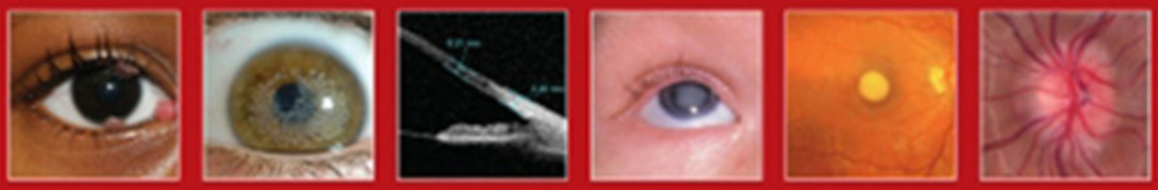


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PEDIATRIC OPHTHALMOLOGY AND STRABISMUS



Scott R. Lambert
Christopher J. Lyons

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Foreword

After publication of the fourth edition of this book we decided it was time that we ask two younger colleagues to assume the role of editors for the fifth edition. We were very pleased when Scott Lambert and Chris Lyons accepted our invitation to assume this responsibility. Both of them have spent time in our training programs and we recognized that they were uniquely qualified for the task. Both of them maintain broad interests in the field of pediatric ophthalmology and strabismus and their clinical and academic expertise is exceptional. They critically reviewed the previous editions of the book before organizing the chapters and contributors for this edition. They have maintained the important goal of masterfully compressing the information discussed in the book in order that it can be presented in a single volume. At the same time, every effort has been made to ensure that each chapter reflects our most current and thorough understanding of the topic under discussion. A wide range of illustrations including clinical and pathological photographs, graphs, and charts enhance and clarify the text. We consider this edition to be an essential resource for all of us interested in the care of children's visual problems and the management of strabismus. We wish to sincerely thank Scott and Chris and their collaborators for producing this excellent fifth edition.

David Taylor
Creig Hoyt

Preface

After editing the first four editions of *Pediatric Ophthalmology and Strabismus*, David Taylor and Creig Hoyt passed the torch to us for the fifth edition. We were honored to be asked, having both been involved since the early editions. However, we did wonder if textbooks are becoming a victim of disruptive innovation in the field of medical education. We are both actively involved in teaching of Medical students, Residents and Fellows and have witnessed the increasing use of online searches by trainees to access medical information. As a result, one of the criteria we decided on from the onset was that the content of each chapter of the fifth edition must be far superior to the results of an internet search on the topic. We believe that every chapter in this book has exceeded this goal.

Each chapter in the fifth edition has been written or updated by one of the foremost experts in the field. Many new chapters have been added to the fifth edition reflecting advances in the field of pediatric ophthalmology. These chapters range from the use of anti-VEGF agents to treat retinopathy of prematurity, the use of optical coherence tomography to image a child's eye, minimally invasive strabismus surgery (MISS), the latest technology for vision screening and apps for pediatric ophthalmology. We have also tried to make the fifth edition very practical, adding chapters on managing refractive errors in children, delivering bad news, as well as many new line drawings to the chapter on strabismus surgery. All of the videos included with the book are now narrated and like the fourth edition, there will be a digital version of the book that can be downloaded to tablets and smart phones. We have found this to be helpful with patient and trainee education in the clinic and also a wonderful resource to look up information when examining a patient.

We have enjoyed the opportunity to make new friendships and to renew old friendships in the process of soliciting and editing chapters for the fifth edition. The level of enthusiasm was invigorating. Our hope is that this textbook will "level the field" throughout the world in the care of disorders of the eye.

The Elsevier team have been wonderful to work with. Sam Crowe has been on the front lines corresponding with authors, reviewing the format of chapters and moving the book along. Russ Gabbedy has helped us understand the production process and the marketing of the book and Julie Taylor has helped considerably with the proof stage and project management.

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A history of pediatric ophthalmology and strabismus

David S Taylor

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Introduction

Aided by ophthalmologists in many countries, I have given an international and a personal perspective to the intertwined specialties of pediatric ophthalmology and strabismology. I had to leave out many important contributors to pediatric ophthalmology, naming mostly those long retired or dead.

Early beginnings

Eye diseases are common in children so they have always been found in doctor's practices. Hippocrates and his pupil Galen, the Greco-Roman philosopher, anatomist (and gladiators' physician), must have had many children as patients. So must the physicians distinguished in the management of eye conditions such as William Briggs in 17th century London and Jacques Daviel in Paris. In the 18th to 19th centuries, William Mackenzie in Glasgow, John Cunningham Saunders (a founder of Moorfields Eye Hospital), Benjamin Travers, James Wardrop, and William Cheselden in London all wrote about children's eye conditions and practiced surgery with techniques and instruments developed for adults (Fig. 1.1). In continental Europe, Georg Joseph Beer, founder of the first eye hospital, in Vienna in 1786, Hermann von Helmholtz, Franciscus Cornelis Donders, and others were pioneers of management of children's eye diseases.

Setting the background

- *Anesthesia*: Joseph Priestley and Thomas Beddoes of the philosophical–scientific 18th century Lunar Society, and Humphry Davy, discovered the anesthetic properties of nitrous oxide. Hepatotoxic chloroform and explosive ether were also used as early anesthetics, the latter being used for infant glaucoma at one hospital, which carried on to nearly the 21st century, until a flashback occurred through a "safety venting" system opening onto a roof being repaired with a blowtorch.
- *Antisepsis*: Alexander Gordon (Scotland), Louis Pasteur (France), Oliver Wendell Holmes (USA), Ignaz Semmelweiss (Hungary), and Charles White (England) pointed towards the germ theory of infection. Joseph Lister proved it with the effects of carbolic acid and layered dressings, leading to previously unbelievable low infection rates.
- *Antibiotics*: The discovery of penicillin by Alexander Fleming, Ernst Chain, and Howard Florey, and of sulfonamides by Gerhard Domagk, revolutionized management of eye diseases in children.

The 19th century: the rise of children's hospitals

Hospitals caring specifically for children by doctors with pediatric skills, if not formal training, led to the pediatric super-specialties. In London in 1741, Captain Thomas Coram, supported by William Hogarth and George Frideric Handel, established of the Foundling Hospital, a home for healthy abandoned "foundlings"; it had no medical role but had



Fig. 1.1 Cataract Surgery as practised by John Cunningham Saunders in 1811. A small team would hold the child still; restrained, the surgery would be over in a flash, the child hopefully young enough and drugged enough with liquor or opium to forget. William Mackenzie of Glasgow said, in answer to the question of when to operate, "The answer decidedly is to operate in infancy". He was aware that late operation was accompanied by a worse visual outlook and more difficult surgery. © Gillian Lee Illustrations.

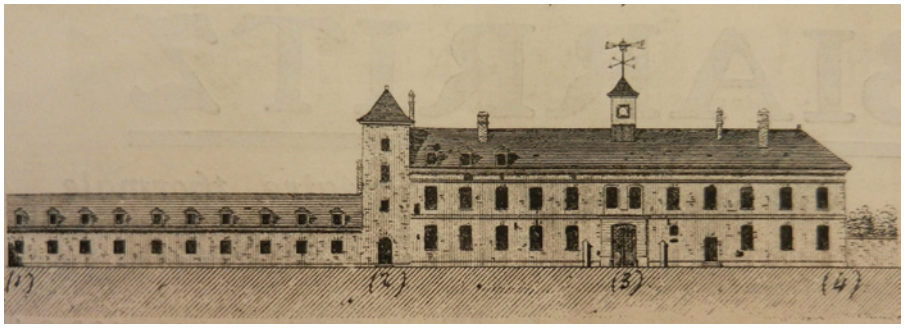


Fig. 1.2 In 1769 the London Dispensary was opened at Holborn by George Armstrong, accepting child out-patients but closed soon after. Similar institutions offered help to children during the chaos of the French Revolution but the first hospital for the treatment of sick children was the Hôpital des Enfants-Malades founded in 1802 on the Rue de Sèvres in Paris (above). Hospitals in Frankfurt, Munich, Hamburg, St. Petersburg soon followed. The Hospital for Sick Children, Great Ormond Street, London was the first in the English speaking world; it opened on the St Valentine's day in 1852. The child mortality rate at that time was truly shocking: of 50,000 persons dying annually in London, 21,000 were children under 10. From Lereboullet, Pierre. L'Hopital Des Enfants-Malades (1802-1913). Paris Médical. 1913–14;1:3–19. Written as the hospital was being demolished.

a profound social influence. Great Ormond Street (GOS) Hospital was later founded in an adjacent street. L'Hôpital des Enfants-Malades was founded in 1802 in Paris (Fig. 1.2), becoming the first effective children's hospital[1]; others in Europe soon followed.

Children's hospitals in Philadelphia (1855) and Toronto (1875), on a similar model to GOS, were for children and their pediatricians – this was the vanguard of scientific medicine. The ophthalmologists there learnt pediatric skills and embraced scientific medicine. Early GOS ophthalmologists included Robert Marcus Gunn, Edward Nettleship, George Coats, and Philip Doyne.

The 20th century: ophthalmology super-specialization in North America

By the early 20th century, the major specialties, including ophthalmology, were established. Specialist societies were often conjoined: the American Academy of Ophthalmology only separated from its partner, Otolaryngology, in 1979.

Dr Frank Costenbader of Washington DC, who had trained in ophthalmology and otolaryngology, developed particular expertise in children's eye disorders. In 1943, he limited his practice to children, becoming the first pediatric ophthalmologist.

After World War II, the pace of specialization and the quality of training quickened. Ophthalmologists trained as super-specialists through dedicated fellowships, replacing the previous apprenticeship system, i.e. "sitting at the feet" of a well-known teacher.

Dr Costenbader's first trainee, Dr Marshall Parks, became the United States' most prominent pediatric ophthalmologist with wide pediatric expertise. This first fellowship program was followed by many others run by Hermann Burian, Arthur Jampolsky, Phil Knapp, Gunter von Noorden, Martin Urist; and in Canada by Jack Crawford in Toronto, William G Pearce in Alberta, and John Pratt-Johnson and Andrew Q McCormick, both in Vancouver. Their fellows included most of the best-known names today; North American Pediatric Ophthalmology is what it is today because of their clinical activity, research, teaching and collegial behavior.

The 20th century in Europe, Asia, South America, the Middle East, Africa and elsewhere

Most European countries had, and many still have, apprenticeship systems to enter pediatric ophthalmology as a consultant. Since the 1970s, many European ophthalmologists have undertaken a fellowship before applying for definitive positions. Fellowship training in pediatric ophthalmology is available worldwide and can be supported by work in state health services, national, or international grants, including grants from the International Council of Ophthalmology for ophthalmologists from developing countries. Table 1.1 shows *some* of those who, by their teaching, research, and clinical acumen, have forged the current state of our profession.

Table 1.1 Key pioneers in pediatric ophthalmology from Europe, Asia, South America, the Middle East, Africa, and elsewhere

Above is a list of *some* of those who by their teaching, research, writing, acumen and example have forged the current state of our profession. I was greatly helped in compiling this list and the chapter as a whole by generous colleagues in 35 countries but it has been impossible to include more than a small proportion of the thousands who have made up our trainers, teachers and those who have taught by example and by lucid writing. I have included a few of those still living and only those whose practices have been predominantly involved with children.
Several countries not mentioned herein have predominantly generalist ophthalmologists who also look after children. They may not be included here despite providing high quality ophthalmology services for children and sometimes outstanding research.

Country	Name and dates (where known)	Distinguished for/in
EUROPE		
Belgium		
Belgium, Ghent	Daniel van Duyse, 1852–1924	Published extensively, mostly developmental anomalies
Belgium, Ghent	Jules François, 1907–1984	Published widely, mostly on genetic diseases
Belgium, Antwerp	Adolphe Neetens	Neuro-ophthalmologist. Vitreoretinal diseases
Belgium, Ghent	Jean-Jaques DeLaey	Retinal diseases. International work
DENMARK		
Denmark, Århus	Mette Warburg, 1926–2015	Co-founder EPOS. Management of child VI. Eponymous syndrome
Holland		
Holland, Utrecht	PJ Waardenburg, 1886–1979	Ophthalmic geneticist. Eponymous syndrome
Holland, Rotterdam	AThM van Balen	Pediatric IOLs, electrophysiology
Italy		
Italy, Rome, etc.	Giovanni B Bietti, 1907–1977	Spoke 7 languages, 14 eponymous signs or diseases. Large practice: child glaucoma. Introduced cryoRx
Italy, Rome, etc.	Bruno Bagolini, 1924–2010	Great teacher, mentor, and inventive strabismologist
Norway		
Norway, Hamar	Ruth Riise, 1934–	Co-founder EPOS. Retinal dystrophies. International work
Norway, Oslo	Sigmund Spetalen, 1937–	Electrophysiology and retinal diseases. King's gold medal
Norway, Ullevål Oslo	Jan Ytteborg, 1925–	Management of congenital glaucoma throughout Norway
Sweden		
Sweden, Stockholm	Eva Lindstedt, –2014	VI and rehabilitation. Screening for amblyopia
Sweden, Goteborg	Kerstin Strömland	Teratology: fetal alcohol and Möbius syndromes
United Kingdom		
UK, London	Arnold Sorsby, 1900–1980	Early ophthalmic geneticist. Refractive development research. Eponymous syndromes
UK	Claud Worth, 1869–1936 Bernard Chavasse, 1888–1941 James H Doggart, 1900–1989 T Keith Lyle, 1904–1987 Kenneth Wybar, 1921–1992	Writers of early publications (see text)
UK, Leeds	Brian Harcourt, 1934–1987	Prominent in national and international pediatric ophthalmology development
UK, London	Barrie Jay, 1929–2007	Co-founder EPOS. Ophthalmic genetics

Continued

Table 1.1 Key pioneers in pediatric ophthalmology from Europe, Asia, South America, the Middle East, Africa, and elsewhere—cont'd

Country	Name and dates (where known)	Distinguished for/in
SOUTH AMERICA		
Argentina, Cordoba	Alberto Urrets-Zavalía, 1920–2010	Spoke 8 languages; cyclovertical disorders, eponymous syndrome
Argentina, BA	Alberto Ciancia, 1924–	Eponymous syndrome, prolific author and teacher
Brazil, Sao Paulo	Carlos Souza Dias	Strabismus; multiple treatises
Brazil, Sao Paulo	Jorge Alberto F Caldeira	Strabismus, prolific author and teacher
ASIA PACIFIC		
Australia, Melbourne	J Ringland Anderson, 1894–1961	Cyclovertical strabismus and nystagmus
Australia, Sydney	Norman Gregg, KB, 1892–1966	Congenital rubella syndrome
Australia, Sydney	Frank Billson	Research and teaching. Political and international work
China, Tianjin	He Yu-shi, 1922–1981	Published on pediatric ophthalmology and strabismus
China, Beijing	Liu Jia-qi	Prolific author and teacher of pediatric ophthalmologists
India, Madurai	P Vijaylakshmi	Worldwide teaching and training and research
Japan, Tokyo	Yasuo Uemura, 1924–1996	Strabismus, amblyopia and ROP
Japan, Kyoto	Makoto Nagata, 1925–	ROP Rx, ERGs, eye surgery textbook in 6th edition
Korea, Seoul	Bong Leen Chang, 1939–	Pediatric neuro-ophthalmologist; prolific author and teacher
Korea, Seoul	Yoonae Choo	Prolific author and trainer of many university teachers
Philippines, Manila	Dr Evelyn Cortes	Founder PSPOS. Wide training. Multiple trainees
MIDDLE EAST AND AFRICA		
Egypt, Alexandria	Hussein Ali Hussein	Founded advanced surgery unit for childhood cataract
Iran, Tehran	Ziaeddin Yazdian	Established pediatric ophthalmology and strabismus in Iran. Prolific author
Jordan, Amman	Hasan Al-Kattan, 1959?–2004	1st Jordanian pediatric ophthalmologist. Prolific teacher
S Africa, Capetown	Justin van Selm, 1919–2009	Strabismus and intraocular surgeon; teacher and traveller

cryoRx, Cryotherapy; EPOS, European Paediatric Ophthalmological Society; ERGs, electroretinograms; IOLs, intraocular lenses; PSPOS, Philippine Society of Pediatric Ophthalmology and Strabismus; ROP, retinopathy of prematurity; VI, visual impairment.

Serendipity, clinical observation, and collaborative science in the advance of pediatric ophthalmology

An ophthalmologist in Sydney during World War II, Dr Norman Gregg, saw an increase in referrals for congenital cataract. He fortuitously overheard some of the mothers say they had rubella during pregnancy. The publication of his observations,[2] even though researched and refined, was not met with universal acclaim. Doggart[3] wrote, "Gregg found himself for a time withered by the pity of his cobbers in the antipodes … 'poor old Norman,' they said, 'he's gone nuts. This rubella's a fair cow' … Soon they were eating their words!" Worldwide honors soon followed, as well as two Nobel Prize nominations.

The management of unilateral congenital cataract illustrates the changing attitudes of ophthalmologists to the risks and benefits of management for the patient's best interests. Before the 20th century, success was measured more by the survival of both the patient and the eye operated on, rather than by measurably better vision. Even bilateral cataracts were left until the child was older. Treacher Collins,[4] in 1908, suggested "… to wait until the child is 10 months before operating … the cornea is so small and the anterior chamber so shallow …" Alexander,[5] in 1928, said, "… I would not hesitate to operate as early as 9 months."

Frank Juler[6] in 1921, on traumatic cataract, stated "… there is such a disease as amblyopia from disuse, that affects the eyes of children up to the age of six years, that it does not attack eyes after the age of seven, that it is not merely a standing still of the development of the retina or certain cerebral associations, but that it causes a real retrogression of the effective power …" Broendstrup,[7] in 1944, noted that not just the cataract but also the aphakia alone may be "ambliopiogenic." No details of refraction, near correction, or of any occlusion of the dominant eye were given.

Prudhommeaux,[8] in 1962, operated 65 cases: 17 were unilateral; all got good light perception or less. "Il faut alors poser la question: pourquoi doit-on opérer les cataractes congénitales unilatérales?" ("We must then ask the question: why should we operate unilateral congenital cataracts?").

Nutt[9] stated, "Uniocular cataracts are better left un-treated, except for cosmetic reasons … the visual result is always bad … the chances are that the affected eye is abnormal in some other respect." Jules François[10] wrote, "Everyone knows the uselessness of operating on unilateral congenital cataract." The general opinion everywhere then was against any intervention.

Along with the growing understanding of amblyopia, things changed. von Noorden and colleagues[11] wrote "It may be well worth while a trial to aspirate a unilateral mature congenital cataract (that is not accompanied by other anomalies) within the first days of life to be followed by immediate contact lens correction." No doubt there were some skeptics but not all were. Frey et al.,[12] a group in Washington DC, operated on and fitted a contact lens that was worn for up to 12 hours daily for 21 idiopathic unilateral congenital cataracts. Occlusion of the phakic eye was attempted. Three of the youngest, with good contact lens wear but unspecified occlusion, achieved 20/40 or better. The team wrote, "… the dictum of extreme conservatism in the management of monocular cataracts in children needs to be re-evaluated."

At this point, several groups were trying to unlock the door to successful treatment. A group in London[13] managed 23 cases with unilateral congenital cataract with surgery, contact lens, and graded occlusion. They agreed that later surgery gave worse visual results. They were looking towards very early surgery, contact lens wear, and graded occlusion, but they found that "… correction before 4 months of age produces less visual loss but we cannot specify the function within this period."

Creig Hoyt's group[14] in San Francisco preceded their study by talking with neonatologists about detecting neonatal cataracts and referring them early: they received cases almost as soon as they were born and published a case series of eight neonates with monocular cataract treated with immediate surgery, vigorous occlusion, and contact lenses. Five developed visual acuities of LogMAR 0.18 (6/9, 20/30, 0.67), three with LogMAR 0.6 (6/24, 20/80, 0.25). This was a stunning achievement, marred only by the time it took the skeptics, including myself, to believe it! It required great expertise and teamwork, the parents being pivotal. Many other cases were then similarly managed by individuals or teams, and good visual results weren't unusual and occasional cases even had high levels of binocular vision.

A debate arose regarding the risks and benefits for the affected baby. It was now possible to achieve good vision in unilateral congenital cataract. However, since the operated eye might become the best and one most used, the risks of glaucoma and other complications are high in the first weeks of life, and sympathetic ophthalmitis has been recorded, these risks may, in the parent's view, outweigh the benefits of having a "spare eye." That parental informed choice was paramount took some time to be accepted, and the weighing of risks and benefits became the basic currency of the contract with a patient.

Government funding has been behind many of the largest and best collaborative studies in many fields of science. In 1997, the Pediatric Eye Disease Investigator Group (PEDIG), a collaborative network facilitating multi-center clinical research in childhood eye disorders was formed in the USA. It has over 100 participant centers and has resulted in the publication of nearly 100 well-constructed collaborative studies. Another study, also government-funded by the National Eye Institute, is the Infant Aphakia Treatment Study (IATS), which asks vital questions on cataract management with intraocular and corneal contact lenses in 114 affected patients with long follow-up.

Although centrally funded research in children's eye diseases is most important in many other countries, much is essentially the result of diversely funded groups of collaborators. In the UK, for instance, these include the European Eye Epidemiology Consortium, the British Isles Congenital Cataract Interest Group, the British Childhood Onset Hereditary Retinal Disorders Network, the 1958 British Birth Cohort, the British Ophthalmological and Paediatric Surveillance Units, and the British Childhood Visual Impairment Interest Group.

Orthoptists and pediatric ophthalmology

Mary Maddox, the daughter of Ernest Maddox, an ophthalmologist with a deep interest in eye muscles, optics, refraction, and binocular vision, started a clinic in London in 1928, and was soon joined by Sheila Mayou, the daughter of a London ophthalmologist. At Moorfields Eye Hospital, High Holborn, they started a public clinic and school of orthoptics. Beryl Mayou travelled extensively during World War II and afterwards ran a training course, launching orthoptics in Brazil. They and other orthoptists, Vivien MacLennan, Sylvia Jackson, Joyce Mein, Jona Yoxall, and Barbara Lee in the UK, Birgitta Neikter in Sweden, Catherine Turbayne Lunn and Geraldine Tillson in Canada, and others in North America, France, Holland, South Africa, Australia, and Japan showed how orthoptists were *vital* colleagues in diagnosis and management of patients with strabismus, to the great benefit of patients and cost savings to service providers.

Early publications on pediatric ophthalmology and strabismus

In 1583, the first ophthalmology textbook, *Augendienst*, by Georg Bartisch, included the management of strabismus. The first strabismus surgery was claimed in 1751 by the English charlatan (and brilliant physiologist?) "Chevalier" John Taylor, but is generally attributed to Johann Dieffenbach in Berlin in 1839, whose tenotomy was practiced by George Critchett in 1855. A small book entitled *Squinting* by Carsten Holthouse was published in London in 1858. In 1903, Claud Worth published *Squint: its Causes, Pathology and Treatment*. It ran to six editions under his authorship and, read today, it is brilliant. Worth was succeeded by Bernard Chavasse on this book. Chevasse worked with the physiologist Charles Sherrington, embracing physiological concepts based on reciprocal innervation and reflexes. After World War II, James Hamilton Doggart published the first book on pediatric ophthalmology, *Diseases of Children's Eyes* (Fig. 1.3): it was meticulously organized and beautifully illustrated.

T Keith Lyle, a strabismologist and neuro-ophthalmologist, and a prolific author and lecturer, collaborated with The Hon Geoffrey Bridgman on the ninth edition of Worth and Chavasse's book and he also wrote prolifically on strabismus. Kenneth Wybar was the author of the strabismus section of Duke-Elder's *System of Ophthalmology*.

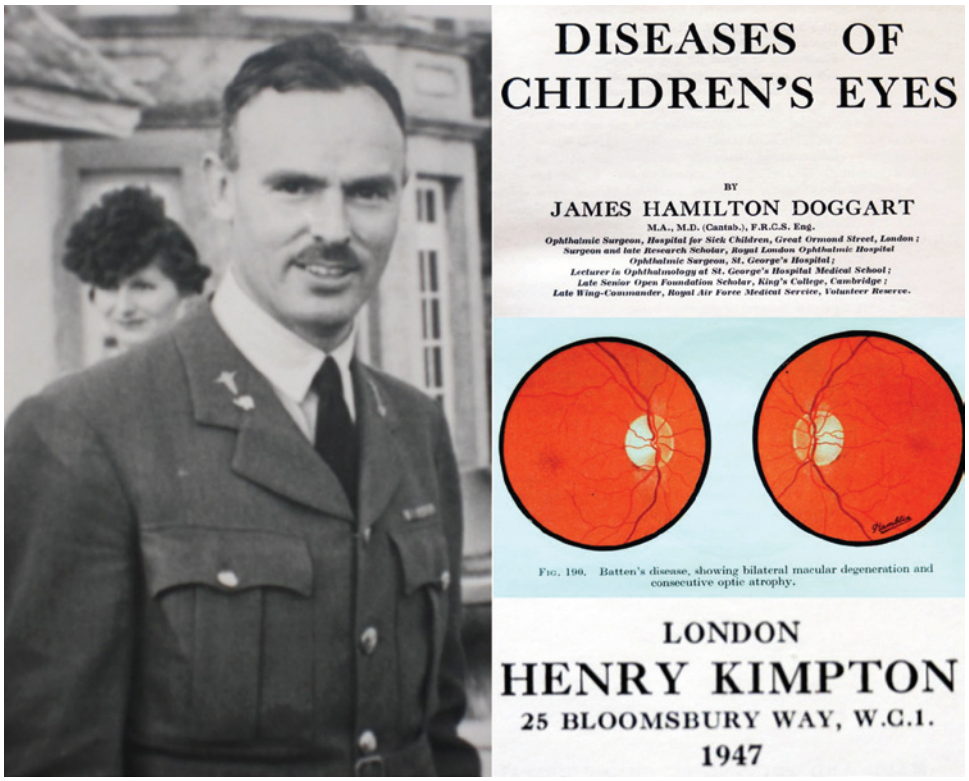


Fig. 1.3 The first textbook on pediatric ophthalmology, *Diseases of Children's Eyes* by James Hamilton Doggart (left) was published in 1947. Doggart was a mostly medical ophthalmologist who had been working in Great Ormond Street in London since at least 1937 and his main interest was in children's eye diseases. He wrote this immaculately prepared text, illustrated with 242 monochrome and colour plates both during and shortly after the World War II which was when this photograph of him was taken: it was published in London and New York in 1947 with a companion book, *Children's Eye Nursing*. This was shortly followed by *Ophthalmic Medicine* and *Slit-Lamp Microscopy* in 1949.

Other contributors to today's pediatric ophthalmology

Where would we be without David Hubel and Torsten Wiesel, Gunter von Noorden (with MLJ Crawford) and the Cambridge group working on amblyopia, the Smith Kettlewell Eye Research Institute, or the Institute of Ophthalmology in London, and so many other scientists, optometrists, instrument manufacturers, and others? It is not just people of the "eye world" to which the field of pediatric ophthalmology is indebted: in the Norwegian mining town of Røros, Dr Otto Christian Stengel (1794–1890), with brilliant observation, described Batten's disease; Carl Credé, a 19th century obstetrician, decimated ophthalmia neonatorum; and Antonie van Leeuwenhoek, a 17th century draper, invented the microscope.

The future

We cannot predict the future, but one thing is certain: the importance of research in pediatric ophthalmology. Furthermore, pediatric ophthalmologists must speak like pediatricians, think like them, and follow their way of managing patients, including the taking of a simple but detailed history, an examination that does not scare the child, well-directed further investigations, and simple, kind, honest explanations, that are understandable by both parents and their child, given by a modest ophthalmologist. We know from history that it is these things which have distinguished successful doctors, far more than the organizing of batteries of tests, brilliance in surgery, or eloquence in the lecture theatre.

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Epidemiology and the worldwide impact of visual impairment in children

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Introduction

This chapter considers important issues about epidemiological studies of childhood visual impairment (VI), severe visual impairment (SVI), or blindness (Boxes 2.1 and 2.2); we synthesize current data to provide a global picture of the frequency, causes, and prevention of VI and blindness in childhood.

Specific issues in the epidemiological study of visual impairment in childhood

- Case definition: A standard definition applicable to all children continues to be challenging, see below.
- Rarity: Visual impairment and blindness in childhood are uncommon; it is difficult to obtain sufficiently large and representative samples of affected children to allow precise and unbiased study.
- Complex, multidisciplinary management: For a complete picture, information must be sought from the professionals involved in the care of VI or blind children. For many children with additional non-ophthalmic impairments or chronic disorders, this adds further complexity.
- Lifecourse approach: It is important in health research to understand the biological, environmental, and lifestyle/social influences at all life stages (preconceptional, prenatal, perinatal, and childhood), and how they combine to set and change health trajectories into adult life. Lifecourse epidemiological and epigenetics approaches are increasingly applied to the study of VI and eye disease affecting children or originating in childhood.[1]
- Developmental perspectives: In all research on children, developmental issues (as distinct from age-related issues *per se*) must be taken into account in assessing outcomes and their relationship with risk factors.
- Long-term outcomes: Assessment of meaningful outcomes, such as final visual function or educational placement, requires long-term follow-up, possibly into adult life for some outcomes. This is challenging and is increasingly addressed through health informatics research. This approach mainly relies on *routinely* collected data, often as electronic or "e" records, in health care (e health records, EHR), and other administrative systems, e.g. educational or welfare. Record (data) linkage using established methods to minimize errors creates complete datasets for analysis. This is a well-established and powerful approach in child health research[2] and has good potential for research in pediatric ophthalmology.
- Ethics. Issues of proxy consent (by parents) and children's autonomy increasingly impact on participation in ophthalmic epidemiological research.

Framing the question

Clinical or service provision decisions are ideally based on "three-part questions" reflected in the PICO mnemonic (**P**opulation **I**ntervention/**C**omparator and **O**utcomes). Thus a good question incorporates the reference population (e.g. children under 2 years with infantile esotropia), the

Box 2.1

What is ophthalmic epidemiology?

Ophthalmic epidemiology (literally "studies upon people") has both its origins and its applications in clinical and public health ophthalmology.

The aim of primary or secondary (e.g. systematic literature review, meta-analysis and modeling) research is to:

- provide quantitative information for planning services
- shed light on the causes and natural history of ophthalmic disorders
- enhance the accuracy and efficiency of diagnosis
- improve the effectiveness of treatment and preventive strategies

Box 2.2

Epidemiological reasoning

This is based on the following principles:

- the occurrence of disease is not random, rather a balance between causal and protective factors
- that disease causation, modification, and prevention are studied by systematic investigation of populations to gain a more complete view than can be achieved by studying individuals
- that any inference that an association between a risk factor and a disease is causal can only be made after two specific steps in reasoning: (1) the exclusion of chance, bias, or confounding as alternative explanations for the observed association, and (2) evidence of a consistent and strong statistical association, which is biologically plausible, in the correct temporal sequence, and preferably exhibits a dose–response relationship

risk factor or the intervention and, where appropriate, a comparator (e.g. preterm versus term birth, or strabismus surgery versus no surgery), and the outcomes (e.g. parent-reported improvement in cosmesis and objective improvement in alignment and stereopsis). The focus of the question – whether frequency, causes, or treatment/prevention of disease – determines the study design required to address it, e.g. a descriptive, cross-sectional prevalence survey, or an analytical study (either observational, e.g. case–control or cohort studies, or interventional, e.g. randomized controlled trials).

Who is a visually impaired child?

The affected child, their parents, teacher, social worker, rehabilitation specialist, pediatrician or ophthalmologist are likely to have differing, but equally valid answers to this question. The issue is not which is "correct" but which definition to choose for epidemiological research, for assessing/planning services and in clinical practice.

A standardized definition is necessary in order to compare the frequency, causes, treatment, or prevention of VI within and between countries and over time. The World Health Organization (WHO) classification (Table 2.1) is based on the acuity in the better-seeing eye (i.e. at the level of the person not the eye) and measured with optical correction, if usually worn. Until recently, uncorrected refractive error fell outside this definition, as the early categories used best corrected visual acuity. It has been adopted for epidemiological research, despite the difficulties of measuring visual acuity in very young children and those unable to cooperate with formal testing.

Table 2.1 World Health Organization classification of visual impairment

Level of visual impairment	Visual acuity in better eye with optical correction (if worn)
Slight, if acuity less than 6/7.5	6/18 or better
Visual impairment (VI)	Worse than 6/18 up to 6/60 (logMAR 0.5 to logMAR 1.0)
Severe visual impairment (SVI)	Worse than 6/60 up to 3/60 (logMAR 1.1 to 1.3)
Blind (BL)	Worse than 3/60 (worse than logMAR 1.3) to no light perception or Visual field <10 degrees around central fixation

MAR, Minimum angle of resolution.
6/7.5 = logMAR 0.10, 20/25, 0.8; 6/18 = logMAR 0.48, 20/60, 0.33; 6/60 = logMAR 1.0, 20/200, 0.10; 3/60 = logMAR 1.3, 20/400, 1.31.0.
Adapted with permission from World Health Organization (WHO). International Statistical Classification of Diseases and Health Related Problems. 10th Revision. Geneva: World Health Organization, 1992.

New methods for testing vision in young children are likely to emerge from technological innovations. Nevertheless, there is a need in epidemiological research and also arguably in clinical practice for a better classification system applicable to children of different ages. This should consider other aspects of vision such as near acuity, visual fields, binocularity, and contrast sensitivity, as well as normal visual development. However its development will be challenging.

Adoption of the WHO International Classification of Functioning, Disability and Health (ICF) reflects the new underpinning framework for understanding disability and the relationship between health conditions, personal, and societal factors.[3] In tandem, the importance of measuring patient-reported outcomes (patient-reported outcome measures, PROMs) conventionally using self-completed questionnaires is now embedded within many health care systems, so as to help improve the quality of care. Two types of PROMs are particularly relevant to pediatric ophthalmology.[4]

1. *Functional vision* assesses the child's ability (difficulty or ease) for tasks of daily living dependent on vision, such as navigating independently.
2. *Vision-related quality of life* elicits the child's and/or parents' view of the gap between the child's expectations and his/her actual experiences with respect to the physical, emotional/psychological, cognitive, and social functioning of the child impacted by the visual disorder and its therapy.[4]

Measures of frequency and burden of childhood visual impairment

The analogy of a barrel of white and red grapes with a hole in the bottom can be used to illustrate measures of frequency and the burden of disease. In this analogy, white grapes represent those without the condition of interest ("healthy") and red grapes represent those who have the condition of interest ("diseased"). The total number of grapes (white plus red) in the barrel represents the population of interest (e.g. all children aged 0–15 years). The *proportion* of all the grapes in the barrel that are red at any given time denotes *prevalence*.

The *total number* of red grapes in the barrel at any given time reflects the *magnitude* or *burden of the disease* in the population. The *speed* at which red grapes enter the barrel equates with *incidence*, i.e. the rate of new occurrence of disease in a given population over a specified time. For example, in the UK the annual incidence of congenital cataract was estimated to be 2.5 per 10,000 children aged ≤1 year in 1995.[5]

However, the proportion in a population that is diseased (i.e. the prevalence) is dynamic, as some grapes (both red and white) leave the barrel through the hole in the bottom. The "diseased" (i.e. red grapes) can leave through mortality, which may be higher amongst those diseased, or by out-migration, or as a result of treatment that means they are no longer classified as diseased. At the same time, more red and white grapes are being added to the barrel. The prevalence (proportion of grapes that are red) at any given time is, therefore, a balance between how fast red (and white) grapes are added and how quickly they leave the barrel. For example, the current UK prevalence in childhood of amblyopia with an acuity of worse than logMAR 0.3 (6/12, 20/40, 0.5) is about 1%.[6]

These measures of disease frequency do not, however, give any indication of the health economic impact or consequences of the disease. These aspects are important in order to determine priorities and allocate resources, providing a metric at population level that complements patient-reported outcomes assessed at an individual level. Measures of "utility" such as disability-adjusted life years (DALYs) or quality-adjusted life years (QALYs) are often used for this purpose, as they incorporate morbidity or mortality into a single measure that can be used to compare different states of health within and between countries. Blindness is categorized in the range 0.43 (blindness from refractive errors) to 0.6 (blindness from glaucoma), where 0 equates to perfect health and 1 equates to death.[7]

Prevalence and incidence data provide *complementary* information. Incidence identifies and monitors trends *over time* that reflects changing exposure to risk factors, or emergence of new exposures. Incidence data are useful for planning the provision of services and research, e.g. estimating likely recruitment time in clinical trials. Prevalence indicates the proportion of the population with the condition *at a given time*. It helps allocate resources and can be used to evaluate services, if changes in prevalence can be attributed solely to changes in outcome or duration of disease as a result of treatment rather than changes in underlying incidence.

Potential sources of information about visual impairment

There are a number of sources of epidemiological information about childhood VI or blindness but, in reality, only a few are available in most countries. This explains the currently incomplete picture (Box 2.3).[8]

1. *Population-based prevalence studies.* These represent a source of precise, representative estimates of burden (frequency) and causes. However, the few studies of whole populations of children with VI, such as prior and upcoming national birth cohort studies in the UK,[9] need to be very large (a study of 100,000 children is required in an industrialized country to identify 100–200 children with VI or blindness): these are costly and difficult to do.
2. *Population-based incidence studies*. Studies of all-cause incident (newly occurring) VI are even more difficult, explaining the rarity of studies of this kind.[10]
3. *Special needs/disability registers, surveys, and surveillance.* Specific studies and/or surveillance systems[11] or registers of childhood disability[12] can provide information about VI, but it is important to recognize the potential for bias, as certain visually impaired children may be over-represented in these sources, e.g. those with multiple impairment.
4. *Studies of intervention/service-based populations*. In developing countries, studies of children in special education provide information on causes, but these may be biased because many affected children (particularly with additional non-ophthalmic impairments) do not have equal access to special education. With other service-based studies, e.g. from clinic attendees, the interpretation of findings and their extrapolation to other populations needs to take these biases into account.
5. *Visual impairment registers*. These exist in many industrialized countries but, if registration is voluntary and not a prerequisite for accessing special educational or social services, registers may be incomplete as well as biased, reflecting differences in parental preferences and professionals' practices regarding registration of eligible children.[13,14]
6. *Visual impairment teams*. Increasingly, children in industrialized countries are evaluated by multidisciplinary teams. They can provide useful information if these teams serve geographically defined populations.
7. *Disorder-specific ophthalmic surveillance schemes.* Uncommon eye conditions in children can be studied using population-based surveillance schemes, such as those for congenital anomalies (e.g. anophthalmia, microphthalmia, congenital glaucoma)[15,16] or others for adverse drug reactions (e.g. visual loss with vigabatrin).[17] Under-ascertainment can occur. In the United Kingdom, the national active surveillance scheme includes all senior ophthalmologists (the British Ophthalmological Surveillance Unit).[11] It supports studies of uncommon disorders, including the first population-based incidence

Box 2.3

Key gaps in current knowledge about epidemiology and the impact of visual impairment on children

For many regions of the world, there is currently very limited contemporary population-based information about frequency, burden, and etiology.

There is limited understanding of the following:

- long-term ophthalmic disease, general and mental health, educational, occupational, and social outcomes for affected children and the adults they become
- social, economic, and personal impact on the families of affected children
- economic consequences – including financial and other costs associated with medical treatment, rehabilitation, social support and care, as well as loss of productivity

The opportunities and infrastructure for research to address these questions are better in industrialized countries, so there is currently a differential information gap.

study of SVI and blindness in childhood.[10] This is an important model for pediatric ophthalmic epidemiological research.

8. *Community-based rehabilitation programs.* In many developing countries, rehabilitation of blind and VI children is occurring within the community. Where the size of the catchment population is known, it is possible to estimate prevalence and obtain population-based data on causes.[18]
9. *Case ascertainment using key informants.* In many developing countries, it may be possible to identify key community and religious leaders, health care workers, and others who know their communities well and thus can identify children believed to have VI or ocular disorders. This can be combined with the size of the population at risk, to estimate prevalence and provide population-based data on the causes.[18,19]
10. *Household surveys* are commonly used in many low-income countries to collect data on a range of health indices. This approach can also be used to identify children who are blind.[20]
11. *Data modeling* can also be used for specific conditions, as has recently been used to estimate the global incidence of blindness and visual impairment from retinopathy of prematurity.[21]

Regardless of the sources, ascertainment is often incomplete and/or biased. For example, in industrialized countries, families from socially disadvantaged groups or ethnic minorities are less likely to participate in research on health services for visually impaired children.[12] Participation/selection bias affects our ability to generalize findings, especially in research on rare disorders. Also, in some communities in low-income countries, having a disabled child is a source of stigma, which can lead to under-ascertainment. Using multiple sources generally provides a more complete and reliable picture of causes and frequency of childhood VI.[22,23]

Impact of visual impairment

Visual impairment in childhood impacts on all aspects of the child's development and shapes the adult he/she becomes, influencing employment, social prospects, and lifelong opportunities.[13–15] Although the prevalence and incidence of VI are lower in children than in adults, the years of life lived with VI ("person-years of visual impairment") are considerable.[24] Personal and social costs are important, but difficult to measure (see Box 2.3). The economic costs of childhood VI in terms of loss of economic productivity are significant,[25] a quarter of the costs of adult blindness in some countries.[26] For example, in India an estimated annual cumulative loss of gross national product attributable to childhood VI was US$ 22 billion.[26]

Visual impairment in the broader context of childhood disability

Multiple impairments

In high-income countries, at least half of all severely visually impaired and blind children also have motor, sensory, or learning impairments or chronic systemic disorders which impact on development, education, and independence.[10,27] In low-income countries, the proportion is probably smaller, reflecting the incidence of conditions such as ophthalmia neonatorum, which causes purely ocular disease, and the high mortality rates among children who are blind from conditions associated with multiple impairment, for example congenital rubella syndrome, meningitis, or brain tumors.

For *research* on etiology and interventions, and for provision of services, it may be helpful to think about two separate populations:

1. children with isolated VI;
2. children with VI and other impairments or systemic diseases.

Mortality

Children with visual impairment are more likely to die than other children. In low-income countries,[28,29] children who become blind from keratomalacia (acute vitamin A deficiency) have a very high mortality rate. Other blinding conditions are also associated with high mortality, e.g. measles infection, meningitis, congenital rubella syndrome. In high-income countries, visually impaired children also may have higher mortality rates: in the UK, 10% of SVI or blind children die within a year of diagnosis.[10]

Prevalence studies of older visually impaired children exclude those who died before school age. This underestimate of the true frequency results in bias.

Groups at high risk of visual impairment

In research and resource allocation, VI should be viewed in the context of other childhood disabilities. The social determinants of visual health are poorly defined, but some children are at increased risk of visual loss: children with low birth weight, those who are socioeconomically deprived or from ethnic minorities.[10] Because these higher risk groups are also less likely to participate in health services research,[30] selection bias may occur through sociodemographic factors.

Frequency of childhood visual impairment and blindness

Prevalence

In the absence of direct data for many settings, an approach has been developed to estimate a proxy prevalence based on the association between the prevalence of blindness in children and the under-5 mortality rates (U5MRs) for a country.[31] In high-income countries with U5MRs less than 20 per 1000 live births, the prevalence of blindness is approximately 3–4 per 10,000 children. By contrast, in countries with U5MRs of >200 per 1000 live births (e.g. the poorest countries in sub-Saharan Africa), the prevalence of blindness is nearer 12–15 per 10,000 children, as shown in Fig. 2.1. This reflects three factors:

1. exposure to risks and potentially blinding conditions not found in affluent regions (e.g. vitamin A deficiency, cerebral malaria);
2. the occurrence of conditions adequately controlled elsewhere (e.g. measles infection through immunization);

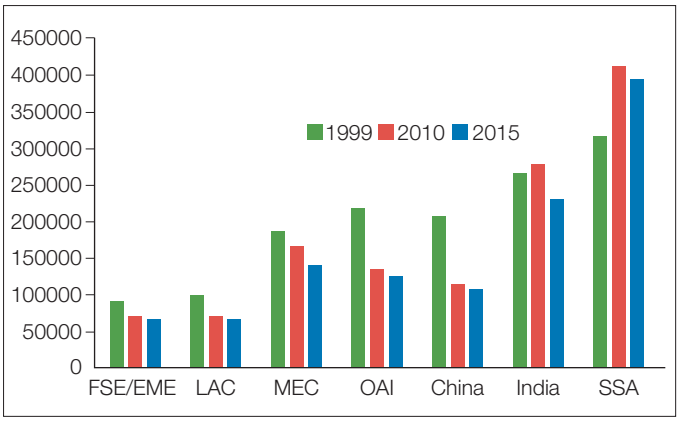


Fig. 2.1 Magnitude of blindness in children, by World Bank region. EME, Established Market Economics; FSE, Former Socialist Economics; LAC, Latin America and Caribbean; MEC, Middle East Crescent; OAI, Other Asia and Islands; SSA, Sub-Saharan Africa. Note: World Bank regions have changed over time. Data are presented according to groupings as in 1990 to allow comparison over time.

3. limited access to services and treatments that ameliorate disease progression (e.g. management of retinopathy of prematurity [ROP]) or that restore visual function (e.g. high-quality management of cataract).

VISION 2020 was launched in 1999, when it was estimated there were 1.4 million blind children in the world,[28] (using U5MRs for 1994 to reflect the midpoint of the 16 years of childhood and total child population of each country for 1999). Fig. 2.1 shows these data by World Bank regions, i.e. grouping countries by composite development indicators, such as maternal education level, which predict general child health and are associated with ophthalmic disease and visual impairment. The figures were revised in 2010 and, because of falling U5MRs, the estimate had fallen by 10% to 1.26 million.[32] A further revision in 2015, also shown in Fig. 2.1, shows an additional decrease to 1.14 million. However, there has been a differential decline by region, being greatest in China and "Other Asia and Islands" regions. In both India and sub-Saharan Africa, the 2015 estimates are lower than in 2010, reflecting improved child survival as well as a leveling off of the number of children aged 0–16 years. Nevertheless, these regions have the highest estimated absolute number of blind children, reflecting higher prevalence in larger total child populations.

Prevalence and incidence studies reported since 2000 have used various approaches. As shown in Table 2.2 and Fig. 2.2, there is a trend of higher prevalence in low-income countries, such as Sudan, Bangladesh and India, which increases as under-5 mortality rates increase. However, the low prevalence estimates for sub-Saharan African countries are probably artefactual, arising from methodological or cultural issues with the key informant method used for case ascertainment. Another explanation is that blind children in Africa have a very high mortality rate. The prevalence of VI is still not known for many regions.[32] In most settings, SVI and blindness (BL) account for one-third of all levels of visual impairment. In high-income countries, the combined prevalence of VI, SVI, and BL is about 10–22 per 10,000 children aged <16 years, while in some developing countries it is 30–40 per 10,000.[29]

Incidence

Contemporary incidence data are lacking for many countries. Since 2000, there have only been two incidence studies reported (see Box 2.3 and Table 2.2). In the UK, from a population-based study, the age group-specific incidence was reported to be highest in the first year of life at 4.0 per 10,000 per year, with the cumulative incidence (lifetime risk) increasing to 5.9 per 10,000 by 16 years of age.[10] This is likely to be applicable to countries with similar socioeconomic development and access to services, but the incidence in many lower income countries is probably higher.

Causes of visual impairment

The WHO classification has helped us to understand the relative importance of the different causes of VI, including comparisons between countries and within countries over time. This uses the principal "anatomical site" affected, as well as the underlying etiology, categorized according to the timing of action (Table 2.3).[33] It is now used extensively worldwide.

Variation by region and over time

The causes of visual impairment in children in a country reflect the balance between the biological, environmental, and social determinants of ophthalmic disorders and the strategies, policies, and resources available for their prevention or treatment – hence the regional variation in the relative importance of different disorders (Tables 2.4 and 2.5). Over the last few decades, levels of socioeconomic development have changed rapidly, together with greater provision of eye care services for children. Both factors influence the pattern of causes of blindness.[34]

Data from studies published since 2000, which used a variety of data sources ranging from special schools to visual impairment registers, are summarized in Table 2.6 (sources listed online). Many studies used the WHO categories of visual loss and classification system, making the data directly comparable. However, where necessary, data from other studies have been re-grouped to allow comparison. Lesions of the higher visual pathways, and the context of prematurity, predominate in the wealthiest countries. Acquired conditions of childhood leading to corneal scarring only occur in the poorest countries.

Insufficient data on the causes have been published between 1999 and 2015 to allow change over time to be assessed for this relatively short time period. Taking a longer-term perspective, several patterns emerge. First, in high-income countries, ophthalmia neonatorum and other causes of corneal scarring have substantially diminished and the outcomes of surgery for cataract and glaucoma have improved. At the same time, survival of extremely preterm infants has improved, meaning that cerebral VI and retinopathy of prematurity (ROP) have increased in incidence, and the inherited retinal dystrophies have become relatively more important.[18] Second, corneal scarring is declining in importance in the poorest regions, reflecting socioeconomic development and public health interventions for the control of measles and vitamin A deficiency among pre-school-age children. In many countries in these regions, un-operated cataract, or poor outcomes after surgery, are now the commonest avoidable cause of blindness. Another change is the dramatic increase in blindness due to

Table 2.5 Causes of blindness in children published between 2000 and 2015, classified using the anatomical site of abnormality, by World Bank region

Reference	Country/area	N	Anatomical site of abnormality																	
			Whole globe		Cornea		Lens		Uvea		Retina		Glaucoma		ON		CVP		Others	
EME/FSE																				
Kocur 2001[57]	Czech Rep	229	6%	14	2%	5	9%	21	5%	11	54%	124	5%	11	15%	34	2%	5	2%	5
Mitry 2013[58]	England/Wales	443	16%	71	1%	4	2%	9	2%	9	23%	102	1%	4	13%	58	34%	151	8%	35
Durnian 2010[59]	England	256	5%	13	0%	0	4%	10	7%	18	31%	79	1%	3	21%	54	27%	69	4%	10
Boonstra 2012[60]	Netherlands	2843	2%	57	0%	0	5%	142	3%	85	21%	597	0%	0	12%	341	27%	768	30%	853
Chong 2013[61]	New Zealand Maori	100	2%	2	1%	1	1%	1	2%	2	11%	11	0%	0	34%	34	41%	41	8%	8
Flanagan 2003[62]	Scotland	19	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%	0	29%	5	0%	0
Alagaratnam 2002[63]	Scotland	107	11%	12	1%	1	0%	0	0%	0	36%	39	2%	2	17%	18	33%	35	0%	0
Bamashmus 2004[64]	Scotland – W	30	0%	0	0%	0	0%	0	0%	0	20%	6	0%	0	23%	7	23%	7	33%	10
Rahi 2003[65]	UK	439	7%	31	2%	9	5%	22	3%	13	29%	127	3%	13	28%	123	48%	211	2%	9
Kong 2012[66]	USA	2760	2%	55	0%	0	3%	83	5%	138	27%	745	3%	83	24%	662	20%	552	16%	442
Hatton 2007[67]	USA	1979	6%	119	0%	0	0%	0	0%	0	29%	574	0%	0	11%	218	26%	515	28%	554
Region overall		**9205**	**4%**	**373**	**0%**	**20**	**3%**	**288**	**3%**	**277**	**26%**	**2404**	**1%**	**117**	**17%**	**1549**	**26%**	**2358**	**21%**	**1926**
LAC																				
Haddad 2007[68]	Brazil	3210	3%	96	1%	32	7%	225	4%	128	38%	1220	7%	225	24%	770	10%	321	6%	193
Zepeda-Romero 2011[69]	Mexico	114	9%	10	2%	2	1%	1	0%	0	48%	55	15%	17	17%	19	0%	0	8%	9
Heijthuijsen 2013[70]	Surinam	65	9%	6	6%	4	15%	10	1%	1	34%	22	5%	3	8%	5	8%	5	14%	9
Overall		**3389**	**3%**	**112**	**1%**	**38**	**7%**	**236**	**4%**	**129**	**38%**	**1297**	**7%**	**245**	**23%**	**795**	**10%**	**326**	**6%**	**211**
EMR																				
Razavi 2010[71]	Iran	27	33%	9	4%	1	0%	0	0%	0	44%	12	7%	2	8%	2	4%	1	0%	0
Mirdehghan 2005[72]	Iran	329	5%	16	9%	30	14%	46	0%	0	51%	168	8%	26	10%	33	0%	0	3%	10
Dehghan 2010[73]	Iran	200	18%	36	4%	8	7%	14	1%	2	63%	126	0%	0	7%	14	0%	0	0%	0
Mehdizadeh 2005[74]	Iran	143	21%	30	1%	1	6%	9	0%	0	54%	77	16%	23	1%	1	0%	0	1%	1
Mezer 2015[75]	Israel	1284	0%	0	0%	0	4%	51	0%	0	39%	501	3%	39	17%	218	0%	0	37%	475
Tabbara 2005[76]	Saudi Arabia	53	0%	0	0%	0	8%	4	8%	4	32%	17	0%	0	40%	21	0%	0	12%	6
Zeidan 2007[77]	Sudan	40	2%	1	40%	16	13%	5	0%	0	8%	3	2%	1	2%	1	0%	0	33%	13
Aksoy 2012[78]	Turkey	185	12%	22	4%	7	15%	28	0%	0	41%	76	3%	6	4%	7	1%	2	20%	37
Region overall		**2261**	**5%**	**114**	**3%**	**64**	**7%**	**157**	**0%**	**6**	**43%**	**980**	**4%**	**96**	**13%**	**298**	**0%**	**3**	**24%**	**543**

Continued

Table 2.5 Causes of blindness in children published between 2000 and 2015, classified using the anatomical site of abnormality, by World Bank region—cont'd

Reference	Country/area	N	Anatomical site of abnormality																	
			Whole globe		Cornea		Lens		Uvea		Retina		Glaucoma		ON		CVP		Others	
CHINA/HONG KONG																				
Fan 2005[79]	Hong Kong	82	2%	2	7%	6	5%	4	2%	2	50%	41	12%	10	17%	14	0%	0	5%	4
Shi 2002[80]	China	356	15%	53	19%	68	28%	100	0%	0	23%	82	0%	0	15%	53	0%	0	0%	0
Region overall		**438**	**13%**	**55**	**17%**	**73**	**24%**	**104**	**0%**	**2**	**28%**	**123**	**2%**	**10**	**15%**	**67**	**0%**	**0**	**1%**	**4**
INDIA																				
Gogate 2009[81]	India S	891	39%	347	14%	125	14%	125	0%	0	20%	178	2%	18	4%	36	0%	0	7%	62
Bhattacharjee 2008[82]	India NE	258	32%	83	36%	93	11%	28	2%	5	6%	15	4%	10	5%	13	1%	3	3%	8
Gogate 2007[83]	India Maharashtra	1778	46%	818	22%	391	6%	107	1%	18	11%	196	0%	0	5%	89	0%	0	9%	160
Hornby 2000[84]	India AP	267	20%	53	24%	64	8%	21	3%	8	31%	83	7%	19	5%	13	0%	0	2%	5
Krishnaiah 2012[85]	India S	113	41%	46	8%	9	10%	11	5%	6	19%	21	8%	9	5%	6	0%	0	4%	5
Magdula 2009[86]	India N and S	103	32%	33	13%	13	13%	13	2%	2	22%	23	4%	4	11%	11	0%	0	3%	3
Pal 2006[87]	India North	133	6%	8	7%	9	31%	41	17%	23	16%	21	0%	0	17%	23	0%	0	6%	8
Titiyal 2003[88]	India North	650	27%	176	22%	143	11%	72	9%	59	15%	98	5%	33	11%	72	0%	0	0%	0
Bhalerao 2015[89]	India	90	51%	46	25%	23	10%	9	1%	1	3%	3	3%	3	7%	6	0%	0	0%	0
Region overall		**4283**	**38%**	**1610**	**20%**	**870**	**10%**	**428**	**3%**	**121**	**15%**	**638**	**2%**	**95**	**6%**	**268**	**0%**	**3**	**6%**	**251**
OAI																				
Muhit 2007[90]	Bangladesh	394	18%	71	31%	122	23%	91	1%	4	17%	67	4%	16	6%	24	0%	0	0%	0
Muhit 2007[90]	Bangladesh	1245	11%	137	25%	311	36%	448	2%	25	12%	149	4%	50	9%	112	0%	0	1%	12
Muhit 2007[90]	Bangladesh	296	15%	44	28%	83	29%	86	2%	6	11%	33	5%	15	9%	27	0%	0	1%	3
Muhit 2010[91]	Bangladesh	45	13%	6	13%	6	38%	17	0%	0	9%	4	0%	0	11%	5	0%	0	16%	7
Mactaggart 2013[92]	Bangladesh	184	9%	17	8%	15	27%	50	0%	0	5%	9	0%	0	18%	33	0%	0	0%	0
Sia 2010[93]	Cambodia	62	13%	8	26%	16	27%	17	3%	2	21%	13	5%	3	3%	2	0%	0	2%	1
Cama 2010[94]	Fiji	81	13%	11	2%	2	0%	0	0%	0	45%	36	0%	0	9%	7	28%	23	3%	2
Sitorus 2007[95]	Indonesia, Java	82	40%	33	6%	5	15%	12	7%	6	21%	17	0%	0	11%	9	0%	0	0%	0
Patel 2011[96]	Malaysia	448	11%	49	8%	36	17%	76	5%	22	33%	148	8%	36	8%	36	2%	9	8%	36
Reddy 2001[97]	Malaysia	332	17%	57	15%	50	22%	74	0%	0	21%	69	0%	0	9%	29	0%	0	49%	163

Table 2.5 Causes of blindness in children published between 2000 and 2015, classified using the anatomical site of abnormality, by World Bank region—cont'd

Reference	Country/area	N	Anatomical site of abnormality																	
			Whole globe		Cornea		Lens		Uvea		Retina		Glaucoma		ON		CVP		Others	
Bulgan 2002[98]	Mongolia	64	14%	9	6%	4	34%	22	3%	2	13%	8	5%	3	14%	9	0%	0	11%	7
Muecke 2009[99]	Myanmar	202	19%	38	44%	89	14%	28	2%	4	7%	14	7%	14	4%	8	1%	2	2%	4
Sapkota 2011[100]	Nepal	43	12%	5	0%	0	16%	7	0%	0	11%	5	0%	0	0%	0	0%	0	26%	11
Gao 2001[101]	Sri Lanka	192	18%	35	8%	15	11%	21	3%	6	36%	69	4%	8	11%	21	3%	6	6%	12
Limburg 2012[102]	Vietnam	411	11%	45	24%	99	15%	62	3%	12	25%	103	5%	21	10%	41	2%	8	5%	21
Limburg 2012[102]	Vietnam	22	9%	2	9%	2	14%	3	14%	3	14%	3	0%	0	14%	3	0%	0	26%	6
Region overall		**4103**	**14%**	**567**	**21%**	**854**	**25%**	**1014**	**2%**	**92**	**18%**	**748**	**4%**	**165**	**9%**	**366**	**1%**	**48**	**7%**	**285**
SSA																				
Nallassamy 2011[103]	Botswana	99	13%	13	7%	7	23%	23	3%	3	7%	7	12%	12	15%	15	3%	3	17%	17
Ruhagaze 2013[104]	Burundi	55	9%	5	18%	10	25%	14	13%	7	2%	1	9%	5	13%	7	0%	0	11%	6
Demisse 2011[105]	Ethiopia	36	9%	3	28%	10	33%	12	0%	0	0%	0	12%	4	3%	1	0%	0	15%	5
Kello 2002[106]	Ethiopia	295	5%	15	62%	183	9%	27	9%	27	2%	6	2%	6	10%	30	0%	0	1%	3
Njunguna 2009[107]	Kenya	182	13%	24	13%	24	12%	22	9%	16	16%	29	2%	4	16%	29	0%	0	19%	35
Njunguna 2009[107]	Malawi	178	20%	36	23%	41	12%	21	6%	11	9%	16	3%	5	8%	14	0%	0	19%	34
Kalua 2012[108]	Malawi S	54	0%	0	14%	8	50%	27	0%	0	0%	0	9%	5	9%	5	14%	8	4%	2
Duke 2013[109]	Nigeria SE	108	11%	12	16%	17	35%	38	0%	0	8%	9	8%	9	8%	9	4%	4	10%	11
Ezegwui 2003[110]	Nigeria SE	46	17%	8	22%	10	30%	14	0%	0	11%	5	11%	5	9%	4	0%	0	0%	0
Aghaji 2014[111]	Nigeria SE	55	16%	9	16%	9	35%	19	0%	0	4%	2	12%	7	7%	4	8%	4	2%	1
Njunguna 2009[107]	Tanzania	192	21%	40	20%	38	15%	29	7%	13	16%	31	2%	4	10%	19	0%	0	9%	17
Njunguna 2009[107]	Uganda	149	7%	10	20%	30	15%	22	4%	6	22%	33	5%	7	16%	24	0%	0	11%	16
Schulze Schwering 2013[112]	Malawi	55	11%	6	11%	6	15%	8	0%	0	16%	9	0%	0	16%	9	0%	0	0%	0
Region overall		**1504**	**12%**	**180**	**26%**	**392**	**18%**	**275**	**6%**	**83**	**10%**	**147**	**5%**	**72**	**11%**	**169**	**1%**	**19**	**10%**	**147**

CVP, Cerebral visual pathways; EME, Established Market Economics; EMR, Eastern Mediterranean Region; FSE, Former Socialist Economics; LAC, Latin America and Caribbean; OAI, Other Asia and Islands; ON, ophthalmia neonatorum; SSA, Sub-Saharan Africa.
Note: The references cited in this table are available online.

Table 2.2 Incidence and prevalence data published since 2000

Reference	Country	Method	Age (years)	Definition	Measure of frequency
ESTABLISHED MARKET ECONOMIES CUMULATIVE INCIDENCE DATA					
Rahi 2003[10]	UK	Active surveillance	<16	<6/60	5.9 (5.3–6.5)/10,000
Al-Merjan 2005[37]	Kuwait	Register	0–20	<6/60; VF <20	7.35/100,000 person years
PREVALENCE DATA					
Flanagan 2003[38]	Scotland	Multiple sources	<19	Not specified	1.61/1000
Crewe 2012[39]	Australia	Surveillance	0–17	<6/60	0.2/1000
Bodeau 2007[12]	UK	Regional register	<12	<6/60	0.4/1000 live births
MIDDLE EAST CRESCENT					
Razavi 2010[19]	Iran	KIM	<15	<6/60	0.4 (0.3–0.5)/1000
Zeidan 2007[40]	Sudan (Khartoum)	Household survey	<16	<6/60	1.4 (1.0–1.8)/1000
Shahriari 2007[41]	Iran	Pop. based survey	10–19	<3/60	0.4 (0.1–0.3)/1000
Mezer 2015[42]	Israel	Register	0–3	Legal blindness	2003: 7.7 (6.5–8.8)/100,000 2013: 3.1 (2.4–3.7)/100,000
CHINA					
Xiao 2011[43]	China SE	KIM	0–13	<6/60	0.3 (0.1–0.5)/1000
Lu 2009[44]	China	Pop. based survey	3–6	<3/60	0.28 (0.04–0.54)/1000
Fu P 2004[45]	China	Pop. based survey	0–6	ND	0.33 (0.43–0.53)/1000
INDIA					
Dorairaj 2008[46]	India S	Household survey	<16	<3/60	1.1 (0.50–1.6)/1000
Nirmalan 2003[47]	India S	Pop. based survey	<16	<6/60	0.62 (1.5–11.0)
Parkar 2007[48]	India C	KIM	0–15	<6/60	0.6 (0.4–0.8)/1000
OTHER ASIA AND ISLANDS					
Muhit 2010[20]	Bangladesh	Household survey	<16	<6/60	0.8 (0.58–1.06/1000)
Mactaggart 2013[49]	Bangladesh	KIM	<18	<6/60	0.7 (0.6–0.8)
Bulgan 2002[50]	Mongolia	Mixed methods	<16	<6/60	0.19 (0.16–0.22)/1000
Adhikari 2014[51]	Nepal	Household survey	0–10	<6/60	0.7 (95% CI 0.2–1.2)/1000
Cama 2010[22]	Fiji	Mixed methods	<16	<6/60	Blind: 0.36 (0.35–0.37)/1000 VI: 0.52 (0.51–0.54)/1000
Limburg 2012[23]	Vietnam	RAAB/KIM	<16	<3/60	0.76 (4.9–11.8)/1000
SUB-SAHARAN AFRICA					
Nallassamy 2011[52]	Botswana	Radio/outreach	<16	<6/18	0.23/1000
Demisse 2011[53]	Ethiopia	KIM	<16	<6/60	0.62 (0.42–0.82)/1000
Kalua 2012[54]	Malawi S	KIM/HSAs	<16	<3/60	0.11/1000
Duke 2013[55]	Nigeria SE	KIM	ND	<6/60	0.09–0.22/1000
Shirima 2009[56]	Tanzania	KIM	<16s	<3/60	0.17/1000

World Bank regions have changed over time. Data are presented according to groupings as in 1990 to allow comparison over time.
HSAs, Health surveillance assistants; KIM, key informant method; pop., population; RAABS, Rapid Assessment of Avoidable Blindness Survey; VF, visual fields; VI, visual impairment.
Note: References 37 to 56 are available online.

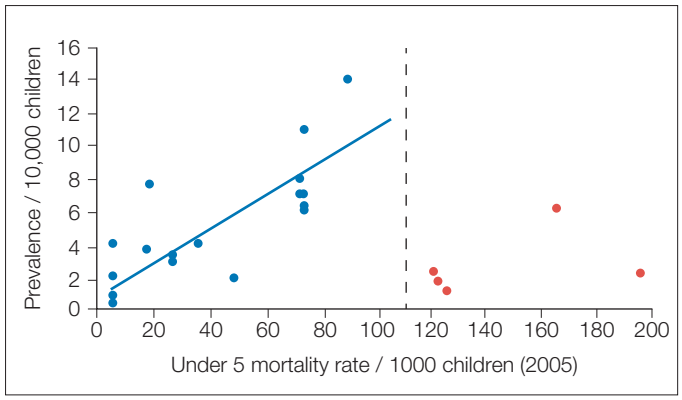


Fig. 2.2 Under-5 mortality rates (for 2005) and blindness prevalence (per 1000 children) – all countries. Studies from non-African countries are shown in blue. Studies from African countries are shown in red.

ROP, initially in Latin America and Eastern Europe in the 1990s and now in South East Asia.[35] This reflects the expansion of neonatal care services of variable quality with increased survival of premature babies. In 2000, it was estimated that 32,300 (uncertainty range 24,800–44,500) infants became blind or visually impaired due to ROP each year.[21]

Other sources of variations in the pattern of causes

The relative importance of disorders will also vary with the level of visual impairment studied. Albinism and congenital cataract are relatively more important if children with all levels of VI (VI, SVI, or BL) are studied, whereas ROP and cortical visual impairment are more important if only those with blindness are studied. Patterns may differ according to whether prevalent or incident cases are studies, as survival may be important. This may be particularly relevant in countries which have limited access to specialist health care.

None of the data presented in this chapter include children with visual impairment due to undiagnosed or uncorrected refractive error alone. This represents a large population of children – possibly 12 million currently – the majority of whom live in Southeast Asia and have uncorrected myopia (see Box 2.3).

Prevention of visual impairment and blindness in childhood: VISION 2020

Children are a priority in VISION 2020,[31] the global initiative for the elimination of avoidable blindness led by WHO and the International Agency for the Prevention of Blindness. As the causes of visual loss vary, country-specific plans and programs are being developed and implemented, based on the priorities for prevention, treatment, and rehabilitation. All programs combine disease-control strategies with the development of human resources, technology, and infrastructure. In many countries, these programs will interface with existing broader governmental initiatives to improve the health of children or improve services for children with disability. For example, reducing blindness due to ROP requires improvement of

Table 2.3 Classification of the causes of childhood visual impairment or blindness, according to the anatomical site(s) affected, and the etiological factors by their timing of action

Anatomical site(s) affected	Etiological factor(s) by timing of action
WHOLE GLOBE/ANTERIOR SEGMENT	**PRENATAL**
Microphthalmia/anophthalmia	Genetic/genomic
Anterior segment dysgenesis	Autosomal recessive or dominant
Coloboma – multiple sites	X-linked
Others	Chromosomal
GLAUCOMA	Mitochondrial
Primary	Hypoxia/ischemia
Secondary	Infection
CORNEA	Prenatal drug
Sclerocornea	Others
Keratomalacia	Presumed, but factor unknown
Other corneal scar	**PERINATAL/NEONATAL**
Dystrophy	Hypoxia/ischemia
LENS	Infection
Cataract	Non-accidental injury
Aphakia/pseudophakia	Others
Subluxed	Presumed, but factor unknown
UVEA	**CHILDHOOD**
Anidiria	Tumor
Uveitis	Nutritional
Coloboma – single site	Infection
RETINA	Hydrocephalus/raised intracranial pressure
Retinopathy of prematurity	Hypoxia/ischemia
Retinal and macular dystrophies	Abusive trauma
Albinism	Accidental injury
Retinitis/neuroretinitis	Harmful traditional practices
Retinal detachment	Specific systemic disorders
Retinoblastoma	Presumed, but factor unknown
Other	**UNDETERMINED TIMING OF INSULT AND FACTORS UNKNOWN**
OPTIC NERVE	
Hypoplasia	
Atrophy – primary or secondary	
Neuritis/neuropathy	
Others	
CEREBRAL/VISUAL PATHWAYS	
Neurodegenerative disorders	
Hypoxic/ischemic encephalopathy	
Abusive head trauma	
Infection	
Structural abnormalities	
Tumor	
Other	
OTHER	
Idiopathic nystagmus	
High refractive error	

Modified with permission from Gilbert C, Foster A, Negrel AD, et al. Childhood blindness: a new form for recording causes of visual loss in children. Bull World Health Organ 1993; 71: 485–9.

Table 2.4 Classification of visual impairment (principally severe visual impairment and blindness) by anatomical site(s)

	FSE/EME	LAC	EMR	China	India	OAI	SSA
Socioeconomic status	**Highest** ←						→ **Lowest**
Studies (n)	11	3	8	2	9	16	13
Children (n)	9205	3389	2261	439	4283	4103	1504
ANATOMICAL SITE (% TOTAL)							
Whole globe	4	3	5	13	38	14	12
Cornea	0	1	3	17	20	21	26
Lens	3	7	7	24	10	25	18
Uvea	3	4	0	0	3	2	18
Retina	26	38	43	28	15	18	10
Glaucoma	1	7	4	2	2	4	5
Optic nerve	17	23	13	15	6	9	5
CVI	25	10	0	0	0	1	1
Other/NK	21	6	24	1	6	7	1

Aggregated data N = 25,000; see onlline for sources published 2000–15.
CVI, Cortical visual impairment; EME, Established Market Economics; EMR, Eastern Mediterranean Region; FSE, Former Socialist Economics; LAC, Latin America and Caribbean; NK, not known; OAI, Other Asia and Islands; SSA, Sub-Saharan Africa.

Table 2.6 Estimates of the number of blind children and the major avoidable causes for a population of 10 million people, by level of economic development

Economic development	Blindness prevalence estimate[a] (/10,000)	Children (N)	Blind children per 10 million total population (N)	Major avoidable causes
High	3–4	2 million	600–800	Cataract Glaucoma Retinopathy of prematurity Non-accidental injury
Medium	5–7	3 million	1500–2100	Retinopathy of prematurity Cataract Glaucoma
Low	8–11	4 million	3200–4400	Cataract Corneal scarring from VADD; ON; measles Retinopathy of prematurity Glaucoma
Very low	12–15	5 million	6000–7500	Corneal scarring from VADD; ON; measles; HTER Cataract Glaucoma

[a]Estimate derived from association with under-5 mortality rates.
HTER, Harmful traditional eye remedies; ON, ophthalmia neonatorum; VADD, vitamin A deficiency disorders.

neonatal services to prevent severe disease from occurring, as well as secondary prevention through screening and early treatment. Table 2.6 lists the main "avoidable" (preventable or treatable) causes of visual impairment across the world.

Strategies to prevent visual impairment or blindness can be categorized as follows:

1. Primary prevention: to prevent the occurrence of ophthalmic disease. Examples include high-coverage rubella immunization programs, preventing congenital rubella-associated cataract; vitamin A supplementation and measles immunization to prevent corneal scarring; face washing and antibiotic treatment to control trachoma; avoidance of ocular teratogens in pregnancy through public and antenatal health education campaigns; excellent neonatal care to prevent ROP, and preconception genetic counseling of families with genetic eye disease.
2. Secondary prevention: to prevent established ophthalmic disease from causing serious visual loss. This includes both screening and surveillance to ensure early detection

and prompt referral of children with suspected ophthalmic disease, such as cataract.[36] It incorporates prompt treatment by pediatric eye care teams specializing in disorders such as ROP, cataract, glaucoma, and amblyopia.

3. Tertiary prevention: to maximize residual visual function and prevent disadvantage due to established visual impairment. This includes interventions aimed at improving visual function even though good vision cannot be achieved, e.g. management of late-presenting childhood cataract or optical iridectomy for central corneal scarring. Tertiary prevention also incorporates assessing and meeting special educational needs, providing low-vision devices and assistive technologies, mobility training, and providing social support and services to families of children with irreversible visual loss.

The role of ophthalmic professionals in prevention of childhood visual impairment

Ophthalmic professionals have a key role in the implementation of strategies through their ability to:

- Provide specialist pediatric ophthalmic care, combining medical, surgical, and optical management of specific disorders;
- Collaborate with non-ophthalmic colleagues. This includes providing education and training as required to pediatricians, family doctors, optometrists, or community eye workers, to ensure implementation of programs aimed at early detection and prompt referral of children suspected of having eye diseases, those at high risk for VI, those with major neurodevelopmental disorders, or those with a family history of blinding eye disease. One such example is working closely with neonatologists to establish appropriate screening and treatment for ROP;
- Contribute to multidisciplinary VI teams, ideally combining medical, educational, and social service professionals, to ensure comprehensive and coordinated care of all VI children and their families;
- Contribute to assessments of special educational needs and certification of eligibility for special services, in particular notification to VI registers;
- Contribute to monitoring VI in their population;
- Participate in epidemiological research that strengthens the evidence base for practice and policy.

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Table 2.5 Causes of blindness in children published between 2000 and 2015, classified using the anatomical site of abnormality, by World Bank region.

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Clinical embryology and development of the eye

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Chapter contents

EMBRYOGENESIS AND EYE DEVELOPMENT
EYE ORGANOGENESIS (FOURTH TO EIGHTH WEEK GESTATION IN HUMAN)
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In this chapter we will discuss the organogenesis of the eye. The differentiation of the components of the eye will then be reviewed separately.

The vertebrate eye is formed through interactions between neuroepithelium, surface ectoderm, and extraocular mesenchyme.[1] The neuroectoderm gives rise to the retina, iris, and optic nerve; the surface ectoderm forms the lens and corneal epithelium; and the extraocular mesenchyme comprising mesodermal and neural crest cells gives rise to the corneal stroma, corneal endothelium, extraocular muscles, and fibrous and vascular coats of the eye.[2]

There are three main periods in the prenatal development of the eye. The first (embryogenesis) includes the establishment of the primary organ rudiments. It finishes around the end of the third gestational week, when the optic groove (optic sulcus), precursor of the eye, appears on either side of midline at the expanded cranial end of the open neural folds. The second period (organogenesis) extends to the end of the eighth week and includes the development of the primary organ rudiments. Thereafter, the third period (differentiation) involves the differentiation of each of the primitive organs into a fully or partially active organ. During this period, the retina, optic nerve, vitreous, lens, and angle structures develop (Table 3.1).[3,4]

Embryogenesis and eye development

Early vertebrate eye formation follows a conserved sequence of events. Following gastrulation, the eye field is specified in the anterior neural plate. The first morphological landmarks are bilateral indentations (optic sulci or pits) at approximately 22 days in the neural folds at the cranial end of the embryo.

Eye organogenesis (fourth to eighth week gestation in human)

Fourth week

The optic pits deepen and form the optic vesicles (OVs), which are evaginations of the lateral walls of the diencephalon. The OVs are connected to the forebrain by the optic stalk (a short tube that eventually forms the optic nerve; Fig. 3.1A,B). During this period, interaction between the OV and surface ectoderm (SE) induces the lens placode, and the wall of the OV in contact with the surface ectoderm also thickens to form the retinal disc. Towards the end of the fourth week a process of invagination begins to transform the OV into the optic cup (OC). Also at this time, the primordia of the extraocular muscles appear as condensations in the periocular mesenchyme. Disruptions in these early steps lead to severe congenital anomalies, including absent eyes (anophthalmia), small eyes (microphthalmia), and optic fissure closure defects (coloboma).[5,6]

Fifth week

Invagination of the OV to form the OC predominates in the fifth week. Invagination involves the retinal disc, lens plate, and the ventrocaudal wall of the optic vesicle (Fig. 3.1C,D). Invagination of the retinal disc of the OV leads to formation of the inner layer of the optic cup, which becomes the neural retina, while the external layer of the optic cup will become the retinal pigment epithelium (RPE; Fig. 3.1E). The optic cup is not continuous, and forms a fold inferiorly and ventrally that is continuous with the optic stalk. This fold is called the embryonic (optic) fissure (Fig. 3.2). The optic fissure allows the hyaloid artery into the optic cup. The primary vitreous develops around the hyaloid vasculature. The process of invagination also involves the lens placode (plate), which leads to the formation of the lens pit. The lens pit deepens to become the lens vesicle. Further development leads to the lens vesicle separating from the surface ectoderm.[7] The

Table 3.1 Overview of eye development[4]

Gestational age	Developmental milestone
22 days	Optic primordia appears
Second month	Hyaloid artery fills embryonic fissure Closure of embryonic fissure begins Lid folds appear Neural crest cells (corneal endothelium) migrate centrally; corneal stroma follows Choroidal vasculature starts to develop Axons from ganglion cells migrate to optic nerve
Third month	Sclera condenses Lid folds meet and fuse
Fourth month	Retinal vessels grow into nerve fiber layer near optic disc Schlemm's canal appears Glands and cilia develop in lids
Fifth month	Photoreceptors develop inner segments Lids begin to separate
Sixth month	Dilator muscle of iris forms
Seventh month	Central fovea thins Fibrous lamina cribrosa forms Choroidal melanocytes produce pigment
Eighth month	Iris sphincter develops Chamber angle completes formation Hyaloid vessels regress Retinal vessels reach periphery Optic nerve myelination complete to lamina cribrosa Pupillary membrane disappears

resulting lens vesicle is relatively large and fills the optic cup.[8] The surface ectoderm will become the corneal epithelium (Fig. 3.1F,G).[1,3]

Sixth week

One of the principal events of the sixth week is the closure of the optic fissure. For the optic fissure to close, the edges of the optic cup must become closely apposed. The embryonic fissure closure begins midway and then extends both anteriorly and posteriorly (see Fig. 3.2). The optic cup is regionalized along several axes: dorsal–ventral, anterior (cornea)–posterior (RPE), nasal–temporal, and central (central neural retina)–peripheral (ciliary epithelium).[9]

The development of the retina progresses with the RPE forming a single layer of cuboidal cells. A primitive Bruch's membrane arises. The sensory retina thickens due to proliferation of cells in the germinative zone of the inner layer of the optic cup. At this stage, retinal ganglion cell (RGC) axons first enter the optic stalk to exit the primitive eye[4] (Fig. 3.1H,I). The secondary vitreous, a cellular structure with associated extracellular matrix, forms and starts to remodel the primary vitreous and fill the remaining retrolenticular space.[10]

Seventh week

The main events include maturation of the RPE and development of the sensory retina with the formation of outer and inner neuroblastic layers at the posterior pole. Primary lens fibers form to obliterate the cavity in the lens vesicle. The periocular mesenchyme evolves with the formation of the choroidal vasculature posteriorly and the development of the anterior segment (Fig. 3.1J,K).

The anterior periocular mesenchyme in the mammal has contributions from cells of neural crest and mesodermal origins, in contrast to the chick where there are only neural crest contributions. The mesenchymal cells migrate forward so that there are cells of neural crest and mesodermal origin contributing to the corneal stroma, endothelium, and trabecular meshwork, whereas Schlemm's canal is of mesodermal origin (Fig. 3.3).

Eighth week

Optic nerve development predominates as more ganglion cells differentiate in the sensory retina, reaching 2.67 million axons by the end of the eighth week. The axons start to make contact with the brain and establish a rudimentary chiasm.[11] RPE nears maturation with the appearance of melanosomes. Müller cells appear and start to extend radial fibers inwards to form the internal limiting membrane and outward toward the prospective external limiting membrane.

Corneal differentiation continues. The corneal endothelial cells start to form Descemet's membrane, the corneal stroma consists of 5–8 rows of cells, and the corneal epithelium is evolving to a stratified squamous epithelium.

The lens develops rapidly with the primary lens fibers filling the lens vesicle. The intracellular organelles disappear. The equatorial epithelial cells begin to divide and new cells are pushed posteriorly, then elongate to become the secondary lens fibers. This leads to development of the lens bow where the nuclei of the secondary lens fibers arc forward convexly (see Fig. 3.1H). The lens sutures develop where the secondary lens fibers meet in a linear pattern at the anterior and posterior poles of the lens. The sutures initially are a line, but then evolve to be Y shaped anteriorly and an inverted Y (Λ) posteriorly.[7,12]

The four rectus muscles insert into the sphenoid bone and the trochlea develops. The lacrimal glands form from the superotemporal quadrant of the conjunctival sac (see Fig. 3.1J).

Differentiation and maturation of elements

Cornea

The cornea forms an optically transparent window for the eye. This function derives from its unique structure and composition.[13] The cornea consists primarily of three layers: an outer layer containing an epithelium; a middle stromal layer consisting of a collagen-rich extracellular matrix (ECM) interspersed with keratocytes; and an inner layer of endothelial cells.

The corneal epithelium develops from surface ectoderm and its maturation is related to eyelid development. Rudimentary lids fuse 8 weeks after ovulation and do not separate (open) until 26 weeks.[14] Bowman's membrane, which underlies the corneal epithelium, develops from the processes of superficial mesenchymal stromal cells. It first becomes apparent around week 16 and is easily recognizable by the fifth month.[15]

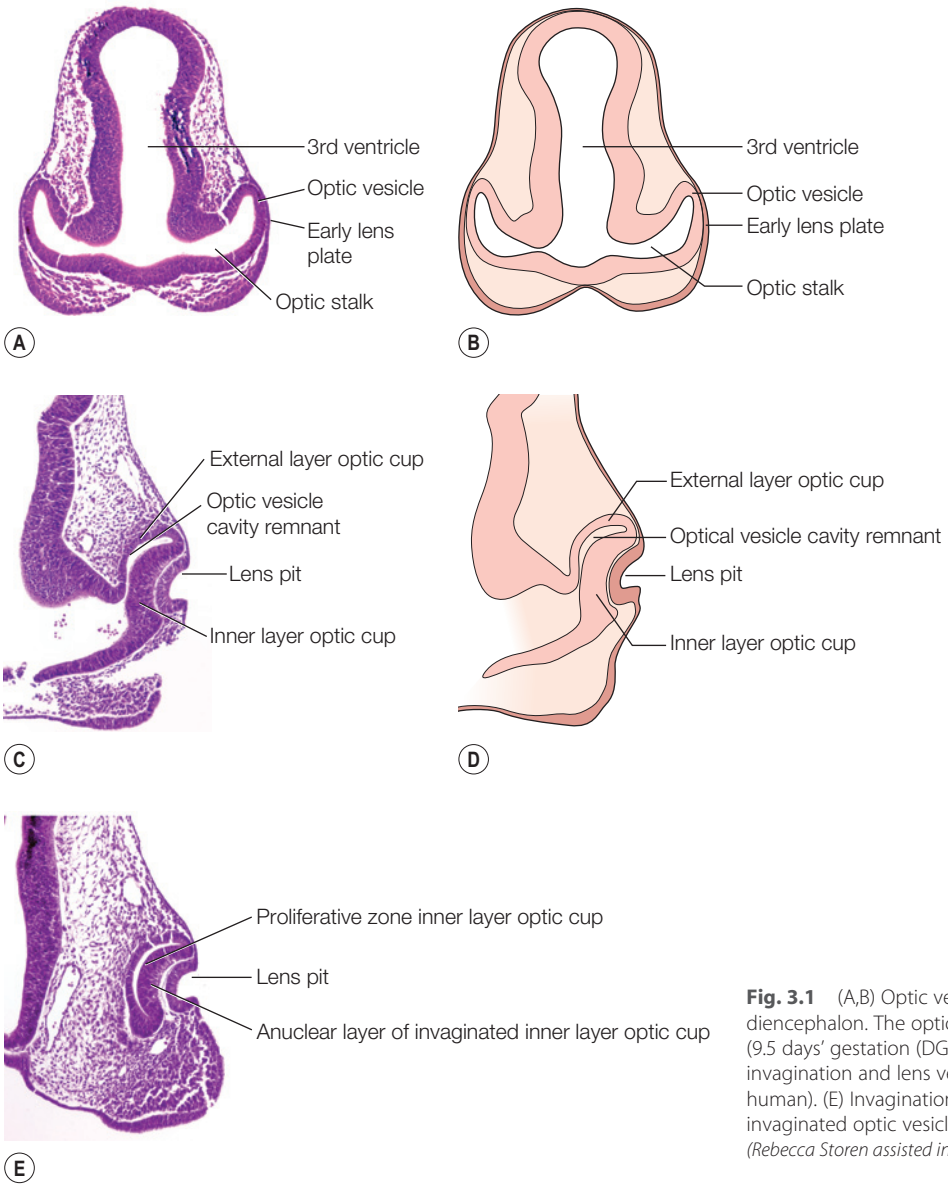


Fig. 3.1 (A,B) Optic vesicle formation on the lateral wall of the diencephalon. The optic stalk connects the optic vesicle to the forebrain (9.5 days' gestation (DG) mouse ≈ 26 DG human). (C,D) Optic vesicle invagination and lens vesicle formation (early 10.5 DG mouse ≈ 28 DG human). (E) Invagination of lens pit and bilayered optic cup forming from invaginated optic vesicle (late day 10.5 DG mouse ≈ 32 DG human). *(Rebecca Storen assisted in preparing the histological sections.)*

Continued

The beginnings of the limbus appear at the end of the eighth week. This is marked by a change in stromal appearance at the periphery of the cornea, with cells acquiring a more polymorphic shape and losing regular orientation. By week 11, this junction is well demarcated. In place of the limbal folds identifiable in adult corneas, a ridge-like structure circumscribes and demarcates the developing cornea. This is thought to represent the primitive corneal epithelial stem cell niche.[15,16]

The mature corneal endothelial and stromal layers, the mesenchymal layer of the limbus, and the trabecular meshwork in mammals each consist of two mature cell lineages, one derived from the neural crest and the other from the mesoderm. The mesoderm-derived cells mature to a mix of antigen-presenting cells. These include dendritic cells and macrophages in the limbus and peripheral cornea. Mesenchymal stromal cells of neural crest and mesodermal origin migrate into the space between the corneal epithelium and corneal endothelium and become keratoblasts. The keratoblasts synthesize high levels of hyaluronan to form the primary embryonic corneal stroma ECM. The keratoblasts differentiate into keratocytes, which synthesize high levels of collagens and keratan sulfate proteoglycans that replace the primary stroma with a densely packed collagen fibril-type ECM.[17] Proper differentiation of the stroma and endothelium depends on signals from the lens epithelium, although the nature of the responsible molecules is not known.[18]

The homogeneous distribution of regularly packed small-diameter (25–30 nm) collagen fibrils develop by processes involving keratocytes, which exhibit long-range associations with collagen bundles in the developing matrix via an extended network of actin-rich tubular cytoplasmic protrusions. These have been termed keratopodia. Synchronized alignment of keratopodia and collagen contributes to lamella formation.[19] The proteoglycans are small enough to fit in the spaces between the collagen fibrils and regulate their spacing.

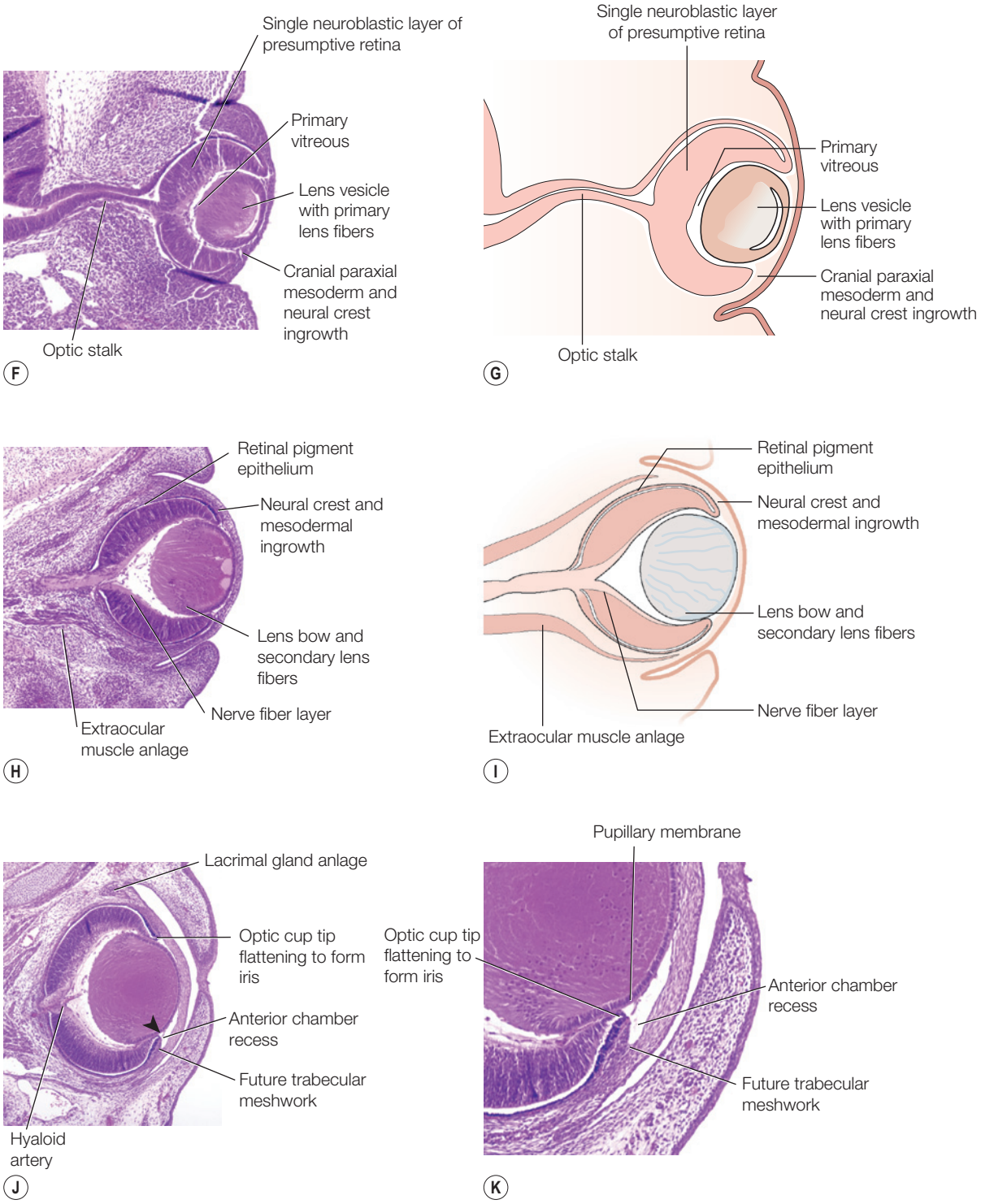


Fig. 3.1, cont'd (F,G) Optic fissure closure, lens vesicle formation and primary vitreous (12.5 DG mouse ≈ 44 DG human). (H,I) Nerve fiber layer formation, neural crest migration, and lens bow formation (14.5 DG mouse ≈ 56–60 DG human). (J) The eye at the end of organogenesis. Cornea, early iris formation, extraocular muscle anlage, and lacrimal gland clearly visible. Arrowhead shows pupillary membrane (16.5 DG mouse ≈ >60 days human). (K) Anterior chamber angle including trabecular meshwork formation results from the differentiation of mesenchymal cells to form a wedge-shaped structure that lies between the corneal endothelium and the stroma of iris. *(Rebecca Storen assisted in preparing the histological sections.)*

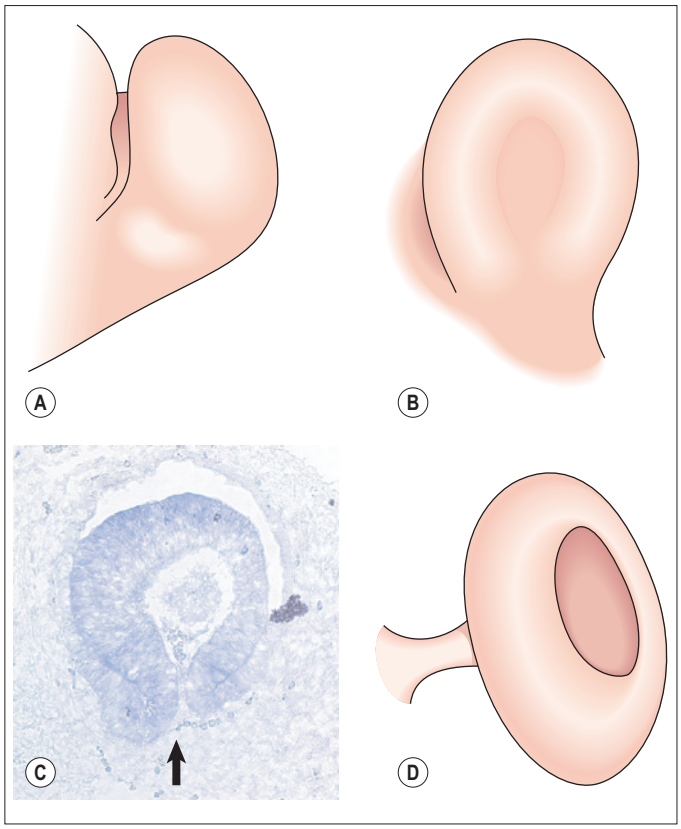


Fig. 3.2 Optic vesicle invagination: three-dimensional representation. (A) Optic vesicle outpouching (9.5 days' gestation (DG) mouse ≈ 32 DG human). (B) Optic fissure closing. (C) Parasaggital section of mouse eye just prior to fissure closure. (D) Fusion of optic fissure. *([A,B,D] Reproduced with permission from Fitzpatrick DR, van Heyningen V. Developmental eye disorders. Curr Opin Genet Dev 2005; 15: 348–53. [C] Reproduced from Mihelec M, Abraham P, Gibson K, et al. Novel SOX2 partner-factor domain mutation in a four-generation family. Eur J Hum Genet 2009; 17 :1417–22.)*

Anterior chamber structures

Iris

The iris arises at the end of embryonic development from both the anterior margin of the optic cup neuroepithelium and the periocular mesenchyme. This includes specification of the peripheral optic cup to a non-neuronal fate (pigmented epithelial layer of iris). Periocular mesenchymal cells proliferate and migrate along the iris epithelial layers and differentiate into the iris stroma. Between the iris stroma and the (pigmented) iris epithelium, the sphincter and dilator smooth muscles arise from neuroectoderm.[20] It is most likely that the iris stroma in mice originates from both neural crest and mesoderm.[21,22]

Ciliary body

The ciliary body (CB) shares a common embryonic origin with the iris, but develops into a functionally different structure. The two cuboidal epithelia of the ciliary body that are derived from the neurectoderm include the outer pigmented layer, which is continuous with the RPE, and the inner non-pigmented layer (NPE), which is continuous with the neural retina.

The ciliary marginal zone (CMZ) is a zone of proliferating neural progenitors at the peripheral edge of the retina in fish, frog, and chicken eyes. These progenitors produce neurons that have the ability to regenerate the retina following injury. The cells of the mammalian ciliary epithelium can be induced to become retinal stem cells (RSC), but may not represent a true CMZ.[23]

Fibrillin-rich zonular fibers produced by the NPE span the narrow cleft between the lens epithelium and the ciliary body and become intimately attached to the capsular surface. As the lens expands, the zonules elongate and fan out over the equator.[24]

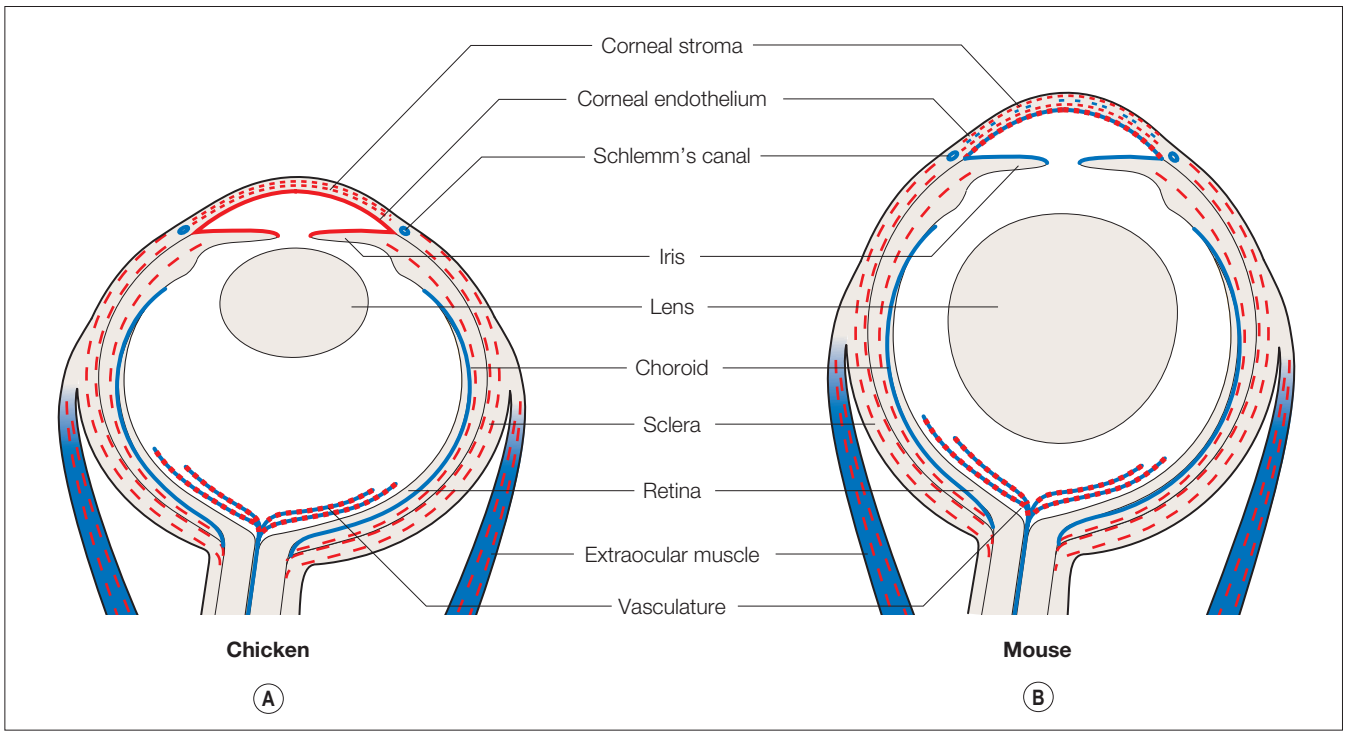


Fig. 3.3 Neural crest and mesoderm fates in bird and mammalian eyes. Cross-sectional diagrams summarizing similarities and differences in contributions of neural crest (red) and mesoderm (blue) to adult chicken and mouse eyes. The major differences occur in the anterior segment. *(Reproduced with permission from Gage PJ, Rhoades W, Prucka SK, et al. Fate maps of neural crest and mesoderm in the mammalian eye. Invest Ophthalmol Vis Sci 2005; 46: 4200–8.)*

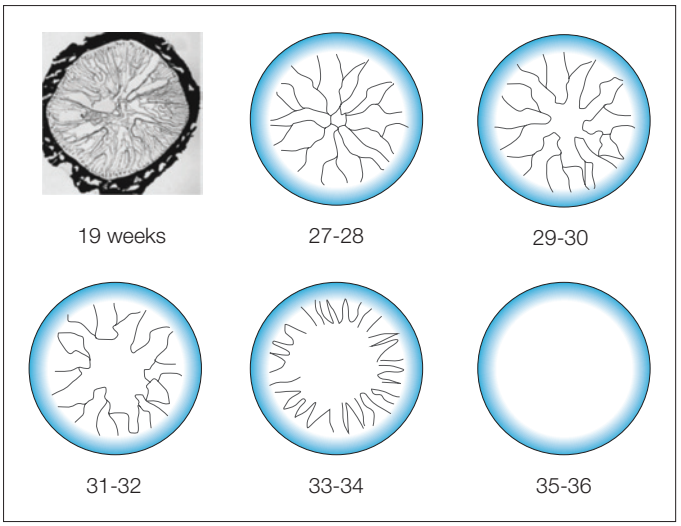


Fig. 3.4 Pupillary membrane regression. The pupillary membrane is fully developed by 13 weeks' gestation. Clinical appearance at 19 weeks' gestation (adapted from Zhu M, Provis JM, Penfold PL. The human hyaloid vasculature: cellular phenotypes and interrelationships. Exp Eye Res 1999; 68: 553–63.). Schematic regression stages modified from Hittner HM, Hirsch NJ, Rudolph AJ. Assessment of gestational age by examination of the anterior vascular capsule of the lens. J Pediatr 1977; 91: 455–8. At around 29–30 weeks, the central quarter of the membrane clears; at 31–32 weeks, the central half clears; at 33–34 weeks, only a peripheral rim of membrane remains; by 35–36 weeks, the membrane has completely regressed.

Trabecular meshwork

Trabecular meshwork formation begins around the fourth month of gestation.[25] The mesenchymal cells of the trabecular meshwork form a wedge-shaped structure that lies between the corneal endothelium and the deeper stroma (see Fig. 3.1K). During the fourth to sixth months, there is a 50% increase in cross-sectional area and a threefold increase in volume of the trabecular anlage.

Schlemm's canal (SC) forms when limbal transcleral veins begin to sprout laterally. It becomes visible in the 16th week of gestation.[26] By 24 weeks, SC is present throughout the entire circumference. By 36 weeks, the SC and outer collecting channels are clearly defined and connected by intercanalicular links. The development of this system continues postnatally, acquires lymphatic identity through upregulation of *PROX1*,[27] until an adult-like configuration is achieved by 8 years.[28]

Pupillary membrane

During mammalian lens development, a transient capillary meshwork known as the pupillary membrane (PM) forms, which is located in the pupil area. The PM reaches its maximal development by 12–13 weeks' gestation[29] (Fig. 3.4 and see Fig. 3.1K). The PM nourishes the anterior surface of the lens and then regresses to make the optical path clear. The regression may be due to iris movement leading to altered blood flow in the PM and regression of the membrane due to apoptosis.[30] The regression of the PM occurs in a programmed manner at consistent time points. The stage of regression of the PM is a useful guide to the gestational age of a premature infant. At 27–28 weeks' gestation, the pupillary membrane fully covers the pupil, and then the central vessels are progressively lost until 35–36 weeks' gestation, when the membrane is no longer present[31] (see Fig. 3.4).

Lens

Lens morphogenesis therefore depends both on the execution of the differentiation program and on the correct assembly of the epithelial and fiber cells into the three-dimensional functional structure. Recent studies exposed a key role for the Wnt/planar cell polarity (PCP) pathway in directing lens fiber morphology.[32] Lens epithelial cells start to differentiate into lens fiber cells at the interface between the lens epithelium and the primary lens fiber core, at the equator. Differentiating lens fiber cells elongate and cover the old lens fiber core, resulting in growth of the lens during development.[33] At term, the lens is approximately 6 mm in diameter and continues to grow to a diameter of approximately 9–10 mm in adult life.

Vitreous and hyaloid system

The hyaloid system is well established by 10 weeks' gestation (see Figs 3.1J and 3.4). The tunica vasculosa lentis (TVL) anastomoses with the annular vessel at the anterior border of the optic cup and connects to the choroidal vasculature. The hyaloid system is characterized by the absence of veins. All hyaloid vessels are arteries and the venous drainage is accomplished by the choroidal veins.[34] The development of the hyaloid vascular system (HVS) is complete around the fourth month and provides all nutrients to the intraocular components of the developing eye. With the appearance of the developing retinal vasculature at approximately the fifth month of gestation, the first signs of hyaloid vessel regression can be detected.[34]

The primary vitreous is a transient collection of cells originating from the neural crest and mesoderm; this structure eventually gives rise to the hyaloid vasculature. Regression of the structures derived from the primary vitreous is a critical event, important for the formation of the crystalline (secondary) vitreous.[35] Failure leads to persistent fetal vasculature. Blood flow in the hyaloid artery ceases around the seventh month, and the vessel is almost completely atrophied by birth.

Retina

The two layers of the optic cup give rise to the outer RPE and the inner neural retina (see Fig. 3.1C,D). The RPE is required for growth of the eye, and it contributes to control of proper lamination of the neural retina. The basal lamina of the RPE, Bruch's membrane (BM), forms a functional unit with the RPE and choriocapillaris.[36]

Differentiation of the neural retina begins at the end of the sixth week. At any location in the retina, there is a fixed birth sequence of retinal cells, so that ganglion cells, horizontal cells, and cone photoreceptors are born first, followed by amacrine and bipolar cells, with rod photoreceptors and Müller cells being the last to differentiate.[37] A region develops in the central retina comprising only differentiating cone photoreceptors at 10–11 weeks' gestation, and is the first indicator of the developing foveal region. Primate retinal studies identify the fovea as the initiation point for most developmental events in the retina, including: cessation of mitosis, morphological maturation, apoptosis, opsin expression, and synaptogenesis.[38] Different developmental events then radiate out from this region across the retina.[38]

Spatiotemporal patterns of neural activity, or "retinal waves," emerge during development and guide the development of

interconnections between different parts of the visual system prior to visual experience.

At week 34, cones and rods near the pure cone area of the fovea have outer segments and are forming elongated axons, which terminate in distinct synaptic pedicles in the outer plexiform layer.[38] The protracted development of the foveal region means that foveal cones are the last to attain adult morphology. In comparison, cones in the periphery are mature in the perinatal human retina.[37] Genetic ablation of the RPE or disruption of RPE specification genes result in microphthalmia, RPE-to-retina transdifferentiation, and coloboma during murine eye development.[1]

Vascularization of the retina involves proliferation and migration of astrocytes and endothelial cells, so that the vessels spread outward from the disc and reach the peripheral retina at around birth.[39] The first vessels appear around 14–15 weeks' gestation. The stimulus for vascular growth is dependent on the retinal neurons becoming metabolically active, resulting in local hypoxia. This "physiological" hypoxia causes retinal astrocytes to secrete vascular endothelial growth factor (VEGF), promoting growth of endothelial cells and formation of retinal blood vessels. In this manner, blood vessel formation is matched to oxygen demand.[40]

The foveal region is never vascularized during normal development, and the foveal avascular zone is fully demarcated by around 28 weeks' gestation in humans.[41]

At the fovea, the retina is adapted morphologically to its blood supply because the development of retinal vessels is inhibited. This is the converse of the rest of the retina and may provide a clue to the susceptibility of the macular to disease.[40]

Optic nerve

The optic nerve develops from the edges of the optic fissure. The optic fissure can be divided into two adjoining parts: the optic groove, which derives from the optic stalk, and the retinal fissure, which derives from the ventral optic vesicle (see Figs 3.1C and 3.1D). The optic disc will form at the transition between the optic groove and retinal fissure.[42] Axons and hyaloid artery at the developing optic disc become encircled by a ring of compact neuroepithelial cells, characterized by the expression of the paired-boxed transcription factor Pax2.[43]

Type I astrocytes arise from PAX2 expressing neuroepithelial cells of embryonic optic stalk and a subpopulation migrate onto the retinal surface where they associate with the surface vasculature to form the blood/retinal barrier.

RGC axons initially extend along the vitreal surface of the neural retina and follow a centripetal route towards the center of the retina. Within the retina, RGC axons grow in close contact with Müller glial cell endfeet and with the vitreal basal lamina.[2,44] The number of RGC axons entering the optic nerve peaks at 3.7 million at around 16–17 weeks' gestation, then declines, stabilizing at an estimated 1.1 million axons (adult number) by week 29 of gestation.[45] This redundancy contributes to the retinotopic organization being mapped to the cortex via activity-dependent mechanisms.

Extraocular muscles

Craniofacial muscles develop from unsegmented prechordal and paraxial mesoderm. They also receive contributions from the neural crest. The extraocular muscles (EOMs) differ from craniofacial muscles formed in the branchial arches by having different upstream activators of the muscle-regulatory transcriptional cassette.[46]

Eye movements depend on correct patterns of connectivity between cranial motor axons and the extraocular muscles.

EOMs also have unique gene expression profiles relative to other skeletal muscles, which include the presence of embryonic and cardiac muscle proteins as well as higher levels of enzymes that lead to improved calcium homeostasis and reduced oxidative stress.[47] These unique properties make the EOMs resistant to many forms of muscular dystrophy.[46]

Cranial nerves

Twelve pairs of cranial nerves (CN) form during the fifth and sixth weeks of development. They are classified into three groups based on their embryological origins. The somatic efferent cranial nerves are: oculomotor (CN III; majority of the nerve), trochlear (CN IV), abducent (CN VI), and hypoglossal (CN XII). The nerves of the branchial arches include: CN V, VII, IX, and X. The special sensory nerves are: CN I, II, and VIII.

Within the brain (as opposed to the spinal cord), motor neuron organization is subservient to neuromeric organization. The cranial motor neurons are organized within individual rhombomeres (neuromeres of the rhombencephalon) or in adjacent neuromeric pairs. The oculomotor (III) nucleus is located in the posterior midbrain, the trochlear (IV) nucleus in anterior rhombomere 1 (r1), the trigeminal (V) nucleus in rhombomeres 2 and 3, the facial (VI) nucleus in rhombomeres 4 and 5, the abducens (VII) nucleus in rhombomeres 5 and 6, and the glossopharyngeal (IX) nucleus in rhomobomeres 6 and 7. The midbrain and each hindbrain segment have their own molecular "address" reflected by the expression of a unique combination of transcription factors.[48]

Normal development and function of the efferent cranial nerves is critical for normal development of the extraocular muscles. Axon pathfinding is essential for the establishment of proper neuronal connections during development. Abnormalities lead to congenital cranial dysinnervation disorders including congenital fibrosis of the extraocular muscles (CFEOM), Duane syndrome, and Marcus Gunn jaw-winking phenomenon.[49]

Lacrimal system

Three stages in lacrimal gland morphogenesis are identified: (1) the presumptive glandular stage at 7 to 8 weeks' gestation, characterized by a thickening of the superior fornix epithelium together with surrounding mesenchymal condensation; (2) the bud stage, characterized initially by the appearance of nodular formations in the region of the superior conjunctival fornix and concluding with the appearance of lumina within the epithelial buds; fibroblast growth factor (FGF) signaling is critical for these steps[50]; (3) the glandular maturity stage at 9 to 16 weeks' gestation, when the gland begins to take on the morphology of adulthood.[51]

The excretory lacrimal system begins to develop at 6 to 7 weeks' gestation when the lacrimal groove is observed between the maxillary and external nasal processes. The lacrimal cord develops at 8 weeks' gestation, and by 9 to 16 weeks the palpebral orbicular muscle primordium has formed along with the lumen of the excretory lacrimal system and formation of the tendon, the medial palpebral ligament.[52]

Emmetropization

The human eye is programmed to achieve emmetropia in youth and to maintain emmetropia with advancing years. Eye growth is regulated in early postnatal life and optically driven mechanisms contribute to this process.[53]

The visual image is critical in refractive development, with the retina having a central role in optically regulating eye growth; each area of retina processes the retinal image and influences the growth and/or biomechanics of the overlying sclera.[54,55]

Embryology resources are well developed online and we refer the reader to http://www.emouseatlas.org/emap/analysis_tools_resources/software/jatlasviewer.html for more detailed images.

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Developmental biology of the eye

David R FitzPatrick

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Introduction

Developmental biology aims to provide an understanding of the mechanisms controlling the four-dimensional changes in shape (*morphogenesis*), cell type diversity (*histogenesis*), and functional maturation during embryogenesis and early brain development. Ocular development has proven to be a popular system for developmental biologists, since the general structure of the eye is similar throughout vertebrate evolution and the molecular basis of development is conserved to a remarkable degree from the well-studied invertebrate animal model, the fruit fly, *Drosophila melanogaster*.

For both ethical and technical reasons, experimental developmental biology has not been possible in humans. However, the ability to induce transdifferentiation of adult human cells into induced pluripotent stem (*iPS*) cells[1] and to then differentiate these into optic vesicle-like structures[2] has significantly reduced this limitation. Combining this technology with our improved understanding of the genetic basis of human eye malformations predicts that human developmental biology will be an important and rapidly growing field in the near future. To date, however, almost all knowledge of eye development comes from model organisms: the fruit fly (*Drosophila melanogaster*); frogs (*Xenopus laevus*, *Xenopus tropicalis*); fish (zebrafish [*Danio rerio*], medaka [*Oryzias latipes*]); chick (*Gallus gallus*); and mouse (*Mus musculus*). Each model has strengths and weaknesses. For example chick embryos have been extensively used for fate mapping and tissue recombination experiments, but there are few natural mutations available for study and genetic manipulation is difficult. In mice one can inactivate almost any gene in a targeted manner via homologous recombination in embryonic stem (ES) cells, but very early development is difficult to visualize since this is a placental mammal. Although exact equivalence of animal model experimental data with orthologous processes in humans is unlikely given the expansion of gene families through evolutionary genome duplication and existence of species-specific phenomena, it is likely that many of the developmental mechanisms will be common and generalizable.

Important concepts and processes in developmental biology

Differentiation

The fertilized egg is a *totipotent* cell, i.e. one cell can give rise to all embryonic and extra-embryonic tissues. *Differentiation* can be thought of as a progressive loss of "stem-ness" associated with increasing functional specialization of the daughter cells. This process ends with *terminal differentiation*, where the cell exits the cell cycle and changes the cellular machinery to fulfill its assigned function, for example, as a rod photoreceptor. The ancestry of this cell would be represented as fertilized egg ⇨ blastomere cell ⇨ inner cell mass cell ⇨ primitive ectodermal cell ⇨ neuroectodermal cell ⇨ optic field cell ⇨ optic vesicle cell ⇨ retinal progenitor cell ⇨ photoreceptor. This sequence of any developing cell is known as the *fate map*.

Cell migration

Embryogenesis involves dramatic shape changes over short periods of time. Much of this change is due to differential rates of cell division within and between tissues. However, there is a subset of cells that migrate from their birthplace to distant regions of the embryo. The best known of these travellers are *neural crest (NC) cells*, which form on the lips of the neural fold along the length of the neural tube. The *cranial neural crest (cNC) cells* are important in eye development and will be discussed further below. The molecular basis of the movement of NC cells is becoming known and many of the master control genes for this process are also important in mediating cancer invasion and metastasis.[3]

Programmed cell death

In many developmental tissues a proportion of the constituent cells will be seen to undergo a process where there is nuclear fragmentation leading to death. This process is microscopically and molecularly distinct from senescence and is known as *apoptosis* or *programmed cell death* (PCD).[4] The correct

functioning of PCD is crucial to the normal development of many organs and appears to be used to prune cells that are excess to requirement.

Signaling

Signaling is one of the fundamental concepts in developmental biology. A diffusible ligand is produced by a cell or group of cells in the embryo that interacts with a receptor to effect a change. Protein phosphorylation and/or the transcriptional profile is altered in the receptor-bearing cell, which can be at some distance from the ligand-producing cells. Ligands can be proteins (e.g. sonic hedgehog) or small molecules (e.g. all-*trans*-retinoic acid). The receptors (e.g. fibroblast growth factor receptors) can be on the cell surface or intracellular (e.g. retinoic acid receptors). The ligand–receptor interaction will often lead to a signal transduction cascade (e.g. MAPK pathway). Some ligand–receptor interactions can activate several different signal transduction pathways. In such cases, the most commonly used pathway is known as canonical (e.g. beta catenin activation in Wnt signaling) and the alternative pathways known as non-canonical. There are many different signaling pathways used during eye development (Fig. 4.1) and many of these will be discussed in more detail below.

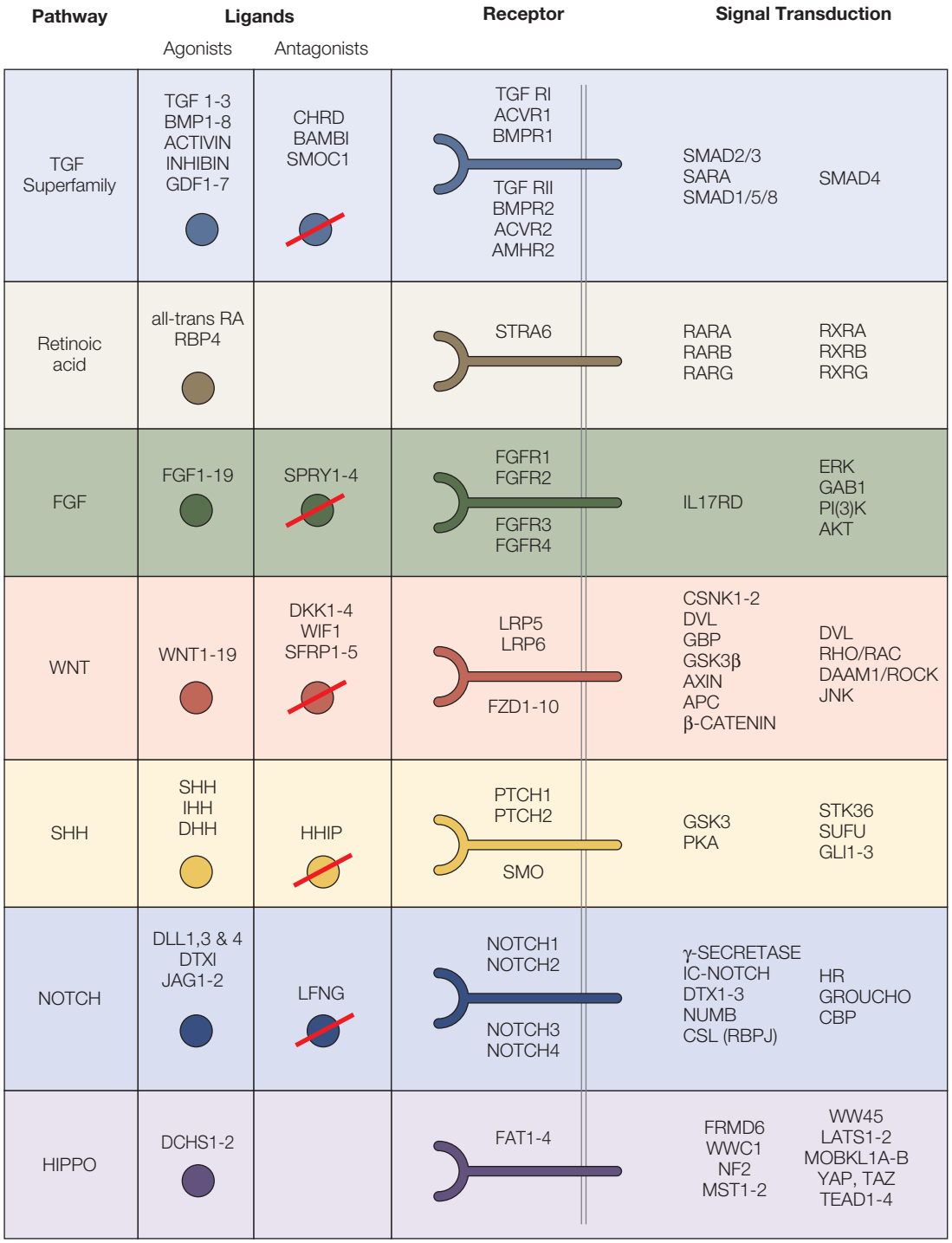


Fig. 4.1 Major signaling pathways used during eye development. The signaling pathways are made up of ligands, antagonists, receptors, and signal transduction effectors. The pathways are named after the ligands, which are either groups of proteins that are related by sequence homology or small molecules. Some receptor–ligand interactions may use more than one signal transduction cascade depending on cell context.

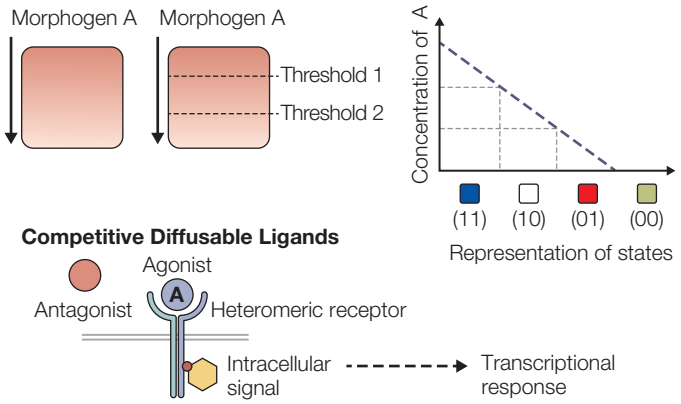


Fig. 4.2 Translation of morphogen gradients into cell state change. Morphogen gradients are created by diffusible ligands for signaling cascade. The source of ligand production will represent the peak of the concentration gradient. Factors such as the nature of the extracellular environment and the catabolism or internalization of the ligand will influence the slope and extent of the gradient. The signaling gradient is translated into changes in cell state using a threshold-dependent mechanism. This can be diagrammatically represented by the French flag model in which specific points on the slope of the signaling gradient will result in a change in the differentiated state of a group of cells that lie between the threshold points. The concept of signal transduction is represented by the competition between soluble ligands and antagonists competing for interaction with the receptor complex. If the ligand binds, it will then trigger the signal transduction to effect the proteomic or transcriptomic change within the cell.

The term "morphogen gradient" means that the diffusible ligand (morphogen) exerts concentration-dependent differential effects on target tissues.[5] This important concept is summarized in the so-called French flag model (Fig. 4.2).

Transcription factor codes

Transcription factors (TF) are proteins that reversibly bind – either alone or in combination with other TFs – to specific sequences of DNA called binding sites to exert a *cis*-regulatory effect on one of more genes. The expression of combinations of TF – the TF code – can be used to mark a region of apparently undifferentiated tissue that will become a specific structure. TFs are thus often used as marker genes to determine tissue fate. An example of this is given in the next section: the TF *RAX* is used to define the eye field.

Specific developmental events in eye development

The eye field and the preplacodal region

Following gastrulation, the three germ layers (endoderm, mesoderm, and ectoderm) are established and neural identity begins with formation of the neural plate (Fig. 4.3A,B). The first molecular evidence of eye development is a single "virtual" structure, the eye field, that extends across the midline and is defined by discrete and overlapping expression domains of different TFs – the eye field transcription factors (EFTF) including OTX2, TBX3, RAX, PAX6, SIX3, SIX6, LHX2 and NR2E1.[6] RAX is the EFTF most commonly used as a marker of the eye field (Fig. 4.3C). Mutations in the human *RAX* gene are a rare cause of human microphthalmia. Homozygous

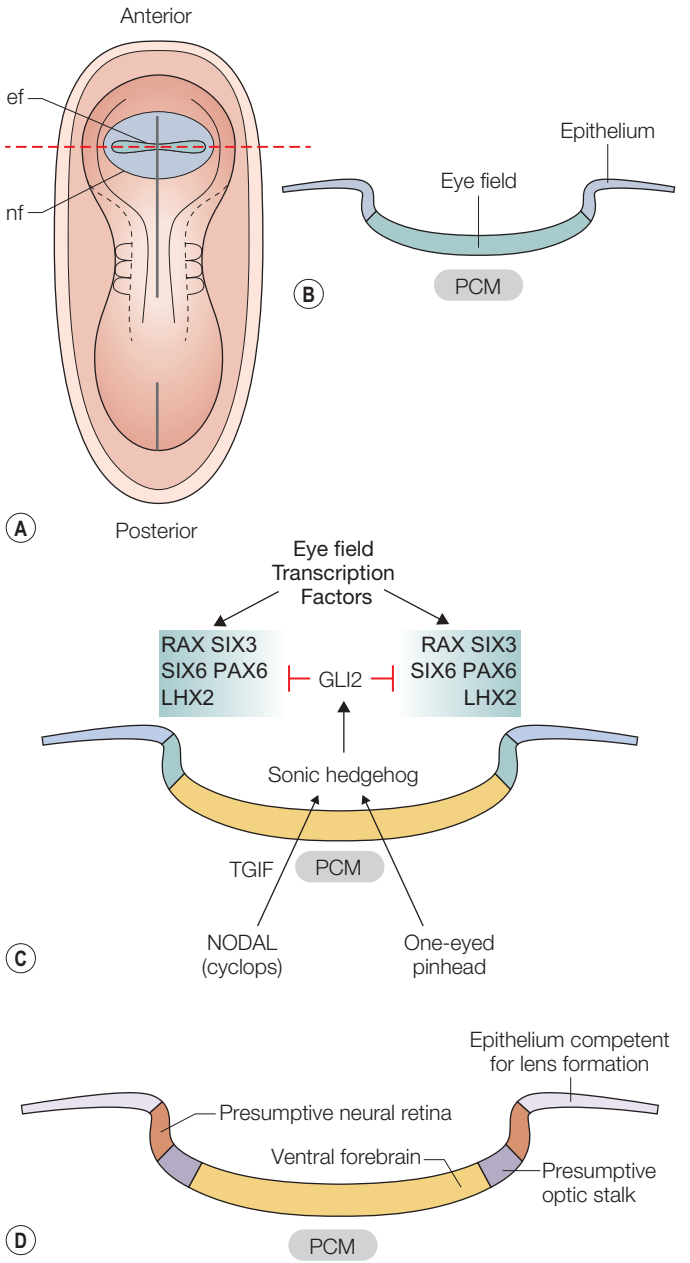


Fig. 4.3 Splitting the eye field. (A) The eye field (ef) is a virtual structure that forms within the neural field (nf) on the dorsum of the early embryo. (B) A section through the eye field shows it to be a plate of neuroepithelial cells spanning the midline and overlying a structure called the prechordal mesenchyme (PCM), which is a rostral continuation of the notochord. Expression of a group of eye field transcription factors (EFTF) mark the eye field at this stage. (C) Sonic hedgehog (SHH) signaling via GLI2 from the PCM acts to inhibit expression of the EFTF in the midline and split the eye field. (D) SHH also acts to pattern the now bilateral eye field into the medial presumptive optic stalk (green) and the more lateral presumptive neural retina (yellow). At this stage, most of the surface ectoderm is competent to produce a lens vesicle.

null mutations *Rax* in mice result in complete absence of eye structures, due to a failure in formation of the optic sulci that give rise to the optic cups. *Otx2* is the earliest molecular delineator of the eye field and heterozygous loss-of-function mutations in *OTX2* cause severe ocular malformations in humans.[7] The EFTF *Lhx2* has an expression domain within that of *Rax*. Targeted mutations in the mouse *Lhx2* gene cause

anophthalmia. As with many EFTF, LHX2 also functions later in eye development.

In common with many developmental processes, the eye field is a result of a balance of different signaling activities with competing morphogen gradients originating in neighboring tissues and often having antagonistic functions – some signals promoting formation of the eye field and others inhibiting it.[8] Ligands of the Wnt signaling system are secreted from the midbrain and paraxial mesoderm regions. A reduction or an increase in Wnt signaling will result in an increase or a decrease in the size of the eye field, respectively. For example, artificially overexpressing an inhibitor of Wnt signaling, *dickkopf1*, in zebrafish causes the eye field to get bigger; whereas, homozygous loss-of-function mutations in a different inhibitor of Wnt signaling, *axin1*, causes reduced eye size.[9] In *Xenopus* embryos, Notch signaling also induces the eye field, and hypomorphic mutations of Notch2 in mice causes bilateral microphthalmia. The eye field is surrounded by the preplacodal region, which is a band of ectoderm that subsequently migrates to form the lens placode mentioned below.

The eye field must split in the midline in order for two separate eyes to form. Failure of this process will result in a single central eye (cyclopia). Nodal signaling from the underlying prechordal plate mesoderm results in downregulation of *Pax6* and *Rax* expression in the ventral midline, with the newly separated domains demarcating the two bilateral optic primordia. Nodal ligands are members of the transforming growth factor beta (TGF-β) superfamily of signaling molecules. In zebrafish, the mutants, *Cyclops*, *oep* (one-eyed pinhead), and *sqt* (squint), all have cyclopia[10] and failure to form ventral forebrain due to a loss-of-function mutation in the Nodal pathway. The Nodal effect is mediated via inductions of *Sonic hedgehog* (*Shh*) expression, which in turn induce expression of the transcriptional repressor *Gli2* (see Fig. 4.3). Both mice and humans with *Shh*/*SHH* mutations develop cyclopia and holoprosencephaly.

Following splitting of the eye field, the bilateral presumptive neural retina (PNR) fields are visible as a pair of shallow grooves (optic sulci) on the anterior neural plate. These will ultimately form the optic vesicles. Definition of the medial and lateral boundaries of the PNR are maintained by continued Shh signaling from the prechordal mesenchyme and bone morphogenetic protein (BMP) signaling from the paraxial mesenchyme, respectively.[11] This process appears to be crucial for normal eye development; the blind cavefish *Astyanax* is anophthalmic because an evolutionary mutation produces hyperactivation of the Shh signaling cascade in the midline.[12,13] This moves the medial boundary of the PNR more laterally, resulting in smaller optic vesicles.

The optic vesicle and optic stalk

The midline gradient of Shh signaling also differentiates the optic stalk from optic cup. *Shh* induces expression of the optic stalk markers, *Pax2*, *Vax1*, and *Vax2*. Overexpression of *Shh* at this stage results in expanded expression of the ventral marker *Pax2* and the suppression of *Pax6*.[14] Reciprocal transcriptional repression between *Pax2* and *Pax6* creates a boundary demarcating the future optic stalk region and the presumptive neural retina.[15] *Pax2* expression is a marker of the presumptive optic stalk and *Pax6* a marker of the presumptive neural retina. Human loss-of-function mutations in *PAX2* cause optic nerve coloboma, a failure to complete optic fissure closure. This is presumed to be the result of an expansion of the PAX6 domain into the presumptive optic stalk region at the expense of the PAX2 domain. Similar to *Pax2*, loss-of-function mutations in *Vax2*, or its paralogue, *Vax1*, cause optic nerve coloboma in mice. Again this appears to be via failure of repression of PAX6 expression.[16] In zebrafish, *Vax1* and *Vax2* genes are expressed in overlapping ventral domains within the developing eyes and their abrogation results in failure of fissure closure and the expansion of neural retina into ventral regions. A further level of control of Vax1/2 function is via the control of the nuclear localization of these proteins through SHH signaling.[17]

Shh, retinoic acid (RA), and bone morphogenetic protein 4 (BMP4) pattern the developing optic vesicle (OV) to confer proximoventral and dorsal–distal characteristics on the neuroectoderm. *Bmp4* is expressed in the distal OV and subsequently within dorsal regions of the optic cup. Overexpression of *Bmp4* expands the *Pax6* expression domain, thus repressing *Pax2* that results in the extension of retinal pigment epithelium (RPE) into forebrain regions.[14] A similar phenotype is associated with loss of Smoc1, a BMP antagonist, in mice. *SMOC1* mutations in humans results in severe anophthalmia as part of the ophthalmo-acromelic syndrome.[18] Overexpression of another BMP antagonist, Noggin, increases *Pax2* and decreases *Pax6* expression. Treatment of *Xenopus* embryos with RA leads to ventralization of the dorsal optic vesicle with expansion of *Vax2* expression domain dorsally.[14] Loss-of-function mutations in RA nuclear receptors reduce the size of the ventral retina, resulting in failure of the optic fissure to close. Loss of multiple RA receptors results in additional ventral abnormalities, including the absence of ventral iris.[15] In humans, loss-of-function mutations in the RA receptors STRA6[19] and RARB[20] or in the enzyme that activates RA, ALDH1A3[21] each result in severe eye malformation.

Patterning of neural retina in the optic vesicle

Shh and BMP4 promote dorsal–ventral (DV) polarity within the presumptive neural retina (PNR) of the optic vesicle (Fig. 4.4). Bmp4 is induced by Lhx2 and in turn induces *Tbx5* expression in the dorsal PNR, while Shh induces *Vax2* expression ventrally. Overexpression of *Bmp4* in *Xenopus* causes expansion of *Tbx5* expression domain ventrally with suppression of *Vax2*. Tbx5 and Vax2 negatively regulate each other in the PNR to impart dorsal and ventral identity. Vsx2 (previously known as *Chx10*), a paired-like homeodomain transcription factor, is expressed in the PNR adjacent to the lens placode in response to inductive fibroblast growth factor (Fgf) signaling from the surface ectoderm. Mutations in *VSX2* lead to microphthalmia in humans and mice.[22] Removal of the lens placode from cultured OV causes abnormal differentiation that can be rescued by exogenous Fgf.

Involvement and development of the retinal pigment epithelium

The retinal pigment epithelium (RPE) develops from dorsal neuroectoderm of the early OV and is required for

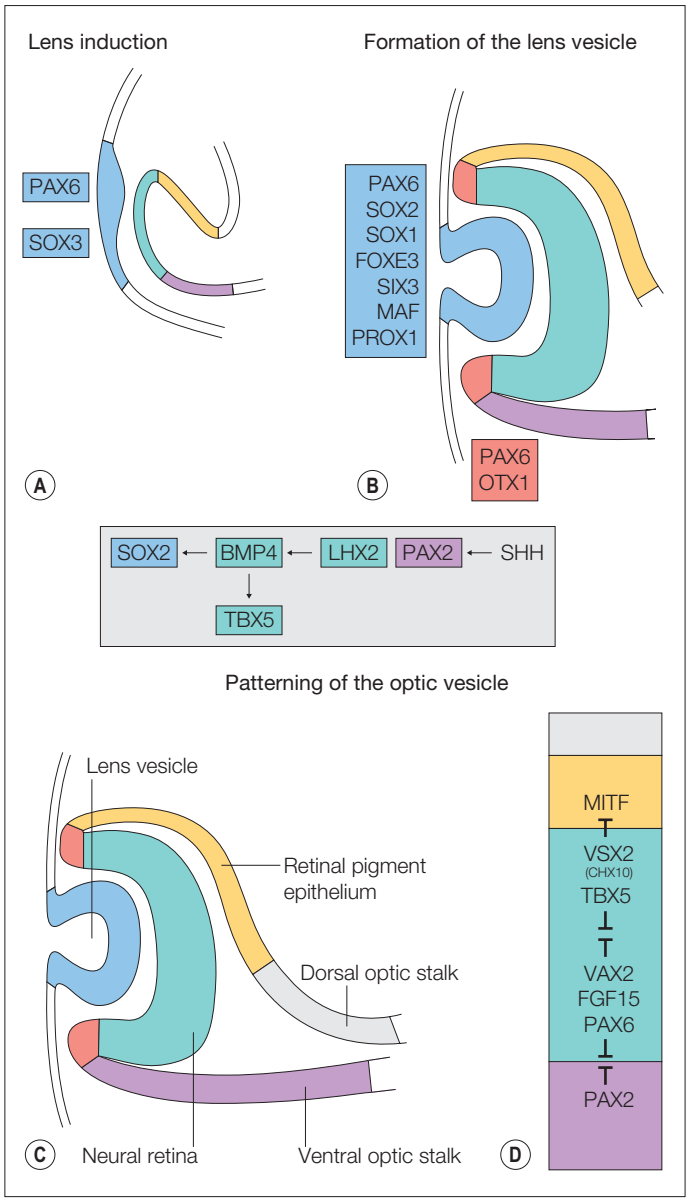


Fig. 4.4 Patterning the lens, retina and retinal pigment epithelium (RPE). (A) The formation of the lens requires signaling between the surface ectoderm and the optic vesicle to form the lens placode. The optic stalk is patterned by induction of PAX2 via SHH. LHX2 induces expression of BMP4 in the presumptive neural retina (PNR), which in turn induces SOX2 expression in the surface ectoderm. This triggers a cascade of transcription factor expression in the lens placode to induce lens vesicle formation (B,C). BMP4 also induces expression of TBX5. (D) A complex network of transcription factors act by induction and repression to form the boundaries between the optic stalk and the PNR and the PNR and the RPE.

morphogenesis of the neural retina. Microphthalmia-associated transcription factor, *Mitf*, a basic helix–loop–helix leucine zipper family gene, is expressed in the future RPE in both mouse and chick. Mutations in *Mitf* cause microphthalmia or anophthalmia in rodents and fish but not humans. *Otx1* and *Otx2* are transcription factors initially expressed throughout the PNR but later mark the presumptive RPE during optic cup formation. Loss-of-function mutations in *Otx* genes in mice result in RPE patterning defects and replacement with ectopic neural retina, while in *Mitf* mutant mice, *Otx2* expression is lost. Both proteins co-localize within nuclei of RPE cells and may cooperate to activate other RPE genes. *Mitf* is also a transcriptional target of *Pax6*; both are co-expressed in the presumptive RPE, with *Pax6* being restricted to the PNR at later stages.[23]

Lens development

As with many parts of eye development, Pax6 is a key player in lens development. Initially Pax6 is expressed throughout the head ectoderm, but then becomes restricted to the presumptive lens placode as the result of TGF-β signals from the underlying migratory cranial neural crest cells. Pax6 mis-expression in *Xenopus* results in ectopic lens formation. In developing optic vesicles,[24] Pax6, the Meis family of transcription factors, Bmp7 and Fgf signaling define the regional localization of the placode prior to ectodermal thickening.[25] Both Bmp4- and Bmp7-null mice do not induce lens development. Disruption of Fgf signaling results in a reduction in placodal Pax6 expression and causes defects in early lens development and lens pit invagination. Co-binding of Sox2 (or Sox1) and Pax6 to enhancers is necessary for early lens crystallin gene expression. The forkhead family gene FoxE3 is a Pax6 target gene, which is expressed in the presumptive lens placode. FoxE3 mutations in humans and mice cause aphakia and microphthalmia.[22] In Mab21l1 mutants, FoxE3 expression is absent in the lens placode, yet Pax6 is unaffected, suggesting that activation of Mab21l1 lies between placodal Pax6 and FoxE3 activation in the developing lens.[25] *Mab21l1-deficient mice have rudimentary lenses as a result of insufficient invagination of the placode due to insufficient expression of FoxE3 with normal expression of Pax6, Sox2, and Six3*. The MAF family of basic-leucine zipper transcription factors is also implicated in lens development and is regulated by Pax6.

Once the lens vesicle has separated from the surface ectoderm, Prox1 expression is essential for the differentiation and elongation of lens fiber cells. Prox1 mutant lenses fail to polarize and elongate, resulting in a hollow lens.[26] Pax6 remains expressed in the lens epithelium until just after the time of vacuole closure, whereas Sox2 is downregulated soon after vacuole formation. Sox1 is expressed throughout the lens at this time, replacing expression of Sox2 and being present in primary fiber cells. Mutations in mouse Sox1 cause cataracts.

Differentiation of the neural retina

The differentiation of the multipotent retinal progenitors involves the interaction of activating and repressing bHLH transcription factors.[27] Each retinal cell type has a unique bHLH factor combinatorial code. Hes1 and Hes5 are both repressive bHLH molecules and double null mutants lack optic vesicles. Retinal ganglion cells (RGCs) are generated from progenitors co-expressing Pax6 and the bHLH activator gene atoh7. Sox2 is expressed widely in neural progenitors. Human heterozygous loss-of-function mutations in Sox2 cause bilateral anophthalmia and severe microphthalmia.[28] Hypomorphic mutations in mouse Sox2 result in the loss of RGCs and cause disrupted cell lamination within the neural retina. The decreased levels of Sox2 are associated with reduced Notch1 and Hes-5 expression, while atoh7 and Pax6

are upregulated. These data are consistent with a key role for Sox2 in the maintenance of retinal neural progenitors.

Shh acts as a retinal precursor cell mitogen, increasing neuron cell numbers in culture experiments.[29] The Shh receptor Patched is expressed in the neuroblastic layer of the retina in a pattern that follows the wave of differentiating ganglion cells – first observed in the ganglion cell layer and then later within the inner nuclear layer. The bHLH activators Neurod1 and Neurod4 are expressed in differentiating amacrine cells. In double mutant mice, amacrine cells are completely missing while ganglion and Müller glial cell numbers are increased. Co-expression of Pax6/Neurod1 or Pax6/Neurod1/Neurod4 promotes amacrine cell differentiation, while co-expression of Pax6/Neurod4 results in more horizontal cells than amacrine. Bipolar cells co-express Vsx2/Neurod4/Ascl1 (another bHLH activator). Horizontal cells require co-expression of Pax6/Neurod4/Prox1/Foxn4. Rods and cones require co-expression of Neurod1, Ascl1, Crx, and Otx2. Crx is necessary for normal cone and rod function and is implicated in human photoreceptor degeneration and Leber congenital amaurosis (LCA; MIM#602225).

Closure of the optic fissure

The optic fissure begins as a deep groove that runs from the ventral rim of the optic vesicle continuously along the ventral aspect of the entire outgrowth. It provides a channel for hyaloid blood vessels that supply the primitive lens and retina. Fusion of the fissure begins with apposition of the inferior lips of the ventral-most optic cup and continues both anteriorly toward its rim and posteriorly along the optic stalk. Little is known about the genetic factors underlying the fusion event; however, failure of this process results in the commonest major eye malformation, optic fissure closure defects (OFCD; e.g. iris, retina, or optic nerve coloboma). *Pax2* and *Vax2* are expressed in the ventral optic stalk and have both been implicated in OFCD. Patients with Pax2 mutations develop optic nerve coloboma,[30] while both Pax2 and Vax2 knockout mice display colobomas, suggesting that genes expressed in the ventral portion of the optic vesicle in the early stages of development may contribute and coordinate the closure of the optic fissure. Heterozygous mutations in YAP1, the effector of the HIPPO signaling pathway, and MAB21L2 have recently been identified as causing OFCD.[22] *CHD7* mutations are a common cause of syndromal OFCD as a component of CHARGE syndrome.[31] The cause of the vast majority of nonsyndromal OFCD cases remains unknown, although *PAX6*, *SOX2*, and *SHH* mutations have been reported in a few cases.

Cornea and anterior segment development

The cornea, lens, and anterior segment structures (ciliary body, iris, vitreous, and trabecular meshwork) are formed by contributions from various cell populations from distinct origins in spatially and temporally coordinated interactions. The cornea is derived from both surface ectoderm and neural crest-derived periocular mesenchyme cells. The ectodermal cells secrete a collagen-rich matrix that attracts the surrounding mesenchymal cells to form the stroma of the future corneal epithelium. A second wave of mesenchyme cells forms the corneal endothelium, or posterior stroma. Other neural crest-derived mesenchyme cells line the anterior chamber, iris stroma, and trabecular meshwork. The transcription factor Lmxb1 is required for the normal development of the latter structure.[32] Normal dosage of PAX6 is required for formation of the iris, with haploinsufficiency leading to aniridia in humans and mice. PITX2 and FOXC1 are also crucial for normal anterior segment development.[33,34] The pigmented region of iris develops from an outgrowth from the tip of the optic cup margin, with iris muscles forming from the outer layer of the optic cup margin. The aqueous humor is secreted into the anterior chamber by the ciliary body epithelium and exits through the trabecular meshwork at the angle of the eye, which has at its anterior the cornea, while the iris is positioned at its posterior. These structures control the flux of aqueous humor in the anterior segment; maintenance of intraocular pressure is very important in both the development of the anterior segment and in the adult organ itself.

Summary

Our understanding of the molecular basis of eye development has benefited from an ongoing dialogue between basic developmental biologists and human geneticists, leading to the elucidation of critical patterning and signaling events involved in early development of the lens, retina, and RPE. The emergence of new high-throughput sequencing technologies should mean that the pace of discovery dramatically increases.

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Clinical aspects of normal and abnormal visual development and delayed visual maturation

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Introduction

The development of normal vision accompanies the development of the eye and brain. As the eye grows, the axons of the retinal ganglion cells find their way via the optic nerve and visual pathways within the brain to reach targets in the visual cortex. As the eye grows, its optical properties change and, normally, emmetropization occurs.[1] In the posterior segment, retinal cells re-distribute to populate the expanding periphery and to create a fovea that normally matures to mediate exquisite visual resolution.[2–4] Myelination of the optic nerve fibers continues into childhood.[5] Also after birth, myelination of brain structures continues, the volume of the brain increases, and the organization of the brain matures.[6,7]

As the infant grows and develops, visual capabilities gradually increase and become more like those in adults. Some developmental changes in visual function can be related to structural changes in the eye or brain. In other instances, the immature molecular substrate surely impacts vision, but the relationship of these immaturities to visual functions may not be demonstrable in the living subject.

Increases in visual capabilities accompany normal development. Diseases of the eye and visual system may decrease these capabilities. In patients, functional deficits may occur even if abnormalities in physical structure and molecular substrate are undetectable. In infants and children, distinguishing immaturity from disease is fundamental to the interpretation of their visual responses. Repeated measures over time may help separate effects of development (improving vision) from effects of disease (worsening vision). Longitudinal data are often of supreme value.

Rigorous, noninvasive psychophysical and electrophysiological tests, originally used to study visual development in healthy infants with normal eyes, have been modified for clinical application. For measurement of vision, stimuli must be specified in precise physical terms.[8,9] Procedures must insure that the child's response is under stimulus control. That is, there must be a reliable relationship between the stimulus and the child's response. Comparison to normal values for age is crucial for valid interpretation of a patient's vision test results. In the authors' experience, measurement provides critical information that complements important clinical history and unstructured observation. Without losing sight of the clinical context, interpretation of the patient's results includes comparison to normal values for age. Additionally, data obtained in serial measurements can be compared to the patient's own prior results in order to chart the patient's course.

In this chapter, we limit our discussion to those visual functions that are regularly measured in the clinic, such as visual acuity and visual fields, and those that have been used to investigate common pediatric disorders of the eye and visual system. In strabismus and amblyopia, the visual functions that are informative, in addition to visual acuity, are contrast sensitivity, Vernier acuity, and stereoacuity. In retinal dystrophies of early onset, the dark-adapted visual threshold provides an assessment of retinal function from infancy onward.

For each visual function, the course of normal development is shown and comment on the putative structural and neurophysiological bases is provided. Examples from patients are presented. Some visual functions discussed here are mediated by the central retina (grating and letter acuity, contrast sensitivity, Vernier acuity, stereoacuity) and others by the peripheral retina (dark-adapted rod-mediated visual threshold, visual field). The most commonly measured visual function, visual acuity, evaluates function of the entire visual pathway. Some visual functions are tested mainly to evaluate the function of the retina (dark-adapted visual threshold). Vernier acuity and stereoacuity are often cited as noninvasive assessments of processes in the brain. This chapter by no means covers all aspects of visual development. Human retinal and visual development is covered in a more comprehensive fashion elsewhere.[6,10–12]

Table 5.1 Acuity development: mean visual acuity and 95% prediction interval

Age	Min arc	Snellen VA	95% Prediction limits*	
			Lower	Upper
GRATING ACUITY				
1 month	32.84		65.68	16.42
2	15.72		31.45	7.86
3	10.63		21.26	5.32
4	8.20		16.39	4.10
5	6.76		13.53	3.38
6	5.82		11.64	2.91
7	5.14		10.29	2.57
8	4.64		9.28	2.32
9	4.24		8.49	2.12
10	3.93		7.85	1.96
11	3.66		7.33	1.83
12	3.45		6.89	1.72
15	2.96		5.91	1.48
18	2.62		5.25	1.31
21	2.38		4.76	1.19
24	2.19		4.39	1.10
30	1.93		3.85	0.96
36	1.74		3.48	0.87
48	1.49		2.99	0.75
SYMBOL ACUITY				
3 years		~20/35	~20/70	~20/17
4		~20/30	~20/60	~20/15
5		~20/27	~20/53	~20/13
6		~20/25	~20/49	~20/12
7		~20/23	~20/46	~20/11
8		~20/22	~20/43	~20/11
9		~20/20	~20/41	~20/10
10		~20/20	~20/39	~20/10
11		~20/19	~20/38	~20/9
12		~20/18	~20/36	~20/9
Adult		~20/15	~20/30	~20/8

CONVERSION OF ACUITY METRICS

Snellen VA	Min arc	cpd	Dec VA	logMAR
20/2400	120.00	0.25	0.008	2.08
20/1600	80.00	0.38	0.013	1.90
20/1200	60.00	0.50	0.017	1.78
20/800	40.00	0.75	0.025	1.60
20/600	30.00	1.00	0.033	1.48
20/400	20.00	1.50	0.050	1.30
20/300	15.00	2.00	0.067	1.18
20/200	10.00	3.00	0.100	1.00
20/150	7.50	4.00	0.133	0.88
20/100	5.00	6.00	0.200	0.70
20/80	4.00	7.50	0.250	0.60
20/60	3.00	10.00	0.333	0.48
20/50	2.50	12.00	0.400	0.40
20/40	2.00	15.00	0.500	0.30
20/30	1.50	20.00	0.667	0.18
20/25	1.25	24.00	0.800	0.10
20/20	1.00	30.00	1.000	0.00
20/15	0.75	40.00	1.333	−0.12
20/10	0.50	60.00	2.000	−0.30

cpd, Cycles per degree; Dec VA, decimal visual acuity; MAR, minimum angle of resolution; Min arc, minutes of arc.
*The prediction interval is the range within which values of 95% of the normal population are expected.[16]

Visual acuity

Visual acuity is mediated by the fovea, which projects to a large region of the primary visual cortex. Visual acuity is defined as the finest detectable detail (minimal angle of resolution MAR).[13–15] Correct identification of letters that subtend, from top to bottom, 5 minutes of arc with stroke and gap widths of 1 minute of arc is designated as 20/20 acuity; 20/20 Snellen is equivalent to 6/6, 1.0 decimal, or 0.0 logMAR (Table 5.1). 20/200 symbols are 10 times larger. Letter acuity of 20/200 is one of the main criteria for legal blindness and thus a determinant of eligibility for vision support services.



Fig. 5.1 Preferential looking test of acuity using the Teller Acuity Cards (TAC). The 15-month-old child is seated on his mother's lap. The examiner shows a series of cards with black and white stripes (gratings) on either the left or the right, starting with wide stripes. The examiner, who is unaware of the right–left position of the stripes, must judge the stripe location based on the child's head and eye movement response.[22] Acuity is taken as the narrowest stripes to which the subject responds. *(Photos courtesy of Pablo Altschwager, MD, and family.)*

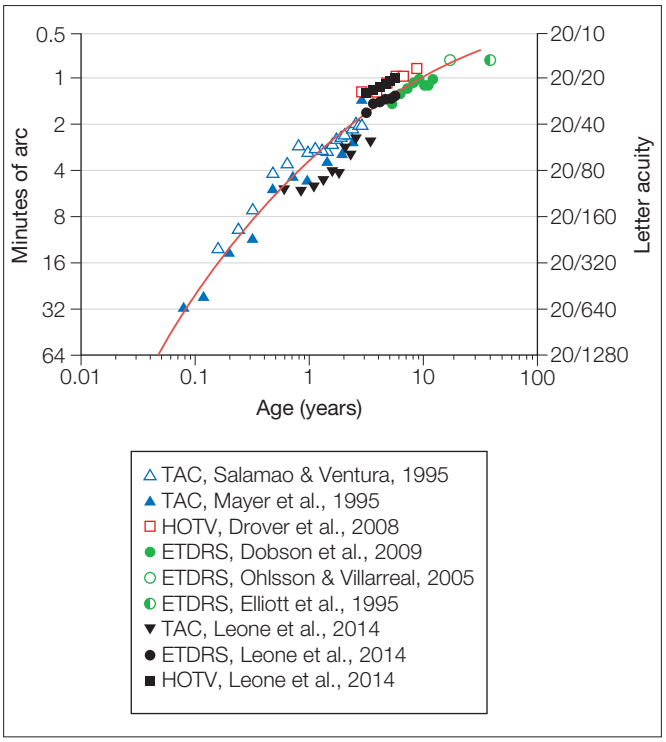


Fig. 5.2 Development of acuity in normal subjects. Mean monocular acuity is shown as a function of age. Grating acuity (triangles) from age 1 month to 4 years was obtained using the Teller Acuity Card (TAC) preferential looking procedure.[21–23] HOTV letters (squares) were used to measure acuity from age 3 to 9 years.[21,137] ETDRS letters (circles) were used for children 5 to 12 years,[21,138] 17 and 18 year olds,[139] and adults.[140] The smooth curve shows a verage acuity as a function of age which increases systematically despite the use of different stimuli (gratings, symbols) and procedures (preferential looking, matching, recognition).

In infants and children who do not have the behavioral repertoire to read letters or follow instructions for matching, acuity is tested using preferential looking (PL), psychophysical (Fig. 5.1) or visual evoked potential (VEP) electrophysiological procedures. The stimuli are repetitive patterns, most often gratings (stripes), that are specified in precise physical units (minutes of arc [min arc], cycles per degree [cpd]). The development of normal acuity is summarized in Figure 5.2. For convenience, mean values of normal acuity along with the prediction interval for normal[16] at selected ages are listed in Table 5.1. In the authors' experience, at age $2\frac{1}{2}$ to 3 years, children with typical development can be tested using symbols and a matching task. Before that age, acuity measurements are most commonly accomplished using preferential looking procedures.

During infancy, acuity measured using VEP[17–20] is better than that obtained using PL[21–23]; whereas in healthy adults, VEP acuity is poorer than letter acuity.[24] In a healthy infant at age 6 months, average PL acuity is 6 min arc and average VEP acuity is approximately 2 min arc.[25,26] A six min arc stripe subtends the same angle as a 20/120 letter; a 2 min arc stripe subtends the same angle as a 20/40 letter. The explanation offered for the VEP–PL difference usually runs along the following lines[19]: VEP acuity is constrained by processes in the eye, the pathway from the eye to the visual cortex, and the visual cortex. The same processes also constrain PL acuity, but additionally, PL acuity requires processing in higher neural areas, attention,[27] and eye–head movement indicating a behavioral looking response. Differences in stimuli, analysis techniques, and response measures also contribute to the VEP–PL difference.

During normal development, acuity is limited in part by immaturities of the fovea. The fetal fovea becomes identifiable as a ~1665 µm diameter rod-free retinal region at approximately 22 weeks' gestation.[4] By term, this diameter has decreased to ~1100 µm. The diameter continues to decrease with age. The adult diameter is approximately 350 µm.[28] Foveal maturation continues into childhood.[2,28–30] The cones first develop inner segments, which are wider than those in adults, and then outer segments. The cone center-to-center spacing decreases and the inner segments become more slender as the fovea develops.[2,31] These features of the foveal cone photoreceptors do not account fully for low acuity in young infants. There are, additionally, postreceptor retinal[32] and brain immaturities.[7,33–35]

Assessments of acuity contribute to diagnosis and to assessment of severity and course of disease (Fig. 5.3). PL acuity tests have been used widely for assessment of infants and children with ophthalmic disorders.[36–40] In pediatric patients with cognitive impairment, acuity is, on average, about one octave (a halving of spatial frequency) below normal for age, even if their eyes are normal.[41] PL and VEP tests also have a place in measurement of acuity in older patients with cognitive impairment.[42]

Grating acuity may appear to be too good. In a study of amblyopia, letter acuity for the amblyopic eye was on average 1.5 times worse than grating acuity,[43] perhaps, in part, because letters have complex spatial content. Thus, a patient's grating acuity must be interpreted with some caution. A practical issue arises if grating acuities are reported to educators and agencies without explanation. Without the ophthalmologist's explanation, children may be unnecessarily declared ineligible for services because their grating acuity test results are better than 20/200, a definition of legal blindness.[44,45]

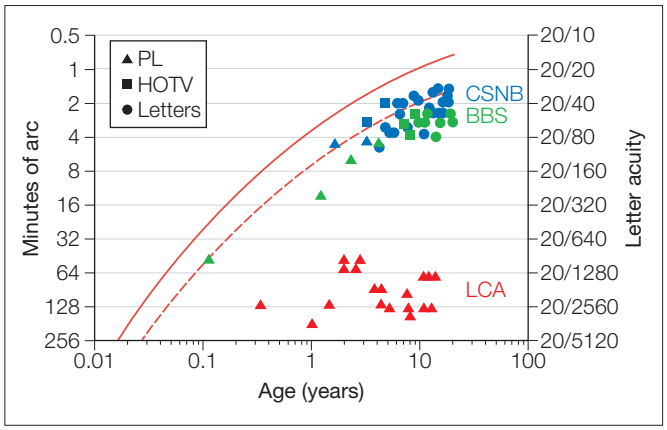


Fig. 5.3 Acuity in three patients. Data from patients with Bardet–Biedl syndrome (BBS, *BBS7*; green symbols), X-linked congenital stationary night blindness (CSNB; blue symbols), and Leber congenital amaurosis (LCA, *CRB1*; red symbols) are shown. The solid red line, re-plotted from Fig. 5.2, describes average acuity as a function of age and the dashed line the lower 95% prediction limit of normal[16]; see also Table 5.1. Age-appropriate tests were used for the patients with BBS and CSNB. In the patient with BBS, acuity remains near the lower limits of normal for age and shows a developmental increase; over the same interval, his dark-adapted visual threshold worsened. In the patient with CSNB, visual acuity remained stable, as did his dark-adapted visual threshold. Acuity in the patient with LCA (*CRB1*), who had marked macular atrophy, was measured using the gratings of the preferential looking test. This patient's dark-adapted visual threshold (youngest patient in Fig. 5.6) worsened significantly during childhood. As a rule of thumb, an octave change in repeated measures of acuity is significant.

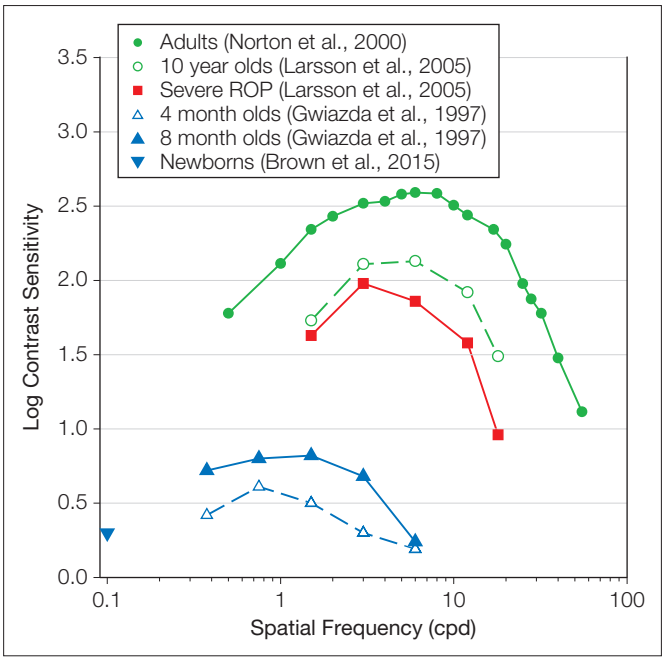


Fig. 5.4 Contrast sensitivity functions for healthy adult,[141] child,[142] and infant subjects[49] and for pediatric patients with a history of treated retinopathy of prematurity (ROP).[142] The reciprocal of the contrast necessary to detect a grating is plotted as a function of the spatial frequency of the grating. Data are re-plotted from the cited references.[48–50,141,142] All data were obtained using psychophysical procedures.

Contrast sensitivity

The real world is full of objects with widely varying contrast. Visual acuity is typically tested using high-contrast stimuli and, therefore, this fails to capture some important information about visual capabilities. For detection at lower contrast, stimulus elements must be larger than at high contrast. PL[46–50] and VEP[51–53] procedures have been modified to study development of normal contrast sensitivity and have also been used to study clinical conditions (Fig. 5.4). Contrast sensitivity is tested in older pediatric patients using commercially available charts with gratings or letters.[54,55]

Patients with retinal degenerations or optic nerve demyelination often have low contrast sensitivity.[56–58] For instance, patients with such disorders may have 20/40, or even 20/20, acuity at high contrast (>95%) and 20/100 acuity at low contrast (10%). On real world tasks, poor contrast sensitivity causes difficulty on everyday vision-mediated tasks, even though acuity measured in high-contrast conditions may indicate only mild-to-moderate deficits. This can baffle educators and other caregivers, but may be readily clarified if recognized by the ophthalmologist. Documentation of low-contrast sensitivity supports requests for appropriate educational planning.

Vernier acuity and stereoacuity

These functions depend upon integrity of the fovea and optic nerve but, importantly, also require complex cortical processing and are, therefore, considered higher-order visual processes.

Vernier acuity

Vernier acuity is the ability to detect discontinuity in a line.[14,15,59] This is critical to pattern perception. In healthy adults, Vernier acuity is nearly an order of magnitude better than letter acuity.[60] It is referred to as hyperacuity. Development of normal Vernier acuity has been studied using PL[61–65] and VEP[66] procedures. Vernier acuity and grating acuity develop at different rates (Fig. 5.5), with the level of Vernier acuity surpassing that of grating acuity during infancy[61,63] or childhood.[64,65] Vernier acuity reaches adult levels later than grating acuity.[64,66,67]

Vernier acuity is relatively tolerant to defocus, motion, and changes in luminance.[68–70] Tests of Vernier acuity are, therefore, potentially robust for clinical application. The advantages, however, are offset by susceptibility of Vernier acuity to practice effects and attention.[71,72] Although Vernier is better than letter acuity in healthy adults (see Fig. 5.5), in amblyopia, deficits in Vernier and letter acuity are similar.[43] In children with cerebral visual impairment, deficits in Vernier acuity are greater than deficits in grating acuity.[73]

Stereoacuity

Stereoacuity is the smallest disparity between images presented to the two eyes that can be detected reliably. Development of normal stereoacuity has been studied by several investigators.[74–78] Infants may demonstrate stereopsis as early as 2–3 months of age, but most show onset at age 3–5 months. Thresholds are 3–5 min arc by age 6 months (Fig. 5.5); in adults, stereoacuity is 1 min arc or better. Disorders of binocular vision, such as strabismus, affect stereopsis and depth perception. Interestingly, infantile esotropia often starts at ages during which normal stereoacuity develops rapidly.[79]

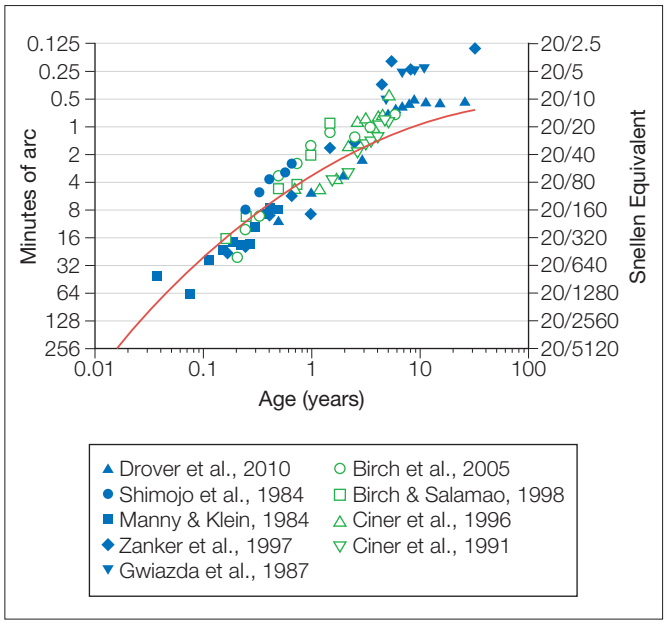


Fig. 5.5 Vernier acuity (filled symbols) and stereoacuity (open symbols) as a function of age in healthy subjects. Data are re-plotted from the cited studies.[61–65,75,77,78,143] The smooth red curve, which shows average visual acuity as a function of age, is re-plotted from Fig. 5.2.

Some investigators have championed tests of stereoacuity as a means of detecting strabismus and amblyopia,[77,80] and stereoacuity has been used to assess outcomes of treatment for esotropia.[81,82]

Dark-adapted visual threshold

The ability to detect dim spots of light in the dark is present in early infancy. The test spot must be brighter to be detected by a young infant than by an adult. With increasing age, the infant can detect dimmer test spots. For instance, at age 4 weeks, threshold is on average 1.4 log unit above that in adults.[11,83,84] By age 6 months, the threshold has become equivalent to that in adults.[84] The course of normal dark-adapted threshold development depends on maturation of the rod photoreceptors.[83,85]

To perform the test, threshold is measured following a period of dark adaptation using a modified preferential looking procedure (Fig. 5.6) as previously detailed.[86] The stimuli must be carefully specified and controlled to minimize spurious results.[11] Stimuli are chosen to favor detection by the rod system. Spectral sensitivity functions in infants as young as 4 weeks old confirm that dark-adapted thresholds are rod mediated.[83,87,88] The threshold is constrained by the rod photoreceptors' capture of quanta. The infant's retina has an adult complement of rods by term. The normal infant's rod outer segments are shorter and the retinal content of the visual pigment rhodopsin is lower than in adults.[85] Therefore, more light must fall on the infant's retina to produce the same response as in an adult.[11] Normally, there is a delay in developmental elongation of the near-peripheral (10° eccentric) rod outer segments compared to those in more peripheral (30° eccentric) retina; this is accompanied by a delay in development of the dark-adapted visual threshold at



Fig. 5.6 The dark-adapted visual threshold test. *The child is seated on his mother's lap; his eyes are positioned 50 cm from the screen when stimuli are presented. The patient reports stimulus location, by looking, pointing, or verbally reporting stimulus location to the right (A) or left (B). An adult observer (not shown) monitors the patient with an infrared viewer and reports the response to the examiner. (Photos courtesy of Pablo Altschwager, MD, and family.)*

10° eccentricity.[84] Studies of rod-mediated spatial summation show that infants' receptive fields are larger than those in the mature retina.[89–92] Rod-mediated temporal summation in infants appears to be constrained by immaturities in the activation of rod phototransduction.[93,94]

The dark-adapted rod-mediated visual threshold has also been studied in children with retinal disease, including degenerations and retinopathy of prematurity (ROP).[86,95–97] Longitudinal measurement of the dark-adapted threshold can be used to follow patients with retinal disease even when the electroretinogram is markedly attenuated.[86,98] Figure 5.7 shows representative results from patients with Leber congenital amaurosis (LCA). A 1 log unit worsening of threshold is evidence of significant progression of disease.[86] In ROP, near-peripheral (10° eccentric) threshold development is delayed relative to that in term born infants.[95] The effects of ROP on rod-mediated threshold persist into adolescence.[93,95,99–101]

Visual fields

In conventional visual field testing using commercially available equipment, adults and older children communicate

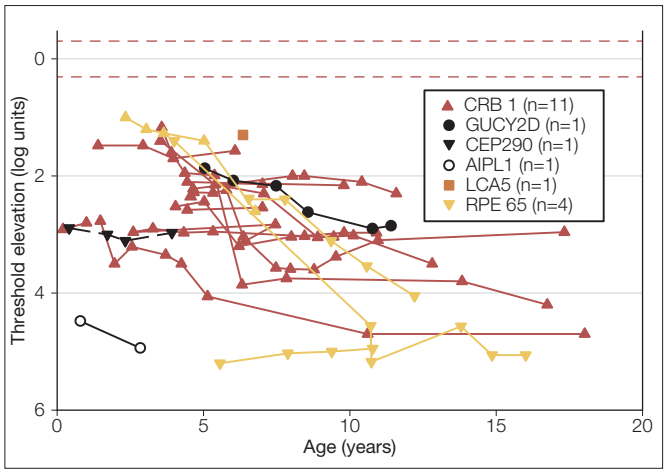


Fig. 5.7 Dark-adapted threshold as a function of age in patients with Leber congenital amaurosis. The key shows the patients' genetic diagnoses. Threshold for detecting 10° diameter, 50 ms duration spots presented 20° to the right or left of a small red fixation light is plotted as a function of age.[11,86] The course for each patient is shown by points connected by line segments. The majority of these patients had worsening thresholds. The normal mean threshold is at zero; the dashed lines indicate ±2 standard deviations.



Fig. 5.8 Confrontation visual field testing. (A) The patient's gaze is attracted to the target centered straight ahead. (B) Then a second target is presented peripherally in one quadrant. The child's looking response, or lack thereof, is noted. Each quadrant is tested in a similar manner. *(Photos courtesy of Pablo Altschwager, MD, and family.)*

their response to the stimuli (small spots of light) by buzzer press or similar activity. An eye movement to the target may be used in those unable to manage the buzzer. Acceptable reliability indices in automated static perimetry can be obtained in typically developing 8-year-olds[102,103] and, after a training session, in some children as young as 5 years.[104]

Conventional, non-automated procedures such as Goldmann kinetic perimetry are feasible in children at approximate developmental age 4 years, particularly if cast as a computer game.[105] The youngster's central fixation and subsequent head and eye movement response to the stimulus must be under strict surveillance by the examiner. Some examiners take successful mapping of the blind spot as an indicator of reliable perimetry. In the authors' opinion, conventional testing should be attempted as young as possible in children at risk for field loss.

Maturation of the peripheral visual field has been studied in typically developing infants and children. The visual field extent in term-born neonates is significantly smaller than in older children and adults.[106,107] The horizontal extent of the visual field increases steadily from age 2 months to 12 months.[106] Binocular and monocular field extent is 90–95% of that in adults by age 1½ to 4 years. In children aged 4–10 years, the visual field extent obtained using arc or hemispheric perimeters approximates that obtained by Goldmann kinetic perimetry.[106,108–115] Maturation of the nasal field may be delayed compared to temporal field, although not all studies find this.[106,110,111] Variability in infant and child visual field extent is high; the 95% confidence interval is typically ±10–20° for monocular field extent.[106,109,110] In infants and young children, visual field extent may be limited by immaturities of the visual pathways as well as by the child's attention.

Infants, young children, and also older patients with cognitive impairment or neurological limitations who cannot sustain attention sufficiently for tests using automated or other conventional perimeters, are tested using alternative procedures.[116] Some of these procedures were originally devised to study development of the peripheral visual field in normal infants.

Confrontation testing is the most commonly used alternative test (Fig. 5.8). The patient must have adequate looking behavior to respond to targets such as toys or lights. The examiner observes the patient's fixation behavior before presentation of the stimulus. The central stimulus (fixation target) is typically a small toy. Once the patient's gaze is on the central fixation target (see Fig. 5.8, upper panel), a peripheral target is presented (see Fig. 5.8, lower panel) and is moved slowly toward the center. Each quadrant must be tested in a similar fashion. To reduce spurious responses to the examiner's movements, a slender wand with lighted tip may be used. Game-like ploys, personalized by the examiner, are important for sustaining the patient's attention. Standard stimuli and procedures for confrontation testing are not established. Each quadrant should be tested using the same stimulus and procedure from one test session to the next. The stimuli are well above detection threshold and the sampling of the peripheral visual space is necessarily coarse. Thus, small scotomata will be missed. These procedures can identify large, absolute defects such as hemianopia or quadrantanopia produced by retrochiasmal disease, inferior altitudinal field loss due to white matter injury of prematurity in the parietal-occipital

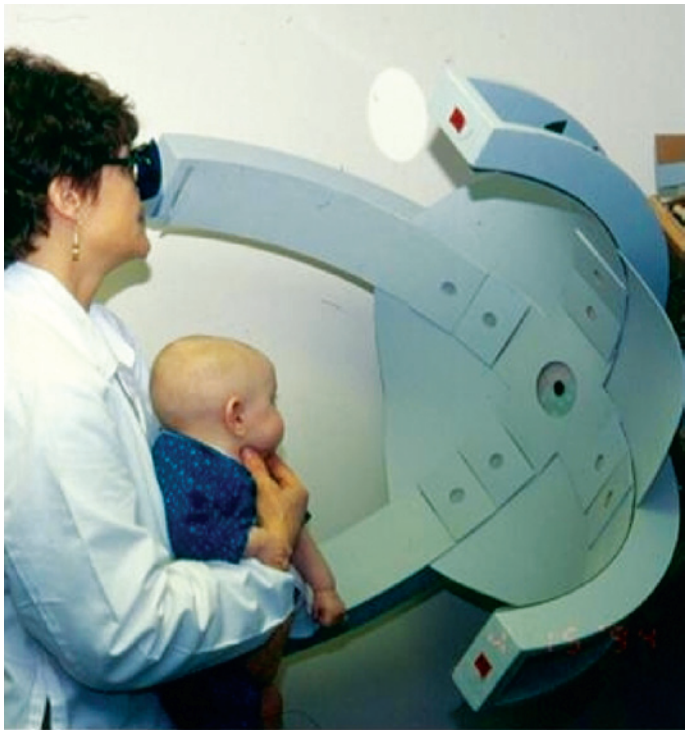


Fig. 5.9 An experimental arc perimeter used to test peripheral field in infants. A healthy infant, age 5 months, is looking at the central fixation display. The peripheral stimulus is a flickering yellow LED presented along the arcs. The infant's orienting eye–head movement response will indicate detection of the peripheral stimulus. The examiner, who is masked to the location of the yellow stimulus by wearing glasses with blue filters, uses a video system (not shown) to monitor the infant's fixation and report responses. *(From SanGiovanni JP, Ho E, Mayer DL. Photopic peripheral sensitivity of 20-week-old infants and adults. Invest Ophthalmol Vis Sci 1994; 35: ARVO Abstract 1393.)*

regions of the brain,[117] and constriction of the visual field caused by retinal degeneration or toxicity.[105,118]

An arc perimeter or modified hemispheric perimeter provides an advantage over confrontation testing because numeric results can be obtained (Fig. 5.9). A map of the patient's responses to stimuli at selected peripheral eccentricities can be drawn. Stimuli have included white spheres, LEDs, and other small lights. The minimum test should evaluate responses in each quadrant along the major obliques (45°, 135°, 225°, and 315°). Children's visual fields mapped using kinetic arc perimetry are highly variable.[116,118,119] A clinician's goal is often to complete monocular visual field testing. If this is not feasible, the results obtained with binocular viewing may yield useful information about the child's disease and/or visual capabilities.

The balance of attention between central and peripheral stimuli influences measured field extent in infants and young children. A central stimulus that is too salient may inhibit ability to disengage and orient toward the peripheral stimulus.[106,120] Ideally, the central stimulus should be similar to the peripheral stimulus in luminance and spatial extent. Stimulus characteristics, including spatial extent, rate of centrad movement, and rate of flicker all have demonstrable effect on field extent in infants and young children.[121–124] Sounds synchronized with presentation of central and peripheral stimuli may enhance attention and orienting in young infants but not in toddlers.[106]

Delayed visual responsiveness

The integrated development of structure and function of the eye and visual pathways enables visual responsiveness at a very young age. A healthy, term-born infant starts smiling responsively at approximately 5 weeks, and fixes and follows readily by age 2 months. In some infants without conspicuous ophthalmic or medical abnormalities, the visual behavior does not meet normal developmental milestones. The term "delayed visual maturation" (DVM) describes this clinical entity.[125,126]

Young infants lacking visual responsiveness are taken to the ophthalmologist because of suspected blindness. Infants with this worrying presentation will include those in whom no ophthalmic or neurological abnormality is found, those who have some ophthalmic disease, and those who have disease of the brain. Others without any specific clinical abnormalities of the eye or the brain will subsequently be diagnosed with a disorder that has associated cognitive impairment or neurodevelopmental disability. In short, the universe of visually unresponsive young infants includes diverse diagnoses. Schemes for categorizing infants with visual delays have sought to organize a mass of information.[127,128] Some generalities emerge. Among those infants in whom the results of ophthalmic and neurological examinations are normal, many rapidly develop normal visual responsiveness. A subset of such infants are subsequently found to have cognitive impairment.[128] Hoyt[126] followed for two decades patients (N=98) who in infancy had isolated delays in visual responsiveness. Nearly all developed excellent visual acuity, but more than half manifested neurodevelopmental disorders, most commonly expressed as learning disabilities.[126]

There are several specific ophthalmic conditions that are encountered repeatedly in infants with visual inattention. Structural abnormalities, should they be present, are typically discovered on the first ophthalmic examination. Optic nerve hypoplasia is a structural abnormality found in some of these infants. Detectable (although sometimes subtle) ophthalmic anomalies occur in the various forms of albinism – perhaps the most common specific diagnosis underlying visual unresponsiveness in infancy.[129]

If another diagnosis cannot be secured, evaluation for severe congenital retinal dystrophy (for example, Leber congenital amaurosis) by electroretinographic testing should be done. Even if visual inattention is profound in early infancy, patients with severe ocular disorders (including optic nerve hypoplasia and Leber congenital amaurosis) may show some developmental increments in acuity on the preferential looking test, presumably due to continuing maturation of the regions of the brain subserving vision.[37,130]

Among young, visually inattentive infants, we also find those with achromatopsia and congenital stationary night blindness – congenital anomalies of retinal function. We narrow the differential diagnosis by electroretinography and then secure the diagnosis by molecular genetic study.

If the eye is not at fault, brain disorders must be considered as the cause of the infant's visual inattention. Approximately half of the brain is dedicated to visual processing.[131] Structural abnormalities of the brain are found by magnetic resonance imaging (MRI). Some infants may have seizure activity; in particular, seizure activity in the frontal or parietal lobes is

associated with reduced visual responsiveness even in the absence of brain malformation.[126]

Acuity measured by PL or VEP in infants with delayed visual responsiveness is variable, ranging from severely reduced[127] to normal for age.[132] Overall, this variability is not too surprising given the diverse underlying diagnoses and the multiple components of the visual system that must mature to mediate visual responsiveness. Furthermore, we are reminded that Fantz and coworkers originally considered preferential looking not for vision testing but for assessment of infants' cognitive development.[133] In our experience, young infants who show little or no visual responsiveness to faces or lights may have measurable PL acuity that is within the rather broad prediction interval of normal for age. Many of these infants proceed to develop good vision. A substantial proportion of them may, however, have neurodevelopmental issues that become apparent later in infancy or childhood.

What underlies the delay in visual responsiveness in infants who clinically have normal eyes? Many answers may eventually be forthcoming. For now, we comment that functional MRI techniques show anomalous organization of vision-driven activity in the brain in mature subjects with achromatopsia or albinism, diagnoses that we find in some infants with delayed visual responsiveness.[134,135] These anomalies of the brain's circuitry are too subtle to be detected by MRI studies that are done in the course of clinical care. With advances in the clinical neurosciences, the processes that govern the turning on of an infant's vision will surely become more completely understood, including the sudden switching on of vision in those with isolated visual delays. We believe that working toward an early, accurate diagnosis is the route to the best possible care of these patients.

Finally, we caution that young infants with poor vision often have delays in motor, social, and even language development. In the absence of visual input (such as facial expressions), coordination of social cues and motor development may not occur. This situation may worry and mislead family and physicians about global developmental delay.[125,136] Early, thorough evaluation of the eyes, including electrodiagnostics if indicated, is the ophthalmologist's contribution to minimizing the likelihood of an incorrect diagnosis of global developmental delay in the visually unresponsive infant.

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Milestones and normative data

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At birth, the corneal diameter is only 1.7 mm smaller than in an adult, but the ocular volume increases threefold and the eye's weight doubles by the time maturity is reached. In the full-term newborn eye, volume is 3.25 cm^3 and weight is 3.40 g. The weight increases 40% by the middle of the second year and 70% by the fifth year.

The development of the eye parts is meticulously sequenced, and understanding the milestones of development is essential to make sense of clinical observations.

Electrophysiological examinations are made according to the International Society for Clinical Electrophysiology of Vision (ISCEV) protocols. However, each laboratory should establish normative data for its own equipment and population. The pediatric ophthalmologist must be aware that electrophysiological maturation proceeds until adulthood.[1] Thus data on electrophysiological investigations will not be discussed in this chapter.

Intercanthal distance and the eyelids

Abnormalities in the distance between the inner and the outer canthi and the size and shape of the palpebral fissure are important features in craniofacial malformations and fetal alcohol syndrome. A fast non-contact method of measuring facial components is provided in Figure 6.1A,B.[2]

Palpebral fissure changes in early childhood have been studied by analyzing digital imaging[3]: During the first 3 months of life, the upper eyelid is at its lowest position, later rising to its maximum between 3 and 6 months of age, and then declining until adulthood. The lower eyelid is close to the pupil center at birth, dropping until the age of 18 months when its position stabilizes. A single lower eyelid crease is common at birth, a double crease at the age of 36 months. Figure 6.2 shows the linear relationship between gestational age and orbital margin horizontal (OMH), as well as vertical (OMV) diameters in the unborn child.[4] There is a linear relationship between gestational age and conjunctival fornix horizontal (CFH) and conjunctival fornix vertical (CFV) diameters (Fig. 6.3).[5]

The palpebral fissure's horizontal length is 15±2 mm at 32 weeks of gestation, 17±2 mm at birth, 24±3 mm at 2 years of age, and 27±3 mm at the age of 14.[5,6] Inter-racial differences exist: The palpebral fissure is longer in Black Americans.[7]

Inner canthal distance and outer orbital distance are 16 and 59 mm, respectively, in premature infants; 20±4 and 69±8 mm in newborn babies; 26±6 and 88±10 mm at the age of 3 years; and 31±5 and 111±12 mm at the age of 14 (Fig. 6.4).[8]

A universal approach is the canthus index:

$$\text{Canthus index} = \frac{\text{Inner canthus distance} \times 100}{\text{Outer canthus distance}}\ \%$$

Normals, unrelated to age, lie between 28.4 and 38%.[9] The canthus index of over 1000 children between 6 and 18 years of age was determined as follows[10]:

	Boys	Girls
6 Years	38.2% (SD 2.1%)	38.3% (SD 1.8%)
16 Years	37.1% (SD 2.6%)	36.6% (SD 1.9%)

Tear secretion

Tearing is not a problem when holding the eyelids of the youngest premature babies open. Later, in preterm babies

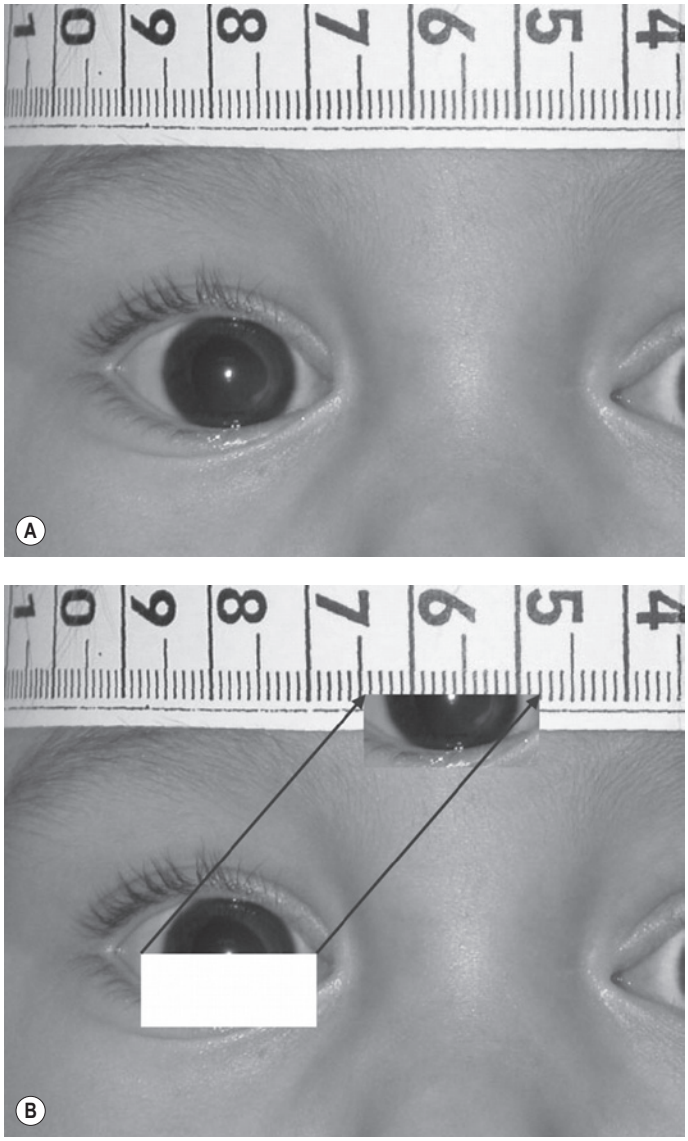


Fig. 6.1 (A) Photograph showing non-contact measurement of corneal diameter in children. Before digital photography of a child's eyes, a paper ruler was taped on the forehead. (B) After uploading the image to a computer, a rectangle is cut using the computer mouse, with the upper line passing through the cornea's widest horizontal diameter. This rectangle then is dragged to the ruler to read the corneal diameter, in this case 12.5 mm. *(From Lagrèze WA, Zobor G. A method for noncontact measurement of corneal diameter in children. Am J Ophthalmol 2007; 144: 141–2.)*

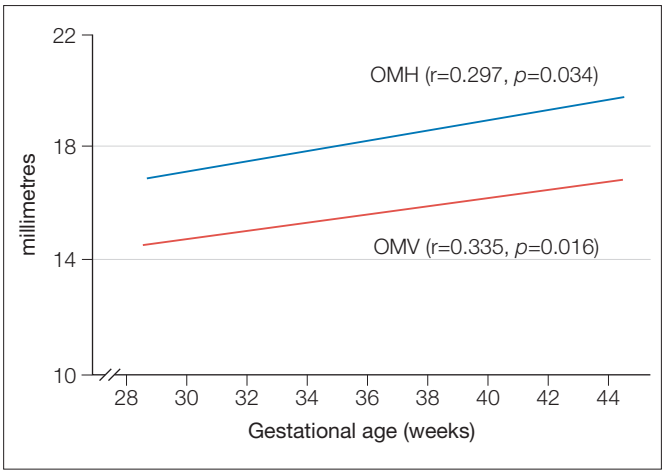


Fig. 6.2 Interocular distance. Linear regression relationship and standard error of the estimate between orbital margin horizontal (OMH) and vertical (OMV) diameters and gestational age. Correlation coefficients with *p* values are indicated. *(Data from Isenberg SJ, McCarty JW, Rich R. Growth of the conjunctival fornix and orbital margin in term and preterm infants. Ophthalmology 1987; 94: 1276–80. With permission from American Academy of Ophthalmology.)*

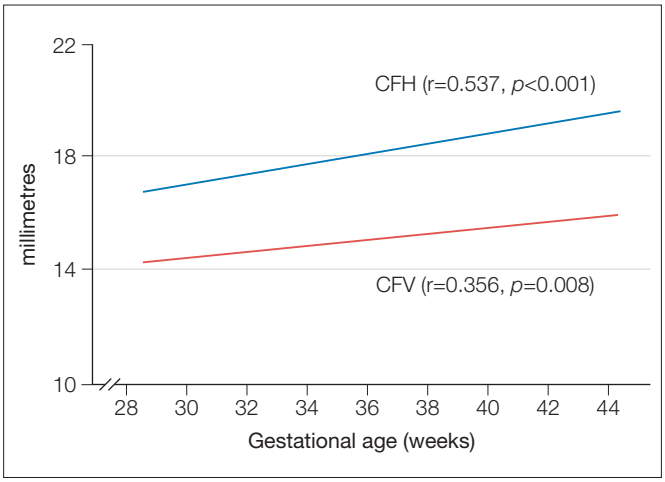


Fig. 6.3 Linear regression relationship and standard error of the estimate between conjunctival fornix horizontal (CFH) and vertical (CFV) diameters and gestational age. Correlation coefficients with *p* values are indicated. *(Data from Isenberg SJ, McCarty JW, Rich R. Growth of the conjunctival fornix and orbital margin in term and preterm infants. Ophthalmology 1987; 94: 1276–80.With permission from American Academy of Ophthalmology.)*

(30–37 weeks after conception), mean basal tear (with topical anesthesia) secretion is 6.2 (±4.5 SD) mm and at term 9.2 (±4.3) mm tested with a Schirmer tear test strip (5 minutes). Mean reflex tear secretion is 7.4 (±4.8) mm in preterm and 13.2 (±6.5) mm in term infants.[11] Non-invasive tear film break-up time in normal children was recently published to be 21.76±4.06 seconds (range 14.9–30.95 s) in children mean age 7.64 years (range 2.16–15.83 years).[12] This is considerably greater in children in comparison to adults. This is in keeping with a lower blink rate of 6 blinks per minute in newborns and 8 blinks per minute for preschool-age children.[13]

Cornea

The premature cornea lacks luster and clarity making some diagnoses difficult. Shallow anterior chambers, miotic pupils, and bluish irides are features of prematurity. The corneal diameter in infants at 25–37 weeks postconceptional age increases by 0.5 mm every 15 days from 6.2 to 9.0 mm (Fig. 6.5).[14,15] The horizontal and vertical diameters of the cornea in full-term boys are 9.8±0.33 mm and 10.4±0.35 mm, respectively, and in girls 10.1±0.33 mm and 10.7±0.29 mm.[16] Two millimeters of growth in corneal diameter (approximately 20%) occurs in early infancy and early childhood. The adult value of 11.7 mm is reached by 7 years.

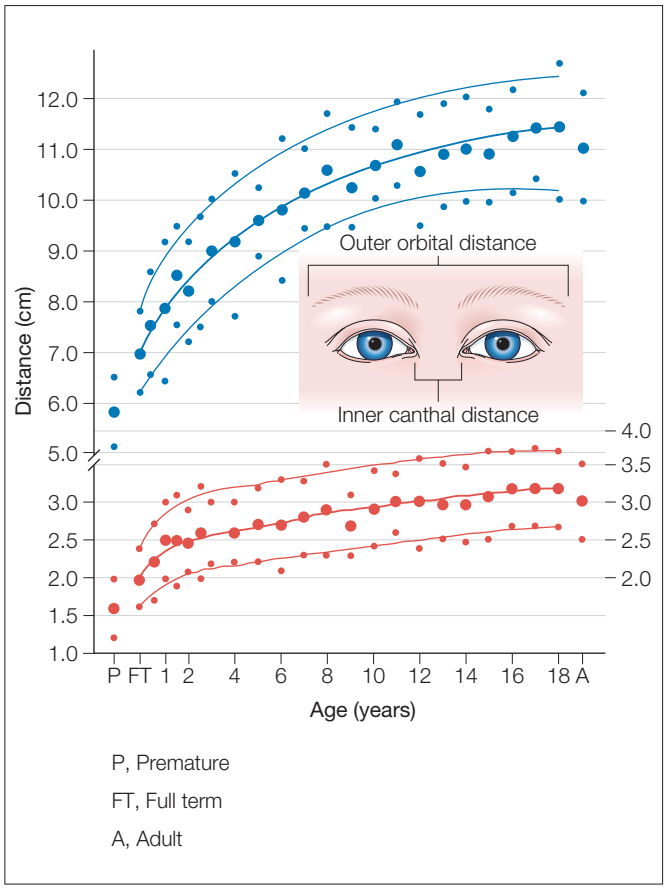


Fig. 6.4 Graphs of inner canthal and outer orbital distances. The large points represent the mean value for each age group, the smaller points represent 2 SD from the mean. The heavy line approximates the 50th percentile, while the shaded area roughly encompasses the range from the 3rd to the 97th percentile. *(Data from Laestadius ND, Aase JM, Smith DW. Normal inner canthal and outer orbital dimensions. J Pediatr 1969; 74: 465–8. With permission from Elsevier.)*

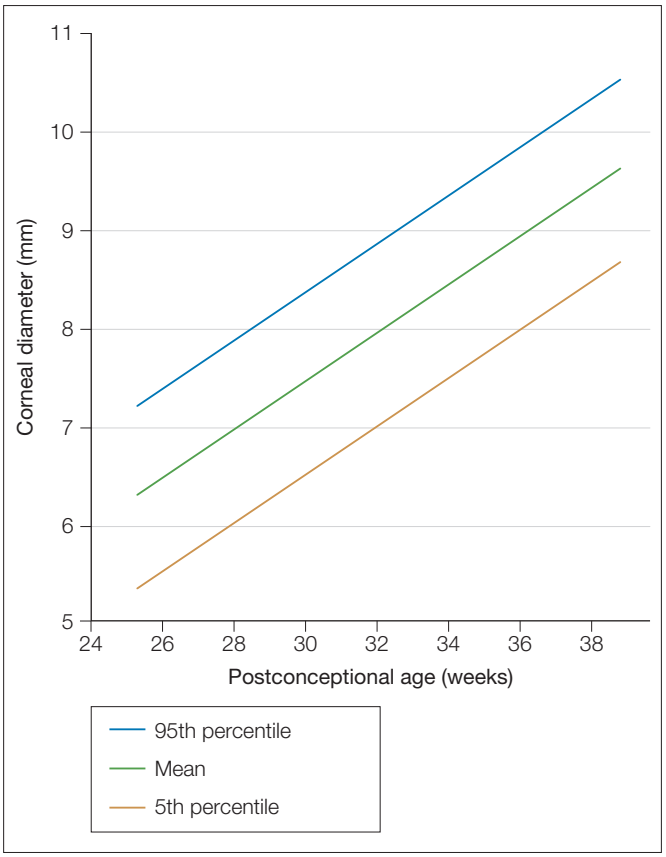


Fig. 6.5 Mean corneal diameter plotted against postconceptional age. *(From Tucker SM, Enzenauer RW, Levin AV, et al. Corneal diameter, axial length, and intraocular pressure in premature infants. Ophthalmology 1992; 99: 1296–300. With permission from American Academy of Ophthalmology.)*

Central corneal thickness

Abnormal thickness of the central cornea influences intraocular pressure measurement; corneal hysteresis may also play a role in children. Central corneal thickness (CCT) in a full-term baby is 0.54 mm which is thicker than in an older child. CCTs measured with optical pachymetry and corneal curvature are given for premature and full-term babies in Table 6.1.[17]

CCT in premature infants below 33 weeks gives a mean of 0.656 mm (SD±0.103 mm) 5 days postnatally, and 0.566 (SD±0.064) at the age of 110 days.[18] In full-term neonates,[17] CCT is 0.573±0.052 mm (range 0.450–0.691 mm) with a peripheral corneal thickness of 0.650±0.062 mm (range 0.520–0.830 mm). Table 6.2 shows the decrease in thickness during the first few days of life.

Another study[19] confirmed the above data and also measured peripheral corneal thickness: Superior corneal thickness was 0.696±0.055 mm, inferior was 0.744±0.062 mm, nasal was 0.742±0.058 mm, and temporal was 0.748±0.055 mm. A recent, very large study concluded that African American children had thinner corneas on average than those of both white and Hispanic children (P<.001 for both) by approximately 20 µm. Thicker median CCT was observed with each successive year of age from age 1 to 11 years, with year-to-year differences steadily decreasing and reaching a plateau after age 11 years at 573 µm in white and Hispanic children and 551 µm in African American children. For every 100 µm of thicker CCT measured, the intraocular pressure was 1.5 mmHg higher on average (P<.001).[20]

Keratocyte density is around 60,000 cells/mm^3 in infancy with a decline of 0.3% per year through life.

Table 6.1 Central corneal thickness (CCT) and curvature (R) in newborns and children

Age group	No.	CCT (mm ± SEM)	R (mm ± SEM)
Premature newborns	6	0.545 ± 0.014	6.35 ± 0.09
Mature newborns	19	0.541 ± 0.006	7.11 ± 0.07
Children 2–4 years	10	0.520 ± 0.007	7.73 ± 0.09
Children 5–9 years	15	0.520 ± 0.005	7.81 ± 0.09
Children 10–14 years	11	0.520 ± 0.007	8.01 ± 0.05
Adults (own group and data from literature)		~0.52	~7.8

From Ehlers N, Sørensen T, Bramsen T, et al. Central corneal thickness in newborns and children. Acta Ophthalmol (Copenh) 1976; 54: 285–90. With permission from Blackwell Publishing Ltd.

Table 6.2 Central and peripheral corneal thickness (mm) in newborn babies

Corneal thickness	Age (hours)		
	0–24	24–48	48–72
Central	0.58	0.56	0.54
Peripheral	0.63	0.63	0.61

From Portellinha W, Belfort R, Jr. Central and peripheral corneal thickness in newborns. Acta Ophthalmol (Copenh) 1991; 69: 247–50. With permission from Blackwell Publishing Ltd.

Table 6.3 Values (mm) of the distance from sclerocorneal limbus to the ora serrata in the nasal, temporal, superior, and inferior meridians (mean ± SD) in fetuses aged 24–40 weeks[23]

Nasal meridian	Temporal meridian	Superior meridian	Inferior meridian
3.22	3.33	3.23	3.27
0.30	0.35	0.36	0.37

From Bonomo PP. Pars plana and ora serrata anatomotopographic study of fetal eyes. Acta Ophthalmol (Copenh) 1989; 67: 145–50. With permission from Blackwell Publishing Ltd.

Endothelial cell counts exceed 10,000 cells/mm^2 at 12 weeks of gestation, 50% of this at birth and 4000 cells/mm^2 in childhood. Mean endothelial cell count was 3500 cells/mm^2 in the unoperated eyes of a large cohort of 5-year-old children who had undergone cataract surgery in their fellow eyes.[21]

Pupil size and reaction to light

The pupil, in relative darkness, has a mean diameter of 4.7 mm at 26 weeks postconceptional age. The pupils subsequently become progressively smaller, reaching 3.4 mm at 29 weeks. There is no reaction to light until 30.6 weeks (±1 week) postconceptional age.[22] Figure 6.6 shows the change of pupil diameter in relative darkness (<10 ft-c) in preterm neonates. The mean pupil size is 3.8 mm (SD ± 0.8 mm) in the newborn period. The incidence of anisocoria of less than 1 mm is 21%; no difference was greater than 1 mm.[23]

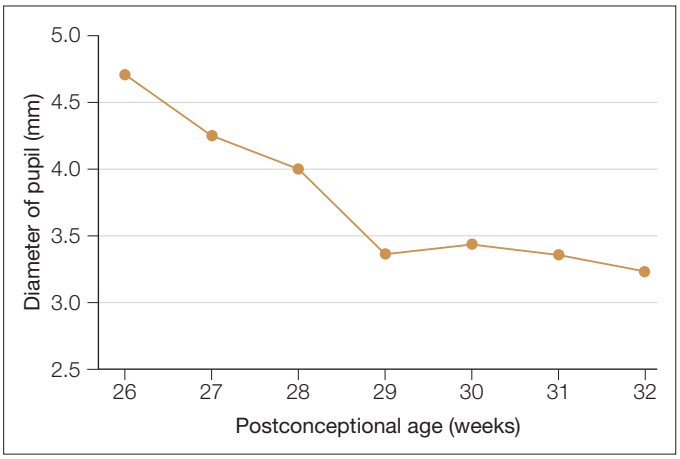


Fig. 6.6 The diameter of the pupil in relative darkness in preterm neonates. *(With permission from Isenberg SJ, Molarte A, Vazquez M. The fixed and dilated pupils of premature neonates. Am J Ophthalmol 1990; 110: 168–71.)*

The crystalline lens

The lens grows throughout life; information on lens thickness is included in the section "Axial length." The lens capsule doubles its thickness from birth to old age.

Pars plana and ora serrata

The average pars plana of third trimester fetuses is 1.17 mm in width, which is one-third that in the adult eye. The distance between the sclerocorneal limbus and the ora serrata is 3.22 mm nasally and 3.33 mm temporally (Table 6.3).[24] Similar figures were obtained from examination of 76 paraffin-embedded normal eyes from 1-week-old to 6-year-old children.[25]

Seventy-six percent of the development of the ciliary body occurs by the age of 24 months. The pars plana, which occupies 75% of the total length of the ciliary body, follows a similar course. The external distance from the limbus to the ora serrata is 0.3–0.4 mm more than the corresponding dimension of the ciliary body in these specimens.

Optic disc parameters

The diagnosis of optic nerve hypoplasia is a subjective one because it is not only optic nerve size that is important. The optic disc dimensions of 66 children of low refraction error aged 2–10 years was studied by fundus photography (Table 6.4A).[26] The vertical disc diameter, the disc area, and the cup-to-disc ratio were significantly larger in black than in white children. The optic disc dimensions (excluding the meninges) studied at autopsy[27] produce slightly different results due to fixation shrinkage (13%), but the measurements correlate well with the photographic study (Tables 6.4B and 6.4C). Approximately 50% of optic disc and nerve growth occurs by 20 weeks of gestation and 75% by birth. Ninety-five percent of the growth of the optic disc and nerve occurs before the age of 1 year. The optic nerve head in 5–16-year-old children has been assessed using Heidelberg retina tomography (HRT). The confocal scanning laser ophthalmoscope creates three-dimensional topographic images and with this technique the mean values of the optic disc area and rim area were 2.16 (SD 0.47) and 1.75 (SD 0.39) mm^2, respectively. In this age group, there were no differences in size of optic disc and rim areas regarding the age or gender of the child.[28]

Axial length

In week 9 of fetal life, the eye has a sagittal diameter of 1 mm, increasing to a mean of 5.1 mm by the age of 12 weeks.[29]

The total axial length of the premature eye (25–37 weeks postconceptional age) increases linearly from 12.6 to 16.2 mm.[14] Measurements from a later study[30] are given in Table 6.5.

Table 6.4A Optic disc parameters in 66 volunteers[25]

No. of volunteers	Race	Sex	Age	Cycloplegic refraction	Vertical disk diameter (mm)	Horizontal disk diameter (mm)	Cup-to-disk ratio	Area (mm^2)	Neuroretinal rim area (mm^2)
16	Black	Female	7.0	+0.8	2.11	1.84	0.32	3.05	2.57
			2.5	1.4	0.21	0.17	0.21	0.54	0.50
14	Black	Male	7.0	+0.5	2.13	1.85	0.40	3.11	2.46
			2.4	0.7	0.19	0.19	0.20	0.56	0.58
18	White	Female	5.2	+1.0	1.88	1.73	0.10	2.57	2.52
			2.4	1.1	0.20	0.17	0.11	0.49	0.48
18	White	Male	6.1	+0.7	1.94	1.79	0.20	2.74	2.54
			2.2	0.7	0.22	0.22	0.18	0.59	0.58

Values are expressed as means; SDs are listed under the means.
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Table 6.4B Mean vertical and horizontal diameters and area of the optic disc for each age group

Age	No. of subjects	Mean diameter (mm) (SD)		Mean area (mm^2) (SD)
		Vertical	Horizontal	
<40 weeks' gestation	20	1.10 (0.21)	0.93 (0.15)	0.82 (0.26)
Term to 6 months	13	1.37 (0.21)	1.13 (0.19)	1.25 (0.40)
6 months to 2 years	12	1.57 (0.15)	1.40 (0.17)	1.73 (0.32)
2–10 years	17	1.64 (0.20)	1.43 (0.19)	1.87 (0.44)
>10 years	31	1.73 (0.23)	1.59 (0.21)	2.19 (0.54)

From Rimmer S, Keating C, Chou T, et al. Growth of the human optic disc and nerve during gestation, childhood, and early adulthood. Am J Ophthalmol 1993; 116: 748–53, with permission.

Table 6.4C Mean vertical and horizontal diameters and area of the optic nerve for each age group

Age	No. of subjects	Mean diameter (mm) (SD)		Mean area (mm^2) (SD)
		Vertical	Horizontal	
<40 weeks' gestation	20	1.96 (0.36)	1.79 (0.43)	2.85 (1.16)
Term to 6 months	13	2.38 (0.22)	2.23 (0.30)	4.22 (0.87)
6 months to 2 years	12	2.70 (0.33)	2.55 (0.32)	5.47 (1.26)
2–10 years	17	2.84 (0.39)	2.64 (0.27)	5.95 (1.26)
>10 years	30	3.06 (0.39)	2.85 (0.32)	6.95 (1.62)

From Rimmer S, Keating C, Chou T, et al. Growth of the human optic disc and nerve during gestation, childhood, and early adulthood. Am J Ophthalmol 1993; 116: 748–53, with permission.

Ultrasound measurements of the newborn eye[31] are as follows[32,33]:

1. average anterior chamber depth (including the cornea) 2.6 mm (2.4–2.9 mm);
2. average lens thickness 3.6 mm (3.4–3.9 mm);
3. average vitreous length 10.4 mm (8.9–11.2 mm);
4. total length of the newborn eye is 16.6 mm (15.3–17.6 mm).

The postnatal growth of the emmetropic eye can be divided into three growth periods (Table 6.6 and Fig. 6.7)[32]:

1. a rapid postnatal phase with an increase in length of 3.7–3.8 mm during the first 18 months;
2. a slower phase from the second to the fifth year of life with an increase in length of 1.1–1.2 mm;
3. a slow juvenile phase lasting until the age of 13 years with an increase of 1.3–1.4 mm, which tapers off towards teenage years (ages 13–18) unless juvenile onset of myopia.[34]

Optical coherence tomography of the macula

Optical coherence tomography (OCT) has been used for quantitative and qualitative assessment of macular morphology. The technique is valuable when examining children with different retinal diseases. As in adults, the central area is the thinnest and the inner circle the thickest. Boys have slightly thicker maculae and young children appear to have thicker maculae than those in adolescence.[35,36]

Extraocular muscles and sclera

Most of the enlargement of the eye is in the first 6 months of extrauterine life. All diameters increase. The cornea and the iris have about 80% of their adult dimensions at birth. The posterior segment grows more postnatally. Therefore, in squint

Table 6.5 Numerical parameters of ocular axial length, and axial growth rate from fetal age 20 weeks to the age of 3 years

Age (weeks)[a]	Axial length (mm)	Growth rate (mm/week)
20	10.08	0.66
30	14.74	0.32
40 (term)	17.02	0.16
50	18.24	0.092
60	18.97	0.059
70	19.48	0.044
80	19.87	0.035
90 (about 1 year)	20.19	0.030
100	20.47	0.026
120	20.93	0.021
140 (about 2 years)	21.31	0.017
170	21.75	0.013
200 (about 3 years)	22.07	0.009

[a]<40 weeks = fetal; >40 weeks = post-term.
From Fledelius HC, Christensen AC. Reappraisal of the human ocular growth curve in fetal life, infancy and early childhood. Br J Ophthalmol 1996; 80: 918–21.

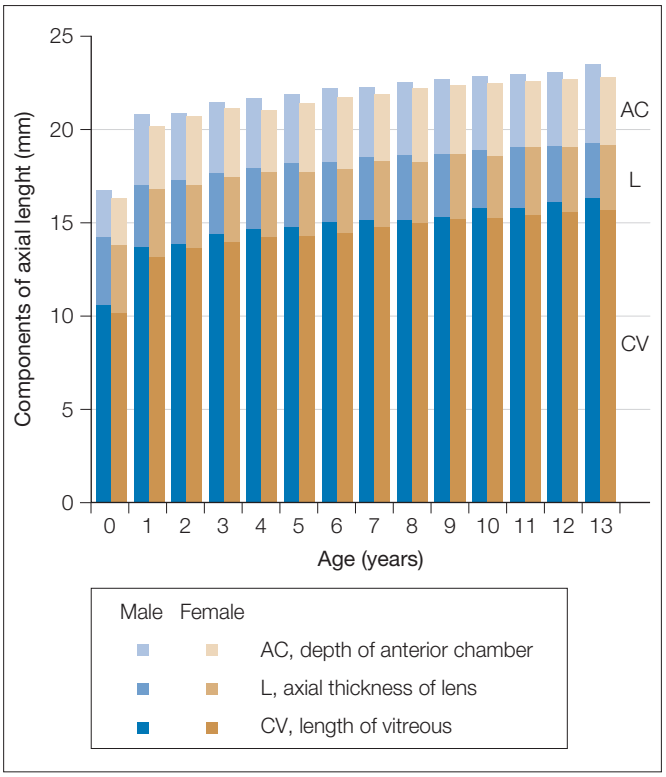


Fig. 6.7 The relationships between the different components of the eye during the growth period. An ultrasound oculometric study. *(From Larsen JS. The sagittal growth of the eye. I–IV. Acta Ophthalmol (Copenh) 1971; 49: 239–62, 427–40, 441–53, 873–86. With permission from Blackwell Publishing Ltd.)*

Table 6.6 Axial length (mm) in male children

	Days	Months		Years												
	1–5	6	9	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12	12–13	13–14
NO. OF EYES																
	86	2	4	36	118	110	100	64	64	70	100	80	56	52	56	24
LENGTH OF AXIS (MM)																
Mean	16.78	18.21	19.05	20.61	20.79	21.27	21.68	21.85	21.97	22.09	22.33	22.43	22.50	22.70	22.97	23.15
SD	0.51	—	—	0.47	0.61	0.55	0.58	0.59	0.71	0.62	0.51	0.47	0.47	0.82	0.71	0.38
SE	0.055	—	—	0.078	0.056	0.052	0.058	0.074	0.089	0.074	0.051	0.053	0.063	0.114	0.095	0.078

SD, standard deviation; SE, standard error.
From Larsen JS. The sagittal growth of the eye. I–IV. Acta Ophthalmol (Copenh) 1971; 49: 239–62, 427–40, 441–53, 873–86. With permission from Blackwell Publishing Ltd.

surgery in the very young child, it is more difficult to predict outcomes (Tables 6.7A–C).

The thickness of the sclera in 6-, 9-, and 20-month specimens is 0.45 mm, similar to that in adult eyes.[37]

Children's visual function questionnaire

An instrument to document quality of life is retrievable from http://www.retinafoundation.org/pdf/questionnaire/cvfq.pdf, describing data for children up to 7 years of age undergoing different treatment modalities to detect resulting changes in quality of life.[38]

Visual acuity

Postnatal maturation of the visual pathways plays an important role in visual development. At birth, the macula is immature. The fovea reaches histological maturity as late as between 15 and 45 months of age. Myelination of the optic nerve is not complete until at least the age of 2 years.

Table 6.7A Breadth of rectus muscle insertions (mm)

Age	No. of specimens	Superior	Medial	Inferior	Lateral
Neonatal	10	7.5	7.6	6.8	6.9
2–3 months	4	7.3	6.8	6.7	7.0
6 months	4	8.9	9.0	8.3	8.4
9 months	4	8.8	8.7	8.3	8.2
20 months	2	10.2	8.9	9.3	7.8
Adult	5	10.8	10.5	9.8	9.2

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Table 6.7B Millimeters from clear cornea to rectus muscle insertions

Age	No. of specimens	Superior		Medial		Inferior		Lateral	
		Nasal end	Temporal end	Sup. end	Inf. end	Nasal end	Temporal end	Sup. end	Inf. end
Neonatal	10	6.1	7.6	4.7	5.3	6.0	6.6	6.4	5.8
2 months	3	5.5	5.8	5.2	6.0	5.2	6.2	7.8	5.8
3 months	3	6.9	7.5	5.1	5.8	6.6	7.5	7.5	7.0
6 months	4	7.4	8.3	5.8	6.6	7.2	9.0	7.2	7.1
9 months	4	7.2	9.3	6.2	6.9	7.7	8.8	7.5	7.1
20 months	2	7.1	8.7	7.3	7.6	8.5	9.3	8.5	8.5
Adult	5	7.4	10.0	7.8	7.7	8.0	9.2	8.4	8.5

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Table 6.7C Distance in millimeters of oblique muscle insertions from clear cornea and optic nerve

Age	No. of specimens	Superior oblique				Inferior oblique			
		To cornea		To optic nerve		To cornea		To optic nerve	
		Ant. edge	Post. edge	Ant. edge	Post. edge	Ant. edge	Post. edge	Ant. edge	Post. edge
Neonatal	8	9.0	11.6	10.6	5.6	10.2	14.8	8.6	2.2
2–3 months	4	10.3	12.8	10.3	5.6	12.1	16.2	8.2	2.3
6–9 months	8	12.3	14.2	12.0	6.4	13.9	18.0	10.8	3.2
20 months	2	14.2	15.3	12.2	7.8	15.5	19.3	11.7	4.6
Adult	3	14.7	17.7	14.6	8.3	16.2	20.5	14.2	6.6

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The period between 1 and 3 months is a period of radical changes in visual capabilities and behavior. A rapid rise in acuity, the appearance of the low-frequency cut in contrast sensitivity, the emergence of smooth pursuit eye movements and of symmetrical optokinetic nystagmus, and possibly the establishment of functional binocular vision all occur roughly together.[39]

Lid closure is seen on illumination with a bright light in babies of 25 weeks' gestation. The pupillary reflex to light is seen from weeks 29 to 31. Discriminative visual function and "tracking" eye movements are present by 31–33 weeks' gestational age.[40]

The acuity of the newborn infant is close to 6/240, and at 7 weeks of age the infant has eye-to-face contact. Visual acuity rapidly increases to 6/180–6/90 at 2–3 months. At 6 months, visual acuity is between 6/18 and 6/9. The assessment of visual acuity, however, depends on the testing method. Table 6.8 summarizes pooled information of visual development.

Table 6.8 Visual acuity according to different methods, given as Snellen equivalents

Technique	Newborn	2 months	4 months	6 months	1 year
Optokinetic nystagmus	20/400	20/400	20/200		20/60
Preferential looking (one study)	20/400	20/200	20/200	20/150	20/50
Preferential looking (other study)	20/800 to 20/1600	20/1200	20/400	20/300	20/100
Visual evoked potential	20/100 to 20/200	20/80	20/80	20/20 to 20/40	20/40

Information pooled from different sources.

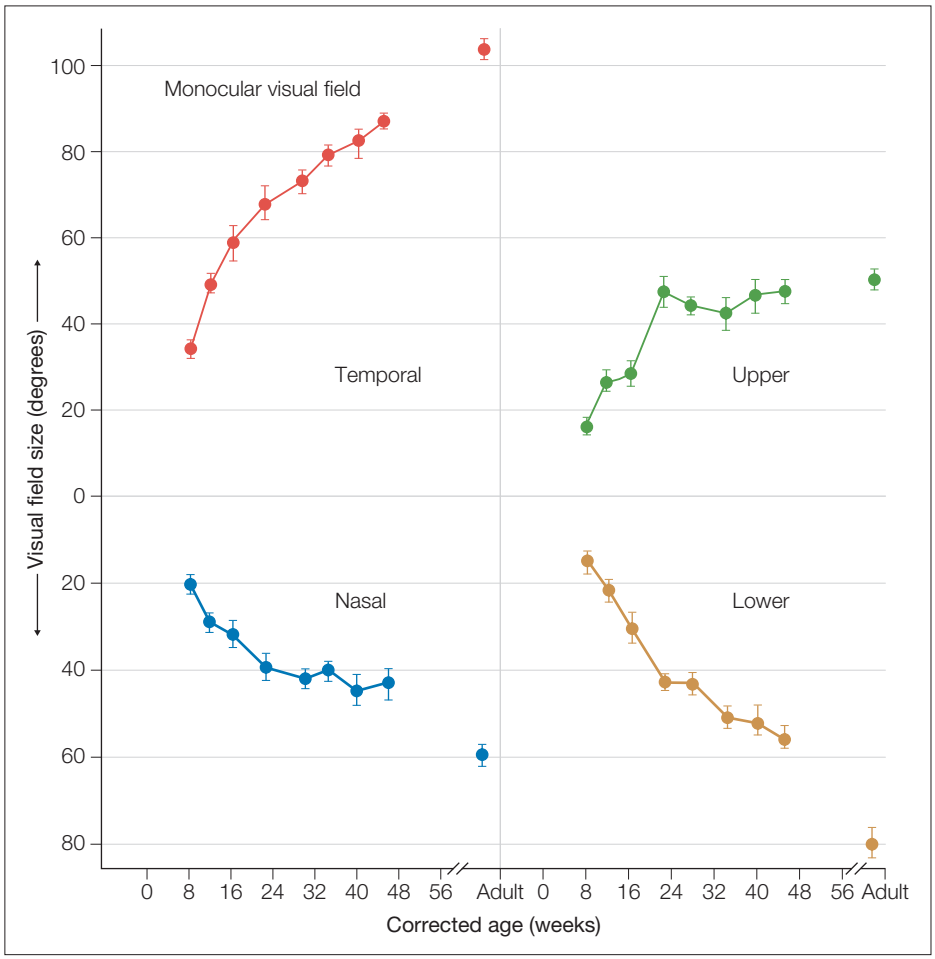


Fig. 6.8 Development of monocular visual field. The horizontal (left) and vertical (right) meridians. Error bars indicate 2 SEM. *(From Mohn G, van Hof-van Duin J. Development of the binocular and monocular visual fields of human infants during the first year of life. Clin Visual Sci 1986; 1: 51–64, as well as personal communication 1994.)*

Full accommodative ability is not established until 3–4 months of age. Yet, it does not appear to be a major limiting factor on reported acuity values.

Stereoacuity can be demonstrated by the age of 16 weeks. By 21 weeks, infants have a stereoacuity of 1 minute of arc or better.[41] Median Randot stereoacuities are 100 seconds of arc for 3-year-olds, 70 seconds of arc for 4-year-olds, 50 seconds of arc for 5-year-olds, 40 seconds of arc for 6-year-olds, and 45 seconds of arc for 7-year-olds.[42]

Results of visuoperceptual testing in a cohort of children aged 4–15 years revealed that visual acuity in the better eye was ≥1.0 (≤0.0 logMAR) in 79% of subjects. None of the children had visual acuity <0.5 (>0.3 logMAR) in the better eye. Amblyopia was found in 0.7% of the subjects. Signs of visuoperceptual problems were reported in 3% of the children.[43] Nevertheless it is difficult to know precisely at what age adult acuity is normally attained!

Visual field

The visual field of the infant depends on the distance at which the target is presented, whether static or kinetic fields are investigated, how interesting the targets are, and whether a fixation target is present. Between 2 and 4 months, the child develops the ability to switch attention to a new object.

The binocular visual field shows little development between birth and 7 weeks. After 2 months there is a rapid expansion of the field until 6–8 months of age. The visual field increases at a slower rate up to 12 months (Fig. 6.8). An asymmetry of 13° or more should be considered pathological.[44,45] Normative data for 4- to 12-year-old children are shown in Table 6.9.[45]

Table 6.9 Mean extent of visual field in degrees (± SEM) in each meridian for five age groups

Age group	ST	IT	IN	SN
RIGHT EYE				
4 years	59.2 (2.1)	84.7 (1.6)	51.4 (2.4)	47.8 (1.8)
5 years	63.4 (2.4)	88.1 (1.9)	52.4 (2.6)	51.7 (1.6)
7 years	66.8 (1.5)	86.0 (2.0)	53.6 (2.0)	58.4 (1.3)
10 years	66.9 (2.3)	86.7 (1.7)	57.9 (1.9)	60.2 (1.3)
Adult	72.6 (2.7)	94.9 (1.4)	54.0 (1.7)	60.2 (2.1)
LEFT EYE				
4 years	66.1 (2.6)	83.8 (2.5)	59.2 (2.9)	49.1 (1.7)
5 years	66.7 (2.8)	83.0 (2.3)	54.8 (2.3)	52.4 (1.9)
7 years	73.7 (1.4)	89.4 (1.7)	51.9 (1.5)	55.9 (1.3)
10 years	71.8 (2.5)	86.7 (1.8)	52.9 (2.1)	55.8 (2.5)
Adult	70.7 (2.5)	93.4 (1.7)	52.4 (2.0)	57.7 (2.1)

I, Inferior; N, nasal; S, superior; T, temporal.
With permission from Wilson M, Quinn G, Dobson V, et al. Normative values for visual fields in 4- to 12-year-old children using kinetic perimetry. J Pediatr Ophthalmol Strabismus 1991; 28: 151–4. © 1991 Slack Inc.

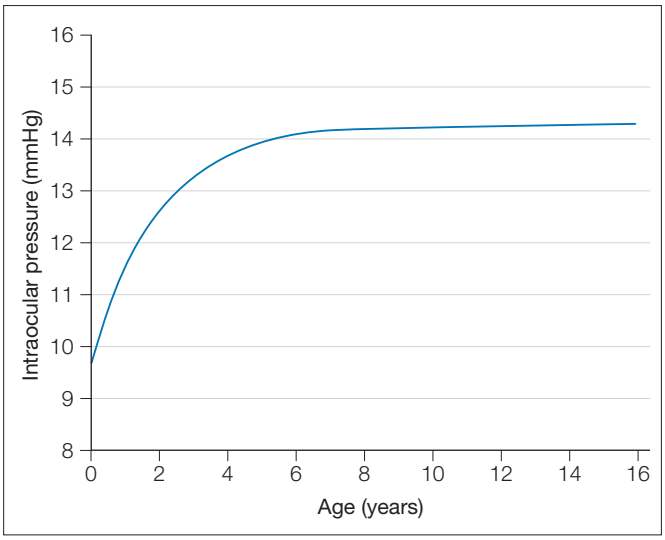


Fig. 6.9 Intraocular pressure by age group. *(From Pensiero S, Da Pozzo S, Perissutti P, et al. Normal intraocular pressure in children. J Pediatr Ophthalmol Strabismus 1992; 29: 79–84. © 1992 Slack Inc.)*

Refraction, corneal curvature, and astigmatism

Most authorities agree that neonatal refractions are distributed in a bell-shaped curve around +2 diopters (D).[46] Later, there is a shift toward emmetropia. In a group of older Swedish children, 68% had no refractive errors, 9% were hyperopic (≥2.0 diopters in spherical equivalent), and 6% were myopic (≥0.5 diopters spherical equivalent).[43] The range of astigmatism is difficult to study due to off-axis retinoscopy errors. One study of non-cycloplegic refractions in children aged 0–6 years revealed a minus cylinder against-the-rule before the age of 4.5 years and a minus cylinder with-the-rule after that age.[47]

The smaller eyes of premature and full-term babies have a more curved cornea of 6.35 mm in curvature radius in contrast to the adult with 7.8 mm (see Table 6.1).[17] Keratometer measurements in one study were: in premature infants 53.1±1.5 diopters, in neonates 48.4±1.7 diopters, at 1 month 45.9±2.3 diopters, and at 36 months 42.9±1.3 diopters. Another study reported 47.59 diopters (SD±2.10; range 44.08–50.75 diopters) in the newborn, 45.56 diopters (SD±2.70; 40.13–52.75 diopters) in the 12- to 18-month age group, and stabilization of the cornea at the age of 54 months with an average of 42.69 diopters (SD±1.89; range 40.50–47.50 diopters).[48] Videokeratography reveals that neonates have steep, high astigmatic (generally with-the-rule) corneas at birth that flatten significantly by the age of 6 months. At birth, the central corneal power measured 48.5 diopters and astigmatism measured 6.0 diopters usually with-the-rule with a mean axis of 95°. Neonates delivered vaginally had a greater frequency of with-the-rule astigmatism than those delivered by cesarean section. By 6 months, the mean central corneal power and astigmatism decreased to 43.0 and 2.3 diopters, respectively.[49]

There is considerable variation in the nature and severity of refractive errors reported from different areas of the world.

Intraocular pressure

Intraocular pressure is easily measured in children with the use of rebound tonometry. Most studies show intraocular pressure is lower in children than in adults. Babies who were 3–11 weeks premature had a mean intraocular pressure of 18 mmHg (13–24 mmHg) with a Perkins tonometer and topical anesthesia.[50] Lower values of 11.4 mmHg have been reported in full-term neonates.[51] Somewhat different results were obtained with a hand-held Tonopen tonometer. With an applanation tonometer, a mean intraocular pressure of 10.3 mmHg was found in 70 premature babies, aged 25–37 weeks.[14]

The intraocular pressure in 460 subjects aged 0–16 years measured with a non-contact Keeler Pulsair tonometer was reported to be 9 mmHg in neonates, increasing to 14 mmHg at the age of 5 years (Fig. 6.9).[52] Averaged Pulsair readings agreed well with Perkins applanation tonometry values in a study of children measured under general anesthesia.[53] The ICare rebound tonometer, in a group of infants, gave a mean intraocular pressure of 11.8±2.7 mmHg with no statistically significant difference between two observers.[54]

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Examination, history and special tests in pediatric ophthalmology

G Robert LaRoche

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A child's problem will likely be easily assessed with a little play, a few key tricks, and, mostly, a reasonable dose of spontaneity and patience. Cookie-cutter or hurried visit plans will rarely yield thorough assessments.

Assent and consent

Bonheoffer said, "The test of the morality of a society is what it does for its children." As caregivers to children and their families, we have important ethical responsibilities. Whereas in the past, the "omniscient doctor" made all the decisions, we live in a time of patient advocacy and participatory decisions, some of which are unique to children. Our responsibility is to act for the good of our young patients and their families. This entrustment of care is a form of guardianship, but we have to consider these same children as full persons with a right to the truth.[1] In the process of consent, we should determine the limits of our patients' autonomy: what decisions can a child make on the information we provide? When do children have the capacity to evaluate risks, consequences, and benefits? Do we need a child's assent before proceeding with an unpleasant examination or treatment, even when we have unequivocal parental consent?

It's all about the child

Personality, timing, and the examination itself will all influence the patient's cooperation. For example, a crying infant will not reveal his visual potential, but just a few minutes of calming breastfeeding can settle the child enough to allow the observation of a visual response to a face. A worried 3-year-old with uveitis might not volunteer for a slit-lamp examination, but given the chance to first talk about a cherished new pair of sneakers, he or she will eagerly hold the "handle bars," allowing a good view of anterior chamber cells. In fact, for the most part, it's all in the act. A teacher of mine once said, "With kids, you have to be ready to put on your monkey suit, and stand on your head."

The equipment

A successful examination room needs a few extra toys to interest the child: small near fixation targets, silent for the most part so as not to test hearing, and transmitting an internal light; an attractive, audible distant fixation target; and, finally, rewards to cap it all. How many visual targets? To paraphrase a colleague (Chris Lyons, personal communication, 2011), "One toy, one look" (Fig. 7.1). In addition to the usual ophthalmic equipment, a portable slit-lamp and tonometer, as well as appropriate vision charts, will complete the full set for a thorough examination of most children. Additional equipment may be necessary in special circumstances: testing infant vision, examining premature infants, a full orthoptic assessment, electrodiagnostic or imaging investigations. Full discussion on these will be found in other chapters.

History: include the child

Taking a history is crucial. With children, time and opportunism are crucial. While it is tempting to get most of the history from the parents, one should never forget the young patient's own story. A child's behavior and perspective on the events can be revealing. For example, a well-intentioned parent might provide a very different account of a poorly compliant amblyopic child who, in turn, describes a great summer at the grandparents' without having to wear "that darn patch," or getting the dreaded morning drop. Important details will be revealed only once we gain the child's confidence. Examples of this include the bullied child who will avoid wearing the prescribed spectacles or emergency room pellet gun stories that drastically change when the parents are not present. In

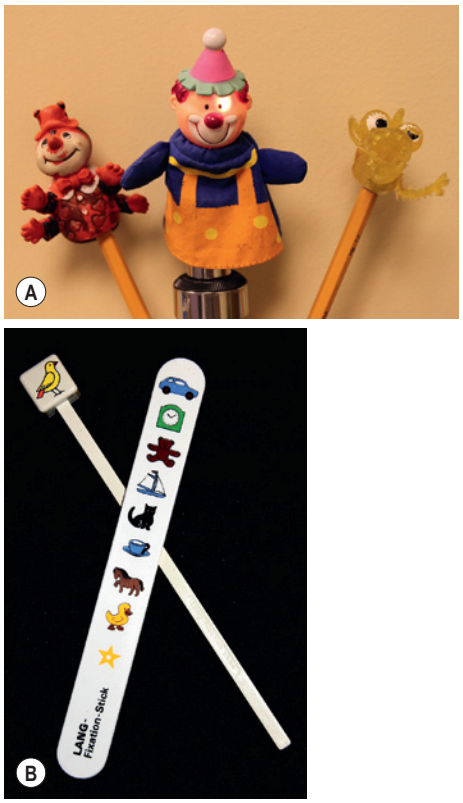


Fig. 7.1 Near fixation targets. (A) Finger puppets: all able to transmit light, giving creative possibilities to enhance their attractiveness. (B) Lang fixation stick and cube. These have become a standard the world around.

other circumstances, disagreements between guardians can suggest poor family dynamics; blame games, avoidance, and miscommunications can all be barriers. But it is also important to recognize socioeconomic and cultural issues that can hamper full cooperation from the family: repeated missed appointments, spectacles that are always "left at home," numerous children in tow at appointments, inability to repeat the instructions given, or evidence of poor hygiene. It has been long recognized in the pediatric literature that education of the mother is key to a successful outcome.[2] This also applies to amblyopia, glaucoma, or uveitis management among others, where understanding, cooperation, and engagement of the family are essential. Finally, pictures can play a big part of the historical record. For example, a few good photographs taken at home can easily give enough clues to target an otherwise difficult examination for a diagnosis of Duane retraction syndrome or Brown syndrome. Likewise, retinoblastoma is often detected from family photographs.

A no-touch approach at first

Ophthalmology is known for its sophisticated and high-tech visuals. But with children, simple observation should be the first priority, with many clues helping to clarify or support clinical findings that can be difficult to obtain otherwise. Time simply watching, while maintaining a "hands off" approach, before intervening is key. The following pages describe the chronological components of the examination for a child presenting to the office of a pediatric ophthalmologist, starting with the least intrusive ones. Specialized ancillary tests are mostly done after the initial clinical assessment and based on specific diagnostic requirements; we refer the reader to the relevant chapters for these.

Say "hi"!

Break the ice, address the child, be friendly, get down to eye level, and avoid white coats. At the first visit, the ophthalmologist is a stranger and, except for infants, most children are reluctant to initially open up to strangers. Outfit, shoes, toys, or stuffed animals' names – these are all good topics of conversation that will help start a warm exchange and create the welcoming atmosphere so important to the rest of the encounter. Remember that children love to play – the examination should therefore remain a game.

Observe

While greeting the child and family, remember to observe: the head position (a cranial nerve dysfunction or nystagmus), photophobia (corneal disease, retinal dystrophies, glaucoma), body language (evidence of a visual handicap) or unusual behavior (extreme hyperactivity of attention deficit, withdrawal in cases of abuse), and the possible clues suggesting developmental delay, especially associated with abnormal visual functions (Table 7.1).

Head/body posture

A visually impaired child will often hold the head down, even in dimmer lighting. On the other hand, the prostration of a photophobic child in regular daylight is an alarming clinical presentation. Head thrusts or nodding can be of diagnostic help with abnormal eye movements in oculomotor apraxia and spasmus nutans. An abnormal head posture that increases with visual efforts is typical of the null position of a nystagmus.

Visual behavior

A classic scenario is that of the allegedly blind infant who brightens up, follows, and fixes objects only when the lights are turned down – a scenario seen in achromatopsia. Sometimes, other clues can be useful: the excessively close focusing of a very high myope or the preferential visual attention toward objects of the autistic child who avoids eye contact.

Where to place the child for the examination

Many young children will be more comfortable, quieter, and more cooperative on their parent's lap. A few will require you to start the visit with them in their parent's arms and away from all the strange machines and equipment (Fig. 7.2).

Parents as a resource

Sometimes the child is nervous being the center of attention. It is easy to involve others in the room to relieve the tension, for instance: "Who are these people? Is this your sister, or your mom? Is that a real baby in that stroller?" This is also the time for a short, targeted history on the current problem with the guardian. With the parental version of the problem at hand, it can be most revealing to follow with the child's own story: a daily headache becomes a rare occurrence, or vice versa; a

Table 7.1 Visual developmental milestones relevant to a pediatric ophthalmology examination in young children

Age group	Fine motor-adaptive	Personal/social	Language (receptive and expressive)
0–4 weeks	Visual following from side to midline (90° arc)	Regards human faces with interest	
2 months		Smiles responsively	
3 months	Looks at object placed in hand Looks promptly at objects in midline Follows visually in 180° arc and in circular pattern		
4 months	Reach and grasp begin Looks at objects in hand	Excited when toys presented	
5 months		Distinguishes strangers from family	
6 months		Pushes adult hand away to reject	
8 months		Finger feeds	Responds to name when called (turns)
9 months	Explores pellet with index finger		
10 months		Imitates nursery tricks (modeled), e.g. pat-a-cake Bangs two cubes together in imitation	
12 months		Hands over toy on request with accompanying hand-out gesture	
24 months	Threads shoelace through hole		
48 months	Picks longer of two lines	Buttons up	Points to colors on request (red/blue, yellow/green)

Adapted from Goldbloom R. Pediatric Clinical Skills, 4th ed. Philadelphia: Elsevier; 2011. With permission from Elsevier.



Fig. 7.2 Indirect ophthalmoscopy in infants. An example of unconventional assessment techniques necessary in infants. Here the examination is carried out successfully in the patient's own comfort zone: a stroller and a good suck on the examiner's finger.

complaint of poor vision is really a wish to wear spectacles like the big sister, and so on. Next comes the family history. Looking at the family photo album is helpful. It may confirm the evolution of an abnormal head posture, or time the onset of an abnormal red reflex. However, all this should not be a protracted affair; things easily get boring or stressful for a child sitting and waiting for something to happen. Details of the history are often better gathered as one goes along with the rest of the visit.

A word of caution: too many people in the room can create havoc, as they can become a source of distraction and noise. The best scenario is to have the child in the office with a cooperative parent or two. A good friend of the same age group can also be a reliable calming agent for a 6–10-year-old. Finally, and unfortunately, in difficult situations, someone might have to *hold* a non-cooperative child. Either in decubitus, a preferred position for drop instillation, or sitting and facing the examiner, the parents quickly learn how they can help, and comfort their child at the same time (Fig. 7.3).

Targeted examination

Since opportunities are often limited by a child's cooperation, the examiner should first target the most promising component of the examination. Guided by the history and the observational clues gathered in the first minutes of the consultation, this approach will increase the yield of the encounter and minimize the frustrations of an incomplete examination. However, keep on hand a checklist to ensure all the components of a full examination are achieved. As the visit progresses, the items are checked. If necessary, other visits may have to be planned to complete the list.

The Brükner test

This is the best way to introduce ophthalmic instruments to a child.[3] It involves a quick look through a direct ophthalmoscope, at a distance of a third of a meter. The brightness, color, and the homogeneity of the pupillary areas are checked and compared in a semi-darkened room, without dilating drops; this will

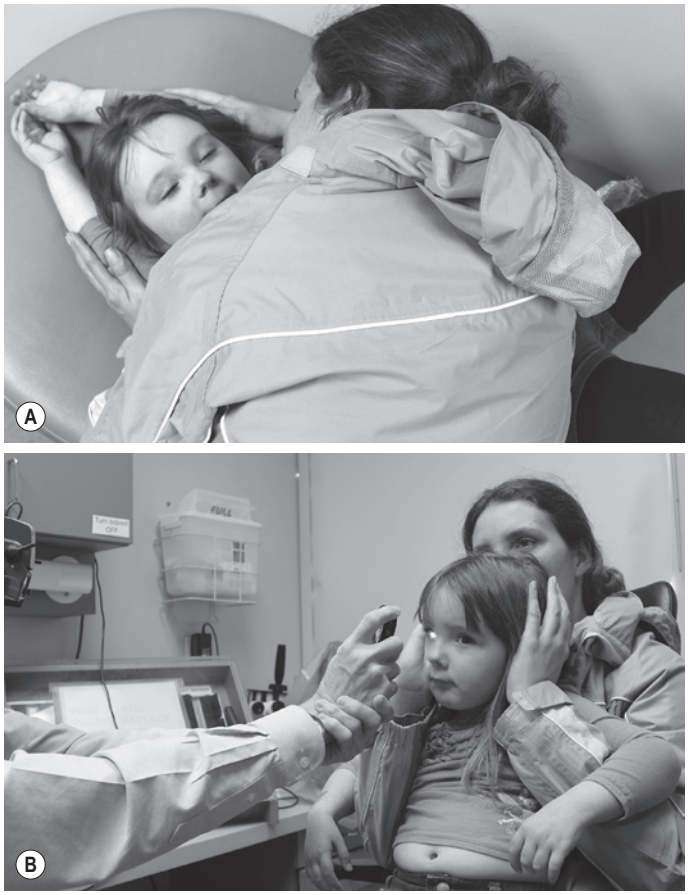


Fig. 7.3 Parent hold. Parents can help physically stabilize their children for crucial parts of the examination, either in the supine position with the elbows pressed against the head (A) or sitting facing the examiner (B). Both positions involve the close proximity of the parent and his/her soothing voice to help calm the child.



Fig. 7.4 Brückner's test. In all cases, make sure the patient is comfortable, least disturbed, and with his or her own things. Stay at about 0.6 m away with the widest beam of the ophthalmoscope encompassing both pupils. Focus the lenses for the working distance and compare both corneal reflection and fundus red reflex for symmetry, homogeneity, and brightness. *(From Goldbloom R. Pediatric Clinical Skills, 4th ed. Philadelphia, PA: Elsevier; 2011. With permission from Elsevier.)*

help detect visually significant opacities, large or asymmetric refractive errors, and some ocular misalignments (Fig. 7.4). The position of the corneal Purkinje images in each eye can reveal misalignment.

The few seconds required for the Brükner in the early stage of a consultation can help answer crucial questions: How is a cataract or corneal scar obstructing the pupillary area? Can light pass through a congenital pupillary membrane? Is this likely to be a "pseudostrabismus" or are the corneal light reflections really off-axis? Is there significant anisometropia?

Binocularity: first no dissociation

From around 2 years of age, a child's binocularity can be assessed clinically. Already at age 3 to 4 months, binocular vision has been established to some degree[4] and, as a result, infants with congenital oculomotor difficulty like Duane retraction syndrome can be seen adopting a compensatory head posture.

For formal testing and to assess a patient's performance "as if in real life," it is important to avoid binocular dissociation by occlusion of one eye or polarizing glasses. The author favors tests that do not involve holding things near the child's face. The two-pencil test (2PT), and the Frisby and the Lang stereotests assess stereopsis without the interference of dissociating components (Fig. 7.5). They can also be easily introduced into games. The 2PT involves matching a real three-dimensional (3D) target in space; it can detect stereopsis in the order of 2000–3000 seconds of arc.[5] The Frisby also involves real spatial separation of its targets, another easy game for toddlers. The Lang stereotest achieves haploscopic image dissociation to produce a stereo effect without the need for glasses and measures at least three stereoacuity levels. Children as young as 2 years of age can be observed to look at the perceived 3D targets. Eventually, more demanding and dissociating tests can be used for older children.

Vision assessment

After binocularity, monocular visual function can be assessed. The degree of intrusiveness increases but, if conducted carefully and cheerfully, testing can fit into a play scenario. The examiner should remain aware of guessing, memorizing, and peeking. The reliability of visual acuity (VA) testing is dependent on the child's concentration. VA tests vary with age, but the strategy is always the same: binocular first, to get a best acuity and establish a comfort zone for the child, then the expected better eye is measured, and finally the poorer side is measured.

Measuring binocular VA can lead to more information than just a level of vision: watch the child. For example, an increasing head turn as he or she reads down the chart will highlight an apparently mild nystagmus. Similarly, a reduced distance binocular acuity in a child with intermittent exotropia can be indicative of the accommodative efforts necessary to help control the deviation.[6]

The preferred vision assessment tools for infants are based on psychophysical observations. Healthy infants will preferentially look at a normal human face almost as soon as they are born.[7] They will do so while awake, but they also need to be calm and happy; the best time for this is halfway through a feed. In this manner, the presence of normal visual

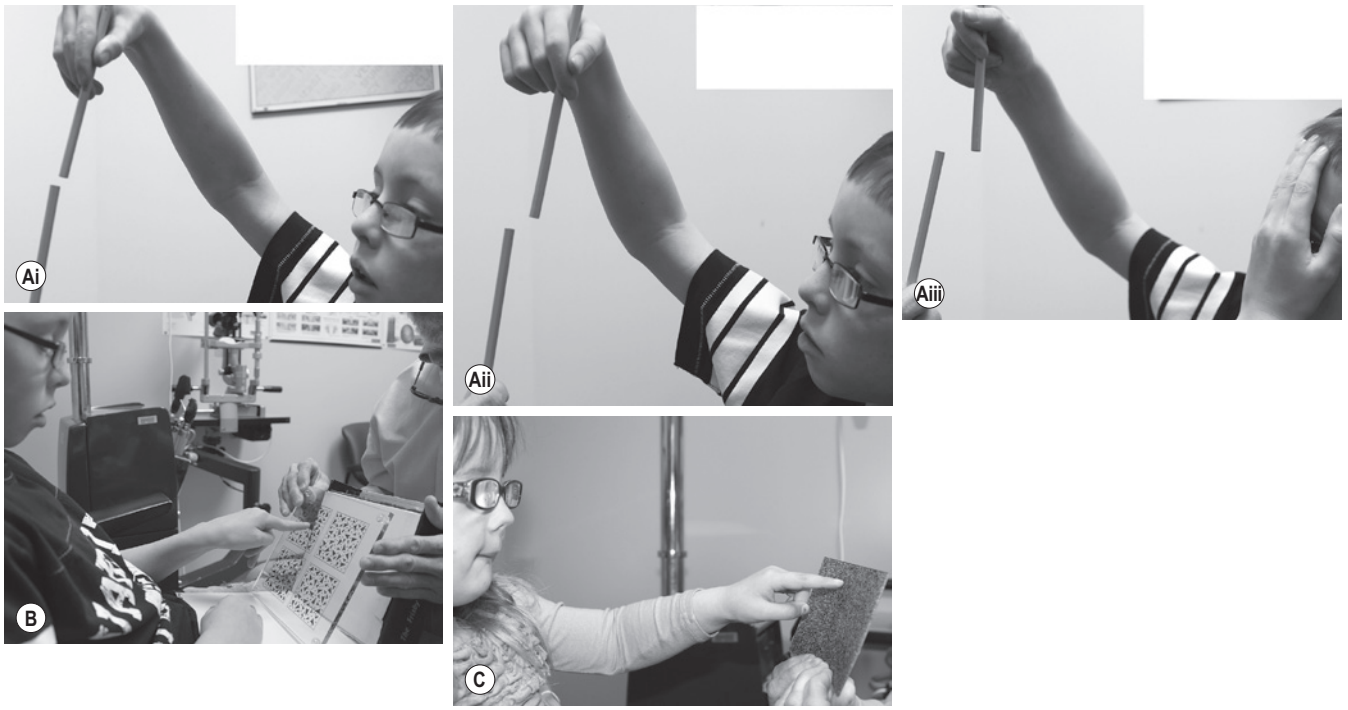


Fig. 7.5 Non-dissociating stereotests. (A) The two-pencil test (2PT) has its limitations because of the many motor components involved, but it provides a real life demonstration of "three-dimensional" vision with straight eyes, as it does here in this esotropic child with high accommodative convergence/accommodation (AC/A) ratio who shows the advantage of looking through his bifocals. Note: keep the targets at eye level. (B) The Frisby test can give false positive clues of stereopsis if the image plate is rotated on its axis or the patient's head shifts sideways. It is easy to administer and is a good test in the right conditions. (C) The Lang stereotest can be interpreted by watching the patient point or simply gaze at the targets seen only stereoscopically. Again, however, movements of either the test card or the patient's head can help find monocular clues (apparent increased scrambling of the random dot array in the location of the stereotargets). Note the curvature given to the card by the examiner to make it match the curvature of Panum's area.



Fig. 7.6 Infant following face. The examiner holds the infant with good support of the head. The child is happy and relaxed, hence receptive. The face of the examiner is slowly panned across the baby's visual field while observing the child's eyes and head turn in unison with the moving target. The intended movements of the head are easily felt by the supporting hand. The eyes of the examiner's face being of such importance here, it is suggested to remove one's glasses to avoid reflections. A moving but silent mouth with its contrasting contours has been shown to enhance the attractiveness of the target face for infants as young as 3–4 months.

processing can be confirmed (Fig. 7.6). More crudely, one can also observe the exaggerated lid opening of a sighted infant when the lights are suddenly dimmed. Similarly, we can see the quick re-fixation of a sighted baby toward a preferred visual target, like a face, after having been submitted to a spin that has generated good oculo-vestibular movements.

Visual behavior is also compared when each eye is obstructed in turn (Fig. 7.7). The CSM (central, steady, maintained) system provides a repeatable assessment of the *ocular* fixation *behavior* to a target (CSM fixation: *central*, in the middle of the pupil; *steady*, without nystagmus or other eye instability; *maintained*, even if a monocular short interruption occurs). The visual or general behavior of the child is compared as each eye is tested separately after the initial binocular assessment. Another useful method of comparing one eye to the other is to challenge a maintained fixation with a vertical prism. A 10 to 16 diopter (10–16Δ) prism is used while watching for a re-fixation movement of either eye.[8] This simple method

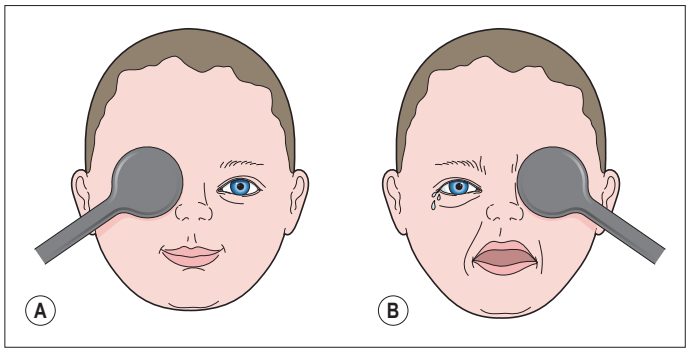


Fig. 7.7 Evaluation of vision in infants. A child with poor vision in one eye (here the right), may not object to having the poorly seeing eye covered (A), but will show displeasure when the good or better eye is covered (B). This can translate to behavioral changes or active avoidance measures with head movements or pushing of the cover with the hand. *(From Goldbloom R. Pediatric Clinical Skills, 4th ed. Philadelphia, PA: Elsevier; 2011. With permission from Elsevier.)*

can be particularly useful in the absence of a horizontal strabismus in a child with suspected vision difference between the two eyes. In esotropic youngsters that are too young for quantitative measurements, symmetry of cross fixation or latent nystagmus are indirect indicators of vision. Conversely, sine wave grating tests, including optokinetic nystagmus, visual evoked potentials, and the so-called "Teller cards" based on preferential looking, all estimate vision levels in children but are not primary diagnostic tools in most clinical settings. While they can be applied to a great number of children because of their exploitation of the visual system's innate hunger for simple high-contrast grating visual targets, they can perform unreliably in detecting interocular vision differences due to amblyopia and can overestimate the potential recognition vision capacity if one is not very careful in interpreting the results.[9,10] On the other hand, recognition quantitative visual acuity tests designed in the last few decades are well adapted to young children. They use comparison games and consist of highly standardized logarithmic distribution of optotypes. These include the HOTV and LH tests that have become standards in visual acuity testing for children who are too young to complete the ETDRS (Early Treatment Diabetic Retinopathy Study) test (Fig. 7.8). Most reports show good reliability starting at age 40 months on average.

Dynamic retinoscopy

This technique, which requires the child to focus on a target placed on the examiner's retinoscope while overcoming minus lenses, detects the presence and degree of accommodation.[11] It may be useful in conditions like trisomy-21, where hypoaccommodation to near targets is evident. Both eyes are observed simultaneously, allowing easy comparison.

Versions, ductions, null position

To evaluate all six extraocular muscles (EOM), a quick and dynamic assessment of versions can be carried by a simple technique involving the mental representation of a virtual picture frame in front of the patient's face, the corners of which are the targets to reach with a fixation object (Fig. 7.9). This facilitates the detection of muscle underaction. In a cooperative child, monocular testing will differentiate version versus duction deficits. All four horizontal muscles – hence





Fig. 7.8 LH logMAR vision chart for children. A well-standardized and validated visual acuity (VA) test, the Leah Hivarinnen comparative recognition VA chart, has become a gold standard in children of all ages. It can be used in children as young as 36 months. At 41 months, the testability in the general population is good.

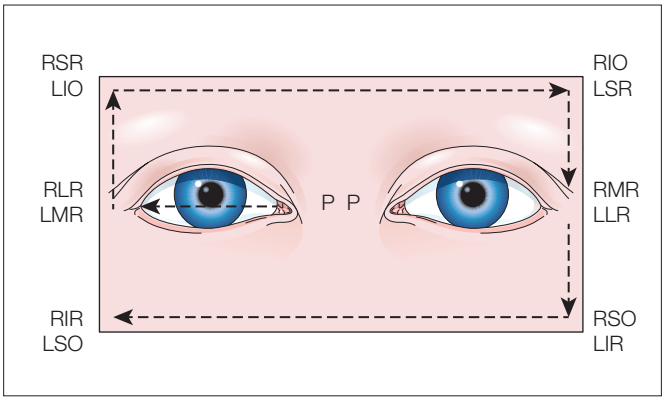


Fig. 7.9 The frame used to evaluate comitance of a strabismus. A slow continuous movement of the dim fixating light along an imaginary frame around the patient's eyes allows the assessment of all 12 extraocular muscles. LIO, left inferior oblique; LIR, left inferior rectus; LLR; left lateral rectus; LMR, left medial rectus; LSO, left superior oblique; LSR, left superior rectus; PP, primary position; RIO, right inferior oblique; RIR, right inferior rectus; RLR, right lateral rectus; RMR, right medial rectus; RSO, right superior oblique; RSR, right superior rectus. *(From Goldbloom R. Pediatric Clinical Skills, 4th ed. Philadelphia, PA: Elsevier; 2011. With permission from Elsevier.)*

cranial nerves II and VI – can easily be assessed with the doll's head maneuver. For infants, a quick turn of the examiner on a rotating stool in each direction while holding the child up in front of one's eyes, with a slight tilt forward to maximize utricular responses, will easily confirm the presence of full



Fig. 7.10 Spin the baby for horizontal extraocular movements. Horizontal strabismus can appear to have limited abduction or adduction in infants. Stimulating an oculocephalic response will elicit full movements by rotating with the child in one's arms while watching the eye movements.
Note the forward tilt of 30° to line-up the horizontal semicircular canal with the plane of rotation, enhancing the response. A sighted child will also have the ability to stop a postrotational nystagmus, in contrast to the tonic eye deviation in the direction of the rotation of the blind patient.

horizontal movements (Fig. 7.10). This can solve the frequent conundrum of a poorly abducting eye in an otherwise normal esotropic infant. For older children, if no neck anomaly exists, a quick short-amplitude forced jerk movement of the head will induce the same response and often help reveal that elusive full eye movement.

Next step: touching and other methods of annoying the child – the second part of the examination

Use the company

Take advantage of those in the room who came with the child; if they are older or looking more at ease, conduct key tests on them first. This will include the parents, of course, but a favorite stuffed animal can play the same role.

Pupils and corneal diameter

These are difficult to examine. One needs attractive and noisy fixation targets, both for near and distance. The use of magnification is sometimes useful to visualize small pupils (surgical loupes come in handy here) and a well-located light switch to change the room lighting while observing the pupils is also an asset. For pupillary light responses, the diameter, as well as the dynamic aspect of the response, provide valuable information. The observation of the pupils' behavior while turning on the room lights after 3–4 seconds of darkness can be sufficient: normal pupils will constrict, while those of an achromat will clearly dilate initially, with the opposite happening when the lights are turned back on. Finally, taking a digital photograph can provide reliable documentation of corneal diameters or anisocoria. Photographing a millimeter ruler held in the limbal plane (Fig. 7.11), the camera zoom function can be used to allow an exact match of the ruler in the photo on the camera screen against a live ruler held over

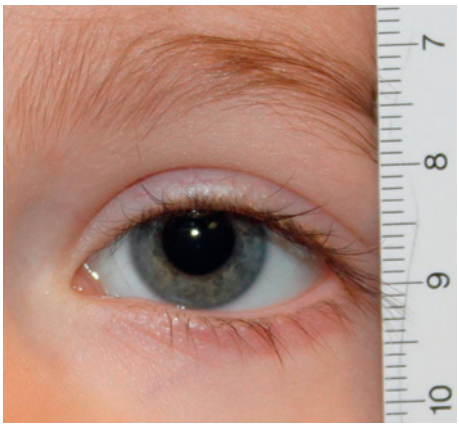


Fig. 7.11 Precise measurements by photograph. A calibrating ruler placed in the same plane as the object of interest of a photograph will provide the accurate reference for the measurement of that object, be it a pupillary or corneal diameter, or an interpalpebral fissure.

the camera screen. Once the ruler on the photo is zoomed accurately to "life size," the pupil, cornea, ptosis (or anything else in the iris plane) can be easily measured.[12]

Lids

Ptosis can be measured even in the youngest children with a bright fixation toy, and using its corneal reflexes as landmarks to measure the lid margin-to-reflex distances. One should note if the lid margin fails to clear the visual axis under normal viewing circumstances, as this could represent an amblyogenic risk. Finally, food (or liquid in a bottle) can be of great use to elicit the typical lid movements of the Marcus Gunn jaw-winking synkinesis.

Binocularity

If the preliminary testing (see above) was not sufficient, more refined binocularity testing can be used at this juncture. The necessary glasses, prisms, and various testing complexities can, nevertheless, require great acumen when interpreting the results in younger children. Note that earlier monocular testing could have dissociated the patient and disrupted fusion, influencing the results at this stage. This is typically the case in intermittent exotropia.

Confrontation fields

A reliable visual field assessment in young patients can be critical. Quantitative Goldman perimetry can be obtained from around 5 years of age in cooperative children by a dedicated perimetrist. Automated machines only become reliable later. Therefore, a good confrontation technique is important. With younger children, moving fingers (MF) are good targets, while in older patients, finger counting (FC) is best (Fig. 7.12). Very young children can mainly do binocular testing. Conversely an older child should be able to cooperate with very accurate confrontation using a 4 mm white pin, documenting the blind spot, similarly to adults.

Strabismus assessment

In addition to the observation of head posture, variable angles, and fixation behavior, the prism cover test and alternate cover

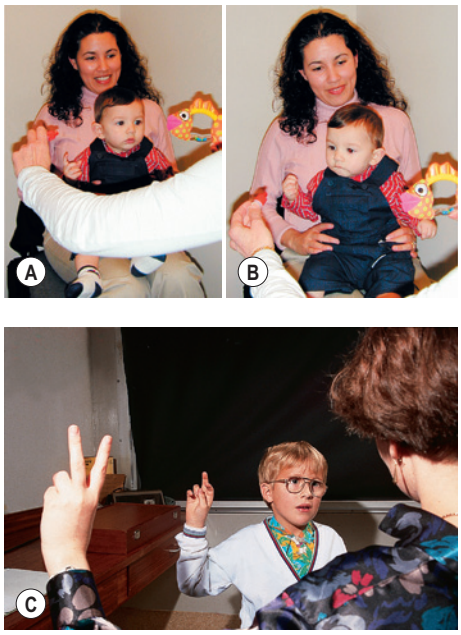


Fig. 7.12 (A) Assessing the visual field of infants. The tester attracts the baby's attention to a toy while bringing in an object, in this case a dropper bottle, silently from the child's right side to see whether the child's attention is drawn to it – which in this case it is! Although seemingly crude, if defects are detected by these methods, they are likely to be functionally significant in the future. (B) Demonstration of finger counting technique to assess visual fields in older children. While the tester watches the fixation, the child tells her when the tester's fingers are wiggling or may watch or count the fingers if able to do so. *([A], Photo by Dr Hung Pham.)*

test, as well as sensory testing, can be performed to a certain degree in children of all ages. Appropriate accommodative targets are essential for reliable measurements. At least one 6-meter target, and ideally a window to the outside world, are essential for exotropic patients. No one carries out these measurements better than a well-trained orthoptist. The great value of these professionals in the successful evaluation of children cannot be overemphasized, especially for strabismus and amblyopia.

Slit-lamp examination

The success of the anterior segment examination in children depends a lot on their degree of comfort. But even in the best of circumstances, the conventional slit-lamp's short working distance may frighten many children. Operating loupes at 2.5× magnification can be useful for surface problems and a high-magnification Brückner with the direct ophthalmoscope set at +5 D can help for media opacities. The less imposing portable slit-lamp can be of help for some less cooperative children or bedside examinations. However, infants can often be propped up with the help of adults for a conventional slit-lamp examination (Fig. 7.13).

Refraction

Good cycloplegia is essential for reliable refractions of children and it is important to achieve that goal with minimal stress and trauma. The author likes to postpone the drops needed to achieve this until the last stage of the first visit. In difficult cases, it may be helpful to teach the parents drop instillation at home. Because one drop of most cycloplegic agents is frequently

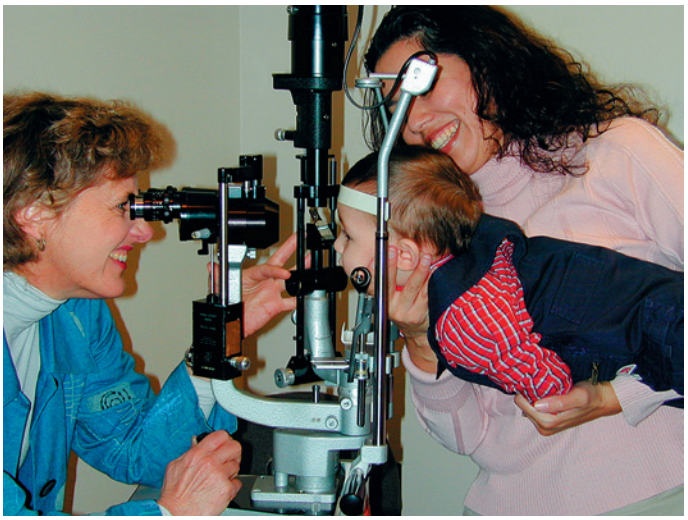


Fig. 7.13 Method for examining infants at the slit-lamp. First, the ophthalmologist sets up the slit-lamp microscope so that it is ready for the most important task (i.e. looking for transillumination using a coaxial beam). While the parent (or clinic assistant) holds the baby with the left arm under his tummy, he/she places his head on the white strap, continually encouraging him.



Fig. 7.14 Sciascopy in the axis, and cylinders. While paying attention to one's working distance, any technique that will ensure a cycloplegic refractive sciascopic measurement in the visual axis will ensure precise measurements. When cylinders are involved, an infant trial frame without temple pieces will serve wonders in providing both a good cache as well as helping to find the correct axis.

insufficient to achieve good accommodative paralysis in dark-eyed individuals, pretreatment with a topical anesthetic may be helpful. Apart from reducing the discomfort, this improves corneal penetration and increases the effectiveness of the cycloplegic agent.

The younger children often dislike having refractive trial lenses placed close to their face; a ±0.12 D lens to hold during the examination can be a great distractor. Astigmatic axis assessment is improved by ensuring a good alignment with the visual axis and by placing the lenses in a trial frame. For younger children, using the frames without the temple pieces greatly helps (Fig. 7.14). It is worth trying the phoropter with

all children who can sit straight in the examination chair and do so voluntarily. For most, it is a fun experience once you point out that their side of the machine is just like looking through the glasses of the most famous mouse cartoon character (Fig. 7.15). Finally, it cannot be emphasized enough that a calm environment is essential for refracting children. A continuous dialogue between child and refractionist in a quiet and darkened room will help even the most challenging cases.

Intraocular pressure measurement

One reliable measurement in clinic can make the difference between a discharge or many more visits, including examinations under sedation or anesthesia. Reliability of readings is a major issue, not only because of the variability of thickness of the pediatric cornea, but also because of the profound effect the conditions of examination can have on the measurements obtained. General anesthetics all modify the pressure to some extent, most decreasing them, and any kind of crying or forceful lid opening will dramatically raise the values. Some instruments are reliable only in a certain range of pressure reading (e.g. Tonopen and iCare types), while others are difficult to use in smaller eyes (e.g. Perkins, Goldmann). All require a relaxed wide-eyed patient and, for that reason, careful scheduling to take advantage of feeding and nap times is essential (Fig. 7.16).

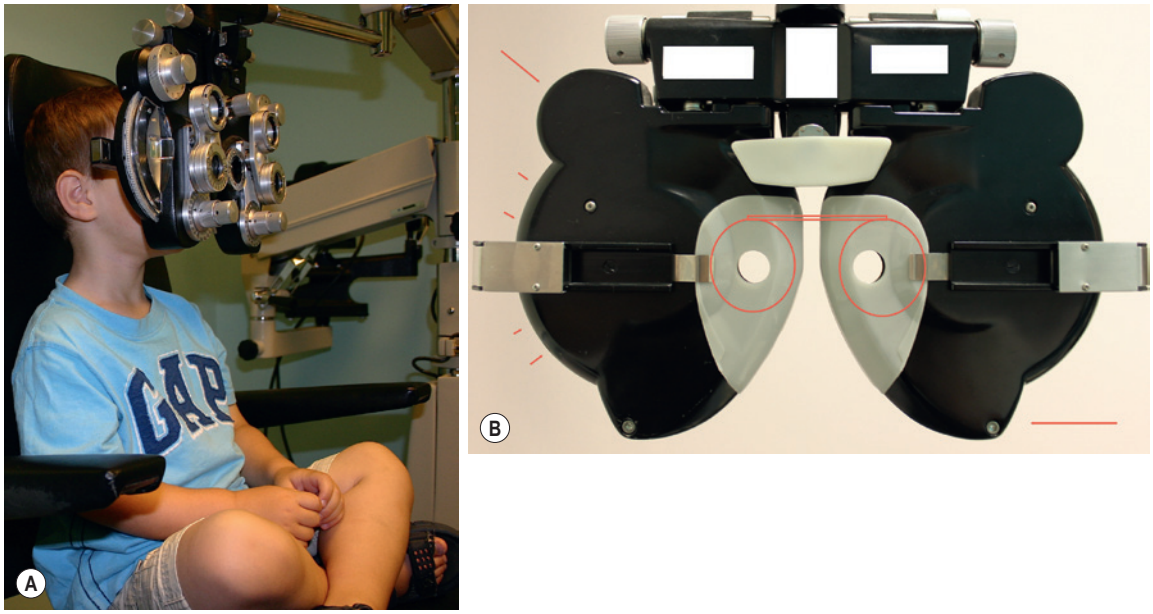


Fig. 7.15 The phoropter and children. (A) As soon as a child can sit, in theory, the phoroptor can be used for refractions. A sitting position with good stable posture is essential. (B) On the patient's side, familial features of the famous iconic cartoon mouse become obvious with a little imagination: ears, cheeks, whiskers.

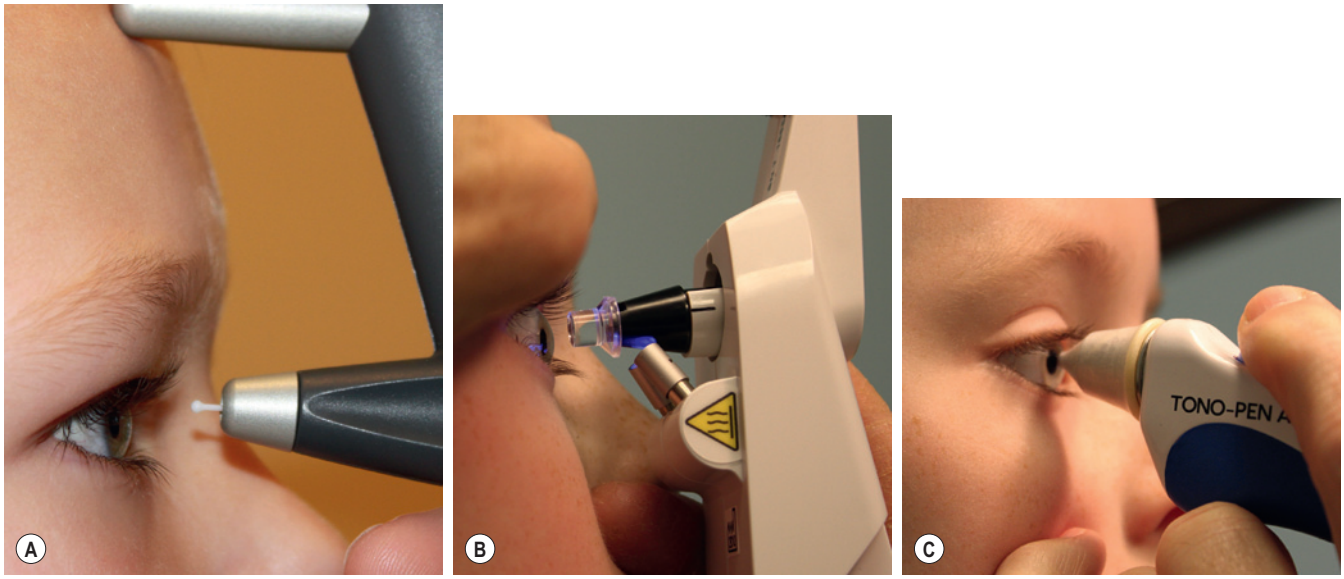


Fig. 7.16 Tonometers in the pediatric age. Note the wide-eyed relaxed-looking child in all these photos. Anything other than this will give you a faulty reading with any instrument.

Fundus examination

This is often what will break the magic spell of a pleasant visit. Most children will not object even to the bright indirect ophthalmoscope, and will cooperate for a direct ophthalmoscopic examination, so long as an interesting fixating target is made available to them for the other eye. The liberal use of fantastical themes to describe what one sees in that fundus helps allay fears and improve cooperation. The child's own body parts are perfect visual targets for the peripheral retinal exam; most know where their left big toe or shoulder is, and will look in the right direction, especially if asked to move the targeted body part. For most examinations, the regular use of the 20 D aspheric lens with the indirect ophthalmoscope will facilitate the estimation of vessel caliber, disk size, and macular health and position. The 28 D is sufficient for an overview of things, but should only be used in conjunction with the 20 D in each case. Here, a word of encouragement: However fleeting the view, a satisfactory mental montage will emerge in most patients. Children who cooperate with the slit-lamp will readily allow a good exam with the 78 D or 90 D lenses for a detailed assessment of the posterior pole structures. These are the same patients who will also readily allow excellent photographic or optical coherence tomography images. For the uncooperative younger individuals, a good restraining technique rarely fails to achieve a reasonable fundus examination. Obviously, the level of suspicion will dictate the quality of the examination required and the efforts put into it; but, for the most part, the clinic setting will be satisfactory. For this, or for some difficult refractions, the parents are always invited to participate and help. It is better for them to know and understand what takes place than be alarmed by cries and screams from the other side of a door.

Finally: rewarding success

A good visit cannot end without celebration. A child who receives positive feedback after showing some goodwill or after controlling great fears will remember that reward, that gift. These are well worth their minimal cost considering the time and efforts saved by a happy child. Stickers are universally welcomed as long as they are current, so keep up with the cultural icons of your young patients. "High fives," handshakes, and hugs all have their place in the right situation, as long as the parents are agreeable. Specific to amblyopia treatment, colorful patches with printed designs are welcome as a novelty by many children. A photo club poster of patching children, and a certificate for those who reach their goal, are popular in our clinic. Parents should also be rewarded: for example, a chart of a child's vision progress helps to celebrate gains and reinforces the need to increase efforts when needed.

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Managing refractive errors in children

Amy K Hutchinson and Buddy Russell

Chapter contents

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COMMON REFRACTIVE ERRORS IN CHILDREN
TREATMENT OF REFRACTIVE ERRORS IN CHILDREN
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Introduction

Refractive errors cause blurred vision and potentially amblyopia through inability to form a perfectly focused image on the retina. Emmetropia is the state of a perfectly focused eye when the focusing power of the cornea and lens are exactly appropriate for the axial length of the eye (Fig. 8.1A); this is uncommon in young children because their eyes have not completely matured and a mild hyperopic refractive error is frequently present.[1] Not all refractive errors require treatment. This chapter reviews the current state of diagnosis, treatment, and prevention of refractive errors in children.

Diagnosis of refractive errors in children

Cycloplegia

In children, cycloplegia is required to measure refractive error accurately because accommodation is active, causing overestimation of myopia and underestimation of hyperopia. Phenylephrine 2.5% is often added to enhance dilation. Toxicity from cycloplegic agents is uncommon. Signs and symptoms of anticholinergic effects include flushing, fever, rash, rapid or irregular heartbeat, dry mouth, and mental status changes. These should be reported immediately. Cycloplegic agents include atropine 1%, cyclopentolate 0.5% or 1%, and tropicamide 0.5% or 1 %. Atropine provides the most complete cycloplegia, but has the longest time to onset, duration of effect, and the most severe side effect profile. Tropicamide has the shortest onset and is better tolerated because of its shorter duration of action and low side effect profile, but residual accommodation remains.[1,2] Table 8.1 outlines the cycloplegic agents employed in the authors' practice based on age. Cyclopentolate 0.2% is available in the USA as "Cyclomydril." It is primarily used for pupillary dilatation of premature infants.

Techniques

Useful techniques for measuring refractive errors in children include retinoscopy, autorefraction, and post-cycloplegic subjective manifest refraction. Ocular biometry and corneal topography are useful adjunctive measures in selected children.

Cycloplegic retinoscopy

Cycloplegic retinoscopy is useful in very young and developmentally delayed children. Cycloplegic retinoscopy is also useful to confirm findings of autorefraction. In addition, cycloplegic retinoscopy performed over existing glasses or contact lenses can be a rapid way to determine whether there has been a significant change in glasses prescription, or whether media irregularities are present that may preclude successful neutralization of refractive error with spectacles. A description of the technique is beyond the scope of this chapter but is published elsewhere.[3]

Dynamic retinoscopy

Dynamic retinoscopy can help to confirm accommodative dysfunction, which is sometimes present in children with cerebral palsy, Down syndrome, and other neurodevelopmental concerns. To perform dynamic retinoscopy, the authors use the monocular estimate method (MEM).[4] The authors have our patient fixate on a detailed target held in the plane of the retinoscope. Testing is performed with the spectacle correction in place. Room lights are dim, but bright enough for the child to be able to see the target. The examiner should use a working distance of about 40 cm. If the patient is accommodating appropriately, the retinoscopy reflex should be neutral when the child fixates on the target. If a "with" reflex is present, there is a "lag" in accommodation, and if an "against" reflex is present, there is a "lead" in accommodation. A small lag in accommodation is normal (1 D or less), but children who have larger amounts of accommodative lag can benefit from correction of hyperopia and possibly even reading glasses or bifocals. Occasionally, infants will present with a delay in development that is due to moderate-to-high hyperopia and poor accommodation. Dynamic retinoscopy is invaluable in identifying this disorder (Fig. 8.2).

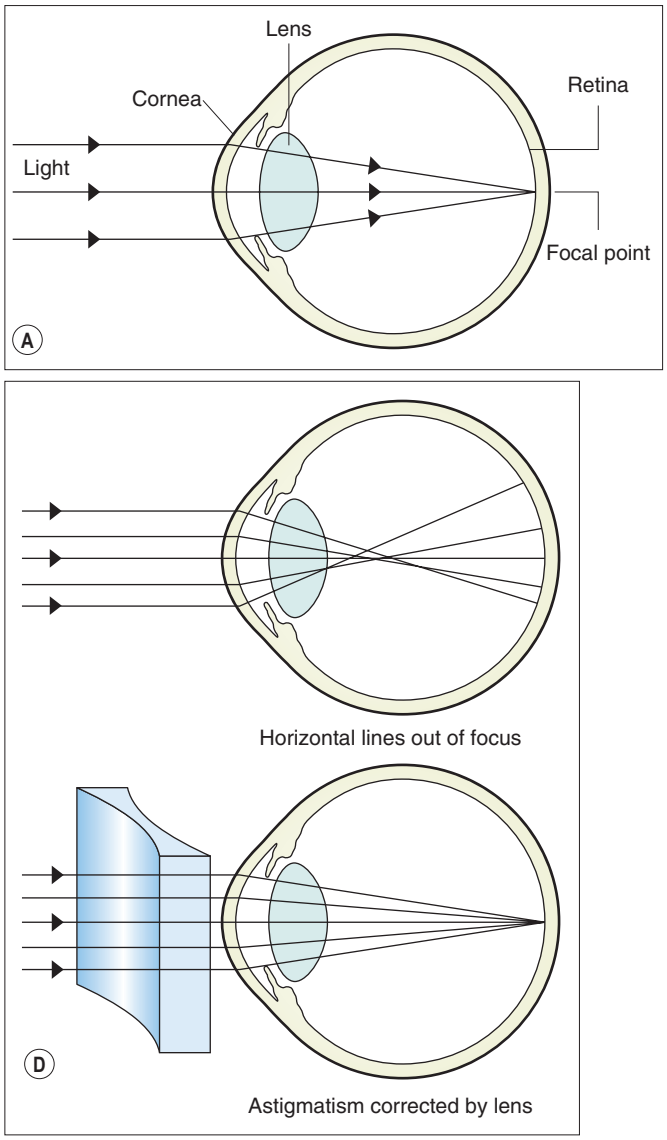


Fig. 8.1 (A) In emmetropia, the focusing power of the lens and cornea are exactly balanced by the length of the eye so that the light emanating from an object forms a perfectly focused image on the plane of the retina. (D) With astigmatism there is a difference in power of the two principal meridians of the eye due to a toric curvature of the cornea and/or lens resulting in an inability to bring light into a point of focus on the retina. A toric lens brings both meridians into focus.

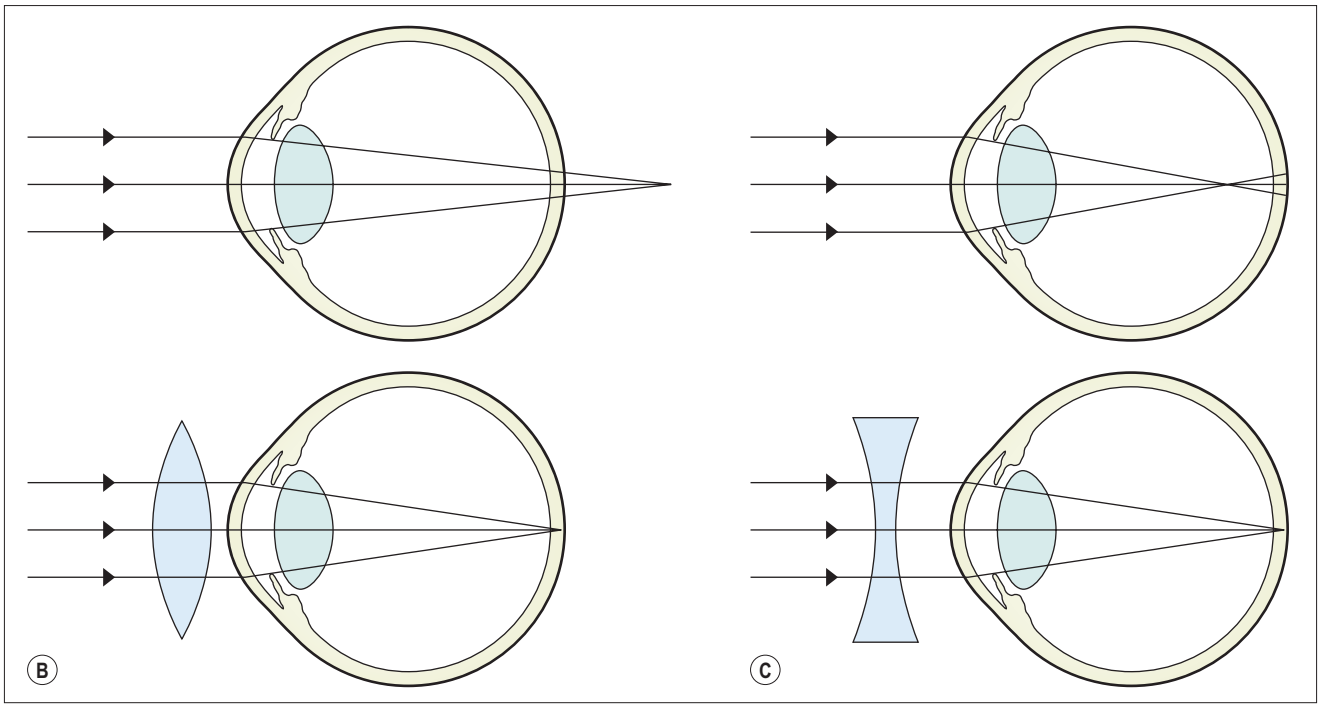


Fig. 8.1 (A) Continued online. (B) Hyperopia occurs when the focusing power of the eye is too weak, and/or the length of the eye is too short, such that the light rays focus behind the retina. A biconvex lens can be used to bring the image into focus. (C) Myopia occurs when the focusing power of the eye is too strong, and/or the length of the eye is too long, such that the light rays focus in front of the retina. A biconcave lens can be used to bring the image into focus. (D) Continued online.

Table 8.1 Recommended cycloplegic agents[2]

Age	Recommended agent	Dosage	Onset of cycloplegia	Duration of cycloplegia + mydriasis	Side effect profile
Preterm to 3 months	Cyclomydril (cyclopentolate 0.2% and phenylephrine 1%)	Two sets of one drop every 5 minutes	20–60 minutes	6–48+ hours	Minimal
3 months to 1 year	Cyclopentolate 0.5%	Two sets of one drop every 5 minutes	20–60 minutes	6–48+ hours	Moderate
1 to 12 years	Cyclopentolate 1% or	Two sets of one drop every 5 minutes	20–60 minutes	6–48+ hours	Moderate
	Atropine 1% drops or ointment	One drop twice a day for 3 days	Hours	1–2+ weeks	High
12 years and older	Tropicamide 1%	Two sets of one drop every 5 minutes	25–40 minutes	2–6+ hours	Low

Adapted from Mutti DO, Zadnik K, Egashira S, et al. The effect of cycloplegia on measurement of the ocular components. Invest Ophthalmol Vis Sci 1994; 35: 515–27.

Autorefraction

The authors have found in their practice that autorefraction performed monocularly and with cycloplegia using late model stationary devices provides very accurate measurements of refractive errors and can be used in cooperative children as young as 2 years of age (Fig. 8.3). Autorefraction may more accurately detect astigmatism than retinoscopy.[5] Nevertheless, we recommend confirming autorefraction findings with retinoscopy and visual acuity measurements rather than prescribing spectacles based on autorefraction alone.

Post-cycloplegic subjective manifest refraction

Post-cycloplegic subjective manifest refraction can be useful in children. Often, a prescription can be written for the full refractive error detected with cycloplegic refraction, but sometimes it can be helpful to have the patient return to the office for manifest refraction after the cycloplegic agent has worn off. Examples include children with high hyperopia who do not tolerate the full plus correction, children who have significant changes in refractive error over relatively short periods of time, children with incomplete cycloplegia, and



Fig. 8.2 This infant was seen at 2.5 months of age for parental concerns about poor visual interest. Hyperopia of 6 D was detected. Parents were reassured but returned when the child was 4 months old for similar concerns. Dynamic retinoscopy revealed 4 D of accommodative lag. Spectacles were prescribed. The parents noted immediate improvement in the child's visual interest and development with the +6 D spectacles.



Fig. 8.3 Autorefraction can be successfully performed on cooperative children as young as 2 years of age.

children with irregular red reflexes that limit the ability to perform retinoscopy or autorefraction.

Corneal topography

Corneal topography can be a useful diagnostic tool in children with significant corneal astigmatism to confirm the axis of astigmatism, to diagnose irregular or asymmetric astigmatism and early keratoconus, and to identify lenticular astigmatism. It can also be useful during contact lens fitting.

Ocular biometry

A-scan ultrasound or non-contact optical biometry measurement of axial length, anterior chamber depth, and lens thickness can be useful to determine the etiology of refractive errors, and is invaluable in determining intraocular lens power for cataract surgery, but is not used routinely to diagnose refractive errors.

Common refractive errors in children

A refractive error is present if parallel incident light rays in a non-accommodating eye with clear media are not perfectly focused on the retina. This occurs if the focusing power of the eye is too strong or weak for the length of the eye.

Hyperopia

In hyperopia, the focusing power of the eye is "too weak" and/or the axial length of the eye is "too short." In the non-accommodating hyperopic eye, the light rays coming from an object at infinity will come into focus behind the retina (Fig. 8.1B). A biconvex (plus powered) lens is needed to bring the light rays onto the retina. Severe hyperopia is seen with aphakia, which occurs because of surgical removal or spontaneous dislocation of the lens.

Mild hyperopia is normal in infancy and early childhood before the eye has reached its full adult size. Newborn infants have about 3 D of hyperopia, which usually decreases to about 1 D by the age of 1 year.[6] Since infants and young children can normally accommodate 14 D or more,[7] correction of mild and symmetric hyperopia in young children is usually not required. However, if esotropia is present, the authors recommend prescribing the full hyperopic correction, as determined by cycloplegic refraction. If the hyperopia exceeds 4.5–5 D, there is accommodative lag, or the child is symptomatic the authors recommend prescribing at least a partial hyperopic correction. If anisometropia is present (hyperopia is not the same magnitude in both eyes) the authors usually prescribe if the hyperopic anisometropia exceeds 1.5 D (sometimes less in children with over 4 D of hyperopia). After the age of 3, correction of hyperopia can be based on subjective testing of visual acuity and patient complaints.

In some cases, children do not tolerate the full hyperopic correction because they have difficulty relaxing their accommodative tone, which renders them myopic when wearing the full correction. In such cases, the authors will either cut up to 2 D of hyperopia from the spectacle prescription, or treat with atropine 1%, one drop daily for 1 week to relax accommodation.

The American Academy of Ophthalmology's (AAO's) consensus-based recommendations for correction of hyperopia in young children to age 3 are listed in Table 8.2.[8] A review of 19,372 pediatric refractions performed at the Children's Hospital of Philadelphia over 4.5 years[9] revealed that the rate of adherence to these guidelines was fairly high in children over the age of 1 year; however, in many cases, treatment of even large amounts of hyperopia in children under the age of 1 was postponed, likely due to the rapid shifts in refractive error expected with growth.

Myopia

In myopia, the focusing power of the eye is "too strong" and/or the eye is "too long." In the myopic eye, the light rays from an object at infinity will come into focus in front of the retina (Fig. 8.1C). A biconcave (minus powered) lens is needed to focus the light rays on the retina. Myopia occurs as a result of a variety of genetic and environmental factors. The decision whether to treat myopia is based on the visual needs of the child, which in turn are heavily dependent on age. The

AAO recommends treatment of isoametropic myopia when it exceeds 5 D in children under age 1, 4 D in children age 2, and 3 D in children age 3 (see Table 8.2).[8] After age 3, treatment is based on subjective visual acuity and patient complaints. Anisometropic myopia is better tolerated, and there is less risk of isoametropic amblyopia than with hyperopia, most likely because each eye will be in focus at some distance. Consequently, the AAO recommendations for the correction of anisomyopia are 4 D in children under age 1, and 3 D in children aged 2–3 years. As with hyperopia, compliance with AAO guidelines is high in children 2 years of age and older, but treatment is often postponed in children less than 1 year of age.[9]

Astigmatism

With regular astigmatism there is a difference in power of the two principle meridians of the eye due to toric curvature of the cornea and/or lens resulting in an inability to bring light into a point of focus on the retina (Fig. 8.1D). Irregular astigmatism, which is less common, occurs when the principle meridians are not 90° apart, and is usually caused by corneal scarring or ectasia. Although moderate levels of astigmatism can be well tolerated, the AAO recommends treatment of over 2 D of bilateral or anisometropic astigmatism in children over the age of 2 years (see Table 8.2),[8] although this recommendation is not consistently followed, especially in symmetric cases.[9] Many patients tolerate astigmatism remarkably well, and are more likely to reject astigmatic correction than correction for myopia or hyperopia. Since anisometropic astigmatism can cause amblyopia, the authors usually recommend correction for 1.5 D or more.

Table 8.2 American Academy of Ophthalmology guidelines for refractive correction in infants and young children

Condition	Refractive errors (diopters)		
	Age <1 years	Age 1–2 years	Age 2–3 years
ISOAMETROPIA (SIMILAR REFRACTIVE ERROR IN BOTH EYES)			
Myopia	−5.00 or more	−4.00 or more	−3.00 or more
Hyperopia (no manifest deviation)	+6.00 or more	+5.00 or more	+4.50 or more
Hyperopia with esotropia	+2.50 or more	+2.00 or more	+1.50 or more
Astigmatism	3.00 or more	2.50 or more	2.00 or more
ANISOMETROPIA (WITHOUT STRABISMUS)*			
Myopia	−4.00 or more	−3.00 or more	−3.00 or more
Hyperopia	+2.50 or more	+2.00 or more	+1.50 or more
Astigmatism	2.50 or more	2.00 or more	2.00 or more

NOTE: These values were generated by consensus and are based solely on professional experience and clinical impressions because there are no scientifically rigorous published data for guidance. The exact values are unknown and may differ among age groups; they are presented as general guidelines that should be tailored to the individual child. Specific guidelines for older children are not provided because refractive correction is determined by the severity of the refractive error, visual acuity, and visual symptoms.
*Threshold for correction of anisometropia should be lower if the child has strabismus. The values represent the minimum difference in the magnitude of refractive error between eyes that would prompt refractive correction.
From AAO. Preferred Practice Pattern Guidelines. Pediatric Eye Evaluations. San Francisco, CA: American Academy of Ophthalmology; 2012. Available at: http://www.aao.org/ppp.

Treatment of refractive errors in children

Spectacles

Because of their safety and availability, spectacles are the most common method of treating refractive errors in children and are usually the authors first line of treatment. Spectacles come in a wide variety of shapes and sizes. Children who are aphakic or pseudophakic or who have a high accommodative convergence to accommodation ratio benefit from bifocal lenses. Spectacles also provide a measure of safety when shatter-resistant lenses such as polycarbonate or trivex are used. Safety is an important consideration in all children, but is especially important in children with moderate to profound amblyopia in one eye to safeguard the healthy eye.

Large amounts of anisometropia can lead to image size disparity when corrected with spectacles. Despite Knapp's law, the authors treat primarily with contact lenses regardless of whether the etiology is axial or refractive (see below). When conditions exist that preclude the use of contact lenses, adjustments in spectacle index of refraction, lens thickness, and vertex distance are required to balance the image size of the two eyes. Commercially available programs such as Aniseikonia Inspector can be employed to facilitate this process.

Contact lenses

Indications for contact lenses in children

There are medical and non-medical indications for using contact lenses in children. The CLIP (Contact Lenses in Pediatrics) study showed children as young as 8–12 years of age are capable of assuming at least some of the responsibility for the insertion, removal, and care of contact lenses, although this age group required more time training than children aged 13–17.[10] In both age groups, over 80% of children were able to manage care and cleaning using 2-week disposable soft lenses. In addition, the self-perception of physical appearance, athletic competence, scholastic competence, and social acceptance in a group of children aged 8–11 years randomized to contact lens wear was higher than an age-matched control group randomized to spectacles.[11,12] In these studies, the rates of contact lens-associated complications were very low. Nevertheless, poor hygiene, lack of maturity, prolonged fitting times, and high cost of contact lens-related complications in children can preclude the use of contact lenses for non-medical indications in children, especially when spectacles are an acceptable alternative.

Medical indications for contact lenses in children include anisometropia, irregular corneal astigmatism, large-magnitude refractive errors, and nystagmus. Correction of anisometropia with spectacles can improve amblyopia, but can result in aniseikonia (unequal image sizes), which can adversely affect stereopsis.[13–15] In practice, the authors usually consider contact

lenses when large amounts (3 D or more) of anisometropia are present. Similarly, optimal correction of the higher-order aberrations of irregular astigmatism is not possible with spectacles and requires contact lenses as the first step toward management of amblyopia in affected children. Spectacle correction of large refractive errors such as aphakia and high myopia induces distortion, prismatic effects, and magnification (hyperopia) or minification (myopia), so contact lenses are sometimes preferred in these settings. Finally, the authors have observed improved quality of life and improved optical correction of refractive errors in patients with nystagmus who wear contact lenses, when compared to spectacles.[16] Although the authors commonly use contact lenses for the above medical indications, they are reluctant to rely on contact lenses alone in settings of moderate-to-profound amblyopia in one eye. In such cases, the preferred option is safety glasses, sometimes in combination with a contact lens in the amblyopic eye only..

Lens selection

A variety of contact lens materials are available. In general, soft contact lenses are better tolerated by children and are preferred over rigid gas-permeable (GP) lenses in most cases of myopia, hyperopia, and mild astigmatism. Soft lens materials range in water content and ionicity and are categorized by the Food and Drug Administration in the United States as 1–5, with 5 representing silicone hydrogel materials. Custom soft contact lenses are available when the parameters needed are not available with conventional lens products. Soft toric contact lenses are practical up to a power of approximately 2 D cylinder. With higher amounts of cylindrical correction, variable vision often results due to lens instability and rotation. Frequent replacement of soft lenses reduces complications, and patients should always adhere to the manufacturers recommendations for replacement. Whenever possible, single-use lenses should be considered for use in children, since they eliminate the need for a care system and promote compliance. GP lenses are preferred in children with severe or irregular astigmatism, since they provide a smooth refracting surface. Hybrid lenses and tandem ("piggy back" lenses) are sometimes useful in children who cannot tolerate a GP lens.[17] Cost of lenses also factors into lens selection.

Lens fitting

Children have small tight palpebral fissures and strong Bell's reflexes, and so it can be challenging to fit contact lenses. Soft contact lenses should demonstrate good centration with full corneal coverage, allowing approximately 2 mm of overlap on the sclera while still allowing for some movement. When digitally displaced to the side, the lens should re-center gradually on the cornea. If it "springs back" immediately, it is probably too tight, and if it stays off-center while manually closing the lid, it is probably too loose. In addition, the red reflex should maintain clarity before, during, and after a blink.

GP fitting in children can be guided by keratometric readings obtained at the time of surgery or an exam under anesthesia, but application and evaluation of a diagnostic lens provides the best results. Good centration and stability of the lens is desired and is easier to achieve with larger-diameter lenses. A good rule of thumb is that if the lens frequently dislodges from the eye, it is too tight, and if it frequently displaces to the bulbar conjunctiva, it is too loose.

Application, removal, and care of contact lenses in children

The application of any contact lens to the eye of a small child by an eye care professional or caregiver is initially a daunting task. Through practice and good technique, the skill can be mastered. In general, GP and silicone hydrogel lenses are easier to apply and remove than soft contact lenses. Proper hand washing should always take place before application or removal of contact lenses. A contact lens can be applied to a small eye by gently sliding the leading edge under the upper lid and then massaging the lens into the correct position. A soft lens can be removed by pinching the lens with the thumb and ring finger to release the lens from the eye. The removal of a GP lens from a young patient can be aided with a DMV suction cup. However, one must be able to hold the eye open wide enough to apply the tool to the anterior lens surface. Scissoring a GP lens off of the eye can be achieved by sliding the lower lid under the lens edge in order to dislodge it. A GP lens can also be removed from the eye by the young patient by "popping" the lens out. By opening both eyes wide and maintaining fixation, the ring finger is placed between the temporal upper and lower lids then pulled laterally. The lens is then easily dislodged by the upper lid with a blink.

Whenever daily-wear disposable lenses are not possible, a care system is required. Daily care of the lens storage case consists of removing the storage solution, wiping the case with a lint free cloth, and allowing it to air dry. In addition, the storage case should be scalded once a week in boiling water and replaced monthly. Lens care systems should include an approved cleaner and lens disinfectant. Approved oxidative care systems for both GP and soft lens modalities should be considered to maximize microbial efficacy and avoid hypersensitivities.

Despite newer lens materials that maximize oxygen delivery, overnight wear of any contact lens carries a greater chance of microbial keratitis.[18,19]

The use of overnight-wear materials can be considered but primarily prescribed as a daily-wear modality. In addition, daily application and removal of the contact lens improves facility in handling and managing the lens.

Safety of contact lenses in children

Contact lens wear in children is safe in most circumstances. Contact lens complications can be categorized as infectious, inflammatory, and mechanical, are usually easily treated, and occur in about 18% of contact lens wearers overall.[20] Children have more mechanical adverse events than adults during their learning period of contact lens wear.[21] Late adolescent and young adult patients have a higher contact lens complication rate than younger children.[22] A child who is motivated to wear contact lenses for specific activities and is instructed properly by the eye care professional can enjoy many years of safe contact lens wear. Children should be given verbal and written instructions concerning lens hygiene, which should be reviewed at each follow-up visit.

Refractive surgery

Refractive surgery is a promising option for correcting refractive errors in children with developmental and other disorders that preclude the use of spectacles and contact lenses (see Chapter 71).

Prevention of onset and progression of myopia

The increasing prevalence of myopia, especially in Asian populations (which reaches 80% in some regions) and other groups with high educational demands, had led to a heightened interest in the factors that contribute to myopia onset and progression.[23] In turn, novel preventative strategies have been introduced to minimize the long-term morbidity associated with moderate-to-high myopia (retinal detachment, early-onset cataract, glaucoma, optic nerve anomalies, and choroidal neovascularization).[24]

In addition, treatment strategies for preventing the progression of keratoconus have been introduced in recent years. This section provides an overview of these evolving practices.

Modification of outdoor and near activities

Several observational studies have shown that outdoor activities seem to protect against myopia. The proposed mechanisms include increased dopamine release in the retina (which inhibits axial elongation in experimental studies), increased light intensity outdoors (which constricts the pupil and improves focus, presumably slowing eye growth), reduced accommodative demand, and possibly a substitution of distance for near work.[24,25] Conversely, a relationship between increased near work and onset or progression of myopia has been shown in some studies, but not others, and the association remains controversial. Multiple genetic and environmental factors contribute to the effect of outdoor time and near work on myopia, and are not completely understood.[24] Nevertheless, the authors recommend counseling patients and their parents about the importance of balancing time spent doing near work and play with time spent working and playing outdoors.

Pharmacologic intervention

The ability of atropine to retard progression of myopia was recognized almost 100 years ago. The mechanism by which atropine and other antimuscarinic agents such as pirenzepine and cyclopentolate work to slow progression of myopia has still not been clearly elucidated. Proposed mechanisms include inhibition of accommodation and increased collagen cross-linking of sclera (caused by increased pupillary dilation/increased ultraviolet light exposure), but are most likely caused by direct biochemical effects on the retina and sclera.[24] Known side effects of traditional concentrations of 0.5% and 1% atropine (pupillary dilation, loss of accommodation) have limited its widespread use. Recent studies have confirmed a dose-dependent effect of atropine on reducing progression of myopia, with concentrations as low as 0.01% showing a significant effect.[26] A rebound effect is observed after discontinuation of all concentrations of atropine; however, a recent report suggests that 0.01% atropine has a more modulated and sustained effect (Fig. 8.4).[26,27] In addition, pupillary dilation and loss of accommodation were mild, and recovered quickly after discontinuing this concentration. Consequently, the authors concluded that 0.01% atropine could be considered a reasonable approach to retarding myopia progression in children. It is commercially available in only a limited number of countries.

Optical treatment strategies to reduce the progression of myopia

Undercorrection of myopia

Undercorrection of myopia has been used in some clinical settings as a strategy to slow myopia progression in children.[28] Although myopic defocus has been shown to slow myopic progression in animal studies, this finding has not been replicated in most human studies.[24] Several recent clinical

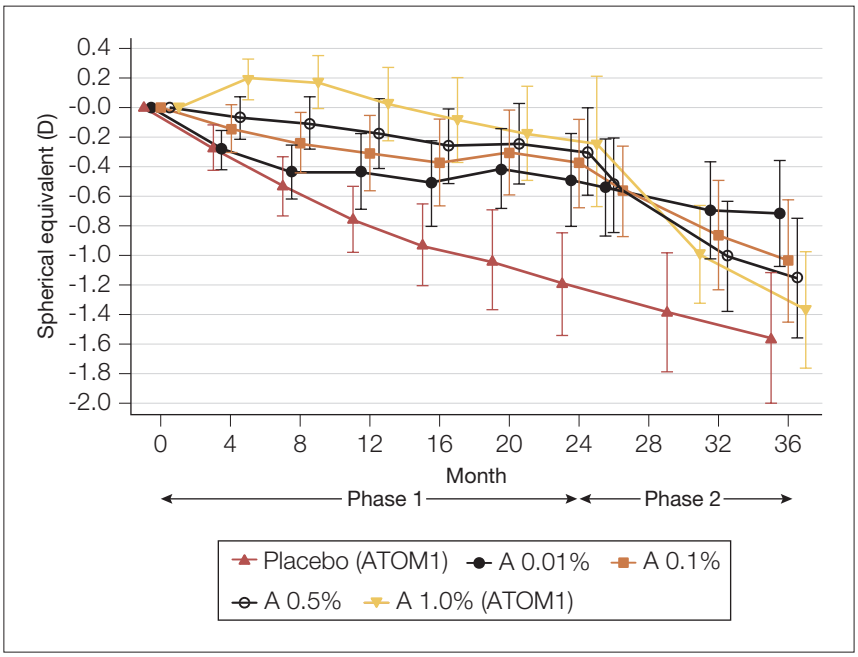


Fig. 8.4 Results of the ATOM1 and ATOM2 study show a sustained effect of 0.01% atropine on retarding progression of myopia. *(From Chia A, Chua W-H, Wen L, et al. Atropine for the treatment of childhood myopia: changes after stopping atropine 0.01%, 0.1% and 0.5%. Am J Ophthalmol 2014; 157: 451–57.e1.)*

studies have concluded that undercorrection of myopia may actually accelerate myopic progression in children.[28–30] Hence, the authors recommend providing the full correction for myopic children.

Reduction of relative peripheral hyperopia

Historically, the use of bifocal and progressive addition spectacle lenses (PALs) to slow myopia progression was based on the belief that accommodative lag during near work causes foveal hyperopic defocus that accelerates axial growth of the eye.[24] Indeed, PALs, flat-top D bifocals, executive bifocals, and executive bifocals with base-in prism (in order of increasing effect) have all been shown to have modest effects on slowing of the progression of myopia, especially in children with high accommodative lag.[24,25,31] An alternative mechanism is that reduction in *peripheral* hyperopic defocus slows myopia progression. Peripheral hyperopic defocus occurs when myopia is corrected with spectacles or single-vision contact lenses, and light rays falling on the peripheral retina are focused behind the plane of the retina (Fig. 8.5A). This theory is supported by animal studies that suggest that visual signals coming from the retinal periphery may dominate refractive development,[25] as well as clinical observations that show significant reduction in myopic progression when bifocal glasses, multifocal contact lenses, or overnight corneal reshaping therapy (orthokeratology) are used to reduce peripheral hyperopic defocus.[32] These lenses place the image shell on to the mid-peripheral retina, reducing peripheral hyperopic defocus in contrast to spectacles or conventional contact lenses (Fig. 8.5B). Although the clinical effect of these optical interventions has been consistently shown in multiple randomized controlled trials (Table 8.3),[3,6,33–39] the underlying mechanism is still a matter of debate.[40]

Orthokeratology (corneal reshaping therapy)

Reverse geometry GP designs are used to redistribute and thin central epithelial power. The initial application for this method of correction allowed patients to wear lenses at night and function during the day without myopic correction. Researchers then found this form of correction also slowed myopic progression, presumably due to the oblate cornea and resultant peripheral retinal focus as described above. However, these designs are not without risks, due to overnight wear. Center distance soft multifocal designs have shown similar

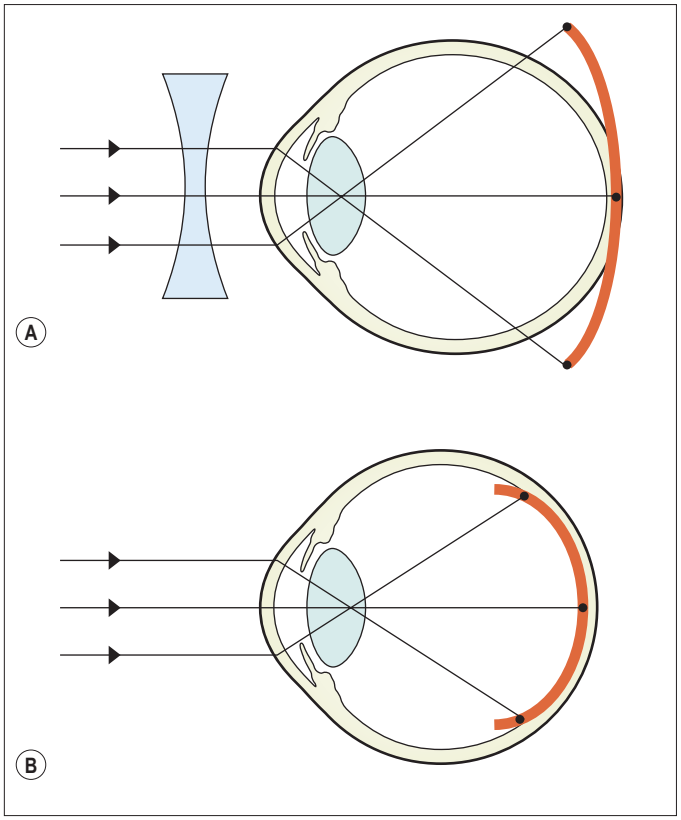


Fig. 8.5 (A) Peripheral hyperopic defocus occurs when a biconcave lens is used to correct myopia. (B) Corneal reshaping therapy (orthokeratology) induces peripheral myopic defocus.

Table 8.3 Randomized clinical trials of contact lenses to slow progression of myopia

Author	Year	Lens type	Range of myopia[a] (D)	Age range	Number of patients	Reduction of axial growth[b]	Duration of study
Sankaridurg et al.[34]	2011	Peripheral gradient contact lens	–0.75 to –3.5	7–14	43	34%	1 year
Anstice et al.[35]	2011	Dual focus contact lens	–1.25 to –4	11–14	40	49%	10 months (phase 1)
Walline et al.[33]	2013	Multifocal contact lens	–1 to –6	8–11	32	29%	2 years
Lam et al.[36]	2014	Defocus incorporated contact lens	–1 to –5	8–13	65	31%	2 years
Cho et al.[37]	2012	CRT	–0.5 to –4	6–10	37	43%	2 years
Charm et al.[38]	2013	Partial CRT	–5 to –8	8–11	26	NR	1 month
Chen et al.[39]	2013	CRT	–0.5 to –5 cyl –1.25 to –3.50	6–12	35	52%	2 years

[a]May include 1 D or less astigmatism in most studies unless otherwise indicated.
[b]Compared to single-vision spectacles or contact lens control group.
CRT, corneal reshaping therapy (orthokeratology).

outcomes related to myopia control while being worn on a daily-wear schedule.[33] The risk of complications associated with modern day orthokeratology has improved in recent years. Good compliance with prescribed maintenance regimen is essential.[41]

Acupuncture

Traditional Chinese medicine practitioners advocate for the use of acupuncture for the treatment of myopia. A Cochrane Review and Preferred Practice Guidelines from the AAO both conclude that the use of acupuncture to treat myopia has not been sufficiently studied, and the decision to use acupuncture to control myopia should be individualized to the patient's needs and preferences.[42]

Collagen cross-linking

Collagen cross-linking has been used to manage progressive pediatric keratoconus. The timing and technique is currently debated. Parents should be informed about the possibility of the need for re-treatment – especially in very aggressive forms.[43]

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Fig. 8.1 (A) In emmetropia, the focusing power of the lens and cornea are exactly balanced by the length of the eye so that the light emanating from an object forms a perfectly focused image on the plane of the retina.

Fig. 8.1 (D) With astigmatism there is a difference in power of the two principal meridians of the eye due to a toric curvature of the cornea and/or lens resulting in an inability to bring light into a point of focus on the retina. A toric lens brings both meridians into focus.

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Visual electrophysiology: how it can help you and your patient

Dorothy A Thompson and Alki Liasis

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Introduction

Pediatric visual electrophysiology can be a challenge, but provides information about the function of the retina and visual pathways that cannot be obtained by other means. This quantifiable functional assessment helps us with early diagnosis, prognosis, and is an objective means of monitoring neurologic and ocular sequelae.

There are international guidelines and minimum standards for performing visual electrophysiologic investigations (e.g. from the International Society for Clinical Electrophysiology of Vision [ISCEV] at http://www.iscev.org or the International Federation of Clinical Neurophysiology at http://www.ifcn.info). The authors use and extend ISCEV adult protocols in children who are able to sit still and follow instructions for 30 minutes or more. With younger or less compliant children, adapted protocols are used that are robust enough to provide comparable information without restraint, sedation, or anesthesia.

Much encouragement and distraction are often needed to obtain reproducible results in children with short attention spans. For these patients, one also has to be flexible and responsive during the test and able to adapt the protocol, and the order of tests within a protocol, to ensure that the clinical question is answered. This may be prompted by ongoing analysis and interpretation of online findings, or by changes in the child's compliance. These modified protocols and distraction techniques enable clinicians to meet the needs of a child in ways they enjoy in a time-efficient way! The overarching aim is to minimize stress and anxiety to child, carer, and staff. This optimizes results and the chance of reliable monitoring in the future.

The tests

Clinical visual electrophysiologic tests include the electro-oculogram (EOG) and the electroretinogram (ERG), which assess the function of the retinal pigment epithelium (RPE) and retina, and the visual evoked potential (VEP), which assesses the integrity of the postretinal pathways to the striate visual cortex, particularly the macular pathways.

Behavioral compliance and tolerance are limiting factors in pediatric visual electrophysiology testing. Full adult protocols are lengthy and demanding. For example an EOG requires a child to make accurate saccades every minute for 15 minutes in the dark then 15 minutes in the light. The multifocal ERG (mfERG) and pattern ERG (PERG) require steady fixation; in addition the PERG needs good focus. A full-field ERG (ffERG) demands 20 minutes of dark adaptation and 10 minutes of light adaptation. PERGs, mfERG, and ffERGs optimally require corneal electrodes. These may be tolerated by exceptional youngsters, but they are more likely to be acceptable from the ages of 5 years upwards. The authors' adaptive protocol may be applied from birth onwards and aims for a total investigation time of 30 minutes, during which time pattern VEPs (PVEPs) are carried out, followed by contemporaneous flash VEPs and ERGs. ERGs are recorded with skin electrodes, natural pupils, and no formal dark adaptation, but use scotopic blue and red flashes to help separate rod and cone contributions after viewing the pattern stimulator in a darkened room. These adapted test data are compared with a robust reference range and provide physiologically similar results to adult protocols.[1]

To illustrate the approach, the authors have applied their Great Ormond Street Hospital (GOSH) protocol to two common questions arising at different ages. The flow chart outlines the diagnostic algorithm and hierarchy of testing (Fig. 9.1). Short notes on the technical aspects of the methodology have been provided at the end of the chapter. Artifacts can mimic physiologic responses and must be excluded before

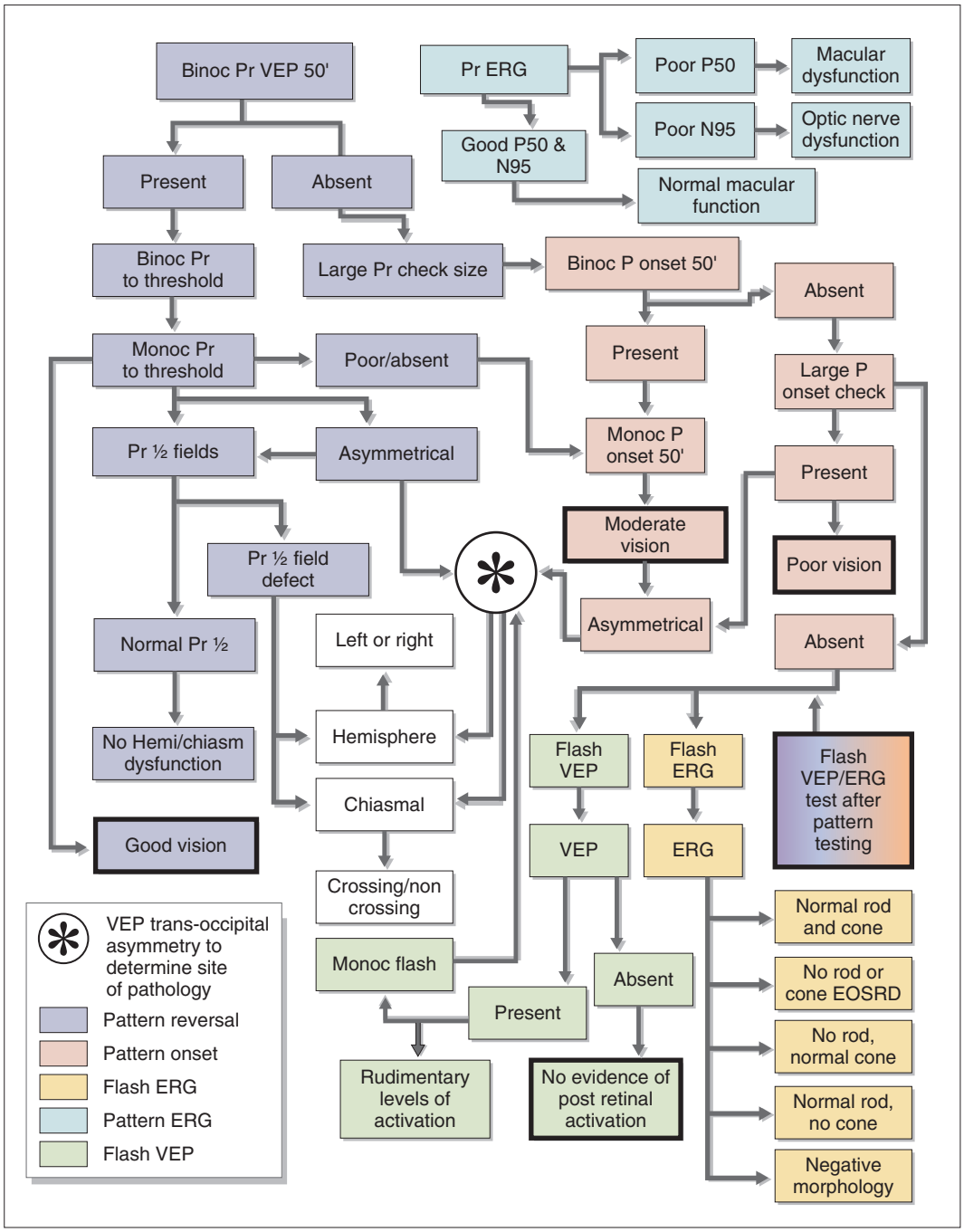


Fig. 9.1 All testing can start with pattern-reversal 50′ checks presented to both eyes. Depending upon the response, one may proceed to smaller reversing checks and monocular testing, or divert to pattern-onset stimulation. After pattern stimulation is completed, flash stimulation is used to contemporaneously record electroretinograms (ERGs) and visual evoked potentials (VEPs). Transoccipital asymmetries are noted throughout and explored in all three stimulus modalities and, when possible, with half-field stimulation. With suspected voluntary defocus, the pattern electroretinogram (PERG) is recorded simultaneously with the pattern-reversal VEP (PVEP). This robust combination strategy can be used to investigate diverse clinical questions as the two examples outlined:

1. Babies: unstable eye movements, is this congenital motor nystagmus? Looking for an anterior visual pathway problem. Possibilities:
   i. Retina: early-onset severe retinal dystrophy (EOSRD), cone dysfunction and congenital stationary night blindness (CSNB) – *need stimuli to separate rod and cone activity and distinguish photoreceptors from inner retina activity (a- and b-wave).*
   ii. Optic nerve: optic nerve hypoplasia – *need monocular flash and PVEPs to compare interocular amplitudes and latency on the midline electrode.*
   iii. Chiasmal anomaly: albinism (require flash infancy and pattern-onset stimulation for older children), chiasmal hypoplasia, glioma – *need monocular stimulation and a transoccipital array of electrodes to look for transoccipital distribution of VEP.*
2. Teenagers: questioning whether there is a functional element to measured subnormal vision:
   Simultaneous PERG and PVEP – *control defocus: cycloplegic full correction for viewing distance, observe direction of gaze.*

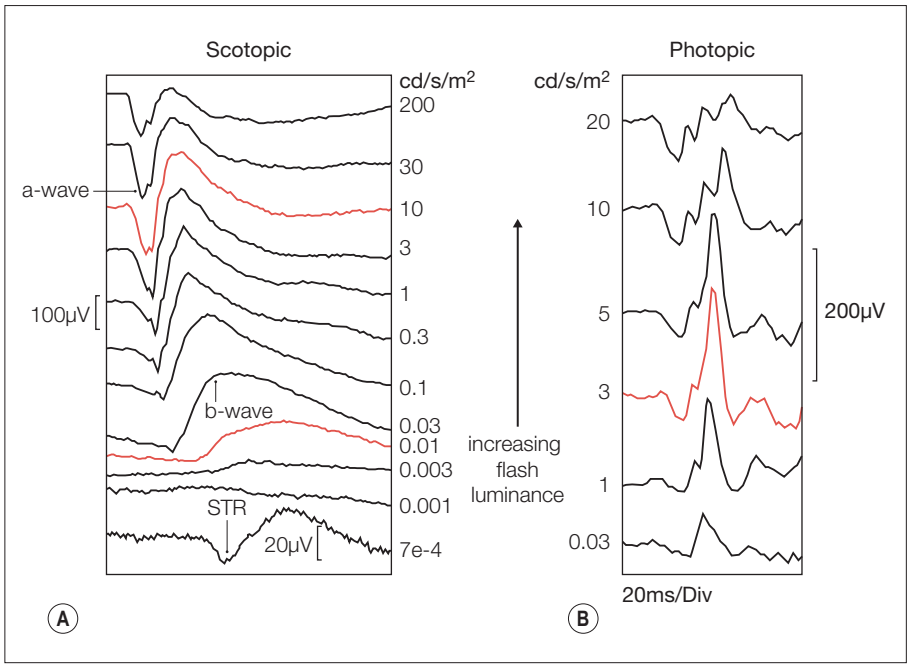


Fig. 9.2 Scotopic (A) and photopic (B) luminance response series. Electroretinograms (ERGs) to International Society for Clinical Electrophysiology of Vision (ISCEV)-standard flash strengths are shown in red. (A) From bottom to top, shows first the development of the rod driven b-wave and then the a-wave as flash strength increases. (B) Shows the photopic hill phenomenon with smaller b-wave amplitude to higher flash strengths.

findings from complementary tests are interpreted as consistent (see Fig. 9.1).

What do the responses tell us? An aide memoire for the busy clinician

The electro-oculogram

The EOG is used to investigate if a maculopathy is due to retinal pigment epitheliopathy. It depends upon the integrity of the RPE interface with photoreceptors. The RPE has a transepithelium potential between its apical and basal surfaces of around 6 mV, with maximal positivity detected at the corneal apex. Electrodes placed on the medial and lateral canthi will record a potential change during a saccade: the electrode closest to the cornea becomes positive relative to the electrode furthest from the cornea. This is the EOG and if it is displayed as a voltage/time plot it can be used to record eye movements, including nystagmus. The transepithelium potential increases in light and decreases in the dark.[2] This variation can be expressed as the Arden ratio (light rise/dark trough) of the maximum and minimum amplitude of EOGs to saccades made in light and dark. Ratios below 1.6–1.8 are considered abnormal. A spuriously normal Arden Index can arise if the dark trough is subnormal due to lowered resistance of RPE tight junctions.[3] An EOG may also reflect the extent of photoreceptor loss, e.g. in pigmentary retinopathy (RP) when the rod ERG is subnormal too. The EOG is diagnostically potent when the Arden ratio is abnormal and the rod ERG is normal as this discriminates a primary retinal condition from an epitheliopathy, e.g. bestrophin mutations.[4]

The flash electroretinogram

The flash ERG is used to distinguish cone from rod and photoreceptor from inner retinal function. The ERG waveform, size, and time to peak will depend upon the relative proportion of rods and cones that are excited and the area of the retina stimulated.[5] The ffERG has no significant contribution from the macula. Rods and cones can be preferentially stimulated by flashes of different colors, strength, and duration presented under different states of dark and light adaptation. Examples of changes in ERG waveforms with increasing flash strength under scotopic and photopic conditions are shown in Figure 9.2. To very dim lights, a small scotopic threshold response (STR) has been described, but clinically this is difficult to achieve and is used rarely. As flash strength increases, a positive b-wave emerges. This is the rod-driven b-wave, DA 0.1, which reflects inner retinal activity of depolarizing on-bipolar cells mainly, and Müller cells. The change of b-wave amplitude with flash strength can be described by a Naka–Rushton function, derived from the Michaelis–Menton equation, but the derived parameters will vary according to the method of curve fitting. In clinical circumstances, these need to be interpreted with care.[6]

$$V/V_{max} = \mathrm{Int}/\mathrm{Int} + K$$

where V = trough-to-peak amplitude of the b-wave, V_{max} = maximum value of trough-to-peak amplitude, Int = flash strength in troland/second, K = semisaturation value, i.e. when Int = K, V is $V_{max}/2$.

As the flash strength further increases an early negative a-wave precedes the b-wave. The a-wave becomes larger and has a shorter time to peak with increasing flash strength reflecting photoreceptor hyperpolarization. To the brightest flashes, DA 200, the leading edge of the scotopic a-wave models rod phototransduction.[7] After light adaptation, the LA 3 b-wave is cone mediated and faster by ~30ms. It reflects both on and off bipolar contributions. Measures of a- and b-waves are most useful clinically, but other ERG waves can be useful. These include:

1. oscillatory potentials – a series of wavelets between the a- and b-waves, vulnerable to disturbances of retinal circulation and spiking neurons.[8]

2. the photopic negative response, the descending limb of the photopic b-wave – reflecting proximal retinal activity, vulnerable in glaucoma and in potassium channelopathies.[9]
3. the c-wave – related to the EOG, due to a depletion of potassium ions in the space between RPE.
4. the d-wave – an off-pathway response. Rods use the on-pathway through the inner retina; cones use both on- and off-pathways. The d-wave is associated with decreases in light under photopic conditions, and is best seen in response to prolonged on–off flashes (on >90 ms).[10] Usually b- and d-waves are superimposed in the ERGs to short-duration (<10 ms) flashes.

ISCEV-standard ffERGs have distinctive shapes and Figure 9.3 shows a reference array of diagnostic standard ERGs with clinical examples in lower rows to aid interpretation of shape changes in pathology.

Flash ERG amplitudes are proportional to the area of functional retina and the summated ERG can mask a small, localized lesion, e.g. maculopathy. Localized areas of retina can be stimulated by focal flashes on bright backgrounds, or with patterned and multifocal stimuli that avoid intraocular light scatter; these methods require steady fixation.

PERGs are elicited by pattern-reversing checks. The waveform is biphasic with positivity at 50 ms and negativity at 95 ms, termed p50 and n95, respectively. The p50 reflects both pre- and postganglion cell activity, whilst the n95 characterizes spiking neuron and ganglion cell function. PERGs are used to investigate suspected early maculopathy, and distinguish it from optic nerve (retinal ganglion cell) dysfunction.[11] The authors record PERGs simultaneously with PVEPs using a large (30°) field and small (15°) fields to additionally distinguish maculopathy and optic nerve dysfunction from visual pathway and cortical dysfunction. The localized retinal area stimulated means PERG signals have small amplitudes, (around 0.5–8 μV). Corneal electrodes that allow good focus, and stringent artifact-rejection criteria and signal averaging to avoid blinks and eye movement artifacts, are needed (Fig. 9.4).

Multifocal stimulation allows focal ERG responses to be recorded simultaneously from many regions of the retina.[12] An array of hexagons are scaled in size with retinal eccentricity to elicit responses of equal size. Each hexagon flashes on and off in pseudorandom sequence (an M-sequence) that guarantees that no stimulus sequence is repeated during an examination. At any one time, on average, half of the hexagons are black and the other half white. The stimulation rate is high, causing a flickering appearance of the screen, but with relatively stable mean luminance. Each element starts the sequence at a different place to every other element. If the difference in starting point in the sequence (the lag) is longer than the response duration, each element generates a response uncorrelated with every other element. Responses unaffected by stimulation of other areas are termed first-order components; second-order components represent temporal interactions between flashes and short lags relative to the duration of the response. It is important to interpret the trace arrays rather than rely on the associated isopotential contour maps, which can be misleading. The mfERG waveforms are mathematical constructs not tiny ERGs, and do not directly reflect a- and b-wave sources. mfERGs, like PERGs, are very sensitive to fixation instabilities and evidence of a blind spot should be sought in trace arrays. Application in children remains largely untried.

The visual evoked potential

The VEP is recorded from the occipital region of the scalp. It reflects depolarization of lamina 4c of the striate cortex (area V_1) by the retinogeniculo afferent volley.[13,14] Retinotopic activity from the central 5°, predominantly lower field, dominates the VEP, and PVEPs in children can act as a surrogate index of macular pathway function. If the PVEP is abnormal, it is important to rule out primary retinal dysfunction at the macula using PERG, mfERG, and/or fundal imaging. Even in the presence of known maculopathy or degraded/absent PERG/mfERGs the PVEP waveform may still provide useful information about residual macular and paramacular function. The authors record PVEPs with both eyes open before monocular testing. They use a transoccipital array of electrodes, large full field (30°) and, where possible, half-field stimulation, to discriminate optic nerve, chiasmal, and hemisphere anomalies (Fig. 9.5).

Use of different types of stimulation: pattern reversal, pattern onset, and flash stimulation

Pattern-reversal VEPs have a simple triphasic waveform that is maintained across the lifespan, with a major positive peak around 100 ms by 7 months of age, called p100 (components are defined by their polarity: p for positive, n negative; the numbers are the latency of the peak after the stimulus). The shape of the full-field pattern-reversal VEP may become bifid (p-n-p) if a central scotoma reduces the macular contribution, e.g. seen in dominant optic atrophy. The bifid waveform is due to enhancement of paramacular contributions n105 and p135. Half-field stimulation can delineate macular and paramacular peaks. The authors use a wide range of check sizes from 400′ to 6.25′ presented at 3/s after 6 weeks of life.

Pattern-onset stimulation is attention grabbing, robust to eye movements, and is preferred in nystagmus or to prevent active defocus. Its waveform is complex and three components have spatially separate generator sources: CI, a positivity around 90 ms; CII, negativity at about 110 ms; and CIII, a prominent positivity at around 180–200 ms.[15,16] Different peaks emerge at different ages: the initial positive CI is most prominent in children and depends upon contrast and luminance. CII emerges in later childhood and depends more on contour. These changes mean it can be difficult to use pattern onset VEPs for monitoring longitudinally.[17]

Flash stimulation is robust and can be effective through closed lids. A control ERG recorded at the same time as the VEP can ensure the level of retinal stimulation. The authors use both flash and pattern stimulation, and often both pattern reversal and onset stimulation to provide corroborating evidence of visual pathway function, particularly transoccipital asymmetries.

Flash and pattern reversal VEPs show paradoxical localization. For example, the right half field stimulates the pathways of the left hemisphere and is detected over the right occipital electrode. This is due to orientation of the cortex activated and is a consequence of the authors' use of large-field stimulation and midfrontal reference electrode site.[18] Pattern-onset VEPs do not show this. The right half field response is recorded

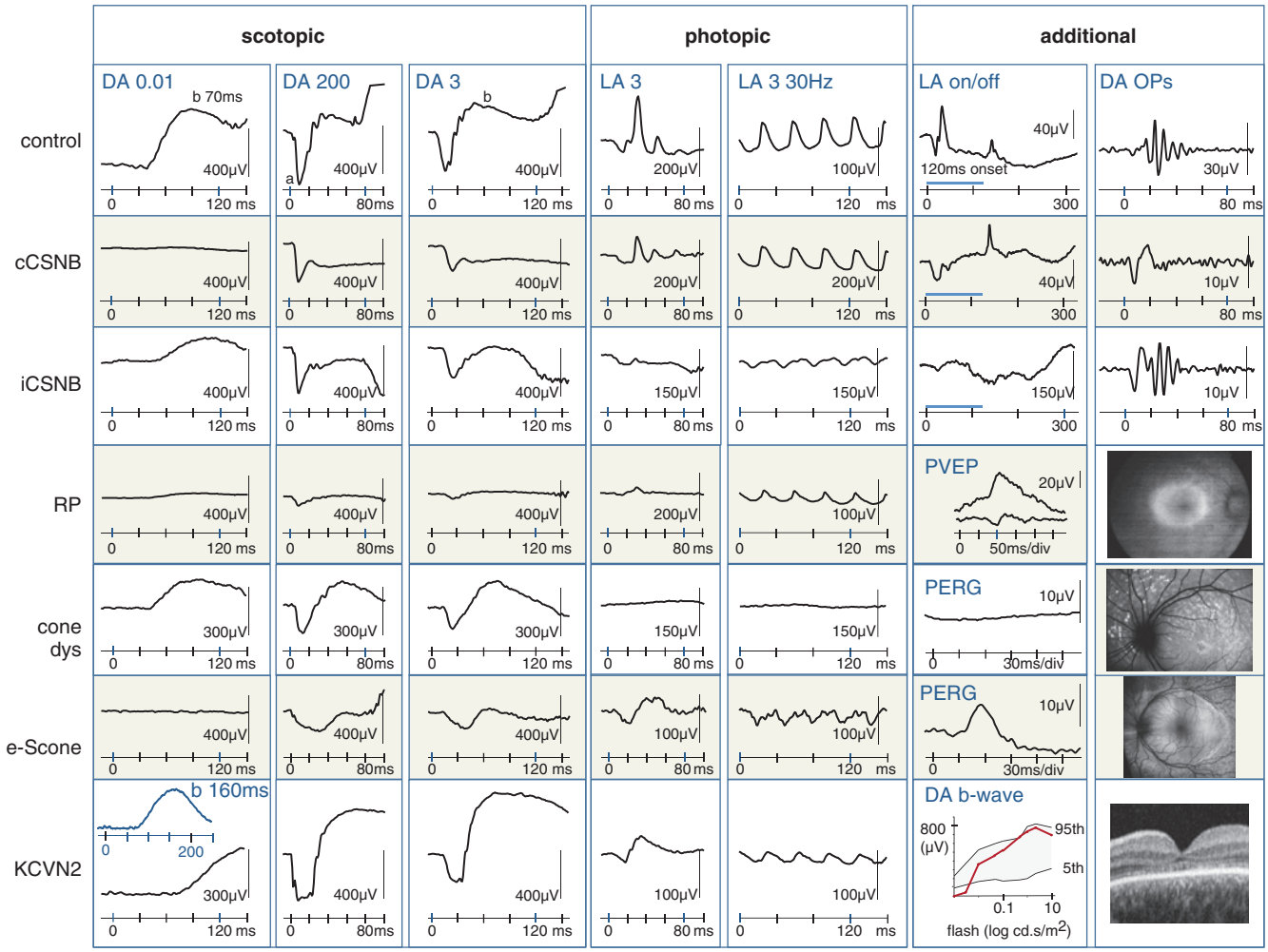


Fig. 9.3 Template of standard diagnostic electroretinograms (ERGs).
Row 1 shows normal traces. The columns moving from left to right show dark-adapted (DA) and light-adapted (LA) ERGs recorded to flashes of different strengths. The last two columns show diagnostically useful additional data, e.g. prolonged on–off ERGs (LA on/off), oscillatory potentials (OPs), pattern-reversal VEP (PVEP), and pattern electroretinogram (PERG). The characteristic ERG waveforms are shown in response to flash stimuli. DA 0.01: large rod-driven b-wave and no a-wave; DA 200: emphasizes the rod a-wave; DA 3: an a- and b-wave mixture of rod and cone contributions; LA 3: a cone-specific response comprised of both on and off bipolar cell activity; LA 3 30 Hz flicker is a cone-sensitivity response reflecting inner retinal responses; LA on/off flashes separate responses of the bipolar on-pathway and off-pathways.
The rows below the normal traces show examples of clinically distinctive electrophysiological findings. Rows 2 and 3 are examples of electronegative ERGs when the b-wave does not rise above the baseline.
Row 2: complete congenital stationary night blindness (cCSNB) is due to a signaling defect, which prevents on-bipolar depolarization. Thus the rod DA 0.01 b-wave is absent and the maximal flash ERG is electronegative. The shape of LA 3 cone a-wave is a broad trough, as the absence of the on-pathway contribution reveals the photoreceptor and off-bipolar responses. The flicker ERG has a saw-tooth shape. LA on–off ERG show an electronegative on-response and a well preserved off response. Later OPs are missing.
Row 3: incomplete CSNB (iCSNB) defects occur at the photoreceptors and affect on- and off-pathways. There is some residual DA 0.01 rod-driven b-wave, a severely attenuated LA 3 cone response and a bifid flicker waveform.
Row 4: pigmentary retinopathy (RP). The very small DA 200 rod a-wave indicates rod photoreceptor loss. Residual cone ERGs reflect peripheral to central progression of photoreceptor loss. If the macula region is preserved, e.g. within the ring of hyper fundus autofluorescence (FAF) shown, then PVEPs may be recorded as they arise from the central 2–5°. PVEPs may help indicate the extent of central retinal preservation when ERGs in RP are non-detectable.
Row 5: cone dysfunction syndrome (conedys). DA rod ERGs are preserved, but the LA cone responses and PERG are attenuated markedly. Such an array of ERGs may occur in Stargardt disease: the typical Stargardt FAF is shown in the last column of this row. Attenuation of the PERG p50 will be noted first indicating maculopathy, but the relative preservation of cone and rod ERGs can be used prognostically.
Rows 6 and 7 are examples of two pathognomonic ERG arrays.
Row 6: e-Scone syndrome (e-Scone). The retina is populated only by S-cones, which use the on-bipolar pathways. There is no DA 0.01 rod driven b-wave. Characteristically, the DA 3 and LA 3 have similar waveforms, the S-cone ERG will be larger than usual, the PERG p50 is typically delayed, as shown, as is the flicker ERG, which may be smaller than the cone a-wave. In childhood hyper FAF dots are seen around the arcades.
Row 7: KCVN2 retinopathy (cone dysfunction with supra normal rod response) shows absent DA rod-driven b-waves to low flash strengths, but to higher flash strengths a very late b-wave suddenly appears (see insert showing the DA 0.01 ERG on a longer time *x*-axis). The DA b-wave amplitude grows rapidly over a small range of flash strengths (plotted as a red line on amplitude vs. flash strength, with the gray area highlighting normal response growth). The DA 200 a-wave shows a distinctive flat-bottomed trough. KCVN2 retinopathy can be associated with bull's eye maculopathy and older children may show a distinctive "toothy" foveal optical coherence tomography (OCT) appearance in the photoreceptor layers.

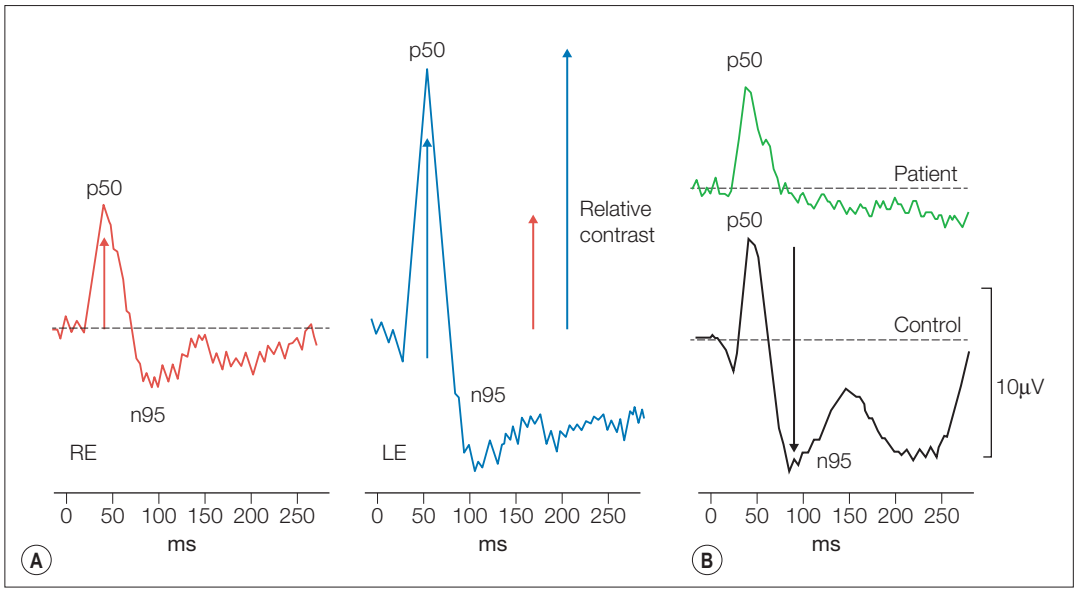


Fig. 9.4 (A) Right eye (RE) and left eye (LE) pattern electroretinograms (PERGs) to 50′ from a 3-year-old patient with RE posterior lenticonus. p50 amplitude is proportional to contrast. The RE PERG amplitude reflects the relative contrast loss due to RE cataract. (B) Top trace is RE PERGs to 25′ from 6-year-old patient with kidney failure. Loss of n95 indicates visual loss due to ON compromise not retinal dysfunction.

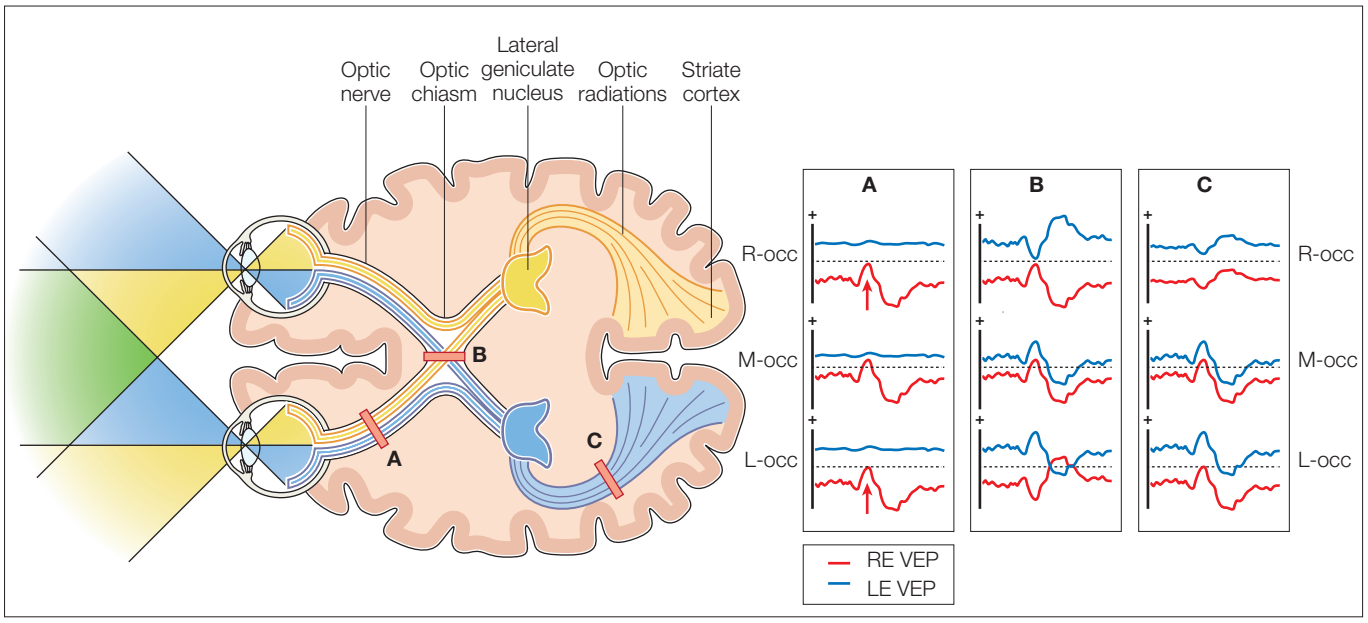


Fig. 9.5 Schematic projection of the right (blue shade) and left (yellow shade) half fields of each eye (RE, right eye; LE, left eye). The black bars superimposed on the pathway represent lesions at (A) left optic nerve, (B) chiasm, and (C) left optic radiations and occipital cortex. The occipital distribution of schematic visual evoked potentials (VEPs) caused by these lesions are shown from RE (in red) and LE (in blue) aligned with the electrode sites right (R-occ) and left (L-occ) lateral and the midoccipital (M-occ) channels. Column A shows a reduced LE VEP and a symmetric distribution of the RE VEP where lateral channel amplitudes are similar (arrowed). Column B shows a crossed asymmetry where the transoccipital distribution of one eye is the mirror image of the other, i.e. the RE VEP is negative (downwards deflection) on the left occiput and the LE VEP is negative over the right occiput. This indicates chiasmal dysfunction. Column C shows that each eye has the same, homonymous, distribution reduced over the right occiput. This homonymous distribution or uncrossed asymmetry suggests hemisphere dysfunction. Due to paradoxical lateralization this distribution of flash and pattern-reversal VEPs means dysfunction of the right half field representation in the left hemisphere.

anatomically appropriately over the left occiput. A comparison of full-field pattern-onset and -reversal VEP transoccipital asymmetries is at times useful to determine if VEP occipital asymmetry is due to pathology, especially in those children with flat or asymmetric skulls who cannot manage half-field stimulation.[19]

Visual acuity and the VEP

It is alluring to try to condense PVEPs into a single-number descriptor of vision acuity; unfortunately, the relationship is not so simple. In normal children, an estimate of visual acuity may be based on the amplitude of PVEPs elicited by patterns of decreasing element size.[20] Threshold VEP acuity is derived from the smallest pattern size to give a response above noise level, or an extrapolation to zero amplitude on a graph of amplitude versus spatial frequency.[21] Although PVEPs show some correlation with behavioral acuity, it is not realistic to expect a direct correlation in a clinical population. For example, as neurons are lost in optic atrophy, the PVEPs will become markedly attenuated and degraded, yet if the receptive fields of the few remaining functioning neurons are closely spaced in the

central field, recognition acuity can be surprisingly good, even with marked optic disc pallor. Estimates of acuity development are higher with VEP techniques in the first 12–18 months of life; after this, behavioral estimates exceed VEP acuity.[22] Recognition acuity is an interpretation of high contrast, static images by higher association areas. Discrepancies from a VEP measure of striate cortex activity should not be surprising. Nevertheless, PVEPs are a useful index of macular pathway function and provide a qualitative indication of the vision level that the retinogeniculate pathway can support. In the authors' opinions, a pattern-reversal VEP to 50′ or smaller checks suggests good vision levels; to 100′–200′, moderate vision levels; and to 400′, poor vision levels. If a flash VEP is detected, but no PVEP is recorded, this suggests vision is rudimentary. PVEPs show little intersession variation and are reliable for serial monitoring. They are particularly useful for interocular comparisons in infancy.[23,24]

When the rate of stimulation increases, individual transient PVEP waveforms merge and become sinusoidal. This is a steady-state response and is used in sweep VEPs, where many different pattern sizes or contrast levels are swept through rapidly.[25,26] The steady-state VEP is analyzed by Fourier techniques into magnitude and phase data. It is possible to determine signal-to-noise thresholds during acquisition before proceeding to smaller patterns – a step acuity VEP. The sweep technique can provide a number (usually in cycles per degree [cpd]) to describe acuity or contrast sensitivity quickly, but there is a loss of information about waveform and often transoccipital distribution. These fast stimulation rates drive the maturing visual system faster than optimal for highest acuity. As VEP waveforms are such important diagnostic indicators the authors prefer transient PVEP recording for routine clinical practice (Fig. 9.6).

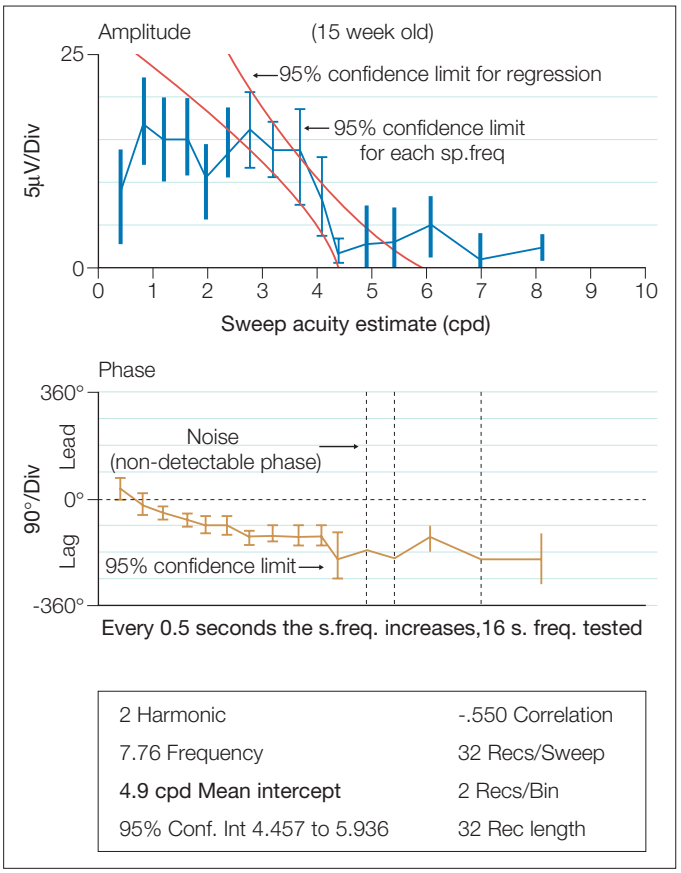


Fig. 9.6 Sweep visual evoked potential (VEP). Rapid stimulation rates are used to elicit a quasi-sinusoidal VEP characterized by its amplitude and phase. A range of spatial frequencies is presented. There is a trend for VEP amplitude to decrease with increasing spatial frequency. A regression to the baseline or noise level is computed to give an acuity estimate, in this case 4.9 cpd.

Technical factors

Visual stimuli include transient flashes of different intensities, durations, temporal rates, colors, patterns, and multifocal mosaics.

Visual stimulators

Flash

Commercial flash stimulators include hand-held strobes, which are helpful for pediatric testing. They can easily follow an alert but restless child, and the child's eye position can be directly observed. Ganzfeld stimulators scatter light uniformly over the retina. They are available as static domes with chin rests, or smaller hand-held LED versions held close to the eye. It is important that these have integral cameras to ensure the eye is open and stimulated properly. Some versions measure natural pupil area and determine flash dose necessary for standard retinal illuminance.

Patterns

Patterned stimuli are computer generated and presented on cathode ray tube (CRT) and plasma display panels (PDP), which are no longer commercially available, or liquid crystal diode (LCD), back projection systems, or super-bright organic light-emitting diode arrays. Triggers for response acquisition with CRTs synchronize with the raster rate generating the image. If running at 50 Hz, there could be a 20-ms difference in latency between a PVEP recorded looking at the top-left of the screen compared to the bottom-right. LCD screens have an inherent luminance flash artifact generated in the pattern due to timing differences in on and off switching. PDPs avoid both these issues. The authors use a large-field PDP with the advantage of the near-simultaneous generation of a pattern uniformly over the screen without luminance artifact. Its multisynch capabilities allow us to switch quickly between the stimulus and a cartoon DVD during the test to maintain attention, whilst a separate audio output keeps soundtrack continuity when patterns are presented.

Field size

Large field sizes (around 30°) are important in pediatric practice, allowing a child some variation of gaze direction whilst still fully stimulating a central, macular, 10° field. Smaller fields are more prone to spurious transoccipital asymmetries when fixation direction varies to the edge of the field.

Check sizes

Patterns prevent light scatter by containing equal numbers of black-and-white elements (usually checks, more rarely gratings) that either counterphase (reverse from black to white) or appear from a background of uniform gray field of equal

mean luminance (pattern onset). A wide range of check sizes is important to ensure consistency, provide a broad baseline for monitoring, and intraocular comparison. The diagonal dimension of a single check gives the cpd equivalent.

ERG electrodes

A range of different sized contact lens electrodes is needed for pediatric work, but these are not used often in the UK and Europe because of concerns about cross-infection. Disposable corneal electrodes (e.g. DTL, gold foil, and HK loop electrodes) are preferred and inferior periorbital skin electrodes are used frequently in younger children.[27] An ERG recorded with a skin electrode is smaller, 12–15% of the amplitude of a corneal electrode, but still substantial, i.e. exceeding 10 μV (with corneal electrodes mfERG are measured in nanovolts, PERGs are under 2–5 μV, and adult VEPs ≤5 μV).[28,29] The skin ERG waveform and timings are similar to corneal electrode ERGs. It is important to ensure the cornea is positioned towards the skin electrode, e.g. a child is encouraged to look downwards, or if there is strabismus, or a shallow midface, the skin electrode may be displaced and gaze directed over it. If the child is asleep and eye rolls up, it is possible to record a completely inverted ERG trace.[29]

Refractive error

The PERG is sensitive to 0.5 DS blur, but the pattern-reversal VEP is robust to 8 D blur of 60′ checks. These two responses can be recorded together to ensure accurate focus. If there is a doubt about focus, as may occur in patients with suspected functional overlay, then PERGs and PVEPs may be recorded after cycloplegia and correction for stimulator distance, e.g. +1 D added for a viewing distance of 1 m.

Dilatation

For the authors' combined protocol, best focus for pattern-reversal VEPs is required. The authors do not dilate for the flash ERG protocol, which immediately follows the PVEP recording. Pupillary dilatation aims to standardize amplitudes, but causes only 12–15% amplitude change.[28,29] Extremes of pupil size or anisocoria are noted, but numerical correction factors for variation in retinal illuminance rarely are applied to clinical ERGs. Recording ERGs to a wide a range of flash strengths ensures this is overcome empirically.

Dark adaptation

It is not practical to have pediatric normative data for abbreviated dark adaptation. Ranges would be required for each 5-minute dark interval for each month of the first year of life. The authors take the same time point under darkened conditions without long dark adaption and stimulate with dim blue flashes to bias the photoreceptor contribution to be predominantly rod driven. The ERG waveform shape provides feedback about the predominant contributing cells as the retina acts like an adaptive photometer.

Maturation

Retinal sensitivity is poor at birth. ISCEV-defined flash stimuli include the possibility of non-detectable ERGs in early infancy.[30] In essence, brighter flash stimuli are needed. If anesthesia is used, this can delay the time to peak and diminish the b-wave in particular.[31] Myelination and synaptogenesis and pruning influence the latency of the pattern reversal VEP, which shortens rapidly to within 10% of adult values in the first 7 months of life. A newborn VEP latency is around 240 ms. It is better to stimulate at 1/second and increase the acquisition time window to 450 ms to capture baby responses. After 8 weeks of age, stimulation of 3/second and shortening the time window to 300 ms speeds up data acquisition. There continue to be morphologic changes throughout life and it is important for each laboratory to acquire full normative reference data sets, sampling frequently in the first 12 months of life.

Summary

Visual electrodiagnostic tests (EDTs) are noninvasive, objective indices of function and are ideal tests for children. To get the most information from each child in the least time, the authors combine and adapt stimulation protocols according to individual need. Distraction is used, interleaving cartoon DVDs with patterned stimuli, having continuous sound tracks, music, audio books, noisy toys, and, most importantly, reassurance and encouragement through personal interaction and play. These are key to directing attention and gaze for a successful recording. Responses are compared against age-matched reference data, after artifacts and confounders are excluded. Data obtained from a combined ERG and VEP assessment can localize dysfunction along the visual pathway and provide a qualitative estimate of vision. The authors provide complementary and supplementary information in many diverse clinical presentations, ranging from an infant who does not fix and follow and has unusual eye movements, to amblyopia not responding to patching, investigation of headaches, and assessment of children who cannot communicate for behavioral assessments.

The prognostic significance of visual EDT results must be weighed in the light of clinical data and with an awareness of maturational changes. Clinical visual EDTs assess the "visual hardware," but do not tell us about the "software." They may suggest the quality of pattern vision that the retinogeniculostriate pathway may support, but clinical EDTs cannot tell how well a child will be able to use the visual data that reaches the striate cortex.

Bonus e-book content online

Fig. 9.1 All testing can start with pattern-reversal 50′ checks presented to both eyes.

Depending upon the response, one may proceed to smaller reversing checks and monocular testing, or divert to pattern-onset stimulation. After pattern stimulation is completed, flash stimulation is used to contemporaneously record electroretinograms (ERGs) and visual evoked potentials (VEPs). Transoccipital asymmetries are noted throughout and explored in all three stimulus modalities and, when possible, with half-field stimulation. With suspected voluntary

Bonus e-book content online—cont'd

defocus, the pattern electroretinogram (PERG) is recorded simultaneously with the pattern-reversal VEP (PVEP). This robust combination strategy can be used to investigate diverse clinical questions as the two examples outlined:

1. Babies: unstable eye movements, is this congenital motor nystagmus? Looking for an anterior visual pathway problem. Possibilities:
   - i. Retina: early-onset severe retinal dystrophy (EOSRD), cone dysfunction and congenital stationary night blindness (CSNB) – *need stimuli to separate rod and cone activity and distinguish photoreceptors from inner retina activity (a- and b-wave).*
   - ii. Optic nerve: optic nerve hypoplasia – *need monocular flash and PVEPs to compare interocular amplitudes and latency on the midline electrode.*
   - iii. Chiasmal anomaly: albinism (require flash infancy and pattern-onset stimulation for older children), chiasmal hypoplasia, glioma – *need monocular stimulation and a transoccipital array of electrodes to look for transoccipital distribution of VEP.*
2. Teenagers: questioning whether there is a functional element to measured subnormal vision:

Simultaneous PERG and PVEP – *control defocus: cycloplegic full correction for viewing distance, observe direction of gaze.*

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Imaging the child's eye, orbit, and visual pathways

Daniel J Salchow and Nadja Kadom

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In 1850/1851, Hermann von Helmholtz (1821–1894) designed the direct ophthalmoscope, enabling the founders of modern ophthalmology to see the living ocular fundus for the first time. Completely new disorders were described, making this instrument essential in establishing the young specialty of ophthalmology. Until ophthalmic photography became available, ophthalmic imaging was performed by artists who meticulously drew and painted detailed renditions of the ocular diseases they had observed. The advent of scanning laser ophthalmoscopy (SLO) in 1981[1] and of optical coherence tomography in 1991[2] dramatically enhanced ophthalmic imaging. Thirty-five millimeter film photography was the standard in external, anterior segment, and fundus photography for decades but has now been replaced by digital photography. Camera systems and optics have remained relatively unchanged, with the exception of the development of non-mydriatic fundus cameras, which allow imaging of the fundus without pupil dilation.[3]

Several new techniques to examine and image the eye have been established over the past few decades. This progress has resulted in a shift in the role of ophthalmic imaging from simple documentation to powerful analysis of the eye and its components, significantly enhancing our understanding of many ocular diseases.

Nevertheless, a careful clinical examination of the patient is essential to decide which type of imaging is needed. Using imaging techniques indiscriminately can result in confusion, the waste of resources, anxiety, and potentially, the provision of unnecessary treatment. Accurate documentation of clinical findings also has a medicolegal dimension. In this chapter, we attempt to provide a framework for the physician to facilitate decisions regarding which imaging technique to use. Specific findings in certain entities are discussed in their respective chapters.

Photography

External photography

In many settings, external ophthalmological findings can be documented. For example, lid fissure height and margin reflex distance are important parameters in patients with upper lid ptosis; ocular motility in patients with strabismus and eyelid swelling and erythema in cellulitis can be photographed. Children might not tolerate instruments close to their face, which makes photography helpful (Fig. 10.1).

Anterior segment photography

In young children, slit-lamp examination is often impossible and photography may allow the clinician to document findings. Measuring the corneal diameter helps to establish the diagnosis in some patients (microphthalmos, infantile glaucoma) and is best done photographically. Judging and comparing lens opacities in pediatric cataract or the extent of subluxation of the lens (e.g. in Marfan syndrome) is facilitated by photographic documentation.

The RetCam (Clarity Medical Systems, Inc., Pleasanton, CA) is a contact digital photography system. With special lenses, it can be used for anterior segment photography. The anterior chamber angle may be visualized and good agreement with slit-lamp gonioscopy in detecting angle closure has been reported.[4]

Fundus photography

When evaluating newborns for retinopathy of prematurity, sequential photographic documentation of retinal findings is helpful. The use of digital fundus photos for remote diagnosis (telemedicine), which holds promise in areas with limited medical care is another possibility. Retinal lesions can be documented, which is particularly important in managing tumors such as retinoblastoma.

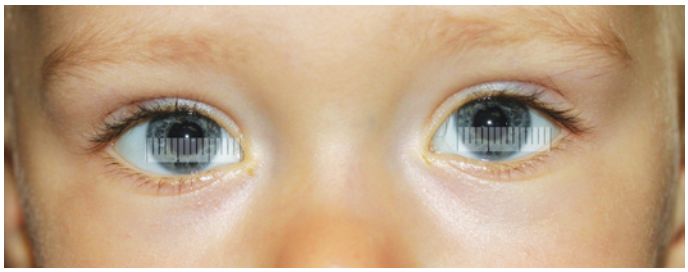


Fig. 10.1 External photograph of a young boy showing symmetric lid fissures and normal corneal diameters. The superimposed scales help to obtain precise measurements, which may be difficult in uncooperative children.

Optic disc characteristics such as the color, sharpness of its borders, as well as size and shape of the optic cup can be assessed on a photograph (using magnification if necessary) and comparison with subsequent photographs is possible, helping to highlight progressive change.

Red-free fundus photography

In red-free fundus photography, the imaging light illuminating the fundus is filtered to remove red colors, allowing light with wavelength 495–570 µm to pass. Since hemoglobin absorbs light of this wavelength well, retinal vessels and hemorrhages appear dark and may be more easily seen than on color photographs. Visualization of retinal holes (darker than surrounding retina) is also facilitated. Drusen (macular and optic disc), exudates, cotton-wool spots, and defects in the retinal pigment epithelium (RPE) are lighter on red-free photography. The retinal nerve fiber layer (RNFL) is lighter and defects appear as darker areas with arcuate borders of RNFL bundles.

Infrared fundus photography

Infrared fundus photography is usually obtained using scanning laser ophthalmoscopy (SLO). Compared with regular white flash fundus photography or photography using a laser with a shorter wavelength (blue, green), it offers better visualization of lesions located in the outer retina or under the retina (Fig. 10.2).

Confocal microscopy

Confocal microscopy (CM) has been used in other tissues since 1955,[5] and was first used to study the cornea in 1990.[6] Like specular microscopy, CM can image the cornea at a cellular level. Unlike light microscopy, which is limited by scattered light and reflections outside the focal plane, in CM the illumination and detection paths have the same focal plane. CM is helpful in diagnosing acanthamoeba keratitis (amoebic cysts and swollen corneal nerves can be detected) and visualizing pathology in individual layers of the cornea (e.g. guttae in endothelium in Fuchs's endothelial dystrophy).

Corneal topography

The first keratoscope was described by Henry Goode in 1847 and used the reflection of a square object on the corneal surface.[7] The *Placido disc* was described by Antonio Placido in 1880. The disc consists of concentric light and dark rings with a central opening to observe the reflections of these rings on the cornea. Any corneal irregularity (astigmatism, scars) will distort the reflection, so that the rings do not appear circular. Videokeratoscopy became available in the 1980s and made analysis of several thousands of sampling points possible. With Placido disc-based topography, a corneal map can be created and color-coded based on corneal curvature or elevation. Advantages of this technology include noninvasiveness and intuitive interpretation. Regular and irregular astigmatism are easily distinguished and corneal disorders such as keratoconus can be identified based on their characteristic appearance. Disadvantages of this technology include the absence of information about the posterior corneal surface and limited corneal coverage (60%).[7]



Fig. 10.2 Infrared image of the normal macula of a 13-year-old girl obtained with a scanning laser ophthalmoscope. The optic disc (right edge of photograph) is sharply demarcated, its neural rim appears dark, the cup white. There is a circular brighter area around the optic disc. Retinal vessels are dark. In the central macula (fovea) a brighter signal is seen.

Slit-scanning elevation topography provides an elevation map of the anterior and posterior corneal surface. The Orbscan II (Bausch and Lomb, Inc., Irvine, CA) is the only commercially available unit using this principle; it provides two-dimensional color-coded maps. Corneal elevation is measured from a reference sphere. This reference sphere is adjusted to each patient's cornea and is called "best-fit sphere." Maps of corneal elevation (anterior and posterior) and curvature as well as corneal thickness can be computed.

Scheimpflug imaging is based on the principle that Theodor Scheimpflug, a captain in the Austrian Navy, described in 1904.[7] Although first used in ophthalmology in the late 1950s, it was not until 1995 that it was used regularly in clinical practice. Diagnostic setups based on the Scheimpflug principle include the Pentacam (Oculus Optikgeräte GmbH, Wetzlar,

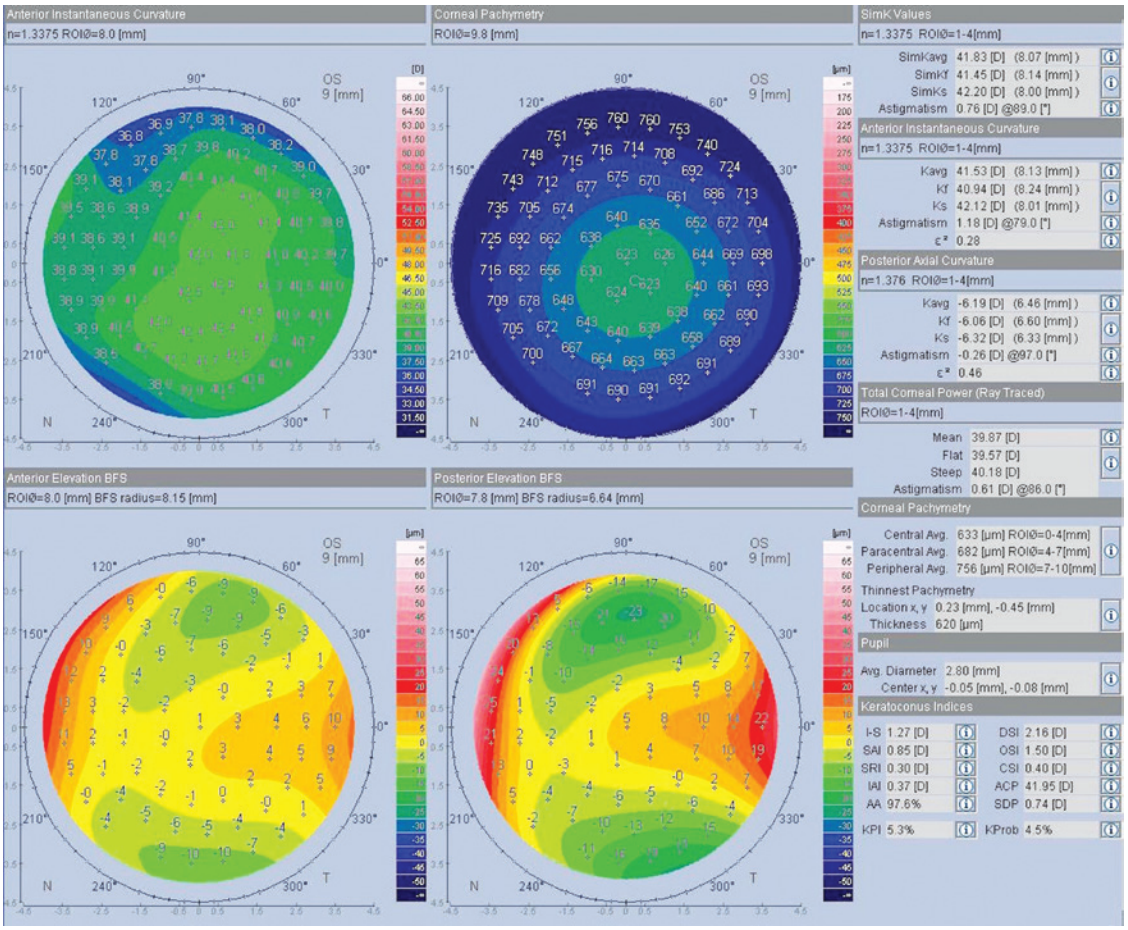


Fig. 10.3 Corneal analysis based on the Scheimpflug principle using Gallilei.* Upper left, anterior corneal curvature is shown (with absolute values and a color-coded corneal map for intuitive interpretation). Upper right, corneal pachymetry is shown; thinner parts are color-coded in warmer colors (red and pink) in order to alert the clinician to corneal thinning. Lower left, an anterior corneal elevation map is shown, in relation to the best-fit sphere (see text). Lower right, a posterior corneal elevation map is shown. Elevation maps are helpful in identifying corneal ectasias such as keratoconus. **Ziemer Ophthalmic Group, Port, Switzerland.*

Germany), the Gallilei (Ziemer Ophthalmic Systems AG, Port, Switzerland) and the Orbscan II (Fig. 10.3). They can measure corneal elevation, thickness, and curvature of the anterior and posterior corneal surface, as well as anterior chamber depth, pupil diameter, anterior chamber angle size, lens opacification, and lens thickness.[7]

Ultrasonography

Ultrasonography can usually be performed without sedation or general anesthesia and is available in many ophthalmologists' offices.[8] It can be performed if fundoscopic examination is inconclusive or not possible. Ultrasonography is based on the emission of high-frequency sound waves, which are reflected by tissues. Shorter wavelengths allow for higher resolution, but tissue penetration is lower. Higher ultrasound frequencies (50 MHz) are used to image the anterior segment (ultrasound biomicroscopy [UBM]), lower frequencies (10–20 MHz) to perform biometry and to image the entire globe.

Ultrasound travels more slowly in fluid and faster in solid material. Velocities in the eye are 1532 m/s in aqueous humor and vitreous and 1641 m/s in the cornea and lens.[9] In silicone oil, sometimes used to fill the vitreous cavity after a vitrectomy, ultrasound has a reduced velocity (980–1040 m/s). Ultrasound is absorbed by any medium it travels through. Denser media absorb more ultrasound, resulting in weaker echoes behind them. It is also reflected by any medium and an echo is generated. Based on the ability to generate an ultrasound echo, the normal cornea is isoechoic to the skin of the eyelids, the fluid-filled anterior chamber is anechoic, iris and ciliary body are isoechoic to the lens, the vitreous is anechoic, and the retina has a relatively strong echo. The optic nerve is a hypoechoic band between the relatively strong echoes of the retina and the choroid anteriorly and the orbital fat posteriorly. Calcium is highly echogenic and casts a dark shadow behind it (posterior extinction).

The ultrasound probe emits sound waves, registers the echoes, and converts them into an electric signal. In an A-scan, a thin ultrasound beam is emitted; vertical spikes on the screen represent the recorded echoes. The height of these spikes corresponds to the strength of the echo (Fig. 10.4). By means of an oscillating beam, A-scans can be combined to form B-scans to image a slice of tissue (Fig. 10.5). Here, reflectivity values are represented by dots of different brightness; stronger echoes generate brighter dots. For both A- and B-scans, the angle of incidence (angle at which the sound beam hits structures) is crucial: the more perpendicular the probe is positioned relative

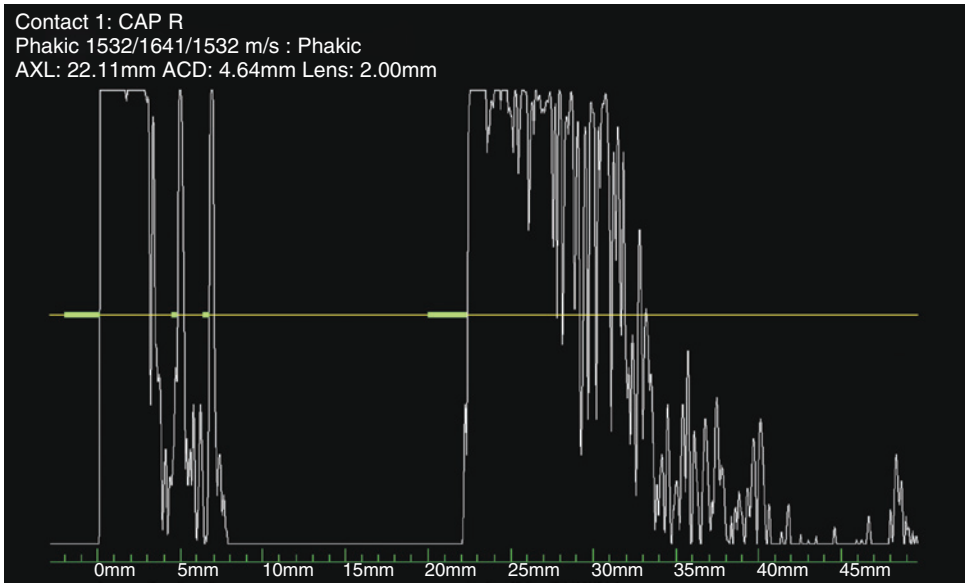


Fig. 10.4 A-scan ultrasound image of the normal eye of a child. This scan was obtained using the contact method, where the ultrasound probe gently touches the anesthetized cornea. From left to right, the first spike represents the cornea, followed by the less echogenic anterior chamber. The two following spikes are the anterior and posterior surface of the lens, followed by the low echo of the vitreous cavity. The steep retinal spike is followed by a gradual decline of the echo, representing the choroid, sclera, and orbital tissues.

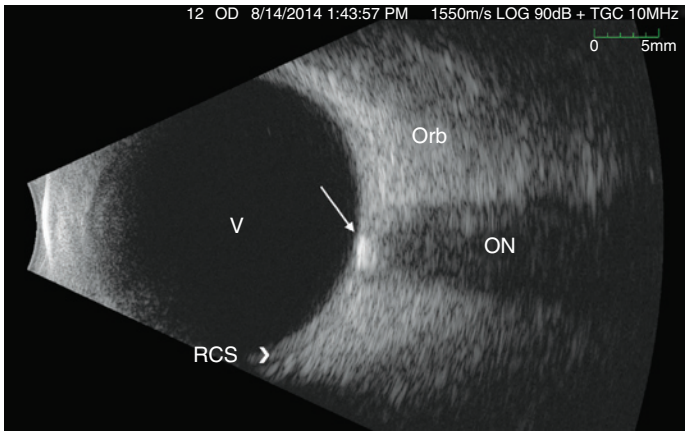


Fig. 10.5 Ocular B-scan ultrasound image of the right eye of a 12-year-old child. Cornea, lens, and iris are not imaged because the scan was obtained through the closed eyelid. The vitreous (V) is clear. Retina, choroid, and sclera (RCS) can be distinguished from the orbital tissue. The optic nerve (ON) is hypoechogenic relative to the orbital tissue (Orb). In this otherwise normal B-scan, a bright (highly echogenic) structure can be seen at the level of the optic disc (arrow) – an optic disc druse.

to the structure of interest, the more the echo is reflected to the probe and the clearer the image becomes. On an A-scan, this is seen as steeply rising spikes (e.g. lens, retina); on a B-scan this results in brighter dots and higher contrast.

Anterior segment ultrasound (ultrasound biomicroscopy)

Various developmental and genetic disorders can cause anterior segment pathology in children (e.g. Peters anomaly and sclerocornea) and need to be identified to select the most appropriate therapeutic approach.[10]

Iris cysts are usually seen on biomicroscopy, but UBM can help distinguish them from solid masses. Ciliary body cysts are usually asymptomatic but they may displace the iris anteriorly and can cause glaucoma. On UBM, they appear as round-walled structures with anechoic interior within the ciliary body.

Posterior segment ultrasound

Posterior segment ultrasonography is important when direct ophthalmoscopic visualization is not possible (opaque media, small pupils). When ruling out intraocular foreign bodies in ocular trauma, ultrasound has the advantage of not using a magnet such as magnetic resonance imaging (MRI). MRI is contraindicated when a metallic foreign body is suspected, because it can dislocate the foreign body and cause more extensive injury.

Ultrasound findings in selected ocular disorders

In eyes with persistent fetal vasculature (PFV), ultrasonography may visualize involvement of the retina. Spectral Doppler ultrasonography can demonstrate blood flow in a persistent hyaloid artery. In Coats disease, exudative retinal detachment may develop and the primary role of the ultrasound is to exclude a tumor in these eyes.

Retinoblastoma is the most common intraocular tumor in children. With ultrasonography, retinoblastoma lesions appear as irregular solid masses with heterogeneous internal reflectivity.[8,11] Calcification is present in 90% of the lesions,[8] and may be more easily detected on ultrasound than on computed tomography (CT).[12]

In retinal detachment (RD), the retina is seen as a curvilinear structure with high reflectivity, which may extend to the optic disc posteriorly and the ora serrata anteriorly. The points of attachment distinguish a RD from a choroidal detachment (biconvex echogenicity not extending to the optic disc) and from vitreous membranes.

In papilledema, the optic nerve sheath diameter (ONSD) may increase. ONSD is measured 3 mm behind the globe. In infants up to 1 year of age, 4 mm is the normal upper limit; in older children, 4.5 mm; and in adults, 5.7 mm.[13,14]

Optic disc drusen may cause the optic disc to appear swollen. They tend to calcify and appear as hyperechoic bodies in the anterior part of the optic nerve (Fig. 10.5).[15] Scleral thickening can be seen in patients with mucopolysaccharidoses.

Orbital ultrasound

Anophthalmos means the absence of ocular tissue. Most often, however, a small cyst can be seen on ultrasound. The term

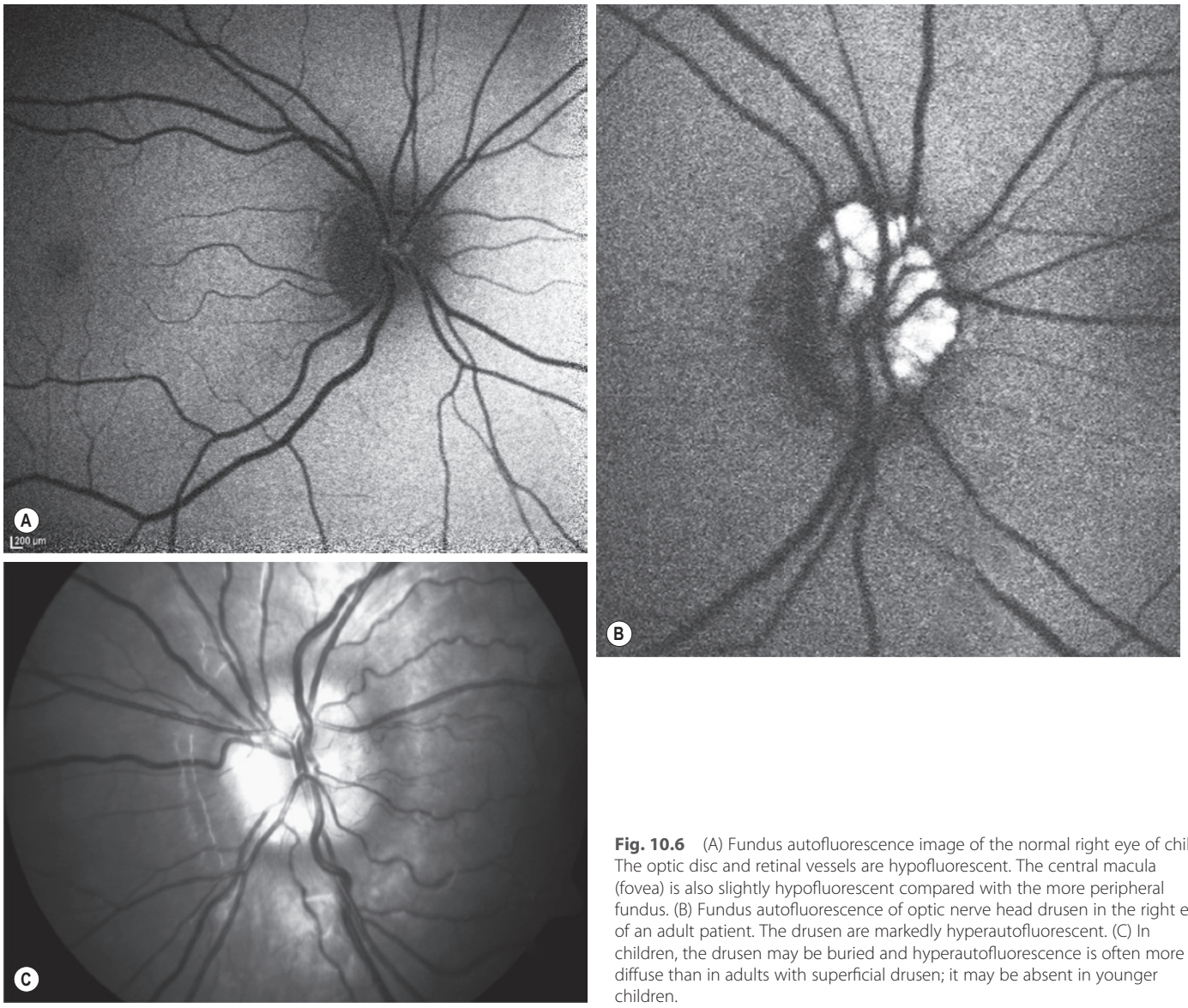


Fig. 10.6 (A) Fundus autofluorescence image of the normal right eye of child. The optic disc and retinal vessels are hypofluorescent. The central macula (fovea) is also slightly hypofluorescent compared with the more peripheral fundus. (B) Fundus autofluorescence of optic nerve head drusen in the right eye of an adult patient. The drusen are markedly hyperautofluorescent. (C) In children, the drusen may be buried and hyperautofluorescence is often more diffuse than in adults with superficial drusen; it may be absent in younger children.

microphthalmos is used when an eye is less than two-thirds of the age-appropriate size and is structurally abnormal. Nanophthalmos describes a small but normally developed eye. Ultrasound helps to make these distinctions. Nanophthalmos or microphthalmos may be present in a number of disorders including CHARGE, Goldenhar syndrome, clefting disorders, and others.[16]

Ultrasound pachymetry

Corneal thickness is increased in corneal edema, for example in congenital hereditary endothelial dystrophy (CHED) or childhood glaucoma. Corneal thickness may have an effect on intraocular pressure measurements, so it is important factor to consider when caring for patients with glaucoma.

Fundus autofluorescence

Normal retinal function depends on photoreceptor and RPE metabolism. RPE cells phagocytose photoreceptor outer segments and break down the ingested material.[17] Some of the breakdown products act as fluorophores: if they are excited by light of a certain wavelength, they emit light of a different wavelength – this is called "fundus autofluorescence" (FAF). Lipofuscin (LF) has been identified as a major source of FAF. A prominent component of LF is *N*-retinyl-*N*-retinylidene ethanolamine (A2E), which is likely toxic to RPE cells. Because LF accumulates in RPE cells, FAF primarily provides information about the state of RPE cells. In Box 10.1, pertinent disorders and their effects on FAF are listed. FAF may identify subtle pathologic findings not visible on funduscopy, for example in retinal dystrophies such as Leber congenital amaurosis and retinitis pigmentosa. In Stargardt disease, a central oval-shaped area of hypoautofluorescence is usually found in children. If pisciform retinal flecks are present, these may be centrally hyperautofluorescent, hyperautofluorescent with surrounding hypoautofluorescence, or hypoautofluorescent.[18,19] FAF is particularly helpful in detecting optic nerve head drusen, which appear as hyperautofluorescent bodies in the optic disc (see Fig. 10.6).

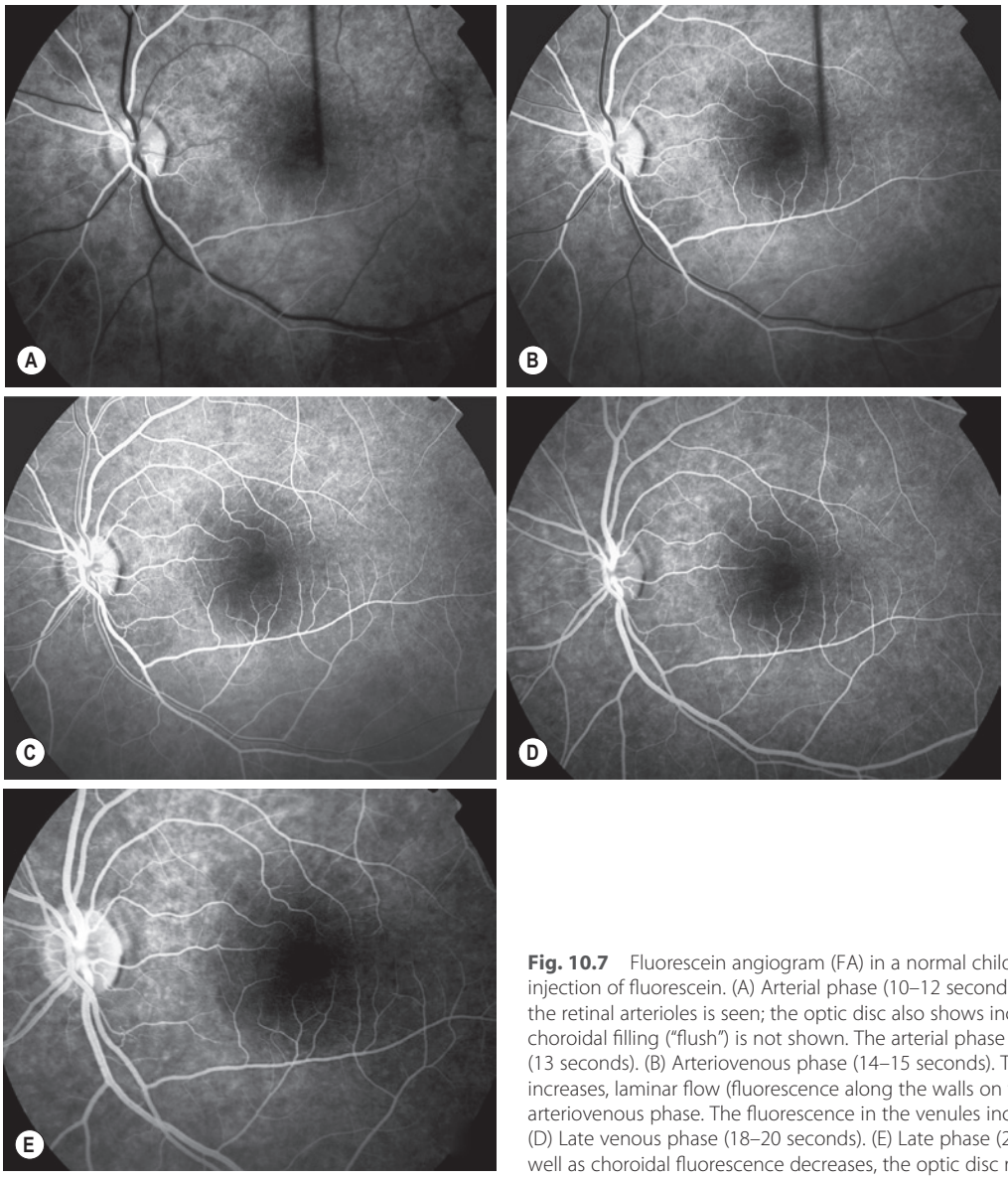


Fig. 10.7 Fluorescein angiogram (FA) in a normal child. Times refer to time point after intravenous injection of fluorescein. (A) Arterial phase (10–12 seconds). Choroidal fluorescence and fluorescence in the retinal arterioles is seen; the optic disc also shows increasing fluorescence. The preceding choroidal filling ("flush") is not shown. The arterial phase is followed by the capillary transition phase (13 seconds). (B) Arteriovenous phase (14–15 seconds). The choroidal and arterial fluorescence increases, laminar flow (fluorescence along the walls on the retinal venules) can be seen. (C) Later arteriovenous phase. The fluorescence in the venules increases, as does the choroidal fluorescence. (D) Late venous phase (18–20 seconds). (E) Late phase (2–5 minutes). Fluorescence in the vessels as well as choroidal fluorescence decreases, the optic disc retains fluorescence (normal staining).

Angiography

To perform angiography, a dye is injected intravenously. Light of a given wavelength (which is passed through a excitation filter) is projected onto the structure of interest (usually the ocular fundus). The light excites the dye, which gives off fluorescence of a different wavelength. The emitted fluorescence is filtered (barrier filter) and detected photographically. In ophthalmology, fluorescein angiography (FA) and indocyanine green angiography (ICG) are used clinically. Angiography is an invasive test with known side effects and risks. Although both FA and ICG are generally well tolerated, nausea and vomiting are observed in 5–10% of patients and allergic as well as anaphylactic reactions (potentially life-threatening) have been reported.

Fluorescein angiography

Fluorescein is a relatively small molecule (molar mass 332.31 g/mol), used to image the retinal circulation. It leaks from the fenestrated choroidal vessels, and is not optimal for angiography of the choroid. Since fluorescein is excreted through the kidneys, the urine will be yellow for several hours after intravenous application. Renal insufficiency or dialysis is not a contraindication to FA.[3] The excitation wavelength illuminating the retina is 465–490 nm (blue light). The barrier filter allows only yellow-green light (usual wavelength of 525 nm) from the fluorescence to reach the camera. After 10–20% fluorescein sodium is injected intravenously, the dye enters the eye through the internal carotid artery via the ophthalmic artery, which supplies the choroid through the short posterior ciliary arteries. The retina is supplied via the central retinal artery. Normal findings are shown in Figure 10.7. Pathological findings are divided into *hyper*fluorescence and *hypo*fluorescence. Causes for hyperfluorescence include (1) transmission or window defects (a layer that normally blocks fluorescence is missing), (2) leakage (e.g. from incompetent blood vessels, aneurysms, neovascularization), (3) pooling (fluorescein gradually fills a fluid-filled space), (4) staining (normally the optic disc and sclera stain;

Box 10.1

Important causes for abnormal fundus autofluorescence (FAF) signal in children and adolescents (modified from Schmitz-Valckenberg et al.[18])

Causes for reduced FAF signal

Absence/reduction in retinal pigment epithelium (RPE) lipofuscin density
Hereditary retinal dystrophies (e.g. *RPE65* mutations)
Increased RPE melanin content (e.g. RPE hypertrophy)
Absorption from extracellular material, cells, or fluid anterior to RPE
Intraretinal fluid (e.g. macular edema*)
Intraretinal and subretinal lipid
Fresh intraretinal and subretinal hemorrhages
Fibrosis, scar tissue, borders of laser scars
Retinal vessels
Angioid streaks
Macular pigment (lutein and zeaxanthin)
Media opacities (vitreous, lens, anterior chamber, cornea)

Causes for increased FAF signal

Excessive RPE lipofuscin accumulation
Lipofuscinopathies including Stargardt disease, Best disease, and adult vitelliform macular dystrophy
Occurrence of fluorophores anterior or posterior to the RPE cell monolayer
Intraretinal fluid (e.g. macular edema*)
Subretinal fluid leading to separation of the outer segments of the photoreceptors from the underlying RPE, which leads to improper outer segment turnover
Macrophages containing lipofuscin in the subretinal space (choroidal tumors such as nevi and melanomas)
Migrated RPE cells or macrophages containing lipofuscin or melanolipofuscin (seen as pigment clumping or hyperpigmentation by funduscopy)
Older intraretinal and subretinal hemorrhages
Choroidal vessel in the presence of RPE and choriocapillaris atrophy (e.g. in the center of laser scars or within patches of RPE atrophy)
Lack of absorbing material
Depletion of luteal pigment (e.g. in idiopathic macular telangiectasia type 2)
Displacement of luteal pigment (e.g. cystoid macular edema)
Optic nerve head drusen
Artifacts

*Some diabetic patients with macular edema can have either increased or decreased autofluorescence.

pathology such as disciform scars or drusen may stain), and (5) abnormal vasculature (e.g. neovascularization). Causes of hypofluorescence include blocking (e.g. blood, retinal or non-vascularized preretinal lesion) and filling defect (e.g. capillary non-perfusion, vascular obstruction).

In clinical practice FA is mainly used to study the ocular fundus. Rarely, iris angiograms are performed for anterior segment ischemia.

Indocyanine angiography

Indocyanine green (ICG, molecular weight 774.96 g/mol) does not leave intact choroidal vessels and is used to image the choroidal circulation. ICG absorbs light between 600–900 nm (peak spectral absorption approximately 800 nm) and emits fluorescence between 750–950 nm. The infrared light used for excitation penetrates the retina well, allowing imaging of deeper layers. Since ICG is excreted via the liver; liver failure is a contraindication to ICG angiography. In practice, ICG angiography is used in age-related macular degeneration (AMD) and other diseases affecting the choroid, such as choroidal tumors, choroidal neovascularization, and other vascular abnormalities.

Optical coherence tomography

Since optical coherence tomography (OCT) was introduced to clinical ophthalmology in 1991,[20] significant advances in technology have increased its resolution and decreased the test time of this noninvasive, non-contact imaging modality. OCT provides high-resolution cross-sectional images of tissues. It uses low-coherence interferometry to determine the time delay of backscattered light reflected by tissue.

Technology

The older time-domain (TD) OCT has an axial resolution of approximately 10 µm, a transverse resolution of 20–25 µm and a scan speed of approximately 400 A-scans per second. TD-OCT uses a moving reference mirror to encode the time information for a given reflection. The process of moving this mirror limits acquisition speed. A detailed review on TD-OCT findings in pediatric ophthalmology is available.[21] TD-OCT has largely been replaced by spectral-domain (SD) OCT, which was first used to image ocular structures in 2002.[22] SD-OCT acquires time delay and reflectivity information simultaneously. It evaluates the frequency spectrum of the interference between the reflected light and a stationary reference mirror,[23] allowing for faster scan acquisition. Current SD-OCT systems acquire 27,000–52,000 A-scans per second, have an axial resolution of 2.5–5 µm and a transverse resolution of 10–15 µm. The development of the human macula has been studied in detail and correlated with histology.[24]

An OCT can usually be obtained in unsedated children aged 4 years and up and sometimes even younger.[25] Reproducibility of the OCT of the RNFL and macula in children is good.[26] Thickness of retinal layers (e.g. RNFL thickness) may not be comparable between TD- and SD-OCT, and different SD-OCT machines may give different results.[27] It is advisable to use the same OCT machine for longitudinal follow-up of a patient.

Artifacts

Several types of image artifacts can affect the accuracy of OCT measurements. Using TD-OCT, one study found artifacts in 43.2% and erroneous retinal thickness measurements in up to 62.2% of all scans.[28] In a study on SD-OCT, 28.2% of macular scans and 19.9% of the RNFL contained artifacts.[29] The most common reason for artifacts is the presence of ocular pathology, especially epiretinal membranes. Because the OCT is an optical method, it depends on clear ocular media. In patients with an opaque cornea or lens, it may be impossible to image the structures posterior to the opacity. Contact lens wear does not seem to affect OCT measurements of the macula and RNFL using TD-OCT,[30,31] but studies

found small effects of contact lens power on RNFL thickness measurement (higher values with stronger minus lenses) using the SD-OCT.[32,33]

Macular analysis

Imaging the macula is one of the most important uses of OCT; it has revolutionized the clinician's ability to detect subtle pathology. Using SD-OCT, retinal sublayers can be discerned (Fig. 10.8).

Retinal thickness in the central 1 mm circle has been reported as 255–274 µm in healthy children irrespective of their gender.[34,35] Central retinal thickness in children also seems to increase with age.[35,36] There are many situations where a macular OCT is helpful, including macular edema (e.g. in children with uveitis or after cataract surgery) and in patients with retinal dystrophies. In children with congenital nystagmus, it may show foveal hypoplasia and help establish the diagnosis of albinism in subtle cases. In X-linked retinoschisis, it can show macular schisis cavities before they are noted with ophthalmoscopy.

Retinal nerve fiber layer

RNFL thickness may be reduced in optic atrophy, optic nerve hypoplasia, or glaucoma. It may be increased in acute optic neuritis, papilledema, and other types of optic neuropathy. Routine RNFL thickness programs offer automatic identification of the RNFL, which is highly reflective (Fig. 10.9). With SD-OCT (Heidelberg Spectralis SD-OCT, Heidelberg Engineering, Heidelberg, Germany), average global RNFL thickness in normal children has been found to be 106–107 µm,[34,35] but may be thinner when measured with different SD-OCT systems (Cirrus, Carl Zeiss Meditec, Dublin, CA).[27] The RNFL is thickest in the superior and inferior quadrants, thinner nasally, and thinnest temporally (Table 10.1). There is considerable inter-individual range in normal subjects, which makes clinical correlation and interpretation of OCT measurements necessary.

Anterior segment

Using anterior segment (AS) OCT, the cornea can be imaged and evaluated, its layers can be differentiated, and their thickness measured (Fig. 10.10). AS-OCT allows for non-contact biometry of the anterior segment and for evaluation of the anterior chamber angle (goniometry), where its findings correlate well with gonioscopy. AS-OCT is particularly helpful in evaluating the anterior chamber angles of children who do not tolerate

Table 10.1 Average retinal nerve fiber layer thickness in normal children (using the Spectralis OCT*) as reported in two studies

Sector	Yanni et al.[35]	Turk et al.[34]
Global	107.6 (1.2)	106.45±9.41 (83.33–141.17)
Temporal	76.5 (1.9)	74.31±9.45 (53–106)
Temporal superior	145.1 (2.2)	138.97±17.58 (104–191)
Temporal inferior	147.0 (2.1)	144.64±17.16 (110–183)
Nasal	84.5 (1.9)	71.54±10.03 (49–102)
Nasal superior	116.2 (2.8)	102.84±15.96 (78–145)
Nasal inferior	125.4 (3.0)	106.4±19.13 (78–162)

*Heidelberg Engineering, Heidelberg, Germany.
Values are in micrometers; for Yanni et al., mean (±standard error of the mean) is given; for Turk et al., mean (±standard deviation [range]) is given.

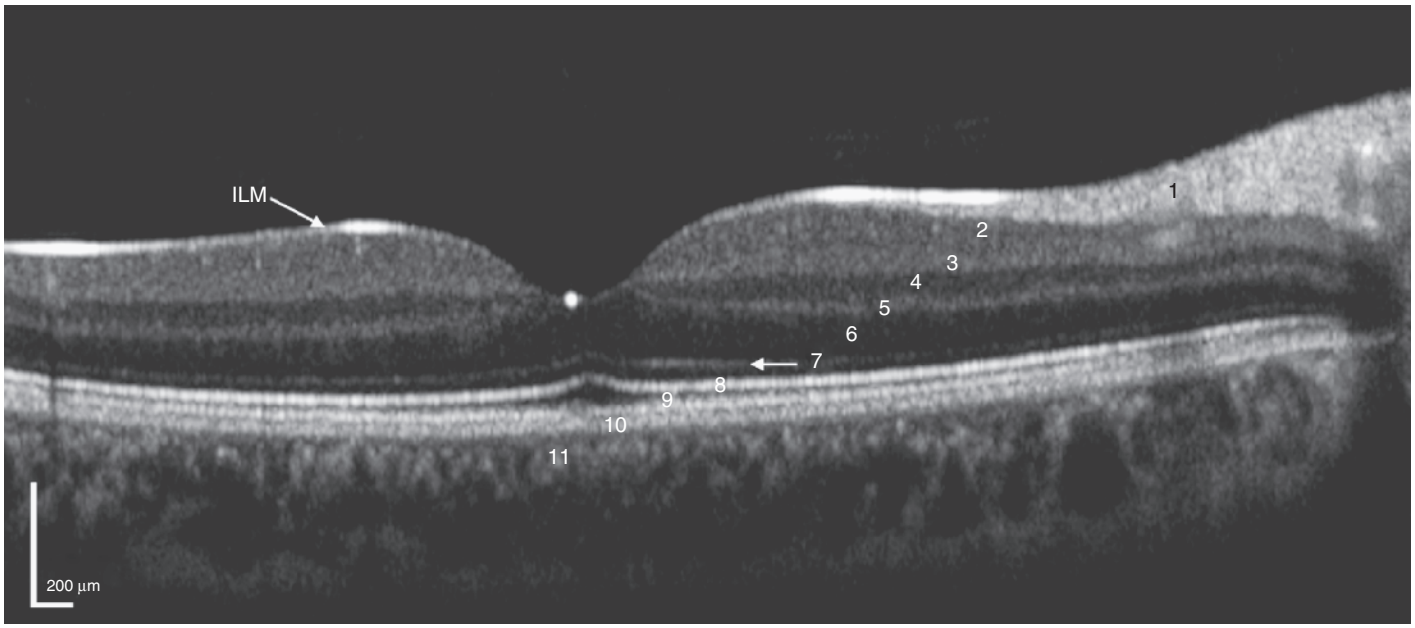


Fig. 10.8 Spectral-domain optical cohere tomography (SD-OCT) line scan through the macula of a 15-year-old boy. The optic nerve is on the right of the picture, where the retinal pigment epithelium (RPE) ends and the retinal nerve fiber layer is thickest. Retinal layers can be distinguished: ILM, internal limiting membrane; 1, retinal nerve fiber layer (high reflectivity); 2, ganglion cell layer (low reflectivity); 3, inner plexiform layer (medium reflectivity); 4, inner nuclear layer (low reflectivity); 5, outer plexiform layer and photoreceptor synapses (high reflectivity); 6, outer nuclear layer (low reflectivity); 7, external limiting membrane (thin band of higher reflectivity); 8, photoreceptor inner segment ellipsoids (high reflectivity); 9, photoreceptor outer segments (low reflectivity); 10, retinal pigment epithelium, consisting of two highly reflective bands; 11, choroid (heterogeneous reflectivity).

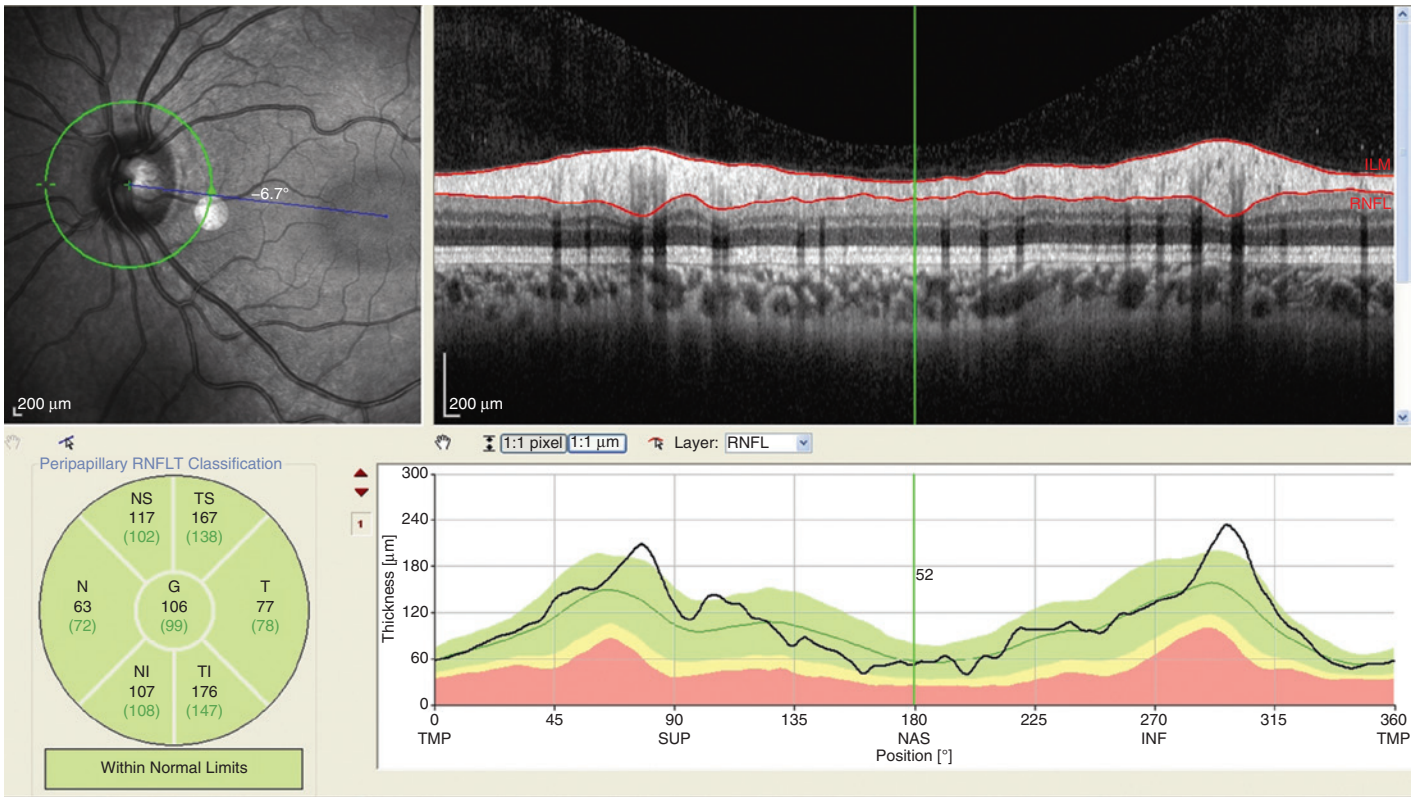


Fig. 10.9 Retinal nerve fiber layer (RNFL) thickness analysis using spectral-domain optical coherence tomography (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). In the upper left corner, location of the circular scan around the optic disc is shown. Below in the lower left, global RNFL thickness (central field) and RNFL thickness in different sector is given. A color scheme indicates whether or not the values fall into the normal range of the database of the OCT machine. In the upper right, the circular scan is shown and the RNFL segmentation is outlined in red. In the lower right, RNFL thickness is plotted against the normative database. Green indicates that the value measured has a probability greater than 5% of falling within the normal range; yellow indicates a probability of less than 5% of being normal; red that the probability is less than 1%.

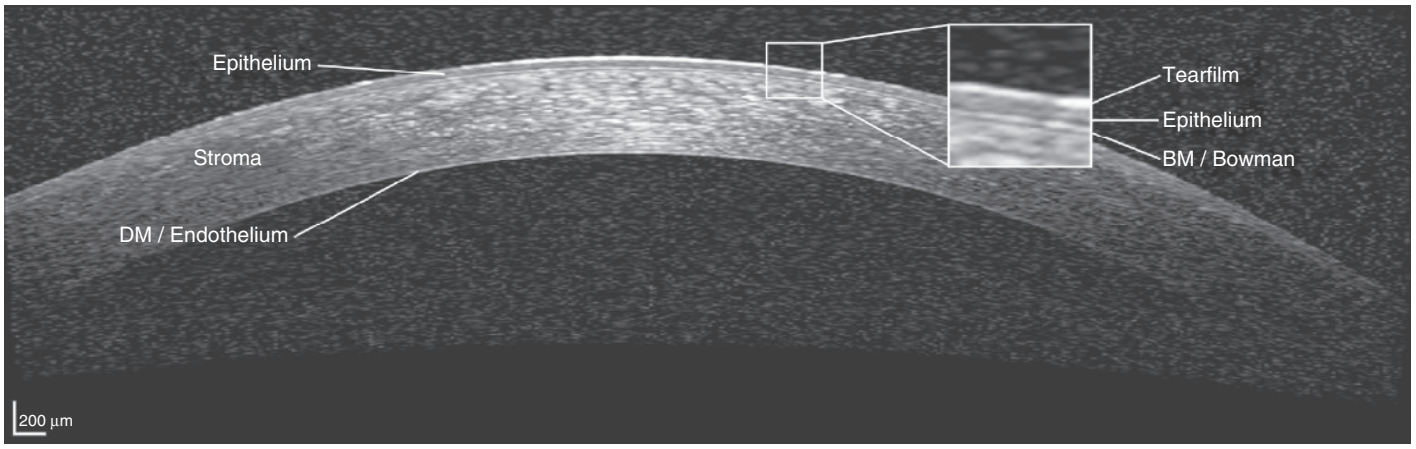


Fig. 10.10 Anterior segment optical coherence tomography of a normal cornea. The interface between air and corneal epithelium/tear film is highly reflective and appears bright. The corneal stroma has less homogenous reflectivity then the epithelium, because of its composition (cells, collagen fibers, extracellular matrix). The Descemet membrane (DM)–endothelium complex is more reflective than the stroma and generates a brighter band; the anterior chamber has practically no reflectivity. Inset, details of the anterior corneal layers can be appreciated (BM, basement membrane of the corneal epithelium; Bowman, Bowman's membrane).

gonioscopy.[37] Sensitivity and specificity of AS-OCT in detecting an occludable angle – identifying patients at risk for angle closure glaucoma – is high.[38] Iris configuration can be assessed, but pigmentation of the angle cannot be evaluated. Important anterior chamber angle parameters include (normal adult values in parentheses): anterior chamber angle (ACA nasal 44.9±9.1°, temporal 47.1±8.7°) and anterior chamber opening distance measured 500µm (AOD500) and 750µm (AOD750) from the scleral spur (AOD500 nasal 0.52±0.18 mm, temporal 0.53±0.15 mm; AOD750 nasal 0.71±0.26 mm, temporal 0.71±0.23 mm),[39] see Figure 10.11. Anterior chamber depth and iris thickness can also be measured.

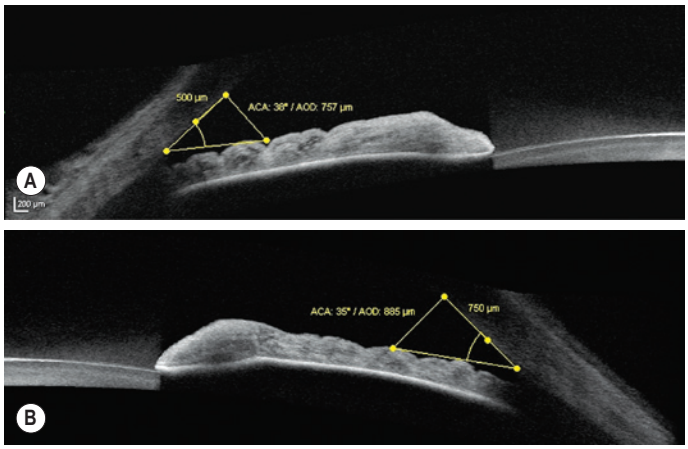


Fig. 10.11 Spectral-domain optical coherence tomography (SD-OCT) imaging of the normal anterior chamber angle, iris, and anterior lens surface. (A) Temporal angle; (B) nasal angle. Anterior chamber angle parameters can be measured, including anterior chamber angle (ACA), anterior chamber opening distance measured 500 µm central to the scleral spur (AOD 500, yellow overlay, upper part) and 750 µm central to the scleral spur (AOD 750, lower part). For these parameters, the distance between the posterior surface of the cornea and the anterior surface of the iris is measured at a right angle to the posterior corneal surface.

Extraocular muscle insertions can be identified and measured using OCT.[40] Although there is considerable variation between individuals, it may become a valuable tool in clinical ophthalmology (e.g. when evaluating a patient for a slipped muscle after strabismus surgery or for myositis).[41] In children, AS-OCT has been used for the following: to image the cornea of patients with Peters anomaly, after penetrating keratoplasty, to visualize tube placement after glaucoma drainage device implantation, to demonstrate closure of the anterior chamber angle, and in other clinical scenarios.[42] Grading inflammation in patients with uveitis is an interesting application and good correlation between clinical anterior chamber cells and OCT findings (bright spots in the normally dark anterior chamber) have been reported.[43,44]

OCT Angiography

Recently, OCT has been used to image retinal and superficial choroidal blood vessels. In contrast to conventional FA and ICG angiography, no dye is required. OCT angiography detects blood flow by using decorrelation of the signals of sequential OCT b-scans. In other words, several OCT scans taken at the same location are compared and the differences registered. Since intravascular blood cells (mainly erythrocytes but also leukocytes) are usually the only moving objects at the ocular fundus (provided the patient fixates steadily), blood flow can thus be registered. OCT angiography can detect blood flow only above a certain minimum threshold, because it relies on change between consecutive b-scans. This slowest detectable velocity is determined by the time lapse between two scans. Increasing this time may increase the sensitivity to detect slow blood flow but also increases motion artifacts.[45]

Most OCT angiography units have preset algorithms to facilitate identification of the retinal vessels. However, the examiner can manually choose the level and thickness of the plane to be examined, depending on the pathology (Fig. 10.12).

OCT angiography affords a higher resolution than FA and ICG angiography (it can image retinal capillaries), but it does not show extravascular blood (in contrast to FA, which can show leakage and staining). Furthermore, OCT angiography lacks the dynamic information which FA and ICG angiography can provide (such as arterio-venous transit time or delayed filling) and does not give information about the characteristics of blood flow in retinal and choroidal vessels.

Nevertheless, it has been shown to add valuable information in disorders such as age-related macular degeneration, choroidal neovascularization, and retinal vascular occlusion.[45] OCT angiography may prove helpful in evaluating children with disorders such as ROP, familial exudative vitreoretinopathy (FEVR), and Coats disease.

Scanning laser ophthalmoscopy

The SLO is a non-contact, noninvasive modality. It uses monochromatic, low-energy laser light for illumination and a confocal scanning laser microscopy technique to image the ocular fundus or cornea. Lasers with different wavelengths (and different tissue penetration) may be combined – the resulting image is a pseudo-color image of the fundus. SLO allows for FA and ICG angiography.

Infrared imaging is helpful when studying subretinal pathology such as drusen or deposits using the SLO. Infrared light penetrates optical media opacities (e.g. cataract, vitreous hemorrhage) better than shorter wavelengths (Fig. 10.13). Infrared reflectance may image epiretinal membranes and cystoid macular edema better than other photographic techniques. Retinal crystals (e.g. in Bietti crystalline retinopathy, metabolic and toxic crystalline retinopathy) are seen as bright dots throughout the fundus.

SLO is also used to image the optic disc (Fig. 10.12). The SLO does not distinguish different retinal layers and does not measure RNFL thickness directly. By longitudinally comparing the images of the same optic disc, changes in its contour and loss of neuroretinal rim can be detected. Normal optic disc values in children have been reported (Table 10.2).[46] Some SLO machines offer real-time eye tracking, so that different images can be superimposed and averaged, improving measurement accuracy. In the case of SLO-based FA, this results in the need for less intravenous dye.

SLO technology can be used to obtain wide-field (up to 200 degrees) fundus pictures. For example, the current Optos camera (Optos plc, Dunfermline, UK) utilizes an ellipsoid mirror eliminating the need for bright illumination lighting or a contact lens. Two lasers (red, 635 nm and green, 523 nm) scan the fundus in 0.4 seconds and these scans may be combined to generate a composite color fundus image with a resolution of up to 14 µm (Fig. 10.14). Red-free and fundus autofluorescence imaging, as well as fluorescein and indocyanine angiography are possible (for angiography, additional laser wavelengths are required). Mydriasis facilitates imaging but is not necessary.

In adaptive optics SLO (AOSLO), the SLO is used in conjunction with adaptive optics to remove optical aberrations from the images. This technique allows for the visualization of individual retinal cells *in vivo*.

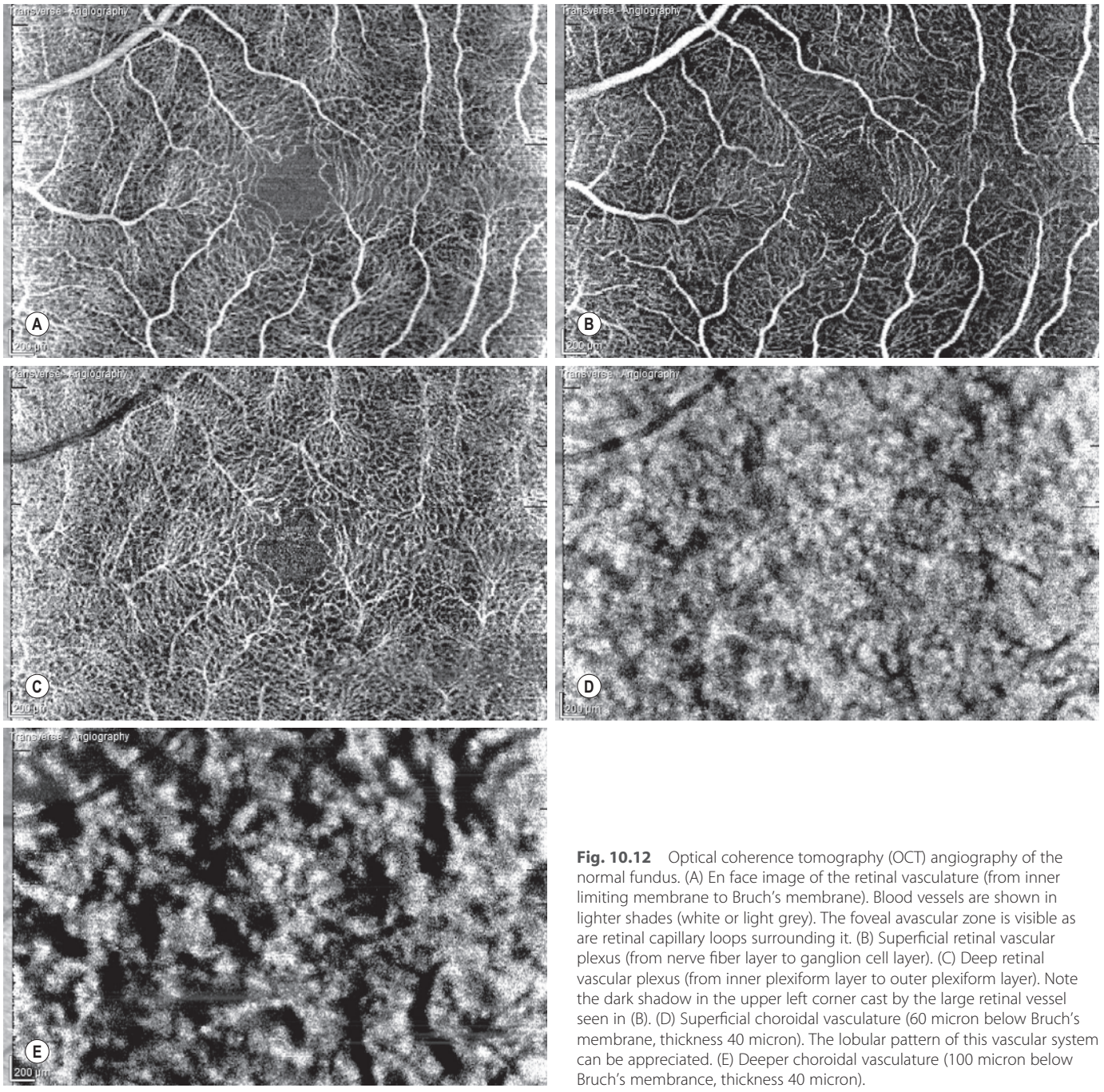


Fig. 10.12 Optical coherence tomography (OCT) angiography of the normal fundus. (A) En face image of the retinal vasculature (from inner limiting membrane to Bruch's membrane). Blood vessels are shown in lighter shades (white or light grey). The foveal avascular zone is visible as are retinal capillary loops surrounding it. (B) Superficial retinal vascular plexus (from nerve fiber layer to ganglion cell layer). (C) Deep retinal vascular plexus (from inner plexiform layer to outer plexiform layer). Note the dark shadow in the upper left corner cast by the large retinal vessel seen in (B). (D) Superficial choroidal vasculature (60 micron below Bruch's membrane, thickness 40 micron). The lobular pattern of this vascular system can be appreciated. (E) Deeper choroidal vasculature (100 micron below Bruch's membrance, thickness 40 micron).

Radiology imaging in pediatric ophthalmology

The following radiology imaging modalities can be used for the evaluation of orbital contents, the intracranial optic pathway, and the visual cortex in children: CT, conventional MRI, advanced MRI techniques such as fetal MRI, diffusion tensor imaging, and functional MRI. There is essentially no diagnostic role for plain film imaging of the orbit currently, because of superior sensitivity and specificity of cross-sectional imaging modalities.[1]

Computed tomography

Many pediatric specialists avoid CT imaging in children due to radiation exposure concerns. Generally, children are at higher risk for radiation-induced morbidities due to higher mitotic rates in growing tissues and a longer lifespan to experience these morbidities. However, the risk is strongly dependent on the imaging technique used by the local radiology practice, the frequency of radiation exposure, and the imaged body part. For example, radiology practices should have dedicated pediatric CT protocols and use radiation-reduction techniques, such as iterative reconstruction algorithms. Patients undergoing

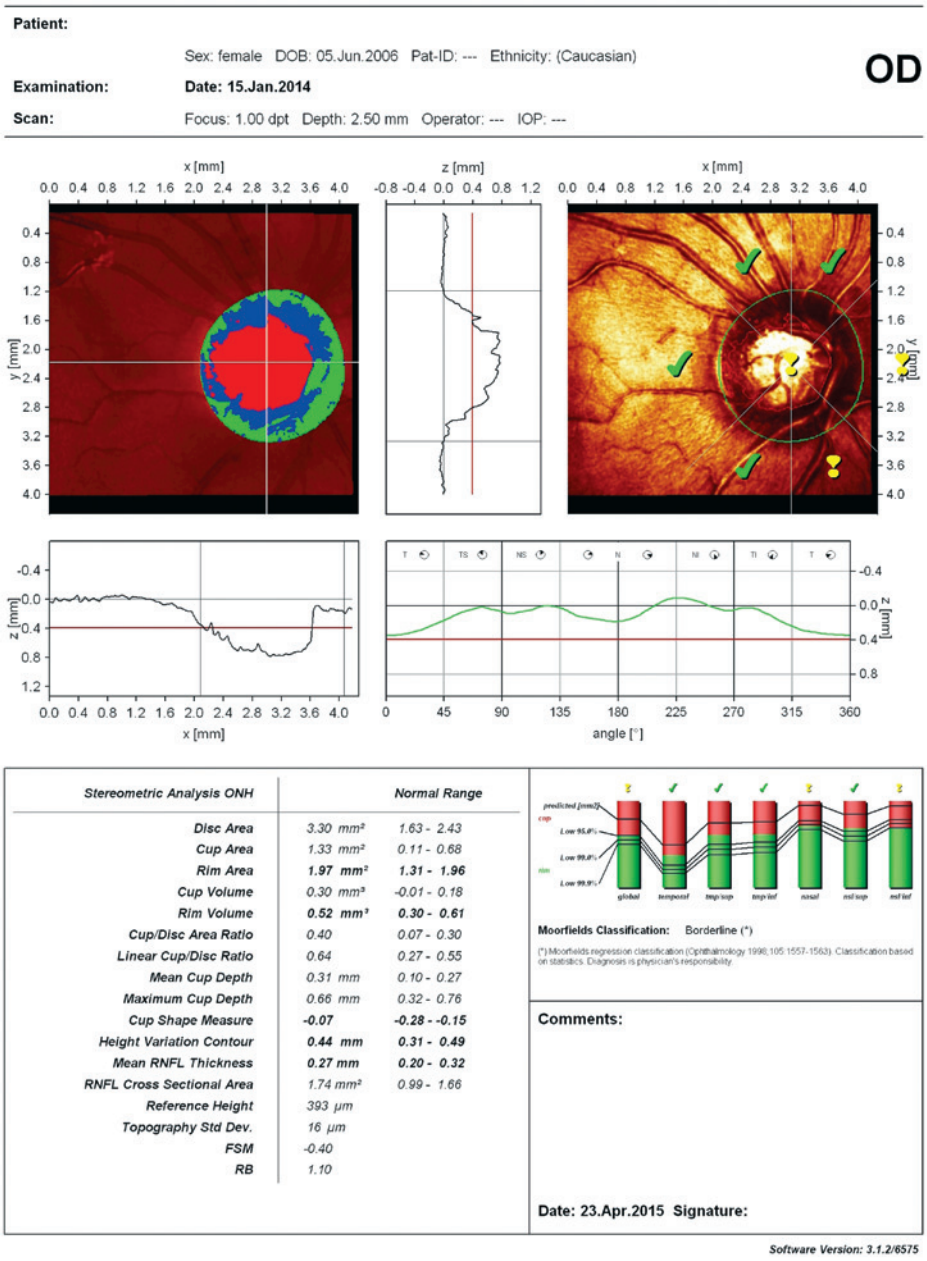


Fig. 10.13 Scanning laser ophthalmoscopy analysis of the optic disc with Heidelberg Retina Tomography.* The upper section contains demographic patient data. Below left, a false color image of the optic disc topography is shown. Green areas represent "stable" neural rim, blue sloping of the neuroretinal rim, red the optic disc cup. Next to it is the vertical height profile (white line in the topography image on the left). On the right, a false color reflection image is shown, the brighter the color, the more light is reflected. Six disc sectors are compared with the normative database and classified using the Moorfields regression analysis. According to the patient's age and optic disc size, findings are classified as "within normal limits" (green check marks), "borderline" (yellow exclamation marks), and "outside normal limits" (red crosses – not shown). The horizontal height profile along the white line in the topography image is shown in the section below on the left. Next to it, the "mean height contour graph" shows the retinal surface height along the drawn green contour line. The lower red line represents the reference line separating the neuroretinal rim and the optic cup, defined as a plane 50 µm below the papillomacular bundle (in the temporal sector between 350° and 356°). The black line represents the mean peripapillary retinal surface height, which serves as the zero point of the height (*z*-axis). The height profile starts temporally at 0° and proceeds clockwise for right eyes and counterclockwise for left eyes. The difference between the height profile line and the reference line corresponds to the retinal nerve fiber layer thickness along the contour line. In the box at the bottom, optic disc parameters are provided, values outside the normal range for the reference database are highlighted in bold. *Cup shape measure* describes the three-dimensional shape of the optic cup, determined as the distribution frequency of depth values within the optic cup. More positive values indicate a more abnormal (glaucomatous) cup shape. *Height variation contour* represents the difference between most elevated and most depressed point along the contour line. It is decreased in diffuse nerve fiber loss and increased if a localized nerve fiber layer defect is present. *Mean RNFL Thickness* is measured along the contour line relative to a reference plane and not directly, which applies also to *RNFL cross sectional area*. A parameter for image quality is *topography std dev*. in micrometer, values <10 are considered excellent; 10–20, very good; 20–30, good; 30–40, acceptable; 40–50 indicates that the study needs improvement; >50 low quality (scan should not be used). *FSM* (discriminant function) is a linear combination of three parameters (cup shape measure, rim volume, and contour line height variation). Positive values are normal, negative values classify the disc as glaucomatous. *RB* (discriminant function) is a linear function, which has a high specificity but poor sensitivity for the detection of early glaucoma; values less than zero suggest glaucomatous damage. **Heidelberg Engineering, Heidelberg, Germany – according to information provided on the manufacturer's website at heidelbergengnieering.com, accessed May 2015.*

Table 10.2 Average optic disc parameters measured with the Heidelberg Retina Tomography (HRT)* in normal children 5–16 years old[46]

Parameter	Mean (standard deviation)	Range
Disc area (mm^2)	2.16 (0.47)	1.15–3.09
Cup area (mm^2)	0.41 (0.33)	0.00–1.37
Rim area (mm^2)	1.75 (0.39)	0.92–2.59
Cup/disc area ratio	0.18 (0.12)	0.00–0.49
Rim/disc area ratio	0.82 (0.12)	0.51–1.00
Cup volume (mm^3)	0.09 (0.12)	0.00–0.58
Rim volume (mm^3)	0.41 (0.17)	0.12–1.01
Mean cup depth (mm)	0.16 (0.08)	0.04–0.41
Maximum cup depth (mm)	0.49 (0.21)	0.10–0.88
Height variation (mm)	0.32 (0.09)	0.17–0.56
Cup shape measure (mm)	–0.24 (0.08)	–0.43 to 0
Mean RNFL thickness (mm)	0.21 (0.05)	0.13–0.34

*Heidelberg Engineering, Heidelberg, Germany.
RNFL, Retinal nerve fiber layer.
"Cup shape measure" describes the overall three-dimensional shape of the optic cup, determined as the distribution frequency of depths values within optic cup. More positive values indicate a more abnormal (glaucomatous) cup shape.

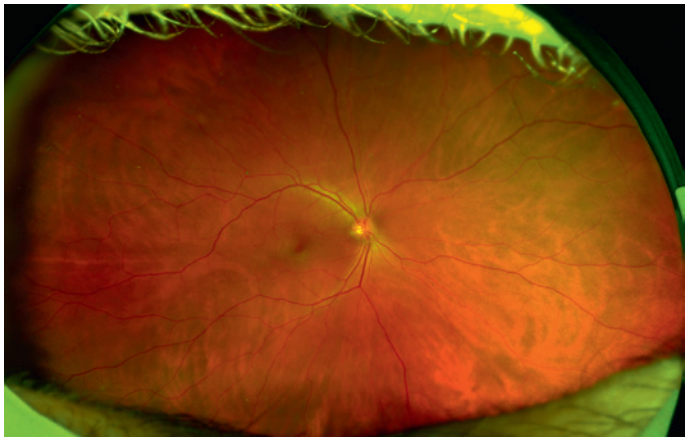


Fig. 10.14 Wide-field imaging of the normal ocular fundus obtained with Optos Daytona scanning laser ophthalmoscope through the undilated pupil (Optos plc, Dunfermline, UK). Composite color image of the green and red laser images is shown.

repeat CT imaging, such as children with chronic diseases, are at higher risk than a patient who undergoes a single CT study in a lifetime. Radiation exposure of the orbit can affect the highly radiosensitive lens, leading to cataracts (based on atomic bomb survivor studies after single brief exposure).[2] Physicians need to weigh risks against benefits when ordering CT orbit and brain studies in children. Benefits of CT imaging in general include the ubiquitous availability, fast access, and fast image acquisition obviating the need for sedation most of the time.

Non-contrast CT is useful in the evaluation of orbital trauma and associated complications and is sufficient in the evaluation of thyroid ophthalmopathy. Dermoid cysts can be evaluated with non-contrast CT. Contrast-enhanced CT is the imaging modality of choice for orbital infections. CT imaging is of little use in the evaluation of the intracranial visual pathway.

Conventional magnetic resonance imaging

Many pediatric specialists prefer MRI over CT to avoid radiation exposure in children. Disadvantages of MRI are limited availability, delayed access, and long study acquisition times requiring sedation in most children under the age of 8 years.

MR imaging is the modality of choice for evaluation of the intracranial visual pathway and the visual cortex. It is also superior to CT in the evaluation of orbital masses. Frequently, MRI of the orbits is performed in conjunction with MRI of the brain, for example in multiple sclerosis or orbital masses. A state-of-the-art MRI study of the orbits should be performed pre- and postcontrast, and should include both orbits in axial and coronal planes, the cavernous sinus, and the brainstem to the level of cranial nerve VI nuclei. Dedicated oblique imaging along the long axis of the intraorbital optic nerve may be acquired for specific clinical questions. Standard whole brain MRI images should include diffusion-weighted imaging (DWI), fluid-attenuated inversion recovery (FLAIR), T2, and pre- and postocontrast T1 images. Generally, non-contrast MRI is sufficient for detection of structural abnormalities or post-traumatic changes, while if there is a concern for infection, inflammatory disease, or neoplastic processes the scan should be performed with the use of intravenous contrast. The use of MRI may be limited in patients who cannot be safely screened, such as patients with certain pacemakers or other metallic implants. The safe use of MRI contrast (Gadolinium) depends on kidney function and other safety considerations, such as pregnancy and lactation status. National screening and safety guidelines should be applied when using these techniques.

Advanced magnetic resonance imaging

Fetal MRI structural assessment of the orbit is an integral part of the fetal imaging evaluation. The assessment includes identification of the lenses and the vitreous, shape of the globe, and various biometrics, such as binocular diameter, interocular distance, ocular diameter, lens diameter, and anteroposterior diameter. These assessments may help in identifying hypo- and hypertelorism, anophthalmia, and coloboma, which can aid in the diagnosis of various genetic disorders.[47]

Diffusion tensor imaging (DTI) infers directions of axonal tracts based on directional diffusion properties of water in the brain. This technique has been used to identify the location of the intracranial optic nerves in children with suprasellar masses and may be helpful in making decisions regarding surgical approach.[48] In children with optic pathway gliomas (OPG), DTI can provide additional information about the integrity of the entire optic pathway and may in the future help differentiate indolent from progressive OPG.[49]

Functional blood-oxygen level dependent (BOLD) MRI is used to detect cortical responses to visual stimuli based on local changes in cortical perfusion that cause differences in the ratio of oxygenated to deoxygenated blood. This technique

has been used in so-called retinotopic mapping,[6] where visual stimuli are presented to different portions of the visual field, generating a map of the visual field on the visual cortex using BOLD-fMRI.

Functional connectivity imaging is fMRI in the absence of external stimuli and can be used to detect resting state activities of the brain and brainstem. This requires advanced MR imaging capability, as well as advanced image postprocessing. The technique explores temporal relationships by selecting specific anatomical regions and searching for distant regions that show activation or deactivation at the exact same point in time, implying the two anatomical regions are related through excitation or depression of stimuli. Recently, the technique has been applied to brainstem nuclei,[50] which could yield future useful insights into eye movement disorders.

Cross-sectional imaging of the orbit

Trauma Non-contrast CT is considered the gold standard in the evaluation of orbital trauma and is superior to MRI in the depiction of fractures and orbital foreign bodies. In fact, the possible presence of metallic foreign bodies in the orbit is considered a contraindication to MRI because when exposed to the magnetic field they could damage adjacent structures through movement and/or heating (Fig. 10.15). CT and MRI can both be used to evaluate traumatic muscle and fat herniations, muscle deformities, hematomas, and orbital fat edema/hematoma (Fig. 10.16). However, optic nerve injury is not well seen on CT and is better evaluated with ophthalmology exam or MRI (Fig. 10.17).

Infection Contrast-enhanced CT is the imaging modality of choice for any infectious process, most commonly used to detect paranasal sinusitis with orbital involvement (Fig. 10.18) and to assess for postseptal involvement in children with orbital cellulitis. MRI of the orbits and brain is preferred in patients with intracranial involvement, such as empyema (Fig. 10.19), encephalitis, and venous sinus thrombosis.

Inflammatory conditions Pediatric *optic neuritis* is frequently immune-mediated in the setting of viral or other infections or after immunizations. However, a small percentage of children may have multiple sclerosis, neuromyelitis optica (NMO), or chronic relapsing inflammatory optic neuropathy (CRION). The imaging work-up should include contrast-enhanced MRI of the orbits and brain to exclude any compressive lesions. The MRI appearance of acute optic neuritis is characterized by increased T2 signal, swelling, and contrast enhancement of the



Fig. 10.15 Axial non-contrast orbit computed tomography. A 13-year-old boy with BB projectile (arrow) within the left vitreous. This represents a contraindication to a magnetic resonance imaging study because the BB could move when exposed to a magnetic field and cause additional injuries.

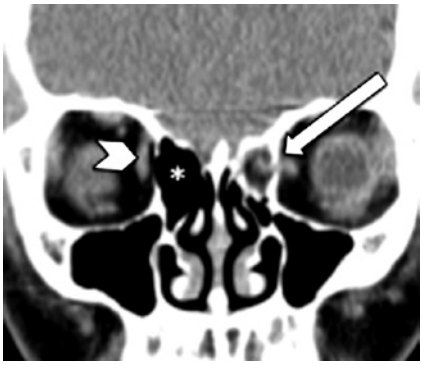


Fig. 10.16 Coronal reformats, axial non-contrast orbit computed tomography. An 8-year-old girl with left lamina papyracea fracture (arrow). Note the entrapment of the left medial rectus muscle and herniation of fat into the left ethmoid air cells when compared to the normal right medial rectus muscle (arrowhead) and normal air within the right ethmoid cells (asterisk).

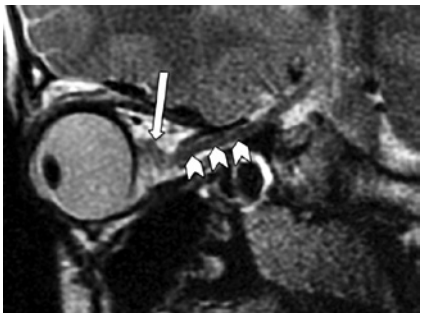


Fig. 10.17 Oblique sagittal T2 magnetic resonance imaging through the left optic nerve. A 16-year-old girl with orbit trauma caused by a motor vehicle collision. The image shows increased T2 signal and abnormal tortuosity of the proximal optic nerve (long arrow), compatible with contusion or rupture. Note normal optic nerve at the apex and within the optic canal (arrowheads).

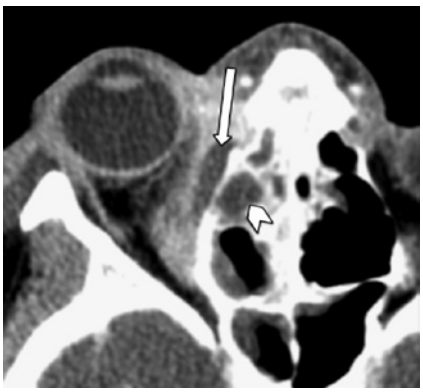


Fig. 10.18 Axial postcontrast orbit computed tomography. A 9-year-old girl with ethmoid sinusitis and orbital involvement. There is a peripherally enhancing subperiostial collection over the right lamina papyracea (arrow), compatible with subperiostial abscess. This collection caused mass effect on the orbit that resulted in proptosis and pain. There is peripherally enhancing fluid in an adjacent ethmoid air cell, compatible with sinusitis (arrowhead).



Fig. 10.19 Axial postcontrast orbit computed tomography (CT). An 8-year-old boy with frontal sinusitis and intracranial involvement. Clinically, the patient has sinusitis and headaches. There is complete opacification of the frontal sinuses (only partially shown, arrowhead). There are multiple extra-axial fluid collections over the left frontal and temporal lobes (arrows), compatible with empyema. Magnetic resonance (MR) imaging is usually required preoperatively and also can depict associated encephalitis better than CT. Both CT and MR venogram can help in detection of associated venous sinus thrombosis.

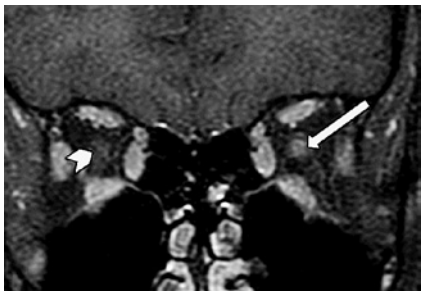


Fig. 10.20 Coronal postcontrast T1 magnetic resonance imaging (with fat suppression) through the optic nerves. An 8-year-old girl with a first episode of left optic neuritis. There is increased size and contrast enhancement of the left optic nerve (arrow) compared to the normal right optic nerve (arrowhead), consistent with optic neuritis.

affected optic nerve (Fig. 10.20). Chronic optic neuritis usually results in T2 bright signal and volume loss of the affected optic nerve; contrast enhancement may not be seen outside the acute flare. Detection of concomitant white matter lesions with brain MRI is associated with a higher risk of developing multiple sclerosis.

Thyroid orbitopathy results in edema of the extraocular muscles as well as the orbital fat. The increased volume of orbital contents causes proptosis and also inhibits venous drainage, which can result in eyelid swelling. In children, non-contrast MRI should be the imaging study of choice. Other inflammatory conditions of the orbit have been lumped under the term *orbital inflammatory disease* (OID) and comprise dacryoadenitis, myositis, cellulitis, optic perineuritis, periscleritis, orbital apicitis, and a focal inflammatory mass.[51] Rarely, OID may be diffuse. Imaging in OID is indicated to exclude other pathology, such as malignancies, infections, and post-traumatic changes. The best imaging modality for OID is contrast-enhanced orbital MRI due to its higher sensitivity in detection of inflammatory changes compared to CT. In the setting of orbital apicitis, the cavernous sinus should be included in the MRI to detect involvement (Tolosa–Hunt syndrome).

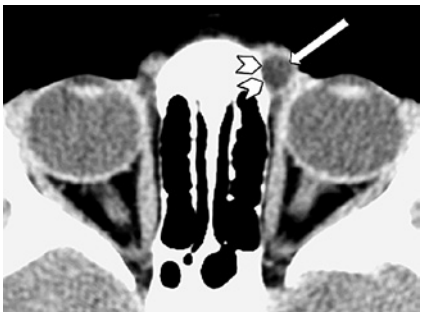


Fig. 10.21 Axial noncontrast orbit computed tomography. A 2-year-old girl with a firm, non-tender and non-discolored mass of the left medial canthus. There is a well-defined cystic lesion (arrow) with flattening of the underlying bone (arrowheads), consistent with a dermoid cyst. Bone flattening usually indicates slow growth and/or longstanding pressure.

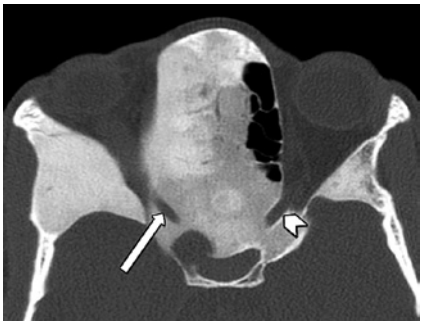


Fig. 10.22 Axial noncontrast orbit computed tomography. A 12-year-old boy with fibrous dysplasia with deterioration of right-sided visual acuity. The patient has groundglass thickening of bilateral temporal, ethmoid, and sphenoid bones, right worse than left. Note the narrowing of the right optic canal (arrow) compared to the less involved left optic canal (arrowhead).

Congenital lesions Non-contrast CT or MRI is usually sufficient to evaluate *dermoid and epidermoid cysts*, which are typically low-density lesions with a thin cyst wall, often related to bony sutures. They may cause some bone remodeling (Fig. 10.21) or may extend into the bone. A variety of *vascular lesions* may be found in the orbits and are best evaluated with contrast enhanced MRI: hemangiomas are typically well-defined, lobulated masses with bright T2 signal, vascular flow voids, and strong homogeneous contrast enhancement; venous malformations are characterized by non-enhancing cysts and presence of phleboliths; lymphatic malformations are macro- or microcystic, with fluid-fluid levels, cyst wall enhancement, and without calcifications. Evaluation of *fibrous dysplasia* is probably best accomplished with CT imaging to better assess mass effect on optic canal and superior orbital fissure (Fig. 10.22). Orbitotemporal plexiform neurofibromas may well be evaluated with contrast enhanced orbital MRI alone. The benefit of MRI evaluation of orbitotemporal plexiform neurofibromas is to better determine worsening over time in patients without significant vision loss and to assess the involved anatomical spaces prior to debulking surgery in patients with vision loss, which is usually caused by ptosis and/or anisometropia.[52]

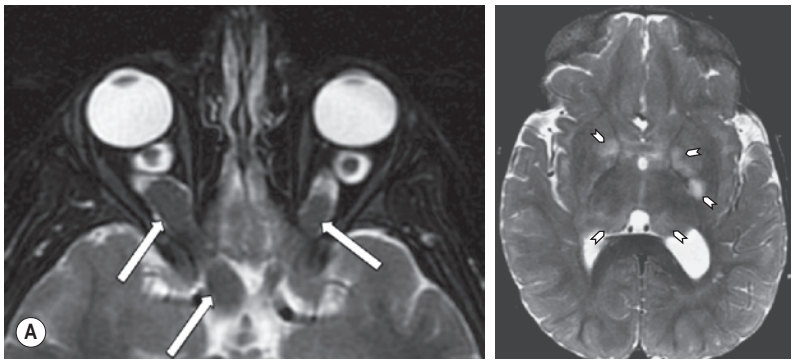


Fig. 10.23 (A) Axial T2 magnetic resonance imaging (MRI) (with fat suppression) through the optic nerves. (B) Axial T2 MRI (with fat suppression) of the brain. A 12-year-old girl with neurofibromatosis type I. (A) Bilateral soft tissue masses of the optic nerves, right larger than left (arrows), compatible with bilateral optic nerve glioma. (B) Numerous T2 bright lesions of the basal ganglia and thalami (arrowheads), consistent with neurofibromatosis type I.

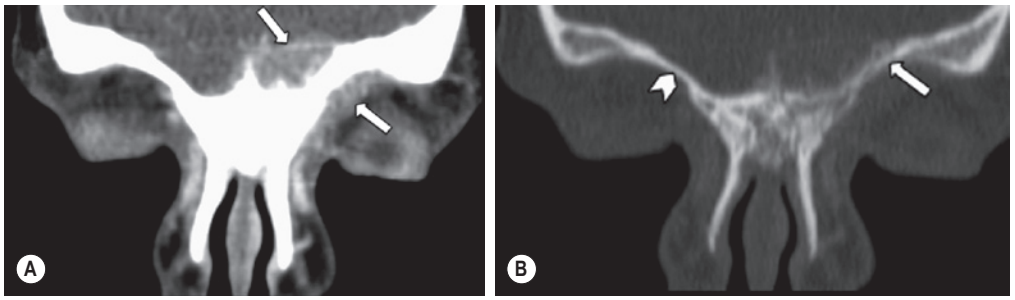


Fig. 10.24 Coronal reformats, axial noncontrast orbit computed tomography: (A) soft tissue window, (B) bone window. A 2-year-old girl with orbital ecchymoses, for evaluation of fracture or infectious process. (A) Soft tissue mass of the anterior skull base, extending both intracranially and into the orbit (arrows). (B) Note the spiculated appearance of the left orbital roof (arrow) when compared to the normal right side (arrowhead).

Cross-sectional imaging of orbit and brain

Orbital tumors Most orbital tumors should be evaluated with MRI and should include both imaging of the orbit and the brain, pre- and postcontrast. In patients with *optic glioma*, MRI is best suited to differentiate masses of the optic nerve from optic nerve sheath tumors, to evaluate for intracranial extension, and to assess for other brain pathology, such as T2 bright lesions that could indicate neurofibromatosis type 1, which can significantly affect prognosis and treatment (Fig. 10.23). In *retinoblastoma*, inclusion of brain imaging is important to detect intracranial involvement and possible trilateral disease affecting the pineal gland. The orbit can be a site for *rhabdomyosarcoma* and imaging of the brain should be included if there is associated bone destruction (parameningeal type). *Langerhans histiocytosis* primarily presents with lytic bone lesions, but it can also cause cerebellar lesions, lesions of the pituitary stalk and hypothalamus, as well as pineal lesions. In children with *leukemic retinopathy*, MRI imaging may be helpful in differentiating optic nerve infiltration from papilledema secondary to central nervous system leukemia.[53] *Metastatic neuroblastoma* is usually detected with CT imaging in children who present with eyelid ecchymosis ("raccoon eyes") and who are initially being evaluated for skull base trauma. Metastatic neuroblastoma typically presents with multiple bone lesions with a soft tissue component and a spiculated periosteal reaction (Fig. 10.24). Contrast-enhanced MRI brain/orbits is more sensitive than CT in further delineating intraorbital and intracranial mass effect of these lesions; rarely intraparenchymal metastatic neuroblastoma lesions may be found.

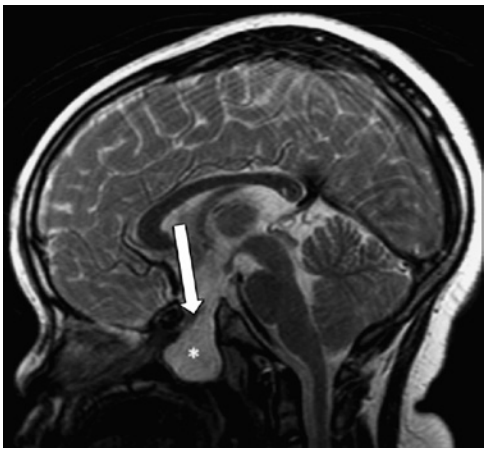


Fig. 10.25 Sagittal T2 magnetic resonance imaging (MRI) through the midline of the brain. An 18-month-old girl with unilateral morning glory and transsphenoidal encephalocele. Lack of chondrification of the intersphenoidal synchondrosis during fetal development results in persistence of the craniopharyngeal canal through which intracranial contents can herniate. Note the inferior displacement of the optic chiasm (arrow) and the extension of the mass into the nasopharynx (asterisk). The pituitary stalk and gland are not definitely seen.

Congenital malformations Malformed optic discs could indicate associated brain malformations and may benefit from non-contrast brain MRI. For example, morning glory disc anomaly may be seen in children with transsphenoidal encephaloceles (Fig. 10.25). Small (hypoplastic) optic nerves can be seen in the setting of septo-optic dysplasia (Fig. 10.26).

Multiple sclerosis While the majority of pediatric optic neuritis is unrelated to multiple sclerosis, it is important to screen

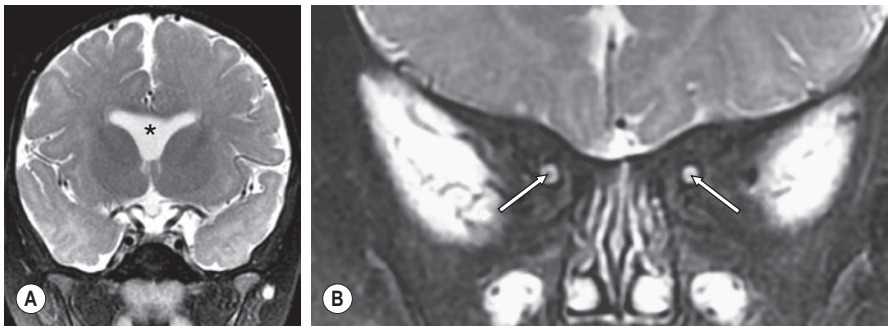


Fig. 10.26 (A) Coronal T2 magnetic resonance imaging (MRI) (with fat suppression) through the brain; (B) coronal T2 MRI (with fat suppression) of the optic nerves. A 6-month-old girl with septo-optic dysplasia. (A) Absence of the interventricular septum (septum pellucidum) (asterisk) and (B) hypoplasia of the optic nerves, left worse than right (arrows), these are typical features of septo-optic dysplasia.

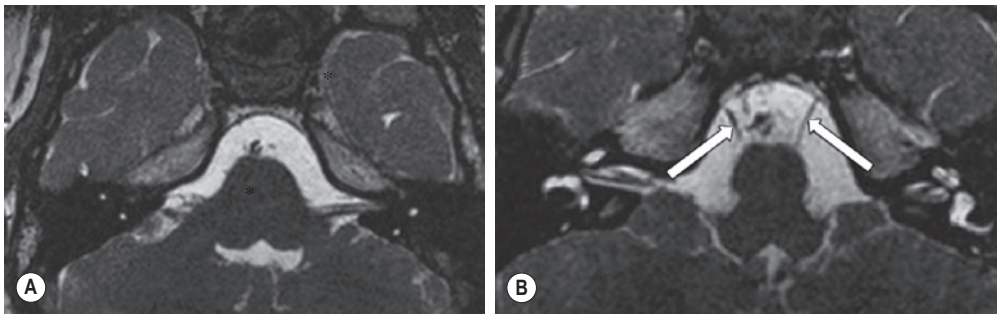


Fig. 10.27 Axial high-resolution T2 magnetic resonance imaging through the brainstem: (A) Duane syndrome, (B) normal anatomy. A 17-year-old boy with Duane syndrome. Note bilateral absence of cranial nerves VI in the prepontine cistern ([A]) compared to normal cranial VI nerves in an unaffected patient ([B], arrows).

children with recurrent optic neuritis for signs of multiple sclerosis or neuromyelitis optica, which requires contrast-enhanced MRI brain and spine imaging in search of enhancing and non-enhancing lesions.

Cranial nerve imaging Children with cranial nerve palsies are best evaluated with contrast-enhanced MRI of brain and orbits to detect/exclude etiologies such as stroke, intracranial masses, traumatic brain injury, infectious disease, or causes of increased intracranial pressure. High-resolution imaging studies of the cranial nerves can also help in confirming congenital abnormalities of cranial nerves, such as absence of the abducens nerve(s) in Duane syndrome (Fig. 10.27). Children may also experience ophthalmoplegic migraines and MRI can detect associated thickened enhancement at the oculomotor nerve root exit zone.[54] MRI angiography can be useful in detection of aneurysms that cause cranial nerve symptoms in patients with disorders that put them at risk for vasculopathy.

Horner syndrome imaging In children with Horner syndrome, the clinical exam may be difficult and may not be possible to determine whether the oculo-sympathetic pathway is affected at the central, preganglionic, or postganglionic level. Rarely, malignancies can account for pediatric Horner syndrome, most notably neuroblastoma. It may, therefore, be prudent to image the orbits, brain neck, and upper chest to the aortic arch, preferably with MRI to avoid radiation exposure.[55]

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Genetics and pediatric ophthalmology

Panagiotis I Sergouniotis and Graeme C M Black

Chapter contents

INTRODUCTION
GENETIC DISORDERS
VARIANTS AND MUTATIONS
GENETIC TESTING
GENETIC COUNSELING AND ETHICAL ISSUES
CONCLUSIONS
REFERENCES

Introduction

The modern era of genetic ophthalmology began in 1985 with the discovery of the retinoblastoma gene[1,2] (Fig. 11.1 sets out a timeline of historic discoveries). Exciting progress in deciphering the genetic bases of eye disease has been made since that time. Hundreds of genes associated with a wide variety of common and rare disorders have been discovered leading to clinically valuable diagnostic tests (e.g. for pediatric cataract[3]), meaningful disease classifications (e.g. for corneal dystrophies[4]), and novel therapeutic strategies (e.g. for retinal dystrophies[5,6]). This chapter focuses on genetics in pediatric ophthalmic practice; we discuss the different types of genetic disorders and modes of inheritance, and the principles of genetic testing and counseling.

Genetic disorders

Genetic conditions account for a third of childhood severe visual impairment/blindness worldwide, a figure that is likely to be an underestimate, especially in medium- and high-income countries.[7–9] Disorders referred to in this context are defined by their predominantly monogenic inheritance. This means that each is caused by a fault or *mutation* in a single gene, and that the detection of such mutations can predict the disease development with relatively high accuracy. Such monogenic or *Mendelian* disorders can be recognized by the characteristic pedigree patterns they give.

The human genome (i.e. the totality of one's DNA) is divided among 46 physically distinct chromosomes: 22 pairs of autosomes (non-sex chromosomes) plus two sex chromosomes (two X chromosomes in female, one X and one Y chromosome in male). Monogenic disorders can be associated with genes on autosomes (chromosomes 1–22) or on the X and Y chromosomes. Autosomal characters in both genders and X-linked characters in females can be dominant or recessive. This section will focus on the three main Mendelian pedigree patterns: autosomal dominant, autosomal recessive, and X-linked recessive (Fig. 11.2A–D). Mitochondrial inheritance, an atypical mode of inheritance that can be viewed as an expansion of Mendelian concepts, is also described (Fig. 11.2E). For a more detailed discussion of pedigree patterns, including the rare X-linked dominant, Y-linked, and digenic inheritance, see[10].

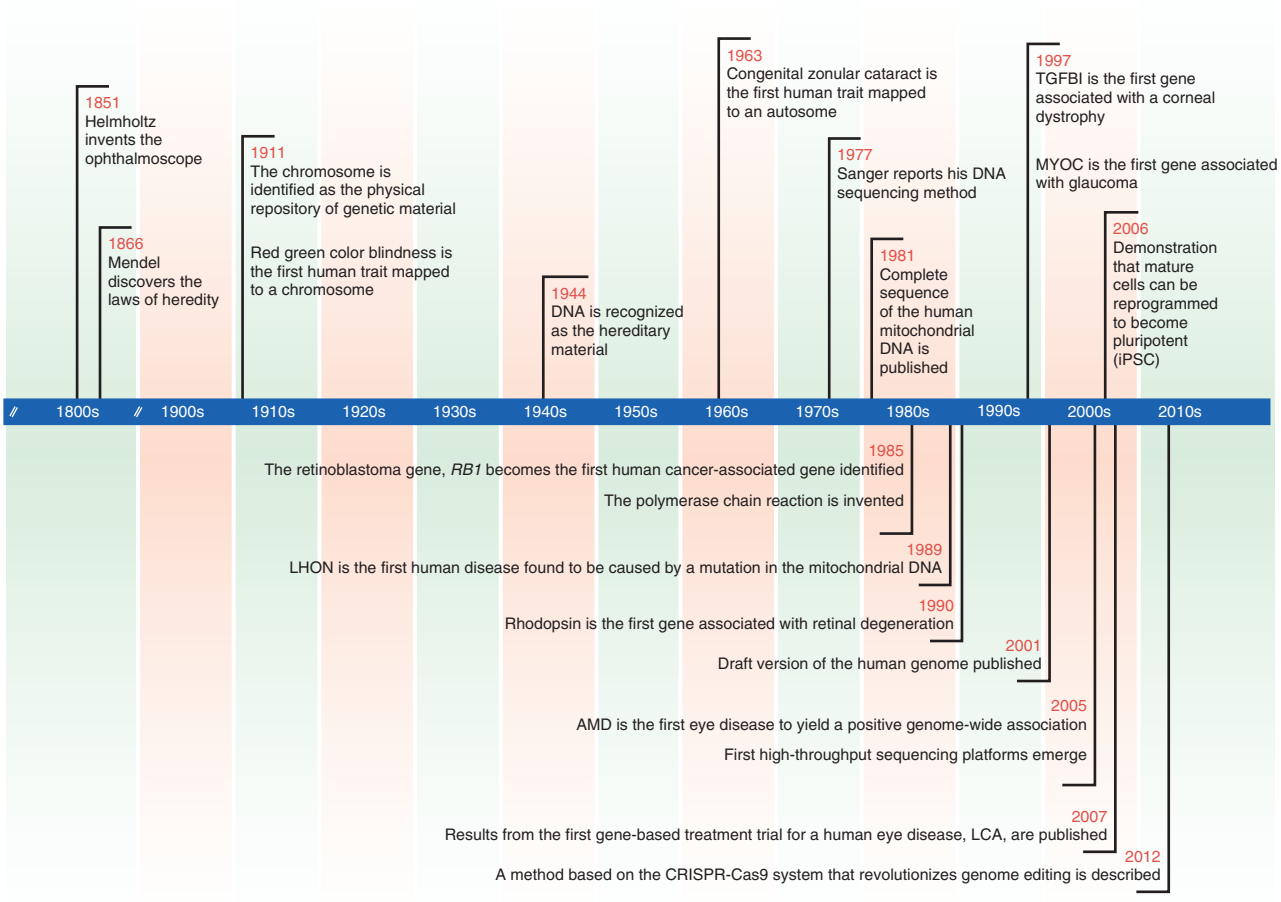
Autosomal dominant inheritance

In autosomal dominant conditions, affected individuals carry one normal and one mutated copy of a gene. This means that a single copy of the mutation is sufficient to cause disease (i.e. the condition is expressed in the *heterozygous* state). Typically, an affected person has at least one affected parent and there are affected individuals in multiple generations. A person with an autosomal dominant disorder has a 1 in 2 chance of passing the mutated gene to an offspring (i.e. of having an affected child). This basic Mendelian pattern can be disguised by phenomena such as non-penetrance (see Fig. 11.2B), variable expressivity, and new/*de novo* mutations (see below).

Autosomal recessive inheritance

In autosomal recessive conditions, affected individuals carry defects on both copies of a given gene. They can be either *homozygotes*, if both copies harbor the same mutation, or *compound heterozygotes*, if each copy carries a different mutation. Typically, affected individuals are born to asymptomatic carrier parents; this means that the parents carry one normal and one mutant gene copy but are not affected, as the normal copy is sufficient to produce normal function and structure. After the birth of a child with an autosomal recessive condition, each subsequent child has a 1 in 4 chance of being affected.

Autosomal recessive disorders can appear as "sporadic" in a family where all parents and siblings are healthy; this is



LHON, AMD and LCA denote Leber hereditary optic neuropathy, age-related macular degeneration, and Leber congenital amaurosis, respectively.

Fig. 11.1 Timeline of landmarks in genetic ophthalmology.

particularly common in small families. In real life, predicting autosomal recessive inheritance can be challenging and may be inferred on the basis of unaffected parents ("lack of vertical transmission") and exclusion of X-linked inheritance.

A major risk factor for autosomal recessive disorders is parental consanguinity.[11] A consanguineous marriage is in general defined as a union between a couple related as second cousins or closer.[12] Although these unions increase the likelihood that spouses carry an identical gene mutation, in many ethnic groups they are an important part of family culture. Personalized genetic counseling should be offered to consanguineous couples, but this must be done with sensitivity and appreciation of cultural issues.

X-linked inheritance

An X-linked condition is caused by a mutation in a gene carried on the X chromosome. Males have only one X chromosome and, consequently, such a mutation will be manifest. Females have two copies of each X chromosome gene and the presence of a normal copy leads to partially or completely preserved structure and function.

The essential features of X-linked inheritance are the presence of affected males (of greater severity than females) and the lack of father-to-son (male-to-male) transmission. The mothers of affected males are obligate carriers and have a 1 in 2 chance of passing the mutation to their offspring; each son has a 1 in 2 chance of being affected and each daughter has a 1 in 2 chance of being a carrier.

Classically, it is assumed that X-linked recessive conditions only affect males. This is true for conditions such as X-linked retinoschisis and Norrie disease. However, for others such as X-linked retinitis pigmentosa, there may be phenotypic manifestations in heterozygous females, although these will usually be milder and of later onset than in males.[13] In these cases, it might be difficult to distinguish X-linked from autosomal dominant inheritance, especially in the absence of a detailed family history. Notably, phenotypic manifestations of X-linked disorders in females are highly variable; this is mainly due to a genetic phenomenon termed *X chromosome inactivation* or lyonization (for more information see Wu et al.[14]). It is of interest that in a number of X-linked conditions including choroideremia and Lowe syndrome, females may show characteristic ocular signs despite the absence of symptoms. These signs can help the identification of apparently unaffected female carriers.[15,16]

Complications to the basic Mendelian pedigree patterns

Various clinical phenomena can often disguise an underlying Mendelian inheritance pattern. An example of such a

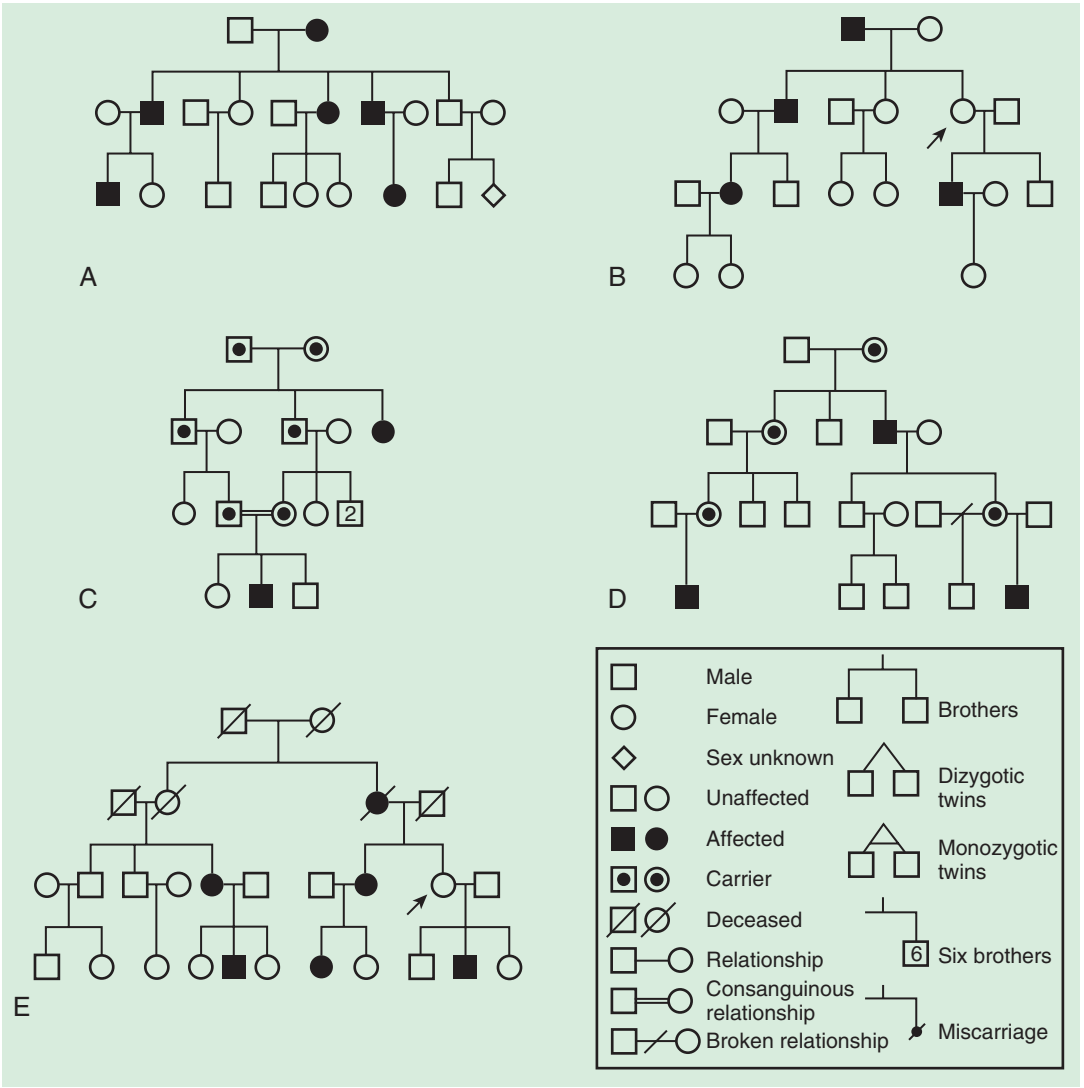


Fig. 11.2 Pedigree patterns of autosomal dominant (A,B), autosomal recessive (C), X-linked recessive (D), and mitochondrial (E) conditions. Arrows highlight non-penetrant carriers of an autosomal dominant (B) and a mitochondrial (E) disorder.

complication is *reduced penetrance*.[17] Reduced penetrance is common in dominant disorders where heterozygous mutation carriers are classically expected to be affected. However, in reality, the probability of a mutation carrier developing symptoms is rarely 100% – that is mutations often show reduced penetrance. In practice, this means that for many conditions including pediatric cataract, coloboma, and some forms of autosomal dominant retinitis pigmentosa, individuals may carry a mutation but have no signs of the disorder. An extreme example is an asymptomatic individual with an affected parent and children; such a pedigree structure would suggest that he/she certainly carries the mutation but there is non-penetrance (see Fig. 11.2B).

Another genetic phenomenon with similarities to reduced penetrance is variable expressivity, also frequently seen in the context of dominant disease. A mutation is said to demonstrate variable expressivity if, within a family, affected individuals carry the same genetic defect but the manifestations of the condition vary widely. The cause for variable expressivity is the same as for reduced penetrance: environmental factors or other genes can have some influence on the development of symptoms.[18] Examples of variable expressivity include von Hippel–Lindau disease and Stickler syndrome, in which ocular and extraocular manifestations vary among those who carry a mutation.[19,20] In these cases, disease severity in one individual may give little or no indication of the likely disease severity for siblings or offspring. Reduced penetrance and variable expressivity are important reasons for examining apparently unaffected parents of children with conditions such as pediatric cataract or anterior segment dysgenesis. Importantly, the presence of mild features can predict the risk for future offspring.

Many cases of severe dominant disease are the result of new mutations.[21] These so-called *de novo* mutational events arise as a result of a copying error from a parent's DNA and manifest without warning in families with no previous history of the disorder. This phenomenon is observed in many individuals with aniridia (Fig. 11.3) or retinoblastoma.[22,23] In such cases, the recurrence risk for future siblings is much lower than 1 in 2. However, the figure will not be zero due to the risk of *gonadal mosaicism* (i.e. one parent carrying the mutation only in a proportion of his sperm or her eggs).

The exact nature of a *de novo* mutation is difficult to predict. For cases of sporadic/non-familial aniridia, a deletion

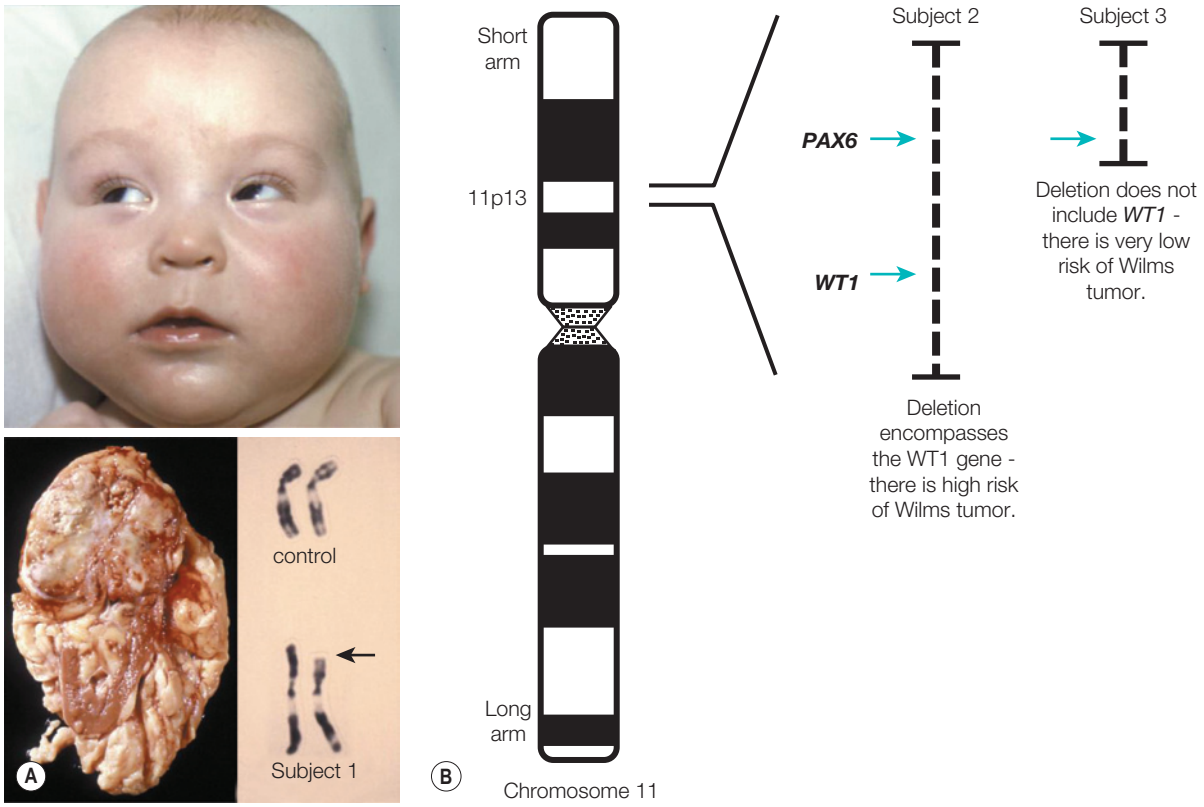


Fig. 11.3 Aniridia caused by deletions in chromosome 11. (A) A child presented with cognitive impairment, genitourinary abnormalities, and aniridia (subject 1, top row); there was no relevant family history. He was subsequently found to have a Wilms tumor in the superior pole of his kidney (bottom row, left). Karyotype analysis revealed a deletion in the short arm of chromosome 11, which encompasses the PAX6 (aniridia) and the WT1 (Wilms tumor) genes (bottom row, right; arrow highlights the deleted region). (B) Individuals 2 and 3 were born with sporadic aniridia. Karyotype analysis was normal but further cytogenetic analysis revealed submicroscopic deletions in both patients. The deletion in subject 2 removed a copy of the PAX6 and WT1 genes (deletion shown as interrupted line). The deletion in subject 3 was smaller and only removed a copy of the PAX6 gene; the WT1 gene was unaffected with two normal copies. Consequently, subject 2 is at high risk of developing Wilms tumor (one WT1 gene copy), while subject 3 is not at risk (two WT1 gene copies).

can remove other neighboring genes; this is seen in WAGR syndrome (Wilms tumor, aniridia, genitourinary abnormalities, and intellectual retardation). These contiguous gene deletions are the reason why individuals with sporadic aniridia require either renal ultrasound screening or molecular evidence that the Wilms tumor gene, *WT1*, is unaffected by the mutation (see Fig. 11.3).[23,24]

Mitochondrial inheritance

Mitochondria are cytoplasmic cellular organelles that contain a small genome (~16,500 bases) that is distinct from the nuclear genome (~3,200,000,000 bases).[25,26] Like mutations carried on the nuclear chromosomes, mutations in the mitochondrial DNA (mtDNA) can be associated with disease. Among the small number of proteins encoded by mtDNA are important components of the electron-transport chain. Mutations in these genes can cause Leber hereditary optic neuropathy (LHON) and Kearnes–Sayre syndrome.[27,28]

Mitochondria are inherited exclusively from the ovum and an mtDNA mutation can only be passed on from a mother to her child. Consequently, while mitochondrially inherited disorders can affect both genders, they are transmitted only by mothers who carry the mtDNA defect. Although, at first sight, the pedigree pattern may appear dominant, it should be noted that affected fathers never transmit the condition.

Maternally inherited conditions are typically highly variable, making the estimation of prognosis challenging. In many cases where individuals carry mtDNA mutations in all of their cells, as is seen for most LHON patients, the basis for this variability is poorly understood.[29,30] However, with mitochondrial myopathies such as Kearnes–Sayre syndrome, only a proportion of the mitochondria carry mtDNA mutations and, since each cell has many mitochondria, variability can arise.[31] This state is termed *heteroplasmy* and is associated with a variable ratio of mutant to normal mitochondria between the cells/tissues of a single individual or between different individuals of the same family.

Heterogeneity in genetic disorders

There is very rarely a one-to-one correspondence between genes and genetic disorders and this has implications for diagnosis, counseling, and genetic testing. Two types of heterogeneity are observed:

1. *Locus heterogeneity* is when defects in more than one gene can cause indistinguishable phenotypic manifestations. Examples include Leber congenital amaurosis and Bardet–Biedl syndrome, which are not single disorders but groups of clinically similar genetic conditions.[32,33]

2. *Clinical heterogeneity* is when mutations in the same gene produce two or more apparently distinct disorders in different individuals (e.g. *SOX2* mutations can cause microphthalmia, anophthalmia, or coloboma[34]). As the clinical outcome of a mutation can be influenced by its position, type, and effect on the encoded protein, clinical heterogeneity may be associated with different effects of distinct mutations.

Multifactorial disorders

Although overall monogenic eye disorders are common, they are individually fairly rare. Notably, many of the common pediatric ophthalmic conditions appear to show familial clustering and are likely to be caused by a complex interplay of multiple genes and the environment (e.g. esodeviations[35,36]). In these multifactorial disorders, the presence of any one of the disease-associated variants is not highly predictive of the development of disease.[37] It is clear that there is a continuum of disorders from fully penetrant monogenic to multifactorial conditions, and that compartmentalizing genetic disorders into "monogenic, simple, and rare" and "multifactorial, complex, and common" is an oversimplification.[38]

Epigenetics

Differences in phenotype often result from chemical modifications of DNA and its associated proteins (histones) rather than changes in the primary DNA sequence. Such *epigenetic modifications* can control gene activity, switching genes on and off. These changes may be induced by the environment (toxins, nutrition, stress) and can endure for varying times.[39] While epigenetic alterations have a role in normal cellular processes and development, they can also be responsible for certain inherited disorders.[40] Furthermore, epigenetically regulated process such as genomic imprinting can influence how some genetic conditions are inherited.[41]

Key molecular mechanisms of epigenetic control include DNA methylation, histone modification and non-coding RNA gene silencing.[42] The expansion of our understanding of these mechanisms has highlighted the potential for translating this knowledge into a new class of treatment options to combat blinding disorders.[42,43]

Variants and mutations

Although the term "mutation" can be used in different senses, it has developed a negative connotation and is typically used to indicate a disease-causing DNA change; that is a change that contributes mechanistically to disease but may not be sufficient in isolation to cause disease (e.g. in cases with reduced penetrance). In contrast, the term "variant" is used to indicate any difference in a DNA sequence in comparison with the normal reference sequence. A variant may or may not affect the function of a gene/protein; variants for which a functional effect is unknown are called "variants of unknown significance".[44,45] Other ways to classify variants include common versus rare and small-scale versus large-scale.

Human genetic variation ranges from single base/nucleotide changes (known as SNPs, single nucleotide polymorphisms) through to structural variants (see Fig. 11.3) and gains or losses of whole chromosomes. Substitutions of a single base/nucleotide are the most numerous variants.[46] These small-scale DNA sequence alterations may result in the substitution of one encoded amino acid for another (missense changes) or convert an internal amino acid of a protein into a termination codon (nonsense changes). Small insertions/deletions (indels), in which up to 21 bases/nucleotides are inserted and/or deleted, are another common subtype of small-scale DNA variation. Notably, if the overall loss or gain of bases is not a multiple of three, the reading frame of the gene will be altered and a premature termination codon will be probably introduced.

Some changes can alter transcription (i.e. the process of copying a particular segment of DNA into mRNA) and in particular the stage during which the immature mRNA molecule (consisting of introns and exons) is modified to form mature mRNA (consisting of joined exons only). This process is called splicing and requires the interaction of a large protein complex, the spliceosome, with mRNA. Many mutations, especially those that lie at or close to the junctions between introns and exons, cause disease by interrupting splicing. These splicing mutations lead to reduced transcription of a gene and therefore reduced gene expression.

Any sequence change can be described using the conventions set out on the website of the Human Genome Variation Society (http://www.hgvs.org/mutnomen/[47,48]); common prefixes include "c." (coding DNA level) and "p." (protein level). Useful variant databases include the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/[49]) and ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/[50–52]), two online repositories of disease-associated variants, as well as the Exome Aggregation Consortium database (http://exac.broadinstitute.org/) which includes variant data from over 60,000 unrelated individuals.

Genetic testing

Genetic testing for ophthalmic disorders aims to provide accurate diagnosis, to facilitate appropriate counseling to the patient and family members, and to determine inclusion in gene-based clinical trials.[53,54] A genetic test, in the broad sense, can be a clinical or a laboratory investigation. For example, the identification of multiple iris nodules in the child of a person with neurofibromatosis type 1 will have similar ramifications as the identification of a NF1 gene mutation in a standard DNA-based test. One key difference though is that a DNA-based method can establish the predisposition to a genetic disease long before the disorder will be detectable by even the most sensitive clinical tools (*presymptomatic testing*).[37]

Advances in DNA sequencing technologies have reduced the cost of genetic testing,[55] shortened the turnaround time of tests, and facilitated the evaluation of numerous genes and molecular hypotheses concurrently (*parallel testing*).[56] As a result, clinically useful tests now exist for dozens of inherited eye disorders.[3,37,53,57] The focus of these tests is presently monogenic disease, and ophthalmologic societies have issued recommendations on when genetic testing is advisable (the current recommendations of the American Academy of Ophthalmology Task Force on Genetic Testing can be found online at http://www.aao.org/).

Genetic testing is typically performed on DNA extracted from a tissue sample. Peripheral blood is the most commonly

used and reliable source, but mouthwashes or buccal scrapes can be used when sampling must be noninvasive; for prenatal diagnosis, amniotic fluid or chorionic villi are normally utilized. Depending on the clinical indication, different techniques can be subsequently employed (see Fig. 11.1).[58] DNA sequencing is by far the most commonly used approach in inherited eye disease.

Testing options that use DNA sequencing have greatly expanded over the past decade. Notably, there has been a fundamental shift away from the traditional Sanger sequencing-based technique to newer technologies, referred to as high-throughput or next-generation sequencing.[56] These approaches have transformed genetic testing and are the basis of tools such as multigene panel testing, exome sequencing (i.e. sequencing the protein-coding, informative 1% of the genome[59]) and genome sequencing (i.e sequencing the totality of the nuclear DNA).

Sanger sequencing is only able to analyze one small portion of DNA at a time. Using this approach may still be a sensible testing strategy in certain conditions associated with one specific gene such as Sorsby dystrophy (*TIMP3* gene[60]) or stromal corneal dystrophies (*TGFBI* gene[61]). However, single-gene eye disorders are rare and most inherited eye diseases are either associated with large and complex genes (e.g. *ABCA4* in Stargardt disease[62]) or exhibit locus heterogeneity (e.g. Usher syndrome[63]). In these cases, Sanger sequencing, a technology unable to generate large sequence output, is an arduous, time-intensive, and expensive means of diagnosis.

In contrast, high-throughput sequencing approaches allow rapid inspection of many genes at once, resulting in high diagnostic rates, especially in heterogeneous disorders.[21,64–66] Multigene panel tests utilizing high-throughput sequencing technologies are presently the preferred method for diagnostic testing of retinal dystrophies[53,67] and pediatric cataract.[3] This approach inspects hundreds of known disease-causing genes and has been shown to not only be more sensitive than exome sequencing but also to reduce the potential for incidental findings (see below).[68] Exome and genome sequencing can assess >95% of the protein-coding sequence of the human genome (~19,000 genes) and have been adopted as standard approaches in genetic research; however, their implementation in the clinical setting has been slower. At present, genome sequencing appears to outperform exome sequencing not only in detecting large-scale/structural variants, but also in covering protein-coding regions.[64,69,70]

With the advent of these high-throughput sequencing technologies, genetic data acquisition and DNA sequence variant identification are no longer the rate limiting steps. However, there is a huge interpretive burden: pinpointing the disease-causing variant among the considerable background of detected rare variants can be an onerous task.[71,72] A well-informed clinical, pre-test hypothesis is key, making a knowledgeable clinician one of the most important components of the genetic testing process. Another major issue with extensive parallel testing, a characteristic of exome and genome sequencing, is the collateral discovery of numerous clinically relevant findings that are unrelated to an individual's presenting symptoms. The terms "incidental" and "secondary" are used to describe these findings.[37,73] One example of such a secondary finding is the discovery of a mutation increasing the risk of breast cancer in a patient who had exome sequencing for childhood-onset glaucoma.

Genetic counseling and ethical issues

The primary aim of genetic counseling is to communicate information, in an appropriate manner, to individuals about a genetic disorder. This includes discussing the risk to family members and the options around reproduction and genetic testing. An accurate diagnosis and a close collaboration between the clinic and the laboratory are central to effective genetic counseling.

A genetic test can have significant and far-reaching consequences for an individual and his/her family. Guiding families through the testing process can be challenging, especially given the increasing complexity of the results of high-throughput sequencing-based tests. Informed consent and effective genetic counseling are essential and can maximize the benefits and minimize the risks associated with each test.

Pre-test considerations

It is crucial to maintain realistic expectations for finding the causative mutation and to alert the patient/family that, in most cases, a positive result is unlikely to change management decisions or to improve the prognosis.[74] If exome or genome sequencing have been identified as appropriate for a child, the parents should be engaged in a decision-making process. They should be aware that these strategies involve a broad evaluation of thousands of genes and, as a result, there is a chance that genetic susceptibility to a condition unrelated to the indication of the test could be identified. Current recommendations are to include analysis of a small set of genes that are deemed to be highly medically actionable (e.g. genes associated with familial hypercholesterolemia) in every subject tested with exome or genome sequencing; this analysis is performed regardless of the specific indication of the test, but it is common to allow a patient opt-out clause.[73,75]

Informed consent

Consent forms can be lengthy and technical, and just asking the parents to navigate the forms on their own is often not appropriate. The consenting individual should make a checklist of the essential points in the form and ensure that these are discussed with the family.[76] According to standard practice, after pre-test counseling to the parents and child, one or both parents with custodial responsibility should agree in writing with the decision to perform the test. Importantly, communication needs of visually impaired individuals should be taken into account and information should be provided in suitable formats.

Post-test considerations

High-throughput sequencing-based tests are rarely positive/negative assays. Distinguishing true- from false-positives can be challenging and may require additional history taking or examination (e.g. one may look for clinical features of a previously unrecognized syndrome). The conclusion that an identified variant is indeed disease-causing is the result of integrating submitted clinical information with laboratory test results; reviewing available data from trusted medical sources (PubMed or textbooks) may also be required.[64] A negative test should prompt re-evaluation of the clinical findings and

the limitations of the conducted test. Notably, a negative result often suggests that the current state of research has not identified the gene that is associated with the patient's condition.

Presymptomatic and carrier testing

In late-onset conditions where the causative gene mutation is known (e.g. *EFEMP1* in autosomal dominant drusen[77]), asymptomatic at-risk individuals may choose to have a predictive genetic test to discover if they are likely to develop the disorder. This will allow them to make informed reproductive or career decisions at a time when the disease is not yet clinically detectable.[37] Another common situation is unaffected females from families segregating an X-linked disorder (e.g. X-linked retinitis pigmentosa), choosing to have carrier testing in order to make decisions around reproduction, prenatal testing, or preimplantation genetic diagnosis.[78]

Testing asymptomatic children for untreatable disorders should be avoided except in exceptional circumstances.[37] For these few cases, careful counseling and engagement of parents in shared decision-making is essential. For conditions that are asymptomatic until adulthood, it is generally advised to wait until an individual is old enough to make their own decisions.

Conclusions

The field of ophthalmic genetics is evolving very rapidly. Genetic tests that greatly enhance diagnostic precision are now available and should be routinely considered as part of the clinical evaluation of children with inherited eye disease. Importantly, recent progress in genome editing, gene transfer, and stem cell biology have made the prospect of halting disease progression in currently untreatable inherited eye disorders a realistic possibility.

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Congenital infections of the eye

Luis Amaya

Chapter contents

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RUBELLA
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Maternal infection during pregnancy can have significant consequences to the developing fetus, including involvement of the visual system; it is an important cause of childhood blindness in the world, particularly in developing countries.[1] The term "TORCHES" refers to toxoplasmosis, other agents (varicella, lymphocytic choriomeningitis, West Nile virus, human immunodeficiency virus [HIV]), rubella, cytomegalovirus, herpes viruses, and syphilis. Improved screening and prophylaxis of pregnant women at risk will reduce these potentially devastating infections.

Toxoplasmosis

Toxoplasma gondii is an obligate intracellular parasite, which typically affects the brain and the eyes in humans. There are three different strains. Congenital disease in humans is associated mostly with types I and II; type III is found only in animals.[2]

Systemic manifestations include hydrocephalus, microcephalus, intracranial calcifications (Fig. 12.1), anemia, petechiae due to thrombocytopenia, deafness, seizures, jaundice, fever, hepatosplenomegaly, mental and growth retardation, spasticity and palsies, lymphadenopathy, maculopapular rash, vomiting, and diarrhea.[3,4] Around 90% of neonates are asymptomatic; however, some of these infants later in life develop retinochoroiditis, hydrocephalus, mental retardation, and, deafness.[5] Clinical manifestations are more severe in premature infants, and congenital abnormalities are worse if the infection is acquired during the first trimester of gestation, but only 10–15% of these babies have serological evidence of vertical transmission.[6] When maternal *Toxoplasma* infection occurs during the third trimester, fetal transmission is around 75%, but there are minimal if any abnormalities.[7]

Ocular manifestations include retinochoroiditis[2] (Fig. 12.2A,B), microphthalmos (Fig. 12.3), cataracts, panuveitis (Fig. 12.4), optic atrophy, retinal detachment, pthisis, active vitritis (Fig. 12.5), active retinitis, nystagmus, and strabismus. Active chorioretinitis (Fig. 12.6) develops in 85% of patients with subclinical congenital infection[8]: it is usually bilateral and has a predilection for the macula; peripheral lesions are found in 64% of cases.[9] The chorioretinal scarring is usually heavily pigmented and associated with areas of chorioretinal atrophy (see Fig. 12.2). Chorioretinitis is progressive; the incidence can increase from 11% at 1 year of age to 23% by 7 years of age.[10]

Human infection is acquired from eating bradyzoites in undercooked meat, but it can also result from ingestion of oocysts in water, soil, or food contaminated by cat feces. Toxoplasmosis can also be a sexually transmitted disease via semen.[11] Marked regional differences in the prevalence of seropositivity occur due to differing dietary practices and sanitation standards. Up to one third of the world's population has serologic evidence of past *Toxoplasma* infection. *Toxoplasma* is responsible for the majority of congenital and acquired infectious uveitis. The incidence of congenital toxoplasmosis syndrome is 1–10 per 10,000 live births.[12,13] The prevalence of *Toxoplasma* seropositivity varies with age; in children under 5 years of age, the antibodies are found in less than 5% of the population, whereas they are present in 60% of adults

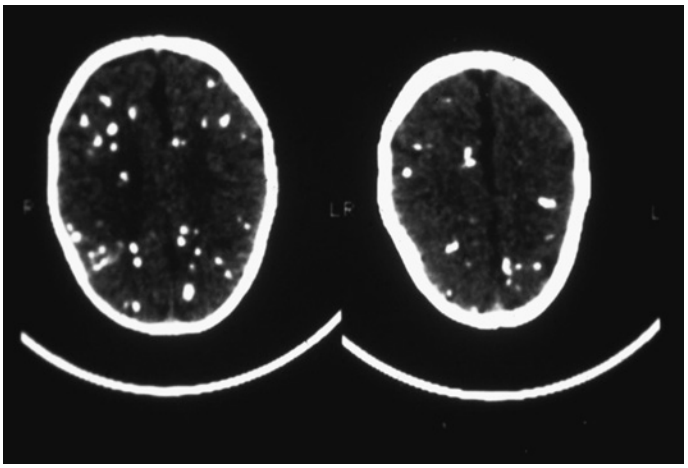


Fig. 12.1 Severe congenital toxoplasmosis with widespread brain calcifications shown on computed tomography scan.

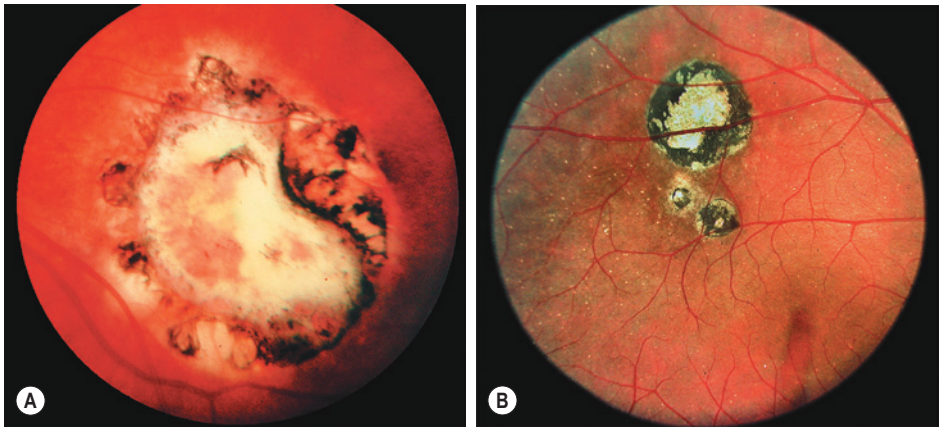


Fig. 12.2 (A) Raised congenital toxoplasmosis retinal scar. (B) Paramacular congenital toxoplasmosis scar.

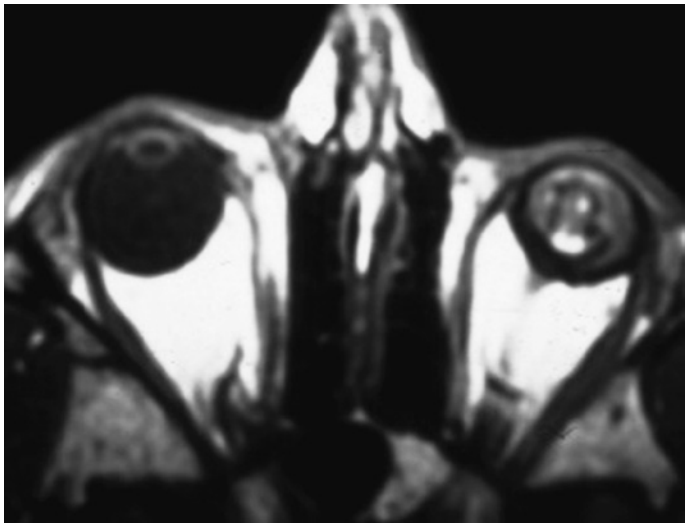


Fig. 12.3 Congenital toxoplasmosis with marked unilateral microphthalmos shown on magnetic resonance imaging.

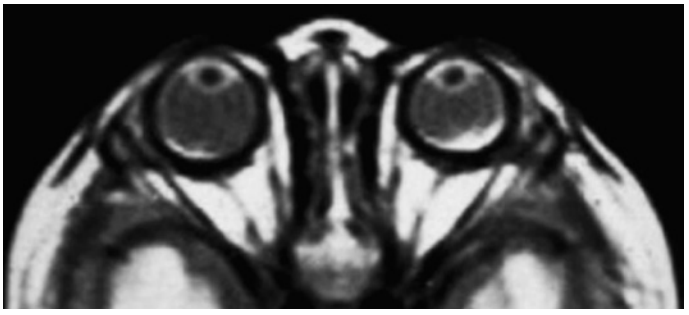


Fig. 12.4 Congenital toxoplasmosis with severe active panuveitis and posterior synechiae.

over age 80 years. Since 70% of the obstetric population has negative antibodies, this is a risk for transmission to the fetus.[14] Likewise, women of childbearing age emigrating from an area of low immunity to a region of high immunity are at the greatest risk of contracting toxoplasmosis.

The diagnosis of maternal toxoplasmosis is confirmed by testing serum for antibodies. If both immunoglobulin (Ig) G and IgM antibodies are absent, infection has not occurred. Positive IgG titers with negative IgM titers suggest prior infection.[15] The presence of IgM antibodies with or without positive IgG titers warrants a further workup with confirmatory testing including the Sabin–Feldman test, IgG avidity (measures the strength of antigen binding to antibody)[15], and enzyme-linked immunosorbent assay (ELISA) for IgG, IgM, and IgA. High IgG avidity indicates a less recent infection.[16] Polymerase chain reaction (PCR) testing of amniotic fluid can have 98% sensitivity and 100% specificity.[17,18] Cerebrospinal fluid PCR is considered to be highly sensitive for diagnosis of congenital toxoplasmosis in infants with neurological disorders.[19]

Women who contract toxoplasmosis during pregnancy must be treated with spiramycin, a macrolide that does not cross the placenta, believed to only reduce the sequelae among infected infants but not the rate of maternal–fetal transmission.[20] However, in a recent prospective cohort trial in Brazil, only 58% of newborns from spiramycin-treated mothers had congenital infection compared to 73% of infants whose mothers were not treated.[21] When maternal infection occurs during the third trimester, maternal treatment with pyrimethamine and sulfadiazine can be administered. In immunocompromised women, vertical transmission can occur without recent acute infection[22]; therefore, HIV-infected women with CD4+ count of 200/mm^3 or less should be treated with spiramycin for the duration of their pregnancy.

Recurrence has been reported to occur in only 13% of treated infants, compared to 44% of untreated patients; recurrences occur in areas contiguous to old scars or in uninvolved retina. It is recommended that all neonates with serological evidence of an intrauterine toxoplasmosis infection, even if there are no chorioretinal lesions or signs of active infection, be treated with a 1-year course of pyrimethamine and sulfadiazine with concurrent administration of folinic acid to reduce the hematotoxicity of pyrimethamine.[3] There is resolution of active disease within weeks of starting the treatment and long term follow-ups confirm improved visual outcomes.[23] Recent studies have shown that diclazuril can be effective and well tolerated for the treatment of maternal and congenital toxoplasmosis in a murine model, and it helps to eliminate the cycle of toxoplasma infection in cats, which are the definitive host.[24]

Prevention includes not eating raw or undercooked meat and avoiding cat feces during pregnancy. Fruits and vegetables that might be contaminated with toxoplasmosis oocytes, should be washed carefully before being eaten. Routine serological screening of pregnant women for toxoplasmosis is still

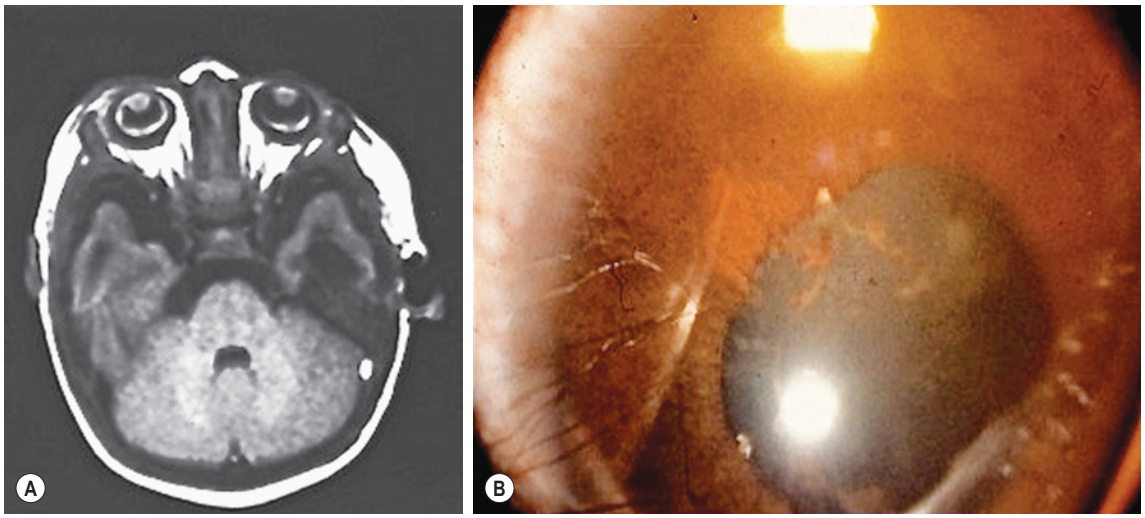


Fig. 12.5 Congenital Toxoplasmosis. (A) CT scan showing bilateral microphthalmos, panuveitis. (B) Slit-lamp view showing marked panuveitis. The vitreous was very hazy making fundal view impossible.

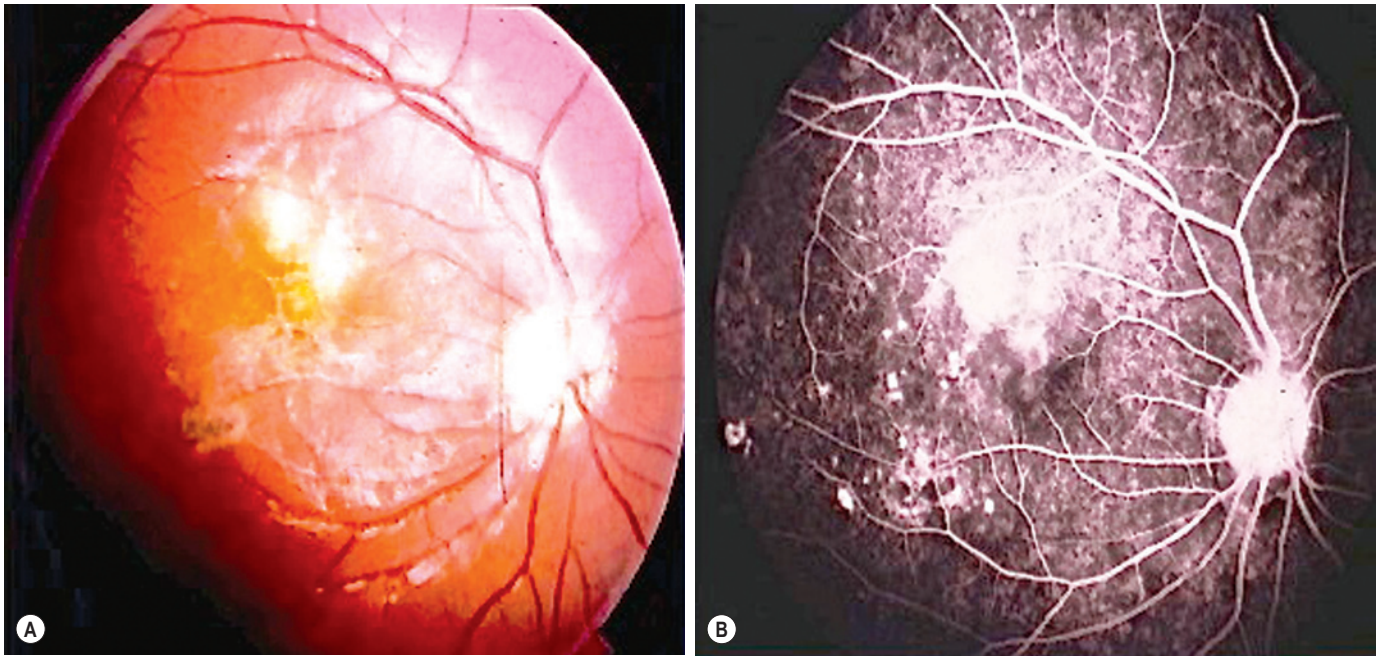


Fig. 12.6 (A) Congenital Toxoplasmosis. Active chorioretinitis due to re-activation of old congenital lesions. (B) Fluorescein angiogram of same patient.

controversial, and it is not carried out in many countries, but in those areas where the disease is endemic, pregnant women should be screened throughout the pregnancy.

Rubella

Congenital rubella was first described in Australia in 1941 by Norman Gregg after an epidemic affecting 78 children. The findings included congenital cataracts, congenital heart disease, and deafness.[25] Other systemic manifestations are intrauterine growth retardation, mental retardation, microcephaly, osteopathy, lymphadenopathy, thrombocytopenic purpura, hepatitis and hepatomegaly, diabetes and other endocrine abnormalities, and hypospadias.[26,27] The most common finding is hearing loss, present in 44% of cases.[28]

The virus is transmitted to the fetus through the placenta during the viremic phase in the mother. The prevalence of abnormalities correlates with the gestational stage at which the infection occurs: the rate of congenital defects is 100% in the first 11 weeks, 30% in weeks 11–20, and 0% after that. The incidence of congenital infection is also dependent on the gestational month when exposure to the virus occurred; it is 90% in the first 11 weeks, 50% during weeks 11–20, 37% during weeks 20–35, and 100% during the last week of pregnancy.[29]

Ocular manifestations include cataracts, present in 20–30% of children with the congenital rubella syndrome,[30] and they

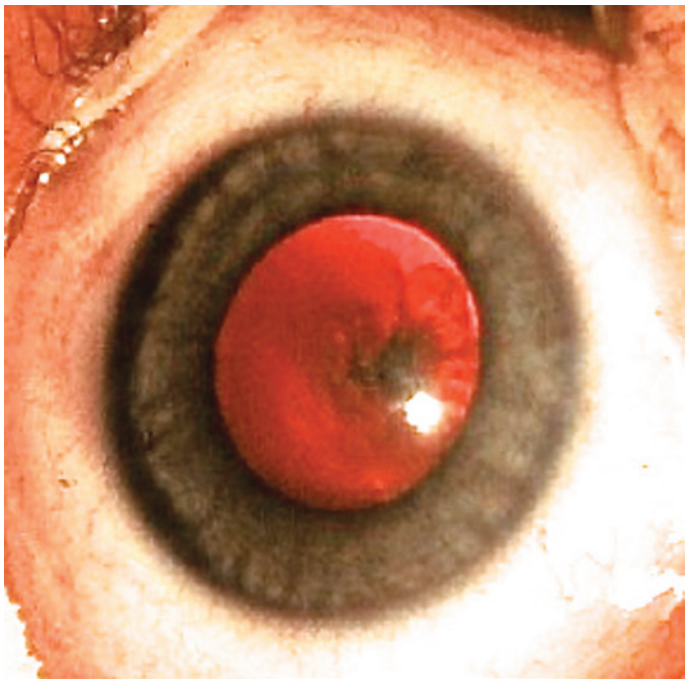


Fig. 12.7 Congenital rubella with cataracts and microphthalmos.



Fig. 12.8 Salt and pepper congenital rubella retinopathy.

occur when the virus infection occurs during the first 3 months of gestation. They are bilateral in 75% of cases. The cataracts can be nuclear, total, or membranous.[27] The virus has been cultured from cataractous lenses of children affected with the rubella syndrome up to 4 years of age, and it causes the severe inflammatory reaction observed after cataract surgery in these babies.[31] Microphthalmos is present in 10% of patients and it is usually associated with cataract[8] (Fig. 12.7).

The cornea may be hazy, due to keratitis secondary to the presence of the virus in the aqueous; it may resolve in weeks or months. Glaucoma can also be present in 10% of cases,[32] and it is seen usually associated with microphthalmic eyes or eyes with iris hypoplasia. It can be due to developmental abnormalities of the angle, chronic iridocyclitis, or even angle closure due to a large cataractous lens.[33] Keratoconus,[27] and dacryostenosis also may occur.[34] Some babies have a chronic granulomatous iridocyclitis,[34] causing focal necrosis of the pigment epithelium of the iris and the ciliary body. Iris colobomas, posterior synechiae, anisocoria, persistent pupillary membrane, and mesodermal dysgenesis have also been reported.[35]

Pigmentary retinopathy is the most common ocular abnormality. Present in 40% of affected babies, it is bilateral and is described as "salt and pepper" retinopathy, characterized by mottled pigmentary changes throughout the fundi (Fig. 12.8). Histopathologically, there is depigmentation of the retinal pigment epithelium without inflammation. The distribution varies, but the changes are most marked in the posterior pole. In spite of striking changes, the visual function is unaffected, and the electroretinogram (ERG) is normal. Primary optic atrophy has also been reported.

The diagnosis is confirmed by the presence of IgM antibodies to rubella in cord blood; serial rising IgG titers from serum sampling or throat virus culture can also be useful.[29]

Treatment of congenital rubella is mainly supportive. Unfortunately the visual outcome after modern surgical management of rubella-induced congenital cataracts remains poor.[36]

Prevention with the introduction of the attenuated rubella virus vaccine (RA-27) has dramatically reduced the incidence of rubella in the developed world. The Americas have eliminated endemic transmission of rubella and congenital rubella syndrome.[37] It is still, however, a major cause of blindness in developing countries where universal vaccination programs are not in place.[38] About 110,000 infants are affected every year with congenital rubella syndrome.[37,39]

Cytomegalovirus

Cytomegalovirus (CMV), which is part of the herpes virus group, is the most common cause of intrauterine infection. It occurs in 0.5–2.4% of live births,[40] but only 10% of children with congenital CMV are symptomatic as newborns.[41] The prevalence of latent infection in young adults is higher in developing countries and with increasing age.[42]

Transmission can occur prenatally during primary maternal infection, re-infection, or re-activation of latent infection[43]; the risk of transmission is highest when primary infection occurs during the third trimester.[44,45] Neonatal infection can occur due to exposure to genital secretions at the time of delivery or the ingestion of breast milk.[29]

Intrauterine CMV infection causes tissue necrosis causing disruption of organogenesis.[46] Systemic manifestations that are exclusively seen in infants born to mothers with primary infection include intrauterine growth retardation, thrombocytopenic purpura, microcephaly, periventricular calcifications (Fig. 12.9), hepatosplenomegaly, jaundice, pneumonia, sensorineural deafness, and psychomotor retardation.[47]

Ocular manifestations are uncommon and include keratopathy, glaucoma, cataracts, microphthalmos, optic atrophy, optic nerve hypoplasia, and optic nerve coloboma.[48] Retinochoroiditis is present in 22% of symptomatic babies.[48] The chorioretinal scars are similar to toxoplasmosis lesions,

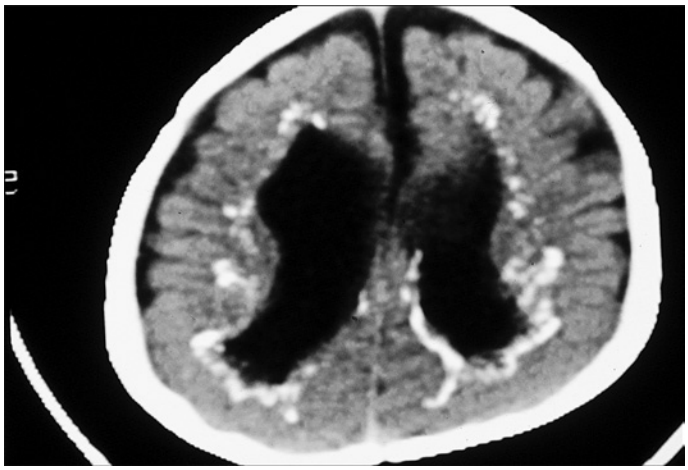


Fig. 12.9 Congenital cytomegalovirus infection with periventricular calcification, hydrocephalus, and cerebral atrophy shown on computed tomography scan.

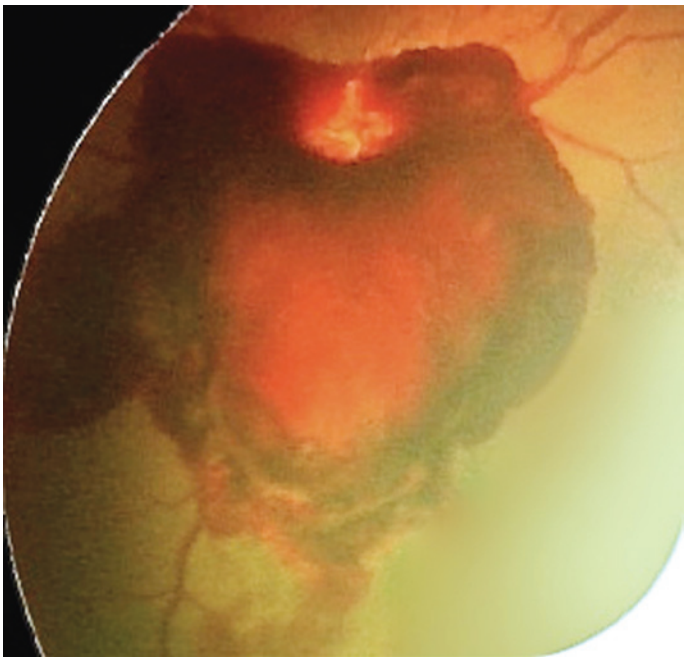


Fig. 12.10 Severe retinal arteritis affecting a newborn baby with congenital herpetic infection.

but less heavily pigmented. Chorioretinal scars can be the only clinical sign of congenital CMV infection, and can develop several weeks after birth.[49] Cyclopia and anophthalmia have also been reported in babies with congenital CMV infection.[50]

Diagnosis is suspected from the presence of IgM antibodies in the baby, and can be definitely confirmed by isolating and culturing the virus from urine or saliva. Culturing the virus from an infant during the first 3 weeks of life confirms the diagnosis.[51]

Intravenous treatment with ganciclovir and foscarnet reduce the severity of hearing loss, but ganciclovir does not seem to alter the time of resolution of CMV retinitis.[52] Trials also show that viruria returns to pretreatment levels after cessation of the drug.[53]

Maternal CMV infection appears to develop after exposure to young children at home or at group childcare settings, so seronegative pregnant women should be vigilant to avoid contracting infection.[47]

Herpes simplex

Infection by herpes simplex virus (HSV) is predominantly a neonatal disease. The transmission occurs at birth by aspirating infected vaginal secretions in 86% of cases usually after a primary genital infection. A congenital infection occurs in 4% of cases, and is due to maternal viremia with transplacental transmission, or an ascending infection into the uterus after premature rupture of the amniotic membranes. Postnatal infection occurs in 10% of cases; possible entry sites include the eyes, scalp, skin, and umbilical cord.[54] The majority of neonatal infections are due to HSV-2, which is the genital strain.[55] HSV-1 is the oral strain, which affects the mouth, eyes, and causes encephalitis.[56]

Neonatal infection can rapidly spread causing systemic involvement and even death; infected infants usually become symptomatic 5–15 days after birth with lethargy, temperature alterations, respiratory distress, anorexia, vomiting, cyanosis, hepatitis, pneumonia, disseminated intravascular coagulation, or encephalitis. The mortality rate of disseminated disease is very high, up to 49%, and a high percentage of babies with encephalitis are neurologically handicapped. Only 26% of survivors develop normally.[56] Patients with the congenital type of disease can have low birthweight, microcephaly, seizures, diffuse brain damage, intracranial calcifications, scars on the skin or digits, pneumonitis, and hepatomegaly.[57]

Ocular manifestations can vary from blepharoconjunctivitis with vesicles on the eyelids, keratitis with epithelial dendrites, to iridocyclitis, iris atrophy, posterior synechiae, and cataracts.[58] Chorioretinitis with vitritis and optic atrophy can occur, especially in infants with central nervous system involvement. Chorioretinal scarring results in well-circumscribed hyperpigmented lesions that typically involve the peripheral retina. White vitreous masses have also been described.[59] Acute retinal necrosis may develop later in life from recrudescence of the virus in scars,[60] which spreads rapidly and circumferentially, with occlusive vasculopathy, arteriolar involvement (Fig. 12.10), and vitreous and anterior chamber inflammation.[61] Microphthalmos may also be associated with microcephaly and intrauterine growth retardation.[59]

The diagnosis should be suspected in infants with progressive icterus, fever, hepatosplenomegaly, and cutaneous vesicular lesions, and is confirmed by isolating the virus from fresh vesicles, nasal secretions, conjunctival secretions, and cerebrospinal fluid (CSF).[56]

Systemic treatment with intravenous acyclovir is the treatment of choice for disseminated disease, but because of the high risk of rapid spread, it also applies for infants with limited cutaneous or ocular involvement, particularly in babies less than 1 month of age. The dose is 30 mg/kg per day for 10 days to 4 weeks.[62] Vidarabine is also administered as a single intravenous infusion of 15 mg/kg per day over 12 hours. Debridement of epithelial keratitis and antiviral topical treatment (acyclovir, vidarabine, idoxuridine, or trifluorothymidine) is also necessary. Herpes simplex blepharoconjunctivitis should

also be treated with topical antiviral therapy as prophylaxis against the development of keratitis.

Syphilis

Congenital syphilis occurs when the fetus is exposed to *Treponema pallidum* after the 16th gestational week. Transmission during the first trimester usually results in death. Virtually 100% of babies exposed to primary maternal infection during pregnancy are affected, and most infants born to mothers with secondary syphilis show signs of congenital syphilis.[63] Half a million pregnancies are affected annually.[64,65] Incidence of the infection decreased in the 1980s and 1990s, but congenital syphilis has increased as a consequence of more primary infections in adults.[63] Transplacental transmission can occur even during periods of maternal seronegativity.[29]

Congenital syphilis has early manifestations due to active infection, or late manifestations that occur later in childhood secondary to ongoing inflammation. Early manifestations include skeletal abnormalities, rhinitis, maculopapular rash, fissures of the lips, nares, and anus, hepatosplenomegaly, anemia, and uveitis. Late manifestations that occur after 2 years of life include nerve deafness, bone changes, dental abnormalities, and interstitial keratitis.[64] Hutchinson's triad is the association of nerve deafness, malformed incisors, and interstitial keratitis.

Ocular manifestations include chorioretinitis, interstitial keratitis, anterior uveitis, iridoschisis, and optic atrophy. Up to 40% of children with untreated congenital syphilis develop interstitial keratitis, which is bilateral in 80% of cases, and develops at 5–20 years of age.[66] This is an infectious and hypersensitivity keratitis, which may progress despite adequate intravenous antibiotics, so treatment with topical steroids is necessary. It is characterized by sectorial or diffuse corneal edema infiltrated by interstitial vessels. It is accompanied by iridocyclitis and iris atrophy. Stromal neovascularization is also usually present and secondary glaucoma can develop. Corneal scarring and residual ghost vessels can cause significant visual loss. Congenital and acquired cataracts are usually due to uveal inflammation. Chorioretinitis affects peripheral areas and manifests as pigment mottling. Severe cases may result in extensive retinal pigmentary changes resembling retinitis pigmentosa.

Pregnant women should be screened for syphilis early in pregnancy and again before delivery to prevent congenital syphilis, which occurs predominantly in the offspring of young, unmarried women with poor antenatal care. Serologic testing includes treponemal tests such as the fluorescein antibody absorption test (FTA-ABS), the microhemagglutination assay for *T. pallidum* (MHA), and the *T. pallidum* particle agglutination assay (TP-PA). Non-treponemal tests include the Venereal Disease Research Laboratory test (VDLR) and the Rapid Plasma Reagin (RPR). Serological tests may be negative in newborns (who can also be asymptomatic initially), making the diagnosis difficult. A quantitative assay of non-treponemal serology with titers four times higher than maternal titers indicates a congenital infection. Treponemal tests are almost always positive in infants with congenital syphilis and should be performed with a non-treponemal test to increase specificity. The treponemes can be isolated from active cutaneous lesions and seen by dark-field microscopy. Additionally, any child with congenital syphilis must have a lumbar puncture and CSF serology examination even if there are no symptoms of neurosyphilis.

Pregnant women with HIV are at a higher risk of having active syphilis, but a higher rate of false negatives occurs in these patients. It is important that infants born to HIV-positive women should be screened for any clinical manifestations of congenital infection in addition to having serologic testing.

The treatment of choice is parenteral penicillin G for 10–14 days, which is usually adequate. Serologic testing should be repeated every 3 months after treatment until serum VDRL or RPR is negative or titers are less than four times their original value. Sometimes repeated parenteral penicillin treatment is necessary if antibody titers remain elevated or begin to rise.

Varicella zoster virus

Intrauterine infection by varicella zoster virus, also known as chickenpox, is rare, since more than 90% of women of childbearing age have virus-specific immunity.[67] However, nearly one-third of affected infants die during the first few months.[68] Infection in the first and second trimesters may lead to congenital varicella syndrome (CVS); maternal infection near term may result in neonatal disseminated infection. Fetal infection occurs by transplacental transmission.

Systemic manifestations include cicatricial skin lesions (Fig. 12.11), limb hypoplasia, and since the virus has high affinity for the central nervous system, seizures, neurologic defects, and cortical atrophy can be present; they can also have low birthweight for gestational age and neuropathic bladder. Ocular manifestations include chorioretinitis, which is the most common ocular manifestation, characterized by single or multiple deeply pigmented chorioretinal scars and atrophy closely resembling toxoplasmosis lesions[69] (Fig. 12.12). Cataracts, microphthalmos, optic nerve hypoplasia, and Horner syndrome have been reported as well.

The congenital varicella syndrome may be overlooked since the clinical findings may be subtle and non-specific. The diagnosis is confirmed by detection of the viral DNA in the infant, presence of specific IgM antibodies and/or persistence of IgG antibodies beyond 7 months of age, or the appearance of zoster during early infancy.

Prevention includes vaccination of seronegative women prior to pregnancy and avoidance of exposure to varicella



Fig. 12.11 Cicatrical skin lesions on a child with congenital varicella.

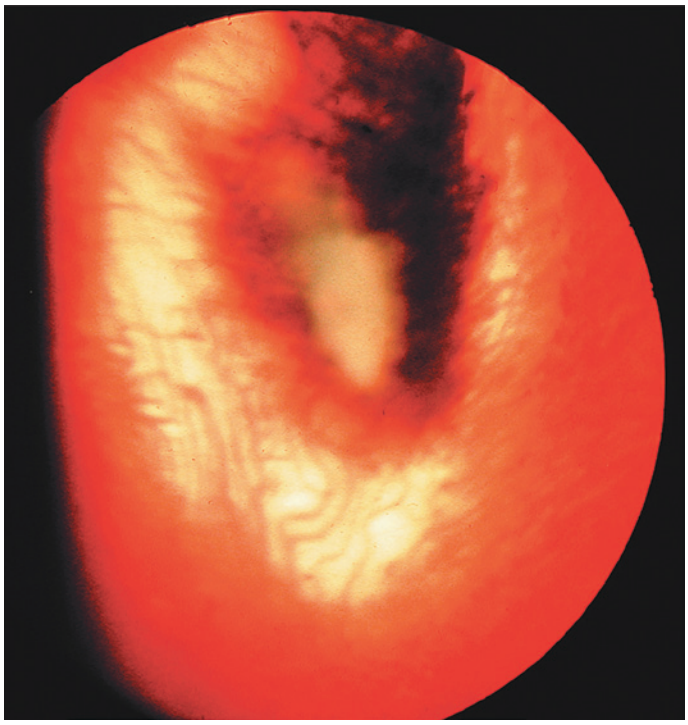


Fig. 12.12 Chorioretinal scar in a child with congenital varicella syndrome.

zoster during pregnancy. Pregnant women exposed to varicella who are seronegative should receive an injection of varicella zoster immunoglobulin. However, there are no controlled studies on the utility of antiviral therapy in preventing fetal transmission.[70]

Other

Lymphocytic choriomeningitis virus is an RNA virus with a rodent reservoir. Transmission to humans may be airborne, from contamination of food by infected mouse urine, feces, and saliva, or from bites of infected mice. Transmission of the fetus occurs during maternal viremia.

Systemic finding in the neonate include macrocephaly or microcephaly, hydrocephalus, meningitis, hepatosplenomegaly, and neurological abnormalities such as cerebral palsy, mental retardation, and seizures. The most common ocular manifestation is chorioretinal scarring, which is indistinguishable from toxoplasmosis scars; they can affect the peripheral retina or the macula. Optic atrophy can also be present.[71,72] There is no known effective treatment.

West nile virus is an RNA flavivirus transmitted to humans by mosquitos. Transmission can occur transplacentally and through breast milk. Most infections are asymptomatic. Systemic manifestations include pharyngitis, arthralgia, skin rash, encephalitis, meningitis, or paralysis. The most common ocular manifestation is chorioretinitis, which has been reported in congenital infection.

Human immunodeficiency syndrome intrauterine infection has decreased significantly with the advent of new drugs. These patients can present with CMV or toxoplasmic chorioretinitis.[73]



Fig. 12.13 Fundus of a 37 week gestation Brazilian baby born with microcephaly. The mother had an asymptomatic pregnancy. The macular area shows an oval, well circumscribed punched out chorioretinal lesion. Courtesy of Dr Camila Ventura.

Zika virus is a member of the Faviviridae virus; mosquitoes from the Aedes family are the vectors, which infect humans by direct inoculation.[74] An infection from a pregnant woman can spread to the foetus causing serious brain malformations and microcephaly,[75-76] as well as ophthalmic abnormalities which including focal pigment mottling and chorioretinal atrophy that can affect the macula (Fig. 12.13). These can be circumscribed areas with no choroidal vessels visible, or circumscribed areas of pigmentary clumping. Other ocular findings include optic nerve hypoplasia, severe optic disc cupping, lens subluxation, and iris colobomas.[77]

A widespread outbreak of Zika virus began in April 2015 in Brazil, and has spread to other countries in South America, Central America, Mexico and the Caribbean. 1.5 million people have been infected by Zika in Brazil, and more than 3,500 cases of microcephaly were reported between October 2015 and January 2016. [78-79]

There is no vaccine to prevent infection, and at present there is no treatment available.[80]

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Conjunctivitis of the newborn

Megan Geloneck and Gil Binenbaum

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Neonatal conjunctivitis or ophthalmia neonatorum is an inflammation or infection of the conjunctiva occurring within the first month of life. It is the most common infection in the first month of life, with an incidence from 1% to 24%, depending upon geographic region.[1] The three etiologies of neonatal conjunctivitis are chemical, bacterial, and viral. Though some types of conjunctivitis are self-limited and not vision threatening, others have important systemic associations or can cause blindness.

Common signs include conjunctival injection, chemosis, discharge, and eyelid edema. Some signs, such as laterality, severity of inflammation, character of discharge, and presence of pseudomembranes or skin vesicles, can be suggestive of a specific etiology, as can the clinical and maternal history. Generally, age at onset of conjunctivitis is not a reliable indicator of etiology.

Prophylaxis

Credé first described the use of ocular prophylaxis in newborns.[2] The widespread use of prophylaxis resulted in a great reduction in conjunctivitis-related blindness, but unfortunately ophthalmia neonatorum-related corneal scarring remains a leading cause of childhood blindness in developing countries.[3,4]

Types of prophylaxis include silver nitrate 1%, povidone iodine 2.5%, erythromycin ointment 0.5%, and tetracycline ointment 1%. These agents are meant to be administered to the inferior conjunctival fornix of both eyes within 1 hour of an infant's delivery. Silver nitrate is the agent most likely to cause a chemical conjunctivitis. Silver nitrate and tetracycline have demonstrated equal efficacy (83–93%) in the prevention of gonococcal ophthalmia neonatorum.[5] In a randomized controlled trial of 3117 Kenyan newborns, povidone iodine 2.5% was more effective than erythromycin or silver nitrate for prophylaxis of infectious conjunctivitis (13.1% vs. 17.5% vs. 15.2%).[6] In a smaller trial involving 410 Israeli newborns, the rate of infectious conjunctivitis appeared higher with povidone iodine (10.4%) than tetracycline (5.4%), but the difference failed to reach statistical significance ($p=0.052$); as expected, povidone iodine was more likely to cause a chemical conjunctivitis compared to tetracycline (5% vs. 0%).[7] When using povidone iodine, care should be taken to use a prep solution and not a scrub formulation, which causes significant chemical conjunctivitis and even corneal decompensation.

In the United States, erythromycin 0.5% is used as the topical prophylactic agent, as the other agents are not commercially available there. During an erythromycin shortage in 2009, the Centers for Disease Control recommended topical azithromycin 1% solution, or, if unavailable, topical gentamicin 0.3% or tobramycin 0.3% ointments. However, azithromycin is approximately 10 times more costly than povidone iodine prepared by a hospital pharmacy,[8] and topical gentamicin can cause periocular ulcerative dermatitis and should be avoided.[9]

Term colostrum shows insufficient antibacterial activity to be used as prophylaxis for neonatal conjunctivitis, and term milk shows no inhibitory activity.[10]

Chemical conjunctivitis

Chemical conjunctivitis develops within 1–2 days after the administration of a topical agent and is bilateral. Gram stain shows leukocytes but no organisms. Conservative management typically results in gradual resolution of symptoms within a couple of days.

Chlamydial conjunctivitis

The prevalence of *Chlamydia trachomatis* among pregnant women ranges from 2% to 20%; the higher rates are among younger women, and those without prenatal care.[11] The likelihood that an infant born to a mother with untreated *C. trachomatis* infection develops symptomatic conjunctivitis ranges from 20% to 50%.[5,12]

Chlamydial conjunctivitis (Fig. 13.1A) typically develops 5–14 days after delivery but can begin earlier. Though more

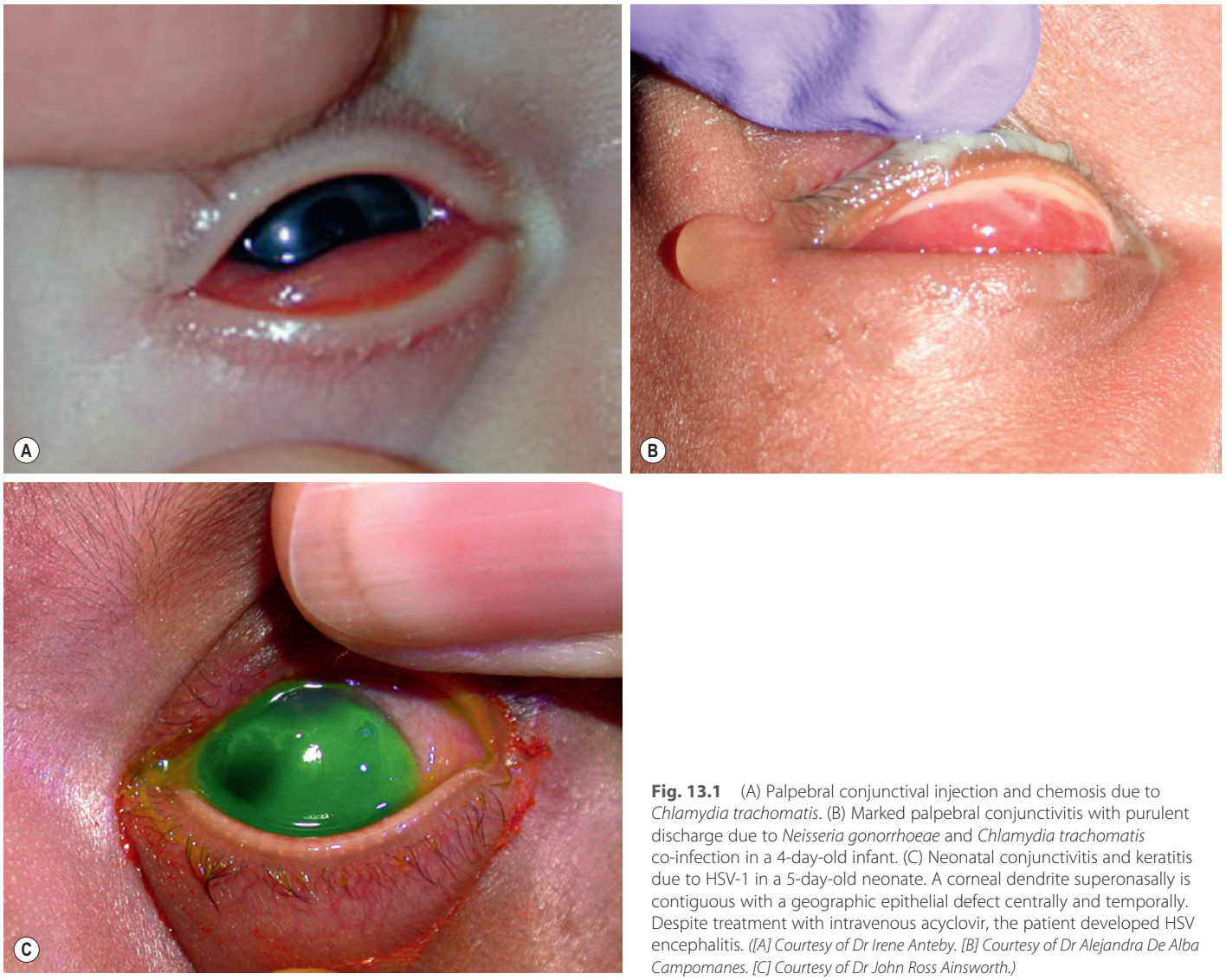


Fig. 13.1 (A) Palpebral conjunctival injection and chemosis due to *Chlamydia trachomatis*. (B) Marked palpebral conjunctivitis with purulent discharge due to *Neisseria gonorrhoeae* and *Chlamydia trachomatis* co-infection in a 4-day-old infant. (C) Neonatal conjunctivitis and keratitis due to HSV-1 in a 5-day-old neonate. A corneal dendrite superonasally is contiguous with a geographic epithelial defect centrally and temporally. Despite treatment with intravenous acyclovir, the patient developed HSV encephalitis. *([A] Courtesy of Dr Irene Anteby. [B] Courtesy of Dr Alejandra De Alba Campomanes. [C] Courtesy of Dr John Ross Ainsworth.)*

common among infants born vaginally, it can follow cesarean section delivery. The conjunctivitis can be unilateral or bilateral, with mucopurulent discharge and possible pseudomembrane formation. Untreated, the conjunctivitis resolves after weeks to months, but can cause conjunctival and corneal scarring, which can be blinding. Furthermore, if left untreated, it is contagious, posing a public health threat to others.

Classically, the diagnosis is made by isolating *Chlamydia* via culture obtained by scraping the palpebral conjunctiva for epithelial cells. Intracellular inclusions can be demonstrated on Giemsa stain. Recently, polymerase chain reaction (PCR) detection was found to have higher sensitivity (100%) and similarly high specificity (95%) compared with culture and Giemsa stain, and may be superior in mild disease.[13,14]

Chlamydial conjunctivitis is associated with systemic disease including otitis media, nasal congestion, and pneumonitis occurring later, at 4–12 weeks of life. Chlamydial conjunctivitis is treated with oral erythromycin (50 mg/kg divided into 4 daily doses) for 14 days.[11] Asymptomatic infants born to mothers with untreated *C. trachomatis* infection are not treated prophylactically, in part because erythromycin can cause infantile hypertrophic pyloric stenosis.[15] For infants with conjunctivitis but no sign of pneumonia, systemic erythromycin can be delayed while awaiting confirmatory diagnostic tests for *Chlamydia*, but the infant should be monitored closely for systemic signs. Oral azithromycin (20 mg/kg daily for 3 days) is an alternative, though experience with its use in neonates is limited. The mother and her sexual partners should be treated with a single dose of oral azithromycin (1 g) and be evaluated for other sexually transmitted diseases. Some areas with a high incidence of trachoma are instituting annual or biannual mass prophylaxis with oral azithromycin to reduce the incidence of *C. trachomatis*, with moderate success.[16]

Gonococcal conjunctivitis

The prevalence of gonococcal cervical infection among women in developed countries is typically less than 1%; however, the prevalence in some countries is as high as 22%.[17] Newborns of mothers with gonococcal infection who do not receive prophylaxis have a 30–47% likelihood of developing conjunctivitis after vaginal delivery.[12,17] The gonococcal transmission rate increases to 68% if the mother is also infected with *Chlamydia*.[12]

Gonococcal conjunctivitis is also possible among infants born by caesarean section.

Infants typically exhibit symptoms 2–5 days after delivery, but can present later. The conjunctivitis has an aggressive course, with profuse purulent discharge, and severe conjunctival injection, chemosis, and eyelid edema (Fig. 13.1B). Gonococcus can invade the cornea through intact epithelium, leading to keratitis, ulceration, perforation, and endophthalmitis, or corneal scarring with neovascularization. Corneal involvement begins with coarse white peripheral infiltrates. Ulceration can progress rapidly, so aggressive treatment is required.[5] One study showed that 4 of 25 patients (16%) with gonococcal conjunctivitis developed corneal involvement.[18]

All infants born to *N. gonorrhoeae*-infected mothers, whether or not conjunctivitis is present, should be treated prophylactically with a single dose of intravenous (IV) or intramuscular (IM) ceftriaxone (25–50 mg/kg up to 125 mg maximal) or cefotaxime (100 mg/kg IM or IV) if the infant has hyperbilirubinemia.[11] Infants with suspected gonococcal conjunctivitis should undergo Gram stain, culture using modified Thayer-Martin medium, and/or PCR testing, if available, prior to beginning antibiotics, though unnecessary delays in treatment should be avoided. Identification of gram-negative diplococci on Gram stain has a sensitivity of 86% and specificity of 90% for gonococcal conjunctivitis.[18] In febrile infants, blood and cerebrospinal fluid (CSF) cultures should be obtained to assess for bacteremia and meningitis, and the baby should be monitored clinically for septic arthritis. Due to frequent maternal co-infection with *Chlamydia*, Giemsa stain and chlamydial culture and/or PCR testing should also be performed. In the presence of systemic infection, the cephalosporin course is extended to 7–14 days. Antibiotic eye drops may be used, particularly if there is corneal involvement, and frequent (i.e. hourly) saline lavage of the purulent discharge should be performed. The mother and her sexual partners should be treated for gonococcus and presumptively for *Chlamydia*, and should be evaluated for other sexually transmitted diseases.

Other bacterial conjunctivitis

Neonatal nasopharyngeal colonization rather than maternal vaginal colonization is implicated in most bacterial conjunctivitides not due to *Chlamydia* or *Gonococcus*.[19] *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Streptococcus viridans*, *Enterococcus* spp., and *Haemophilus* spp. are more commonly isolated from conjunctival swabs in neonates with conjunctivitis compared to controls without.[19,20] Bacterial conjunctivitis typically presents at days 5–14 of life and can be unilateral or bilateral. Bacteria can be cultured on chocolate and blood agar. Some positive cultures represent colonizing rather than disease-causing bacteria. A broad-spectrum topical antibiotic can be used until culture results are available, but many cases resolve without treatment.

Herpetic conjunctivitis

Herpes simplex virus (HSV) can rarely cause neonatal conjunctivitis. Neonates can become infected via vaginal delivery or ascending intrauterine infection if the mother has genital HSV. The risk of infection is far greater if the mother has primary rather than re-activated genital HSV (25–60% vs. 2%). Neonates can also become infected via direct contact with caregivers who have herpes labialis or herpetic whitlow.[11]

Ophthalmic manifestations of neonatal HSV include eyelid vesicles and erythema, conjunctivitis, keratitis, and anterior uveitis (Fig. 13.1C). The keratitis can involve all layers of the cornea and does not follow the disease patterns seen in adults. Ophthalmic manifestations usually occur 5–14 days after exposure. Neonatal HSV keratoconjunctivitis typically occurs in the setting of systemic disease, which can include disseminated disease (pneumonitis, hepatitis), skin disease (dermatitis, mucositis), and central nervous system (CNS) disease (meningoencephalitis). The onset of systemic disease can be delayed up to 6 weeks from birth.

HSV culture or PCR testing (of conjunctiva, corneal epithelium, or skin vesicle scraping), CSF analysis, including HSV PCR, and liver function tests should be obtained in neonates with suspected HSV keratoconjunctivitis. Other rapid diagnostic techniques include direct fluorescent antibody staining or enzyme immunoassay detection of HSV antigens within scrapings. However, serum HSV antibody testing is not useful in neonates.

Asymptomatic infants are treated with prophylactic IV acyclovir if they are born to mothers with primary genital HSV at the time of vaginal delivery or if surface testing detects HSV. Neonatal HSV infection is treated with IV acyclovir (60 mg/kg per day divided into three doses) for 14 days, or for 21 days in the presence of disseminated or CNS disease.[11] Adjunctive therapy with topical trifluorouridine 1%, iododeoxyuridine 0.1%, or vidarabine 3% can be considered, but topical ganciclovir 0.15% ophthalmic gel has less corneal toxicity. A topical steroid may be added for corneal stromal and endothelial disease if the corneal epithelium is intact, and topical steroid and cycloplegia for uveitis. Babies with neonatal HSV have a high risk of death and are hospitalized for the duration of IV treatment.[11] They are also at high risk of HSV re-activation, and prophylactic acyclovir should be continued for at least 6 months after hospital discharge.[21]

Neonatal conjunctivitis in the hospital

Hospitalized neonates acquire infection via hospital workers and instruments, and via assisted ventilation, which is thought to increase the contact of nasopharyngeal flora with the eye.[21] Most of these infants are premature or have multiple comorbidities. Coagulase-negative staphylococci, *Staphylococcus aureus* and *Klebsiella* spp. were the most commonly isolated species in a study of 200 neonates in a US intensive care nursery.[22] *Serratia marcescens* is another common cause of conjunctivitis outbreaks in neonatal intensive care nurseries, and has been found to cause 27% of conjunctivitis in some parts of the world.[23,24] Methicillin-resistant *Staphylococcus aureus* has also caused conjunctivitis outbreaks in neonatal intensive care units,[25] and its incidence is possibly increasing.[26]

Laboratory testing

While the clinical history can sometimes help to guide appropriate laboratory testing, multiple infectious causes are

typically in the differential diagnosis, so broad laboratory testing including the following is usually required:

- Gram stain.
- Chlamydial culture, PCR, or Giemsa stain.
- Gonococcal culture on Thayer-Martin medium or PCR.
- Bacterial cultures using blood or chocolate agar.
- HSV culture, PCR, direct fluorescent antibody, or enzyme immunoassays.

Approximately half of clinically evident neonatal conjunctivitides have negative culture results; therefore, empiric treatment is often the mainstay of management.[19]

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Preseptal and orbital cellulitis

Richard L Scawn and Jimmy M Uddin

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The diagnosis of infective preseptal and orbital cellulitis is clinical. The goal is to prevent rapid deterioration and serious sequelae such as visual loss, cavernous sinus thrombosis, cerebral abscess, osteomyelitis, and septicemia. It must be managed promptly with appropriate antibiotics and medical support from a multidisciplinary team consisting of pediatricians, ophthalmologists, ear, nose and throat (ENT) surgeons, nurses, and radiologists. Regular evaluation for progression of signs or deterioration of the clinical picture is essential. Neuroimaging may be necessary to determine the extent of the disease.

Anatomy and terminology

The orbital septum marks the anterior extent of the orbit. Its firm attachment to the orbital rim along with the attachment of the orbital periosteum is referred to as the arcus marginalis; it extends to the upper and lower tarsal plates. Preseptal cellulitis is a descriptive term for patients who present with symptoms and signs of inflammation confined largely to the eyelids: pain, redness, and swelling. The orbital septum acts as a physical barrier to lesions spreading posteriorly to the orbit. Orbital cellulitis involves infection of the postseptal space and usually results from adjacent infected sinuses, commonly the ethmoids. Many vessels and nerves pierce the thin lamina papyracea between the ethmoid sinuses and the orbit: infection easily spreads through these and other naturally occurring perforations, and may lift off the loosely attached periosteum within the anterior orbit, resulting in a subperiosteal abscess. An orbital abscess results from an infectious breach of the periosteum or seeding into the orbit. Extension of infection from the ethmoids into the brain may result in meningitis and cerebral abscesses. The presence of decreased, painful eye movements, proptosis, optic neuropathy, or radiological evidence of orbital inflammation or collections signifies orbital cellulitis.

The drainage of the eyelids, sinuses, and orbits is largely by the orbital venous system, which empties into the cavernous sinus via the superior and inferior orbital veins. Since it is devoid of valves, infection may spread in both preseptal and orbital cellulitis, leading to the serious sight- and life-threatening complication of cavernous sinus thrombosis.

Classification

Infective orbital cellulitis and its complications can be classified into five types that are not mutually exclusive and do not necessarily progress in that order[1] (Table 14.1):

1. preseptal cellulitis;
2. orbital cellulitis;
3. subperiosteal abscess;
4. orbital abscess;
5. cavernous sinus thrombosis.

Preseptal cellulitis

Preseptal cellulitis is five times more common than orbital cellulitis, especially in children under the age of 5 years.[2,3] It is often secondary to lid and cutaneous infections – styes, impetigo, erysipelas, herpes simplex, varicella, or dacryocystitis (Figs 14.1, 14.2, and 14.3). It is also associated with upper respiratory tract infections, uncomplicated sinusitis (Fig. 14.4), or lid trauma.

Infective preseptal cellulitis must be distinguished from other causes of lid edema such as adenoviral keratoconjunctivitis, atopic conjunctivitis, or, rarely, Kawasaki disease.[4] In one series, 16% of children referred with preseptal cellulitis were found to have adenoviral keratoconjunctivitis.[5]

Clinical assessment

History

Children with preseptal cellulitis associated with an upper respiratory tract infection or sinusitis present in the winter

months with preceding nasal discharge, cough, fever, localized tenderness, and general malaise, followed by unilateral eyelid swelling. Bilateral involvement is rare. There is history of a localized lid infection or trauma with swelling spreading from an identifiable point.

Examination

The child may be generally unwell and febrile. The cellulitis ranges from a mild localized involvement, with or without an abscess, to generalized tense upper and lower lid edema spreading to the cheek and brow, precluding examination of the eye. Localized causes such as styes, trauma, and dacryocystitis should be evident. There is an absence of proptosis; optic nerve functions and extraocular movements are normal.

It can be difficult to differentiate between preseptal and orbital cellulitis and the diagnosis may change from preseptal to orbital cellulitis if orbital signs become more obvious, clinically or by imaging.[6]

Table 14.1 Classification of orbital cellulitis

Stage	Signs and symptoms	Computed tomography findings
Preseptal cellulitis	Eyelid swelling, occasional fever	If performed, sinusitis may be present
Orbital cellulitis	Proptosis, decreased painful eye movements, chemosis	Sinusitis, mild soft tissue changes in the orbit
Subperiosteal abscess	Signs of orbital cellulitis, systemic involvement	Subperiosteal abscess, globe displacement, soft tissue changes in the orbit
Orbital abscess	Signs of orbital cellulitis, systemic involvement, ophthalmoplegia, visual loss	Orbital collection of pus with marked soft tissue changes of the fat and muscles
Intracranial complication	Signs of orbital or rarely preseptal cellulitis, marked proptosis, cranial nerve palsies (III, IV, V, VI)	Intracranial changes: cavernous sinus thrombosis, extradural abscess, meningitis, and osteomyelitis

Modified from Uzcategui N, Warman R, Smith A, et al. Clinical practice guidelines for the management of orbital cellulitis. J Pediatr Ophthalmol Strabismus 1998; 35: 73–9. © 1998 Slack Inc.



Fig. 14.1 Preseptal cellulitis secondary to eczema herpeticum.



Fig. 14.2 (A) Preseptal cellulitis associated with a lid abscess. Normal eye movements with a white eye (patient looking up). (B) Intravenous antibiotics and surgical drainage resolved her condition.



Fig. 14.3 (A) Cellulitis associated with dacryocystitis in a 1-year-old child. (B) Acute infection resolved with antibiotics. Patient subsequently underwent probing to treat the underlying nasolacrimal duct obstruction.



Fig. 14.4 Preseptal/orbital cellulitis treated successfully with intravenous antibiotics. (A) At presentation with swollen lids and possibly mild proptosis. Patient was admitted under pediatricians, ophthalmologist, and ENT. She was treated immediately with intravenous antibiotics. No imaging was performed. (B) Responding to antibiotics within 12 hours. (C) Fully resolved at 4 days.

The clinical picture varies with the organism involved. In staphylococcal infections there is a purulent discharge, while *Haemophilus* infection leads to a non-purulent cellulitis with a characteristic bluish-purple discoloration of the eyelid with irritability, raised temperature, and sometimes otitis media (Fig. 14.5). In streptococcal infection there is usually a sharply demarcated red area of induration,[7] heat, and marked tenderness (Fig. 14.6A,B). Preseptal cellulitis may be complicated by meningitis, particularly if the infection is due to *Haemophilus influenzae* type B.[8]

Management

In children who develop preseptal cellulitis following an upper respiratory tract infection, cultures should be taken from the nose, throat, conjunctiva, and any accessible aspirates of the periorbital edema.

Children with mild-to-moderate preseptal cellulitis can be managed in the same way as uncomplicated sinusitis on an outpatient basis with oral broad-spectrum antibiotics, or as an inpatient with intravenous antibiotics if more severe (Table 14.2).[9,10]

Admission, intravenous antibiotics, and close observation may be more appropriate in more severe preseptal cellulitis, young children, the immunocompromised, or those who are systemically unwell.

Neuroimaging to assess orbital, sinus, and brain involvement is indicated when lid swelling prevents an adequate examination of the eye.[11]

Children with a local cause for the periorbital edema, such as dacryocystitis, need specific treatment for the underlying condition and rarely need further investigation.



Fig. 14.5 Preseptal cellulitis due to *Haemophilus influenzae* in a 6-month-old infant.

Table 14.2 Initial antibiotic treatment of preseptal and orbital cellulitis

Preseptal cellulitis	Associated with upper respiratory tract infection Cefuroxime 100–150 mg/kg per day or amoxicillin-clavulanate (Augmentin) or ampicillin 50–100 mg/kg per day
Orbital cellulitis	Empiric combination of two or more antibiotics may be initiated. This may include a third-generation cephalosporin with good CNS penetrance coupled with gram-positive antibiotic cover. Metronidazole can be added according to clinical suspicion of anaerobic organisms. Flucloxacillin: 50 mg/kg qds IV (max 2 g/dose) Co-amoxiclav: 30 mg/kg tds (max 1.2 g/dose) Metronidazole: 7.5 mg/kg tds (max 500 mg/dose) Vancomycin should be considered in resistant cases Clindamycin should be added in necrotizing fasciitis

Note: You should consult your own pharmacy for correct doses.
The exact dose will vary with age and severity of infection.
There may be local variations in pathogens and antibiotic resistance.
Development of a local antibiotic policy in conjunction with a microbiologist is recommended



Fig. 14.6 (A) Streptoccocal preseptal cellulitis in a 12-month-old child. (B) It is useful to mark the extent of cellulitis for monitoring purposes. This 10-year-old girl had proptosis and responded to intravenous antibiotics.



Fig. 14.7 Beta-hemolytic *Streptococcus* may cause necrotizing fasciitis, as shown here. *(Courtesy of Mr G. Rose.)*

Lid trauma may result in suppurative cellulitis, when the causative agent is *Staphylococcus aureus* or a beta-hemolytic *Streptococcus*. It is usually sufficient to culture the wound discharge, as there is rarely any bacteremia; blood cultures are usually negative.[12] Parenteral antibiotics are administered and tetanus prophylaxis is provided, if appropriate. If the skin has been penetrated by organic material or animal bites, antibiotics should include coverage for anaerobic organisms.

Rarely, beta-hemolytic *Streptococcus* may cause necrotizing fasciitis. It is characterized by a rapidly progressive tense and shiny cellulitis with excessive edema and poorly demarcated borders with a violaceous skin discoloration. Necrosis develops and streptococcal toxic shock syndrome is common (Fig. 14.7). Treatment is with immediate hospitalization involving a multidisciplinary team implementing resuscitation and medical support with immediate high-dose intravenous antibiotics including a penicillin or third-generation cephalosporin and clindamycin. Surgical debridement should be considered if there is not a clear response to medical treatment.[13,14]

Orbital cellulitis

Etiology

Infective orbital cellulitis is more frequent in children over 5 years (average age 7 years). In over 90% it is secondary to sinusitis,[12,15] especially of the ethmoid. It is more common in cold weather when the frequency of sinusitis increases. Other less common causes are penetrating orbital trauma, especially when there is a retained foreign body, dental infections,[16] extraocular muscle and retinal surgery,[17] and hematogenous spread during a systemic infectious illness.

Orbital cellulitis is always serious and potentially sight- and life-threatening, giving rise to a variety of systemic and ocular complications (Box 14.1). In the pre-antibiotic era, one-fifth of patients died from septic intracranial complications; one-third of the survivors lost vision in the affected eye.[18] This poor outlook has been dramatically altered by effective antibiotics and the changing spectrum of causative organisms, but prompt diagnosis and vigorous treatment are still essential.

History

The usual presentation is with a painful red eye and increasing lid edema in a child who has had a recent upper respiratory tract infection. The child is usually miserable, pyrexial, and unwell.

Box 14.1

Complications of orbital cellulitis

Optic neuritis
Optic atrophy
Exposure keratitis
Central retinal artery occlusion[19]
Retinal and choroidal ischemia[20]
Subperiosteal and orbital abscess[23,24]
Cavernous sinus thrombosis
Meningitis[12]
Brain abscess
Septicemia[22]

Table 14.3 The differential diagnosis of inflammatory proptosis

Infection	Orbital cellulitis or cavernous sinus thrombosis
Idiopathic and specific inflammation	Orbital idiopathic inflammation, myositis, sarcoidosis, and Wegener granulomatosis
Neoplasia	Leukemia, Burkitt lymphoma, rhabdomyosarcoma, extra-scleral retinoblastoma, metastatic carcinoma, histiocytosis X (Letterer–Siwe variety), dermoid cyst (rupture and inflammation), and ethmoid osteoma
Trauma	Traumatic hematoma, orbital emphysema, retained foreign body
Systemic	Sickle cell disease (bone infarction) conditions
Endocrine	Dysthyroid exophthalmos (very rare) dysfunction

Modified from Jain A, Rubin PA. Orbital cellulitis in children. Int Ophthalmol Clin 2001; 41: 71–86.

Examination

There are signs of orbital dysfunction, including proptosis, reduced and painful extraocular movements, and optic nerve dysfunction. There may be involvement of cranial nerves III, IV, and VI, especially with superior orbital fissure and cavernous sinus involvement. Visual loss, when it occurs, is usually due to an optic neuropathy but may also be caused by exposure keratitis or a retinal vascular occlusion.[19,20]

The acute, sometimes explosive, onset of pain, fever, and systemic illness helps to differentiate orbital cellulitis from most other causes of inflammatory proptosis, which should always be considered when seeing a patient with cellulitis (Table 14.3 and Fig. 14.8A–D).

Orbital cellulitis is partially constrained by the septum at the arcus marginalis; the preseptal soft tissue signs may be less dramatic than those in preseptal cellulitis. Conjunctival chemosis and injection may be subtle or even absent.

Management

Children with orbital cellulitis should be admitted under the care of pediatricians, ophthalmologists, ENT surgeons, and the infectious disease team. Blood cultures, nasal, throat, and conjunctival microbiology swabs may be taken. These are often negative, but a positive result is helpful in planning antibiotic treatment. This should not delay immediate and appropriate intravenous antibiotics and fluid resuscitation where necessary.

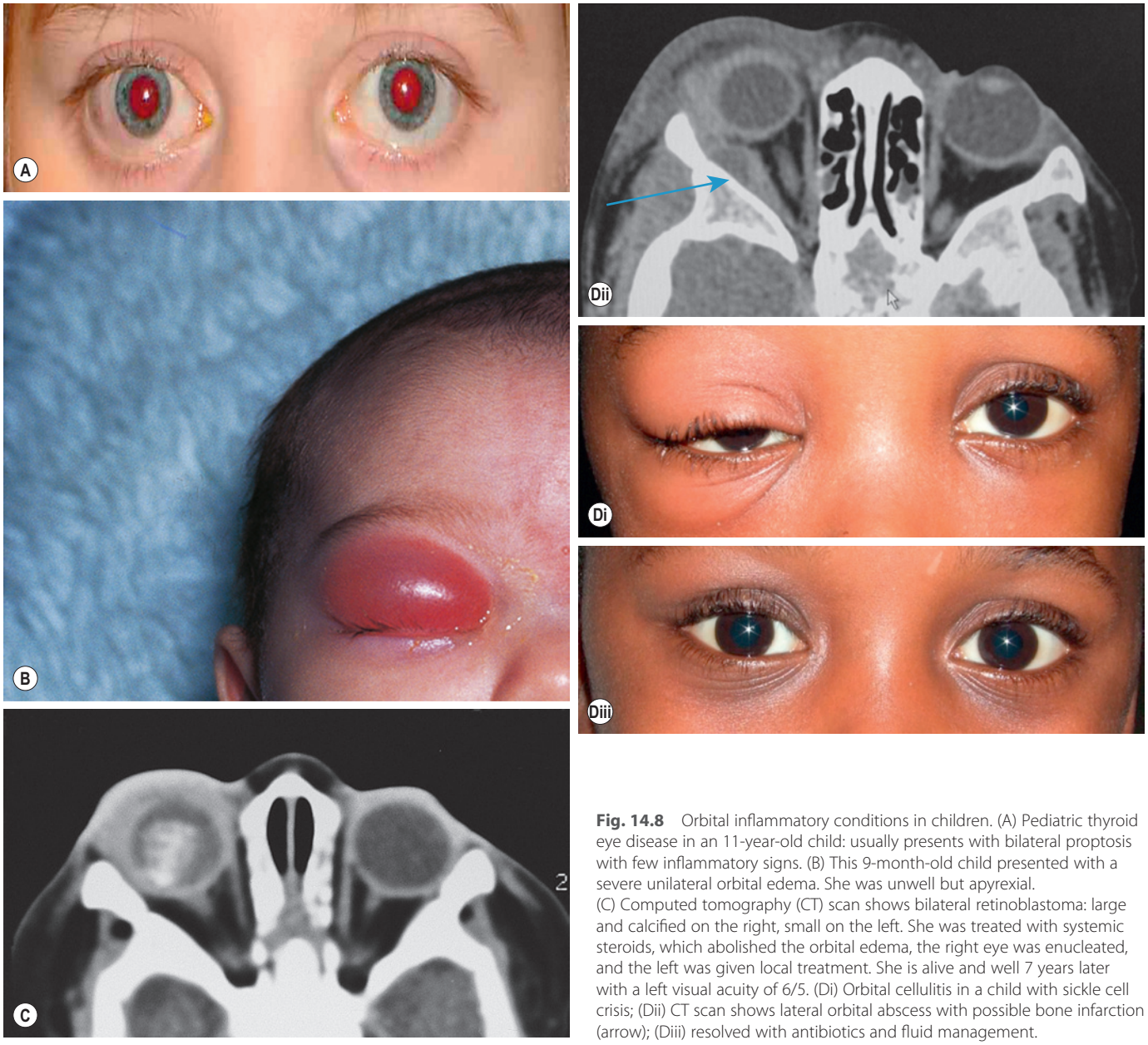


Fig. 14.8 Orbital inflammatory conditions in children. (A) Pediatric thyroid eye disease in an 11-year-old child: usually presents with bilateral proptosis with few inflammatory signs. (B) This 9-month-old child presented with a severe unilateral orbital edema. She was unwell but apyrexial. (C) Computed tomography (CT) scan shows bilateral retinoblastoma: large and calcified on the right, small on the left. She was treated with systemic steroids, which abolished the orbital edema, the right eye was enucleated, and the left was given local treatment. She is alive and well 7 years later with a left visual acuity of 6/5. (Di) Orbital cellulitis in a child with sickle cell crisis; (Dii) CT scan shows lateral orbital abscess with possible bone infarction (arrow); (Diii) resolved with antibiotics and fluid management.

The initial treatment of orbital cellulitis in infants should be with a high-dose intravenous third-generation cephalosporin, such as cefotaxime, ceftazidime, or ceftriaxone, combined with a penicillinase-resistant penicillin. Given the potential intracranial complications of orbital cellulitis, antibiotics with good blood–brain barrier penetration are thought to be advantageous.[21] In older children, sinusitis is frequently caused by mixed aerobic and anaerobic organisms so clindamycin may be substituted for penicillinase-resistant penicillin. Metronidazole is now being increasingly used in younger children. An alternative regimen is the combination of penicillinase-resistant penicillin with chloramphenicol (see Table 14.2). The initial regime may be modified after culture results. Nasal decongestants such as ephedrine may be helpful in promoting intranasal drainage of infected sinuses. The child should be monitored closely for deterioration of ocular and systemic signs and management modified.

Steroids in orbital cellulitis

Evidence for the use of steroids in pediatric orbital cellulitis is emerging, but remains limited.[22,23] The potential for immunosuppression in the presence of infection courts controversy. However, advocates of adjuvant steroids cite improved outcomes with steroids in meningitis and two recent studies of orbital cellulitis within pediatric populations demonstrated some benefits when steroids were added. One of these studies randomized patients with orbital cellulitis over 10 years age who had already received intravenous antibiotics for 3–5 days and shown a clinical response to either receive steroids or continue antibiotic therapy.[22] Steroids appeared to hasten clinical recovery, although long-term outcomes were similar in each treatment group. The second study investigated whether systemic steroids offered a benefit and also used C-reactive protein (CFP) as a marker for initiating treatment.[23]

The authors concluded that children receiving oral steroids once the CRP has fallen below 4 g/dl were discharged from hospital earlier. It will be interesting to see whether further evidence leads to wider adoption of steroids and at what point in treatment algorithms steroids should be considered.

Orbital imaging

Computed tomography (CT) is the investigation of choice. CT is usually readily available. The quick acquisition of images (compared to magnetic resonance imaging [MRI]) makes it ideal for children in the urgent-care setting of orbital cellulitis. CT will define the extent of sinus disease, intracranial involvement, subperiosteal or orbital abscesses, and should include coronal views to avoid potentially missing an abscess in a third of patients.[24] Although a CT scan may detect subperiosteal (Figs 14.9 and 14.10) and orbital abscesses not apparent clinically or on plain films,[11,25] the management of mild and moderate orbital cellulitis without optic nerve compromise or intracranial complications is initially medical. Imaging may be unnecessary unless there is a poor response to intravenous antibiotics, increasing systemic signs, progression of orbital signs, or expectant surgical management. MRI scanning is advantageous in that there is no radiation exposure, but the long acquisition time and the need for sedation or anesthesia in children makes it a second-line modality. It is more sensitive than CT in detecting intracranial complications such as cavernous sinus thrombosis where a false negative CT is more likely in early disease. MRI may be more sensitive than CT in delineating the extent of fungal sinus disease. The T2-weighted MRI in mycotic infection may appear hypodense due to paramagnetic material produced by the fungi.[26]

Sinus X-rays may be difficult to interpret in small children due to the lack of development of the sinuses and are generally unhelpful.

Microbiology of preseptal and orbital cellulitis

Historically, the most feared pathogen in both preseptal and orbital cellulitis, as well as sinusitis, was *H. influenzae* type B (Hib). Vaccination against Hib was widely available from 1990. In a study of 315 preseptal and orbital cellulitis cases, 297 were preseptal and 18 were orbital cellulitis. Before 1990, 12% were found to be Hib-related cellulitis and after 1990, 3.5%. The overall rate of cellulitis also declined by 60% in the 1990s.[3] The dramatic decline of culture-positive infection may be due to higher threshold for admission (managed care), improved general child health, and earlier and more aggressive outpatient use of antibiotics (e.g. oral cephalosporins).

In younger children, the most common pathogens, in the post-Hib-vaccine era, became *Staphylococcus aureus* and *Staphylococcus epidermidis*; *Streptococcus pneumoniae*, *Strep. pyogenes*, and *Strep. sanguinis*; and *Moraxella catarrhalis*.[3,6] These organisms mirror the microbiology of sinusitis. Older children have bacteriologically more complex sinus infections and, therefore, orbital cellulitis.[27] Polymicrobial infections and anaerobic infections are more common in older children

Methicillin-resistant *Staph. aureus* (MRSA) orbital cellulitis is a serious concern. Increasing prevalence, especially in the community, has led to empiric antibiotic choices changing, with the increasing use of vancomycin. MRSA was reported in as many as 73% of all *Staph. aureus* orbital cellulitis isolates in one US study.[28] However, two other contemporary studies reported 1% of patients or 12% of *Staph. aureus* isolates to be methicillin resistant.[29,30] The variation highlights the need for obtaining microbiology samples where possible and developing a locally tailored antibiotic policy in conjunction with a microbiologist. Treatment options for MRSA orbital cellulitis include vancomycin or clindamycin.[31] MRSA infections present a challenge, not only due to their antibiotic resistance, but also because of the production of powerful leucocidins and enterotoxins blunting the immune response and enhancing their pathogenicity.[32,33] In Liao and Harris's 2002–2012 pediatric and adult orbital subperiosteal abscess (SPA) series, all four MRSA-positive pediatric cases presented with advanced disease prompting emergency drainage.[33] MRSA orbital cellulitis infections may also present in an atypical fashion.[31] A preceding upper respiratory tract infection with sinusitis is typically absent, as is any penetrating skin injury. Lacrimal gland abscess was a feature in five of six children in a series of MRSA orbital cellulitis reported by Mathias et al., and surgical drainage was required in almost all cases.[31]

Fungal infections are rare but should be considered when orbital cellulitis occurs in an immunosuppressed or diabetic child.[34] Children with cystic fibrosis are more likely to be infected with *Pseudomonas aeruginosa* or *Staph. aureus*.

Subperiosteal and orbital abscess

The incidence of subperiosteal and orbital abscesses complicating orbital cellulitis was about 10%,[35] but is now declining. Most have sinus infection. In subperiosteal abscess, a purulent infection within a sinus, usually the ethmoid, breaks through the thin orbital bony wall (lamina papyracea) and lies beneath the loosely adherent periosteum, which is easily lifted off the bone, giving a convex "lens" type of appearance on CT scan. An orbital abscess occurs either when a subperiosteal abscess breaches the periorbita or when a collection of pus forms within the orbit.

The most common causative organism is *Staphylococcus*, but *Streptococcus*, *H. influenzae*, and anaerobic organisms may also be responsible. MRSA may be suspected when there is marked systemic toxicity and orbital signs, or when orbital cellulitis is slow to respond to adequate intravenous antibiotics.[33] The presence of subperiosteal abscess may be indicated by lateral displacement of the globe away from the infected sinus, impaired adduction, and resistance to retropulsion.[36]

All studies have recommended hospitalization for intravenous antibiotic therapy (see Table 14.2) and repeated eye examinations to evaluate progression of infection or involvement of the optic nerve.

CT scanning (see Fig. 14.4) at presentation is not always necessary, especially if there is mild orbital cellulitis with sinusitis and no optic nerve compromise or intracranial signs. It is indicated if the presentation is unusual, severe, in an older child, or there are optic nerve or intracranial signs. If the child does not respond to treatment, it is advisable to image the sinuses, orbits, and intracranial compartment with a CT scan (Figs 14.11 and 14.12). A contrast-enhanced scan gives additional information in differentiating an abscess, which

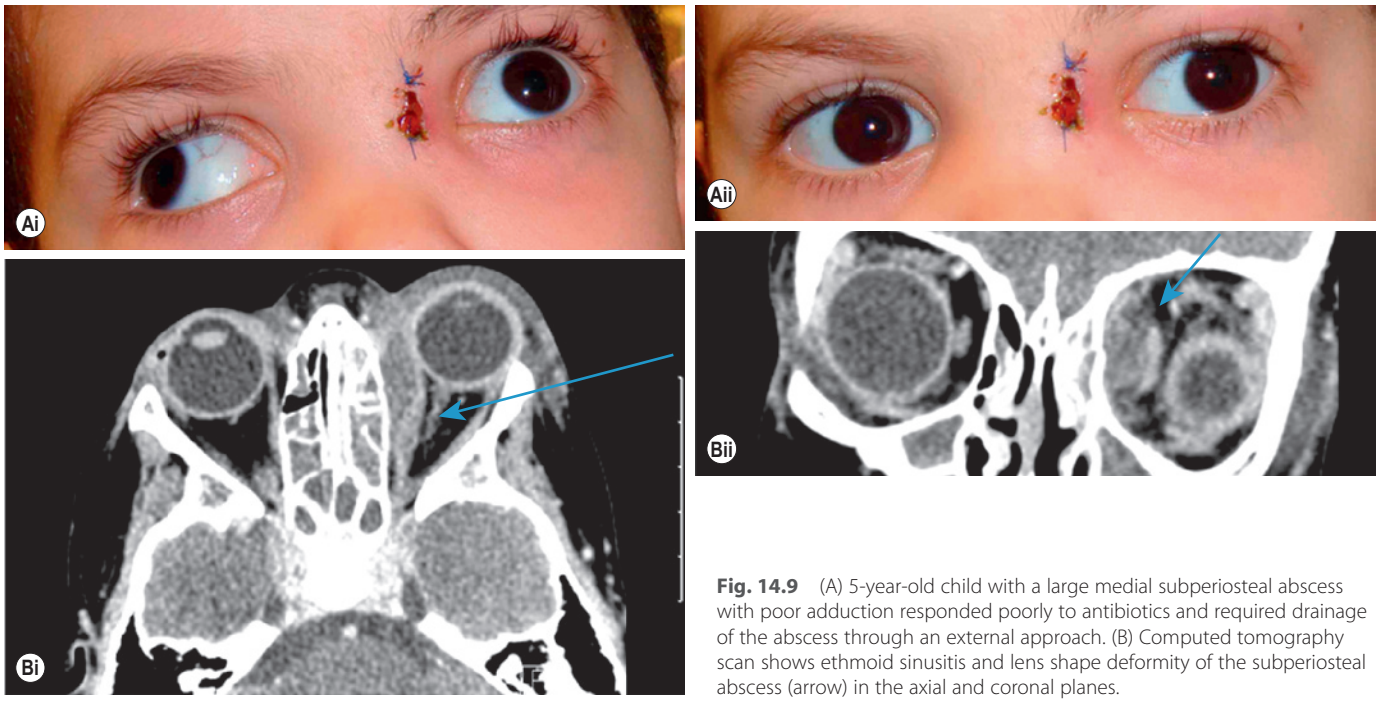


Fig. 14.9 (A) 5-year-old child with a large medial subperiosteal abscess with poor adduction responded poorly to antibiotics and required drainage of the abscess through an external approach. (B) Computed tomography scan shows ethmoid sinusitis and lens shape deformity of the subperiosteal abscess (arrow) in the axial and coronal planes.

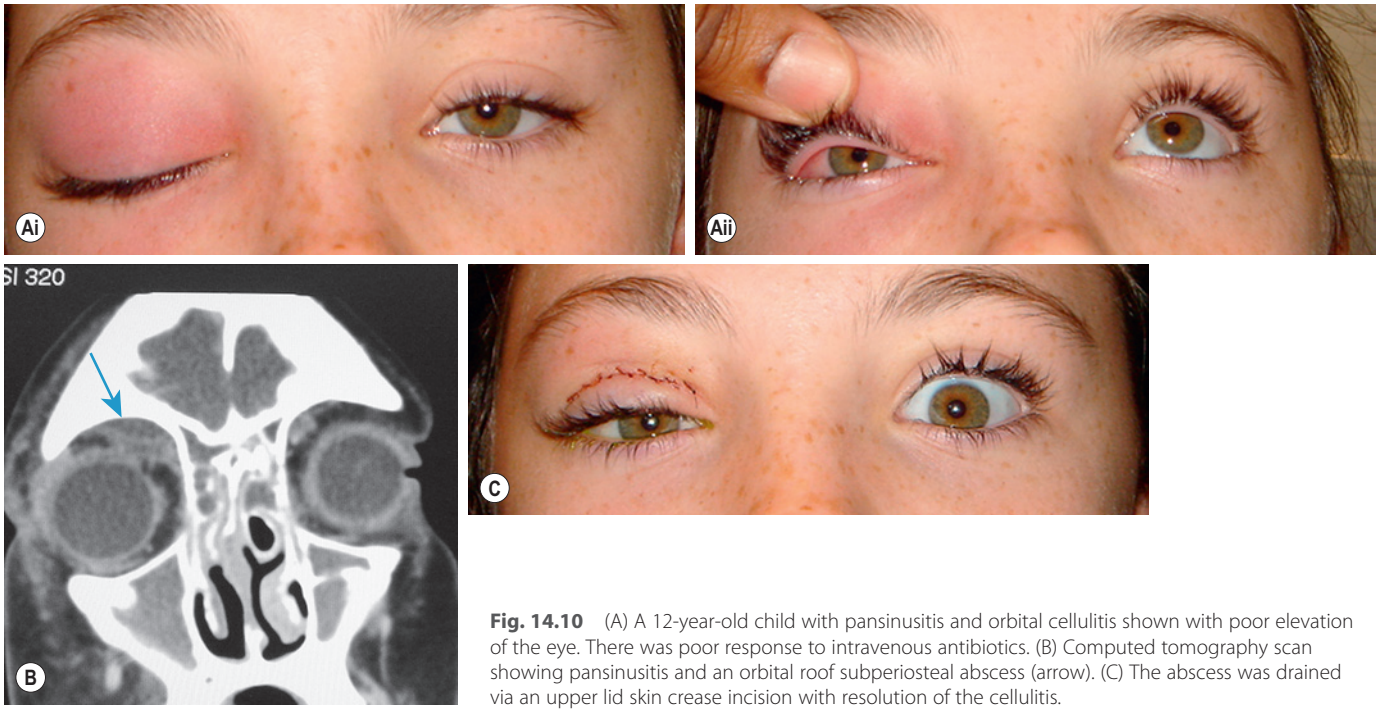


Fig. 14.10 (A) A 12-year-old child with pansinusitis and orbital cellulitis shown with poor elevation of the eye. There was poor response to intravenous antibiotics. (B) Computed tomography scan showing pansinusitis and an orbital roof subperiosteal abscess (arrow). (C) The abscess was drained via an upper lid skin crease incision with resolution of the cellulitis.

is amenable to drainage, from a phlegmon (purulent tissue inflammation), which is not.

An orbital abscess should be drained. The management of subperiosteal abscess is more controversial[6] because they may resolve with medical treatment.[6,27,37]

In a review of 37 patients with subperiosteal abscess secondary to sinusitis, resolution occurred in 83% of patients under 9 years of age who were treated medically or who had negative cultures on drainage.[38] In contrast, only 25% of those aged between 9 and 14 years cleared without drainage or had negative cultures on drainage. The remaining group, aged 15 years and over, were refractory to medical therapy alone. In a review of the management of subperiosteal abscess, the authors found that if the maximum abscess width was smaller than 10 mm medical treatment alone was successful in 81% of patients. In contrast, 92% of patients with an abscess larger than 10 mm underwent surgery.[39]

Nine children (2 months to 4 years) with subperiosteal abscesses were managed with a third-generation cephalosporin and vancomycin in the first 24–36 hours; only one required



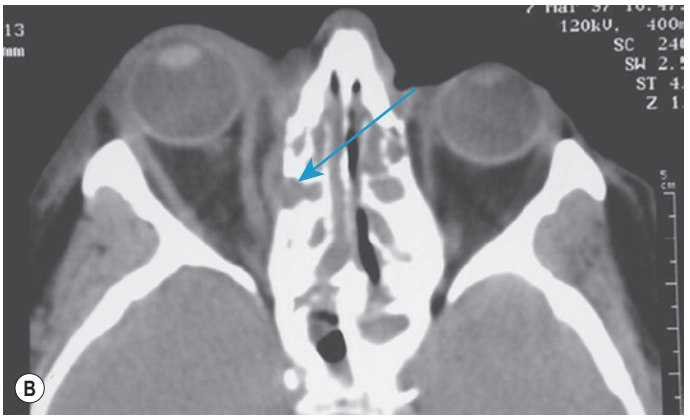
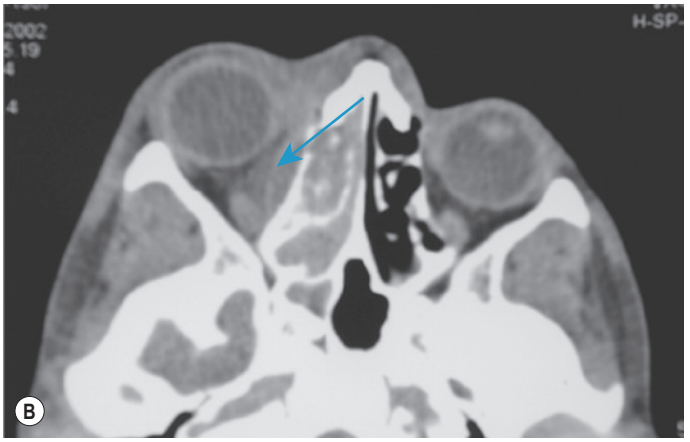


Fig. 14.11 (A) 7-year-old child with right orbital cellulitis, proptosis, white eye, limitation of eye movements, but no optic nerve compromise. (B) Computed tomography scan shows ethmoid sinusitis, significant proptosis, and a small medial subperiosteal abscess (arrow). He was successfully treated with antibiotics alone and did not need surgical intervention.









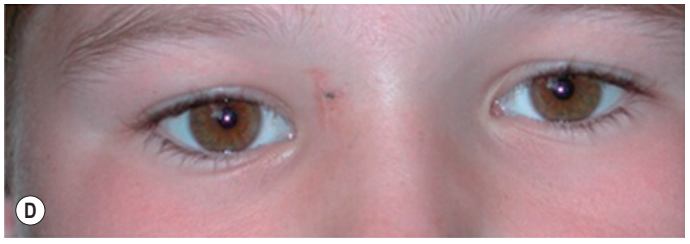


Fig. 14.12 (A) Orbital cellulitis with a white eye. (B) Computed tomography scan shows sinusitis and a subperiosteal abscess (arrow). Child deteriorated despite adequate intravenous antibiotics. (C) Drainage of ethmoid sinus and subperiosteal abscess was performed. (D) Patient made a good recovery.

surgical drainage and this case was culture-negative. This supports an initial medical management approach for most patients with subperiosteal or orbital abscesses resulting in orbital cellulitis.[6]

Garcia and Harris[27] advocate a non-surgical management of subperiosteal abscess if four criteria are met:

1. age less than 9 years;
2. no visual compromise;
3. medial abscess of modest size;
4. no intracranial or frontal sinus involvement.

In their prospective study of 29 patients fulfilling the above criteria, 27 (93%) were managed successfully with only medical therapy. Only two patients had surgical intervention with successful outcomes.[27]

It seems reasonable to initially treat medically if vision is normal, there is no intracranial extension, the subperiosteal abscess is of moderate size, and the child is under 9 years of age (see Figs 14.11 and 14.12). The recently published follow-up series by Liau and Harris concluded that these guidelines remain appropriate. However they noted in younger children, who might classically be expected to resolve with conservative

management, the emergence of more aggressive organisms, such as MRSA, makes emergent drainage necessary more often due to advanced clinical disease at presentation.[33]

Osteomyelitis of the superior maxilla

This rare condition, which usually presents in the first few months of life with fever, general malaise, and marked periorbital edema, may be confused with orbital cellulitis or subperiosteal abscess. The diagnosis should be suspected if there is pus in the nostril and edema of the alveolus and palate on the affected side. An oral fistula may be present. Imaging supports the diagnosis. *Staphylococcus aureus* is the usual infecting organism. Treatment is with high-dose intravenous antibiotics chosen on the basis of culture and sensitivity, and surgical drainage of the abscess preferably via the nose.

Cavernous sinus thrombosis

Since the introduction of antibiotics, this dreaded complication of orbital cellulitis has become rare. Previously, mortality was almost 100%.[40] In its early stages, cavernous sinus thrombosis may be difficult to distinguish clinically from orbital cellulitis. There is more severe pain, a marked systemic illness, proptosis develops rapidly, and there may be third, fourth, and sixth cranial nerve palsies, in contrast to the mechanical limitation seen in orbital cellulitis.

Hyperalgesia in the distribution of the fifth cranial nerve is common. The presence of retinal venous dilatation and optic disc swelling, especially if bilateral, is very suggestive of cavernous sinus thrombosis. In the later stages, bilateral involvement in cavernous sinus thrombosis makes the clinical distinction from orbital cellulitis easier.

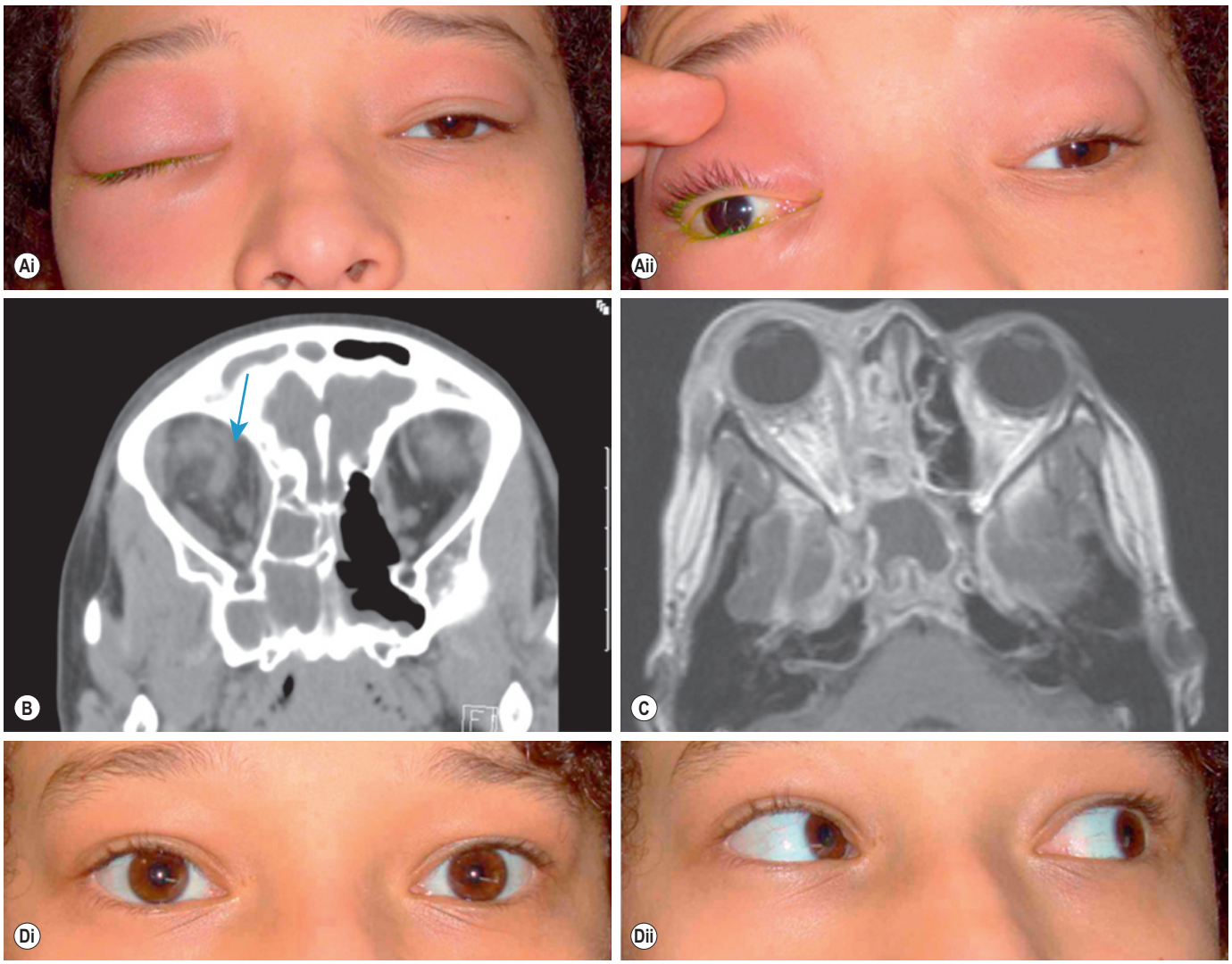


Fig. 14.13 (A) A very unwell 13-year-child with orbital cellulitis, proptosis, and reduced eye movements. (B) Computed tomography scan showed pansinusitis including the ethmoids and sphenoid sinus, and a dilated cavernous sinus and superior ophthalmic vein (arrows). (C) Magnetic resonance imaging confirmed a cavernous sinus thrombosis, with flow voids. (D) She made an excellent recovery with antibiotics and anticoagulation.

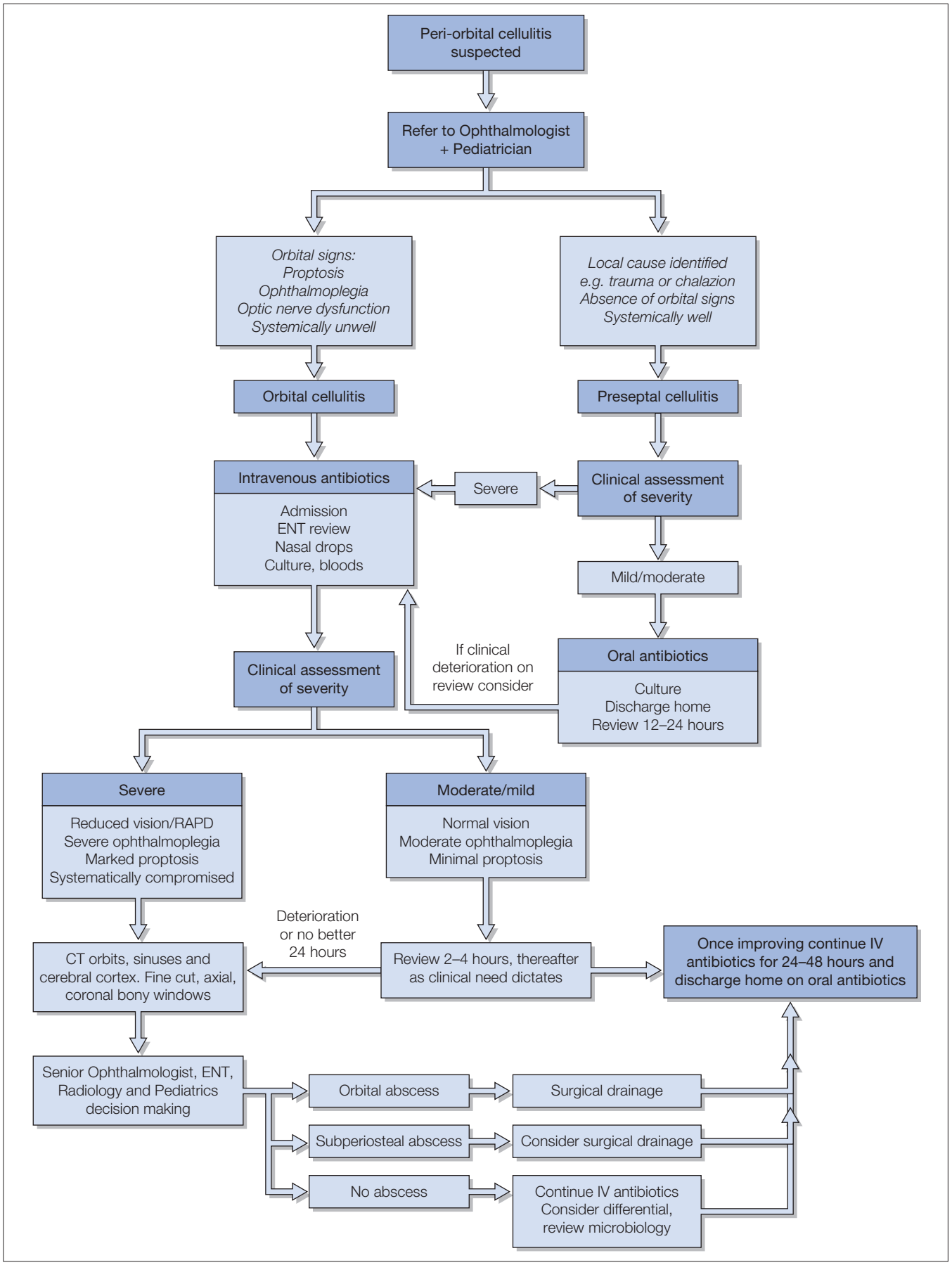


Fig. 14.14 Management of preseptal and orbital cellulitis.

Diagnosis can be supported by CT findings but is better confirmed with an MRI scan. Cavernous sinus thrombosis is most frequently associated with *Staph. aureus* infection[41] (Fig. 14.13).

Management is best undertaken by a pediatric neurologist or neurosurgeon and involves treatment with high-dose intravenous antibiotics. The use of anticoagulants and systemic steroids requires careful consideration.

Fungal orbital cellulitis orbital mucormycosis

Orbital fungal infection should be suspected in any diabetic or immunosuppressed[25] child or one with gastroenteritis and metabolic acidosis[42] who develops a rapidly progressive orbital cellulitis, especially if accompanied by necrosis of the skin or nasal mucosa.

Fungal orbital cellulitis has been described in otherwise healthy children.[43,44] Untreated, it is rapidly fatal.

Colonization of the sinuses by spores followed by direct or hematogenous spread to the orbit occurs, which is heralded by periorbital pain, marked lid edema, conjunctival chemosis, and proptosis. Later, spread to the orbital apex results in third, fourth, and sixth cranial nerve palsies and optic neuropathy. Mucomycosis and aspergillosis have a tendency to invade vessel walls causing thrombosis and subsequent ischemia. Involvement of the facial arteries causes gangrene of the nose, palate, and facial tissues resulting in necrosis. Central retinal artery occlusion and cerebral infarction can result. Once spread to the cavernous sinus and intracranial vessels occurs, the prognosis is very poor.

Scrapings from infected tissues should be cultured and Gram and Giemsa stained. Larger tissue biopsies should be fixed in 10% formalin and processed for histologic examination. These fungi have an affinity for hematoxylin and are, therefore, easily recognized in hematoxylin and eosin sections.

The management consists of specific antifungal therapy, correction of the underlying metabolic or immunologic abnormality, and surgical debridement of necrotic tissues. The specific treatment of choice is amphotericin B, which should be given intravenously and may also be used locally to irrigate infected sinuses.[45] It is nephrotoxic so renal function should be carefully monitored.

For further information on the management of preseptal and orbital cellulitis please see Figure 14.14.

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Endophthalmitis

Donal Brosnahan

Chapter contents

CLINICAL PRESENTATION
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Infectious endophthalmitis occurs when bacteria, fungi, parasites, or viruses enter the eye following a breach of the outer wall of the eye (exogenous endophthalmitis), or when microorganisms enter the eye from a source elsewhere in the body (endogenous endophthalmitis). Exogenous endophthalmitis most frequently arises following surgery but may be a consequence of trauma. Endogenous endophthalmitis usually results from hematogenous spread of infection. Exogenous endophthalmitis may be subclassified into acute and chronic. The classification of endophthalmitis is important as each type has a characteristic clinical setting, differing spectrum of microorganisms, and varying visual prognosis.

Clinical presentation

The presentation of bacterial endophthalmitis depends on the route of infection and the virulence of the microorganism. Acute postoperative endophthalmitis typically presents 1–3 days after surgery with pain and decreased vision. There is often lid swelling, conjunctival injection, corneal edema, and chemosis. Intraocular findings include uveitis, hypopyon, vitreous cells, and occasionally sheathing of blood vessels. In children, presentation and treatment are often delayed, particularly following trauma where occult penetration may go undetected.

Infection with less virulent organisms may result in chronic or late-onset endophthalmitis, which may run an indolent course with exacerbations and remissions. Intraocular inflammation is less severe, but hypopyon and vitreous activity may be present. The presence of creamy white plaques on the posterior capsule following cataract surgery is suggestive of *Propionibacterium* infection. In endophthalmitis following penetrating injury, there may be a persistent severe uveitis and vitreous haze with infiltration of the wound edges. Retinal periphlebitis may be an early sign of bacterial endophthalmitis. Endophthalmitis should be suspected after intraocular surgery or traumatic perforation whenever the inflammation is greater than expected. Serial and frequent examinations may be necessary. The main differential diagnoses are fungal endophthalmitis and severe uveitis. Rarely, retinoblastoma or metastatic tumor may present with uveitis and hypopyon.

Exogenous bacterial endophthalmitis

Cataract surgery

Exogenous endophthalmitis in adults occurs most frequently following intraocular surgery (70–80%). Cataract extraction has a reported incidence of postoperative endophthalmitis of 0.029–0.38%[1,2] (Fig. 15.1). Good et al. reported an incidence of 0.45% in a retrospective review of 641 cases of cataract extraction in children.[3] Wheeler et al. reported an incidence of 0.07% in children undergoing cataract and glaucoma surgery.[4]

A study of 464,996 cataract surgeries undertaken in Sweden over 6 years found perioperative communication with the vitreous and non-use of intracameral cefuroxime showed a statistically significant association with endophthalmitis.[2] Surgery for congenital cataract, whether lensectomy or lens aspiration, usually involves breach of the posterior capsule. Therefore, one might expect a higher incidence of postoperative endophthalmitis similar to that reported in intracapsular cataract, posterior capsular tear, and anterior vitrectomy.

Toxic anterior segment syndrome (TASS) may be difficult to distinguish from infective endophthalmitis. TASS is a sterile inflammatory response usually occurring in the first 48 hours following cataract surgery. Clinical features include corneal edema, raised intraocular pressure, and absent vitritis. If doubt exists as to whether the patient has endophthalmitis or TASS, vitreous biopsy and intravitreal antibiotics are warranted.

The Endophthalmitis Vitrectomy Study (EVS) studied 420 cases of infectious endophthalmitis presenting within 6 weeks of cataract extraction or secondary intraocular lens implantation.[5] Positive culture was obtained from 69.3% of intraocular specimens. Gram-positive bacteria were isolated in 94.2% of cases and gram-negative bacteria in 6.5% of isolates. *Staphylococcus epidermidis*, normal skin flora, was by far the most common gram-positive isolate (70%), followed by *Staphylococcus aureus* (9.9%), *Streptococcus* spp. (2.2%), and *Propionibacterium acnes*. *Proteus* and *Pseudomonas* were



Fig. 15.1 Bacterial endophthalmitis following infant cataract surgery and intraocular lens implantation.

the most common gram-negative organisms. *Haemophilus influenzae* has also been identified in other series.[6] Gower et al. noted patients developing streptococcal endophthalmitis following cataract surgery were 10 times more likely to have poor final visual acuity than patients with coagulase-negative staphylococcal endophthalmitis.[7] Weinstein's study of children with endophthalmitis reported similar results, 75% of culture-positive cases being caused by gram-positive organisms.[8] *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, and *Staphylococcus aureus* have been identified as the most frequent infecting agents in children following cataract extraction.

Trauma

Trauma is a significant cause of exogenous endophthalmitis in children. Endophthalmitis following penetrating injury accounted for 44% of cases in a 10-year review of pediatric endophthalmitis.[9] The incidence of endophthalmitis after penetrating injury ranges from 4% to 20% and is particularly high when injury occurs in a rural setting.[10] Eight-five percent of patients in the EVS achieved final visual acuity of 20/400 or better, while only 22–42% achieved this level of acuity following post-traumatic endophthalmitis.[4,11]

Poor visual outcome results from delayed diagnosis and treatment. Damage to ocular structures and retained intraocular foreign body are also contributory factors to poor visual outcome. In adults with post-traumatic endophthalmitis, *Staphylococcus epidermidis* and *Bacillus* spp. are the most frequent pathogens. In a review of post-traumatic endophthalmitis in children *Streptococcal* spp. were isolated in 25.9%, *Staphylococcus* in 18.5%, and *Bacillus* spp. in 22% of cases.

Glaucoma filtration surgery

Infection associated with filtration surgery is often subclassified into blebitis, defined as mucopurulent material in and around the bleb associated with anterior segment activity but without hypopyon. If a hypopyon is present, or there is evidence of vitreous activity, a diagnosis of endophthalmitis is made. Endophthalmitis may occur soon after surgery, but is frequently reported many years after surgery. Antimetabolites such as 5-fluorouracil (5-FU) and mitomycin C are used to augment filtration surgery in childhood glaucoma. While improving the success rate of filtration surgery, they increase the risk of postoperative endophthalmitis. When intraoperative 5-FU is used, the reported incidence of endophthalmitis is 1–5.7%. The incidence of endophthalmitis is 0.3–4.9% when mitomycin C is applied.[12] Use of antimetabolites may result in thin and avascular blebs that are predisposed to infection.

Implantation of glaucoma drainage devices is associated with increased rates of endophthalmitis. A review of 542 eyes with Ahmed valve insertion noted a significantly higher endophthalmitis rate in children. The incidence in adults was 1.7%, compared to 4.4% in children.[13] Endophthalmitis is often associated with conjunctival erosion and tube exposure; inferior placement of bleb or drainage device is also associated with higher rates of infection. When endophthalmitis is related to glaucoma surgery, the spectrum of microorganisms differs from that in cataract surgery in that streptococcal species predominate. *Haemophilus influenzae* is also isolated more frequently than *Staphylococcus epidermidis*. This difference may reflect the fact that endophthalmitis is often of late onset with invasion of microorganisms through thin-walled or leaking blebs.[14] Jampel et al. found increased incidence of endophthalmitis associated with full-thickness filtration procedures, inferior-placed blebs, bleb leakage, and the use of mitomycin.[15] If endophthalmitis develops in the early post-operative period, *Staphylococcus epidermidis* is more frequently cultured.

Strabismus surgery

Endophthalmitis following strabismus surgery is rare, with an incidence of 1:3,500 to 1:185,000.[16] Scleral perforation is thought to be a prerequisite for the development of endophthalmitis following strabismus surgery. Spatulated needles have greatly reduced the frequency of scleral perforation during strabismus surgery. Needles and sutures are frequently contaminated despite the use of preoperative povidone-iodine. Carothers et al. noted 19% of needles and 24% of sutures were culture positive in patients undergoing strabismus surgery.[17] When scleral perforation has been noted, a dilated fundal examination is indicated and laser photocoagulation of any retinal lesions should be considered. Many surgeons would ask a retinal surgeon to help with this (see Chapter 86). Periocular and systemic antibiotics may reduce the risk of endophthalmitis following perforation.

Streptococcus pneumoniae, *Staphylococcus aureus*, *Haemophilus influenzae*, and *Staphylococcus epidermidis* have been isolated in cases of endophthalmitis associated with strabismus surgery. It appears that infection with more virulent organisms is more frequent than after cataract surgery. Visual prognosis is poor as a consequence of delayed diagnosis and the virulence of the infecting organisms.

Intravitreal injection

Anti-vascular endothelial growth factor (anti-VEGF) is an effective treatment for some forms of retinopathy of prematurity. Anti-VEGF is delivered by intravitreal injection. In adults, endophthalmitis rates range from 0.019% to 0.07% when it is used to treat age-related macular degeneration.[18] In contrast to endophthalmitis following incisional surgery, *Staphylococcus* species (38.24%) and *Streptococcus* species (29.41%) were identified more frequently in a meta-analysis of infectious endophthalmitis after injection of anti-VEGF agents for age-related macular degeneration, diabetic macular edema,

and retinal vein occlusion.[19] Endophthalmitis caused by *Streptococcus* species is associated with poorer visual prognosis.

Exogenous endophthalmitis may also arise secondary to infectious keratitis associated with exposure or trauma.

Prevention

The patient is the most common source of postoperative infection. Children with extraocular infection, blepharitis, conjunctivitis, or with impaired nasolacrimal drainage should have their surgery delayed until these are remedied. Surgery should also be deferred in the presence of upper respiratory tract infection.

Preoperative application of aqueous povidone-iodine 5% solution to the conjunctival sac decreases bacterial counts and is the only prophylaxis, apart from intracameral antibiotics, for which there is an evidence base. It must be applied at least 3 minutes prior to surgery. In cases of penetrating injury, povidone-iodine should not be applied.

A prospective study by the European Society of Cataract and Refractive Surgeons demonstrated a five-fold decrease in the incidence of postoperative endophthalmitis in patients undergoing phacoemulsification surgery when intracameral cefuroxime (1 mg in 0.1 ml of normal saline) was administered at the end of surgery.[20] It is likely that intracameral cefuroxime results in reduced infection rates in pediatric cataract surgery. Antibiotics in irrigating solutions and subconjunctivally have largely been supplanted by the intracameral approach. There may be a beneficial effect from administering intravitreal antibiotics after repair of penetrating injuries, where there is a known higher rate of endophthalmitis.

Management

If endophthalmitis is suspected, it is essential to proceed rapidly and obtain aqueous and vitreous samples before starting antibiotic treatment (Box 15.1). General anesthesia will be required to allow thorough examination, collection of specimens, and delivery of intravitreal antibiotics. The microbiologist should be informed to ensure that appropriate culture media are available in the operating room and also to perform Gram and Giemsa stains. Specimens should be sent immediately to the laboratory. Aqueous and vitreous specimens are plated on appropriate agar to facilitate culture of the potential pathogens, e.g. blood agar, chocolate agar, and Sabouraud dextrose agar. Specimens should be placed on glass slides for Gram and Giemsa stains. Culture for up to 2 weeks is required to allow growth of anaerobes such as *Propionibacterium* spp. and fungal species. *Propionibacterium acnes* may be sequestered in folds of the posterior capsule and, if suspected, removal of capsular remnants for culture may be helpful in confirming the diagnosis.

Polymerase chain reaction (PCR) is a highly sensitive and specific test, which can be employed to rapidly identify bacteria, fungi, and viruses resulting in early diagnosis and appropriate antibiotic therapy. It is particularly helpful in culture-negative cases or when the patient has been commenced on antimicrobial therapy before samples are obtained. Care must be taken to minimize the risk of contamination of the specimen with environmental organisms, which may cause a false-positive PCR result. Positive PCR results with a negative culture must be interpreted with caution; always consider whether the PCR result is a recognized ocular pathogen and also consider the clinical context. Newer techniques such as real-time PCR have been shown to identify the bacteria from aqueous and vitreous in 95% of patients with endophthalmitis in one case series.[21]

Vitreous samples are preferably obtained using a mechanical cutter: 0.2 ml is removed for culture and staining. Care must be taken in infants as the pars plana is poorly developed; therefore, sclerotomies should be anteriorly placed. If an intraocular lens has not been inserted, an anterior approach is possible.

Once vitreous sampling has been completed, antibiotics are injected into the vitreous cavity: vancomycin, 1 mg in 0.1 ml of normal saline, and ceftazidime, 2 mg in 0.1 ml of normal saline. Vancomycin is effective against gram-positive bacteria and ceftazidime against gram-negative organisms. Dexamethasone, 0.4 mg in 0.1 ml, may also be given intravitreally to reduce the inflammatory response. Antibiotics are delivered with a 30-gauge needle using separate syringes for each antibiotic. Most antibiotic has left the eye by 48 hours and consideration should be given to repeating the injections after this period depending on clinical response.

The EVS did not show any additional benefit from using systemic antibiotics to supplement intravitreal therapy. In the EVS, systemic treatment consisted of amikacin and ceftazidime; however, this may be suboptimal as vancomycin is more effective against gram-positive cocci. As intravitreal antibiotics only remain in the eye for a short period, patients with severe endophthalmitis should have systemic antibiotics. Systemic antimicrobial therapy is indicated in cases of endogenous endophthalmitis secondary to bloodstream infection or infection at a distant focus.

Subconjunctival antibiotics do not penetrate the vitreous cavity well and have limited use. Topical antibiotics may be used to supplement intravitreal injection if there is superficial infection or infectious keratitis (vancomycin 50 mg/ml and ceftazidime 50 mg/ml or amikacin 25 mg/ml). Treatment regimens need to take into account the clinical setting and the likely infecting microorganisms. Antibiotic therapy should be reviewed in the light of clinical response and culture results.

Box 15.1

Initial antibiotic treatment of bacterial endophthalmitis

Intravitreal antibiotics

Vancomycin 1 mg in 0.1 ml of normal saline and ceftazidime 2 mg in 0.1 ml of normal saline

or

Amikacin 0.4 mg in 0.1 ml of normal saline and ceftazidime 2 mg in 0.1 ml of normal saline

Systemic antibiotics

Vancomycin 44 mg/kg per day and ceftazidime 100–150 mg/kg per day

or

Ciprofloxacin 5–10 mg/kg per day

Topical antibiotics

Vancomycin 50 mg/ml hourly and ceftazidime 50 mg/ml hourly

or

Gentamicin 14 mg/ml hourly

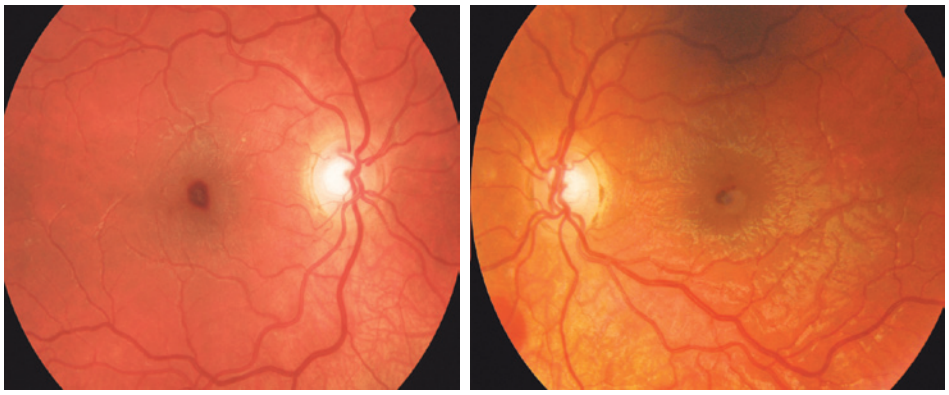


Fig. 15.2 Bilateral Roth's spots in a case of bacterial endocarditis.

Consult with your vitreoretinal colleagues for consideration of early virectomy. The management of endophthalmitis following cataract has been greatly influenced by the EVS. The key findings of this study were:

1. Immediate vitrectomy is not indicated if the visual acuity is better than light perception.
2. If visual acuity is light perception only, then there is a significant benefit from vitrectomy.

It should be noted that the EVS study was undertaken 20 years ago and improved vitreoretinal instrumentation and techniques now favor a more aggressive surgical approach with better visual outcomes. Vitrectomy decreases the bacterial load and removes toxins and inflammatory mediators from the eye. Removal of opaque vitreous will hasten visual rehabilitation. It may be very difficult in some children to establish a reliable visual acuity. It should be noted that in this study the systemic antibiotics used differed from those given intravitreally and therefore would not have helped to maintain intraocular antibiotic levels. The role of vitrectomy in endophthalmitis associated with strabismus or glaucoma surgery has not been established. However, the same general principles apply.

Endogenous bacterial endophthalmitis

Endogenous or metastatic bacterial endophthalmitis results from hematogenous spread from a distant focus such as bacterial endocarditis (Fig. 15.2), meningitis (Fig. 15.3), abdominal sepsis or otitis media (Box 15.2). Between 2% and 8% of all bacterial endophthalmitis cases are endogenous and are frequently bilateral (14–50%).[22] Although symptoms and signs are similar to exogenous endophthalmitis, the clinical setting is different. Systemic symptoms may predominate. Initially, ophthalmological features may be mild, delaying the diagnosis. The presence of red eye in a patient with sepsis should prompt early and full ophthalmological examination.

Endogenous endophthalmitis most frequently results from gram-positive organisms such as *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Listeria monocytogenes*. Gram-negative infection results from *Neisseria meningitides*, *Haemophilus influenzae*, *Klebsiella* spp., and *Escherichia coli*. gram-positive organisms predominate in North America and Europe with gram-negative organisms more frequently isolated in Asia.[23] *Klebsiella* species predominate in East Asia, often associated with cholangiohepatitis and liver abscess. Premature infants are more likely to develop endophthalmitis secondary to *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*. These infants are immunocompromised and often dependent on ventilators and humidifiers, which may be a source of nosocomial infection.

Once the diagnosis is suspected, systemic antimicrobial therapy should be commenced. If an infective agent has not

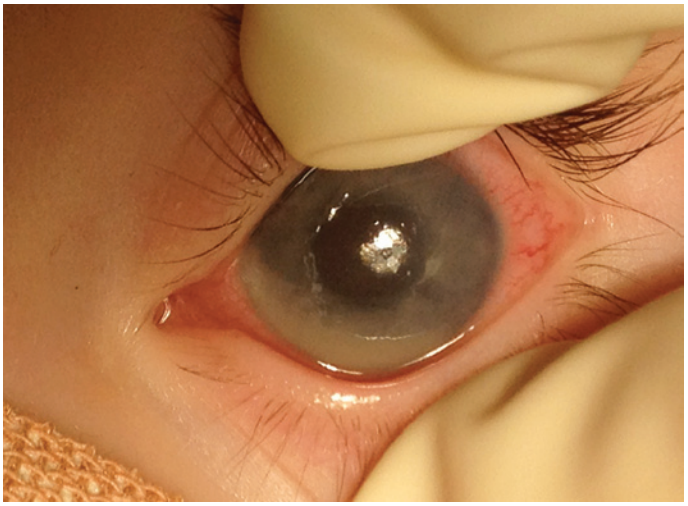


Fig. 15.3 Endogenous endophthalmititis in an infant with meningococcal septicemia.

Box 15.2

Risk factors for endogenous endophthalmitis in children

Bacterial

Immunosuppression
Bacterial endocarditis
Meningococcal infection
Gastrointestinal sepsis

Fungal

Prematurity
Parenteral nutrition
Immunosuppression
Broad-spectrum antibiotics
Retinopathy of prematurity

been identified from blood culture, aqueous and vitreous specimens should be obtained and intravitreal antibiotics administered covering both gram-positive and gram-negative organisms. Blood cultures are positive in up to 72% of cases and are useful in guiding initial antibiotic therapy. Should the child present to the ophthalmologist, urgent assessment by a pediatrician or infectious diseases specialist is indicated. The role of vitrectomy is not established; no prospective studies have been undertaken.

Exogenous fungal endophthalmitis

Exogenous fungal endophthalmitis may complicate penetrating eye injury, especially when it occurs in a rural setting and in the presence of a retained organic foreign body or fungal keratitis. Presentation may not be until weeks or months after injury. Progressive uveitis, hypopyon, vitritis, and vitreous abscess following penetrating injury should give rise to suspicion of fungal endophthalmitis. Aqueous and vitreous samples should be obtained promptly. Giemsa stain may identify hyphae, confirming the diagnosis and facilitating early treatment with intravitreal amphotericin B. Vitrectomy should be considered if there is significant vitreous involvement.

Endogenous fungal endophthalmitis

Endogenous fungal endophthalmitis is usually associated with candida septicemia. Risk factors include immunosuppression, intravenous feeding, and prematurity (see Box 15.2). *Candida albicans* is the organism most commonly identified in endogenous fungal endophthalmitis although *Aspergillus fumigatus* and *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatiditis*, *Cryptococcus neoformans*, and *Sporotrichum schenckii* have all been implicated.

Neonatal endophthalmitis is almost always endogenous and results from systemic candidiasis. In neonates, candidemia is associated with central venous catheters, parenteral nutrition, and the use of broad-spectrum antibiotics. A recent review of the incidence of neonatal endogenous endophthalmitis in the United States demonstrated a significant reduction in the incidence (8.71 cases per 100,000 live births in 1998 and 4.14 cases per 100,000 live births in 2006).[24] This decrease may result from improved care and earlier treatment of neonates with candidemia. Candidemia, retinopathy of prematurity, and low birth weight were significant risk factors in the development of endophthalmitis in this study. The presence of retinopathy of prematurity was associated with a two-fold increase in the rate of endophthalmitis.

Ocular involvement may take the form of chorioretinitis where pale creamy-white lesions are noted in the choroid with a predilection for the posterior pole. These lesions may extend into the vitreous to form "puff balls" which, when multiple, have a "string of pearls" appearance (Fig. 15.4). There may be areas of retinal hemorrhage with white centers similar to Roth's spots. Vitreous inflammation is variable. The anterior segment may be involved and secondary cataract has been reported. Early diagnosis and systemic treatment will prevent the progression of chorioretinal lesions to diffuse endophthalmitis. *Aspergillus* endophthalmitis is typically more severe with large confluent areas of chorioretinitis.

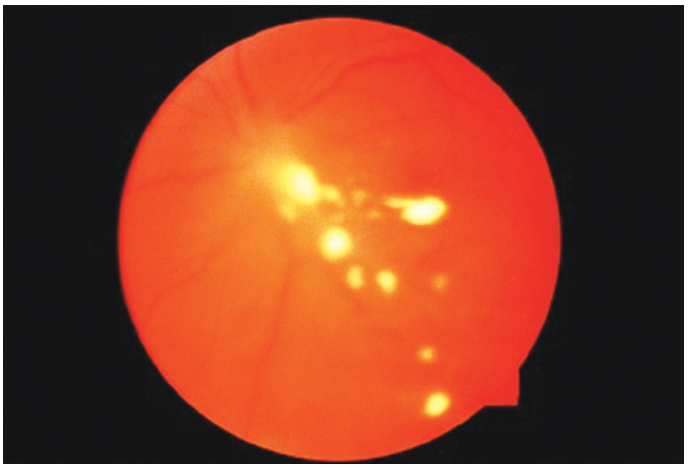


Fig. 15.4 Endogenous *Candida* endophthalmitis in an immunosuppressed child. Note characteristic "string of pearls" appearance of vitreous infiltrates.

Clinical features may suggest the diagnosis; however, blood and urine cultures are useful in diagnosis. If there are positive cultures from blood or urine, it is not necessary to perform vitreous sampling. Giemsa stain and Sabouraud media are used to identify and culture fungi. PCR is also employed and can rapidly identify fungi from intraocular samples.

In endophthalmitis associated with candidemia, systemic administration of fluocytosine is indicated. Fluocytosine has superior ocular penetration to amphotericin B and is less toxic. If a species other than *Candida* is suspected or confirmed, amphotericin B is more appropriate as it is active against a broader range of fungi. Amphotericin B has significant systemic side effects including nephrotoxicity, neutropenia, and hypokalemia. The use of the liposomal version of amphotericin B (L-AMB) is less toxic than the deoxycholate forms. In cases where there is only chorioretinal involvement without significant vitreous involvement, systemic treatment may suffice. In the presence of vitreous involvement, intravitreal amphotericin B (5 μg in 0.1 ml of normal saline) may be given as an adjunct to systemic therapy. The use of intravitreal steroid remains controversial.

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External eye disease and the oculocutaneous disorders

Stephen J Tuft

Chapter contents

BLEPHAROKERATOCONJUNCTIVITIS
CONJUNCTIVITIS
KERATITIS
REFERENCES

This chapter focuses on the most common external eye conditions in children (Fig. 16.1).

Blepharokeratoconjunctivitis

Blepharitis is a disorder of the lid margins with or without ocular surface inflammation. Lid disease can involve the anterior lid margin (lash follicles) or posterior lid margin (meibomian glands). Corneal disease occurs with both. The clinical features include:

- styes and meibomian cysts;
- conjunctivitis, phlyctenulosis and episcleritis;
- keratitis with vascularization and scar;
- dermatologic disease.

In children, dermatologic associations (facial rosacea and acne vulgaris) are less common than in adults and may be mild or absent, but corneal disease is more likely to progress to significant vision loss without obvious surface inflammation, termed blepharokeratoconjunctivitis (BKC) or ocular rosacea (Table 16.1). In developed countries it is second only to allergy as a cause for ocular surface disease in children.

Keratitis is uncommon in *acute* blepharitis, commonly caused by styes, impetigo, herpes simplex infection, or infected meibomian cysts.

Pathogenesis of blepharokeratoconjunctivitis

BKC is a delayed hypersensitivity response to *Staphylococcus aureus* or *Propionibacterium acnes* bacterial antigens and lipases released into the tear film. A proposed role for *Demodex* is unproven. Breakdown products of meibomian gland lipid may also cause inflammation and an unstable tear film that amplifies the effect through surface drying. Posterior lid margin disease is not the result of infection. Histologically, there is keratinization of the ductules of the meibomian glands and meibomian gland "drop out" can be demonstrated with infrared imaging. The prevalence is thought to be higher in females and in South and East Asian than white populations.[1]

The age of onset of BKC is bimodal with a peak at 5–7 years and a second peak at adolescence. However, onset can be in the first months of life. There is often a delay of months or years between the onset of symptoms and diagnosis. The symptoms of early cases of BKC are eye rubbing with chronically uncomfortable red eyes (Fig. 16.2). The disease can be very asymmetric or unilateral, with photophobia and epiphora if there is keratitis (see Table 16.1). There may be crusting in the morning, but discharge is not a major feature. The disease can be relatively asymptomatic until reduced vision or a corneal opacity alerts the patient or parents.

Table 16.1 Features of pediatric blepharokeratoconjunctivitis

Associated skin disease (absent in 50% of cases)	Symptoms[a]	Signs[b]		
		Lids[c]	Conjunctiva[c]	Cornea
Acne rosacea Acne vulgaris	Photophobia Pain Eye rubbing Redness Watering Discharge Blur (older children)	Inspissated meibomian ducts Crusting and collarettes Telagiectasia Notching of lid margins Meibomian cysts Styes	Bulbar hyperemia Tarsal papillary hyperplasia Tarsal follicles Lipid crystals Phlyctenules	Punctate epitheliopathy Marginal keratitis Phlyctenules Axial supepithelial scar Thinning Sectorial vascularization

[a]Some patients may be asymptomatic until visual loss is detected.
[b]Signs may be very asymmetric or even unilateral.
[c]Lid and conjunctival change can be minimal even with corneal disease.

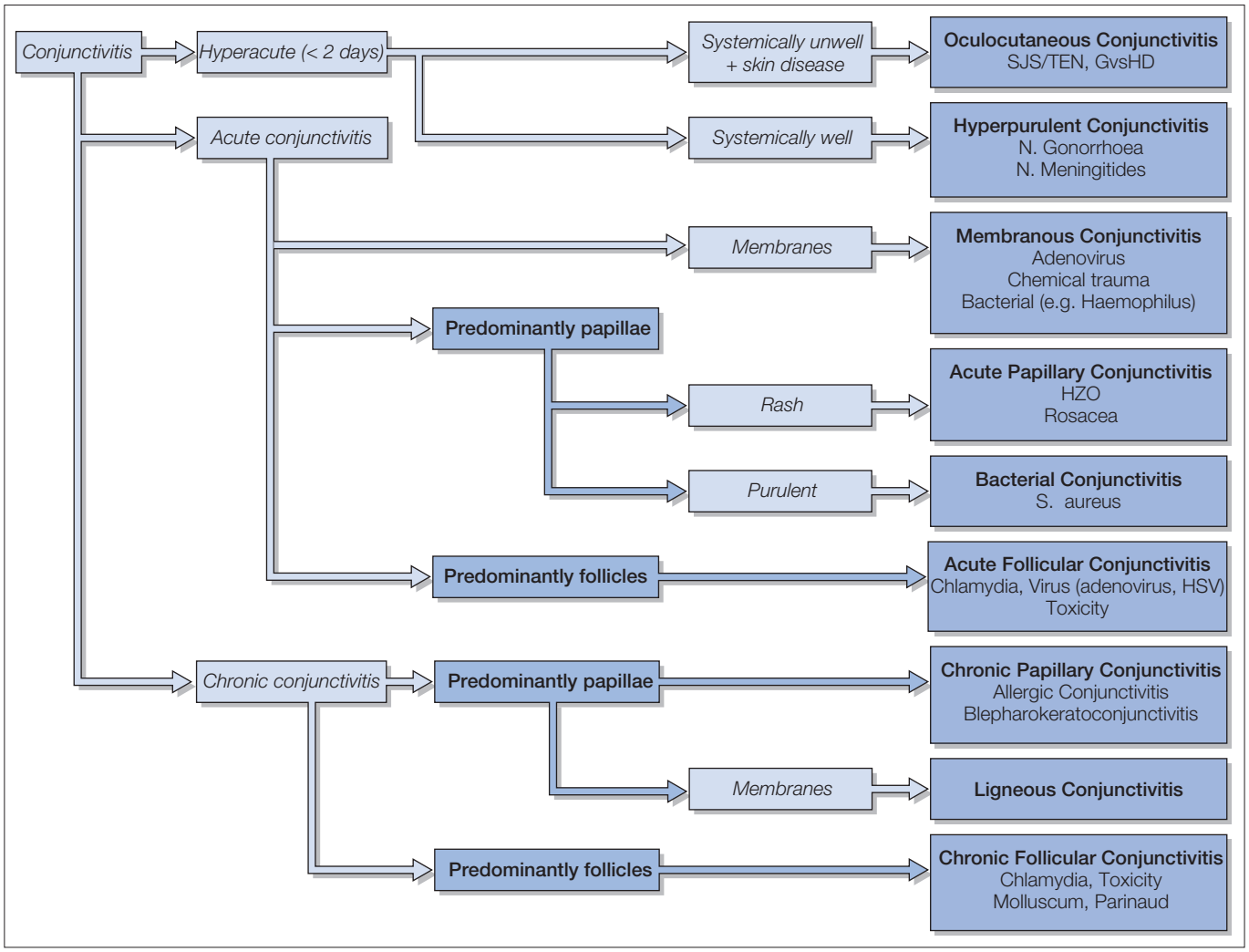


Fig. 16.1 Algorithm for assessment of conjunctivitis.



Fig. 16.2 Red and watery right eye of child with blepharokeratoconjunctivitis. There is anterior blepharitis and a reactive ptosis.

Approximately half of patients with BKC do not have facial skin changes, but a papular rash on the cheeks or acne can develop. Lid signs of anterior blepharitis include scales and collarettes at the bases of the lashes (Fig. 16.3). The appearance of the posterior lid margin can be surprisingly normal, or there may be telangiectasia and inspissation of the meibomian gland openings with expression of white sebum following gentle lid pressure. In more active disease, there is a mixed papillary and follicular change, especially in the upper and lower tarsal conjunctiva (Fig. 16.4), with limbitis and conjunctival or corneal phlyctenules (Figs 16.5 and 16.6). A phlyctenule

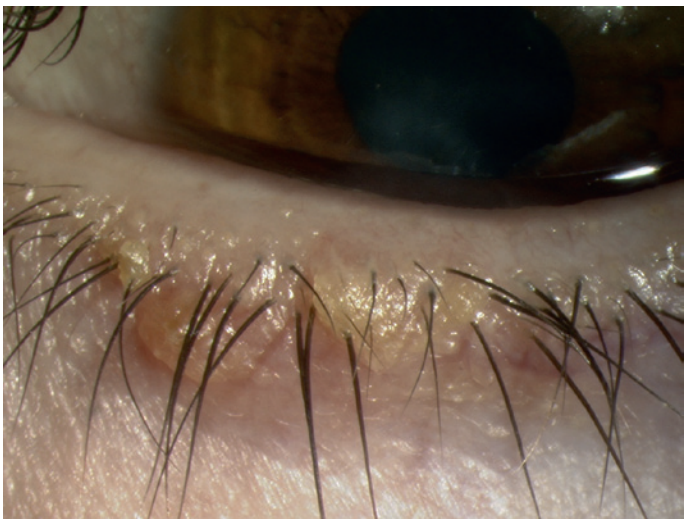


Fig. 16.3 Crusting at the base of the lashes in anterior blepharitis.

(or phlycten) is a small white collection of polymorphs and leukocytes with an overlying epithelial defect. Subconjunctival crystals are not always present but are a specific sign for this condition (Fig. 16.7). The corneal epithelial signs range from a reversible mild inferior punctate keratopathy to diffuse

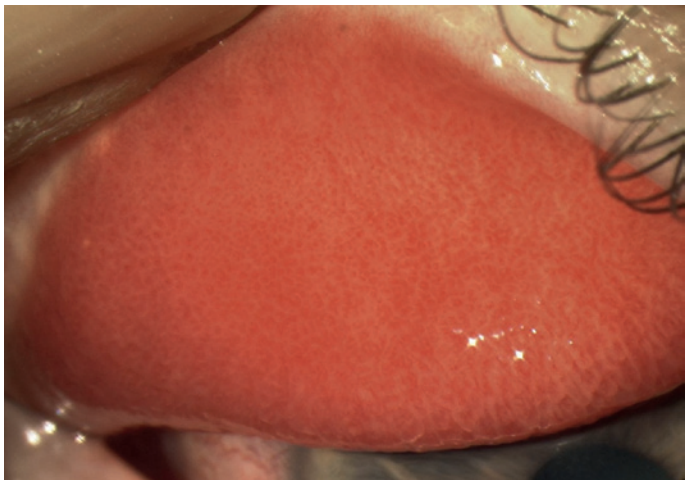


Fig. 16.4 A predominantly papillary response in a patient with very active blepharokeratoconjunctivitis.

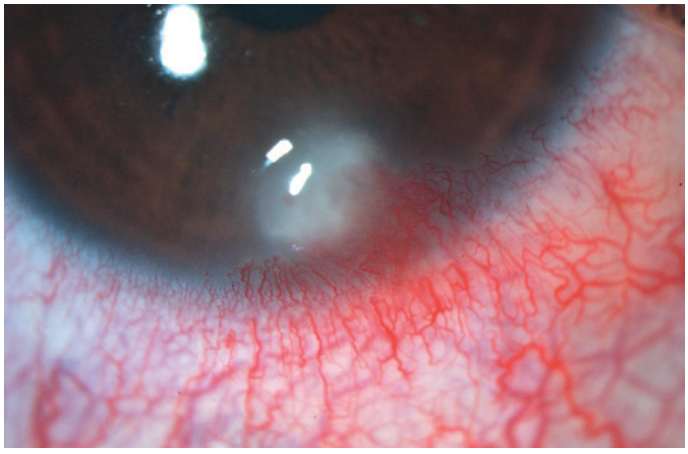


Fig. 16.5 Acute phlyctenule at the limbus. The lesion is raised with an epithelial defect. There is early corneal vascularization.

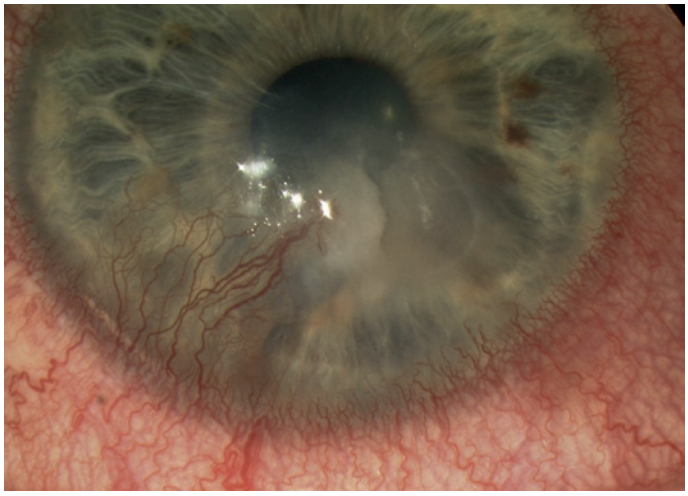


Fig. 16.6 A recurrent corneal phlyctenule. There is scar, thinning, and vascularization of the cornea that reduce vision.

corneal stain with fluorescein (Fig. 16.8). More severe corneal changes include corneal thinning or perforation and sectorial vascularization at the site of previous phlyctenules (Fig. 16.9). Vision loss may be insidious and severe.

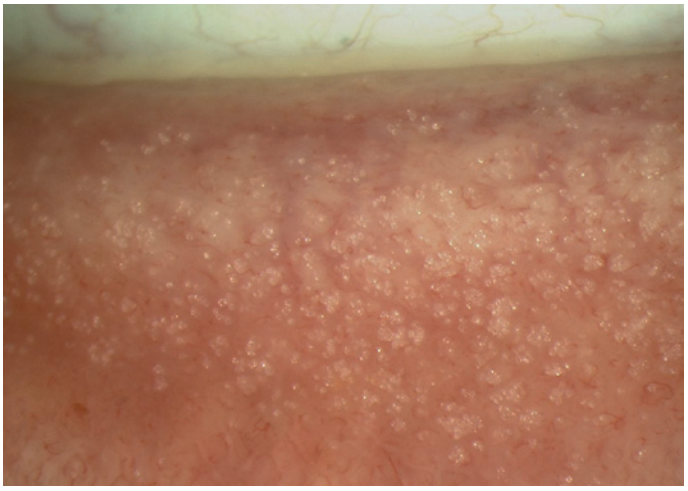


Fig. 16.7 Numerous subconjunctival crystalline deposits in blepharokeratoconjunctivitis shown in the tarsal conjunctiva of the everted lower lid.

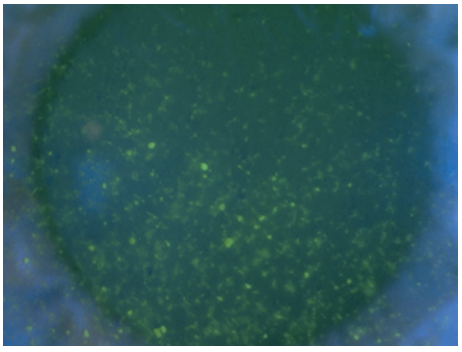


Fig. 16.8 Punctate epithelial erosion and microcysts secondary to blepharitis. Stained with fluorescein.

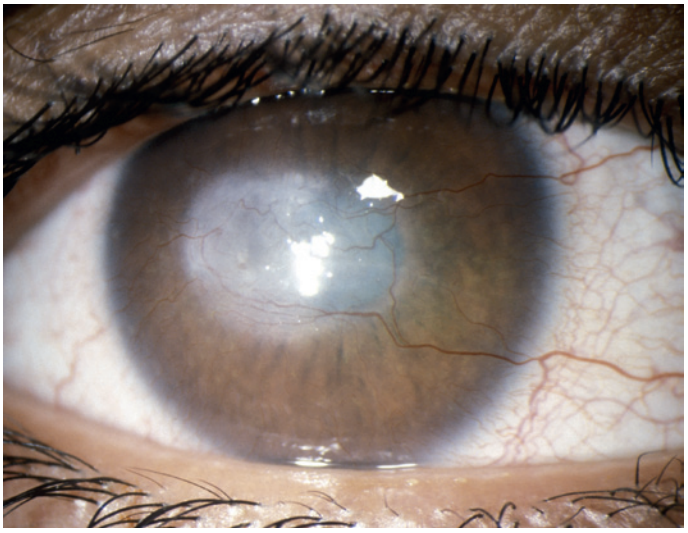


Fig. 16.9 Dense axial cornea scar associated with blepharokeratoconjunctivitis. The patient was relatively asymptomatic until a corneal opacity was noted.

Treatment of blepharokeratoconjunctivitis

There are no controlled clinical trials to guide therapy.[2] A hierarchical treatment strategy has been suggested.[3] Options include the following:

- Treat acute infection or styes with a warm compress and a short course of topical antibiotic (Table 16.2).

Table 16.2 Management options for blepharokeratoconjunctivitis

Option	Agent	Protocol
1. Lid scrubs		Daily
2. Topical antibiotic	Oc chloramphenicol 1% Oc azithromycin 1.5% Oc metronidazole 0.75%	Nocte bd Skin of face
3. Oral antibiotic	Erythromicin (<9 years) Doxycycline[a] (>9 years) Azithromycin	20 mg/kg/day for 3 months 2.2 mg/kg/day for 3 months 5 mg/kg/day for 5 days
4. Topical anti-inflammatory	e.g. Fluoromethalone 1% or cyclosporin 2%	As required
5. Omega-3 oil	Flaxseed	2.5 ml for 6 months
6. Immunosuppression[b]	Mycophenolate Corticosteroid	Supervision by pediatrician
7. Non-medical management	Fine-needle diathermy Corneal glue Lamellar keratoplasty Rigid contact lens	For progressive vascularization For perforation For perforation and scar For irregular astigmatism

[a]Doxycycline should not be used in children under 9 years and patients should be warned about skin sensitivity to sunlight and gastrointestinal side effects.
[b]Immunosuppression is reserved for sight-threatening and uncontrolled inflammation.

- Meibomian cysts tend to resolve spontaneously, but they should be incised if they do not resolve after 3 months or if they affect vision by altering lid position. A course of oral antibiotic (e.g. erythromycin, doxycycline, or azithromycin) should be considered if there are recurrent cysts.
- For chronic disease, a daily warm compress followed by lid cleaning with a cotton bud moistened in boiled water followed by application of a topical antibiotic (e.g. chloramphenicol, azithromycin). This can take 4–6 weeks to work and long-term maintenance therapy may be required. Long-term low dose (sub-antimicrobial) oral tetracycline or macrolide antibiotic, e.g. erythromycin, azithromycin, or doxycycline, are thought to work through an anti-inflammatory effect. Lid scrubs with chlorhexidine 0.02% may help if there is severe lid margin inflammation.[3]
- Topical immunosuppression with corticosteroid is the basis of treatment for most cases of BKC if there are conjunctival phlyctenules or significant corneal disease. For example, fluoromethalone 0.1% four times a day, reducing to once daily or less after 4 weeks. Long-term treatment (i.e. for years) with low-dose steroid may be required. Intraocular pressure should be monitored even with very low-dose therapy. A short course of intensive treatment (e.g. prednisolone 1% hourly) may be required to control intense inflammation. Topical cyclosporin or tacrolimus are alternatives to topical corticosteroid.
- Topical metronidazole gel can help facial skin disease.
- Treat visually significant keratitis with long-term (8–12 weeks) low-dose oral antibiotic. Systemic antibiotics reduce the frequency and severity of relapses.
- The effect of manual expression of the meibomian gland secretions or duct probing is debated and it is difficult to perform without sedation in young children.
- Dietary supplement with oral omega-3 (e.g. flaxseed oil) has been recommended.
- Rarely, for inexorable corneal opacification, or if corneal surgery is planned, systemic immunosuppression (e.g. oral corticosteroid, mycophenolate, or azathioprin) is required.
- Secondary microbial keratitis should be treated immediately.
- An axial corneal opacity or irregular astigmatism may cause amblyopia. Visual correction may be possible in older children using a rigid contact lens.
- Corneal perforation should be managed immediately with application of cyanacrylate glue before lamellar keratoplasty.[4]

Many cases of BKC require very prolonged treatment and even with all these options an estimated 10% of cases do not respond.

The great majority of cases of phlyctenular disease in developed countries are associated with staphylococcal lid margin disease, but phlyctenules are a reported association with tuberculosis, and very rarely with helminthiasis, leishmaniasis, and candidiasis. In areas where tuberculosis is endemic, a child with a phlyctenule should be screened for tuberculosis.

Other uncommon causes of chronic blepharokeratoconjunctivitis

Lesions of discoid lupus erythematosus at the lash margin may mimic chronic blepharitis. These may respond to topical treatment with corticosteroid but systemic therapy (e.g. hydroxychloroquine) is usually required. Lash or eyebrow infestation by crab lice (*Phthirus pubis*) can cause low-grade irritation and conjunctivitis (Fig. 16.10). Manual removal of the eggs (nits) and lice at the slit-lamp, followed by application of white soft paraffin eye ointment to the lid margin twice daily

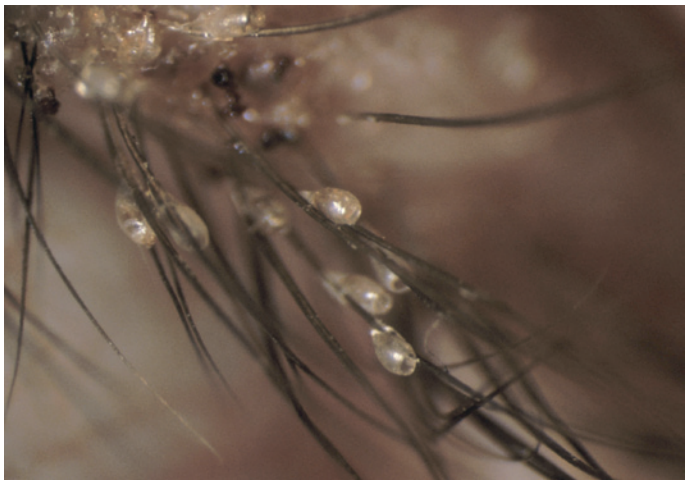


Fig. 16.10 *Phthirus pubis* infestation of the lashes. Adults can be seen superiorly at the bases of the lashes with eggs (nits) adherent to the shaft of the lashes.

for 10 days to smother the lice and eggs, is effective. Insecticides (e.g. permethrin 5%, malathion 1%) are not licensed for ocular use; they are used in shampoos or creams, but they cause ocular irritation. Decontamination of bed wear is essential. Because of the possibility of child abuse, a pediatrician should be involved and screening for sexually transmitted infections such as chlamydia may also be indicated.

Conjunctivitis

The causes of conjunctivitis are outlined in Fig. 16.1. Cultures are only necessary when there is:

1. associated corneal disease (microbial keratitis);
2. hyperacute conjunctivitis;
3. chronic conjunctivitis (symptoms >2 weeks);
4. ophthalmia neonatorum (infection before 28 days) (discussed in Chapter 13).

Acute conjunctivitis

Acute bacterial conjunctivitis is common in young children. It is bilateral in 70% of cases with a mucopurulent discharge, diffuse bulbar redness, and papillary hypertrophy of the upper tarsal plate conjunctiva. *Haemphilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Staphylococcus aureus* are the most common pathogens. One-quarter of children with conjunctivitis have a symptomatic otitis media, which usually resolves spontaneously. Viruses (adenovirus, picornovirus, herpes simplex virus [HSV]) are isolated in 6% of community acquired cases,[5] and preauricular adenopathy is a characteristic feature of viral infection. Chemical irritation (toxicity), BKC, and allergic conjunctivitis should be considered as alternative causes.

Acute infective conjunctivitis is typically self-limiting and resolves spontaneously over 2 weeks (65% in 2–5 days) (Fig. 16.11). Sight-threatening complications are uncommon. Management for most cases is irrigation with boiled water and is generally sufficient, with removal of secretions on the lid with a moist cotton pad. Antibiotics are unnecessary for most cases, although if used within 5 days of onset, they accelerate the resolution of symptoms and bacterial clearance. Complications of untreated disease are unusual. There is no evidence to support the superiority of any particular antibiotic. It is not necessary to exclude children from school unless adenoviral infection is suspected.[6]



Fig. 16.11 Acute bacterial conjunctivitis. Bilateral purulent discharge is an index of bacterial infection.

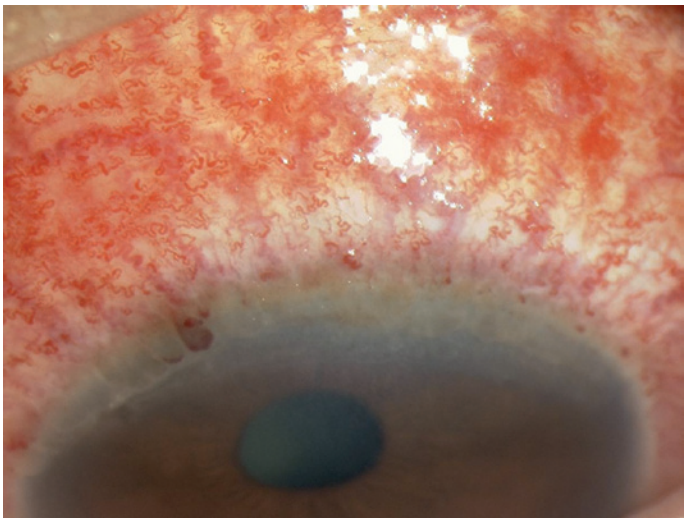


Fig. 16.12 *Neisseria gonorrhoeae* conjunctivitis. There is intense congestion of the vessels with petechial hemorrhages. There may be a hyperpurulent discharge and a tendency for corneal thinning at the superior limbus.

Hyperpurulent conjunctivitis

Hyperpurulent conjunctivitis requires urgent attention: it may be associated with severe corneal and systemic disease. Patients are typically febrile with a rapid onset of periocular swelling, mucopurulent discharge, pain, hemorrhagic conjunctivitis, and chemosis, with possible preauricular lymphadenopathy. Lid swelling and photophobia may make examination difficult. It is important to exclude infection with *Neisseria gonorrhoeae* and *N. meningitidis*, although *Staphylococcus*, *Streptococcus*, *Haemophilus*, and *Pseudomonas* spp. may rarely cause a similar picture (Figs 16.12 and 16.13). *Neisseria gonorrhoeae* conjunctivitis is not always sexually acquired, although this possibility should be excluded. Infection has occurred with the use of traditional medicines containing infected urine. *Neisseria gonorrhoeae* causes a rapidly progressive ulcerative keratitis with a characteristic superior corneal gutter that can rapidly perforate. *Neisseria meningitidis* conjunctivitis is usually acquired by airborne spread within schools or colleges. Although less severe, in 15% it causes epithelial breakdown

and ulcerative keratitis. Metastatic spread of *N. meningitidis* to the eye can occur as a terminal event following septicemia.

Membranous conjunctivitis

Differentiating membranous and pseudomembranous conjunctivitis is not useful. Any severe conjunctivitis (infectious, chemical, immune) can lead to membrane formation with corneal infiltrates and epithelial sloughing. Resolution may be accompanied by conjunctival scarring with non-progressive symblepharon and secondary entropion or trichiasis. Potential causes include:

- adenovirus and HSV
- *Neisseria* spp.

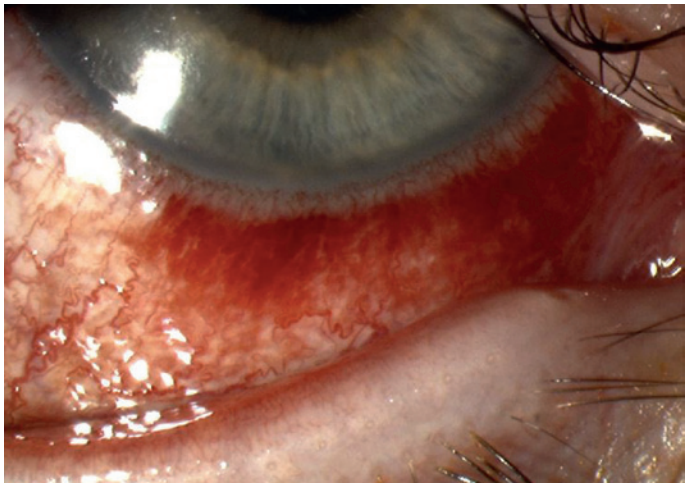


Fig. 16.13 Primary *Neisseria meningitidis* conjunctivitis in a child. Subconjunctival hemorrhages and epithelial defects are a common feature.

- Stevens–Johnson syndrome, toxic epidermal necrolysis;
- *Corynebacterium diphtheriae* (rare in developed countries);
- *Streptococcus pyogenes, Haemophilus influenzae, Staphylococcus aureus;*
- accidental or non-accidental chemical injury.

Diagnosis and investigation of conjunctivitis

Microbial investigation is only indicated for chronic conjunctivitis or hyperpurulent conjunctivitis. Samples should include an urgent Gram stain and culture on blood agar. Polymerase chain reaction (PCR) should exclude *Neisseria* spp., *Chlamydia*, adenovirus, and HSV. Treatment guidelines are presented in Table 16.3.

Systemic treatment for microbial conjunctivitis

Systemic treatment is usually required for patients with hyperpurulent conjunctivitis, if there is evidence of generalized infection, and immunosuppressed patients. These patients should be admitted until the diagnosis and management have been confirmed. Consultation with an infectious diseases specialist should be made. Patients with otitis media and hyperpurulent conjunctivitis may harbor identical strains of *Haemophilus influenzae* in both sites and systemic therapy is indicated.

Acute follicular conjunctivitis

Acute follicular/mixed conjunctivitis is characteristic of infection by viral or chlamydial organisms.

Table 16.3 Antibiotic treatment for conjunctivitis

Indication + common pathogens	First-line treatment	Alternative
Acute conjunctivitis[a]		
• *Haemophilus influenzae* • *Moraxella catarrhalis* • *Streptococcus pneumoniae* • *Staphylococcus aureus*	Observation, or G chloramphenicol 0.5% qds for 7–10 days	A fluoroquinolone, e.g. G Levofloxacin 0.5% qds for 7 days (prescribe if Gram-negative infection suspected)
Hyperacute bacterial conjunctivitis		
• *Neisseria gonorrhoeae*[b] • *Neisseria meningitidis*	IM Ceftriaxone once daily for 3 days	IM Spectinomycin once daily for 3 days (if penicillin allergy)
Note: Seek opinion from genitourinary and infectious diseases specialist	PLUS G Cefuroxime (PF) 5% hourly for 24 hours, then six times a day until resolved	PLUS G Ceftazidime (PF) 5% or a fluoroquinolone hourly for 24 hours, then six times a day until resolved
***Chlamydia* conjunctivitis**		
• *Chlamydia trachomatis*	G Azithromycin 1.5% tds for 3 days	PO Doxycycline 100 mg bd OR 200 mg daily for 7 days for children over 12 years of age
Note: Seek genitourinary opinion Treat sexual partners of parents/carers if necessary	PLUS PO Azithromycin 1 g STAT (for children who weigh ≥45 kg)	

[a]Acute conjunctivitis has a 65% chance of resolving without treatment within 2–5 days.
[b]Culture essential due to problems with resistance.

Viral infectious keratoconjunctivitis

This is an important cause of ocular morbidity and visual loss worldwide. HSV, varicella-zoster virus (VZV), adenovirus, and enterovirus are common causes.

Adenoviral keratoconjunctivitis

In many parts of the world, adenoviral keratoconjunctivitis is the most common viral infection of the ocular surface, causing community- or clinic-based epidemics. It accounts for approximately 8% of cases seen in primary care and 62% of cases seen in the ophthalmic emergency room. The clinical signs of the ocular pathogenic strains (serotypes 8, 19, and 37) are indistinguishable. Classification of disease subtypes (pharyngoconjunctival fever, epidemic keratoconjunctivitis) related to specific serotypes is of limited value.

Adenovirus infection causes acute lid swelling, a mixed papillary and follicular conjunctivitis, petechial hemorrhages, conjunctival membranes, and preauricular lymphadenopathy (Fig. 16.14). There may be an upper respiratory tract infection, vomiting and abdominal pain, urethritis, and cervicitis. Corneal epithelial sloughing and anterior uveitis can occur. Usually, a focal epithelial keratitis develops in 3–5 days, followed after 2 weeks by the development of immune-mediated focal subepithelial infiltrates (Fig. 16.15). After 3 weeks, the epithelial changes subside, leaving subepithelial scarring that can result in irregular astigmatism that often resolves over 6 months but which may be permanent. Subconjunctival scarring is common but not progressive or clinically significant. Diagnosis in the acute stage can be confirmed by PCR or commercially available enzyme-linked immunosorbent assay (ELISA)-based kits for use in the clinic. Because there may be 4–10 days of virus shedding before clinical disease is apparent, and because adenovirus can survive for days on dry surfaces, spread of infection between patients and clinicians is common.

There are no controlled trials showing benefit of topical steroid or antiviral therapy for the final outcome of adenoviral keratoconjunctivitis.[7] Treatment is based on symptomatic relief such as cold compress. Removal of conjunctival membranes can improve comfort but not the final outcome.

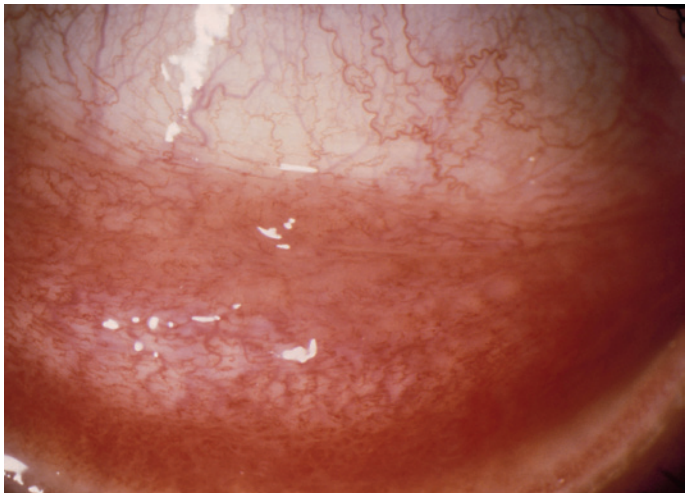


Fig. 16.14 Conjunctival follicular response in acute adenovirus infection. A papillary change may predominate over the upper tarsal conjunctiva.

Topical corticosteroid should be restricted to cases with visual reduction secondary to keratitis or if there is a membranous conjunctivitis or uveitis, but this may lengthen the period of virus shedding. Topical steroid is unlikely to precipitate herpetic epithelial disease even if there is HSV conjunctivitis. Topical non-steroidal agents, interferon, and antivirals (e.g. acyclovir, trifluorothymidine) have no effect and should not be used (Table 16.4). The lack of effective treatment has led to strict protocols to limit nosocomial virus spread. Patients with an acute conjunctivitis should be seen promptly in a separate area of the clinic where they cannot mix with other patients; equipment should be decontaminated after use.[8]

Herpes simplex blepharoconjunctivitis

Herpes simplex conjunctivitis or blepharoconjunctivitis (Fig. 16.16) is less common than bacterial conjunctivitis in children. It may be the result of a primary infection or recurrent disease following asymptomatic primary infection. It is often unilateral, with a mixed papillary and follicular response, and is associated with preauricular lymphadenopathy. Blepharoconjunctivitis can be particularly severe if there is co-existing atopic dermatitis (eczema herpeticum). There

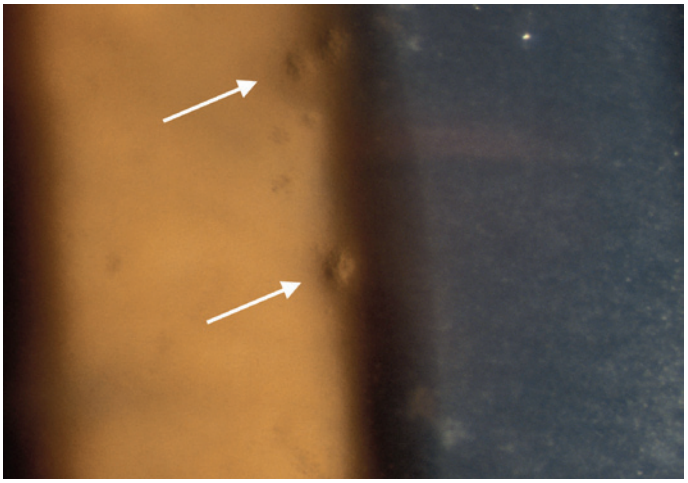


Fig. 16.15 Raised epithelial lesions of acute adenovirus keratitis (arrows). After a week the lesions flatten with the onset of anterior stromal scarring and irregular astigmatism.

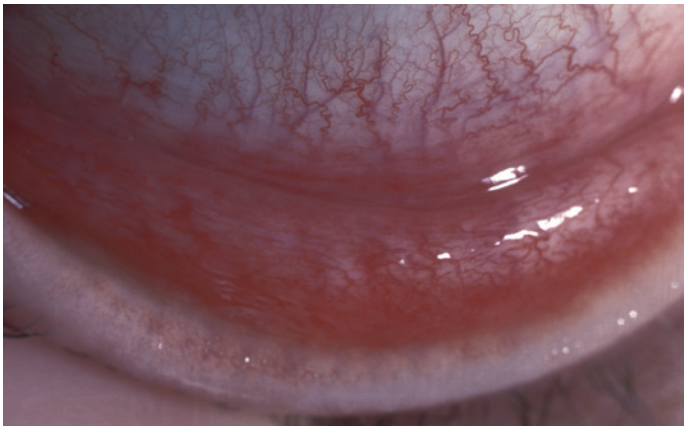


Fig. 16.16 A mild follicular conjunctivitis associated with herpes simplex infection. Confirmed by polymerase chain reaction.

Table 16.4 Treatment options for viral conjunctivitis

Common pathogens	First-line treatment[b]	Alternative
• Herpes simplex virus Note: Usually subsides without treatment within 4–7 days unless complications occur	Acyclovir eye ointment 3% or trifluorothymidine eye drops 1% 5× daily for 7 days (or continue for at least 3 days after complete healing) or Oral acyclovir 200 mg 5× daily for 5 days	Ganciclovir 0.15% gel 5× daily for 7 days
• Varicella (herpes) zoster virus Note: Exclude HIV/immunosuppression	Oral acyclovir 5× daily for 3 days	
• Adenovirus[a] • Enterovirus Note: Highly contagious. Self-limited, with improvement of symptoms and signs within 5–14 days	Nil	

[a]For adenovirus infection, instruct patient to avoid sharing personal items (towels, sheets, pillows, etc.), use meticulous hand washing, and avoid close personal contact for approximately 2 weeks. There is no effective treatment for adenovirus infection; however, artificial tears, topical antihistamines, or cold compresses may be used to mitigate symptoms.
[b]Dose reduction required when using oral antivirals in renally impaired patients.

may be a diffuse punctate keratitis or a dendritic ulcer, with multiple dendrites or geographic lesions in the presence of vernal keratoconjunctivitis. It is often self-limiting, but healing is accelerated by treatment with an antiviral such as acyclovir ointment or trifluorothymidine drops five times a day for 1 week. Oral acyclovir and an oral antibiotic (e.g. erythromycin) to treat staphylococcal superinfection is effective for eczema herpeticum.

Acute hemorrhagic conjunctivitis

Large outbreaks of acute hemorrhagic conjunctivitis caused by enterovirus 70 or coxsackievirus A24 occurred in central Africa and Asia in the 1980s. It has a rapid onset and resolution with characteristic petechial subconjunctival hemorrhages, without permanent corneal change. Direct inoculation and the use of traditional eye medicines, rather than the fecal–oral route, spreads the infection. Confirmation of infection is by PCR. There is no effective treatment; management relies on infection control. The outcome is usually benign, although a polio-like paralysis (radiculomyelitis) has rarely been reported with enterovirus 70 infection.

Chlamydia conjunctivitis

Outside the neonatal period, infection with *Chlamydia trachomatis* serotypes D–K is usually sexually acquired. There is a mixed follicular and papillary conjunctivitis with mucopurulent discharge and preauricular lymphadenopathy. The follicles may be prominent in the lower tarsal and bulbar conjunctiva. These should be distinguished from normal childhood follicles that are often present in the fornix and at the superior border of the tarsal plate. Keratitis is infrequent but the superior cornea can show a superficial punctate keratitis followed by subepithelial opacities and peripheral vessels. Diagnosis is by PCR of tear fluid. Local treatment is with topical azithromycin but systemic treatment with a single dose of oral azithromycin or a course of erythromycin or doxycycline is required to eradicate infection. Children should be investigated for other sexually transmitted diseases (e.g. *N. gonorrheae)*, and assessed for potential sexual abuse.

Trachoma

This is an important cause of external eye disease and the leading infectious cause of blindness. Repeated infection with serotypes A–C of *Chlamydia trachomatis* can cause conjunctivitis in children that progresses to scarring and blindness as adults. Without re-infection, it is a self-limiting disease. In 2014, it was estimated that 232 million people had blinding trachoma. It is endemic in 51 countries, principally in poor rural communities in developing countries. It has disappeared from most developed countries. Transmission is by direct contact with eye or nasal secretions, eye-seeking flies, or by aerosol.[9]

In some endemic areas, 80% of children have active disease and scarring disease can be seen in late childhood. Active disease in children is usually characterized by a mixed follicular and papillary response, best seen over the everted upper tarsal plate, often accompanied by a severe inflammatory response that obscures the underlying vessels over the tarsal plate, and a superior corneal pannus. Resolved follicles at the superior limbus leave depressions (Herbert's pits) that are pathognomonic of previous infection. Corneal blindness is the result of trichiasis, dry eye, secondary infection, and vascularization.

Control of the disease is by implementation of the SAFE strategy:[10]

S=**S**urgery for trichiasis
A=mass distribution of **A**ntibiotics
F=**F**acial cleanliness
E=**E**nvironmental improvement

Treatment of acute conjunctivitis is with a single dose of oral azithromycin (20 mg/kg body weight), or 6 weeks of 1% tetracycline ointment or azithromycin drops. Mass treatment is recommended when the prevalence of active infection is >5%. Clinical signs may persist for months after active infection has been eliminated. If there is trichiasis, lash epilation and lid taping are short-term options prior to lid eversion surgery.

Chronic follicular conjunctivitis

Chronic re-infection with *Chlamydia trachomatis* is a cause of chronic follicular conjunctivitis along with other rare chlamydial infections (feline pneumonitis, psittacosis, and

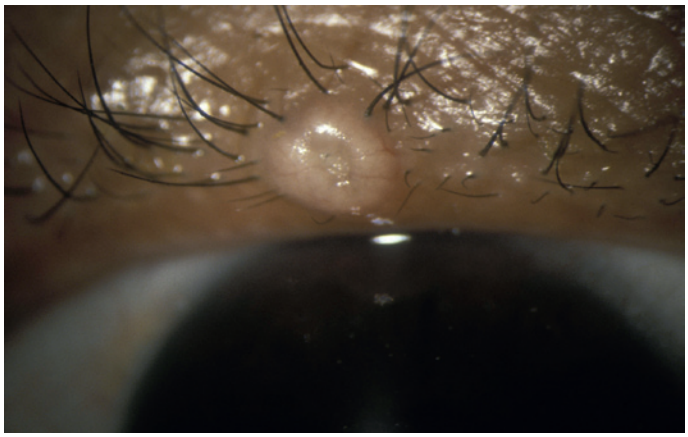


Fig. 16.17 An umbilicated lesion of molluscum contagiosum on the lid margin. There may be an associated follicular conjunctivitis and corneal vascularization in neglected cases.

lymphogranuloma venereum). Chronic canaliculitis and secondary conjunctivitis caused by *Actinomyces* spp. is rare in children. Hypersensitivity or toxicity to medications (preservatives such as benzalkonium chloride, especially in ocular hypotensives) can produce a follicular response. Other potential causes are described below.

Molluscum contagiosum

Molluscum contagiosum is a double-stranded DNA poxvirus. Transmission is by direct contact or autoinoculation to the eye. Molluscum lesions are umbilicated; when on the lid or close to the lash line they can easily be missed (Fig. 16.17). In this location they can cause a chronic follicular conjunctivitis, usually unilateral with a peak incidence at ages 2–4 years. Multiple facial lesions can develop in patients with atopy and in the immunosuppressed. Treatment is by expression or curettage of the core of the lesion, facilitated by making a small incision in the inner margin of the lesion with the tip of a needle – cautery or cryotherapy may cause depigmentation of the lid margin and loss of lashes; resolution is then rapid and topical steroid is not required. Chronic cases can develop a punctate keratopathy with secondary peripheral vascularization.

Parinaud oculoglandular syndrome

This rare condition causes a unilateral granulomatous conjunctivitis with surrounding follicles, often associated with fever and ipsilateral regional lymphadenopathy. It is a rare feature of cat-scratch disease, which is usually caused by a Gram-negative bacterium, *Bartonella henselae*, following a scratch from a cat or inoculation of contaminated cat flea feces into the conjunctiva. The diagnosis is confirmed by a rising immunoglobulin (Ig)G serology, indirect fluorescent antibody for *Bartonella* spp., or PCR from tears. There is a tendency to spontaneous resolution but treatment is with oral azithromycin, doxycycline, or ciprofloxacin. Other rarer causative agents are tularemia (*Francisella tularensis*), HSV, sporotrichosis, tuberculosis, and chlamydia.

Ophthalmia nodosa

This is a granulomatous reaction of the conjunctiva or cornea to implanted plant or insect hairs. There is rapid onset of irritation, photophobia, and chemosis after exposure. Migration of barbed hairs into the tissue is aggravated by eye rubbing. Intraocular penetration of the hairs can occur, with symptoms of chronic keratoconjunctivitis, uveitis, vitritis or chorioretinitis. Caterpillar hairs (setae) were the first reported causative agent, but hairs from pet tarantulas (e.g. Chilean rose tarantula – *Grammostola rosea*) are now more common. Tarantulas release a cloud of hairs as a defensive ploy when threatened. Protruding hairs can be removed, but physical removal of buried hairs is usually impossible. Mild topical steroid is effective to control inflammation. Conjunctival granulomas can be excised (Fig. 16.18).

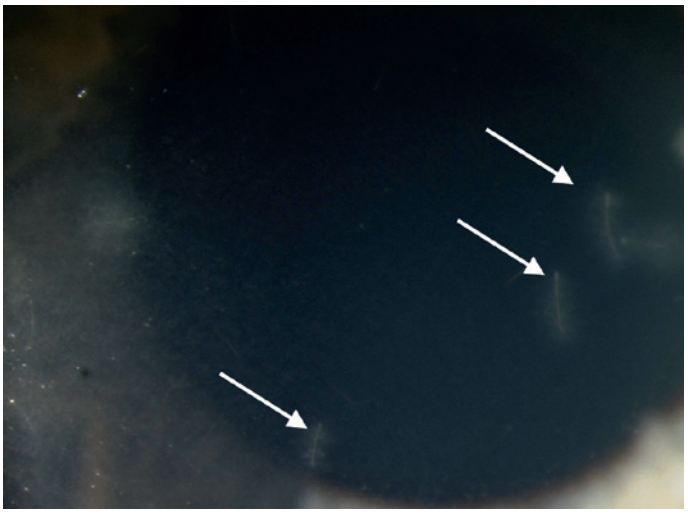


Fig. 16.18 Tarantula hairs embedded in the cornea (arrows). There was an associated mild conjunctivitis but no granuloma.

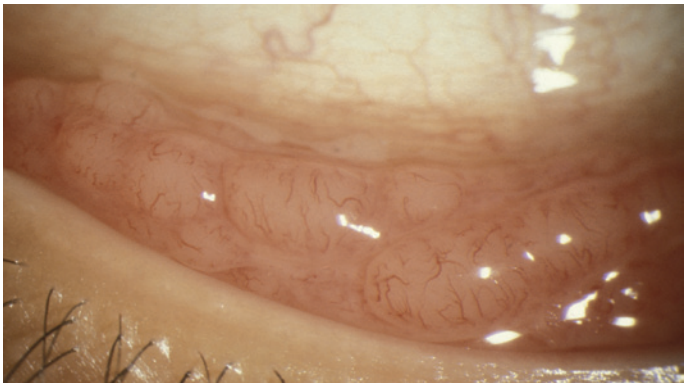


Fig. 16.19 Numerous large follicles in the inferior fornix (folliculosis). The patient was asymptomatic.

Conjunctival folliculosis

Folliculosis is a marked follicular response without other signs of ocular inflammation mostly seen in adolescents and young adults. There may be only mild discomfort; the follicles may have been noted coincidentally. The follicles may be present on the tarsal, forniceal, and bulbar conjunctiva (Fig. 16.19). Treatment or investigation is not usually required. A trial of topical steroid or oral doxycycline is appropriate but spontaneous resolution occurs; it may take years.

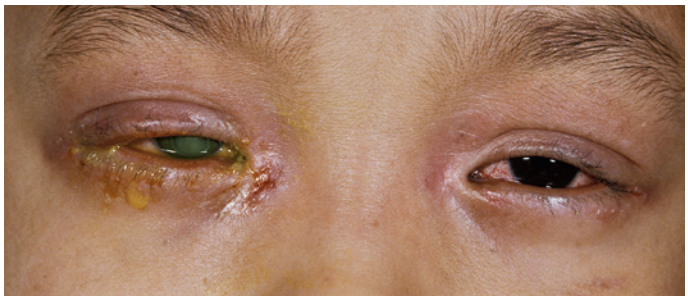


Fig. 16.20 Severe signs in a 6-year-old child with vernal keratoconjunctivitis. The lids are thickened with loss of lashes. There is also an abrasion on the side of the nose from eye rubbing. A right corneal plaque has developed.

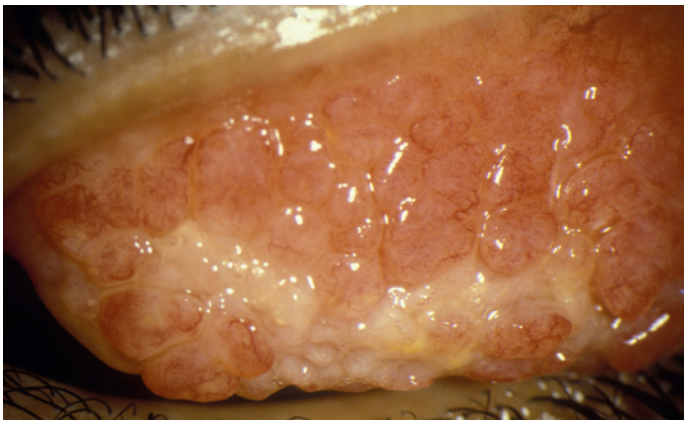


Fig. 16.21 Active palpebral vernal keratoconjunctivitis. There are giant papillae with adherent mucus.

Chronic papillary conjunctivitis

Vernal keratoconjunctivitis

Vernal keratoconjunctivitis (VKC) is an atopic disease in which an allergic response is mounted to common environmental allergens, dust or pollen. The mild ocular allergic diseases are seasonal and perennial allergic conjunctivitis. The severe allergic eye diseases are VKC that has an early onset with a high expectation for eventual resolution, and atopic keratoconjunctivitis that is unremitting, typically developing in older patients with severe facial atopic dermatitis (eczema).

Clinical features

VKC usually develops in the first decade of life (82% by age 10 years, with a mean age of 7 years). In 95% of cases there is remission by the late teens. In Africa, India, and the Middle East, it is a substantial public health problem, accounting for 3% of eye clinic patients and 10% of outpatient attendances. It affects 3–10% of children in Africa and the Middle East. The prevalence in Western Europe is less than 0.03%.[11] VKC is more common in males, although the gender difference is less marked in the tropics. In temperate regions, 45–75% of patients have a history of asthma or eczema; in tropical regions this is lower (0–40%). There is a family history of atopy in 50% of patients, although the expression (eczema, asthma, or allergic rhinitis) may vary in different family members. Limbal VKC is more frequent in patients of African or South Asian descent; this racial predisposition persists after migration to temperate regions.

Symptoms of VKC consist of itch, photophobia, discomfort, blepharospasm, blurred vision, and mucous discharge. The disease can be markedly asymmetric. The skin of the lids may be eczematous with excoriation at the canthi and a reactive ptosis (Fig. 16.20). Papillary hypertrophy and cellular infiltration over the upper tarsal plates obscures the pattern of underlying vessels. Giant papillae (>1 mm diameter) give a cobblestone appearance and, in active disease, mucus accumulates between the papillae (Fig. 16.21). Papillae can form at the limbus, appearing as gelatinous or vascular mounds with white Horner–Trantas dots (aggregates of degenerated eosinophils and epithelial cells) on the apices (Fig. 16.22). Reticular scarring can develop over the upper tarsal plate, rarely of clinical significance. VKC is classified as palpebral, limbal, or combined disease according to the distribution of the giant papillae. Palpebral or combined limbal and palpebral diseases behave similarly, whereas purely limbal disease, which is the more common form in tropical regions, is a more benign variant in temperate regions.

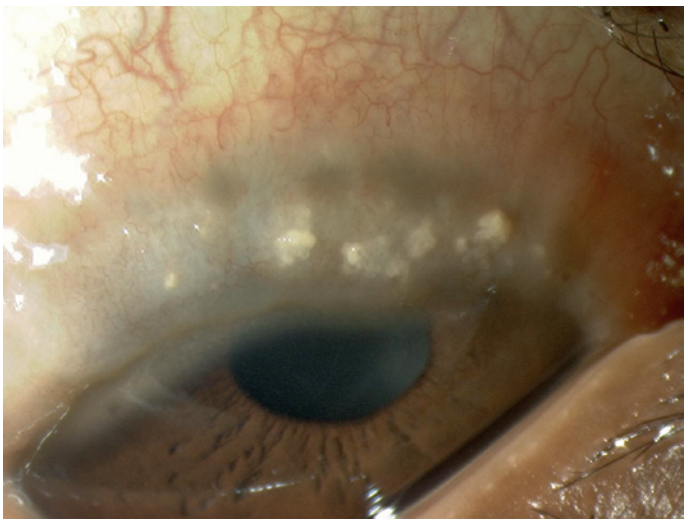


Fig. 16.22 Limbal vernal keratoconjunctivitis. White Trantas' dots have formed on the apices of the limbal papillae. There is a secondary pseudogerontoxon centrally.

Corneal changes

In mild disease there may be punctate epithelial erosions on the superior and central cornea. If there is active palpebral disease, mucus may be deposited on the superior corneal epithelium (Fig. 16.23), which can stimulate the formation of superficial corneal neovascularization. If there is severe palpebral disease, this may progress to corneal epithelial necrosis (macroerosion) caused by the toxic agents (e.g. eosinophilic major basic protein) released from the epithelium of the upper tarsal conjunctiva (Fig. 16.24). An epithelial erosion may heal completely with early intensive treatment, but in neglected cases mucus and calcium deposition on Bowman's layer can prevent re-epithelialization and a vernal plaque (shield ulcer) develops (Fig. 16.25). These plaques rarely vascularize, but they cause intense discomfort. Because there is a risk of secondary

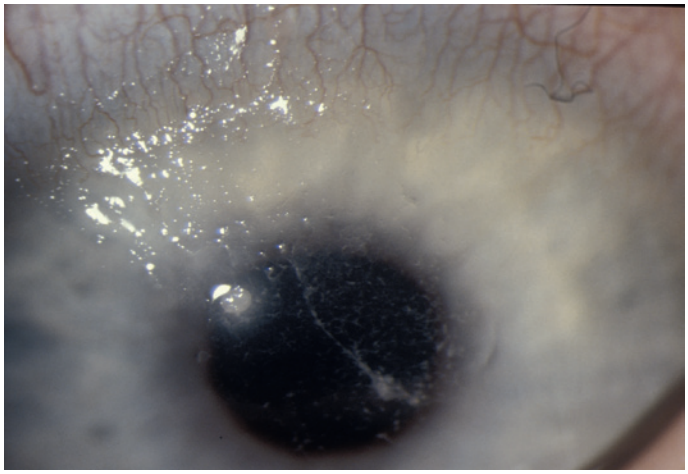


Fig. 16.23 Mucus adherent to the superior corneal epithelium in a case with palpebral vernal keratoconjunctivitis.

infection, including crystalline keratopathy, a prophylactic antibiotic should be prescribed (Fig. 16.26). Although visual loss from limbal disease is uncommon, an arcuate infiltrate can develop adjacent to limbal papillae (pseudogerontoxon), and there may be cystic degeneration of the conjunctiva in previously affected areas. In tropical regions, untreated limbal VKC is an important cause of visual loss.

Associated disease

Patients with VKC may have other conditions that affect their vision, including:

1. herpes simplex keratitis;
2. keratoconus in up to 26% of patients;
3. a characteristic anterior capsular cataract in 8%;
4. complications of unsupervised steroid treatment (glaucoma, cataract) in up to 20%.

The risk of visual loss is greatest in tropical regions, varying between 0% and 10%. The higher rate of visual loss in tropical

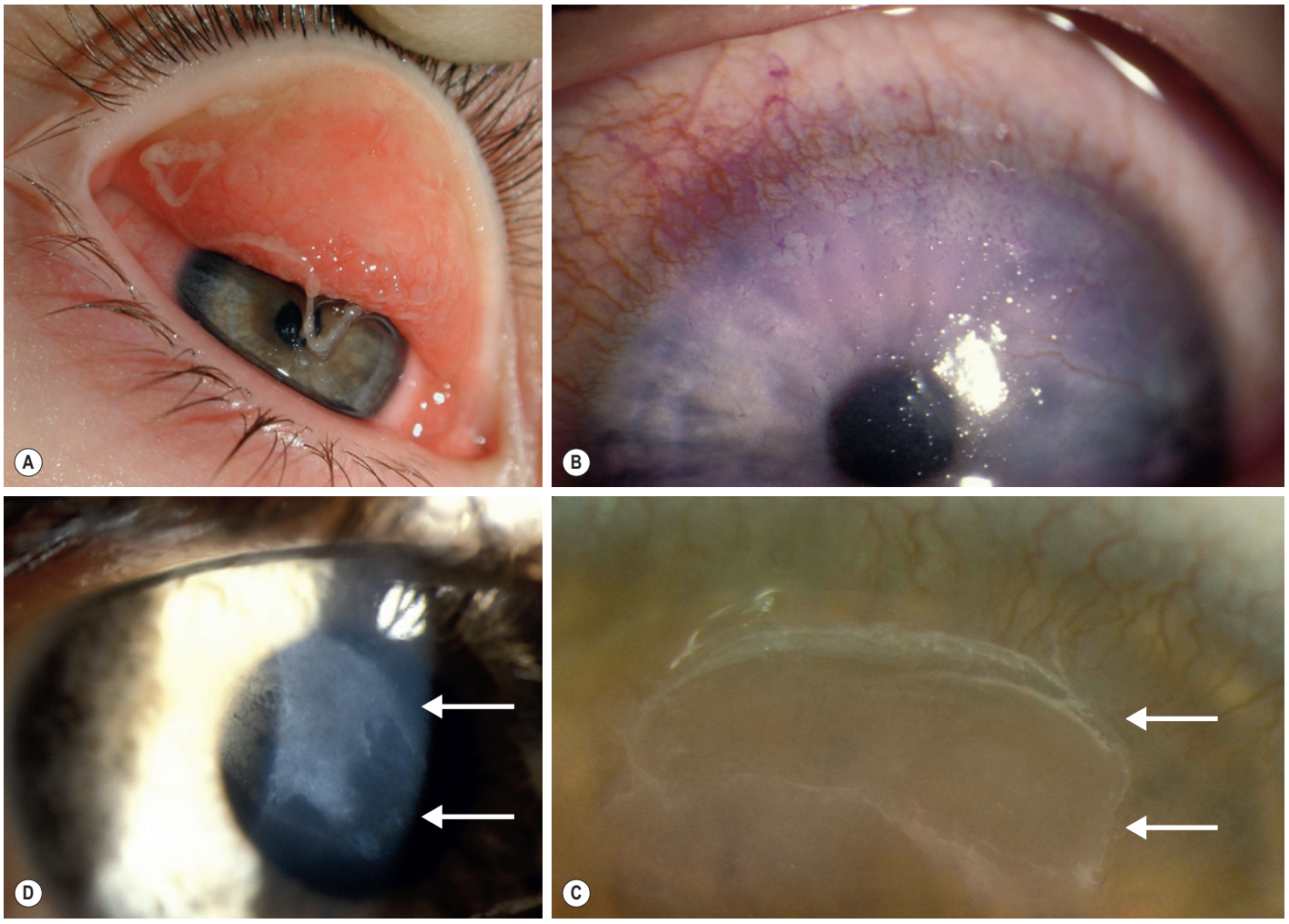


Fig. 16.24 The pathogenesis of vernal plaque. (A) The tarsal conjunctiva becomes inflamed with increased mucus production due to mast cell degranulation and histamine release. Eosinophil degranulation releases cationic proteins that are epitheliotoxic resulting in (B) associated corneal punctate keratopathy with adherent mucus highlighted with Rose Bengal stain. (C) If the inflammation continues, a confluent area of epithelium breaks down to form a macroerosion. Epithelial and eosinophilic debris are deposited on Bowman's membrane in the base of the macroerosion to form a vernal plaque (arrows). (D) Whether this is removed with lamellar dissection or epithelializes a ring scar results.

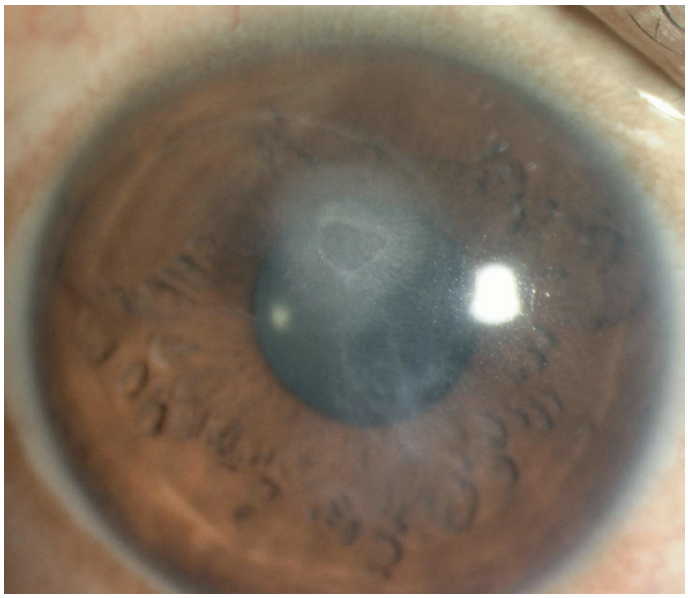


Fig. 16.25 Large corneal plaque in a case with palpebral vernal keratoconjunctivitis. The base of the defect is calcified.

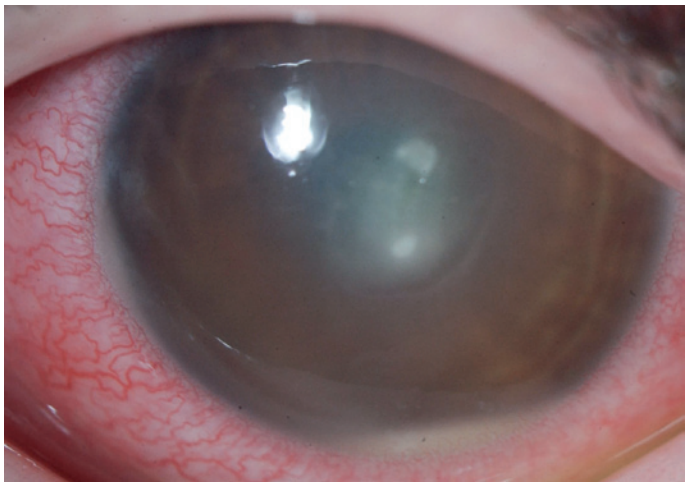


Fig. 16.26 Secondary bacterial infection of a vernal plaque with small hypopyon. Prophylactic antibiotic should be used until a plaque has healed.

areas is related to poor access to treatment and co-existent disease such as trachoma and bacterial conjunctivitis. In developed countries, minor visual loss from corneal scar occurs in about 6% of patients; 25% of patients with palpebral VKC in Western Europe develop corneal complications.

Disease mechanisms

In atopy, a subpopulation of T lymphocytes (Th2) is abnormally expanded; these cells drive the disease process via the type I (IgE-mediated) immediate hypersensitivity response. Th2 cells generate cytokines and interleukins (IL-3, IL-4, and IL-13) that promote the synthesis of IgE by B cells. When an allergen comes into contact with conjunctival mast cells coated with IgE antibodies specific to that allergen, the mast cell degranulates and releases histamine and other cytokines that recruit other inflammatory cells such as eosinophils, which in turn attract more inflammatory cells. Additional inflammatory mediators are released into the tissue and tears. Tarsal and limbal papillae consist of a central vascular core of mononuclear cells surrounded by edematous connective tissue infiltrated with plasma cells, mast cells, activated eosinophils, and lymphocytes. Squamous metaplasia of the overlying epithelium may also contain mast cells but a reduced number of goblet cells. Scar tissue (collagen type III) forms in the core of the papillae.

Mechanical irritation can precipitate a clinical picture similar to VKC termed "contact lens-associated giant papillary conjunctivitis" (GPC). The role of secondary irritation (diesel particles, infection, or smoke) amplifying the symptoms of VKC has not been fully explored. The genetic basis for VKC is not fully determined. An altered epithelial and mucosal barrier function is important, allowing environmental allergens access to the immune system. Truncation mutations in the filaggrin gene, a protein crucial to maintaining the epithelial barrier function, may be significant.

The diagnosis of VKC is based on characteristic clinical signs. Investigations to support the diagnosis are not usually necessary or widely available. The following may be helpful:

- Total serum IgE and tear IgE are usually elevated, but these measurements are also non-specifically elevated if there is atopic dermatitis. Commercial kits to measure total tear IgE are available.
- Measurement of local IgE production by radio-allergosorbent test, and conjunctival challenge to allergens can confirm allergic conjunctivitis but they are only available in some specialist departments.
- A conjunctival biopsy or a cytology specimen, taken by swabbing the conjunctiva with a nylon brush, will contain eosinophils and MC_T mast cells (tryptase positive, chymase negative) if there is severe allergic eye disease.
- "Allergy skin testing" is not indicated in the majority of patients. In temperate regions, epidermal or conjunctival challenge testing shows that at least 50% of patients are sensitive to house dust mite allergen, pollens, and animal dander. Testing for local environmental allergens (pollens, house dust mite, etc.) can support an atopic basis for the disease, but patients may react to several allergens with no indication as to which is causing the allergic conjunctivitis. Conversely, allergen-specific conjunctival provocation may reveal sensitivity to allergens that do not provoke a response by skin testing. In the same individual, the allergens provoking asthma and allergic conjunctivitis may be different. Advice should be sought from a clinical allergist if the disease is refractory.

Management

There is an excellent potential to retain good vision in the majority of cases of VKC, and iatrogenic disease must be avoided.[12] The presence of papillae alone is not a good indicator of activity. This is best reflected by conjunctival injection, the presence of mucus between the papillae, Trantas dots, mucus adherent to the corneal epithelium, as well as corneal epithelial breakdown, vascularization, and ulceration. Medical management is proportional to symptoms and signs; intensive topical corticosteroid is reserved for crises (Fig. 16.27). The following should be considered[13]:

- Allergen avoidance by eliminating feather pillows, carpets, pets. Allergens are often locally distributed, but

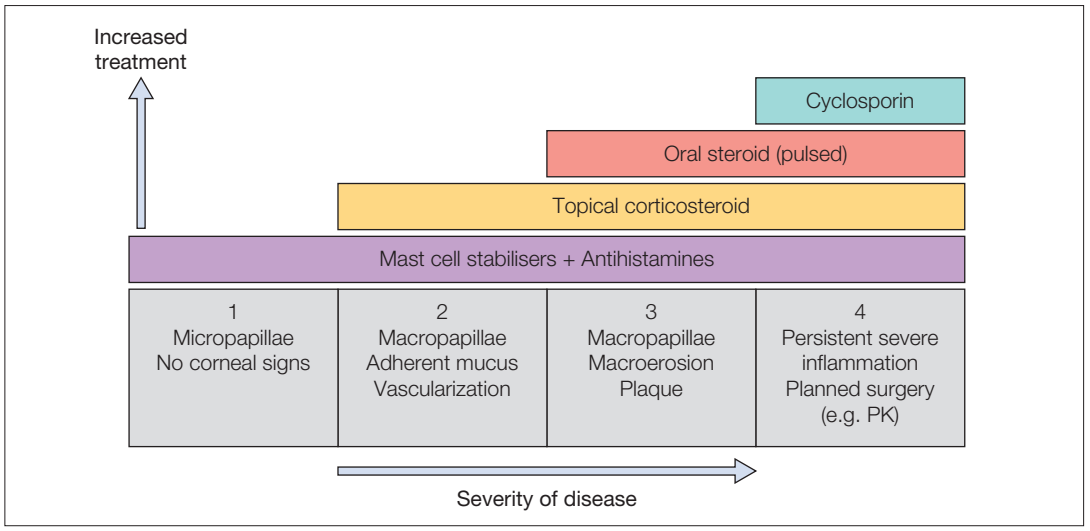


Fig. 16.27 The stepladder of treatment for severe allergic eye disease. With increasing severity of clinical signs (grades 1–4) treatment is added to control the disease. PK, penetrating keratoplasty.

geographic treatment by relocation may not be practical. The patient's school may need to be informed that VKC is not an infection. School staff may need to administer treatment during the school day.

- An oral antihistamine can help sleep and reduce nocturnal eye rubbing.
- Topical non-steroidal medications are effective, but no one agent is superior. For mild disease, topical histamine (H_1) antagonists (levocobastine 0.05%, emedastine 0.05%) produce rapid symptomatic relief. Topical cromones (sodium cromoglycate 2–4%, nedocromil sodium 2%) and other mast cell stabilizers (lodoxamide 0.1%) prevent mast cell degranulation. Dual action agents active against H_1 receptors and mast cell degranulation (e.g. olopatadine 0.1%) are well tolerated. All are safe for long-term maintenance therapy, reducing the number and severity of exacerbations and the need for supplementary topical corticosteroid.
- Topical acetylcysteine 5–10% reduces mucus adherence to the cornea during exacerbations.
- The role of topical non-steroidal agents (diclofenac 0.1%, ketorolac 0.5%), a potentially safe option, needs better evaluation.
- Topical corticosteroid is very effective, but patients should be carefully monitored for side effects (glaucoma, cataract, and ocular herpetic infection). Synthetic steroids (fluoromethalone, loteprednol, rimexolone) may reduce the risk of glaucoma and cataract. Steroid ointment, such as betamethasone, may be useful at night to reduce treatment frequency.
- Steroid injected into the supratarsal space after lid eversion (0.5–1.0 ml of either dexamethasone [4 mg/ml] or triamcinolone [40 mg/ml]) is reserved for severe disease not responding to topical treatment, or given at the time of surgery for a vernal plaque.
- Cyclosporin A (0.05% to 2%) or tacrolimus 0.03% is safe in children. It is an alternative to topical corticosteroid, but generally less well tolerated.
- Systemic immunosuppression with corticosteroids, cyclosporin A, tacrolimus, or azathioprine is reserved for severe unremitting disease with corneal complications. Leukotriene receptor antagonists (e.g. montelukast) appear to only be effective if there is associated atopic asthma. Molecular antagonists of IgE (e.g. omalizumab) and immunoglobulin are very expensive but may have a role in the acute management of severe disease.
- Surgical excision or cryotherapy of papillae produces only temporary remission as the papillae tend to re-grow. Application of mitomycin 0.02% after excision may reduce the rate of recurrence. Cryotherapy for limbal papillae risks causing corneal stem cell failure.
- Treatment of vernal plaque is by superficial keratectomy after the local allergic disease has been medically controlled. A short (3-day) course of oral corticosteroid (prednisolone 1 mg/kg) can help to rapidly bring severe disease under control. The epithelium should be reflected to show the full extent of the plaque and the plaque debrided or "peeled" from the surface. A minimum depth of tissue should be removed. There is no advantage in using laser phototherapeutic keratectomy. An amniotic membrane graft may rarely be required for a large persistent epithelial defect. A bandage contact lens is not an alternative to effective medical management. It increases the risk of secondary infection.

For severe unremitting disease, a short period of supervised treatment in hospital may be required to confirm compliance with treatment.

Treatment for GPC includes replacing scratched contact lenses or prostheses, optimizing their fit to reduce conjunctival trauma, and the use of a rigorous hygiene and protein-removing tablets 1–2 times weekly. Topical corticosteroids can be used freely if there is a prostheses. Protruding sutures should be removed.

Stevens–Johnson syndrome and toxic epidermal necrolysis

Stevens–Johnson syndrome (SJS) and the more severe variant, toxic epidermal necrolysis (TEN), are a spectrum of disease with potentially devastating ocular consequences. SJS is

defined as having <10% body surface area skin involvement and TEN as >30% affected. There is a characteristic prodrome of fever, malaise, and upper respiratory infection. The typical erythematous skin macules and target lesions can progress to vesicular lesions and necrosis. In severe disease, even slight rubbing leads to exfoliation of the outer epidermis (Nikolsky's sign). Any mucosal surface can be affected; lesions are most common on the lips and oral mucosa. The mortality rate of SJS is 1–5%, and of TEN is 25–35%; this can rise to 90% if large areas of epidermis are involved. The annual incidence in all ages is approximately 1.9 per 10^6 in Europe, lower in some ethnic groups. The incidence in human immunodeficiency virus (HIV)-positive patients is much higher. Eighty percent of patients hospitalized for treatment of SJS/TEN will develop eye disease, and 35% continue with chronic disease.[14] Acute eye involvement is usually more common with TEN than SJS but the proportions with late complications are similar.[15] It is the eye disease that causes the most profound long-term morbidity because it can progress over years after the acute episode has resolved.

The most commonly associated trigger factor for these diseases is exposure to drugs. HSV infection and mycoplasma is less common. Sulfonamides, phenobarbital, carbamazepine, and lamotrigine are strongly associated with a risk of SJS or TEN in children, with lesser associations with valproic acid, non-steroidal anti-inflammatory drugs, and paracetamol. In some cases no precipitating factor is identified.

The mechanism of disease involves Fas–Fas ligand interaction and cytotoxic T-lymphocyte activation that results in keratinocyte apoptosis, which is the basis of the skin and mucosal lesions. Histologically, there is lymphocyte aggregation at the dermal/epidermal interface and a perivasculitis.

It is essential that an ophthalmologist examines patients at the onset of disease. Acute ocular complications usually occur concurrently with the skin disease but may precede it by several days. The early signs include conjunctivitis with a mucous discharge, conjunctival membranes, and sloughing of the conjunctival epithelium (Figs 16.28 and 16.29). Conjunctival ulceration over the tarsal plates is common but may be difficult to confirm due to lid swelling. Corneal epithelial defects may progress to corneal ulceration with the potential for microbial superinfection (Fig. 16.30). Progressive sight-threatening corneal complications require lifelong management and can



Fig. 16.28 Skin lesions in acute Stevens–Johnson syndrome (three monitoring pads are in position). *(Courtesy of Dr Saaeha Rauz.)*

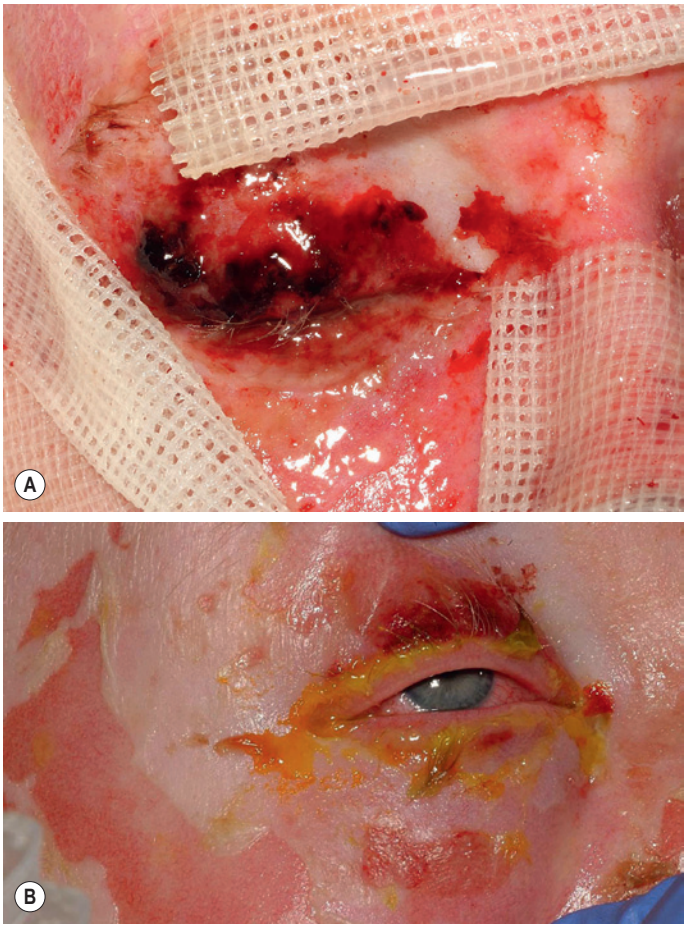


Fig. 16.29 Toxic epidermal necrolysis. There is necrosis and haemorrhage of the lid skin (A) with protective skin gauze. The appearance during skin healing (B). There is still conjunctival chemosis and a corneal epithelial defect (not shown). *(Courtesy of Dr Saaeha Rauz.)*

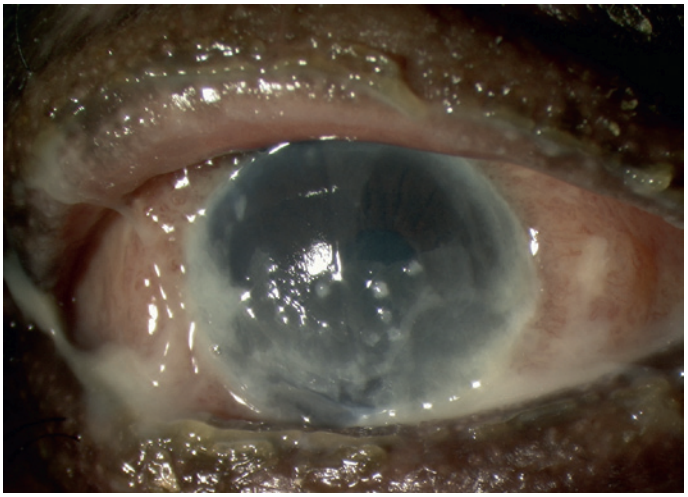


Fig. 16.30 Eye 3 weeks after onset of Stevens–Johnson syndrome. There is a subtotal epithelial defect over the cornea and conjunctiva with excessive mucus accumulation.

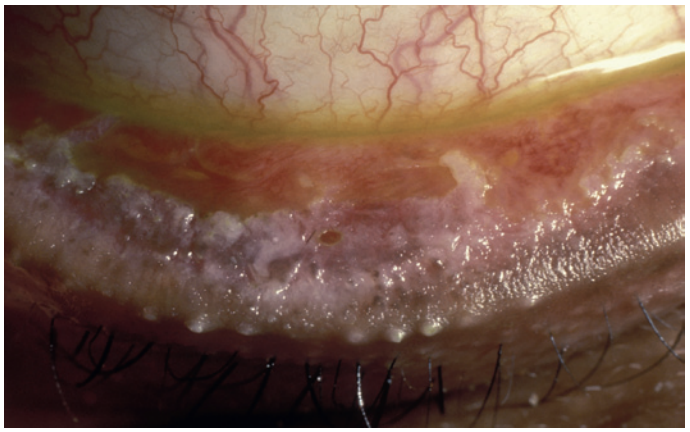


Fig. 16.31 Keratinization of the posterior surface of the lower lid margin in Stevens–Johnson syndrome. Keratinization is an important risk for microbial keratitis and vascularization.

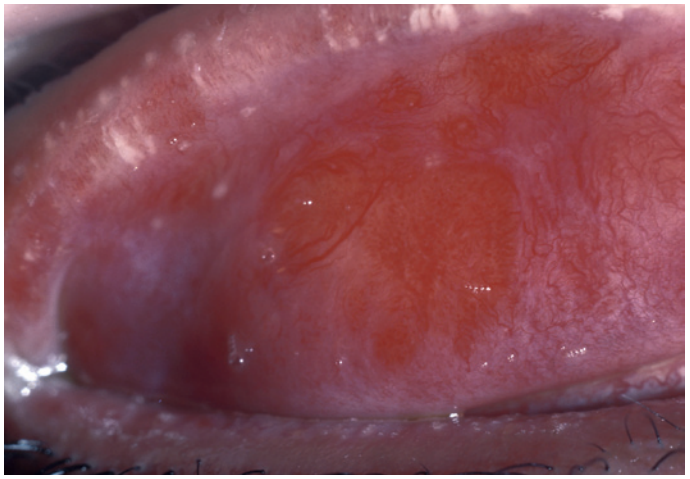


Fig. 16.32 The characteristic reticular pattern of scarring over the upper tarsal plate that is a consequence of acute Stevens–Johnson syndrome. The meibomian gland orifices open onto the posterior lid margin.

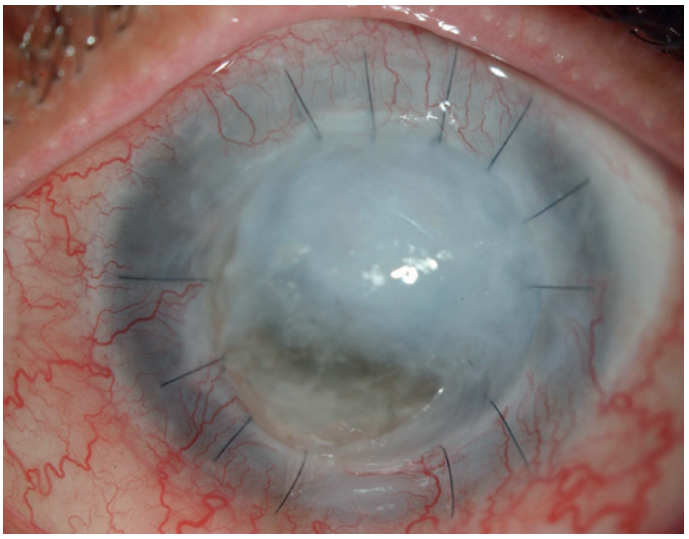


Fig. 16.33 Persistent epithelial defect and melting in a graft required to treat a perforated cornea in late stage Stevens–Johnson syndrome.

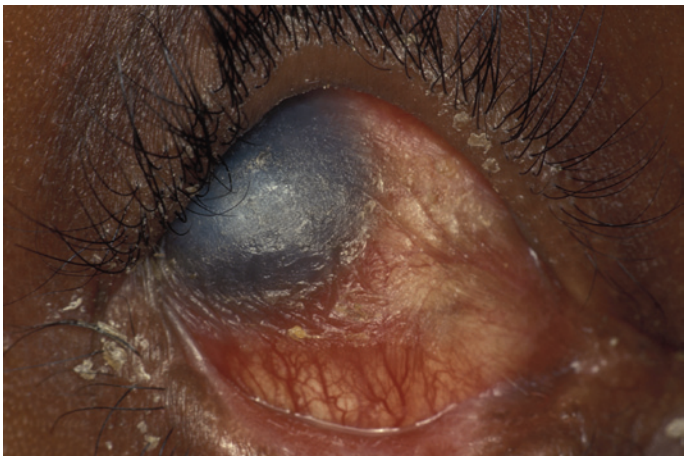


Fig. 16.34 A dry keratinized ocular surface in end-stage ocular disease following Stevens–Johnson syndrome.

result from conjunctival scarring involving the lid margin, tarsus, and loss of the fornix. Late complications may result from damage to the limbal epithelial stem cells, dry eye disease from obliteration of the lacrimal ductules and goblet cell loss, and from chronic inflammation or infection causing corneal opacity and neovascularization (Figs 16.31–16.34).

Management of SJS/TEN

Supportive management in the acute phase of the disease is essential. Patients are critically ill and require transfer to a regional burns unit or intensive care department for skin care and medical support. Identification and removal of the inciting agent is important. There is some evidence that systemic corticosteroids or intravenous immunoglobulin (IVIG) improve the prognosis of SJS compared to supportive care alone, while IVIG or other agents such as tumor necrosis factor alpha inhibitors (e.g. infliximab) and oral cyclosporin improve the prognosis of TEN. However, this is controversial.[16] There is no robust evidence that any of these systemic treatments improve the final visual outcome.

The goals of acute management of ocular involvement are minimization of inflammation and adhesions, infection prophylaxis, and the prompt identification and treatment of complications such as exposure and microbial keratitis. There is no standardized treatment for the prevention of ocular complications. Ocular hygiene with topical anesthetic and saline will remove inflammatory debris and periodic lysis of conjunctival adhesions with a squint hook or forceps to remove membranes, or scissors to divide early adhesions, is often performed, although there is no proof of long-term benefit. Lid taping or lubricant ointment and a moist chamber with polyethylene film must be used if the patient is anesthetized to prevent exposure keratitis. A topical antibiotic (quinolone) should be used if there is corneal epithelial breakdown. Topical corticosteroid or cyclosporin may help reduce severe conjunctival inflammation, but they should be used cautiously when there is a corneal epithelial defect because they may mask signs of infection, and bacterial or candida superinfection of an epithelial defect can progress rapidly. An amniotic membrane secured with absorbable sutures to cover the entire ocular surface, or secured over a conformer, may limit symblepharon formation and prevent limbal stem cell

Table 16.5 Ocular effects of chronic ocular surface disease

Ocular effects	Symptoms and signs
Loss of goblet cells	Poor tear film
Loss of lacrimal gland	Dry eye disease
Meibomian gland drop out	Punctate corneal epithelial stain
Posterior lid margin loss	Persistent epithelial defect
Posterior migration of meibomian gland orifices	Vascularization
Keratinization, particularly of the posterior lid margin	Scar
Conjunctival scarring and symblepharon	Visual loss
Entropion	Pain
Trichiasis	
Exposure	
Ocular surface stem cell failure	

failure if performed within 2 days of onset of symptoms.[17,18] Episodes of conjunctival inflammation may persist after the systemic disease has resolved or recur much later (recurrent SJS) in a clinical pattern similar to ocular mucous membrane pemphigoid. These recurrences do not occur in non-ocular tissues; their pathogenesis is obscure.

In the chronic phase of the disease (>1 month from onset), treatment focuses on management of chronic ocular surface disease by eliminating or minimizing toxicity from topical treatments and the introduction of immunosuppressive therapy if there is recurrent inflammation or progressive cicatrization. Successful management depends on the identification of the contributing components of the ocular surface disease, which must all be managed for successful control of the disease (see below). Severe conjunctival inflammation leads to the following sequence of events (Table 16.5):

- Loss of goblet cells and the accessory conjunctival lacrimal glands.
- Loss of the posterior lid margin with migration of the openings of the meibomian glands onto the posterior lid surface with meibomian gland dysfunction. Metaplasia of the meibomian gland duct epithelium is accompanied by abnormal lashes that grow from the gland opening (distichiasis). Keratinization extending onto the posterior lid margin is a particular risk for progressive corneal vascularization and opacification.
- An unstable tear film and a secondary punctate keratopathy causes chronic discomfort, photophobia, and reduced vision. Keratinization of the corneal surface results in severe discomfort and loss of vision.
- Conjunctival inflammation leads to a coarse reticular pattern of scarring over the upper tarsal plate. Conjunctival scarring can lead to lid shortening and entropion, resulting in corneal abrasion from trichiasis. Incomplete lid closure (lagophthalmos) is common.
- Trichiasis, dry eye disease, exposure, and poor surface healing mean that any abrasion can lead to a persistent corneal epithelial defect. This may progress rapidly to corneal stromal melt and perforation, particularly if there is microbial infection.
- Acute severe inflammation or chronic ocular surface disease may lead to ocular surface failure from loss of corneal epithelial stem cells.

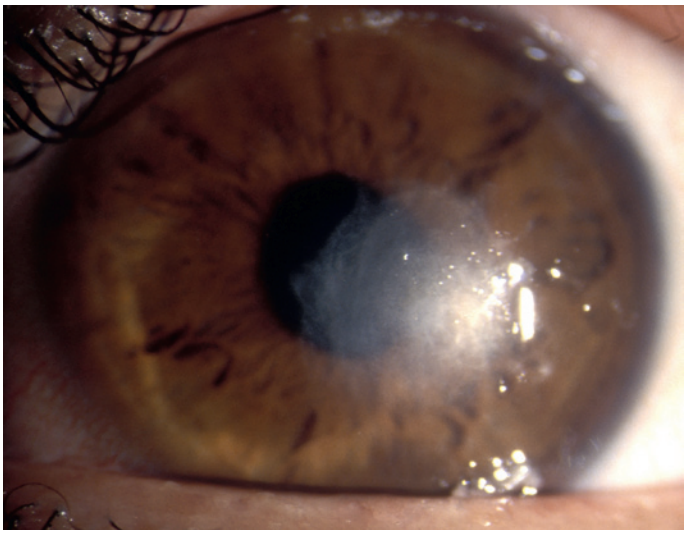


Fig. 16.35 Bacterial keratitis complicating dry eye disease in a child who developed graft-versus-host disease following bone marrow transplantation.

Graft-versus-host disease

Hemopoietic allogeneic stem cell transplantation (allo-HSCT) is used to treat a number of malignant and non-malignant hematologic disorders and some inherited diseases. The main complication of allo-HSCT developing in 40% to 60% of patients after an HLA-matched graft (<3 months after graft) is acute systemic graft-versus-host disease (GVHD). A proportion progress to chronic disease. The mechanism is the recognition by donor cytotoxic T lymphocytes of host alloantigens on antigen-presenting cells. GVHD affects the gastrointestinal tract, liver, skin, and lungs. Ten percent of patients develop conjunctival involvement during acute GVHD, with hyperemia and edema, the formation of conjunctival membranes, subconjunctival hemorrhage, and corneal epithelial breakdown. The severity of acute GVHD, and skin and mouth involvement, are all predictors of the development of chronic GVHD. The reported incidence of ocular involvement in chronic GVHD varies widely between 30% and 85% with a median onset of about 9 months and ocular can precede systemic disease. Corneal disease and chronic uveitis are the primary causes of visual loss. The principal ocular complication is dry eye disease from goblet cell loss and fibrosis of the lacrimal ducts, developing in 40–60% of patients, with a poor tear film, punctate erosions, and filamentary keratitis. There may be necrosis of the lid margins with secondary keratinization of the posterior lid margin and conjunctiva, trichiasis, and entropion. GVHD is a potentially blinding disease. In one study, severe ocular complications (bacterial keratitis or corneal perforation) occurred in 13% of 620 patients who had received bone marrow transplantation or allo-HSCT (Fig. 16.35). The incidence of severe ocular complications may be reduced by regular ophthalmic review and early treatment. Patients are also at risk during the required bone marrow suppression before an allo-HSCT of corneal involvement from herpes virus infections (simplex, zoster, Epstein–Barr).[19,20]

Initial management is intensive preservative-free lubricants (e.g. hyaluronic acid). A hematologist should supervise the management of systemic GVHD with treatment with systemic corticosteroid, cyclosporin A, or mycophenolate.[21] Additional

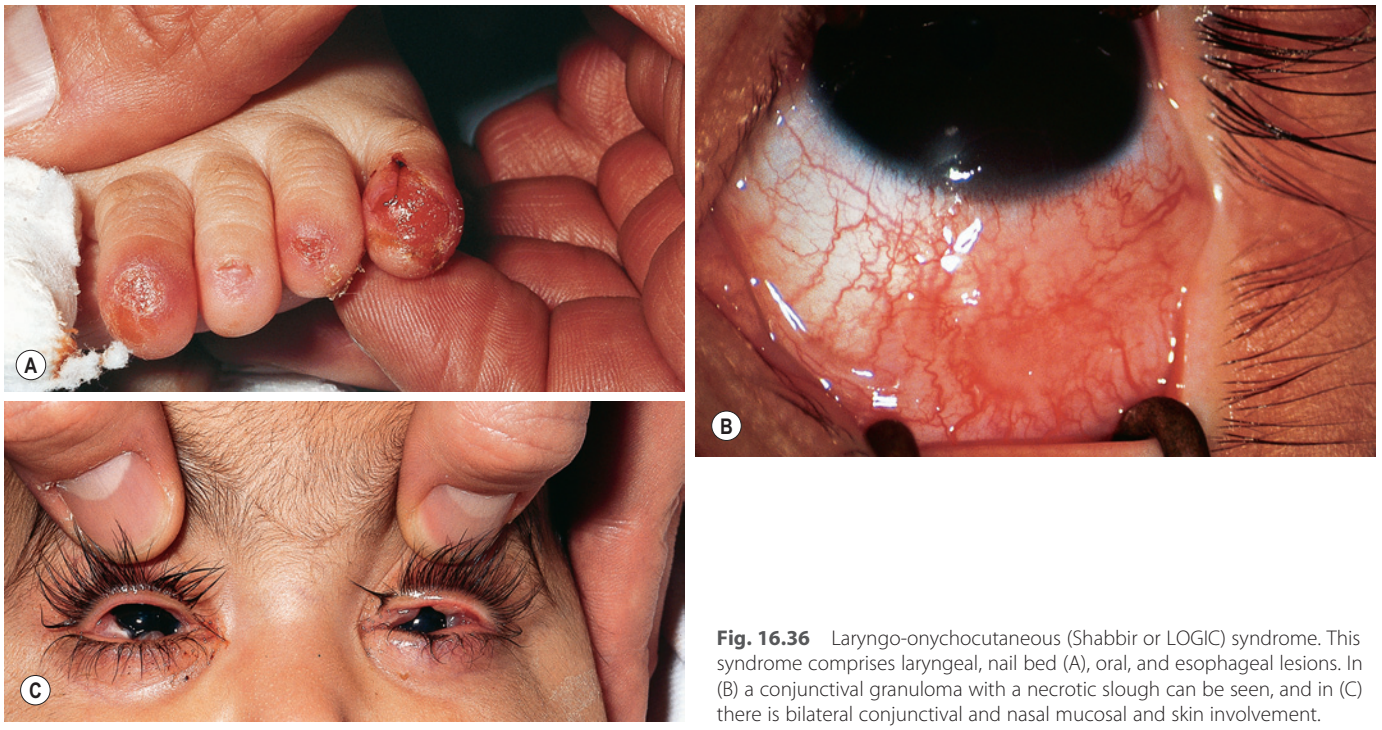


Fig. 16.36 Laryngo-onychocutaneous (Shabbir or LOGIC) syndrome. This syndrome comprises laryngeal, nail bed (A), oral, and esophageal lesions. In (B) a conjunctival granuloma with a necrotic slough can be seen, and in (C) there is bilateral conjunctival and nasal mucosal and skin involvement.

management options for chronic ocular surface disease are described below.

Inherited abnormalities of the epidermal microfilament assembly structure can cause severe corneal and ocular surface disease. Epidermolysis bullosa is described in Chapter 34. Laryngo-onychocutaneous syndrome (LOGIC or Shabbir syndrome) is another example that falls within this group of diseases. It is a very rare autosomal recessive condition described in consanguineous Punjabi Muslim families that comprises skin, laryngeal, and ocular mucous membrane sloughing and granulation tissue. It is evident in the first year of life and is relentlessly progressive (Fig. 16.36). The conjunctival changes are resistant to treatment, although fornix reconstruction using amniotic membrane may be partly effective. The condition is the result of mutations of the *LAMA3* gene that encodes the laminin subunit alpha-3.[22] Other loss-of-function mutations of this gene cause the lethal skin disorder Herlitz type junctional epidermolysis bullosa.

Corneal limbus stem cell failure (ocular surface failure)

Corneal epithelial stem cells are located in the basal layer of the epithelium at the limbus. Epithelial stem cell deficiency can result from chemical or thermal injury, or develop after acquired inflammation in conditions such as SJS of VKC. Congenital causes include aniridia, ectodermal dysplasia, in which there is an absence of the meibomian gland orifices, and the autoimmune polyendocrinopathies (Fig. 16.37). The final common pathway of disease is conjunctivalization of the surface of the cornea in which the epithelial layer contains goblet cells and the epithelial cells themselves express an altered cytokeratin profile (CK19) that is characteristic of conjunctiva (Fig. 16.38). There is often poor vision from vascularization

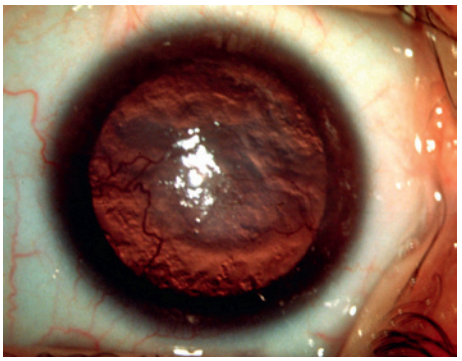


Fig. 16.37 Corneal vascularization and scarring in a child with autoimmune polyendocrinopathy. The mechanism is thought to be corneal limbus stem cell failure.

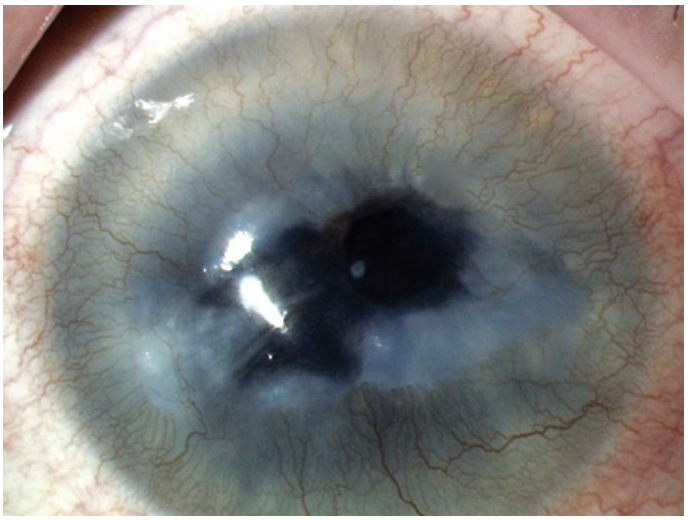


Fig. 16.38 Peripheral conjunctivalization of the cornea in a child with aniridia. There is superficial vascularization and scar of the peripheral cornea. With time the abnormal epithelium may advance to cover the whole cornea.

and subepithelial scarring. In aniridia, vision is further reduced by macular hypoplasia. The eye is uncomfortable due to an unstable epithelial surface. In bilateral disease there is often a severe reduction in quality of life.

Ocular surface failure is a difficult management problem. For unilateral disease (e.g. burns) a corneal epithelial phenotype can be restored by direct transfer of limbal tissue from the unaffected eye or the use of laboratory-cultivated cells.[23] In bilateral disease, a living related donor (parent, sibling) may donate tissue, or a cadaveric donor can be used, but this must be combined with systemic immunosuppression. An oversized or eccentric keratoplasty that includes part of the limbus can also be used if there is associated corneal stromal opacity. In adults, a successful outcome at 3 years following an autograft has been reported in 74–100% of cases; in childhood, the outcome is not clear. The results using unrelated donor tissue are much worse (21–54%). Laboratory-based techniques of cultured limbal epithelial transplantation have also been developed. The cells are obtained from a biopsy of limbal tissue or oral mucosa. A sheet of cultured epithelial cells, rich in stem cells or transient amplifying cells, attached to a carrier such as amniotic membrane or fibrin is transplanted onto the prepared surface of the recipient cornea. Laboratory-based methods are expensive and only available in a small number of specialist centers.

Management of severe ocular surface disease

The following options apply to the management of severe ocular surface disease, whatever the cause:

- Dry eye disease: use non-preserved lubricants with an ointment (e.g. white soft paraffin) at bedtime. Hyaluronic acid drops 0.1% to 0.4% have a long surface residence time. Autologous or pooled donor serum drops are effective. Temporary punctual occlusion with silicone plugs or permanent punctal occlusion with diathermy conserves tears.
- Chronic surface inflammation: preservative-free topical corticosteroid (e.g. prednisolone 0.5%); calcineurin antagonists (cyclosporin 0.05% to 2%, or tacrolimus 0.03%, if available). Filamentary keratitis: mucolytic drops – acetylcysteine 5–10%.
- Toxicity: eliminate preservatives in drops, especially benzalkonium chloride. Avoid aminoglycoside antibiotics. Recovery from the effects of toxicity may take several weeks.
- Trichiasis: epilate lashes in the short term. Electrolysis for occasional lashes, cryotherapy for groups of misdirected lashes, and surgery for trichiasis with entropion.
- Blepharitis: lid hygiene, topical antibiotic ointment, and oral erythromycin or doxycycline.
- Keratinization: topical all-*trans* retinoic acid 0.05% (not vitamin A) is effective but only available from specialized manufacturing pharmacies.
- Persistent corneal epithelial defect: treat exposure, infection, and trichiasis if present. Try intensive preservative-free lubricants, then therapeutic lenses (e.g. silicone hydrogel, or rigid corneal lens, or scleral lenses in very dry eyes) (Fig. 16.39). If this is unsuccessful, close the eye with tape, a temporary botulinum toxin tarsorrhaphy or a lid suture. Alternatively, an amniotic membrane onlay graft with a protective soft contact lens or temporary tarsorrhaphy.
- Corneal perforation: temporize with therapeutic contact lenses and/or corneal glue. If a keratoplasty is necessary, perform a lamellar rather than a penetrating procedure.
- Disease unresponsive to topical therapy (intense conjunctival inflammation, secondary corneal disease, progressive conjunctival scarring): systemic immunosuppressives may be required. Azathioprine and cyclosporin can be used separately or combined. A short course of high-dose oral prednisolone (1 mg/kg) can be used for rapid control until other agents are effective.
- Secondary corneal neovascularization: isolated vessels can be occluded by fine-needle diathermy. Topical steroid or subconjunctival bevacizumab are options for more diffuse vascularization.
- Management of end-stage bilateral corneal opacity due to scarring, neovascularization, and keratinization can be formidable, especially with severe dry eye disease. The results of ocular surface reconstruction by limbal allograft are poor in the presence of dry eye. A Boston keratoprosthesis, if the eye is moist, or osteo-odontokeratoprosthesis for cases with severe dry eye, may be considered. A conjunctival flap may be more appropriate if the eye is uncomfortable and there is no visual potential.

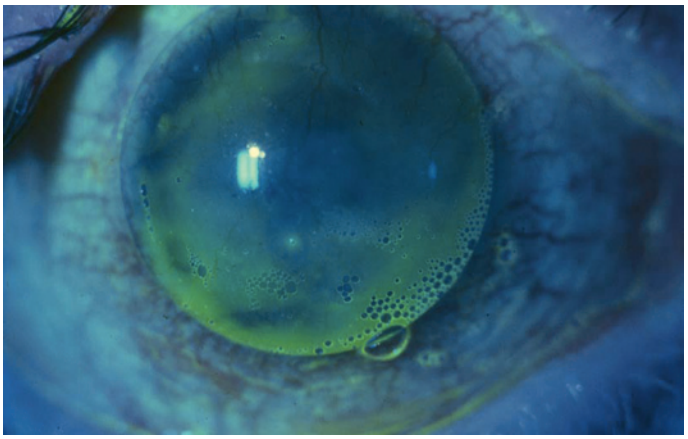


Fig. 16.39 A limbal-fit rigid contact lens used to improve vision following corneal scarring from Stevens–Johnson syndrome. This may also help correct the irregular astigmatism of aniridic keratopathy.

Toxic and hypersensitivity keratoconjunctivitis

In children who require long-term topical medication for glaucoma, allergic conjunctivitis, or recurrent herpes simplex keratitis, toxicity should be considered as a cause for conjunctival hyperemia, follicular and papillary conjunctival reactions, or delayed epithelial healing (Fig. 16.40). Secondary conjunctival scarring (pseudopemphigoid) and punctal stenosis can occur. There may be redness and an eczematous change of the periorbital skin. The most common sensitizing agents are atropine, pilocarpine, guanethidine, epinephrine, antivirals, benzalkonium chloride (as a preservative), and aminoglycosides. Treatment is elimination of the causative agent and a short course of topical steroid if there is severe inflammation.[24]



Fig. 16.40 Severe contact dermatitis following topical application of a cromoglycate for allergic eye disease.



Fig. 16.41 Ligneous conjunctivitis showing typical membranes. The central area of thickened hyperemic conjunctiva on the upper tarsus is the appearance that is sometimes seen in chronic cases, which may no longer have membranes.

Corneal or conjunctival artefacta

Conjunctivitis artefacta is uncommon in children. Self-medication (e.g. topical anesthetic abuse) or self-harm are common causes in adults and may be seen in older children. Non-accidental injury from parents or carers should be considered (see Chapter 70). Suggestive features of artefacta are signs that do not fit established patterns of disease, such as epithelial defects extending onto the conjunctiva, unilateral disease, involvement of only a defined region of the ocular surface, and failure to improve on therapy. It is often very difficult to be certain of the diagnosis. "Mucous fishing" in allergic conjunctivitis, corneal anesthesia, and molluscum should be excluded. There should be a frank discussion with the child and parents of the possibility that this may be the diagnosis, and involvement of a pediatrician and social services if necessary.

Ligneous conjunctivitis

Ligneous conjunctivitis is the most common manifestation of type I plasminogen deficiency (hypoplasminogenemia). There is an inability to break down fibrin clots due to an absence of plasmin; wound healing is arrested at the stage of granulation tissue formation. It is usually seen in infants and young children of all ethnic groups, with a slight female preponderance. Untreated the disease can persist for decades.[25] It is usually an autosomal recessive disorder with a homozygous or compound heterozygous defect in the plasminogen gene (*PLG*; 6q26). Typically, it involves the upper tarsal conjunctiva although the bulbar and lower tarsal conjunctiva may be involved (Fig. 16.41). Lesions have a yellow-white or red appearance and a woody texture. The disease may be precipitated by infection, trauma, or surgery. Fifty percent of cases are bilateral. Secondary corneal involvement occurs in 30% of cases with associated loss of vision. Lesions of extraocular mucosal sites are less common but include the gingiva, ear, respiratory tract, female genitourinary tract, skin, and renal collecting system. Several children with ligneous conjunctivitis have developed hydrocephalus.

Management should involve a hematologist. There will be early recurrence if surgical excision is performed without appropriate ancillary treatment. Conservative therapy should be considered in patients who are asymptomatic without corneal involvement. Before the demonstration of the role of plasminogen, or if plasminogen is unavailable, a success of 75% was achieved with excision with meticulous hemostasis, and immediate hourly application of topical heparin and steroid continued until inflammation had subsided.[26] Multiple treatments were sometimes required. Systemic or topical plasminogen concentrates are now the treatment of choice; systemic treatment is preferred as this is a multisystem disorder. Unfortunately, plasminogen concentrate is currently not available commercially for either systemic or local treatment. Topical plasmin is ineffective; it is rapidly broken down in the tear film.

Keratoconjunctivitis is one of the ocular manifestations of biotinidase deficiency, a condition treated with oral biotin (vitamin B_7) supplements. If untreated, children may have seizures, hypotonia, alopecia, seborrhoic dermatitis, and optic atrophy.

Keratitis

Corneal infection is rare in the normal eye because of the protective effects of corneal sensation and the blink reflex, as well as the presence of innate antimicrobial agents (e.g. defensins) in the tear film and ocular surface. Keratitis can occur if any of these are compromised. Visual rehabilitation and prevention of amblyopia are particular concerns in younger children with corneal inflammation.

Microbial keratitis

The main risk factors for microbial infection in children are trauma, ocular surface disease (VKC, trichiasis, BKC), congenital corneal anesthesia, exposure from propotosis or lagophthalmos, dry eye disease, systemic disease (systemic immunodeficiency, SJS/TEN, vitamin A deficiency and measles), and prior corneal surgery. Orthokeratology (correction of refractive error by molding the cornea with a soft contact lens) in adolescents is a particular risk, reported mostly from East Asian countries. The relative contribution of these risk factors varies with age, gender, and geographic location. In children up to 3 years of age, systemic illness and congenital external ocular disease are the main risk factors. In developing countries, protein-energy malnutrition and vitamin A deficiency is a significant risk factor under 5 years. In adolescents, contact lens wear has become an important cause of microbial keratitis in the developed world. Boys have a higher rate of microbial keratitis than girls, possibly because of higher rates of trauma (Figs 16.42–16.45).

The organisms responsible vary. All centers report high rates of coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, and *Streptococcus* spp. in younger children. *Pseudomonas* infection

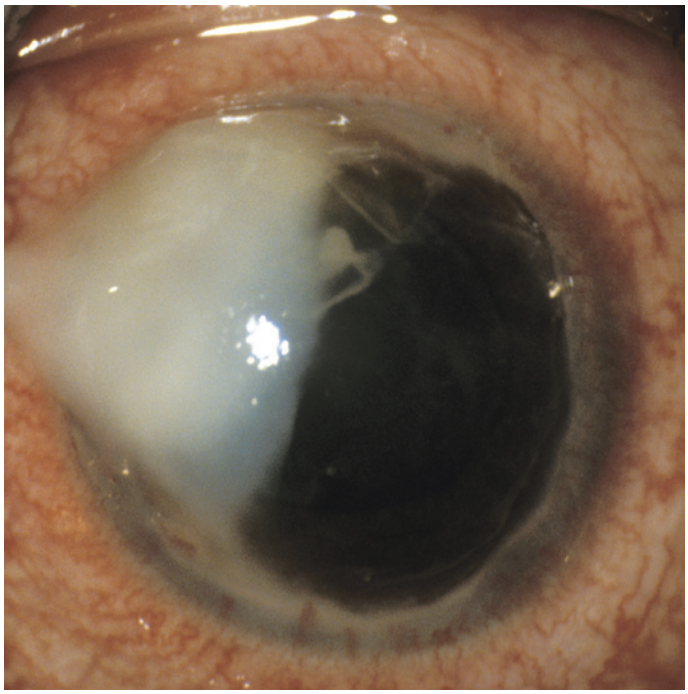


Fig. 16.42 Severe corneal ulceration and lysis secondary *Pseudomonas aeruginosa* in a 10-year-old girl with dry eye disease from graft-versus-host disease. A large-diameter tectonic keratoplasty was required.

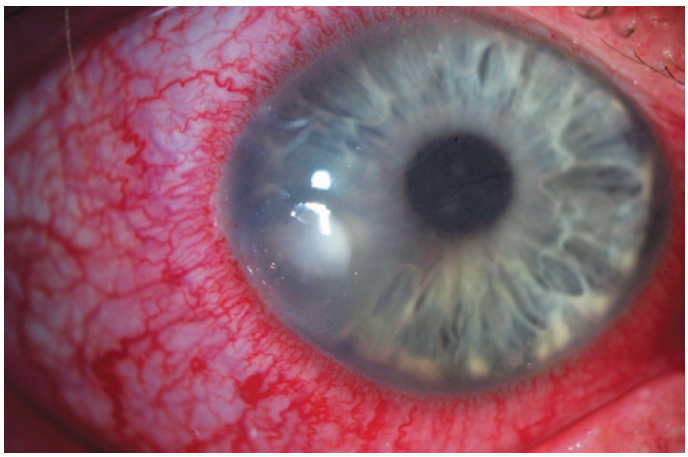


Fig. 16.43 Peripheral corneal ulceration secondary to *Pseudomonas aeruginosa* in an adolescent wearing a soft contact lens for myopia.

is more common in older children and is associated with contact lens wear. Because of the high risk of Gram-negative infection, contact lens-associated keratitis should never be treated with chloramphenicol. Fungus infection accounts for 10–18% of cases and filamentary fungal infections (*Fusarium*, *Aspergillus*) are common following trauma in subtropical and tropical environments, with yeast (*Candida* spp.) a particular risk factor in debilitated children. Polymicrobial infections can occur and should be considered if there is a failure to respond to treatment.

Immune (sterile) keratitis can occur. It results from immune-mediated inflammation. Immune infiltrates tend to be small and peripheral on the cornea, without a large epithelial defect. They respond rapidly to topical antibiotic and low-dose topical

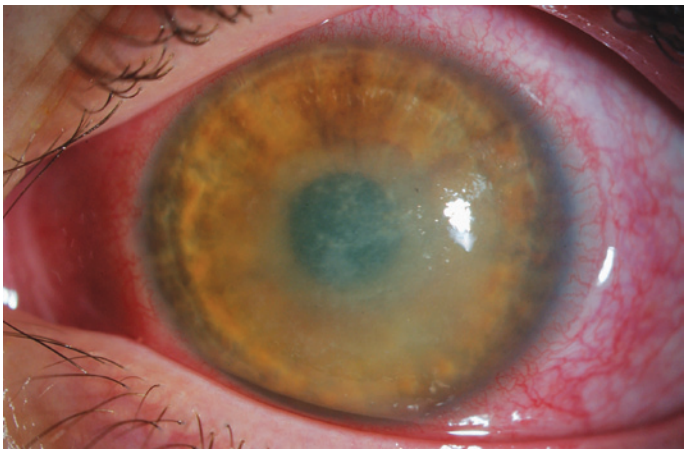


Fig. 16.44 *Acanthamoeba* keratitis in a 12 year old. Initial diagnosis was herpes keratitis, which delayed the initiation of the correct treatment for several weeks.

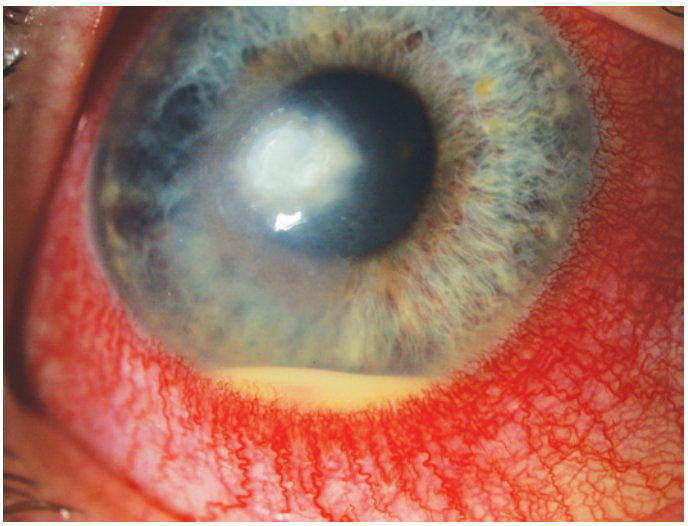


Fig. 16.45 Filamentary fungal keratitis following trauma. The edges of the lesion are "feathered" and there is a hypopyon.

Table 16.6 Distinguishing features of suppurative keratitis and sterile keratitis

Presumed microbial	Presumed sterile
Central lesions	Peripheral lesions
Lesions >1 mm diameter	Lesions <1 mm in diameter, or >1 mm diameter at the limbus
Epithelial defect	Intact epithelium (early) or small epithelial defect
Severe, progressive pain	Mild, non-progressive pain
Severe corneal suppuration with lysis	Mild corneal suppuration
Uveitis	No uveitis

corticosteroid. If the diagnosis is in doubt, they should be managed as infectious keratitis (Table 16.6).

Initial examination

This should record:

- dimensions of the lesion: the maximum length and width of the epithelial defect and infiltrate, and distance from limbus;

- stromal thinning, expressed as a percentage of normal corneal thickness;
- anterior chamber activity, including presence of fibrin, cells, and flare;
- the presence and height of a hypopyon;
- evidence of perforation;
- remediable risk factors for infection such as trichiasis or exposure;
- specific risk factors, e.g. contact lens (amoeba), trauma (filamentary fungus).

Investigation

Children with suspected microbial infection should be treated immediately with an appropriate broad-spectrum antibiotic. Diagnostic tests are not essential and may require sedation of the patient. Obtaining a sample for culture and sensitivity testing provides epidemiologic data and guidance for alternative treatment if there is failure to respond or deterioration on treatment. Culture is essential if:

- the clinical diagnosis is uncertain;
- there is a failure to respond to empiric first-line treatment;
- an unusual pathogen is suspected (e.g. fungus, amoeba).

Minimum investigation should include a slide for microscopy and Gram stain with material inoculated on blood agar plates (Table 16.7). Most fungi will grow on blood agar. Non-nutrient agar and Sabaraud agar should be included if *Acanthamoeba* or fungi are suspected. Samples should be inoculated directly onto the media or placed in transport culture media (e.g. brain heart infusion) before processing in the laboratory. Samples can be taken with a blade or a 21-guage hypodermic needle from the edges of the lesion. Growth of most pathogens can be expected after 48 hours. Cultures for fungi and *Acanthamoeba* should be incubated for up to 7 days. Sensitivity testing is normally reported for bacteria, but not *Acanthamoeba*, and fungal samples will need to be forwarded to a reference laboratory. Samples should also be taken for PCR (bacteria, fungi, *Acanthamoeba*) if this is available. Confocal microscopy can confirm the presence of fungi and *Acanthamoeba* cysts; this procedure may be possible in older children. Biopsy is only necessary for cases with chronic or progressive keratitis with prior negative cultures. Histologic examination should include immunohistochemistry for *Acanthamoeba* cysts and trophozoites and a silver stain for fungal hyphae.

Table 16.7 Investigations for suspected microbial keratitis

Organism	Histology	Culture
Common bacterial isolates[a]	Gram stain	Blood agar Nutrient broth
Facultative bacterial isolates		
• *Mycobacteria* spp.	Ziehl–Neelson	Lowenstein–Jensen
• *Nocardia* spp.	Gram stain	
Anaerobes	Gram stain	Thioglycolate broth
Acanthamoeba[a]	Immunofluorescence Calcofluor white	Non-nutrient agar seeded with killed *Escherichia coli*
Fungi[a]	Silver stain Calcofluor white	Sabouraud agar Blood agar
Microsporidia	Gram stain Periodic acid–Schiff	No growth *in vitro*

[a]Polymerase chain reaction probes available for all of these organisms

Treatment

The goals of treatment are sterilization of the cornea and healing. Sterilization may be rapid; it precedes epithelial healing and resolution of inflammation.

Choice of initial antibiotics

This depends on local epidemiologic data on the common corneal pathogens and their antimicrobial susceptibilities (Table 16.8). In temperate climates, bacterial isolates account for over 90% of the infections. In tropical climates, 50% may be fungal infection. Polymicrobial infection is present in 5–10% of cases. The choice of topical antibiotics for bacterial keratitis is outlined in Table 16.8 but selections should be modified if regionally appropriate. The first-line option should be broad-spectrum therapy to cover Gram-positive and Gram-negative bacteria, such as a fluoroquinolone monotherapy or a combination of a fortified aminoglycoside and fortified cephalosporin (neither are commercially available). In adults, these alternatives are comparable in effect. Although aminoglycoside and fluoroquinolone resistance is a problem in some parts of the USA and India, it is not currently in the UK. Because fluoroquinolones may not adequately treat streptococcal species, it is prudent to use a combination of a fluoroquinolone and a fortified cephalosporin if streptococcal infection is suspected in young children.

Sterilization phase

Treatment with hourly drops is given initially: 48 hours' duration gives a wide margin of safety. Admission is preferable unless good compliance is guaranteed. Topical treatment is reduced to four times daily until healing has occurred (i.e. re-epithelialization of the cornea). Fungal and amoebic infections require prolonged treatment to ensure sterilization. Systemic antimicrobials are only necessary for ulcers adjacent to the limbus to prevent scleral spread, or if there is actual or incipient corneal perforation, or if there is recent perforating corneal surgery (e.g. penetrating keratoplasty). Adjunctive therapies may include cycloplegia, analgesics, and hypotensive agents for secondary glaucoma. A subconjunctival injection of a broad-spectrum antibiotic can be given if an examination under anesthesia has been necessary or if there is poor compliance, but it does not achieve a sustained higher corneal concentration than topical treatment.

Once treatment has been started, there can be an initial increase in inflammatory signs due to endotoxin release. Definite evidence of progression after 48 hours (increased stromal thinning or a clear expansion of the ulcer) implies the patient is insensitive to treatment or there is poor compliance. Patients should be admitted if necessary and the microbiology results reviewed. A change to an alternative therapy is not indicated at this stage unless there is antimicrobial resistance to the primary therapy. Complications are common in children. Even with early recognition and appropriate management surgery rates range from 6% to 28%. If there is threatened

Table 16.8 Treatment options for microbial keratitis

Common pathogens	First-line treatment	Alternatives
• *Staphylococcus aureus* • *Streptococcus pneumoniae* • *Pseudomonas aeruginosa* • *Serratia marcescens*	Fluoroquinolone, e.g. G Levofloxacin 0.5% hourly (day and night) for 2 days, then hourly (day) for 3 days, then qds until resolution	G Cefuroxime 5% hourly then taper according to severity until resolution PLUS G Gentamicin 1.5% hourly then taper The following antibiotics can be used if available according to sensitivity results: G Penicillin 0.3% G Amikacin 2.5% G Ceftazidime 5% G Vancomycin 5%
Mycobacterium keratitis		
• *M. chelonae* • *M. fortuitum* • *M. flavescens*	G Amikacin 2.5% hourly PLUS G Levofloxacin 0.5% hourly	G Clarithromycin 1% hourly PLUS G Azithromycin
Fungal keratitis[31]		
• *Candida* spp. • *Aspergillus* spp. • *Fusarium* spp.	G Natamycin 5% hourly, then taper frequency until resolution (active against *Candida* spp. and some *Aspergillus* spp.) OR G Voriconazole 1% (active against *Candida* spp., *Aspergillus* spp. and *Fusarium* spp.) OR G Amphotericin 0.15% (active against *Candida* spp. and *Aspergillus* spp.) For lesions that potentially extend into the anterior chamber or into the sclera: add systemic therapy PO Fluconazole bd (active against *Candida*) OR PO Voriconazole bd (active against *Aspergillus*) – dose adjusted by weight and age	G Econazole 1% OR Miconazole 1% (arachis oil) (active against *Candida* spp. and some *Aspergillus* spp.) ADD G Chlorhexidine 0.2% for severe infection (no evidence for benefit of dual therapy) PO Voriconazole (active against *Fusarium* spp., *Aspergillus* spp., and fluconazole-resistant *Candida* spp.) Intralesional voriconazole or amphotericin 50 μg in 0.1 ml repeat weekly as needed (reconstituted from a 200 mg IV vial)[a]
Acanthamoeba spp.		
Recommended regimen: Hourly day and night for 48 hours, then hourly by day for 72 hours, then every 2 hours for 3–4 weeks, then tailored to each individual case No clinical evidence to suggest that dual therapy is more effective than monotherapy with polyhexamethylene biguanide alone	G Polyhexamide (polyhexamethylene biguanide) 0.02% OR G Chlorhexidine digluconate 0.02% PLUS G Propamidine 0.1% isethionate (Brolene) OR G Hexamidine 0.1% diisethionate (Desomedine)	If unresponsive to both combinations of first-line therapy consider G PHMB 0.06% OR G Chlorhexidine 0.2%

[a]May increase risk of perforation

or actual perforation, application of cyanoacrylate glue may stabilize the situation. Urgent lamellar or penetrating keratoplasty (PK) may be required, although there is a high risk of graft failure and amblyopia. A conjunctival flap may be more appropriate for large perforations in infants. If there is deterioration or indolent inflammation after 1 week, repeat culture for fastidious organisms or a biopsy are indicated.

The healing phase

Even after sterilization of the corneal ulcer, healing may be delayed by persistent inflammation, toxicity to treatment, or failure to treat the precipitating causes (e.g. exposure, trichiasis, dry eye disease). Non-preserved medications should be used if possible, and ocular surface disease should be treated (Fig. 16.46).

Use of topical corticosteroids

Topical corticosteroids reduce inflammation that may be delaying healing. However, they must be introduced cautiously because they potentiate the growth of fungi and herpes simplex infection. In adults, there is no clear benefit for the use of corticosteroids as adjunctive therapy in the management of bacterial keratitis.[27] Healing without topical steroid will occur but is slower than when steroid is used. Early treatment with topical corticosteroid has an adverse effect on the outcome of *Acanthamoeba* keratitis and filamentary fungus.[28] In patients with a PK in whom fungal infection is excluded, topical corticosteroid therapy should be introduced at the outset of infection to protect against allograft rejection. Topical cyclosporin is an alternative to control inflammation in cases of fungal infection; this does not potentiate fungal growth.

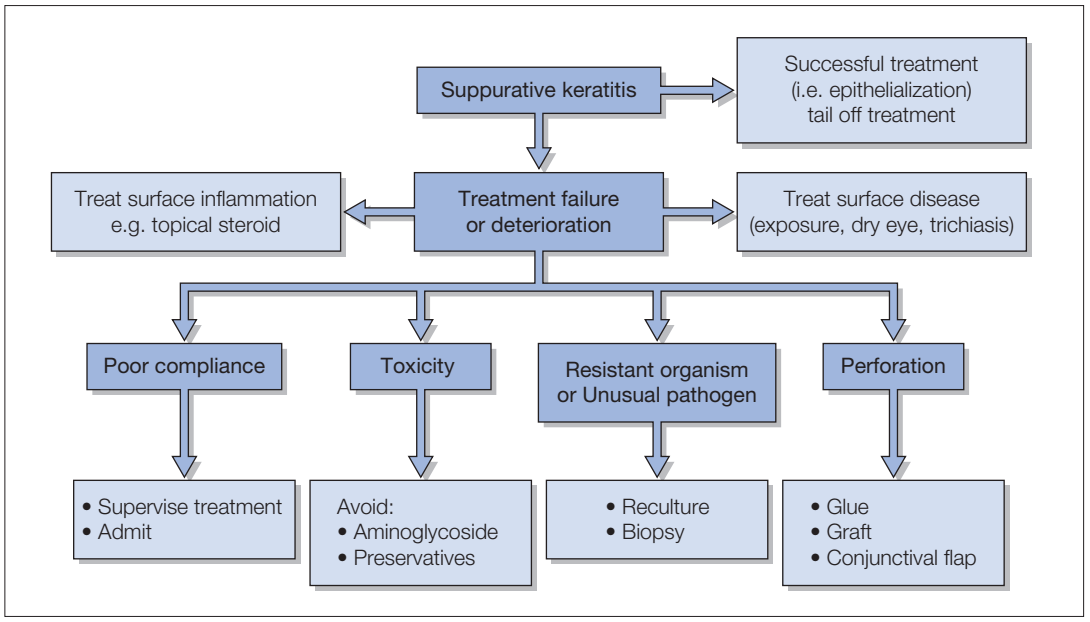


Fig. 16.46 Algorithm for evaluating response to treatment of suppurative keratitis.

Progressive or indolent microbial keratitis

Progressive microbial keratitis after 5 days of intensive broad-spectrum topical antibiotic treatment is an indication for re-culture using specialist media (see Table 16.7) or corneal biopsy. Stopping treatment for 24 hours prior to re-culture may increase the chance of recovering a pathogen, but this must be balanced against the risk that an infection could advance rapidly during this time. When a biopsy is performed, half should be sent for histology, the other half pulverized and cultured. A microbiologist should be consulted regarding optimum media for isolation, which would normally include a modified Ziehl–Neelsen plate. Slow-growing pathogens can take 3 weeks to grow in culture and the laboratory should be asked to perform extended incubation. A trial of therapy directed at the organism most likely to be causing the infection on clinical and epidemiologic grounds can be started while waiting for the pathology results.

Fungal keratitis is characterized by a raised white stromal infiltrate with feathery borders, satellite lesions, "solid" hypopyon, and endothelial plaque formation. Treatment is dependent on local epidemiologic data. Suggested antifungal therapies are shown in Table 16.8. Commercially available natamycin 5% is the drug of choice for filamentary fungal infection, with amphotericin B used for *Candida* spp. Oral treatment is recommended for deep stromal filamentary fungal infection because of risk of hyphal growth through Descemet's layer into the anterior chamber. Subconjunctival or intracameral injection of amphotericin are additional treatment options to achieve therapeutic levels of drug, but intrastromal injection can increase the risk of perforation. Early excisional keratoplasty may be required to control progressive filamentary fungal infections.

Acanthamoeba infection in children is rare but may be associated with contact lens wear, with showering or swimming in lenses a particular risk. Delay in diagnosis and early treatment with topical steroid can seriously affect outcome. Treatment options are presented in Table 16.8. While epithelial disease is relatively easy to eliminate, stromal infection can require months of treatment before the *Acanthamoeba* cysts are killed. More detailed management options are presented elsewhere.[29]

Microsporidium keratitis is an emerging cause of corneal infection in some regions. Large series from Singapore and Southern India report infections in immunocompetent patients, related to soil contamination, trauma, and contact lens wear. The most common appearance is a coarse punctate epitheliopathy. Diagnosis is confirmed by histologic examination of an epithelial biopsy. Although topical fluoroquinolones have been recommended, the disease is self-limiting with a good visual outcome. *Microsporidium* stromal disease is extremely rare and difficult to eradicate. Excisional keratoplasty is often required. Treatment options for stromal disease include topical Fumadil-B 0.3% (active drug fumagillin) and oral albendazole.

There is currently no convincing evidence of a benefit of corneal collagen cross-linkage as an ancillary option to standard therapy for antimicrobial keratitis.

Herpes simplex virus keratitis

HSV is the most common infectious cause of corneal blindness in developed countries. It is also an important cause of visual loss in developing countries, particularly in association with endemic measles. It is less common in children than adults.

Primary infection with HSV may be subclinical and remote from the site of recurrent disease. Acute conjunctivitis may represent primary infection. After infection, the virus is carried to the sensory ganglion where a latent infection is established. Stimuli such as fever, hormonal change, ultraviolet radiation, trauma, and trigeminal nerve injury may then reactivate HSV, which is transported in axons to the ocular surface causing recurrent disease. The virus may maintain latency within the cornea and HSV can be spread by corneal transplantation. The HSV-1 strain is usually responsible for ocular or labial disease; HSV-2 causes urogenital infection and is associated with herpetic ophthalmia neonatorum. HSV-1 and HSV-2 reside equally in almost all ganglia; local factors favor HSV-1 reactivation from the trigeminal ganglion. Transmission of HSV is facilitated in conditions of crowding and poor hygiene.

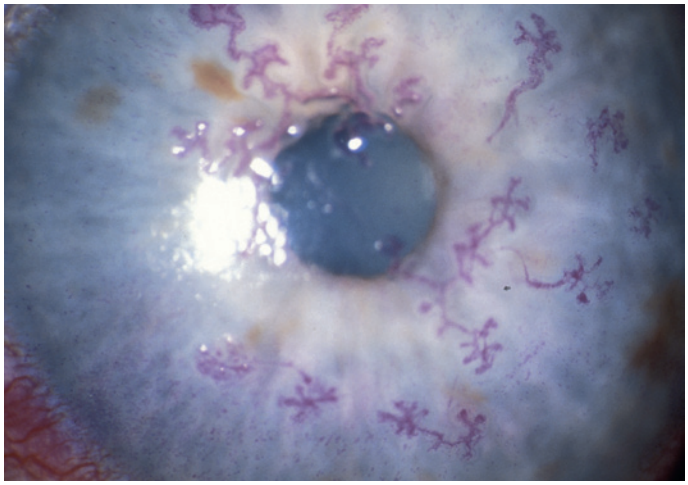


Fig. 16.47 Multiple dendrites from herpes simplex infection complicating vernal keratoconjunctivitis.

Malnutrition, measles, and malaria may suppress cell-mediated immunity and be associated with severe unilateral and bilateral HSV infection.

Because primary HSV infections may be asymptomatic in two-thirds of cases, clinical surveys underestimate the incidence and prevalence. Serology is used to define the prevalence of prior infection, and this reflects latency. Age, geographic location, and socioeconomic status affect the prevalence. Using PCR, the detection of HSV in the trigeminal ganglion suggests a prevalence of 18.2% by 20 years of age, but crowding may be a risk factor for early exposure and in Africa 70–80% have HSV-1 antibodies by adolescence. Ten million people worldwide may have herpetic eye disease.

There are different patterns of HSV keratitis. The clinical picture may vary over time and multiple features may be present in the same cornea:

- Epithelial lesions (dendritic ulcer, geographic ulcer): This is the result of virus replication and is the most common presentation of recurrent ocular HSV (Fig. 16.47). A geographic ulcer is nominally >1 mm diameter and associated with concurrent topical corticosteroid treatment or allergic eye disease.
- Neurotrophic keratitis (metaherpetic ulceration, persistent epithelial defect) is secondary to corneal anesthesia or toxicity from treatment.
- Necrotizing keratitis (immune keratitis): Active stromal infection with an inflammatory response causing stromal melting.
- Endothelialitis (disciform keratitis): The primary target of viral replication is the corneal endothelium, which is damaged, with secondary edema of the overlying stroma.

Following a first episode of keratitis, the rate for recurrence of ocular HSV increases from 20% at 2 years postinfection, to 40% at 5 years, and 70% at 7 years. After the first episode of corneal involvement, 32–40% of the patients experience a recurrent herpetic ulcer: 25% experience disciform keratitis or stromal keratouveitis; 5% experience ocular hypertension; and 6% develop scarring sufficient to decrease visual acuity. Bilateral disease occurs in 12% of patients, especially in atopes (who are at risk of eczema herpeticum) and the immunosuppressed. HSV is more severe in children than in adults, especially if they are immunosuppressed, in whom viral shedding and recurrences are more common. Recurrent disease is associated with visual loss, but with prompt treatment the visual consequences can be minimized; 90–94% of patients maintain vision of >6/12 but 3% are ≤6/36. HSV keratitis accounts for 3–10% of all PKs performed in the UK and the USA.

Table 16.9 Treatment options for viral keratitis

Pathogen	First-line treatment	Alternative
• Herpes simplex virus (HSV)	Oc acyclovir 3% or G trifluoridine 1% 5× daily For prophylaxis of stromal keratitis and keratouveitis: PO acyclovir 400 mg bd under specialist supervision (modify dose according to age)	G Ganciclovir 0.15% 5× daily Valacyclovir 500 mg

Management

Summary guidelines are:

- Epithelial HSV disease (dendritic ulcer or geographic ulcer) is the result of viral replication, and is treated with a topical antiviral agent (Table 16.9). Oral antiviral and topical corticosteroid is not required.[30]
- Stromal disease is treated with steroid to reduce destructive inflammation, but covered with an antiviral agent to prevent enhanced viral replication (dendritic keratitis). Both treatments are gradually reduced as the inflammation subsides.
- Latent virus cannot be eliminated. Although acquired viral resistance is uncommon, it can occur following prolonged antiviral treatment and in the immunosuppressed.

The antiviral agents used to treat HSV disease are purine or pyrimidine analogs that are incorporated to form abnormal viral DNA (see Table 16.9). Topical trifluorothymidine (F_3T, trifluridine), acycloguanosine (acyclovir), and or ganciclovir (Virgan) have low toxicity and achieve virucidal concentrations in the stroma and anterior chamber, effectively covering adjunctive steroid treatment. Acyclovir has the advantage that it can be used systemically. All are active against HSV-1 and HSV-2 and are equivalent for the treatment of dendritic or geographic ulcers. Foscarnet should be considered if thymidine kinase-resistant HSV is suspected. Topical interferon α2 has a small additional effect when used in conjunction with a topical antiviral, but it is expensive and not generally available. Oral acyclovir did not hasten healing of epithelial disease when used in combination with topical treatment. Debriding infected corneal epithelium is effective, but adjunctive virucidal agents are needed to avert an early recurrence of epithelial keratitis. The sample obtained from epithelial debridement can be sent for PCR confirmation of HSV infection.

Other Herpes Eye Disease Study Group treatment guidelines are as follows:

- For stromal disease (e.g. disciform keratitis), topical steroid (1% prednisolone phosphate four times daily), in conjunction with topical antiviral cover, reduces recovery time by 68% with no increased risk of recurrence at 6 months.

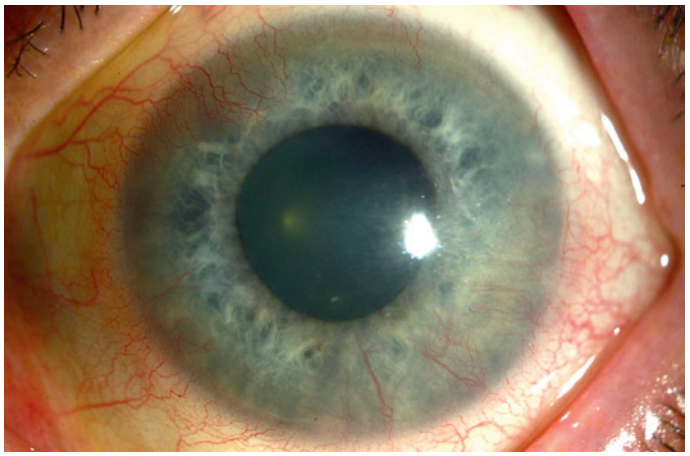


Fig. 16.48 Peripheral corneal vascularization and opacity following herpes zoster ophthalmicus.

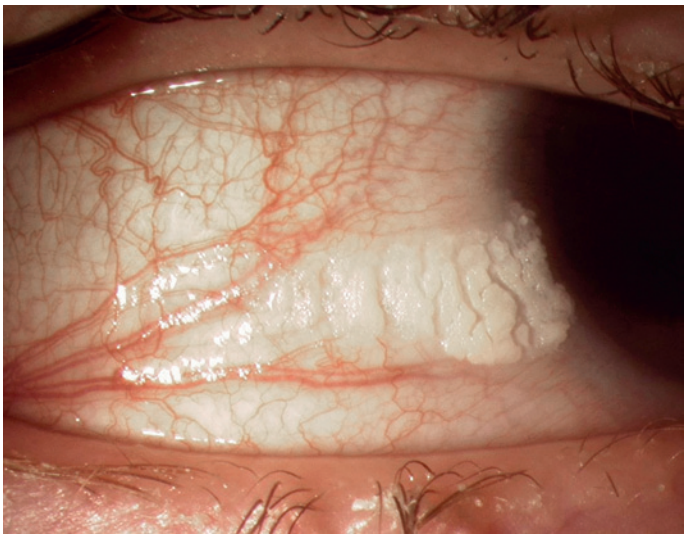


Fig. 16.49 Conjunctival keratin plaque associated with hereditary benign intraepithelial dyskeratosis.

- There is no additional effect of oral acyclovir over topical steroid and F_3T when treating stromal keratitis.
- After epithelial HSV, a 3-week course of oral acyclovir (400 mg five times a day) does not prevent stromal disease in the subsequent year.
- Prophylactic treatment with acyclovir (400 mg bd) reduces epithelial recurrences and stromal recurrences in patients with prior stromal disease by about 50% over 12 months. Prophylactic antiviral treatment is usually restricted to patients with bilateral disease, prior HSV keratitis in atopes, or the immunosuppressed, especially following corneal surgery.
- Oral acyclovir (400 mg bd for 6 months) reduces the risk of HSV recurrence and graft failure after PK.

Herpes zoster ophthalmicus

Following a primary infection (chicken pox) the varicella virus can become latent in sensory ganglia in up to 100% of cases. The diagnosis of herpes zoster ophthalmicus (HZO) is usually clinical, with a painful rash over the upper lid and forehead with a particular risk of corneal involvement if the side of the nose is involved (Hutchinson's sign). However, the rash may be minimal and PCR testing can be used to confirm infection. There is a gradual increase in exposure to VZV with age; in developed countries antibodies to VZV are present in 99% of the population by the age of 40 years. The incidence of HZO in children <18 years is less than 1.5 : 1000 individuals. HZO is normally associated with reducing antibodies to VZV and it is, therefore, uncommon in children unless they are immunosuppressed (e.g. chemotherapy or radiotherapy). Immunosuppression can trigger a re-activation of vesicular rash. Between 9% and 16% of patients have trigeminal involvement (HZO), of whom 50–72% have ocular involvement, and 20% have corneal involvement. It is not known how vaccination of children for VZV (against chickenpox) will affect the incidence and severity of HZO.

Corneal involvement during the early stages of herpes zoster ophthalmicus can present as a dendritic or stromal keratitis (Fig. 16.48), occasionally associated with uveitis, glaucoma, progressive outer retinal necrosis, and scleritis. The epithelial disease of acute HZO is the result of mucus accumulation on the epithelial surface rather than viral replication, but co-infection with HSV is possible. The use of topical antiviral at this stage is a wise precaution. Recurrent corneal inflammatory disease after 2–3 months is not always the result of viral replication and a topical antiviral is not normally prescribed.

Oral antivirals reduce the severity of acute HZO and the frequency of late-onset inflammatory corneal disease by 50%, but have no proven effect on reducing late complications such as neurotrophic keratitis or postherpetic neuralgia. Oral acyclovir is generally prescribed for 3 days within 72 hours of the onset of rash. Topical acyclovir is not recommended to treat the rash of zoster. Management of neurotrophic keratitis is with topical lubricants or corneal protection (e.g. tarsorrhaphy) (see Chapter 34).

Hereditary benign intraepithelial dyskeratosis

Hereditary benign intraepithelial dyskeratosis is an autosomal dominant disorder characterized by elevated epithelial plaques on the ocular and oral mucous membranes (Fig. 16.49). It occurs primarily, but not exclusively, in individuals of American Indian heritage. It is the result of a duplication in chromosome 4 (4q35). There is photophobia and blepharospasm with secondary corneal scarring and vascularization. Vitamin A deficiency should be excluded as a cause of conjunctival keratinization. Topical lubricants provide symptomatic relief.

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Ocular manifestations of HIV/AIDS in children

Emmett T Cunningham Jr and Philippe Kestelyn

Chapter contents

HIV/AIDS: GLOBAL AND REGIONAL EPIDEMIOLOGY
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While the annual incidence of human immunodeficiency virus (HIV) infection has decreased steadily over the past two decades, HIV/acquired immune deficiency syndrome (AIDS)-related illnesses continue to be among the leading causes of morbidity and mortality worldwide.[1] In 2014, roughly 36.9 million people were living with HIV/AIDS, 2.6 million (7.0%) of whom were children 15 years of age or less (Table 17.1). Approximately 220,000 (8.5%) of these children were newly infected during that year – an incidence of about 600 children per day. This number decreased by approximately 40% since 2009, due, in large part, to increased use of antiretroviral therapy by HIV-positive pregnant woman. Ocular complications occur in at least 70% of adults and up to 50% of children with HIV/AIDS if not treated with antiretroviral therapy.[1,2]

The introduction of multidrug combination therapy changed the face of HIV/AIDS-related eye disease. Termed "highly active antiretroviral therapy" (HAART), this regimen uses a combination of potent antiretrovirals to inhibit replication of HIV. Patients on HAART experience a dramatic improvement in helper CD4+ T cell populations and a marked decline in viral titers, resulting in fewer opportunistic infections, reduced morbidity and mortality, and improved quality of life. Despite the decline in the incidence of ocular complications in patients taking HAART, they continue to occur and remain an important cause of disability in HIV-infected patients. This is particularly true in the developing world, where access to HAART varies considerably from country to country.[2]

HIV/AIDS: global and regional epidemiology

The 2014 report from the Joint United Nations Program on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) on the global HIV/AIDS epidemic estimated that 36.9 million (34.3–41.4 million) people were living with HIV in 2014, 90% of whom were unaware of their infection. Roughly 17.4 million (16.1–20.0 million) were women and 2.6 million (2.4–2.8 million) were children under 15 years of age (Table 17.1). The prevalence of HIV infection in children varies, with over 85% of all children with HIV/AIDS living in sub-Saharan Africa (Fig. 17.1). Roughly 1.4 million (1.2–1.5 million) people were newly infected with HIV in 2014, 220,000 (190,000–230,000) of whom were children. During that same year, 1.2 million (980,000–1.6 million) people died from HIV/AIDS, 150,000 (12.5%; 140,000–170,000) were children.[1]

Transmission of HIV in children

While high-risk behaviors such as injection drug use, unprotected commercial sex, and unprotected sex between men contributes to HIV transmission, most HIV infections in adults occur during unprotected heterosexual intercourse.[2] Most HIV-positive children acquired their infection *in utero*, at delivery, or while breastfeeding – so-called mother-to-child transmission (MTCT). Prior to the advent of obstetric and antiretroviral interventions, up to 40% of infants born to infected mothers contracted HIV infection. This included 20–25% of infections that occurred *in utero*, 35–50% that occurred during delivery, and 25–35% who were HIV negative at birth and within the first 6 weeks of delivery, but who became infected later, presumably as a result of transmission through breast milk.[3] These rates have since declined dramatically in North America, Western Europe, and other resource-rich regions, where current total perinatal transmission rates vary from 1% to 3%. The incidence of MTCT in many resource-poor regions remains high due to the high prevalence of HIV in women of childbearing age, a lack of access to antiretroviral prophylaxis, and few feasible alternatives to breastfeeding. Sub-Saharan Africa has the highest burden of HIV disease overall, accounting for 80–90% of perinatal infections and children infected by HIV (Fig. 17.1).[1]

Diagnosis of HIV/AIDS in children

The Centers for Disease Control and Prevention (CDC) case definition[4] of HIV infection among children aged less than 18 months recognizes four categories:

1. definitely HIV infected;
2. presumptively HIV infected;

3. presumptively uninfected with HIV;
4. definitively uninfected with HIV.

The presence of maternal antibodies can make diagnostic laboratory testing for HIV infection among children aged less than 18 months unreliable; these children with perinatal HIV exposure who develop an AIDS-defining illness (Box 17.1) are considered presumptively HIV infected.

Table 17.1 Global summary of HIV/AIDS as of 2014

Number of people living with HIV/AIDS in 2014	
Total	36.9 million (34.3–41.4 million)
Adults	34.3 million (31.8–38.5 million)
Women	17.4 million (16.1–20.0 million)
Children under 15 years of age	2.6 million (2.4–2.8 million)
Number of people newly infected with HIV in 2014	
Total	2.0 million (1.9–2.2 million)
Adults	1.8 million (1.7–2.0 million)
Children under 15 years of age	220,000 (190,000–260,000)
Number of HIV/AIDS-related deaths in 2014	
Total	1.2 million (980,000–2.2 million)
Adults	1.8 million (1.7–2.0 million)
Children under 15 years of age	150,000 (140,000–170,000)

The numbers in parentheses represent confidence intervals based on the best available information.
From UNAIDS. 2014 Global Statistics: http://www.unaids.org/sites/default/files/media_asset/20150714_FS_MDG6_Report_en.pdf (accessed January 2016).

A child aged less than 18 months is categorized as definitively HIV infected if born to an HIV-infected mother and testing of the infant (excluding cord blood testing) shows a positive result on two separate specimens from one or more of the following HIV-virologic (non-antibody) tests:

- HIV nucleic acid (DNA or RNA) detection;
- HIV p24 antigen test, including neutralization assay, for a child aged ≤1 month;
- HIV isolation (viral culture).

A child aged less than 18 months born to an HIV-infected mother is categorized as definitively uninfected with HIV if:

1. the criteria for definitive HIV infection are not met, and;
2. at least two negative HIV DNA or RNA virologic tests from separate specimens are obtained.

The CDC laboratory criteria for reportable HIV infection among persons aged 18 months to less than 13 years exclude confirmation of HIV infection through the diagnosis of AIDS-defining conditions alone. Laboratory confirmation of HIV infection is required for all reported cases of HIV infection among children in this age group.

Children aged 18 months to less than 13 years are categorized as having AIDS if the criteria for HIV infection are met and at least one of the AIDS-defining conditions has been documented (see Box 17.1). Once HIV infection has been established, early initiation of both HAART and *Pneumocystis jirovecii* pneumonia prophylaxis, followed by scheduled administration of routine vaccinations for infants is recommended.[5]

In 2007, the World Health Organization (WHO) revised the HIV infection and AIDS clinical staging system and the clinical and surveillance case definitions.[6] They recommended reporting cases of HIV infection as HIV infection or advanced HIV disease (AHD), which includes AIDS. All cases of HIV infection, AHD, and AIDS require a confirmed diagnosis of HIV infection based on laboratory testing. The revised WHO surveillance case definitions include the following four stages:

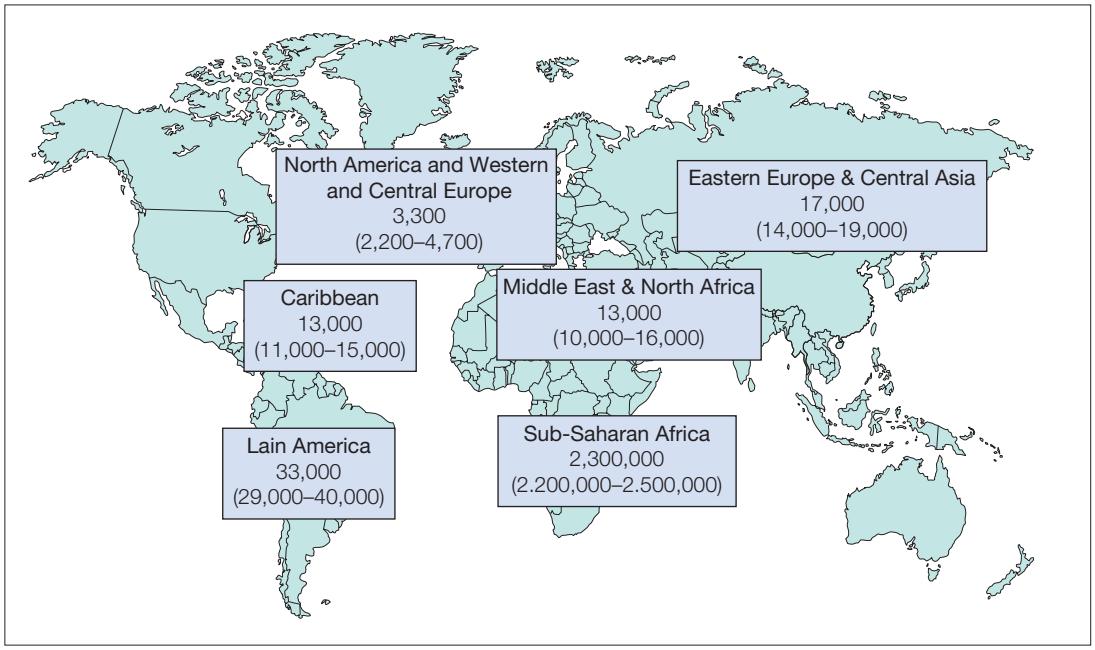


Fig. 17.1 The number of children <15 years of age with HIV/AIDS by region in 2014. Roughly 85% of the 2.6 million children estimated to be infected by HIV live in sub-Saharan Africa. *(From UNAIDS. 2014 Global Statistics: http://www.unaids.org/sites/default/files/media_asset/20150714_FS_MDG6_Report_en.pdf [accessed January 2016].)*

Box 17.1

AIDS-defining conditions for children less than 13 years of age, adolescents, and adults

- Bacterial infections, multiple or recurrent[a]
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus[b]
- Cervical cancer, invasive[c]
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)[b]
- Encephalopathy, HIV related
- Herpes simplex: chronic ulcers (greater than 1 month's duration) or bronchitis, pneumonitis, or esophagitis (onset at age greater than 1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi sarcoma[b]
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex[a,b]
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary[b]
- *Mycobacterium tuberculosis* of any site, pulmonary,[b,c] disseminated,[b] or extrapulmonary[b]
- *Mycobacterium*, other species or unidentified species, disseminated[b] or extrapulmonary[b]
- *Pneumocystis jirovecii* pneumonia[b]
- Pneumonia, recurrent[b,c]
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain, onset at age less than 1 month[b]
- Wasting syndrome attributed to HIV

[a]Only among children aged less than 13 years. (CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR 1994; 43[No. RR-12].)
[b]Condition that might be diagnosed presumptively.
[c]Only among adults and adolescents aged ≥13 years. (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR 1992; 41[No. RR-17].)
For surveillance purposes patients are categorized as having AIDS only if the criteria for HIV infection are met.
Adapted from Schneider E, Whitmore S, Glynn KM, et al. Centers for Disease Control and Prevention (CDC). Revised surveillance case definitions for HIV infection among adults, adolescents, and children aged <18 months and for HIV infection and AIDS among children aged 18 months to <13 years – United States, 2008. MMWR Recomm Rep. 2008; 57(RR-10): 1–12.

asymptomatic HIV infection, or stage 1; mildly symptomatic HIV infection, or stage 2; AHD, or stage 3; and AIDS, or stage 4.[6,7] An HIV-positive child's level of immunosuppression may be staged using circulating CD4+ T cell levels. Whereas absolute CD4+ T cell counts are typically used in adults, absolute counts normally decline dramatically over the first 5 years of life; so, for young children, CD4+ T cell percentages provide best estimates of disease severity. The WHO classification of HIV-associated immunodeficiency in young children is shown in Table 17.2. A similar system recommended by the CDC grades the immune status of HIV-infected children using either CD4+ T cell counts or percentages as stages 1, 2, and 3 (Table 17.3).[8] In comparison, adults with an absolute CD4+ T cell count less than 200 cells/mm^3 are characterized as having AIDS; those with a count less than 100 cells/mm^3 are considered profoundly immunosuppressed and at greatest risk of developing one or more ocular complications, including cytomegalovirus (CMV) and other necrotizing herpetic retinitis.[8]

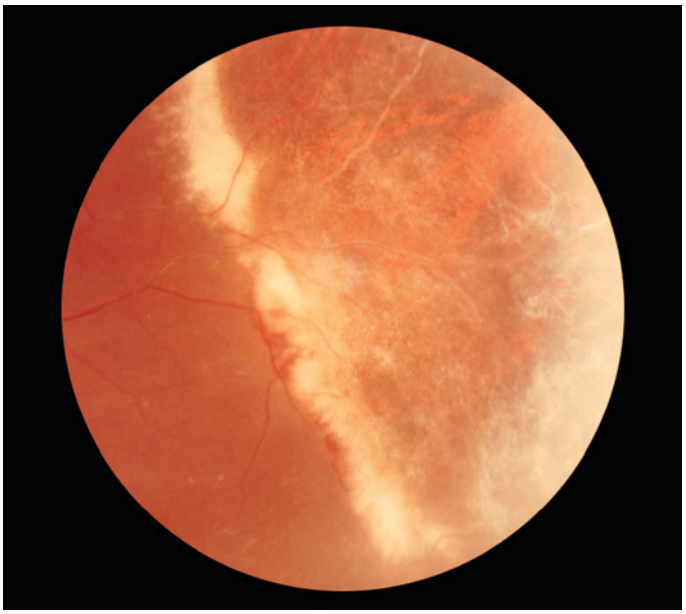


Fig. 17.2 Cytomegalovirus retinitis with an active leading edge in a child with AIDS from Rwanda.

Ocular manifestations of HIV/AIDS in children

Literature on the ocular manifestation of HIV/AIDS in children is limited (Table 17.4),[8–22] but suggests that ocular aspects of HIV infection differ between children and adults in several important respects. First, ocular complications of HIV/AIDS are less common in children than in adults. This is particularly true for CMV retinitis (Fig. 17.2) and HIV retinopathy (cotton-wool spots), which occur in fewer than 5% of untreated HIV-positive children, compared to 30% or more of untreated adults.[8] Herpes zoster ophthalmicus (HZO; Fig. 17.3) appears to be less common in HIV-infected children as compared to adults,[23] although zoster dermatitis has been reported as an early complication of immune reconstitution in children receiving HAART.[24,25] Second, a distinctive retinal vasculitis[26] (Fig. 17.4), not commonly recognized in adults, is seen in about 3% of HIV-infected children in the USA[10] and France,[11] and from approximately 10% to 40% of HIV-positive children in Africa and India.[14,15,20,21] Vascular inflammation is typically bilateral and peripheral with periphlebitis occurring three times more often than periarteritis. This peripheral retinal vasculitis may be associated with a generalized lymphadenopathy, including salivary and lacrimal gland involvement, and lymphocytic interstitial pneumonia (LIP), suggesting that these children

Table 17.2 WHO classification of HIV-associated immunodeficiency using CD4+ T cell counts and percentages

Classification of HIV-associated immunodeficiency	Age-related CD4+ T cell values			
	≤11 months (CD4%)	12–35 months (CD4%)	36–59 months (CD4%)	≥5 years (cells/mm^3 or CD4%)
Not significant	>35%	>30%	>25%	>500 cells/mm^3
Mild	30–35%	25–30%	20–25%	350–499 cells/mm^3
Advanced	25–29%	20–24%	15–19%	200–349 cells/mm^3
Severe	<25%	<20%	<15%	<200 cells/mm^3 or <15%

Table 17.3 Surveillance case definition for HIV infection among adults and adolescents (aged ≥13 years) – United States, 2008

Stage	Laboratory evidence[a]	Clinical evidence
Stage 1	Laboratory confirmation of HIV infection *and* CD4+ T-lymphocyte count of ≥500 cells/μl *or* CD4+ T-lymphocyte percentage of ≥29	None required (but no AIDS-defining condition)
Stage 2	Laboratory confirmation of HIV infection *and* CD4+ T-lymphocyte count of 200–499 cells/μl *or* CD4+ T-lymphocyte percentage of 14–28	None required (but no AIDS-defining condition)
Stage 3 (AIDS)	Laboratory confirmation of HIV infection *and* CD4+ T-lymphocyte count of <200 cells/μl *or* CD4+ T-lymphocyte percentage of <14[b]	*Or* documentation of an AIDS-defining condition (with laboratory confirmation of HIV infection)[b]
Stage unknown[c]	Laboratory confirmation of HIV infection *and* no information on CD4+ T-lymphocyte count or percentage	*And* no information on presence of AIDS-defining conditions

[a]The CD4+ T-lymphocyte percentage is the percentage of total lymphocytes. If the CD4+ T-lymphocyte count and percentage do not correspond to the same HIV infection stage, select the more severe stage.
[b]Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of ≥200 cells/μL and a CD4+ T-lymphocyte percentage of total lymphocytes of ≥14. Definitive diagnostic methods of these are in the 1993 revised HIV classification system and the expanded AIDS case definition (CDC. 1993 Revised classification system for HIV infection and expanded surveillance case definition of AIDS among adolescents and adults. MMWR 1992;41 (No. RR-17) and from the National Notifiable Diseases Surveillance System.
[c]Although cases with no information on CD4+ T-lymphocyte count or percentage or on the presence of AIDS-defining conditions can be classified as stage unknown, every effort should be made to report CD4+ T-lymphocyte counts or percentages and the presence of AIDS-defining conditions at the time of diagnosis. Additional CD4+ T-lymphocyte counts or percentages and any identified AIDS-defining conditions can be reported as recommended. (Council of State and Territorial Epidemiologists. Laboratory reporting of clinical test results indicative of HIV infection: new standards for a new era of surveillance and prevention [Position Statement 04-ID-07]; 2004. Available at http://c.ymcdn.com/sites/www.cste.org/resource/resmgr/PS/04-ID-07-FINAL.pdf.)

might have the same immunopathological response occurring at different body sites. Prior to the introduction of HAART, HIV-positive children with LIP had a relatively good survival as compared to overall cohorts of HIV-infected children. LIP with salivary and lacrimal gland involvement in HIV-positive children may be analogous to diffuse infiltrative lymphocytosis syndrome (DILS) in adults – an HIV-associated disorder characterized by chronic circulating and visceral CD8+ T cell infiltration, including involvement of the lung and salivary and lacrimal glands.[14]



Fig. 17.3 An HIV-positive adolescent with active herpes zoster ophthalmicus.

Orbital and adnexal complications of HIV/AIDS occur in adults, and include orbital cellulitis and tumors, most notably lymphoma and Kaposi sarcoma.[8] Orbital and adnexal involvement in HIV-positive infants and children is less common, although a single HIV-infected child with preseptal cellulitis was reported[9] (see Table 17.4). A "fetal AIDS syndrome" consisting of downward obliquity of the eyes, prominent palpebral fissures, hypertelorism, and blue sclerae has been described.[26]

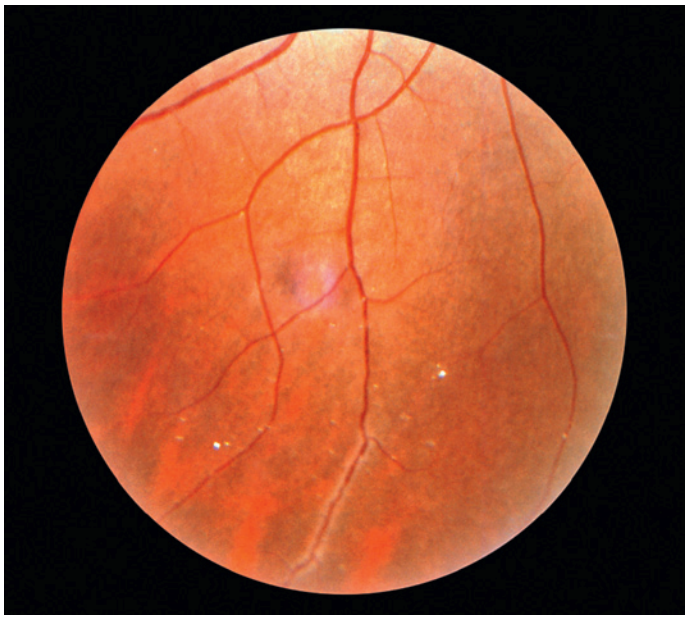


Fig. 17.4 An HIV-positive child from Africa with peripheral retinal vasculitis and several nearby superficial, small, punctate, white retinal lesions.

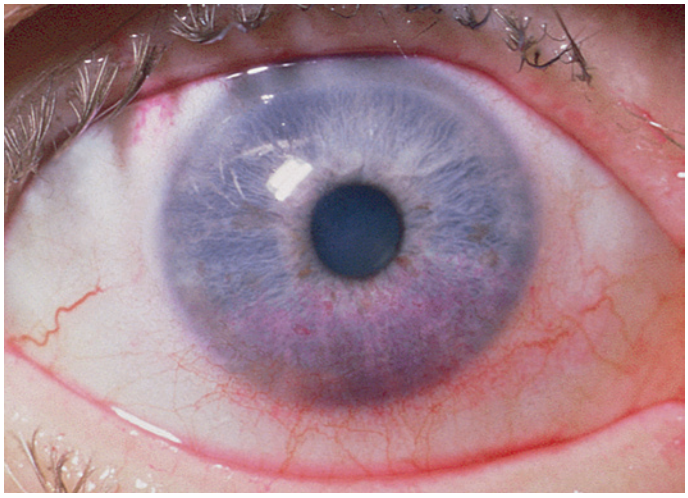


Fig. 17.5 An HIV-positive patient with keratoconjunctivitis sicca and prominent Rose Bengal staining of the inferior conjunctiva and cornea.

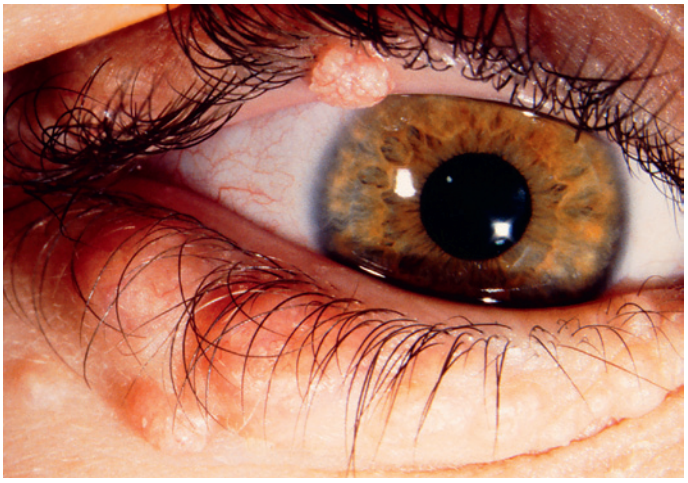


Fig. 17.6 An HIV-positive adolescent with hemophilia and both upper and lower lid molluscum contagiosum lesions.



Fig. 17.7 Severe conjunctival and corneal xerosis in a young Asian boy. A prominent mucus strand is evident near the lateral canthus. *(Courtesy of Dr Alfred Sommer.)*

Prior to the introduction of HAART, up to 20% of HIV/AIDS adults had anterior segment complications, most notably conjunctival telangiectasis, keratoconjunctivitis sicca (Fig. 17.5), infectious keratitis, and molluscum contagiosum (Fig. 17.6).[8] Similar complications occur in children (see Table 17.4). Almeida et al.[18] observed dry eye in 2 of 111 HIV-infected children in Brazil. Conjunctival xerosis (Fig. 17.7), presumably due to the combined effects of malnutrition, vitamin A deficiency, and HIV-related malabsorption and diarrhea, has been noted in Africa[13–16] in 1.2%[14] to 24.2%[14] of pediatric HIV/AIDS patients. Zaborowski et al.[27] described seven black African boys from South Africa with HIV-associated arthritis and bilateral intraocular inflammation, including three with anterior uveitis and four with intermediate uveitis. Five of 10 affected eyes had cataract and two had cystoid macular edema. Although the intraocular inflammation resembled juvenile idiopathic arthritis-associated uveitis, being insidious and asymptomatic in onset and bilateral and non-granulomatous in character, patients with HIV-associated arthritis and uveitis are different. They all were male, antinuclear antibody negative, and six of the seven had polyarticular joint involvement. Isolated cases of bacterial conjunctivitis, allergic conjunctivitis, otherwise unspecified keratitis and conjunctivitis, conjunctival telangiectasis, subconjunctival hemorrhage, and blepharitis have also been noted in HIV-infected children (see Table 17.2). The relationship of these findings to the child's underlying HIV infection has yet to be established.

In addition to isolated cases of CMV retinitis, HIV retinopathy, and the distinctive peripheral retinal vasculitis, posterior segment complications in children with HIV/AIDS include isolated cases of increased retinal vascular tortuosity, disc swelling, macular edema, *Toxoplasma* retinochoroiditis, non-CMV herpetic retinitis,[28] small punctate white retinal lesions (see Fig. 17.4), chorioretinitis of undetermined cause, and dideoxyinosine toxicity (see Table 17.4). Some of these

Table 17.4 Prevalence of ocular complications in clinic-based pediatric cohorts

Study	Location	Sample size	Male : female	Age range (months)	Average age (months)	Number (%) with eye involvement	Peripheral retinal vasculitis – number (%)	Cytomegalovirus retinitis – number (%)	HIV retinopathy (cotton-wool spots) number (%)	Chorioretinitis – number (%)	Herpes zoster ophthalmicus – number (%)	Other – number (%)
Rutar et al., 2015[21]	USA	22	0.69 : 1.0	144–276	199	9 (40.9%)	0 (0%)	0 (0%)	0 (0%)	1 (4.5%)	0 (0%)	Strabismus – 4 (18.2%); amblyopia – 2 (9.1%); corneal pannus – 1 (4.5%); corneal ectasia and scarring – 1 (4.5%); subretinal fibrosis – 1 (4.5%)
Nsiangani et al., 2013[20]	Africa	100	0.8 : 1.0	6–180	96	22 (22.0%)	8 (8.0%)	0 (0%)	2 (2.0%)	4 (4.0%)	0 (0%)	Mucopurulent conjunctivitis – 7 (7.0%); allergic conjunctivitis – 5 (5.0%); optic atrophy – 3 (3.0%); molluscum contagiosum – 2 (2.0%); verruca vulgaris – 2 (2.0%); blepharitis – 1 (1%); anterior uveitis – 1 (1.0%); nystagmus – 1 (1.0%); oculomotor palsy –1 (1.0%); fungal dermatitis – 1 (1.0%)
Venkatesh et al., 2013[19]	India	187	2.74 : 1	6–156	108	39 (20.9%)	23 (12.3%)	3 (1.6%)	0 (0%)	2 (1.1%)	0 (0%)	Adnexal molluscum contagiosum – 4 (2.1%); corneal opacity – 3 (1.6%); optic atrophy – 3 (1.6%); vitritis – 1 (0.53%); retinal hemorrhage – 1 (0.53%)
Almeida et al., 2007[18]	Brazil	111	0.63 : 1	5–153	26.4	19 (17.1%)	0 (0)	1 (0.9%)	0 (0%)	2 (1.8%)	1 (0.9%)	Blepharitis – 6 (5.4%); allergic conjunctivitis – 4 (3.6%); dry eye – 2 (1.8%)
Esposito et al., 2006[17]	Italy	117	1.09 : 1	1–268	196	9 (8.1%)	0 (0%)	8 (6.8%)	0 (0%)	1 (0.9%)	0 (0%)	
Ikoona et al., 2003[16]	Uganda	158	0.82–1	6–183	42	55 (34.8%)	49 (31.0%)	6 (3.8%)	0 (0%)		3 (1.9%)	Molluscum contagiosum – 16 (10.1%); conjunctival xerosis – 14 (8.9%); keratitis – 11 (7.0%); optic atrophy – 5 (3.2%)
Kestelyn et al., 2000[15]	Rwanda	162	1.25 : 1	2–168	30	88 (54.3%)	63 (38.9%)	3 (1.9%)	4 (2.5%)	8 (4.9%)	2 (1.2%)	Conjunctival xerosis – 2 (1.2%); subconjunctival hemorrhage – 2 (1.2%); conjunctival telangiectasis – 1 (0.6%); palpebral abscesses – 1 (0.6%)
Padhani et al., 2000[14]	Tanzania	62	1.06 : 1	18–168	44.5	24 (38.7%)	2 (3.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	Conjunctival xerosis – 15 (24.2%); phlyctenules – 3 (4.8%); macular edema – 8 (12.9%); retinal hemorrhages – 2 (3.2%); optic atrophy – 1 (1.6%); retinal NV – 1 (1.6%)
Livingston et al., 1998[13]	USA	33	1.36 : 1.0	NR	45	10 (30.3%)	0 (0%)	2 (6.1%)	1 (3.0%)	0 (0%)	1 (3.0%)	Strabismus – 2 (6.1%); viral conjunctivitis 1(3.0%); anterior uveitis 1 (3.0%); nystagmus – 1 (3.0%); molluscum contagiosum – 1 (3.0%); corneal scars – 1 (3.0%); HSV blepharitis – 1 (3.0%)
Hammond et al., 1997[12]	UK	98	NR	8–122	NR	5 (5.1%)	0 (0%)	3 (3.1%)	0 (0%)	0 (0%)	0 (0%)	Progressive outer retinal necrosis – 1 (1.0S%); allergic conjunctivitis – 1 (1.0%)
Girard et al., 1997[11]	France	33	1.09 : 1	20–192	57	7 (21.2%)	1 (3.0%)	0 (0%)	0 (0%)	1 (3.0%)	1 (3.0%)	Bacterial conjunctivitis – 3 (9.1%); conjunctivitis associated with febrile rash – 3 (9.1%); retinal vascular tortuosity – 2 (6.1%); disc swelling – 2 (6.1%); molluscum contagiosum – 1 (3.0%); herpetic keratitis – 1 (3.0%); chalazion – 1 (3.0%); small, punctate, white retinal lesions – 1 (3.0%)
de Smet et al., 1992[10]	USA	160	NR	NR	73	29 (18.1%)	5 (3.1%)	10 (6.3%)	4 (2.5%)	1 (0.6%)	0 (0%)	Heterotrophia – 10 (6.3%); 2,3′-dideoxyinosine retinal toxicity – 15 (9.4%)
Dennehy et al., 1989[9]	USA	40	1.11–1	1–68	23	8 (20%)	0 (0%)	2 (5.0%)	3 (7.5%)	0 (0%)	0 (0%)	Retinal hemorrhages – 2 (5%); molluscum contagiosum – 2 (5%); preseptal cellulitis – 1 (2.5%)

HSV, Herpes simplex virus; NR, not reported.

findings may have been unrelated to the HIV status of the children.

Children infected by HIV are at increased risk of neurodevelopmental delay and increased incidence of neuro-ophthalmic complications. Isolated cases of optic atrophy of undetermined cause have been noted in children with HIV/AIDS.[13,15,20,21] De Smet et al.[10] and Livingston et al.[13] each found heterotropia in approximately 6% of their cohorts, whereas Rutar et al.[22] identified various forms of strabismus in over 18% of HIV-positive children. Kasi et al. described a 15-year-old boy from Zimbabwe, Africa, with HIV-related vitritis, phlebitis, optic neuritis, and multifocal retinal infiltrates.[29] All ocular findings resolved following treatment with HAART.

Ophthalmic screening and monitoring of HIV-infected children

Recommendations for ophthalmic screening and monitoring of HIV-infected children are not available. However, we recommend that all infants of HIV-positive mothers be screened for ocular complications shortly following birth and then every 2–3 months until their HIV status is known. Once HIV positivity is established, screening of children without ocular complications should be determined by overall level of immunosuppression (see Table 17.2). In the absence of ocular signs or symptoms, we recommend that children with severe immunosuppression receive a dilated eye examination every 2–3 months, that those with advanced immunosuppression be examined every 6 months, and that those with mild or no immunosuppression be seen annually. Once one or more ocular complications of HIV/AIDS have been identified, follow-up varies and depends upon the treatment status of the complication(s), as well as the age and immune status of the child.

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Disorders of the eye as a whole

Sunju Park and Elias I Traboulsi

Chapter contents

ANOPHTHALMOS AND MICROPHTHALMOS
OTHER DISORDERS OF THE EYE AS A WHOLE
CLINICAL EVALUATION AND MANAGEMENT OF ANOPHTHALMOS AND MICROPHTHALMOS
REFERENCES

The ophthalmologist needs to make an exact diagnosis in patients with eyes that are smaller than normal, or with malformations affecting anterior or posterior structures. A precise diagnosis allows good counseling of patients and families and an educated guess at visual outcomes and screening for possible future complications. Conditions that are associated with a small ocular size include microphthalmos and anophthalmos, nanophthalmos, persistent fetal vasculature, and some cases of aniridia and Peters' anomaly.

Anophthalmos and microphthalmos

Anophthalmos and microphthalmos are rare, with an incidence of between 6 and 13 per 100,000 live births.[1–4] The birth prevalence of anophthamos ranges from 0.6 to 4.2 per 100,000 births, whereas the birth prevalence of microphthalmos ranges from 2 to 17 per 100,000 births.[5] They are often associated with systemic malformations. Although reported risk factors include maternal age over 40 years, multiple births, low birth weight, and low gestational age, there is no unifying causation. Clustering of cases, which might suggest an environmental cause, probably does not occur.[1,2,6,7]

Anophthalmos

The term "anophthalmos" is used when the eye is non-existent (Fig. 18.1) or, more commonly, when it is not visible and a very small cystic remnant of the eye is identified on pathology. The term "clinical anophthalmos" emphasizes that there is a spectrum in which anophthalmos merges with microphthalmos. True anophthalmos is sometimes associated with absence of the optic nerve and chiasm, as in some patients with *SRY-BOX2* (*SOX2*) mutations.[8]

Secondary abnormalities of the orbit occur; orbital growth is always retarded to some extent. Extraocular muscles may be absent and the optic foramen size is often decreased. The conjunctival sac may be small. Although the absence of a developing eye does not affect the initial development of a bony orbit,[9] the growth of the orbit is highly influenced by the presence or absence of the globe and its size. The mean axial length of the human full-term neonatal and adult eyes are approximately 17.0 and 23.8 mm, respectively,[10] with the normal neonatal eye measuring 70% of the adult size.[11] Orbital volume increases dramatically during the first 3 years of life, especially in the first year.

While orbital volume cannot be assessed using plain radiographs, the horizontal and vertical sizes of the orbital openings from the orbital rim can be measured and are reduced in adults with congenital anophthalmos, or in those enucleated within the first year of life. This retardation of orbital growth is halved when an orbital implant is used, and the severity of the overall reduction in volume diminishes if the insult occurs at a later date. Orbital growth appears to be complete by the age of 15 years; subsequent enucleation will not result in appreciable size difference.[12]

In anophthalmos, there is a complete failure of budding of the optic vesicle or early arrest of its development. In consecutive or degenerative anophthalmos, an optic vesicle forms, but subsequently degenerates. The presence of optic nerves, chiasm, or tract with anophthalmos may indicate this pathogenesis.

Many causes for anophthalmos have been proposed; these merge with the causes of microphthalmos (see below). Bilaterality and increased severity imply an early teratogenic or genetic developmental event.[13] In isolated cases, inheritance may be autosomal dominant[14] or autosomal recessive.[15] In families with clear Mendelian inheritance, ocular pathology may be asymmetric or even unilateral. Mutations in *SOX2* are one of the more common causes of anophthalmos.[16] Several other genes have been implicated in anophthalmos as well (Table 18.1).

Microphthalmos

It is important for the clinician to distinguish between isolated microphthalmos, colobomatous microphthalmos, and microphthalmos associated with systemic disorders. Making the proper diagnosis will direct appropriate counseling of patients and their families.

The volume of a microphthalmic eye is reduced. Often, clinical suspicion arises from a corneal diameter less than

10 mm in adults. Although microphthalmos is usually associated with a small cornea, there may be microphthalmos with a normal cornea, and microcornea without microphthalmos.[17,18] Ultrasonographic determination of an axial length less than 21 mm in an adult or 19 mm in a 1-year-old child substantiates a diagnosis of microphthalmos.[19] This represents a reduction of 2 standard deviations or more from normal.

Bilateral microphthalmos[20] occurs in approximately 10% of blind children.[21] The effect of microphthalmos on vision depends on whether it is bilateral, the severity of the microphthalmos, and the presence of concurrent ocular malformations – specifically, the degree of retinal maldevelopment, involvement of the macula and optic nerve head, and the presence or absence of cataract and coloboma.[22]



Fig. 18.1 Bilateral anophthalmos in a girl with a *SOX2* mutation. There was absence of all visual pathways.

Microphthalmos may be simple (without other ocular defects) or complex (associated with anterior segment malformations, cataracts, colobomas, retinal or vitreous disease, or more complex malformations).[19,23] It can be further divided into colobomatous (Fig. 18.2) and non-colobomatous on the basis of associated uveal abnormalities.[17,24] The association between eye growth and closure of the fetal fissure is important since closure of the cleft is completed early in development.[25]

Microphthalmos represents a non-specific growth failure of the eye in response to prenatal insults and/or genetic defects. Inadequate postnatal growth, secondary to decreased size of the optic cup, altered vitreous composition, and low intraocular pressure, may play a role in the pathogenesis of simple micophthalmos.[23] Posterior segment abnormalities and complex microphthalmos may be secondary to inadequate production of secondary vitreous.[19] Microphthalmos can be classified according to mode of inheritance, environmental causes, chromosomal aberration, as well as syndromic associations that have additional systemic abnormalities. (For a complete search of inherited conditions associated with microphthalmos and anophthalmos, consult Online Mendelian Inheritance in Man (OMIM) at http://omim.org/).[9,17]

Table 18.1 Genes linked to anophthalmos

Gene symbol	Gene	Locus	Inheritance	Description
ALDH1A3	*Aldehyde Dehydrogenase 1 Family, A3*	15q26.3	Autosomal recessive	Encodes A3 isoform of aldehyde dehydrogenase 1
BMP4	*Bone Morphogenetic Protein 4*	14q22–23	Sporadic; complex inheritance	Secretes signaling molecule in the TGF-β superfamily
BMP7	*Bone Morphogenetic Protein 7*	20q13.31	Sporadic; complex inheritance	Secretes signaling molecule in the TGF-β superfamily
GDF3	*Growth Differentiation Factor 3*	12p13.1	Autosomal dominant	Secretes signaling molecule in the TGF-β superfamily
GDF6	*Growth Differentiation Factor 6*	8q22.1	Autosomal dominant	Secretes signaling molecule in the TGF-β superfamily
OTX2	*Orthodenticle, Drosophila, Homolog of, 2*	14q22–23	Sporadic; complex inheritance	Bicoid homeodomain transcription expressed in neuroretina and brain
PAX6	*Paired Box 6*	11p13	Autosomal dominant	Encodes a transcriptional regulator involved in oculogenesis and other developmental processes
RAX	*Retina and Anterior Neural Fold Homeobox*	18q21.32	Autosomal recessive	Encodes retina and anterior neural fold homeobox
RBP4	*Retinol-Binding Protein 4*	10q23.33	Autosomal dominant	Encodes retinol-binding protein
SOX2	*SRY-Box 2*	3q26.3–27	Autosomal dominant	Encodes transcription factor containing an HMG domain
STRA6	*Stimulated By Retinoic Acid 6*	15q24.1	Autosomal recessive	Encodes cell membrane receptor for retinol binding protein

HMG, High-mobility-group; TGF-β, transforming growth factor beta.
Data from Online Mendelian Inheritance in Man (http://omim.org).

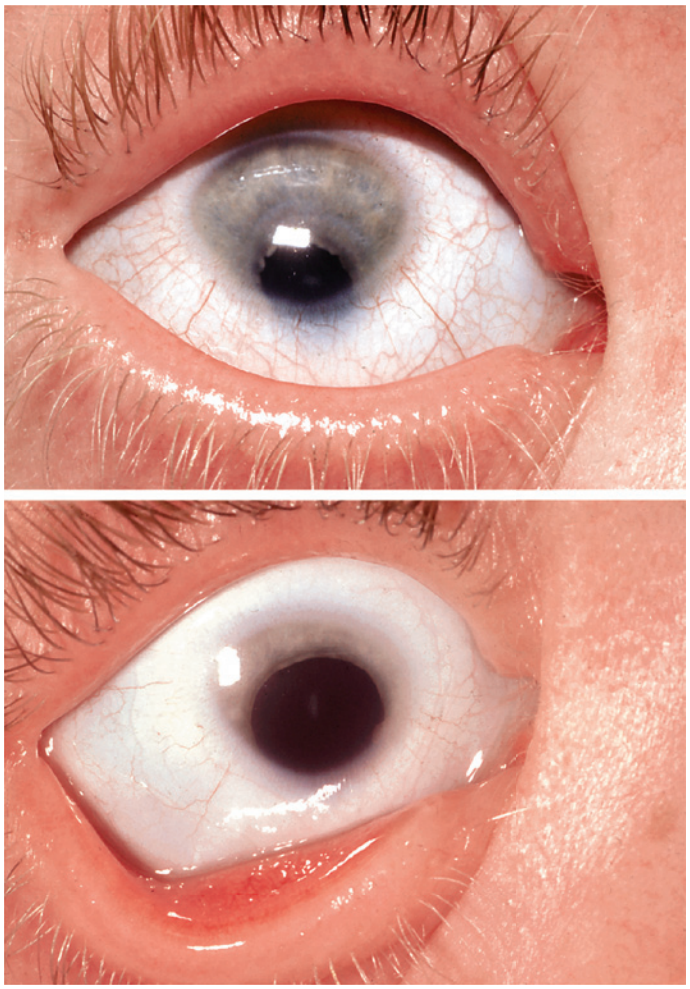


Fig. 18.2 Colobomatous microphthalmos. Both eyes are generally small with an inferior coloboma in the fundus. Although vision was limited to an acuity of 2/60 in each eye, the patient had a useful field and navigated without problems.



Fig. 18.3 (A) Bilateral marked non-colobomatous microphthalmos. (B) Mother of the child in (A) showing bilateral non-colobomatous microphthalmos.

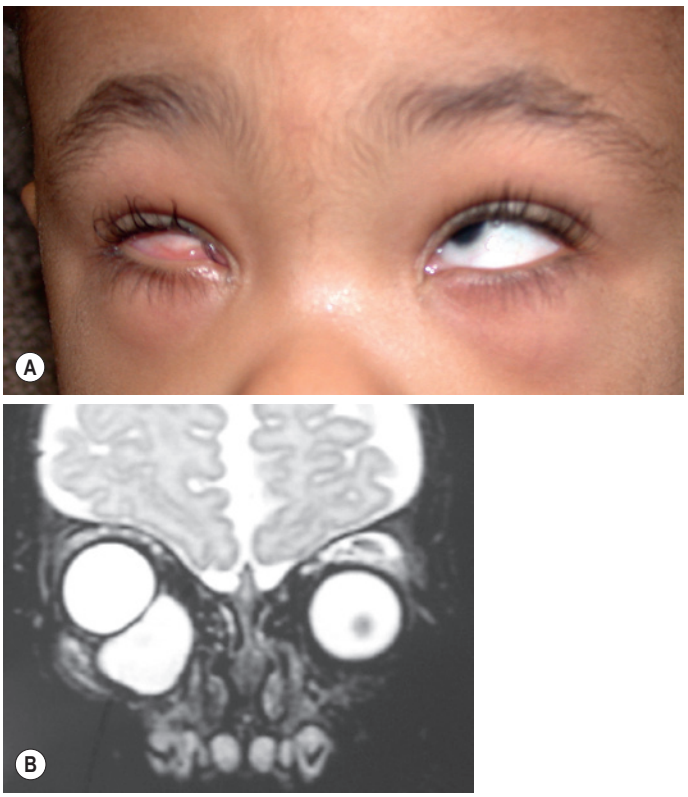


Fig. 18.4 (A) Bulge in right lower lid is due to pressure from cyst behind it. Ipsilateral eye is microphthalmic and has a coloboma. (B) Magnetic resonance imaging of same patient shows small eye with attached cyst.

Idiopathic isolated microphthalmos

Vision is variably affected, depending on the degree to which the eye is microphthalmic as well as associated high errors of refraction and consequent amblyopia.

Inherited isolated microphthalmos

Although most cases were previously thought to be sporadic,[26] many have been found to be autosomal dominant or autosomal recessive.[27,28] Some families (Fig. 18.3) have dominant inheritance of colobomatous microphthalmos and variable expression, with extreme microphthalmos at one end of the spectrum and coloboma at the other. A high rate of consanguinity suggests an autosomal recessive inheritance in some cases.[15,29] X-linked recessive inheritance occurs, sometimes with mental retardation.[30]

Microphthalmos with orbital cyst

This form of microphthalmos presents with a bulge behind the lower lid from birth (Fig. 18.4A). It is secondary to failure of optic fissure closure and the protrusion of a cyst from the coloboma. It has been confused with a congenital cystic eye,[31]

but the two are different. In the latter, the eye is replaced by a cystic structure and there is no lens or other normal eye structures. In microphthalmos with cyst, the small eye often cannot be seen and a neoplasm may be suspected. The cyst usually communicates with the eye.[32–34] Presentation may be as an orbital mass distending the lids and hiding the eye, or as proptosis in which a microphthalmic eye is visible. Ultrasonography and computed tomography (CT) or magnetic resonance imaging (MRI) aid in diagnosis (Fig. 18.4B).[33] Most cases of microphthalmos with cyst are sporadic; familial cases have been reported, with presumed autosomal recessive inheritance.[32,35,36]

Management is initially conservative, especially for small cysts. Large cysts may be managed with repeated aspiration or by surgical removal.[35,37–39] If the cyst is not growing rapidly, it may be left in place until some orbital growth is achieved. Because the cyst communicates with the eye, its removal may deflate the microphthalmic eye necessitating the removal of the latter.

Microphthalmos with cryptophthalmos

Cryptophthalmos implies varying degree of skin covering the eyeball, with variable cutaneous adhesions to the cornea.[40] It is usually bilateral with asymmetric degrees of severity. Unilateral cases have been described.

Francois described three subgroups of cryptophthalmos[41]:

1. Complete cryptophthalmos (Fig. 18.5): the lids are replaced by a layer of skin without lashes or glands that is fused with the microphthalmic eye without a conjunctival sac. Normal electrophysiological responses have been recorded.[42]
2. Incomplete cryptophthalmos (Fig. 18.6): the lids are colobomatous (often medially) or rudimentary and there is a small conjunctival sac. The exposed cornea is often opaque.
3. An abortive form: the upper lid is partly fused with the upper cornea and conjunctiva and may be colobomatous.[40] The globe is often small.

A fourth autosomal dominant type exists in which the upper lid is very tall and fused with the lower one at the margins. There is a normal complement of lashes. A dimple in the upper lid indicates where it is attached to the underlying eyeball.[43]

The systemic associations of cryptophthalmos and microphthalmos include nose deformities, cleft lip and palate, syndactyly, abnormal genitalia, renal agenesis, mental retardation, and many others.[40,44,45]

Microphthalmos with ocular and systemic malformations

Other eye malformations and systemic abnormalities are frequent in microphthalmos. Numerous syndromes are associated with microphthalmos. (http://omim.org/).[46]

Microphthalmos with ocular abnormalities

Microphthalmos represents the outcome of a non-specific response to a wide variety of influences. It occurs in conjunction with a number of severe eye diseases, including anterior segment malformations such as Peters' anomaly or cataracts, especially in the context of a chromosomal abnormality,[47] persistent fetal vasculature (PFV),[48] and multisystem syndromes such as the oculo-dento-digital syndrome.[49] Microphthalmos may be secondary to severe, widespread intraocular disease including retinopathy of prematurity, retinal dysplasia, retinal folds,[50] retinal degeneration, and glaucoma. A three-generation family has been described with aniridia, anophthalmos, and microcephaly.[51] Coloboma is the most common associated ocular malformation with microphthalmos and is found in many microphthalmos syndromes.[52,53]

Microphthalmos with systemic malformations

Up to 50% of patients with anophthalmos and microphthalmos have associated systemic abnormalities.[11,54] Many patients with microphthalmos-associated syndromes, especially chromosomal disorders, are developmentally delayed[30,55,56] or have cleft palate with and without macrosomia.[57]

The most common syndromic cause of colobomatous microphthalmos is the CHARGE syndrome (coloboma, heart abnormalities, atresia of the choanae, retardation of growth and development, genitourinary abnormalities, and ear/hearing abnormalities).[52] Affected patients can have cranial nerve abnormalities such as facial nerve palsy, craniofacial clefting, dysphagia/esophageal abnormalities, duplication of the thumb, and congenital brain abnormalities, particularly of the forebrain.[58,59] Although most cases are sporadic, autosomal dominant transmission has been reported.[60] Mutations in the *Chromodomain Helicase DNA-Binding Protein 7* (*CHD7*) gene are responsible for 60% of CHARGE cases, with possible genotype–phenotype correlation.[61,62] *CHD7* encodes a putative



Fig. 18.5 Complete cryptophthalmos. Note the characteristic continuation of the forehead skin onto the cheek. There is an abnormal hairline extending to the brow.



Fig. 18.6 Partial cryptophthalmos of the left eye. The eye is small and the cornea is opaque. There is a colobomatous upper lid and a characteristic "lick" of hair from the temple to the brow with a unilateral nose abnormality.

chromodomain protein widely expressed in the neuroectoderm and in neural crest cells during human development.[63] Mutations in the *Semaphorin 3E* (*SEMA3E*) gene can also result in CHARGE syndrome.[64]

The Temple–al-Gazali syndrome (Fig. 18.7) also referred to as X-linked dominant microphthalmos with linear skin defects (MLS) syndrome, and also known as the microphthalmos, dermal aplasia, and sclerocornea (MIDAS) syndrome, results from mutation of the *Holocytochrome C Synthase* (*HCCS*) gene and maps to Xp22.2.[65–68] Patients have linear, irregular areas of skin aplasia especially of the head and neck, microphthalmos with variable sclerocornea, and, sometimes, abnormal intelligence.[69–71] The condition is lethal in XY males.

Fryns "anophthalmos plus" syndrome is microphthalmos or anophthalmos, cleft lip or palate, and sacral neural tube defect.[72] The branchio-oculo-facial syndrome combines a broad nose with large lateral pillars, branchial sinuses, and orbital cysts.[73,74] Other microphthalmos syndromes with facial defects include fronto-facio-nasal dysplasia (Fig. 18.8),[75] and the cerebro-oculo-nasal syndrome in which there is an association of anophthalmos/microphthalmos, abnormal nares, and central nervous system anomalies.[76]

In Delleman syndrome, there is an association of skin tags, punched-out lesions of the skin on the ears and elsewhere, mental retardation, hydrocephalus, brain malformations, and orbital cysts.[77,78]

Microphthalmos has been described in patients with growth retardation, microcephaly, brachycephaly, oligophrenia syndrome (GOMBO syndrome).[79]

The eyes can be quite small in some patients with the oculo-dento-digital syndrome, characterized by bilateral digital anomalies (Fig. 18.9) with cutaneous syndactyly of fingers and camptodactyly,[49,80] thin nose with hypoplastic alae nasi and small nares, partial dental agenesis, enamel hypoplasia, and glaucoma.[81,82]

Patients with the less common recessive variety are more likely to have microphthalmos.[83] The syndrome results from mutations in Connexin 43. Iris cysts and anomalous retinal development may occur.[84]

Waardenburg recessive anophthalmos syndrome includes microphthalmos with syndactyly, oligodactyly, and other limb defects, and mental retardation.[85]

Patients with the X-linked recessive Lenz microphthalmos syndrome have microphthalmos with mental retardation, malformed ears, and skeletal anomalies.[53,86,87] The gene has been identified as *BCL6 Corepressor* (*BCOR*) and maps to Xq27–q28.[88,89]

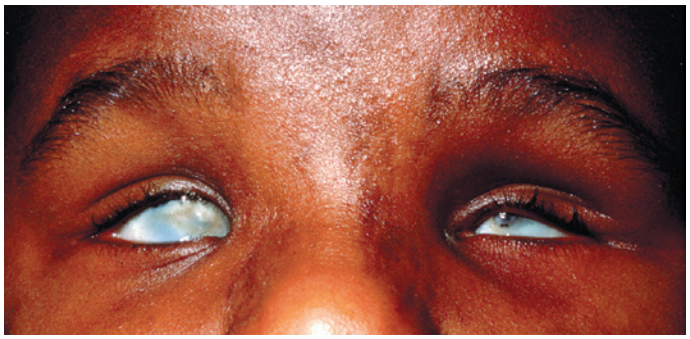


Fig. 18.7 Microphthalmos, dermal aplasia, and sclerocornea (MIDAS or Temple–al-Gazali) syndrome showing extreme microphthalmos and characteristic skin lesions.



Fig. 18.8 Right clinical anophthalmos, left microphthalmos in a child with bilateral cleft lip and palate associated with fronto-facio-nasal dysplasia.

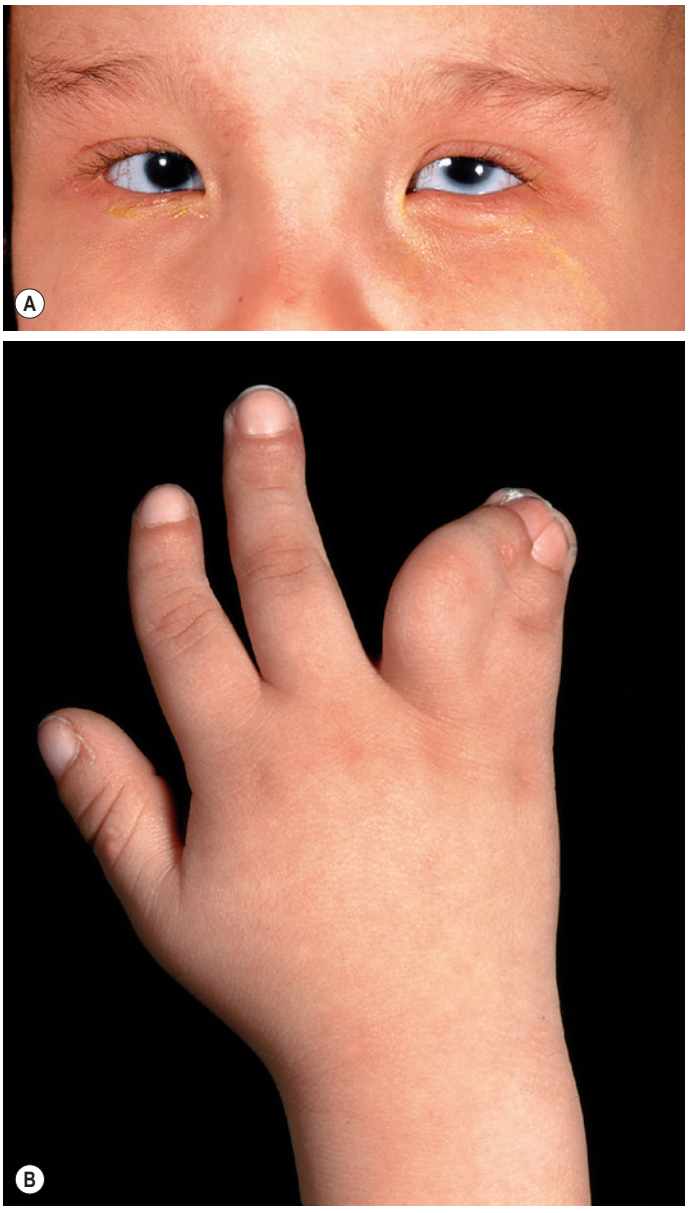


Fig. 18.9 (A) Bilateral microphthalmos, thin nose, and epicanthic folds in a patient with the oculo-dento-digital syndrome. (B) Cutaneous syndactyly of fingers and camptodactyly in the oculo-dento-digital syndrome.

The autosomal recessive Warburg MICRO syndrome comprises microphakia, microphthalmos, characteristic lens opacity, atonic pupils, cortical visual impairment, microcephaly, developmental delay by 6 months of age, and microgenitalia in males.[90,91] It can be caused by mutations in the *RAS-Associated Protein RAAB18* (*RAB18*) gene encoding the catalytic subunit of the RAB3 GTPase-activating protein complex (RAB3GAP).[92,93]

Gene mutations associated with anophthalmos and microphthalmos

A large number of chromosomal deletions, duplications, and translocations have been linked to anophthalmos and microphthalmos, often in association with well-delineated syndromic conditions.[94] Mutations in single genes have also been identified as causes of anophthalmos and microphthalmos.

SOX2 (*SRY-Box 2*)

The *SOX2* gene located at 3q26.3–27 is a major causative gene of microphthalmos and anophthalmos with an autosomal dominant inheritance pattern. *De novo* heterozygous loss-of-function point mutations account for 10–20% of bilateral anophthalmos and severe microphthalmos.[16] It is expressed at critical stages of eye development[95] and mutations have been associated with sclerocornea, cataract, persistent fetal vasculature, optic disc dysplasia, mental retardation, neurologic abnormalities,[8] facial dysmorphism, failure to thrive, and anomalies of the gastrointestinal, pituitary gland, and genital systems.

PAX6 (*Paired Box Gene 6*)

Mutations in this gene on chromosome 11p13 generally cause aniridia, but may rarely cause autosomal dominant panocular malformations, microphthalmos, and anophthalmos.[3,96] *PAX6* and *SOX2* interact and play a regulatory role in lens induction in several animal models.[97]

PAX2 (*Paired Box Gene 2*)

Mutations in *PAX2* are found in cases of the renal-coloboma syndrome (ocular colobomas, vesicoureteral reflux, and kidney anomalies).[98] The eyes are sometimes small (see Chapter 53).

VSX2 (Visual System Homeobox 2)

Formerly known as *CEH10 Homeodomain-Containing Homolog* (*CHX10*).

Human *VSX2* is expressed in progenitor cells of the developing neuroretina and in the inner nuclear layer of the mature retina. The human microphthalmos locus was mapped on chromosome 14q24.3; *VSX2* mutations were identified in non-syndromic autosomal recessive microphthalmos, cataracts, and severe abnormalities of the iris.[99]

FOXE3 (*Forkhead Box E3*)

Mutations in this gene on chromosome 1p32 have been associated with microphthalmos and lens agenesis.[100] The locus had been previously linked to congenital primary aphakia.

OTX2 (*Orthodenticle, Drosophila, Homolog of, 2*)

This gene located at 14q22–23, is a bicoid-type homeodomain transcription factor expressed in the neuroretina and brain. Heterozygous loss-of-function mutations account for 2% of anophthalmos and severe microphthalmos.[95]

BMP4 (*Bone Morphogenetic Protein 4*)

This gene, also at 14q22–23, is associated with anophthalmos and microphthalmos.[28] As a member of the transforming growth factor-β1 superfamily of secretory signaling molecules, it is important in optic vesicle formation, lens induction, and anterior and posterior segment development.[95]

ALDH1A3 (*Aldehyde Dehydrogenase 1 Family, A3*)

Mutations in this gene encoding the A3 isoform of the aldehyde dehydrogenase 1 have been linked to both anopthalmos and microphthalmos. This enzyme is critical in the formation of a retinoic acid gradient along the dorsoventral axis during early eye formation. Inheritance is autosomal recessive and occurs primarily in the setting of consanguinity. This gene maps to chromosome 15q26.3.[28,101–107]

Additional mutations associated with microphthalmos and anophthalmos have been identified in *Retina and Anterior Neural Fold Homoeobox* (*RAX*) gene,[108,109] *BCL6 Corepressor* (*BCOR*),[110] *Stimulated by Retinoic Acid 6* (*STRA6*), and *Growth/Differentiation Factor 6* (*GDF6*) among others.[111,112] Several loci for dominant, recessive, and X-linked inherited microphthalmos have been identified (http://omim.org; Tables 18.2–18.4)

While cluster studies have failed to identify causal links between environmental factors and microphthalmos/anophthalmos,[7] prenatal infection with rubella, toxoplasmosis, varicella, cytomegalovirus, parvovirus B19, influenza, and coxsackie A9 have been implicated.[2,11,113,114] Maternal vitamin A toxicity,[115] hyperthermia,[116] X-ray exposure, and prenatal drug exposure (thalidomide, warfarin, alcohol, the fungicide benomyl) have been postulated as potential non-infectious etiologies.[10]

Other disorders of the eye as a whole

Nanophthalmos

Nanophthalmos (Fig. 18.10) is a rare condition characterized by eyes whose axial length is less than 20 mm in adults. There is high hypermetropia, a weak but thick sclera with abnormal collagen,[117] a tendency toward angle closure glaucoma in young patients,[118] and uveal effusion. Some cases are autosomal recessive. Sundin and associates found a frameshift mutation in the original recessive nanophthalmos kindred and four independent mutations in the *MFRP* gene on 11q23.3.[119,120] Additional genes have been identified for nanophthalmos (Table 18.5). There is an increased fibronectin level in nanophthalmic sclera and cells; fibronectin is involved with cellular adhesion and healing.[121]

Intraocular surgery on nanophthalmic eyes may be complicated by severe uveal effusion.[122–125]

Cyclopia and synophthalmos

Complete (cyclopia) or partial (synophthalmos) fusion of the two eyes is very rare. The brain fails to develop two hemispheres and the orbit has gross deformities.[126–128] Fetuses with cyclopia generally do not survive. The brain is almost always malformed; the telencephalon fails to divide and a large dorsal cyst develops. The orbit is markedly affected as a consequence of the abnormal development of midline mesodermal structures. The normal nasal cavity is replaced

Table 18.2 Genes linked to isolated microphthalmos

Gene symbol	Gene	Locus	Inheritance	Description
ALDH1A3	*Aldehyde Dehydrogenase 1 Family, A3*	15q26.3	Autosomal recessive	Encodes A3 isoform of aldehyde dehydrogenase 1
BMP4	*Bone Morphogenetic Protein 4*	14q22–23	Autosomal dominant	Secretes signaling molecule in the TGF-β superfamily
FOXE3	*Forkhead Box E3*	1p32	Autosomal dominant or recessive with variable expressivity	Encodes forkhead box E3
GDF3	*Growth Differentiation Factor 3*	12p13.1	Autosomal dominant	Secretes signaling molecule in the TGF-β superfamily
GDF6	*Growth Differentiation Factor 6*	8q22.1	Autosomal dominant	Secretes signaling molecule in the TGF-β superfamily
PAX6	*Paired Box 6*	11p13	Autosomal dominant	Encodes a transcriptional regulator involved in oculogenesis and other developmental processes
RAX	*Retina and Anterior Neural Fold Homeobox*	18q21.32	Autosomal recessive	Encodes retina and anterior neural fold homeobox
RBP4	*Retinol-Binding Protein 4*	10q23.33	Autosomal dominant	Encodes retinol-binding protein
VSX2	*Visual System Homeobox 2*	14q24.3	Autosomal recessive	Encodes visual system homeobox 2

TGF-β, Transforming growth factor beta.
Data from Online Mendelian Inheritance in Man (http://omim.org).

Table 18.3 Genes linked to colobomatous microphthalmos

Gene symbol	Gene	Locus	Inheritance	Description
ABCB6	*ATP-Binding Cassette, Subfamily B, Member 6*	2q35	Autosomal dominant	Encodes transporter protein
ALDH1A3	*Aldehyde Dehydrogenase 1 Family, A3*	15q26.3	Autosomal recessive	Encodes A3 isoform of aldehyde dehydrogenase 1
BMP7	*Bone Morphogenetic Protein 7*	20q13.31	Sporadic; complex inheritance	Secretes signaling molecule in the TGF-β superfamily
FOXE3	*Forkhead Box E3*	1p32	Autosomal dominant or recessive with variable expressivity	Encodes forkhead box E3
GDF3	*Growth Differentiation Factor 3*	12p13.1	Autosomal dominant	Secretes signaling molecule in the TGF-β superfamily
GDF6	*Growth Differentiation Factor 6*	8q22.1	Autosomal dominant	Secretes signaling molecule in the TGF-β superfamily
PAX6	*Paired Box 6*	11p13	Autosomal dominant	Encodes a transcriptional regulator involved in oculogenesis and other developmental processes
RAX	*Retina And Anterior Neural Fold Homeobox*	18q21.32	Autosomal recessive	Encodes retina and anterior neural fold homeobox
RBP4	*Retinol-Binding Protein 4*	10q23.33	Autosomal dominant	Encodes retinol-binding protein
SHH	*Sonic Hedgehog*	7q36.3	Autosomal dominant	Encodes sonic hedgehog protein involved in establishing cell fates during development
STRA6	*Stimulated By Retinoic Acid 6*	15q24.1	Autosomal recessive	Encodes cell membrane receptor for retinol binding protein
TENM3	*Teneurin Transmembrane Protein 3*	4q34.3–q35.1	Autosomal recessive	Encodes transmembrane protein
VSX2	*Visual System Homeobox 2*	14q24.3	Autosomal recessive	Encodes visual system homeobox 2

TGF-β, Transforming growth factor beta.
Data from Online Mendelian Inheritance in Man (http://omim.org).

Table 18.4 Genes linked to microphthalmos associated with systemic disorders

Gene symbol	Gene	Locus	Inheritance	Description	Findings
BCOR	*BCL6 Corepressor*	Xp11.4	X-linked recessive	BCL6 corepressor gene	Lenz microphthalmos syndrome
BMP4	*Bone Morphogenetic Protein 4*	14q22–23	Autosomal dominant	Secretes signaling molecule in the TGF-β superfamily	Microphthalmos or clinical anophthalmos with brain and digit developmental anomalies
CHD7	*Chromodomain Helicase DNA-Binding Protein 7*	8q12.1–q12.2	Autosomal dominant	Encodes CHD7 trascriptional regulator	CHARGE syndrome
GJA1	*Gap Junction Protein, Alpha-1*	6q22.31	Autosomal dominant	Encodes connexin-43	Oculo-dento-digital syndrome
HCCS	*Holocytochrome C Synthase*	Xp22.2	X-linked dominant	Mitochondrial holocytochrome synthetase	Microphthalmos with linear skin defects (MLS); microphthalmos, dermal aplasia, sclerocornea syndrome (MIDAS)
HMGB3	*High Mobility Group 3*	Xq28	X-linked dominant	Inhibits B-cell and myeloid differentiation	Colobomatous microphthalmos with microcephaly, short stature, psychomotor retardation
HMX1	*H6 Family Homeobox 1*	4p16.1	Autosomal recessive	Encodes transcription factor	Oculoauricular syndrome (OCACS)
MAB21L2	*Mab21 C. Elegans, Homolog-Like 2*	4q31.3	Autosomal dominant or autosomal recessive	Cell fate specification gene; participates in formation of sensory organs	Colobomatous microphthalmos or clinical anophthalmos with or without rhizomelic skeletal dysplasia
OTX2	*Orthodenticle, Drosophila, Homolog of, 2*	14q22–23	Autosomal dominant	Bicoid homeodomain transcription expressed in neuroretina and brain	Microphthalmos or clinical anophthalmos with coloboma, microcornea, retinal dystrophy, hypoplasia or agenesis of optic nerve, possible agenesis of corpus callosum or other pituitary abnormalities
RAB18	*Ras-Associated Protein RAAB18*	10p12.1	Autosomal recessive	Encodes catalytic subunit of the RAB3 GTPase-activating protein complex	Warburg MICRO syndrome
SEMA3E	*Semaphorin 3E*	7q21.11	Autosomal dominant	Encodes semaphorin 3E	CHARGE syndrome
SMOC1	*SPARC-Related Modular Calcium-Binding 1*	14q24.2	Autosomal recessive	Encodes calcium-dependent glycoprotein	Microphthalmos with limb anomalies
SOX2	*SRY-Box 2*	3q26.3–27	Autosomal dominant	Encodes transcription factor containing an HMG domain	Microphthalmos, anophthalmos, coloboma, sclerocornea, cataract, persistent fetal vasculature, optic disc dysplasia, mental retardation, neurologic abnormalities, facial dysmorphism, failure to thrive, anomalies of gastrointestinal/pituitary gland/genital systems
STRA6	*Stimulated by Retinoic Acid 6*	15q24.1	Autosomal recessive	Encodes cell membrane receptor for retinol-binding protein	Pulmonary hypoplasia, diaphragmatic hernia/eventration, anophthalmos/microphthalmos, cardiac defect (PDAC)
TFAP2A	*Transcription Factor AP2-Alpha*	6p24.3	Autosomal dominant	Encodes activating enhancer-binding protein 2-alpha	Branchio-oculo-facial syndrome
YAP1	*YES-Associated Protein 1, 65-KD*	11q22.1–q22.2	Autosomal dominant	Encodes protein that binds to SH3 domain of YES tyrosine kinase	Colobomatous microphthalmos with or without hearing impairment, cleft lip/palate, and/or mental retardation

CHARGE, **C**oloboma of the eye, **h**eart defects, **a**tresia of the nasal choanae, **r**etardation of **g**rowth and/or development, **g**enital and/or urinary abnormalities, and **e**ar abnormalities and deafness HMG, high-mobility-group; SH3, SRC homology 3; TGF-β, transforming growth factor beta.
Data from Online Mendelian Inheritance in Man (http://omim.org).



Fig. 18.10 (A) Patient with nanophthalmos wearing high hypermetropic glasses. The phakic correction was +10.00 D right, +11.00 D left. (B) Patient with nanophthalmos with small eyes and abnormal red reflex with co-axial illumination. (C) Shallow anterior chamber in patient with nanophthalmos. The eyes are prone to angle closure glaucoma. (D) Retinal appearance in a patient with nanophthalmos showing a crowded optic disc and prominent yellow foveal pigment with a fold between the fovea and the macula. Nanophthalmic eyes are very prone to choroidal effusions spontaneously or in response to intraocular surgery.

Table 18.5 Genes linked to nanophthalmos

Gene symbol	Gene	Locus	Inheritance	Description
MFRP	*Membrane-Type Frizzled-Related Protein*	11q23.3	Autosomal recessive	Encodes membrane-type frizzled-related protein
NNO1	*Nanophthalmos 1*	11p	Autosomal dominant	Associated with high incidence of angle closure glaucoma
NNO2	*In progress*	11q23.3	In progress	Caused by homozygous or compound heterozygous mutation in *MFRP* gene
NNO3	*In progress*	2q11–q14	In progress	
NNO4	*Nanophthalmos 4*	17q11.2	Autosomal dominant	Caused by heterozygous mutation in *TMEM98* gene
TMEM98	*Transmembrane Protein 98*	17q11.2	Autosomal dominant	Encodes transmembrane protein

Data from Online Mendelian Inheritance in Man (http://omim.org).

by the "pseudo-orbit."[129] The eyes are more commonly partly fused with one optic nerve and no chiasm. Other intraocular abnormalities such as fetal vasculature, cataract, coloboma, and microcornea may exist.[130] Chromosomal aberrations are common.[131] Several causative genes have been identified (Table 18.6). Familial occurrences and association with consanguineous marriages have also been noted.[132] Other etiologic considerations include maternal health and toxic factors.[133]

Clinical evaluation and management of anophthalmos and microphthalmos

The ophthalmologist faced with a new patient with microphthalmos must address several questions:

1. Is this an isolated ocular problem or are there associated systemic malformations?
2. What is the level of vision?
3. What is the refractive error? Is amblyopia present?
4. Are colobomas present? Do they involve the fovea?
5. Are there other ocular malformations?
6. Is there evidence of congenital infection, chromosomal abnormality, or environmental factors?
7. Is this genetically determined and heritable with recurrence risks in siblings?
8. Are there life-threatening associations (cardiac, brain, or renal defects) or factors that may alter parental expectations (mental retardation or deafness)?

Following family and medical history, physical examination, review of systems, appropriate chromosomal tests and molecular genetic tests are ordered. Neuro- and orbital imaging and possibly renal ultrasonography and audiological assessment may be needed.

Clinical diagnosis of anophthalmos may be difficult. To differentiate between anophthalmos and extreme microphthalmos, the examiner can palpate the lids to feel for any globe movements from residual extraocular muscle function. Bulging of the lower lid may be observed in patients with microphthalmos with cyst. Unilateral anophthalmos is often associated with anomalies of the other eye. Detailed examination of both eyes is crucial.[134] Parents and siblings should also be examined. Small visually insignificant colobomas in otherwise normal eyes indicate carrier state of the mutation.

Vision should be assessed and may require electrodiagnostic testing in infants (see Chapter 9). Visual evoked potential may demonstrate reduced, but useful, function in patients with

Table 18.6 Genes linked to cyclopia

Gene symbol	Gene	Locus	Inheritance	Description
CDON	*Cell Adhesion Molecule-Related/ Downregulated by Oncogenes*	11q24.2	In progress	Encodes cell surface receptor of immunoglobulin/fibronectin type III
GLI2	*GLI-Kruppel Family Member 2*	2q14.2	Autosomal dominant	Encodes vertebral transcription factor involved in *SHH* signal transduction
HPE1	*Holoprosencephaly 1*	21q22.3	Autosomal recessive	
HPE2	*Holoprosencephaly 2*	2p21	Autosomal dominant	Caused by mutation in *SIX3* gene
HPE3	*Holoprosencephaly 3*	7q36.3	Autosomal dominant	Caused by mutation in *SHH* gene
HPE4	*Holoprosencephaly 4*	18p11.31	Autosomal dominant	Caused by mutation in *TGIF* gene
HPE5	*Holoprosencephaly 5*	13q32.3	Autosomal dominant	Caused by heterogzygous mutation in *ZIC2* gene
HPE6	*Holoprosencephaly 6*	2q37.1–q37.3	In progress	
HPE7	*Holoprosencephaly 7*	9q22.32	In progress	Caused by heterozygous mutation in *PTCH1* gene
HPE8	*Holoprosencephaly 8*	14q13	In progress	
HPE9	*Holoprosencephaly 9*	2q14.2	Autosomal dominant	Caused by heterozygous mutation in *GLI2* gene
HPE10	*Holoprosencephaly 10*	1q41–q42	Isolated cases	
HPE11	*Holoprosencephaly 11*	11q24.2	In progress	Caused by heterozygous mutation in *CDON* gene
PTCH1	*Patched, Drosophila, Homolog of, 1*	9q22.32	In progress	Encodes transmembrane protein
SHH	*Sonic Hedgehog*	7q36.3	Autosomal dominant	Encodes sonic hedgehog protein involved in establishing cell fates during development
SIX3	*Sine Oculis Homeobox, Drosophila, Homolog of, 3*	2p21	Autosomal dominant	Encodes proteins which may be involved in determining DNA-binding specificity and in mediating protein–protein interactions
ZIC2	*Zinc Finger Protein of Cerebellum 2*	13q32.3	Autosomal dominant	Homolog of Drosophila "odd-paired" gene; encodes proteins important in brain and distal limb development

Data from Online Mendelian Inheritance in Man (http://omim.org).

clinical anophthalmos. The evaluation of visual potential is imperative; it may guide the approach to socket expansion if indicated. Ophthalmologists should withhold prognostication of visual potential based on degree of microphthalmos and ocular malformation. Patients with very small eyes and even large colobomas may have preserved vision.

Neuroimaging or ultrasound may demonstrate extremely microphthalmic eyes, but histological sectioning is needed to determine the presence of neural ectoderm-derived cells (in microphthalmos) or their absence (in anophthalmos). Ultrasound is useful to determine a decreased axial length in microphthalmic eyes. MRI is important as many conditions associated with microphthalmos and anophthalmos affect brain development.[135]

Ophthalmic interventions may be limited to the prescription of glasses to offset amblyogenic refractive errors, helping the ocularist in management and fitting of cosmetic shells or contact lenses in non-seeing eyes, and diagnosing and treating glaucoma and cataracts. Cataract extraction may improve vision.[136] Microphthalmic eyes with corneal opacities may rarely require corneal grafting, but such interventions should be weighed against the risk of making the situation worse by precipitating glaucoma or more corneal opacification with graft failure. In patients with unilateral microphthalmos and poor vision, protective glasses should be prescribed.

Underdevelopment of the bony orbit, eyelids, and fornices leads to the inability to retain a prosthesis later in life. Mild microphthalmos may be managed with enlarging conformers, which should be transparent if there is vision. While anophthalmos is initially managed similarly with a conformer in the first several weeks of life, serial static implants or expandable implants may be used after 6 months of age to increase orbital volume. Complications of orbital implants include wound dehiscence, extrusion, or inadequate stimulation of bony growth.[10] Hydrophilic expanders held in place by tarsorrhaphy may allow growth of the bony orbit.[11] Controversially, some advocate early removal of a non-seeing microphthalmic eye with replacement of tissue by dermis fat graft or ball implant. In cases of microphthalmos with cyst, surgical intervention may be delayed, as orbital growth is more likely if the eye and cyst are left in place.[11]

Management by multidisciplinary teams is optimal. Because midline neurologic and pituitary abnormalities are common, referral to neurology and endocrinology may be indicated. In cases of bilateral anophthalmos or severe microphthalmos with no light perception, melatonin may establish regular nocturnal sleep patterns.[11] If no syndromic findings are identified initially, evaluation may be repeated at 3–5 years. Many syndromes may not fully manifest until later in childhood. Referral to a low vision specialist, occupational therapist, and other agencies may be indicated.

The benefits of genetic evaluation are three-fold. In cases of severe vision loss, identification of a potential cause may ease the guilt felt by some parents. Known syndromic findings of mutations of certain genes or chromosomal rearrangements may drive multidisciplinary approach and screening. Genetic counseling may aid in risk assessment for future siblings of the affected child. However, given the number of genes identified with a link to anophthalmos and microphthalmos, genetic counseling may be difficult. Even when a causal mutation is identified, gonadal mosaicism and variable penetrance may make recurrence risk prediction difficult.[10,95] For example, there have been observations of normal parents of affected children carrying loss-of-function *SOX2* and *OTX2* mutations.[10] Given systemic comorbidities identified with many mutations, the patient's siblings may be tested for genetic abnormalities. With unbalanced chromosomal translocation, with parents having rearrangements, the risk to siblings is higher and genetic testing should be recommended.

Prenatal diagnosis can be made by ultrasound early in the second trimester[137] when transvaginal ultrasound can identify anophthalmos and microphthalmos. Cytogenetic studies may be conducted on amniotic fluid samples at 14 weeks' gestation, or on chorionic villus samples at 10–12 weeks' gestation. These may be useful when an anomaly is identified on ultrasonography, to identify gene mutations associated with neurologic anomalies and other systemic findings.

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Lids: congenital and acquired abnormalities – practical management

Robert C Kersten and Richard Collin

Chapter contents

MANAGEMENT OF CONGENITAL LID CONDITIONS
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See online for supporting video for this chapter.

This chapter concentrates on the practical management of congenital and acquired eyelid lesions. The main indications for eyelid surgery in children are to optimize the potential for useful vision in severe congenital malformations, to prevent amblyopia, to control exposure and breakdown of the ocular surface, and to improve cosmesis. These aims are aligned, as reconstructive lid surgery usually results in both improved function and cosmesis.

Complex cases require a careful treatment plan. However, flexibility is often required in oculoplastic surgery, and the surgeon often enters the operating room with the realization that plans may need to be modified.

Management of congenital lid conditions

Lid coloboma

The treatment of lid coloboma is directed toward treating sight-threatening corneal exposure, preventing amblyopia, and improving cosmesis. Occasionally, underlying abnormalities that limit ocular motility may need to be addressed.

The coloboma is described in terms of its position using the Tessier classification,[1] and in terms of its extent. An examination is carried out to exclude associated ocular and systemic abnormalities. Initial management aims to protect the ocular surface with lubrication and occlusive dressing – taking care not to induce amblyopia with them. A forced duction test is performed on all children with an eyelid coloboma for underlying adhesions,[2] which need early treatment. This usually requires an examination under anesthesia. A small coloboma can be closed under the same anesthetic. If a more complicated repair is required, timing depends on the underlying ocular surface protection, but delaying repair allows growth of soft tissues, increasing options for advancement and closure. If corneal exposure cannot be controlled, the eyelid reconstruction is urgent. A defect of less than 25% of the lid length can be repaired by excision of the coloboma margins and direct closure. For defects of 25–50% of lid length, a lateral canthotomy and cantholysis allows the wound edges to come together. For defects of 50% or more, tissue will need to be added from elsewhere. In the lower eyelid, the posterior lamella can be reconstructed using tarsoconjunctival grafts from the upper lid, together with advancement myocutaneous eyelid flaps or skin grafts. In the upper eyelid, larger defects are generally better closed with a lower lid rotation flap, provided there is sufficient lower lid tissue available. The lower lid is rotated into the upper lid. The pedicle is divided after about 2 weeks and aggressive occlusion therapy is started to limit amblyopia.

The coloboma in Treacher Collins syndrome (see Chapter 28) is a pseudocoloboma in which there is a defect of subcutaneous tissue rather than a true eyelid discontinuity. The syndrome is variably severe, including an abortive form. Severe cases may require craniofacial surgery prior to eyelid surgery in order to re-establish malar support. In less severe cases, the lids can be built with oculoplastic surgery alone. In mild cases, the lateral canthus can be repositioned with a lateral canthoplasty, but extensive undermining and repositioning of the periocular soft tissues is necessary to maintain the new canthal position. In moderate cases, with absence of vertical and horizontal eyelid soft tissue, the lid can be reconstructed with the use of mucous membrane grafts, ear cartilage, or a spacer to support the lid. The lateral canthus can be secured with wire fixation to bore holes in the lateral orbital rim. Moderately severe cases may require transposition flaps from the upper to lower lids with a lateral canthal strip.

Cryptophthalmos

Cryptophthalmos is a rare condition in which the upper eyelid and eyebrow fail to develop and the cutaneous epithelium is

continuous with conjunctiva at the superior fornix. There is usually severe dysgenesis of the anterior segment as well. The condition can be complete, incomplete, or partial (congenital symblepharon) (see Chapter 31).

In complete cryptophthalmos there is no real chance of gaining vision, even with reconstructive surgery. In incomplete cryptophthalmos there may be some chance of achieving useful vision or reasonable cosmesis, but this is unusual: then the same concerns pertain as in eyelid colobomas. The urgency of surgery depends on whether the condition is unilateral or bilateral, the presence of visual potential, and the degree of corneal exposure. If the condition is unilateral, no visual potential exists, and exposure is controlled, surgery should be delayed to allow for the relaxation of tissues, which occurs as the infant matures.[3]

Surgery reconstitutes the components of the anterior and posterior lamellae. Pedicle rotation flaps from the cheek or brow, eyelid sharing, full-thickness skin grafts, and mucous membrane grafts are used. The success of complex lid reconstruction is limited by defective tear production, a lack of healthy conjunctiva, and underlying ocular defects associated with the condition, such as corneal and anterior segment dysgenesis.

Ablepharon

Complete failure of eyelid development is rare. Urgent treatment is required to protect the ocular surface followed by early lid reconstruction. The results depend on the severity of the lid changes and the integrity of the underlying structures. Treatment of true ablepharon has poor results; however, treatment of milder cases (microblepharon), by vertical stretching of the lid and anchoring at the lateral orbital rim, is more successful. Although the eyelid may open minimally initially due to "bow-stringing" of the tight eyelid, this improves significantly within 6–8 weeks of surgery.

Ankyloblepharon

In ankyloblepharon the eyelid margins are partially or completely fused together with a reduction in the palpebral aperture. Ankyloblepharon filiforme adnatum is a similar condition in which one or more skin tags join the two lids and there is usually a normal horizontal palpebral aperture: it is treated by division of the tag or tags.

Ankyloblepharon must be differentiated from blepharophimosis, in which the palpebral aperture is reduced and there is telecanthus, but the eyelid margins are normal. Recognition of ankyloblepharon necessitates systemic examination to detect associated abnormalities such as genitourinary, cardiac, and syndactyly. The lids are opened along the line of fusion with sharp scissors or a scalpel. A thin strip of skin and orbicularis is excised and the bare lid margin allowed to conjunctivalize. The lid structure and tarsus are usually otherwise normal.

Euryblepharon

Euryblepharon is congenital primary enlargement of the palpebral aperture, usually greatest laterally. There is a localized outward and downward displacement of the lateral canthus and downward displacement of the lower lid. Mild cases may require no treatment or simple lubrication. If there is a danger of corneal exposure, the lateral canthus may be tightened and positioned more superiorly and posteriorly. Wide undermining and repositioning of the soft tissues is necessary or the tissues tend to migrate to their original location. If the eyelid is short vertically, skin grafts and/or posterior lamellar grafts with overlying soft tissue advancement may be required. Free grafts usually result in suboptimal cosmesis in young children.



Fig. 19.1 Bilateral ectropion due to shortage of the anterior lamella in a patient with euryblepharon and blepharophimosis.

Ectropion

The initial treatment of ectropion in childhood is conservative, using lubrication to prevent exposure keratitis. Surgery is aimed at treating the underlying cause: shortage of skin or increased lid laxity (paralytic ectropion is discussed later) and is usually delayed until the child is older and has more soft tissue with which to work. Ectropion associated with a shortage of skin occurs in congenital conditions such as Down syndrome, blepharophimosis (Fig. 19.1), and acquired conditions such as ichthyosis, dermatomyositis, and trauma. A localized scar can be lengthened with a Z-plasty, and a generalized shortage of skin corrected with a skin flap or graft. Increased lid laxity causing ectropion is found in congenital conditions such as megaloblepharon and euryblepharon and can occur after trauma. It is treated with lid-tightening procedures.[4]

Eversion

Treatment of congenital eversion is aimed at repositioning the everted eyelids so that the underlying soft tissue swelling and chemosis can resolve. Once this has occurred, the eyelids remain in proper position. Repositioning the eyelids and pressure patching or taping for 5–7 days is usually sufficient. More severe cases can be treated by intermarginal sutures.

Epiblepharon

Epiblepharon is a horizontal fold of skin across the upper or lower eyelid that may push the lashes against the cornea. The lid margin remains in a normal position. Epiblepharon usually resolves by 5–6 years of age as the facial bones grow. It is usually asymptomatic and is seldom associated with keratitis (Fig. 19.2). Surgical intervention is reserved for those patients in whom it causes corneal compromise despite conservative treatment (i.e. lubrication) or it persists into adolescence. Quickert sutures can be used in milder cases, or excision of an ellipse of skin and orbicularis muscle with tarsal fixation is used in more severe cases.[5,6]

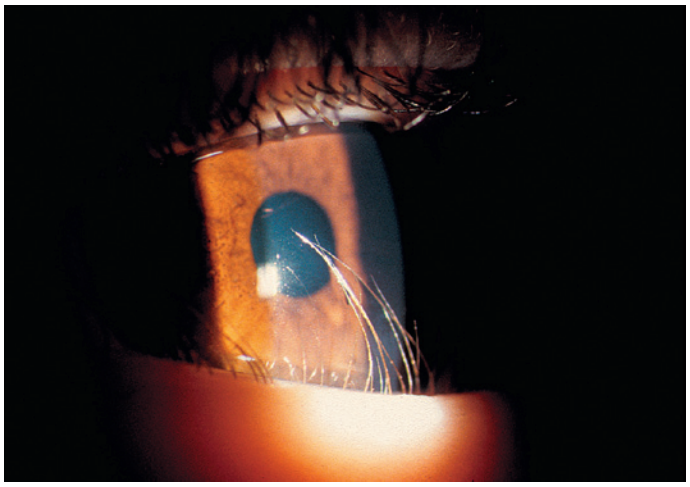


Fig. 19.2 Epiblepharon. In this child the lower lid lashes have turned in from birth, but the cornea has remained undamaged. Spontaneous improvement usually occurs.

Entropion

In congenital entropion the eyelid margin is inverted (Figs 19.3 and 19.4). This often requires prompt surgical intervention to prevent corneal infection and scarring. It should be distinguished from epiblepharon, where a skin fold causes a secondary turning of the lower lid lashes. Surgery is directed toward re-everting and stabilizing the eyelid with excision of skin and orbicularis, reattachment of the lower eyelid retractors to the inferior border of the tarsus, and then re-fixating the skin edges to the inferior tarsal border.

Tarsal kink/upper lid entropion

Congenital upper lid entropion is rare but often associated with a horizontal kinking of the tarsus. As with lower lid entropion, there is a risk of corneal scarring and infection. It can be corrected by incising the tarsus along the kink, and then repositioning the anterior lamella of the eyelid (Fig. 19.5).

Distichiasis

Distichiasis is a developmental abnormality in which a second row of cilia emerges from the meibomian gland orifices posterior to the normal eyelashes. The abnormal lashes may be asymptomatic or cause superficial corneal problems. If the patient is symptomatic or has significant corneal staining, treatment is indicated. Electrolysis is the treatment of choice, but is time consuming and has a high failure rate unless the lash roots can be exposed and destroyed directly. The lid is everted with a clamp under the microscope. A small, partial-thicknesss, vertical cut is made through the conjunctivalized surface of the tarsus to expose the whole eyelash from the lid margin to the lash root. This is then electrolyzed under direct vision. The alternative for large numbers of lashes is cryotherapy with a double freeze–thaw cycle for 20 seconds. In the upper lid, a gray line split between the anterior and posterior lamellae allows cryotherapy to be applied directly to the tarsus, avoiding damage to the normal lash roots and, in dark-skinned patients, discoloration of the skin. The posterior lamella is then advanced, leaving the raw surface of the tarsal plate to granulate. This prevents contraction of the tarsal plate leading to entropion.

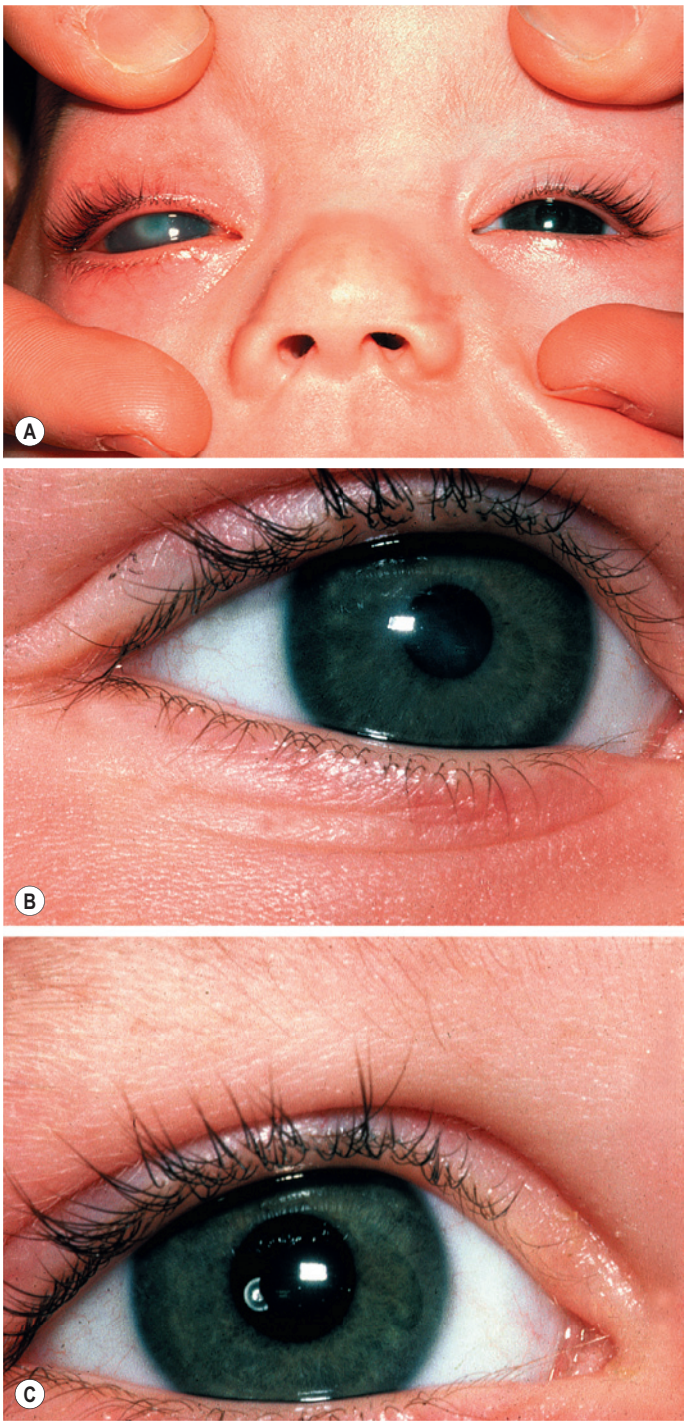


Fig. 19.3 Congenital entropion. (A) Shortly after birth this child's eye was found to be swollen. During examination under anesthetic right upper lid entropion was found with a corneal abrasion caused by the entropion. (B) After taping the lids, the entropion resolved, and (C) ultimately there was only minimal subepithelial opacity.

Epicanthic folds

Epicanthal folds are folds of skin that extend from the upper eyelid toward the medial canthus. The fundamental difference

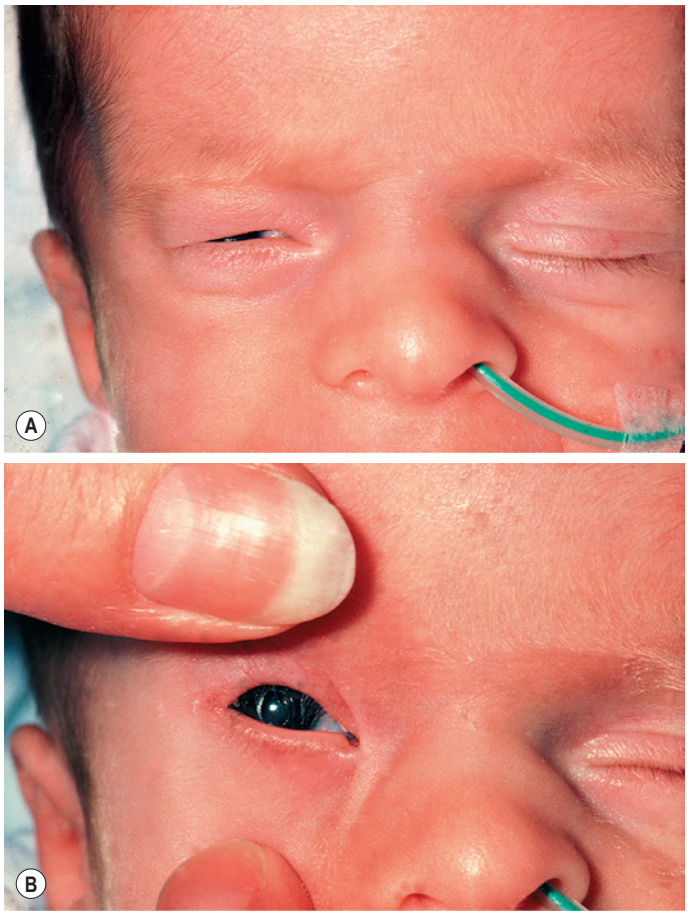


Fig. 19.4 Congenital entropion. (A) This child presented with irritability and an abnormality of the right lids, which were slightly swollen. (B) Same child with the lid everted, showing the lashes inturned and abrading the cornea without damage at this stage. It was treated with simple lid suture and resolved without complication.

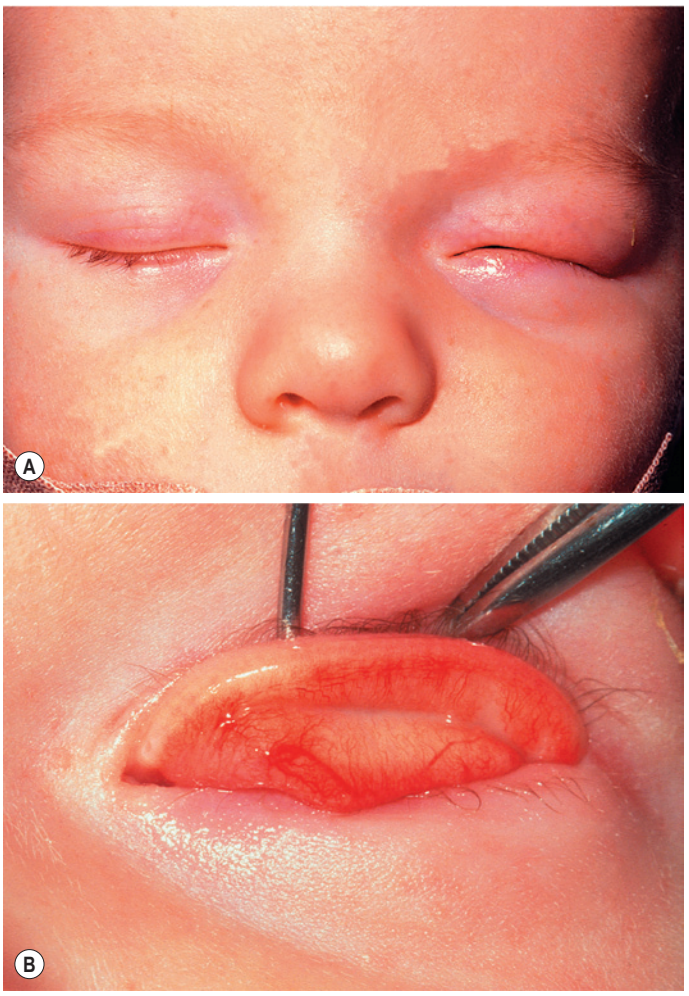


Fig. 19.5 Horizontal tarsal kink. (A) This child presented with a swollen and sore left eye with blepharospasm. (B) On eversion of the lid the horizontal kink in the tarsus can be seen. It runs the whole length of the tarsal plate, which is bent to 90°. It was treated by forced eversion using a strabismus hook to straighten the tarsus by force while the margin of the lid was held. This was followed by a week of lid suture, and the condition resolved following that treatment, but there was severe corneal scarring and the eye was blind.

between epicanthic folds and epiblepharon is that epicanthic folds are caused by a relative shortage of skin where the soft tissue is stretched tautly between the medial eyelid and the medial canthus instead of following the contour of the nasal angle. Epicanthic folds only require urgent treatment if they cause trichiasis or obstruct vision. They are largely an esthetic issue and become less prominent with development of the bridge of the nose and stretching of the overlying skin. As the folds represent lines of skin shortage, they can be broken up and lengthened with various different flaps. A simple epicanthic fold can be treated with a Z-plasty. Two separate Z-plasties can be used when a fold affects both the upper and lower lids. A mild epicanthic fold associated with telecanthus can be treated with a Y–V plasty and shortening of the underlying medial canthal tendon. If there is a marked epicanthic fold associated with telecanthus, a double Z-plasty can be combined with a Y–V plasty.[7,8]

Telecanthus

Telecanthus is an increased width between the medial canthi, with a normal interpupillary distance. If there is an overgrowth of bone with an increase in the interorbital and interpupillary width the condition is referred to as hypertelorism. Telecanthus can usually be improved by shortening the medial canthal tendons without involving a significant reduction in bone.[9] Mild cases can be treated by medial canthal plication with a non-absorbable or wire suture combined with a Y–V plasty. More severe cases may require transnasal wiring combined with a Y–V plasty. Posterior placement of the wire is necessary for a good cosmetic result. The thickness of the anterior lacrimal crest and medial orbital wall bone can be reduced with a burr at the same procedure. If a transnasal wire is required, it is essential to have preoperative radiologic evidence of the height of the cribriform plate to avoid damage to the intracranial structures. The correction of hypertelorism requires craniofacial surgery to mobilize the orbital rims and reduce the intervening ethmoid bones.

Blepharophimosis

Blepharophimosis means "small eyelids." In the blepharophimosis syndrome, the horizontal palpebral aperture is reduced

and this is associated with epicanthus inversus, ptosis, and telecanthus. Treatment is directed first toward promoting visual development and then improving cosmesis.

If the resting lid level obstructs a significant part of the pupillary aperture or causes astigmatism, urgent ptosis surgery is indicated. This is to prevent amblyopia and strabismus, which are common.[10] It usually involves a frontalis sling with non-autogenous material that, in severe cases, may be indicated in the first few months of life. The procedure may need to be repeated if the lid level drops and, again, starts to occlude the pupillary aperture.

When the child is about 3½–4 years old, a decision can be taken about if and when to repair hypertelorism, telecanthus, and epicanthic folds. Various techniques have been described to rearrange the medial canthal tissues, but a simple Y-to-V advancement with medial canthal tendon plication, or, in the case of more severe telecanthus, transnasal wiring, is most effective. The epicanthic folds can be corrected at the same time or left until the bridge of the nose has developed at puberty, which may by itself improve the cosmesis. After any medial canthal surgery there may be a need to correct residual ptosis. This usually involves a frontalis sling procedure using autogenous fascia lata or temporalis fascia, as the levator function is very poor (Fig. 19.6). Any lateral canthoplasty to widen the horizontal palpebral aperture is best delayed until after puberty when there is less scarring.

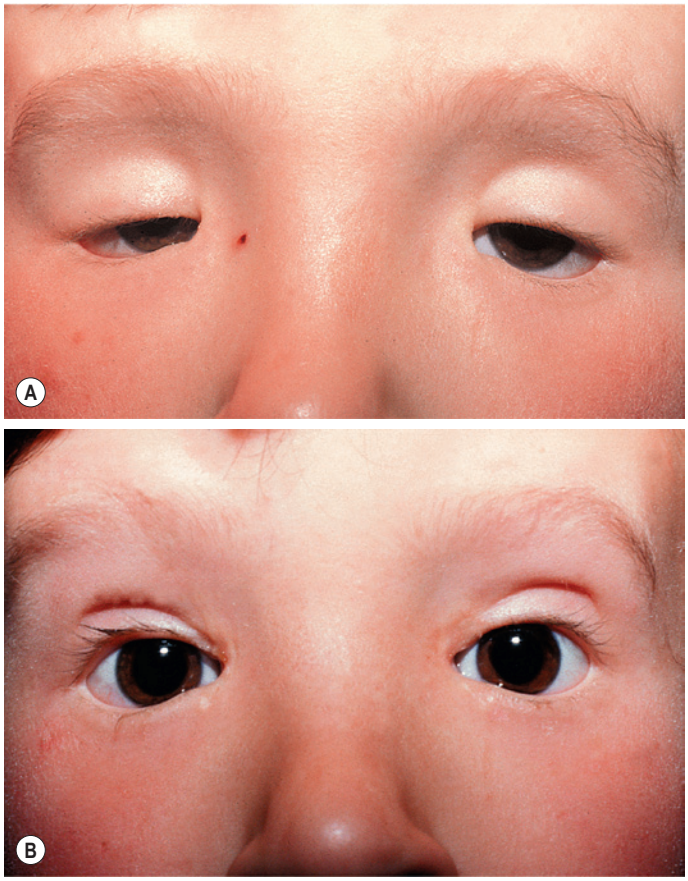


Fig. 19.6 Blepharophimosis. (A) This patient has blepharophimosis syndrome with blepharophimosis, ptosis, and telecanthus. (B) The same child after Y–V canthoplasties followed by brow suspensions with autogenous fascia lata.

Management of congenital and acquired ptosis

Congenital ptosis is usually associated with a dysgenesis of the levator muscle. There is a direct relationship between the levator muscle function, i.e. the excursion of the upper lid between full upgaze and downgaze, and the number of healthy striated muscle fibers. This is the main factor influencing the choice of ptosis surgery. Causes of acquired ptosis include aponeurotic defects, third nerve palsy and associated syndromes, Horner syndrome, ocular myopathies, and myasthenia. These will influence the choice of surgery by affecting Bell phenomenon, levator function, the variability of ptosis, etc.

History and examination

A careful history to confirm the congenital or acquired nature of the condition and associated phenomenon is important. With congenital ptosis, the parents may report that the condition seemed to improve initially after birth and then plateaued after a few months.

A full eye examination should be performed, with attention to the position of the lid on downgaze, levator excursion from down- to upgaze, extraocular motility, facial or eyelid dysmorphism or mass, aberrant movements of the lid associated with ocular or jaw movements, pupillary size and reactivity, and variability in eyelid height. Best corrected visual acuity, fixation preference, and retinoscopy or subjective refraction should be performed to rule out associated amblyopia. Further investigations may be indicated, for instance with third nerve palsies or Horner syndrome.[11] Early acquired Horner syndrome may be associated with neuroblatoma in the cervical region or internal carotid abnormalities. True congenital Horner syndrome should have associated heterochromia, the ipsilateral iris having lighter pigmentation.

The degree of ptosis should be assessed by comparing the vertical interpalpebral aperture measurements on both sides and assessing the height of the lid above the corneal reflex from a spot source of light (margin–reflex distance). This obviates inaccuracies from malposition of the lower eyelid. The levator function should be measured by pressing over the brow to prevent any frontalis action and then measuring the excursion of the lid between full up- and downgaze, if the child is old enough to cooperate. The position of the skin crease on both sides and the presence or absence of Bell phenomenon should be noted, as well as orbicularis strength.

Treatment

This depends on the diagnosis and physical findings. Surgical correction is urgent only if there is a risk of amblyopia because the eyelid is inducing asymmetric astigmatism or occluding part of the pupillary aperture. Even in the setting of severe unilateral ptosis, a chin-up head position is often adopted to maintain binocular fusion. Hence, ptosis surgery often may be delayed until the child is old enough for an accurate assessment of levator function, but regular examinations to monitor amblyopia are mandatory. Underlying strabismus should be corrected before undertaking ptosis repair, as eyelid height may be affected by strabismus surgery.

With congenital ptosis, the levator function and degree of ptosis govern the choice of operation. In mild congenital

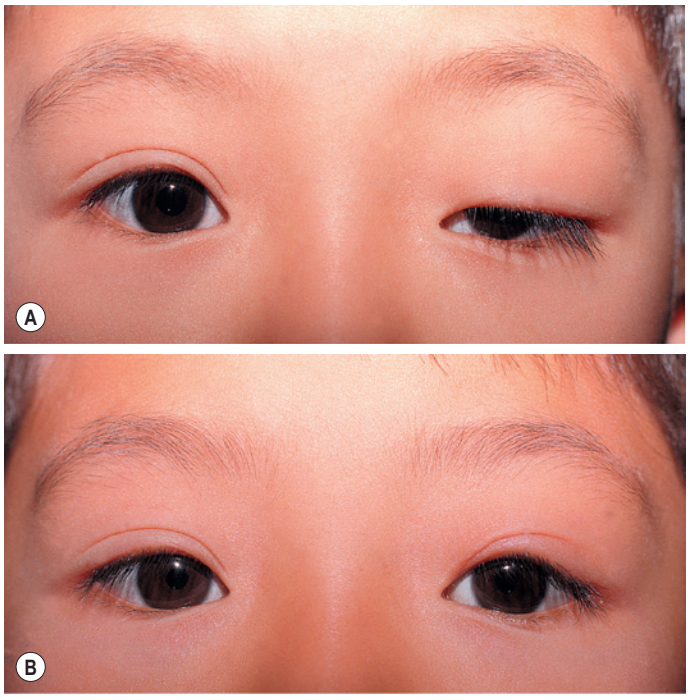


Fig. 19.7 (A) Unilateral simple congenital ptosis. (B) The same child after levator resection.

ptosis, if there is about 2 mm of ptosis with good levator function of 10 mm or more, a Fasanella Servat procedure or Müller muscle resection predictably elevates the eyelid.

In moderate congenital ptosis with levator function between 5 and 10 mm, a graded levator resection, depending on the amount of levator function and degree of ptosis (Fig. 19.7), is attempted. Either an anterior or a posterior approach to the levator can give satisfactory results. The posterior approach has the advantage that the resected levator muscle is held by pull-out sutures that are tied in the skin crease. If an overcorrection occurs, these can be removed in the early postoperative period and the eyelid lowered. The anterior approach is suitable for a maximum levator resection; it allows wider exposure of the levator muscle and the creation of an enhanced lid fold by directly fixating skin to the underlying distal edge of the cut levator muscle. The disadvantage of a large levator resection is that it increases lagophthalmos and lid lag on downgaze.

In severe congenital ptosis with less than 5 mm of levator function, a frontalis sling is usually necessary. The success of this procedure relies on the intrinsic reflex recruitment of the ipsilateral frontalis muscle. Internal attachment between the frontalis and the eyelid is carried out so that frontalis elevation results in a more efficient eyelid elevation. If it is necessary to elevate an eyelid urgently to prevent amblyopia, this can be done with a unilateral procedure using a non-autogenous material. Many materials have been utilized, but non-autogenous materials carry risk of infection, extrusion, migration due to "cheese-wiring," or degradation with breakage or loss of strength. Of the various options, a 4-0 prolene suture, 3-0 Supramid, or 1 mm silicon rod are the simplest to insert and do not carry the risk of granuloma formation associated with integratable materials such as Mersilene mesh or Gore-Tex. If there is no concern about amblyopia, it is better to wait until the child's leg is large enough to harvest autogenous fascia lata (usually 3–4 years) to use as the sling material. A pentagonal sling with opening of the eyelid crease and direct suturing the sling material to tarsal plate allows for excellent symmetry of eyelid creases. Intraoperative adjustment of lid height and contour can be effected depending on placement of the fixation sutures on the tarsal plate. Controversy exists as to whether unilateral ptosis with poor levator function should be treated with a unilateral sling or whether better symmetry can be achieved by excising the normal levator muscle and lifting both eyelids symmetrically with a bilateral brow suspension (Fig. 19.8). Excellent symmetry in the primary position can usually be obtained with unilateral surgery, but asymmetric lid lag will be visible in downgaze. Bilateral surgery involves sacrificing the normal anatomy, which may be unacceptable to some parents. Although excellent symmetry may be obtained if both brows work symmetrically, asymmetrical swelling or bleeding at the time of surgery may produce some degree of asymmetry in the final lid levels. A frontalis sling is usually ineffective if there is amblyopia, as there will be no stimulus for recruitment of the frontalis to clear the visual axis if there is no drive to obtain binocular vision. In this case, a maximal levator resection may be performed. The levator muscle is dissected free of it attachments, including Whitnall ligament, and the muscle maximally resected (up to 30 mm) and re-sutured to the tarsal plate through an anterior approach. The goal is to leave the eyelid margin at the level of the superior limbus. This approach may lead to lagophthalmos and exposure keratopathy, but most young patients will tolerate this with the aid of initial aggressive corneal lubrication. Lagophthalmos usually improves over time because a severely dysgenetic levator muscle is heavily infiltrated with fatty tissue and tends to stretch, but this can also lead to recurrence of the ptosis over time.

Specific conditions

In the blepharophimosis syndrome, levator function is usually poor and bilateral autogenous fascia lata brow suspensions are required. If the levator function is good, bilateral levator resections can be performed. The epicanthus inversus is usually best treated with a medial canthoplasty about 6 months before the lids are lifted.

In Marcus Gunn syndrome, if the jaw-winking element is unobtrusive, the ptosis alone can be corrected based on the levator function. If the jaw-winking is severe, it can be abolished or diminished by transecting the levator muscle and attaching it to periorbita behind the supraorbital rim. The ptosis must then be corrected with a brow suspension procedure. In some patients, the "wink" becomes less noticeable over time if they learn to control their jaw movements. It may be justifiable to delay surgery until the child is old enough to determine the ultimate degree of jaw-wink.

With cranial nerve III lesions, the eye should be straightened first with strabismus surgery. Correction of the ptosis depends on the levator function. If Bell phenomenon is defective, there is a risk of exposure keratitis, and ptosis surgery should be more conservative. Congenital third nerve lesions may often display aberrant innervation with cross-signaling between the medial rectus and levator palpebrae superioris (see Chapter 84). In this case, extirpation of the levator and frontalis sling surgery is required. A similar approach is used if there is cyclic third nerve dysfunction.



Fig 19.8 (A) Left ptosis with poor levator function in a 6-month-old baby. It can be seen that there is no lid crease on the right while it is present on the left. The child is looking down during this photograph and the normally ptotic lid is slightly higher than the normal lid. The failure of the affected levator to relax in downgaze suggests a dysgenetic etiology. (B) Same child at 2 years of age preoperatively. (C) Same child after a bilateral levator sling procedure.

Horner syndrome usually does well with a Fasanella Servat or Müller muscle resection procedure.

Patients with myasthenia gravis should first be managed medically. If ptosis persists, silicone rod frontalis sling allows elevation of the eyelid and postoperative adjustment of eyelid height, if necessary. The two ends of the rod are attached to each other by placing them through a Watzke sleeve; the ends are left long with about 1 cm of excess rod on either side. If necessary, the eyebrow incision may be re-opened later over the sleeve to loosen the sling.

Aponeurotic defects occurring congenitally, traumatically, or secondary to blepharochalasis syndrome should be repaired by advancing the levator aponeurosis. This is best done under local anesthesia when the child is older, so that eyelid height and contour can be adjusted intraoperatively.

In the congenital cranial dysinnervation disorders (see Chapter 83), a brow suspension with careful postoperative management to prevent exposure may give good results.

Lid retraction in infancy

Lid retraction in infancy can be caused by various conditions. Major lid retraction with corneal exposure requires urgent treatment with lubrication and early surgery to protect the cornea. Cases of mild lid retraction may benefit from cosmetic surgery that may be delayed into early childhood.

The upper lid can be lowered and the lower lid elevated by recessing the lid retractors, provided there is no shortage of skin or conjunctiva. Upper lid retractor recessions through a posterior approach can be used to release Müller muscle and aponeurosis and correct up to 2 mm of lid retraction. However, posterior approach upper lid retractor recessions inevitably cause a raised skin crease. This does not matter in mild or bilateral cases, but is important in severe unilateral cases. In these, the retractors should be lengthened via an anterior approach levator recession or Z-myotomy, or a spacer graft, and the skin crease reformed at the desired level. More recently, transverse blepharotomy has proven useful, with full-thickness transverse blepharotomy followed by skin closure. Lower lid retraction may be corrected by retractor recession, usually in combination with a spacer graft.[12]

Seventh nerve palsy

In the newborn, the incidence of facial palsy is 0.2%. Birth trauma is the cause of 78% of facial paralyses in this group, and can be caused by forceps delivery, pressure from the maternal sacrum, pressure from the fetal shoulder, or intracranial hemorrhage. Nearly 90% of newborn facial palsies completely recover without treatment, usually by 5 months of age.[13] In infancy or childhood, acquired facial palsy is most often associated with otitis media and mastoiditis, or idiopathic Bell palsy, which is less common in children than in adults. It is manifest as a sudden onset of paralysis of all five divisions of the facial nerve without signs of ear or cerebellopontine angle disease. It is bilateral in 0.3–2% of cases, and recurrent in 9% of cases.

In bilateral palsies, the resultant disability is dramatically more severe, and can be associated with severe feeding problems. In the newborn it may be associated with Möbius syndrome (see Chapter 83). In childhood, the most common cause in endemic areas is Lyme disease, followed by otitis media and idiopathy.[14]

Although facial nerve palsy in children has a good prognosis, it may be the initial manifestation of a life-threatening disorder such as an intracranial neoplasm or vascular malformation.

If there are other neurologic findings, imaging studies are indicated. Progression of facial nerve palsy is usually due to a tumor; in 20% of patients with recurrent facial weakness, a tumor is eventually discovered.

The main problems caused by a seventh nerve palsy are corneal exposure, paralytic ectropion, epiphora, and poor cosmesis.[15]

Corneal exposure

Corneal exposure does not usually result from poor lid closure alone, as Bell phenomenon is good in infants; there are usually additional risk factors. These include inadequate Bell phenomenon, reduction in corneal sensation, lower lid ectropion, treatment on a ventilator, prematurity, or reduction in tear production if the lesion is proximal to the geniculate ganglion. A reduction in corneal sensation is more common after surgical treatment of intracranial tumors, although it may be present in Möbius syndrome.

Initial treatment is with lubricants, taping at night, and occasionally occlusive dressings may be required. The lubricants can be stopped for 2–3 hours a day, or the other eye patched in order to avoid amblyopia. Occasionally, a temporary lateral tarsorrhaphy may be required to protect the cornea. If there is continued corneal exposure after 6 months, or earlier if there is no chance of recovery, the palpebral aperture can be reduced permanently. The vertical palpebral aperture can be reduced by raising the lower lid with a lateral tarsorrhaphy and medial canthoplasty, by lowering the upper lid with a recession of Müller muscle and the levator muscle, or with a full-thickness blepharotomy. Lid closure can be improved mechanically with upper lid gold weights or springs.

Paralytic ectropion

Paralytic ectropion can be treated by a medial canthoplasty. If required, this can be combined with lateral canthal tightening.

Epiphora (see Chapter 21)

Epiphora is due to the loss of the lacrimal pump mechanism and is exacerbated by lower lid ectropion. Persistent watering after 6 months may be improved by correction of any ectropion with a lateral canthal tightening and medial canthoplasty.

Watering may also occur due to "crocodile tears" in which tearing is associated with salivation due to aberrant innervation of the lacrimal gland by parasympathetic fibers intended for the salivary glands. Crocodile tears may be improved by injections of 2.5 units of botulinum toxin into the palpebral lobe of the lacrimal gland, but this requires a general anesthetic in a child. Severe epiphora of any cause may require a Lester Jones tube: this is difficult to manage in a small child.

Cosmesis

Surgery to raise the brow, reduce the palpebral aperture, and correct ectropion may help. Lower facial paralysis tends to cause progressive facial asymmetry; facial slings or nerve grafting may help restore facial tone and position.

Lid tumors

Nevi

Surgery for nevi is indicated if there is malignant potential, amblyopia due to lid malposition, and for cosmetic reasons.

Large, or giant, congenital nevi are associated with a risk of malignant transformation. The risk is proportional to the size of the lesion and may be up to 20% in very large congenital hairy nevi. The incidence of malignant transformation in small and medium congenital nevi is controversial, but probably is negligible. Divided nevi ("kissing nevi") are a form of congenital melanocytic nevus that involves mirror surfaces of the upper and lower lids (Fig. 19.9). Malignant transformation has not been reported in congenital nevi limited to the eyelids. Peak onset of malignant transformation occurs by 2–3 years of age. The lesions are difficult to treat due to their size. Surgery may require numerous stages, with skin grafts and flaps, and the use of tissue expanders. The multiple procedures may result in marked scarring. Dermabrasion, within the first few months and preferably weeks of life, may reduce the chance of malignant transformation, improve cosmesis, and reduce the extent of further surgery.[16]

Acquired nevi are rarely a concern in children, but these lesions are monitored.

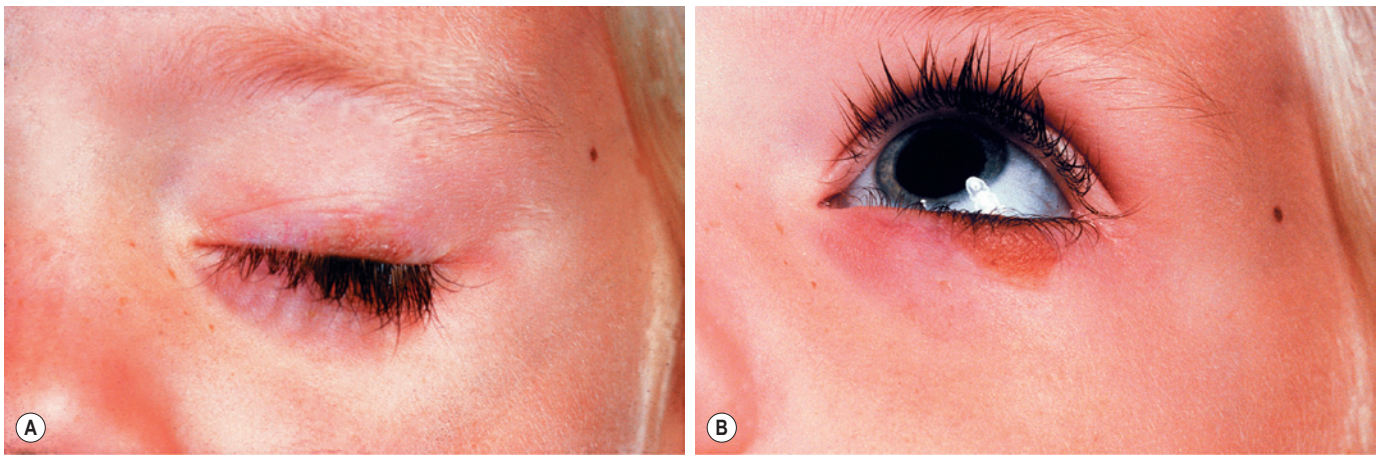


Fig. 19.9 Divided nevus.



Fig. 19.10 Large molluscum contagiosum lesion. *(Dr Susan Day's patient.)*



Fig. 19.11 Molluscum contagiosum showing multiple lesions and a follicular conjunctivitis.



Fig. 19.12 Molluscum contagiosum showing "kiss" lesions on upper and lower lids.

Molluscum contagiosum

Molluscum contagiosum are viral lesions that frequently occur on the eyelids (Fig. 19.10). They may rarely obtain large size; "kissing" lesions may occur on the upper and lower lids (Fig. 19.11). They are often associated with a follicular conjunctivitis (Fig. 19.12), which does not resolve until the lesions near the eyelid are eradicated (see Chapter 16). Treatment modalities include curettage and diathermy of the core of the lesion, cryotherapy, and chemical ablatives.

Juvenile xanthogranuloma

Juvenile xanthogranuloma (see Chapter 27) is a benign disease characterized by the development of small yellowish rubbery cutaneous lesions, including eyelid lesions, measuring 1–10 mm, in the first 1–9 months of life. They are occasionally associated with ocular xanthogranuloma lesions, particularly in the iris; spontaneous hyphema and glaucoma may result.

Complex choristoma

These are rare lid tumors that consist of variable combinations of ectopic tissues (see Chapter 29). They resemble other choristomas such as dermoids and lipodermoids. When acinar elements compose the majority of the tissue, they may have a fleshy appearance or resemble an ectopic lacrimal gland. Mild growth may occur during puberty, but malignant transformation is very rare. They can involve the underlying tissue. Conjunctival lesions may involve the underlying globe; therefore, excision is performed with caution.

Pilomatrixoma (calcifying epithelioma of Malherbe)

A small hard nodule in the eyebrow is likely to be a pilomatrixoma. The overlying skin is intact and may have a pink to purple discoloration. It may be mistaken for a chalazion or dermoid. Treatment is excision.

Lid hamartoma

Lid hamartomas include infantile hemangiomas (see Chapter 20), plexiform neurofibromas (see Chapter 68), lymphangiomas (venolymphatic malformations) (see Chapter 20), and congenital nevi.

Indications for surgery for plexiform neurofibroma and lymphangioma include mechanical ptosis, occlusion amblyopia, astigmatic anisometropic amblyopia, and cosmetic deformity. Surgery for both these lesions is challenging. The lesions may be extensive, involving the lids, orbits, and surrounding facial tissues. Due to their infiltrative nature there may be an increase in growth around puberty. Treatment should be planned in conjunction with allied surgical specialties. In general, less surgical intervention is better than more. Serial procedures may be necessary over the lifetime of the patient.

Meibomian gland diseases

Chalazia (meibomian cysts)

A chalazion is a lipogranulomatous inflammatory reaction of the meibomian gland that results from obstruction of the gland duct and is usually located in the mid-portion of the tarsus. It may occur on the lid margin if the opening of the duct is involved. A secondary bacterial infection of the surrounding tissue may develop with swelling of the entire lid. Chalazia may cause pressure on the globe and induce astigmatism. Most chalazia ultimately resolve spontaneously; this may be

hastened by frequent application of warm compresses. These can be made using a cup of uncooked rice placed in a thin sock and heated for 1 minute in a microwave oven. If the chalazion is inflamed or secondarily infected, treatment with oral azithromycin (once a week for 3 weeks) is often helpful. There is little role for topical antibiotic drops or ointment since these do not penetrate the tarsal plate. Incision of the posterior tarsal wall of the lesion and curettage is sometimes necessary. This is avoided whenever possible in young children since it requires general anesthesia. Chronic meibomitis and blepharitis may predispose to recurrent chalazia, and can be treated by lid cleaning and antibiotic/hydrocortisone ointment and oral azithromycin (see Chapter 16).

Other diseases of the meibomian glands include the following:

1. absent or deficient glands: primary congenital ectodermal dysplasia or ichthyosis, or secondary to lid disease;
2. replacement: primary distichiasis, or secondary distichiasis due to metaplasia;
3. meibomian seborrhea: associated with seborrheic dermatitis and acne rosacea. The meibum is greasy and solidified;
4. meibomitis: often occurs with blepharitis. The orifices are red and swollen and sometimes there is tenderness to palpation with associated lid edema. Treatment is similar to blepharitis.

Acute blepharitis

Acute blepharitis (see Chapter 16) presents with ulceration of the lid margins and is usually caused by *Staphylococcus aureus*, other organisms, and viruses, including *Moraxella* spp., herpes simplex, and various fungi in immunosuppressed patients (Fig. 19.13). Staphylococcal and *Moraxella* blepharitis usually respond well to antibiotic cream and lid hygiene.

Chronic blepharitis

Chronic blepharitis (see Chapter 16) is much more common than the acute form. It presents as irritable, red, and scaly eyelids that are sometimes edematous (Fig. 19.14). The anterior lid margin is usually most affected, but occasionally the posterior lid margin is more red and swollen when the meibomian glands are affected (chronic meibomitis). Chronic infection with *S. aureus*, *Propionibacterium acnes*, or coagulase-negative staphylococcal species may play a role.[17]

Most of the cases of chronic blepharitis have a seborrheic element with greasy, scaly lids associated in some cases with seborrheic dermatitis of the scalp (dandruff), or elsewhere.

Treatment is by regular lid cleaning, with particular attention to the lid margins. Expression of meibomian secretion by firm pressure may help the symptoms of burning and irritation. A 3-week course of oral azithromycin may be effective in reducing inflammation. Recurrent or severe cases, associated with keratoconjunctivitis, may be treated by a short course of steroid–antibiotic combination ointment.

Lid lice

Lid lice (see Chapter 16) are usually pubic lice rather than head lice because their body shape is more suited to the wider spacing of the lashes. They may be found on slit-lamp examination of the bases of the lashes; their eggs ("nits") may be found attached to the lashes. The pubic hair must be treated with a topical anti-lice shampoo. The lice and nits can be manually removed from the eyelashes and topical non-medicated ointment applied to the lashes three times a day will often asphyxiate remaining lice. Topical physostigmine or pilogel can be applied.

Trichiasis

Trichiasis is an acquired condition of the eyelash roots in which the cilia are misdirected posteriorly causing corneal and conjunctival irritation. In the large majority of cases, it is caused by subtle cicatricial entropion, as evidenced by the anterior migration of the mucocutaneous junction relative to its normal location at the posterior lid margin. The more common causes of trichiasis include chronic blepharitis, Stevens–Johnson syndrome, burns, trachoma, and pemphigus (usually in adults).

The treatment of trichiasis depends on the number of abnormal lashes. One or a few lashes can be treated with electrolysis or surgery to excise the lash roots or resect the affected portion of the eyelid margin. More numerous lashes are best treated with cryotherapy, but all the lashes in



Fig. 19.13 Acute blepharitis with lid ulceration and stye formation.



Fig. 19.14 Chronic blepharitis associated with chronic *Staphylococcus* infection.

the treated area are liable to be destroyed and it may cause depigmentation. In heavily pigmented patients, cryotherapy can be combined with a lid-splitting technique as described above for distichiasis. Tarsal fracture and rotation provides a superior cosmetic result, but may be followed by recurrence in cases of severe cicatricial entropion.

Socket management

Contracted socket

Early socket growth is rapid (see Chapter 6). At 3 months, the face is only 40% of its adult size; by 5½ years it is 80% of its adult size. The presence of an eye is necessary for normal orbital growth. The loss of an eye, microphthalmia, or anophthalmia all result in abnormal orbital growth, but lack of a normal globe during development *in utero* leads to much more severe socket hypoplasia than loss of an eye after birth. The aims of socket management in infants are to increase the size of the bony orbit, conjunctival space, and palpebral length, and to promote the normal development of the lid margins and lashes.

Treatment must be started early to avoid a poor esthetic result. If the patient has an orbital cyst associated with microphthalmos or anophthalmos, this may be left to aid socket expansion (see Chapter 18).[18] The socket soft tissues can be expanded using increasing sizes of orbital conformer. Expandable conformers that do not require serial changes and can be increased in size by injecting saline through a port have become available. These can be placed in the intraconal space and connected to a remote injection port under the skin (e.g. over the ear) or in the conjunctival sac with an anterior port directly accessible through the palpebral fissure.

An alternative is the self-inflating hydrogel expander. This is made of a modified copolymer of methylmethacrylate and vinylpyrrolidone, similar to contact lens material but with more capacity for fluid imbibition (i.e. the capacity to absorb fluid). It swells 10–12 times in volume, taking about 2–6 weeks to expand to its full size in the orbit.

Orbital volume replacement

Sometimes orbital expansion results in an increase in the anteroposterior dimension of the socket without increasing the palpebral fissure length and forniceal depth. The resultant conformer is round and deep and will not promote an increase in vertical and horizontal lid length, and will be difficult to retain. An orbital implant can be inserted, and a thinner conformer used to improve the fornices. Alternatively, if hydrogel expanders are used, a lens-shaped expander can be used to expand the conjunctival space, followed by a spherical expander for the orbit.

The lateral fornix is often difficult to enlarge. It may need to be constructed surgically with a mucous membrane graft in order to retain a prosthesis.

Orbital implants available include porous implants of hydroxyapatite and polypropylene, non-porous implants made from silicone and acrylic, and dermis fat grafts. The porous implants have the advantage that they may become integrated into the socket and may be less likely to extrude. However, their more abrasive surface may increase the erosion of the overlying conjunctiva and Tenon capsule, resulting in increased likelihood of exposure. There may be the option of pegging the porous implant to improve motility later. However, integration into the socket tissues makes these implants more difficult to remove if an implant needs to be replaced for a larger size. No study has supported the concept that porous implants give better motility unless they are pegged. Since pegging is rarely done due to a 30–40% incidence of complications, silicone or acrylic implants are generally preferred. Dermis fat grafts have several advantages.[19] In adults, they tend to atrophy, but in children they grow as the child grows and help with socket expansion. They may grow so much that they require debulking.[20] The conjunctiva can be attached to the edge of the graft, allowing the conjunctival epithelium to grow over the surface of the graft and increase the size of the conjunctival sac. If further volume augmentation is required, an orbital implant can be placed posterior to the graft.[21] The main disadvantage is donor site morbidity (usually the abdomen), although this is seldom a problem.

If treatment has failed to achieve adequate orbital expansion, resulting in marked facial asymmetry, craniofacial surgery may be required to augment or repair the orbit. Vascularized flaps to increase soft tissue may be used, for example, in cases of tissue atrophy secondary to radiotherapy.

Discharging sockets

Socket discharge is a common problem in patients with a prosthesis. The common causes are[22]:

1. prosthesis: poor fit, mechanical irritation, hypersensitive reaction, and poor prosthetic hygiene;
2. orbital implant: extrusion of implant, conjunctival inclusion cyst, and granuloma formation;
3. lid: poor closure and infected focus;
4. socket lining: contracture resulting in a mixture of skin and mucous membrane;
5. lacrimal system: defective tear production or drainage and dacryocystitis.

Management is to treat the underlying cause.

Lid and adnexal trauma (see Chapter 69)

Etiology

The majority of pediatric lid and adnexal injuries are accidental in nature, most commonly occurring during domestic activity, play time, or sporting activity.[23,24] Injuries from dog bites are frequent. Accidental penetration by common objects such as pencils or toys occurs frequently when a child stumbles and falls. Lid injuries include contusions, crush injuries, abrasions, lacerations, puncture wounds, and burns. These frequently occur in combination.

Immediate management

A history is taken, noting the time of the injury, nature of any projectile (was it sharp or blunt, metallic or vegetable), the speed of the projectile (was it thrown or shot), height of a fall and the type of surface the child landed on, any loss of consciousness, and any witnesses.

The assessment of the patient starts by examining and treating all injuries. Any necessary basic life support is given, and a full systemic examination may be required, including a neurologic examination if there is any suspicion of intracranial injury. It is not uncommon for long narrow objects such as pencils to penetrate the intracranial cavity via the orbit when a child carrying them stumbles and falls. A full ocular examination is performed. Visual function is assessed; if possible the visual acuity is taken. In a young child, one evaluates fixation and checks the patient's tolerance of occlusion of the uninjured eye. Check the pupil responses for a relative afferent defect.

The injury is assessed by looking for any damage not readily visible. A small penetrating lid laceration may have extensive underlying damage, including intracranial injury, orbital fractures, optic neuropathy, and injury to the globe. Avulsion injuries of the upper or lower eyelid (e.g. dog bites) are usually accompanied by canalicular injury; since this is the weakest part of the eyelid it is often the first to tear. The patient is examined for any evidence of a retained foreign body, missing tissue, and damage to the lacrimal system. The levator function should be noted in upper lid lacerations. If a large hematoma is present, there should be a greater suspicion of damage to the orbit and globe. Computed tomography (CT) scans are used to look for retained foreign bodies and fractures; magnetic resonance imaging (MRI) can be useful to look for a retained organic foreign body and more fully assess intracranial injury. Photographs are taken of any injury for future reference. A tetanus toxoid booster is given as appropriate.

The results of eyelid surgery are not prejudiced by waiting for up to 48–72 hours if this allows more time and better facilities to be available.[25] However, upon initial exam, the wound should be cleansed and irrigated copiously to prevent infection, subsequent tattooing, or retained foreign bodies. It is examined carefully and the tissues repositioned as accurately as possible. The skin can be closed with absorbable sutures, such as 6-0 Vicryl, avoiding a further anesthetic for suture removal. Tissue should not be excised or discarded, as the eyelid region has an excellent blood supply; any pedicle should be preserved. It is not usually necessary to cut or "freshen" the wound. In contaminated wounds such as animal bites, copious irrigation is paramount. Prophylactic intravenous antibiotics are given within 1 hour followed by a 1-week course of oral antibiotics.

After initial repair, major revision should be delayed for 6–9 months. At that time, secondary defects such as lid retraction or ptosis can be addressed unless the patient develops symptoms of corneal exposure that cannot be controlled with simple lubrication or is at risk of developing amblyopia.[25]

Lid margin defects require careful approximation of the lash line and tarsal plate to avoid lid notch, rotation of the lid, and lash abnormalities. The lid margin sutures are usually incorporated in the lash line sutures to prevent their coming in contact with the cornea.

Traumatic ptosis

Traumatic ptosis can be caused by:

1. direct injury or stretching of the aponeurosis or levator muscle;
2. loss of orbital contents or phthisical eye, lowering the fulcrum of the levator complex;
3. injury to the superior division of the third nerve or sympathetic nerve supply;
4. mechanical restriction due to conjunctival, lid, or deep orbital scarring.

Most levator defects should be sutured at the time of the primary repair; however, minor defects can be left, as they are likely to heal spontaneously and excessive surgery may lead to lid retraction. Residual ptosis may be repaired at a later date, usually after 6 months or after any improvement has ceased. Early intervention is indicated if there is any risk of amblyopia. A temporary frontalis sling using removable material such as a Prolene or Supramid suture or a silicone rod may be required. Secondary repair is via an anterior approach. Excision of the scar tissue may leave a gap in the levator complex, requiring a spacer. A dermis fat graft can be used to prevent the reformation of dense adhesions. Treatment of ptosis due to nerve injury is described earlier in this chapter.

Lacrimal drainage injuries

It was formerly believed that the lower canaliculus played a greater role in tear drainage than the upper system. Therefore, some authors recommended that only inferior canalicular lacerations be repaired. Studies of lacrimal scintigraphy after occlusion of either upper or lower punctum have concluded that both play an equal role in tear drainage; injury to either one deserves surgical repair. Although many patients will be asymptomatic as long one of their two canaliculi remains functioning, at least 10% of patients will have epiphora if one punctum is occluded. This increases to more than 50% when subject to globe irritation by exposure to the elements.

The canaliculus should be repaired by suturing the two severed ends over an indwelling silicone stent, which is usually left in place for 3 or more months. The white color of the canalicular epithelium can usually be seen with loupe magnification, although the aid of an operating microscope may be required. Injection of fluorescein-stained viscoelastic via the opposite punctum (or directly into the sac in cases of upper and lower canalicular damage) may help to identify the canaliculus. Use of a pigtail probe passed through the intact punctum in an attempt to find the lacerated cut end is controversial; it may damage healthy tissue (especially the older hooked instruments). With the use of an operating microscope, good hemostasis, and a thorough knowledge of the anatomy, this is seldom required.

If the canaliculi are to be anastomosed, they are intubated with a self-retaining monocanalicular stent, or with bicanalicular stents. The peri-canalicular soft tissues are closed with 7-0 Vicryl sutures. Care is taken to repair the posterior limb of the medial canthal tendon, which is immediately posterior to the medial canaliculus. This maintains the lid in apposition to the globe. In repairing the canaliculus, the sutures should be passed into the tissues immediately around the canaliculus and not through its epithelium.[26]

Common canalicular injury is repaired, or opened into the lacrimal sac, the canaliculi intubated, and a dacryocystorhinostomy performed.

Canalicular damage near the punctum can be treated by a retrograde dacryocystorhinostomy with marsupialization of the canaliculus into the conjunctival sac. Blockage near the lacrimal sac can be re-treated by excision of the scar and connection of the patent canaliculus to the sac. In either case, at least 8 mm of one canaliculus is necessary for success.

Medial canthal tendon injuries

The anterior limb of the medial canthal tendon seldom needs repair; however, if the posterior limb is damaged and only the anterior limb is repaired, the lid will be anteropositioned. The method of repair of the posterior limb depends on the posterior fixation point available. If the lacrimal drainage system is intact and there is a firm and reasonably positioned medial wall fixation point, the posterior limb and eyelid tissues can be directly attached to the medial orbital wall. If the lacrimal sac must be opened for dacryocystorhinostomy and the tissues behind the lacrimal sac are adequate, a non-absorbable suture can be passed behind the opened lacrimal sac and used to re-attach the medial canthus and eyelid tissues medially and posterior to the posterior lacrimal fascia. If there is no adequate ipsilateral fixation point, a "T-shaped" mini-plate can be attached to the anterior lacrimal crest and the tendon sutured to one of its posterior fixation points, or a transnasal wire can be used to reposition the medial canthus posteriorly.

Burns

In the acute stage, burns are treated with heavy lubrication or occlusive therapy to protect the cornea. To avoid amblyopia in the young child, the eye may be left for 2–3 hours a day without lubrication or the other eye can be patched. In severe cases of exposure, a conjunctival flap may be required to protect the cornea in the chronic stage. Cicatricial contracture of the eyelids is a frequent problem and tarsorrhaphies, lid-sharing procedures, split-thickness skin grafting, and Frost sutures may be necessary to protect the ocular surface. Re-operation is often required due to progressive wound contracture, which may continue for months. After 30 days, the lids are reconstructed. Split skin grafts may be required; lid-sharing procedures are avoided where possible to avoid the risk of amblyopia.

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Lid and orbital infantile periocular hemangiomas (capillary hemangiomas) and other vascular diseases

Christopher J Lyons

Chapter contents

TUMORS
VASCULAR MALFORMATIONS
REFERENCES

Vascular lesions of the orbit include tumors such as infantile hemangioma and hemangiopericytoma, as well as malformations such as venous-lymphatic malformations (lymphangiomas), orbital varices, and arteriovenous malformations. Infantile periocular hemangiomas (capillary hemangiomas) are common benign vascular tumors that are characterized by rapid growth during the first year of life and show regression over the next several years.[1,2] Venous-lymphatic malformations are vascular malformations that infrequently present in early childhood and are complicated by bouts of hemorrhage and rapidly progressive enlargement. Varices and arteriovenous malformations primarily present in the second and third decades.

Tumors

Infantile periocular hemangioma (capillary hemangioma)

Infantile periocular hemangioma, a hamartoma, is the most common childhood orbital tumor. It occurs more frequently in females than males in a ratio of 3:2 with no inheritance pattern.[3] There is an increasing incidence with prematurity and reduced birth weight: up to 23% in infants weighing less than 1000 g have at least one infantile hemangioma, compared with 1–4% of full-term infants.[4,5] It is distinguished from other orbital vascular lesions by spontaneous regression. Numerous techniques are available to manage this potentially disfiguring disorder, which can affect vision. There is no "one size fits all" approach for this unpredictable tumor; lesions that resolve rapidly with treatment could have done so without treatment. We are fearful of uncontrolled growth, as illustrated by Fig. 20.1. Treatment of periocular hemangiomas is a team effort involving pediatricians, dermatologists, and ophthalmologists. Decisions to treat are based on the position of the lesion, the potential for amblyopia, rapidity of growth, and discussion of risk/benefits with informed parents. Children must be followed closely, watching for rebound growth and for amblyopia.

The histopathology varies with the clinical phase: in its early proliferative phase, it consists mostly of numerous dividing endothelial cells; vascular spaces are rare and small. It is rich in mast cells, whose function is not clear. There may be numerous mitotic figures, which could lead to an incorrect diagnosis of malignancy in rapidly enlarging lesions. The characterization of poorly differentiated lesions may be helped by reticulin stains or by the identification of factor VIII, which is produced by the endothelial cells, using peroxidase or fluorescein antibody techniques.[3] In more mature tumors, vascular spaces are larger, with fewer flattened endothelial cells. The tumor is not encapsulated and tends to infiltrate surrounding structures. In the involutional phase, the endothelial cells are replaced by adipocytes and there is deposition of fibrous tissue.

The natural history of infantile periocular hemangioma, with its rapid enlargement followed by spontaneous involution, is unique for vascular tumors. The vascular endothelium expresses placenta-associated antigens,[6] which are not expressed by other vascular tumors or normal skin, leading some to speculate that infantile hemangiomas develop either from angioblasts abnormally differentiating toward placental vascular phenotypes or as the result of placental cell embolization into fetal tissues.[6,7] Infantile hemangiomas could also be the result of somatic mutations in a gene mediating endothelial cell proliferation. Alternatively, an endothelial progenitor cell could be implicated.[8] Hypoxia has also been implicated, either systemically or in localized areas of poorly perfused tissue. This could stimulate endothelial progenitor cells to proliferate inappropriately.[9]

Clinical features

One-third of infantile periocular hemangiomas (Fig. 20.2) are present at birth; all have appeared by the age of 6 months. The appearance of the tumor may be preceded by a faint cutaneous flush. Usually, rapid growth lasting 3–6 months is followed by a period of stabilization and then regression (Fig. 20.3). Margileth and Museles[1] found that 30% of 336 hemangiomas had regressed by the age of 3 years, 60% by 4 years, and 76% by 7 years.

Infantile periocular hemangiomas are most commonly found in the upper lid or orbit (see Fig. 20.3). Their appearance varies according to the depth of involvement (see Fig. 20.3A); superficial cutaneous lesions have a red lobulated appearance, giving rise to the name "strawberry nevus" (see Fig. 20.8A). These superficial lesions consist initially of a confluence of telangiectasias that progress to raised, nodular lesions. They may enlarge and become bluish in color with crying. Subcutaneous hemangiomas are often bluish in color. Lesions situated deep to the orbital septum may present with proptosis without cutaneous discoloration. Occasionally, the proptosis is severe enough to cause corneal exposure. One-third of hemangiomas involve several levels of depth. A deeply situated lesion causing only proptosis with no cutaneous signs may present a diagnostic dilemma. A helpful diagnostic sign is the increase in proptosis with crying (see Fig. 20.2). In 30% of patients, "strawberry nevi" are found at other cutaneous sites.[2] Occasionally, enormous growth occurs, obliterating facial structures (see Fig. 20.1).

Amblyopia is common with orbital infantile hemangioma, with a prevalence between 43% and 60%.[2,10] This can result from occlusion of the visual axis by a bulky tumor, but more often,



Fig. 20.1 Massive facial and orbital infantile periocular hemangioma (capillary hemangioma).

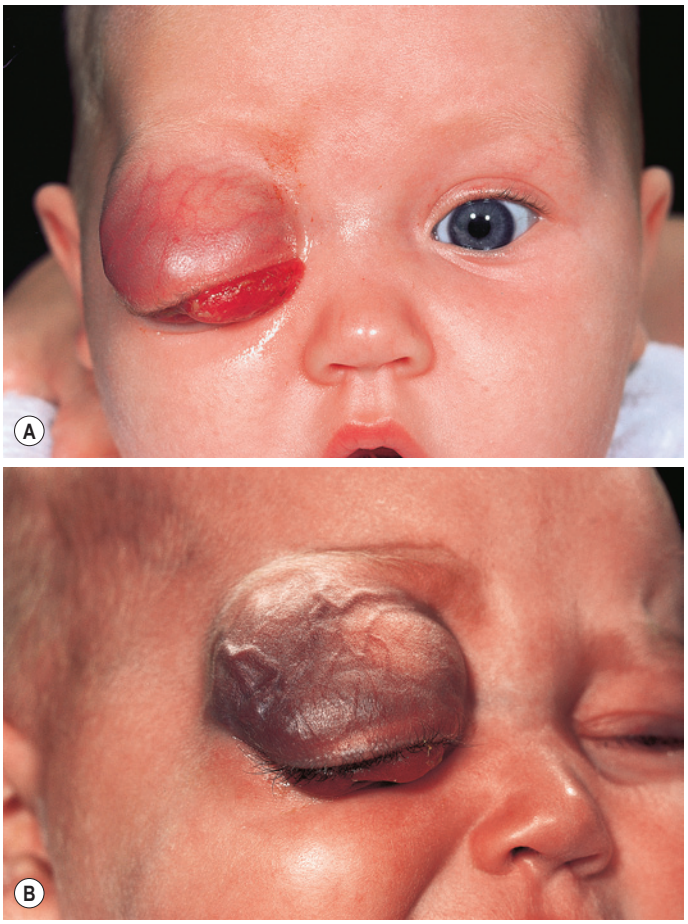


Fig. 20.2 (A) Infantile periocular hemangioma of the anterior orbit and lid. (B) Same patient when crying, showing engorgement and mild increase in size.



Fig. 20.3 (A) Orbital infantile periocular hemangioma. The mother of this child was accused of having injured her child. (B) Orbital infantile periocular hemangioma in a child aged 2 months. (C) Same patient as (B) aged 9 years after some spontaneous resolution and surgery. Surgery is usually not necessary and best avoided in most instances.

distortion of the globe by tumor causes corneal astigmatism; generally, the axis of the corrective plus cylinder is directed toward the tumor. This may persist after the hemangioma has regressed but usually resolves, at least partially, particularly if the hemangioma resolves or is treated early.[11,12] Prolonged occlusion can result in ipsilateral myopia[13] and the resultant anisometropia may be another amblyogenic factor. Secondary strabismus is common as a result of the interruption of fusion and binocularity.

Systemic complications of infantile periocular hemangiomas are rare; they include[3]:

1. Kasabach–Merritt syndrome: a potentially life-threatening coagulopathy resulting from consumption of fibrinogen and platelet entrapment within a large vascular hemangioma. It usually responds to platelet replacement and corticosteroids.
2. PHACE(S) syndrome (**p**osterior fossa abnormalities, **h**emangioma, **a**rterial lesions, **c**ardiac abnormalities, **e**ye and **s**ternal abnormalities): this condition has serious cardiovascular and neurologic complications and frequent ocular involvement, including amblyopia, strabismus, anterior polar cataract, ptosis, and optic neuropathy.[14] A careful ocular, cardiac, and neurologic examination is necessary for patients with extensive facial infantile periocular hemangiomas.

Investigation

In the majority of children presenting with proptosis, lid involvement or the presence of other cutaneous hemangiomas suggest the diagnosis.

Doppler ultrasound may help to secure the diagnosis.[15] The extent of the lesion can be assessed by computed tomography (CT) scanning. A soft tissue density mass is seen to infiltrate the orbit, with smooth or nodular margins, often crossing boundaries between compartments such as the muscle cone or orbital septum. Bony erosion may be seen. Enhancement is variable, according to the vascularity of the lesion and its stage of development. T2-weighted magnetic resonance imaging (MRI) is useful to delineate the tumor since the lesion is hyperintense due to its intrinsic blood flow (Fig. 20.4). T1-weighted gadolinium-enhanced views with fat suppression to improve contrast give the best assessment of the anatomic

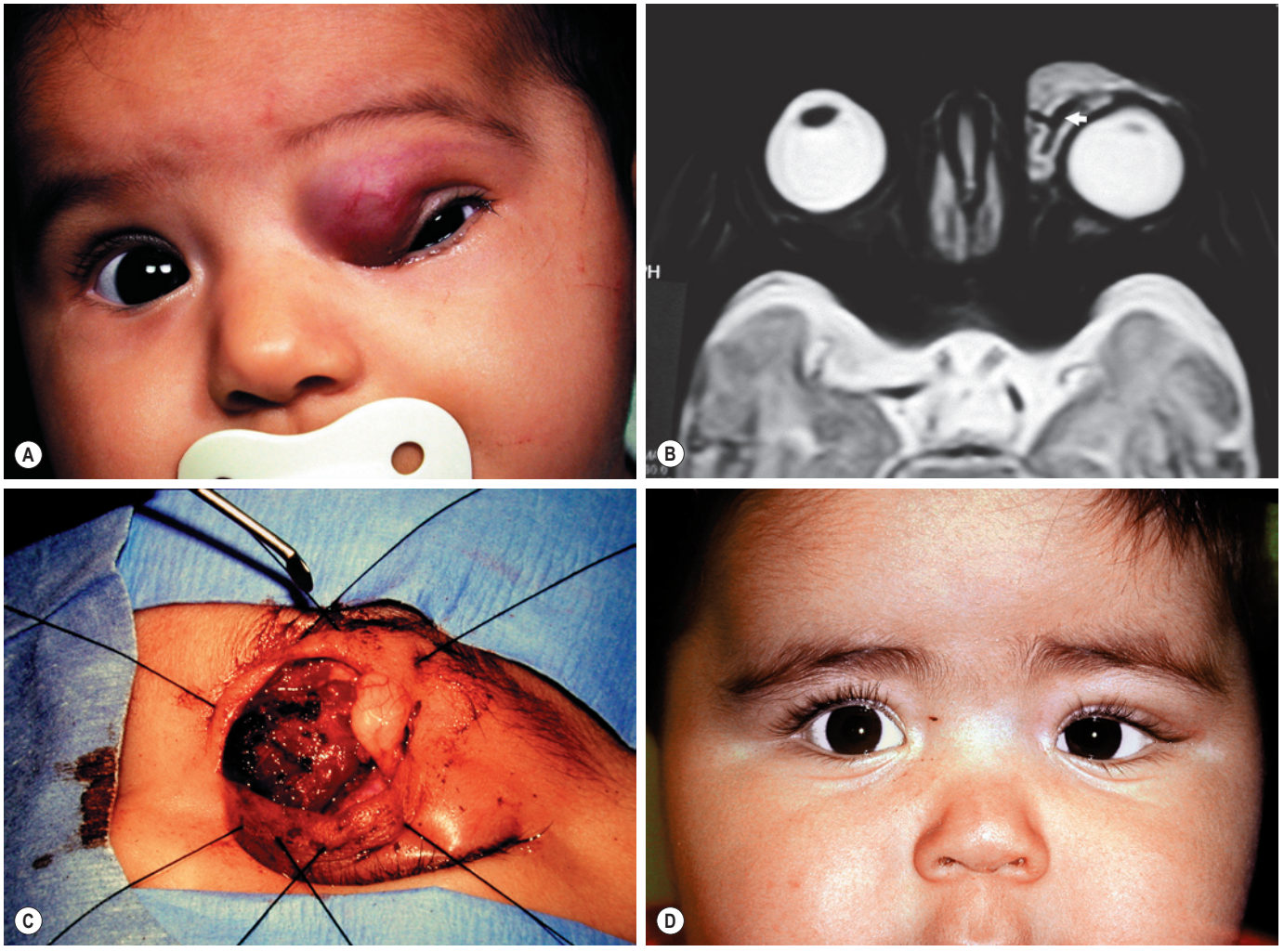


Fig. 20.4 (A) This child aged 2½ months presented with a large subcutaneous infantile periocular hemangioma that was unresponsive to steroids and inducing significant astigmatism. (B) T2-weighted MRI demonstrated a relatively well-defined anterior orbital mass with a large central flow void (arrow). (C) Operative photo of the same lesion during excision. (D) After surgery, she had minimal ptosis, and her astigmatism regressed. *(Patient of the University of British Columbia. (A) and (B) reproduced with permission from Rootman J. Diseases of the Orbit: A Multidisciplinary Approach, 2nd ed. Philadelphia: Lippincott Williams and Wilkins, 2002: 542.)*

relationships of the tumor. Obtaining a magnetic resonance angiogram and venogram (MRA and MRV) at the time of the MRI may rule out other vascular anomalies that can mimic hemangiomas. Lesions confined to the posterior orbit, especially during a period of growth, may occasionally be mistaken for a malignant tumor such as rhabdomyosarcoma; biopsy may be indicated.

Management

Management should be conservative, with treatment of significant refractive error and amblyopia while awaiting spontaneous regression (Fig. 20.5). The appearance of superficial pale stellate areas of scarring ("herald spots") on a "strawberry" lesion is a useful early indicator of spontaneous regression. Amblyopia therapy should be accompanied by correction of the astigmatic error of the affected eye with appropriate glasses (Fig. 20.6).

Active treatment to reduce the size of the tumor is only indicated if there is occlusion of the visual axis or if a posterior lesion results in progressive proptosis with optic nerve compression, corneal exposure, and significant or progressive amblyopia. Many methods of treatment are available. Topical or systemic beta-blockers are considered "first line."[16–19] Local or systemic steroids,[12,20,21] or surgical excision may be used for patients in whom beta-blockers are ineffective or contraindicated.[22] Cryotherapy is another potentially useful treatment modality.[23] Radiotherapy, laser,[24] and injection of sclerosing agents are rarely indicated.

A dramatic reduction was noted in the size of infantile hemangiomas (IH) in children treated with propranolol (Fig. 20.7).[25] At doses of 1–3 mg/kg/day, a response may be seen within a few days. Subsequent studies have shown a response rate of up to 90%; side effects such as hypotension, bronchospasm, bradycardia, heart block, and hypoglycemia can be avoided with careful monitoring.[16,17] This method of treatment is now the first choice for most ophthalmologists.[19] Topical timolol 0.5% solution or gel rubbed gently onto the surface of the IH twice daily is also effective, with fewer side effects than systemic treatment.

Steroids may still be a useful "second line" alternative to beta-blockers. Slow intralesional injection of a depot preparation such as triamcinolone (Kenalog)[26] results in tumor regression within 2–4 weeks. Further injections may be necessary (Fig. 20.8). Complications are rare but may include visual loss from central retinal artery embolization. Adrenal suppression,[3,20] local fat atrophy, skin hypopigmentation, eyelid necrosis, and periorbital calcification have also been reported.

Systemic steroids (1.5–5.0 mg/kg/day) may be preferable for very extensive or posteriorly situated lesions (Fig. 20.9). The response is over 90% for doses greater than 3 mg/kg/day but falls to less than 70% for doses of 2 mg/kg/day and less.[20] The side effects of growth retardation, gastrointestinal bleeding, behavior changes, and adrenal suppression make this therapy less attractive. A rebound increase in size has been noted after discontinuation of oral steroid.

Sight-threatening lesions that have failed to respond to beta-blockers or steroids may respond to treatment with interferon alpha-2a,[27,28] although the response to this treatment may be slow and the side effects uncertain in infants. Other immunomodulators, vincristine and cyclophosphamide, have been used to treat hemangiomas (primarily visceral). The

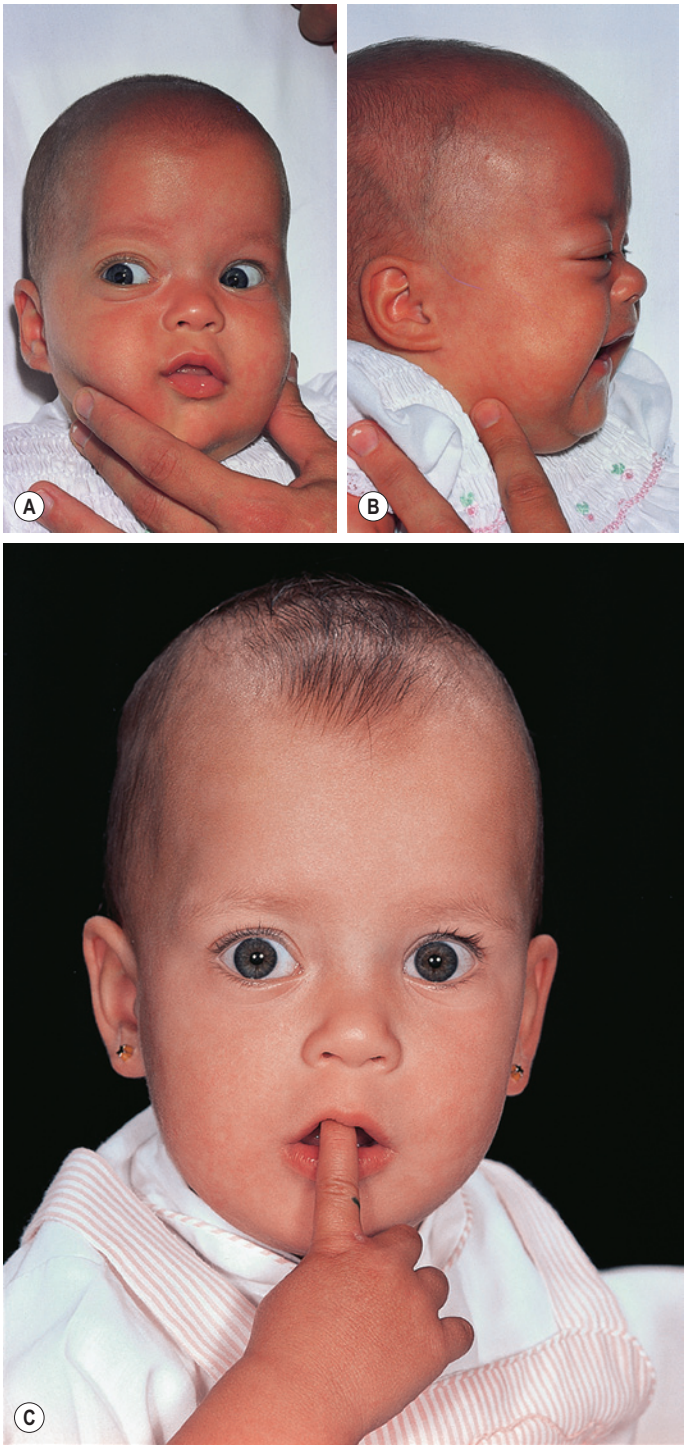


Fig. 20.5 (A,B) Right orbital infantile periocular hemangioma in a child aged 5 months. (C) Complete resolution without treatment.

carbon dioxide, argon, yttrium–aluminum–garnet (YAG), and dye lasers have been used to treat hemangiomas. Their use is limited by scarring, although the dye laser tuned to 577 or 585 nm with a 10-ms pulse duration may allow selective thermal damage of capillary tissue with minimal scarring and accelerated regression.[24,29] Radiotherapy and sclerosing agents should no longer be used.

Previously, surgical excision was deferred until the lesion stopped regressing, often after 6 or 7 years of age when any

residual cosmetic defect was corrected.[30] However, well-defined lesions causing significant amblyopia through obstruction or astigmatism can safely be removed surgically. The technique requires meticulous hemostasis, but the tumor is readily removed microsurgically after failure to respond to treatment with beta-blockers or steroids, or as a primary treatment[22,31] (Fig. 20.10).

Diffuse neonatal hemangiomatosis

This rare condition is characterized by the presence at birth or in the first month of life of multiple (sometimes 100 or more) hemangiomas involving the skin, bones and viscera.[32] These have similar growth and involutional characteristics to cutaneous infantile hemangiomas. Complications, related to visceral and notably liver involvement, include high-output cardiac failure, hemorrhage, involvement of brain or lung, as well as severe hypothyroidism.[33] These result in a mortality rate of approximately 60% for this condition.

Clinicians should recognize this rare disorder. Hepatic involvement, a significant risk factor, is more likely in infants with five or more cutaneous hemangiomas.[34] Treatment modalities include systemic corticosteroid, embolization, vincristine or interferon. More recently, propranolol has been shown to be effective.[35]



Fig. 20.6 Deep infantile periocular hemangioma in a 6-month-old boy. A faint bluish tinge is evident in the left lower lid. There is a +·4.0 diopter induced cylinder. Occlusion is vital in virtually every case. This child's inventive parents devised a novel method of preventing him from removing the patch. Eighteen months later the lesion had resolved, as had the cylinder. *(Patient of the University of British Columbia.)*

Hemangiopericytoma

This rare tumor, which ranges from benign to malignant, is derived from the pericyte. It is usually seen in adults but has been reported in childhood[36] and early infancy.[37] Its behavior is unpredictable; the usual presentation is with gradually



Fig. 20.7 (A) A large segmental infantile periocular hemangioma in a 4-month-old old girl causing inverse ptosis and astigmatism. The hemangioma had grown rapidly in the first month of life and was unresponsive to oral and intralesional steroid treatment. A systemic work up for PHACE syndrome was negative. (B) After 2 months of oral propranolol treatment, the size and thickness of the lesion decreased and the visual axis cleared. *(Courtesy of Tina Rutar.)*

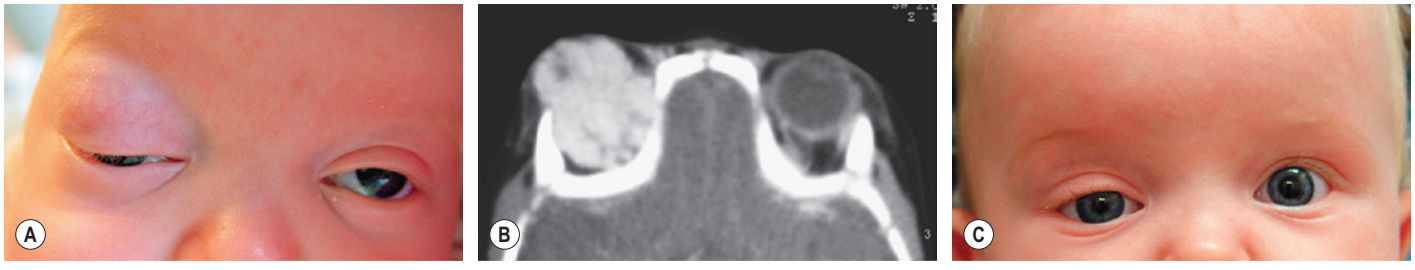


Fig. 20.8 This infant was born at 27 weeks' gestation. Right upper lid swelling was noted at age 6 weeks, and she was seen in our clinic at 16 weeks of age (A). (B) Computed tomography scan confirmed infantile periocular hemangioma showing a poorly defined, enhancing lesion in the superior orbit. An intralesional injection of 40 mg triamcinolone and 20 mg methylprednisolone was given at this time. Repeat injection was planned for 8 weeks later but was deferred due to her clinical improvement. Part-time occlusion of the left eye was used. (C) Three months later, she was equally visually attentive with each eye. No further treatment was necessary. *(Patient of the University of British Columbia.)*

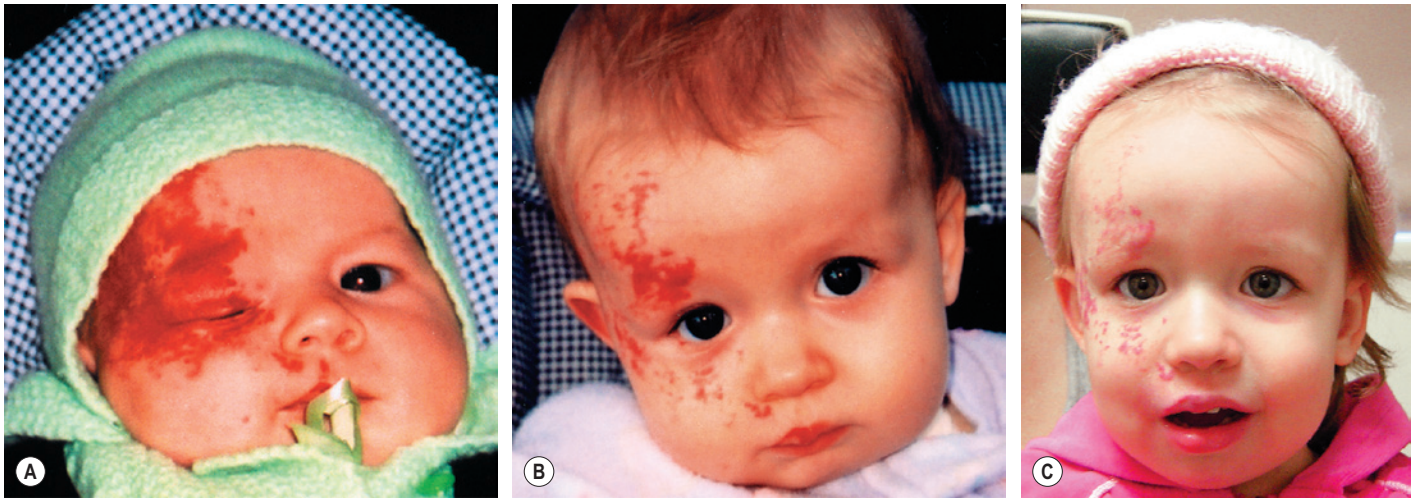


Fig. 20.9 (A) This 6-week-old infant was noted to have right upper lid swelling and discoloration from the second week of life, increasing on crying. There is complete closure of the right eye. Oral steroids were started at 6 weeks of age at 5 mg/kg/day, tapering to nothing over 6 months. (B) By 9 months of age, her cushingoid features have resolved; the infantile periocular hemangioma no longer obstructs the right visual axis. (C) At 11 months, the cutaneous changes have largely disappeared. There is no amblyopia. *(Patient of the University of British Columbia.)*

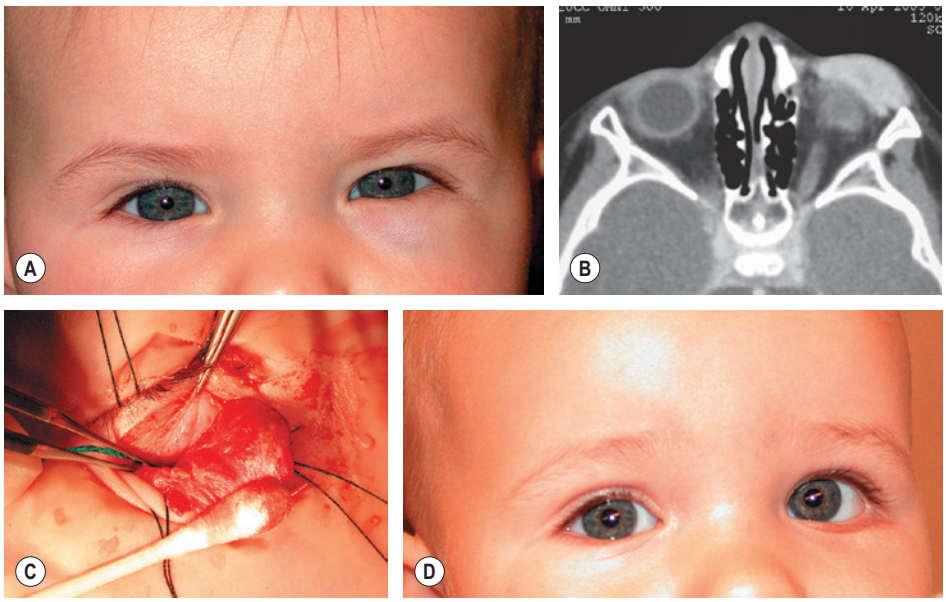


Fig. 20.10 (A) Clinical photograph of an 8-month-old child who presented with a progressive mass of the lower lid, causing astigmatism (+2.50 cylinder at 90°) and upward displacement of the left globe. (B) Contrast-enhanced CT scan demonstrates a relatively well-defined anterior orbital mass involving the left lid and inferior orbit. (C) Intraoperative photo of the same patient at the time of excision of the infantile periocular hemangioma. (D) One month after surgery, his astigmatism resolved. *(Patient of the University of British Columbia.)*

increasing proptosis and mass effect related to a tumor that is usually superiorly placed. On CT scan, it is well circumscribed, showing marked, homogeneous contrast enhancement. There is a pronounced early blush on angiography. It is usually a locally invasive tumor, which recurs locally unless completely excised within its pseudocapsule. This is technically challenging, as the tumor is very friable. Between 10% and 15% develop distant metastasis. Occasionally, these tumors behave very aggressively. In these cases, exenteration may be necessary.

Vascular malformations

Vascular malformations of the orbit are derived from venous (varices and venous-lymphatic malformations [lymphangiomas]) and arterial (arteriovenous malformations) vascular anlagen, and constitute an important cause of orbital tumors in childhood. They are best understood in the context of their hemodynamics and can be divided into three types.[38]

1. High-flow lesions such as aneurysm, arteriovenous fistula or malformation.
2. Low-flow lesions, which may be: venous malformations (distensible or non-distensible-cavernous) or lymphatic malformations (macrocystic, microcystic, or mixed).
3. Combined lymphaticovenous malformations, in which venous or lymphatic components may be predominant.

Venous-lymphatic malformations (lymphangiomas)

These vascular anomalies usually arise in childhood and are often difficult to manage. They may enlarge gradually, but their expansion can be sudden from hemorrhage into the lesion. Unlike infantile hemangiomas, they do not undergo

spontaneous regression. Deeply situated lesions are difficult to excise; their margins are poorly defined and they arborize widely throughout the orbit.

Venous-lymphatic malformations (lymphangiomas) account for a small proportion of orbital tumors.[39] In one-third of cases, the lesion is apparent at birth or within the first weeks of life,[40] and over three-quarters of patients present in the first decade. A female preponderance (ratio 2–3 : 1) has been reported.[40]

Their occurrence within the orbit is puzzling in view of the absence of lymphatic drainage from the retroseptal tissues. It has been suggested that venous-lymphatic malformations arise from primitive vascular elements within the orbit.[41] However, ultrastructural analysis and immunochemistry have identified lymphatic endothelium in orbital venous-lymphatic malformation.[42] They do not appear to grow by cellular proliferation; the full extent of the malformation is present at birth, insinuating itself within the normal orbital tissues. Since the vascular channels have characteristics of both lymphatic and venous vessels, the histologic differentiation of venous-lymphatic malformations from orbital varices has been a source of debate.[43–45] Hemodynamically, venous-lymphatic malformations and varices are part of a continuum of venous-derived lesions, differentiated according to the presence or lack of connection to the venous system. Whereas varices are connected, and therefore expand with Valsalva maneuver or supine posture, venous-lymphatic malformations are isolated and do not. Lesions may be mixed with both venous and lymphatic components represented within a single mass. The extremes of the spectrum can be differentiated histopathologically; the venous-lymphatic malformations element has distinctive electron microscopic features.[46] The pathogenesis of these lesions relates to the lack of blood flow and the tendency for sludging, neovascularization, hemorrhage with recurrent inflammatory episodes, and the formation of isolated "chocolate cysts."[47]

Histopathologically, they consist of diaphanous, serous fluid-filled channels lined by endothelium. These have characteristics of true lymphatic channels as well as areas of dysplastic channels. Lymphoid follicles are often present in the stromal components.

The clinical features of venous-lymphatic malformations vary with the extent and depth of orbital involvement.

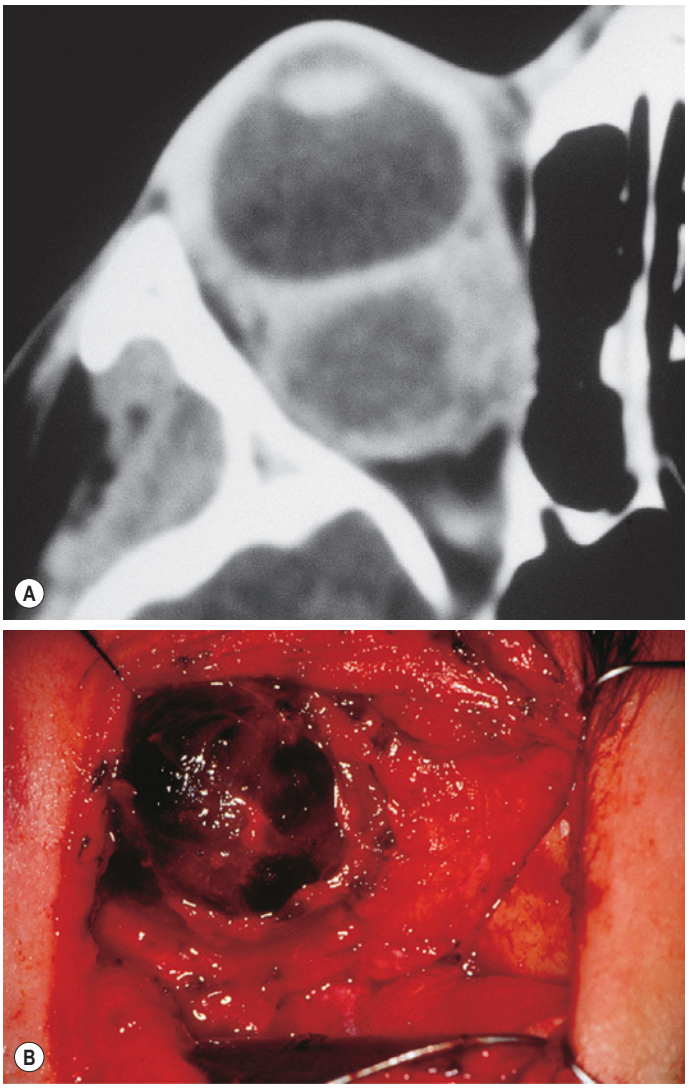


Fig. 20.11 Previously asymptomatic 8-year-old presenting with sudden-onset axial proptosis overnight, decreased vision, afferent pupillary defect, and optic disc swelling. (A) Computed tomography shows a cystic mass indenting the globe posteriorly. (B) At surgery, the chocolate cyst was identified and decompressed. *(Patient of the University of British Columbia.)*

Superficial

Isolated superficial involvement is comparatively rare and consists of multiple conjunctival cysts filled with clear or xanthochromic fluid, or a subcutaneous bluish cystic swelling of the eyelid. The latter may transilluminate and present with an abrupt localized change in color due to hemorrhage into a pre-existing lesion.[48] Superficial venous-lymphatic malformations are easily accessible and, if unsightly, may be excised with good results.

Deep

The hallmark of deeply situated orbital venous-lymphatic malformations is proptosis (Figs 20.11 and 20.12). Deep venous-lymphatic malformations may present with gradually increasing proptosis, with or without ptosis. In contrast to infantile hemangiomas, the proptosis is variable. An increase with upper respiratory tract infections and other generalized inflammatory states has been attributed to lymphoid activity within the lesion.

The most typical presentation, however, is with sudden proptosis resulting from hemorrhage into a hitherto-unsuspected lesion. The differential diagnoses include other causes of rapidly increasing proptosis such as rhabdomyosarcoma (see Chapter 24), neuroblastoma (see Chapter 26), etc. Examination of the nasal and palatal mucosa may be helpful if it reveals mixed clear fluid and blood-filled blebs of widespread venous-lymphatic malformation (Fig. 20.13). Optic nerve compression may occur with rapidly expanding blood-filled "chocolate cyst"[49] (see Fig. 20.11) with decreased visual acuity and disc swelling. It is an indication for urgent orbital intervention to decompress or excise the lesion.

Combined lesions (lymphohemangiomas)

These usually present in infancy, gradually enlarging over many years. Long-standing lesions may be associated with

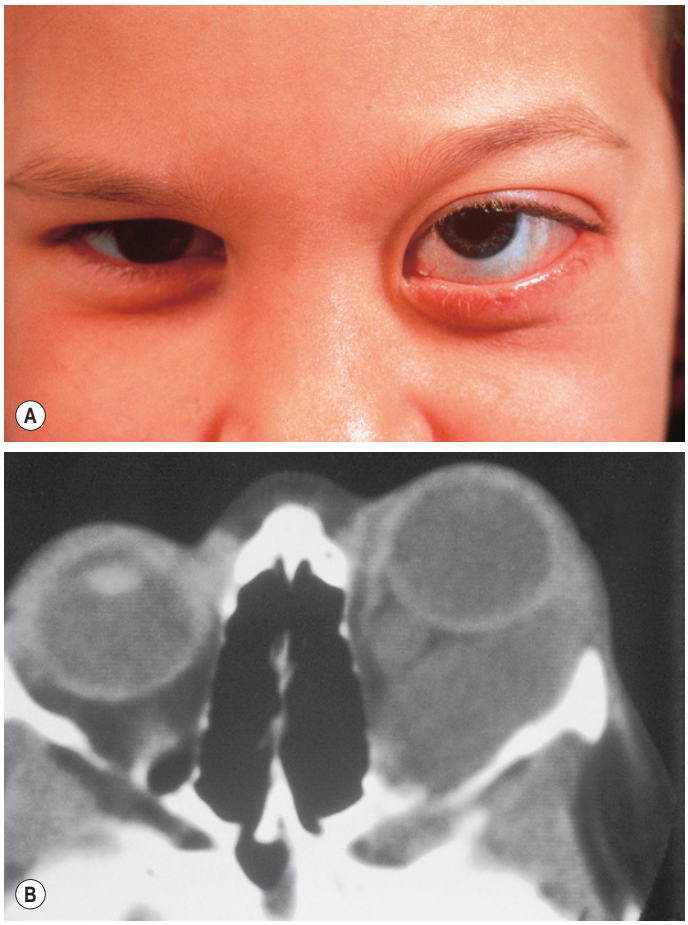


Fig. 20.12 Orbital venous-lymphatic malformation (lymphangioma). (A) Sudden onset of proptosis in the left eye of a previously asymptomatic 5-year-old child. (B) Computed tomography scan shows diffuse soft tissue density lesion arborizing through the retrobulbar tissues. *(Patient of the University of British Columbia.)*

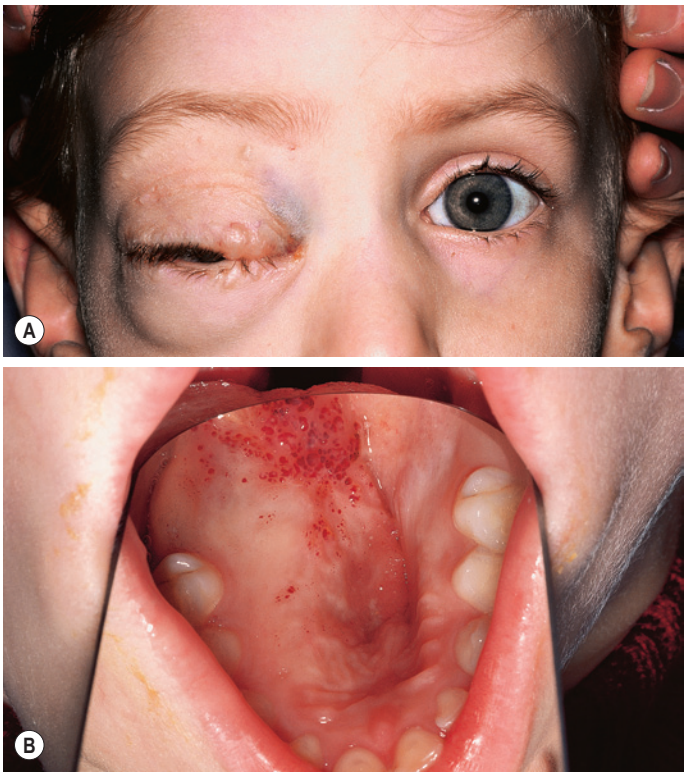


Fig. 20.13 (A) This 4-year-old boy was born after a 32-week gestation. Right proptosis developed by 4 weeks and was progressive despite orbital surgery, until the age of 3 years. It has been static since then. The diagnosis was a venous-lymphatic malformation. (B) Same patient showing clear and blood-filled cystic lesions on the palate.

orbital enlargement. The presence of telltale conjunctival and lid changes is helpful in making the diagnosis of venous-lymphatic malformation (see Fig. 20.13). Hemorrhage into superficial lesions may result in the striking appearance of blood menisci within the conjunctival cysts (Fig. 20.14). These may be accompanied by recurrent subconjunctival hemorrhage and lid ecchymosis. Deep hemorrhage results in proptosis, commonly associated with compressive optic neuropathy. Combined lesions may be large enough to simultaneously involve every orbital space, producing gross proptosis and facial deformity, some from extension through the superior orbital fissure. Non-contiguous intracranial vascular abnormalities may occur.[50] Since the latter are at risk of bleeding, brain imaging is indicated in patients with orbital venous-lymphatic malformation.

Investigation

CT scanning shows a soft tissue density mass with poorly defined margins and non-homogeneous enhancement after injection of contrast medium. Bony destruction is absent but large lesions can result in smooth enlargement of the orbit. The presence of a cystic component helps differentiate venous-lymphatic malformations from infantile hemangiomas. Since hemoglobin has paramagnetic qualities that change as blood denatures, blood-containing "chocolate cysts" are well visualized by MRI scanning[51] (Fig. 20.15). The age of intralesional hemorrhages can be assessed since oxyhemoglobin in fresh hemorrhage is hypointense on T1- and T2-weighted images, gradually becoming hyperintense as it is converted to methemoglobin. Later, degradation to ferritin and hemosiderin once again produces a hypointense image. Intravenous contrast in the case of CT scan or gadolinium in MRI is helpful in imaging the most active component of the lesion, which should be removed if surgery is contemplated. A review of brain images is indicated for non-contiguous intracranial vascular anomalies.[50]

Management

Complete surgical excision is difficult in all but the most superficial lesions and can precipitate further hemorrhage. Since hemorrhagic cysts tend to shrink with time, a conservative approach is usually preferable. Bed rest, alone or with cold compresses, can result in a good outcome, even in cases with marked acute proptosis.[52]

Impressive early results have been reported from interventional radiology for patients with macrocysts. Image-guided intralesional injection of bleomycin resulted in significant reduction in lesion volume with few complications.[53,54]

Surgery or neuroradiological intervention is indicated if there is optic nerve dysfunction, corneal exposure, pain and nausea from raised orbital pressure, or the risk of amblyopia from astigmatism or strabismus. It is possible to temporize by aspirating the cyst contents through a needle under ultrasound

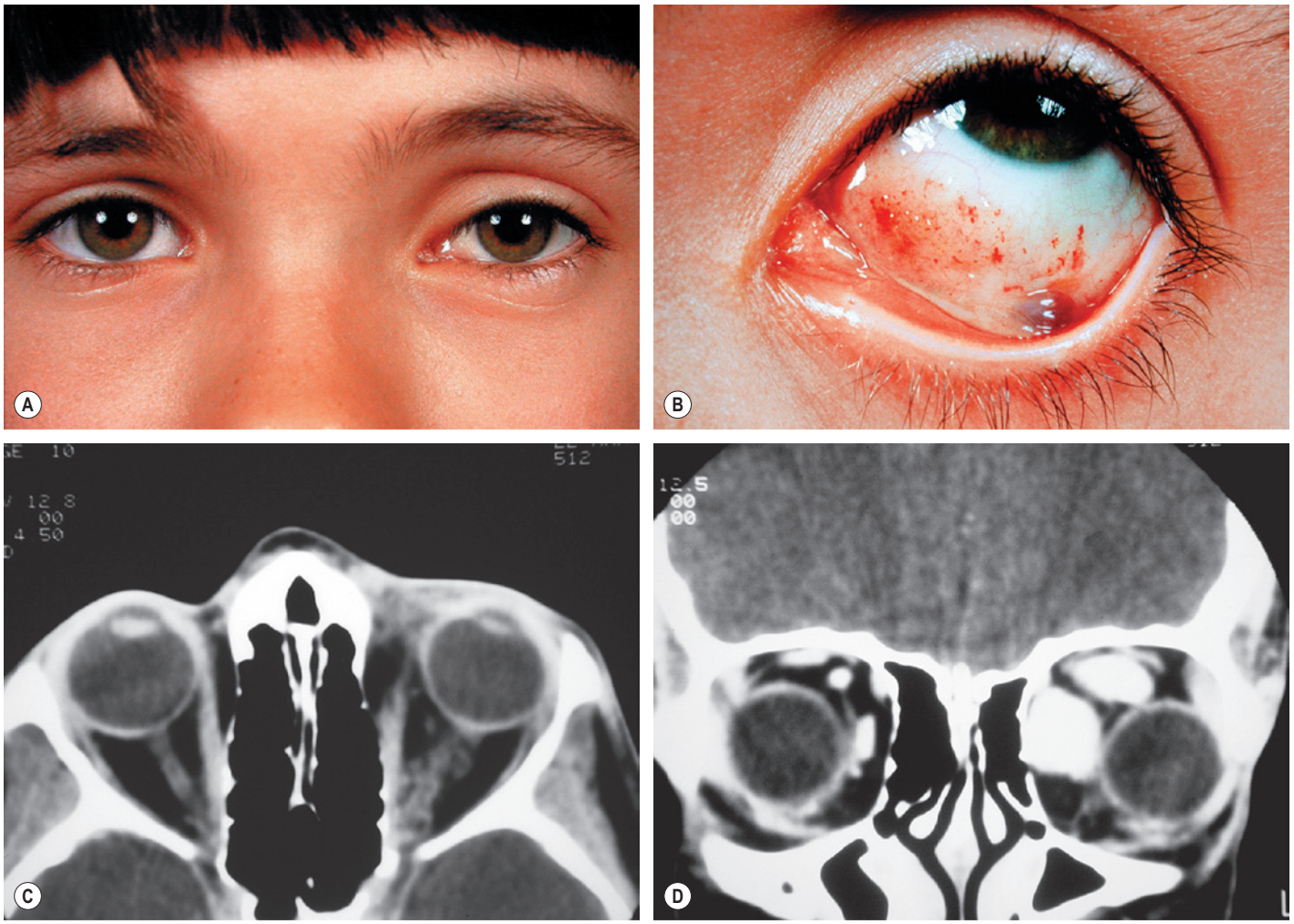


Fig. 20.14 (A) This 12-year-old child presented with an epibulbar lesion on the left side associated with fullness of the upper and lower lids and slight ptosis. (B) The epibulbar surface demonstrates a gelatinous-appearing lesion medially containing many clear fluid-filled cysts along with focal blood cysts, many of which appear to have menisci. In addition, in the inferolateral fornix, there appears to be a dark varix. The conjunctival lesion was proven on biopsy to be consistent with a venous-lymphatic malformation histologically and by electron microscopy. It was noted also that the superior sulcus appeared somewhat deepened on the left. (C) Post-contrast computed tomography scan in the axial view shows an irregular lesion occupying the anteromedial orbit around and behind the caruncle. On direct coronal view (D), there is evidence of a posterior orbital varix that appeared with increased venous pressure. This lesion represents a combined venous-lymphatic malformation and varix. *(Patient of the University of British Columbia.)*

guidance. Poor results and frequent morbidity have been reported from attempts at subtotal excision. The authors feel that surgery, when indicated, should excise as much of the venous-lymphatic malformation as is safe, particularly removing the active tissue as well as draining blood cysts with release of their contents. Unlike dermoid or sebaceous cysts, excision of the whole cyst wall is not necessary to avoid recurrence. The carbon dioxide laser may be useful in reducing hemorrhagic complications associated with subtotal excision surgery.[55] Systemic steroids[56] or intralesional OK-432 (group A *Streptococcus pyogenes* of human origin)[57] may reduce the size of these tumors. Recently sildenafil (Viagra) has been shown to be effective in two children with extensive orbital venous-lymphatic malformations.[58]

Congenital orbital varices

Varices are of high- and low-flow types. Low-flow varices are clinically similar to venous-lymphatic malformations, with a tendency for sudden, often recurrent, hemorrhage,[59] whilst high-flow varices expand with increased jugular venous pressure and rarely bleed.[47]

Distensible orbital varices expand only slowly during childhood and rarely give rise to visual problems. There is often a subconjunctival component (see Fig. 20.14). They often present in adolescence with discomfort on bending over and slow development of enophthalmos and deepening superior sulcus due to fat atrophy and enlargement of the orbit, which may be seen on plain X-rays, along with phleboliths. The main indications for surgical excision are removal of the superficial component for cosmetic reasons or removal of deeper lesions for grave, persistent pain. A combined neuroradiologic method with gluing followed by excision may be worthwhile in cases that demonstrate isolation from the venous system and do not share out-flow with critical orbital structures.[60] Detachable coil embolization may be considered before proceeding with surgery.[61] Some orbital varices may be associated with intracranial varicosities (Fig. 20.16).

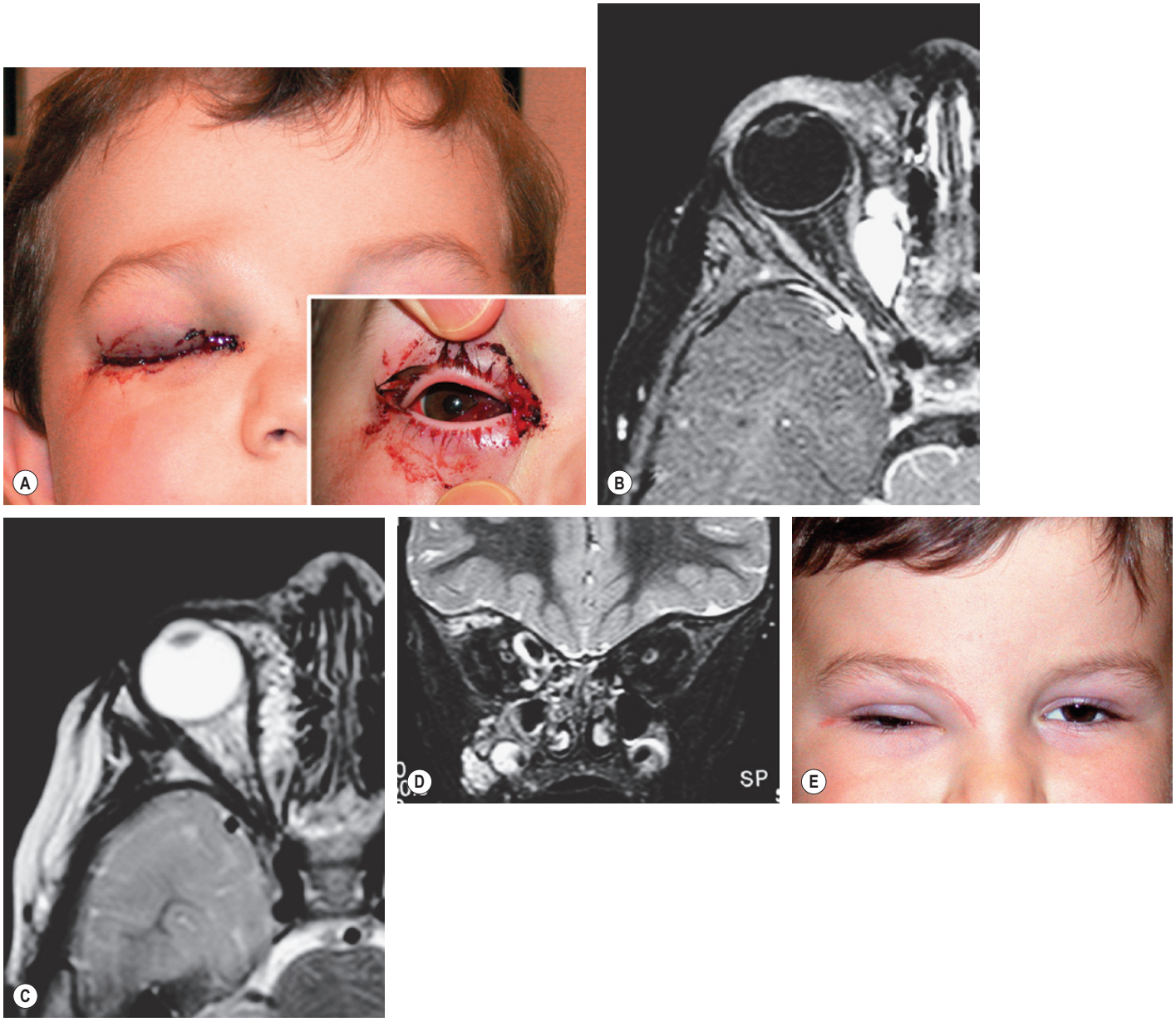


Fig. 20.15 (A) This 2½-year-old boy was born with a swollen right eye. At age 1, he developed spontaneous bruising and a gelatinous lesion on the surface of the right globe, treated at the time with steroids with improvement. He continued, however, to have constant bleeding from the epibulbar surface, progressive lid closure, and swelling. (B–D) MRI scans demonstrate an extraconal medial lesion that involves the lid and forehead and extends to the apex of the right orbit. Posteriorly, note the cystic components consistent with venous-lymphatic malformation. The patient underwent excision of his venous-lymphatic malformation. (E) He did well postoperatively (seen here at 1 month following surgery) with a residual ptosis and persistent lid involvement, which will require future surgery. *(Patient of the University of British Columbia. (B–D) with permission from Rootman J. Vascular malformations of the orbit: hemodynamic concepts. Orbit 2003; 22: 103–20.)*

Arteriovenous malformations

Arteriovenous malformations are characterized by the development of pulsating exophthalmos with episodes of hemorrhage, thrombosis, or extended, tortuous and engorged vessels secondary to arterialization of out-flow venous channels. They may have an audible bruit and can cause pain when engorged by Valsalva maneuver. Typically, they present in late adolescence or early adult life.

On imaging, arteriovenous malformations are characterized by irregular, rapidly enhancing masses. Doppler studies and CT or MR angiography demonstrate high-flow characteristics. With selective angiography, the lesions consist of engorged proximal arterial supply, a tangled malformation, and a distal venous out-flow (Fig. 20.17).

Arteriovenous malformations can largely be observed. The indications for intervention include recurrent hemorrhage or persistent pain. The malformations can be removed using selective gluing or embolization of in-flow vessels followed by excision.[62]

Sturge–Weber syndrome (SWS) (see Chapters 38 and 68)

This neurocutaneous disorder is a sporadic congenital condition affecting 1 in 20,000–50,000 live births.[63] A child

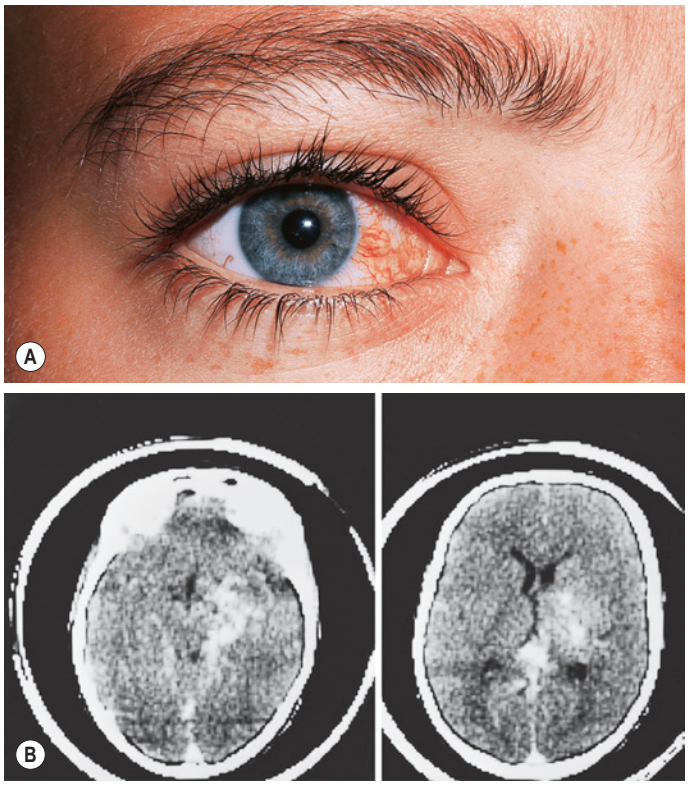


Fig. 20.16 (A) Subconjunctival varicosities in a patient with an orbital and intracranial hemangioma. (B) Contrast-enhanced computed tomography scans showing the intracranial lesion (same patient).

with a facial port wine stain has approximately 6% chance of having SWS[64]; if the cutaneous lesion is in the V1 distribution, this probability increases to 26%.[65] The disorder is thought to be due to a somatic mutation of GNAQ.[66]

The port wine stain in Sturge–Weber syndrome can be confused with early-stage infantile hemangioma. Infantile hemangiomas grow in thickness and breadth within the first few weeks of life; in contrast, the vascular lesion of Sturge–Weber syndrome remains unchanged. In addition to the triad of glaucoma, port wine stain, and cerebral vascular malformation, SWS can be associated with choroidal hemangioma leading to serous retinal detachment. Orbital involvement is rare,[67] with ipsilateral nevus flammeus and orbital vascular malformation causing proptosis without intracranial involvement.

Early results of the use of pulsed dye lasers for nevus flammeus have been encouraging. Treatment with pulsed dye laser in the first few years of life can prevent thickening of the skin lesion and results in lightening of the color. The associated local hypertrophy may also be reduced. Regular intraocular pressure monitoring is indicated.

Rare vascular lesions of the orbit

Klippel–Trénaunay–Weber syndrome (see Chapter 68)

This syndrome comprises multiple cutaneous nevi associated with various angiomas of one or more limbs, which may show hypertrophy of the soft tissues. Orbital varix is a rare finding.[68]

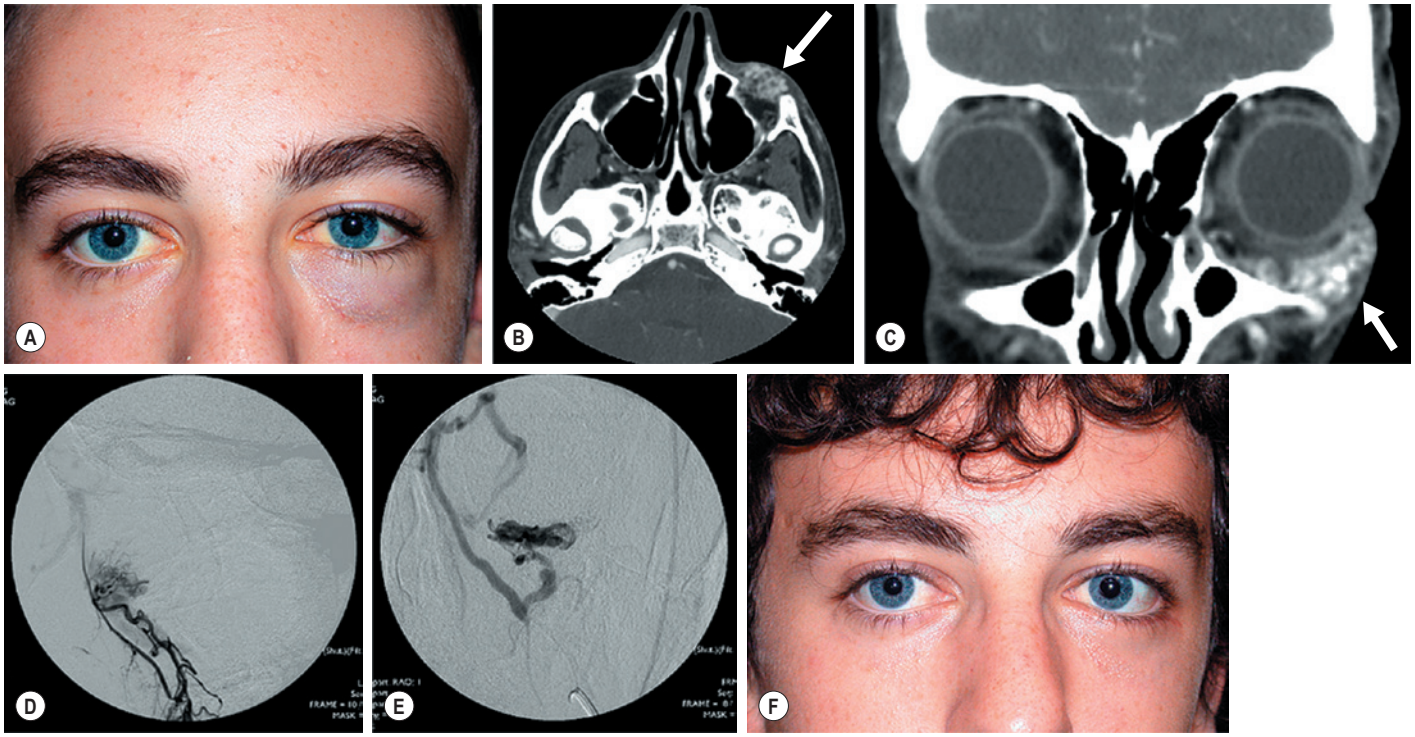


Fig. 20.17 (A) This 15-year-old boy presented first at age 12 with a fullness of the left lower lid and transient visual obscuration episodes on exertion, due to an arteriovenous malformation. He was observed for 2½ years, during which time the lesion progressed, and it was decided to intervene. He underwent combined embolization and excision of his mass. (B,C) Computed tomography angiograms demonstrate the tangle of the arteriovenous malformation in the left inferior orbit and lid (arrow). (D) Selective external carotid angiogram shows the external maxillary supply, while the anterior–posterior venous phase angiogram (E) reveals the venous out-flow to the facial and superior ophthalmic veins with facial compression. (F) Photograph of the patient 4 months after his surgery shows his postoperative result. *(Patient of the University of British Columbia.)*

Blue rubber bleb nevus syndrome

This rare syndrome usually presents in childhood. It consists of multiple bluish cutaneous vascular anomalies associated with angiomas of the gastrointestinal tract, lung, heart, and central nervous system.[69] Gastrointestinal hemorrhage is a rare complication of this disorder. The cutaneous lesions are soft, rubbery, and compressible. Most cases are sporadic, but autosomal dominant inheritance has been reported. Conjunctival, iris, and retinal angiomas may occur, as well as orbital venous malformation.[70]

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Lacrimal system

Caroline J MacEwen and Una O'Colmain

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See online for supporting video for this chapter.

Introduction

The lacrimal system consists of a secretory portion and a drainage system. The secretory portion is the lacrimal and accessory lacrimal glands. With the meibomian glands and the goblet cells, they secrete the components of the tear film. The tear film has three layers: the inner mucin layer secreted by the conjunctival goblet cells, the intermediate aqueous layer secreted by the lacrimal and accessory lacrimal glands, and the outer, oily layer secreted by the meibomian glands. The accessory lacrimal glands produce basal tear secretion; the lacrimal gland is responsible for reflex tearing in response to noxious or emotional stimuli.

The drainage system consists of the lacrimal puncta, canaliculi, lacrimal sac, and the nasolacrimal duct. This active system pumps tears from the conjunctival sac into the inferior meatus of the nose.

Tears flow along the lid margins and conjunctival fornices. They are spread across the surface of the eye by blinking. Tears protect the eye by surface lubrication, provision of oxygen and antibacterial substances such as immunoglobulin (Ig)A, IgG, and lysozyme, and mechanical removal of irritating substances and cellular debris.

Lacrimal problems in children usually relate to underproduction of tears, causing dry eyes, which is rare but potentially sight threatening, or reduced drainage of tears, which is much more common but less serious (Box 21.1).

Lacrimal gland

Embryology

The lacrimal gland develops from ectoderm that is supported by mesodermal connective tissue. It continues to grow 3–4 years after birth. Basal tearing is present in infants from birth, and reflex tearing begins at any time from birth to several months of age.[1]

Anatomy

The lacrimal gland is an exocrine gland in the anterior aspect of the superotemporal orbit within the bony lacrimal fossa. The majority of the gland lies within this fossa, but the lateral horn of the levator palpebrae superioris separates this orbital part from the palpebral lobe, which extends anteriorly into the superotemporal conjunctival cul-de-sac. The ducts of the gland pass through the palpebral lobe and open on to the conjunctiva in the superior fornix. The lacrimal gland is innervated via the facial (afferent) and trigeminal (efferent) nerves. The accessory glands of Kraus and Wolfring sit in the superior conjunctival fornix.

Congenital abnormalities

Congenital absence of the lacrimal gland is rare, usually occurring in conditions with reduced conjunctiva: anophthalmos, cryptophthalmos, and the lacrimo-auriculo-dento-digital (LADD) syndrome. Anomalous lacrimal ductules that secrete tears on to the skin rather than the conjunctival sac may be found near the lacrimal gland, around the lateral canthus, or in the preauricular region. These are rare but may require dissection and excision.[2]

The embryology of the lacrimal gland is closely linked to that of the conjunctival epithelium.

Other congenital anomalies include orbital ectopic lacrimal gland tissue. A drainage system may not be present in such cases and an enlarging orbital mass may develop. Neoplasms can occur within such ectopic tissue.

Crocodile tears (see Chapter 95) occur from congenital aberrant innervation between the fifth and seventh cranial nerves causing tearing with chewing or sucking.[3]

Dry eyes in children

Congenital causes

Congenital alacrima is rare. It may be due to absence of the lacrimal gland or to it being ectopic in the orbit. Alacrima may be associated with systemic conditions such as the Riley–Day syndrome (familial dysautonomia), anhydrotic ectodermal dysplasia, and Allgrove syndrome (familial alacrima, achalasia of the cardia, and adrenal deficiency).

Box 21.1

Causes of watery eyes in children

Excess tear production (lacrimation)

Allergic rhinitis
Upper respiratory tract infection
Epiblepharon
Subtarsal foreign body
Iritis
Corneal abrasion/ulceration
Conjunctivitis
Glaucoma

Drainage failure (epiphora)

Congenital nasolacrimal duct obstruction
Skeletal and sinus abnormalities
Lid malposition
Punctal malposition
Punctal occlusion
Anomalous drainage system

Acquired causes

Acquired tear deficiency may be due to pathology of the lacrimal gland, causing failure of tear production, or to conjunctival damage (see Chapter 31), leading to ductule obliteration. The lacrimal gland may be damaged by Epstein–Barr infection, as the result of human immunodeficiency virus (HIV) infection, or in patients with bone marrow transplantation (often associated with graft-versus-host disease). The conjunctiva may be affected by injury (burns), infection, the sequelae of trachoma, Stevens–Johnson syndrome, or toxic epidermal necrolysis.

Sjögren syndrome is rare in children. It can be a primary autoimmune event or associated with rheumatoid arthritis or systemic lupus erythematosus. Children with Sjögren syndrome often have lacrimal gland enlargement. They may have recurrent parotid gland swelling and salivary gland involvement. Sjögren syndrome should be considered in any child with recurrent parotiditis, keratoconjunctivitis sicca, and early tooth decay due to xerostomia.[4]

Chronic blepharitis is uncommon. It usually presents with recurrent chalazia, although the lids may appear normal. The tear film is deficient causing surface dryness. The associated peripheral corneal vascularization and scarring can be sight threatening.

Isotretinoin treatment for acne is a cause of dry eyes in adolescence. This is usually reversible at cessation of the drug.

Children with dry eyes present with irritable, uncomfortable, gritty, red eyes. A reduced tear meniscus is evident with punctate keratopathy, particularly affecting the interpalpebral zone. Staining occurs with fluorescein and Rose Bengal dyes. Severe keratopathy due to concomitant corneal hypoesthesia can be a problem in the Riley–Day syndrome.

Treatment of dry eyes involves copious use of artificial tears and temporary or permanent punctal occlusion in severe cases. Immunomodulation may have a role to play in secondary lacrimal gland failure, including that due to infections. Blepharitis should be treated with lid hygiene, lubricants, and systemic antibiotics such as erythromycin or azithromycin. Oral tetracyclines should be avoided in children prior to their second dentition.

Dacryoadenitis

Dacryoadenitis is usually associated with viral infection, mumps, infectious mononucleosis, herpes zoster, tuberculosis, brucellosis, histoplasmosis, or gonococcal infection. Lacrimal gland swelling may rarely be a sign of childhood Sjögren disease.

A primary clinical feature of dacryoadenitis is the "S sign" in which there is drooping of the lateral aspect of the upper lid. In acute inflammatory cases, the overlying skin is inflamed. Neuroimaging confirms enlargement and helps rule out other orbital masses. In the long term, dacryoadenitis may damage the lacrimal gland and cause reduced tear secretion.

Dacryoadenitis must be differentiated from a lacrimal gland infarct, which occurs in children with a sickle cell crisis. The onset is rapid, like acute dacryoadenitis.

Treatment of acute dacryocystitis is aimed at the underlying cause.

Lacrimal tumors (see Chapter 26)

Lacrimal tumors are very rare in children. Pseudotumor causing painful swelling may affect the lacrimal gland.[5] Malignant epithelial tumors, including mixed cell adenocystic and other carcinomas, have been recorded in childhood.[6]

Lacrimal gland enlargement is also found in conditions such as sarcoidosis or leukemia. Prolapse of the lacrimal gland, which is commonly bilateral, may present as a subconjunctival mass in the upper outer fornix. This may occur with craniofacial anomalies (see Chapter 28) due to reduced orbital volume and increased orbital pressure.

The lacrimal drainage system

Embryology

The lacrimal outflow system develops between the maxilla and the lateral nasal process from surface ectoderm. By the end of the first trimester, this tissue begins to canalize. The puncta usually open with the eyelids during the sixth month of gestation. The nasolacrimal duct opens into the inferior meatus of the nose just before or after term birth. There may be a failure of this canalization process at any part of the system, but this is most frequent at the lower end.[7]

Anatomy

Understanding the lacrimal outflow system is important for the pediatric ophthalmologist, especially for performing probing.

The puncta should be in contact with the globe at the medial aspect of the upper and lower lids. The proximal part of the canaliculus, the ampulla, is a slightly dilated vertical portion 1 mm in length in the young child. The canaliculus then turns 90° to run medially in a horizontal direction. The upper and lower canaliculi join to form the common canaliculus that enters the lateral wall of the lacrimal sac. Rosenmüller's valve prevents reflux of tears from the sac into the canaliculus. The lacrimal sac sits in the bony lacrimal fossa, separated from the

middle meatus of the nose by the maxilla and lacrimal bone. The lacrimal sac extends superiorly under the medial canthal ligament to form its fundus. The nasolacrimal duct exits from the lower end of the sac and passes in a downward, lateral, and slightly posterior direction. This duct is surrounded by bone in its upper part but becomes membranous inferiorly. The nasolacrimal duct opens into the medial wall of the inferior meatus of the nose via the valve of Hasner. This ostium is found under the inferior turbinate of the nose, approximately 1 cm directly behind the entrance of the nose in the baby.

Physiology

Tears are actively pumped through the outflow system. During blinking, when the lids close, the canaliculi are shortened and narrowed by contraction of the pretarsal orbicularis muscles. Simultaneously, the same muscles pull the lateral sac wall, creating negative pressure inside the sac, sucking fluid into the expanded sac. Further lid closure causes contraction of the orbicularis oculi muscle, which squeezes the tears from the sac into the nasolacrimal duct. At the end of each blink, the sac is empty. As the lids open, the canaliculi and the sac elastically expand. This causes a vacuum within the system into which tears enter via the puncta, and the cycle begins again.

Congenital abnormalities

Common abnormalities, include narrowing (stenosis), blockage (atresia), complete absence (agenesis), or duplication (accessory channels) of any part of the system. A membranous obstruction at the distal end of the nasolacrimal duct is the commonest abnormality, causing congenital nasolacrimal duct obstruction.[7] Obstruction at other sites is rare, but more relevant in older children.

Children with craniofacial abnormalities (see Chapter 28), particularly clefting syndromes, have complex anomalies of the lacrimal outflow system that may involve large areas being either blocked or absent.

Congenital dacryocystocele (dacryocele)

A dacryocystocele (syn. dacryocele) is a congenital swelling located at the medial canthus due to trapped fluid inside the lacrimal sac and nasolacrimal duct.[8] The fluid is unable to escape from either the upper or lower end of the drainage system as both are blocked. This presents as a tense, blue, non-pulsatile swelling below the medial canthus. It is evident at, or shortly after, birth (Fig. 21.1A). The inferior end of the dacryocystocele projects into the nose (Fig. 21.1B) and in some cases may be responsible for breathing difficulties.[9] If respiratory compromise occurs, urgent treatment is required.

Congenital dacryocystocele must be differentiated from a meningoencephalocele, a meningocele, a midline nasal dermoid cyst (see Chapter 29), or an infantile hemangioma (see Chapter 20). Routine imaging is unnecessary; the diagnosis is usually made clinically but in ambiguous cases a magnetic resonance imaging (MRI) scan is helpful in identifying the dilated sac and nasolacrimal duct and excluding other pathology.

Treatment of a dacryocystocele involves observation during the first 2 weeks of life, during which time most spontaneously improve. Massage over the lacrimal sac may be undertaken to encourage rupture of the distal cyst into the nasal cavity.[10] If

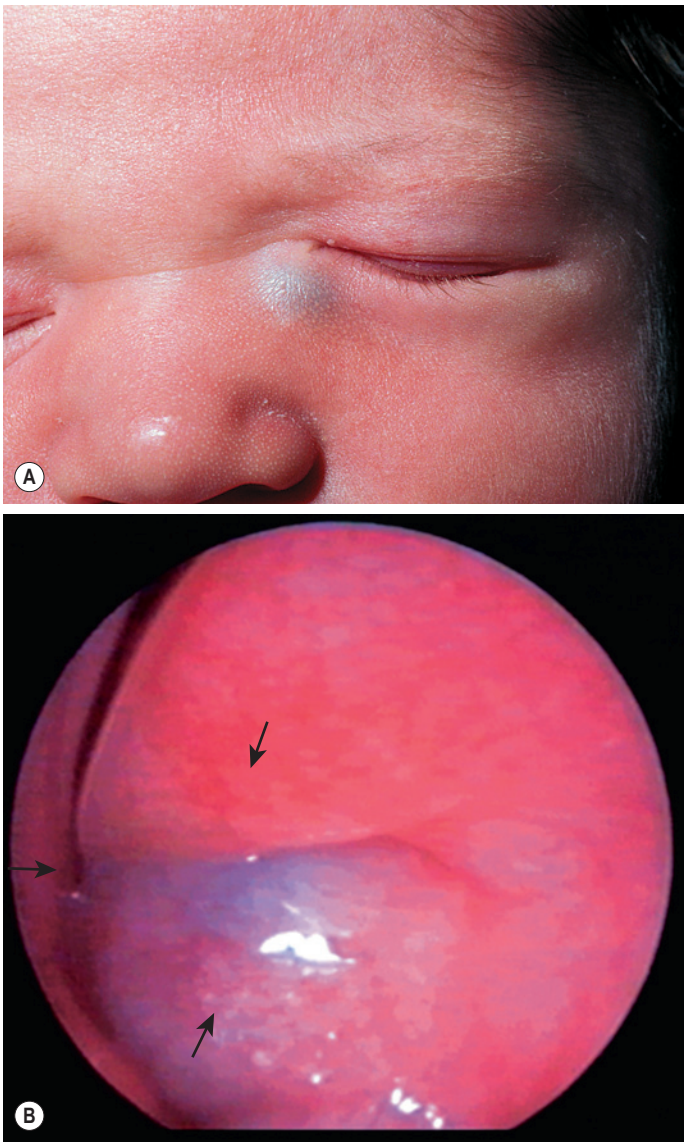


Fig. 21.1 Congenital dacryocystocele. (A) A bluish swelling is seen below the medial canthal tendon. It can present as nasal obstruction. (B) Dacryocystocele viewed from inside the nose, demonstrating the dilated nasolacrimal duct protruding into the nasal cavity, which may cause respiratory distress (left nostril).

it does not settle within the first 2 weeks of life, or if acute dacryocystitis (Fig. 21.2) or respiratory difficulties develop, then endoscopic drainage of the dacryocystocele into the nose is indicated and the nasal mucosa over the dacryocystocele excised. If acute dacryocystitis develops, intravenous antibiotics should be given prior to surgery.

Congenital nasolacrimal duct obstruction

Congenital nasolacrimal duct obstruction results from delayed maturation of the lacrimal system where it enters the nose, resulting in a persistent membranous obstruction at the valve of Hasner. The diagnosis is made on a history of a watery eye that has been present from the first few weeks of birth. This is usually unilateral but may be bilateral. If so, it is commonly asymmetrical. Some children develop a

mucopurulent discharge that may be constant or intermittent. The eye remains "white" without evidence of active infection, although conjunctivitis may complicate the condition. The child is well with no evidence of irritation or photophobia. The skin around the eye may become red and excoriated. Although usually an isolated abnormality, congenital nasolacrimal duct obstruction may be more frequent in certain conditions, such as EEC syndrome (ectrodactyly, ectodermal dysplasia, clefting; Fig. 21.3) branchio-oculo-facial syndrome, craniometaphyseal or craniodiaphysial dysplasia, Down syndrome, LADD syndrome, and the CHARGE syndrome (**c**oloboma of the eye, **h**eart defects, **a**tresia of the nasal choanae, **r**etardation of growth and/or development, **g**enital and/or urinary abnormalities, and **e**ar abnormalities and deafness; Table 21.1).

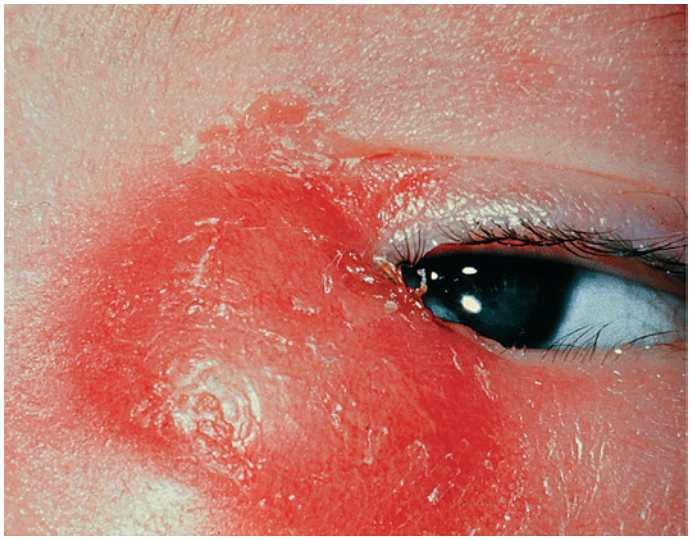


Fig. 21.2 Acute dacryocystitis in a baby with a congenital dacryocystocele. A dacryocystocele is not normally inflamed.

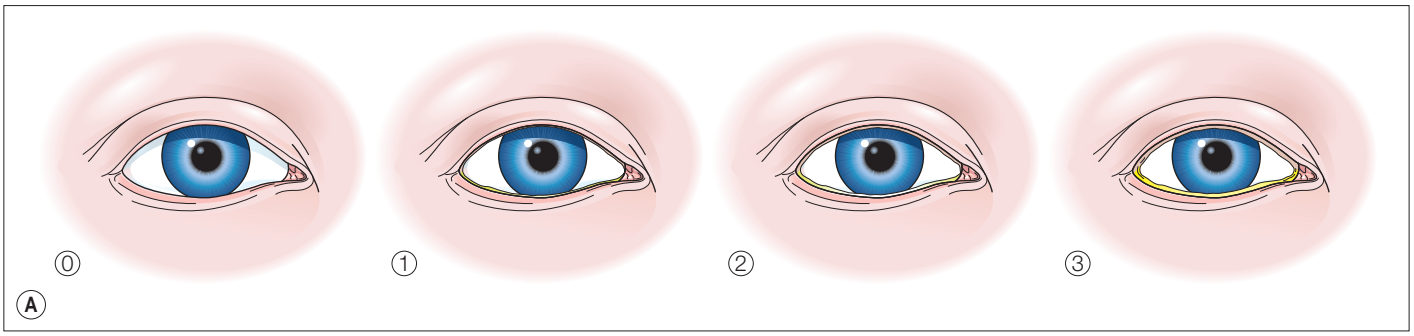


Fig. 21.3 (A) The ectrodactyly, ectodermal dysplasia, clefting (EEC) syndrome is associated with nasolacrimal duct obstruction and (B) "lobster claw" deformity of the hands.

Table 21.1 Systemic associations of nasolacrimal duct obstruction in children

Syndrome	Genetics	Other eye findings	Systemic findings
Down syndrome (see Chapters 37, 39)	Trisomy 21, mosaic or translocation	Up-slanting palpebral fissures, strabismus amblyopia, cataract, blepharitis	Short stature, hypotonia, simian crease, mental retardation, flat nose, small mouth and ears
EEC (see Chapters 16, 46; see Fig. 21.3)	AD	Photophobia, absent eye lashes	Ectrodactlyly, hypoplasia or aplasia of middle digits, ectodermal dysplasia (absent sweat glands, hair, eyelashes, and brows), clefts (palate/lip)
Branchio-oculo-facial	AD; mutations in *TFAP2A* gene	Hypertelorism, microphthalmos, cataract, coloboma	Postauricular branchial cleft defects, cleft lip/palate, low-set ears, malformed nose, hemangiomas of chest and neck
Craniometaphyseal dysplasia	AD/AR; mutations in ANK membrane protein gene	Optic atrophy	Hyperostosis of cranial bones, splayed metaphyses, palsies cranial nerve VII and VIII, delayed teething
Craniodiaphyseal dysplasia	AR/AD	Optic atrophy, strabismus, hypertelorism, exophthalmos	Generalized hyperostosis and sclerosis, growth retardation, parasnasal bossing, deafness, cylindrical long bones
LADD (lacrimo-auriculo-dento-digital)	AD Loss of FGF signaling	Ptosis, keratitis sicca	Hypoplasia, aplasia, or atresia of lacrimal and salivary glands, abnormalities of forearms and fingers, ear anomalies
CHARGE syndrome (see Chapter 53)	AD/sporadic mutations in *CHD7*	Coloboma	Coloboma, heart defects, atresia choanae, retardation of growth and development, genitourinary problems, ear abnormalities/deafness
Goldenhar syndrome (see Chapters 28, 29)	Usually sporadic	Lid coloboma, epibulbar/limbal dermoid, Duane syndrome	Macrostoma, hemifacial microsomia, atresia ear canal, ear deformity, misshapen tongue, hemivertebrae, preauricular tags

AD, Autosomal dominant; AR, autosomal recessive; FGF, fibroblast growth factor.
Further information: http://www.orpha.net; http://rarediseases.info.nih.gov.



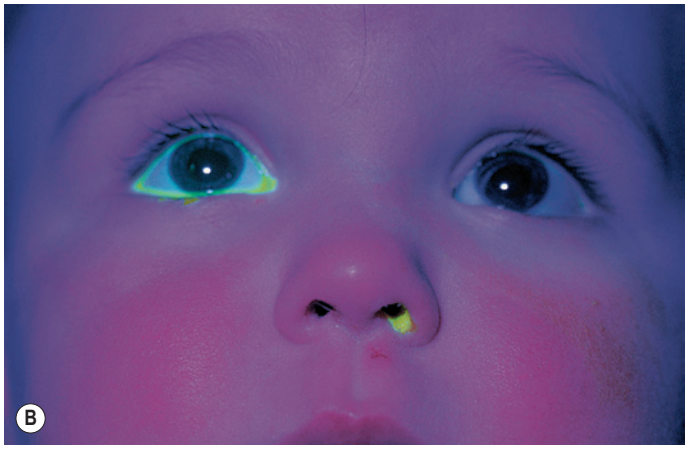


Fig. 21.4 The fluorescein disappearance test. (A) Grading the test is usually performed at 5 or 10 minutes.[24] (B) This child has evidence of delayed fluorescein disappearance test from the right eye, and a patent left system is confirmed in cobalt blue light by the presence of fluorescein in the nostril.

There is an increased tear meniscus and there may be stickiness or crusting on the lashes. A mucocele may develop. The contents can be expressed into the conjunctival sac.

A fluorescein disappearance test should be performed on children with epiphora to determine if there is evidence of lacrimal outflow obstruction.[11] Fluorescein 1% is instilled into each lower conjunctival fornix and cobalt blue light from the slit-lamp or indirect ophthalmoscope illuminates the eyes. The tear meniscus is evaluated at 2 and 5 minutes (and at 10 minutes in equivocal cases). Normally, the fluorescein disappears by 5 minutes (graded 0 or 1), but it remains present in children with obstruction, helping to secure this diagnosis (Fig. 21.4).

Natural history

Congenital nasolacrimal duct obstruction is evident in up to 20% of infants, of which the vast majority become symptomatic during the first month. The natural history is spontaneous resolution with maturation.[12–15] Spontaneous resolution is rapid[12–15] (Fig. 21.5) during the first year of life and continues, at a reduced rate, beyond this into childhood.[16,17]

Conservative treatment

Because of the high rate of spontaneous resolution, observation is recommended until the child is at least 1 year old and even older. Parental education should provide reassurance and information about the etiology and natural history.

Cleansing the lids and lashes with cooled boiled water, gently expressing the contents of the lacrimal sac proximally into the conjunctival sac,[18] maintains flow in the system and prevents stagnation, reducing any sticky discharge. Massage of the sac may also increase hydrostatic pressure within the lacrimal system. This increases resolution by rupturing the membranous obstruction.[19–21] Parents find this difficult and need clear instructions: press on the sac below the medial canthus with the little finger 2–3 times per day if possible. Vaseline (or liquid paraffin) should be applied to the periocular skin to protect and treat any areas of redness or broken skin.

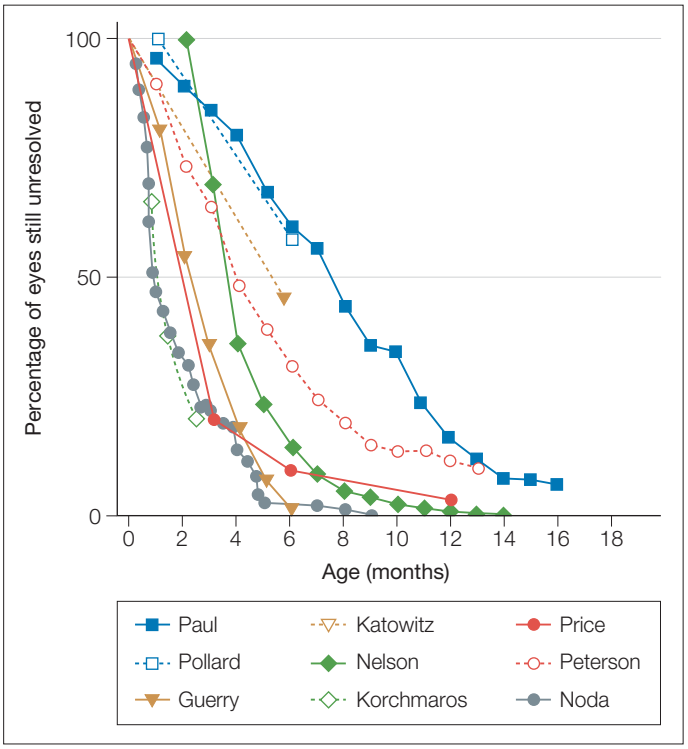


Fig. 21.5 The rate of spontaneous resolution of nasolacrimal duct obstruction expressed as a percentage of those still unresolved at a given age in months.

Antibiotics are not required and should be avoided unless there is evidence of conjunctivitis. Swabs for bacterial growth should only be performed under these conditions, as "pathogenic" bacteria are frequently commensals in the conjunctival sacs of normal infants and do not require antibiotic treatment in white watering eyes.[22]

Syringing and probing

If epiphora persists, syringing and probing the lacrimal drainage system is the treatment of choice. The optimum time to intervene remains controversial. In the past, probing was advocated at presentation or after a short period of conservative treatment.[23,24] However, this has become less favored due to better understanding of the natural history of the condition. It has been shown that the earlier probing is performed, the greater is the success rate.[25,26] However, the higher failure rate in older children is probably unrelated to the age of the child, but is due to a process of natural selection.[27–32] As children grow older, more complex and severe obstructions become common because cases of simple membranous obstruction spontaneously resolve. This reduces the success rate of probing in older children and increases the requirement for more extensive surgery.[16] Observation is as effective as probing in children up to the age of 2 years, but probing provides a more rapid result if performed around 12 months of age.[16]

The decision to probe is based on the natural history, severity, and informed parental request. Probing under 12 months of age is generally not recommended, and there is no evidence that it is detrimental to wait until 2 years of age[16,27–31] and probably later, if desired, with regards to spontaneous resolution.

"Office probing," carried out on awake, restrained babies, which is favored in the USA, is less popular elsewhere because it must be performed at an age when between 50 and 73% of those undergoing probing would not require intervention if left until 1 year of age.[14,33] In environments where office probing is performed, the parents should be fully counseled about the possible benefits of earlier resolution against the risks of it being an unnecessary intervention in the majority of children.[33]

Probing should be carried out in a pediatric environment with the child anesthetized. Probing is diagnostic, as well as therapeutic. In the small number of cases that remain symptomatic, the cause of failure can be identified and a management plan formed. This can only be achieved under general anesthesia using a laryngeal mask following full nasal preparation. Probing should be carried out in a step-wise fashion, identifying the patency or obstruction of each area between the puncta and end of the nasolacrimal duct. Probing is a blind procedure and depends on awareness of resistance to the probe as it passes through the system. The use of a nasal endoscope permits direct visualization of the lower end of the nasolacrimal duct, which assists in the diagnosis and management.[31]

Each punctum is dilated using a Nettleship dilator. This is introduced in a vertical direction for approximately 1 mm and then rotated through 90° medially to run horizontally parallel to the lid margin to dilate the proximal canaliculus. This is easier if the lid is held taut by pulling the eyelid laterally to straighten out the canaliculus. The lacrimal system should be syringed with fluorescein-stained saline using a disposable cannula. Syringing takes place via each punctum and any areas of resistance or any regurgitation of fluid or mucus are noted. The inside of the nose should be inspected with an endoscope or fluorescein retrieved via a nasal or pharyngeal aspirate. The passage of fluorescein and the amount of resistance are important factors in deciding the site and nature of any abnormality of the lacrimal outflow system.

The following features of syringing are useful in identifying the nature of the obstruction:

- Stenosis at the valve of Hasner, or a narrow inferior meatus caused by a tight inferior turbinate: difficulty in injecting the fluid, regurgitation of clear fluid via the other punctum and fluorescein is identified in the nose.
- Atresia at the lower end of the nasolacrimal duct: resistance to flow of fluid, regurgitation of mucus via the other punctum, and no fluorescein is retrieved from the nose.
- Agenesis (rare): severe resistance to flow, clear fluid regurgitation, no fluorescein in nose.
- Physiologic/functional blockage: free and easy flow of fluorescein into the nose in symptomatic children, indicating a normal anatomic pathway.

If a nasal endoscope is used, it should be introduced into the inferior meatus after infracture of the inferior turbinate. This maneuver is often therapeutic as it opens up a narrow inferior meatus and may stretch a stenotic ostium.[34] The fluorescein-stained fluid should be syringed through the system and observed through the endoscope.

- Atresia is identified as ballooning of the submucosa with no passage of fluorescein.
- Stenosis appears as a poor flow through the narrow valve (Fig. 21.6A).
- A clear free flow indicates either that the infracture has been effective or that the patient has "functional" epiphora.

The system should then be probed via the upper canaliculus, as this is anatomically favorable for the onward, downward passage of the probe into the nasolacrimal duct and therefore may be less likely to result in canalicular damage. The smallest probe available should be used (usually a Bowman size 0000). The probe is passed in the same manner as the dilator until it reaches a hard stop that indicates the medial wall of the sac. The probe is withdrawn slightly and rotated 90° so that its tip is pointing downward. It is then advanced gently downward but also slightly posteriorly and laterally to follow the path of the nasolacrimal duct. During passage of the probe, the operator should note the level of any resistance. If the probe perforates a persistent membrane at the valve of Hasner, this may be felt as it enters the inferior meatus.

If being performed with endonasal control, in a successful procedure, the probe will be observed entering the inferior meatus through the valve of Hasner (Fig. 21.6B).

Unsuccessful probings are observed when the probe:

- fails to perforate the atretic mucosa (Fig. 21.6C); or
- creates a false passage by missing the valve of Hasner, and either carries on in a submucosal plane to the floor of the nose or enters the meatus through a false and usually ineffective passage.

In the first instance, a cut down onto the probe may be required; in the other it may be possible to steer the probe

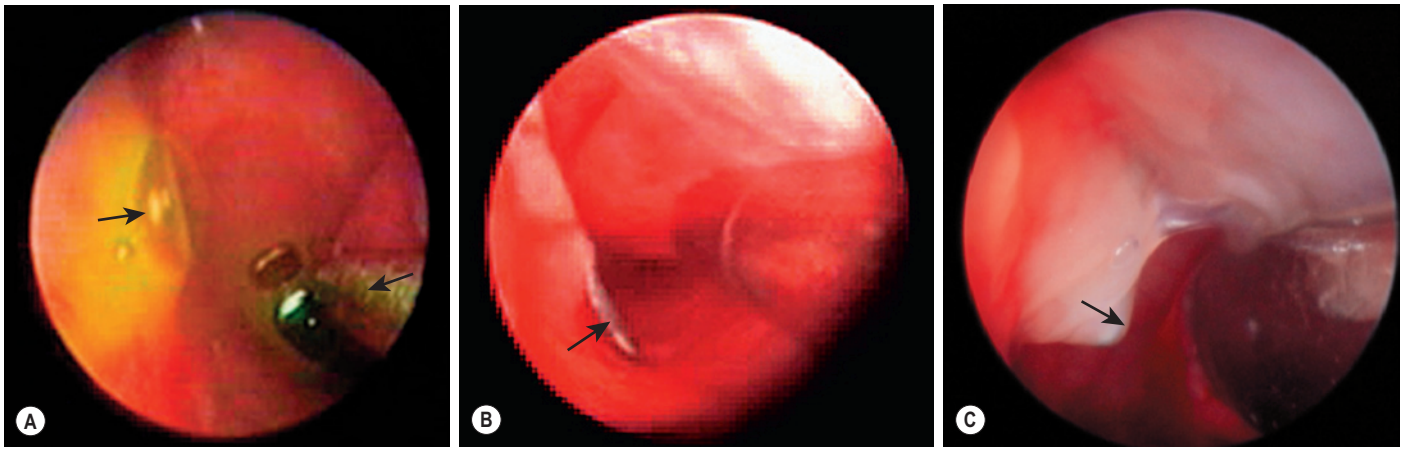


Fig. 21.6 (A) Stenotic flow through the valve of Hasner – right nostril. (B) Probe entering the inferior meatus via the valve of Hasner – right nostril. (C) Probe distending, but not perforating, the mucosa in a case of atresia of the lower end of the nasolacrimal duct – right nostril. *(Courtesy of Paul White.)*

under direct visualization toward and through the stenotic or atretic valve of Hasner. If the perforation is inadequate and felt to be tight, the probe size should be increased to a maximum size 1. Larger probes should be avoided as they may induce canalicular damage. To confirm patency, the syringing should be repeated with fluorescein-stained saline.

Postoperatively a steroid/antibiotic combination should be instilled for 2 weeks. Improvement is usually noted within a few days of the probing. If there has been no improvement by 1 month, it is unlikely that the treatment has been successful.

What to do if probing fails

If probing fails, it is important to identify the reason for failure. Failure is generally due to one of three causes:

1. Failure to create an anatomically patent passage due to:
   - **a.** a tight inferior meatus due to a large inferior turbinate;
   - **b.** failure to perforate the mucosa with the probe;
   - **c.** submucosal passage of the probe;
   - **d.** false passage formation; or
   - **e.** inadequate size of the perforation.
2. Physiologic (functional) epiphora. Functional epiphora is persistent watering despite a clear, patent, free-flowing syringing, observed endoscopically in the inferior meatus and no resistance felt on probing. All other causes of lacrimation or epiphora must be eliminated. The fluorescein disappearance test demonstrates delay. The cause is probably physiologic pump failure. Such children may have an upper respiratory cause, such as large adenoids. A history regarding nasal symptoms should be taken.
3. Complex abnormalities of the outflow system. Abnormalities of the canaliculi or the proximal nasolacrimal duct become commoner in older children. These abnormalities may be complex, especially in children with abnormal bony facial structure.[35–37]

A major advantage of endoscopic probing is that these common causes of failure can be identified and treated at the first probing, improving the success rate.[38]

If endoscopic probing was not performed on the first occasion, then this approach is useful in re-probings. It will identify the most frequent causes of failure and permit appropriate treatment.[38] If the initial procedure was an endoscopic procedure, subsequent treatment is dependent on the original findings. Another option is intubation of the system with silicone tubes.[39] However, intubation carries risk of damage to the ocular surface and lacrimal system. It may be unnecessary (e.g. in functional cases), and is no more effective than endoscopic probing in repeat cases.[40]

One of the possible complications of probing is the creation of a false passage, a situation when the probe passes out with the anatomical lacrimal outflow system. This can occur in a variety of places along the lacrimal outflow channels but the commonest sites are: (1) when the probe perforates the nasal mucosa at the end of the bony nasolacrimal duct above the valve of Hasner (which may be stenosed or atretic); and (2) when the probe misses the valve of Hasner and continues submucosally towards the roof of the mouth. These are easy to see when using an endoscope and the probe can be directed towards the correct exit point – the valve of Hasner – which can be seen as a small dimple in the mucosa. It is more difficult to envisage without endoscopy, but if there is no sensation of overcoming a small resistance or if no fluorescein can be retrieved from the nose following the post-probing flush, then the possibility of false passage should be considered.

Intubation

Indications for silicone tubes include upper nasolacrimal duct obstruction and canalicular stenosis.[39] Intubation can be employed to treat "failed probings,"[41] but the etiology of the failure should be clarified prior to intubation. Tubes may be bicanalicular or monocanalicular; insertion of monocanalicular tubes can require either retrieval of the distal end of the tube from the nasal cavity ("Monoka") or "pushed" insertion of the tube from the proximal end using a metal introducer ("Masterka"). Both techniques have been used with successful outcomes.[42–44]

Intubation should take place under general anesthetic after the nose has been prepared with decongestant. Nasal endoscopic guidance is used to view the inferior meatus. Tubes come with a metal introducer. Each end is placed through the system via the canaliculi, into the sac, and down the nasolacrimal duct into the inferior meatus. They should be

retrieved under direct visualization. Ritleng tubes – silicone tubes, inserted via hollow probes which are placed in the lacrimal system – are easier to insert, less traumatic, and more likely to be successful, especially in the hands of a novice.[45] Postoperative treatment consists of a topical antibiotic and steroid preparation into the conjunctival sac.

Possible complications of intubation include cheese-wiring through the canaliculi, dislocation superiorly or inferiorly, infection, epistaxis, sinusitis, granulomatous reaction, and scarring of the drainage system; the ocular surface can be affected by conjunctival irritation and corneal abrasion.[46]

The optimal time to leave tubes in place is not known, but 3–6 months is usually recommended.[41–47] Tubes should be removed under general anesthetic via the nose to prevent aspiration of the tube. The system is then irrigated to remove debris and to confirm patency.

Balloon catheter dilatation of the lacrimal system is an alternative to intubation in patients with failed probing.[48] This has a high success rate, similar to that of intubation,[49] but is significantly more expensive. It has been suggested that balloons have a role in the primary treatment of congenital nasolacrimal duct obstruction, but the results are no better than "blind probing."[50] The role of balloon dacryoplasty in the management of congenital nasolacrimal duct obstruction still needs to be fully evaluated.

Dacryocystorhinostomy

Children rarely require a dacryocystorhinostomy (DCR), but indications include persistent epiphora despite probing and intubation, complex congenital abnormalities of the lacrimal outflow apparatus (particularly involving the upper nasolacrimal duct), and acquired disease usually caused by infection or trauma.[51] External and endoscopic routes are possible. Excellent success rates, comparable to those of adult DCR, have been reported.[52–54]

Congenital fistulae of the lacrimal outflow system

Fistulae of the lacrimal system in which tracts open onto the skin directly from the puncta, canaliculi, lacrimal sac, or nasolacrimal duct are rare. They may appear as double puncta, or appear in the region of the medial canthus (Fig. 21.7). They are usually non-functioning and should be left untreated unless they allow flow of tears onto the face or result in epiphora (rare). Treatment involves excision of the fistula after ensuring that the remaining outflow system is patent.

Punctal and canalicular abnormalities

Failure of the proximal end of the lacrimal drainage system to canalize may result in punctal stenosis or atresia. This is often asymptomatic especially if only one punctum is abnormal. Narrow puncta should be dilated. Membranous obstruction should be pierced with a needle and dilated. These cases do well, but are often associated with distal abnormalities and a syringing should always be performed.

Abnormalities proximal to the sac result in surprisingly few symptoms. Agenesis should be suspected if the papilla is not readily obvious.[55] If only one punctum is missing, syringing via the other one detects the extent of the damage. Surgery to construct these areas is specialized. Retrograde probing from an external DCR incision may be attempted through the sac; otherwise, a Jones tube is required. This type of surgery may be left until the child is in their teens.

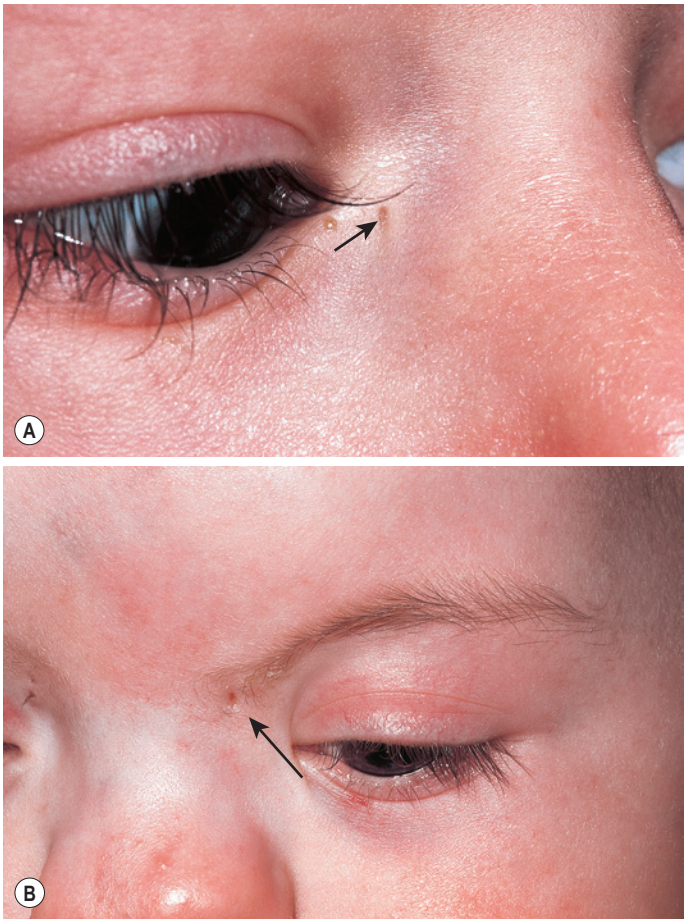


Fig. 21.7 Congenital fistula of the nasolacrimal system. A fistula can be seen as a tiny mark (A) below or (B) above the medial canthus.

Acquired conditions of the lacrimal drainage apparatus

Canaliculitis

Canaliculitis in children is uncommon but may be due to bacterial or primary herpes simplex infection. Management involves obtaining viral and bacterial cultures and treatment with antibiotics or antiviral agents depending on the clinical and laboratory findings. Probing in the active phase should be avoided.

Acute dacryocystitis

Acute dacryocystitis may accompany non-patent nasolacrimal systems or may occur as a primary event. This is particularly common in infants with dacryocystocele.[56] Treatment comprises prompt intervention with intravenous antibiotics as retrobulbar abscesses may occur. Cultures should be taken of any pus or discharge that can be expressed through the punctum. Probing should not be performed as damage to the congested epithelium may cause false passage and lead to orbital cellulitis and fistula formation.[57] Skin incisions should not be made during the acute phase as an external fistula may occur. If a mass remains after resolution, evacuation can

be performed through the skin with a needle through the lower pole of the sac, although the pus may be inspissated or loculated. Once the infection has resolved, probing should be performed if epiphora persists.

Acquired nasolacrimal duct obstruction

Acquired nasolacrimal duct obstruction may be caused by diseases of the nose or paranasal sinuses, especially chronic allergic rhinitis or persistent upper respiratory tract infections with enlarged adenoidal lymphoid tissue. These are commoner in older children and adolescents.[58] Rarely, acquired obstruction may herald a more sinister cause such as fibrous dysplasia, cranial metaphysial or cranial diaphysial dysplasia, or tumor formation (see Chapter 25). Treatment should be aimed at the underlying cause.

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The management of orbital disease in children

Alan A McNab

Chapter contents

ORBITAL DISEASE AND AGE
CLINICAL ASSESSMENT
INVESTIGATIONS
SURGERY
REFERENCES

Orbital abnormalities in childhood may be congenital or acquired. Congenital developmental abnormalities can be confined to the orbit or part of a more widespread craniofacial malformation. For example, proptosis may be related to shallow or small orbits in the craniosynostoses (Fig. 22.1). The relationship between the orbits may also be disturbed: in hypertelorism the orbits are widely separated; in hypotelorism, they are set close together. An orbital wall defect may allow prolapse of intracranial tissue with pulsating exophthalmos or enophthalmos. Orbital growth occurs throughout childhood and congenital absence of the globe, enucleation, or radiotherapy results in failure of normal growth of the orbits and the adjacent facial structures (Fig. 22.2).

Children with acquired orbital disorders most commonly present with signs and symptoms of a mass leading to proptosis, either axial or non-axial, soft tissue signs, and in some cases a palpable mass. Other presentations include reduced vision, restriction of eye movements, pain, and inflammation. Occasionally, a child may present with enophthalmos, for example following orbital fracture.

The relative frequency of the conditions causing proptosis in childhood varies considerably,[1–8] depending, in part, on the source of the report. Series from eye hospitals[3] differ from those from neurosurgical[2] or pediatric units.[6] Geographic factors can have a major impact. The major causes of proptosis in African,[4] Indian,[9] or Turkish[10] children are different from those seen in Europe and North America. In developing countries, secondary involvement of the orbit by advanced and neglected retinoblastoma is a common cause of proptosis, but this is a rare cause in developed countries. Series that rely solely on tissues specimens[1,5,7,8] exclude the many conditions that can be diagnosed and treated without biopsy or surgery, such as infantile periocular hemangioma, or those in which biopsy may be more conveniently obtained at another site of involvement, such as neuroblastoma or Langerhans cell histiocytosis. Population-based studies have shown that the incidence of pediatric orbital tumors has remained fairly constant. Conversely, there has been a steady increase in the incidence of orbital tumors, particularly lymphoma, in adults.[11]

Orbital disease and age

Within the childhood years, defined here as ages up to and including 16 years, knowledge of the trends in the incidence of orbital disorders at different ages can help the diagnostic process.

Clinical data of 326 children seen by the orbital service in Vancouver, Canada, from 1976 provide useful information (Table 22.1). Neoplasia and structural abnormalities (including cysts) account for the great majority of children presenting with orbital disease (Fig. 22.3). This is quite different from adults, in whom over 60% of presentations are due to inflammatory diseases, most commonly Graves' orbitopathy, and structural abnormalities account for less than 15% of cases. The distribution of orbital disease in children aged over 11 years resembles the adult pattern (Fig. 22.4).

Fortunately, only a small proportion of pediatric orbital neoplasms are malignant, similar to other published series from North America.[6,7,12] Under 2 years of age, the major causes of proptosis are infantile hemangiomas and venous-lymphatic malformations (lymphangioma), dermoids and other epithelial cysts, and other structural abnormalities. Fig. 22.5 shows that while some lesions are distributed evenly throughout childhood (venous-lymphatic malformation, varices, and arteriovenous malformations), others tend to occur within a specific age range. Seven patients with rhabdomyosarcoma were seen, whose ages ranged from 2 to 11 years. The seven patients with Langerhans cell histiocytosis ranged in age from 3 to 9 years. Infantile hemangioma was overwhelmingly more common in early infancy. Inflammatory conditions were increasingly frequent after the age of 5 years, especially orbital cellulitis, idiopathic orbital inflammatory disease (6 years and over), and thyroid orbitopathy (11 years and over). It is noteworthy that there were two cases of lacrimal gland carcinoma and four of granulomatosis with polyangiitis in this series, a reminder that, although rare, these potentially lethal conditions can occur in childhood.



Fig. 22.1 A child with bilateral proptosis due to shallow orbits in Crouzon syndrome.



Fig. 22.2 Left enophthalmos following radiotherapy for retinoblastoma. *(Patient of the University of British Columbia.)*

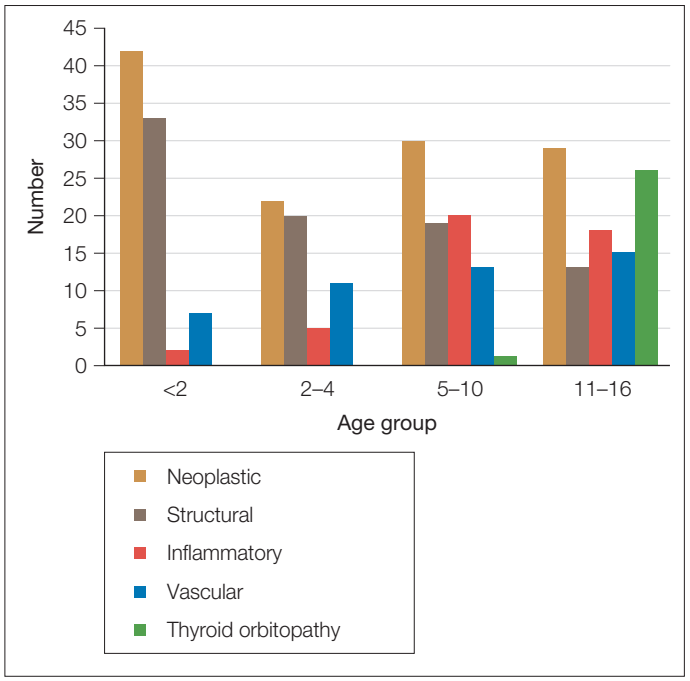


Fig. 22.3 Distribution of orbital disease by age group in patients less than 17 years of age.

Clinical assessment

When assessing a child with orbital disease, a history, examination, and differential diagnosis in the context of the child's age are essential before investigations can be planned.

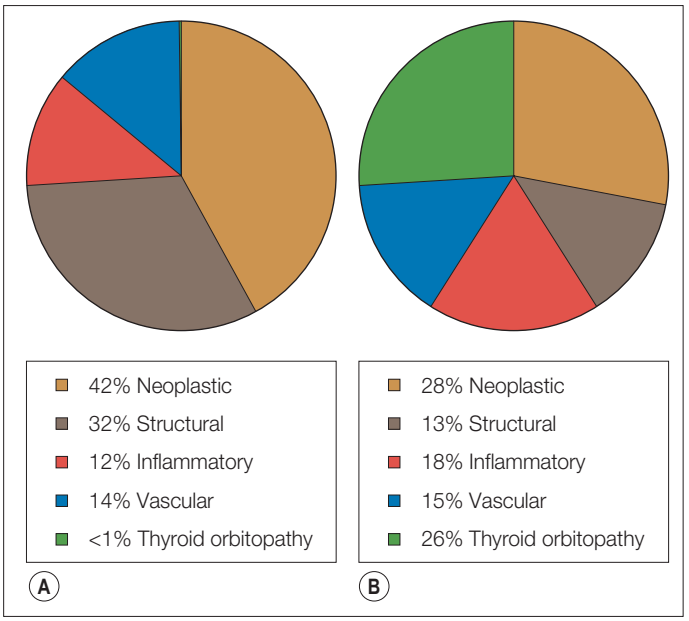


Fig. 22.4 (A) Distribution of orbital disease in patients less than 11 years of age. (B) Distribution of orbital disease in patients 11–17 years.

History

The age of onset, laterality (unilateral or bilateral), and the tempo of onset are important clues to the diagnosis. The duration may be difficult to determine accurately and a review of old photographs may be helpful.

Bilateral proptosis in early infancy is often due to shallow orbits in craniofacial malformations (see Fig. 22.1). This can occasionally be unilateral, as in plagiocephaly. Usually, however, unilateral proptosis is due to the globe being displaced by a mass within the orbit.

Some masses such as optic nerve glioma or dermoid cyst grow slowly. Rapidly increasing proptosis suggests a metastatic deposit or rapidly growing tumor such as rhabdomyosarcoma. Rapid tumor growth may be associated with necrosis and hemorrhage, resulting in signs of inflammation and periorbital ecchymosis. The presence of bilateral ecchymosis is suggestive of metastatic neuroblastoma.

A catastrophic onset (within hours) implies hemorrhage within an often unsuspected, pre-existing lesion, such as a venous-lymphatic malformation (lymphangioma). Occasionally, the onset of orbital cellulitis may be very sudden. It is usually accompanied by pain, local inflammation, and limitation of ocular motility in a child who is generally ill and febrile. The presence of clinically detectable orbital and periorbital inflammatory symptoms and signs in childhood is overwhelmingly associated with infection or non-specific orbital inflammatory disease. Although inflammation is part of the classical description of rhabdomyosarcoma, it is not typical and was absent in all six patients in the above series from Vancouver, even though all had a rapid onset of symptoms.

Most round-cell tumors in childhood, including rhabdomyosarcoma, granulocytic sarcoma (chloroma, or tumefactive extramedullary myeloid leukemia) and Ewing sarcoma, present as a mass developing over weeks in a subacute manner. Metastatic neuroblastoma can present with onset of proptosis over days.

Table 22.1 Orbital disease in children: multiseries data comparison

	Rootman[16]		Bullock et al.[12]		Crawford[6]		All series	
	No.	% of series	No.	% of series	No.	% of series	No.	% of all series
NEOPLASIA								
Optic nerve glioma	17	5.2	5	3.6	17	3.0	39	3.8
Meningioma	2	0.6	2	1.4			4	0.4
Other neurogenic tumor	6	1.8					1	0.1
PNS tumors	19	5.8	9	6.4	14	2.5	42	4.1
Lymphocytic	1	0.3	1	0.7	3	0.5	5	0.5
Other lymphocytic	3	0.9	4	2.9	20	3.6	27	2.6
Histiocytic	7	2.1	1	0.7	20	3.6	28	2.7
Vascular	36	11.0	14	13.6	14	2.5	64	6.2
Secondary/metastatic	5	1.5	4	2.9	21	3.8	30	2.9
MESENCHYMAL								
Rhabdomyosarcoma	7	2.1	3	2.1	11	2.0	21	2.0
Fibrous	1	0.3	3	2.1	1	0.2	5	0.5
Histiocytic	2	0.6	2	1.4			4	0.4
Bone	3	0.9					3	0.3
Neoplasia	6	1.8	2	1.4	5	0.9	13	1.3
Other	2	0.6	1	0.7			3	0.3
Unknown neoplasia			1	0.7	3	0.5	4	0.4
Lacrimal	2	0.6					2	0.2
Teratoma					1	0.2	1	0.1
STRUCTURAL								
Cystic	60	18.4	59	42.1	6	1.1	122	11.9
Bone anomalies	9	2.8			50	8.9	59	5.8
Ectopia	13	4.0	11	7.9			24	2.3
Other	3	0.9			2	0.4	4	0.4
INFLAMMATORY								
Infectious diseases	21	6.4			232	41.5	253	24.7
NSOIS	14	4.3	6	4.3	5	0.9	25	2.4
Inflammatory, other	10	3.1	3	2.1			13	1.3
OTHER								
Thyroid orbitopathy	27	8.3			107	19.1	134	13.1
Vascular	46	14.1	9	2.9	14	2.5	69	6.7
Atrophy/degeneration	2	0.6					2	0.2
Unknown	2	0.6			13	2.3	15	1.5
TOTAL	**326**		**140**		**559**		**1025**	

NSOIS, Non-specific orbital inflammatory syndrome; PNS, peripheral nerve sheath.

An increase in proptosis with crying or straining is suggestive of infantile periocular hemangioma, venous malformations, or absence of the sphenoid wing (as in neurofibromatosis type 1 [NF1]). When very obvious, its presence helps to exclude malignancy as a cause of the proptosis.

Pulsating exophthalmos may be associated with congenital defects of the orbital wall (as seen in NF1 or encephalocele). Occasionally, large periocular infantile hemangiomas (capillary hemangiomas) pulsate due to their rich arterial blood supply, as may high-flow arteriovenous malformations, though the

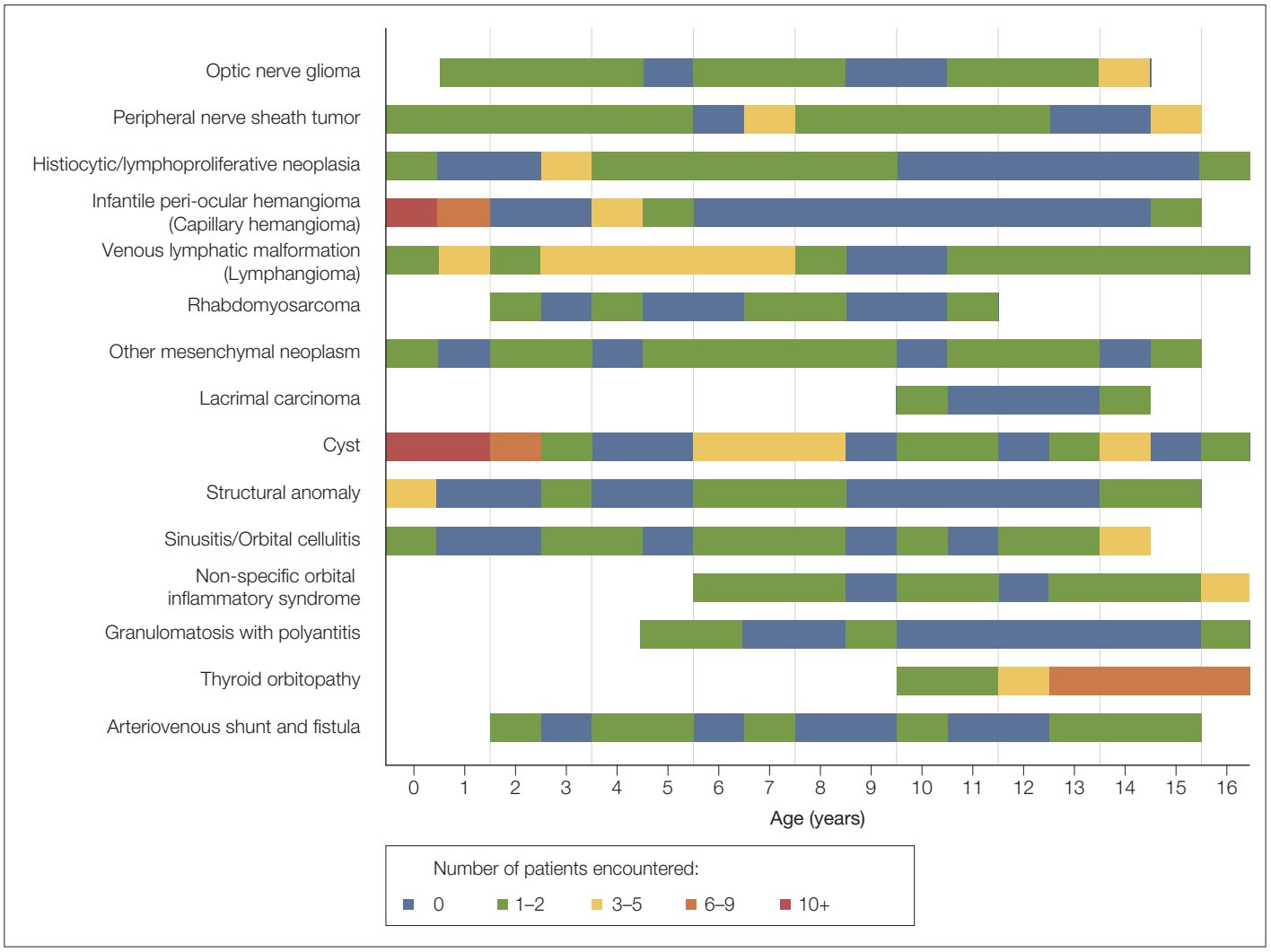


Fig. 22.5 Age distribution of common orbital diseases.

latter are rare in childhood and more common in adolescence or young adulthood.

Skin discoloration may offer a clue to the underlying etiology. Red is suggestive of the arterial supply of infantile periocular hemangioma, which, when superficial to the septum, almost invariably involves the overlying skin. When deep, these may have a blue or purple hue. Venous or venous-lymphatic malformations (lymphangiomas) appear blue or purple, as do some cystic lesions, lacrimal or conjunctival cysts. Some cystic lesions, for instance the cysts associated with colobomatous microphthalmos, are bluish but transilluminate with a focal light. The brownish cutaneous discoloration of hemosiderin is usually caused by previous bleeds into a venous-lymphatic malformation (lymphangioma) or, rarely, by metastatic neuroblastoma. Both of these may present with spontaneous ecchymosis.

Children with blunt orbital trauma and orbital wall fractures may present with severe restrictive strabismus and symptoms of vagal stimulation such as nausea, vomiting, and hypotension, often induced by attempted eye movements.[13] The absence of external signs of orbital trauma may make the diagnosis less obvious (Fig. 22.6).

Examination

Children with proptosis must have a visual assessment. In infants, this may be limited to observing fixation. Resentment to covering of the contralateral eye suggests poor vision. The 10-prism diopter base down test may be useful if poor vision is suspected in an orthotropic child. A cover test should be performed, and ocular ductions and versions assessed. Limitation of ductions may be due to mechanical restriction by tumor, muscle infiltration, inflammation, edema, or entrapment. Third, fourth, and sixth cranial nerve function should be tested, as well as sensory testing of the first and second divisions of the trigeminal nerve, if possible. Occasionally, in an older child with a blow-out fracture, a forced duction test may be useful to detect muscle restriction, but clinical signs will usually suggest the diagnosis without subjecting the child to this intervention.

The site of an orbital mass may be indicated by the direction in which the eye is displaced. A posterior or intraconal tumor results in axial proptosis (Fig. 22.7); an extraconal tumor will usually displace the eye vertically or horizontally. For example, in fibrous dysplasia of the orbit, which most commonly affects

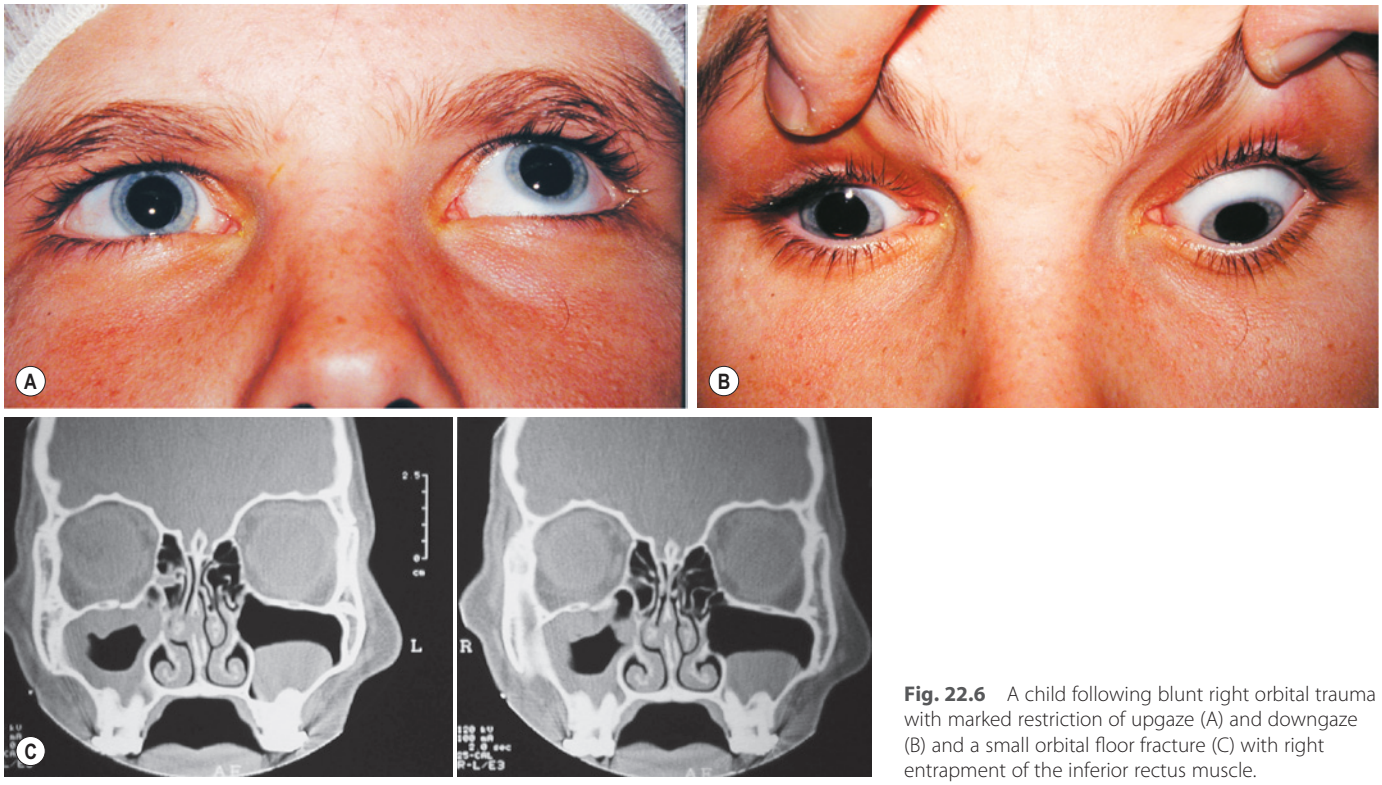


Fig. 22.6 A child following blunt right orbital trauma with marked restriction of upgaze (A) and downgaze (B) and a small orbital floor fracture (C) with right entrapment of the inferior rectus muscle.

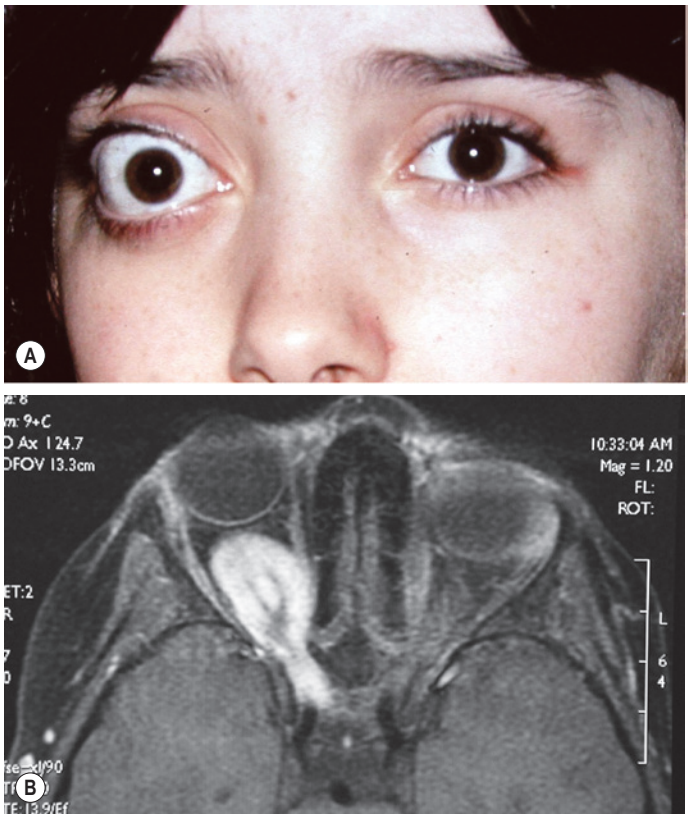


Fig. 22.7 An 11-year-old girl with right axial proptosis (A) due to an optic nerve glioma that extends through the optic canal (B).

the frontal bone, and in juvenile ossifying fibroma, which also commonly involves the orbital roof, the globe is usually displaced downwards and forwards (Fig. 22.8). Orbital cellulitis secondary to ethmoidal sinus infection usually displaces the globe laterally. Although the globe is displaced away from most mass lesions, it can be displaced toward them, as in the case of cicatrizing lesions within the orbit.

Enophthalmos may occur in several childhood scenarios, including following radiotherapy (see Fig. 22.2), with sphenoid wing dysplasia (in NF1), in Parry–Romberg syndrome or hemifacial atrophy, and as the result of orbital wall fractures.

Globe position should be recorded using an exophthalmometer and a transparent ruler is used to measure the amount of vertical and horizontal displacement. It is difficult to measure proptosis accurately in infants, but careful observation from above or below often helps to highlight its presence.

Eyelid position should be recorded. Eyelid retraction or lag on downgaze may suggest thyroid orbitopathy, but may also indicate tethering by tumors.

Slit-lamp examination may show dilated dysmorphic venous channels in the conjunctiva of patients with vascular malformations. Venous-lymphatic malformations (lymphangioma) may be associated with visible conjunctival lymphangiectasis or cysts, which occasionally contain a meniscus of blood. Lisch nodules on the iris are diagnostic of NF1, increasing in number with age, and may assist in the diagnosis of plexiform neurofibroma (Fig. 22.9) or sphenoid wing dysplasia with encephalocele as causes of proptosis. Juvenile cataract is a marker for NF2. Meningioma and schwannoma are important causes of orbital mass in this disorder.

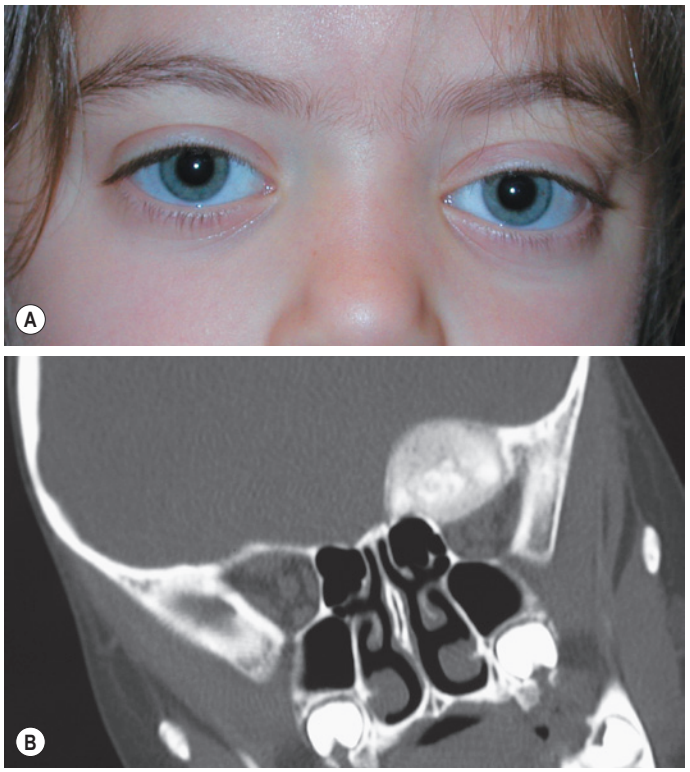


Fig. 22.8 A 7-year-old girl with non-axial left proptosis (A) due to an ossifying fibroma of the orbital roof (B).



Fig. 22.9 A 13-year-old girl with left hypoglobus, a thickened and hyperpigmented upper eyelid and temple due to plexiform neurofibroma in neurofibromatosis type 1.

The presence of an afferent pupillary defect suggests optic neuropathy, which may be due to intrinsic optic nerve disease, such as glioma, or to extrinsic compression, as in fibrous dysplasia involving the optic canal, which is rare. Visual field testing, if feasible in older children, is helpful in assessing and documenting optic neuropathy. In older children, color vision can be assessed using subjective red desaturation or an Ishihara chart to confirm the presence of optic neuropathy.

Cycloplegic refraction is important to detect astigmatism due to distortion of the globe by an orbital mass. Retrobulbar lesions tend to result in a hyperopic shift, and lesions anterior to the equator may produce astigmatism. These are important causes of amblyopia.[14] Occasionally, unilateral axial myopia or buphthalmos may mimic proptosis. Long-term occlusion of an eye, as in uncorrected unilateral ptosis due to infantile periocular hemangioma (capillary hemangioma), can result in ipsilateral axial myopia.

Optic disc swelling or atrophy can appear in patients with optic nerve compression or glioma. If the mass is close behind the globe, choroidal folds may be present. Optico-ciliary shunt vessels, classically associated with primary optic nerve sheath meningioma (PONM), are much more frequently seen in optic nerve glioma in children, because PONM is much rarer in children.

Palpation of the orbit reveals the consistency of a localized mass. Infantile periocular hemangiomas (capillary hemangiomas) feel firm and spongy. Their contents cannot be expelled by applied pressure, whereas orbital varices are easily drained of blood, even with gentle pressure. Dermoids should be examined for mobility or fixation and the presence of a posterior margin or a tail extending into the orbit or temporalis fossa. A posterior extension or extension through the lateral wall of the orbit is more likely to be present in dermoids that are situated inside the orbital rim than in those directly overlying the rim.

The evaluation of children with orbital disease should include a general examination, as this may give useful clues to the diagnosis. Café-au-lait spots suggest NF1, and skin pigmentation may be seen in some forms of fibrous dysplasia (McCune–Albright syndrome). Characteristic skin lesions may also be present in Langerhans cell histiocytosis and juvenile xanthogranuloma. Infantile periocular hemangioma (capillary hemangioma) of the orbit is often associated with cutaneous infantile periocular hemangiomas (capillary hemangiomas) elsewhere. In suspected metastatic disease there may be other involved sites such as an abdominal mass in neuroblastoma or skin, scalp, or bony lesions in Langerhans cell histiocytosis. Thyroid orbitopathy may be accompanied by general symptoms and signs of hyperthyroidism.

Finally, obtaining opinions from other specialists, particularly general pediatricians, pediatric neurologists and ear, nose, and throat (ENT) surgeons, may help to determine the cause of proptosis in a child.

Investigations

Investigating children with proptosis should be guided by the history and clinical findings and tailored to each patient. Some disorders can be diagnosed clinically without the need for further diagnostic tests. In others, further tests will be necessary to confirm the suspected diagnosis or to assess the degree of orbital involvement. When other systems are involved, such as extension of tumor into the brain or sinuses or systemic involvement in malignancy, investigation of the child should be planned with the other specialists who may become involved in the child's care.

Radiology

Plain X-rays

Except where computed tomography (CT) or magnetic resonance imaging (MRI) is unavailable, plain X-ray has a very limited role. Detection of a radio-opaque foreign body is one potential use of plain X-rays. In general, plain X-rays are inadequate in the evaluation of orbital disease or trauma.

Computed tomography and magnetic resonance imaging

Diagnostic imaging of orbital structures was revolutionized by CT, and later by MRI. Modern CT scanners have very short acquisition times, which means that younger children may be scanned without the need for general anesthesia, and often with relatively mild sedation. If possible, children should be scanned on the most modern scanners available in order to minimize exposure to radiation. Modern scanners are able to provide high-resolution reconstructed images in coronal, sagittal and other planes. CT provides information about intracranial as well as orbital structures.[15] It yields more information on the presence of calcification and on bony detail, which can be important in assessing orbital fractures, and in surgical planning. CT can also be used when a ferromagnetic foreign body is suspected. The differential diagnostic yield is increased by the use of contrast agents, which enhance vascular lesions, inflammations, and some malignancies.

Sedation is usually necessary under the age of 3–4 years, though the speed of data acquisition has increased significantly. Data capture for orbital CT scan with a 16-slice scanner takes under 10 seconds, and more modern 32- or even 64-slice scanners reduce this to a fraction of that time. The relatively high dose of radiation makes CT useful for initial diagnosis but undesirable for regular follow-up, especially for patients with tumor suppressor gene mutations (retinoblastoma, neurofibromatosis, and rhabdomyosarcoma).

MRI provides higher resolution of soft tissue without exposure to ionizing radiation.[12] This is important if repeat imaging is necessary, for example a child with NF1 and optic nerve glioma who is being followed regularly. Any plane can be chosen at the time of the examination. Orbital views may be obtained with a 0.5–3.0 tesla field, and surface coils should be used to increase the surface-to-noise ratio. Contrast enhancement can be obtained for similar indications to those outlined above for CT, using gadolinium, which results in T1 shortening. Because fat has a bright signal on T1-weighted images, fat saturation techniques must be used to maximize the effect of contrast enhancement in the orbit. This is essential to examine the optic nerve, which would otherwise be swamped by the bright fat signal, potentially obscuring an important finding such as optic nerve sheath meningioma, which would be more obvious with CT.

Multiple image sequences can provide characteristic signal patterns, such as the fluid/fluid levels typical of low- or no-flow vascular malformations and aneurysmal bone cysts. Identification and dating of blood within hemorrhagic lesions such as venous-lymphatic malformations (lymphangiomas), presence or absence of flow within mass lesions, and contrast enhancement of the optic nerve in optic neuritis are further strengths of this technique.

Disadvantages include the time taken to image an orbit – 20 to 30 minutes – compared with CT, which takes seconds; CT can be used without sedation for much younger patients who can lie still for 2 or 3 minutes. Conversely, most patients under the age of 6 years require sedation or anesthesia (often using only intravenous propofol as opposed to intubation or laryngeal mask) for MRI because of the noise and duration of the procedure. MRI is generally contraindicated for patients with ferromagnetic foreign bodies which is often relevant to teenagers with their dental braces. A more specific problem of MRI for orbital work is its relative inability to image bone and calcification clearly, which may be important when differentiating glioma from meningioma in the orbit.

Surgery

The surgical approach to the child's orbit differs significantly from that taken in adult orbital disease. This is due to the relative shallowness of the orbit in childhood. Lateral orbitotomy, with lateral orbital wall removal, is unnecessary in most cases since lesions can usually be reached via the anterior approach. If possible, incisions should be hidden in the upper eyelid crease, or transconjunctival approaches used, to avoid obvious scars.

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Neurogenic tumors

Peter J Dolman and Yvonne Chung

Chapter contents

INTRODUCTION
FUNDAMENTAL SCIENCE
OPTIC PATHWAY GLIOMAS
PRIMARY OPTIC NERVE MENINGIOMAS
ORBITAL NEUROFIBROMAS
ORBITAL SCHWANNOMAS (NEURILEMMOMAS)
PERINEURIOMA
PERIPHERAL NERVE SHEATH MALIGNANCIES (PNSM)
PARAGANGLIOMAS
REFERENCES

Introduction

Primary neurogenic tumors of the orbit arise from the optic nerve, from peripheral sensory or motor nerves, or from the autonomic ciliary ganglion. Secondary neurogenic tumors include retinoblastomas and intracranial meningiomas that invade directly from contiguous structures or neuroblastomas and peripheral neuroectodermal tumors (Ewing sarcoma) that spread hematogenously; these are discussed in other chapters.

Fundamental science

Basic anatomy and origin of primary orbital neurogenic tumors

The optic nerve (cranial nerve [CN] II) extends from the optic disc to the chiasm and is divided into four parts: the intraocular portion within the sclera; the intraorbital portion, which pursues a sinuous course from the globe to the orbital apex; the intracanalicular portion within the narrow bony optic canal; and the intracranial portion from the canal to the chiasm.[1] The nerve carries axonal bundles (95% retinal ganglion axons and 5% supportive astrocytes) and is surrounded by a pial sheath containing capillaries, the arachnoid layer, and a thick protective dural coat.[2] The nerve is an extension of the central nervous system (CNS), and the myelin surrounding its axons is produced by CNS oligodendrocytes rather than by perineural Schwann cells, as seen in peripheral nerves. Unlike peripheral nerves, it is not surrounded by neurilemma and so cannot regenerate itself.[3] Optic nerve gliomas arise from pial astrocytes within the substance of the nerve, while primary optic nerve sheath meningiomas arise from cap cells of the arachnoid around the intraorbital or intracanalicular portion of the nerve.

The orbital peripheral nerves are either sensory branches of the trigeminal nerve (CN V) or motor branches to the extraocular muscles and eyelid retractors. These consist of bundles of axons, each of which is an extension of a single nerve cell, and is surrounded by Schwann cells that myelinate the fibers to improve conductivity. The endoneurium is a loose matrix of collagen and extracellular matrix between the axons. Perineurium surrounds individual fascicles and the epineurium is the fibrous coating encasing the complete nerve, and contains within it the blood supply (Fig. 23.1).[4] Common benign peripheral nerve sheath tumors include neurofibromas (proliferations of axons, fibroblasts, and Schwann cells) and schwannomas (composed predominantly of Schwann cells). Rare lesions include the perineurioma and malignant peripheral nerve sheath tumors.

The ciliary ganglion lies just temporal to the optic nerve, 1 cm behind the globe, and houses the parasympathetic short ciliary cell bodies. A rare tumor arising from non-chromaffin tissue around the ganglion and ciliary nerves is the paraganglioma.[5]

All of these specific primary neurogenic tumors will be described individually.

Pediatric versus adult orbital neurogenic tumors

Orbital neurogenic tumors differ between the pediatric and adult population in incidence and behavior. The optic nerve glioma is the most common neurogenic tumor in children and is relatively benign when isolated to the orbit, in contrast to the adult form, which is rare and often highly aggressive.[6] Neurofibromas are the next most common lesions in children. These are often plexiform neurofibromas associated with neurofibromatosis type 1 (NF1; see below), which may rarely transform into a malignant variant after adolescence. Adult-onset neurofibromas are rare and typically are solitary benign lesions.[7] Primary optic nerve sheath meningiomas are more common in adults and tend to be relatively indolent sporadic lesions, whereas in children they are more aggressive lesions often associated with neurofibromatosis type 2 (NF2).[8]

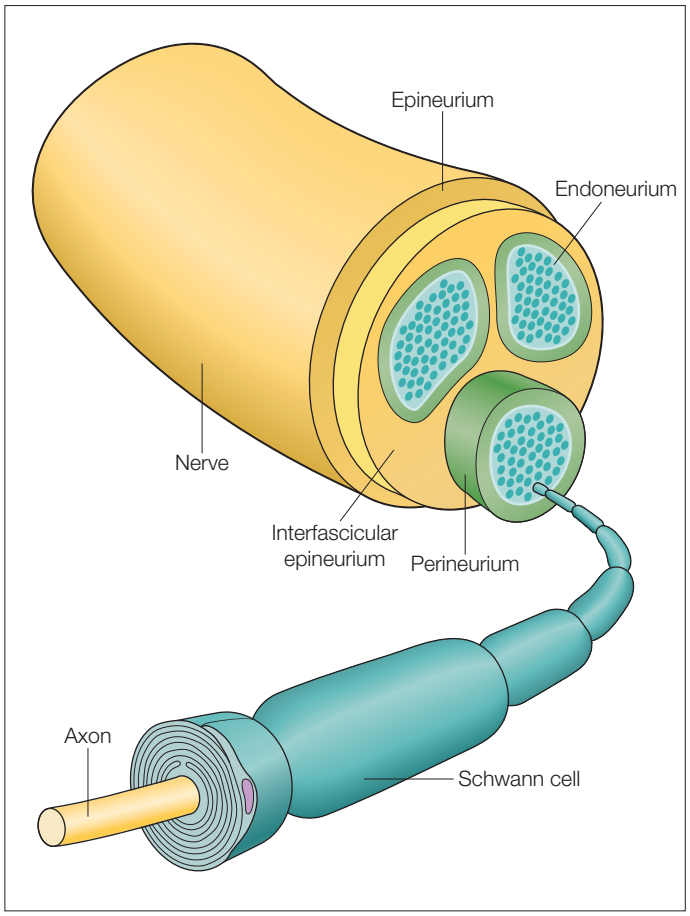


Fig. 23.1 Illustration of peripheral nerve with nerve fascicles containing bundles of axons, each wrapped with Schwann cells. The perineurium surrounds each fascicle and the epineurium surrounds the entire nerve.

Neurofibromatosis (NF1 and NF2)

Most pediatric neurogenic tumors may be associated with one of the seven neurofibromatoses. These syndromes are caused by specific gene mutations and are characterized by various cutaneous pigmentary disorders, and peripheral or central nervous system benign and malignant neurogenic tumors. They are discussed in detail in Chapter 68, but features of the two most common variants, NF1 and NF2, are summarized here.

NF1 (von Recklinghausen disease) is an autosomal dominant genetic disorder occurring in 1 in 2600 births, and is due to a mutation in the *NF1* gene at chromosome 17q11.[9] Cutaneous lesions are the first manifestations and include multiple café-au-lait macules, axillary freckles, iris Lisch nodules and neurofibromas.[10] Sphenoid wing bone anomalies and optic pathway gliomas (occurring in 15% of NF1 patients) appear by the age of 3 years. Malignant transformation of tumors may occur in late adolescence or adulthood.[11]

NF2 is a much rarer autosomal dominant genetic disorder caused by abnormalities in the *NF2* gene on chromosome 22[12]; this gene produces merlin, a tumor suppressor protein, and affected individuals are predisposed to various nervous system neoplasia including bilateral vestibular schwannomas, intracranial and optic nerve sheath meningiomas, and spine tumors.[13]

Optic pathway gliomas

Pathogenesis

Optic pathway gliomas (OPG) are pilocytic astrocytomas arising from astrocytes within the optic nerve or its surrounding pial layer.[14] Anterior OPG involve the intraorbital or intracanalicular optic nerve, while posterior OPG involve the chiasm or post-chiasmal radiations near the hypothalamus.

Although some have suggested they are hamartomas based on their benign behavior, most consider them to be neoplastic as they are histologically indistinguishable from other intracranial pilocytic astrocytomas and they can behave aggressively. Also, BRAF-KIAA and other chromosomal deletions associated with tumor suppression genes have been identified in sporadic tumors.[15]

Epidemiology

Optic pathway gliomas comprise 2% of cerebral gliomas. They occur primarily in children; 90% have been identified before the age of 20.[16] Thirty percent are associated with NF1 and usually appear early in childhood involving the anterior pathway.[6] A small number are associated with NF2, but most occur sporadically.

Clinical presentation

Orbital optic nerve gliomas are slow-growing masses typically presenting in early childhood with proptosis or globe displacement, often first noticed by the parents or relatives. Strabismus and restriction in ocular ductions (particularly upgaze) may develop with growth of the tumor (Fig. 23.2A). Decreased central, color, and peripheral vision may be detected on first presentation (Fig. 23.2B), and often deteriorate over time with growth of the tumor and gradual compression of the nerve or its blood supply. The child may be aware of diplopia but is often not as bothered by the loss of visual acuity. Occasionally corneal exposure or pressure on sensory nerves may cause discomfort or pain. Optic nerve edema and later pallor may develop with ensuing optic atrophy.[17]

In some cases, the clinical features may wax and wane over time, and even some large lesions have been reported to spontaneously involute (possibly as a result of resorption of cystic degeneration), so that several follow-up visits may be required to assess the behavior of a particular case.

Posterior pathway gliomas have no orbital findings, but present with visual disturbances, with bitemporal visual field defects for chiasmal lesions or hemifield loss for post-chiasmal lesions. Precocious puberty may develop in over a third of children with NF1-associated chiasmal gliomas.[18] Sporadic cases of posterior OPGs tend to present more with raised intracranial pressure and obstructive hydrocephalus.[19]

Investigations

Computed tomography (CT) scans

CT scans identify tubular optic nerve enlargement of the orbital portion of an optic nerve glioma, often with a characteristic kink or bend at the junction of the tumor with normal nerve.[20] Calcification within the tumor is considered to be evidence of slow growth and a lower grade histology. Clear zones within the tumor mass may be areas of cystic degeneration.

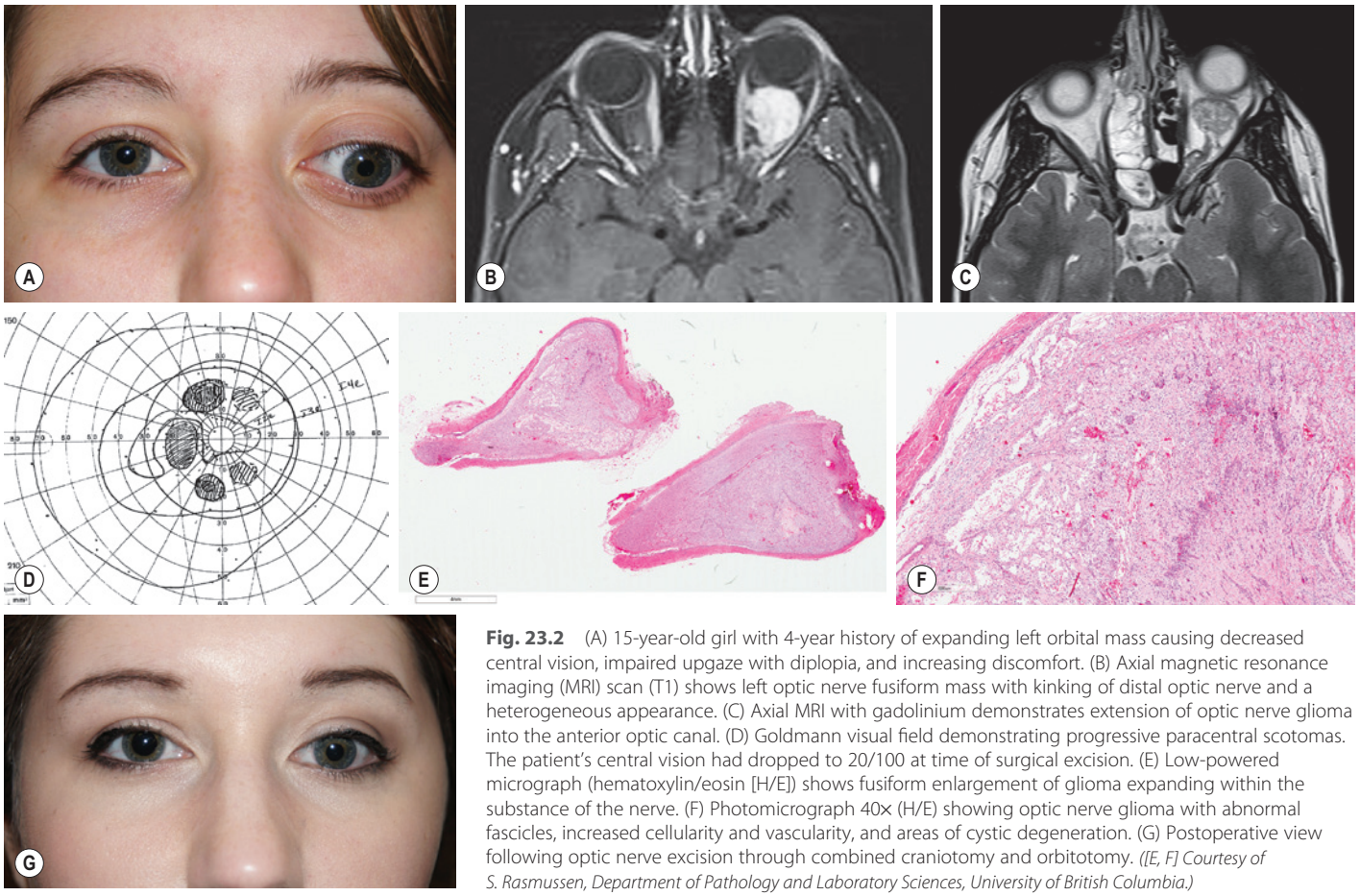


Fig. 23.2 (A) 15-year-old girl with 4-year history of expanding left orbital mass causing decreased central vision, impaired upgaze with diplopia, and increasing discomfort. (B) Axial magnetic resonance imaging (MRI) scan (T1) shows left optic nerve fusiform mass with kinking of distal optic nerve and a heterogeneous appearance. (C) Axial MRI with gadolinium demonstrates extension of optic nerve glioma into the anterior optic canal. (D) Goldmann visual field demonstrating progressive paracentral scotomas. The patient's central vision had dropped to 20/100 at time of surgical excision. (E) Low-powered micrograph (hematoxylin/eosin [H/E]) shows fusiform enlargement of glioma expanding within the substance of the nerve. (F) Photomicrograph 40× (H/E) showing optic nerve glioma with abnormal fascicles, increased cellularity and vascularity, and areas of cystic degeneration. (G) Postoperative view following optic nerve excision through combined craniotomy and orbitotomy. *([E, F] Courtesy of S. Rasmussen, Department of Pathology and Laboratory Sciences, University of British Columbia.)*

Bone erosion or remodeling within the optic canal may indicate presence or invasiveness of the glioma and are best seen with CT.[21]

Suprasellar tumors may extend into the optic nerves, or posteriorly into the optic tracts.

Magnetic resonance imaging (MRI) scans

MRI scans are the best modality to identify the extent of spread of tumor along the optic nerve or tracts and also helps delineate involvement of surrounding intracranial tissues including the hypothalamus (Fig. 23.2B,C).[22]

Visual fields

Visual fields are useful for following visual decline associated with these tumors (Fig. 23.2D).

Differential diagnosis

The differential diagnosis for pediatric orbital optic nerve masses includes primary optic nerve sheath meningiomas, optic nerve sarcoidosis, and leukemic infiltrates. Optic nerve meningiomas may have a more exophytic growth pattern and a more aggressive growth pattern in children. Their primary association with NF2 rather than NF1 may help in their differentiation. Optic nerve sarcoidosis is rare in children, appears as a more exophytic mass radiologically, and may be associated with elevated serum angiotensin-converting enzyme or hilar adenopathy identified on chest X-ray or CT scans. Leukemic infiltrates of the optic nerve may be ruled out with blood counts and lumbar puncture.[23]

The differential diagnosis for suprasellar masses includes craniopharyngioma, germinoma, sarcoidosis, and lymphoma. If MRI scan does not show evidence of optic nerve or tract involvement, these other choices are more likely than glioma, and biopsy is recommended.

Management

In most cases, management is decided through consensus of a multidisciplinary team including the ophthalmologist, pediatric oncologist, radiologist, radiation oncologist, and neurosurgeon.

Anterior (optic nerve) gliomas

Optic nerve gliomas restricted to the orbit are best observed with serial ocular examinations (checking for pain, visual disruption, cosmetic concerns, visual deterioration, exposure, or strabismus). Serial MR scans allow monitoring of tumor growth with particular attention to the speed of growth, and extension intracranially. The intervals between checks depends on the association with NF1 (these tend to progress more slowly than sporadic cases), proximity to the optic canal or chiasm, and the documented growth rate.[24]

Chemotherapy may be considered for progressive cases where vision remains good and the globe is not excessively displaced or exposed. Various combination therapies are available, including cycles every 3 weeks with vincristine in combination with carboplatin or cisplatin. Single therapy with vinblastine has also been described. This may delay progression of disease for several years, particularly in NF1-associated gliomas.[25]

Radiotherapy is avoided in patients with NF1 because of the risk of inducing malignant transformation of pre-existing peripheral nerve sheath tumors or new-onset rhabdomyosarcomas. It may be employed for progressive sporadic optic nerve gliomas that have failed chemotherapy, in order to avoid or delay surgery.[26]

Surgical excision of the optic nerve is the definitive treatment for optic nerve gliomas that are expanding in size with poor vision and significant cosmetic concerns, or pain from nerve compression, or corneal breakdown. This is typically performed by an orbital surgeon and pediatric neurosurgeon through a combined craniotomy and orbitotomy, with resection of the optic nerve from the back of the globe to the chiasm (Fig. 23.2E,F). A small portion of the nerve anterior to the chiasm may be spared to prevent a visual field defect on the opposite eye from von Willebrand's knee. Complications of surgery include transient or permanent facial nerve palsy (from the craniotomy) or oculomotor or trochlear palsy from the orbital resection.

Posterior (intracranial) optic pathway gliomas

These lesions carry a worse prognosis and are more commonly seen in adults and non-NF1 patients.

Initial observation may be considered for younger patients with NF1 as these tumors are likely to grow more slowly. Surgery is indicated in cases of obstructive hydrocephalus with possible tumor resection and shunting. Chemotherapy is offered in younger children to delay or avoid the cognitive and endocrine side effects associated with radiotherapy around the chiasm.[27] Radiotherapy has shown efficacy at shrinking chiasmal OPGs, reducing obstructive hydrocephalus, improving vision, and delaying recurrences. In children less than 5 years of age, it carries significant morbidity from cognitive impairment and endocrine disruption. Stereotactic radiotherapy and proton beam therapy may improve accuracy of treatment with fewer side effects.[28]

Prognosis

Although gliomas in adults follow a very aggressive course similar to a malignant glioma, in children they follow a generally indolent course, particularly NF1-associated gliomas, which tend to involve the anterior nerves alone. In most cases of optic nerve glioma, the tumor progresses slowly, and management ranges from observation through chemotherapy and ultimately surgery. In some cases, spontaneous improvement has been reported. While vision is sacrificed in surgery, the cosmesis is usually restored with globe-sparing surgery and subsequent strabismus repair if needed, and median survival is 15 years (Fig. 23.2G).

Chiasmal gliomas have a worse prognosis, often requiring chemotherapy, radiotherapy, and surgery. However, if associated with NF1, these tumors may also stabilize or even regress spontaneously.

Primary optic nerve meningiomas

Pathogenesis

Primary optic nerve meningiomas arise from arachnoid cap cells within the optic nerve dural sheath; tumors typically expand within the sheath, compressing the underlying optic nerve, but eventually grow through the dura.[29]

They are distinguished from secondary orbital meningiomas, which expand into the orbit from intracranial meningiomas, usually through the posterior and lateral bony walls.

Epidemiology

Primary optic nerve sheath meningiomas account for 20% of all orbital meningiomas. The majority occur in adults with a mean age of presentation in the fourth decade. However, 25% occur in children, usually associated with NF2.[13] Those occurring in children behave more aggressively. There is a strong male preponderance in children.[30]

Clinical presentation

These lesions are characterized by progressive, painless vision loss. Transient visual obscurations may be an initial symptom, although depending on the age of the child, this may not be reported.

Anterior lesions are usually associated with proptosis, while apical lesions may develop fullness in the temporal fossa or impaired ocular motility because of hyperostosis within the lateral and posterior orbital bone.

Most cases are unilateral, although bilateral cases may occur in those associated with NF2.[31]

Investigations

CT scans

CT is often the initial imaging modality and best shows degenerative calcification, if present. Meningiomas enhance with contrast but may be missed on non-contrast CT scans. Extension into the optic canal may cause widening of the canal or surrounding hyperostosis.[32]

MRI scans

MRI is best suited to identify posterior extension. Gadolinium scans on T1 fat-suppressed images show homogeneous enhancement of the lesions while T2-weighted fat-suppressed scans may demonstrate distension of the arachnoid space between the tumor and the posterior globe because of impaired cerebrospinal fluid flow from tumor blockage (Fig. 23.3A,B).[33]

Growth patterns are most commonly tubular (expansion parallel to the optic nerve because of sheath confinement), exophytic (outpouching at the site of a break in the durad), and fusiform (oval shape as a result of a combination of the previous two patterns).

Differential diagnosis

The differential diagnosis and the means of distinguishing them was discussed in the preceding section on optic nerve gliomas.

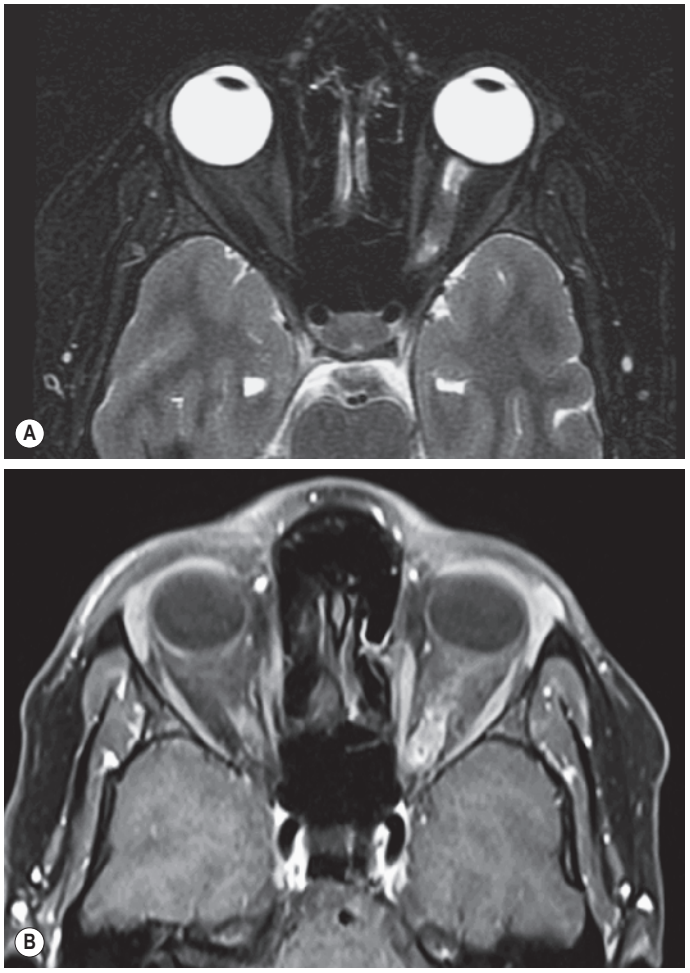


Fig. 23.3 (A) Magnetic resonance imaging (MRI) axial scan (T2) in a 24-year-old with neurofibromatosis type 1 and blind left eye from optic nerve meningioma. (B) MRI axial scan (T1 with gadolinium and fat suppression) shows a possible right subclinical apical meningioma.

Management

Conservative management

Conservative management with regular clinical and radiologic screening is recommended for cases with minimal vision loss and tolerable levels of proptosis. The ophthalmologist should assess for progressive visual loss (including central, color, and peripheral vision) or advancing proptosis.

Surgical biopsy is occasionally indicated where diagnosis is uncertain and specific conditions need to be ruled out. Sheath fenestration or excision of exophytic lesions have been tried with disappointing results.[34]

In cases of progressive posterior growth threatening intracranial spread or involvement of the opposite optic nerve, excision of the nerve with consequent loss of vision is recommended.

External beam radiotherapy or stereotactic radiotherapy

This modality may be employed as primary therapy and has been shown to delay growth of the tumor in adults.[35] It may also be used as an adjunct to excisional surgery, both pre- and postoperatively. In pediatric cases with NF2, it should be used with caution to avoid risk of malignant transformation of other nerve sheath tumors.

Orbital neurofibromas

Pathogenesis

Neurofibromas are benign peripheral nerve tumors composed of a mixture of Schwann cells, perineural cells, and fibroblasts. They typically grow within peripheral nerves and so are interspersed with axons separated by the tumor mass, a feature that distinguishes them from schwannomas histologically.[36]

They are classified by their pattern of growth: plexiform, isolated, or diffuse.

Epidemiology

Plexiform neurofibromas are the most common orbital subtype, usually manifest within the first decade of life, and are commonly associated with NF1.

Isolated neurofibromas (which may be solitary or multiple) may involve the skin of the eyelids and body, or grow along larger sensory, motor, and autonomic nerves. Solitary neurofibromas are most typically encountered in adults and typically are not associated with the neurofibromatoses.[37] However, multiple cutaneous neurofibromas are highly suggestive of NF1.

Diffuse neurofibromas infiltrate soft tissues and cause generalized hypertrophy: these occur rarely in the orbit, but should also raise suspicion for NF1.

Clinical presentation

Plexiform neurofibromas

These are poorly defined lesions commonly appearing early in the first decade of life, often involving the lateral third of the upper lid, temporal orbit, and temporal fossa. These poorly defined tumors are comprised of an infiltrating tangle of thickened peripheral nerves, with a characteristic ropy consistency like a "bag of worms." The overlying skin and eyelid tissue often becomes hypertrophic and stretched, and there may be an associated S-shaped mechanical ptosis with the risk of amblyopia, strabismus, and anisometropia in more than half of individuals with these lesions (Fig. 23.4A).[38,39] Proptosis, pulsatile enophthalmos, and temple swelling suggest orbital extension with underlying craniofacial bony abnormalities, including absence of the greater wing of sphenoid, and hypoplastic ethmoid and maxillary sinuses. Optic atrophy has been known to occur in severe cases.[39]

Isolated neurofibromas

Although common elsewhere in the body, they are relatively rare in the orbit, and very rare in children, unless an early manifestation (with reduced penetrance) of NF1.[38] Solitary tumors also present later in middle-aged adults but are slow growing, discrete, and well circumscribed on imaging. Patients may present with a mass, associated with local or radicular pain, or with sensorimotor neurologic symptoms and signs.

Diffuse neurofibromas

These rarely may diffusely infiltrate orbital fat or muscle but are uncommon in children unless associated with NF1.

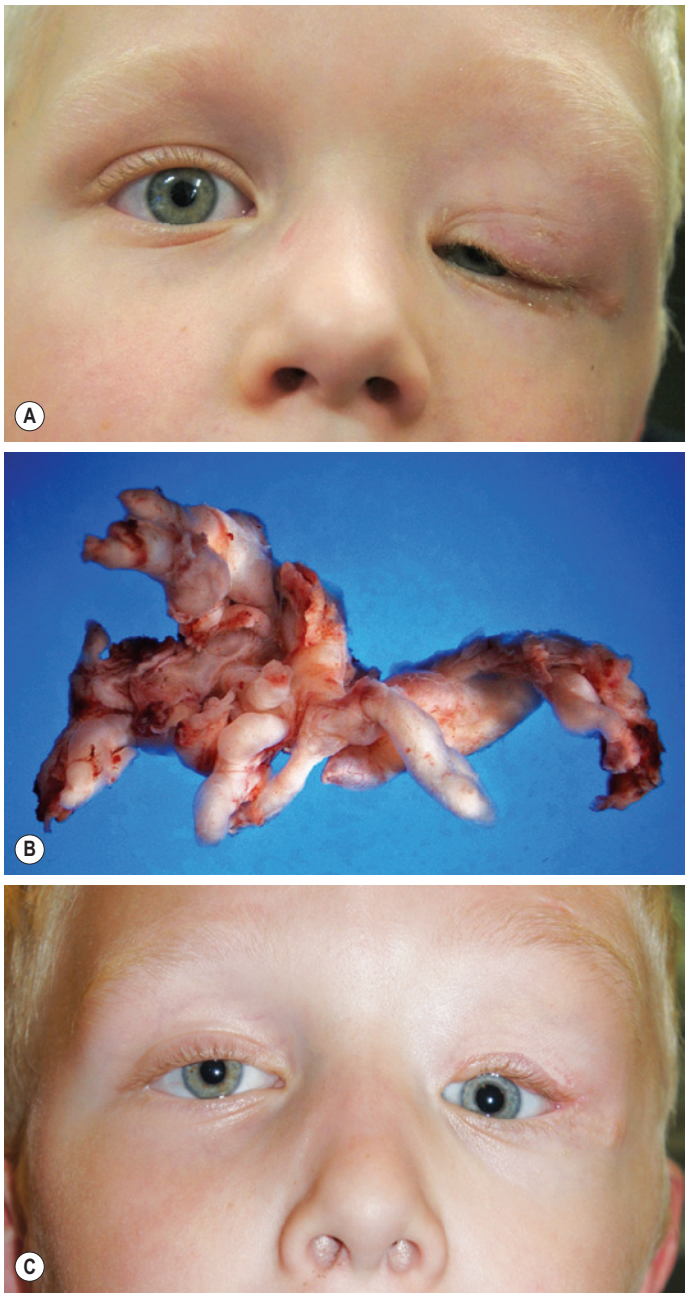


Fig. 23.4 (A) A 5-year-old boy with neurofibromatosis type 1 and plexiform neurofibroma of left upper lid and anterior orbit and temple. He developed amblyopia and patching was instituted. (B) Intraoperative surgical specimen of plexiform neurofibroma with a network of enlarged lacrimal branch of cranial nerve V sensory nerve. (C) Postoperative view following a debulking of tumor mass and horizontal shortening of lid followed at a later surgery with a frontalis sling (brow suspension).

Investigations

CT and MRI of plexiform neurofibromas show large multilobulated, poorly defined, irregular soft tissue infiltration of affected structures and neural tissue. Expansion of the tumor through the orbital fissures or through defects in the sphenoid wing may also be seen. Involvement of motor nerves may cause extraocular muscle enlargement. They are highly vascular and show enhanced signal on MR T2-weighted images.[40]

Isolated neurofibromas are well circumscribed and usually associated with a specific sensory or motor nerve.

Differential diagnosis

Orbital plexiform neurofibromas might be confused with infantile hemangiomas or possibly cutaneous lymphatic malformations. Infantile hemangiomas grow for the first 2 years and then involute, and are highly vascular on imaging. Lymphatic malformations wax and wane and are avascular, with cystic spaces on imaging.

Orbital discrete neurofibromas may be confused with schwannomas and perineuromas.

Management

A child with plexiform neurofibroma should be evaluated to identify the genetic cause, to determine other clinical manifestations, to identify pathology in family members, and to counsel the family about the syndrome.

Initial management is observation unless a lid lesion becomes cosmetically unsightly or there is a risk of occlusion amblyopia, or an orbital lesion expands to cause significant globe displacement.[41] Patching should be instituted to prevent amlyopia, and definitive treatment for strabismus delayed until the disease has stabilized.[39]

Surgical intervention is challenging because of the vascular and diffuse infiltrative nature of these lesions (Fig. 23.4B).[42,43] Debulking is often associated with significant bleeding and care must be taken to avoid damage to normal structures. Enlargement and mechanical stretching of the soft tissues of the eyelid may require surgical horizontal shortening. Damage to the levator muscle through tumor infiltration or aggressive surgery may result in significant ptosis requiring a frontalis sling (Fig. 23.4C). Lesions in the orbit and temporal fossa or forehead may be debulked, but care must be taken to avoid damage to frontalis and temporal branches of the facial nerve.

Multiple sequential surgeries may be required and the results are often suboptimal. In severe cases with significant globe displacement, enucleation or exenteration may ultimately be considered.[42,43]

Discrete orbital neurofibromas may be observed or surgically excised if they cause pain or significant proptosis, but anesthesia or paresthesia may ensue.

Orbital schwannomas (neurilemmomas)

Pathogenesis

These are well-defined, benign, solitary tumors arising from differentiated Schwann cells within the sheath of either orbital sensory or motor nerves. They are histologically characterized by two patterns: Antoni A (tight, compact bundles) and Antoni B (more random, looser, myxoid pattern). Verocay bodies (palisading nuclei) and a fibrous capsule incorporating the peripheral nerve may be identified. They contain less mucopolysaccharide than neurofibromas and are S100 protein positive. Degenerative changes, such as vessel hyalinization, hemorrhage, focal necrosis, and calcifications may be seen in chronic cases.

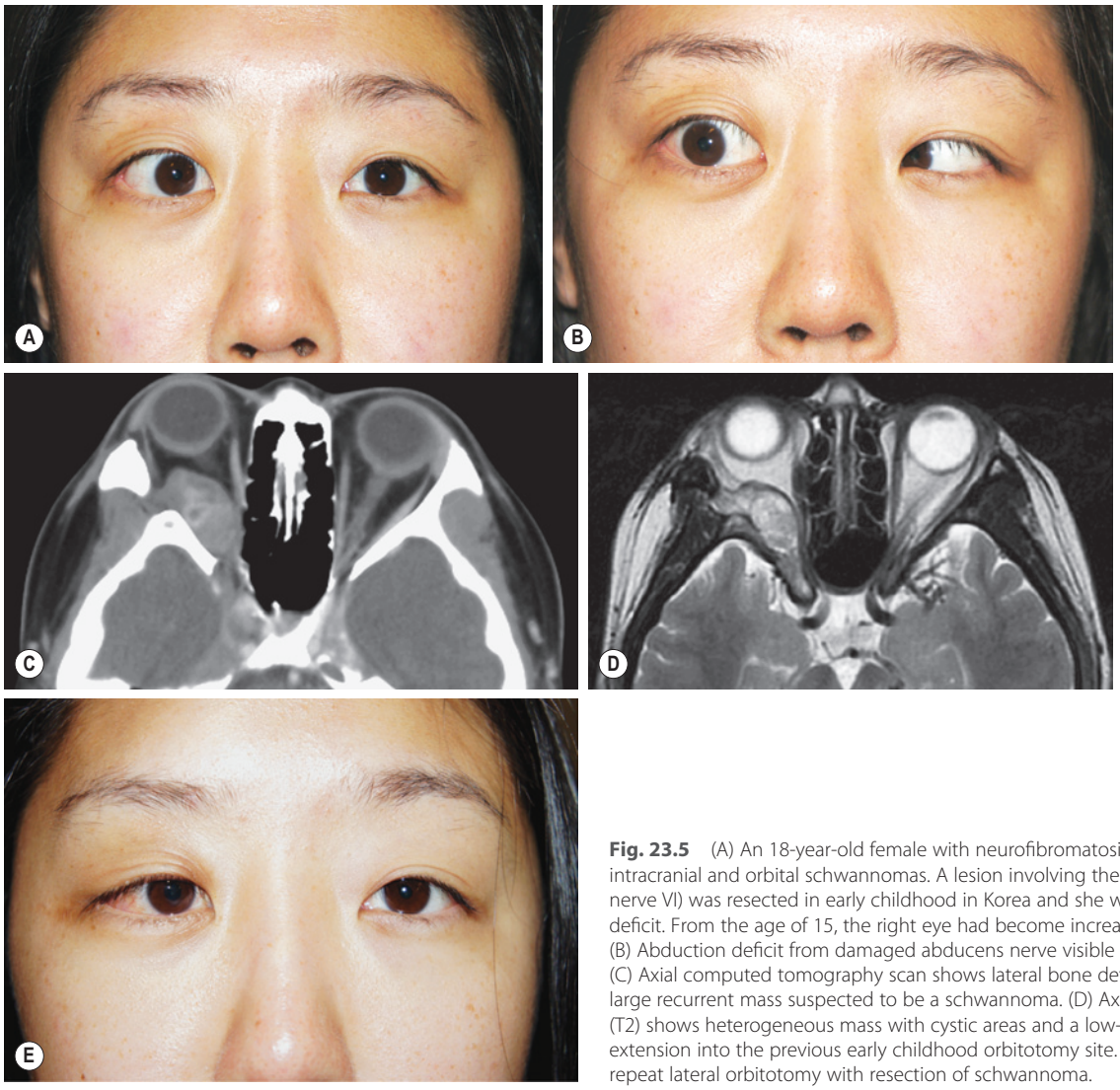


Fig. 23.5 (A) An 18-year-old female with neurofibromatosis type 2 and multiple intracranial and orbital schwannomas. A lesion involving the right abducens nerve (cranial nerve VI) was resected in early childhood in Korea and she was left with an abduction deficit. From the age of 15, the right eye had become increasingly proptotic again. (B) Abduction deficit from damaged abducens nerve visible with attempted right gaze. (C) Axial computed tomography scan shows lateral bone defect from previous surgery and large recurrent mass suspected to be a schwannoma. (D) Axial magnetic resonance imaging (T2) shows heterogeneous mass with cystic areas and a low-signal capsule, with an extension into the previous early childhood orbitotomy site. (E) One month following right repeat lateral orbitotomy with resection of schwannoma.

Epidemiology

While orbital schwannomas are more common in adults than neurofibromas, constituting 3% of orbital neoplasia, they are relatively rare in childhood. They typically arise between 20–50 years of age. They may be associated with NF2 (where bilaterality or multifocal lesions may be seen) and less commonly with NF1. Most arise from the trigeminal sensory nerve, with a propensity for the superior and lateral orbit, sometimes extending through the superior orbital fissure into the cavernous sinus.[42]

Clinical presentation

Schwannomas are slow growing and non-invasive masses. Early signs may include proptosis, globe displacement and lid swelling (Fig. 23.5A). Numbness or paresthesia from involvement of the first division of the trigeminal nerve has been reported; pain may occur with larger lesions. Involvement of the motor nerves or compression of nerves within the cavernous sinus may cause diplopia (Fig. 23.5B). Apical tumors may cause visual compromise or an orbital apex syndrome.

Investigations

Imaging confirms the suspicion of a discrete orbital mass, with the differential including other peripheral nerve sheath tumors (solitary neurofibroma), solitary fibrous tumor, or cavernous hemangioma.[40]

CT scans show a well-defined ovoid lesion, hypodense to muscle with mild enhancement to contrast (Fig. 23.5C).

MRI shows a signal intensity similar to muscle on T1-weighted scans and high intensity on T2-weighted scans (with low intensity in cystic spaces and in the surrounding capsule).[40] The peripheral nerve may be identified coursing adjacent to the tumor (unlike the neurofibroma that incorporates the nerve) and low-density cystic areas are more typical of schwannomas (Fig. 23.5D).

Visual fields are useful in documenting visual impairment and monitoring tumor progression.

Differential diagnosis

The differential diagnoses for Schwannoma include peripheral nerve sheath tumors (neurofibromas, perineurinoma, and

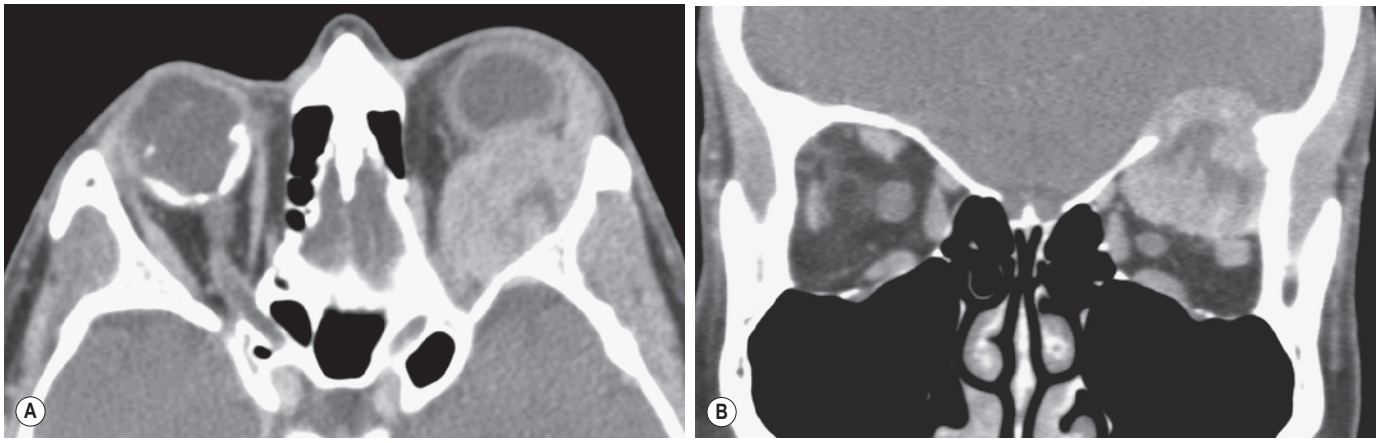


Fig. 23.6 (A) Axial computed tomography (CT) scan of a 35-year-old woman with neurofibromatosis type 1 and a malignant transformation of a plexiform neurofibroma of right thigh, present since age 5. She was treated with radiotherapy to the leg lesion in childhood. This peripheral nerve sheath sarcoma metastasized to her left orbit and brain. (B) Coronal CT scan shows extension through the orbital roof into the cranium.

malignant peripheral nerve sheath tumors), as well as other discrete encapsulated orbital lesions (solitary fibrous tumor, fibrous histiocytoma, cavernous venous malformation). In many cases, the diagnosis is only confirmed at time of biopsy.

Management

These well-circumscribed lesions may be observed clinically and radiologically, especially if small, asymptomatic, and difficult to reach surgically.

Tumors causing proptosis, discomfort, or visual compromise are best surgically removed. Care should be taken to dissect the lesion off important sensory or motor nerves, but often they may arise from small sensory branches, so that sensory loss may be minimal even if the associated nerve is damaged. Dissection into the superior orbital fissure may require careful piecemeal removal (Fig. 23.5E).[44,45]

Prognosis

Prognosis after surgical resection is good, although recurrences may occur if the tumor is only partially removed.[45,46] Malignant transformation is rare and occurs only in adults.

Perineurioma

Perineuriomas are tumors arising from perineurial cells, and so are most commonly seen growing extraneurally within the orbit. Their fusiform shape and contiguity with peripheral nerves makes them indistinguishable from schwannomas, so they are usually only diagnosed histologically. They are most common in young adults (20–30 years old). Surgical excision is recommended for neurologic compromise or pain.[47]

Peripheral nerve sheath malignancies (PNSM)

Pathogenesis

PNSM are malignant sarcomas arising from peripheral nerve cells: they may arise *de novo* or from pre-existing plexiform neurofibromas, schwannomas, perineuriomas, or secondary to radiation therapy.[48–50] Orbital PNSM usually arise from major nerve trunks, such as the trigeminal nerve and its branches.[51]

Typical histopathology shows highly cellular, spindle cells with cytologic atypia and necrosis.[52] Immunohistochemistry reveals positivity for S100, CD56 (myelin basic protein) and p53. BRAF V600E mutations[53] and somatic mutations of *SUZ12*[54] have been identified in certain cases.

Epidemiology

Orbital PNSM are rare. Cases have been reported in children as young as 2 years of age, but most occur in adults. Roughly 50% are associated with NF1, often with an earlier onset of disease.[55,56]

Clinical presentation

Orbital PNSM may present with periorbital swelling, proptosis, and radicular pain that may be associated with hypo- or hyperesthesia. PNSMs associated with NF1 can also present as a rapidly expanding orbital mass over several months. Involvement of the eyelid has also been reported.[57]

Investigations

Imaging features for PNSMs are similar to other orbital peripheral nerve tumors.

CT scans show a heterogenous intraorbital mass with potential invasion through bone into sinus or brain (Fig. 23.6A,B). CT body scans help identify distant metastases.

MR scans demonstrate heterogeneity with low-to-intermediate signal intensity on T1-weighted imaging and high intensity on T2-weighted scans. Margins may be ill-defined.

Management

Treatment of these aggressive tumors is with exenteration of the orbit, sometimes requiring a combined craniotomy to resect intracranial extension. Adjuvant chemotherapy and radiotherapy are often offered, but their benefit remains unproven.[58,59]

Paragangliomas

These are very rare, slow-growing, large tumors arising from mature sympathetic ganglion cells. Few orbital cases have been reported in the literature.[5] They usually present as encapsulated large tumors in adolescent children or adults, with a female preponderance.

Orbital involvement is often heralded with proptosis or occasionally pupil abnormalities from ciliary ganglion dysfunction. Treatment is surgical excision.

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Orbital rhabdomyosarcoma

Carol L Shields and Jerry A Shields

Chapter contents

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General points

Rhabdomyosarcoma (RMS) is a highly malignant neoplasm that can develop in children or adults. This is the most common soft tissue sarcoma of the head and neck in children and represents 5% of childhood cancers.[1–10] RMS can occur in any anatomic location of the body where there is skeletal muscle, as well as other sites without skeletal muscle, such as the soft tissues of the orbit. The primary sites of RMS include head and neck (including orbit, 40%), genitourinary tract (20%), extremities (20%), trunk (10%), and others (10%).[10]

The ocular region, particularly the orbital soft tissues, is an important anatomic location for RMS, which is the most common primary orbital malignancy of childhood.[5,6] In rare instances, RMS has been known to arise in the eyelid, conjunctiva, and the intraocular structures.[2,3] Furthermore, this malignancy can invade the orbit as a metastatic tumor from a distant location or secondarily extend in the orbit from an adjacent primary neoplasm in the paranasal sinuses. In a clinical series of 1264 patients with orbital tumors in children and adults, there were 35 cases (3%) of orbital RMS, but this accounted for 97% of myogenic tumors.[5]

Orbital RMS generally occurs in the first two decades of life with a mean age at diagnosis of 8 years; however, orbital RMS has been observed in adults and has occurred as a second cancer following treatment of primary retinoblastoma.[2–4]

Prompt diagnosis and treatment by the ophthalmologist can save the life of the affected patient. Therefore, eye care physicians should be aware of this tumor, recognize the clinical features, and refer the patient for immediate treatment.

Clinical features

The clinical features of orbital RMS include proptosis (80%), globe displacement (80%), blepharoptosis (55%), conjunctival swelling (60%), and eyelid edema (60%)[1–4] (Figs 24.1–24.3) More advanced cases show downward and lateral displacement of the globe due to the typical superior or superonasal location of the mass.

Ophthalmoscopy can occasionally reveal choroidal folds, retinal venous tortuosity, and optic disc edema. Pain is an uncommon symptom and usually occurs in more advanced cases. Visual impairment is usually minimal unless the tumor becomes advanced. In regions where medical care is not readily available, RMS can attain immense proportions and destroy the eye.

Diagnostic approaches

Any child in the first two decades of life who presents with symptoms and signs of an orbital mass should be evaluated for RMS. The child should have a detailed history, office examination, and imaging studies, particularly computed tomography (CT) or magnetic resonance imaging (MRI).

Computed tomography

Computed tomography is important in the assessment of children with suspected RMS, particularly for the detection of bony involvement by the tumor. With CT, the tumor appears in the early stages as a well-circumscribed, homogeneous, round-to-ovoid mass that is isodense to muscle.[1–4] It is usually extraconal in location and most often found in the superonasal aspect of the orbit. It is usually confined to the orbital soft tissues and does not appear to arise from the extraocular muscles or bone, although it can often cause displacement of the rectus muscles. In general, the smaller tumors do not invade bone, but larger ones can occasionally erode bone and

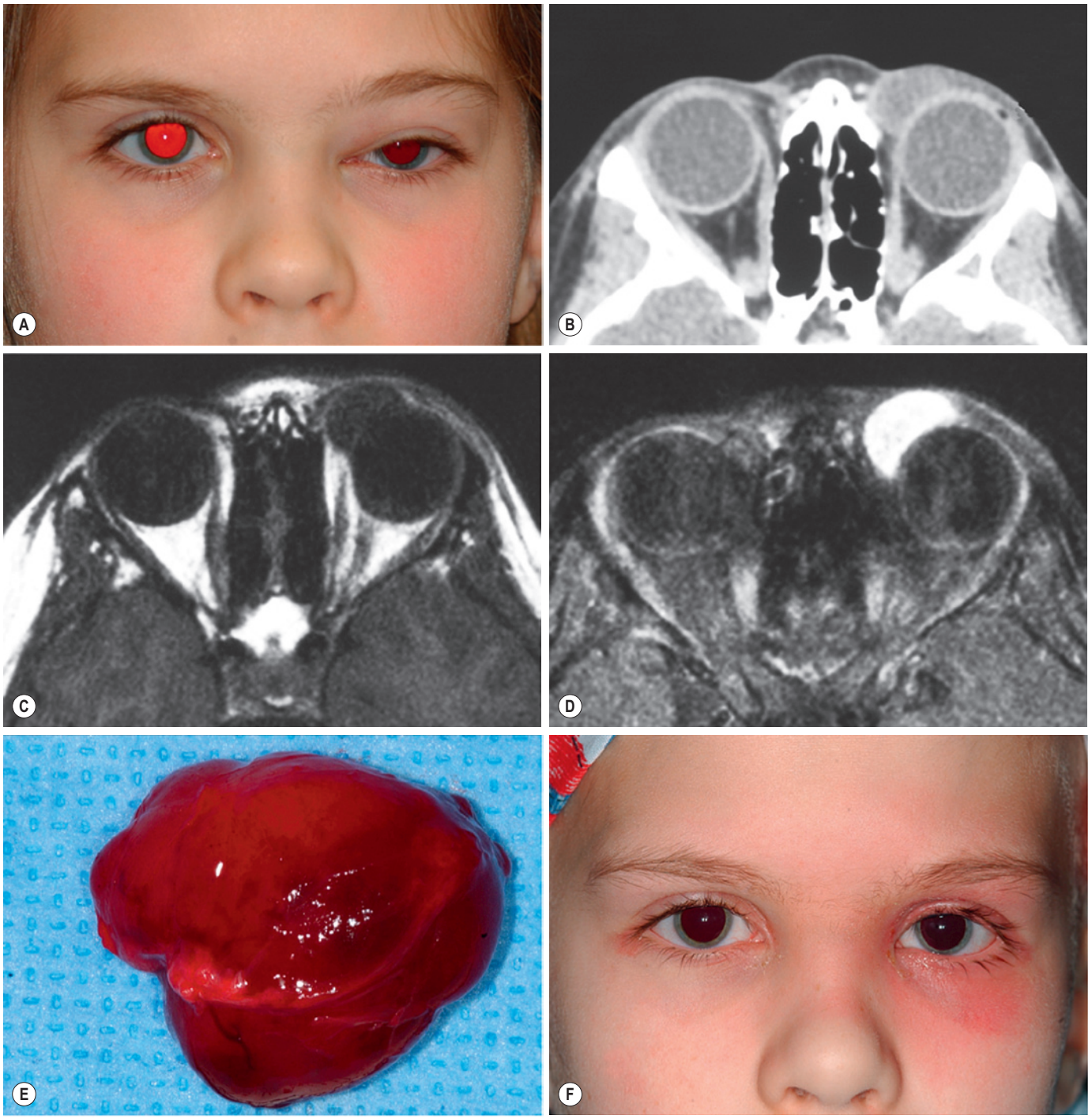


Fig. 24.1 Orbital rhabdomyosarcoma in a young girl. (A) Facial appearance showing downward displacement of left eye. (B) Computed tomography showing solid mass in orbit superonasally. (C) Magnetic resonance imaging (MRI) in T1-weighted image without enhancement depicting circumscribed orbital mass. (D) MRI in T1-weighted image with gadolinium showing uniform enhancement of the malignancy. (E) Circumscribed tumor after surgical excision. (F) Slight erythema of periocular skin following radiotherapy.

extend into the sinuses or nasopharynx. Orbital RMS shows moderate to marked enhancement with contrast agents.

Magnetic resonance imaging

MRI is a valuable method for diagnosis of soft tissue tumors and surgical planning for treatment. With T1-weighted MRI images, the tumor appears as a round-to-ovoid mass that is most commonly located in the orbital soft tissue superonasally. RMS typically has a hypointense signal with respect to orbital fat, but is isointense with respect to extraocular muscles. RMS generally shows moderate to marked enhancement with gadolinium and is best delineated with fat suppression techniques.[1–4] On T2-weighted images, RMS is hyperintense to extraocular muscles and orbital fat. It is usually noncystic, but rare cavitary RMS can resemble a cystic lesion.

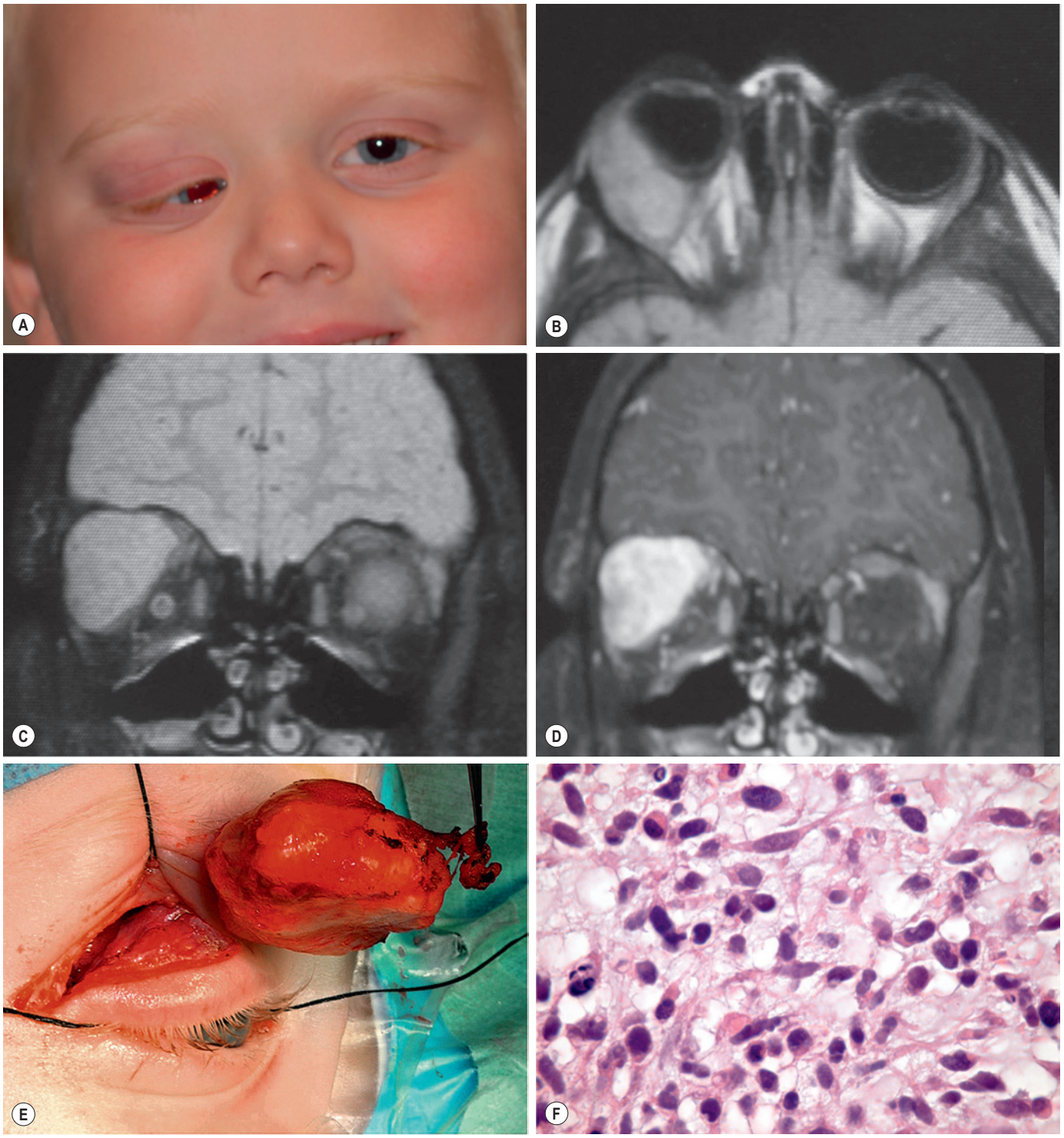


Fig. 24.2 Orbital rhabdomyosarcoma in a young boy. (A) Facial appearance showing proptosis and downward and medial displacement of right eye. (B) Axial magnetic resonance imaging (MRI) showing large superotemporal orbital mass. (C) Coronal MRI showing superotemporal mass. (D) Coronal MRI after gadolinium enhancement showing uniform enhancement of the vascular malignancy. (E) Tumor removed by superolateral orbitotomy. (F) Histopathology showing malignant elongated strap cells and round cells, consistent with orbital rhabdomyosarcoma.

Biopsy

A complete excisional biopsy is preferred in cases of suspected RMS in order to establish the diagnosis and minimize adjuvant therapy. Excisional or incisional biopsy can be considered, depending on the degree of involvement. Care is made to avoid local dissemination of tumor cells with incisional biopsy. Occasionally, fine-needle aspiration biopsy (FNAB) is performed to establish the diagnosis and avoid open surgery.

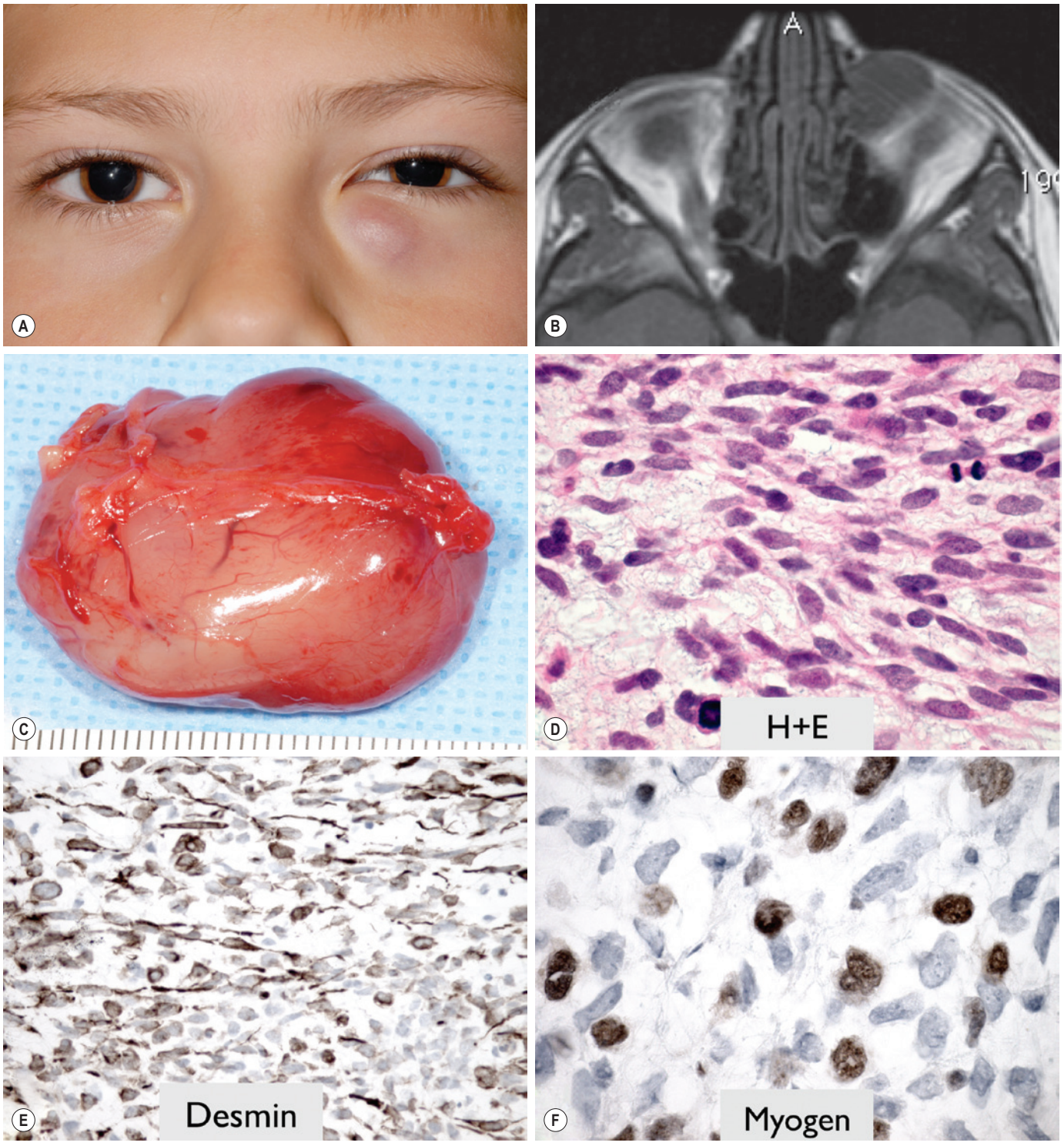


Fig. 24.3 Orbital rhabdomyosarcoma following trauma. (A) Facial appearance showing presumed, traumatic hemorrhagic mass below left lower eyelid. (B) Axial magnetic resonance imaging (MRI) showing low signal inferonasal orbital mass. (C) At surgery the mass was excised completely. (D) Histopathology revealing spindle-shaped cells (hematoxylin and eosin, ×150). (E) Special stain revealing positive desmin stain (×100). (F) Special stain revealing positive myogen stain (×250).

Pathology

Orbital RMS probably arises from primitive pluripotential mesenchymal cells with a propensity to differentiate toward skeletal muscle. Several histopathologic variations of RMS occur in the orbit. Generally, RMS is classified into four major subtypes including embryonal (57%), alveolar (19%), botryoid (6%), and pleomorphic (1%), with the remainder too undifferentiated (10%) or heterogenous (7%) for classification.[1–4,11] The embryonal type is most common, whereas the alveolar type appears to be the most malignant.

Embryonal RMS is characterized histopathologically by spindle-to-round cells that show features of skeletal muscle in various stages of embryogenesis.[11] The predominant cell is an elongated spindle cell that can assume a variety of arrangements and degree of differentiation. The cytoplasm is generally eosinophilic, and cross-striations can sometimes be identified on routine histopathologic sections or with special stains. The alveolar type appears as loosely arranged, malignant cells with septae that are reminiscent of the pulmonary alveoli. The botryoid type may be a variant of the embryonal type that assumes a papillary configuration.

Immunohistochemical studies have provided assistance in the confirmation of RMS and in the differentiation from other spindle cell tumors. Immunohistochemical markers include antibodies against desmin, muscle-specific actin, and myogen (myoglobin) that typically show positive reaction to RMS, but negative reaction to other round or spindle cell tumors (Fig. 24.3).

Classification

Intergroup rhabdomyosarcoma study

In 1972, the Intergroup Rhabdomyosarcoma Study Group (IRSG) was established to increase knowledge and to improve therapeutic results for RMS. Over the past four decades, several treatment protocols have been tested in multicenter trials, and dramatic improvements in patient outcomes have been achieved as a result of these trials.[12–20] Following biopsy, the patient is staged according to the IRSG classification (Table 24.1) and therapy with chemotherapy plus possible radiotherapy is provided. Slightly modified therapeutic protocols are delivered according to the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) and, more recently, the Soft Tissue Sarcoma Committee of the Children's Oncology Group.[21–23]

AJCC classification

The American Joint Committee on Cancer (AJCC) classification of orbital sarcoma (including RMS) has been introduced. This classification depends on tumor (T), node (N), and metastasis (M) localization. For the AJCC clinical classification of RMS see Table 24.2.

Management

Historical aspects

Until the late 1960s, orbital exenteration was considered the treatment of choice for orbital RMS. It was believed that complete surgical removal of the tumor would offer the patient the best chance of survival. However, the mortality rate continued to be poor at 70% death rate in the early 1970s. Subsequently, as a result of the IRSG, there has been major improvement in diagnosis and treatment of orbital RMS. Education of physicians, use of CT and MRI, and better treatment protocols have been introduced for improved survival. Currently, over 90% of patients with orbital RMS demonstrate survival at mean 8 years follow up.[1–10]

Table 24.1 Intergroup Rhabdomyosarcoma Study Group (IRSG) staging classification

Group	Description	Treatment
I	Completely resected localized disease with gross and microscopic confirmation of complete resection and absence of regional lymph node involvement	VA × 32 weeks
Ia	Confined to muscle or organ of origin	
Ib	Contiguous involvement outside the muscle or organ of origin	
II	Residual disease and/or regional lymph node involvement	VAC × 32 weeks plus 3600 cGy CFI
IIa	Grossly resected localized tumor with microscopic residual disease and no evidence of gross residual tumor or regional lymph node involvement	
IIb	Completely resected regional lymph node and no microscopic residual tumor	
IIc	Grossly resected regional lymph nodes with microscopic residual tumor	
III	Incomplete resection with gross residual disease	VAC × 52 weeks plus 4500 cGy CFI or VAI × 52 weeks plus 4500 cGy HFI or VIE × 52 weeks
IV	Distant metastatic disease present at onset	Management based on metastatic site

A, Actinomycin D; C, cyclophosphamide; CFI, conventional fractionated irradiation, E, etoposide, HFI, hyperfractionated irradiation; I, ifosfamide; V, vincristine.

Table 24.2 The American Joint Committee on Cancer (AJCC) clinical classification of rhabdomyosarcoma

Clinical feature	Tumor
Tx	Tumor cannot be assessed
T0	Tumor not evident
T1	Tumor ≤15 mm in greatest dimension
T2	Tumor >15 mm in greatest dimension and without invasion of globe or bony wall
T3	Tumor any size with invasion of orbital tissues and/or bony walls
T4	Tumor invasion of globe, eyelids, temporal fossa, nasal cavity, paranasal sinuses, and/or central nervous system
Nx	Regional lymph node cannot be assessed
N0	Regional lymph node metastasis absent
N1	Regional lymph node metastasis present
M0	Distant metastasis absent
M1	Distant metastasis present

Surgery

The diagnosis of orbital RMS is based on histopathologic findings following surgery. The ultimate goal of surgery is complete removal of the tumor intact; however, that is not always possible, especially when the tumor is large and invasive into normal orbital structures. The excised tissue should be submitted immediately for routine histopathologic examination and special immunohistochemical staining. The orbital surgeon should decide on the approach to biopsy and preferably do a complete excisional biopsy, if possible, to confirm the diagnosis, debulk the mass, and promptly refer the patient to a pediatric oncologist where further management is decided based on tumor stage and published protocols. This often involves a collaborative decision by the ocular oncologist, pathologist, pediatric oncologist, and radiation oncologist, preferably following the guidelines of IRSG. The surgical method of orbital exenteration is rarely used as a primary treatment, but can be utilized if there is recurrent deep tumor.

Chemotherapy

Chemotherapy is the first line of treatment for children with orbital RMS. The exact regimen varies depending on the IRSG stage and involves agents including vincristine, actinomycin D, cyclophosphamide, etoposide, or ifosfamide.[12–23] These agents are generally prescribed for 32–52 weeks.

Radiotherapy

External beam radiotherapy, proton beam radiotherapy, or intensity-modulated radiotherapy are considered for patients with IRSG stages II, III, and IV (see Table 24.1). The use of radiotherapy is controversial and varies from center to center, depending on the stage of disease. The radiation dose has varied from 3600 cGy to 4500 cGy or more and can be associated with short-term and long-term ocular complications. Irradiation is often necessary following orbital exenteration for tumor recurrence after standard irradiation and chemotherapy have failed to control the tumor.

Prognosis

Orbital RMS is a highly aggressive, fast-growing malignancy with tendency for local invasion and remote metastases to lung, lymph nodes, and other sites. However, using modern therapeutic regimen described above, the survival has improved. Today, the survival is greater than 95% for orbital RMS.[1–4] Factors responsible for the better prognosis for RMS in the orbital region include a more favorable anatomic location, earlier stage of disease at detection, more favorable tumor morphology, and perhaps patient age. Overall survival at 5-year follow-up is 92% and at 10 years is 87% for stages I, II, and III.[8]

Summary

RMS is the most common primary orbital malignancy of childhood. It requires prompt diagnosis and treatment. This tumor most commonly occurs in the first two decades of life, at which time the patient develops rapidly progressive proptosis and displacement of the eye. The tumor can arise primarily in the orbit or it can arise in the adjacent sinuses or nasal cavity and secondarily extend to involve the orbit.

Orbital RMS probably arises from primitive pluripotential mesenchymal cells with a propensity to differentiate toward skeletal muscle. Several histopathologic variations of RMS occur in the orbit. The embryonal type is most common whereas the alveolar type appears to be the most malignant.

Ophthalmologists should be aware of the clinical features of RMS and understand the need for high-quality imaging studies to determine the extent of the disease. A carefully planned biopsy should be performed with tumor confirmation on histopathology and staging according to the IRSG protocol. Collaboration with pediatric oncologists and radiation oncologists to plan therapy is advised.

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Other mesenchymal abnormalities

Christopher J Lyons

Chapter contents

DYSPLASIAS
BONE TUMORS
NEOPLASIAS
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Rhabdomyosarcoma is discussed in Chapter 24. Every mesenchymal component of the orbit can give rise to sarcomatous tumors, but these are exceedingly rare and will not be discussed. Nevertheless, they are part of the differential diagnosis of rhabdomyosarcoma.

Dysplasias

Fibrous dysplasia of the orbit

Fibrous dysplasia (FD) is a rare benign disorder, characterized by the replacement of normal bone by a cellular fibrous stroma containing islands of immature bone and osteoid, which does not remodel along lines of stress into lamellar bone. It has no predilection for either gender. It has been reported in infancy[1] but usually presents in childhood; its onset is insidious and it may remain asymptomatic until adulthood. Progression usually slows in the second or third decade, when "bone maturity" is reached, although growth may continue into the fourth decade in some cases. It is important to distinguish it from meningioma[2] and osteosarcoma.

FD may be confined to a single site (monostotic form) that tends to occur after the late teens. Conversely, the rarer polyostotic form, which involves multiple bony sites, tends to occur in childhood and stabilizes around puberty. Polyostotic FD co-existing with cutaneous pigmentation and endocrine abnormalities constitutes the McCune–Albright syndrome.[3] FD is a non-inheritable disorder caused by missense mutations occurring post-zygotically. Activating *GNAS* complex mutations on chromosome 20 result in upregulation of osteoclast function, causing excessive bone resorption and dysplastic fibrous growth.[4] The GSα mutation can be tested for in peripheral blood.[5]

Clinical features

Three-quarters of patients with orbital FD have the monostotic form affecting several contiguous bones but the disease usually remains unilateral. The craniofacial area is affected in 20% of patients, with a predilection for the frontal, sphenoid, and ethmoid bones. Typically, there is a painless, firm, bony swelling with contour distortion; in the orbit, there is an accompanying mass effect. The clinical presentation depends on the predominant wall involved, most commonly the roof, resulting in proptosis and downward displacement of the globe and orbit.[6,7] The lacrimal fossa may be affected, mimicking a lacrimal gland tumor.[8] Maxillary disease (Fig. 25.1) displaces the eye upwards, with persistent epiphora if the nasolacrimal duct is affected.[9] Sphenoid involvement results in optic nerve compression[6,7] from narrowing of the optic canal (Fig. 25.2) or by an associated sphenoid sinus mucocele.[10] Rarely, involvement of the sella turcica may result in chiasmal compression.[11] Other uncommon neuro-ophthalmic complications include cranial nerve palsies,[12] trigeminal neuralgia, raised intracranial pressure, and papilledema.[12,13] Extensive craniofacial involvement can result in severe cosmetic deformity. Pain may occur, either localized or as a diffuse ipsilateral headache. Visual loss is not uncommon.[6,14] Malignant transformation to osteosarcoma, fibrosarcoma, chondrosarcoma, and giant cell sarcoma occurs in 0.5% of cases, increasing to 15% if there has been previous radiotherapy.[14] The accompanying signs are rapid progression, worsening pain, and infiltration of surrounding structures.

The main radiographic feature of FD is expansion of bone. The lesions may be sclerotic, with a dense ground-glass homogeneity, lytic, with increased lucency, or show a mixed picture with alternating areas of lucency and increased density. Most orbital cases are easily diagnosed since they are sclerotic.[6] The main radiologic differential diagnosis includes histiocytosis-X, hyperostotic meningioma, Paget disease (both rare in children), and some bone tumors. On magnetic resonance imaging (MRI) there is a correlation between T1 and T2 signal intensity and clinical and pathologic activity of the lesion.[15] Occasionally, large cystic lesions form in the orbital wall.[6] These may contain blood (Fig. 25.3) and necrotic debris and can be mistaken for aneurysmal bone cysts.[14] Involvement of a neighboring sinus may mimic mucocele.[14,16] Computed tomography (CT) scanning with the possible addition of MRI is the best modality to evaluate the extent of cranial and orbital involvement. The optic canal and chiasm should be assessed for signs of compression.

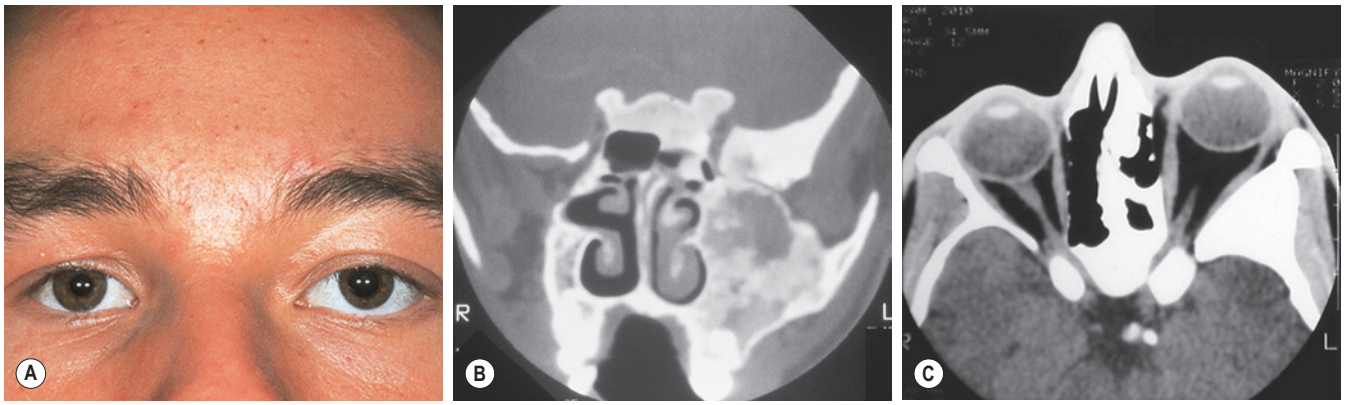


Fig. 25.1 (A) This 16-year-old presented with a history of progressive facial distortion and decreasing vision in the left eye to 20/40. Compressive optic neuropathy was diagnosed secondary to fibrous dysplasia. (B) Computed tomography (CT) scan of the same case showing cystic fibrous dysplasia involving the orbital apex. (C) Axial CT scan shows optic canal involvement. This was surgically decompressed. *(Patient of the University of British Columbia.)*

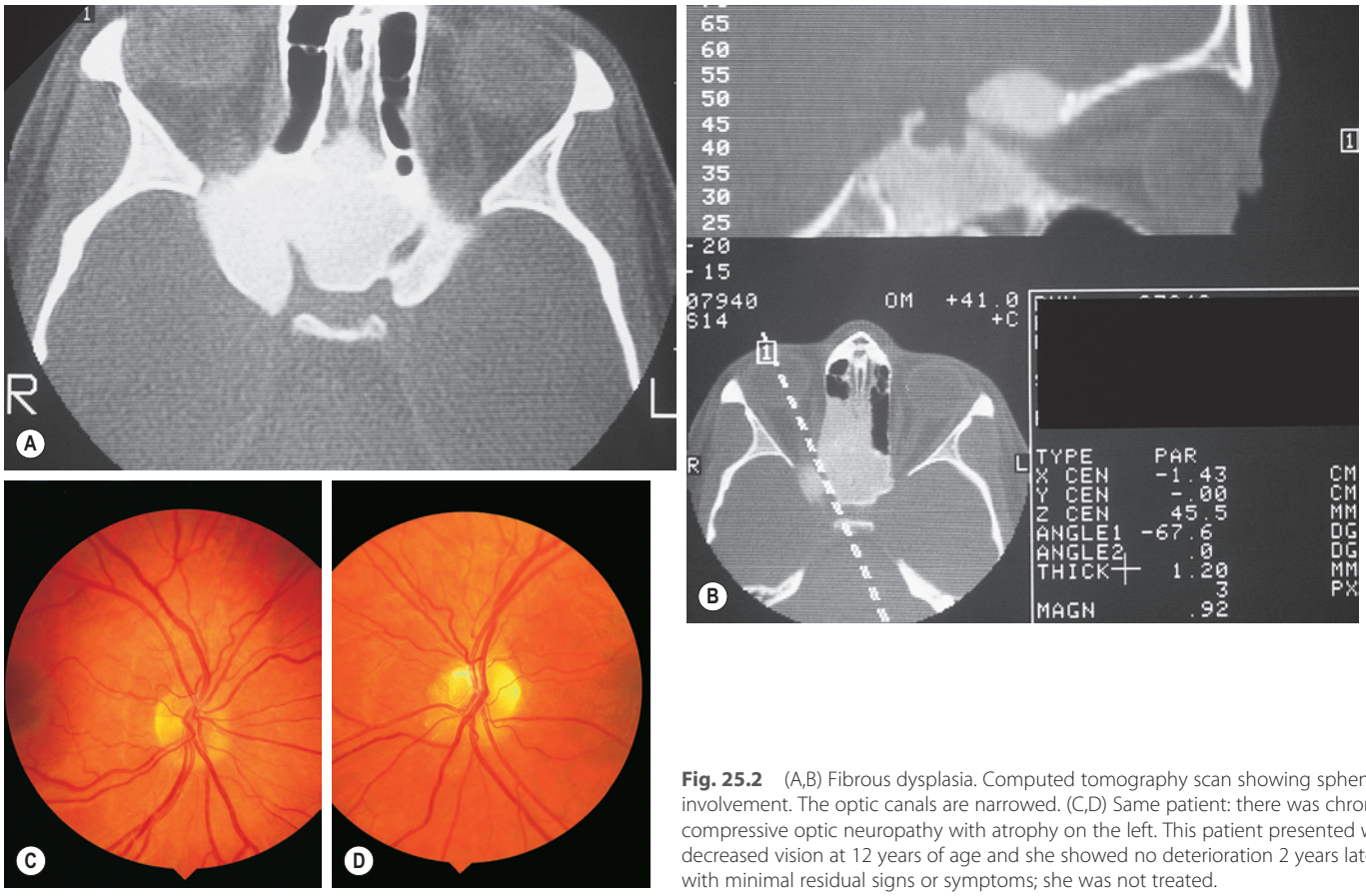


Fig. 25.2 (A,B) Fibrous dysplasia. Computed tomography scan showing sphenoid involvement. The optic canals are narrowed. (C,D) Same patient: there was chronic compressive optic neuropathy with atrophy on the left. This patient presented with decreased vision at 12 years of age and she showed no deterioration 2 years later with minimal residual signs or symptoms; she was not treated.

Management

FD is usually benign and self-limiting. However, the final extent and time of arrest of the lesion are unpredictable. Treatment aims to prevent complications, especially optic nerve compression, and improve cosmesis while waiting for spontaneous arrest.

When there is little doubt about the diagnosis, initial observation and repeat radiologic assessment is best. If the lesion in the orbital wall is lytic or cystic, biopsy is usually necessary to confirm the diagnosis. Outside the orbit, the risk of malignant change after radiotherapy is high[17] and is not used.

Surgery is indicated for cosmetic disfigurement, intractable pain, or optic nerve compression. Since dysplastic bone can be vascular, preoperative blood cross-matching is advisable. Resection of dysplastic bone around the optic canal can reverse visual loss of early compressive optic neuropathy.[10,14] Steroids may also be useful.[18] When decompressing the optic nerve, rongeurs rather than high-speed drills (heat producing) should be used to protect the nerve. Surgery traditionally consisted of debulking the lesion. However, the margins of the affected bone are difficult to define clinically and recurrence was common.[7] In the last 20 years, there has been a shift toward more radical excision of all diseased bone and immediate facial



Fig. 25.3 (A) This 22-year-old developed sudden proptosis of the right eye after a history of slowly progressive facial asymmetry from early childhood. (B) Computed tomography scan showed the fluid level of a hemorrhage within the cystic dysplastic bone. The diagnosis was fibrous dysplasia. *(Patient of the University of British Columbia.)*

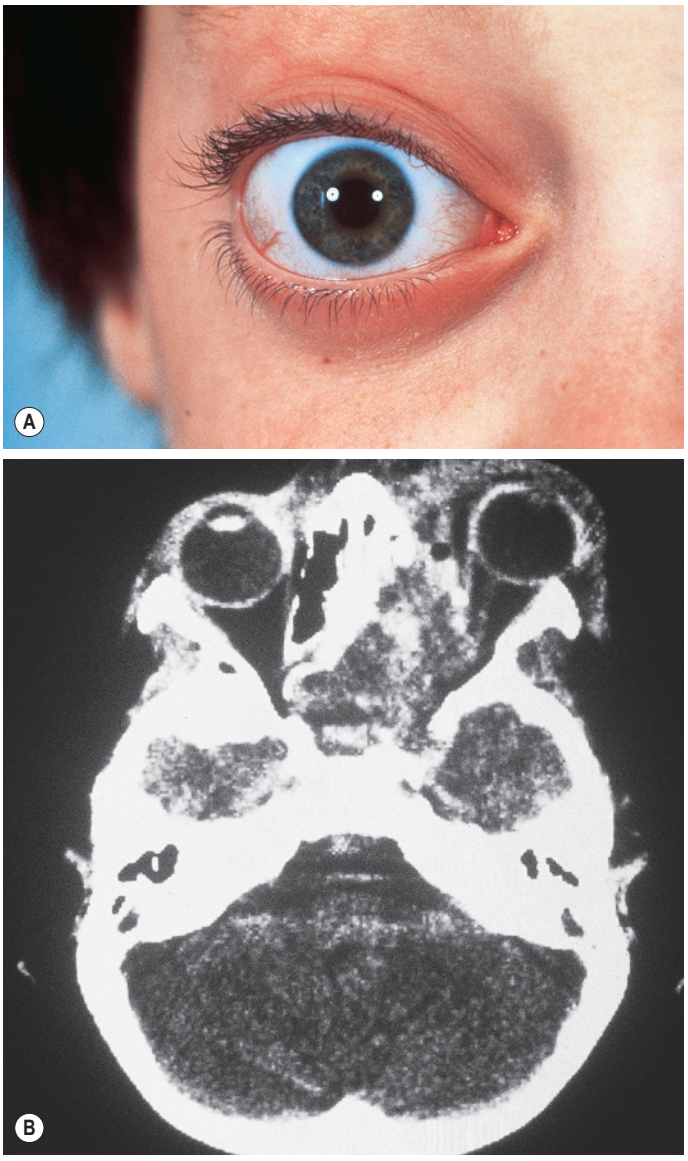


Fig. 25.4 This 10-year-old had a 1-month history of progressive proptosis of the right eye and lateral displacement of the globe. There was gradual loss of vision. Reparative granuloma was diagnosed by intranasal biopsy and the patient underwent lateral rhinotomy and excision of lesion via the ethmoid and maxillary sinuses. *(Patient of the University of British Columbia.)*

and orbital reconstruction using bone grafts[6,19] by combined ophthalmology/craniofacial teams. While some groups report no visual function deterioration following early optic canal decompression, there have been reports of blindness complicating prophylactic nerve decompression.[20] Visual loss is not usually the result of progressive optic canal stenosis, but from the rapid expansion of cystic components, FD mucoceles, or hemorrhage.[21] Prophylactic optic canal decompression is not indicated and a conservative approach is warranted. In this context, serial visual fields, color vision and optical coherence tomography can be helpful.[22] Optic canal decompression should be reserved for patients with progressive or sudden deterioration of visual function.[23]

Bone tumors

Reparative granuloma

Reparative granuloma and aneurysmal bone cyst are parts of a spectrum of reactive giant cell lesions; it may be difficult to differentiate them histologically.

Reparative granulomas (also known as giant cell granulomas) are rare. They affect patients in the first and second decades of life and occur in the mandible, maxilla, and phalanges.[14] The lesion may spread to the maxilla, ethmoid,[24] and sphenoid bones, involving the orbit (Fig. 25.4) and causing proptosis.[25,26] The presentation may be sudden and dramatic if intralesional hemorrhage occurs.[14] Histopathologically, there is a spindle cell stroma with profuse hemorrhagic and hemosiderin content. Osteoblastic giant cells are present within the stroma and new bone may be laid down at the edge of the lesion.

The course is usually benign. Treatment is by surgical curettage; healing occurs by new bone formation. Curettage may need to be repeated or the bony margins resected if the lesion recurs. Radiotherapy is rarely necessary.[25]

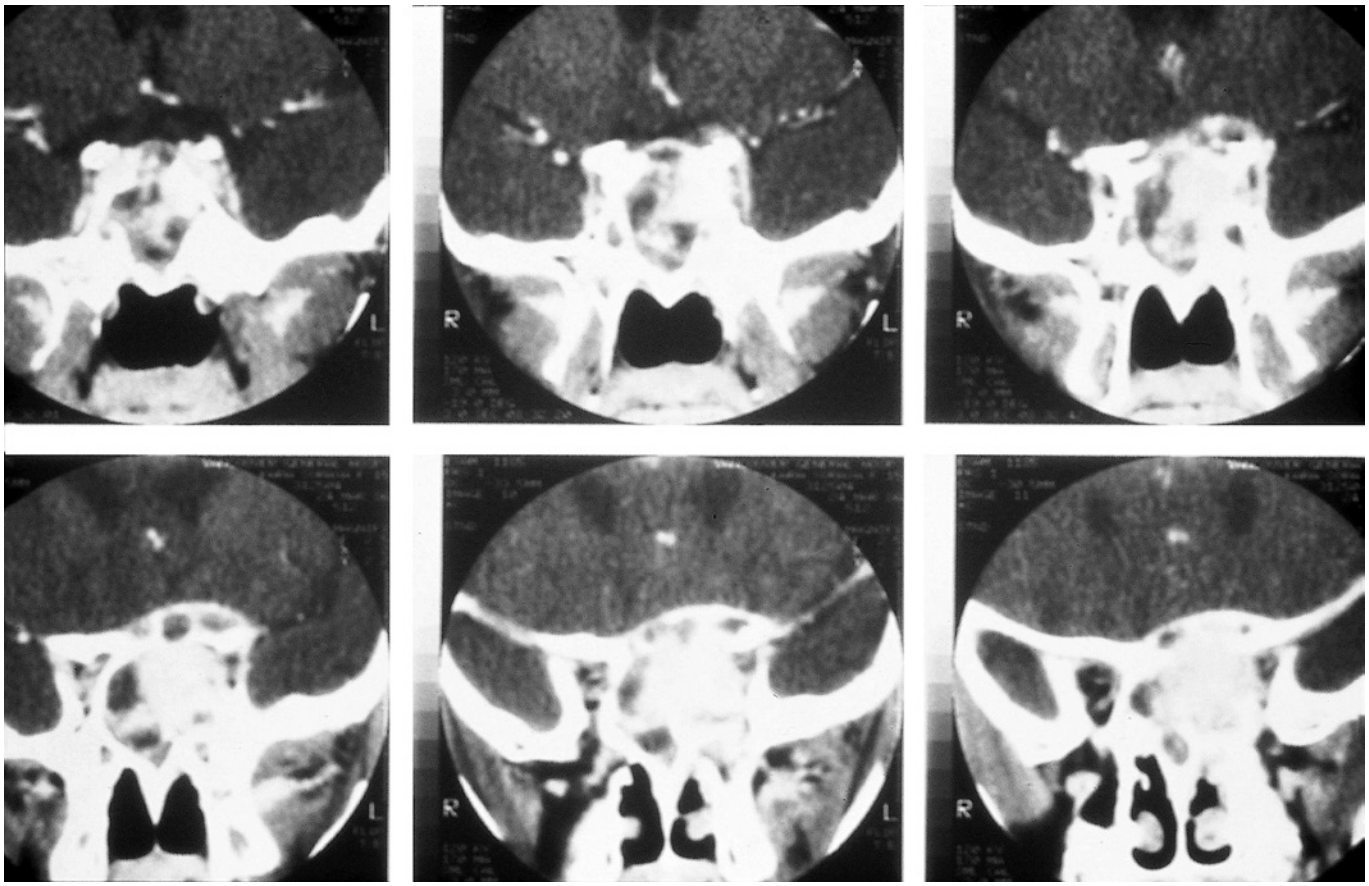


Fig. 25.5 This 12-year-old girl presented with gradual loss of vision. A sphenoid and ethmoid mass was apparent on computed tomography scan. This was shown to be an aneurysmal bone cyst by intranasal biopsy and she underwent cranio-orbitotomy. *(Patient of the University of British Columbia.)*

Aneurysmal bone cyst

This uncommon lesion usually affects the metaphysis of long bones or the spine, often preceded by trivial trauma. The skull is affected in less than 1% of cases; about one-quarter of these affect the orbit.[27] It is a benign lesion that can usually be differentiated from reparative granuloma by the presence of large blood-filled channels lined by multinucleate giant cells and fibroblasts. However, they can be solid, making this differentiation difficult. The two may co-exist.[28]

Aneurysmal bone cysts of the orbit (Fig. 25.5) have been periodically reviewed.[29–31] Most present in the second decade; there is a 5:3 female:male ratio. The history is usually shorter than 3 months, with presentations including proptosis, diplopia, ophthalmoplegia,[32] ptosis, headache, visual deterioration due to optic nerve compression, nasal congestion,[27] epistaxis,[33] and epiphora.[34] Most cases involve the orbital roof and result in gradually increasing unilateral proptosis and downward displacement of the globe.[35] The medial and lateral orbital walls can also be involved. Like reparative granulomas, intralesional hemorrhage may occur, leading to a sudden presentation with signs related to mass effect, occasionally mimicking orbital malignancy in early childhood.[36] Large cysts with intracranial extension may give rise to raised intracranial pressure, papilledema,[37] and optic nerve compression.[14]

Radiologically, irregular expansion with destruction of bone is seen on CT scan, with a thin shell of bone outlining the limits of the lesion. There may be patchy enhancement of the mass or its rim. Hemorrhage and multiple fluid-fluid levels[30] may be evident on MRI or ultrasound.

The treatment of choice is complete surgical excision or curettage with frozen section[14] and grafting with autogenous bone chips. Repair of the orbital wall with a plate,[30] or craniofacial reconstruction may be indicated at the time of surgery.[29,38] The prognosis is good despite a recurrence rate as high as 66%,[39] usually within 2 years of treatment. Cryotherapy and irradiation have also been used, although the latter carries a later risk of osteosarcoma.

Neoplasias

Juvenile ossifying fibroma of the orbit

This rare disorder arises in the bony wall of the orbit, presenting with slowly progressive proptosis. It is similar to, but distinct from, FD.[14]

It usually presents with slowly progressive painless globe displacement in adolescence or early adulthood; younger cases have been reported. The orbital roof (Fig. 25.6) or ethmoid bone are the most common sites[40,41]; rarely, maxillary involvement may cause upward displacement of the globe.[42] There may be massive enlargement with considerable morbidity and disfigurement.[41] Diplopia may occur, and posterior tumors

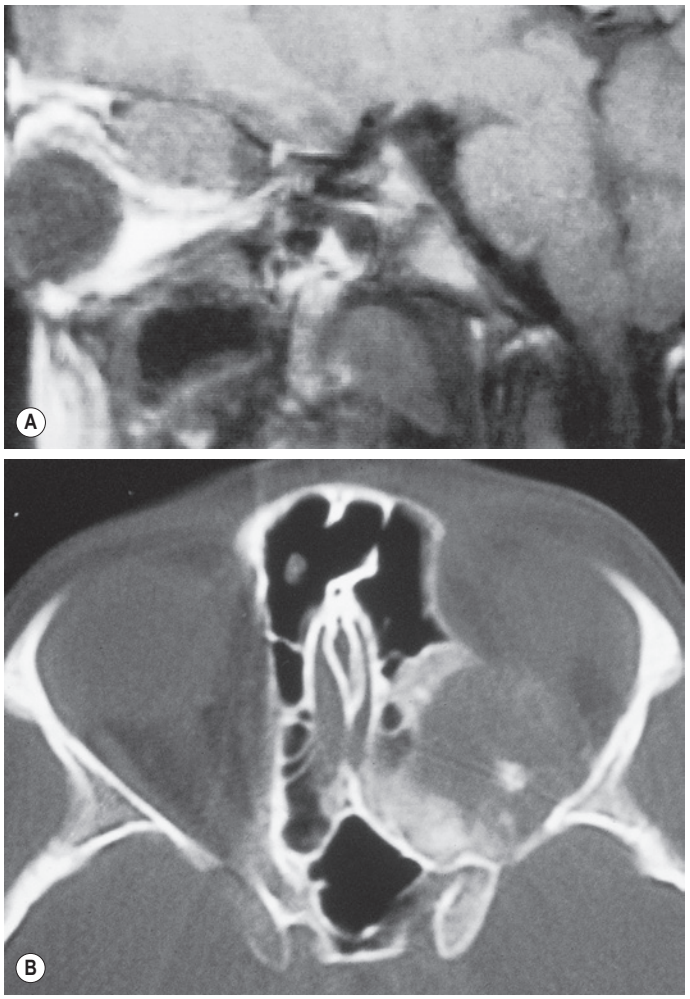


Fig. 25.6 (A) Ossifying fibroma. This 7-year-old child presented with progressive proptosis of the right eye and downward displacement of the globe. The magnetic resonance imaging scan shows a mass in the orbital roof displacing the levator–superior rectus complex, the globe and the optic nerve downwards. (B) Same patient: computed tomography scan showing the sclerotic margin of the fibroma.

may cause apical crowding. Occasionally, inflammation is a feature.[43]

CT scan, which is preferable to MRI,[44] shows a homogeneous central zone with a sclerotic margin expanding a single bone. The lesion is usually clearly demarcated but may grow to involve surrounding bones, sometimes crossing the midline to the other orbit.

Histopathologically, the predominant feature is a central whorled, cellular, vascular stroma surrounded by varying amounts of bone. The more aggressive psammomatoid variant contains islands of lamellar bone or "ossicles", surrounded by a rim of osteoid and osteoblasts resembling the psammoma bodies of meningioma. The tumors enlarge insidiously; surgery becomes necessary for most cases. The treatment of choice is complete excision since recurrence is common, especially in the presence of residual tumor and with psammomatoid histopathology,[41] when regular follow-up is indicated by a multidisciplinary team.[45] Extragnathic cementomas are tumors that behave in a similar fashion.

Other mesenchymal tumors

Osteoblastoma

This benign tumor rarely involves the orbit[46] but can originate from the orbital roof and ethmoid sinuses. It presents with mass effect, globe displacement, reduced ocular motility, and headache.[46,47] Radiologically, osteoblastomas are well circumscribed and may have a lucent center with foci of calcification. The treatment of choice is surgical, either with curettage or more radical excision and reconstruction; both of these may be associated with profuse bleeding due to the vascularity of the tumor. Histologically, it may be difficult to differentiate these from osteoid osteomas.[48] Osteoblastomas tend to be larger, more vascular, and have potential for progressive growth and recurrence. The prognosis is reasonably good, but in the spine and long bones they have a 10–15% recurrence rate after curettage.[49] Since recurrence and sarcomatous transformation have been reported in the skull,[50] complete excision is indicated, preferably by a multidisciplinary team.

Post-irradiation osteosarcoma of the orbit (also see Chapter 43)

Survivors of familial retinoblastoma are at greater risk of developing a second tumor,[51,52] even in the absence of radiotherapy, due to their genetic predisposition. Current retinoblastoma treatment regimes avoid or minimize the use of radiotherapy for this reason. Most of these tumors are osteosarcomas,[52] which may occur within the field of radiation or at a distant site. In 1984, Abramson et al. reported 693 patients with bilateral retinoblastoma. Eighty-nine developed second tumors[52]; 58 occurred within the radiation field and 31 outside. The latent period from completion of radiotherapy to development of the second tumor ranged from 10 months to 23 years (mean 10.4 years). The prognosis of osteosarcoma of the orbit is extremely poor; most patients die within a year of diagnosis.

Infantile cortical hyperostosis (Caffey disease)

This uncommon disorder of unknown etiology affects infants in the first few months of life. It is characterized by sudden onset of fever, irritability, and soft tissue swelling. The soft tissue over the involved bone is swollen and tender. Plain X-rays show subperiosteal new bone formation and cortical thickening. There is usually leukocytosis and raised erythrocyte sedimentation rate. The mandible is the most common bone to be involved, in which case the infants have a characteristic facial appearance with swollen cheeks. It is generally self-limiting and the radiologic appearance reverts to normal within a few months. Involvement of the facial and skull bones may lead to periorbital edema and even proptosis.[53,54] The management is conservative: initially, observation and follow-up radiologic examination of the involved bones. Systemic steroids may be used for persistent disease, or to hasten remission if there is gross swelling.

Osteopetrosis

This is a group of rare genetic bone disorders caused by mutations in at least eight genes,[55] in which defective bone

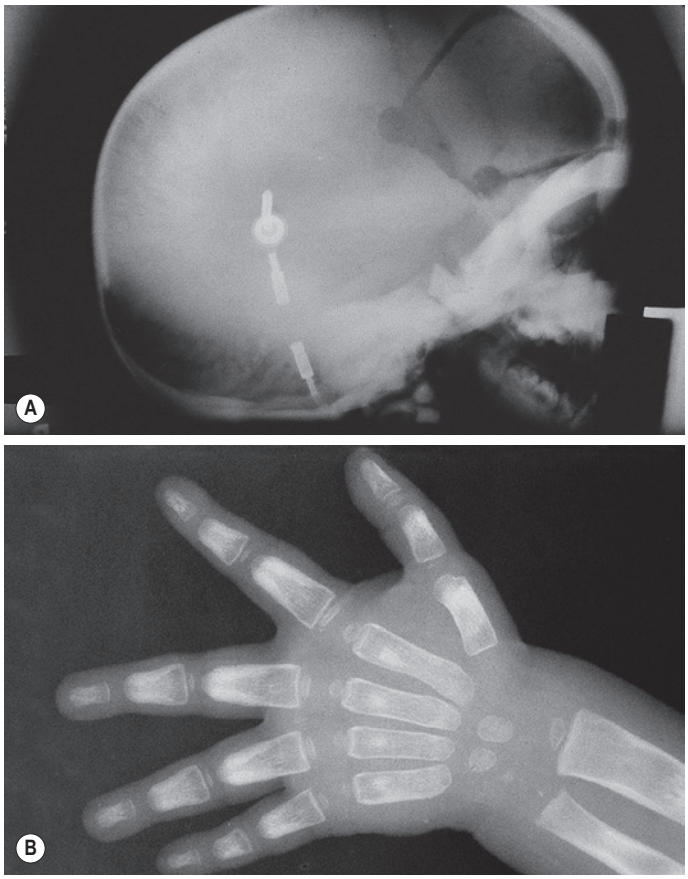


Fig. 25.7 (A) Osteopetrosis. This infant had a bilateral compressive optic neuropathy that failed to respond to optic nerve decompression. He also has a shunt *in situ*. Bone marrow transplantation has been successful in some cases. (B) X-ray of the hands showing increased density of distal ends of the phalanges (same patient).



Fig. 25.8 X-linked hypophosphatemic rickets. Computed tomography scan showing increased bone density, especially of the cortical bone. There was chronic optic nerve compression, which did not deteriorate over a 10-year period while it was monitored by measuring acuity, color vision, pupil reactions, visual fields, and visual evoked potentials.

resorption by osteoclasts results in increased bony thickness and density. There is increased fragility of long bones with narrowing of the marrow cavity. The bony foramina of the skull are also narrowed (Fig. 25.7). Most patients presenting in childhood have one of the autosomal recessive forms of osteopetrosis characterized by a presentation in infancy. This very severe disease, formerly called "malignant" osteopetrosis, is soon fatal if untreated. Another less aggressive form appears in the first decade.

The malignant form presents in infancy with failure to thrive, anemia, and thrombocytopenia. Extramedullary hematopoiesis results in hepatosplenomegaly and lymphadenopathy. Affected infants may present with neonatal hypocalcemia due to defective calcium absorption[55] and unopposed osteoblastic function,[56] which may cause seizures. Bony involvement may result in small orbits with proptosis,[57] narrowing of the cranial foramina, temporal bossing, and nasolacrimal duct obstruction.[58] Narrowing of the optic canal may cause optic nerve compression resulting in optic atrophy.[59,60] Compression of other cranial nerves may result in facial palsy and deafness.

The bone density on X-ray is uniform without corticomedullary demarcation (see Fig. 25.7). There is broadening of the metaphyses and pathologic fractures are common.

Visual function needs to be monitored with electrophysiology in affected infants.[61,62] Vision may be preserved or improved by early decompression of the optic canal,[63,64] but the procedure is difficult due to the increased density of the bone. *LRP5* mutations have been implicated in autosomal dominant osteopetrosis.[65] Also, in a subgroup of patients with infantile malignant osteopetrosis, visual loss results from a rod–cone dystrophy[61,62,66,67]; they may have evidence of widespread neuronal degeneration. A macular chorioretinal abnormality has also been reported.[67] Ocular involvement by age 2 months occurred in half of 33 patients with autosomal recessive osteopetrosis[68]; three had retinal degeneration. Thus, in evaluating a child with osteopetrosis with visual loss, an electroretinogram should always precede optic nerve decompression. Depending on the underlying mutation and severity of the disease, treatment with bone marrow or hematopoietic stem cell transplantation is the best option.[69]

Some forms of autosomal dominant osteopetrosis may be discovered in adulthood, with no ophthalmic complications and a normal life expectancy but numerous orthopedic problems.

Other bone dysplasias

These include craniometaphyseal dysplasia, cranioepiphyseal dysplasia, X-linked hypophosphatemic rickets (Fig. 25.8), and many others, which may be characterized by bone thickening, foraminal occlusion, and orbital narrowing.

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Metastatic, secondary and lacrimal gland tumors

Alan A McNab and Christopher J Lyons

Chapter contents

METASTATIC DISEASE
SECONDARY DISEASE
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Neuroblastoma and Ewing sarcoma account for most childhood orbital metastatic disease.[1] Wilms tumor, testicular embryonal sarcoma, ovarian sarcoma, and renal embryonal sarcoma occasionally metastasize to the orbit.[2]

It is important to differentiate between blood-borne deposits of a malignant tumor (metastatic disease) and direct extension of a tumor into the orbital tissues from an adjacent structure (secondary disease). Rhabdomyosarcoma and retinoblastoma are the most important sources of secondary orbital disease in children (see Chapters 24 and 43).

Metastatic disease

Neuroblastoma

Neuroblastoma is the most common extracranial solid tumor of childhood, accounting for 9% of all childhood cancers, and is the third leading cause of cancer-related death in children. Its incidence peaks in infancy with a median age at diagnosis of 17 months. It arises from postganglionic sympathetic neuroblasts. Most primary tumors involve the adrenal medulla but they can occur anywhere within the sympathetic nervous system in paraspinal ganglia, the neck, or pelvis. It is the commonest source of pediatric orbital metastasis, accounting for 41 of 46 cases reported by Albert et al.,[1] but is a rare cause of orbital disease overall, representing only 1.5% and 3% of pediatric orbital tumors in two large series.[2,3]

Biologic subtypes and genetics

Based on biologic factors and a better understanding of the molecular development of neural crest cells, neuroblastic tumors have been categorized into three biological types:

- *Type 1*: characterized by gains and losses of whole chromosomes. It expresses the TrkA neurotrophin receptor, is hyperdiploid, and tends to spontaneously regress.
- *Type 2A:* characterized by copy number alterations in portions of chromosomes. Type 2A expresses the TrkB neurotrophin receptor and its ligand, has gained an additional copy of chromosome 17q, has loss of heterozygosity of 14q or 11q, and is genomically unstable.
- *Type 2B:* generally has the *MYCN* gene amplified and has a gain of chromosome 17q, loss of chromosome 1p, and expression of the TrkB neurotrophin receptor and its ligand.[4]

Up to 1–2% of cases have a positive family history. Neuroblastoma arises from the interaction of multiple common predisposing genomic variations. The genetic characteristics of each tumor have important prognostic significance; high levels of *MYCN* (N-myc) proto-oncogene amplification are found in approximately 20% of primary tumors and are associated with a worse prognosis.[5,6]

Hyperdiploidy of tumor cell DNA content confers an improved prognosis for infants under 1 year of age at diagnosis. Conversely, segmental chromosomal alterations are associated with more aggressive disease.[7] The most frequent somatically acquired copy number abnormality is allelic gain of distal chromosome 17q, identified in over 50% of primary tumors. An unbalanced gain is associated with more aggressive disease and decreased survival. Cellular genomic aberrations are a better prognostic predictor of the tumor's biological behavior than clinical factors such as age and stage at diagnosis. This is important for treatment planning since it is not uncommon for these tumors to regress spontaneously (stage 4s), even if already widely disseminated. If identified early, these infants can be spared the harmful adverse effects of chemotherapy since their survival rate exceeds 95%.[8] In contrast, children with high-risk neuroblastoma are often resistant to multimodality treatment and have a 5-year survival rate of 40%.

Clinical presentation

Most cases occur under 3 years of age[9] and 90% are diagnosed by age 5, with fewer cases occurring up to the late teens. The adrenals are the primary site in 51% of cases, but it can arise in the cervical sympathetic chain, mediastinum, or pelvis.[10] Neuroblastoma is also more common in patients with neurofibromatosis type 1 (NF1).

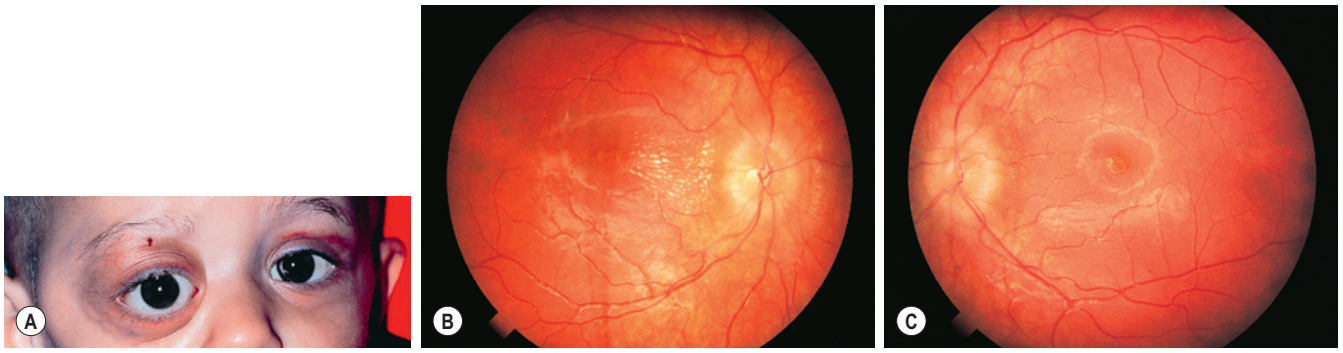


Fig. 26.1 Neuroblastoma. (A) This child presented with bilateral orbital bruising and right proptosis. (B,C) This patient had widespread orbital and cranial bone involvement with raised intracranial pressure and papilledema. *([A] Patient of Dr S. Day.)*

The clinical features vary according to the site of origin, tendency for multiple metastases, any hormone secretion, or paraneoplastic syndrome. Pain, fever, and weight loss are common; cerebellar encephalopathy (ataxia, myoclonic jerks, opsoclonus of unknown cause), diarrhea (from tumor vasoactive peptide production), Horner syndrome (sympathetic chain involvement), and hypertension with flushing episodes (catecholamine production) are classic signs of neuroblastoma.

The diagnosis is often not made until the patient has widespread metastases[11]; 40% have metastases at presentation, increasing to 55% in patients over the age of 1 year. As noted, about 10% of tumors and their metastases (stages 1 to 4s) undergo spontaneous regression, a feature occurring 100 times more commonly than for any other cancer.[12] This underlies the cautious treatment approach outlined below.

Tumor histology ranges from undifferentiated (neuroblastoma) to mature ganglion cells (ganglioneuroblastoma or ganglioneuroma). The histopathological characteristics such as the amount of stroma, degree of differentiation, and number of mitotic figures, reflected in the Shimada classification, do have some prognostic value.

Ninety percent of patients have abnormally high levels of vanillylmandelic acid (VMA) in their urine due to catecholamine secretion. The urinary VMA concentration can be useful for diagnosis and to monitor treatment.

Ophthalmic and orbital features

Neuroblastoma in the mediastinum or cervical sympathetic chain may present with Horner syndrome. This caused two of 10 childhood cases of Horner syndrome reviewed by Woodruff et al.[13] Tonic pupils have been reported as a paraneoplastic effect of adrenal neuroblastoma.[14] Uveal metastases from abdominal neuroblastoma have rarely been described.

The presence of opsoclonus (see Chapter 90), a striking large-amplitude erratic ocular flutter, also known as "dancing eyes syndrome," with or without ataxia and myoclonus, suggests occult localized neuroblastoma.[11] The primary tumor is in the chest or abdomen and not the brain. It is usually associated with a good prognosis, possibly because only single copies of the *MYCN* oncogene are present within the tumor cells,[15] but opsoclonus can also be present with multiple *MYCN* copies, signaling a poorer outcome.[16]

Presentation

In 93% of 46 cases reported by Albert et al.,[1] the primary tumor was diagnosed prior to presentation with orbital signs.



Fig. 26.2 Periorbital ecchymoses in a patient with orbital neuroblastoma.

Ninety percent of the 60 patients with orbital metastases reviewed by Musarella et al.[11] had a primary abdominal tumor. Orbital metastases commonly present with sudden onset and rapidly progressive proptosis (Fig. 26.1), unilateral or bilateral. Eyelid ecchymosis (Fig. 26.2) is present in 25% of cases.[11] The lesion is usually in the superolateral orbit and zygoma but may occur anywhere within the orbit. Bony lesions give rise to swelling of overlying tissues, so periorbital swelling and ptosis may be present. This may mimic orbital cellulitis or other rapidly progressive orbital tumors such as rhabdomyosarcoma, Ewing sarcoma, medulloblastoma, Wilms tumor, and acute lymphoblastic leukemia.[17] Hemorrhage into a pre-existing undiagnosed venous lymphatic malformation (lymphangioma) may also present with sudden proptosis and ecchymosis. The ecchymosis can also lead to suspicion of child abuse and diagnostic delay.[18]

Treatment

The main prognostic factors are the age at diagnosis, stage of disease (Table 26.1), *MYCN* status, Shimada histology, and ploidy for infants. Survival rates for low-risk groups are 90–100%, whilst those for high-risk groups range from 20% to 60%. Infants under 1 year have a 92% 5-year survival; those aged 1 to 4 years, 68%; 5 to 9 years, 52%; and 10 to 14 years, 66%.

Low-risk neuroblastoma (stages 1 and 2) is treated surgically. The cure rate is greater than 90% for stage 2 neuroblastomas

Table 26.1 International neuroblastoma staging system (INSS)

Stage	Description
1	Tumor confined to organ or origin
2	Tumor extends beyond organ of origin but not beyond midline
2a	No lymph node involvement
3	Tumor extends beyond midline with or without bilateral lymph node involvement
4	Tumor disseminated to distant sites
4s	Children younger than 1 year of age with dissemination to liver, skin, or bone marrow without bone involvement and a primary tumor that would otherwise be stage 1 or 2

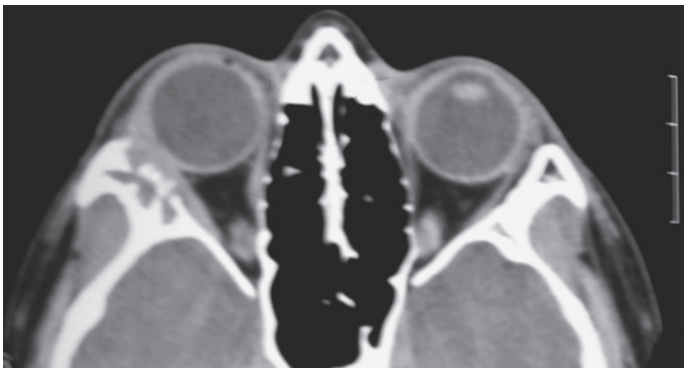


Fig. 26.3 Ewing sarcoma. An axial computed tomography scan of a 9-year-old boy with Ewing sarcoma of the lateral orbital wall. Systemic investigation revealed no other lesions and it was treated with chemotherapy to shrink the lesion followed by complete excision, with long-term cure.

with no further treatment, even if small amounts of tumor remain after surgery.[19] Chemotherapy or radiation can cure local recurrence. Stage 4s has a favorable prognosis; the survival rate is almost 100% with observation and supportive care only.[20] Treatment for intermediate-risk neuroblastoma includes surgery and chemotherapy with agents including carboplatin, cyclophosphamide, cisplatin, etoposide, and doxorubicin over several months. Radiotherapy is used for incomplete response to chemotherapy. Children with stage 3 and infants with stage 4 under 1 year of age and otherwise favorable features have an excellent prognosis of more than 90% survival with moderate treatment. It is important to obtain sufficient material for histopathological and genetic study to determine these patients' moderate risk and spare them the high doses necessary for higher-risk groups. High-risk patients receive induction chemotherapy followed by high-dose chemotherapy and bone marrow transplantation with additional *cis*-retinoic acid treatment.[21]

Ewing sarcoma

Ewing sarcoma is highly malignant and an important cause of mortality and morbidity. The usual age of onset is 10–25 years, with highest incidence in the early teens. It is very rare in African and Chinese children. Four percent of primary tumors arise in the head and neck, usually the maxilla or mandible.[22] Spread from contiguous structures such as the sinuses may occur. There is a marked tendency to spread to adjacent soft tissues, other bones, and the lungs.[23] Immunohistochemical characteristics differentiate Ewing's from other small round cell tumors such as rhabdomyosarcoma, neuroblastoma, and lymphoma. Ewing sarcomas are often S100, neuron-specific enolase, and surface glycoprotein MIC-2 positive, and negative for muscle markers such as desmin or actin. A reciprocal translocation, t(11 : 22)(q24;q12) is present in 83% of tumors.[24] There is a cytogenetic rearrangement on the long arm of chromosome 22 fusing the *EWS* gene (whose function is unknown) and members of the ETS family of transcription factors (FLI-1, ERG). This causes deregulation of other genes within the cell and development of the malignant phenotype.[25] In undifferentiated tumors, the diagnosis may be secured by cytogenetic analysis for the translocation or polymerase chain reaction (PCR) for chimeric fusion gene products EWS/FLII or EWS/ERG.

There are numerous reports of primary Ewing sarcoma involving the orbit, arising from the ethmoid and sphenoid sinuses, roof of the orbit, lesser wing of the sphenoid, and temporal bone. A short history is typical, featuring swelling, globe displacement, strabismus with duction limitation, headache, visual loss, pain, and localized bony tenderness.[1,26]

On computed tomography (CT) scan, there is a "moth-eaten" unevenly enhancing appearance of the involved bone, associated with a soft tissue mass (Fig. 26.3). The differential diagnosis includes neuroblastoma, rhabdomyosarcoma (if extraskeletal), Langerhans cell histiocytosis, and osteomyelitis.

In apparently primary orbital tumors, the patient should be evaluated for metastatic disease. Adequate amounts of fresh tissue should be obtained for histopathologic and cytogenetic studies. Treatment of the primary tumor is with multiagent chemotherapy to shrink the tumor before surgical excision. Vincristine, doxorubicin, and cyclophosphamide are the main treatments with, in addition, ifosfamide and etoposide. Although these tumors are radiosensitive and local control may be achieved by radiotherapy, surgery is preferable due to the risk of late radiotherapy complications including osteosarcoma. Histologically clear margins are essential. The prognosis for metastatic disease remains poor and only one-third survive long term. Since there is an appreciable risk of late recurrence or development of a second malignancy, such as osteogenic sarcoma, prolonged follow-up is indicated.

Secondary disease

Retinoblastoma (see Chapter 43)

Retinoblastoma confined within the eye poses little threat to life and is curable.[23] The prognosis is greatly worsened by extension into the orbit (Fig. 26.4) or central nervous system, or by metastatic disease. The consequences of trans-scleral spread to the orbit and extension into the optic nerve are considered in Chapter 43.

Malignant melanoma

Intraocular melanoma very rarely occurs in infancy and childhood and secondary orbital melanoma is exceedingly rare. Occasionally, orbital malignant melanoma occurs in the neonatal period with extensive involvement of orbital and other facial tissues at presentation.

Lacrimal gland tumors

Dermoid cysts are the commonest lesion of the lacrimal fossa region in childhood.[2] Inflammatory lesions, including non-specific dacryoadenitis, granulomatosis with polyangiitis, immunoglobulin G4 (IgG4)-related dacryoadenitis, and angiolymphoid hyperplasia may also occur in childhood. Granulocytic sarcoma (chloroma) is rare but can present with a mass in the region of the lacrimal gland.

Primary epithelial tumors of the lacrimal gland are rare in children, and more frequent over the age of 10 years. Pleomorphic adenoma of the lacrimal gland can occur in childhood[3]; Rose and Wright reported that three of their 78 cases had onset of symptoms in the second decade of life.[27] Cure is effected by complete removal of the tumor, with recurrence and possible late malignant transformation if excision is incomplete.[27]

Adenoid cystic carcinoma does rarely occur in children, and is commoner than pleomorphic adenoma in this age group.[3,28,29] Six of 38 cases from Moorfields Hospital had their first symptom in the first two decades of life.[30] These tumors often develop rapidly. Alternatively, a longer standing lesion can present acutely with symptoms of pain and paresthesia due to perineural invasion, which often extends microscopically well beyond the tumor mass.



Fig. 26.4 Retinoblastoma. This child with extensive orbital involvement with lymphatic spread (note the preauricular gland involvement) is a common presentation in developing countries.

Radiologically, bone erosion is highly suggestive of malignancy. However, it is important to note that absence of erosion does not exclude malignancy (Fig. 26.5). Since bony remodeling occurs rapidly in childhood, localized bony expansion may still be seen with rapidly growing masses such as adenoid cystic carcinoma, whereas in adults, this sign would indicate a slow-growing mass such as pleomorphic adenoma.

These tumors may be difficult to distinguish clinically from other lacrimal lesions such as low-grade infections, non-specific

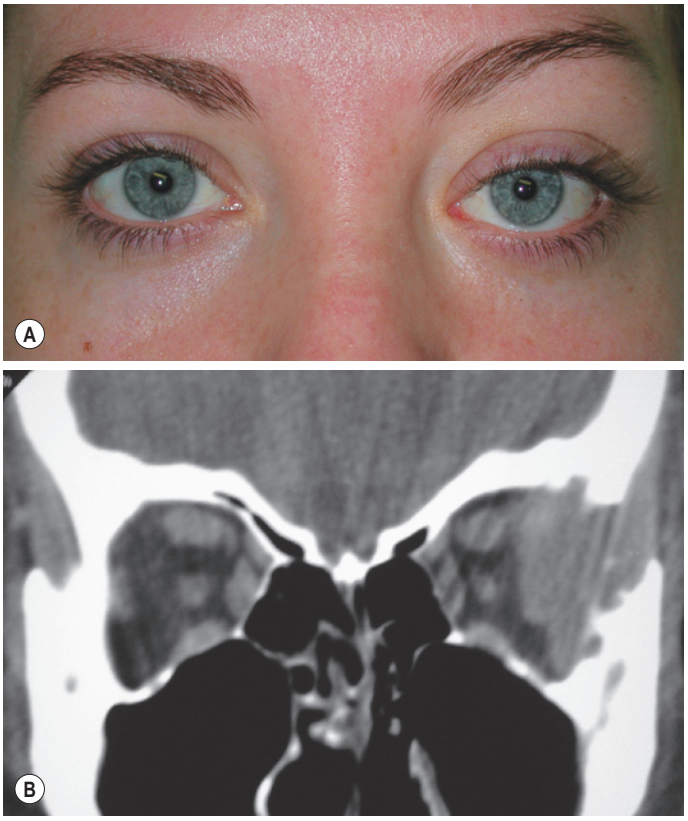


Fig. 26.6 Adenoid cystic carcinoma. (A) A 16-year-old girl had 9 months of increasing left globe dystopia, pain, and numbness over the lateral upper eyelid. (B) A coronal computed tomography scan shows a mass in the region of the lacrimal gland with adjacent bone destruction. Biopsy confirmed basaloid adenoid cystic carcinoma with bone and perineural invasion. She died from metastatic disease within 12 months despite surgery, radiation, and chemotherapy.

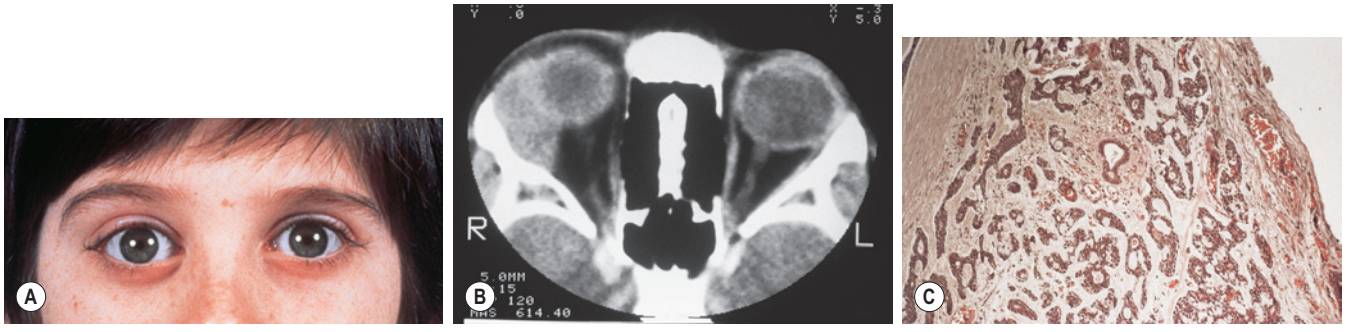


Fig. 26.5 Adenoid cystic carcinoma. (A) This 10-year-old boy presented with a 1-year history of gradual right proptosis and upper lid swelling. There was no pain or sensory loss. (B) Computed tomography scan showed a lacrimal gland mass excavating the frontal bone, without erosion. Even rapidly growing lesions may cause excavation in childhood. (C) It was an adenoid cystic carcinoma of the lacrimal gland. The patient was alive and well 23 years later. *(Patient of the University of British Columbia.)*

inflammation, or leukemic deposits, and biopsy is required for diagnosis.

Adenoid cystic carcinoma is locally invasive, may metastasize, and has a poor prognosis despite surgery, radiotherapy, and chemotherapy (Fig. 26.6).[30] Local excision and radical proton beam irradiation may provide longer disease-free survival.[31]

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Histiocytic, hematopoietic, and lymphoproliferative disorders

Timothy John Sullivan

Chapter contents

LANGERHANS CELL HISTIOCYTOSIS
JUVENILE XANTHOGRANULOMA
ROSAI–DORFMAN DISEASE
LEUKEMIA
LYMPHOMA
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Histiocytic disorders occasionally affect the eye and ocular adnexae. The broad histology-based categories of histiocytic lesions seen by the ophthalmologist are: Langerhans cell histiocytosis (LCH), juvenile xanthogranuloma (JXG), Rosai–Dorfman disease (RDD), and Erdheim–Chester disease (ECD). While LCH and JXG are predominately pediatric disorders, there are many pediatric adnexal RDD cases and a few ECD adnexal cases in children.

Langerhans cell histiocytosis

Early in the twentieth century, Hand–Schüller–Christian disease was described as a combination of a skin rash, bony lesions, and diabetes insipidus. Letterer, in 1924, and Siwe, in 1933, described a histologically similar entity with more extensive involvement including hepatic, splenic, and marrow abnormalities.[1] Solitary eosinophilic granulomas were subsequently reported.[2] The common histopathological features of these three disorders was noted by Lichtenstein who suggested the term "histiocytosis X" to denote the histiocytic origin but unknown pathogenesis.[3] Breathnach and Birbeck described pentalaminar zipper-like intracytoplasmic inclusions (Birbeck granules) in cutaneous Langerhans cells contemporaneously with Nezelof and Bassett, describing identical structures in the lesions of histiocytosis X using electron microscopy.[4]

This led to the belief that the Langerhans cell was the cell of origin in these disorders, henceforth dubbed Langerhans cell histiocytosis. The pathological histiocyte demonstrates a nucleus with a central stripe, reminiscent of a coffee bean, eosinophilic cytoplasm, and positivity for CD1a, CD207 (langerin), and S100 (Fig. 27.1). Standard light microscopy also revealed an abundant infiltrate of eosinophils, lymphocytes, and macrophages, suggesting an inflammatory process rather than a neoplastic process.[5] However, clonality was demonstrated by Yu and Wilmann in 1994. It is now known that *BRAF* mutations are found in 60% of cases, mutually exclusive *MAP2K1* mutations in 15–40%, as well as rarer *ARAF* mutations, confirming LCH to be a neoplastic process with an associated inflammatory response.[5] The pathological histiocytes do have some differences from epidermal Langerhans cells, lacking the typical dendritic spines and demonstrating a gene expression profile consistent with a precursor myeloid dendritic cell rather than a cutaneous dendritic cell. Thus, importantly, LCH is now classified as a myeloid neoplasia.[6]

All the mutations in LCH appear to be directed to the mitogen-activated protein kinase (MAPK, ERK) signaling pathway, which has numerous roles but influences cell cycle in terms of proliferation, apoptosis, and senescence. ERK is extracellular signal-regulated kinase, a key enzyme late in the pathway. The other mutations (*BRAF*, *MAK2K1*) lead to ERK activation. This pathway is the same one involved in neurofibromatosis and melanoma development. The timing of the mutation appears to determine which clinical syndrome manifests. BRAF mutations were present in peripheral blood of all patients with widespread high-risk disease, a small number of those with multifocal low-risk disease and no patients with single-system disease.[7] Other epigenetic influences or additional mutations might also account for variations in disease behavior.

The pediatric incidence of LCH is about five cases per million in population-based studies.[8] The majority of ocular adnexal involvement is from single site, single-system disease, the so-called eosinophilic granuloma (Fig. 27.2A). This is more common in boys. In one large series, 80% presented with a painless swelling of the superior orbit (eosinophilic granuloma). Only 6% manifested multifocal multisystem disease, presenting with signs of diabetes insipidus due to posterior pituitary involvement associated with bilateral proptosis[9] (Fig. 27.2B). Visual loss is unusual but can occur due to optic nerve compression or prolonged raised intracranial pressure. It is important for ophthalmologists to be aware of the possibility of systemic involvement and arrange for appropriate systemic investigation and oncological assessment. Usually imaging with computed tomography (CT) or magnetic resonance imaging (MRI) will be performed to assess the orbital lesion[9] (Fig. 27.3). While MRI is the preferred initial investigation in children, CT does delineate the lytic bony lesions well. Subsequent biopsy will confirm the diagnosis,

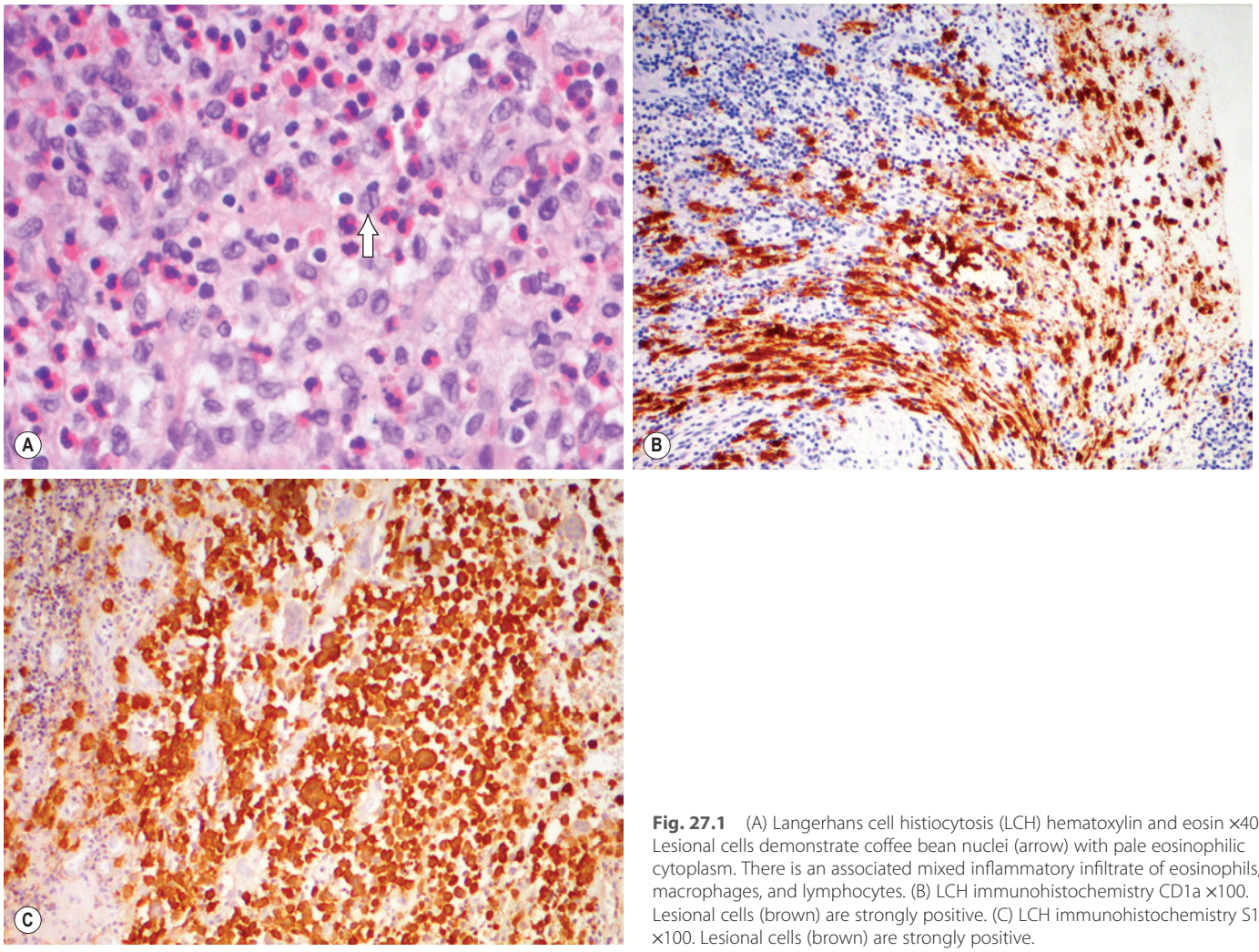


Fig. 27.1 (A) Langerhans cell histiocytosis (LCH) hematoxylin and eosin ×400. Lesional cells demonstrate coffee bean nuclei (arrow) with pale eosinophilic cytoplasm. There is an associated mixed inflammatory infiltrate of eosinophils, macrophages, and lymphocytes. (B) LCH immunohistochemistry CD1a ×100. Lesional cells (brown) are strongly positive. (C) LCH immunohistochemistry S100 ×100. Lesional cells (brown) are strongly positive.



Fig. 27.2 (A) Typical presentation of adnexal Langerhans cell histiocytosis (LCH) with left proptosis and downward globe displacement. (B) Bilateral proptosis associated with LCH multisystem multifocal disease.

pre-empting further investigation and referral. The initial evaluation should include full blood count, liver function tests, electrolytes, coagulation studies, sedimentation rate, lactate dehydrogenase, immunoglobulins, uric acid, and ferritin. Positron-emission tomography (PET)/CT scanning, systemic CT and MRI, and bone marrow and lower gastrointestinal endoscopy are also mandated.[10] One of the characteristic MRI findings in LCH is the loss of the normal posterior pituitary enhancement due to infiltration with affected tissue. Other central nervous involvement includes various soft tissue deposits and diabetes insipidus.

Management of the orbital lesion generally involves confirmatory biopsy with curettage, to remove as much lesion tissue as possible, and perilesional steroids. With a unifocal,

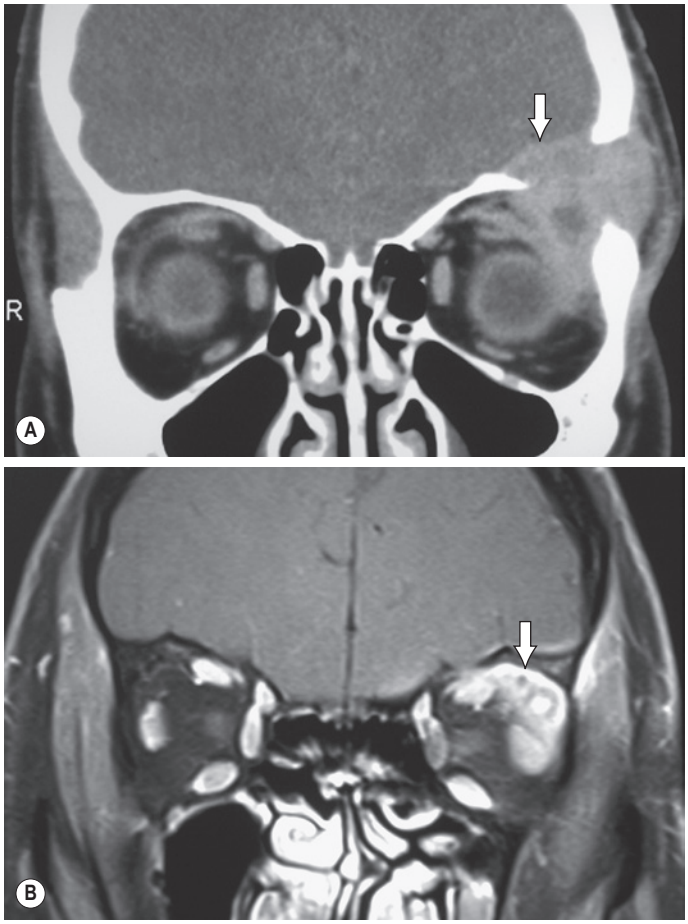


Fig. 27.3 (A) Langerhans cell histiocytosis (LCH) coronal computed tomography scan showing marked destruction of the left frontal bone and orbital roof with an associated soft tissue lesion. (B) LCH coronal magnetic resonance imaging scan, T1 weighted with gadolinium enhancement, showing the enhancing soft tissue component of LCH.

unisystem involvement, other treatment is unnecessary.[10,11] However, appropriate systemic investigation must be performed and if there is multifocal or multisystem disease, oncological management is appropriate. The Histiocyte Society has conducted international multicenter randomized trials, LCH I–IV, and other multicenter studies in Europe and Japan have contributed to management approaches, which have largely been vinblastine- and prednisolone-based from the LCH trials, with cytarabine regarded as a sound option from the Japanese studies and LCH IV. With multisystem, multifocal disease, refractory or relapsed lesions occur frequently and cladribine, clofarabine, and cytarabine have all been used in this setting. Targeted therapy with BRAF inhibitors such as vemurafenib has induced strong response in patients with the *BRAF* mutation. Other agents directed toward the MAPK pathway may also have a role, especially in BRAF-negative lesions. Bony lesions have also responded to prostaglandin therapy, especially for symptomatic unifocal osseous involvement. Where patients do not respond to these treatments, stem cell transplantation has a role. The vast majority of the lesions seen by ophthalmologists are unifocal single-system lesions, and they do well. The prognosis for multisystem multifocal disease remains guarded, but is improving with improved understanding of the pathogenesis, the cell of origin, and the use of targeted therapies.[10]

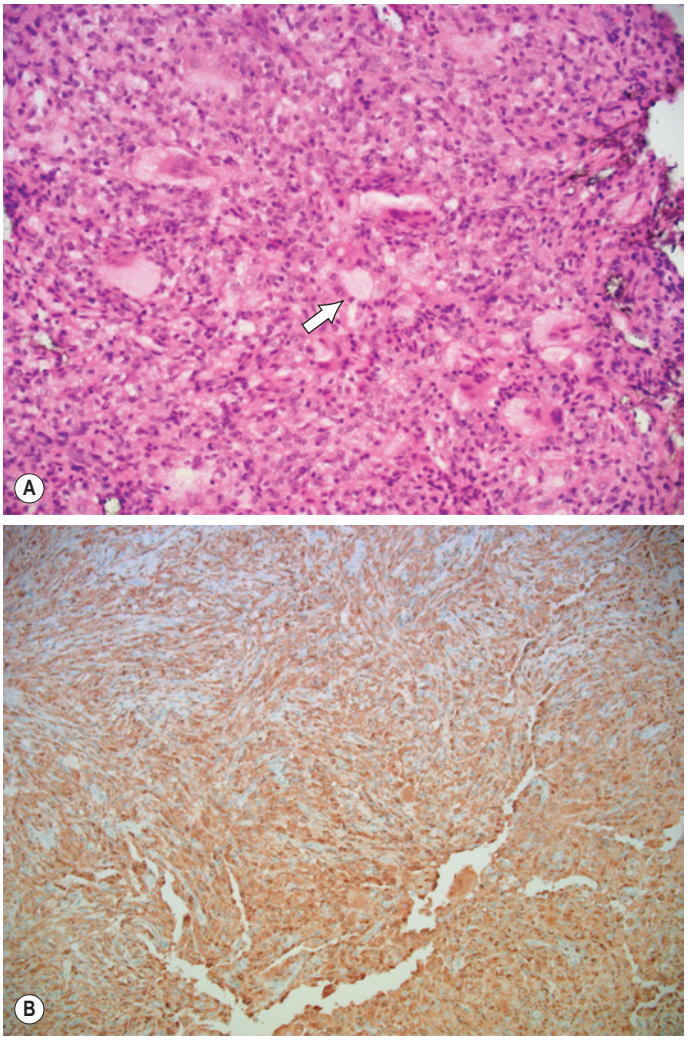


Fig. 27.4 (A) Juvenile xanthogranuloma (JXG) histology, hematoxylin and eosin ×200. Shows a mixed inflammatory cell infiltrate characterized by Touton giant cells. (B) JXG immunohistochemistry CD68, showing strong positivity.

Juvenile xanthogranuloma

The pathology of JXG is different from that of LCH. The cells are epithelioid with an eosinophilic cytoplasm and do not have the coffee bean nucleus. CD1a and CD207 are not expressed, differentiating JXG from LCH. Cells have a consistent immunophenotype for CD14, CD163, CD68, fascin, and factor 13a. Birbeck granules are absent on electron microscopy. There is a mixed inflammatory infiltrate characterized by the presence of Touton giant cells[5] (Fig. 27.4). The presentation is also different, usually with skin lesions. These may be transient in patients with neurofibromatosis type 1 (NF1), sometimes as the initial feature. There is also an association with juvenile myelomonocytic leukemia. Ophthalmic series generally report a preponderance of ocular lesions involving the iris, conjunctiva, or, less commonly, the choroid, with a mean age at presentation of 3 years. Ocular adnexal eyelid or orbital involvement is seen much less frequently but does occur.[12] This may present as a domed xanthomatous skin lesion or a deeper orbital mass in a slightly older child with a mean age of presentation of 6 years (Fig. 27.5). Extraocular muscle



Fig. 27.5 Juvenile xanthogranuloma showing a typical anterior left orbital mass. Note the typical xanthomatous (yellow) color.



Fig. 27.6 (A) Massive bilateral proptosis in acute lymphoblastic lymphoma (ALL). (B) Extensive orbital involvement with ALL demonstrated on computed tomography scan.

involvement may be seen. There is a case report of extensive involvement of the orbit, sinus, infratemporal fossa, and brain in a newborn, which was managed expectantly.[13] The yellowish cutaneous and other lesions are an important clue to the underlying diagnosis. This is confirmed by excisional biopsy of the most accessible lesions, which normally represents adequate therapy. Iris involvement is often complicated by recurrent hyphema and glaucoma. Biopsy is liable to precipitate bleeding, and treatment with topical steroids with frequent careful follow-up is often efficacious in this context.

Rosai–Dorfman disease

RDD is a benign, idiopathic, inflammatory lesion that may include a range of manifestations, including extranodal disease, typically seen in the orbit and ocular adnexa.[5] RDD was formerly known as "sinus histiocytosis with massive lymphadenopathy". These patients usually present with a painless soft tissue mass causing proptosis, or with ptosis or motility disturbances and diplopia. The orbital disease may present well before sinus involvement or lymphadenopathy.[14] CT imaging findings are generally of an homogenous extraconal mass with some contrast enhancement but no associated tissue or bone destruction, although sphenoid wing erosion may occur. MRI reveals lesional tissue to be hypointense with respect to brain, and with significant enhancement with gadolinium contrast.[15] Biopsy reveals pathology characterized by a process known as "emperipolesis." Typically, large histiocytes phagocytose intact erythrocytes, lymphocytes, and plasma cells, contained within intracellular vacuoles in the abundant pale to clear cytoplasm. These cells are CD14-, CD68-, CD163- and S100-positive but negative for CD1a and CD207. Some cells may stain for immunoglobulin G4 but usually do not meet the criteria for diagnosis of that disorder.[5]

Treatment of this unusual histiocytic disorder is not always necessary since about half the cases resolve spontaneously. Surgical excision or debulking at the time of initial biopsy is appropriate if this can be performed without significant risk to vital orbital structures. Occasional orbital cases result in optic neuropathy that may warrant chemotherapy or even low-dose radiotherapy.

Most cases resolve spontaneously or respond to treatment; however, a small number of recalcitrant cases result in disseminated chronic lymphadenopathy. There is a low mortality associated with RDD, predictably in people with multiple nodal and concomitant extranodal lesions.

Leukemia

Leukemia can involve any ocular adnexal structure, either directly from tumor infiltration or deposits, or with secondary effects due to hemorrhage, infection, or neuro-ophthalmic signs[16] (Fig. 27.6). Pediatric leukemias include acute lymphoblastic (ALL) (75%), acute myelogenous (AML) (20%), and

chronic myelogenous (CML) (5%). The incidence of ophthalmic involvement varies widely in different reports from 10–90%, which might reflect the different methodologies.[17] Rigorous prospective evaluation yields a higher incidence, and many patients who are asymptomatic may harbor adnexal involvement.[18] Ophthalmic involvement may be the presenting feature of leukemia, and in one series of 31 cases of granulocytic sarcoma, there was no prior history of leukemia in any case, but 40% were found to have AML on systemic investigation and 75% of the remainder developed AML within 21 months.[19] Granulocytic sarcoma was previously named "chloroma" due to its greenish color from the myeloperoxidase present in lesional cells.[20]

Adnexal disease may also be a sign of a relapse after treatment, representing the most common site for relapse of ALL in one series. For these reasons, ophthalmic examination at diagnosis is recommended. Generally these patients demonstrate unilateral or bilateral proptosis, eyelid swelling or edema, or pain. The deposits may involve the intra- or extraconal spaces, the extraocular muscles, or the lacrimal gland. The presence of orbital or ocular lesions is adversely associated with prognosis for both acute myeloblastic and acute lymphoblastic leukemia. The prognosis for granulocytic sarcoma remains poor, with a majority of patients surviving only 30 months in Zimmerman and Font's 1975 series.[5] In 2014, Aggarwal published a series of patients with granulocytic sarcoma who progressed to AML; their average survival was 9.2 months.

Lymphoma

Ocular adnexal lymphoma is much less common in the pediatric population than in adults. Nonetheless, it occurs in a few settings. Historically there has been an awareness of the Epstein–Barr virus-mediated Burkitt lymphoma in the sub-Saharan African population, but this same lesion can occur sporadically in non-endemic situations.[21]

There have also been limited reports of both B cell and T cell lesions, classified according to the World Health Organization's modification of the Revised European–American Classification of Lymphoid Neoplasms (REAL classification)[22] (Fig. 27.7). These include primary extranodal marginal zone lymphoma (EMZL), diffuse large B cell lymphoma (DLBCL), and B-precursor lymphoblastic lymphoma of the orbit.[23,24] These tumors have presented as mass lesions, proptosis, or eyelid swelling. Imaging findings with CT and MRI show well-circumscribed molded-mass lesions that enhance moderately. Once a tissue diagnosis has been established, systemic staging using the American Joint Committee for Cancer, 7th edition, is undertaken.[25] Primary orbital disease without systemic involvement is usually treated with radiotherapy or with chemotherapy/immunotherapy. The indolent EMZL generally responds well and has a better prognosis. DLBCL is more aggressive but seems to have good survival in the pediatric population, whereas T cell lymphomas have a poorer prognosis.

The final setting for lymphoma or lymphoproliferative disease is as a manifestation of the post-transplantation lymphoproliferative disorder (PTLD), which is strongly associated with Epstein–Barr virus infection.[26,27] In this setting, the post-transplant immunosuppression is reduced or discontinued, in conjunction with chemotherapy and immunotherapy with rituximab, with resolution of the lesions and reduction in the Epstein–Barr viral titer.



Fig. 27.7 Cutaneous ocular adnexal T cell lymphoma.

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Craniofacial abnormalities

Joanna Black and John Crompton

Chapter contents

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CLEFTING SYNDROMES
FRONTOETHMOIDAL MENINGOENCEPHALOCELE
MIDLINE FACIAL CLEFT
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Introduction

This chapter discusses two main groups of disorders:

1. Craniosynostoses, in which premature closure of sutures causes an abnormally shaped skull, e.g. Crouzon and Apert syndromes.
2. The clefting syndromes, in which there is a failure of apposition or fusion of fetal tissues. These include the mandibulofacial dysostoses, e.g. Treacher Collins and Goldenhar syndromes.

In addition, frontoethmoidal meningoencephaloceles, midline facial clefts, and amniotic bands are discussed.

Craniosynostosis

Craniosynostosis is premature fusion of one or more cranial vault sutures with resultant skull deformity. It occurs in approximately 1 in 2500 births and may be primary or secondary. Thirty percent of cases are syndromic, usually with multiple suture involvement and associated primary malformations in the face, trunk, or extremities. Syndromic craniosynostosis patients present with significant cosmetic challenges and face complex neurologic, ophthalmologic, and airway difficulties. Non-syndromic ("simple") craniosynostosis may have neurologic or ophthalmologic complications. Some cases of simple craniosynostosis represent the mild end of a spectrum of syndromic disease.[1]

Pathophysiology

Pathogenesis and genetics[1]

Between 30% and 70% of cases are caused by mutations in hotspots in the fibroblast growth factor receptor genes FGFR1, FGFR2, and FGFR3 or in the TWIST1 gene. Other genes unequivocally associated with the condition when mutated include MSX2, EFNB1 and EFNB2, RAB23, and FREM1. The majority are involved in the process of cell proliferation and ossification, and many belong to a common molecular pathway.[2] The most common syndromes are autosomal dominant. *De novo* mutations are of paternal origin and increase with paternal age, thought to be due to a co-location with mutations promoting clonal expansion within male germline progenitors (the "selfish spermatological selection" theory). The reader is referred to genetic databases such as the Online Mendelian Inheritance in Man (OMIM) Database (http://www.omim.org/). Environmental factors have also been implicated in the etiology of craniosynostosis, including maternal smoking and altitude, and intrauterine head constraint.[3] Craniosynostosis may occur secondary to various conditions, including shunted hydrocephalus, metabolic disorders such as hyperthyroidism and rickets, and hematologic disorders such as thalassemia and sickle cell anemia.[3]

Effects on the skull

Cranial sutures are fibrous joints providing a malleable quality to the head, allowing vaginal birth and growth of the brain during early development. Although a particular skull suture prematurely fused does not always correlate with a specific head shape abnormality, most commonly cranial growth perpendicular to the fused suture is restricted and compensatory growth occurs at the remaining open sutures (Fig. 28.1). The principal clinical manifestations have been given Greek or Latin descriptors; recently synostotic disorders have tended to simply be named according to the suture involved. Trigonocephaly ("triangular head") is metopic suture synostosis; scaphocephaly ("boat-shaped head") is sagittal suture synostosis; plagiocephaly ("twisted head") is either unilateral coronal or unilateral lambdoid suture synostosis; and brachycephaly ("short head") is bilateral coronal suture synostosis (Table 28.1). Multiple suture involvement results in more complex head morphologies, such as tryphyllocephaly (Kleeblatschadel, clover leaf, or trilobed skull) or oxycephaly ("towering head"). Premature synostosis also occurs in the

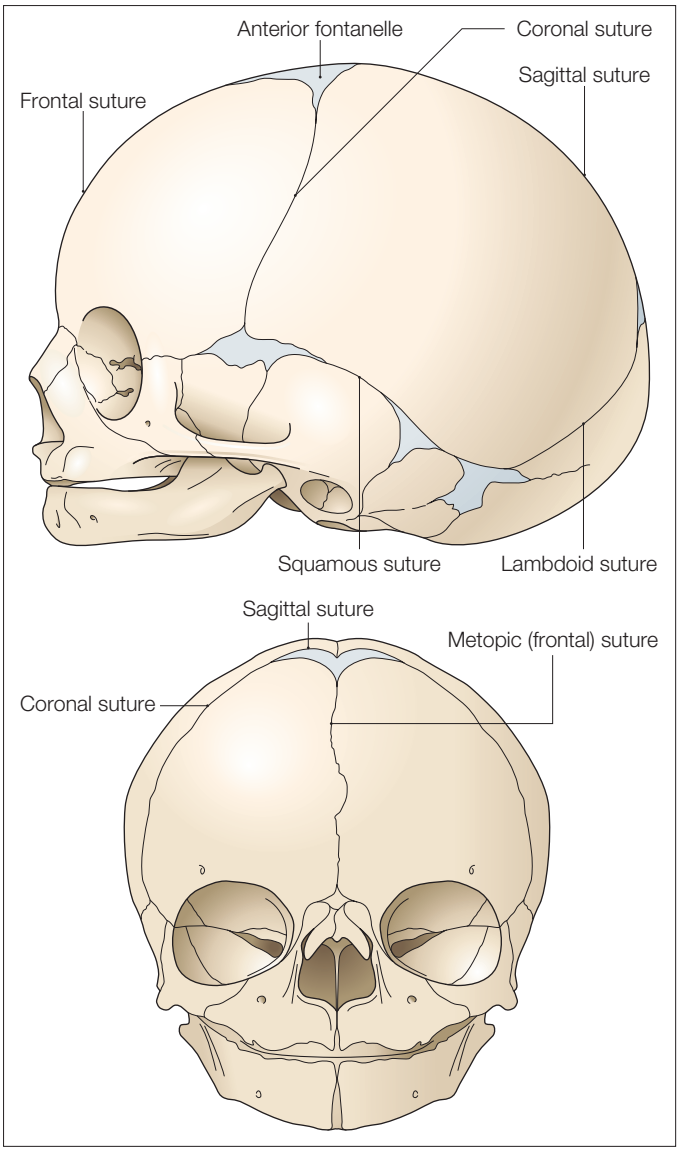


Fig. 28.1 The cranial sutures and fontanelles in an infant skull.

cranial base and facial skeleton. Cranial base underdevelopment compounds primary midfacial hypoplasia through its indirect effects on midfacial growth. The resulting abnormalities of palate, dentition, airway, and hearing may be severe.

Effects on intracranial pressure, the brain, and optic nerve

Brain development is intimately tied to growth of the skull; children with craniosynostosis may have developmental delay.[4,5] Reported incidences vary widely. Increased intracranial pressure (ICP) may occur in 75% of syndromic patients and 20% of single-suture craniosynostosis patients. In syndromic patients, four dynamic factors may contribute to raised ICP: restricted skull volume ("craniostenosis"), intracranial venous hypertension, hydrocephalus, and sleep apnea caused by facial deformity.[6] Due to its slowly progressive nature, the majority of patients have no warning symptoms. Radiologic findings are not necessarily related to intracranial pressure recordings and optic nerve swelling is frequently absent. Fibroblast growth factor receptor (FGFR) gene products are found in the optic



Fig. 28.2 Saethre–Chotzen syndrome. Axial computed tomography of a patient with Saethre–Chotzen syndrome demonstrating shortened orbits and proptosis.

nerve sheath and, when these are mutated, its failure to dilate may be due to abnormal fibrous tissue in the optic nerve sheath or lamina cribrosa.[7] This increased resistance and the limited autoregulatory capacity within the sheath increases the susceptibility of the optic nerve to decreased cerebral perfusion pressure due to raised ICP, venous hypertension, and obstructive sleep apnea-related CO_2 retention.[8] Sleep apnea-related hypoxia may also contribute to brain and optic nerve damage.

Effects on the orbit

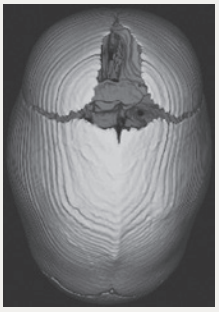
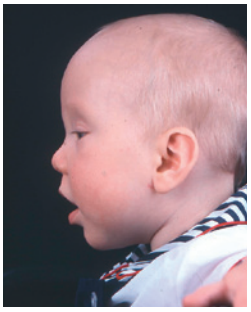
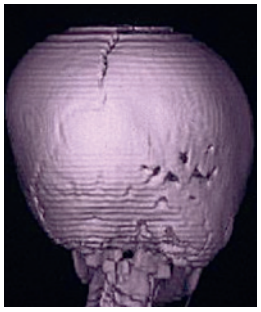
In syndromic craniosynostosis, midfacial hypoplasia and underdevelopment of the skull base lead to shallowing of the orbits, retrusion of the orbital rims, and proptosis (Fig. 28.2). Vision–threatening corneal exposure or globe prolapse may occur. Keratinocyte growth factor receptor is a splice variant of FGFR2, and corneal epithelial healing may be abnormal with some FGFR mutations. Lowering of the cribriform plate and anterior cranial fossa floor with overgrowth of the ethmoid complex results in failure of anterior rotation of the orbital axes in fetal life (see Chapter 3), creating divergent orbital axes and hypertelorism (see Chapter 22). This divergence may be greater in the frontal than maxillary planes, resulting in ex-cyclorotation of the orbits (Fig. 28.3). The external manifestation of this is the antimongoloid palpebral fissure. Premature closure of the metopic suture may result in hypotelorism. These changes in orbital axis and angulation increase the likelihood of strabismus, which is seen in up to 90% of patients. FGFR2 is expressed in the extraocular muscles (EOMs); this may explain some of the EOM abnormalities, including bifid, hypoplastic or absent muscles, microscopic abnormalities, and a gristly, inelastic feel.[7] FGFR2 is also expressed in the embryonic rat lens and cornea. This may account for the high incidence of refractive error in these patients.

Management

Diagnosis[2]

Simple craniosynostoses are summarized in Table 28.1 and the most common craniosynostosis syndromes are described in Table 28.2. Syndromic craniosynostosis is readily detected

Table 28.1 Simple craniosynostosis

Suture involved	Features
METOPIC   	Ridging of metopic suture Depressed superolateral orbital rims Narrowed intercanthal distance
UNILATERAL CORONAL  	Ipsilateral forehead and frontoparietal flattening Contralateral frontoparietal bulging Ipsilateral anterior displacement of the zygoma and ear Deviation of nose to contralateral side Shortened orbital roof and superior oblique imbalance
SAGITTAL   	Biparietal narrowing Frontal bossing Ridging of the sagittal suture
UNILATERAL LAMBDOID    	Ipsilateral occipital flattening Ipsilateral frontal bossing

and may be diagnosed *in utero* (Fig. 28.4). There are a number of differential diagnoses to consider with simple synostoses. History and examination will usually resolve any uncertainty. Attention should be paid to:

1. the angle of the palpebral fissure;
2. the position of the ear;
3. any twisting of the nasal tip;
4. a "bird's eye view" of the head.

The sutures may be palpated for abnormal ridging or immobility. Deformational plagiocephaly, a common condition since the introduction of the "back to sleep" intervention to reduce the risk of sudden infant death syndrome, may be confused

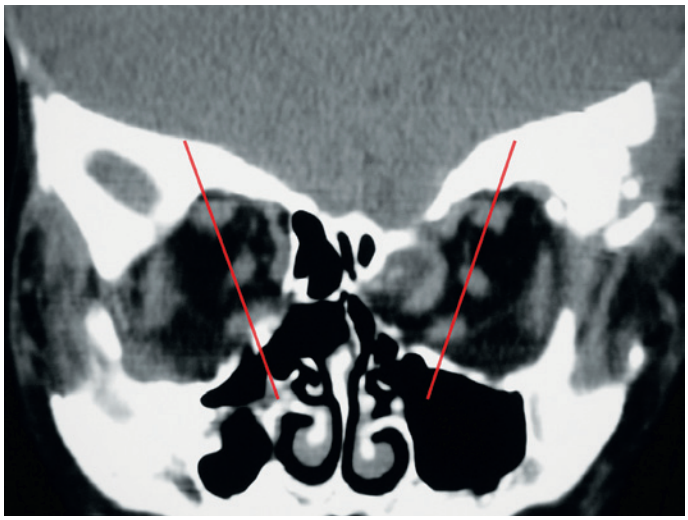


Fig. 28.3 Crouzon syndrome. Coronal computed tomography in a patient with Crouzon syndrome demonstrating ex-cyclorotation of the orbits and their contents. A line drawn between the centers of the superior and inferior rectus muscles emphasizes the angle.

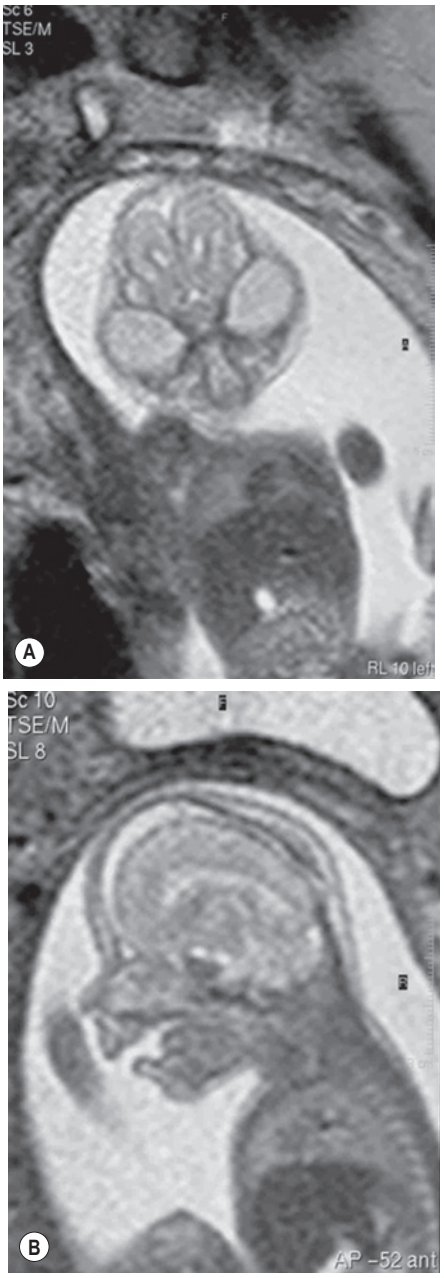


Fig. 28.4 Antenatal ultrasound images of a fetus with Pfeiffer syndrome.

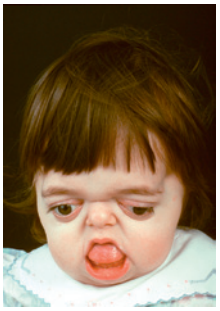
with lambdoid synostosis, which is exceptionally rare. Deformational plagiocephaly is characterized by a history of development of the head shape in the first few months of life in association with persistent positioning on one side, torticollis, or an inactive or developmentally delayed infant. The resultant occipitoparietal flattening may be differentiated from unilateral lambdoid synostosis by a parallelogram-shaped head seen from above and anterior displacement of the ipsilateral ear. Unilateral lambdoid synostosis results in a trapezoidal-shaped head from above with the ear posteriorly displaced (Figs 28.5 and 28.6). The relatively large head and poor neck muscle tone of the premature baby results in a laterally turned head, and may result in a long narrow head. The distinction from sagittal synostosis can be made by the mobile sagittal suture and correction of the head shape at 3 months of age as head control increases. Metopic synostosis may present some diagnostic difficulty; it is a spectrum of disease. At one end is the development of a metopic ridge in the first year of life, which usually requires no treatment. This may be differentiated from premature closure of the metopic suture seen in primary microcephaly by normal head circumference. At the other end of the spectrum is classic trigonocephaly, characterized by metopic ridging in association with supraorbital recession and hypotelorism (see Chapter 22). Where doubt arises, a skull X-ray to check for suture patency is useful, if performed and interpreted by an experienced pediatric radiologist. A computed tomography (CT) scan can be considered where head shape is worsening or doubt persists.

Craniosynostosis is very complex. Decisions about timing and indications for surgery are made with input from specialists from craniofacial, neurosurgical, ear, nose and throat, dental, orthodontic, anesthetic, psychology, audiology, speech therapy, nursing, and ophthalmologic services, forming a craniofacial team. Patients require care from birth until their growth is complete at maturity. Treatment options are exclusively surgical, with a broad range of available surgical techniques. A primary procedure is typically performed in the first 6 months of life, to allow safe growth of a rapidly expanding brain. Removal of the affected suture by strip craniectomy has largely been replaced by more extensive remodeling procedures and expansion of the cranial cavity, most commonly by fronto-orbital advancement. The growing brain may then exert pressure on the released calvaria and dura, allowing for good correction of the cerebrocranial disproportion and deformity. Bone growth is also good and minimizes the risk of bone defects. From this age until the age of 10 years, craniosynostosis should be managed expectantly, with careful monitoring for evidence of raised intracranial pressure, corneal exposure, and airway problems. Some cases may require further cranial expansion surgery or midfacial distraction; expectation would be for recurrence where surgery has been performed at a young age. Surgery in the second decade of life is directed at reducing residual deformity. Best results are achieved the closer to completion of growth the procedure is performed.

Table 28.2 The most common craniosynostosis syndromes

Syndrome	Clinical features
APERT  	Genetics: AD, FGFR3 CS: bicoronal (antenatal), lambdoid, brachycephaly, cranial base (late childhood) CNS (up to 90%): megalencephaly, anomalies septum pellucidum, low IQ, hydrocephalus Face: cleft palate, dental crowding, malocclusion Other: syndactyly (universal), cervical spine fusions, tracheal cartilaginous fusions
CROUZON  	Genetics: AD, variable expressivity, FGFR2, FGFR3 CS (usually in infancy): bicoronal +/– sagittal or lambdoid, cranial base. Head shape variable (scaphocephaly, trigonocephaly, trilobed) CNS (common): Chiari malformation, jugular foramen stenosis, hydrocephalus Face: exorbitism, midfacial hypoplasia, beaked nose, narrow palate, dental crowding, malocclusion Other: cervical vertebral fusion, tracheal cartilaginous fusions, conductive hearing loss
PFEIFFER     	Genetics: AD, incomplete penetrance, FGFR1, FGFR2, FGFR3 Type 1: coronal +/– sagittal CS, normal IQ and life expectancy Type 2: cloverleaf skull, low IQ, synostosis of elbow and forearm Type 3: simple CS, short cranial base, synostosis of elbow and forearm Face: exorbitism, ptosis, ocular anterior segment dysgenesis, midfacial hypoplasia, malocclusion Other (all 3 types): low set ears, ear tags, broad thumbs and great toes, brachydactyly, syndactyly, cervical vertebral fusions, tracheal cartilaginous fusions, cardiovascular, gastrointestinal, urogenital anomalies

Table 28.2 The most common craniosynostosis syndromes—cont'd

Syndrome	Clinical features
MUENKE 	Genetics: AD, FGFR3, variable expressivity CS: coronal Other: low IQ, midfacial hypoplasia, ptosis, hand anomalies
SAETHRE–CHOTZEN  	Genetics: AD, TWIST CS (not universal): coronal, metopic, lambdoid. Often asymmetric Other: ptosis, high forehead, low hairline, maxillary hypoplasia, narrow or cleft palate, broad great toes, brachydactyly, partial cutaneous syndactyly
ANTLEY–BIXLER 	Genetics: AR, FGFR2 (POR) CS: coronal, lambdoid Other: severe midfacial hypoplasia, stenosis or atresia of choanae, low set protruding ears

AD, Autosomal dominant; CNS, central nervous system; CS, craniosynostosis; IQ, intelligence quotient.

Complications include blood loss, bone defects, scalp scarring, and, most commonly, incomplete correction of the deformity. Residual deformity is particularly common in unilateral or asymmetric synostosis. Although fever is common in any surgery penetrating the dura, infection is very rare in procedures not entering the nasopharynx. Despite extensive subperiorbital dissection in fronto-orbital advancement surgery, ophthalmic complications are rare. The effects on ocular alignment are discussed below. Genetic studies have provided potential targets for pharmacologic or genetic treatment modalities. The development of such nonsurgical treatment options may complement or replace current invasive techniques.[9]

Ophthalmic management in craniosynostosis

The ophthalmologist should manage craniosynostosis patients in conjunction with a multidisciplinary specialized craniofacial unit. Examination may be limited by developmental and speech delay, breathing difficulties, and exposure keratopathy-related photophobia. Ophthalmic genotype–phenotype correlations have been reported in syndromic craniosynostosis.[10,11] The visual complications among non-syndromic craniosynostosis will vary with diagnosis.[12,13] However, similar ophthalmic complications may be seen in patients with any diagnosis.

Vision loss

The most important roles of the ophthalmologist are to ensure adequate protection of exposed corneas, monitor for raised intracranial pressure, and detect and treat vision loss. Syndromic craniosynostosis patients have a visual acuity of 6/12 or worse in at least one eye in 65% of cases – in 40% of cases in the better eye.[14,15] Vision loss is rare in simple metopic and sagittal suture synostosis, but is frequent in unilateral coronal synostosis. The majority of non-syndromic and



Fig. 28.5 Bird's eye views demonstrating the parallelogram head malformation seen in deformational plagiocephaly (A) and the trapezoidal head malformation seen in lambdoid suture synostosis (B).

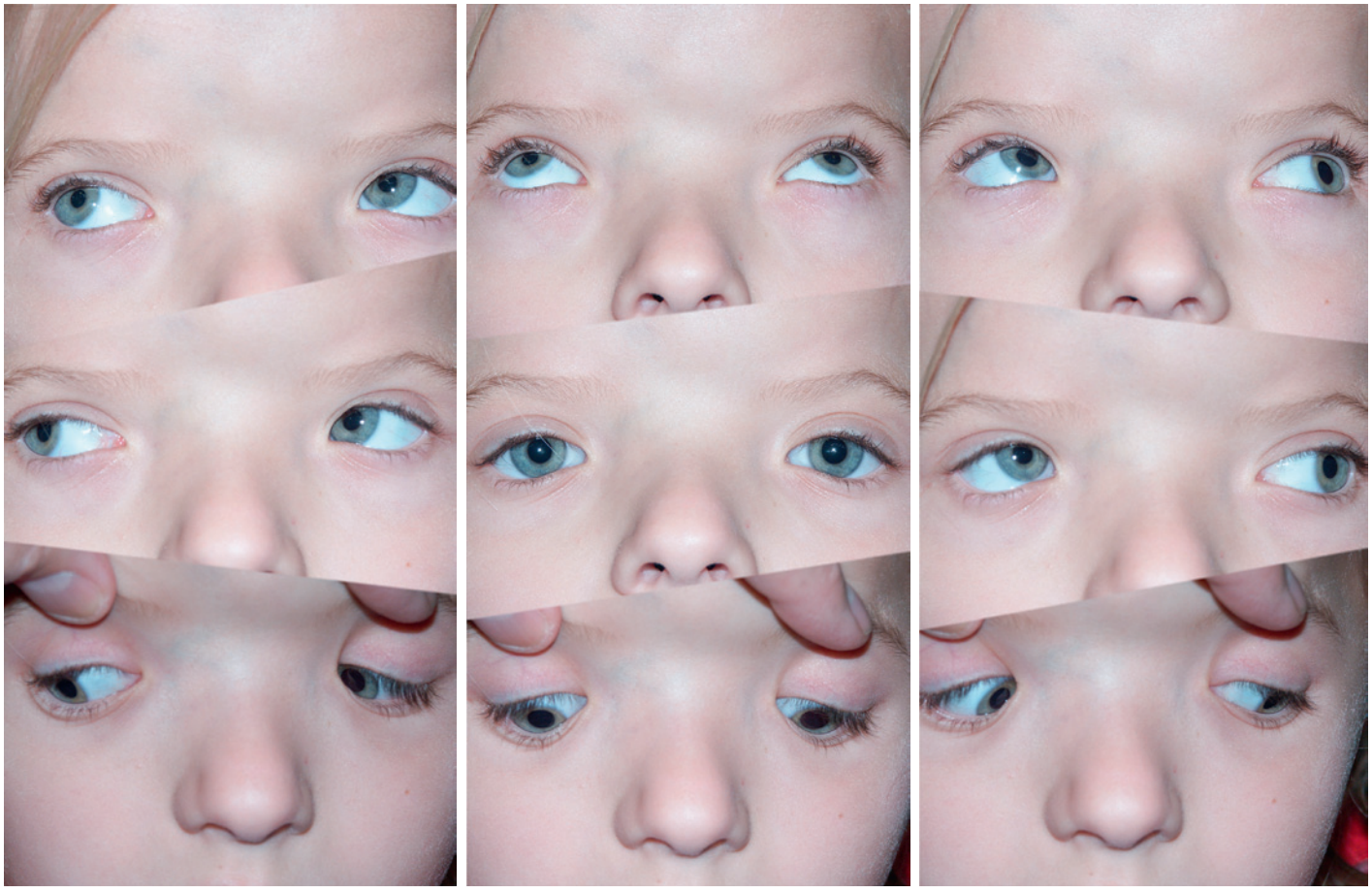


Fig. 28.6 V pattern and pseudo inferior oblique overaction in a patient with Crouzon syndrome.

nearly half of syndromic vision loss is due to treatable causes: astigmatism, anisometropia, and amblyopia.[15–17] Astigmatism may be severe, secondary to the shape of the orbits, ptosis, and corneal scarring. Spectacles may need to be customized to allow comfort and acceptance of wear. Atropine penalization may be preferable to occlusion therapy for amblyopia when there is significant proptosis of the globe. Exposure keratopathy due to a shortened orbit is common in syndromic craniosynostosis and causes discomfort, photophobia, examination difficulties, infection, vision loss, and scarring. The cornea should be protected with lubricants; tarsorrhaphy may be necessary, especially in cases of spontaneous globe prolapse or during periods of significant perioperative chemosis and swelling. In some cases with apparent tissue shortage, levator division may

be necessary to achieve closure. Tarsorrhaphy, however, may result in lid margin changes, which will undermine ocular surface health in the long term. The definitive treatment is midfacial or frontofacial advancement, something which the ophthalmologist may need to advocate for in discussions with the craniofacial team. Distraction devices are the method of choice for this in younger patients; in older patients, surgery may be considered

The optic nerve is susceptible to damage in craniosynostosis, and optic neuropathy may manifest as visual acuity or field loss. Photophobia may make assessment of the optic nerve difficult. Papilledema is frequently absent despite raised ICP. Serial pattern reversal visual evoked potentials (VEPs) are a sensitive and reversible marker of visual pathway dysfunction in raised intracranial pressure due to craniosynostosis.[18,19] Since radiology is also unreliable in detecting raised ICP in craniosynostosis, prolonged invasive ICP monitoring is often required to select patients needing early cranial vault expansion surgery. VEP monitoring provides a valuable noninvasive alternative.[19]

Anterior segment dysgenesis has been reported in Pfeiffer syndrome.[20] Findings include prominent Schwalbe's lines, corectopia, and Peters anomaly. It is prudent to monitor Pfeiffer syndrome patients for glaucoma.

Strabismus

Strabismus is reported in as many as 90% of craniosynostosis patients; exotropia is more frequent than esotropia. Dissociated eye movements, most commonly overelevation in adduction and V pattern, occur in as many as 44%. Theories as to the cause include desagittalization of the obliques due to divergent orbital axes, increased contact of the inferior oblique and globe due to short orbits, and ex-cyclorotated orbits and EOMs.[21] Ex-cyclorotation of all the EOMs will create an abnormal abducting force in elevation from the superior rectus muscles and an abnormal adducting force in depression from the inferior rectus muscles, resulting in a V pattern. The medial rectus muscles will have an abnormal elevating force in adduction and lateral rectus muscles an abnormal depressing force in abduction, mimicking inferior oblique overaction. Craniosynostosis patients have an abnormally high incidence of absent EOMs: superior oblique and superior rectus muscles are the most commonly affected. Strabismus may be multifactorial in some patients.

Success may be limited in strabismus surgery in craniosynostosis patients; however, a patient's condition is rarely worsened and a measured degree of optimism may be held. The timing of surgery takes into account any prior or planned craniofacial reconstruction. Routine fronto-orbital advancement has little effect on strabismus, but surgery to correct hypertelorism often results in an eso-shift. Craniofacial surgery may involve extensive subperiosteal orbital dissection and may result in subconjunctival fibrosis, making surgery more difficult. For these reasons, strabismus surgery should usually be deferred for some time postoperatively.[22] Some surgeons advocate early surgery when craniofacial reconstruction has been deferred beyond the first year of life, to establish binocularity. However, the likelihood of a second, post-reconstruction procedure must be considered. Perfect alignment may be very difficult to achieve and a binocular patient may face a higher risk of postoperative diplopia.

In V patterns and overelevation in adduction, the surgeon should have a high index of suspicion of ex-cyclorotation or muscle anomaly. Other indicators of ex-cyclorotation include ex-cyclorotation of the fundus and torsional movements with vertical optokinetic nystagmus stimulation. Preoperative imaging is useful. The EOMs are most easily identified on coronal CT or magnetic resonance imaging (MRI) immediately posterior to the globe (see Fig. 28.3). Although MRI is the "gold standard" imaging technique, three-dimensional ultrasound imaging is a safe and accurate alternative. Due to short reconstruction times, it may be performed at the time of surgery. It is less accurate at determining extraocular muscle position.[23] If imaging is not possible, surgical alternatives should be planned prior to operation. Some advocate exploration of all six EOMs, although anterior segment ischemia is a risk, especially if muscles are absent.

Horizontal deviations in primary gaze may be treated by standard recession and/or resection surgery; transposition of the rectus muscles may improve the dissociated movements. Coats et al. reported on 14 operated craniosynostosis patients with V pattern with severe oblique dysfunction.[24] Only inferior oblique (IO) myectomy or denervation and extirpation were consistently effective at treating IO overaction; only IO denervation and extirpation improved the superior oblique (SO) underaction. Isolated IO anteriorization and infraplacement of the medial rectus muscles were ineffective. The antielevation syndrome seen after temporal spreading of the insertion in IO anteriorization could worsen the IO overaction of the opposite, adducting eye. Hussein et al. reported nine cases of absent superior oblique tendon, confirmed by the exaggerated traction test, seven of which had craniosynostosis.[25] They reported good reduction in IO overaction and divergence in upgaze with IO nasal and anterior transposition. The best responses were seen in those with unilateral absent SO. Holmes et al.[26] believe that superior oblique tuck surgery addresses ex-cyclorotation of the globe, normalizing the vector forces of the rectus muscles, and they reported a good result in one patient in association with inferior transposition of the medial rectus. Good correction of hypotropia due to imaging-confirmed superior rectus muscle absence can be obtained with a Foster modification of the Knapp procedure.[22] The surgery in one case induced a horizontal deviation.

Clefting syndromes

The second major group of craniofacial abnormalities comprises the clefting syndromes and results from defective apposition or failure of fusion of neighboring structures during embryonic development. Tessier[27] introduced a descriptive classification, numbering clefts from 0 to 14 in clockwise rotation around the orbit (Fig. 28.7). Clefts of midline structures of the nose and forehead are numbered 0 and 1 below the level of the medial canthus and 13 and 14 above. Nasolacrimal and medial canthal clefts are numbered 2, 3, and 4 below and 10, 11, and 12 above, and so on. Cleft number 30 is of the mandibular symphysis. Clefts resulting from failure of embryonic closure of the nasolacrimal furrow or from amniotic bands are simply numbered according to their location relative to the eye.

Tessier's system encompasses the eponymously named syndromes of the face including Treacher Collins and Goldenhar, as well as craniofacial microsomia, formerly grouped together as mandibulofacial dysostoses, that are primarily due to retarded differentiation of the first branchial arch mesoderm.

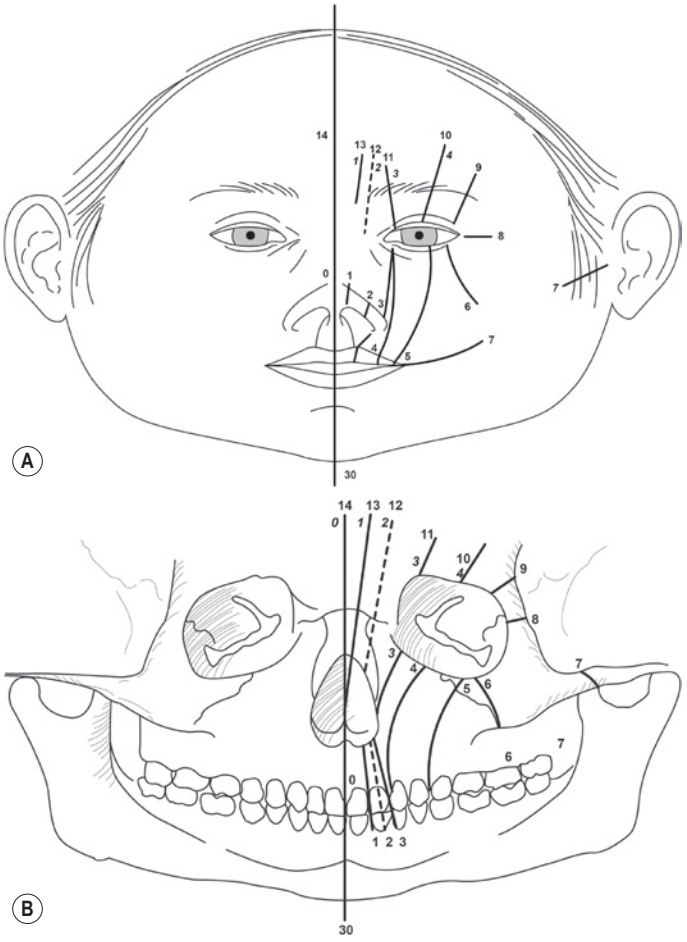


Fig. 28.7 Tessier classification of craniofacial clefts. (A) Soft tissue. (B) Skeletal. *(Modified from David DJ, Moore MH, Cooter RD. Tessier clefts revisited with a third dimension. Cleft Palate J 1989; 26: 163–84.)*

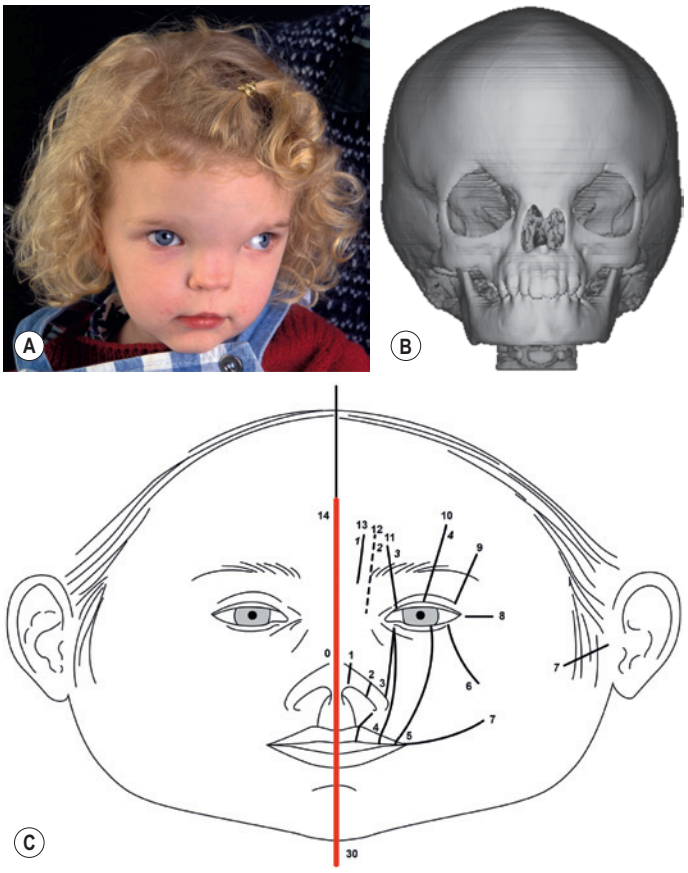


Fig. 28.8 (A) A 5-year-old girl with untreated midline craniofacial cleft (Tessier type 0–14) showing midline depression of the nose, and exotropia. (B) Computed tomography reconstruction shows widely displaced orbits and widened nasoethmoid region. (C) Cleft marked in red.

Van der Muelen et al.[28] have developed a different classification, replacing "cleft" with "dysplasia" based on the embryology of the brain, face, and cranium. This classification explains deformities ranging from anencephaly to lymphangioma by facial clefting and craniosynostosis. However, this system competes with the more simplistic topographic classification of Tessier used here.

Figures 28.8–28.13 are examples of the individual numbered clefts (with the cleft highlighted on the three-dimensional CT scan) – some have combinations of clefts.

Cleft number	Common ocular problem
3 & 11	epibulbar dermoid
4 & 10	iris coloboma
5 & 9	microphthalmos
9, 10, 11	upper lid cleft
3, 4, 5, 6	lower lid cleft

Types of lacrimal problems include: the puncta may be displaced laterally or be absent and the canaliculi may be disrupted or elongated; the lacrimal sac and/or nasolacrimal duct may be absent, and there may be bony defects of the lacrimal fossa.

Treacher Collins syndrome

Although Treacher Collins syndrome (TCS) was first described by Berry, Treacher Collins emphasized the malar deformity; it was expanded by Franceschetti and Zwahlen. The incidence is 1 : 50,000 live births.[29] The mode of inheritance is autosomal dominant with complete penetrance but variable expressivity of a gene on the long arm of chromosome 5 (5q32–33.3).[30] Various gene deletions encoding RNA polymerases 1 and 111 have been identified, confirming the heterogeneity of TCS, thus supporting the hypothesis that TCS is a ribosomopathy.[31]

General findings

- Complete form of TCS involves Tessier clefts 6, 7, and 8 (see Fig. 28.13).
- Characteristic facies include hypoplasia of malar and zygomatic bones with deficient inferolateral orbital angles (Fig. 28.14A).
- Bird- or fish-like profile results from absence of the nasofrontal angle (Fig. 28.14B).
- Lower jaw is hypoplastic with abnormal dentition.
- Respiratory problems result from choanal atresia and mandibular retrusion.
- Malformations of the external ear are common.
- Deafness (50% of cases) results from ossicular chain or inner ear malformations. *Early audiologic assessment is essential.*
- Accessory auricular appendages and blind fistulae occur between the angle of the mouth and ear.

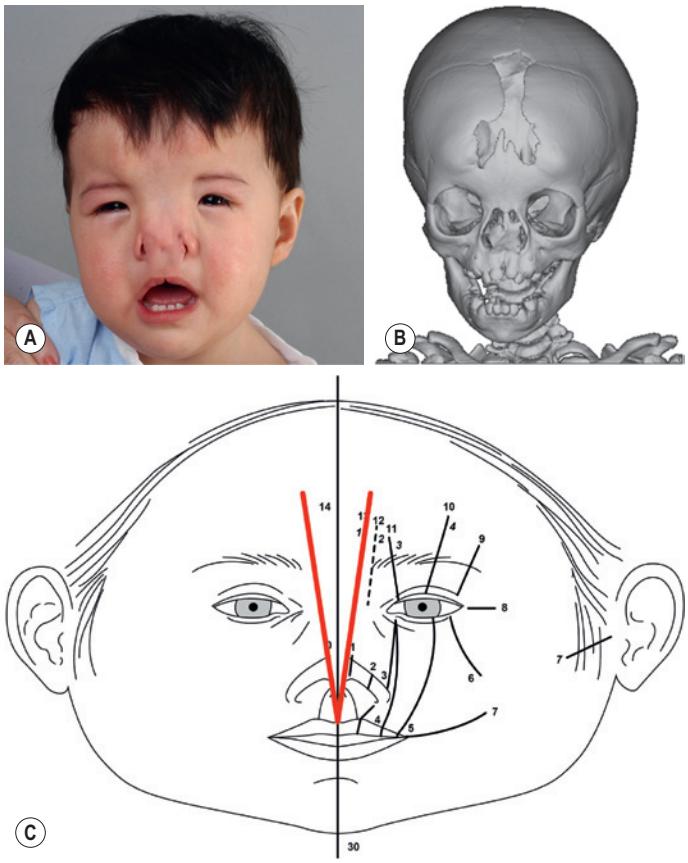


Fig. 28.9 (A) A boy with Tessier type 1–13 cleft: central cleft lip and cleft alae with flattened dorsum of nose. (B) Computed tomography reconstruction: widened nasoethmoid region. (C) Clefts marked in red.

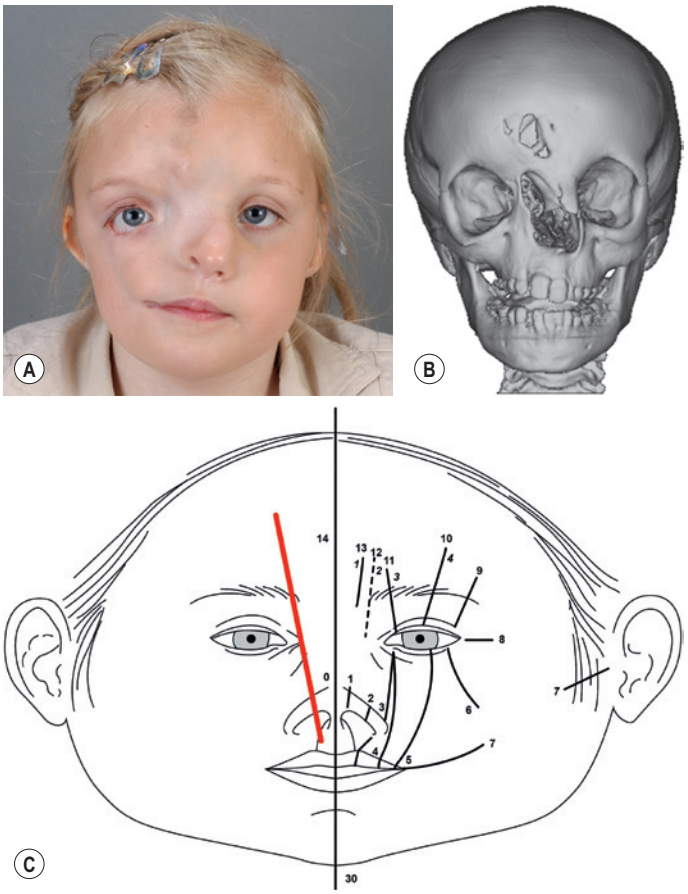


Fig. 28.10 (A) This girl with Tessier type 2–12 cleft shows a soft tissue groove above the distorted right nostril extending up her forehead and a type 5 cleft with vertical soft tissue deficiency between the lateral portion of the lip and the right lower eyelid cleft. (B) Computed tomography reconstruction: 2–12 cleft through ethmoids to frontal bone displacing the orbit laterally; 5: abnormal inferolateral orbital rim. (C) Only the 2–12 cleft is shown in red while her right 5 cleft corresponds to that shown in black on the left.

Ocular findings

- Antimongoloid slant of palpebral fissure.
- Coloboma of lateral one-third of lower lid (common) or pseudocoloboma with hypoplastic cilia, subcutaneous tissues, and muscle; absent lashes on the medial one-third of lower lids (common).
- Canthal dystopia.
- Nasolacrimal obstruction.
- Limbal or orbital dermoids (common), high astigmatism in severely affected cases.
- Severe risk of cognitive deprivation due to astigmatism plus deafness.
- Difficult to fit spectacles in presence of hearing aids and external ear abnormalities.

Management protocol[32]

1. Birth–2 years: airways and feeding problems, hearing problems.
2. 2–12 years: speech therapy and education, removal of limbal dermoid, oculoplastic repair of lid coloboma, and facial reconstruction with bone or vascular bone flaps.
3. 13–18 years: orthognathic surgery, final facial revision.
4. The abnormal anatomy causes airway management difficulties necessitating anesthetic expertise.

Goldenhar syndrome

Goldenhar described a syndrome of epibulbar dermoids, preauricular appendages, and mandibular hypoplasia (or hemifacial microsomia), which was expanded by Gorlin et al.[29] to the "oculoauriculovertebral spectrum." Most cases are sporadic but familial cases have been associated with a deletion on the long arm of chromosome 22 (22q11.2).[33]

Expression is variable, ranging from a few preauricular appendages only to bilateral clefting extending from the angles of the mouth to the tragus as well as of the palate and from either side of the frontonasal process to the medial canthi.

General findings

- Facial abnormalities may be bilateral but are usually more severe on one side (Fig. 28.15).
- Preauricular appendages – usually anterior to the tragus +/– fistula to ear.
- Facial asymmetry.
- Bilateral clefting from angle of mouth to tragus and of palate and either side of frontonasal process to medial canthi.

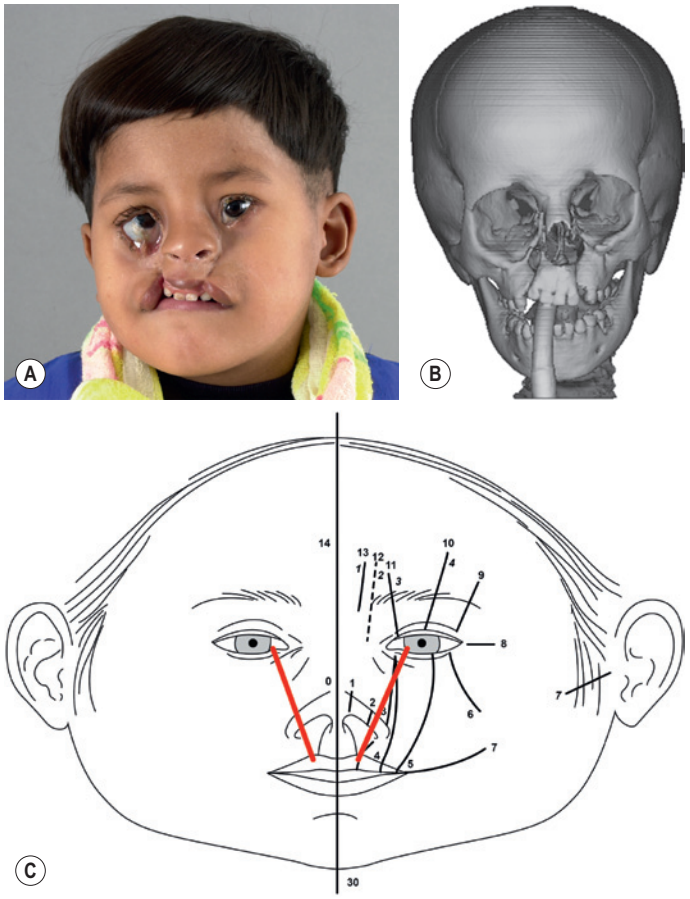


Fig. 28.11 (A) This boy has bilateral Tessier type 4 clefts with severe vertical soft tissue deficiency in the medial cleft lip extending toward the medially placed clefts in the lower and upper eyelids together with marked right orbital dystopia. (B) Computed tomography reconstruction shows bilateral clefts of anterior maxillae into orbital rims and the right orbital dystopia. (C) The no. 4 clefts are shown in red.

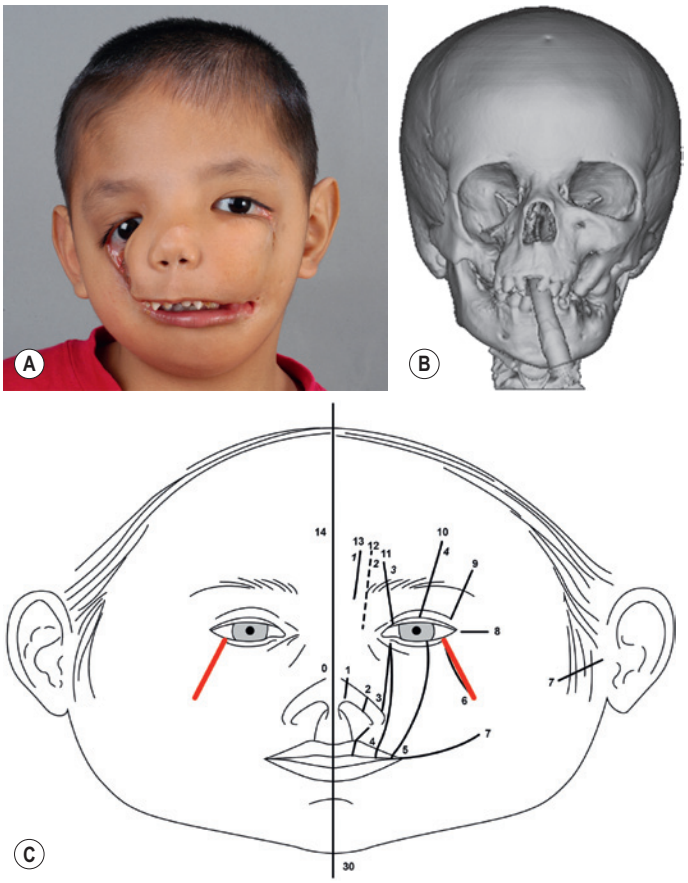


Fig. 28.12 (A) A boy with bilateral Tessier type 6 clefts: severe vertical soft tissue cleft from the oral commissure on the right and a furrow on the left to laterally placed lower eyelid clefts. There is antimongoloid obliquity of the palpebral fissures, some ectropion, and marked right orbital dystopia. (B) Computed tomography reconstruction: cleft in region of the right zygomaticomaxillary suture with hypoplasia of the maxilla and orbital rim. (C) Both no. 6 clefts shown in red.

- The "expanded Goldenhar complex" includes vertebral, cardiac, renal, pulmonary, and central nervous system abnormalities (including severe hydrocephalus and mental retardation).

Ocular findings

- Dermolipoma: usually yellowish, subconjunctival, superotemporal orbit. Rarely enlarges – can often be left alone (Fig. 28.16A).
- Epibulbar dermoid: unilateral 50%, bilateral 25%; nil 25%, usually inferotemporal limbus but can occur anywhere on the globe or within the orbit. White but often infiltrate of lipid at leading edge in cornea (Fig. 28.16B). May have irritating hairs (Fig. 28.16C). Can increase in size and cause astigmatism and amblyopia.
- Coloboma of iris: cosmetic defect +/– glare problems. May need cosmetic contact lens with painted iris.
- Microphthalmos – common.
- Ocular motility disturbance – common. Duane syndrome/esotropia/exotropia found in about 25%.[29]
- Ptosis.
- Nasolacrimal duct obstruction and fistula.
- Coloboma of mid-third of upper lid in 20%, often with ipsilateral epibulbar lesion.

Goldenhar syndrome shares a number of features with Treacher Collin syndrome; a combination of both has been reported.

Frontoethmoidal meningoencephalocele

These are subclassified as to their location: nasofrontal, nasoethmoidal and naso-orbital, their exit hole from the anterior cranial fossa being the foramen cecum. The extruding intracranial contents covered in meninges distort the developing face producing telecanthus, orbital dystopia, elongation of the face, and dental malocclusion (Fig. 28.17).

The clinical presentation depends on the location and extent of the lesion and can vary between a small soft cystic swelling over the bridge of the nose, depressing the nasal structures, to nasal obstruction causing difficulty with breathing and eating. Hypertelorism occurs, particularly if there is associated facial clefting producing a midline defect. Ocular problems include strabismus, amblyopia, and nasolacrimal drainage problems.

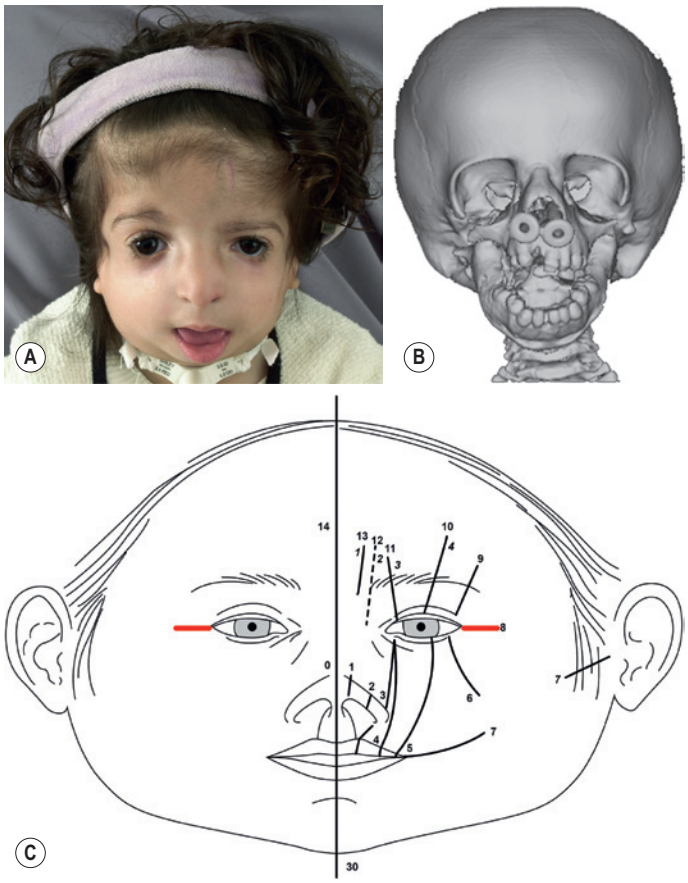


Fig. 28.13 (A) This girl has severe Treacher Collins syndrome and Tessier cleft type 8 with choanal atresia and mandibular retrusion (hence the tracheostomy), lower eyelid pseudocolobomata, and external ear abnormalities. (B) Computed tomography reconstruction: deficient lateral orbital wall, rim, and floor with hypoplastic malar and zygomatic bones bilaterally. (C) Type 8 clefts shown in red.

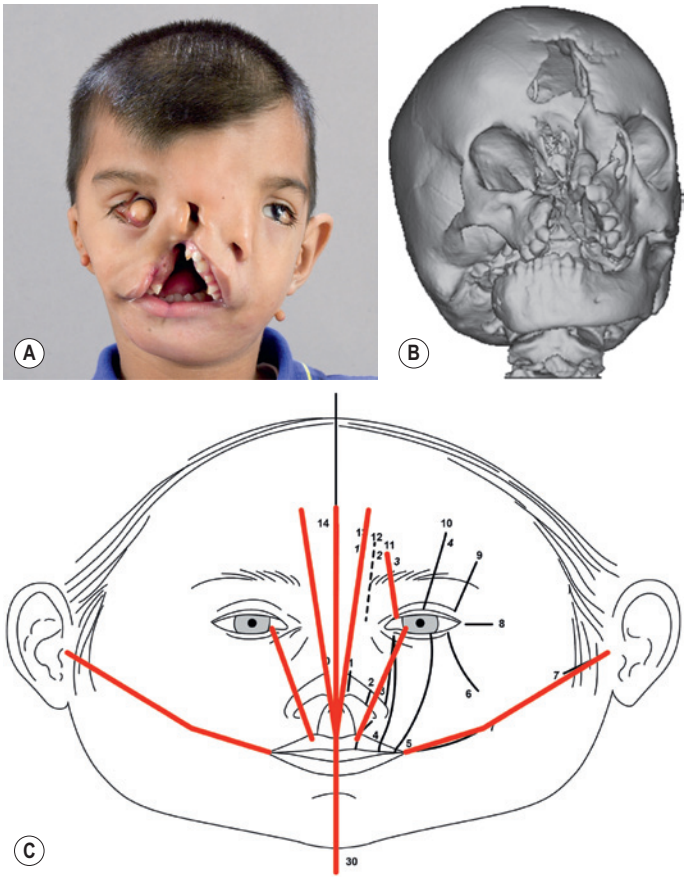


Fig. 28.15 (A) This highly intelligent boy has all the elements of Goldenhar syndrome combined with complex, multiple midline clefts (Tessier types 30, 0–14, 1–13, 3, 7) with a coloboma of the middle third of the right upper lid with bilateral inferotemporal epibulbar dermoids impairing vision and preauricular appendages. The right lower lid coloboma was part of his maxillary cleft. (B) Computed tomography reconstruction shows the frontal defect, the gross orbital dystopia, the maxillary cleft, and the absence of the right mandible and temporomandibular joint. (C) His multiple clefts are shown in red.

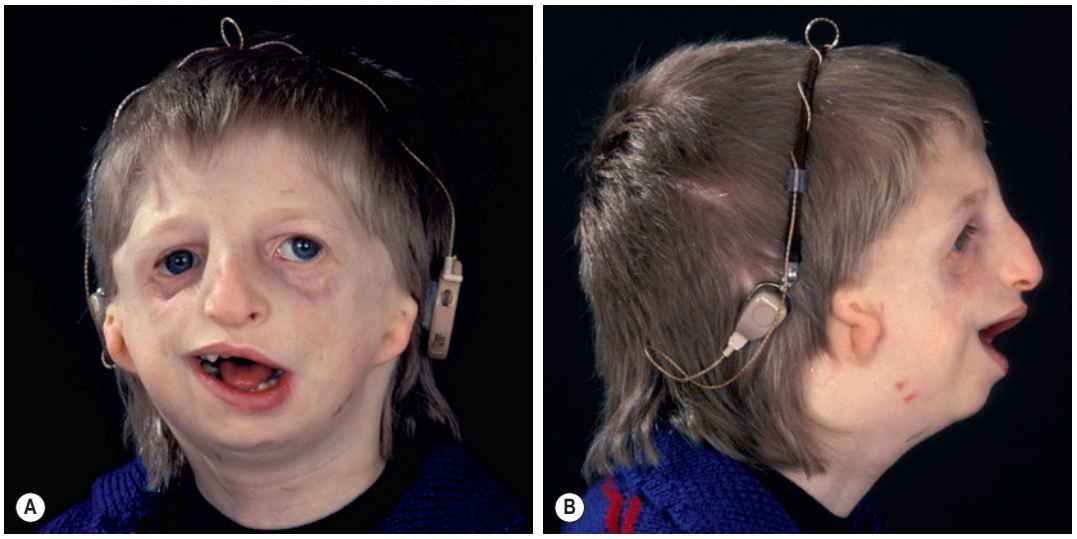


Fig. 28.14 (A) A boy with Treacher Collins syndrome with midface hypoplasia, antimongoloid slant of palpebral fissures, pseudocoloboma of lateral one-third of lower lid, nasolacrimal obstruction, deafness, and external ear abnormalities. (B) Typical "fish-like" profile (absent nasofrontal angle), hypoplastic lower jaw, and mouth breathing due to nasal airway obstruction.



Fig. 28.16 (A) Yellowish subconjunctival dermolipoma in the superotemporal orbit. (B) Epibulbar dermoid at inferotemporal limbus with leading edge lipid infiltrate in cornea. (C) This epibulbar dermoid had irritating hairs growing from it.

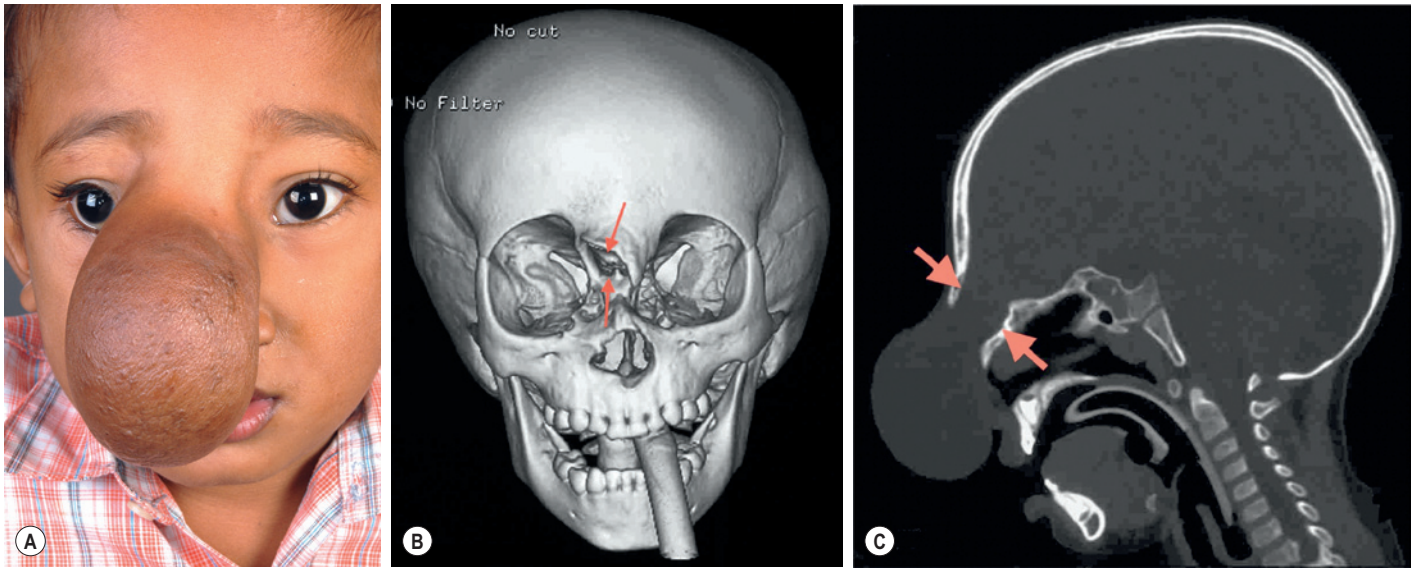


Fig. 28.17 (A) This boy from South East Asia has a very large nasoethmoidal variety of frontoethmoidal meningoencephalocele causing an exotropia and typical elongation of the face. (B) Computed tomography (CT) reconstruction with arrows indicating the bony cranial base defect. (C) This sagittal CT scan shows the dysfunctional brain tissue extruding through the region of the foramen cecum (arrowed).

Frontoethmoidal encephaloceles are more frequent in South East Asia (1:5000 live births), Africa, Malaysia, and Russia.

Management

Hydrocephalus, when present, must be dealt with first, then excision of the cele, watertight closure of the dural defect, followed by reconstruction of the skull defect. Early removal of the meningoencephalocele by the craniofacial route allows re-establishment of normal facial growth.[34] The prognosis depends on the presence of additional congenital anomalies.[35] Post craniofacial surgical problems include hydrocephalus, rhinorrhea, secondary encephalocele (if there is raised ICP and inadequate reconstruction of the frontal bone). Postoperative strabismus nearly always resolves, as does epiphora, which is surprising as the lacrimal drainage system is significantly distorted by the developing cele.

Midline facial cleft

These may include cleft lip and palate, midline bifid nose, and midline encephalocele plus other intracranial abnormalities.

Subtle signs such as a small notch in the upper lip or in the middle of the nose should alert the clinician to an underlying defect (Fig. 28.18).

Six patients in one series[36] all had midline cleft lip and palate, hypertelorism, absent corpus callosum, and sphenoethmoidal (basal) encephalocele, and five of the six had pituitary deficiency. Two had unilateral and one had bilateral peripapillary staphyloma. Two had bilateral optic disc hypoplasia, whereas another had a staphyloma in one eye and a morning glory disc anomaly (MGDA) in the other. An MGDA or optic disc hypoplasia should trigger neuroradiologic investigation to rule out these midline brain defects.

Amniotic bands

These occur when bands of amnion encircle parts of the developing fetus, restricting local growth. When the head is affected, the resulting clefts do not follow usual developmental patterns. However, major craniofacial malformations may occur (Fig. 28.19). This sporadic condition affects both sexes equally.[37]

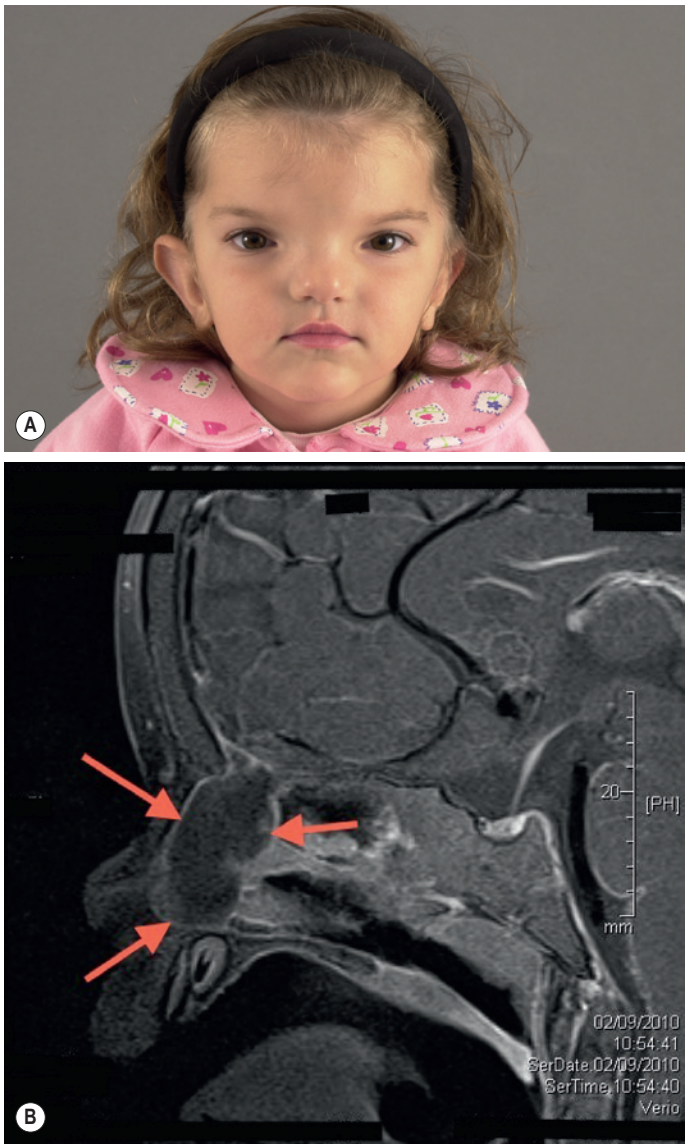


Fig. 28.18 (A) This little girl has subtle external signs of her midline cleft and basal encephalocele: midline nasal furrow and hypertelorism. (B) This other girl's sagittal magnetic resonance imaging scan shows a midline basal encephalocele (arrows). She presented with noisy breathing and examination showed cerebrospinal fluid rhinorrhea and a whitish mass up her nostril.

The most common ocular malformations are congenital corneal leukomas or acquired corneal opacities secondary to exposure and eyelid colobomas. The eyelid defects appear to be extensions of facial clefts and are often located adjacent to the corneal opacities. Other associations are microphthalmos, strabismus, hypertelorism, and rarely coloboma of iris and retina.

Craniofacial surgery

The use of nylon skulls,[38] created from three-dimensional CT scans of the patient, facilitates planning of complex staged reconstructions (Fig. 28.20).

While bone grafting and craniofacial osteotomies correct the underlying skeletal abnormalities, the ultimate success of these reconstructions is limited by the deficiency of skin and soft tissue. Tissue expansion (Fig. 28.21) prior to the primary correction or the secondary surgery allows tension-free closure and improved aesthetic results. Surgical protocols for the various conditions will often need to be individualized. The relative rarity of many of these syndromes makes outcome comparison and statistical analysis of results difficult.

The ophthalmologist needs to be aware of the various complications of this specialized surgery.[39]

Neurosurgical and ophthalmic complications

- Dural damage, more common in surgical correction of craniosynostosis, leading to cerebrospinal fluid (CSF) leak with potential for infection and, rarely, a growing fracture.
- Persisting CSF fistula, especially with hypertelorism or frontoethmoidal encephalocele correction.
- Intracranial hematoma, especially from vascular lesions found in midline clefts.
- Acute hydrocephalus, especially after correction of frontoethmoidal meningoencephaloceles.
- Cerebral ischemia can lead to gliosis and epilepsy.

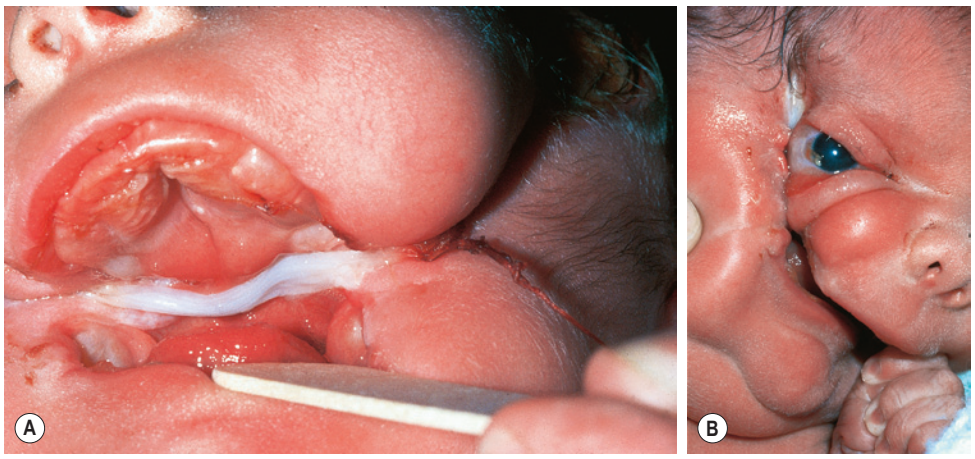


Fig. 28.19 Amniotic bands. (A) A white band can be seen traversing the palate, ending as a cord. (B) The cord cleaves the right maxilla and orbit.



Fig. 28.20 This nylon model constructed from a three-dimensional computed tomography scan of a patient with a midline cleft shows not only the deformity but also how the model can be used for surgical planning and rehearsal.

Aspects of ocular complications prior to, during, and after craniofacial surgery include:

- Adequate corneal protection to prevent drying, ulceration, and scarring with long-term measures required if poor lid function.
- Monitoring visual acuity and its correction to prevent amblyopia.
- Correction of strabismus.
- Canthal and lid position must be optimized prior to lacrimal surgery.

Diplopia can complicate malposition of the whole orbit, malposition of the globe within the orbit, or injury to the EOMs. However, few of the children with very significant orbital deformities are binocular; alternating strabismus is common with suppression of the deviating eye. Binocularity, when present, will be retained postoperatively provided the visual axes remain parallel. About 10% require squint surgery.

Dystopia can be minimized if the craniofacial surgeon preserves a frontal bar of bone as a reference point for orbital repositioning. Following orbital repositioning, for example for hypertelorism, sixth cranial nerve palsies are common but transient: 90% recover in 6–12 months in the authors' experience.

Canthal dystopia is a frequent problem medially with clefts with a medial lid coloboma or deficient canthal ligament. Wedge excision, lower lid advancement, Z-plasties, or other flaps may be needed.

Epiphora is common and probably due to crumpling of the canaliculi. The drainage system is often not present or functional in Tessier no. 3 clefts and in frontoethmoidal meningoencephaloceles. If dacryocystorhinostomy is indicated, it may not be possible to fashion usual nasolacrimal flaps and so out-fracturing techniques from sac to nasal cavity with dilators (e.g. Hegar's cervical) followed by packing with cellulose sponge is often required. Use of Lester Jones or other tubes may not be practical, as they require careful follow-up care.

Enophthalmos is common after correction of naso-orbital frontoethmoidal meningoencephalocele. It is difficult to correct, even with extensive bone grafting.

A "tight orbit" or "orbital compartment syndrome" is a dreaded (early?) postoperative complication due to marked edema or hemorrhage, causing optic nerve or retinal ischemia or infarction. Pupillary responses and visual acuity must be closely monitored. In such an event, the appropriate orbital decompressive technique will be dictated by the previous operative procedure.

Pressure on the globe or optic nerve by a malpositioned bone graft can occur, but direct trauma to those structures is very rare.

The authors are aware of only three cases of postoperative blindness from 17,000 individual non-trauma craniofacial patients treated to date by their clinic – the last occurring 3 years ago in a patient with Pfeiffer syndrome who lost vision in one eye while being operated on in a prone position. Infection is rare considering the nasal sinuses are opened in craniofacial procedures. Appropriate aseptic techniques and postoperative antibiotic regimes must be followed.

The ophthalmologist as an important member of the craniofacial team

These developmental conditions obviously involve more than just the eye and adnexae. Hence the ophthalmologist should be a member of the craniofacial surgical team taking a coordinated role in the assessment, planning, surgical correction, and rehabilitation of the patient.

The ophthalmologist must accurately record the preoperative state including visual acuity, presence or otherwise of binocular vision, strabismus, and ptosis. The team planning meeting coordinates the sequence of management and surgical steps required by the many surgical specialties involved. Postoperatively, the role is reassessment and management of any surgical complications, followed by visual rehabilitation. The whole process usually extends over many years – at least until after visual system maturation and often well after cessation of craniofacial growth.

Sadly, patients with craniofacial defects may be stigmatized by society. The ophthalmologist can contribute by improving their visual function and cosmesis and is richly rewarded when the patient is enabled to take their rightful place in society.

Acknowledgment

Signed parental consent for publication of all the clinical photographs is held by the Australian Cranio-Facial Unit, Adelaide, South Australia.



Fig. 28.21 This sequence shows stages in the management of this boy with Tessier 4–5 clefts. (A) The defect before surgery. (B) After bone grafting to reconstruct the alveolar, orbital, and maxillary defects plus cheek flap rotation. (C) Tissue expansion prior to further bone grafting and soft tissue revision as a teenager. (D) Final appearance at completion of growth.

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Cystic lesions and ectopias

Alan A McNab

Chapter contents

CYSTIC LESIONS
ECTOPIAS
REFERENCES

Cystic lesions

A variety of cystic lesions may occur in and around children's orbits.[1] By far the commonest is the dermoid cyst, but other cystic choristomas may occur in and around the orbit, including congenital cysts lined by conjunctival and respiratory epithelium. Other cystic lesions include microphthalmos with cyst, congenital cystic eyeball, lacrimal ductal cyst, meningocele and encephalocele, sinus mucocele, and teratoma. In some parts of the world, parasitic cysts involving organisms such as *Echinococcus* (hydatid cyst) and *Cysticercosus* are common, but they are rare in Europe and North America.[2] Hemorrhage within orbital venous-lymphatic malformations (lymphangiomas) may give rise to "chocolate" cysts. Cystic lesions of the orbital bones may be seen in fibrous dysplasia, ossifying fibroma, and aneurysmal bone cyst.

Dermoid cyst

Dermoid cysts of the orbit and periorbital region are common in childhood, accounting for between 3% and 42% of orbital lesions in children in different reported series.[2–5] They are developmental cystic choristomas, which arise from ectodermal rests trapped at suture lines or within mesenchyme during orbital development.

The cysts are lined by keratinized stratified squamous epithelium. Adnexal structures such as hair follicles, sebaceous and sweat glands are found within their wall. Cyst leakage or rupture may give rise to an acute inflammatory response, followed by a chronic low-grade granulomatous inflammation. This inflammatory response is often subclinical, but is commonly seen surrounding longer-standing dermoid cysts.

Dermoids may be superficial or deep.[6] Superficial dermoids are usually outside the orbit, and overlie the orbital rim, without a component deep to the orbital septum, and are therefore strictly periorbital rather than orbital. Most dermoids presenting in childhood are superficial.

Some orbital cystic choristomas are lined by other types of epithelium, such as conjunctiva or respiratory epithelium, or even a mixture of these with stratified squamous epithelium (see below).

Superficial dermoids

These often present in infancy as a rounded mass, typically at the superotemporal (Fig. 29.1) margin of the orbit.[7] One-quarter arise in the superomedial orbit[7,8] (Fig. 29.2A,B). They are painless, smooth, non-tender, firm, non-fluctuant, often mobile, or in some cases relatively fixed to the underlying periosteum and bone. Since they are usually situated outside the orbit, they cause no displacement of the globe. The orbital rim is usually palpable behind their posterior edge. Unsuspected deep extension into the temporal fossa, posterior orbit, or even intracranial space occasionally occurs in apparently superficial dermoid cysts, but these deeper-extending dermoid cysts are usually clinically more deeply located, less mobile, and it is not possible to pass a finger behind their medial margin to palpate the orbital rim.

The radiologic appearance of a dermoid cyst is characteristic: on computed tomography (CT) scan, the best modality to highlight bony features, a rounded discrete mass is associated with thinning and smooth erosion or remodeling of the underlying bone. The contents are often of heterogeneous density on CT and magnetic resonance imaging (MRI). Fat lucency was noted in 71% of 70 patients,[9] and its presence within the cyst is considered diagnostic.[10] Fluid levels within the cyst may sometimes be seen as the lighter oily secretions of sebaceous glands float upon more aqueous fluid.



Fig. 29.1 A right external angular dermoid.

Preoperative assessment of any dermoid cyst is essential to rule out deep extension. If the cyst is small, mobile, and easily palpable for its entire extent, imaging may not be necessary. Larger cysts with ill-defined, deep margins are best assessed with a CT scan or MRI.

Excision of superficial dermoid cysts is relatively simple (Fig. 29.2C). It is preferable to do this by the age of 5 years to avoid accidental rupture or inflammatory episodes related to spontaneous leakage.[11] The incision may be situated directly over the lesion, above, below, or through the eyebrow. A skin-crease approach[12,13] or endoscopic removal[14] leaves a less conspicuous postoperative scar, but often these lesions lie beyond the natural upper lid crease. Although excision of the intact cyst is desirable, intraoperative rupture is not disastrous if the contents and the entire cyst wall are carefully removed.



Fig. 29.2 (A) An adolescent boy with a superomedial dermoid cyst. (B) Computed tomography scan shows the rounded low-density lesion medial to the left globe. (C) The cyst was excised intact through an upper eyelid skin crease incision.

Decompression of larger cysts may be helpful to expose the underlying bone. Failure to excise the cyst wall completely, or residual cyst contents, can elicit a chronic inflammatory reaction with sinus formation and persistent discharge. In the series by Satorre et al., dramatic inflammatory signs were present in only four of 17 patients with ruptured cysts.[15] A low-grade lipogranulomatous response was more common.

Deep dermoids

These usually present in adolescence and adulthood with gradual enlargement and displacement of orbital contents, but they can present similarly in infancy.[16] Deeper cysts may have only a squamous epithelial lining, and are therefore classified as epidermoid cysts. Deep dermoids are often not palpable, but sometimes their smooth and rounded anterior margin can be palpated, although they may extend to the orbital apex.[17,18] Proptosis and/or globe displacement are predominant features but ocular motility,[7,19] visual disturbances, and pain may occur. Dermoid cysts rarely may be within[19,20] or attached to the lateral rectus muscle.[21]

Some orbital dermoids may straddle the orbit and temporal fossa, with a communication between the two parts passing through the lateral orbital rim or wall (Figs 29.3 and 29.4). These "dumbbell" dermoids may present with the typical signs of a more superficial dermoid, but extend into the temporal

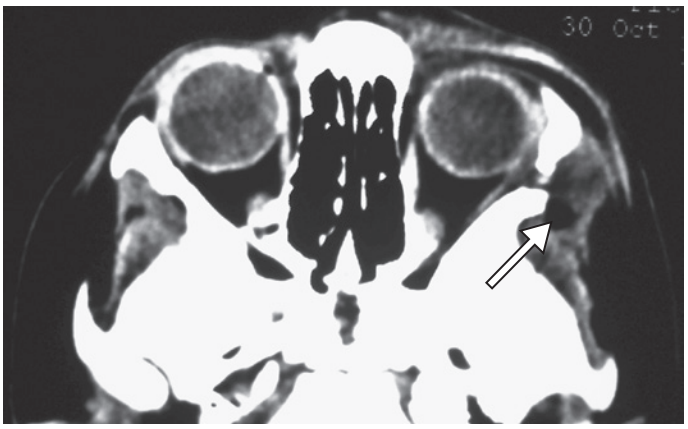


Fig. 29.3 An axial computed tomography scan of a "dumbbell" dermoid cyst with low-density contents extending through a defect behind the lateral orbital rim to involve both the orbit and temporal fossa (arrow).

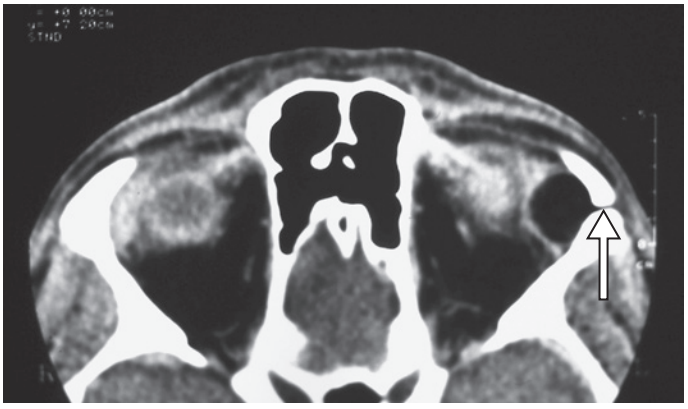


Fig. 29.4 An axial computed tomography scan shows a superotemporal dermoid cyst with a very narrow defect in the underlying lateral orbital wall (arrow), with a small extension of the cyst into the temporal fossa.

fossa in an hour-glass configuration (see Fig. 29.3) and may be associated with temporalis swelling in 1.5–34% of such cases.[9,12] Very rarely, proptosis with or without visual impairment triggered by mastication (masticatory oscillopsia) can result from pressure on a communicating cyst by temporalis muscle contraction with chewing.[22] Presentation with orbital cellulitis related to a discharging sinus tract arising from an orbital dermoid has been reported.[23] Very rarely, simultaneous orbital and temporalis fossa dermoid cysts without communication have been described.[24]

The CT findings of deep dermoids are similar to those of superficial dermoids except for the frequent presence of irregular orbital wall defects as well as sclerosis, irregular scalloping, or notching of the underlying bone (Figs 29.5 and 29.6). The walls of large dermoid cysts may demonstrate irregular "egg-shell" calcification. There may be evidence of surrounding inflammation and scarring from subclinical episodic leakage of the cyst contents.

The management of deep dermoids can be difficult[17,25,26] since total surgical excision is necessary to prevent complications. Preoperative clinical and radiologic assessment is essential to plan the appropriate surgical approach, which may involve combined anterior and lateral orbitotomies or focal marginotomies.[17] Although it has been recommended that this surgery be delayed until bone growth has ceased,[26] such delay may not be necessary to safeguard facial bony growth. A neurosurgical approach with craniectomy may be necessary for safe and complete excision of an orbital dermoid extending intracranially.[27]

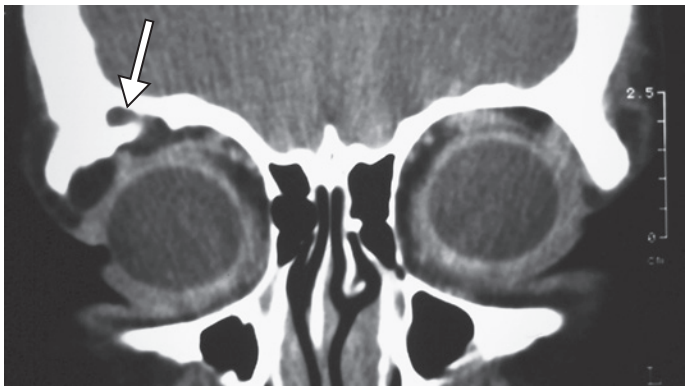


Fig. 29.5 Computed tomography coronal scan of deep dermoid, showing the presence of irregular orbital wall defects (arrow).

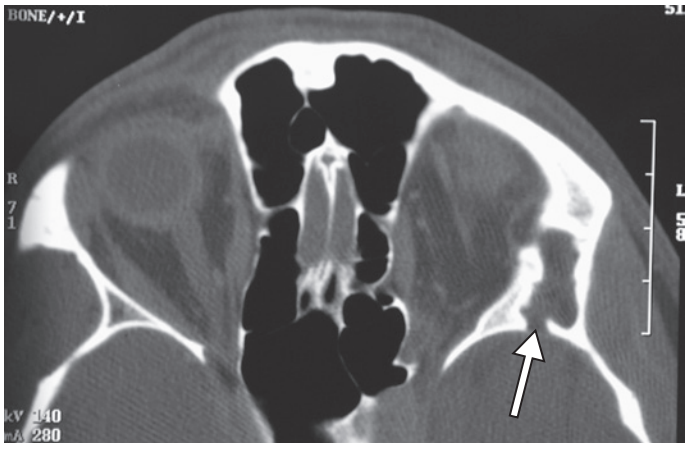


Fig. 29.6 Computed tomography axial scan of deep dermoid, showing the presence of irregular orbital wall defects (arrow).

Conjunctival cysts

Cystic choristomas lined by conjunctival epithelium are usually called "conjunctival dermoids." One-half of these arise in the medial orbit, usually in teenagers and young adults[17] (Figs 29.7 and 29.8). They are not attached to the orbital bones, and are lined by typical conjunctival epithelium with goblet cells and, sometimes, adnexal structures with mucinous or mixed content in the cyst. They are managed by complete excision (Fig. 29.9). Such cysts may have a mixture of conjunctival and dermal lining. Congenital cysts lined by conjunctiva in the region of the common sheath of the superior rectus and levator palpebrae muscles have been described.[28,29]

Conjunctival dermoids should not be confused with conjunctival inclusion cysts, which are acquired lesions due to the implantation of conjunctival epithelium within the orbit after trauma or surgery, most commonly strabismus or vitreoretinal surgery. They may present many decades after trauma or surgery.[30]

Respiratory epithelial cysts

Cysts lined by respiratory epithelium can occur in the orbit as congenital lesions, but also may occur after trauma, with the implantation of respiratory epithelium from the nasal cavity or paranasal sinuses. A mucocele arising from the paranasal sinuses is also lined by respiratory epithelium, often very attenuated, but is a different entity (see below).

Congenital respiratory epithelial cysts are rare.[31–33] They may present in childhood or later in adult life, particularly deeper lesions.[32]

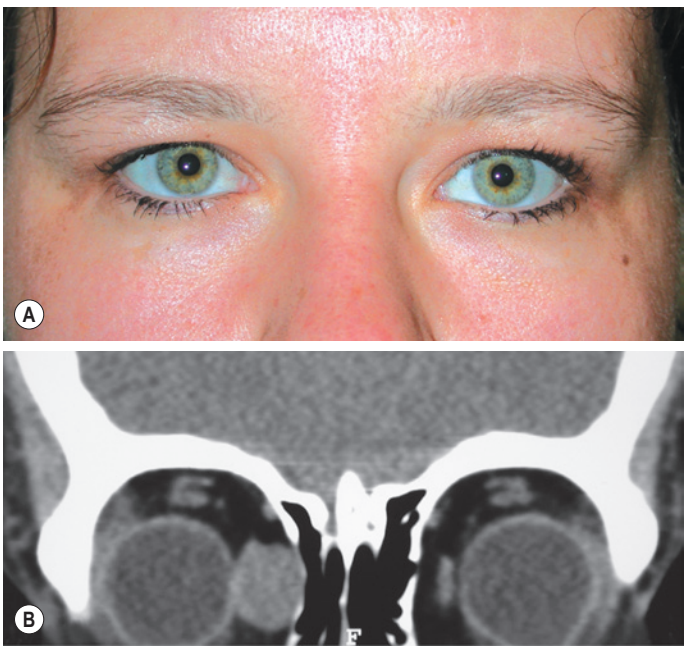


Fig. 29.7 (A) A teenage girl with right globe dystopia due to a medial "conjunctival dermoid" cyst. (B) A coronal computed tomography scan shows the well-circumscribed cyst with contents of higher density than seen on true dermoids.

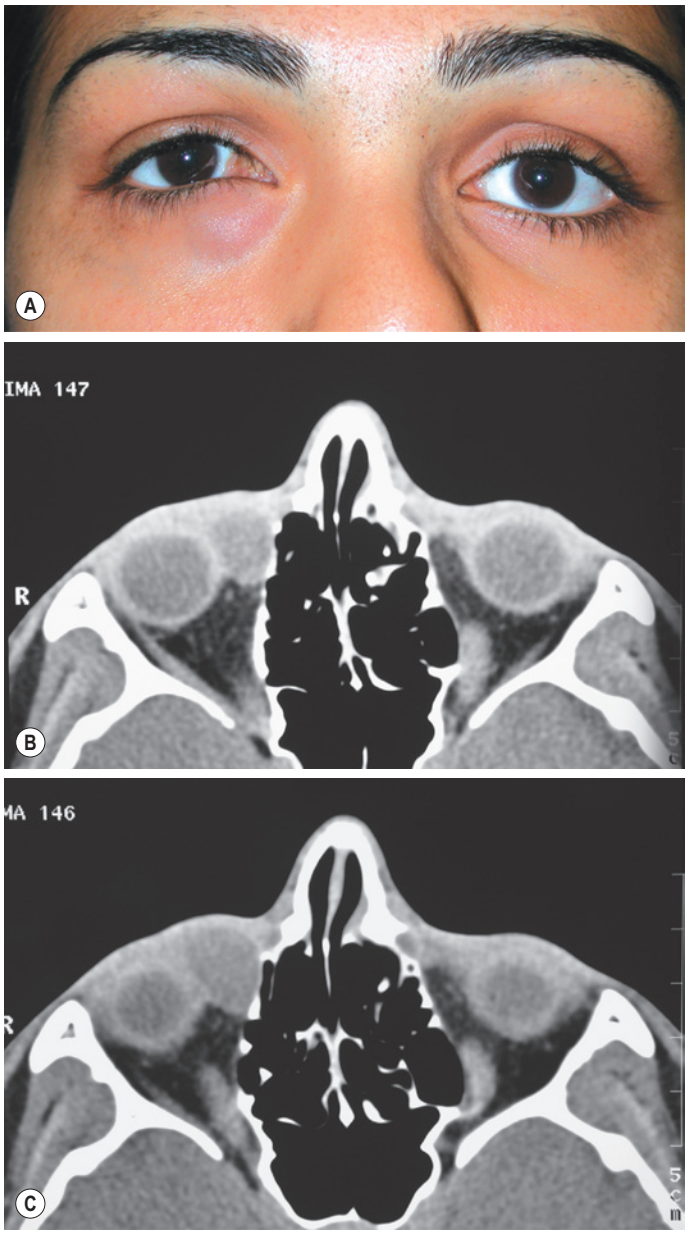


Fig. 29.8 (A) A young woman with longstanding and increasing right globe displacement upward from an inferomedial congenital "conjunctival dermoid" cyst. (B and C) An axial computed tomography scan showing the cyst lying inferomedial to the globe with contents similar in density to the vitreous.

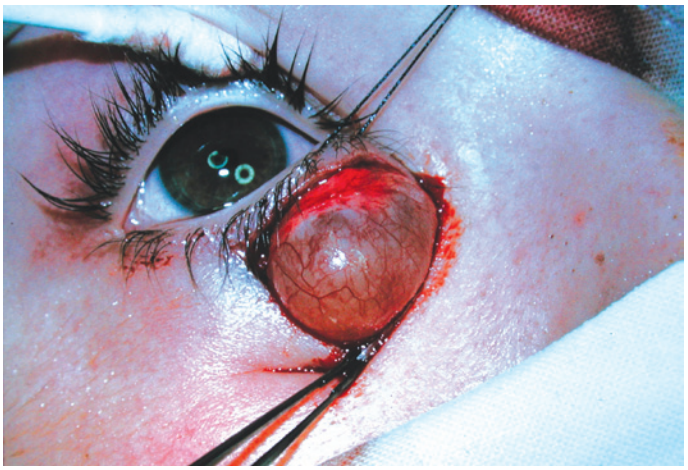


Fig. 29.9 Surgical removal of an inferomedial thin-walled "conjunctival dermoid."

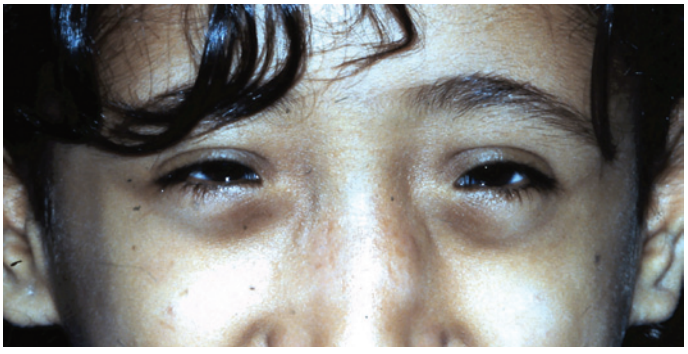


Fig. 29.10 A young girl with hypertelorism and telecanthus from a midline encephalocele.

Orbital meningocele and meningoencephalocele (see Chapter 60)

These rare abnormalities may be congenital or acquired. Congenital lesions arise from a presumed defective separation of neuroectoderm from surface ectoderm, resulting in a bony dehiscence with a "cystic" herniation of dura into the orbit, either alone (meningocele) or with brain tissue (meningoencephalocele). They may be associated with an optic disc anomaly;[34] basal encephalocele should always be excluded in a child with a morning glory disc, especially if there is a midline facial anomaly such as hypertelorism (Fig. 29.10), notched or cleft lip or palate[35] (see Chapters 28 and 53). Significant cerebral vascular anomalies may accompany the presence of a morning glory disc.[36] Orbital encephaloceles may be acquired as a result of head injury and orbital fracture, with herniation of the dura, with or without brain, through the bony defect.[37,38] Occasionally, after relatively trivial trauma, an orbital roof fracture in a child may progressively expand (a "growing fracture") as the leptomeninges herniate into the fracture, forming a "cyst." This may expand, leading to progressive proptosis which may be pulsatile.[39,40]

Congenital orbital encephaloceles may be anterior or posterior.[41] Anterior lesions herniate through single or multiple defects[42] in the region of the sutures dividing the frontal, ethmoid, lacrimal, and maxillary bones. They usually present as a congenital cystic swelling of the medial orbit extending onto the face, accompanied by telecanthus and, frequently, epiphora. They may present in infancy and early childhood with gradually increasing forward and lateral globe displacement. The medial canthal tendon is usually displaced in an inferolateral direction. Atypical presentations occur, such as the 10-mm bluish cystic mass in the superonasal fornix of a 1-month-old patient, which was found to be a meningoencephalocele.[43]

Classically, the cyst increases in size on straining or crying.[44,45] It may be fluctuant, pulsatile, reducible with gentle pressure, and it may transilluminate. Anterior encephaloceles are important in the differential diagnosis of any medial canthal swelling.

They may be mistaken for sinus mucoceles, dermoid cysts, or nasolacrimal duct mucoceles.[46] A bony defect with intracranial communication is evident on CT scan. Three-dimensional CT reconstruction may be helpful in planning surgery,[47] which is usually performed by craniofacial, neurosurgical and/or maxillofacial teams. Posterior encephaloceles herniate into the orbit via the optic foramen, orbital fissures, or a bony defect. They present with slowly progressive, sometimes pulsatile, proptosis. Occasionally, posterior encephaloceles present later in life.

Typically, the eye is displaced forward and downward[44] and the proptosis increases on straining or crying. Plain X-rays demonstrate enlarged foramina or a bony defect of the posterior orbit. CT scan demonstrates the size and contents of the cyst. Posterior encephaloceles are particularly associated with the sphenoid wing dysplasia of neurofibromatosis type 1 (NF1). They can also be associated with enophthalmos.

Paranasal sinus mucocele

The paranasal sinuses are of clinical relevance to childhood orbital disease and it is important to be familiar with their development. All the sinuses are present at birth in a rudimentary form, except the frontal sinus, which first appears at the age of 2 years. There are two spurts of enlargement: at the age of 6 or 7 years, coinciding with the eruption of the second dentition, and again at puberty.[48] Since the frontal sinus is the source of most mucoceles, this disorder is rare in childhood. Ethmoidal sinus mucoceles, however, may present in early life,[49] particularly with cystic fibrosis. In one series of paranasal sinus mucoceles, six of 10 children had cystic fibrosis.[50] Infants and children with cystic fibrosis more commonly develop sinus mucoceles from the maxillary sinuses, which may be bilateral.[51–53]

A mucocele is a cystic expansion of a paranasal sinus, resulting from obstruction of its ostium. The normal mucous secretions of the respiratory epithelial lining accumulate within the sinus, leading to a gradual expansion, with loss of its bony structure. With further expansion, the cystic mass transgresses the orbital wall and displaces the orbital contents. It may also erode into the intracranial space.[54] Eventually, the cyst contents consist of viscous material which may be white, yellow, or brown, and enclosed by a fibrous capsule.

Most mucoceles arise anteriorly, affecting frontal or anterior ethmoid sinuses. The usual presentation is with gradually increasing proptosis with inferolateral or lateral displacement of the globe, appearing clinically as hypertelorism. A firm cystic non-compressible, non-inflammatory swelling may be palpable in the medial orbit. Its extension above the medial canthal tendon should differentiate it from a mucocele of the lacrimal sac. The absence of pulsatility, expansion with straining, and bony skull defect differentiate it from an encephalocele. Sphenoid sinus mucoceles are rare in childhood,[55] but sudden blindness from optic nerve compression by a sphenoid sinus mucocele has been reported.[56]

On CT scan, a smooth-walled cystic lesion, sometimes with egg-shell calcification of the margins, arises from the affected sinus (Fig. 29.11). In childhood, this is most commonly the ethmoid, and there is expansion into the medial orbit with thinning of the wall and destruction of the internal septae.

The mucocele should be marsuplialized to the nasal cavity to prevent recurrence and to re-establish sinus drainage.



Fig. 29.11 An axial computed tomography scan of an ethmoidal mucocele expanding into the medial orbit (arrow), and with egg-shell new bone formation.

Excision or drainage of the mucocele is usually performed endoscopically by an ear, nose and throat surgeon.[57] The transcaruncular approach has been recommended for the management of frontoethmoidal mucoceles.[58] After medial incisions are used, careful repositioning of the trochlea is advised to avoid postoperative superior oblique underaction.[59] Other cystic lesions arising in the sinuses, including dentigerous cysts, may also cause proptosis.[60]

Congenital cystic eyeball (anophthalmos with cyst) (see Chapter 18)

True anophthalmia is very rare. More commonly, complete or partial failure of invagination of the optic vesicle before the 7 mm stage results in a "congenital cystic eye" or "anophthalmos with cyst."[61] No recognizable globe is present within the orbit. The congenital cystic "eye" is lined by neuroglial tissue without any normal ocular structures such as lens, ciliary body, or retina. The wall of the cyst is fibrous connective tissue with attached extraocular muscles. The absence of surface ectoderm-derived ocular structures is a common feature, which may help with the correct diagnosis. Congenital cystic eyeball is rare compared to microphthalmos with cyst, caused by a later defect in embryogenesis.[62]

It presents at birth as a large cystic swelling within the orbit. In contrast to microphthalmos with cyst, the cystic eyeball is usually centrally placed or distends the upper lid.[61,63] The cyst may occasionally be inferior.[62] The fellow eye is usually normal, but contralateral microphthalmos with cyst,[64] persistent hyperplastic primary vitreous, or bilateral congenital cystic eyes have been reported.[62]

The histology is similar to the cystic portion of anophthalmos with cyst: multiple cavities filled with proliferating glial tissue.[62,63] These cystic orbital lesions, occurring in neonates, should be distinguished from teratomas.

Microphthalmos with cyst

Incomplete closure of the fetal fissure between the 7 and 14 mm stage of embryonic development may result in a variety of

colobomatous defects of the eye.[65] Eyes with severe colobomas are often microphthalmic, and proliferation of neuroectoderm at the lips of the persistent fetal fissure may result in the formation of an orbital cyst that communicates with the eye. The size of the cyst varies enormously.

Several genetic mutations are known to cause anophthalmia and microphthalmia (see Chapter 18). Their association with systemic abnormalities makes their identification particularly important. Many are autosomal dominantly inherited, so future siblings are at risk. SOX2,[66] OTX2, PAX2, and PAX6, as well as CHD7 (CHARGE syndrome) are the most frequently implicated mutations. Involvement of a geneticist is advisable. Ragge et al. have reviewed the diagnosis and multidisciplinary management of anophthalmia and microphthalmia.[67]

Clinical presentation

The manifestations are variable, ranging from an apparently normal eye with a clinically unapparent cyst, an obvious cyst in association with a deformed eye, to an invisible eye displaced by a cyst occupying the whole orbit. Typically, a bluish cystic transilluminating lesion bulges inferiorly into the lower fornix and lid, displacing a microphthalmic or rudimentary eye under the upper lid[68] (Fig. 29.12). Rarely, the cyst may be present in the upper lid and the eye is displaced downward[69] (Fig. 29.13). Occasionally, the eye cannot be identified clinically,[68] even under anesthesia. Bilateral involvement is not uncommon. The cyst communicates with the eye via a variably narrow stalk. The microphthalmic eye usually has extremely poor vision and an associated optic nerve and retinal coloboma. The eye, though often very small, usually achieves differentiation with cornea, iris, ciliary body, and lens choroid and retina. The other eye may be normal or may also have an optic nerve or retinal coloboma.[68,70] The extent of the cystic component is best delineated by CT scan, although B-scan ultrasound can also be useful. Small asymptomatic cysts may be found incidentally on CT scan. The glial nature of the cyst lining can be demonstrated by immunohistochemistry.[71]

Management

Most cases require no immediate surgical intervention[70] since the cyst contributes to socket expansion.[64,67] Cyst enlargement resulting in an unsightly appearance can be managed by aspiration; repeated aspiration may be necessary and after multiple aspirations surgery may be indicated. Although it may be difficult to excise the cyst without sacrificing the globe, this can be achieved in patients with mild microphthalmos, with a satisfactory cosmetic outcome.[72]

The presence of an eye is important in inducing normal bony orbital growth. A congenitally anophthalmic socket will have deficient orbital and eyelid growth and shallow conjunctival fornices, which may prevent satisfactory prosthetic fitting. Early orbital volume replacement with an appropriate implant and/or prosthesis is advocated if the globe is small or absent. Various types of conformers and socket expanders can be used to maintain the conjunctival fornices, palpebral fissures, and, perhaps, promote orbital growth.[67] Small sockets and eyelids can be expanded with hydrophilic expanders.[73]

Early enucleation produces a bony volume reduction. Good cosmetic results may be achieved with the use of a large orbital implant at the time of enucleation.[74]

Orbital teratoma

Teratomas are tumors that arise from pluripotent embryonic stem cells and consist of elements derived from more than one germ cell layer. Although classically all three layers are represented, only mesoderm is invariable; ectodermal or



Fig. 29.12 Microphthalmos with cyst. This boy was born with a bluish swelling of the right lower lid, which gradually enlarged. At 6 months, a large cyst filled the right orbit and distorted the lower lid, leading to conjunctival prolapse and exposure.

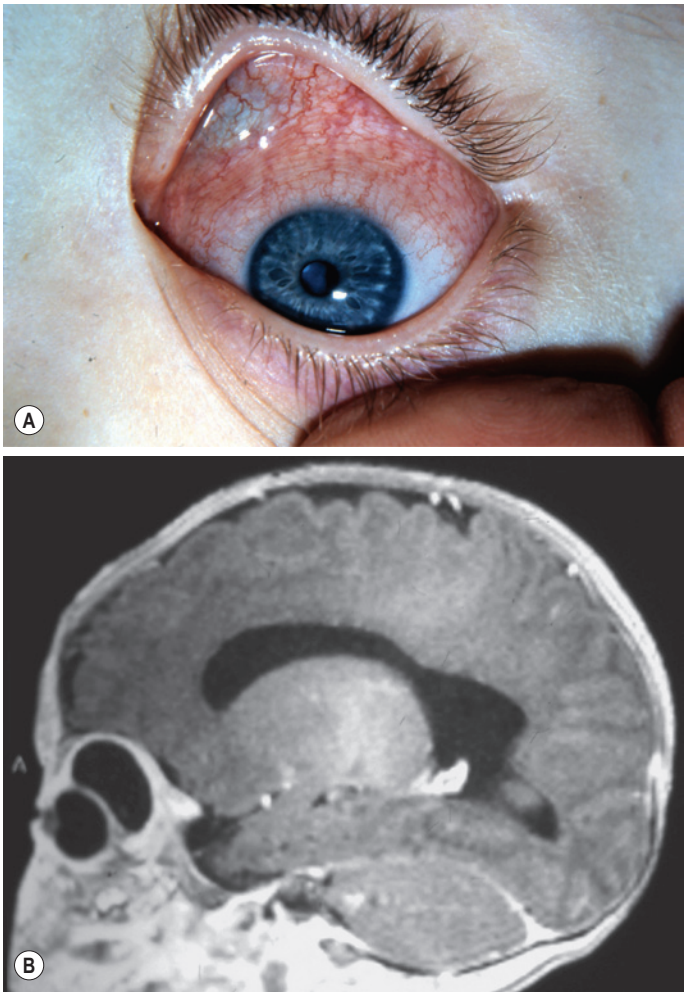


Fig. 29.13 (A) A 4-year-old boy with a bluish superomedial orbital cyst, displacing a small but well-formed microphthalmic eye downward. (B) A sagittal magnetic resonance image shows the cyst with material within it indistinguishable from vitreous.

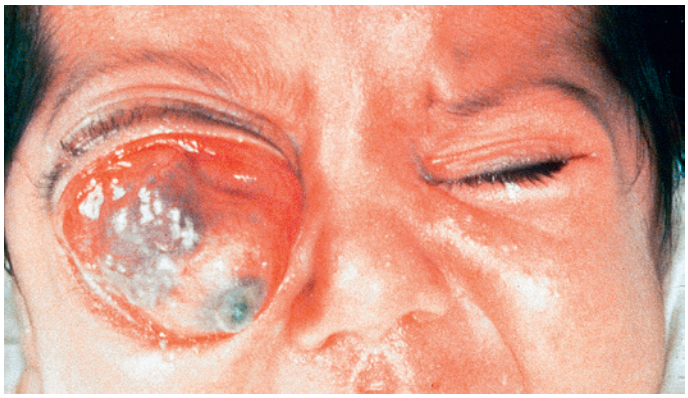


Fig. 29.14 Orbital teratoma in an infant with massive proptosis from a multiloculated cystic lesion.

endodermal elements can be absent. Such tumors should be called "teratoid." The extent of the tumor can be limited to the orbit (primary orbital teratoma) or it may involve the intracranial compartment, cavernous sinus,[75] nose, and sinuses. Occasionally, a much larger primary intracranial tumor invades the orbit secondarily. This usually manifests prenatally as polyhydramnios and is rarely compatible with life.

The usual presentation of a primary orbital teratoma is with unilateral, often massive, proptosis in a newborn child[76] (Fig. 29.14). Teratomas are more common in females by a ratio of 2:1. The globe is often of normal size or slightly small but it is surrounded by intensely chemotic conjunctiva. It is displaced by a large cystic mass, which is often fluctuant and transilluminates but may appear solid. The mass is often intraconal, giving rise to axial displacement with indentation by the four recti. Superior or inferior teratomas can occur. Typically, there is rapid growth after birth as secretions from the epithelial elements of the tumor accumulate within its cystic spaces. Exposure keratopathy, ulceration, and even perforation can complicate the resultant lagophthalmos. The tumor may stretch and adhere to the optic nerve, with optic atrophy. Occasionally, teratomas grow very slowly.[77] They may also rarely present later in childhood, with preserved vision.[78]

On ultrasound, the tumor is of heterogeneous density and may contain foci of calcification, which, along with orbital enlargement, are evident on plain X-rays. CT and MRI delineate the lesion, define any intracranial extension, and highlight variable density with cystic elements, fat, and, occasionally, teeth (Fig. 29.15).

The treatment of choice is early surgical excision, with preservation of the globe if possible.[76,77,79] Intraoperative aspiration of fluid from the cystic mass may facilitate tumor removal. With intracranial involvement, a combined orbitotomy and craniotomy is necessary to remove the tumor. Total excision can be difficult. Vision may be preserved in the affected eye.[80,81] The long-term outlook depends on the histologic differentiation and the extent of the tumor. Respiratory obstruction carries a poor prognosis.[82] Residual tumor can give rise to late recurrence and malignant change,[83] but this is rare in the orbit.[84]

Lacrimal ductal cyst

Lacrimal ductal cysts (also called dacryops) are very rare in childhood but form a part of the differential diagnosis of

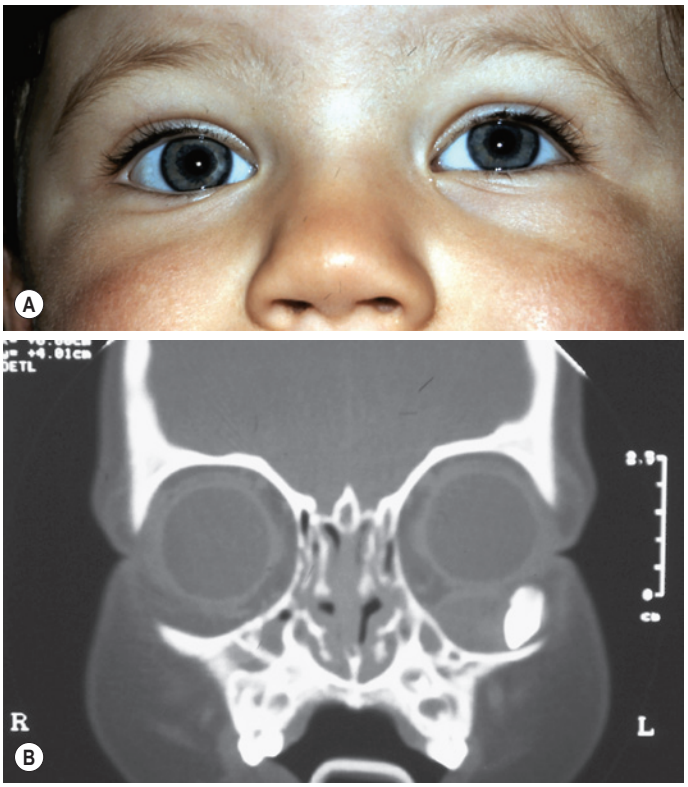


Fig. 29.15 (A) A 3-year-old girl presented with gradually increasing left proptosis and globe dystopia. (B) Computed tomography scans revealed a multiloculated inferior orbital lesion in an expanded orbit with a fully formed tooth within it.



Fig. 29.16 A typical lacrimal ductal cyst.

an orbital mass in the lacrimal gland region. Bullock et al.[85] suggested that lacrimal cysts should be classified by their site of origin: palpebral lobe (simple dacryops), orbital lobe, accessory glands, or ectopic lacrimal gland. Clinically, they may be confused with a superficial conjunctival dermoid cyst (though these are more commonly medial) or inclusion cysts, as well as parasitic cysts.

Lacrimal ductal cysts most commonly arise from the palpebral lobe in adults but they may occur in teenagers, sometimes with a history of trauma or inflammation. A smooth, transilluminating mass slowly enlarges in the lateral aspect of the upper lid (Fig. 29.16) and may be evident on lid eversion as a bluish cyst. Rarely, they enlarge with crying and

can be tender or painful, occasionally resolving spontaneously as the cyst decompresses with a gush of tears. Histologically, ductal cysts of the palpebral lobe are lined by an outer layer of myoepithelium and an inner layer of cuboidal cells, unlike congenital orbital lobe cysts whose epithelial lining is cuboidal. If the patient is symptomatic, careful surgical excision of the intact cyst is curative, with care to avoid damage to adjacent ductules. Marsupialization of larger cysts may be necessary.

Cysts in the orbital lobe are very rare, but may present in infancy or early childhood as a tense mass in the lacrimal fossa.[44] Cysts of the accessory glands of Krause and Wolfring may occur, resulting in swelling in the conjunctival fornix. These can be excised via the conjunctiva.

Lacrimal tissue may occasionally occur ectopically within the eye and orbit with an associated cystic component (see below).

Parasitic cysts

Echinococcosis (hydatid cyst)

The tapeworm *Echinococcus* is an intestinal parasite of dogs and foxes. Sheep, cattle, or rodents may ingest contaminated feces and become hosts, and dogs become infected by eating their carcasses. Humans ingest ova in contaminated meat, berries, unclean vegetables, or feces from poor hand hygiene. The ova hatch in the intestine, and larvae migrate throughout the body, settling in various organs to form slowly enlarging, fluid-filled cysts full of larvae. Due to the distribution of blood from the portal tract, there is a predilection for the right lobe of the liver. Approximately 1% of infestations involve the orbit,[2] especially the superior and posterior orbit.

Sheep- and cattle-rearing areas in the developing world may have a high prevalence. It has largely been eliminated in the developed world. Clinically, orbital echinococcosis presents with insidious signs of mass effect, which may be accompanied by chemosis, diplopia, restricted ocular motility, visual loss, and optic atrophy. Rupture of the cyst can result in an acute inflammatory episode.

The diagnosis of orbital echinococcosis is aided by ultrasonography, CT (Fig. 29.17), or MRI scanning, which show a cystic mass whose wall is occasionally calcified and contains fluid that is isodense with vitreous. Other confirmatory findings include eosinophilia on a blood film, and positive enzyme-linked immunosorbent assay (ELISA) for echinococcal antibodies. This has over 90% sensitivity and specificity for *Echinococcus*.

Systemic treatment with albendazole is effective and a suitable alternative to surgery in uncomplicated cases.[86] Orbital cysts may be excised intact via a direct or lateral orbitotomy. Intraoperative rupture should be avoided if possible, since it may be complicated by inflammation and implantation of daughter cysts.[87] Cyst aspiration followed by irrigation with hypertonic saline may destroy daughter cysts.[88] Hydatid cyst surgery should be accompanied by treatment with albendazole.

Other parasitic infestations of the orbit include cysticercosis and trichinosis, both acquired from pork. Cysticercosis is a common cause of proptosis in children in India. In a series of 171 cases of orbital cysticercosis from India, the median age was 13 years.[89] Over 80% had cysts in relation to the extraocular muscles. Nearly all patients are managed with oral albendazole and prednisolone.

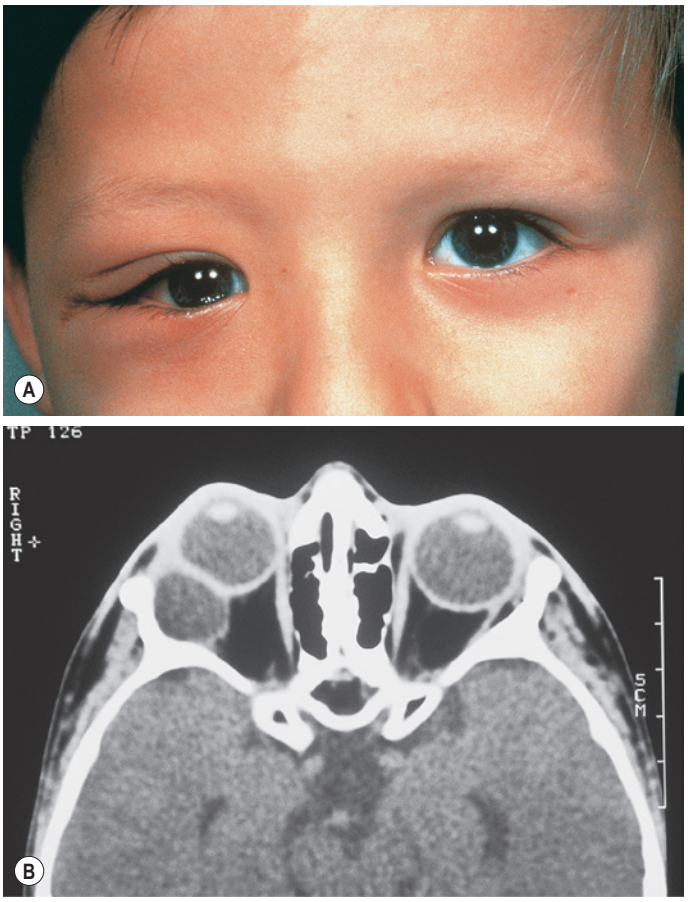


Fig. 29.17 (A) This 9-year-old refugee, who lived in unsanitary conditions, presented with a 6-month history of increasing right upper lid swelling. He had 4 mm of right proptosis, downward displacement of the globe, and lateral ptosis. (B) On computed tomography scan, a cystic lesion was found situated posterolaterally to the globe; this was an echinococcal cyst, which was excised intact. *(Patient of the University of British Columbia.)*

Ectopias

Dermolipoma

These congenital lesions are a maldevelopment of the lateral canthal area and lateral bulbar epithelium. They can be classified as solid choristomas. They may occur alone or as part of the oculoauriculovertebral spectrum (OAVS, Goldenhar syndrome) with combinations of lid coloboma, limbal dermoids, preauricular skin tags, hemifacial microsomia (Fig. 29.18), jaw and cervical spine, facial nerve, palatal, and ear and hearing abnormalities. About one-third of patients with dermolipomas will have features of OAVS.[90] They are situated laterally on the bulbar surface, are pink to yellow in color, with surface epithelium closer to skin than conjunctiva (Fig. 29.19). They may have surface hairs, which can cause irritation. Rarely, they may contain bony tissue.[91] Frequently, their superior and posterior extensions are close to the lacrimal ducts and levator muscle.[92] There is often a poorly formed lateral canthus with a band of fibrous tissue from the canthus to the lesion. The fatty tissue under the surface epithelium is usually continuous with the orbital fat with no clear separation.

Surgery, in response to symptoms of irritation, should be performed with great care. The lesion can be debulked with



Fig. 29.18 A young girl with a right dermolipoma and ipsilateral hemifacial microsomia, but no other features of oculoauriculovertebral (Goldenhar) syndrome.



Fig. 29.19 A typical dermolipoma with slightly thickened whitish surface epithelium and underlying adipose tissue. Note the typical improperly formed lateral canthus with a band from the canthus to the surface of the lesion.

preservation of the surface epithelium, and this minimizes the risk of scarring leading to limited eye adduction.[44,93] The excision should spare the component of the lesion adjacent to the palpebral lobe of the lacrimal gland to avoid damaging its ductules. Additionally, the lateral rectus muscle should be isolated and protected. Attempts at complete excision of dermolipoma with orbital dissection are risky and may cause dry eye, restrictive symblepharon, strabismus, and ptosis.[91,94]

Ectopic lacrimal gland

Lacrimal gland tissue may occasionally occur at ectopic sites within the orbit. Most commonly, it is found in the eyelid or conjunctiva, but it may occur on the cornea or even the iris and choroid.[95] Green and Zimmerman reported eight cases,[96] and more have since been added to the literature, often in children or teenagers. The ectopic tissue may be situated intra- or extraconally. Typically, the patients present with proptosis. Double vision is a common symptom due to muscle restriction from the inflammatory response, which the ectopic tissue often incites. The differential diagnosis includes true orbital neoplasms. Investigation, including CT scan, often shows a cystic component.[97] The treatment of choice is surgical excision. If this is incomplete, proptosis may recur.[96] The aberrant tissue may give rise to tumors such as pleomorphic adenoma or adenocarcinoma.[96]

Ectopic brain in the orbit

There have been rare reports of ectopic brain occurring in the orbit.[98–101] Most cases present in infancy. In some cases, the ectopic tissue has grown slowly, in others it has appeared static over several years' follow-up.[102] When ectopic brain is reported in association with clinical anophthalmia, it is more likely that the abnormal tissue is neural tissue that is well described to occur with congenital anophthalmia, microphthalmia, and congenitally cystic eye.[103] Cases with abnormal extraocular muscle development have been reported.[104]

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Inflammatory disorders

Alan A McNab and Christopher J Lyons

Chapter contents

THYROID-ASSOCIATED ORBITOPATHY
SPECIFIC CAUSES OF ORBITAL INFLAMMATION
NON-SPECIFIC (IDIOPATHIC) ORBITAL INFLAMMATORY SYNDROMES
REFERENCES

Non-infectious orbital inflammation in childhood is uncommon. As in adults, the commonest cause is thyroid-associated orbitopathy (TAO). The remainder can be divided into: (1) specific forms of inflammation, which include granulomatosis with polyangiitis (GPA, previously called Wegener granulomatosis), sarcoidosis, and the more recently characterized entity of immunoglobulin (Ig)G4-related ophthalmic disease; and (2) non-specific orbital inflammation or idiopathic orbital inflammation (IOI). Infective orbital inflammation is most commonly due to bacterial orbital cellulitis and this is discussed in Chapter 14.

Thyroid-associated orbitopathy

TAO is by far the commonest cause of proptosis in adults, but it is relatively rare in children. In most series, about half develop ophthalmic signs.[1,2] Despite its relative rarity, if several large series of orbital disorders are combined, TAO is the second commonest cause of orbital disease after orbital cellulitis (see Table 22.1). Neonatal TAO may affect the infant of a mother with Graves disease, due to transplacental passage of thyroid-stimulating hormone receptor and other antibodies. In the neonate, it tends to be a self-limiting disease.

Although TAO may occur in early childhood, it becomes commoner in the second decade of life (Fig. 30.1). It is more prevalent in girls, by a ratio of between 2 and 7:1.[2–5] There is commonly a family or past history of hyperthyroidism. Associations with other autoimmune disorders and diabetes have been reported. Most patients will be hyperthyroid at the time of diagnosis of TAO (88.6%), with a small number being hypothyroid (2.9%) or euthyroid (8.6%).[5]

The orbital involvement is generally relatively mild, and signs of active inflammation are generally absent.[3] There may be proptosis, sometimes asymmetric, which rarely warrants orbital decompression.[5,6] Lid retraction and lagophthalmos are also common. In East Asian children, an acquired form of lower lid epiblepharon with trichiasis may develop and lead to keratopathy.[3]

Up to 1 in 4 patients will develop restriction of ductions[2] (Fig. 30.2 A,B). The severity of the orbitopathy tends to increase with age.[1] Optic neuropathy and sight-threatening corneal problems have not been described in children. Orbital imaging may show enlarged muscles (Fig. 30.1C) with characteristic sparing of the tendons, or an increase in orbital fat volume.

Treatment is usually conservative with supportive measures. Eyelid or orbital decompression surgery is rarely required.[5]

Specific causes of orbital inflammation

The most common cause of orbital inflammation in childhood is bacterial orbital cellulitis (see Chapter 14). Other childhood orbital inflammatory diseases are comparatively rare, and called "specific" since they have a defined clinical, radiologic, biochemical, and histopathologic spectrum, though their underlying cause has not been clearly determined.

Granulomatosis with polyangiitis (GPA, previously called Wegener granulomatosis)

This is a necrotizing granulomatous vasculitis, which has a predilection for the upper and lower airways and the kidneys. The limited form of the disease in which the kidneys are spared has a better prognosis and is more commonly associated with orbital disease.[7] Both forms have the same incidence of ocular and orbital involvement, ranging in different studies from 28% to 45%.[8] Before the introduction of cyclophosphamide, over 90% of affected patients died within 2 years. Although this is not a common disease of childhood, it does occur under the age of 18. Its rarity in childhood commonly leads to a delay in diagnosis.[9]

Clinical features

In childhood GPA, the median age of onset is about 11 years.[9,10] In pediatric series of GPA, the incidence of ophthalmic disease has been between 18% and 35%.[9,10] The onset of orbital GPA is often preceded by a history of subacute or chronic low-grade disease, with sudden aggravation leading to presentation. The main features are proptosis, which is frequently bilateral, with ocular and facial pain, which may be severe. An orbital mass usually develops (Fig. 30.3), displacing the globe,

even in patients who initially present with scleritis. The latter is typically nodular and necrotizing, accompanied by characteristic marginal corneal infiltration, which can progress to ulceration. Decreased vision is common and can be related to optic neuropathy.



Fig. 30.1 8-year-old girl with Graves orbitopathy and a 6-month history of proptosis. Four months earlier she underwent a total thyroidectomy. She subsequently underwent bilateral orbital decompression.

Lacrimal gland involvement with lid swelling and brawny discoloration may occur. The orbital disease may be bilateral. Midline disease (nasal and paranasal sinus disease) and lacrimal gland involvement are common. Nasal symptoms frequently precede presentation by several months. These include nasal blockage, discharge or bleeding, pain over the paranasal or mastoid sinuses, and hearing loss or tinnitus. Ocular involvement may be the presenting feature of GPA in children.[11]

Computer tomography (CT) scans show an orbital mass with infiltrative margins obscuring fat and adjacent muscles. Midline bony erosion and sinus involvement may be evident. Histologic changes include areas of fat disruption and focal necrosis with lipid-laden macrophages, giant cells, and evidence of acute inflammatory cells. Vasculitis is often difficult to find in these specimens.[7] Fibrosis is common. Stains for fungi and mycobacteria should be performed to exclude these important differential diagnoses.

The antibiotic combination of trimethoprim and sulfamethoxazole is a first-line treatment for this condition. Azathioprine is a second-line drug. Cyclophosphamide is effective in GPA but, due to its oncogenic potential, it is reserved for children who have not responded to the above or who present with severe disease. Rituximab has also been shown to be effective in GPA,[12] and may be used in the pediatric age group. Antineutrophil cytoplasmic antibodies (cANCA) are specific markers for GPA if there is a "cytoplasmic" staining

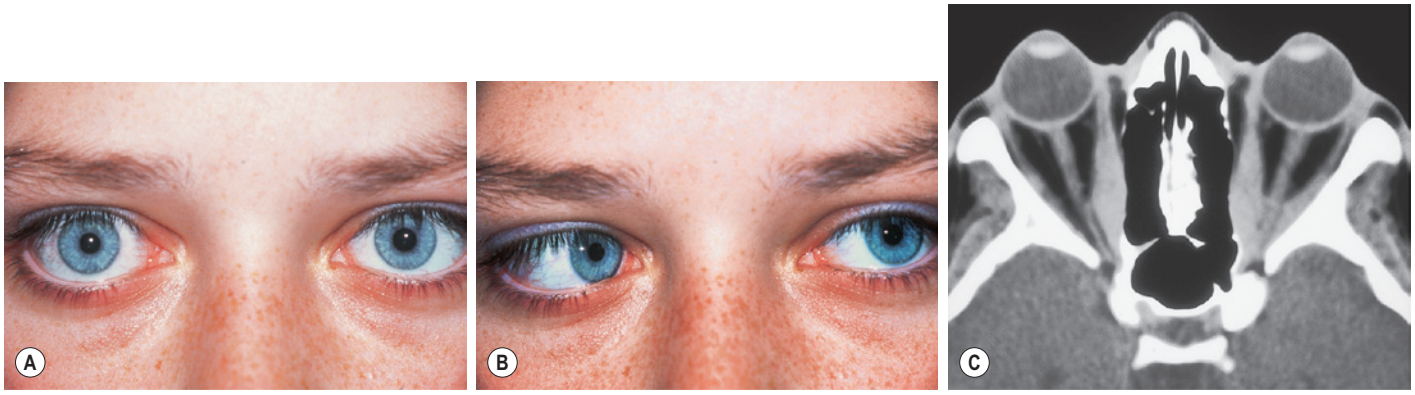


Fig. 30.2 This girl had a 6-year history of double vision at the extremes of gaze. Her past medical history included autoimmune hepatitis and hyperthyroidism, treated with radioiodine. There is lid retraction (A), lid lag, and restriction of abduction with esotropia in lateral gaze (B). Bilateral medial rectus enlargement involving the muscle belly but sparing the tendons is evident on computed tomography scanning (C). *(Patient from the University of British Columbia.)*

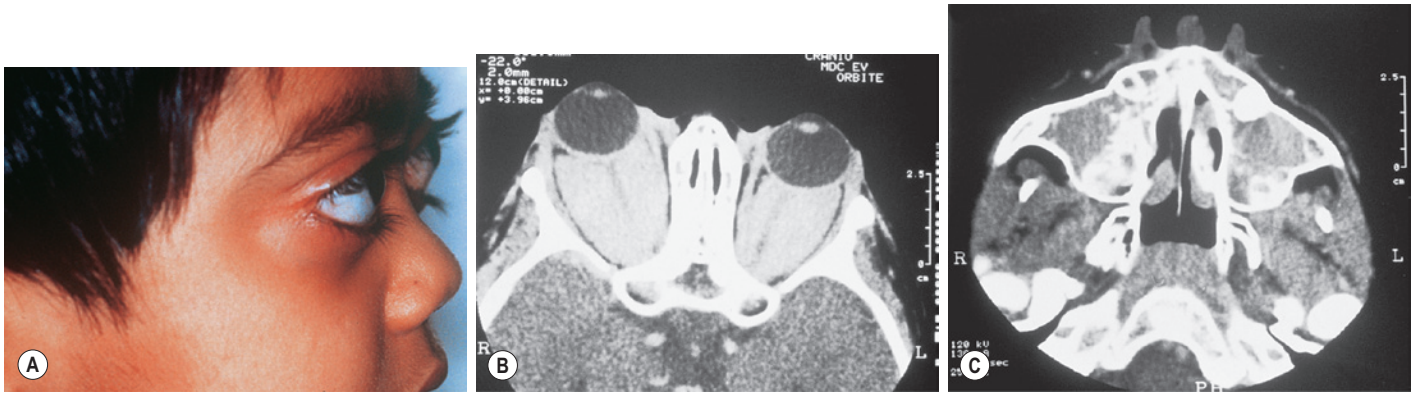


Fig. 30.3 A 7-year-old boy presented with a 3-month history of progressive bilateral proptosis (A). He has positive antineutrophil cytoplasmic antibodies (ANCA) titers. Computed tomography (B,C) shows widespread involvement of the orbital soft tissues and maxillary sinuses. *(Patient from the University of British Columbia.)*

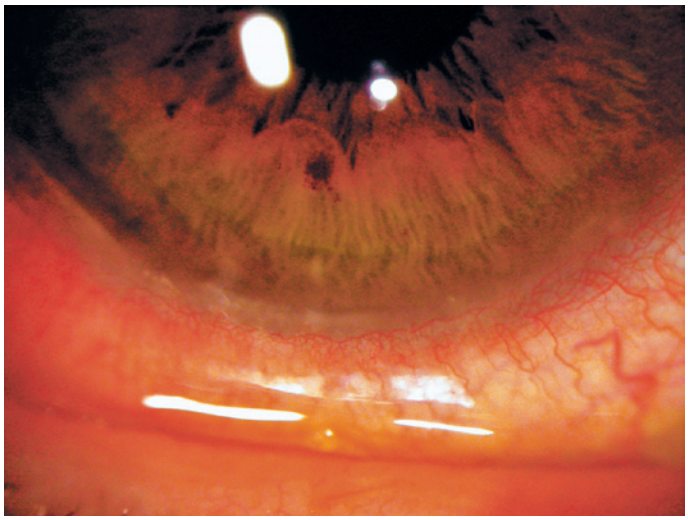


Fig. 30.4 Granulomatosis with polyangiitis (GPA, or Wegener granulomatosis). Photograph or cornea demonstrates marginal infiltration with a clear zone between the infiltrate and limbus, a feature characteristic of the disease. *(Patient from the University of British Columbia.)*

pattern. Their plasma level correlates with disease activity. Failure of these to return to normal after clinical improvement with treatment indicates a high risk of relapse.[13]

GPA is rare but it does occur in childhood. Clinicians should remain alert for this potentially lethal disorder especially in patients with bilateral orbital involvement, particularly with scleritis accompanied by characteristic marginal corneal infiltration (Fig. 30.4). Respiratory tract or sinus (including the mastoid sinuses) involvement further supports the diagnosis.

Sarcoidosis

This chronic granulomatous inflammatory disease of unknown cause occasionally affects children; several hundred cases have been documented in children under the age of 15 years. The incidence of the disease rapidly increases in the late teens, peaking in the third decade. The risk is increased 3–10 times in African-Americans versus Caucasians, with a slight female preponderance. Age defines to some extent the pattern of systemic involvement: children aged 5 years or less develop uveitis, arthropathy, and skin rash; those aged 8 to 15 have lung involvement with ocular, skin, and spleen involvement in approximately one-third.[14]

Anterior uveitis, which may be chronic and granulomatous or acute, is the commonest finding at presentation, affecting one-quarter to one-half of patients. The eyelid, conjunctiva, sclera, episclera, and lacrimal glands may be involved. Orbital infiltration causing unilateral proptosis has been reported in a 5-year-old child with arthritis.[15] Cornblath et al.[16] reported a 15-year-old boy with pain, diplopia, and ophthalmoplegia from generalized involvement of the extraocular muscles. There was diffuse enlargement of all the muscles on CT, suggesting orbital myositis or thyroid orbitopathy. Unlike the latter, the muscle insertions were enlarged on CT scan.

IgG4-related ophthalmic disease (IgG4-ROD)

IgG4-related disease is a recently recognized fibro-inflammatory disorder, characterized by tumefactions infiltrated with large numbers of IgG4-postive plasma cells. Almost any organ can be affected, but the most common are pancreas, hepatobiliary tract, salivary glands, lymph nodes, retroperitoneum, and orbit. Orbital disease, in various patterns, is relatively common.[17] Ophthalmic disease (IgG4-ROD) has been described in several children[18] including in the form of dacryoadenitis.[19]

The diagnosis depends on finding large numbers of IgG4-positive plasma cells in tissues using immunohistochemical stains, in a ratio of over 40% compared to IgG-postive plasma cells, as well as a characteristic lymphoproliferative infiltration, significant numbers of eosinophils, and fibrosis, classically described as storiform. The pathological changes must be correlated with the clinical and imaging findings to reach an appropriate diagnosis; the finding of increased numbers of IgG4+ plasma cells alone is insufficient as it occurs in many other conditions, including GPA, xanthogranulomatous disease, rheumatoid arthritis, Castleman disease, and others.[18]

IgG4-ROD highlights the need to obtain tissue for histopathological examination whenever possible to secure a diagnosis in orbital inflammatory disease. Without tissue, this and many other forms of specific inflammation cannot be diagnosed. IgG4-ROD responds well to oral corticosteroids, but relapse is common. Other immunosuppressants and rituximab may be used in recalcitrant cases.[17]

Non-specific (idiopathic) orbital inflammatory syndromes

Definition

The child's orbit is occasionally the site of acute or subacute inflammation of unknown cause.[20,21] This entity was previously known as "orbital inflammatory pseudotumor," a term which, with the advent of CT and magnetic resonance imaging (MRI) and pathologic studies, has been abandoned. Instead, the site of inflammation is identified,[22] including anterior, diffuse, apical, myositic, and lacrimal types. Children tend to develop the anterior and diffuse types, but myositis and lacrimal gland inflammation may occur. Apical involvement is rare. Non-specific sclerosing inflammation of the orbit is very rare in childhood.

These syndromes present acutely or subacutely with inflammatory signs. Although apparently idiopathic, they have many features of an orbital immune reaction.[23] Histologically, there is an influx of lymphocytes, plasma cells, sparse neutrophils, and macrophages. Inflammatory mediators cause edema, vascular dilatation and pain without systemic malaise. In contrast, more chronic inflammations, including IgG4-ROD, and granulomatous diseases cause mass effect as their predominant feature, without clinical features of acute inflammation. The common CT profile of acute or subacute non-specific orbital inflammatory syndromes (NSOIS) is a poorly defined margin to the inflammatory focus, as well as contrast enhancement.[24] With MRI, T2-weighted sequences with fat suppression and gadolinium can highlight areas of fluid accumulation indicative of inflammatory foci.

Anterior idiopathic orbital inflammation: acute and subacute

This is the most common type of NSOIS in childhood. The inflammatory process is centered on the anterior orbit and

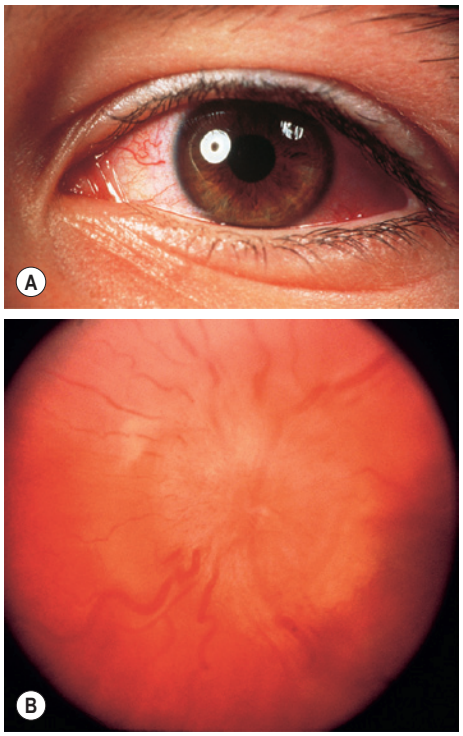


Fig. 30.5 Anterior non-specific orbital inflammatory syndrome in a 6-year-old boy who presented with a red eye (A), pain on eye movement and decreased vision of 3 days, duration. Fundoscopy (B) shows choroidal swelling and papillitis. *(Patient from the University of British Columbia.)*

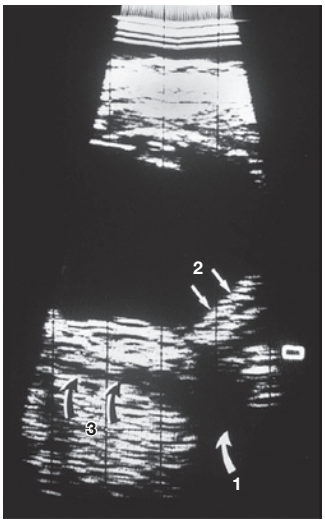


Fig. 30.6 Ultrasound scan of anterior non-specific orbital inflammatory syndrome showing the T-sign. There is doubling of the optic nerve shadow (1), shallow retinal detachment (2), and accentuation of Tenon's space (3). *(Patient from the University of British Columbia.)*

adjacent globe (Fig. 30.5). Pain, proptosis, lid swelling, conjunctival injection, and decreased vision are the main presenting features, with an onset over days or occasionally weeks. Children are more likely to have an associated anterior and posterior uveitis, which can potentially lead to misdiagnosis and erroneous treatment with topical steroid.[25] The disc may be swollen. Systemically, the erythrocyte sedimentation rate may be raised, and there is often cerebrospinal fluid pleocytosis. Disturbances in thyroid function tests and hypothyroidism have also been reported in association with NSOIS.[26] CT scans show diffuse anterior orbital inflammation centered on the globe, producing scleral and choroidal thickening with or without serous retinal detachment. The junction of the globe and optic nerve is characteristically obscured on CT scan with inflammatory changes extending along the nerve sheath. On ultrasound, there is a uniform-density infiltrate corresponding to sclerotenonitis, with accentuation of the sub-Tenon's space and doubling of the optic nerve shadow producing a T-shaped shadow (or T-sign) (Fig. 30.6).

Diffuse idiopathic orbital inflammation: acute and subacute

This is clinically similar to the anterior form, although the symptoms and clinical signs are more severe (Fig. 30.7). The eye movements are more restricted and the visual acuity is worse due to serous retinal detachment and/or optic neuropathy. Inflammatory soft tissue changes permeate the whole orbit on CT scan, with a white-out appearance whose density is proportional to the severity of the clinical signs, and which resolves as the condition settles. Again, the T-sign is evident on ultrasonography.

Anterior and diffuse non-specific orbital inflammatory syndromes: differential diagnoses and management

The differential diagnoses include infection such as orbital cellulitis, scleritis, sudden enlargement of a pre-existing lesion such as a ruptured dermoid, hemorrhage into a venous-lymphatic malformation (lymphangioma) or malignancy, which, in childhood, may be rhabdomyosarcoma, neuroblastoma, Ewing sarcoma, or leukemic infiltration. Anterior and diffuse NSOIS are also part of the differential diagnoses of uveitis and serous retinal detachment in childhood. Biopsy of involved orbital tissues should be considered in all but the most typical cases.

Treatment with oral non-steroidal anti-inflammatory drugs such as flurbiprofen is tried first. Systemic steroids may be used in addition, or as an alternative, in doses for prednisolone of 1–1.5 mg/kg per day. There is usually rapid improvement in symptoms, especially pain, as well as clinical signs. Progress can be monitored by resolution of the clinical, CT, and ultrasound features. This disease may have a recalcitrant course, with frequent recurrences and steroid dependence. High-dose steroid is re-started for recurrence and tapered as quickly as clinical progress will allow, usually over a few weeks. Failure to respond suggests the need for biopsy and the renewed search for a specific etiology. Low-dose radiotherapy has been advocated for biopsy-proven cases that do not respond to steroids. Combined steroids and immunosuppressives may be necessary.

Idiopathic orbital myositis: acute and subacute

This is characterized by proptosis, pain and limitation of eye movement with diplopia, ptosis, lid edema, and conjunctival chemosis. Strabismus is often present with duction limitation in the direction of action of the involved muscle(s).[27] Spasm of the affected muscle also causes restriction of the ipsilateral antagonist with a positive forced duction test. Globe retraction and narrowing of the lid fissure similar to Duane syndrome is a frequent finding.

CT scan shows diffuse muscle enlargement with irregular margins. The muscle enlargement frequently involves the tendon, in contradistinction to thyroid-associated orbitopathy

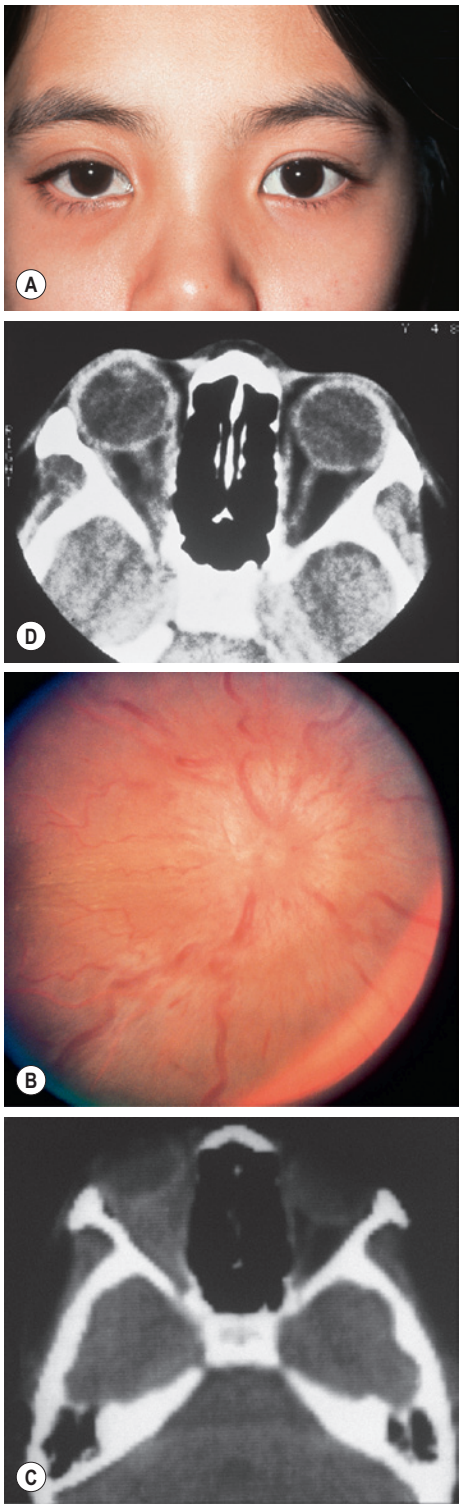


Fig. 30.7 Diffuse non-specific orbital inflammatory syndrome in a 12-year-old girl who presented with a retrobulbar ache, associated with ptosis (A), and pain on eye movement. There was right-sided uveitis with marked disc swelling (B). On computed tomography scanning (C), there was a "white-out" appearance of the right orbit (similar patient), which resolved after treatment with systemic steroids (D). *(Same patient from the University of British Columbia.)*



Fig. 30.8 Left superior rectus myositis in a 16-year-old boy. Ptosis (A) and pain limitation of upgaze with diplopia were the presenting signs; this was due to left superior rectus myositis shown as a thickened muscle complex on computed tomography scan (B). *(Patient from the University of British Columbia.)*

where, typically, the tendon is spared. The superior rectus–levator complex (Fig. 30.8) or medial rectus are the most common muscles to be involved, but any muscle can be affected, including the obliques. More than one muscle may simultaneously be involved and bilateral disease may occur.

The cause of orbital myositis is unknown but a number of associations have been reported, including upper respiratory tract infection,[28] Lyme disease, Whipple disease, and other autoimmune diseases.[29]

The differential diagnoses include thyroid-associated orbitopathy, which differs from idiopathic orbital myositis in that a preceding or concurrent history of thyroid disorder is common, pain is absent, the inferior recti tend to be the first muscles involved (although any muscle may be involved), and sparing of the tendon is apparent on CT scan. In some cases, differentiating between these two conditions can be very difficult and misdiagnosis is not uncommon. Early orbital cellulitis, orbital metastasis, and trichinosis are other differential diagnoses.

Non-steroidal anti-inflammatory treatment has been advocated,[8] but the rapid and dramatic response to steroids is almost diagnostic. We recommend an initial dose of prednisolone of 0.5–1 mg/kg per day, tapering to nothing over 2–4 weeks. Delay in diagnosis and initiation of therapy is associated with recurrence and incomplete resolution of signs. Biologic agents such as adalimumab, a monoclonal antibody directed against tumor necrosis factor alpha, has been reported to be effective in recalcitrant cases of orbital myositis in children.[30]

Idiopathic lacrimal gland inflammation (dacryoadenitis): acute and subacute

Pain, tenderness, and swelling over the lateral aspect of the upper lid are typical presenting features of this disorder.[31] The lid may have an S-shaped configuration with ptosis, which is more marked laterally than medially. The globe is often slightly displaced downward and medially. This may be accompanied by superotemporal conjunctival injection, and chemosis and pouting of the excretory lacrimal duct orifices. Limited abduction may be seen. There is no uveitis. On CT scans, the inflammation is centered on the lacrimal gland, often extending diffusely into the lateral orbit and involving the adjacent globe. The differential diagnoses include bacterial and viral dacryoadenitis, the latter often occurring in association with childhood infections such as mumps or

infectious mononucleosis (Epstein–Barr virus infection), and IgG4-related dacryoadenitis. In this situation, the child is likely to be ill, and generalized lymphadenopathy or salivary gland enlargement may be noted, along with lymphocytosis. Inflammation related to leakage from a dermoid cyst and neoplasia, including chloroma (granulocytic sarcoma), are other rare possibilities. Lacrimal gland involvement in orbital sarcoid tends to be chronic, presenting with signs and symptoms of dry eyes, and is rare in childhood.

Acute or subacute lacrimal gland swellings in childhood do not need biopsy if they are related to an obvious viral illness such as mumps, or if there are other findings suggestive of mononucleosis. Atypical lesions in patients whose signs and symptoms fail to respond to treatment should have an early biopsy to exclude specific forms of inflammation.

Idiopathic lacrimal gland inflammation is usually treated with moderate-dose systemic steroids, tapering with resolution of symptoms and signs.

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Conjunctiva and subconjunctival tissue

Venkatesh Prajna and Perumalsamy Vijayalakshmi

Chapter contents

ANATOMY
CONJUNCTIVA IN SYSTEMIC DISEASE
MISCELLANEOUS DISORDERS OF CONJUNCTIVA
REFERENCES

See online for supporting video for this chapter.

Anatomy

The conjunctiva is a thin, translucent, vascular mucous membrane that lines the inner surface of the eyelids and the anterior surface of the eyeball as far as the limbus. This tissue is arranged in a sac-like fashion and is composed of a palpebral region (covering the inner aspects of the lids), a bulbar region (covering the surface of the sclera), a forniceal region, and a medial semilunar fold.

The palpebral part of the conjunctiva is more adherent to the underlying tarsus than the bulbar part. The loose adherence is responsible for the occurrence of chemosis of the bulbar conjunctiva during inflammation. The bulbar conjunctiva has attachments with the lateral rectus muscle through fine fibrous slips, and hence plays a role in the maintenance of the horizontal movements of the eyeball. While the palpebral conjunctiva shares its blood supply with the eyelids, the bulbar component is supplied by the anterior ciliary arteries. The nerve supply to the conjunctiva is through the lacrimal, supraorbital, supratrochlear, and infraorbital branches of the trigeminal nerve.

The conjunctival epithelium varies from two to five cells in thickness and is continuous with the corneal epithelium at the limbus and with the skin at the margin of the lids. While the bulbar conjunctiva is lined by a stratified non-keratinized squamous epithelium, the forniceal and tarsal regions are lined by columnar and cuboidal types, respectively. A key constituent of the cellular architecture is the presence of goblet cells, which accounts for 10% of the basal cells of the conjunctival epithelium. These cells are more prevalent in the medial forniceal and palpebral regions, and play a vital part in secreting the mucin component of the tear film. There is an increase in the number of these cells during chronic inflammation of conjunctiva, while conditions like pemphigoid and vitamin A deficiency causes a decrease. Other cell types that nestle within the epithelial layers include melanocytes, Langerhans cells, and intraepithelial lymphocytes.

Beneath the epithelium lies a loose structure called the substantia propria. This structure contains different cell types that mediate immune responses (mast cells, plasma cells, eosinophils, and lymphocytes) interspersed in a vascular network. This arrangement of immune cells, commonly referred to as conjunctiva-associated lymphoid tissue, existing in a vascular environment, is continuously exposed to potential external infective agents and allergens and thus serves as a perfect setting for inflammation to set in.

Beneath the conjunctiva lies a fibroelastic tissue, Tenon's capsule, which surrounds the eyeball from the corneoscleral junction to the optic nerve. In children, the conjunctiva–tenon complex is thicker, with a larger proportion of fibroblasts, compared to adults. In consequence, surgeries like trabeculectomy performed in children, especially without adjuvant procedures like intraoperative use of antimetabolites, may fail due to the aggressive healing response induced by these fibroblasts.[1]

Conjunctiva in systemic disease

Vitamin A deficiency

The ocular manifestation of vitamin A deficiency is termed xerophthalmia, and affected individuals present with night blindness, conjunctival xerosis, Bitot's spots, corneal xerosis, keratomalacia, and the "xerophthalmic" fundus (see Chapter 50).

In xerophthalmia, the conjunctival epithelium is transformed from the normal columnar to the stratified squamous type. There is an associated loss of goblet cells, formation of a granular cell layer, and keratinization of the surface. The conjunctiva loses its normal luster and becomes dry or unwettable (Fig. 31.1). It is almost always bilateral. A classic ocular sign is Bitot's spots, which is a superficial, scaly, gray area on the interpalpebral region of the bulbar conjunctiva (Fig. 31.2). *Corynebacterium xerosis* can colonize these spots, and produce a foamy appearance because of the gas-forming nature of these organisms. If untreated, the condition involves the cornea, causing corneal xerosis and finally corneal melting (keratomalacia).

The diagnosis of xerophthalmia can usually be made clinically. In doubtful cases, impression cytology of the

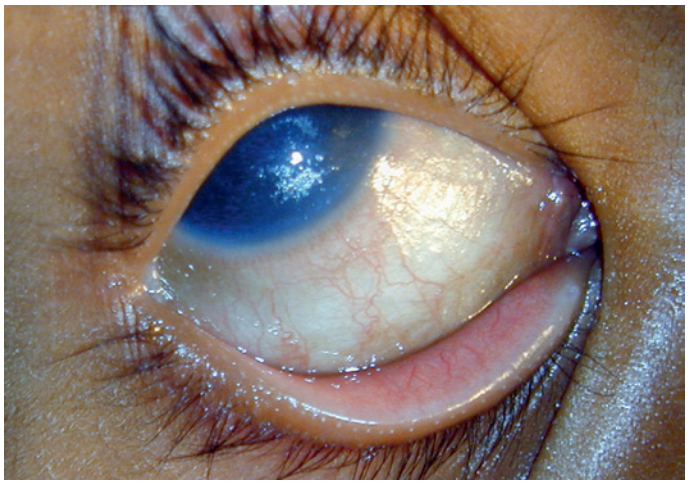


Fig. 31.1 Xerophthalmia. Dry, lusterless, inferior bulbar conjunctiva showing a wrinkled appearance. Associated corneal xerosis is also seen. *(Courtesy of Dr P. Vijayalakshmi, MS.)*

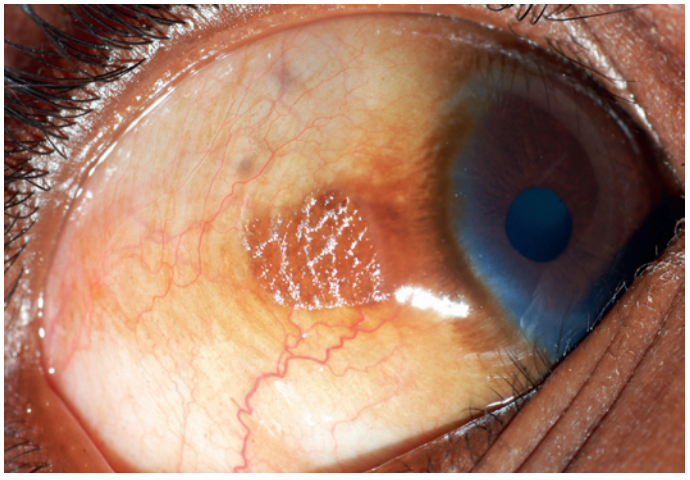


Fig. 31.2 Bitot's spot. A superficial, scaly, foamy Bitot's spot of the bulbar conjunctiva.

superficial layers of the conjunctival epithelium may be helpful to show the loss of goblet cells and keratinization of epithelial cells. In children 12 months of age or older, retinol palmitate (110 mg) or retinol acetate (200 000 IU) are given orally immediately, and the dose is repeated the following day. An additional dose should be given 2 weeks later to boost liver resources. Children between 6 and 11 months should receive only half this dose, and children less than 6 months only one-quarter.

Parenteral administration is indicated in children with gastrointestinal problems. In these cases, intramuscular injection of 55 mg of water-miscible retinol palmitate (100 000 IU) is administered, which replaces the first oral dose. This is repeated the next day. Children less than 1 year old are treated with vitamin A in half the prescribed dosage. After the acute phase is over, dietary supplements with provitamin A-rich foods, should be provided.[2]

Xeroderma pigmentosa

Symptoms appear in early childhood. (Fig. 31.3A). Conjunctival involvement occurs mostly in the interpalpebral area

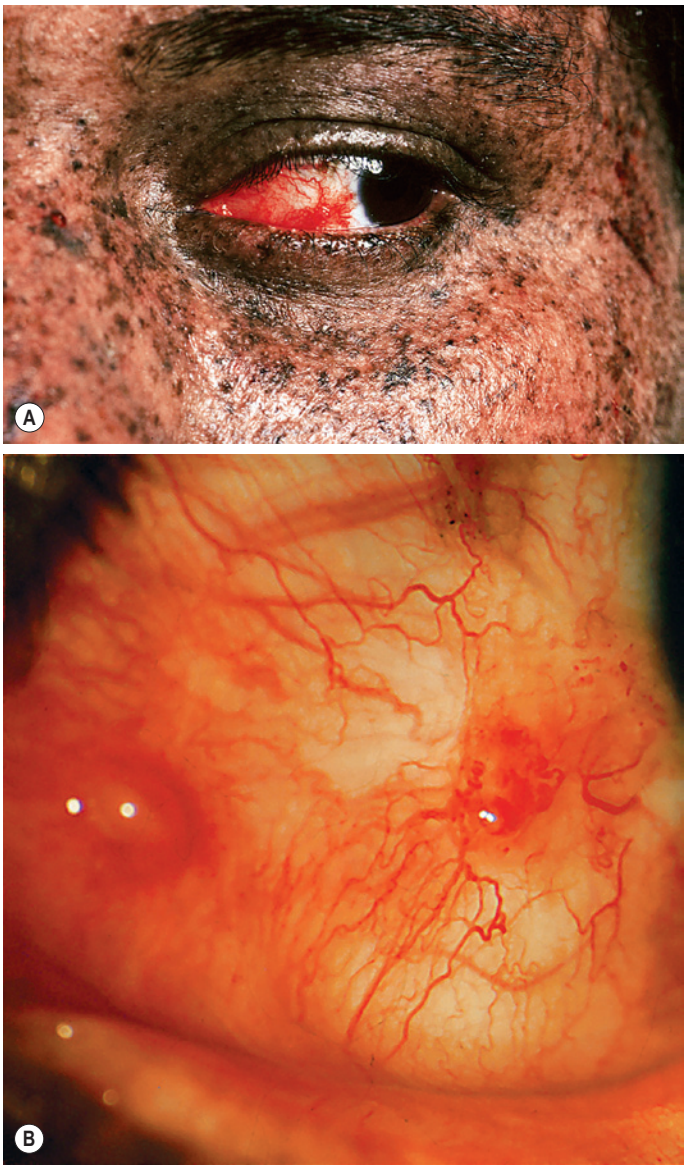


Fig. 31.3 Xeroderma pigmentosa. (A) The widespread skin pigmentation can be seen in this girl of Indian origin. (B) The conjunctiva was affected by multifocal recurrent squamous cell carcinomas.

in the form of xerosis, telangiectasia, chronic conjunctival congestion, pigmentation, pinguecula, and pterygium. Ocular surface neoplasms such as squamous cell carcinoma, basal cell carcinoma, and malignant melanoma may occur, with a predilection for the limbal area (see Chapter 32) (Fig. 31.3B). Corneal changes include exposure keratitis, band-shaped nodular keratopathy, scarring, ulceration, vascularization, and perforation.

Sturge–Weber syndrome

This is a congenital disorder with a classical triad of cutaneous facial angioma, leptomeningeal angioma, and ocular involvement (see Chapters 20 and 68). The facial angioma typically occurs in the distribution of the ophthalmic division of the trigeminal nerve. Dilated episcleral and conjunctival vessels with aneurysm formation in the limbal area are commonly seen.



Fig. 31.4 Ichthyosis. (A) There is keratinization of the upper palpebral conjunctiva secondary to ectropion of the upper lids. (B) The classical "stretched out" skin lesions are seen predominantly around the mouth and neck.

Glaucoma is a frequent accompaniment (see Chapter 38), especially in patients with severe conjunctival involvement.[3]

Ichthyosis

Ichthyosis is a heterogeneous family of at least 28 genetic skin disorders. Most pedigrees are either autosomal dominant or X-linked in their inheritance pattern. A rare autosomal recessive form, lamellar ichthyosis, occurs. In all these conditions, dry scaly lesions are present, predominantly over the upper half of the body, mainly around the neck, mouth, and trunk. The conjunctiva may become inflamed, primarily or secondarily, due to lid anomalies like ectropion.[4] A papillary reaction may develop (Fig. 31.4). The treatment is to provide adequate lubrication and to correct the lid abnormalities, if present.

Measles keratoconjunctivitis

Measles typically produces a bilateral keratoconjunctivitis. The characteristic Koplik's spots may be seen in the conjunctiva. The plica semilunaris may be swollen. Epithelial keratitis may supervene early in children and late in adults. Treatment is symptomatic and topical anti-inflammatory therapy may provide relief. In children with protein/energy malnutrition, this disease can be particularly devastating. If vitamin A deficiency is also present, this may rapidly progress to keratomalacia.

Ataxia telangiectasia (Louis-Bar syndrome)

This is a rare autosomal recessive disorder characterized by early onset cerebellar ataxia, oculocutaneous telangiectasia, ocular motor apraxia (saccadic initiation failure), dysarthria, and immunodeficiency. Ataxia is the first sign and is progressive. Chromosomal fragility and increased susceptibility to ionizing radiation result in a predilection to malignant disorders such as lymphomas and leukemias. Affected individuals tend to have raised serum levels of alpha-fetoprotein.

The most characteristic ocular sign is conjunctival telangiectasia that appears around 10 years of age. This is usually seen in the interpalpebral bulbar conjunctiva, but may extend to the fornices. It is caused by ultraviolet (UV) damage and can be prevented or minimized by early and consistent use of 100% UV filter lenses. Other associated disorders include hypometric saccades, horizontal ocular motor apraxia, deficient accommodative ability, strabismus, and nystagmus.[5]

Osler–Weber–Rendu syndrome

This is a rare autosomal dominant disorder of blood vessels that can cause excessive bleeding. It is characterized by vascular dilatations in a variety of organ systems. Systemic features include epistaxis, dyspnea on exertion, gastrointestinal bleeding, hemoptysis, and hematuria. The classical ocular abnormality detected is conjunctival telangiectasia.[6] It may present with bloody tears or frank external hemorrhage. Retinal telangiectasia and arteriovenous malformations have also been reported. Fabry disease is another entity where conjuctival vascular tortuosity, telangiectasia, and cornea verticillata are seen (see Chapter 65).

Sickle cell disease

The conjunctival signs in this condition are fairly specific. Comma-shaped capillary and venular microaneurysms, which disappear under the heat of the examining lamp, are noted in the inferotemporal quadrant of an otherwise pale conjunctiva. These aneurysms reappear after application of a mild vasoconstrictor. These vascular anomalies are exaggerated during sickling crises.

Ocular cicatricial pemphigoid (OCP)

This group of systemic autoimmune diseases may affect the skin and other mucous membranes. Their hallmark feature is chronic cicatrizing conjunctivitis.[7] The lids may have trichiatic lashes, chronic blepharitis, cicatricial fornix foreshortening, conjunctival shrinkage, keratinization, and subepithelial fibrosis. The cornea may also become involved in advanced disease. Immunohistochemical studies are diagnostic and reveal linear deposition of immunoreactants (immunoglobulin [Ig]G, IgA, complement component C3 or C4). Treatment is mainly systemic immunosuppression. Adjunct surgical modalities include epilation, punctal occlusion, fornix reconstruction, amniotic membrane transplantation, and keratoprosthesis.

Miscellaneous disorders of conjunctiva

Pyogenic granuloma

An aberrant healing response following trauma or surgery involving the conjunctiva can result in an exaggerated fibrovascular response, erroneously referred to as pyogenic granuloma. However, this condition is neither an infection nor a typical granulomatous reaction, but a granulation tissue formation. Rapid growth may simulate a malignancy. A history of preceding trauma or surgery helps in making the diagnosis. The condition may resolve spontaneously, but usually some form of treatment is required. A short course of topical steroids may be given, but excision biopsy is the treatment of choice.

Subconjunctival hemorrhage

A subconjunctival hemorrhage may occur after trivial blunt trauma (Fig. 31.5). It can also be seen in conditions that cause a rise in central venous pressure such as a seizure, violent coughing, or sudden straining. Its presentation may be dramatic and cause considerable worry. It usually resolves spontaneously within 2 weeks and does not require any treatment. Subconjunctival hemorrhages are also seen in conditions such as leukemia

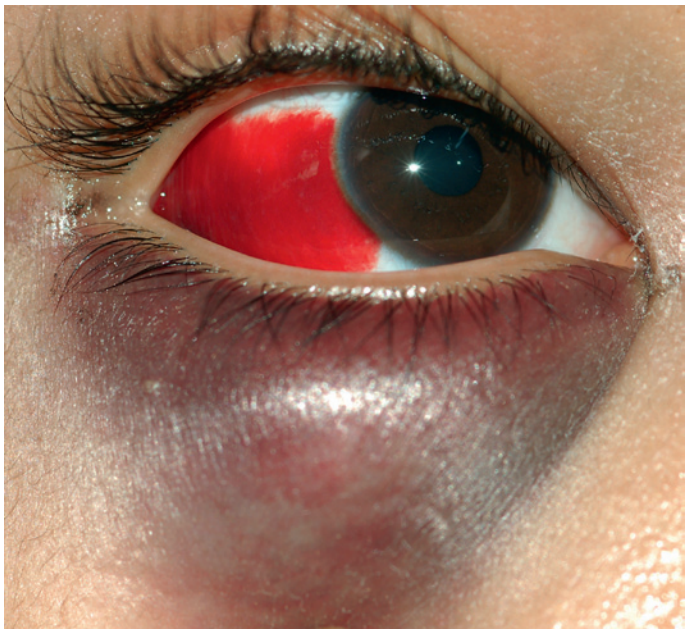


Fig. 31.5 Subconjunctival hemorrhage following a fist injury to the eye. An associated ecchymosis of the lower lid is also seen.

and as a sequel to some forms of conjunctivitis. After head injury, the presence of a subconjunctival hemorrhage with a poorly defined posterior margin could be an indication of a possible intracranial etiology, a matter of concern that has to be investigated radiologically.

Conjunctival inclusion cyst

These are smooth, thin walled lesions that commonly occur in inferior fornix. They are lined with epithelial cells and usually filled with clear fluid (Fig. 31.6). There may be a history of trauma (surgical or non-surgical). Symptomatic lesions may need surgical excision.

Conjunctival granulomas

The presence of a variety of lymphoid cells in the substantia propria serves as a perfect setting for the development of inflammatory granulomas following some systemic and local disorders. The systemic diseases and disorders that can cause conjunctival granulomas include sarcoidois, tuberculosis, Parinaud oculoglandular syndrome, Wegener granulomatosis, trematode-induced granulomas, and rhinosporidiosis and trauma.

Sarcoid nodules are small light-brown nodules in the conjunctiva[8] and show aggregates of epithelioid histiocytes on histopathological evaluation.

Tuberculosis of the conjunctiva may cause granulomas, tarsal necrosis, conjunctival masses, and small miliary palpebral conjunctival ulcers. A phlyctenular conjunctival response can also be seen in some cases (Fig. 31.7). Although the phlyctenular response is correlated with various organisms, *Mycobacterium tuberculosis* is the main causative agent for phlycten[9] in developing countries. It appears as a raised pink-to-gray amorphous nodule, 1–2 mm in diameter, surrounded by conjunctival injection (Fig. 31.8).

Trematodes are known to cause conjunctival granulomas.[10] They are acquired by children while swimming in infested



Fig. 31.6 A freely mobile subconjuctival cyst.

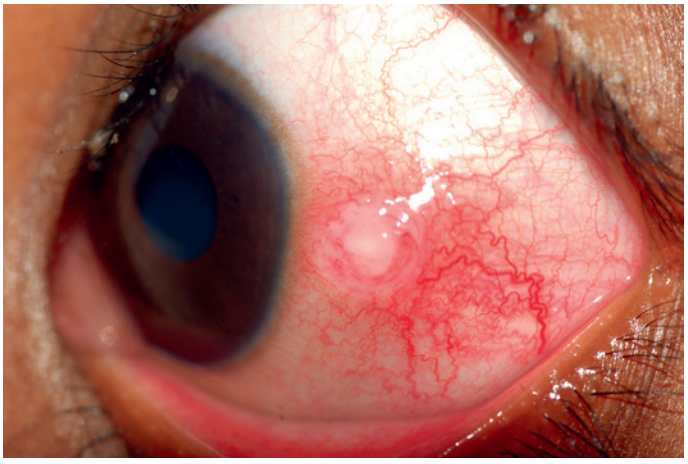


Fig. 31.7 An elevated nodular lesion seen in a 7-year-old girl on anti-tuberculous treatment.

fresh water ponds. The granuloma is usually seen as a smooth, nodular lesion in the bulbar conjunctiva (Fig. 31.9). Co-existent anterior chamber granuloma and corneal inflammation are evident in some cases. A specific inflammatory reaction known as Splendore–Hoeppli phenomenon has been described with helminthic infections, though the helminths themselves have rarely been isolated. Histopathologically, a central deposit of granular, acellular eosinophilic material is surrounded by eosinophils, epithelioid cells, histiocytes, and lymphocytes. Small granulomas may be treated with topical corticosteroids. Large lesions and those that fail conservative management should undergo an excisional biopsy.

Rhinosporidiosis may present as pedunculated granulomas, commonly in in the palpebral conjunctiva[11] (Fig. 31.10). The surface is granular and careful examination reveals pearly white studded spores, which have a tendency to bleed on contact. Treatment is by complete excision followed by cryotherapy. This lesion has an extraordinary tendency to bleed during surgery.

Ophthalmia nodosa is a granulomatous nodular conjunctivitis caused by irritation of the eye due to retained capillary hairs of caterpillars, spiders, or bees. Children presenting with this condition often give a history of a fall. Small nodules may be seen in the conjunctiva along with patterned corneal abrasions.

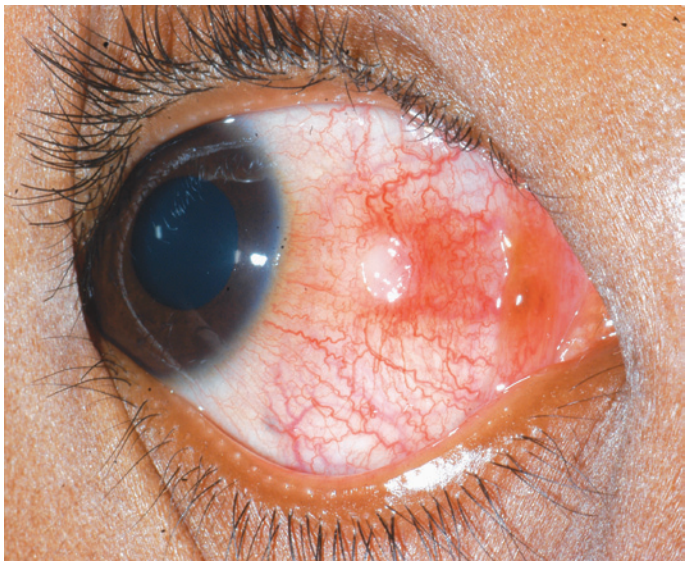


Fig. 31.8 Ulcerative phlycten. A raised nodular elevation with surrounding conjunctival congestion in a patient with a history of tuberculosis.

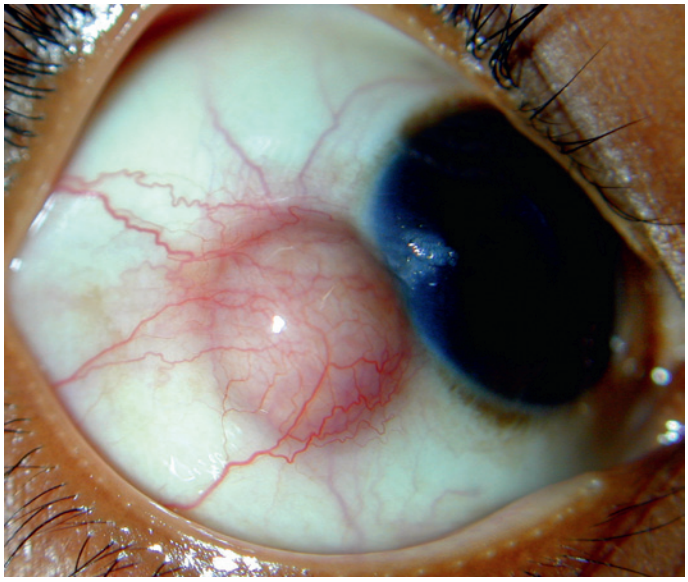


Fig. 31.9 River water granuloma. Well-circumscribed smooth elevated nodular lesion seen in the bulbar conjunctiva. *(Courtesy of Dr Rathinam, DNB.)*

Parasitic infestation of the conjunctiva

This condition is common in endemic areas and usually presents in the cyst form. The common parasitic cysts are cysticercus and hydatid. They may present with inflammation. These parasitic cysts have to be removed *in toto* along with cryotherapy of the base. Cysticercosis is caused by the larval form of *Taenia solium* known as cysticercosis cellulosae. The cysts are usually subconjunctival in location with a thin translucent wall (Fig. 31.11). Adjacent orbital structures and muscles may be involved. A chalky white area representing the scolex may be seen, which clinches the diagnosis.[12] Spontaneous expulsion of these cysts has been reported. A complete ophthalmic and systemic evaluation is needed to look for other involved areas. Treatment is by mechanical removal with supplementation of

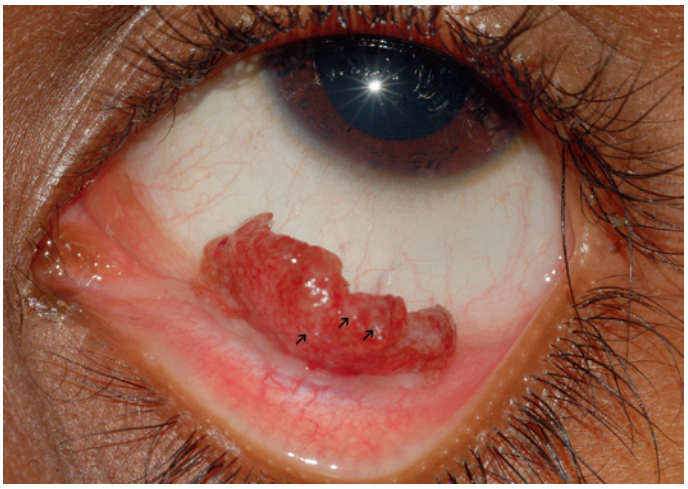


Fig. 31.10 Rhinosporidiosis. Pedunculated irregular granuloma seen in the inferior palpebral conjunctiva. Note the white spherules over the surface of the granuloma (arrows). *(Courtesy of Dr Usha Kim, DNB.)*

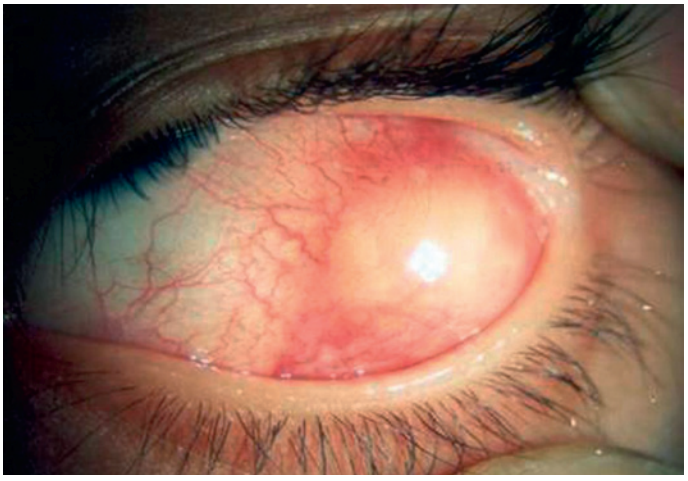


Fig. 31.11 Cysticercosis of the conjunctiva. A subconjunctival translucent cyst in the bulbar conjunctiva caused by cysticercosis.

systemic antihelminthic treatment. Exuberant inflammatory responses may need a course of systemic steroid therapy.

Ophthalmomyiasis

This term refers to the infestation of the eye by the larval forms of flies (maggots), the order Diptera. Implicated species include *Oestrus ovis* (transmitted from sheep and goats by gravid adult flies), *Dermatolabia hominis* (transmitted from cattle and fowl by mosquitoes), *Cuterebra*, *Hipoderma bovi*, *Chrysomyia*, and *Cordylobia*.[13]

In the United States, conjunctival myiasis is usually caused by the cattle fly *Hipoderma bovi*. Conjunctival involvement causes irritation, foreign body sensation, redness, and chemosis. There may be pseudomembrane formation with petechial hemorrhages. Patients may experience the perception of movements and slit-lamp examination shows the larvae. The aim of the treatment is to extract the worm mechanically. The worm may be caught with a forceps or pulled out with a suture passed through the larva.

Occasionally, adult worms can be seen presenting in the subconjunctival space (Fig. 31.12). The treatment is by

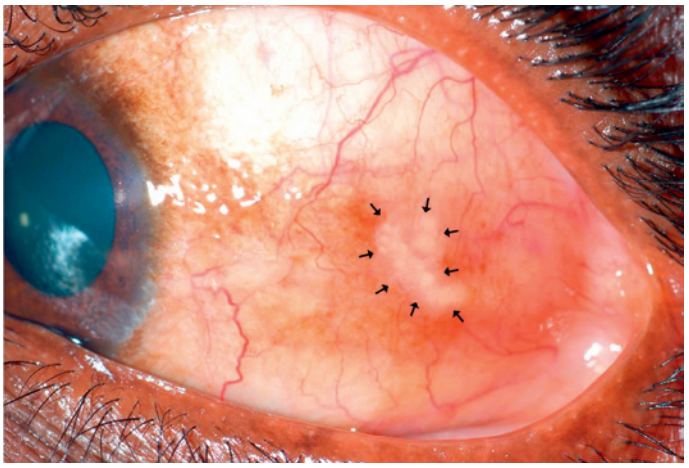


Fig. 31.12 Subconjunctival worm. The contour of this worm, identified later as *Filaria,* is clearly seen (arrows).

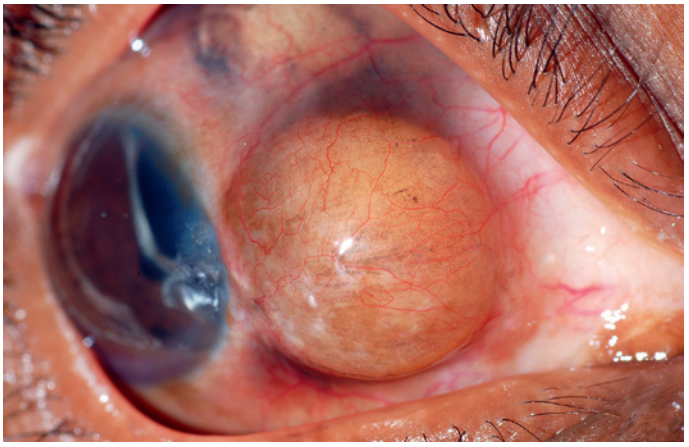


Fig. 31.14 Phacocele. A traumatically anteriorly dislocated lens mimicking a subconjunctival cyst.



Fig. 31.13 Subconjunctival foreign body. A small twig embedded in the conjunctiva required mechanical removal.



Fig. 31.15 Pseudopterigium with symblepharon. This condition warrants a surgical removal because of severe astigmatism.

mechanical removal of the worm using a forceps. In some instances, the worm is entrapped beneath the conjunctiva in close proximity to the extraocular muscles. In these situations, care should be taken to isolate the muscle and extract the worm without injuring the muscle.

Conjunctival trauma and foreign bodies

The upper tarsal conjunctiva is a common site for foreign bodies. An examination after lid eversion is mandatory for any history of trauma and suspicion of foreign body. Various foreign bodies that have been described include insect wings, beetles, cilia, caterpillar hair, seed husk, pieces of wood, twigs (Fig. 31.13), and natural and synthetic fibers. Any foreign body lodged in the conjunctiva evokes an acute inflammatory reaction with a copious outpouring of tears. However, if the foreign body has a large surface area, it may become embedded, resulting in a chronic inflammatory response. This causes a granuloma containing epithelioid and foreign body giant cells. The symptoms rapidly abate after the removal of the foreign body. Very rarely, blunt injuries in the eye, especially in older children and young adults, can cause the lens to dislocate anteriorly into the subconjunctival space and may present as a cystic lesion beneath the conjunctiva. This condition, which may mimic a subconjunctival cyst, is called a phacocele (Fig. 31.14), which may also be a presenting sign of Ehlers–Danlos syndrome type 6.

Symblepharon

In this condition, there is an adhesion between the bulbar and palpebral conjunctiva. It commonly occurs in association with congenital lid coloboma. Other causes include a chronic dry eye, chemical burns, and Stevens–Johnson syndrome where the goblet cells are destroyed. Localized symblepharon, without compromise to the visual apparatus, need not be treated. Surgical release and forniceal reconstruction using amniotic membrane or mucous membrane grafts is indicated in patients with visual symptoms or significant lagophthalmos (Fig. 31.15)

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Conjunctival tumors

Jill Razor Wells and Hans Grossniklaus

Chapter contents

ANATOMY
EXAMINATION
CLASSIFICATION
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REFERENCES

See online for supporting video for this chapter.

Although rare, several conjunctival tumors can occur in the pediatric population. These tumors range from benign lesions including the most common, conjunctival nevi, to malignant lesions such as melanoma or Kaposi sarcoma. Fortunately, most pediatric conjunctival tumors are benign. However, even benign lesions can lead to ocular morbidity and loss of vision; therefore, an understanding of the clinical appearance, diagnosis, and treatment is necessary.

Compared to publications on conjunctival tumors in adults, the number of articles regarding conjunctival tumors in children is quite small. There are only three published large series on conjunctival tumors in children, two of which are from a histopathological perspective.[1–3] The only large clinical series of this entity was published in 2007 by Drs Jerry and Carol Shields and included 262 children.[1]

Anatomy

The conjunctiva is a translucent, vascularized mucous membrane that is freely mobile over the globe and in the fornix, but firmly adherent to the posterior eyelid surface at the tarsal plate. It is composed of: (1) epithelium, which contains goblet cells and melanocytes; and (2) stroma, a fibrovascular connective tissue, which contains collagenous and elastic tissue as well as lymphocytes, plasma cells, vessels, mast cells, and accessory lacrimal glands.

Examination

When examining the conjunctiva, a slit-lamp examination is helpful. In addition to the easily viewed bulbar conjunctiva, it is important to evaluate the fornices and, if possible, to evert the upper lid to check for extension of a lesion or a second tumor. If a malignancy is suspected, palpate the preauricular and submandibular lymph nodes for enlargement. When describing the lesion, note the location (bulbar, palpebral, fornix, or caruncle), size including thickness, consistency of the surface (smooth, rough with keratin, granular, gelatinous, or papillary), mobility over underlying sclera (freely mobile or firmly adherent), shape (flat, nodular, or pedunculated), and composition (cystic or solid).

Classification

Pediatric conjunctival tumors are typically classified as congenital (including choristomas and hamartomas), epithelial, or stromal tumors. Epithelial tumors are further grouped into non-melanocytic and melanocytic subtypes. Non-melanocytic tumors include benign entities (squamous papilloma, keratoacanthoma, oncocytoma, and dacryoadenoma) as well as premalignant and malignant entities (actinic keratosis, conjunctival intraepithelial neoplasia, and squamous cell carcinoma). Melanocytic tumors are also compromised of benign lesions (nevus) and malignant lesions (melanoma). Stromal lesions include vascular, fibrous, xanthomatous, neural, myxoid, leukemic, and lymphoproliferative. It is also important to be aware of non-neoplastic conditions simulating tumors including epithelial inclusion cysts, inflammatory lesions, foreign bodies, and granulomas. (Table 32.1).

Specific tumors

Hamartomas

Hamartomas are congenital overgrowths of normal tissue at their naturally occurring site. The most common are hemangiomas including infantile periocular (capillary) and cavernous. Infantile hemangioma is the more common and occurs as an isolated conjunctival lesion or may be continuous with an orbital or lid lesion. They appear as soft, red, vascular nodules shortly after birth and may grow for the first year and then involute years later[4] (Fig. 32.1). Most of these isolated conjunctival capillary hemangiomas do not need treatment. However, they often involute more rapidly if treated with topical timolol. Cavernous hemangiomas are typically larger and appear as multiloculated vascular masses. Because these do not regress spontaneously and may cause recurrent spontaneous subconjunctival hemorrhages, excision is the best treatment.

Table 32.1 Types of conjunctival tumors

Classification	Subtypes
Epithelial	Melanocytic; non-melanocytic
Stromal	Vascular; fibrous
	Xanthomatous; neural
	Myxoid; leukemic
	Lymphoproliferative
Congenital	
Simulating lesions	



Fig. 32.1 Conjunctival capillary hemangioma. This lesion was prone to repeated subconjunctival hemorrhages.

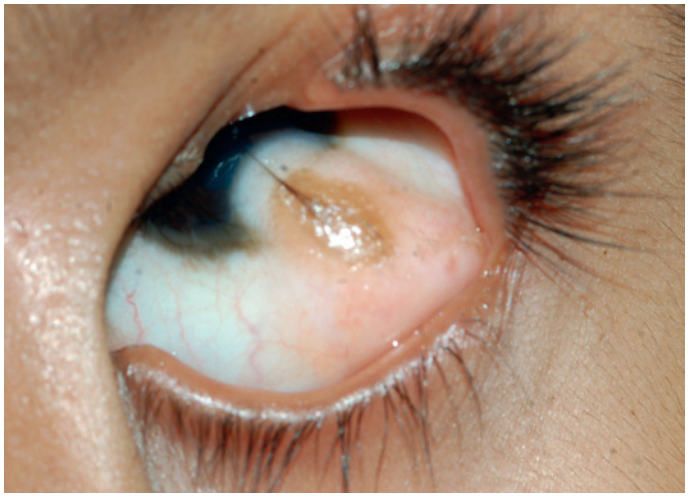


Fig. 32.2 Dermoid. A temporal limbal dermoid in a 5-year-old boy causing significant astigmatism. Hair growth is seen on the surface.

Choristomas

Choristomas are congenital tumors consisting of displaced tissue elements in an abnormal location. The most common conjunctival choristomas are dermoids and lipodermoids. Conjunctival dermoids are congenital, well-circumscribed, firm yellow-white solid masses with a predilection for the limbus. The surface can be smooth or coarse, with keratin and even hair formation (Fig. 32.2). They may appear in isolation or as part of Goldenhar syndrome, which is also known as oculoauriculovertebral dysplasia, in which structures derived from the first branchial arch are affected resulting in preauricular appendages, deafness, and vertebral anomalies.[5] Dermoids may be observed if asymptomatic, or excised if causing disfigurement or significant astigmatism. Lipodermoids (dermolipomas) are soft, mobile, yellow-colored lesions arising at the lateral canthal region and are typically observed (Fig. 32.3).

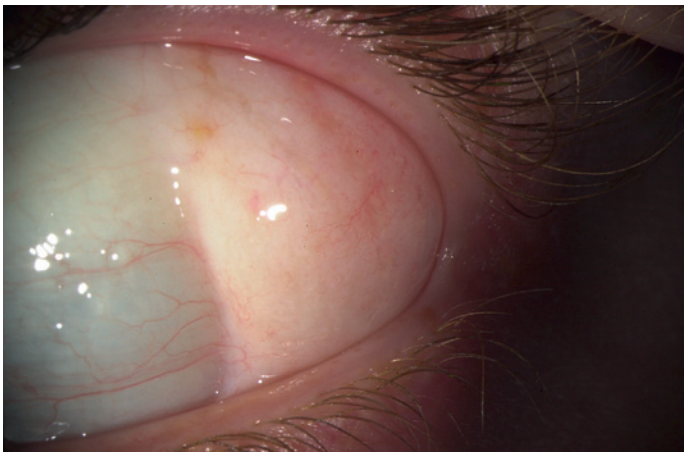


Fig. 32.3 Lipodermoid. Soft, mobile, yellow-white lesion arising at the lateral canthal region.

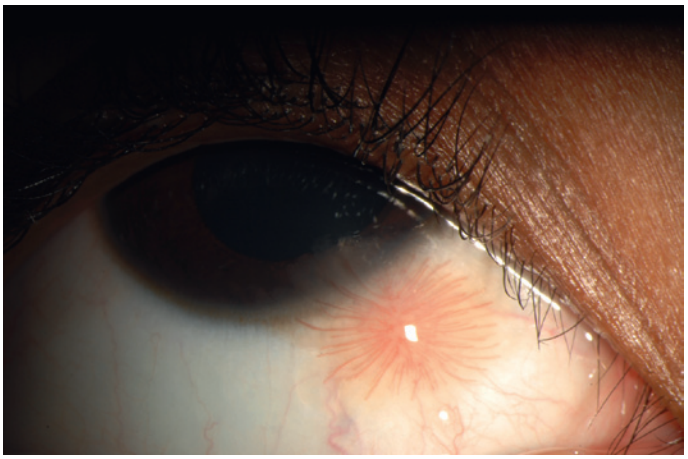


Fig. 32.4 Conjunctival papilloma. Sessile papilloma in a 5-year-old girl.

Papilloma

Squamous papillomas are benign tumors that appear as pink vascular fronds of tissue arranged in a sessile or pedunculated configuration, often with corkscrew vessels (Fig. 32.4). In children, papillomas have been documented to be associated with human papilloma virus (HPV; mostly subtypes 6, 11, and 16).[6] They are often located in the inferior fornix or bulbar conjunctiva. They are typically solitary, but can be bilateral and multiple. Small lesions may be observed for spontaneous resolution, but larger tumors require excision with a no-touch technique in order to prevent the spread of the papilloma-related virus.[7] Cryotherapy should be applied in a double freeze–thaw fashion to the surrounding conjunctival edges and the base of the tumor in order to reduce the risk of recurrence.[8]



Fig. 32.5 Conjunctival papillomas. Multiple pedunculated papillomas in a 5-year-old. These recurred after initial excision and were then treated with excision, cryotherapy, and interferon alpha-2b. Three years later she has had no recurrence.

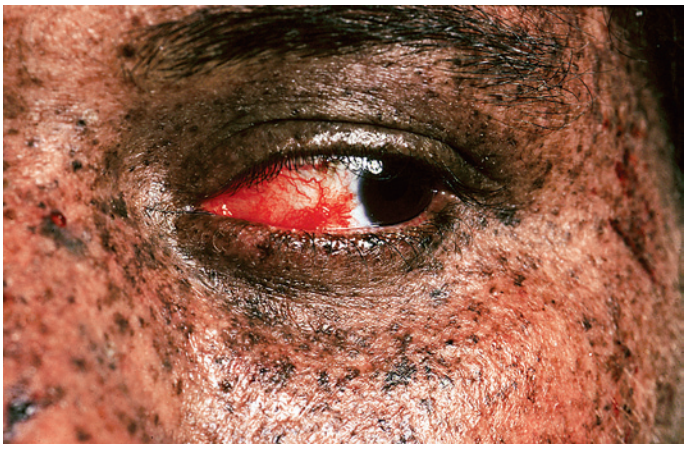


Fig. 32.6 Xeroderma pigmentosa. Widespread skin pigmentation can be seen in this girl of Indian origin.

Conjunctival papillomas tend to recur and, for these cases, topical or subconjunctival interferon alpha-2b may be used to prevent recurrence (Fig. 32.5).[9, 10] Other treatment options include mitomycin C, oral cimetidine, and carbon dioxide laser vaporation.[11–13]

A conjunctival papilloma in an infant or young child could result from acquisition of HPV during a vaginal delivery. The mother should be notified of this and referred for evaluation and treatment if necessary. If dysplasia is noted histopathologically, then the term "premalignant" is often used. If no dysplasia is noted, then the papilloma is benign.

Keratoacanthoma

Keratoacanthomas appear as solitary, gelatinous or leukoplakic, grayish-white nodules that grow rapidly over 3–4 weeks. Although benign, these lesions clinically may simulate squamous cell carcinoma and therefore the treatment is surgical excision with cryotherapy.

Hereditary benign intraepithelial dyskeratosis

This is a rare, benign, autosomal dominant condition that originated in North Carolina among an isolated number of Caucasians, African Americans, and Native Americans.[8] It is characterized by bilateral elevated fleshy plaques in the interpalpebral conjunctiva. Patients appear to have a chronic red eye and may complain of foreign body sensation, photophobia, and tearing. On histopathologic examination, there is acanthosis, dyskeratosis on the surface and deep epithelium, and severe chronic inflammation in the stroma.

Conjunctival intraepithelial neoplasia/ Squamous cell carcinoma

These entities encompass malignancies of the surface epithelial cells. Dysplasia is a term used to define various degrees of cellular atypia that involve various thicknesses of the epithelium starting with the basal layer outwards. Carcinoma *in situ* represents total loss of normal cellular maturation affecting the full thickness of the epithelium but the basement membrane is intact. Invasive squamous cell carcinoma shows features similar to carcinoma *in situ*, but the basement membrane is violated and the subepithelial tissue is invaded. Clinically, these lesions can be difficult to differentiate between one another and histopathologic examination is necessary. They typically occur in the interpalpebral fissure near the limbus, but may appear anywhere on the conjunctiva. They may appear papillary, gelatinous, leukoplakic, nodular, and, in some cases, pigmented. Most cases appear in adults, but it is important to remember that children who are medically immunosuppressed, who are infected with human immunodeficiency virus, or who have underlying DNA-repair abnormalities like xeroderma pigmentosa are at a higher risk of developing conjunctival squamous cell carcinoma.

Xeroderma pigmentosa is a genetic disorder inherited as an autosomal recessive disease. It is due to mutations of one of eight genes that are involved in nucleotide-excision repair. Ultraviolet light causes DNA damage to everyone's cells, but people without this mutation are able to repair their DNA. Xeroderma pigmentosa patients incur an accumulation of DNA damage leading to chromosomal mutations and cell death resulting in neoplasia.[14] They are at an increased risk for malignant lesions in the sun-exposed skin, ocular structures, and mucocutaneous areas. There is a 1000-fold increased risk of developing cutaneous malignancies.[15] Ophthalmic complications are present in about 20% of cases and may include eyelid pigmentary changes, keratitis, eyelid basal cell carcinoma, squamous cell carcinoma, and melanoma (Fig. 32.6).[16] Conjunctival involvement takes the form of xerosis, pigmentation, squamous cell carcinoma, and melanoma, which can result in corneal changes consisting of exposure keratitis, band keratopathy, vascularization, and even perforation (Fig. 32.7). Treatment includes excision with double freeze–thaw cryotherapy. If the cornea is involved with neoplasia, epitheliectomy with alcohol is recommended. Extensive tumors or those that are recurrent may be successfully managed with adjuvant topical and subconjunctival interferon alpha-2b.

Ocular melanocytosis

While this condition does not affect the conjunctiva, it is included in this section because it may be mistaken for a pigmented conjunctival lesion and should be considered in the differential diagnosis. This is a congenital pigmentary

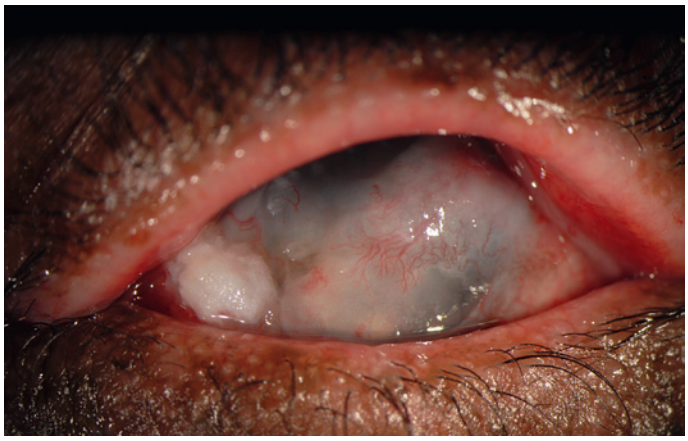


Fig. 32.7 Xeroderma pigmentosa. Conjunctival dysplasia in a young male. His other orbit was exenterated for squamous cell carcinoma 5 years previously as a teenager.

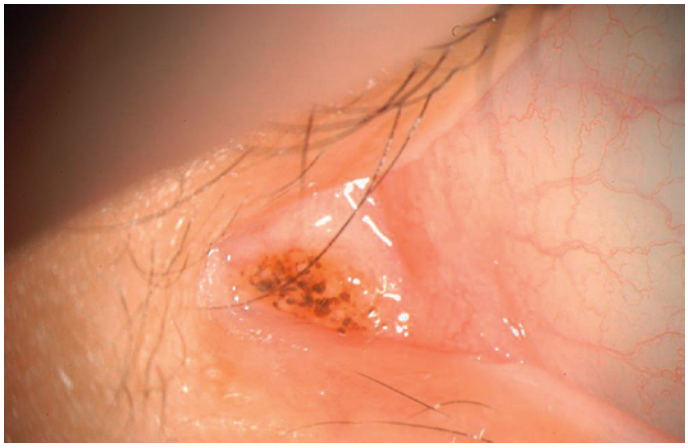


Fig. 32.8 Conjunctival nevus. A pigmented conjunctival nevus in the caruncle. Note the presence of clear cysts.

condition of the periocular skin, sclera, orbit, meninges, and soft palate. The uvea may also show a diffuse darker degree of pigmentation compared to the other eye. There is a 1/400 risk of developing uveal melanoma but no extra risk for conjunctival melanoma.[17] A recent study showed that the risk of metastasis from uveal melanoma is higher if the patient has a ocular melanocytosis.[18]

Nevus

Conjunctival nevus is the most common melanocytic tumor. In a clinical series of 262 pediatric patients with conjunctival tumors, 65% were found to be melanocytic.[1] A nevus typically becomes clinically apparent in the first two decades of life as a discrete, variably pigmented, elevated mass. Most are located in the interpalpebral bulbar conjunctiva near the limbus and rarely involve the cornea. They may become darker or lighter, but usually do not change after adolescence. A key feature of a nevus is the presence of clear cysts within the lesion, found in 65% of cases (Fig. 32.8).[1] While most are pigmented, 16% are completely non-pigmented (Fig. 32.9).[1] Histopathologically, nevi can be classified as junctional, compound, or subepithelial. In junctional nevi, the melanocytes are restricted to the basilar epithelium. Compound nevi extend into the substantia propria,

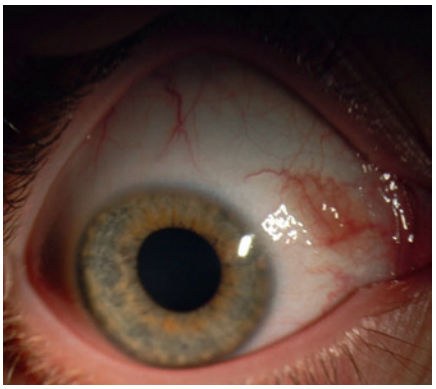


Fig. 32.9 Conjunctival nevus. A non-pigmented conjunctival nevus in a 3-year-old. The lesion was excised and the histopathology confirmed the diagnosis.

but maintain an intraepithelial component. The subepithelial type loses its connection with the basilar epithelium and is confined within the substantia propria.

The overall risk of malignant transformation is about 1%.[19] The management is periodic observation with photographic comparison. Indications for complete excision include documented growth, recent color change, cosmetic concerns, clinical suspicion of melanoma, interference with contact lenses, and recurrence of an excised lesion. At the time of excision, the lesion is completely removed. Cryotherapy may be applied in a double freeze–thaw fashion to the conjunctival margins to help prevent a recurrence.[8]

Melanoma

Conjunctival melanoma typically arises in middle-aged to older adults but rarely can occur in children. Conditions such as dysplastic nevus syndrome, xeroderma pigmentosa, and neurofibromatosis increase the risk of children developing a malignant melanoma. Clinically, the melanoma can appear pigmented or non-pigmented, yellow or pink, and may show rapid growth with feeder vessels. Involvement of Tenon's capsule and the sclera may restrict the mobility of the tumor over the ocular surface. It is important to check the preauricular and submandibular lymph nodes for enlargement. The primary treatment of conjunctival melanoma is excision of the entire tumor with a surgical margin of at least 3 mm. When deep limbal and scleral involvement is suspected, scleroconjuntivectomy should be considered. Cryotherapy in a double freeze–thaw fashion should be applied to the base and the conjunctival margins.[20]

Lymphangioma

Conjunctival lymphangiomas are rare and are hamartomatous proliferations lined by endothelium. There is no known hereditary or systemic association. They can occur in isolation, but more often represent the superficial component of an orbital lymphangioma. They typically appear in the first decade of life and present as clear vessels with variable sized clear fluid-filled cysts, either alone or interspersed amongst blood-filled hemangioma vessels. They have been referred to as "chocolate cysts." They may increase in size with Valsalva maneuvers. The treatment is often difficult because surgical resection or radiotherapy may not completely remove the mass and therefore observation may be preferred. Carbon dioxide laser and brachytherapy have been used to treat conjunctival lymphangiomas with partial success.[21–22]

Rhabdomyosarcoma

Rhabdomyosarcoma is the most common malignant orbital tumor in children (see Chapter 24). Conjunctiva is the source of the primary tumor in around 12% of patients with orbital rhabdomyosarcoma.[23] The superior and superonasal areas are commonly involved. They present as light-brown colored elevated lesions and may be confused with focal areas of inflammation, papillomas, capillary hemangiomas, or conjunctival cysts. Lack of response to medical management and rapid progression is a characteristic feature that should alert the clinician. Histopathologically, this tumor comprises loosely coherent spindle cells in a myxoid stroma. Magnetic resonance imaging is needed to reveal orbital extension if present.

Kaposi sarcoma

The diagnosis of Kaposi sarcoma is made less frequently now that there are more effective treatments for acquired immunodeficiency disorder (AIDS) in medically advanced countries. This tumor is rare in children but can be found in those with AIDS or those who are immunosuppressed while receiving treatment for leukemia. Clinically, this sarcoma appears as one or more painless, reddish vascular masses that resemble hemorrhagic conjunctivitis. Histopathology shows a malignant tumor composed of spindle-shaped cells with elongated oval nuclei, well-formed capillary channels, and vascular slits containing erythrocytes, but without an endothelial lining. They have been shown to respond to chemotherapy and low-dose radiotherapy.[24] Surgical excision may be appropriate for small lesions.

Xanthogranuloma

Conjunctival xanthogranulomas may appear in children as a manifestation of juvenile xanthogranuloma. This is an idiopathic cutaneous condition that results in the presence of painless, pink skin papules with spontaneous resolution, generally in young children under the age of 2 years. Conjunctival involvement is very rare and these lesions usually appear as a solitary, elevated round orange-pink stromal mass, typically near the corneoscleral limbus (Fig. 32.10). If the classic skin lesions are noted or the patient has a known diagnosis of juvenile granulomatosis, the conjunctival lesion may be observed for spontaneous resolution or treated with topical steroids.[8] If the diagnosis has not been established, excisional biopsy is recommended, looking for typical findings of histiocytes and Touton's giant cells in addition to lymphocytes, plasma cells, and eosinophils.

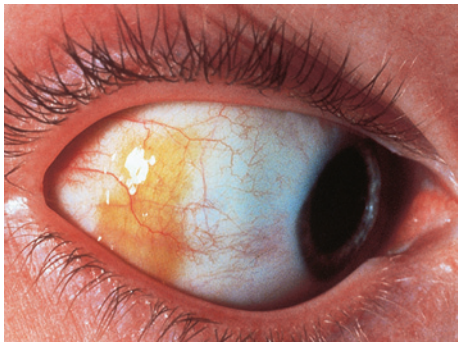


Fig. 32.10 Juvenile xanthogranuloma. A slowly enlarging yellowish lesion was noted in the conjunctiva of this 15-year-old boy. Histopathology showed Touton's giant cells, characteristic of juvenile xanthogranuloma. *(Patient of the University of British Columbia)*

Lymphoid tumors

Lymphoid tumors can occur in the conjunctiva as isolated tumors or as a manifestation of systemic lymphoma.[25] This is more common in adults and rarely occurs in children. They typically appear as a diffuse, slightly elevated, pink mass resembling smoked salmon, frequently referred to as a "salmon patch." Clinically, it is not possible to differentiate benign lymphoid tumors such as reactive lymphoid hyperplasia and atypical lymphoid hyperplasia from the malignant variant, conjunctival lymphoma. Therefore, a biopsy is needed to confirm the diagnosis and a systemic evaluation should be performed. The lymphoid tumors found in children are typically reactive or atypical lymphoid hyperplasia and are not associated with systemic lymphoma (Fig. 32.11).[1] Treatment includes chemotherapy if the patient has systemic lymphoma. If the lesion is localized to the conjunctiva and is found to be reactive lymphoid hyperplasia, topical steroid may help with resolution. Other options include external beam radiation, excision and cryotherapy, and local interferon injections.[8]

Leukemic tumors

Leukemic infiltrates of the eye are most commonly found in the choroid and retina but may occur in the conjunctiva. Conjunctival involvement of leukemia generally manifests as hemorrhages from anemia and thrombocytopenia rather than leukemic infiltration.[26] However, leukemic infiltration may be the initial sign of disease or of a relapse and therefore early recognition is important. Affected individuals present initially with congestion of the bulbar or the palpebral conjunctiva. In some instances, the conjunctiva may be erythematous and chemotic. The lesions are firm and non-tender and often associated with subconjunctival hemorrhage. Histopathologically, the cells infiltrate all layers of the substantia propia. The infiltration may be diffuse or patchy and typically localized around blood vessels. Treatment of the systemic condition with systemic chemotherapy will usually result in rapid resolution.

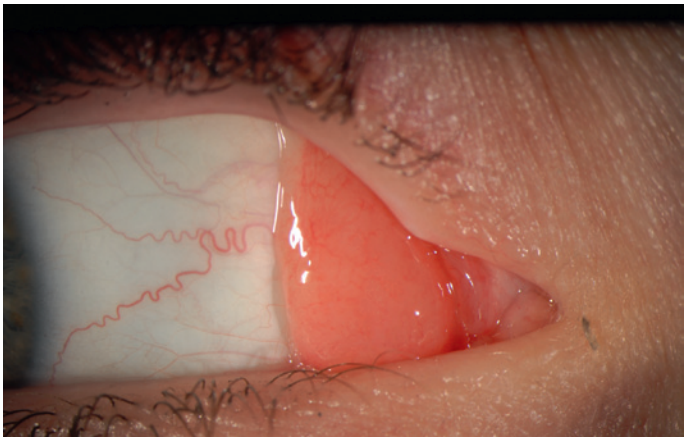


Fig. 32.11 Biopsy of this smooth, pink, "salmon patch" lesion showed atypical lymphoid hyperplasia.



Fig. 32.12 A 5-year-old with a pyogenic granuloma.

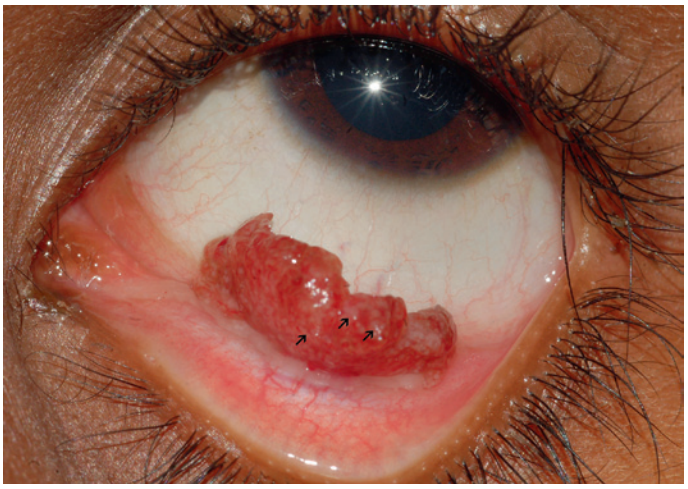


Fig. 32.14 Rhinosporidiosis. Pedunculated irregular granuloma seen in the inferior palpebral conjunctiva. Note the white spherules over the surface of the granuloma. *(Courtesy of Dr Usha Kim, DNB.)*

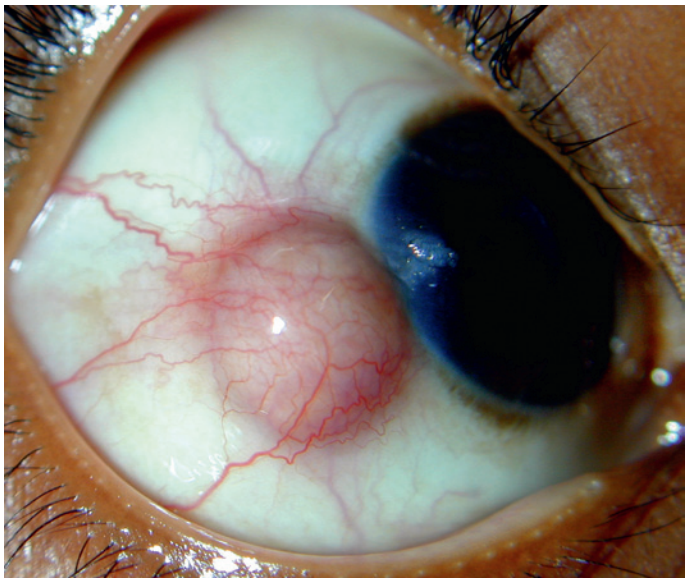


Fig. 32.13 River water (trematode-induced) granuloma. Well-circumscribed, smooth, elevated nodular lesion seen in the bulbar conjunctiva. *(Courtesy of Dr Rathinam, DNB.)*

Non-neoplastic lesions simulating conjunctival tumors

There are a number of non-neoplastic lesions that may be confused with a neoplasm. A pyogenic granuloma is a common condition that can be mistaken for a tumor (Fig. 32.12). A pyogenic granuloma is an exaggerated fibrovascular response following trauma or surgery.[27] The term is a misnomer, as it is neither an infection nor a typical granulomatous reaction, but a granulation tissue formation. Rapid growth may simulate a malignancy. A history of preceding trauma or surgery helps in making the diagnosis. The condition may spontaneously resolute, but some form of treatment is typically necessary. A short course of topical steroids may be attempted, but most will require excisional biopsy.

The presence of a variety of lymphoid cells in the substantia propia serves as a perfect setting for the development of inflammatory granules following some systemic and local disorders. The common systemic diseases that can cause conjunctival granulomas include sarcoidosis,[28] tuberculosis, Parinaud oculoglandular syndrome, Wegener granulomatosis, trematode-induced granulomas[29] (Fig. 32.13), and rhinosporidiosis[30] (Fig. 32.14).

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Anterior segment developmental anomalies including aniridia

Ken K Nischal

Chapter contents

GENE MUTATIONS CAUSING ANTERIOR SEGMENT DEVELOPMENTAL ANOMALIES
GENE EXPRESSION IN THE DEVELOPING ANTERIOR SEGMENT: SITES OF GENE ACTION
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Anterior segment developmental anomalies (ASDA) are rare but potentially visually devastating. It is important for the pediatric ophthalmologist to be aware of the causes, evaluation, and treatment of these conditions. However, their etiology is just as important, because associated extraocular conditions may need to be treated and the family may need counseling for future pregnancies.

Gene mutations causing anterior segment developmental anomalies

The majority of several disease-causing genes proven to play critical roles in ASDA all encode transcription factors (Table 33.1), which act by regulating the transcription of their downstream target genes. Examples of the commonest transcription factors involved in the etiology of ASDA are PAX6, PITX2, FOXC1, FOXE3, and MAF.[1,2]

Gene expression in the developing anterior segment: sites of gene action

The patterns of expression of genes whose mutation causes ASDAs can be considered as three types: those expressed within migrating periocular neural crest cells (*FOXC1*, *PITX2*); those expressed only within the developing lens (*FOXE3*, *MAF*); and those expressed within the whole eye including the lens, of which *PAX6* is the only example.[2]

The lens plays an essential role in the induction of anterior segment differentiation.[3] Two genes are implicated in causing ASDA by affecting the inductive properties of the lens. *MAF* and *FOXE3* mutation both cause ASDA with cataracts. Recent work has shown that homozygous mutations in *FOXE3* result in primary congenital aphakia.[4]

Clinical conditions due to anterior segment developmental anomalies

ASDAs may be considered in terms of their embryologic origin. Therefore they may be:

- of neural crest cell origin;
- of ectodermal origin;
- of global origin.

Anterior segment developmental anomalies of neural crest cell origin

Posterior embryotoxon

This prominent, anteriorly displaced Schwalbe's line, seen in 8–15% of the normal population appears as a whitish, irregular ridge up to several millimeters from the limbus and is often incomplete (Fig. 33.1). It may be inherited in an autosomal dominant fashion.

Ocular associations may include iris adhesions with or without iris changes such as hypoplasia, pseudopolycoria, or corectopia, in which case it forms part of the spectrum of the Axenfeld–Rieger anomaly or syndrome (Fig. 33.2).

The presence of posterior embryotoxon in a jaundiced neonate is suggestive of the autosomal dominant condition Alagille syndrome (arteriohepatic dysplasia),[5] which is characterized by intrahepatic cholestasis, peripheral pulmonary artery stenosis, peculiar facies, and butterfly vertebral arch defects. Posterior embryotoxon is seen in 90% of all cases and 77% of cases also have iris strands.[5]

Since isolated posterior embryotoxon is not associated with glaucoma, there is no need for regular review unless

Table 33.1 Genes essential for the normal development of the anterior segment and whose mutation causes ASDAs

Human gene	Type	Chromosome location	Human disease	OMIM number
CYP1B1	Enzyme	2p22	Congenital glaucoma	601771
EYA1	Transcription factor	8q13	Branchiootorenal dysplasia ASDA	601653
FOXC1	Transcription factor	6p25	ASDA (iridogoniodysgenesis anomaly, iris hypoplasia, Axenfeld–Rieger anomaly, Axenfeld–Rieger syndrome) Congenital glaucoma	601090
FOXE3	Transcription factor	1p23	ASDA and cataracts Peters' anomaly	601094
LMX1B	Transcription factor	9q34	Nail-patella syndrome	602575
MAF	Transcription factor	16q23	ASDA and cataracts	177075
PAX6	Transcription factor	11p13	Aniridia Peters' anomaly Cataracts ASDA Keratitis Optic nerve hypoplasia and glaucoma Foveal hypoplasia	106210
PITX2	Transcription factor	4q25	ASDA (Axenfeld–Rieger syndrome, iris hypoplasia, iridogoniodysgenesis) Glaucoma	601542
PITX3	Transcription factor	10q25	ASDA and cataracts	602669
LTBP2	Latent TGFβ-binding protein 2	14q24.3	Megalocornea, microspherophakia, congenital glaucoma	602091
COL4A1	Collagen, type IV, alpha-1	13q34	Cataract/ASDA	120130
B3GALTL	UDP-Gal:beta-GlcNAc beta-1,3-galactosyltransferase-like	13q12.3	Peters-plus syndrome	610308
KERA	Keratan sulfate proteoglycan	12q21.33	Corneal plana	603228
PXDN	Extracellular matrix-associated protein, peroxidasin	2q25.3	ASDA cataracts microcornea	605158
SLC4A11	Sodium borate cotransporter	20p13–p12	Corneal dystrophy, Fuchs endothelial, 4	610206
JAG1	Ligand of the Notch Receptor	20p12	Alagille syndrome with posterior embryotoxon, iris hypoplasia, small corneal diameter, iridocorneal synechiae, and corectopia	601920
LAMB2	Extracellular matrix protein, laminin	3p21	Pierson syndrome with microcoria or ASDA	15032
BMP4	Regulatory molecule	14q22–q23	ASDA with or without anophthalmia/microphthalmia	112262

other members of the family have features of Axenfeld–Rieger anomaly/syndrome.

Axenfeld–Rieger anomaly and syndrome

Axenfeld–Rieger syndrome (ARS) has ocular and non-ocular features.[6–9] The ocular features consist of posterior embryotoxon with iris strands attached, some of which may be very broad and thick and others thread-like. Historically, if these were the only findings, the term Axenfeld anomaly was used. If, in addition, iris defects were present, then this was termed Rieger anomaly. Axenfeld–Rieger anomaly (ARA) now encompasses both. Iris findings range from stromal hypoplasia, pseudopolycoria, corectopia (displaced anomalous pupil; Figs 33.2–33.4), and ectropion uveae. Occasionally the iris may be almost completely absent – a severe form of hypoplasia. It is important to differentiate this from PAX6-related aniridia; the lack of foveal hypoplasia, polar lens opacities, nystagmus, and sometimes corneal pannus gives the clue to the diagnosis of ARA. The anterior chamber angle is usually open though there may be a high insertion of the iris into the posterior portion of the trabecular meshwork. Occasionally the pupil corectopia is severe enough to warrant surgical pupilloplasty. The pupil may still become progressively more eccentric over years despite surgery.

Angle and iris changes are usually stable. Glaucoma develops in 50–60% of patients with ARS, usually manifesting itself

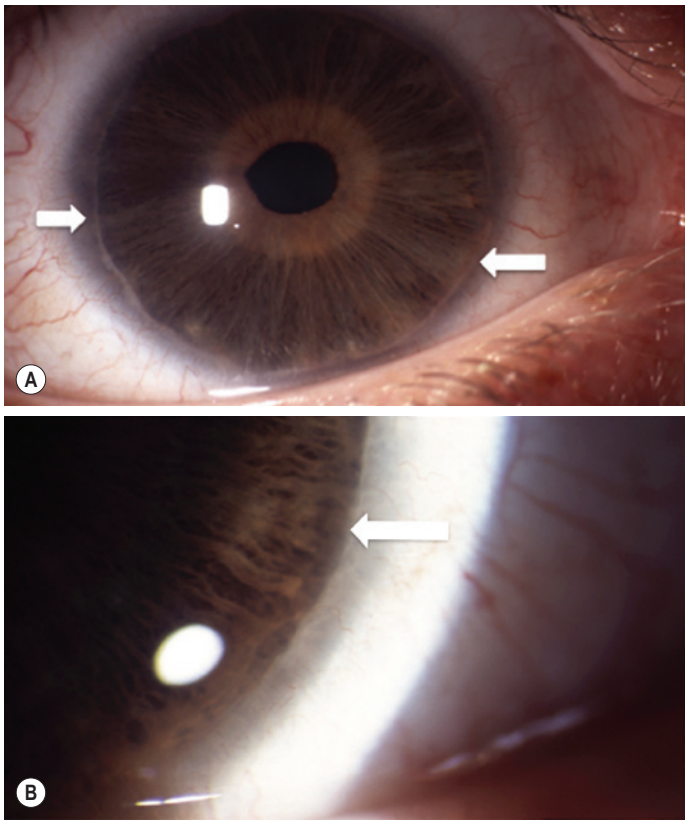


Fig. 33.1 Posterior embryotoxon. (A) Marked posterior embryotoxon with iris strands attached (Axenfeld–Rieger anomaly), white arrows. (B) Posterior embryotoxon with no associated ocular anomalies is a common but subtle anomaly seen on slit-lamp examination.

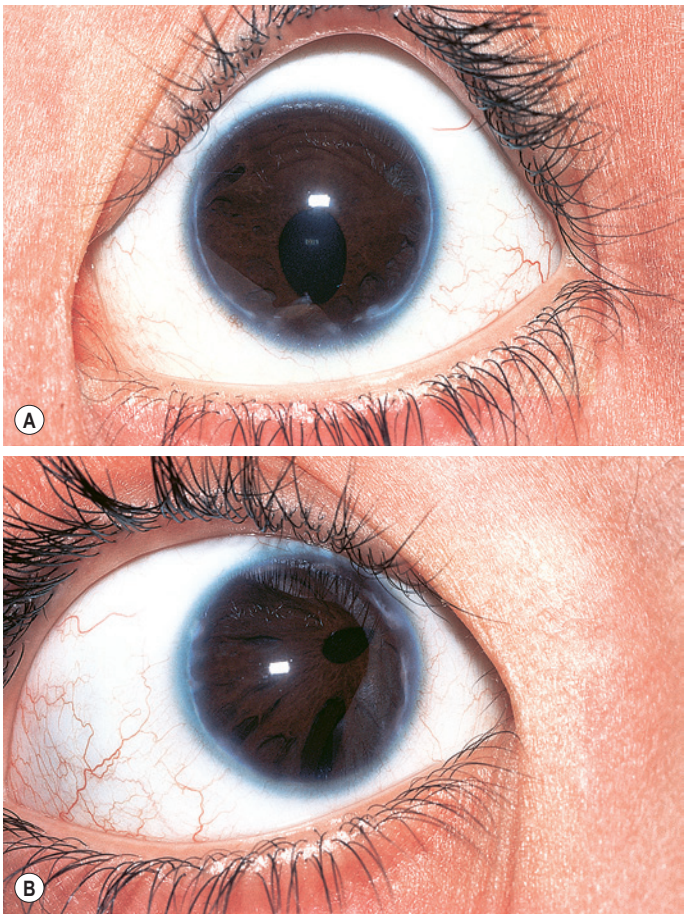


Fig. 33.2 Axenfeld–Rieger anomaly. There is iris hypoplasia, posterior embryotoxon, pseudopolycoria (A), and corectopia with the pupil drawn peripherally (B).

in childhood or young adulthood. Incomplete development of the trabecular meshwork and Schlemm's canal is thought to result from development arrest occurring during the third trimester, causing obstruction to aqueous outflow.[6–9] Other ocular features may include strabismus, cataracts, limbal dermoids, retinal detachment, macular degeneration, chorioretinal colobomas, and choroidal and optic nerve head hypoplasia.

Familial glaucoma iridogoniodysplasia has been described in one pedigree and entails marked iris hypoplasia, iridocorneal angle anomalies, and, frequently, glaucoma.[7] Iridogoniodysgenesis anomaly (IGDA) has been described as iridocorneal angle anomalies, iris stromal hypoplasia, and glaucoma in 50% of cases.[7] Iridogoniodysgenesis syndrome (IGDS) is a rare condition in which iris hypoplasia and iridocorneal angle anomalies are associated with non-ocular features such as jaw and dental abnormalities.[6–9] Both IGDA and IGDS are caused by mutations in *PITX2* and *FOXC1*.

The characteristic non-ocular features of ARS are maxillary hypoplasia, mild prognathism, hypodontia (decreased but evenly spaced teeth), anodontia/oligodontia (focal absence of teeth), microdontia (reduction in crown size), cone-shaped teeth (Fig. 33.5), and excess periumbilical skin (Fig. 33.6) with or without hernia. Hypertelorism, telecanthus, and a broad flat nose have also been described.[6–9] Other systemic features may include growth hormone deficiency and short stature, heart defects, middle ear deafness, mental deficiency, cerebellar anomalies (*FOXC1* mutations), oculocutaneous albinism,

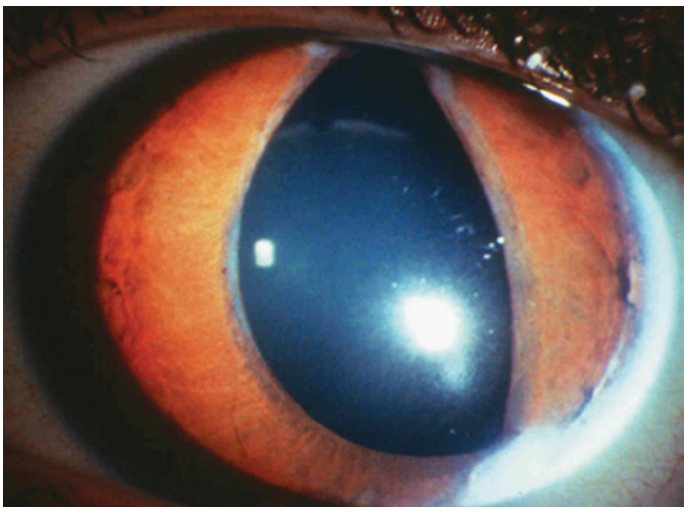


Fig. 33.3 Axenfeld–Rieger syndrome. Marked corectopia with pupil distortion and posterior embryotoxon.

hypospadias, abnormal ears, and, in one pedigree, myotonic dystrophy and Peters' anomaly.[6–9]

Management depends on the presenting complication of the structural anomalies. Some authors suggest that every child with ARS should get a magnetic resonance imaging (MRI) scan

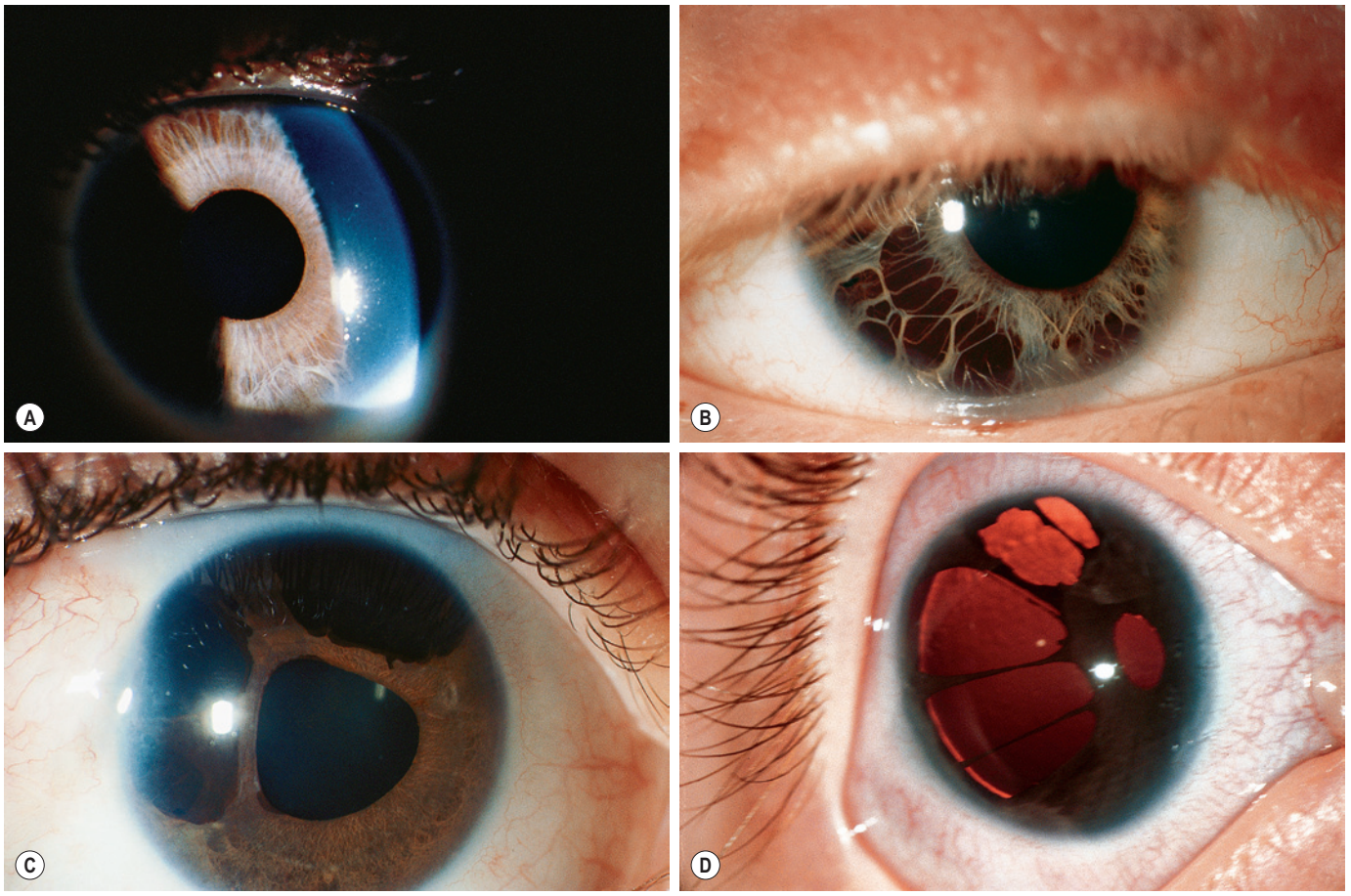


Fig. 33.4 Iris hypoplasia. (A) Iris hypoplasia showing the loss of stroma giving rise to prominence of the sphincter muscle. (B) Marked stromal hypoplasia revealing the posterior pigmented epithelium. (C) Marked stromal hypoplasia giving rise to pseudopolycoria in Axenfeld–Rieger anomaly (ARA). (D) Pseudopolycoria in ARA seen in retroillumination.

given the increased incidence of intracranial anomalies found in PITX2- or FOXC1-positive ARS.

Occasionally there is severe pupillary stenosis for which a large pupilloplasty is required, which may be complicated by lens damage and/or late contraction. Severe corectopia without severe stenosis can be adequately treated with occlusion therapy of the less affected eye. Sometimes the pupil is very large, irregular and, distorted (see Fig. 33.5).

Medical therapy should be used for glaucoma prior to surgical intervention with the exception of infantile cases, where goniotomy/trabeculotomy is first choice of treatment. Miotics should be used with caution, since they may cause trabecular meshwork collapse, with a reduction in aqueous outflow.

Trabeculectomy with antimetabolite augmentation appears to be the procedure of choice for most patients with glaucoma secondary to ARS, especially in older children. The use of cycloablation should be considered for children with limited cooperation where a drainage procedure would be unsuitable. Draining procedures other than trabeculectomy include the use of drainage tubes with or without antimetabolite.[10]

Congenital iris ectropion

This is a rare, usually unilateral, condition in which there is a congenital, non-progressive, non-tractional hyperplasia of the posterior pigment iris epithelium onto the anterior surface of the iris (ectropion).[11] The child is often thought to have mydriasis and anisocoria because of the dark color of the posterior pigment epithelium. The ectropion may be circumferential (Fig. 33.7) or sectorial. Other ocular features include iris stromal hypoplasia, a high iris insertion into the trabeculum with goniodysgenesis, and secondary glaucoma.

The clinical features are thought to result from an arrest in development with abnormal retention of primordial endothelium, which explains the central iris and angle changes. Although the affected pupil reacts to light and accommodation, it may not do so at the same speed as the unaffected eye.[11] Glaucoma occurs in the majority of these patients, usually between early childhood and puberty. Neurofibromatosis type 1 and Prader–Willi syndrome may be associated.

Management of the glaucoma can be difficult, with medical therapy often being unsuccessful; augmented trabeculectomy is often the surgical operation of choice.[11] Goniotomy is usually unsuccessful in these cases and if trabeculectomy fails, a drainage tube is often needed. Some authors prefer to use the drainage tube as the first line of treatment if medical management fails. Recently success with trabeculotomy has been reported in this condition.[12]

Congenital mydriasis

Congenital fixed dilated pupils (congenital mydriasis) is due to hypoplasia of the iris muscles, with absence of iris between the collarette and pupillary border resulting in a scalloped

pupillary margin. Often there are wisps of persistent pupillary membrane. This condition has been shown to be part of a multisystem smooth muscle cell dysfunction syndrome with associated moyamoya-like cerebrovascular disease, patent ductus arteriosus, thoracic aorta aneurysm, and other dysfunction of smooth muscle cells throughout the body. As of now, every affected individual has been shown to have a p.R179H heterozygous mutation in the *ACTA2* gene (see Chapter 39).[13]



Fig. 33.5 Axenfeld–Rieger syndrome (ARS). (A) Widely spaced teeth, some conical; partial anodontia and caries. (B) Dental X-ray of a patient with ARS.

Congenital hereditary endothelial dystrophy (CHED)

Please see Chapter 35, but it is noteworthy that there is only one recognized form of CHED now, with clear evidence suggesting that all previous dystrophies referred to as CHED1 were, in fact, posterior polymorphous dystrophy.[14]

Posterior polymorphous dystrophy

Please see Chapter 35.

Primary congenital glaucoma

Please see Chapter 38.

ICE syndromes

The iridocorneal endothelial (ICE) syndromes, thought to be due to a primary neural crest cell abnormality, include



Fig. 33.6 Axenfeld–Rieger syndrome (ARS). Excess periumbilical skin in ARS.

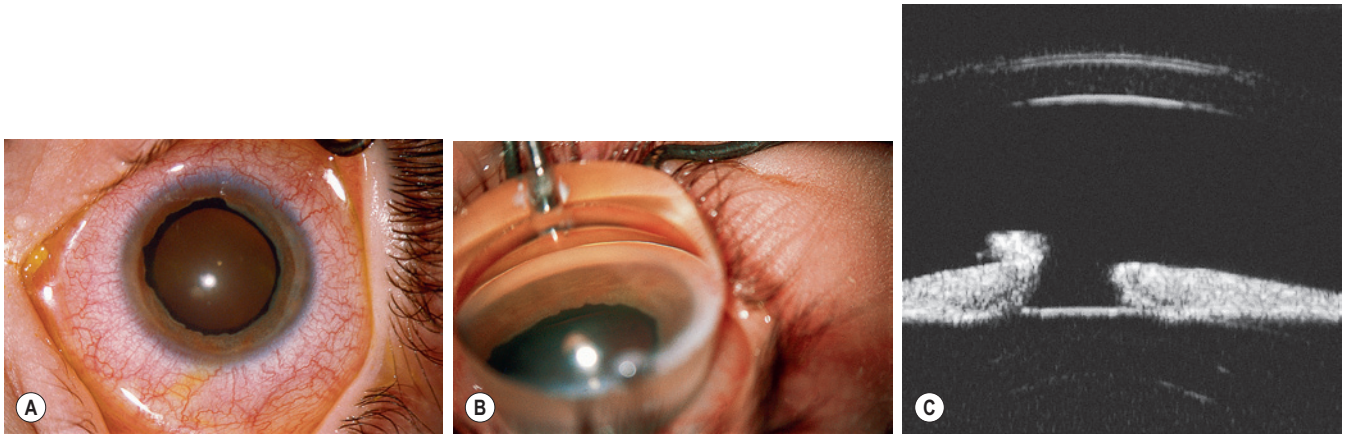


Fig. 33.7 Congenital ectropion uveae. (A) Ectropion uveae, shown as a wide, irregular, dark-brown margin to the pupil in a child with glaucoma. (B) Gonioscopic view showing high iris insertion. (C) High-frequency ultrasound image of a child with congenital iris ectropion. Note the frill of posterior pigment epithelium displaced anteriorly.

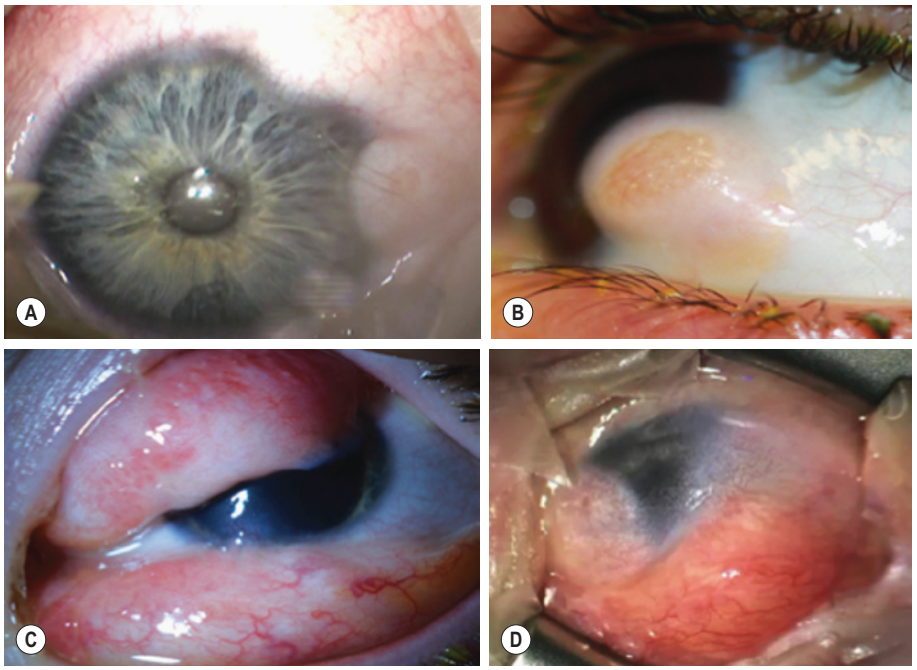


Fig. 33.8 Composite showing variations of limbal dermoids that can be isolated or associated with Goldenhar syndrome (A,B and C); and extensive corneal dermoids seen in encephalocraniocutaneous syndrome (D).

progressive essential iris atrophy, Chandler syndrome, and the iris-nevus syndrome (also known as Cogan–Reese syndrome).[15]

These rare syndromes are even rarer in children, and in fact the youngest reported case is in a 16-year-old. Descriptions of the trabecular meshwork in this 16-year-old with ICE syndrome show collapsed trabecular beams and decreased intertrabecular spaces.[16]

These disorders are unilateral; females are affected more frequently than males and they almost exclusively affect in Caucasians. Specular microscopy almost always reveals mild corneal and iris abnormalities in the "unaffected" eye.

Specular microscopy studies[15] of early cases of ICE syndrome suggest that a subpopulation of corneal endothelial cells are congenitally abnormal and subsequently slowly migrate/proliferate, resulting in a delayed onset of symptoms or diagnosis. These cells may migrate over the angle and onto the iris to cause glaucoma and peripheral anterior synechiae. While the condition can look like Axenfeld–Rieger anomaly (corectopia, iris ectropion, pseudopolycoria, peripheral anterior synechiae, and glaucoma) the conditions can be distinguished by the unilaterality of ICE syndromes and the progressive nature of the ocular features. The cornea can appear normal in this condition but the endothelium may appear similar to that of Fuchs dystrophy.

Iris-nevus syndrome consists of iris changes either of a nodular type or a flattish, pigmented type. These lesions may be associated with varying degrees of iris atrophy and/or corneal endothelial changes.[15–16] Older patients present with visual disturbance, whereas younger ones usually present due to the finding of pupil disturbance, pseudopolycoria, or pigmentary change of the iris.

Management is purely of any glaucoma that may occur in the first instance. Children are unlikely to require corneal grafting, but may do so in their adult lives.[17] Glaucoma management should be attempted initially with aqueous production-suppressing topical treatment, but filtering surgery may be needed. Usually antimetabolite augmented trabeculectomy is favored, but some authors also advocate the use of drainage tubes.

Anterior segment developmental anomalies of ectodermal origin

The two main conditions in this category are limbal and corneal dermoids, which may be associated with Goldenhar syndrome with up to 30% of patients being affected[18,19] (Fig. 33.8 and see Chapter 28). In addition to the systemic association of Goldenhar (in which case the reader is forewarned to check the child's corneal sensation, as hypoesthesia can be seen in Goldenhar syndrome), there is also linear sebaceous nevus syndrome (also known as encephalocraniocutaneous syndrome). The dermoids here are usually more flat and more extensive than those usually seen in Goldenhar. The clue is that the child often has areas of waxy alopecia on the same side as the affected eye. An MRI scan is important because there can be intracranial abnormalities predisposing to seizures.[19]

One further type of corneal dermoid is described as flat and reticular. This is pathognomonic almost for trisomy 8 mosaicism.[19,20] This sign is so important that if the evaluation for trisomy 8 mosaicism returns as negative, the laboratory doing the test must be asked to repeat the test but with a greater number of cells tested for the trisomy 8 anomaly (200 cells instead of the routine 50).

Anterior segment developmental anomalies of a global origin

The anomalies in this category include megalocornea, microcornea, aniridia, autosomal dominant keratitis, Peters' anomaly, cornea plana, sclerocornea, microphthalmos, and

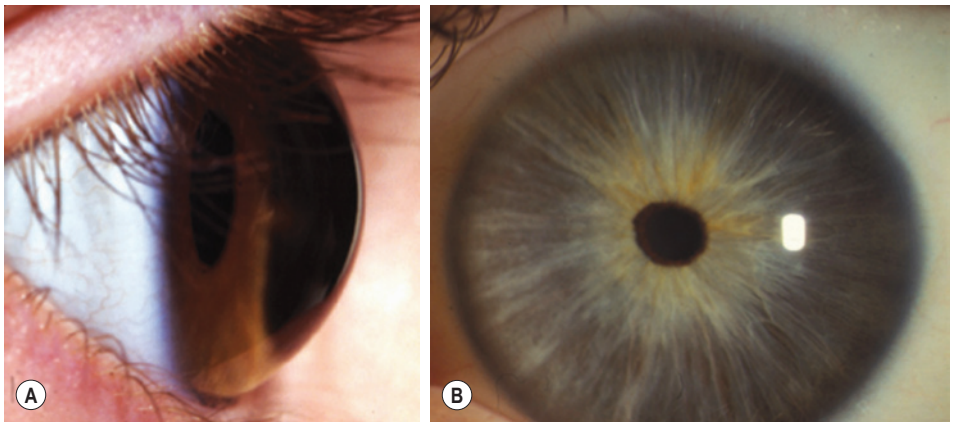


Fig. 33.9 Congenital megalocornea. The horizontal corneal diameter is 13.5 mm (B), and the anterior chamber is deep as seen in (A). In (A) it is possible to view the iridocorneal angle without a gonioscope.

anophthalmos. Of these, microphthalmos and anophthalmos are discussed in Chapter 18.

Congenital megalocornea

This rare, usually bilateral, condition, thought to be due to defective optic cup growth, results in the cornea growing larger in an attempt to close the gap. Usually inherited as an X-linked recessive trait, mapping to Xq21.3–q22, 90% of patients are males.[21–22] Female carriers may have slightly enlarged corneal diameters. The remaining cases are autosomal dominant or occasionally autosomal recessive. It is a non-progressive corneal enlargement with a horizontal diameter of more than 13 mm, without glaucoma and without Haab striae (Fig. 33.9). Myopia is most commonly seen, often accompanied by with-the-rule astigmatism. Associated ocular features include Krukenberg's spindle, increased pigmentation in the trabecular meshwork, iris stromal hypoplasia with iris transillumination, cataracts, ectopia lentis, mosaic corneal dystrophy, and later-onset glaucoma. This can be difficult to assess because the cornea is usually thinner than it should be centrally, which can result in artificially lower intraocular pressure measurements using applanation tonometry. Reported associations include Alport syndrome, craniosynostosis, dwarfism, Down syndrome, facial hemiatrophy, Marfan syndrome, mucolipidosis type II, Frank–ter Haar syndrome (OMIM 249420), and megalocornea-mental retardation syndrome (also known as Neuhauser syndrome).[21]

Management consists of careful observation for complications such as cataract formation, dislocated lens, and glaucoma. The iris transillumination can result in difficulty in bright light (usually outdoors), and some patients benefit from tinted spectacles. Lagophthalmos can be a problem due to improper closure of the eyelids at night, and a lubricating eye ointment may be used to prevent exposure problems. The lower lid can often turn in and cause irritation and corneal erosions. Lubrication at night is especially helpful. Contact lenses can be considered for children with high astigmatism.

Microcornea

This is an uncommon condition defined as any cornea with a horizontal diameter less than normal for age. It may be the result of overgrowth of the tips of the optic cup and may be inherited in an autosomal dominant or recessive manner. If it is an isolated finding and the rest of the eye is normal, it is called "microcornea," whereas if the anterior segment and the rest of the eye is small, the term is "microphthalmos."

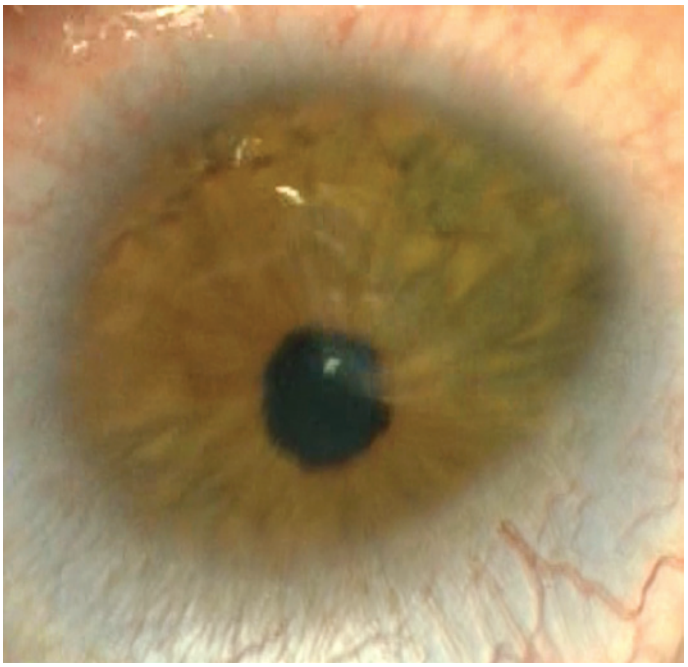


Fig. 33.10 Microcornea in a child with cornea plana.

Microcornea may be unilateral or bilateral and is usually associated with hypermetropia. Associated ocular findings may include cornea plana, iris colobomas, corectopia, cataracts, microphakia, persistent hyperplastic primary vitreous, retinopathy of prematurity, angle closure glaucoma, infantile glaucoma, and chronic open angle glaucoma (occurring in up to 20% of patients later in life) (Fig. 33.10).

Systemic associations include Ehlers–Danlos syndrome, Marfan syndrome, Rieger syndrome, Norrie syndrome, trisomy 21, rubella, Turner syndrome, Waardenburg syndrome, acrorenoocular syndrome, microsyndrome, and oculodentodigital syndrome.[23–26]

Visual acuity may be normal if it is an isolated finding and if any refractive error is corrected early to avoid amblyopia but often complex contact lens fitting needs to be considered to give maximum visual rehabilitation (see Fig. 33.18).

Developmental anomalies affecting corneal clarity

The prevalence of congenital corneal opacity (CCO), including Peters' anomaly, "sclerocornea," congenital hereditary endothelial dystrophy (CHED), and posterior polymorphous dystrophy is approximately 3/100,000.[27]

The terminology for neonatal corneal opacities is at best confused and at worst misleading. In a large review of the literature, only five reports used anterior segment imaging of any description to assess the anterior segment in cases of corneal opacity.[20]

This has led to confusion when attempting phenotype–genotype correlation. Recent publications emphasize the use of a classification system that considers corneal opacities to be primary corneal disease or secondary corneal disease (Box 33.1).[19,28]

Peters' anomaly

This is also considered as a secondary corneal opacity to either iridocorneal adhesion or keratolenticular adhesion resulting in central or eccentric, localized, or total corneal opacification (Fig. 33.11). The pathogenesis of Peters' anomaly is controversial. None of the theories adequately explains all the clinical and histopathologic findings in all forms of Peters' anomaly. Peters' anomaly should be regarded as a sign and not a disease entity *per se*. It is likely that where a genetic basis is responsible for this sign, accompanying ocular conditions may point to the likely mutation, e.g. aniridia and Peters' anomaly is likely to be due to a *PAX6* mutation whereas Axenfeld–Rieger anomaly/syndrome with Peters' anomaly is likely to be due to *FOXC1* or *PITX2* mutations.[19]

Most cases are sporadic, but autosomal recessive and dominant inheritance have been reported. Classical Peters' anomaly is defined as a congenital central corneal opacity with corresponding defects in the posterior corneal stroma, Descemet's membrane, and endothelium. Eighty percent of cases are bilateral. Glaucoma is present in 50% to 70% of cases.

Peters' anomaly has been often classified into three groups[29,30]:

1. Posterior corneal defect with leukoma alone.
2. Posterior corneal defect with leukoma and adherent iris strands.
3. Posterior corneal defect with leukoma, adherent iris strands, and keratolenticular contact or cataract.

Posterior corneal defect with leukoma alone is the simplest form of Peters' anomaly and the least documented in the literature.[31] The iris and lens are normal, but a defect in the posterior cornea has produced an overlying opacity, which varies from a mild haze to an elevated vascularized lesion. This may decrease in the first few years of life. Occasionally the defect is so severe as to cause relative clearing centrally with opacification in the mid-periphery of the cornea (Fig. 33.12). The peripheral cornea is usually clear, allowing visualization of the lens–cornea adhesion with a gonioscope (see Fig. 33.16), although scleralization of the limbus is common.[32] In a recent publication, the author showed mutations in *CYP1B1* associated with congenital corneal opacification and suggest that the original description of von Hippel's ulcer could be explained by such a *CYP1B1* "cytopathy"[31]; besides glaucoma, no additional ocular sign is seen. If glaucoma is present and not treated aggressively, the eye can become severely ectatic (Fig. 33.13).

If there are iridocorneal adhesions, these usually arise from the collarette and vary from fine strands to broad bands. Keratolenticular adhesions may occur and can be described as one of the following types:

Box 33.1

Classification of congenital corneal opacities (CCO)[19]

A. Primary CCO

Developmental anomalies of cornea only

i. Corneal dystrophies
   - CHED
   - PPMD
   - X-linked endothelial dystrophy

ii. Isolated sclerocornea (cornea plana)

iii. Corneal structural defects due to dermoids
   - Peripheral due to limbal dermoid
   - Central corneal dermoid

B. Secondary CCO

I. Kerato-irido-lenticular dysgenesis

a. Lens fails to separate from cornea
   i. Developmental
   ii. Mechanical: clues to this include
      - Lens epithelium discernible
      - Evidence of persistent pupillary type membrane(s)
      - Intact iris stroma architecture on high frequency ultrasound

b. Lens separates but fails to form thereafter
   - More likely to present as total corneal opacification

c. Lens fails to form (primary congenital aphakia – see text)

d. Due to PHPV
   - Pushing lens forward and causing keratolenticular touch/adhesion (again may present as PA)

e. Iridocorneal adhesions

II. Iridotrabecular dysgenesis

a. Infantile glaucoma

b. Axenfeld-Rieger anomaly/syndrome

c. Aniridia

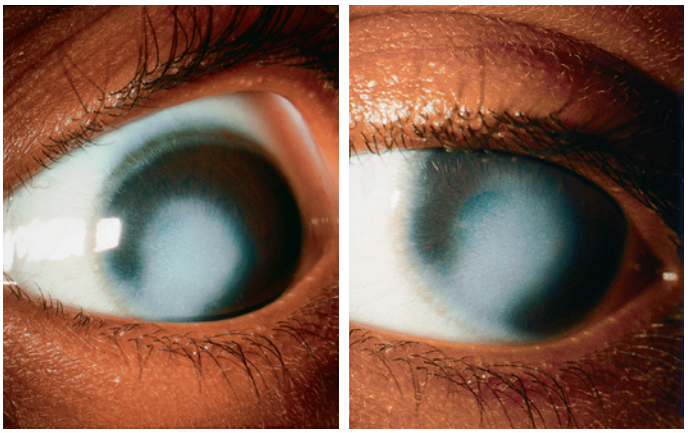


Fig. 33.11 Bilateral Peters' anomaly with eccentric opacification. Anterior segment imaging will determine whether the cause is iridocorneal adhesions and/or keratolenticular adhesion.

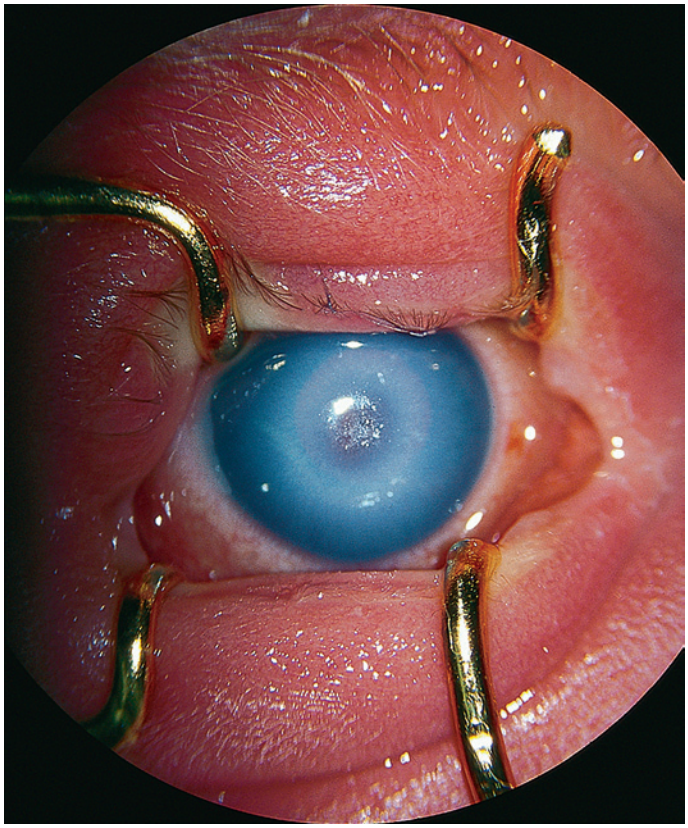


Fig. 33.12 A variant of Peters' anomaly. The posterior corneal defect is so great so as to give relatively clear appearance centrally.

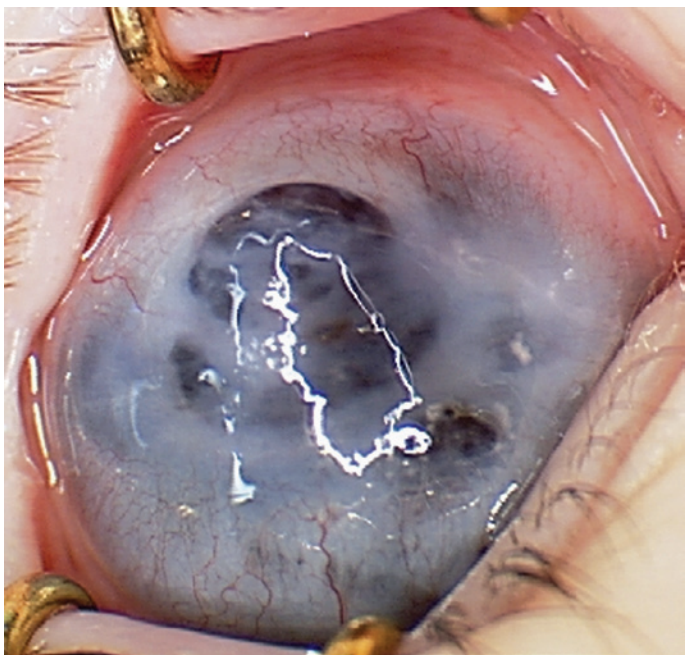


Fig. 33.13 Severe corneal ectasia secondary to glaucoma and congenital corneal opacity.

1. The lens may be adherent to the corneal stroma with absence of Descemet's membrane and lens capsule.
2. The lens may be located in a forward position, but only apposed and not adherent to the posterior surface of the cornea.
3. The lens may be in place, but with a portion of the anterior capsule and lens cortex in contact with or embedded in the posterior corneal surface.
4. The lens is in place but has a cone-shaped pyramidal cataract axially aligned with a posterior corneal defect.
5. The lens may be in place, but has an axial anterior polar or nuclear cataract.

Associated ocular features include Axenfeld–Rieger syndrome or aniridia, microphthalmia, persistent fetal vasculature, and retinal dysplasia.[32]

Systemic associations include craniofacial anomalies, congenital heart disease, pulmonary hypoplasia, syndactyly, ear anomalies, genitourinary disorders, central nervous system abnormalities, dwarfism, fetal alcohol syndrome, and chromosomal abnormalities. Peters'-plus syndrome[33] is a rare autosomal recessive disorder comprising short-limb dwarfism, smooth philtrum with thin upper lip, hearing loss, cleft lip/palate, brachymorphism, with short hands and tapering brachydactyly, mental retardation, and bilateral Peters' anomaly. It is associated with mutations in the *B3GALTL* gene.[33]

Histologically findings may vary, but include diffuse thickening of Bowman layer, mild atrophic changes in the overlying epithelium, normal anterior stroma, compressed posterior stromal lamellae partially replaced by fibrous tissue, and a broad central defect of Descemet membrane and endothelium. The periphery of the cornea usually has an intact Descemet's membrane and endothelium. The anterior chamber is usually deep, except in areas of iridocorneal or keratolenticular adhesions (Fig. 33.14). In other cases, absence of Bowman's layer with anterior stromal edema and posterior corneal defect has been described.[34]

Management of congenital corneal opacification is quite difficult and, despite early diagnosis and prompt medical treatment or surgery, many of these cases have a poor outcome. Essentially, however, by determining the etiology, parents can be counseled much better. For example, evidence exists that Peters' anomaly due to iridocorneal adhesions alone (type 1) fares much better than corneal transplantation for those cases with keratolenticular adhesion.[35]

Early penetrating keratoplasty, within the first 3 months, offers the infant the best hope for good vision. Suture removal after 4–6 weeks, followed by contact lens fitting and treatment of any amblyopia, is only successful if all involved are committed and motivated. If the reader keeps in mind that the goal of treatment is to achieve developmental vision at the very least, then this allows a better way to counsel parents. Graft rejection is a real issue, but evidence for the use of artificial corneas such as the Boston K-pro in infants is probably not robust yet.[36] However, the use of the Boston K-pro in children who have undergone previous corneal grafts that have eventually been rejected should be considered.

Sclerocornea

This is a poor term if describing total corneal opacification, mainly because it is usually due to an intraocular abnormality often involving the lens[19] and this may be due to keratolenticular adhesion or even absence of the lens (primary aphakia)[4,19] (Fig. 33.15). However, when it describes peripheral scleralization with central clearing, it refers to an uncommon, non-inflammatory, non-progressive condition where there is

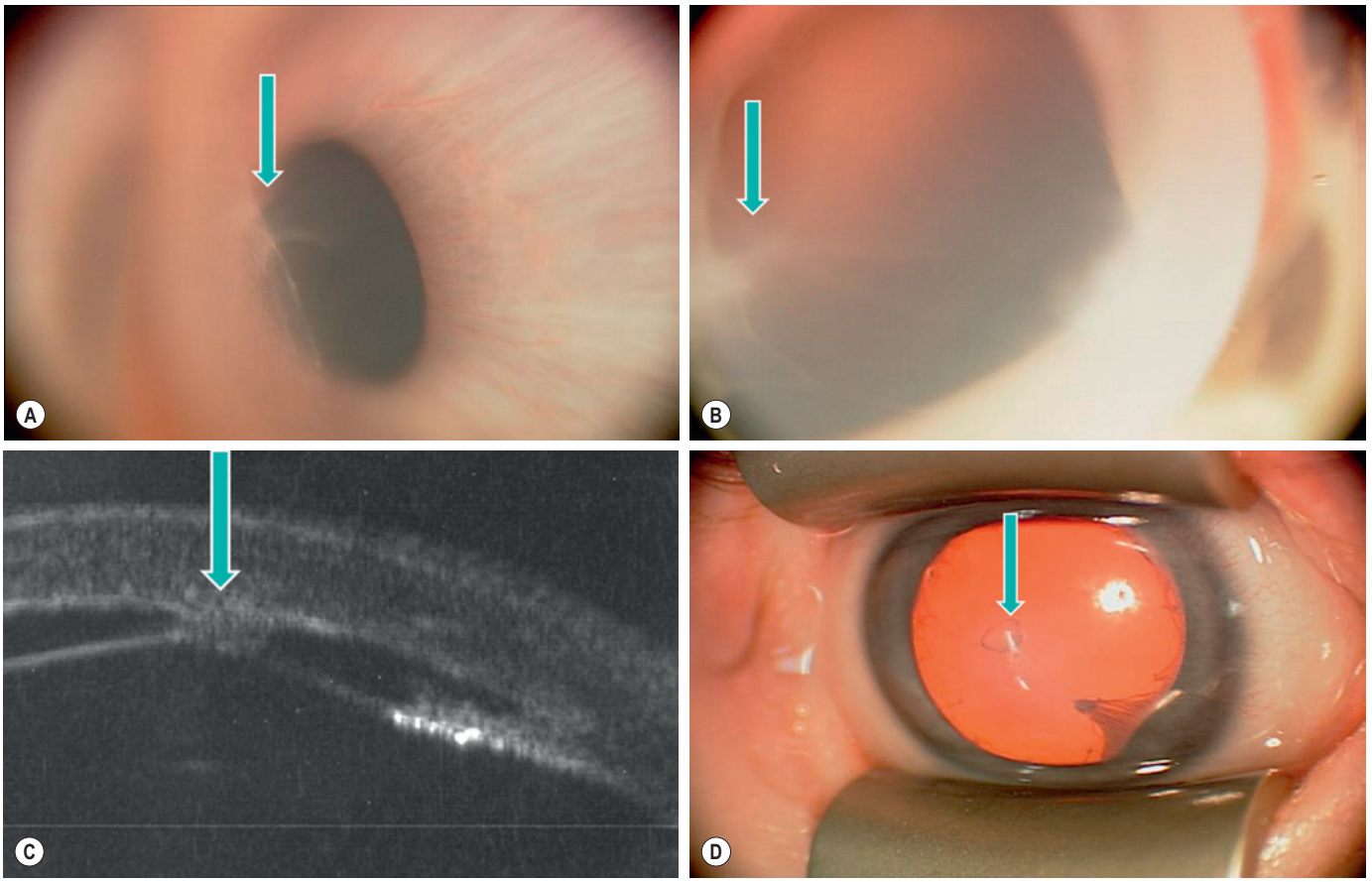


Fig. 33.14 Keratolenticular adhesion (arrow) seen with ultrasound biomicroscopy and clinically. This is a very mild Peters' anomaly.

extension of opaque scleral tissue and fine vascular conjunctival and episcleral tissue into the peripheral cornea, obscuring the limbus. It is bilateral in 90% of cases and almost always associated with cornea plana. It may be autosomal dominant or recessive (more severe), with 50% of cases being sporadic.

Management of sclerocornea consists of surveillance for glaucoma or cataract with correction of the often high hypermetropia seen. In bilateral cases where there is total corneal opacification, penetrating keratoplasty may be performed but postoperative glaucoma is a major problem. Preoperative assessment with high-frequency ultrasound is advisable to assess the presence of iridocorneal and keratolenticular adhesions, so that appropriate counseling can be given with respect to prognosis and so surgical planning can be done more methodically.[37]

Cornea plana

Cornea plana may be due to an arrest in development at the 4-month fetal stage, which results in a bilateral or unilateral flattening of the corneal curvature with a curvature of less than 43 D (Fig. 33.16). The cornea is almost always associated with sclerocornea characterized by peripheral corneal scleralization (Fig. 33.17) but a view of the eye through the center of the cornea is possible (Figs 33.18 and 33.19).

Hypermetropia and microcornea are commonly also seen. The recessive and dominant forms share clinical signs such as reduced corneal curvature, indistinct limbus, and arcus lipoides at an early age. The two forms are distinguished by a central, round, and opaque thickening, approximately 5 mm in width, only seen in recessive cases. Both forms may be associated with fine iridocorneal adhesions.[24]

Autosomal recessive cornea plana (CNA2) may be caused by mutations in the *KERA* gene (12q22), which encodes for keratocan. Keratocan, lumican, and mimecan are keratan sulfate proteoglycans, which are important to the transparency of the cornea.[38]

Associated ocular findings include peripheral sclerocornea, infantile glaucoma, angle closure glaucoma and chronic open angle glaucoma, retinal aplasia, anterior synechiae, aniridia, congenital cataracts, ectopia lentis, choroidal and iris coloboma (Fig. 33.20), blue sclera, pseudoptosis, and microphthalmos. Reported systemic associations include osteogenesis imperfecta, epidermolysis bullosa, and oculodentodigital syndrome.[39]

Management consists of cycloplegic refraction and correction of any refractive error and surveillance for glaucoma.



Fig. 33.15 A composite showing four different eyes from four different patients. All four were labeled as sclerocornea (when describing total corneal opacification). Anterior segment ultrasound showed that (A) had keratolenticular adhesion, as did (C), but (B) had primary aphakia, and (D) showed a very shallow anterior chamber but with normal lens. This demonstrates that the term "sclerocornea" for total corneal opacity is not useful.

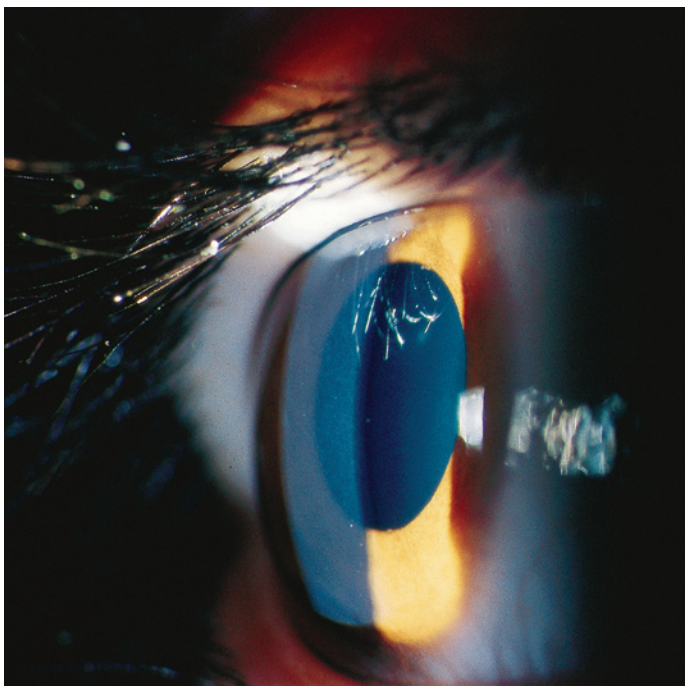


Fig. 33.16 Cornea plana. In profile, the flat nature of the cornea is clearly seen.

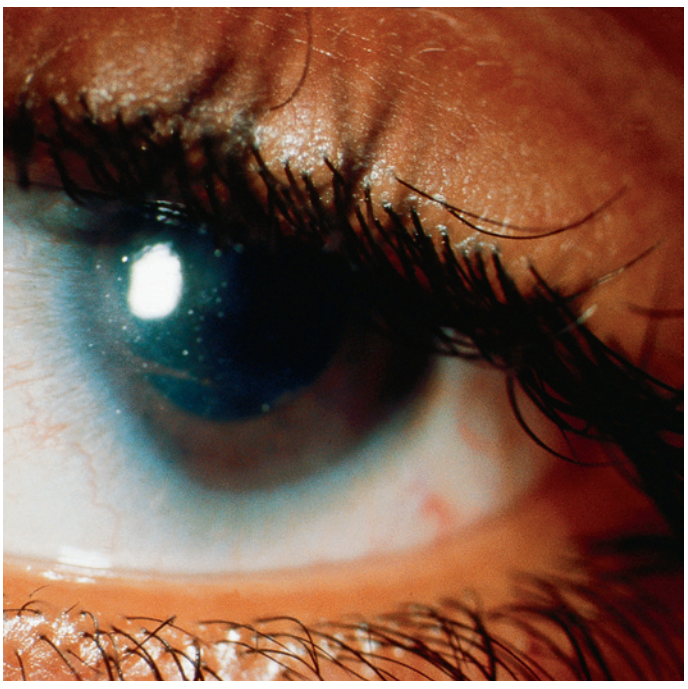


Fig. 33.17 Sclerocornea with cornea plana (S-CNA[20]). There is peripheral scleralization, most likely CNA2.



Fig. 33.18 A child with cornea plana (CNA2) in whom the hypermetropia is so high that his optic disc is visible without an ophthalmoscope.

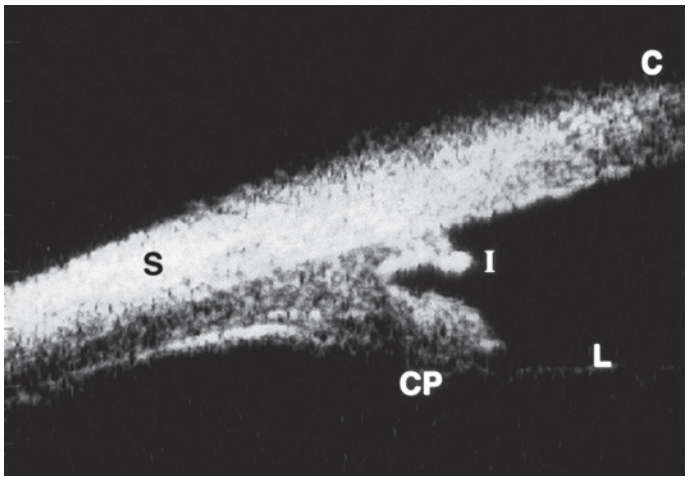


Fig. 33.19 Aniridia. A high-frequency ultrasound of an adolescent with aniridia. Note the iris stump (I), ciliary processes (CP), cornea (C), sclera (S), and lens (L).

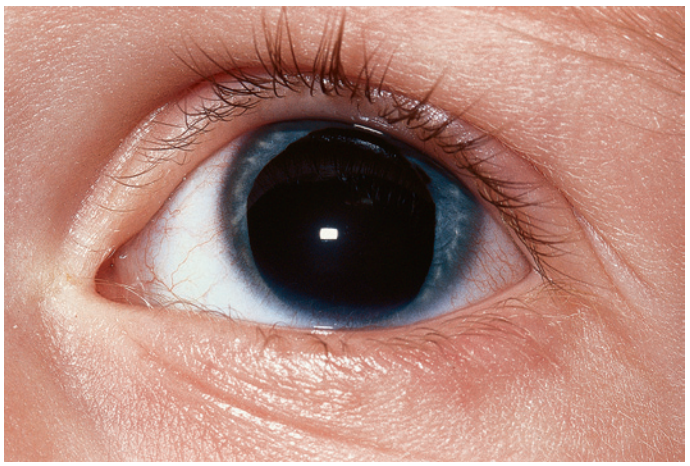


Fig. 33.20 Partial aniridia in a member of an autosomal dominant pedigree.

Complex contact lenses may be needed to give maximal visual rehabilitation (see Figs 33.17 and 33.18).

Autosomal dominant keratitis

This rare recurrent stromal keratitis and corneal vascularization has been shown to be due to mutations in *PAX6*, which are also known to cause aniridia.

The child usually presents with an irritated red eye and is photophobic. It may be associated with foveal hypoplasia. Being autosomal dominant, there is variable expressivity and penetrance within the same pedigree, with the mildest phenotype resulting in a 1 or 2 mm circumferential band of corneal opacification and vascularization contiguous with the limbus.[40,41]

Management is difficult and examination under anesthesia may be needed to clinch the diagnosis. Lubrication with artificial tears and ointments is essential. The role of limbal stem cell transplantation is unclear in this condition but early recurrence after penetrating keratoplasty has been noted. It is thought that this condition may be a variant of aniridia. If this is so, limbal stem cell transplantation might be a viable option.[41]

Aniridia

Aniridia has a prevalence of 1 in 50,000.[42] It is now well established that mutation or deletion of the *PAX6* gene and/or chromosomal rearrangements involving the *PAX6* gene on 11p13 underlies most cases of aniridia.[42]

Mutations in *PAX6* are responsible for human aniridia,[42] which is a panocular, bilateral disorder with absence of much (Figs 33.19–33.22) or most of the iris tissue, although iris hypoplasia may also be seen. Foveal and optic nerve hypoplasia are variably present (Fig. 33.23), resulting in a congenital nystagmus and leading to reduced visual acuity to 6/30 or worse.

Associated ocular features include anterior polar cataracts, often with attached persistent pupillary membrane strands, cortical cataract glaucoma, and corneal opacification, all of which often develop later in childhood. Glaucoma occurs in up to half of all cases; a recent study suggested that up to the age of 40 years, 15% of patients are diagnosed with glaucoma per age decade.[43]

Corneal opacification occurs secondary to limbal stem cell deficiency. Lens subluxation (Fig. 33.24) can also be associated with aniridia, often with glaucoma.[42,43] The typical presentation is a baby with nystagmus who has the appearance of absent irides or dilated unresponsive pupils. Photophobia may be present.

Aniridia can be sporadic or familial. The familial autosomal dominant form has complete penetrance but variable expressivity. Two-thirds of all aniridia children have affected parents. It is said that sporadic aniridia is associated with Wilms tumor in up to one-third of cases.[44]

The Wilms tumor gene *WT1* locus lies close to the *PAX6* gene locus on 11p13. A chromosomal deletion involving both loci results in the association of Wilms tumor with aniridia. In Denmark,[44] patients with sporadic aniridia have a relative risk of 67 (confidence interval: 8.1–241) of developing Wilms tumor. None of the patients with smaller chromosomal deletions or intragenic mutations were found to develop Wilms tumor. Familial aniridia patients are said not to be at risk for Wilms tumor; however, one case has been reported in a child with familial aniridia, but this probably represents a familial 11p13 deletion.[44]

When associated with aniridia, Wilms tumor is diagnosed before the age of 5 years in 80% of cases. The median age at diagnosis is 3 years.

Sporadic aniridia has also been associated with genitourinary abnormalities and mental retardation (AGR triad), a constellation that has been linked with a deletion of the short arm of chromosome 11 (11p-). Some, but not all, of these patients get Wilms tumor (WAGR association), a syndrome due to a contiguous gene deletion encompassing both *PAX6* and *WT1*. Individuals, particularly children under 6 years old, with *WT1* deletion may predispose to Wilms tumor, a kidney tumor with childhood onset. Defining the accurate breakpoints of the 11p13 deletion may contribute to the genetic counseling, disease prognosis, and prevention.[45]

Aniridia can also rarely be associated with ataxia and mental retardation (Gillespie syndrome). Multisystem syndromes and chromosomal abnormalities such as ring chromosome 6 can also include aniridia.[45]

Management includes genetic analysis to exclude chromosomal deletion. Until the result is known, all children with sporadic aniridia should have repeated abdominal ultrasonographic and clinical examinations. One protocol advised that the child be examined every 3 months until the age of 5 years, every 6 months until the age of 10 years, and once a year until the age of 16 years. However, the examinations are best continued until chromosomal and then intragenic mutational analyses have confirmed a *PAX6* mutation only. If a contiguous deletion involving *WT1* is found, then 3-monthly scans should be performed and the child transferred to the care of a nephrologist.

Management of the ocular condition consists of conservative measures such as correction of any refractive errors with filter lenses to reduce glare, and surveillance for onset of glaucoma. These patients often suffer from chronic angle closure glaucoma, which usually develops later and is difficult to treat. For this reason,[46] prophylactic goniotomy is sometimes advocated (Fig. 33.25). Cyclodiode laser, drainage tubes, and trabeculectomy with antimetabolite (usually mitomycin) have all been advocated for treatment of established glaucoma uncontrolled by topical medication alone. It is essential that the ocular microenvironment be assessed for dry eyes or meibomian gland dysfunction as this can accelerate the corneal opacification due to limbal stem cell abnormality. Usually corneal opacification occurs in adulthood but may occur in children. This may necessitate limbal stem cell transplant and corneal graft.[47]

Recent work has demonstrated a potential treatment to arrest or retard at least the corneal opacification. The majority (72%) of intragenic mutations in *PAX6* causing aniridia do so because they result in premature stop codons that result in a truncated protein and approximately 50% of all these mutations are in-frame nonsense mutations. Workers have shown that by adopting a nonsense mutation-suppression approach for in-frame premature stop codons, as long as the premature termination codon is not in a critical position for protein activity, then a functional protein could be produced

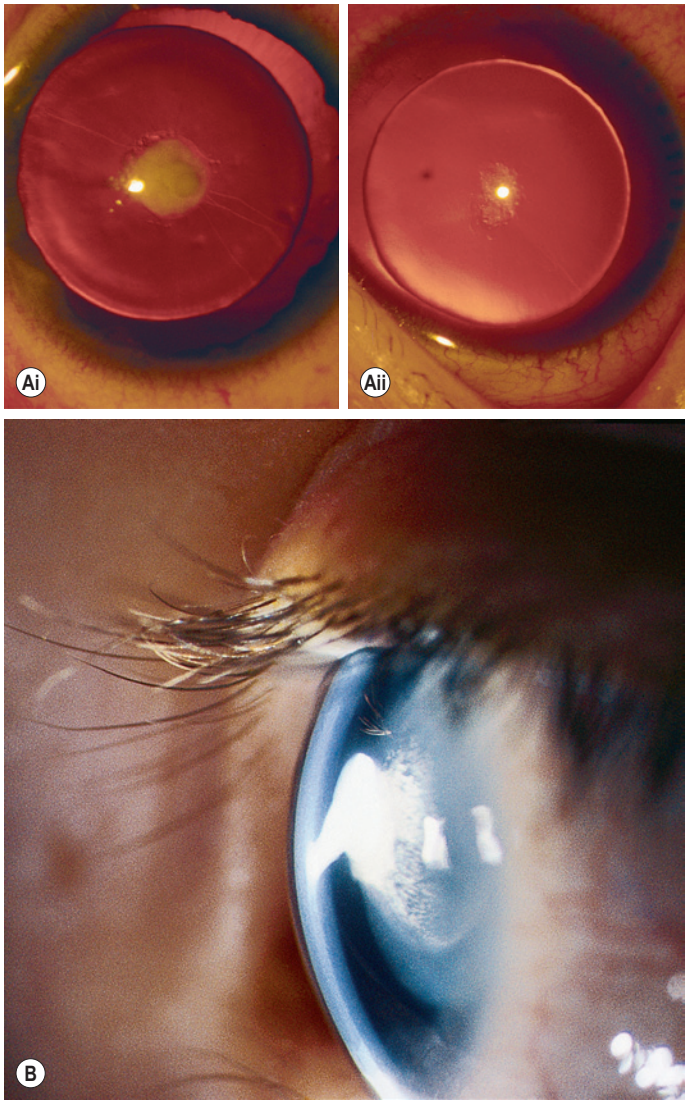


Fig. 33.21 Aniridia. (A) Aniridia with anterior polar cataract. (B) Aniridia with anterior extension of an anterior polar cataract with attachment to the cornea.

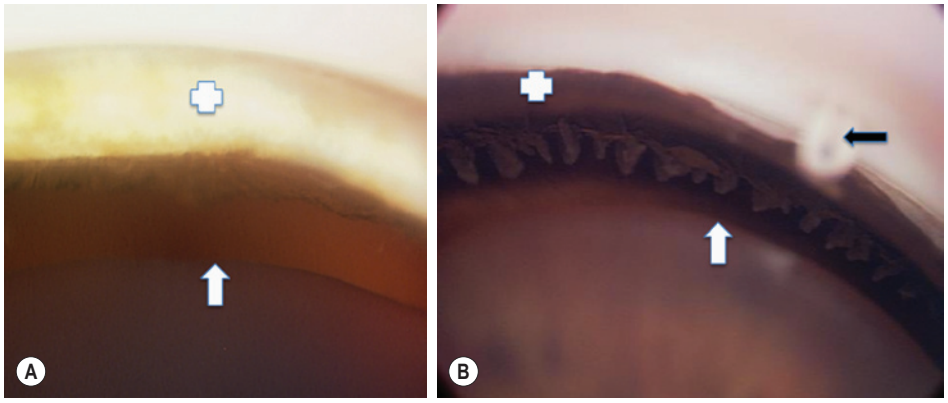


Fig. 33.22 Gonio views of the angle in two cases of aniridia. In (A) the cause is a mutation in *PAX6* but in (B) the cause is a mutation in *FOXC1*. This is a reminder that absence of the iris, while most commonly associated with mutations in *PAX6*, may also be seen in mutations in *FOXC1*. White arrows = lens edge; white crosses = iris remnant; black arrow = Ahmed tube in eye.

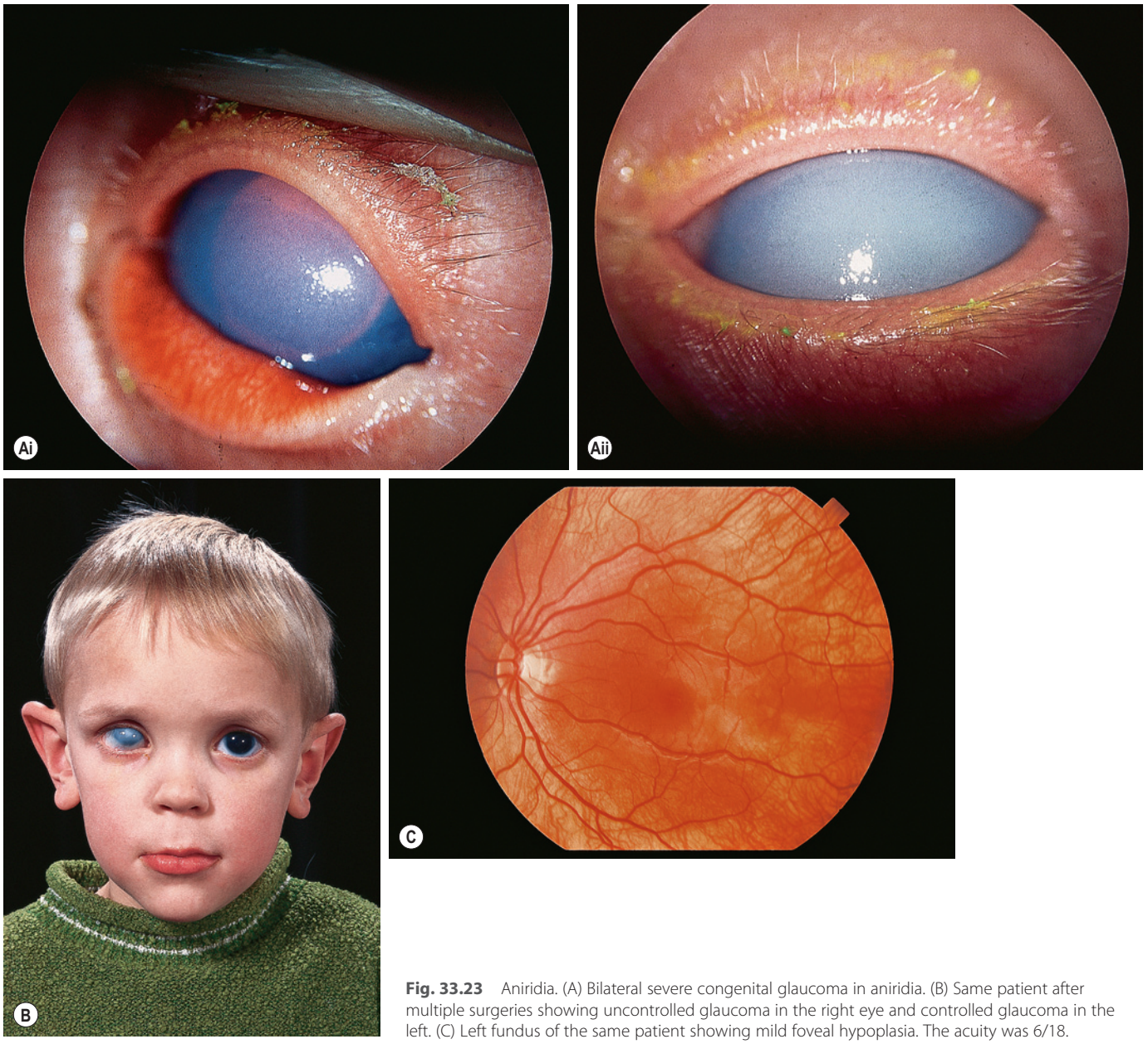


Fig. 33.23 Aniridia. (A) Bilateral severe congenital glaucoma in aniridia. (B) Same patient after multiple surgeries showing uncontrolled glaucoma in the right eye and controlled glaucoma in the left. (C) Left fundus of the same patient showing mild foveal hypoplasia. The acuity was 6/18.

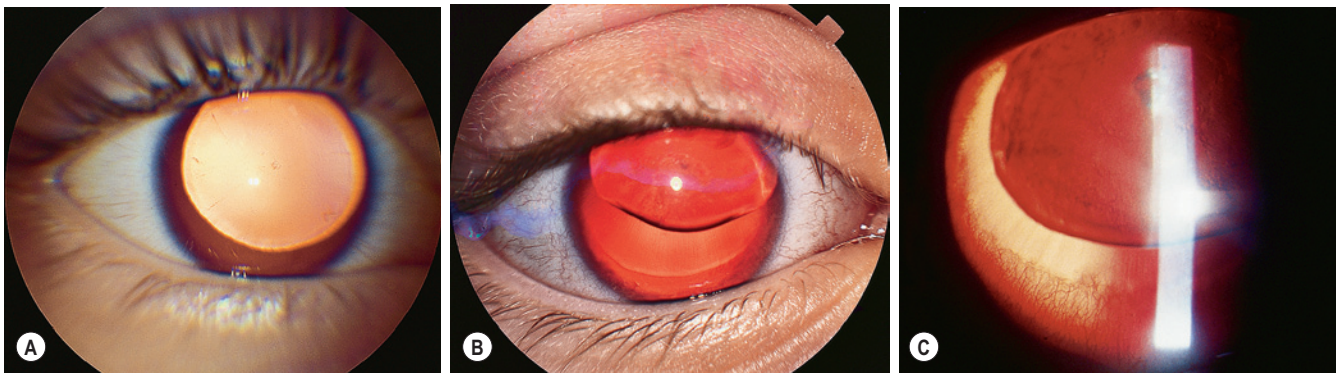


Fig. 33.24 Aniridia. (A) Aniridia with lens subluxation in 1979. (B) Same patient in 1985, showing progressive subluxation. (C) In 1995 there is further subluxation and corneal vascularization.

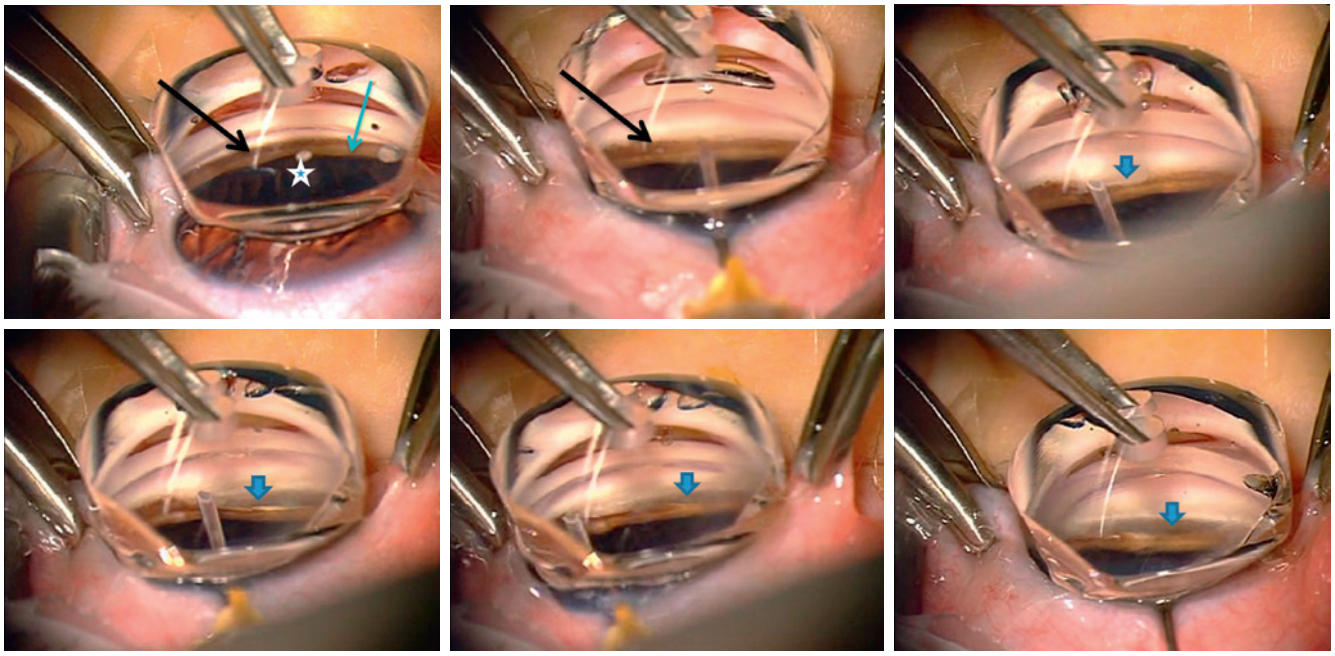


Fig. 33.25 Aniridia: child undergoing goniotomy. The star shows the ciliary processes. There is iris root remnant (child is *not* dilated), and the angle is anomalous. The arrow indicates the developing cleft during successful goniotomy.

with the potential to provide therapeutic benefit. Recently, nonsense-suppressing small molecules with limited toxic effects have been described.[48]

Penetrating keratoplasty for anterior segment developmental anomalies

Infant penetrating keratoplasty has historically been thought to be a thankless endeavor with poor results.[49,50] However, 35% graft survival at 7 years post-graft has been reported in cases of Peters' anomaly,[51] and good visual results have been reported following early penetrating keratoplasty (PKP).[51,52] The definition of success, however, needs to be re-aligned for the infant, since we are dealing with a developing neurobiological system, in which lack of sensory input has a profound effect on global development. The role of amblyopia also plays an enormous part, such that a clear surviving graft in the presence of dense amblyopia cannot be considered an outright success.[53]

Crucial to penetrating keratoplasty in children is the acknowledgment that pediatric ocular tissue behaves differently from that of the adult. The age at which the child's eye becomes more like that of an adult is controversial, but experience suggests that a child over the age of 10 years will have ocular tissue that behaves almost like that of an adult.[54–56]

High-frequency ultrasound is a well-established tool for the examination of the anterior segment, especially in eyes with corneal opacity.[37] It is one of the most challenging conditions to treat surgically, but the use of high-frequency ultrasound evaluation helps determine a more appropriate entry into the anterior chamber.

All cases require a Flieringa ring because the sclera is much less rigid than that of an adult (Fig. 33.26). This is sutured using 8/0 nylon in four quadrants, and the suture is left long so as to stabilize the eye with the long suture ends using Steri-Strips.[52] A pediatric radial corneal marker is used to mark the cornea and allow centration, which aids placement of the trephine. A small paracentesis is made and the anterior chamber hyperinflated with viscoelastic, usually Healon GV.

Prior to trephination of the host, mannitol is infused according to the weight and age of the child to reduce the intraocular pressure and reduce the risk of expulsive hemorrhage. To this end, the child should be paralyzed and the end tidal pCO_2 should be below 30.

A manual trephine is used and, if keratolenticular adhesions or extensive iridocorneal adhesions are present, the anterior chamber is not entered with the trephine. Vacuum trephines such as the Barron-Hessburg are usually not manufactured to a small enough diameter.

The host button is fashioned after initial trephination with a 15° disposable blade so as to avoid excessive damage to the iris and/or lens. In cases of keratolenticular adhesion, the lens may be carefully peeled off the cornea but this usually results in cataract formation within a few weeks of the graft. Therefore, there is an argument for lens aspiration with sparing of the posterior capsule; this needs surgical capsulectomy through a pars plicata approach, usually within a few weeks also, but at least the donor cornea is a little more protected from trauma, since the capsulectomy occurs a little deeper in the eye away from the corneal endothelium. All cases of congenital corneal opacification have an iridectomy in four quadrants to try to reduce the incidence of glaucoma. The donor corneal button is oversized by 1 mm in all these cases, also to increase the anterior chamber depth. There is evidence that this improves outcome.[56] Grafts are sutured using at least 16 10/0 nylon interrupted sutures.[52,54]

All cases receive subconjunctival antibiotic and steroid injection at the end of the procedure. The author uses intracameral dexamethasone routinely, although some have advocated use of intracameral triamcinolone.

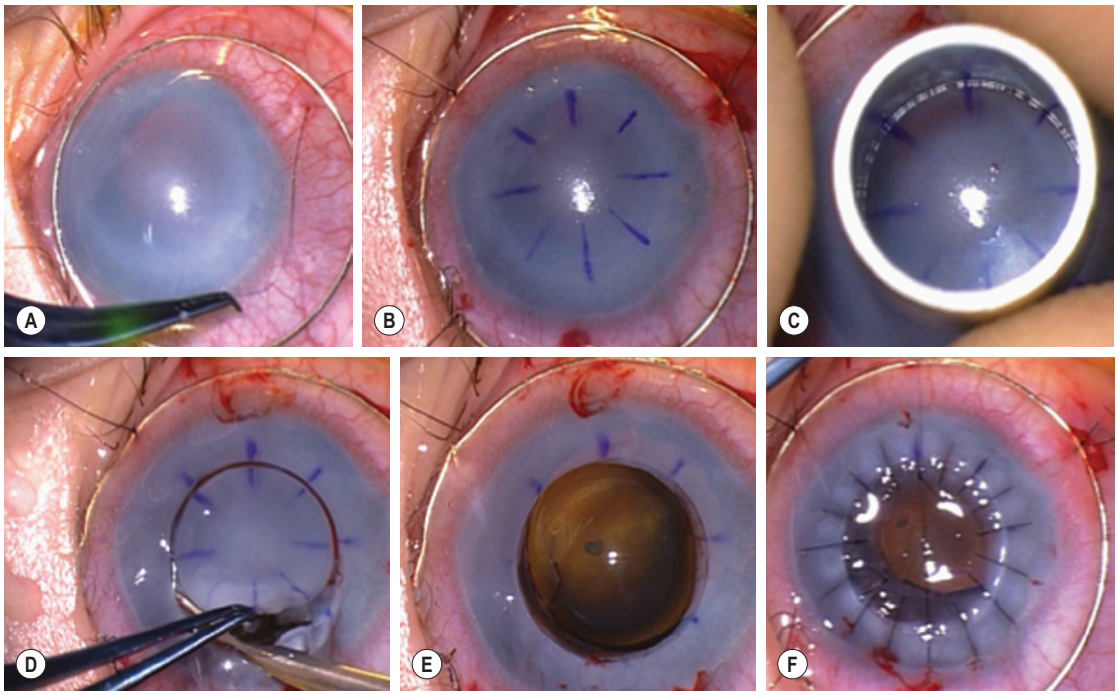


Fig. 33.26 Composite showing penetrating keratoplasty in an infant. The Flieringa ring is secured with four interrupted 8/0 nylon sutures and secured to brow and cheek with Steri-Strips (A,B). A manual trephine is used (C) for a partial-thickness trephine and the host button then excised with scissors so as not to damage the lens (D). The donor is then secured with 16 interrupted 10/0 nylon sutures (E,F).



Fig. 33.27 Infant keratoplasty. (A) There is mucous plug formation around loose sutures only 4 weeks post penetrating keratoplasty (PKP) for this case of complete sclerocornea. (B) The same case as in (A) 4 months later. There is peripheral opacification and scarring encroaching on the visual axis. (C) Two years post PKP for Peters' anomaly (not the same case as that shown in [A] and [B]).

The presence or absence of glaucoma must be assessed. If glaucoma is present preoperatively, this again is a poor prognosticator. In these circumstances, and if the corneal opacification is bilateral, laser cycloablation (usually cyclodiode laser) is used under ultrasound biomicroscopy guidance to treat the inferior half of the ciliary processes.[57] This allows control of the glaucoma with appropriate topical medication, and penetrating keratoplasty can then be performed with the expectation that a drainage tube will probably be needed to be placed at a later stage to control the glaucoma. Simultaneous PKP and drainage tube placement in infant eyes is not a route favored by this author.

The tissue reactivity in infants is such that intensive topical steroid/antibiotic preparations are a necessity to prevent fibrin formation, synechiae, and rejection. These are applied half-hourly for the first 24 hours, with cycloplegic drops three times daily and antibiotic/steroid ointment at night to allow the infant to sleep. The intensity of drops is tailed off over 2 months, and cycloplegia may continue for the same period. Infants are reviewed twice weekly for the first 6 weeks because the slightest hint of a loose suture or suture vascularization necessitates removal of the offending suture under anesthesia within 24 hours (Fig. 33.27). Failure to do so results in rapid epithelial rejection. In any case, all sutures are removed in infants at the latest by 6 weeks postoperatively.

There is no doubt that if it is understood that the aim of surgery is to give functional vision and not perfect vision and that a partially clear graft that allows delivery of functional vision is still a successful outcome, then infant PKP can be very rewarding for the patient and the surgeon[50,53] (see Figs 33.27 and 33.28).

Alternatives to PKP

There are occasions where penetrating keratoplasty may not be appropriate and the social circumstances (multiple children,

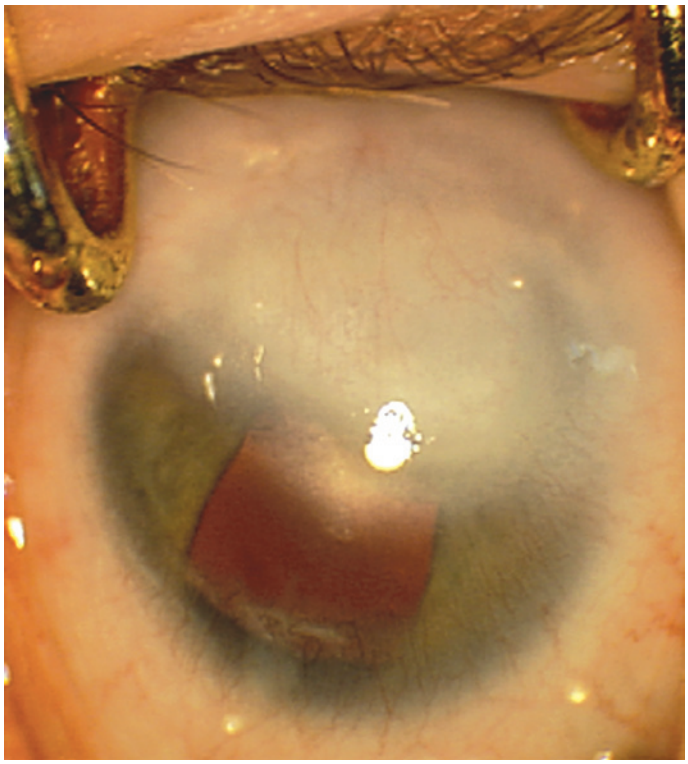


Fig. 33.28 A child with Peters' anomaly due to iridocorneal adhesion causing an eccentric corneal opacity in his only functioning eye. A broad iridectomy has been done to visually rehabilitate the child.

economic considerations, distance to travel for intense follow up) make PKP ill advised. Under these circumstances, if the opacity is eccentric, a broad iridectomy may work very well indeed and should be considered[58] (Fig. 33.28). Autorotational keratoplasty has also been described[59] but in this author's opinion is not an advisable option in developmental corneal opacities due to the crowded or shallow anterior chambers usually present. Also, reports recently have described the use of deep stromal and endothelial keratoplasty (DSEK) in Peter' anomaly; although the long-term visual outcomes are questionable, the rate of rejection appears lower than for PKP (see chapter 35).[60]

One other option is to consider if the coincidental presence of cataract in Peters' anomaly due to keratolenticular adhesion is causing a significant part of the visual deprivation. In such cases, removal of the cataract with judicious iridectomy may allow adequate visual rehabilitation.[61]

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Corneal abnormalities in childhood

Stephen J Tuft

Chapter contents

ABNORMAL CORNEAL SHAPE
ABNORMAL CORNEAL DIAMETER
CORNEAL OPACITY
CORNEAL VASCULARIZATION
PROMINENT CORNEAL NERVES
NEUROTROPHIC KERATITIS
CORNEAL DEGENERATION
REFERENCES

Abnormalities of the cornea may be classed as an abnormality of shape or opacity. The etiology determines the management of any associated visual loss or amblyopia (Fig. 34.1).

Abnormal corneal shape

Keratoconus

Keratoconus is bilateral progressive thinning and ectasia of the cornea.[1] This results in visual loss from keratometric myopia and irregular astigmatism (Fig. 34.2). Rare variants are pellucid marginal degeneration, in which there is an arc of thinning close to the inferior limbus, and keratoglobus in which there is diffuse thinning of the whole cornea. The incidence of keratoconus in North European adults has been estimated to be 1 : 1105,[2] although the disease is significantly more common in South Asian and black populations. Early onset and South Asian ethnicity are associated with rapid progression. There is a strong genetic contribution to the disease with modification by environmental factors such as eye rubbing or allergic conjunctivitis. At present, the etiology is unknown. Although several genetic loci have been mapped for the disease, no causative genes have been identified.[3] Only a small proportion of individuals with keratoconus are syndromic, and although a large number of associations have been reported it is likely the majority result from chance. The main conditions associated with keratoconus are chronic allergic eye disease, Down syndrome, and Leber congenital amaurosis – all of which may act through a tendency for severe eye rubbing. Keratoconus may also be a feature of some connective tissue disorders, e.g. Ehlers–Danlos syndrome and brittle cornea syndrome, although it is rarely a presenting sign for these conditions. The onset of keratoconus is rare before the age of 10 years.

Early diagnosis of keratoconus is important as corneal collagen cross-linking can arrest its progression. Diagnosis depends on the documentation of increasing astigmatism, a scissors reflex at refraction, and characteristic changes on computerized corneal tomography. Serial computerized imaging is now the standard of care to monitor for progression.

Complications of keratoconus are uncommon and include corneal hydrops, from an acute split in the Descemet's layer, leading to corneal scar but rarely infection or perforation. In children, an acute corneal hydrops may be the presenting sign of keratoconus. It is associated with sudden onset of discomfort and blur with a dense central corneal opacity with tissue swelling due to entry of aqueous into the corneal stroma (Fig. 34.3). The natural history of a corneal hydrops is for gradual resolution over 3–4 months, but there is often a residual corneal scar that can flatten the corneal contour but reduce vision due to opacity. Secondary corneal neovascularization can occur if there is a large hydrops adjacent to the limbus, or if there is severe allergic eye disease, in which case topical corticosteroid should be considered until the hydrops resolves. Topical antibiotic is indicated if there is an epithelial defect, but other treatments such as hypertonic 5% saline are ineffective. Intracameral injection of a long-acting gas, e.g. perfluoropropane, has been proposed to speed up the resolution of a hydrops, but it is not always effective and the visual outcome is unchanged. Gas injection also carries a significant risk of iris ischemia and cataract from pupil block.

The management of keratoconus aims to restore functional vision. In early disease this may be achieved with glasses, but as the disease progresses glasses will not correct the irregular component of the astigmatism and contact lenses may then be required. Rigid gas-permeable contact lenses give a better level of vision than soft or soft toric contact lenses, with less risk of secondary complications (infection, corneal neovascularization). Keratoplasty for keratoconus is only indicated if there is advanced bilateral disease when a contact lens cannot be retained, or if there is poor vision (<6/12) even with contact lens correction. It is uncommon for the disease to progress to this stage in childhood. In the absence of a prior corneal hydrops, a deep anterior lamellar keratoplasty (DALK) is the treatment of choice rather than a penetrating keratoplasty because there is a lower risk of allograft rejection and less risk of wound dehiscence following injury. If there is

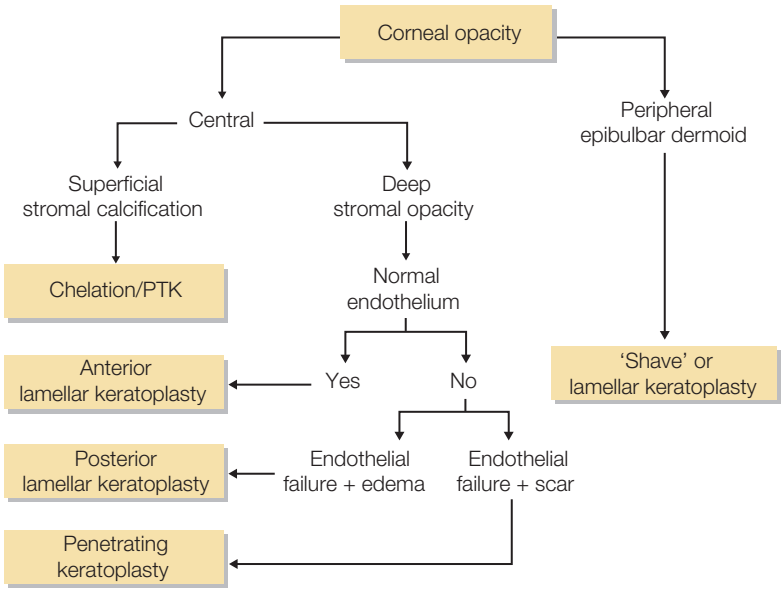


Fig. 34.1 Simplified algorithm for the surgical management of corneal opacity.

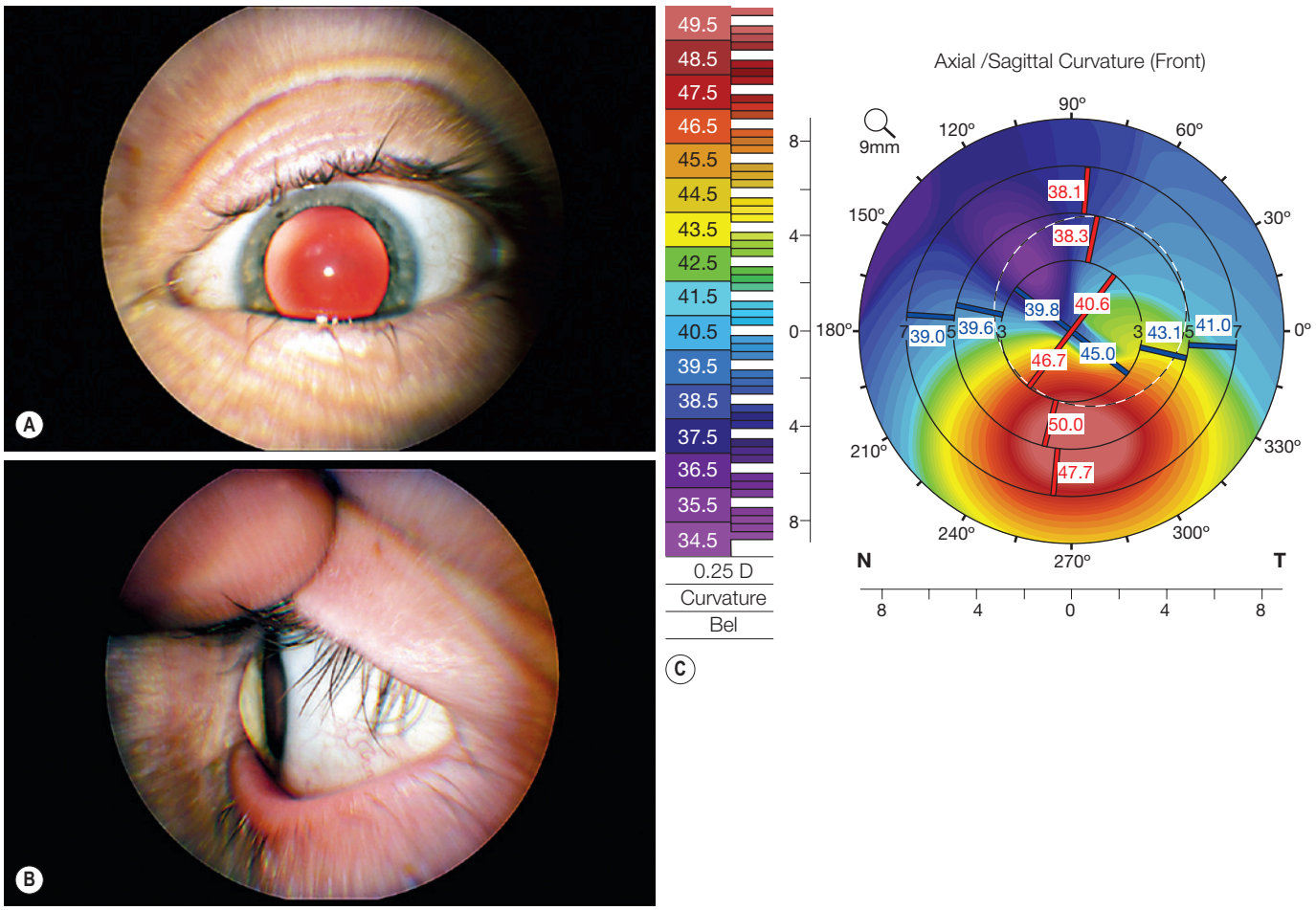


Fig. 34.2 Keratoconus. (A) The retinoscopy reflex in keratoconus has no clear end point and may have a scissors pattern. (B) Lateral view showing the conical cornea. (C) Computed tomography showing ectasia of the inferior cornea.

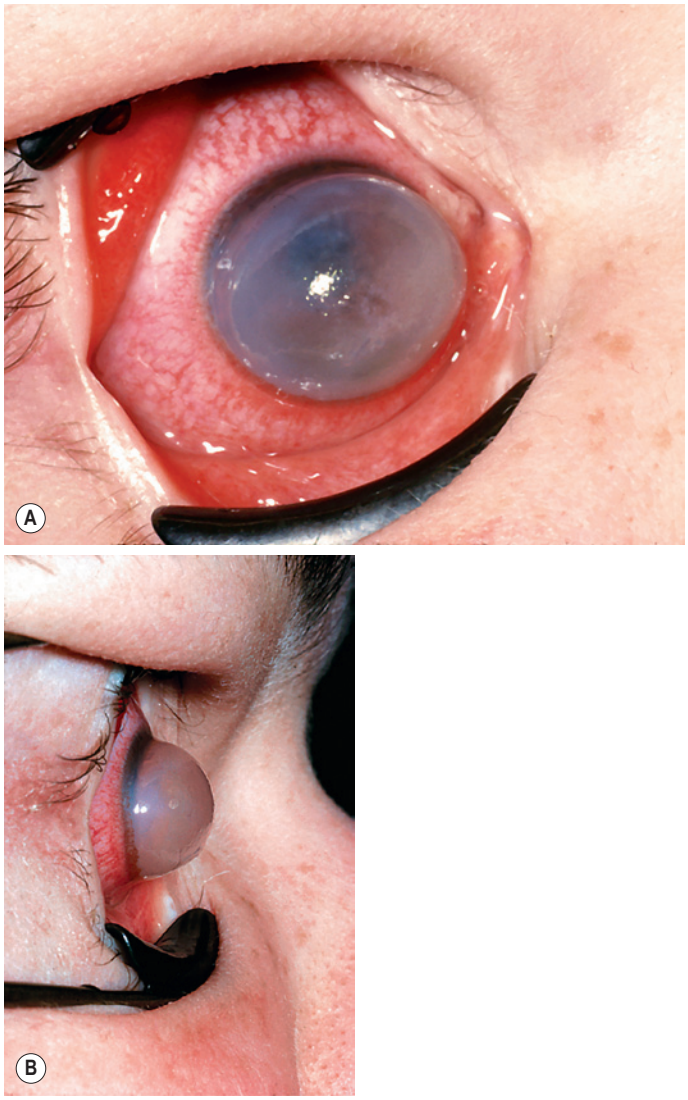


Fig. 34.3 Keratoconus. (A) Acute hydrops in a child with Down syndrome and keratoconus. (B) Side view showing extreme ectasia due to corneal swelling. The swelling will resolve over months but with a risk of secondary vascularization.

poor compliance, e.g. in Down syndrome, an epikeratoplasty should be considered as an alternative.

Corneal collagen cross-linking (CXL) is the only intervention that has been demonstrated to arrest the progression of keratoconus.[4] The ability to do this at a stage when there is still useful spectacle-corrected vision is a major benefit and early referral of suspected cases is therefore imperative. The preferred technique is to remove the corneal epithelium to allow penetration of topical riboflavin into the corneal stroma, followed by irradiation with ultraviolet B (UVB). This can normally be performed in children with topical anesthetic, although mild sedation may be required. Controlled clinical trials of CXL have, as yet, only been performed in adults, and the safety and efficacy of CXL in children has not been demonstrated.[5] The clinical criteria for treatment are under review (Table 34.1), but it is usual practice to confirm that the keratoconus has progressed before treatment is performed. Treatment failure has been documented in 10% of cases and it is not known whether repeat CXL treatment is safe. Potential complications include microbial infection and corneal scar.

Table 34.1 Minimum criteria to confirm progression of keratoconus

Parameter	Change
Refractive astigmatism increase	>1 D
CDVA loss	>1 line lost
Kmax increase if Kmax <55 D	>1.0 D
Minimum corneal thickness loss	>16 μm

Demonstrated progression is a reason for collagen cross-linking to stabilize the cornea.
CDVA, Corrected distance visual acuity; Kmax, maximum keratometry.

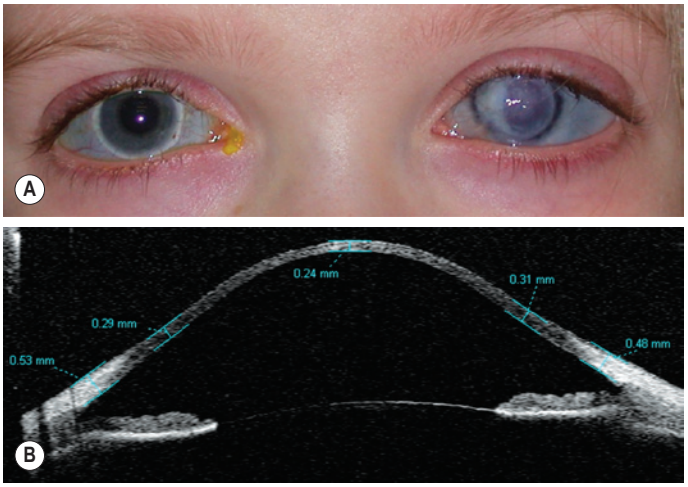


Fig. 34.4 Brittle cornea syndrome. (A) There is blue sclera. The right eye has had an onlay lamellar keratoplasty. The left eye is blind following corneal rupture. (B) Ocular coherence tomography of the anterior segment showing generalized thinning of the cornea and sclera. Central corneal thickness was 240 microns and thickness at the limbus was 310 microns.

Brittle cornea syndrome

Brittle cornea syndrome (BCS) is a rare autosomal recessive condition characterized by blue sclera and extreme thinning of the cornea, with a risk of corneal rupture after minor trauma (Fig. 34.4). BCS1 is caused by mutations in *ZNF469* and BCS2 is caused by mutations in *PRDM5*, although the corneal phenotype is similar.[6] It is a generalized connective tissue disorder with associated joint hypermobility and hyperelasticity of the skin. Affected individuals should wear protective acrylic glasses at all times to reduce the risk of accidental traumatic eye rupture. Scleral lenses may be an alternative in older patients. Extreme secondary central corneal ectasia (keratoconus) can occur, and in these individuals the option of a limbal-sparing onlay graft to reinforce the cornea should be considered.

Blue sclera

Blue-tinged sclera is a rare sign that is usually the result of scleral translucency or thin sclera with choroidal show-through. It may be present in normal children, particularly if there is high myopia. Blue sclera is associated with a wide range of skin and musculoskeletal abnormalities, but it is most frequently seen

in association with pseudoxanthoma elasticum, osteogenesis imperfecta, Ehlers–Danlos syndrome, Marfan syndrome, alkaptonuria, or hypophosphatasia syndrome. Early referral to a pediatrician for systemic review is essential. The multiple fractures of osteogenesis imperfecta may occasionally prompt erroneous referral for suspected non-accidental injury; the finding of a blue sclera in this context is an important diagnostic marker.

Abnormal corneal diameter

Increased diameter

Buphthalmos

This is enlargement of the cornea associated with a raised intraocular pressure from congenital glaucoma. Although the corneal diameter is enlarged (>13.0 mm) and the cornea thin, the anterior chamber depth may be relatively normal (in contrast to the deep anterior chamber that is a feature of X-linked megalocornea). Chronically raised intraocular pressure, splits in Descemet's layer (Haab striae), or subsequent cataract or glaucoma surgery can lead to endothelial decompensation and irreversible corneal edema (Fig. 34.5). If the edema does not clear after the intraocular pressure has been controlled, a keratoplasty should be considered. A posterior lamellar endothelial keratoplasty (DSAEK) will give more rapid visual recovery than a penetrating keratoplasty, with less risk of globe rupture following accidental injury.[7] However, a penetrating keratoplasty may be required if there is significant stromal scar. Interrupted sutures should be used if the peripheral host cornea is markedly thinned. Cataract surgery may also be required with an iridoplasty if the pupil is markedly eccentric.

Forceps injury can cause unilateral corneal edema from birth, although the cornea is not enlarged. The edema will usually resolve leaving characteristic oblique splits in Descemet's layer (Fig. 34.6), with oblique astigmatism. There is a high risk of amblyopia.

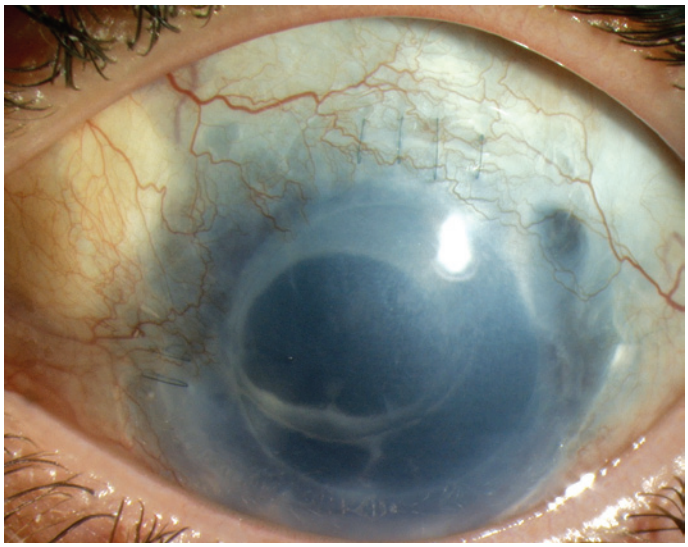


Fig. 34.5 Buphthalmos. The corneal diameter is enlarged and the eye is pseudophakic. There is a scleral patch over a drainage tube superiorly. A posterior lamellar keratoplasty has been performed to treat secondary corneal decompensation.

X-linked megalocornea (MGC1)

X-linked megalocornea is a disorder in which both corneas are symmetrically and markedly enlarged from birth. Features include clear corneas with bilateral horizontal diameters of 14–16 mm, a deep anterior chamber (4–6 mm), generalized reduced corneal thickness (470–500 µm) but with normal intraocular pressures (Fig. 34.7). Secondary changes in older individuals include shagreen corneal degeneration, corneal arcus juvenilis, lens dislocation, and mild iris atrophy with pigment dispersion. The genetic cause is a mutation in the *CHRDL1* gene, which encodes ventroptin, a secreted bone morphogenetic protein (BMP) antagonist. It is proposed that an absence of ventroptin during development permits unrestricted growth of the anterior segment.[8]

MGC1 is almost always a benign condition. The corneal thinning does not progress and it is not associated with juvenile glaucoma. It is therefore important to distinguish MGC1 from primary congenital glaucoma (PCG) during infancy. The limbal architecture is normal in MGC1 with a crisp cornea–sclera transition as opposed to the broadened

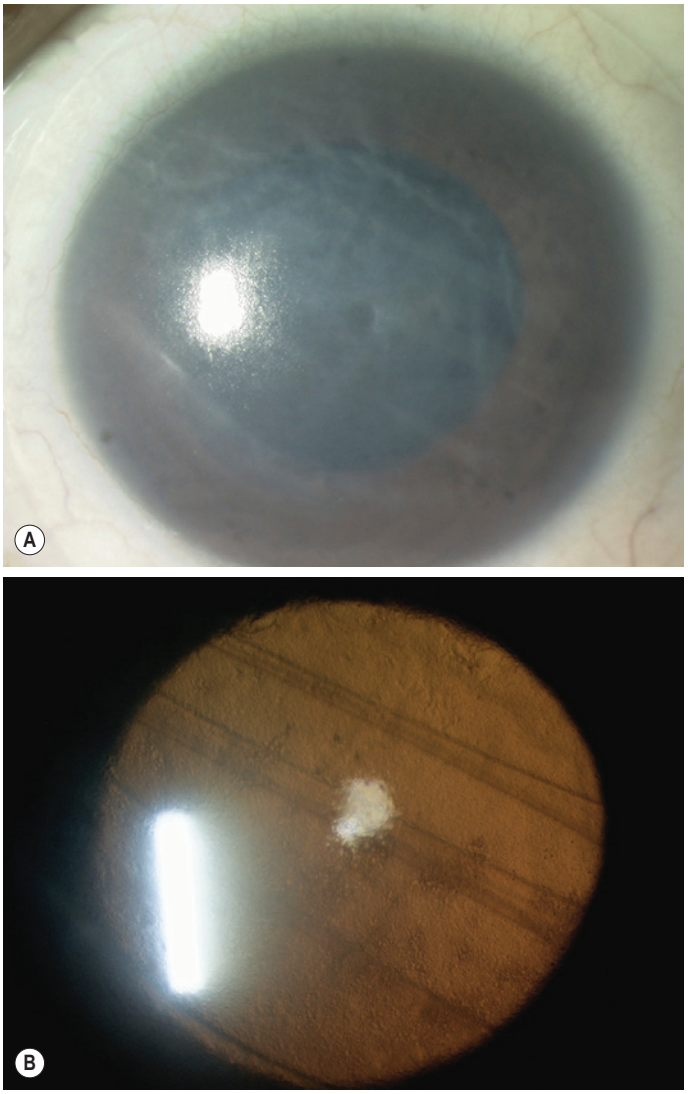


Fig. 34.6 Descemet breaks following presumed forceps injury. (A) There is diffuse unilateral corneal edema with normal intraocular pressure. (B) Oblique breaks in Descemet's layer can be seen on retroillumination.

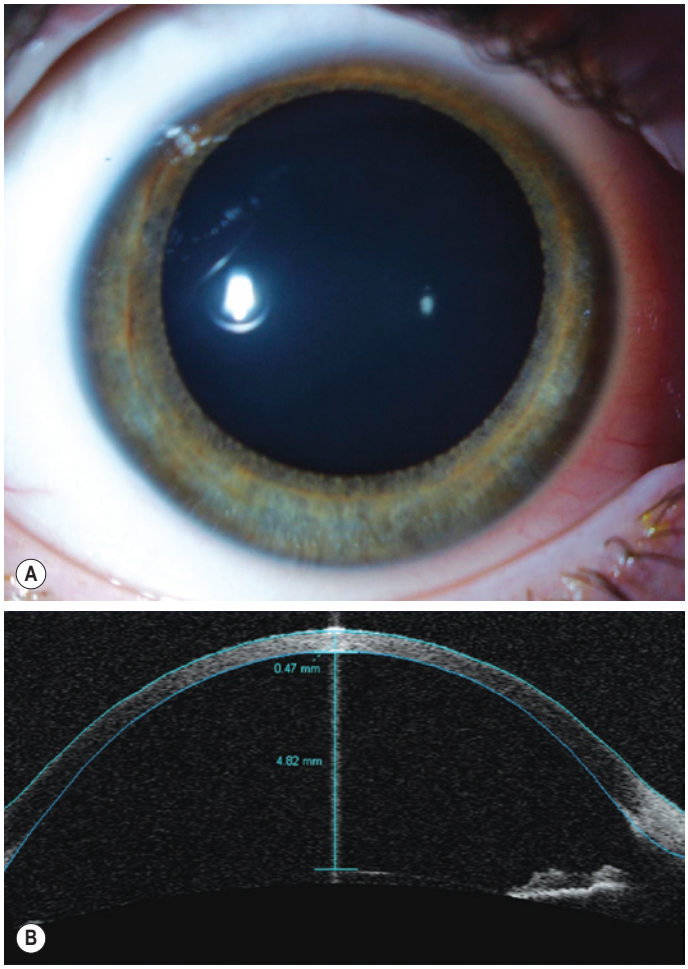


Fig. 34.7 X-linked megalocornea. (A) The cornea is clear with a diameter of 16 mm (pupil has been dilated). (B) Ocular coherence tomography showing reduced corneal thickness and deep anterior chamber.

"smeary" limbus of buphthalmic glaucomatous eyes. Infants with suspected MGC1 should have genetic screening for changes in the *CHRDL1* gene to exclude PCG. In the absence of genetic testing the deep anterior chamber in MGC1 and the low ratio of anterior chamber depth to axial length is a reliable indicator.[9]

Megalocornea is also a feature of megalocornea–mental retardation (MMR; Neuhäuser syndrome). The condition is rare and associated with neurological symptoms including mental retardation, hypotonia, and seizures. Syndromic facial features include a prominent forehead, broad nasal root, epicanthus, large low-set ears, long upper lip, and anteverted nostrils. The genetic cause of MMR syndrome is currently unknown.[9]

Microcornea

Microcornea is a corneal horizontal diameter of ≤9 mm. It may be uni- or bilateral and may be an isolated finding or associated with dysmorphism, microphthalmos or nanophthalmos. It may be associated with posterior polar cataract (microcornea–cataract syndrome with mutations of crystallin genes) (Fig. 34.8), coloboma, sclerocornea, Peter's anomaly, or oculocerebrofacial syndrome.[10] B scan ultrasonography is essential for a full assessment.[11] The cornea can be clear with a normal thickness, but is more usually flat with low keratometry values and a resultant hyperopia, with a risk of secondary glaucoma. When microcornea is an isolated finding, there is a good visual prognosis with correction of refractive error, but other ocular or systemic associations often reduce the vision.

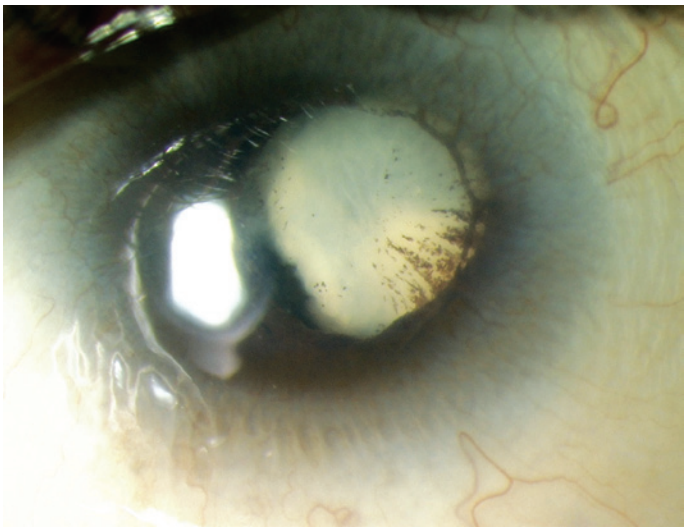


Fig. 34.8 Microcornea and cataract. The corneal diameter was reduced (10 mm) with a flat keratometry (32 diopters). There is a dense cataract and iris abnormality.

Corneal opacity

Congenital corneal opacity is most commonly a feature of (1) genetically determined abnormalities of the anterior segment (dysgenesis) in which there are associated abnormalities of the iris, anterior chamber angle and lens (e.g. Peter's anomaly, congenital glaucoma; see Chapter 33); (2) corneal dystrophy, in which the cornea is usually affected in isolation (e.g. CHED2, sclerocornea/cornea plana; see (Chapter 35); (3) metabolic disease in which abnormal products are deposited in the cornea (e.g. mucopolysaccharidosis; see Chapter 65); (4) choristoma (e.g. dermoid); or (5) external injury from trauma, inflammation or infection (see Chapters 16, 30 and 69). An algorithm for the initial interpretation of congenital corneal opacity is presented in Figure 34.9.

Corneal opacity in older children includes the following conditions.

Superficial keratopathy

This may be a focal, linear, or vortex pattern. The common causes for focal superficial lesions include punctate epitheliopathy from dry eye disease, Thygeson superficial keratopathy (Fig. 34.10), staphylococcal hypersensitivity spots, and adenoviral keratoconjunctivitis. Linear epithelial lesions include dendritic ulceration (herpes simplex) or mucous plaque keratopathy (herpes zoster). A very rare linear kerotopathy associated with tyrosinemia type II is also described as pseudodendritic. Tyrosinemia type II (Fig. 34.11) is due to mutation of the *TAT* gene encoding tyrosine aminotransferase. There is bilateral keratitis with intense photophobia and associated palmar and plantar lesions (palmoplantar keratoderma) and

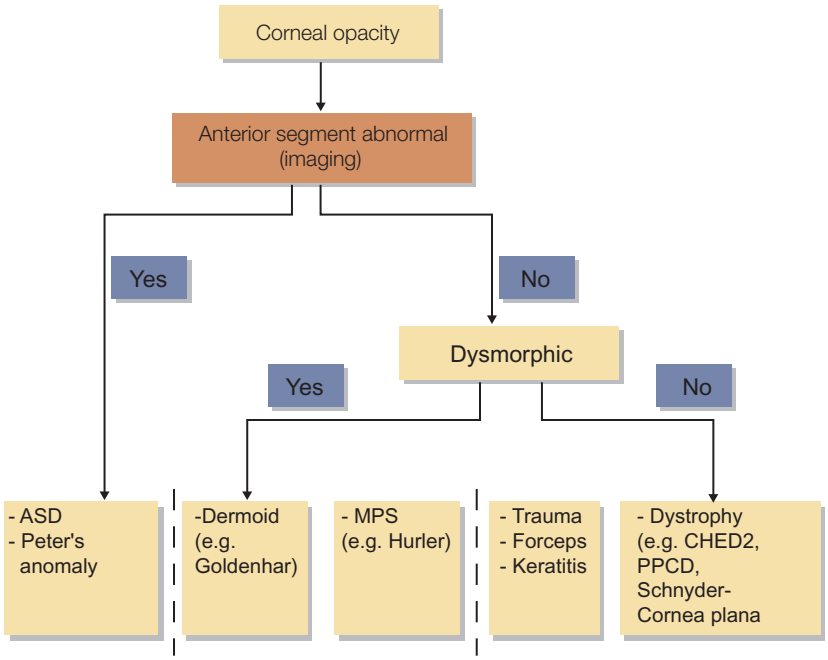


Fig. 34.9 Algorithm for the interpretation of congenital corneal opacity. ASD, Anterior segment dysgenesis, MPS, mucopolysaccharidosis; CHED, congenital hereditary endothelial dystrophy; PPCD, posterior polymorphous dystrophy.

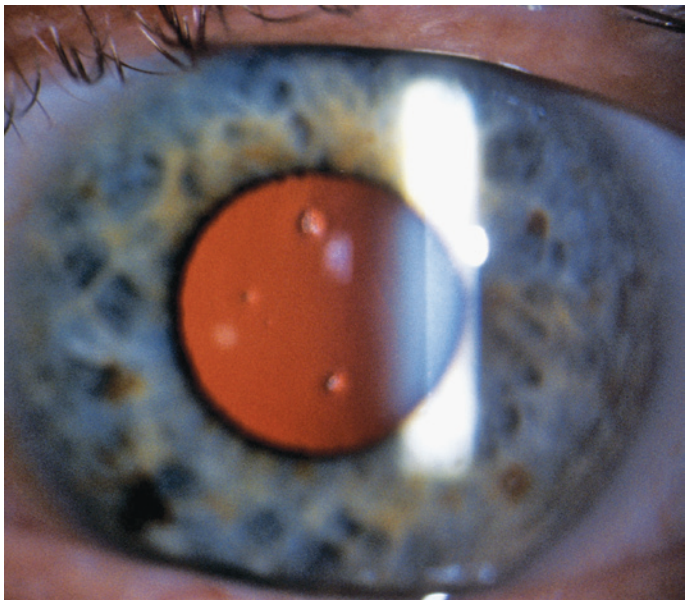


Fig. 34.10 Thygeson superficial keratopathy. Focal lesions are seen in retroillumination. There is no associated inflammation.



Fig. 34.11 Tyrosinemia type II. (A) Skin lesions on pressure points of the sole. (B) Skin lesions on the pressure points of the palms.

developmental delay in 50% of individuals.[12] It is treatable with a low-tyrosine and low-phenylalanine diet.

Vortex keratopathy occurs during epithelial healing, but may also develop following chronic drug ingestion (e.g. amiodarone) (Fig. 34.12), and it is also a feature of Fabry disease, an X-linked recessive lipidosis caused by α-galactosidase-A deficiency, with deposition of glycosphingolipid in the cytoplasm of the epithelial cells. There may also be conjunctival and retinal vascular tortuosity and spoke-shaped cataract.[13]

Thygeson superficial punctate keratitis

This can occur even in children as young as 2 years. There may be photophobia, discomfort, and blurred vision. Coarse elevated epithelial lesions (1 to 50) with minimal stromal

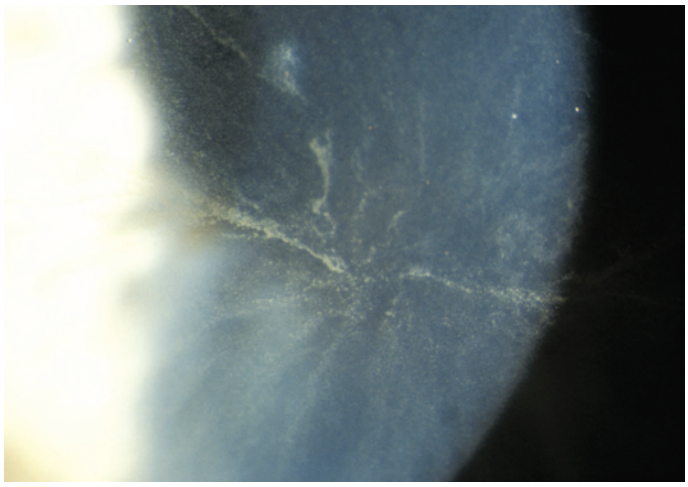


Fig. 34.12 Vortex keratopathy due to chronic drug ingestion (amiodarone).

reaction and an absence of peripheral corneal vascularization or upper tarsal conjunctival inflammation are characteristic (see Fig. 34.10). The cause is a presumed immune response against an, as yet, unidentified pathogen (possibly viral). Initial treatment is with topical lubricants. Low-dose topical steroid (e.g. fluoromethalone 0.1% once daily or less) is effective but may prolong the course of the disease. Topical cyclosporin drops or ointment are also effective.[14] Daily-wear therapeutic contact lenses may be an option for chronic irritation in older children. The lesions recur after epithelial debridement or laser phototherapeutic keratectomy (PTK). Despite a potentially protracted course, the visual prognosis is excellent.

Corneal deposits and crystals

Corneal deposits occur in several conditions; some indicate localized disease, but some have important systemic associations. Corneal deposits are of different types: (1) lipid (e.g. Schnyder crystalline corneal dystrophy), Tangier disease (lecithin–cholesterol acyltransferase deficiency [LCAT]); (2) protein (cystinosis, monoclonal gammopathy); (3) mucopolysaccharide, including Hurler, Scheie, and Hurler–Scheie syndromes (MPS I), Morquio syndrome (MPS IV), and Maroteaux–Lamy syndrome (MPS VI) (Fig. 34.13); (4) bacteria and bacterial biofilm (infectious crystalline keratopathy); (5) mineral deposits (band-shaped degeneration of calcium, calcareous degeneration, hyperuricemia, iron, copper, silver, lead, gold); (6) drug (topical ciprofloxacin, chlorpromazine, chloroquine). In the majority of cases a history of drug therapy, or associated systemic or ocular pathology, will help guide the diagnosis. Biopsy is only rarely indicated for diagnosis.

Cystinosis

Cystinosis is a rare lysosomal storage disease caused by accumulation of the amino acid cystine in lysosomes. There is intracellular crystal formation in tissues including the kidneys, bone marrow, pancreas, muscles, brain, and eye. It is autosomal recessive and caused by mutation of the *CTNS* gene that encodes cystinosin, which is the membrane transport protein for cystine. Cystinosis is classified as nephropathic cystinosis that is further classified as (a) infantile or juvenile onset, accompanied by Fanconi syndrome, or (b) isolated (adult) ocular cystinosis with corneal crystal deposition (Fig. 34.14) but without

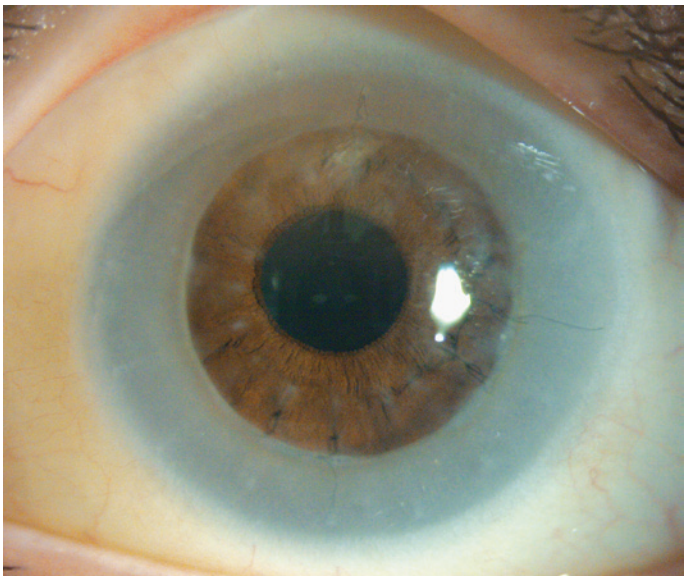


Fig. 34.13 Mucopolysaccharidosis. Lamellar corneal graft 4 years after surgery for a patient with Hurler–Sheie syndrome. The peripheral cornea is hazy but the cornea over the visual axis is clear.

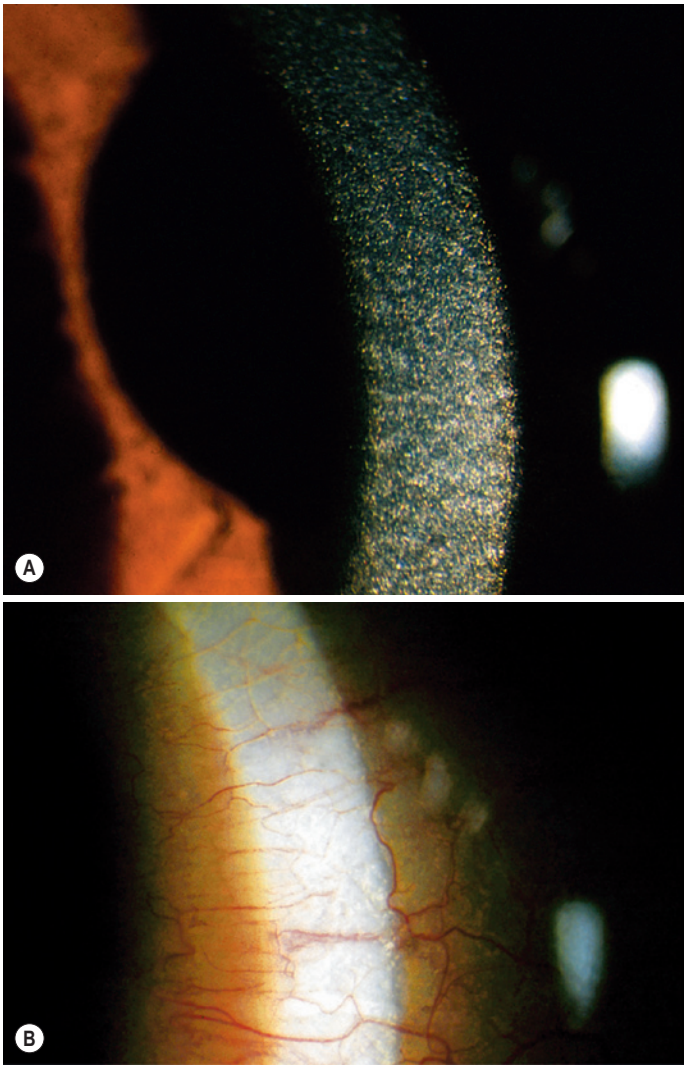


Fig. 34.14 Cystinosis. (A) Corneal crystals can be seen by slit-lamp microscopy. These children are often very photophobic. (B) Crystal deposition occurs in many tissues throughout the body, including the conjunctiva.

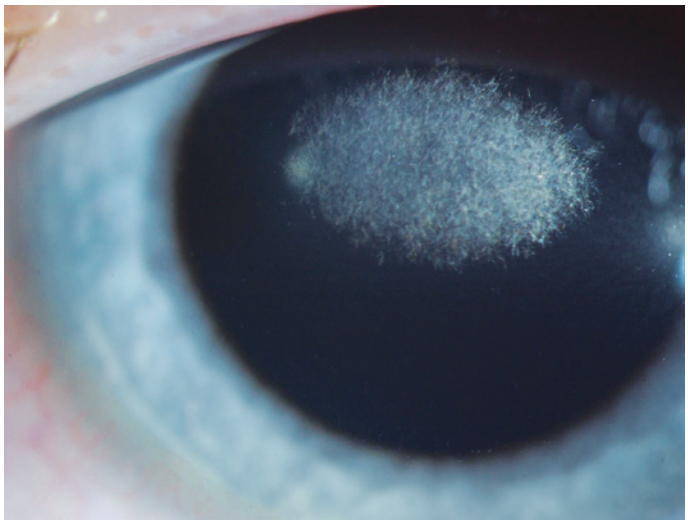


Fig. 34.15 Schnyder corneal dystrophy. Deep stromal crystals present at 8 years of age and acuity of 6/24. The family history was not available.

systemic disease. If there is renal disease, tubular damage leads to loss of carbohydrates and amino acids in the urine with polyuria. Infantile nephropathic cystinosis is the most common and severe form. Systemic manifestations include growth retardation and renal failure between 6 and 12 months of age, with later onset in the juvenile form. There may be end-stage renal disease by 10 years of age. Retinal depigmentation also appears by 3–7 years of age, progressing to legal blindness in 15% of cases. Abnormalities of the anterior chamber angle from crystal deposition in the trabecular meshwork can lead to secondary glaucoma. In the adult form, corneal crystals are present but without significant renal disease.[15]

Patients in all subtypes may be severely photophobic, although the visual acuity may be preserved in reduced light. The corneal appearance is of myriads of needle-shaped, highly refractile crystals, initially concentrated in the anterior periphery, but with spread to involve all layers of the cornea including the endothelium. They are easily identified at the slit-lamp. Secondary corneal changes include superficial punctate keratopathy, recurrent corneal epithelial erosion, filamentary keratitis, and band-shaped keratopathy.

Systemic cysteamine is the treatment of choice for nephropathic disease. This breaks down cystine into smaller products that can traverse the lysosome membrane. Early treatment can protect tubular function and minimize any retinopathy. Oral treatment does not reduce corneal crystal accumulation, probably due to inadequate tissue concentration, but topical cysteamine is a safe and effective alternative. The recommended dose is 0.44% cysteamine hydrochloride solution used 10–12 times per day.[16,17]

Other causes of corneal crystalline deposits include Schnyder corneal dystrophy (Fig. 34.15),[18] which is an uncommon autosomal dominant corneal dystrophy caused by mutation of the *UBIAD1* gene.[19] It presents in young children from 3 to 4 years of age with axial stromal crystalline deposits of lipid (cholesterol), as opposed to the diffuse stromal haze seen in adults. Corneal arcus and superficial stromal crystals are also more characteristic of the disease in adults. Lamellar keratoplasty may be indicated if there is glare and reduced vision. The stromal crystals are normally too deep to be removed by laser phototherapeutic keratectomy.

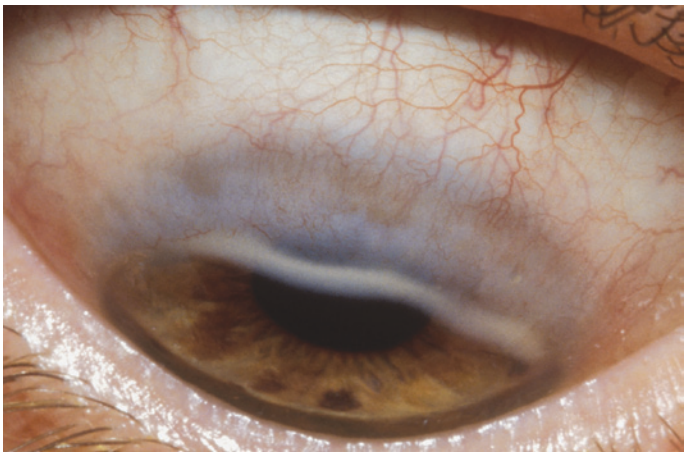


Fig. 34.16 Corneal arcus (pseudogerontoxon). There is lipid deposition central to an area of recurrent inflammation from limbal vernal keratoconjunctivitis.

The corneal crystals of Bietti retinopathy are tiny, peripheral, and do not affect vision.

Lipid deposition

The deposition of lipid in the cornea is normally preceded by corneal neovascularization (e.g. following recurrent stromal herpes simplex virus [HSV] keratitis or vernal keratoconjunctivitis), but may also develop in an arc (pseudogerontoxon) central to an area of recurrent conjunctival or episcleral inflammation at the limbus (e.g. limbal vernal keratoconjunctivitis) (Fig. 34.16). It may also develop as a complication of congenital vascularization (e.g. perilimbal dermoid or aniridic keratopathy). Treatment is only required if the lipid is progressive and approaches the visual axis.

Corneal arcus

Corneal arcus is the deposition of phospholipids, low-density lipoproteins, and triglycerides in the stroma and of the peripheral cornea in the absence of an epithelial defect (Fig. 34.17). When this appears in children, familial hypercholesterolemia (Fredrickson type II) and hyperlipoproteinemia (type III) should be excluded.[20]

Diffuse lipid infiltration and opacity can occur in other diseases of lipid metabolism such as lecithin–cholesterol acyltransferase deficiency (LCAT) deficiency, fish eye disease and Tangier disease.[18]

Corneal vascularization

Acquired corneal neovascularization is most frequently seen as a result of ocular surface diseases. The primary stimulus in tissue is thought to be hypoxia. It can affect vision by opacity, secondary lipid deposition, or irregular astigmatism. The first step in management is to remove the precipitating stimulus (e.g. contact lens wear) and control any ocular surface inflammation (e.g. chronic allergic eye disease, herpes simplex infection). This can be supplemented by the careful use of topical steroid. If secondary lipid deposition threatens to cross the visual axis, the feeder arteriole can be ablated by fine-needle diathermy.[21] To guide treatment, the feeder arteriole can be visualized by indocyanine green angiography.[22] Although it

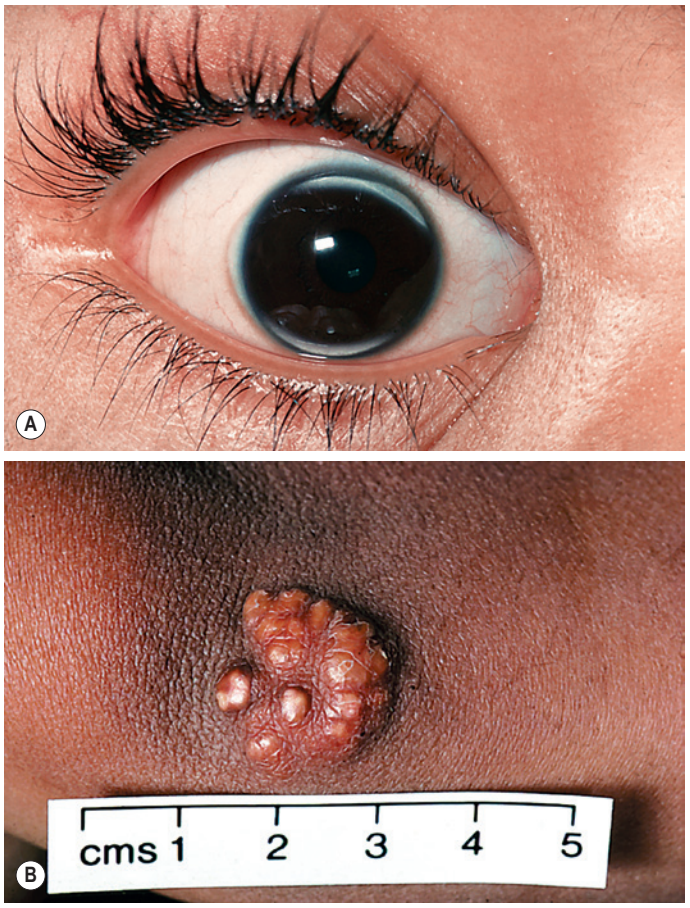


Fig. 34.17 Corneal arcus. (A) Corneal arcus in a patient with hyperlipidemia. (B) Skin xanthoma in hypercholesterolemia.

is used in adults, the safety of local anti-vascular endothelial growth factor (VEGF) treatment (e.g. bevacizumab) in children has not been confirmed.[23,24] Even after the feeder vessels have regressed, the lipid may takes months or years to regress, and only partial regression is usual. Established vascularization (>6 months duration) will not respond to anti-VEGF therapy and lamellar keratoplasty may be indicated.

Epibulbar dermoid

A dermoid is a choristoma, which is a collection of normal tissues in an abnormal location. They are a combination of ectodermal (keratinized epithelium, hair, sebaceous glands) and mesodermal elements (fibrous tissue, fat, and blood vessels) (Figs 34.18–34.20). Most are sporadic and unilateral (Chapter 29), but they may be multiple and associated with oculoauriculovertebral dysplasia (Goldenhar–Gorlin syndrome) or the sebaceous nevus syndrome (Fig. 34.21). Epibulbar (limbal) dermoids are usually situated at the inferotemporal corneoscleral junction but they may be much more widespread and overlie a microphthalmic or staphylomatous eye. They can involve the entire thickness of the cornea and sclera and may affect vision by occlusion of the visual axis, induced astigmatism or secondary lipid keratopathy, any of which can result in amblyopia.[25] A central corneal choristoma may occur sporadically but may also be a feature of trisomy 8 mosaic (see Fig. 34.20).

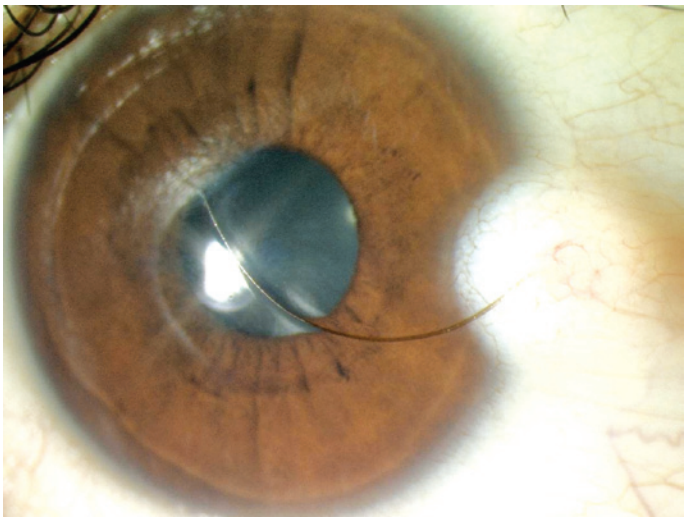


Fig. 34.18 Epibulbar dermoid. An aberrant lash is abrading the cornea.

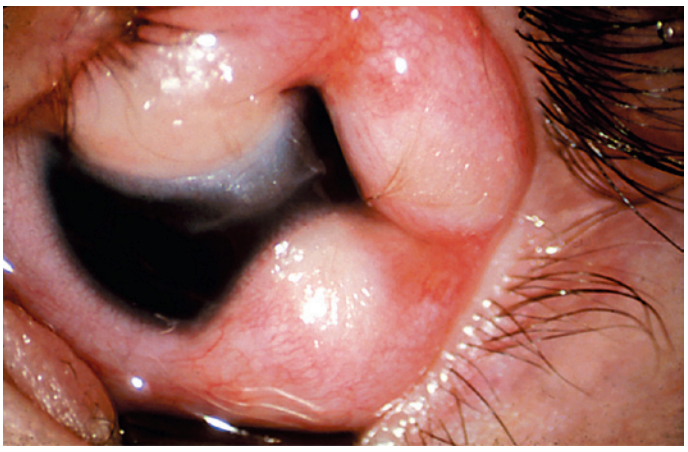


Fig. 34.19 Multiple epibulbar dermoids in a patient with Goldenhar syndrome.

The primary indications for treatment are for cosmesis, to remove irritating keratin or abrading lashes, for dellen formation from drying, or to prevent progressive lipid keratopathy. Because the lesion is often full thickness, excision may not improve vision or reduce astigmatism. High-resolution biomicroscopy can help determine the extent of the mass. Elevated dermoids can simply be resected to a plane level with the surrounding tissue. Alternatively, a deeper lamellar keratectomy can be performed with placement of a donor corneal lamellar graft (Fig. 34.22). Lamellar excision should be performed with care as there may be no plane for deep dissection through the abnormal tissue, and perforation is possible. The cosmetic result following lamellar keratoplasty may not be substantially better than "shaving" if there is deep opacity. Topical mitomicin applied to the base of the excision during surgery may reduce the risk of secondary conjunctival overgrowth onto the cornea (pseudopterygium).[26] If there are multiple dermoids over a microphthalmic eye, enucleation may be considered, delaying treatment if possible to allow for orbital growth.

Corneal vascularization can also be a component of presumed limbal epithelial stem cell failure, related to inherited

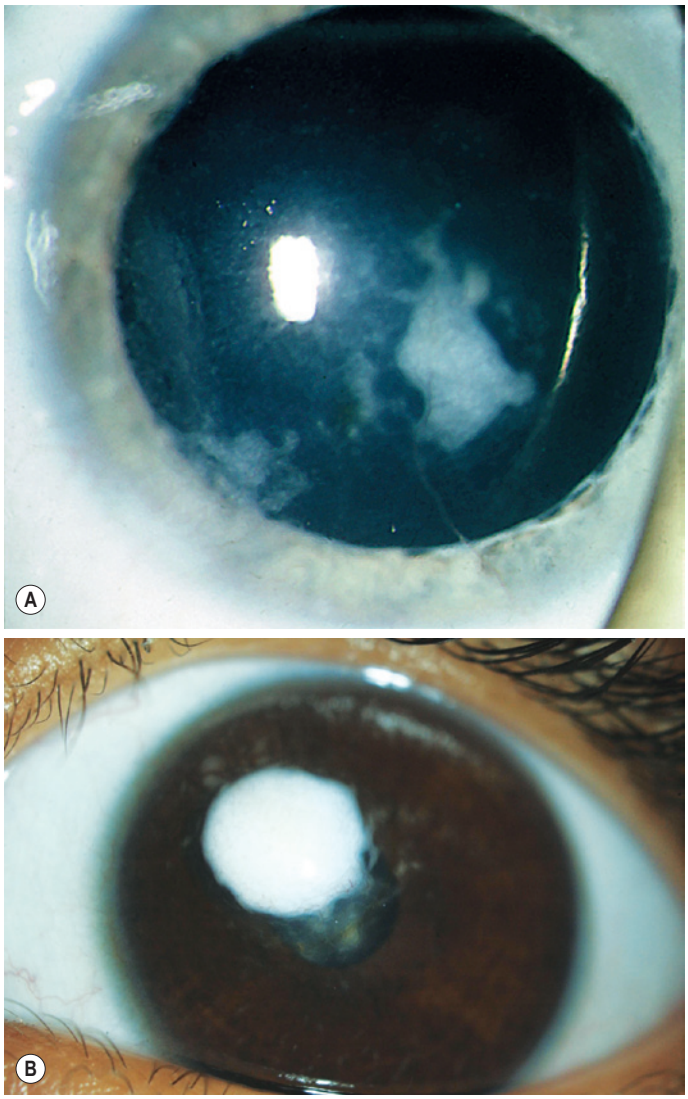


Fig. 34.20 Central corneal dermoid (choristoma). (A) Trisomy 8 mosaic syndrome with characteristic geographic corneal opacity. (B) Sporadic case without other association.

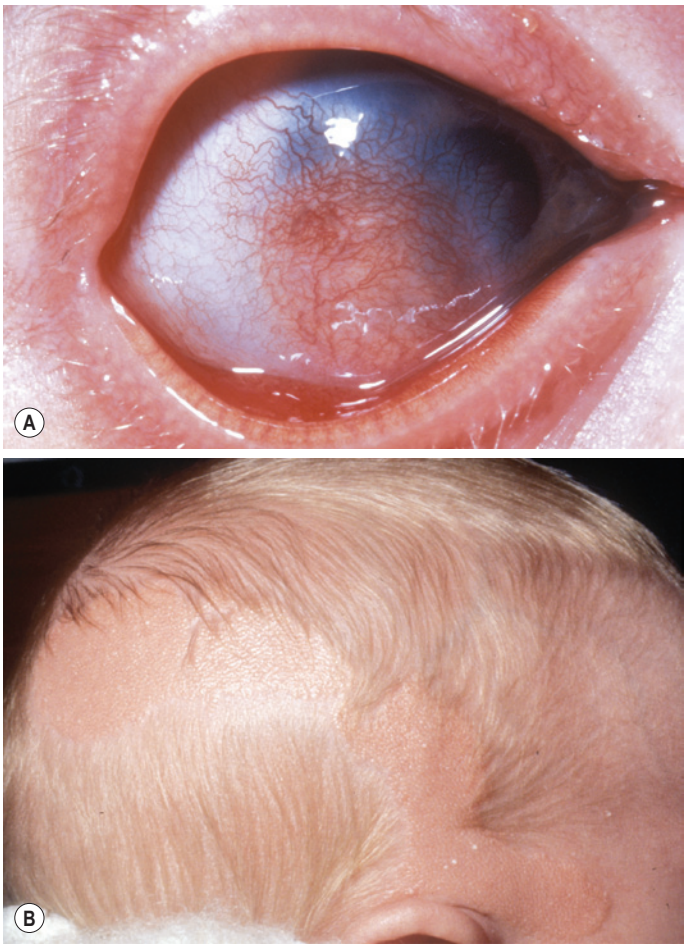


Fig. 34.21 Sebaceous nevus syndrome. (A) Associated with a flat limbal dermoid. (B) Characteristic scalp lesion of patient with sebaceous nevus syndrome.

conditions such as anirida and ectodermal dysplasia, or injury following chemical or thermal burns.

Aniridic keratopathy

Aniridia is an anterior segment developmental disorder (see Chapter 33). In sporadic cases, the WAGR (Wilms tumor, aniridia, genitourinary abnormality, retardation) syndrome should be excluded. WAGR is the result of deletion of a contiguous region of genes on chromosome 11, including the *PAX6* gene. One component of aniridia is peripheral superficial corneal vascularization and subepithelial scarring that is thought to be the result of limbal epithelial stem cell failure (Fig. 34.23). The changes typically progress very slowly but can eventually involve the entire corneal surface. The more severe changes in familial cases are linked to loss of function and *C*-terminal mutations of *PAX6*.[27] Children with poor vision and an unexplained corneal vascularization with scar in the absence of inflammation should be screened for *PAX6* mutations as part of any genetic work-up. Topical corticosteroid or fine-needle diathermy does not prevent progression of the keratopathy and is not indicated. If cataract surgery is required, the axial subepithelial scar can be peeled off to improve visualization during surgery. Unfortunately, there is a strong tendency for recurrence of aniridic keratopathy after simple excision. It is unknown if the topical application of mitomycin during surgery reduces the risk of recurrence. A tinted rigid contact lens should be considered for older children if there is irregular astigmatism.

Ectodermal dysplasia

The ectodermal dysplasias are a large heterogenous group of disorders in which there are abnormalities of the ectoderm, involving the skin and its appendages. Many are X-linked or autosomal recessively inherited with abnormal or absent eccrine glands, wispy or absent hair, and abnormal teeth or nails. One of the most frequently encountered for ophthalmic review is the ectrodactyly, ectodermal dysplasia, cleft (EEC) syndrome in which there are obvious cleft palate and hand and foot deformities associated with mutations in the *TP63* gene.

Ocular abnormalities include anterior blepharitis, conjunctivitis, superficial corneal vascularization with scarring, and symblepharon, entropion, and trichiasis (Fig. 34.24). Meibomian and lacrimal abnormalities may lead to secondary ocular surface disease resulting in keratopathy, infection, and

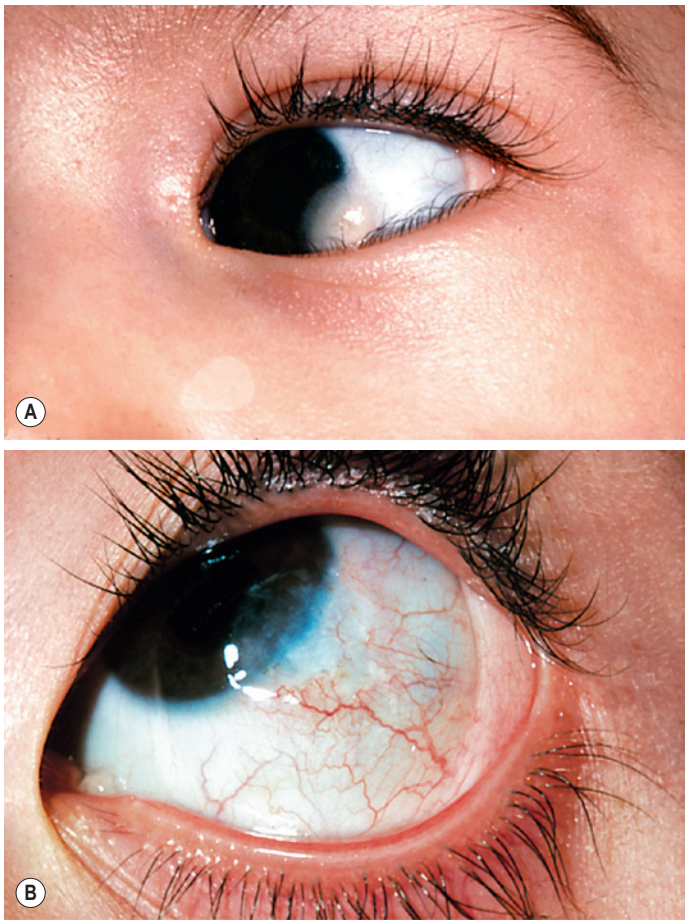


Fig. 34.22 Limbal dermoid. (A) The indication for surgery was the cosmetic appearance. (B) Same case as in (A) after lamellar keratectomy. Although there is still some residual corneal opacity the lesion is now flat and cosmetically improved.

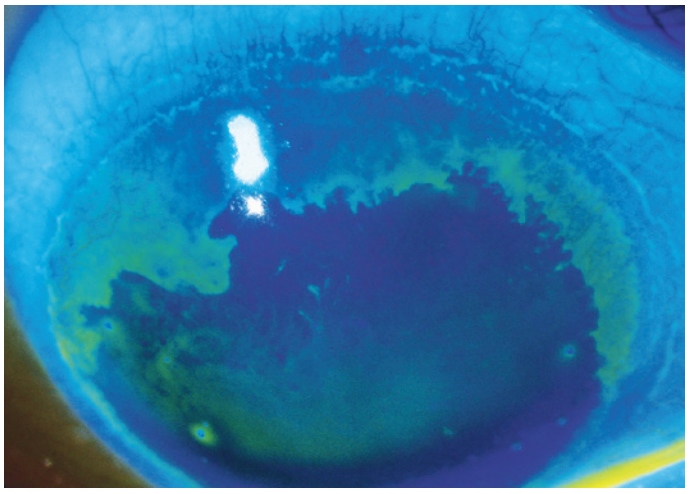


Fig. 34.23 Aniridic keratopathy. There is late stain with fluorescein in the peripheral cornea. This is thought to represent encroachment on a conjunctival cell phenotype. This can progress to vascularization and scar involving the visual axis.

scarring. Management is generally supportive with topical lubricants. Primary or secondary limbal stem cell deficiency is thought to be the mechanism for corneal vascularization and a limbal allograft has been suggested as a strategy to improve the ocular surface.

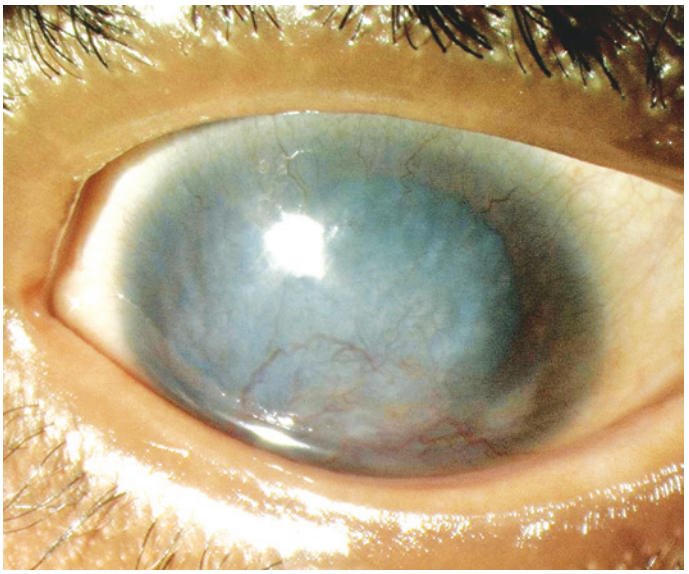


Fig. 34.24 Ectodermal dysplasia. Severe ocular surface failure in a patient with EEC (ectrodactyly, ectodermal dysplasia, cleft) syndrome. Many cases are not as severe as this. Note that the meibomian gland orifices are absent.

Prominent corneal nerves

Corneal nerves and nodules are normally visible passing radially from the periphery toward the center of the cornea. They may be more prominent in children in certain conditions, but their presence is rarely of diagnostic or prognostic value except if there is a perineural infiltrate (*Acanthamoeba* infection). Prominent nerves may be present in:

1. keratoconus
2. Riley–Day dysautonomia
3. leprosy
4. Refsum disease
5. ichthyosis
6. multiple endocrine neoplasia (MEN) type IIa and IIb

Neurotrophic keratitis

Corneal sensation is provided by the fifth cranial nerve. The origin of neurotrophic keratitis is the result of loss of the trophic stimuli (e.g. nerve growth factors) delivered to the cornea by retrograde axonal flow. This can be exacerbated by corneal exposure, mechanical trauma, and drying.[28] Any severe keratitis can lead to a reduced corneal sensation, and a recurrent keratitis with a relative lack of symptoms is suggestive of anesthesia.

Neurotrophic keratitis can be chronic, recurrent, and severe. It is rarely congenital in familial dysautonomia (Riley–Day syndrome) (Fig. 34.25), but is more commonly acquired following trauma, herpes zoster or simplex infection, and brain stem lesions or tumors, particularly of the cerebello-pontine angle or pons. The presence of scars on the forehead may suggest trigeminal anesthesia or previous shingles. Corneal anesthesia can be profound and care should be taken during an assessment to avoid causing an abrasion. Patients with

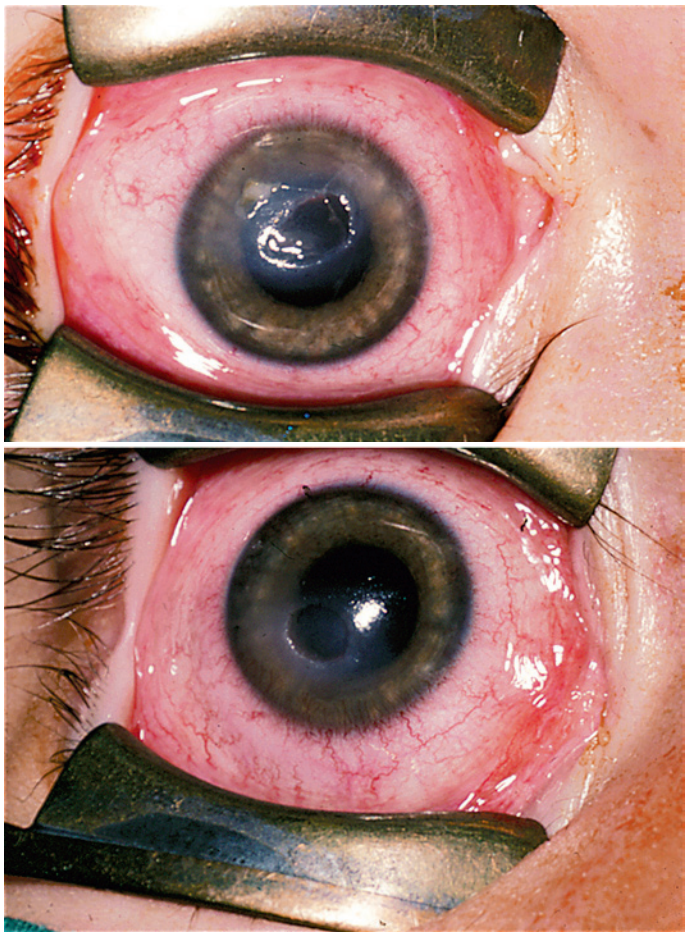


Fig. 34.25 Riley–Day syndrome. This child had a combination of anesthetic corneas and dry eyes that had been treated for several months by topical wetting agents without success. He responded well to a bilateral tarsorrhaphy and lubricant ointment. Later, punctal occlusion allowed enough wetting of his eyes to allow the tarsorrhaphies to be undone.

acquired loss of corneal sensation in the absence of prior keratopathy should be referred for neurological evaluation.

Treatment in infancy

A high level of parental involvement is essential. In mild cases, the frequent use of topical (non-preserved) lubricant drops can help prevent epithelial breakdown. An acute epithelial defect should be treated with antibiotic drops or ointment or temporary taping of the eye. If there is recurrent epithelial breakdown or a persistent epithelial defect, the eye should be closed. Taping is a useful temporary measure, but a tarsorrhaphy is more effective. An outer-third tarsorrhaphy can be partially opened at a later date. A period of arm-splinting may be necessary to prevent eye rubbing in infants.

Treatment in childhood

In older children a therapeutic soft contact lens should be considered. A scleral contact lens will maintain a reservoir of tears on front of the cornea, even if there is incomplete lid closure. Serum tears drops (autologous or pooled) are an option if there is a persistent epithelial defect. Synthetic nerve growth factor is a promising option, although it is not yet widely available.

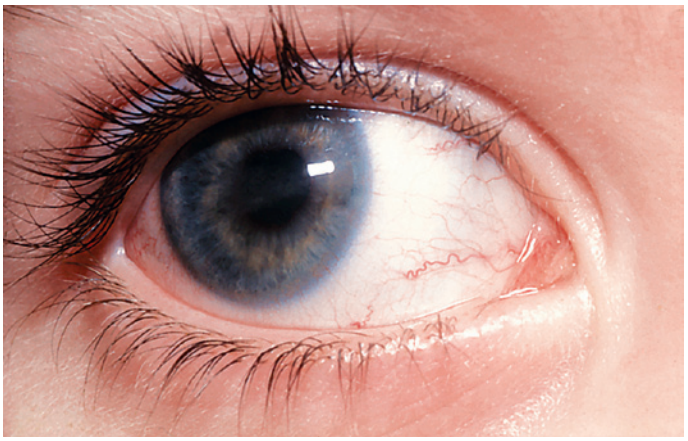


Fig. 34.26 Band keratopathy. A patient with juvenile idiopathic arthritis (see Chapter 40).

Corneal degeneration

Band-shaped corneal degeneration

Superficial band keratopathy occurs in children with juvenile idiopathic arthritis (see Chapter 40), chronic corneal edema (congenital glaucoma), or following vitrectomy, particularly if silicone oil is left *in situ*. The band (Fig. 34.26) is a precipitate of calcium hydroxyapatite in Bowman's layer and the superficial corneal stroma.[29] It typically develops in the interpalpebral zone, often with a clear zone between the deposit and the limbus, and there may be clear areas in the band surrounding perforating nerves. Less commonly, conditions causing systemic hypercalcemia or hyperphosphatemia can cause band keratopathy, e.g. chronic renal failure, sarcoidosis, or hyperparathyroidism. Deep corneal calcification (calchosis) is more common in phthisis bulbi, chemical trauma, Stevens–Johnson syndrome, and graft-versus-host disease. It can also occur following the use of drops with a high concentration of phosphate buffer.

In cooperative older children, a superficial smooth band keratopathy can be removed by excimer laser PTK using topical anesthesia. This removes 30–50 µm of stromal tissue. Unfortunately, because of the location of most lasers, this is rarely an option if general anesthesia is required. An alternative is chelation of the superficial band following debridement of the epithelium and direct application of 3.8% EDTA on a soaked cotton-tipped applicator. EDTA is an irritant, so avoid the conjunctiva. It can take several minutes for the band to disperse. A dense irregular band keratopathy that is eroding the epithelium is more easily removed by a limited superficial keratectomy using a crescent blade. There is a strong tendency for the band to recur, but the treatment can be repeated as required. There is no topical treatment that will reduce the tendency for recurrence.

Dermatological associations

The most common skin changes associated with corneal opacity are acne vulgaris and rosacea, atopic dermatitis (see Chapter 16), Stevens–Johnson syndrome/toxic epidermal necrolysis (TEN), and graft-versus-host disease (see Chapter 16). Other recognized associations are given below.

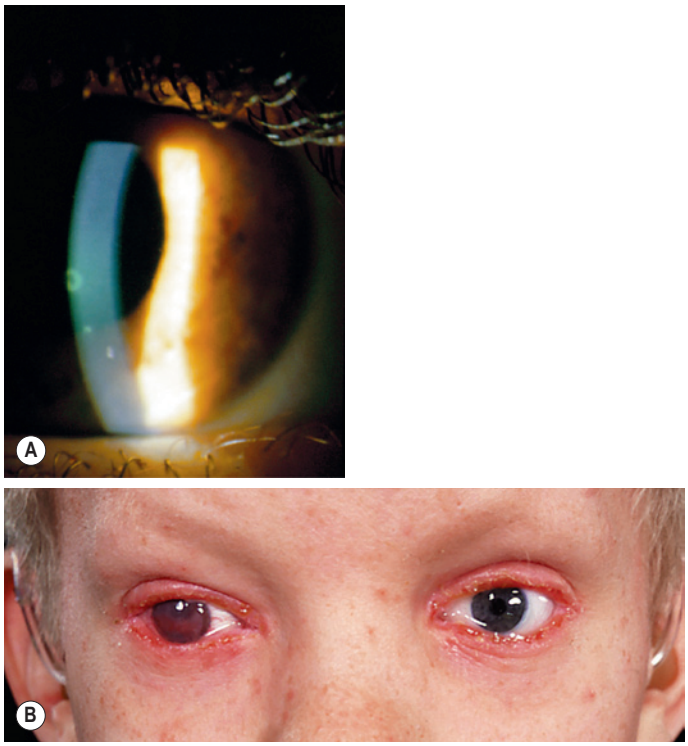


Fig. 34.27 Ichthyosis. (A) Fluorescein-staining superficial corneal lesions. (B) KID (keratitis, ichthyosis, deafness) syndrome with deafness (the patient is using hearing aids) and severe bilateral keratopathy. The left is an artifical eye following enucleation.

Ichthyosis

Lamellar ichthyosis and ichthyosis linearis circumflexa are severe autosomal recessive disorders associated with tight skin that gives rise to secondary ectropion and corneal disease from exposure, with scarring, infection, and perforation. Keratitis is also a major feature of the KID (keratitis, ichthyosis, deafness) syndrome (Fig. 34.27). KID syndrome is caused by mutations in the *GJB2* gene that codes the epithelial gap junction protein connexion 26. The keratitis has variously been attributed to keratin obstruction of the lacrimal gland ductules, recurrent epithelial breakdown, or limbal stem cell deficiency. Treatment with lubricants and topical corticosteroids has a limited effect.

X-linked ichthyosis is the result of mutations in the steroid sulfatase (*STS*) gene. Affected individuals have scaling of the scalp, face and neck, abdomen, and limbs. Superficial punctate keratopathy occurs and scarring may be exacerbated by eyelid abnormalities. A diffuse pre-Descemet's "dystrophy" is rarely visually significant.

Incontinentia pigmenti

This autosomal dominant condition is due to an X-linked dominant mutation of the *NEMO* (*IKBKG*) gene and is thus much more common in females. It is associated with retinopathy and characteristic linear pigmented changes (Chinese writing) of the skin in older children (see Chapter 42). Some individuals develop large numbers of small intraepithelial cyst-like corneal deposits (Fig. 34.28). These may be associated with photophobia and discomfort, but rarely cause erosion. They rapidly recur after epithelial debridement. There is no specific treatment but topical lubricants or a therapeutic bandage contact lens may be helpful.

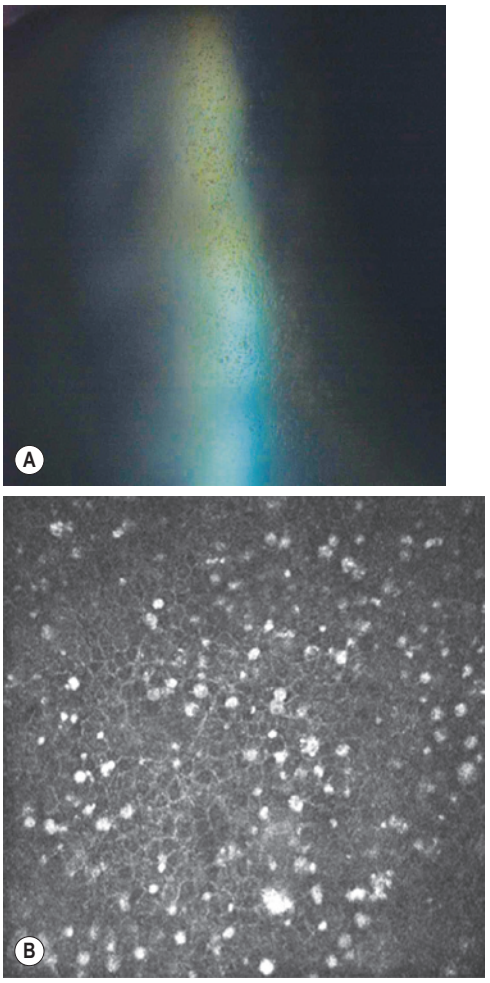


Fig. 34.28 Incontinentia pigmenti. (A) Tiny intraepithelial inclusions associated with photophobia and discomfort. (B) Inclusions visualized with confocal microscopy.

Recurrent corneal epithelial erosion

This occurs less commonly following an injury (e.g. finger nail) in children than adults. Management is with topical lubricants and an ointment at night, continued for several weeks after symptoms resolve to prevent recurrence. An extended-wear soft contact lens should be considered if symptoms persist. Alcohol delamination of the epithelium, or laser PTK, are options for severe cases. Meesmann dystrophy (mutations of *KRT3* or *KRT12*) and epithelial recurrent erosion dystrophy (ERED; *Col17a1* mutation) can both cause pain and photophobia in children, however they are rare and there is usually a strong family history. The *TGFB1*-associated corneal dystrophies (e.g. Reis–Buckler, lattice dystrophy) rarely progress to cause epithelial erosion in childhood (see Chapter 35). Recurrent erosion and scar can also be a feature of epidermolysis bullosa (Fig. 34.29).

Interstitial keratitis

Interstitial keratitis (IK) is an immune-mediated, non-ulcerative inflammation of the corneal stroma (Fig. 34.30). The epithelium and endothelium are often unaffected. In a minority of cases, it is associated with potentially severe systemic disease that requires medical management. HSV is the

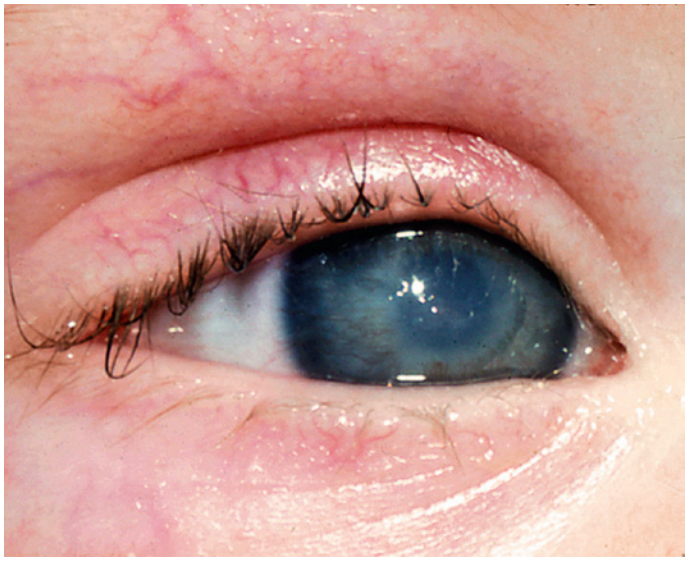


Fig. 34.29 Epidermolysis bullosa. Although many cases of epidermolysis bullosa do not have corneal changes, some, like this patient, develop acute epithelial erosions as a result of minor trauma, which if repeated result in permanent corneal opacity and vascularization.

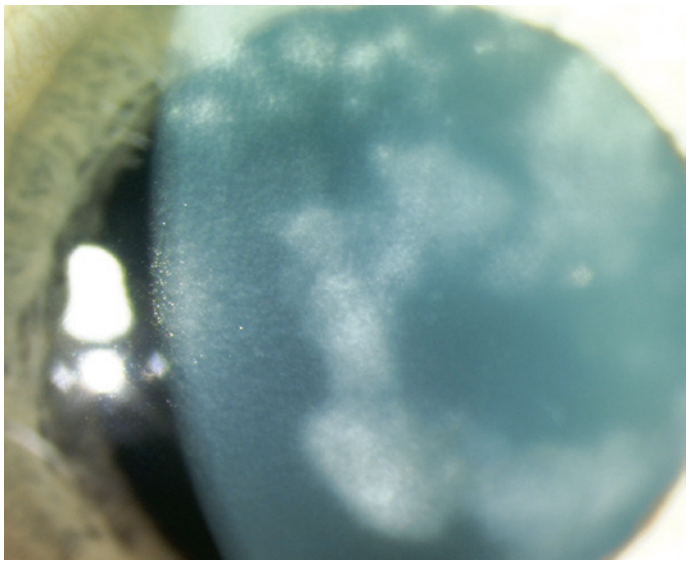


Fig. 34.30 Interstitial keratitis. Deep stromal opacities in a 10-year-old associated with Epstein–Barr virus infection.

most common cause, and although there are numerous other causes the majority are rare. IK may be unilateral or bilateral, diffuse, sectorial, peripheral, or focal, and may affect any layer of the stroma. There may be vascularization or an associated uveitis. It should be distinguished from lipid infiltration or scar.

Symptoms include photophobia and discomfort, although some cases may be asymptomatic and first noted by the parents. There is corneal opacity often with perilimbal injection. Untreated the inflammation can lead to secondary neovascularization, with residual ghost vessels when the acute phase settles, and Descemet's layer wrinkles or scrolls. It is thought to be the result of a hypersensitivity response to antigens, or antigen-bearing cells, in the corneal stroma. Treatment with topical steroids is effective unless there is associated secondary scarring or lipid keratopathy, which will be permanent. If HSV is a potential diagnosis, treatment should include topical or oral acyclovir.

The principal causes are viral, bacterial, and protozoal. However, if the IK is inactive, the majority of cases have no identifiable cause (i.e. idiopathic).

- Herpes simplex stromal keratitis is the most common cause for active IK in developed countries, accounting for over 70% of cases.
- Herpes zoster stromal keratitis is the second most common cause, presenting as either a focal anterior stromal keratitis or a late diffuse keratitis associated with scarring, vascularization, and lipid deposition. There may be a history of shingles or forehead scarring.
- Epstein–Barr virus and mumps virus can cause multifocal discrete anterior stromal opacities that develop several days or weeks after systemic disease. It may respond to topical steroid. Systemic antiviral therapy is not required.
- Congenital syphilis (acquired infection with the spirochete *Treponema pallidum*) is rare in children, although it was once synonymous with IK and is still a major cause of IK worldwide. Screening during pregnancy and treatment with antibiotics has dramatically reduced the incidence. The features are diffuse corneal edema that is bilateral in 80% of cases followed by circumferential intense deep vascularization (salmon patch). Secondary degenerative changes progress into adulthood. The associated signs of congenital syphilis are nerve deafness, abnormal teeth, and characteristic changes of the nose and face. Diagnosis in collaboration with an infectious diseases consultant is confirmed by serologic testing, a positive non-treponemal test (the Venereal Disease Research Laboratory test [VDRL] or rapid plasma reagin test [RPR]) confirmed with a treponemal test (the fluorescent treponemal antibody absorption test [FTA-ABS]) or microhemagglutination. Systemic treatment is essential, but the corneal changes are helped by topical steroid.
- Tuberculosis is most frequently associated with granulomatous uveitis, but IK may be associated with sectorial sclerokeratitis.
- Leprosy is uncommon in children. The stromal infiltration of leprosy is a bilateral superotemporal wedge of infiltration followed by vascularization. Secondary corneal anesthesia and lagophthalmos due to involvement of the fifth and seventh cranial nerves is more common in adults.
- Lyme disease is caused by tick-transmitted infection with a number of different species of the spirochete *Borrelia*. There may be a history of travel to endemic areas in North America and Eurasia and preceding flu-like symptoms and skin lesions (bull's eye rash, erythema migrans), central nervous system, heart, and joint involvement. The commonest ocular feature (10% of cases) is a mild transient conjunctivitis and periorbital edema, with corneal changes (3% of cases) a late feature, with nummular opacities that may vascularize in untreated disease. Optic neuritis, intermediate uveitis, retinal vasculitis, and cranial nerve palsies may occur. Diagnosis is confirmed by an enzyme-linked immunosorbent assay (ELISA) or polymerase chain

reaction (PCR) of serum, and systemic treatment with amoxicillin or doxycycline is required, although the corneal changes respond to topical steroid.

- Onchocerciasis (river blindness) is a regionally important cause of corneal opacity that is becoming less common with eradication programs. It is caused by infection by the parasitic helminth *Onchocerca volvulus* that is transmitted by *Similium* blackflies in endemic areas. Inflammation is stimulated by microfilaria that have migrated from the conjunctiva into the cornea where they have died. In children, a pattern of superficial punctate lesions (snowflake keratitis) due to inflammation stimulated by dead parasites in the cornea is seen. In adults, this may progress to sclerosing keratitis that spreads centrally from the limbus in the interpalpebral zone accompanied by deep vascularization. Vision may be lost as a result of retinitis or secondary glaucoma. Treatment is with oral ivermectin, usually given as part of a community-based eradication program.

  Leishmaniasis and trypanosomiasis are protozoal infections that can cause IK.
- Cogan syndrome is a rare autoimmune disease that can occur in children, although the mean age of onset is in the 30s. There is inflammation directed against an antigen found in the cornea and inner ear, with an associated vasculitis. Onset of eye discomfort, redness, and photophobia is preceded by an upper respiratory tract infection in half of cases. The early corneal changes are bilateral peripheral focal posterior stromal opacities with subepithelial infiltrates, with mild secondary vascularization. There may be a gradual onset of symptoms of nausea, vertigo, and tinnitus similar to Ménière disease. Atypical Cogan syndrome may have conjunctivitis, subconjunctival hemorrhage, episcleritis, uveitis, and retinal vasculitis. Atypical features should alert the clinician to the possibility of alternative diagnoses, such as juvenile arthritis, ulcerative keratitis, etc. There are no specific laboratory abnormalities. The importance of recognizing this condition is the association with deafness and vestibular symptoms. Urgent treatment with high doses of oral corticosteroid and subsequent immunosuppression is required to prevent rapid progression of auditory loss, although this develops in 50% of cases despite treatment. Late onset aortitis can occur.[30]
- Reactive arthritis (Reiter syndrome) characterized by inflammatory arthritis of large joints, urethritis, and ocular inflammation is commonly associated with conjunctivitis and iridocyclitis. Approximately 75% of individuals are HLA-B27-positive, with inflammation possibly triggered by infection (e.g. *Chlamydia*). Mainly peripheral anterior stromal keratitis, epithelial erosions, and more diffuse subepithelial and anterior stromal infiltrates associated with fine conjunctival papillae occur. These lesions resolve with topical corticosteroids but systemic management is also required.

Keratomalacia

The conjunctival features of hypovitaminosis A are described in Chapter 31. If there is severe and chronic A deficiency, the corneal surface can become involved with severe punctate keratitis, vascularization, and edema. Keratomalacia is acute liquefactive necrosis of the cornea, often precipitated by measles infection, diarrhea, herpes simplex, or the use of traditional eye medicines. Management for superficial changes is vitamin supplements. The natural history of keratomalacia is adherent leukoma and vascularization of the cornea, or phthisis (Fig. 34.31). Systemic vitamin supplements and topical antibiotic may halt the progression of the corneal melting. A tectonic keratoplasty (if available) may be required, although the visual outcome is poor, or a conjunctival flap.[31]

Corneal exposure

Exposure keratitis is damage to the ocular surface from inadequate lid protection. This initially results in epitheliopathy, subepithelial and anterior stromal scarring, and, later, corneal neovascularization. In severe cases, often associated with infection, persistent epithelial defect, stromal thinning, and corneal perforation can occur (Fig. 34.32).

Eyelid defects (colobomas, etc.), seventh cranial nerve palsy, or tight skin (lamellar ichthyosis) may cause exposure keratitis. Amniotic bands may be associated with congenital

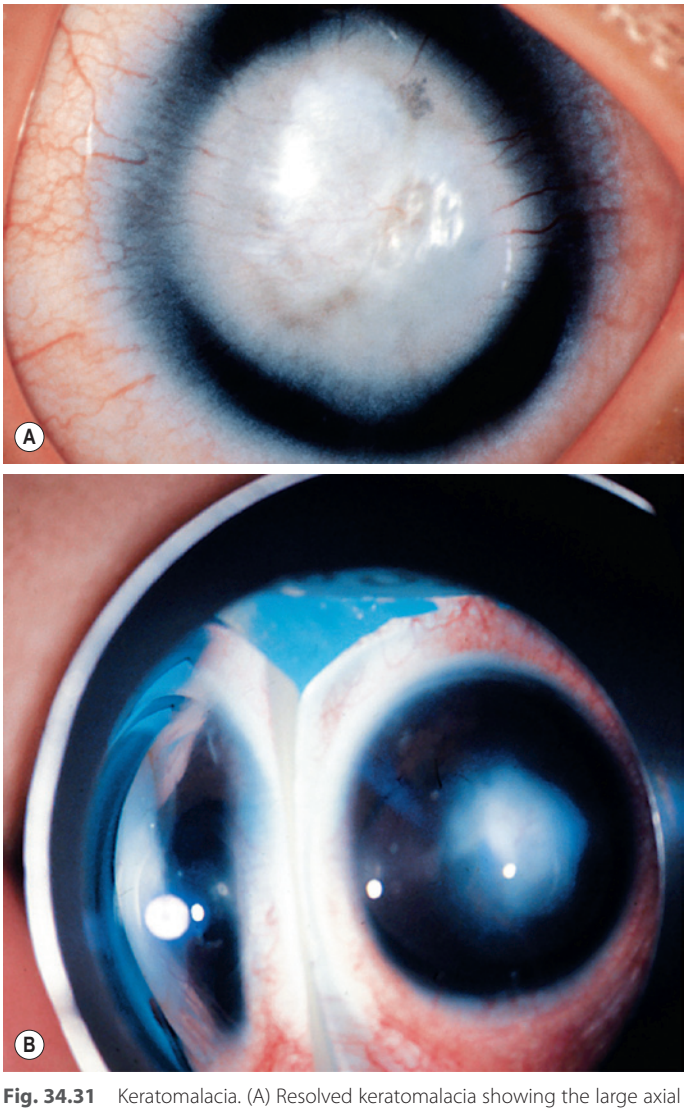


Fig. 34.31 Keratomalacia. (A) Resolved keratomalacia showing the large axial scar. (B) Gonioscopic view showing the iris attached to the posterior surface of the cornea – an adherent leukoma.

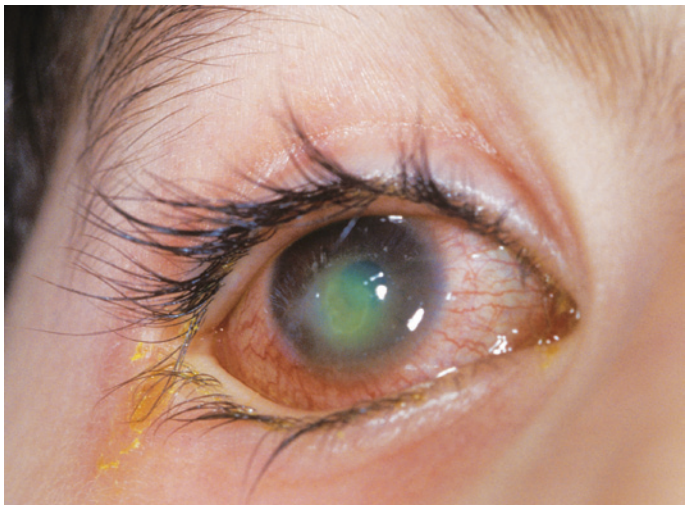


Fig. 34.32 Corneal exposure. Patient with Möbius syndrome. There is poor eye movement and incomplete lid closure leading to epithelial breakdown.

corneal leukomas or with exposure keratitis from lid defects. Exophthalmos from orbit disease or craniofacial abnormalities (see Chapter 28) can result in poor lid closure. The combination of exposure from seventh nerve palsy and neurotrophic keratopathy from fifth nerve palsy, as in Möbius syndrome, is a major management problem. Immediate management requires protection of the eye with ointment and lubrication, or a moist chamber fashioned from plastic drape taped to the periocular skin; however, surgical intervention, usually tarsorrhaphy, to establish better eyelid protection of the ocular surface is usually required.

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Corneal dystrophies

Hans Ulrik Møller and Barry Lee

Chapter contents

DEFINITION
CLASSIFICATION
MUTATION RATE
MANAGEMENT
REFERENCES

Corneal dystrophies are rare Mendelian inherited conditions that exhibit bilateral and usually symmetrical corneal changes.

Nomenclature has been difficult because of controversies about phenotype definitions. Many authors have reported different phenotypes using the same headings, or the same phenotype using different headings (see below under "Classification"). This chapter will focus on a few classic dystrophies, highlighting the clinical presentation in children and emphasizing the differences from adults. It is difficult to document photographically the subtle changes associated with corneal dystrophies in children. The clinical pictures in this chapter look almost alike. However, when examining children for a corneal dystrophy, do not look for the slit-lamp appearance found in adults. You need to look for subtle opacities, which may be similar to the adult clinical picture, but the final diagnosis is made after examining the whole family. Most of the dystrophies are progressive, and the figures illustrate how different the clinical picture may be in children.

The literature on pediatric corneal dystrophies is meager.[1] The one exception is lattice corneal dystrophy.[2] Only a few of the 22 entities called *Corneal Dystrophies* in the International Committee for Classification of Corneal Dystrophies (IC3D)[3] system are included in this chapter.

Definition

The term "dystrophy" is derived from the Greek words *dys* (wrong or difficult) and *trophe* (nourishment). There is no universally accepted definition of the term dystrophy. The word was first used 150 years ago for a group of entities that were clearly not traumatic or infectious in origin. They were believed to be due to poor nerve supply or nourishment and later proved to be genetic in origin, but the word "dystrophy" stuck to this group of inherited diseases.

Corneal opacification associated with systemic conditions such as cystinosis are not included in this chapter. Degenerations are secondary, non-genetic processes resulting from aging or previous corneal inflammation.

Classification

Recently, an international group of cornea specialists published the second version of a list of conditions considered to be dystrophies.[3] The committee developed a series of descriptive categories as shown in Box 35.1 and a paper that included hundreds of references and clinical pictures of adults with these dystrophies.

Mutation rate

The prevalence and clinical significance of the conditions vary. The founder effect (i.e. an increase in the number of cases of a certain genetic trait due to the occurrence of a new mutation in an isolated population) has, in some countries, given rise to large pedigrees of conditions that may be almost non-existent elsewhere.

As the mutation rates for many of the corneal dystrophies are low, it is important to be cautious when diagnosing sporadic cases. A family history *and examination* of family members are mandatory.

Dystrophies related to mutations in the *TGFBI* gene

Genetic information describes the different allelic mutations within the *TGFBI* (transforming growth factor-beta induced) gene on chromosome 5q31. They account for many of the classic corneal dystrophies, which are allelic variations of dominant entities of the same gene. Thus, genetic knowledge is bringing order to this field of ophthalmology. Although naming the diseases according to mutation number has not gained universal recognition, most ophthalmologists rely on a genetic analysis to distinguish between the rarer varieties.

Granular dystrophies

Granular corneal dystrophy, type 1 (a category 1 dystrophy)
Granular corneal dystrophy, type 1 is distinguished by discrete granular-appearing corneal opacities in an otherwise clear cornea. This type has several hundred granules in one cornea (mutation R555W).

Box 35.1

The International Committee for Classification of Corneal Dystrophies (IC3D): the four levels of corneal dystrophies

Category 1: A well-defined corneal dystrophy in which the gene has been mapped and identified and specific mutations are known

Category 2: A well-defined corneal dystrophy that has been mapped to one or more specific chromosomal loci, but the gene(s) remains to be identified

Category 3: A well-defined clinical corneal dystrophy in which the disorder has not yet been mapped to a chromosomal locus

Category 4: This category is reserved for a suspected new, or previously documented, corneal dystrophy, although the evidence for it being a distinct entity is not yet convincing

The category of a specific corneal dystrophy can be expected to change over time as knowledge advances. Eventually, all valid corneal dystrophies should attain category 1.

Note: The classification paper comprising an extensive description of each condition, clinical pictures, key references, and a few words on onset in childhood can be retrieved as a PDF file free of charge probably best by searching online for IC3D Classification of corneal dystrophies version 2.

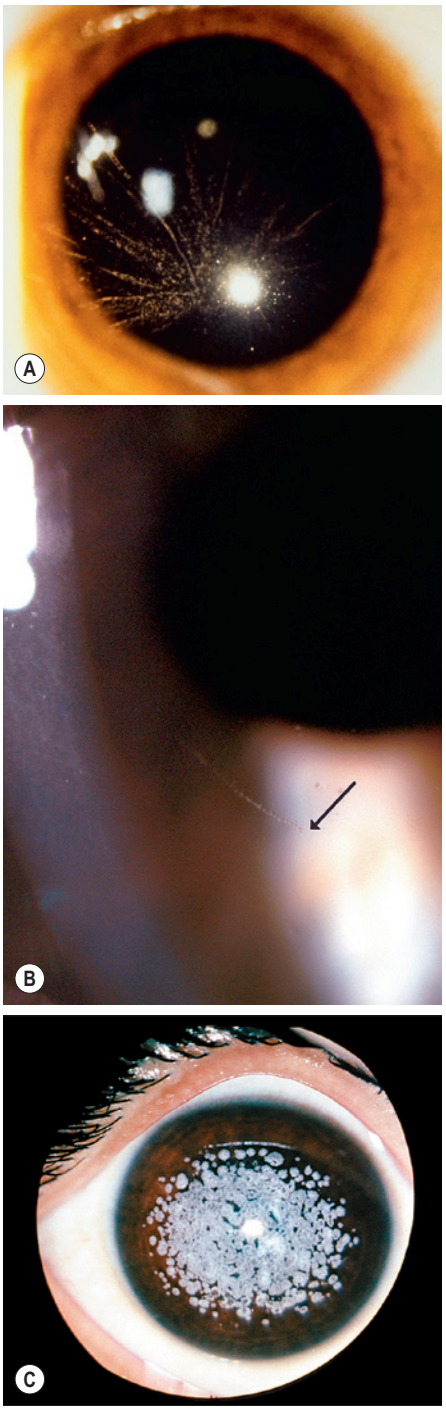


Fig. 35.1 (A) Granular corneal dystrophy, type 1 showing a verticillata-like configuration of the corneal opacities. (B) Granular corneal dystrophy, type 2. A few of these discrete opacities may be all that is visible in a young child. (C) A 7-year-old homozygous patient; granular corneal dystrophy, type 2.

The opacities are white in direct illumination, and transparent, like a crack in glass, by retroillumination. At about 5 years of age, these may be brownish and superficial to Bowman's membrane and present in a verticillata configuration (Fig. 35.1A). The granules increase in number and size and progress into the stroma during late childhood when visual deterioration is moderate. There is always a 2-mm clear limbal zone. Unlike most dominant disorders, the expressivity is nearly constant between generations.

Granular corneal dystrophy, type 2 (a category 1 dystrophy)

Granular corneal dystrophy, type 2 (mutation R124H) is probably the most common corneal dystrophy worldwide. In the past, it was incorrectly called Avellino dystrophy. When patients with this condition from the Italian province of Avellino were first described, it was not recognized that the phenotype had been described decades earlier by others. Clinically and on electron microscopy, this mutation looks like a mixture of a granular and lattice dystrophy with fewer, but larger, opacities in the cornea, particularly later in life. Vision is affected only if the granules are located in the central cornea. It is rarely possible to diagnose this condition until the late teen years. Thus a parent carrying this mutation may need genetic analysis to know whether their children have inherited the trait (Fig. 35.1B). A variety (Fig. 35.1C) with almost a white central cornea before the age of 10 years has also been described. These patients are homozygous for this dominant gene.

Molecular genetic testing is now available for granular dystrophies using buccal mucosal swabs.

Lattice corneal dystrophy (a category 1 dystrophy)

Lattice dystrophy (type I, mutation R124C) is also an autosomal dominant condition of the *TGFBI* gene. Several subtypes have been described; they should be distinguished by genetic analysis. Its hallmark is deposition of amyloid, recognized in a child by three distinct slit-lamp findings[2]:

1. tiny, non-refractile, whitish spots that are round or ovoid (Fig. 35.2A);
2. diffuse axial, anterior stromal haze;
3. white, anterior, stromal dots and filamentary lines that are refractile on indirect illumination in older patients (Fig. 35.2B).

The deposition may be symmetrical or asymmetrical. The stroma becomes increasingly hazy over time, resulting in glare and worsening of vision. Lattice lines gives rise to the name of the condition, but usually are only present in adults. Many patients with this condition have recurrent corneal erosions.

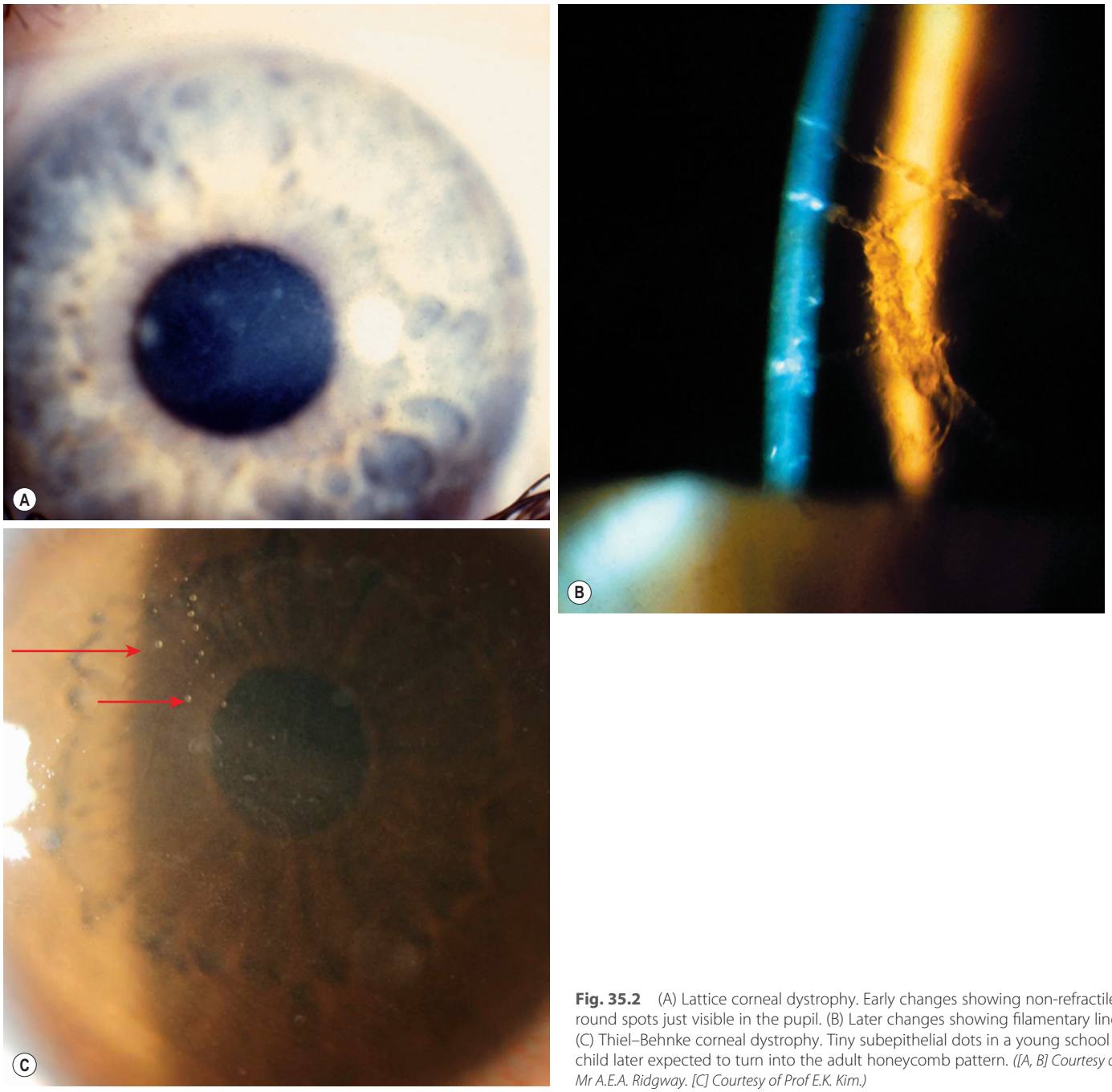


Fig. 35.2 (A) Lattice corneal dystrophy. Early changes showing non-refractile round spots just visible in the pupil. (B) Later changes showing filamentary lines. (C) Thiel–Behnke corneal dystrophy. Tiny subepithelial dots in a young school child later expected to turn into the adult honeycomb pattern. *([A, B] Courtesy of Mr A.E.A. Ridgway. [C] Courtesy of Prof E.K. Kim.)*

Reis–Bücklers and Thiel–Behnke corneal dystrophies (category 1 dystrophies)

Mutations in the same gene also give rise to Reis–Bücklers (mutation R124L) and Thiel–Behnke corneal dystrophy (mutation R555Q). Both have early-onset recurrent corneal erosions. Reis–Bücklers has confluent irregular subepithelial opacities showing rod-shaped bodies on electron microscopy similar to granular corneal dystrophy. Thiel–Behnke corneal dystrophy has a honeycomb slit-lamp appearance and curly fibers on electron microscopy. Both have subtle superficial opacities at presentation that progress to create visual problems (Fig. 35.2C).

Dystrophy due to mutations in other genes

Macular corneal dystrophy (a category 1 dystrophy)

Macular dystrophy is rarely diagnosed in young children since the findings are very subtle and hard to diagnose, particularly if there is no family history of the disease. They comprise nebulous, whitish opacities in the center of the cornea (Fig. 35.3). Over the years, the corneal stroma becomes increasingly hazy between the opacities with an irregular surface. Deposition of glycosaminoglycan in the cornea causes the opacification. As it is inherited as an autosomal recessive trait, there is often a history of consanguinity. The high prevalence of macular



Fig. 35.3 Macular corneal dystrophy in a 13-year-old girl. Typical macular opacities. What cannot be seen in the picture is the opaque ground substance between opacities.

dystrophy in Iceland is an example of the founder effect. Macular dystrophy has been linked to chromosome 16; several mutations exist in the *CHST6* gene. Progressive visual deterioration is symmetrical and usually occurs in the second or third decade.

Posterior polymorphous corneal dystrophy (some subtypes are a category 1, some a category 2 dystrophy)

This autosomal dominant dystrophy may be seen in the very young. The acronym PPCD is suggested by the recent corneal dystrophy classification system. It is often asymmetrical and progression, if it occurs, is slow. Thus the corneas in affected children and adults appear similar. Slit-lamp examination shows small, round, discrete, transparent, vesicular lesions (Fig. 35.4) surrounded by a ring of opacity deep in the cornea at the level of Descemet's membrane; geographical and band varieties exist. As the name suggests, there is usually deep involvement in contrast to most other corneal dystrophies and the opacities may have varying appearances. The opacities are best seen on retroillumination.

Three subtypes of posterior polymorphous dystrophy have been linked to chromosome 20q11 (unknown gene) and 1p34.3–p32.3 in the *COL8A* gene and 10p11.2 in the *ZEB1* gene. The symptoms are often mild and vision unaffected.

Meesmann corneal dystrophy (a category 1 dystrophy)

This condition has a variable expression. It may be asymptomatic or present in early childhood with ocular irritation and photophobia due to recurrent erosions and a mild blurring of vision. Scarring may later cause changes in the slit-lamp appearance. The typical patient has a large number of tiny epithelial vesicles (Fig. 35.5). In the young child, small areas may be spared. Vision is rarely affected in children.

Mutations at two loci, 12q13 and 17q12, of the *KRT3*/*KRT12* gene have been reported.

Schnyder corneal dystrophy (a category 1 dystrophy)

This autosomal dominant corneal dystrophy can be diagnosed in children but may have a variable expression. The central anterior cornea has a slowly progressing, disc-like central opacification with or without polychromatic crystals (Fig. 35.6). It may be visible in the first decade of life. However, it is not until their twenties that patients develop arcus lipoides and a diffuse stromal haze. Vision is variably affected, as some patients have no central crystals. The crystals contain cholesterol and other lipids. The affected gene, *UBIAD1*, is localized on 1-p36.

Congenital hereditary endothelial dystrophy

Congenital hereditary endothelial dystrophy was first described by Maumenee. His name is still used as an eponym, although the dystrophy is more commonly referred to using the acronym CHED. It is recessive (chromosome 20p13, *SLC4A11* gene) and presents at birth with diffuse avascular haziness, ground-glass, bluish-white opacity of the cornea (Fig. 35.7), and nystagmus. The cornea is thicker than normal. The previously so-called dominant form (chromosome 20p11.2–q11.2) that develops during the first or second year of life and progresses slowly and is now considered a variety of posterior polymorphous corneal dystrophy.[3]

It is important to differentiate CHED from congenital glaucoma using corneal pachymetry, intraocular pressure, and corneal diameter measurements.

Management

Most children with corneal dystrophies in the anterior layers of the cornea do not need treatment. Symptoms requiring treatment include decreased vision from corneal opacity or corneal edema and recurrent corneal erosions. The latter may produce photophobia, redness, irritation, blurred vision, or pain. Medical management may be useful for recurrent erosion symptoms with temporary therapeutic contact lens wear, isotonic or hypertonic artificial tear supplementation, or lubricant ointments. Surgical treatments may include superficial keratectomy or phototherapeutic keratectomy (PTK). However, in granular type 1, it may cause scarring.[4] While excimer laser ablation may be helpful in treating some dystrophies, the logistics of administering general anesthesia to these young children at the time of laser treatment remains a challenge. Superficial keratectomy is performed under general anesthesia followed by placement of a therapeutic contact lens. While this may be helpful in severe cases, supportive medical therapy is typically the mainstay of therapy with placement of a therapeutic soft contact lens and topical lubricants. Meesmann dystrophy is particularly challenging to treat with surgical methods, as recurrence is rapid and persistent over time. Promotion of scarring of the cornea with superficial keratectomies may be helpful in rare situations but may lead to reduced visual acuity. The mainstay of treatment for Meesmann dystrophy is supportive, with therapeutic bandage soft contact lenses, and topical lubricants.

In cases with significant corneal opacification and decreased vision from dystrophic deposition in the central cornea, penetrating keratoplasty (PK) or anterior lamellar keratoplasty (ALK) may be indicated. Any dystrophy with normal endothelium such as the *TGFBI* dystrophies can be treated with deep or superficial anterior lamellar keratoplasty depending on the depth of the dystrophic lesions. Dissections can be made using air (Anwar's technique), femtosecond

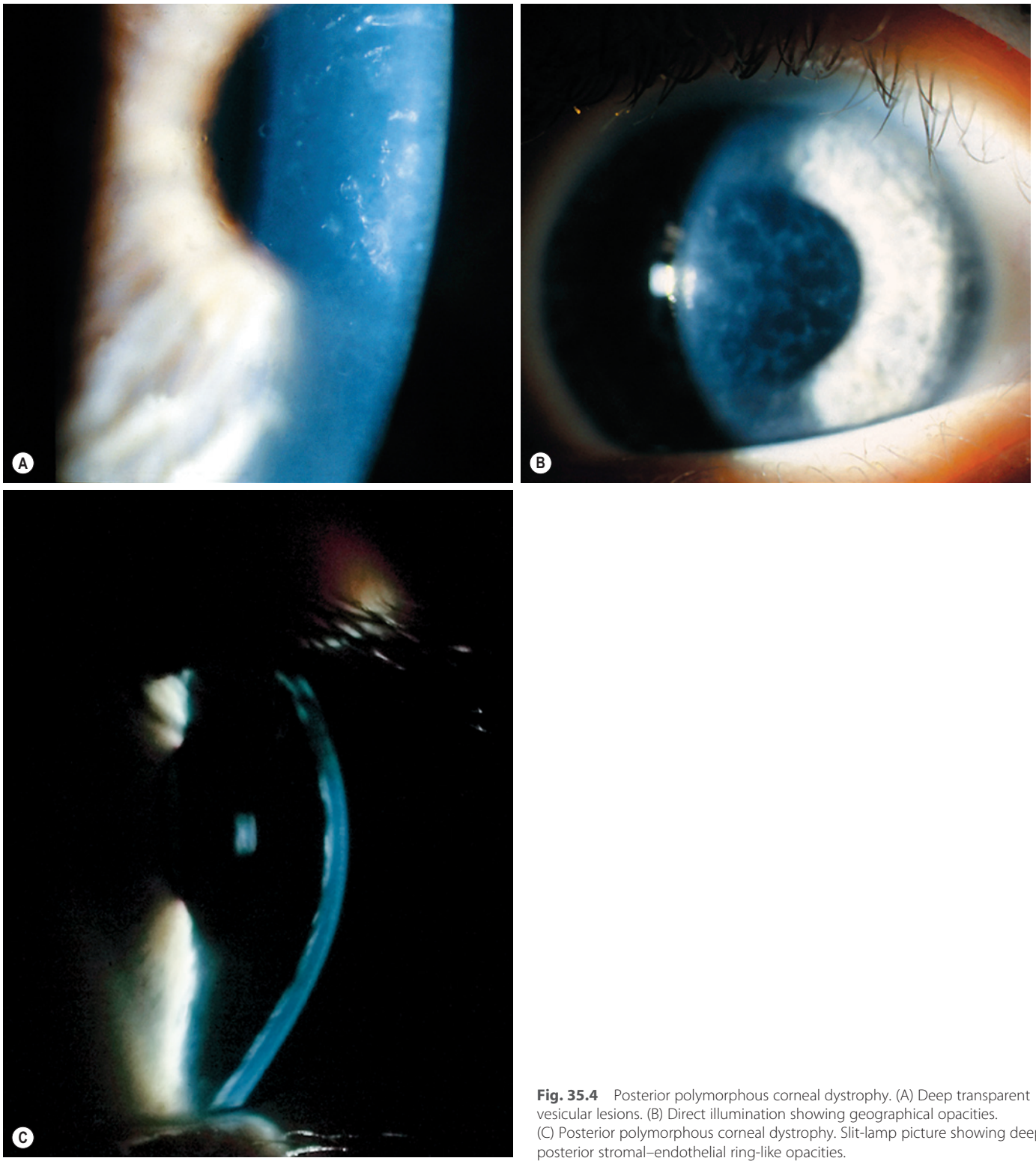


Fig. 35.4 Posterior polymorphous corneal dystrophy. (A) Deep transparent vesicular lesions. (B) Direct illumination showing geographical opacities. (C) Posterior polymorphous corneal dystrophy. Slit-lamp picture showing deep posterior stromal–endothelial ring-like opacities.

lasers, or mechanical microkeratomes.[5] Advantages of ALK techniques over PK are particularly evident in children and include avoidance of endothelial graft rejection, avoidance of an intraoperative open sky, quicker taper of corticosteroids, and increased resistance to trauma from better tectonic stability.[6] Graft success, whether PK or ALK, is high for anterior/stromal corneal dystrophies, yet recurrence of dystrophic material remains a high risk over the patient's lifetime.

When pediatric endothelial dystrophies such as PPCD and CHED cause severe vision loss from severe corneal edema, endothelial keratoplasty is the treatment of choice over PK to reduce the risk of amblyopia. Fortunately most cases of PPCD

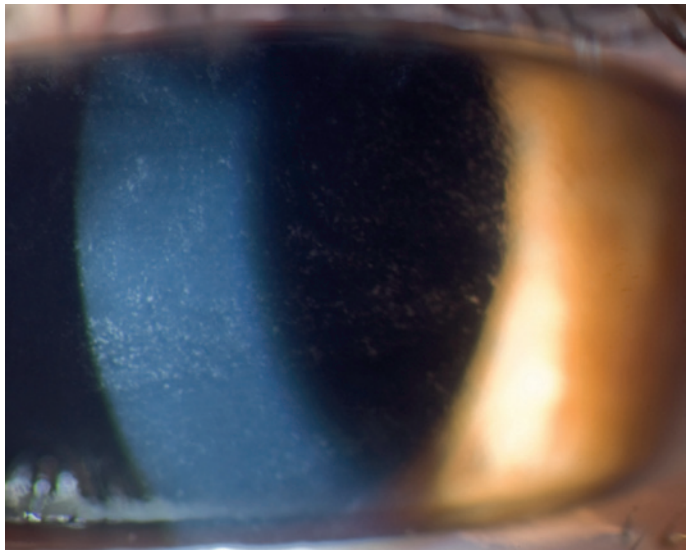


Fig. 35.5 Meesmann corneal dystrophy showing multiple epithelial vesicles. *(Courtesy of K.K. Nischal.)*

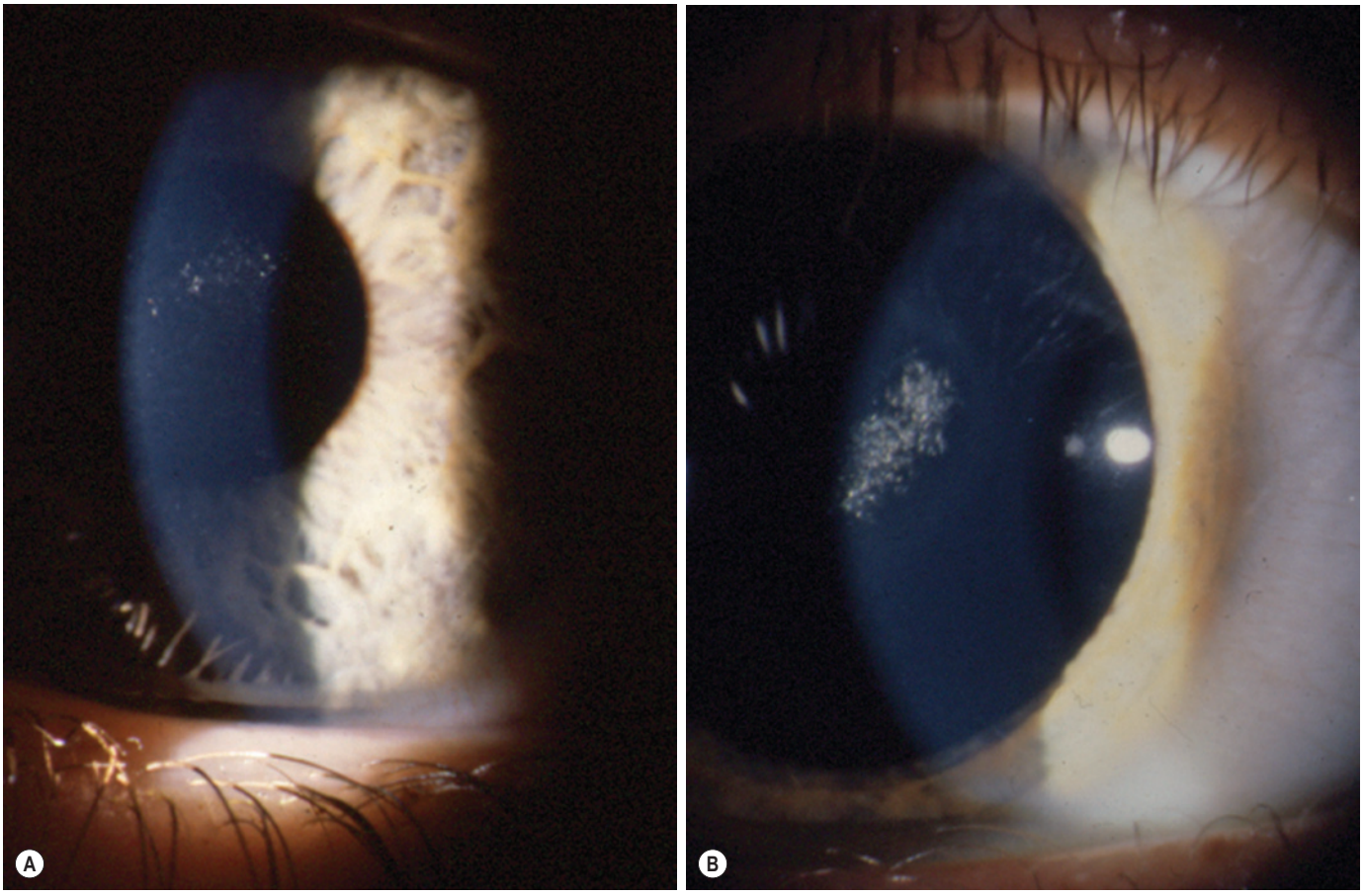


Fig. 35.6 Schnyder corneal dystrophy. Very discrete subepithelial crystals in a 4-year-old (A) and a 10-year-old patient (B) without any arcus. *(Patients of Dr Weiss.)*

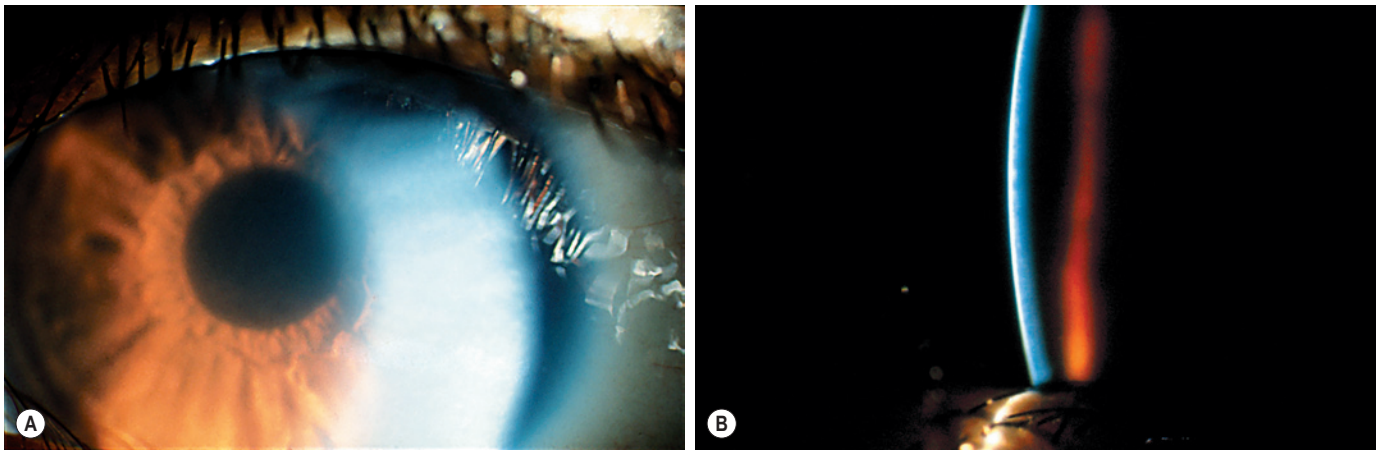


Fig. 35.7 Congenital hereditary endothelial dystrophy. (A) Opaque cornea. (B) Opaque and thickened cornea on slit-lamp illumination.

do not need treatment, whereas probably most cases of CHED do. The most often utilized endothelial keratoplasty technique is Descemet-stripping automated endothelial keratoplasty (DSAEK).[7,8] Endothelial keratoplasty affords a smaller incision size, avoidance of an open sky, quicker visual recovery, quicker vision stability, and less induced astigmatism compared to PK.[9] Due to the smaller incision size, minimal corneal sutures are needed for endothelial keratoplasty so suture related complications are virtually negated with added increased tectonic stability compared to PK.[9] Descemet membrane endothelial keratoplasty (DMEK) is a newer technique of endothelial keratoplasty that has been shown to provide better best-corrected visual acuity and less risk of endothelial rejection compared to DSAEK in adults. The anatomic differences in pediatric eyes compared to adults including smaller corneal diameters, tighter adherence of Descemet's membrane to the stroma (more challenging to strip Descemet's membrane), shallow anterior chambers, and increased posterior pressure remain challenges for DMEK in children. Thus DSAEK may remain the procedure of choice for children requiring surgical treatment for endothelial dystrophies.

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The lens

Jay Self and Christopher Lloyd

Chapter contents

ANATOMY
EMBRYOLOGY
DEVELOPMENTAL ABNORMALITIES OF THE LENS
ECTOPIA LENTIS
MANAGEMENT OF ECTOPIA LENTIS
REFERENCES

See online for supporting video for this chapter.

Anatomy

The crystalline lens, like the cornea, has two principal optical properties: transparency and refractive power. Its structure reflects this. It is a transparent, biconvex, avascular mass of uniquely differentiated epithelial cells. It lies immediately posterior to the iris and is held in position behind the pupil by zonular fibers from the ciliary body.

The lens has an equatorial diameter of 6.5 mm at birth and a maximum anteroposterior thickness of 3.5 mm at the poles. It is completely enveloped by a collagenous capsule, the basement membrane of the cuboidal epithelial cells, which lie beneath it in a single layer. The cuboidal cells at the equatorial region of the lens develop throughout life to form spindle-shaped secondary lens fibers. This addition of fibers at the equatorial region slowly changes the morphology of the lens from a near-spherical fetal shape, to an elliptical biconvex shape (with a diameter of approximately 9 mm and an anteroposterior depth of 5 mm) in childhood and early adulthood. The embryonic and fetal nuclei are present at birth. The fetal nucleus is demarcated from the embryonic nucleus by Y-shaped upright sutures anteriorly and inverted Y-shaped sutures posteriorly. Successive nuclear zones are laid down during development and those deposited after birth contribute to the adult nucleus. The surrounding cortex is formed from less densely packed lens fibers.

Embryology

The lens develops as a thickening of the surface ectoderm overlying the optic vesicle. This "lens placoid" appears on day 26–27 in the human embryo. The mitotically active surface ectoderm is fixed in place, resulting in cell crowding, elongation, and thickening of the placoid.[1] Adhesion of the optic vesicle to the lens placode ensures eventual alignment of the lens and retina in the visual axis. However, there is no direct cellular contact between the basement membranes of the optic vesicle and surface ectoderm. The lens placode then invaginates to form the lens pit. This becomes the lens vesicle. Lens vesicle detachment is the initial event leading to formation of the anterior segment of the eye (day 33). It is accompanied by migration of epithelial cells via a keratolenticular stalk, cellular necrosis, and basement membrane breakdown.[2] This goes someway to explaining the common association of major or minor anterior segment developmental abnormalities (see Chapter 33) in children with lens disorders. The detached lens vesicle is lined by a single layer of columnar epithelial cells surrounded by a basal lamina, the future lens capsule. Primary lens fiber formation occurs in the epithelial cells lining the posterior surface of the lens vesicle and is promoted by the adjacent retinal primordium.[3] The primary lens fibers fill the lumen of the lens vesicle. Elongation of lens cells adjacent to the retina forms the embryonal lens nucleus. The anterior lens cells nearest the corneal primordium remain a cuboidal monolayer and become the lens epithelium. This remains mitotically active for life, providing future lens fiber cells. Epithelial cells differentiate into secondary lens fibers at the lens equator (lens bow). These fibers elongate both anteriorly and posteriorly and insert over the primary lens fibers. They are thickest at the equator. Secondary lens fibers meet anteriorly and posteriorly at the Y sutures.

Zonular fibers are derived from the non-pigmented ciliary epithelium during the fifth month of gestation. The glycoprotein fibrillin is the main component of the ciliary zonules. There are two well-studied isoforms (FBN1 and FBN2) and the more recently discovered FBN3 isoform, which is unique to humans.[4] The monomers are long, flexible molecules that form extended polymers and comprise the backbone of microfibrils, which are important scaffolding structures and are arranged in parallel bundles to form the lens zonules. Fibrillin isoforms interact with many related proteins including the transforming growth factor (TGF)β complex, elastin, and the ADAMTS-like proteins, and are involved in TGFβ and bone morphogenetic protein (BMP) signaling.[5] Interestingly, all isoforms are present in the eye during human embryonic development, but fibrillin-1 predominates in the postnatal zonule, suggesting that fibrillin-2 and -3 play an early scaffolding role for ocular development.[4]

Disorders affecting the structure or function of these interacting proteins result in zonular dysfunction, in particular ectopia lentis, and are discussed below.

The tunica vasculosa lentis (TVL) is a vascular network derived from the hyaloid artery posteriorly and a parallel radial palisade of anastomoses with the annular blood vessel laterally. It envelops the developing lens and nourishes it at a time when aqueous production and formation of the anterior chamber have not yet begun. This intraocular network of vessels begins to develop in the first month of gestation, is maximal in the second to third month, and begins to regress by the fourth month. It has largely disappeared at birth.[6] Persistent TVL is commonly seen in premature neonates and failure of regression of the TVL, hyaloid arteries, and anterior structures can cause a range of developmental anomalies collectively termed persistent fetal vasculature (PFV).

Developmental abnormalities of the lens

Anomalous lens development can often be seen in the context of more global developmental abnormalities of the eye and broadly include: complete absence of the lens (primary aphakia) and anomalies of lens size, shape, position, and transparency.

Congenital aphakia

Congenital aphakia is rare and is invariably associated with significant anterior/posterior segment developmental abnormalities. Primary congenital aphakia (PCA) can result from a variety of teratogenic events (e.g. congenital rubella) in the first 4 weeks of embryogenesis and usually results in microphthalmos, and severe anterior and posterior segment developmental abnormalities.[7,8] Recently, autosomal recessive mutations in the *FOXE3* gene have been identified in some pedigrees with PCA.[8] Secondary congenital aphakia occurs as a result of spontaneous absorption or expulsion of the developing lens. It is associated with less severe ocular anomalies such as PFV.

Microspherophakia

Microspherophakia is a developmental anomaly characterized by a spherically shaped lens of reduced size and diameter (Fig. 36.1). It can occur as an isolated autosomal recessive disorder with mutations in the *LTBP2* gene identified in one pedigree[9] or as part of a known systemic disorder such as Weill–Marchesani syndrome (WMS) or homocystinuria[10] (discussed later). It has also been described in other more global ocular developmental disorders such as aniridia and Axenfeld–Rieger syndrome.[11] It is often accompanied by ectopia lentis and glaucoma (Fig. 36.2).

Lens duplication

Duplication of the lens is a very rare anomaly associated with corneal metaplasia, uveal coloboma, and cornea plana.[12] It is presumed that metaplastic changes in the surface ectoderm prevent normal lens placode formation and thus lead to multiple lens vesicles.

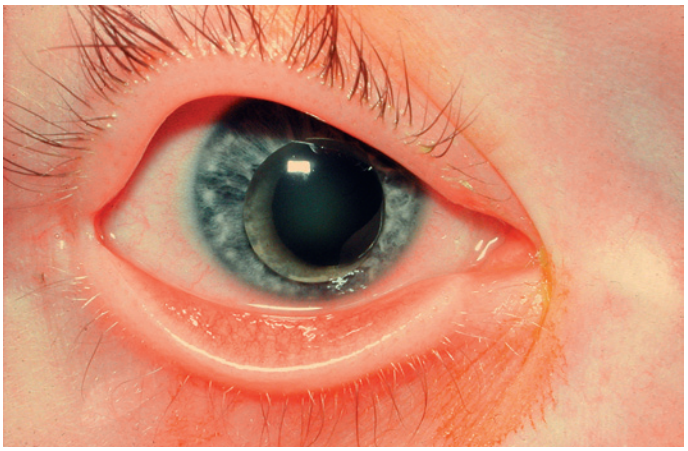


Fig. 36.1 Weill–Marchesani syndrome. Microspherophakia with anterior dislocation.

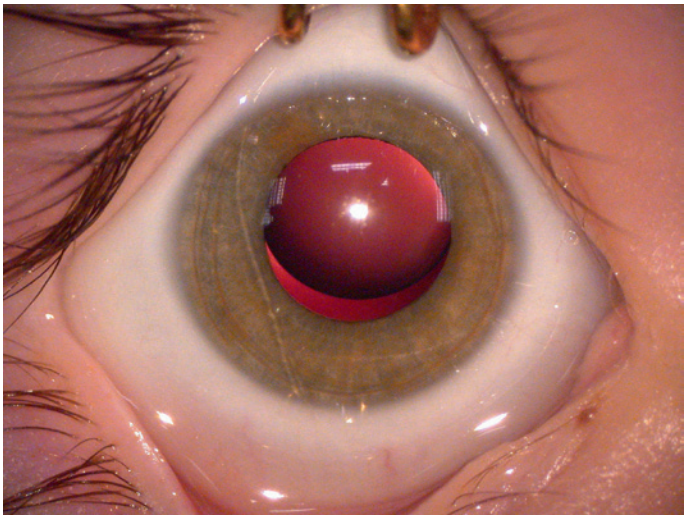


Fig. 36.2 Weill–Marchesani syndrome. Microspherophakia and upward lens subluxation.

Lens coloboma

Lens coloboma (Fig. 36.3) occurs in areas of the lens where there is a failure of zonular development. Scalloped defects in the lens edge demarcate areas of absent zonules. They may occur unilaterally as an isolated anomaly or bilaterally as part of a uveoretinal coloboma phenotype. Lens colobomas may be seen secondary to zonular damage by a congenital ciliary body tumor medulloepithelioma.[13] A localized opacity is often found in the region of the lens coloboma.

Lenticonus and lentiglobus

Lenticonus (Figs 36.4–36.6) and lentiglobus are developmental malformations of the anterior or posterior lens surfaces. Lenticonus is a conical defect and lentiglobus a spherical defect. However, distinguishing lenticonus from lentiglobus can be difficult clinically; accordingly, there has been significant overlap in the use of these terms in the literature. Therefore, the laterality of the defect, and especially its anterior or posterior location, are of greater clinical utility than the defect's conical or spherical morphology. Broadly, posterior

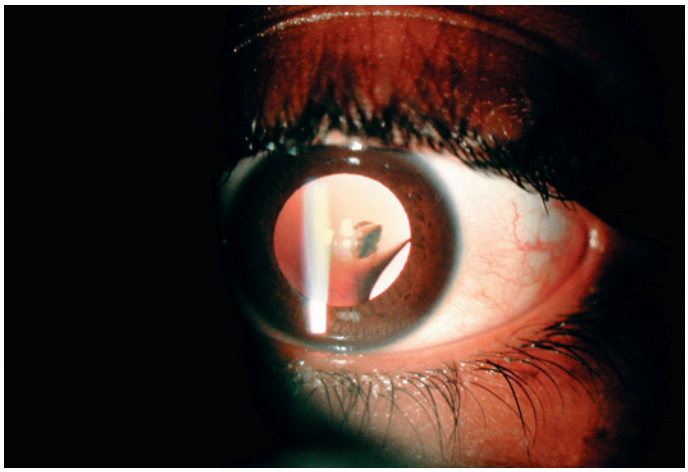


Fig. 36.3 Lens coloboma. Note small cataract adjacent to the coloboma. *(Patient of Dr S. Day.)*

surface abnormalities are more common than anterior surface anomalies and all are usually axial. The resulting refractive error through the central lens is often much more myopic and astigmatic than through the peripheral lens.

Posterior lentiglobus is possibly more common than lenticonus and is usually unilateral.[14] Most cases (95%) are not associated with systemic or other ocular anomalies. When unilateral, there is usually little evidence of a genetic cause. By contrast, bilateral posterior lentiglobus more often has a genetic cause, can be inherited as an X-linked or an autosomal dominant trait,[12] and is occasionally associated with microcornea, Duane syndrome, and anterior lenticonus. The associated cataract is thought to be caused by mechanical stretching of lens fibers.

Posterior lenticonus, like posterior lentiglobus, when unilateral is rarely genetic in origin and can be seen in the presence of a persistent hyaloid artery remnant (see Fig. 36.6). Bilateral posterior lenticonus is more commonly associated

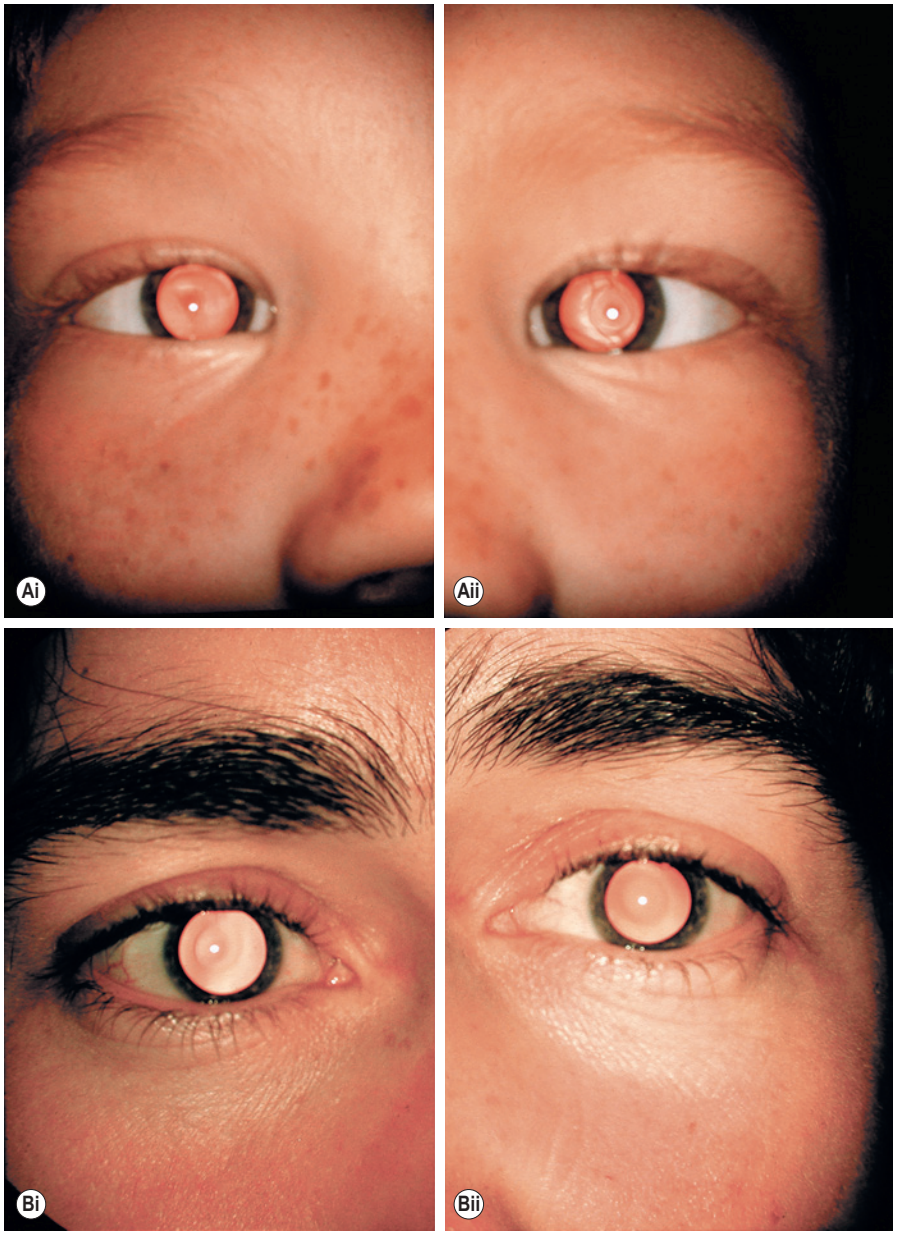


Fig. 36.4 Lenticonus. (A) Although the reflex is a dynamic phenomenon seen on retinoscopy, it can be seen here as a static change in the homogeneity of the red reflex. (B) Mother of patient in (A). Posterior lenticonus is more frequent in boys and may be X-linked.

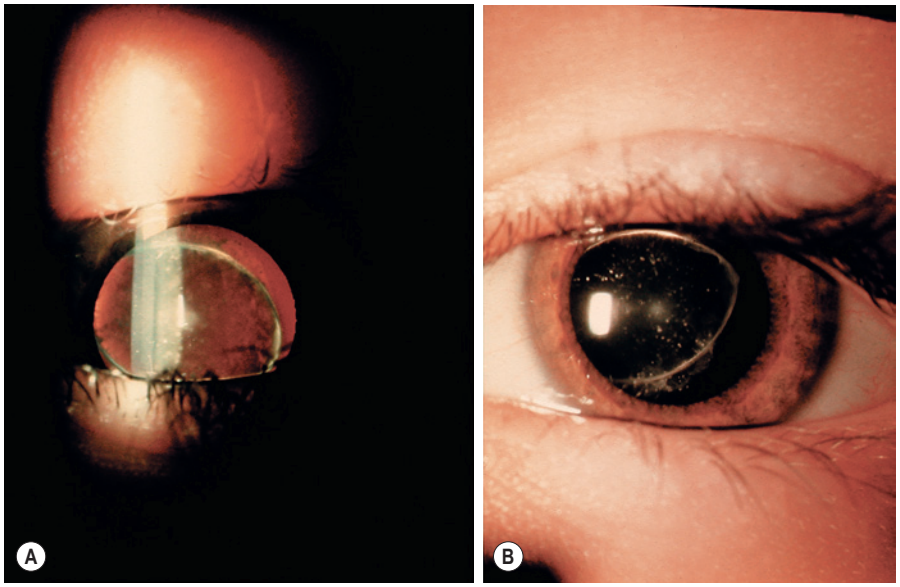


Fig. 36.5 (A) Lenticonus with posterior extension and cataract formation occurring in a healthy girl. (B) Operative photograph with retroillumination on the left showing the defect in the posterior capsule (same patient).

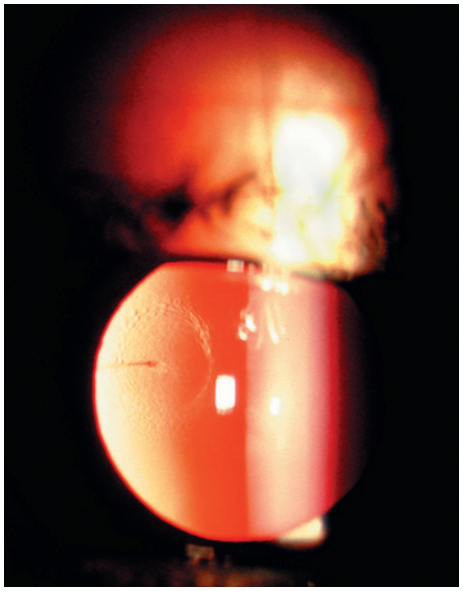


Fig. 36.6 Lenticonic area on the posterior surface of the lens associated with a hyaloid remnant. The presence of the persistent hyaloid remnant suggested that it was important in the pathogenesis.

with an underlying genetic etiology and has been described in many congenital cataract pedigrees, Down syndrome, Pai syndrome,[15] and Pierson syndrome.[16] It can be also be inherited as an isolated autosomal dominant or X-linked recessive trait (see Figs 36.4 and 36.5).

Anterior lentiglobus has rarely been described in the literature and anterior lenticonus is more commonly described. It occurs secondary to an abnormally thin anterior capsule centrally. Approximately 90% of bilateral cases are seen in association with Alport syndrome, which is a rare basement membrane disorder caused by anomalous type IV collagen and is characterized by progressive renal failure, sensorineural hearing loss, and ocular abnormalities. Alport syndrome is often X-linked (85%), although it can be autosomal recessive (10%) or dominant (5%). Mutations have been identified in *COL4A1–6* genes on three different chromosomes, all of which encode type IV collagen. Males with the X-linked form (*COL4A5*) are usually severely affected but females tend to have a mild form, often with only microscopic hematuria and normal renal function. The ocular abnormalities include: a dot-and-fleck retinopathy (85%), peripheral retinal thinning, anterior lenticonus (25%), corneal opacity, and, more rarely, a posterior polymorphous corneal dystrophy and giant macular hole.[17]

Persistent fetal vasculature (PFV)

Persistence of components of the fetal lens vasculature system (PFV) can lead to persistent pupillary membranes, epicapsular stars, iridohyaloid blood vessels, persistence of the posterior fetal fibrovascular sheath, posterior lenticonus, and Mittendorff dots (see Chapter 37).

Ectopia lentis

Ectopia lentis or lens dislocation is most commonly due to disorders that disrupt the fibrillin-rich microfibrils of the ciliary zonule, affecting its structure and function. Displacement of the lens can range from subtle subluxation, to total dislocation due to breakage of most or all of the zonular attachments. Ectopia lentis usually results in reduced visual acuity due to induced refractive error in the first instance. The most common causes of ectopia lentis include Marfan syndrome and related type-1 fibrillinopathies, trauma, homocystinuria, and Weill–Marchesani syndrome. In addition to the refractive effects, subluxation or luxation can lead to sectoral shallowing of the anterior chamber, subluxation of the lens into the anterior chamber, and glaucoma.

Marfan syndrome and the type-1 fibrillinopathies

The fibrillin-1 gene (*FBN1*, ch:15) codes for the FBN1 protein, which is a major constituent of microfibrils and the lens zonules. As detailed above, the fibrillin glycoproteins include FBN1 to 3. Types FBN2 and the newly described FBN3 are important for early ocular development, whereas FBN1 is a major constituent of the mature lens zonule. FBN1

interacts closely with many of the other proteins implicated in ectopia lentis, including ADAMTS10, ADAMTS-like proteins, and the TGFβ complex. Mutations in the *FBN1* gene result in the connective tissue disorder Marfan syndrome (MFS), as well as a group of related clinical phenotypes collectively termed the type-1 fibrillinopathies.[18] These range from the severe neonatal MFS (usually fatal by the age of 2 years) to isolated "simple" ectopia lentis. Autosomal dominant Weill–Marchesani syndrome type 2 has been described due to a *FBN1* mutation in one pedigree. Over 2000 unique mutations have been identified in the *FBN1* gene but, with the exception of a clustering of mutations associated with neonatal MFS, there is no clear genotype–phenotype correlation. MFS has an incidence of approximately 1 in 10,000 births and is an autosomal dominant disorder, although recessive inheritance has been rarely described. Diagnosis is made using the Ghent criteria, which incorporate major clinical findings with family history and the results of molecular studies. Associated skeletal abnormalities include tall stature (Fig. 36.7), arachnodactyly (Fig. 36.8), chest wall deformities, and scoliosis. The typical cardiac abnormalities are dilation of the aortic root, mitral valve prolapse, and aortic aneurysm. Ocular findings include ectopia lentis in 60%, axial myopia, corneal flattening, cataract, hypoplasia of the ciliary muscle and iris, open angle glaucoma, and strabismus. The lens in MFS can sublux in any direction, but most commonly upward (Fig. 36.9). Zonular fibers in ectopia lentis are fewer in number, thin, stretched, and irregular in diameter.[19] The insertion and ultrastructure of zonular fibers

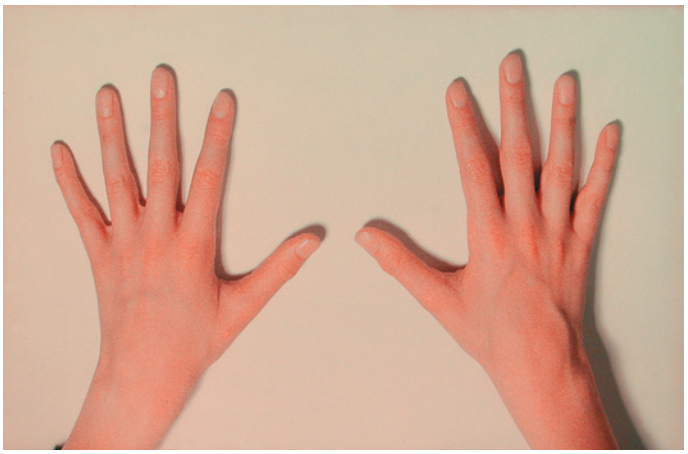


Fig. 36.8 Marfan syndrome. Arachnodactyly.

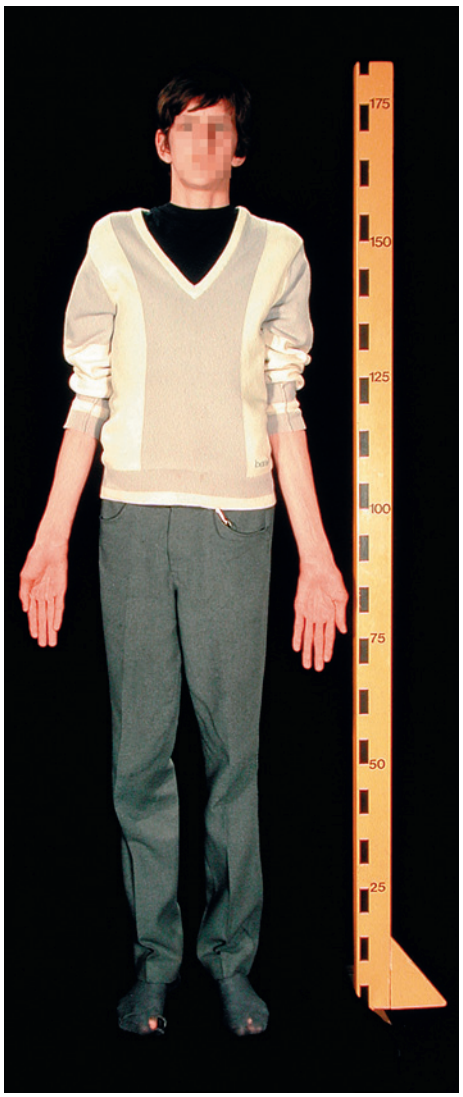
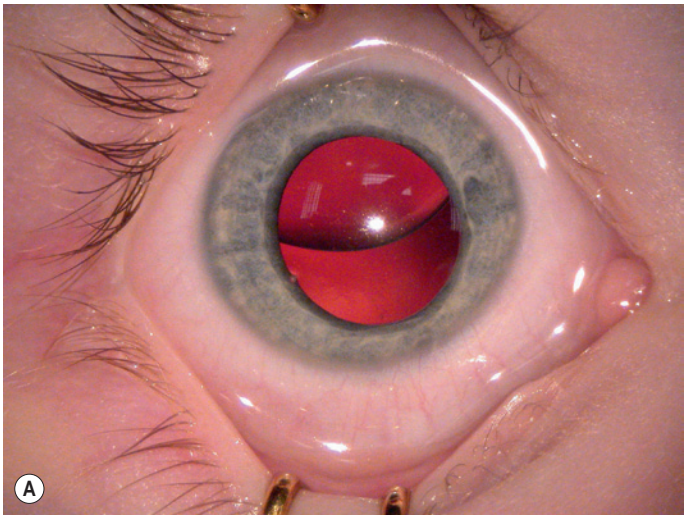


Fig. 36.7 Marfan syndrome. At 15 years of age he is 1.75 m in height. He has very long limbs, arachnodactyly, and pectus excavatum.



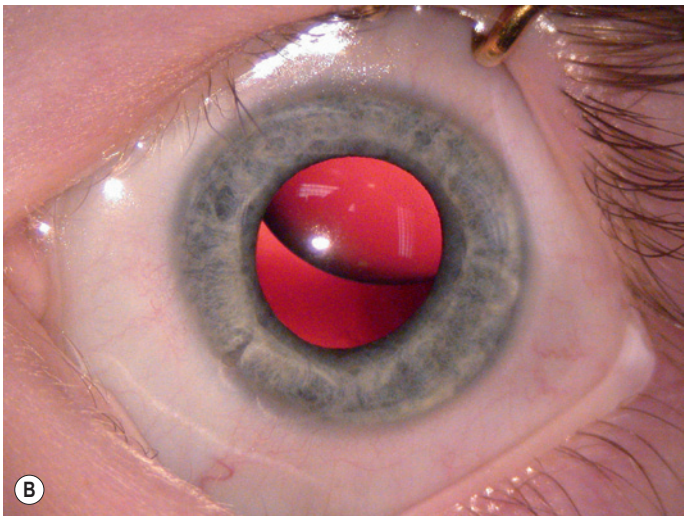


Fig. 36.9 Marfan syndrome. Upward lens subluxation in the right (A) and left (B) eyes of the same child.

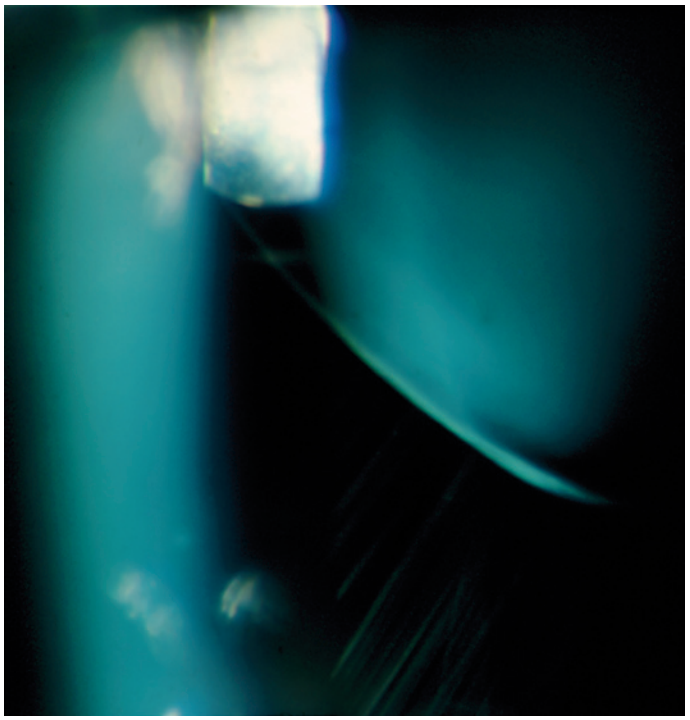


Fig. 36.10 Marfan syndrome. Dislocated lens with intact stretched zonules. The shadow on the left is the slit beam (out of focus) passing through the cornea.

attached to the lens capsule in MFS is also abnormal. Reduced synthesis of fibrillin-1 combined with proteolytic degradation of microfibrils accounts for the variable and occasionally progressive nature of some of the clinical manifestations of MFS.[19]

Zonular fibers typically elongate (Fig. 36.10) and accommodation may be affected. Progression of subluxation is relatively unusual in older childhood and in our experience rarely requires surgical intervention after the age of 10.

Mutations in the *TGFβR2* and *TGFβR1* genes have also been described in MFS-like disorders, which, in some cases, lack the ocular phenotype of MFS and are referred to as MFS-related connective tissue disorders under the heading of the TGFβ signallopathies. *FBN2* mutations can cause Beals syndrome, which has many overlapping clinical features with MFS but, importantly, lacks the ocular features, including ectopia lentis.

Similarly, there is clinical overlap with disorders caused by another FBN1-interacting protein, *ADAMTSL4*. Mutations in this gene are a common finding in pedigrees with apparent isolated ectopia lentis[20] and have been described in patients with ectopia lentis et pupillae (ELeP).[21]

Homocystinuria

Most homocystine, an intermediate compound of methionine degradation, is remethylated to methionine. It is not ordinarily detectable in plasma or urine. The accumulation of homocysteine and its metabolites (homocystinemia or homocystinuria) is caused by disruption of any of the three interrelated pathways of methionine metabolism:

- Type 1: deficiency in the enzyme cystathionine beta-synthase (CBS).
- Type 2: defective methylcobalamin synthesis.

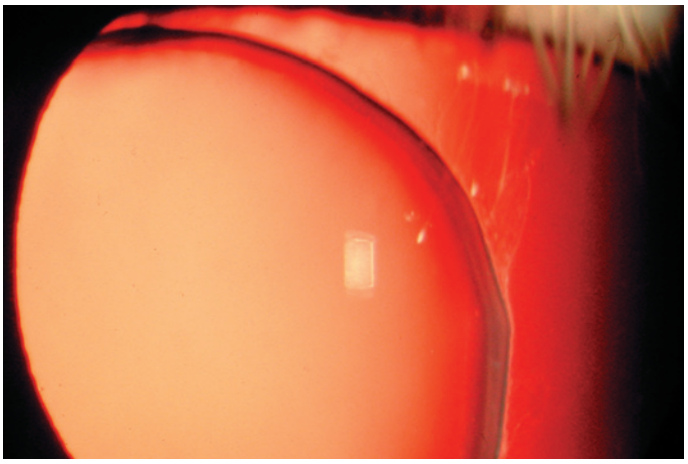


Fig. 36.11 Homocystinuria. Inferiorly dislocated lens with broken, short, and curly zonules. In homocystinuria, the zonules tend to break in their central portion and curl up adjacent to the lens.

- Type 3: abnormality in the enzyme methylene tetrahydrofolate reductase.

Homocystinemia is a milder clinical entity than homocystinuria and describes raised plasma levels of homocysteine. It is associated with cardiovascular disease. It may occur in the absence of homocysteinuria and can be caused by genetic predisposition ± environmental factors.

Type 1 homocystinuria is the most prevalent inborn error of methionine metabolism and is an autosomal recessive condition. It occurs in 1:300,000 to 1:500,000 live births. It is more common in Ireland, where there is an incidence of 1:52,000. Affected individuals are normal at birth but during early childhood may show neurodevelopmental delay and failure to thrive. Ectopia lentis occurs later, along with osteoporosis, fits, psychiatric disorders, and thromboembolic phenomena. However, diagnostic delay is common. Untreated, 90% of individuals develop progressive ectopia lentis.[22] Slit-lamp examination of individuals with ectopia lentis reveals broken and matted zonular fibers (Fig. 36.11). The lens typically subluxates inferiorly or anteriorly and may cause pupil block glaucoma (Fig. 36.12). Patients with homocystinuria are usually tall with elongated limbs and arachnodactyly. They have fair complexions, blue irides, and a malar flush (Fig. 36.13). Kyphoscoliosis, pectus excavatum, high arched palate, and generalized osteoporosis are also common. Other ophthalmic features include progressive myopia, iridodonesis, cataract, iris atrophy, retinal detachment, central retinal artery occlusion, optic atrophy, anterior staphylomas, and corneal opacities.[23] Early diagnosis and medical treatment significantly improve ophthalmic and non-ophthalmic outcomes.[24] Anesthesia can be complicated by thromboembolic events. Lens dislocation and pupil block glaucoma are common indication for surgery.[23] Heel prick testing for this disorder is performed in many countries and so new, undiagnosed presentations in infancy are rare.

Weill–Marchesani syndrome

Weill–Marchesani syndrome (WMS) is a rare systemic connective tissue disorder. Features include: microspherophakia, ectopia

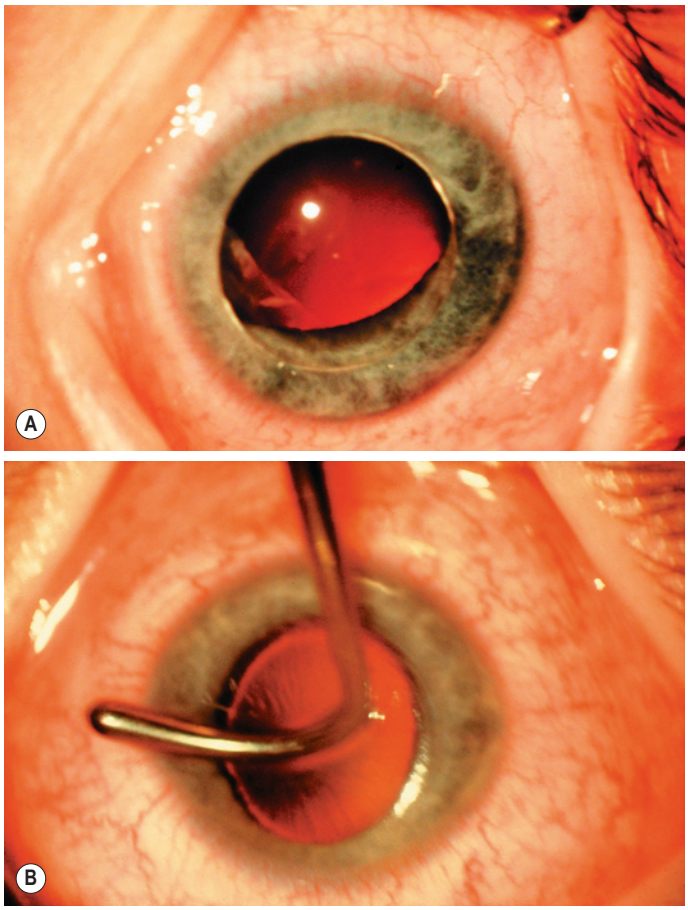


Fig. 36.12 Homocystinuria. (A) Anterior/inferior dislocation of the lens, which is jammed in the pupil. (B) Homocystinuria with anterior dislocation and glaucoma. The lens is being repositioned under local anesthetic with a strabismus hook.

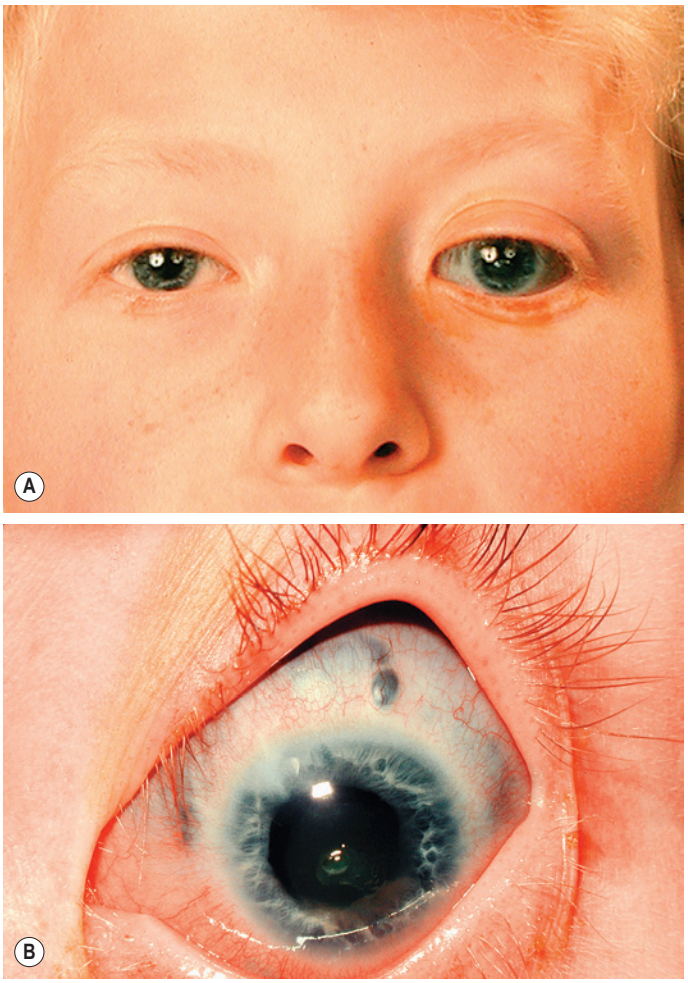


Fig. 36.13 Homocystinuria. (A) Fair-haired boy with chronic glaucoma following unreported anterior dislocation of the lens. (B) Despite his age the left eye had become buphthalmic.

lentis, lenticular myopia, and glaucoma in association with short stature, brachydactyly, and joint stiffness. The lens commonly dislocates into the anterior chamber, causing pupil block glaucoma. Presenile vitreous liquefaction is also reported.[25] It is usually an autosomal recessive disorder, which can be caused by mutations in the *ADAMTS10* gene.[26] Autosomal dominant WMS has also been described in a pedigree with a mutation in the *FBN1* gene (which more commonly causes MFS). A WMS-like syndrome has also been described in association with a mutation in the *ADAMTS17* gene on chromosome 15.[27] ADAMTS10 and ADAMTS17 belong to a family of proteins called the ADAMTS proteases. A related family of proteins, the ADAMTS-like proteins, includes the ADAMTSL4 protein, the gene which has been found to be mutated in some pedigrees with isolated autosomal recessive ectopia lentis and ELeP. Again, the clinical overlap between these conditions and MFS is explained by the known protein interactions of FBN1, the TGFβ complex, ADAMTS, and ADAMTS-like proteins.

Ectopia lentis et pupillae

ELeP is a rare condition that usually exhibits an autosomal recessive inheritance pattern, although a dominant pedigree has been described.[21] It is closely related to autosomal recessive ectopia lentis. Lenticular and pupillary ectopia occur in opposite directions, resulting in an oval- or slit-shaped pupil. Poor pupillary dilatation, axial myopia, glaucoma, megalocornea, and iris transillumination defects are also described. Membrane formation on the posterior aspect of the iris has been observed both in histologic sections and on ultrasound biomicroscopy and suggests that the pathogenesis of this condition may be mechanical tethering of the pupil by a membranous structure with co-existent zonular disruption.[21] Mutations in the *ADAMTSL4* gene have been identified in some pedigrees with ELeP and some with autosomal recessive ectopia lentis.

Aniridia (see Chapter 33) and congenital glaucoma (see Chapter 38)

Aniridia is rarely complicated by ectopia lentis. This may be secondary to associated advanced infantile glaucoma and buphthalmos. Sturge–Weber syndrome may also cause secondary ectopia lentis by the same mechanism.

Megalocornea

Ectopia lentis (often inferior) in association with megalocornea (in the absence of raised intraocular pressure) has been described. Cataract may co-exist.[28]

Ehlers–Danlos syndrome

Ectopia lentis may rarely occur in association with high myopia in Ehlers–Danlos syndrome.

Trauma

Trauma to the eye may result in zonular damage and ectopia lentis.[29] Rarely this may occur as a result of non-accidental injury.

Sulfite oxidase deficiency and molybdenum cofactor deficiency

These related disorders are rare autosomal recessive inborn errors of sulfite metabolism. The diagnosis is suggested in neonates by the association of seizures, abnormal tone, severe neurodevelopmental delay, and ectopia lentis. Affected children usually die in early childhood.[30]

Xanthine oxidase deficiency

This is a very rare cause of ectopia lentis. It is associated with low serum uric acid levels.

Management of ectopia lentis

The ophthalmologist's primary aims for eyes affected by ectopia lentis are restoration of visual function, avoidance of, or treatment of, amblyopia, and the appropriate management of any complications such as glaucoma. Correction of acquired myopia/astigmatism with simple optical measures is all that is required for many children. However, where there is asymmetrical (or unilateral) ectopia lentis, the use of a contact lens may be necessary to avoid aniseikonia. If the crystalline lens is extensively subluxed, correction of the refractive error of the aphakic zone of the pupil can be attempted; however, in most instances, this degree of subluxation leads to significant lens edge effects, anterior chamber sectoral shallowing, and possible glaucoma.

Bilateral ametropic amblyopia has been reported in up to 50% of individuals with ectopia lentis despite good conservative management.[31] This was found to be particularly evident where the lens edge was adjacent to the center of the pupil but where the visual axis was still primarily phakic. Axial high myopia is common in such cases and is possibly secondary to amblyopia.[32] It has been postulated that early lens surgery may avoid induced axial myopia and the subsequent increased risk of retinal detachment. Posteriorly dislocated lenses may be managed conservatively but should be monitored. Signs of glaucoma, uveitis, or retinal degenerative changes are indications for vitreo-lensectomy. The lens is most likely to dislocate anteriorly in homocystinuria. This is often associated with pupil block glaucoma. Lens repositioning can be carried out after pupillary dilatation by using supine positioning of the patient and allowing gravity to direct the lens posteriorly behind the pupil. In addition, mechanical pressure on the cornea with a squint hook can be used, although this may cause some endothelial damage. The pupil is then miosed (see Fig. 36.12B).

Microsurgical techniques yield very good results following either limbal or pars plana approach lensectomy for ectopia lentis.[32,33] If the limbal technique is adopted, the vitreous cutter should be introduced into the area of greatest subluxation (Fig. 36.14). Aspiration of the lens material from within the capsular bag prior to completing the capsulectomy and anterior vitrectomy ensures lens material is not displaced into the vitreous cavity. Retinal detachment, a frequent problem prior

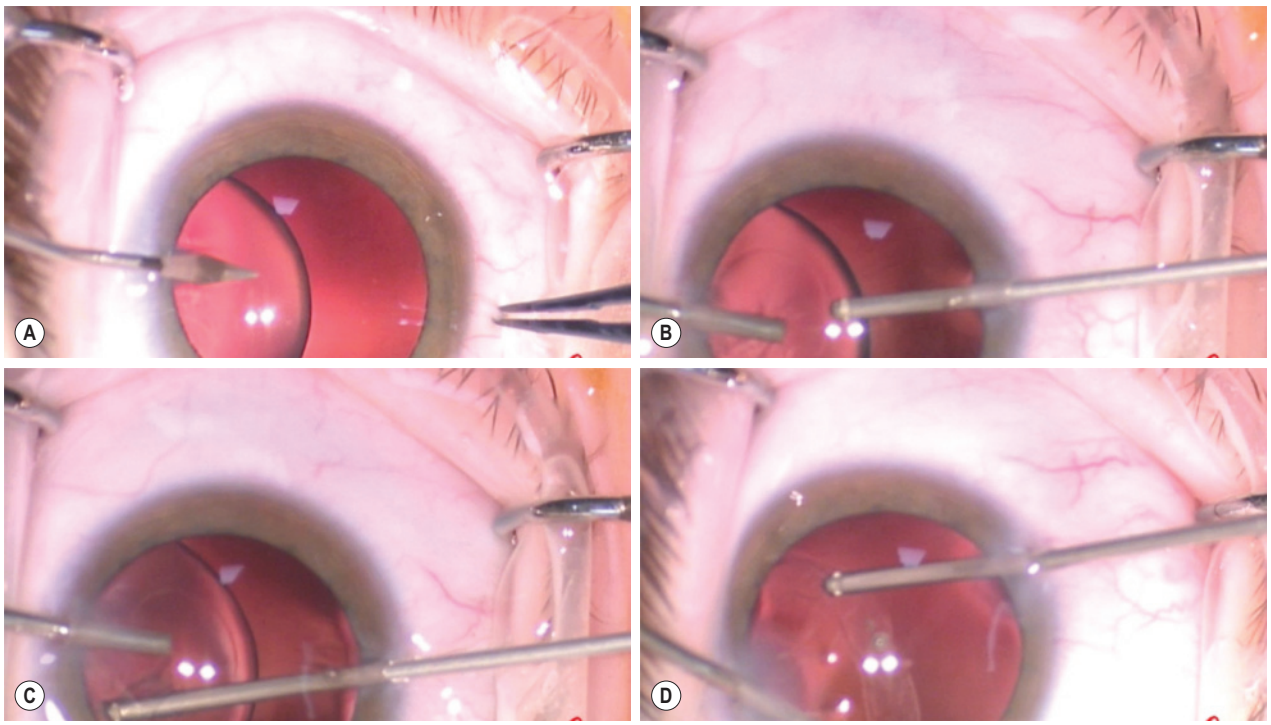


Fig. 36.14 Marfan syndrome: lens surgery. (A) A 23G knife is used to make a corneal incision and to pierce the lens capsule. (B) After completion of a small anterior continuous curvilinear capsulorhexis (CCC) using microrhexis forceps and a bimanual technique, a 23G cutter is inserted into the lens. (C) All of the lens material is aspirated. (D) A 23G vitrector is used to clear the remains of the capsule and perform a small anterior vitrectomy.

to lensectomy procedures using vitreous-cutting instruments, is now a rare complication.[34] Many centers will now use a 23G technique. Contact lens or spectacle correction of subsequent aphakia is effective and relatively straightforward for many children. In one large study, the best-corrected visual acuity of approximately 90% of eyes with ectopia lentis was improved by 2 Snellen lines or more following lensectomy.[34]

YAG laser zonulysis is an alternative technique for moving a lens edge out of the pupillary axis[35] and allows subsequent aphakic correction. However, this technique is now rarely employed.

The use of intraocular lenses (IOLs) for treatment of aphakia following lensectomy for ectopia lentis has been a controversial topic. Techniques include sclerally fixed IOLs, iris claw lenses, iris clip lenses, and "in the bag" surgery utilizing capsular anchoring devices or sutured CTRs.[36–39] Reported complications include corneal endothelial cell loss (an average of 14% in the early postoperative period in one study), suture breakage, and/or lens decentration (33% within a few years follow-up in one study) and visual axis opacification requiring surgery for "in the bag" techniques (70% of cases in some studies). Most studies describing techniques utilizing IOLs in the management of ectopia lentis have little long-term outcome data and tend to describe non-inferiority to aphakia corrected with contact lenses rather than superior visual outcomes.

However, in recent years, the use of anteriorly placed iris claw lenses has been gaining popularity. Data from a number of groups have shown good results in children, with small case series reporting over 10-year follow-up.[37,40,41] Complications requiring explantation or replacement occur, but are rare. The use of iris claw lenses in children following ocular trauma and in aphakic adults is well described, but there are no large, long-term case series in children following surgery for non-traumatic ectopia lentis. Concerns about long-term endothelial damage in already abnormal pediatric eyes, compounded by a lack of specular microscopy technology suitable for young children, limits the more widespread use of these IOLs for children. Posterior fixation of iris claw lenses has been described[42] in an attempt to minimize long-term endothelial damage, but this approach can be technically more challenging and is associated with iris pigment cell loss. It is rarely employed in children.

Given the abnormal ocular morphology in children with ectopia lentis, the lack of large, long-term case series, and the reported complications with IOLs, many pediatric ophthalmic surgeons continue to prefer the traditional gold standard for management of children with significant ectopia lentis requiring surgery, i.e. contact lenses/spectacles to treat aphakia following lensectomy. However, concurrent (or subsequent) insertion of an iris claw IOL is now a well-accepted technique in some centers, and continues to gain popularity in others.

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Childhood cataracts

Scott R Lambert

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See online for supporting video for this chapter.

Incidence

Cataracts, which are opacities of the crystalline lens, are an important problem in children worldwide. The incidence varies, but in the UK the adjusted cumulative incidence at age 1 year is 2.49/10,000, increasing to 3.46/10,000 by age 15 years.[1] Bilateral cataracts are more common than unilateral.

Detection

Because of visual deprivation with both unilateral and bilateral cataracts, successful management requires early detection and referral for treatment. The red reflex should be assessed by direct ophthalmoscopy in the newborn nursery and at well-child check-ups. If an abnormality is detected, referral should be made to an ophthalmologist. Pupillary dilation may be necessary to detect some incomplete cataracts.

Children with visually significant unilateral cataracts often present with strabismus and dense amblyopia. However, visual behavior will usually be unaffected by a unilateral cataract, and for this reason the parents may not be aware of it. In contrast, dense bilateral cataracts are usually associated with impaired visual behavior (Fig. 37.1). If nystagmus develops, visual prognosis is worse, although it may be reversed by prompt treatment.[2]

Morphology

The morphology of cataracts offers important clues to their age of onset and visual prognosis. In addition, it provides insights into the etiology of a cataract. When possible, a slit-lamp examination is invaluable in identifying the morphology. Refinements in the morphology can be obtained intraoperatively.[3] The morphology is largely determined by the timing and nature of the insult and the anatomy of the lens (Box 37.1).

Some types of cataracts have a better prognosis than others. For example, anterior polar (Figs 37.2 and 37.3), lamellar (Fig. 37.4), and posterior lentiglobus (Figs 37.5 and 37.6) cataracts are associated with the best visual prognoses, whereas nuclear (Fig. 37.7), and posterior polar (Fig. 37.8) cataracts have poorer visual prognoses.[4] Acquired cataracts generally have a more favorable visual prognosis than congenital cataracts.

Certain types of cataracts are frequently associated with other ocular abnormalities. For example, nuclear cataracts are often associated with microphthalmos (see Fig. 37.7) while anterior polar cataracts (see Figs 37.2 and 37.3) are more commonly associated with astigmatism. Partially reabsorbed cataracts in an infant boy are suggestive of Lowe syndrome or Hallermann–Streiff–François syndrome (Fig. 37.9). Wedge-shaped or sectional cataracts (Fig. 37.10) may occur with Stickler syndrome and Conradi syndrome and may be due to lyonization.

Persistent fetal vasculature

The term "persistent fetal vasculature" (PFV) describes a wide spectrum of ocular anomalies that may include a retrolental plaque (Fig. 37.11) in a microphthalmic eye with prominent blood vessels on the iris and lens capsule, a shallow anterior chamber, and elongated ciliary processes.[5] Less commonly, these patients may present with a vascularized pupillary

Box 37.1

Morphological classification of infantile cataract

Anterior polar Central opacity on anterior capsule.

Nuclear Opaque lens material between anterior and posterior "Y" suture that may spread into the surrounding (especially posterior) cortex and often associated with posterior capsule plaque.

Lamellar Anterior and/or posterior cortical opacity not involving the nucleus.

Persistent fetal vasculature A combination of one or more of the following: retrolental membrane with or without visible vessels, patent or non-patent persistent hyaloid vessel, or stretched ciliary processes.

Posterior polar Opacity of the posterior capsule often with opacification of the adjacent cortex.

Posterior lentiglobus Posterior bowing of the posterior capsule with or without a pre-existing posterior capsule defect.

Total Entire lens is white.



Fig. 37.1 Nuclear cataracts. This 4-month-old child presented with nystagmus and bilateral nuclear cataracts. His parents had noted that he would stare at room lights. After bilateral lensectomies and contact lens correction, his nystagmus improved. After long-term follow-up, his best-corrected visual acuity is 20/25 when both eyes are tested together, but 20/50 when each of his eyes are tested separately due to latent nystagmus.

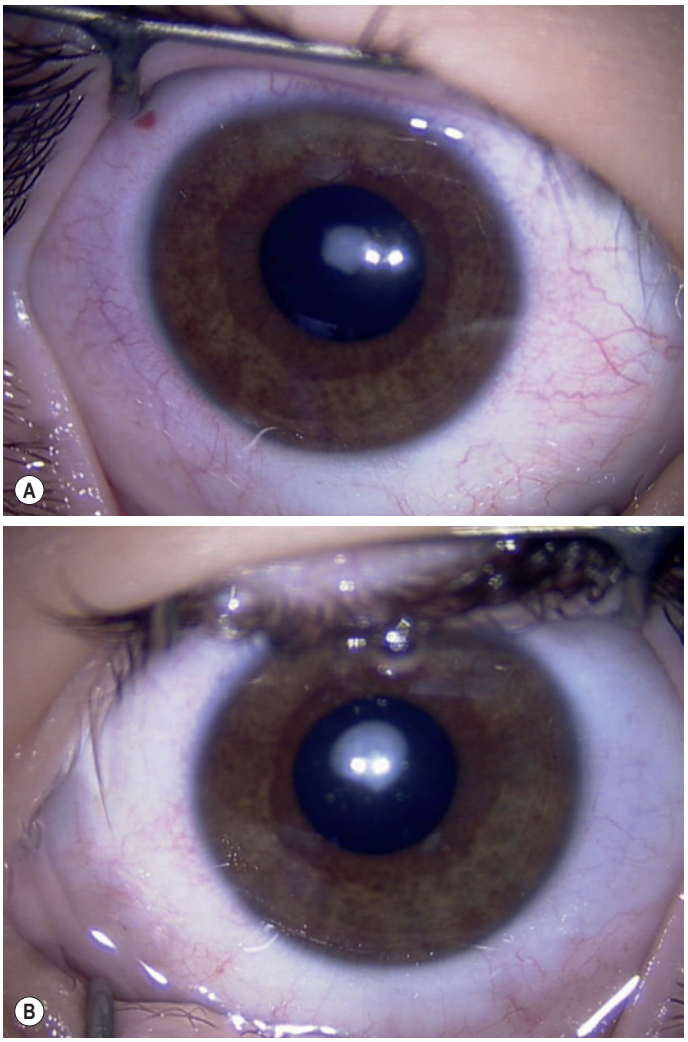


Fig. 37.3 Anterior polar cataracts in the right (A) and left (B) eyes. The child's mother, sister, and brother also had bilateral anterior polar cataracts.



Fig. 37.2 Anterior polar cataract. A small anterior polar cataract generally results in minimal visual deprivation, but may be associated with anisometropic amblyopia.

membrane, microcoria, and an anterior capsular cataract (Fig. 37.12).[6] PFV is almost always unilateral. Over time, the lens may undergo spontaneous absorption or become swollen with loss of the anterior chamber and glaucoma. Usually the posterior pole is normal, but fibrous tissue from the hyaloid remnants may contract, causing peripapillary distortion or tractional retinal detachment. In some cases, the retrolental plaque may be adherent to the peripheral retina and a retinotomy may be required to extricate the retina from the retrolental plaque.

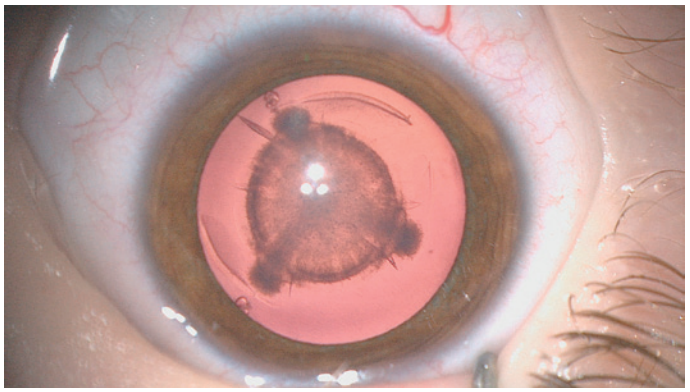


Fig. 37.4 Lamellar cataract.

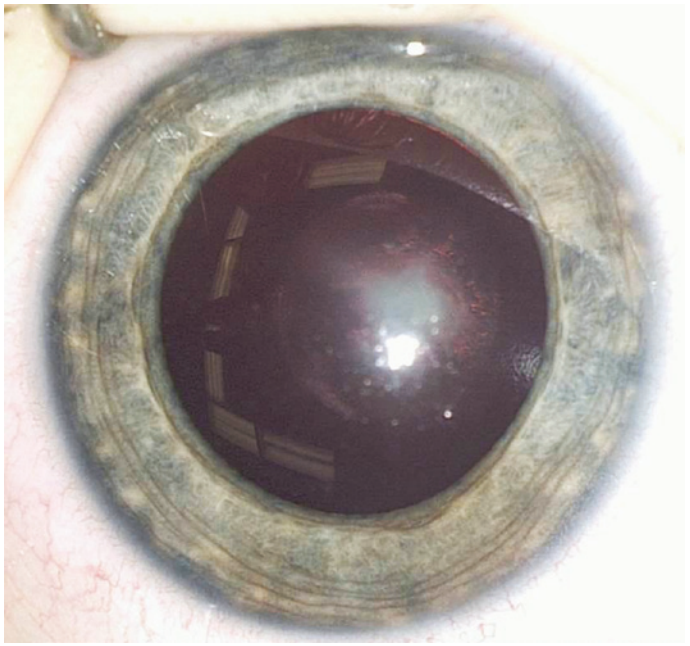


Fig. 37.5 Posterior lentiglobus.

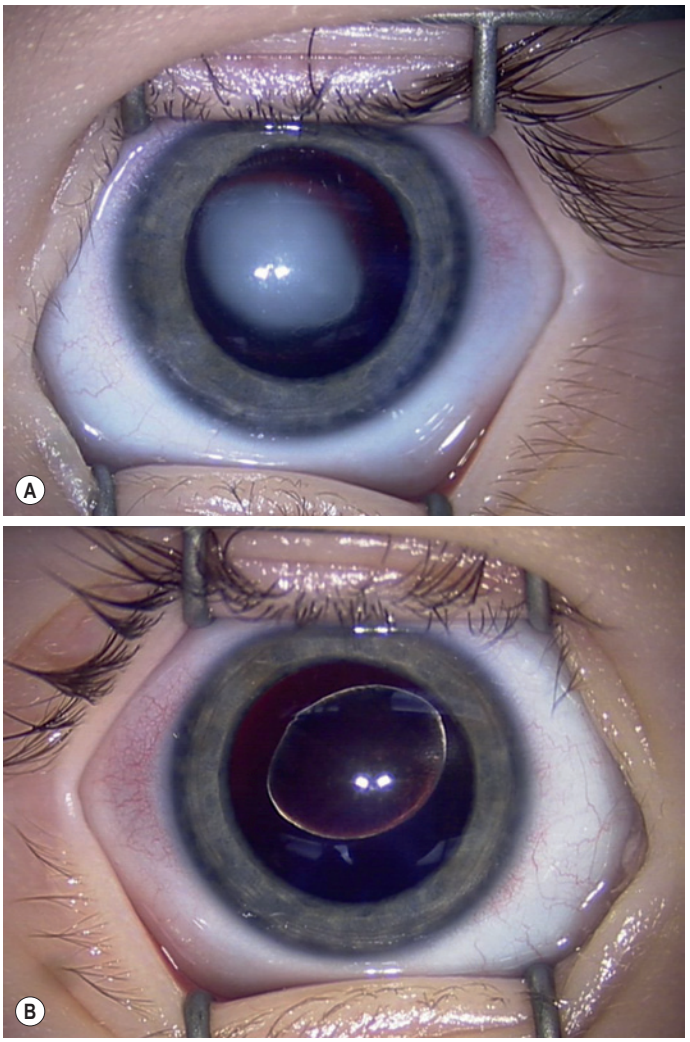


Fig. 37.6 Bilateral posterior lentiglobus. This 8-month-old child presented with lentiglobus in both eyes. (A) There is a dense cataract overlying the lentiglobus in the left eye. (B) The lens cortex is still clear over the lentiglobus in the right eye.

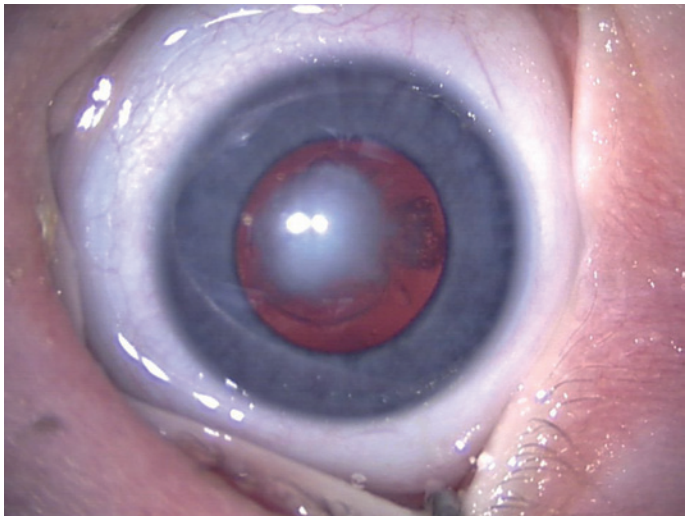


Fig. 37.7 Nuclear cataract. This child underwent a lensectomy and anterior vitrectomy in the right eye when 4 weeks of age. The lens was normal in the left eye. Both eyes had corneal diameters of 10 mm, but the axial length was only 15.74 mm in the right eye compared to 17.32 mm in the left eye.

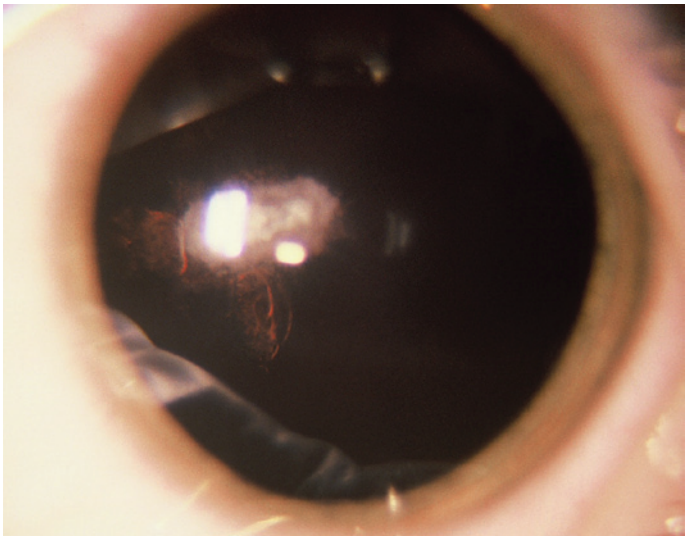


Fig 37.8 Posterior polar cataract. This 4-year-old child was found to have 20/100 visual acuity in his left eye at preschool vision screening. Visual acuity improved to 20/40 with patching therapy. Visual acuity improved further to 20/25 after cataract extraction and intraocular lens implantation.

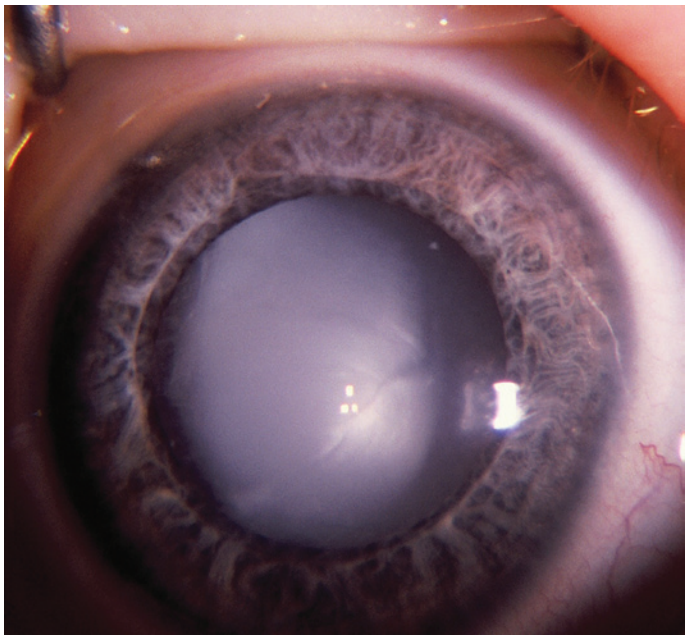


Fig. 37.9 Membraneous cataract. Partially reabsorbed membraneous cataract in a child with Hallermann–Streiff–François syndrome.

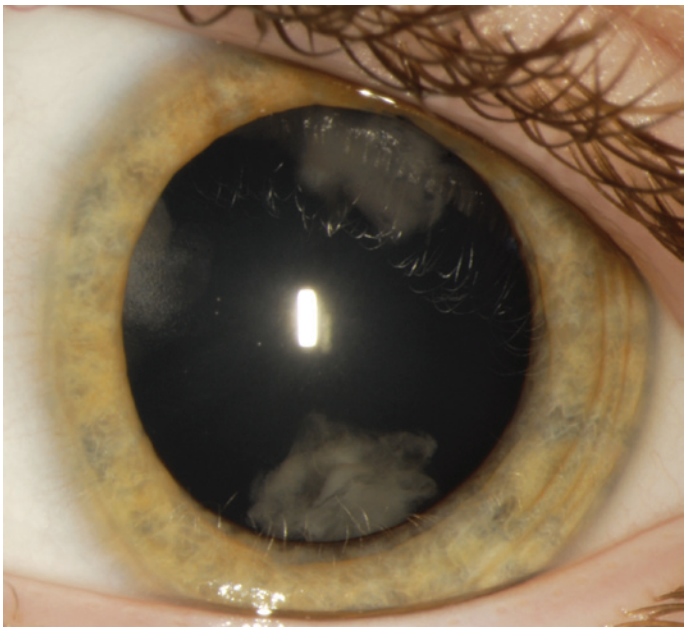
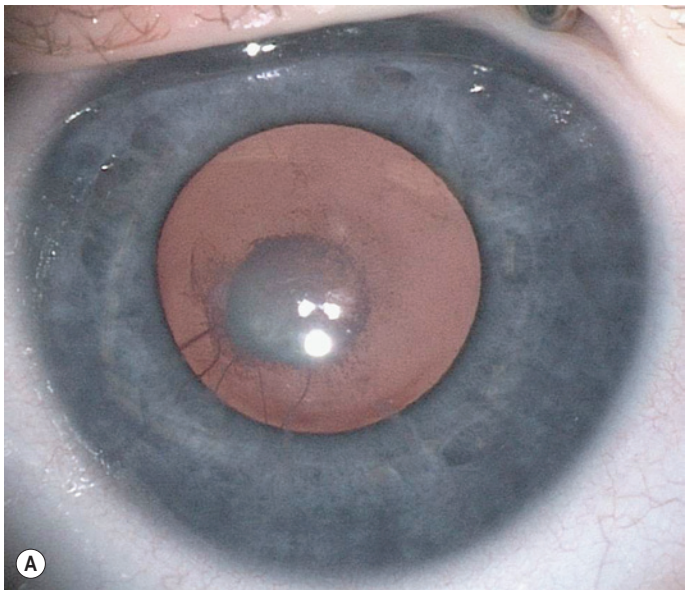
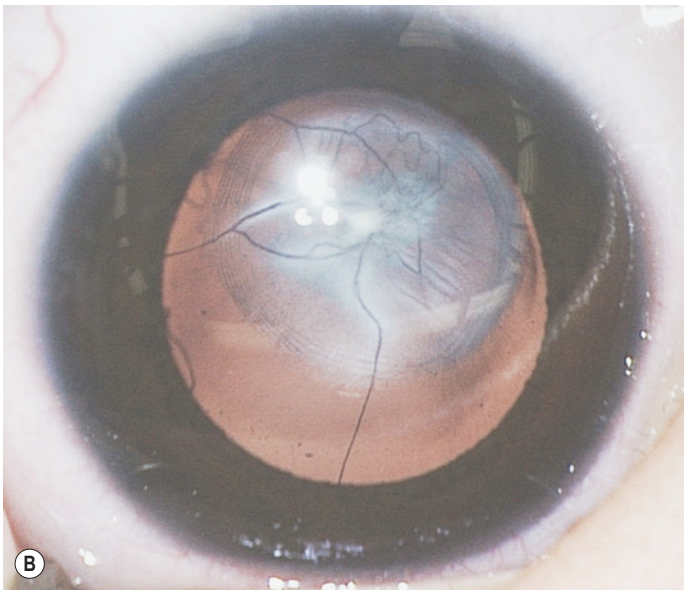


Fig 37.10 Wedge-shaped cataracts. Peripheral wedge-shaped cataracts in a child with autism. Similar appearing cataracts occur in children with Stickler syndrome.





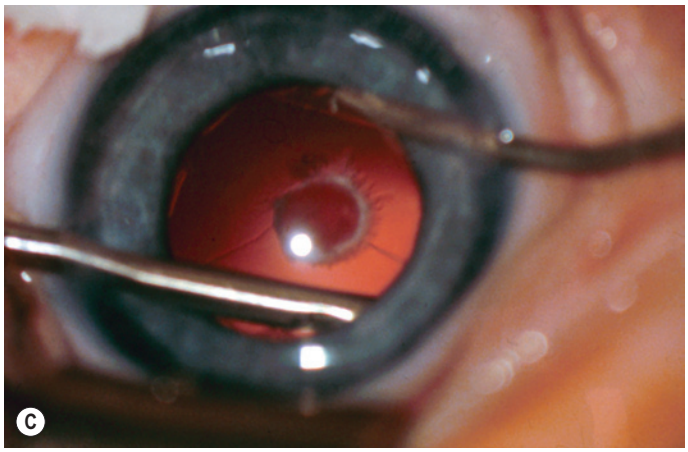
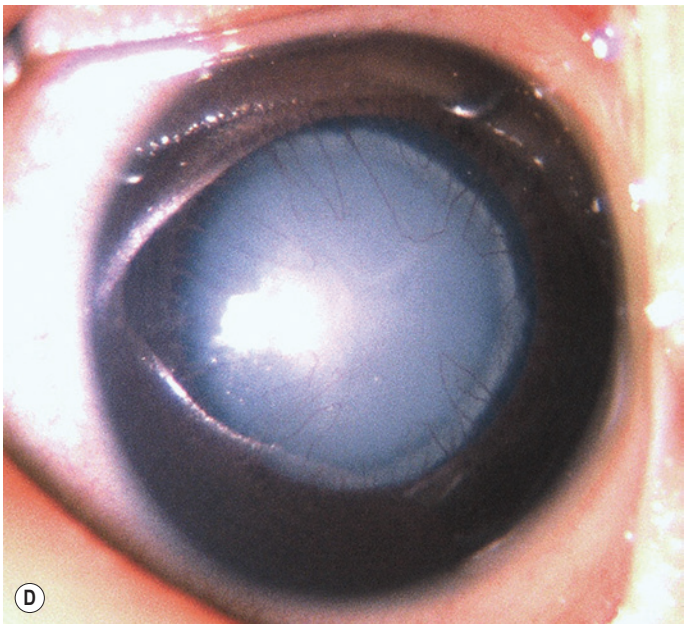


Fig. 37.11 Persistent fetal vasculature (PFV). (A) Mild PFV with hyaloid vessels attached to retrolenticular plaque. (B) Mild PFV with prominent iridohyaloid vessels and a large retrolenticular plaque. (C) Small vascular PRF with a "blood lake" representing a low flow shunt centrally in an eye with PFV.



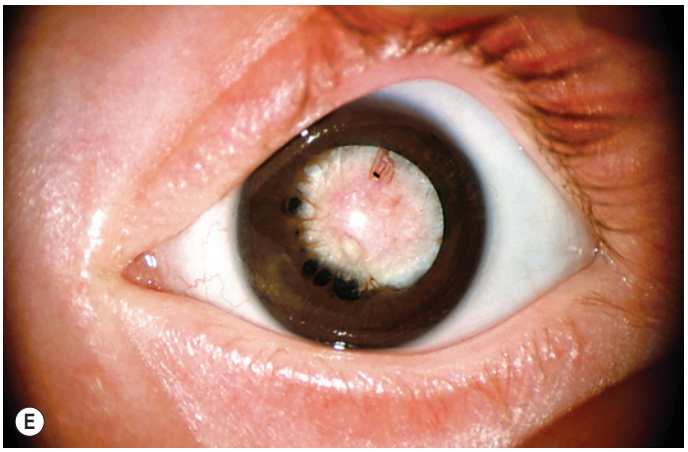


Fig. 37.11 (D) PFV with a dense cataract and hairpin loops. (E) Severe PFV with stretching of the ciliary processes nasally and a dense cataract.

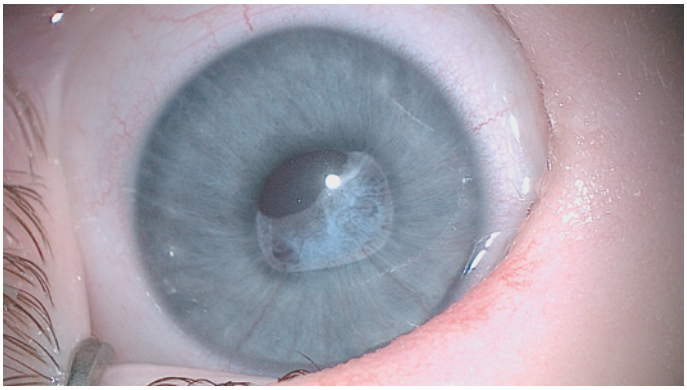


Fig. 37.12 Anterior persistent fetal vasculature. Vascularized pupillary membrane and prominent iridohyaloid vessels in an infant with microcoria.

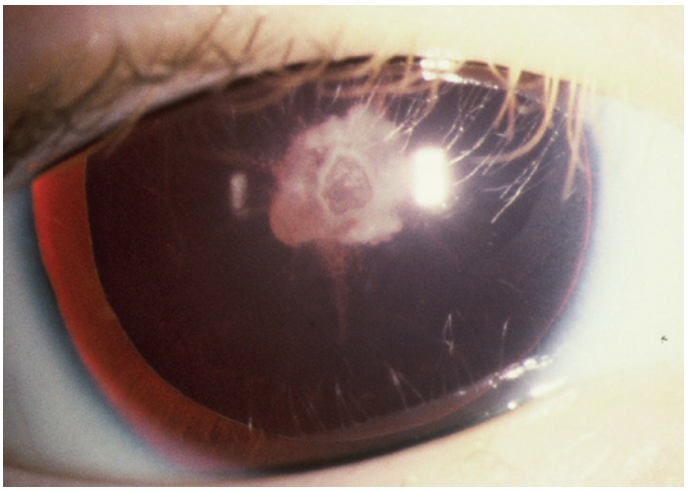


Fig. 37.13 Aniridia. Polar cataracts in a child with aniridia. Macular hypoplasia is the limiting factor for vision in this eye rather than cataract.

Etiology

Bilateral

An etiology can be established in about 50% of children with bilateral congenital cataracts. The most common etiology in Europe and the US is autosomal dominantly inherited cataracts. Less frequently, cataracts can be associated with aniridia (Fig. 37.13), trisomy 21 (Figs 37.14–37.16), Lowe syndrome (Fig. 37.17), Hallermann–Streiff–François syndrome (Fig. 37.18), or a variety of other ocular disorders and syndromes (Box 37.2). Congenital rubella syndrome is a common cause of cataracts where rubella immunization rates are low.[7]

Acquired cataracts may arise secondary to poorly controlled diabetes mellitus, the use of corticosteroids, or external beam radiation therapy (Fig. 37.19).

Unilateral

Many eyes with unilateral congenital cataracts have PFV.[8] They are infrequently associated with systemic disorders. Trauma is the most common cause of an acquired unilateral cataract in a child. On occasion, there is no history of ocular trauma, but iris sphincter tears or a corneal scar can help to establish a traumatic etiology (Fig. 37.20). Cataracts also may develop after laser photoablative therapy for retinopathy of prematurity (Fig. 37.21)[9] or intraocular surgery.

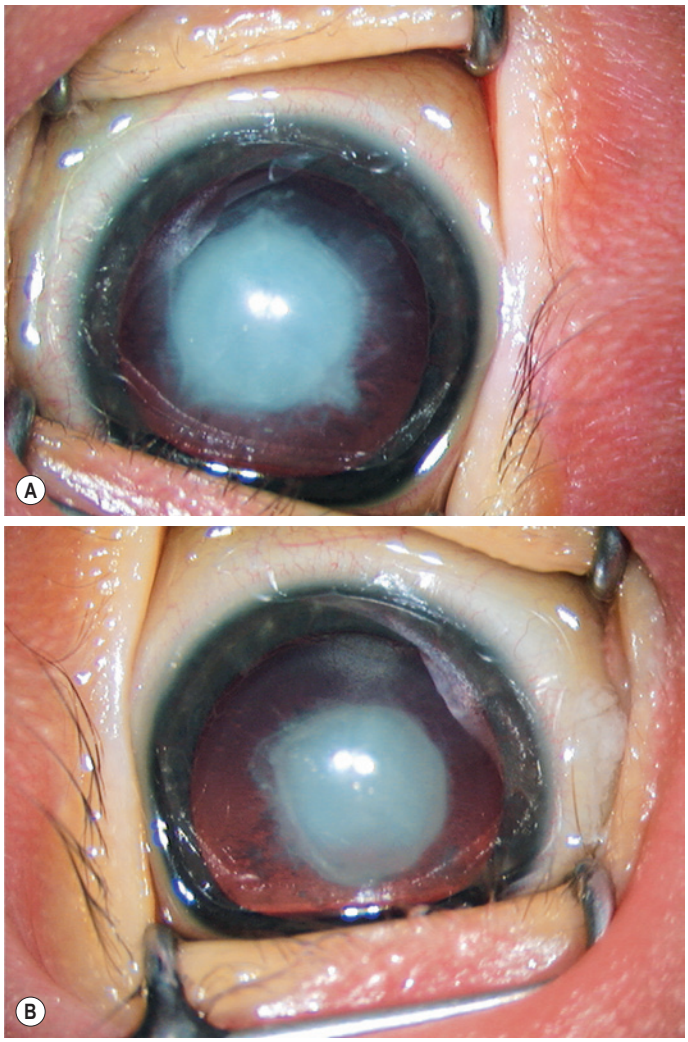


Fig. 37.14 Trisomy 21. Nuclear cataracts in right (A) and left (B) eyes of an infant with trisomy 21.

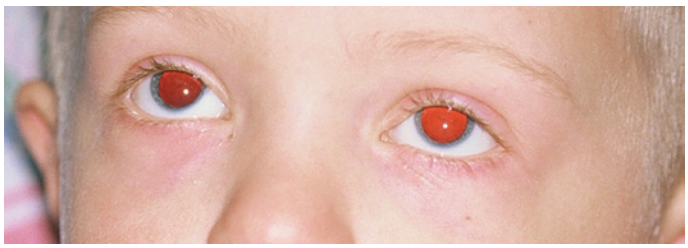


Fig 37.15 Trisomy 21. Lamellar cataracts in a 3-year-old child with trisomy 21.

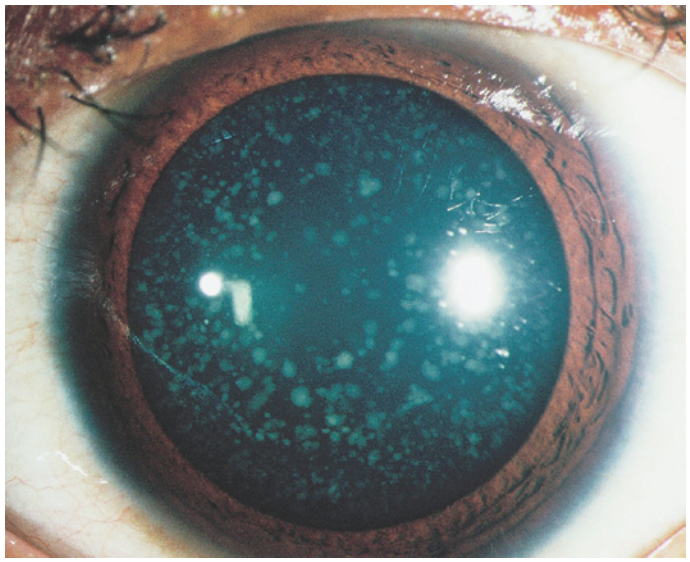
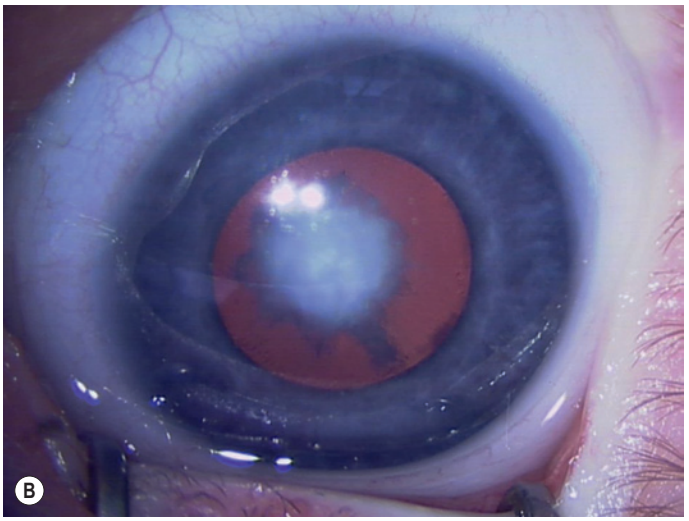


Fig 37.16 Trisomy 21. Cerulean cataract in a teenager with trisomy 21. A similar cataract was present in the fellow eye. Visual acuity was normal.





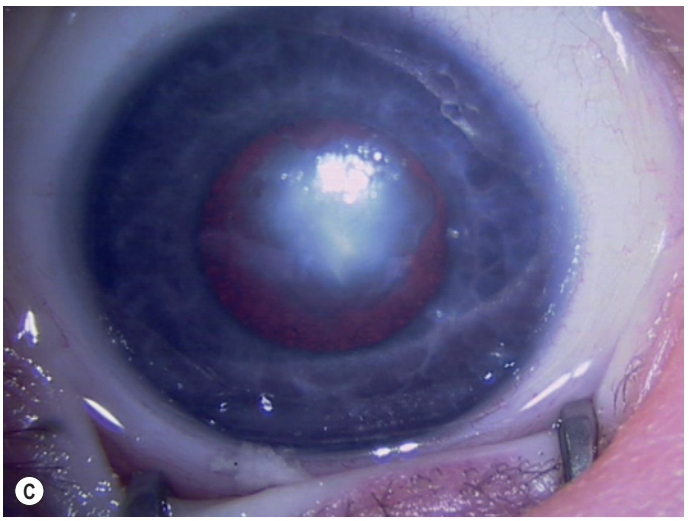


Fig. 37.17 Lowe syndrome. (A) "Chubby" cheeks and rounded forehead. Dense nuclear cataracts in right (B) and left (C) eyes.



Fig. 37.18 Hallermann–Streiff–François syndrome. Note the receding hairline and the vascular, small, red, upturned nose.

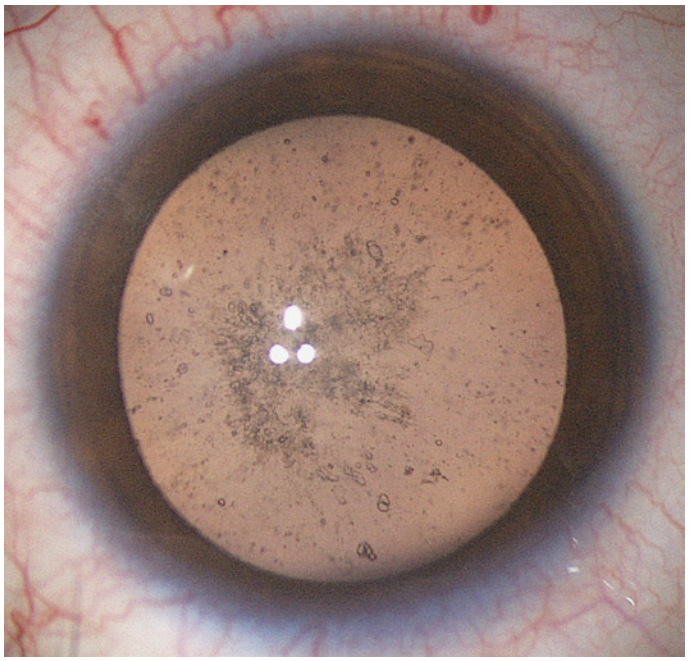


Fig. 37.19 Posterior subcapsular cataract. A posterior subcapsular cataract in a 9-year-old child following external beam radiation therapy for orbital rhabdomyosarcoma.

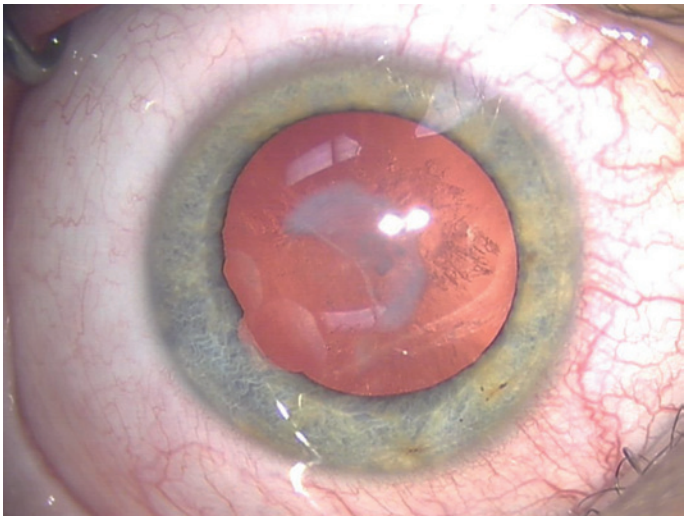


Fig. 37.20 Traumatic cataract. This teenager developed a hyphema, iris sphincter tears, and an anterior subcapsular cataract in his right eye after a paintball injury.



Fig. 37.21 Cataract following diode laser retinal photoablation. This 4-month-old baby developed a dense cataract immediately following diode laser photoablation of the peripheral retina to treat retinopathy of prematurity.

History

The history should determine if there is a family history of childhood cataracts, exposure to corticosteroids or radiation therapy, and ocular trauma. Comorbidities may suggest certain systemic diseases such as diarrhea with cerebrotendinous xanthomatosis.[10] The age the child was first noted to squint or to have leukocoria should be noted. In children with bilateral cataracts, the parents should be asked when they first noted abnormal visual behavior or nystagmus. Reviewing photographs of the child is particularly helpful in children with unilateral cataracts because the abnormal red reflex can be compared to the normal red reflex in the fellow eye (Fig. 37.22). The most informative photographs are taken indoors with a flash and the child looking slightly eccentrically.[11]

Ocular examination

The visual acuity of older children should be assessed using optotypes. In younger children, the ability to fix and follow with each eye should be assessed. The pupillary reflexes should be evaluated for an afferent pupillary defect suggesting associated retinal or optic nerve disease. A slit-lamp examination should

Box 37.2

Etiology of cataracts in childhood

Idiopathic

Intrauterine infection
Rubella
Varicella
Toxoplasmosis
Herpes simplex
Uveitis or acquired infection
Pars planitis
Juvenile idiopathic arthritis
Toxocara canis
Drug-induced
Corticosteroids
Chlorpromazine
Metabolic disorders
Cerebrotendinous xanthomatosis
Galactosemia
Galactokinase deficiency
Hypocalcemia
Hypoglycemia
Diabetes mellitus
Mannosidosis
Hyperferritinemia
Trauma
Accidental
Laser photocoagulation
Non-accidental
Radiation-induced
Other diseases
Microphthalmia
Aniridia
Retinitis pigmentosa
Persistent hyperplastic primary vitreous
Retinopathy of prematurity
Endophthalmitis
Inherited
Autosomal dominant
Autosomal recessive
X-linked
Mental retardation
See text

Inherited with systemic abnormalities

Chromosomal
Trisomy 21
Turner syndrome
Trisomy 13
Trisomy 18
Cri du chat syndrome
Craniofacial syndromes
Cerebro-oculofacial skeletal syndrome
Renal disease
Lowe syndrome
Alport syndrome
Hallermann–Streiff–François syndrome
Skeletal disease
Smith–Lemli–Opitz syndrome
Conradi syndrome
Weill–Marchesani syndrome
Stickler syndrome
Syndactyly, polydactyly, or digital anomalies
Bardet–Biedl syndrome
Rubinstein–Taybi syndrome
Neurometabolic disease
Zellweger syndrome
Meckel–Gruber syndrome
Marinesco–Sjögren syndrome
Infantile neuronal ceroid-lipofuscinosis
Muscular disease
Myotonic dystrophy
Dermatological
Crystalline cataract and uncombable hair
Cockayne syndrome
Rothmund–Thomson syndrome
Atopic dermatitis
Incontinentia pigmenti
Progeria
Congenital ichthyosis
Ectodermal dysplasia
Werner syndrome

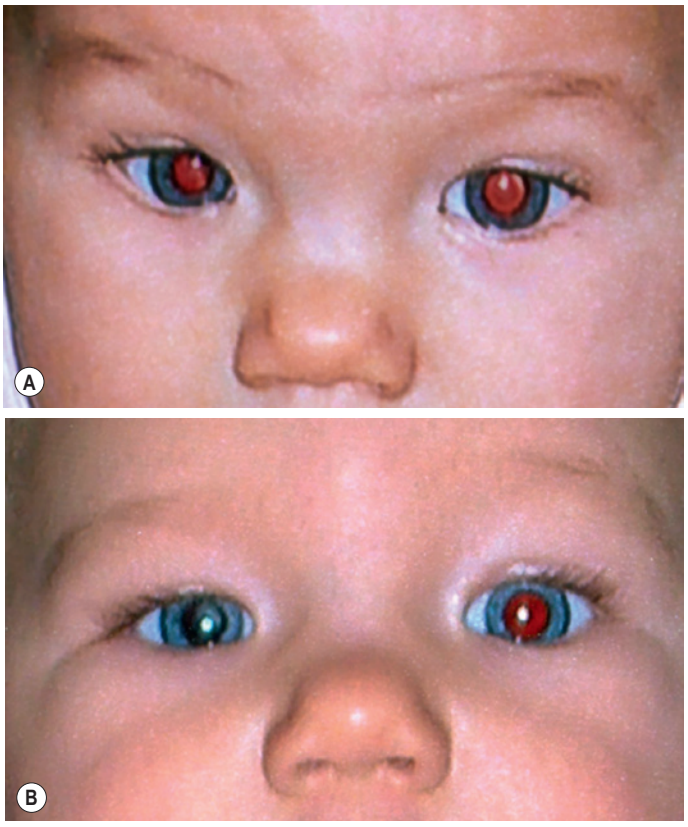


Fig. 37.22 Personal photographs. (A) Personal photograph of an infant taken when 4 months of age showing normal red reflexes in both eyes. (B) Personal photograph of the same infant 2 months later showing loss of the red reflex in the right eye. At the time of cataract surgery, the right eye was found to have a dense central cataract and persistent fetal vasculature.

be performed to evaluate the cornea, iris, and morphology of the cataract. In young children, a hand-held slit lamp is often better tolerated. Slit-lamp examination of other family members can be helpful in establishing a hereditary basis for the cataracts (Fig. 37.23). The retina and optic discs should be assessed using indirect ophthalmoscopy. If the density of the cataract precludes an adequate view of the fundus, a B-scan ultrasound examination should be performed prior to surgery to exclude disease of the posterior segment of the eye that might alter the management of the cataract (e.g. retinal detachment).

Laboratory work-up

A systemic investigation is not usually indicated for children with unilateral cataracts since most are isolated ocular problems, but it can be helpful in selected children with bilateral cataracts. Where rubella vaccination is not routinely performed, infants with bilateral congenital cataracts should be screened for rubella immunoglobulin M (IgM) titers. Male infants with cataracts, hypotonia, problems with weight gain, delayed milestones, and feeding difficulties should be screened for Lowe syndrome by assaying urine amino acids. If urine amino acids are elevated, the diagnosis can be confirmed by testing inositol polyphosphate 5-phosphatase (*OCRL-1*) activity in cultured skin fibroblasts (affected males have <10% normal activity) and *OCRL* gene testing. Children with acquired cataracts and chronic infantile-onset diarrhea should be screened for cerebrotendinous xanthomatosis by measuring plasma levels of cholestanol. Infants with cataracts and failure to thrive should undergo metabolic and genetic testing for galactosemia. While newborn metabolic screening usually diagnoses neonates with galactosemia, false negatives may occur. Children with cataracts and systemic findings

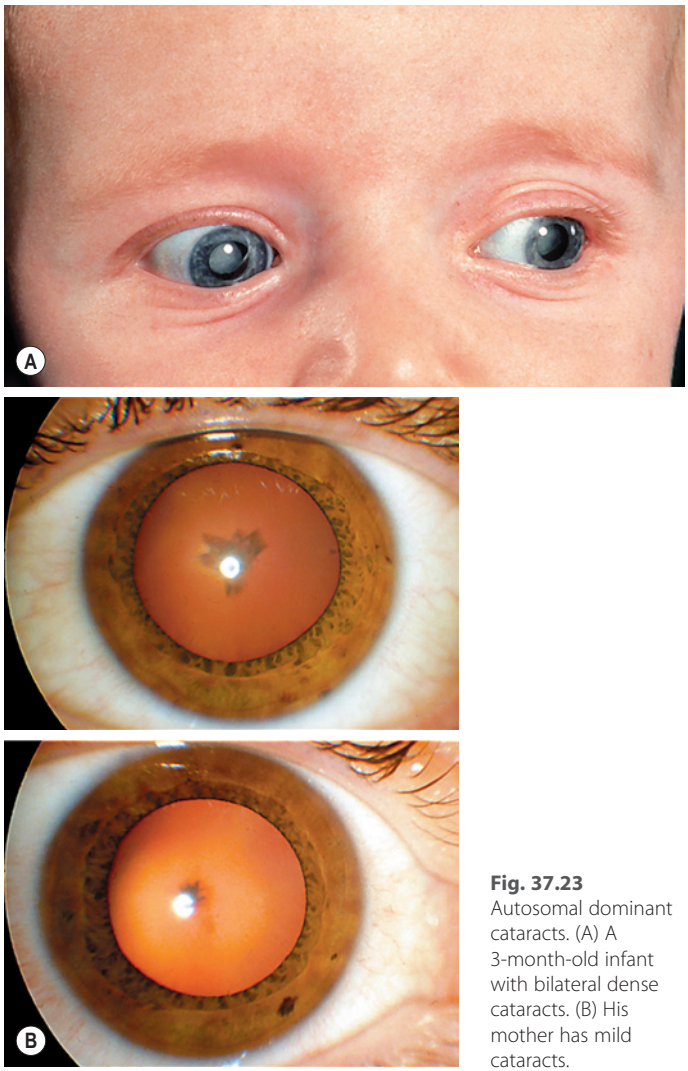


Fig. 37.23 Autosomal dominant cataracts. (A) A 3-month-old infant with bilateral dense cataracts. (B) His mother has mild cataracts.

suggestive of an intrauterine infection should be evaluated by a pediatrician (Fig. 37.24). Children with cataracts and dysmorphic features should be referred to a geneticist. Next-generation sequencing has made it possible to screen children for >100 genes associated with childhood-onset cataracts.[12] Genetic testing will have a more important role in establishing the etiology of congenital and childhood-onset cataracts as these tests become more readily available and affordable. Most autosomal dominant cataracts are caused by mutations of the genes encoding for crystallins and connexins.[13] Since there can be marked heterogeneity in the age of onset and pheonotypes of autosomal dominant cataracts, genetic testing may make it possible to identify asymptomatic children with an increased risk of developing cataracts (Fig. 37.25).

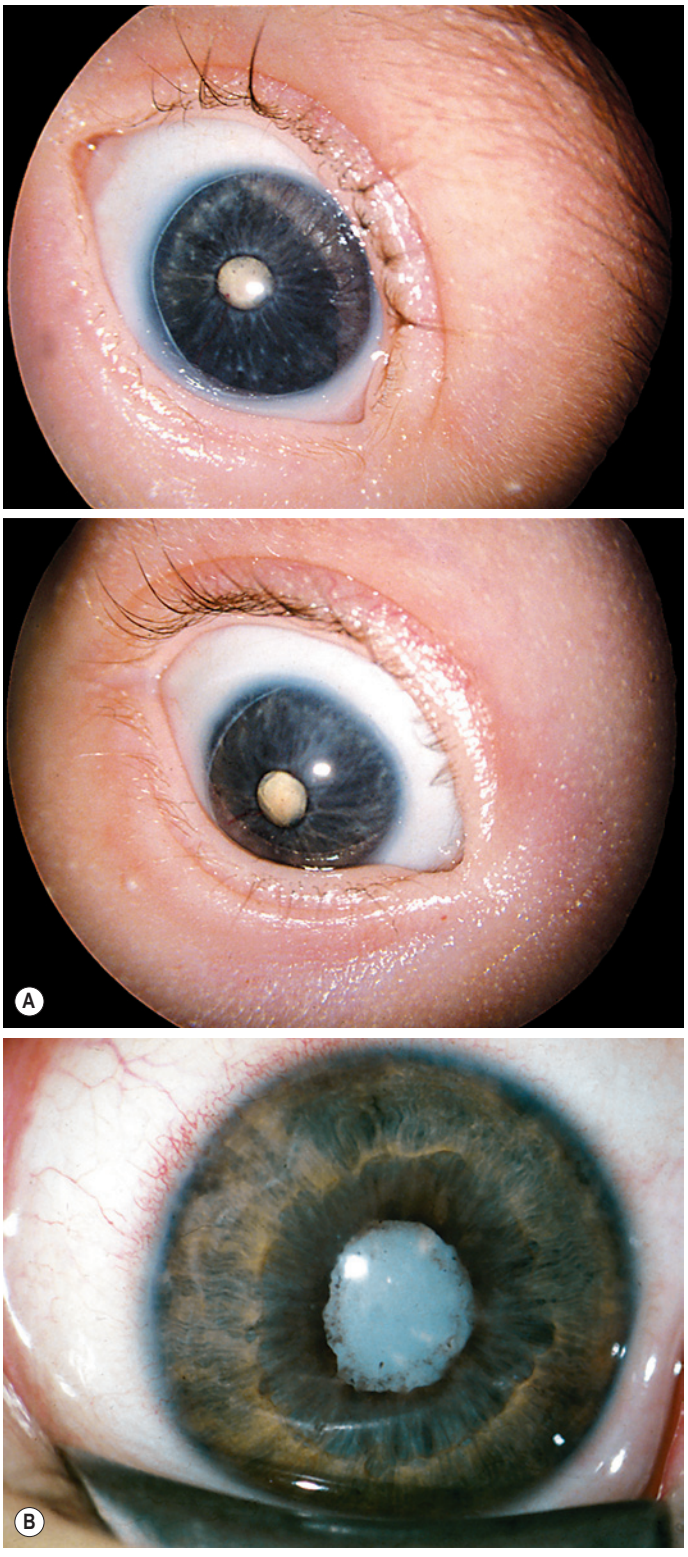


Fig. 37.24 Congenital cataracts with intrauterine infections. (A) Bilateral cataracts and microphthalmos in a child with congenital toxoplasmosis syndrome. (B) Congenital cataract in a child with congenital varicella syndrome. If there is a cataract in a child with an intrauterine infection, it is very likely that there is severe intraocular disease.

Management

Nonsurgical: patching, dilation

Although dense bilateral congenital cataracts should be removed during infancy, incomplete bilateral cataracts should only be removed after a careful assessment of the child's visual

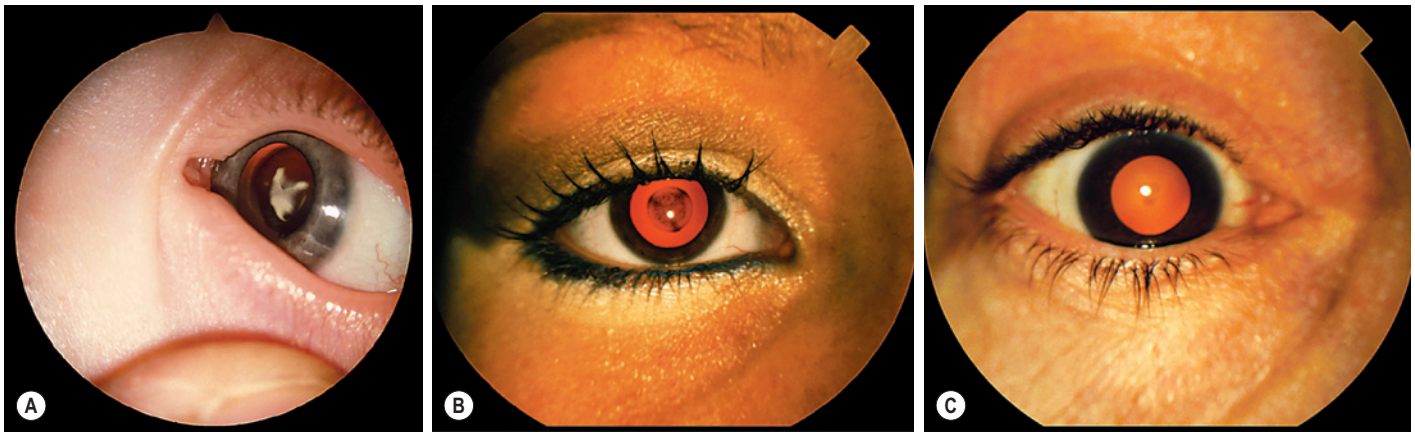


Fig. 37.25 Heterogeneity in autosomal dominant cataracts. (A) A dense central cataract in an infant who presented with leukocoria in both eyes. (B) His asymptomatic mother had mild lamellar cataracts in both eyes. Her vision is good enough to drive a car. (C) His grandmother had visually insignificant lamellar cataracts in both eyes.

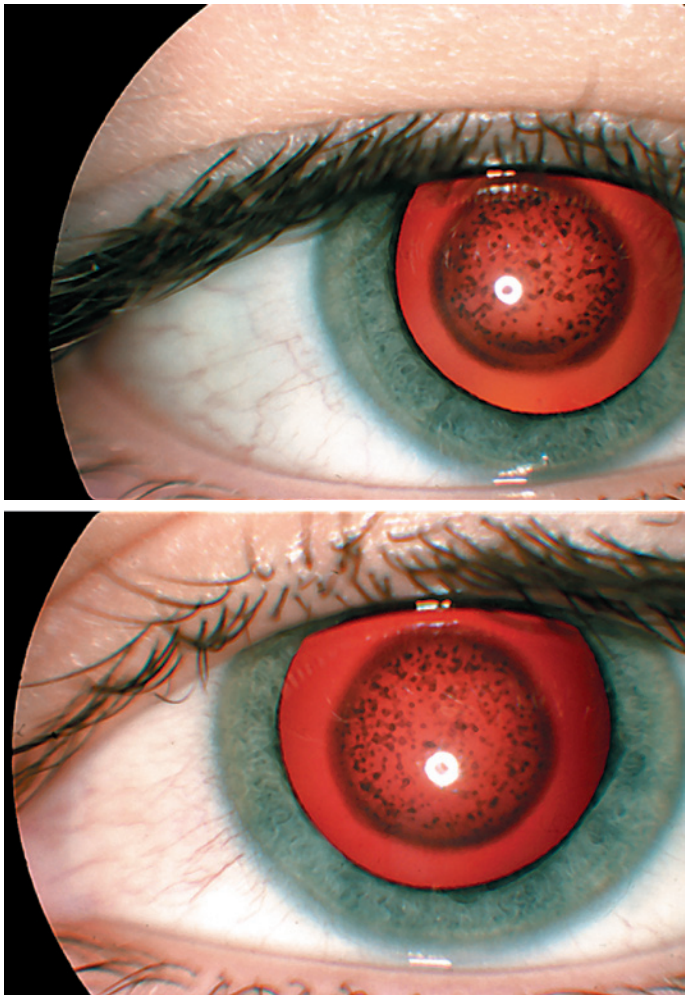


Fig. 37.26 Bilateral symmetrical lamellar cataracts in retroillumination. The acuity is 20/30 in both eyes.

behavior (Fig. 37.26). The density rather than the size of the lenticular opacity correlates best with the visual prognosis for children with bilateral incomplete cataracts. Nuclear cataracts, although smaller in size than lamellar cataracts, have a worse visual prognosis. If major blood vessels in the fundus cannot be distinguished through the central portion of the cataract, significant visual deprivation can be expected. If the incomplete cataract(s) is unilateral or asymmetrical, part-time patching therapy of the normal/better eye may be beneficial to improve or maintain vision in the most affected eye. Chronic dilation of the pupils may be helpful in some children with bilateral incomplete cataracts, particularly if the lens opacities are central and the child has miotic pupils. If a cycloplegic drop is used to achieve long-term dilation, bifocals should be used to correct any hypermetropia and to facilitate near vision.

Surgical

Cataract surgery should be performed during infancy if the cataracts are visually significant. Most surgeons prefer to wait until children are 4 weeks of age to perform cataract surgery since there is evidence that surgery during the first month of life increases the risk of an eye developing glaucoma.[14] The optimal time to perform cataract surgery for a full-term infant with a visually significant unilateral congenital cataract is between 4 and 6 weeks of age, and before 8 weeks of age if the cataracts are bilateral. For premature infants, cataract surgery is usually deferred until the child has a postmenstrual age of at least 40 weeks, but other comorbidities may result in the cataract surgery being delayed until a later age. For children with bilateral cataracts, surgery on the second eye should not be performed more than one week after the first eye to minimize the risk of amblyopia developing in the second eye. Immediate sequential bilateral cataract surgery should be considered for infants with comorbidities that increase the risk of general anesthesia.[15] However, parents should be informed that this increases the risk of bilateral endophthalmitis. Precautions should be taken to reduce this risk such as using different trays of instruments for each eye, disposable cannulas, re-draping between eyes, and using different lots of irrigating solution and medications for each eye.

Surgical techniques

In infants, cataract surgery should be performed using a closed eye system. A scleral tunnel, limbal, or clear corneal incision should be created superiorly to introduce a 20- or 23-gauge vitrector and a lateral incision should be created at the limbus for inserting an infusion cannula into the

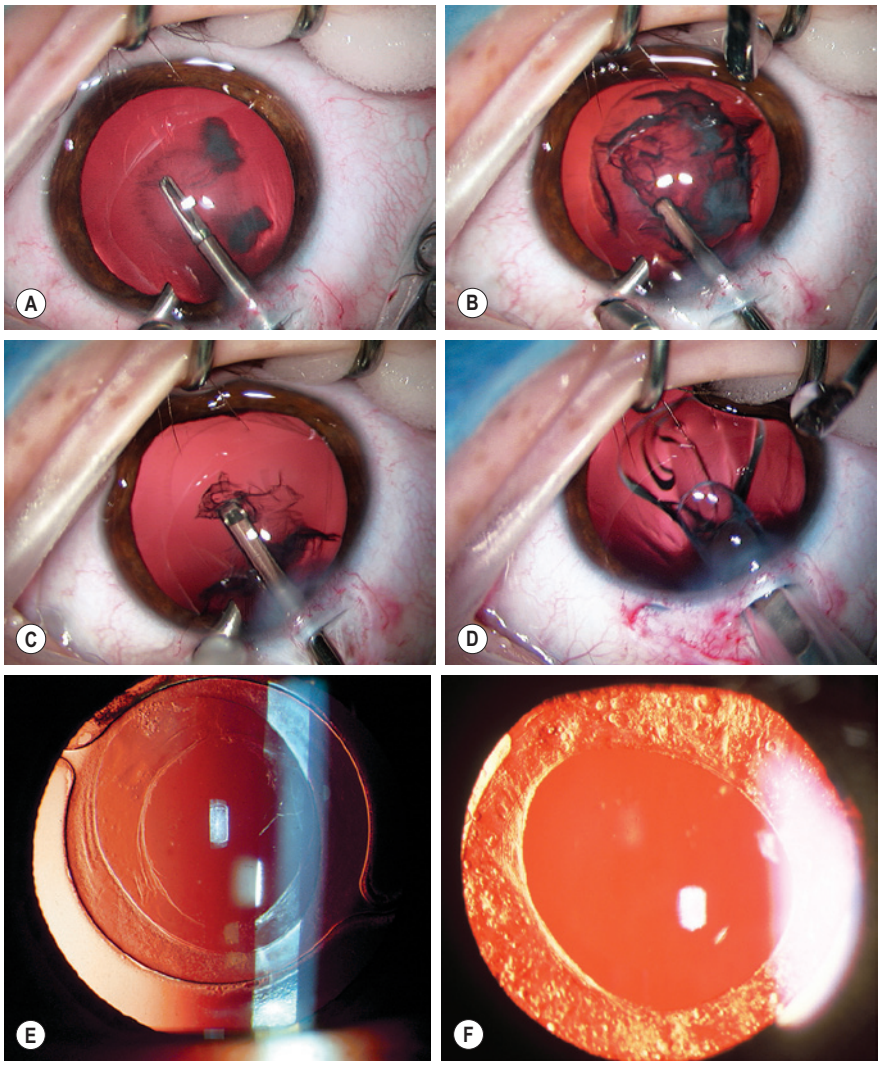


Fig. 37.27 Extracapsular cataract extraction and intraocular lens implantation in a 3-year-old child with a lamellar cataract. After (A) performing a manual anterior capsulorrhexis, (B) the lens cortex is aspirated, (C) a primary posterior capsulotomy and anterior vitrectomy is performed, and (D) a foldable acrylic lens is then implanted in the capsular bag. (E) Polymethylmethacrylate (PMMA) intraocular lens (IOL) in an infant's eye. The central posterior capsulotomy is smaller than the anterior capsulotomy, which facilitated in-the-bag fixation of the IOL. (F) Soemmerring ring in a child following in-the-bag IOL implantation.

anterior chamber. If a lensectomy is planned, an anterior capsule vitrectorrhexis should be performed so the entire cataract surgery can be performed without having to insert and remove additional instruments from the eye. With a low cutting speed, the vitrectorrhexis is initiated by making an opening in the center of the anterior capsule with the port of the vitrector facing downwards. The vitrectorrhexis is then gradually enlarged to 5–6 mm by moving the vitrector away from the center of the lens. If cataract extraction with intraocular lens (IOL) implantation is planned, a continuous curvilinear capsulorrhexis is preferable since the capsular edge created using this technique is less likely to tear during IOL implantation. The capsulorrhexis should be performed with the anterior chamber filled with an ophthalmic viscoelastic device. In infants and young children, vector forces should be directly centripetal rather than tangential during the capsulorrhexis to compensate for the increased elasticity of the anterior capsule. Trypan blue staining of the anterior capsule can be helpful to enhance visualization of the anterior capsule in a patient with a white cataract. If the lens is intumescent, the center of the lens should be decompressed with a needle prior to initiating the capsulorrhexis to prevent the capsule from tearing peripherally. Ideally, the capsulorrhexis should be slightly smaller than the optic of the IOL that will be implanted. Alternatively, a femtosecond laser may be used to create an anterior capsulotomy to more precisely control the size and centration of the anterior capsulotomy.[16] In almost all cases, the lens nucleus and cortex of a pediatric cataract can then be aspirated using a vitrector. Phacoemulsification is rarely required in children. Removing subincisional cortex can be facilitated by switching the entry sites for the vitrector and the infusion cannula. A foldable IOL is preferred in children to minimize the width of the entry site. A smaller entry site reduces the risk of iris prolapse intraoperatively and wound dehiscence postoperatively. When implanting an IOL in the eye of a child <5 years of age, a primary posterior capsulotomy and anterior vitrectomy should be performed given the rapidity of posterior capsular opacification in young children (Fig. 37.27). Posterior capsular opacification makes it difficult to refract children and can also result in amblyopia. In older children, in whom posterior capsular opacification may be delayed for several years and who are less susceptible to amblyopia, a primary posterior capsulotomy and anterior vitrectomy may be omitted if it is possible to follow the child at regular intervals and the child will cooperate with a YAG laser capsulotomy performed in a clinic setting. The posterior capsulotomy can



Fig 37.28 Aphakic contact lenses. The child has successfully worn contact lenses since undergoing lensectomies at 3 weeks of age.

be performed using a limbal or a pars plana approach. The limbal approach has the advantage that the same incision site used for cataract surgery can be used, but it makes it more difficult to implant the IOL in the capsular bag. Capsular bag fixation can be facilitated after creating posterior capsulotomy using a limbal approach by separating the capsular leaflets with a high-viscosity ophthalmic viscoelastic device. A primary capsulotomy can also be performed through the pars plana after implanting the IOL. This simplifies IOL implantation into the capsular bag, but does require a second entry site in the pars plana. The distance of the entry site from the corneal limbus can be based partially on the age of the child (<12 months, 1.5–2.0 mm; 1–4 years, 2.0–2.5 mm; >4 years 3.0–3.5 mm), but the axial length of the eye must also be taken into consideration. After completing the cataract surgery, the limbal incision sites should be closed with 9-0 or 10-0 absorbable sutures and the pars plana incision site with an 8-0 absorbable suture. Any ophthalmic viscoelastic material remaining in the eye should be aspirated and the anterior chamber should be re-formed with balanced salt solution. Antibiotics should then be injected into the anterior chamber[17] and topical 1% atropine and a combination steroid/antibiotic ointment should be applied to the eye. Lastly, the eye should be patched and covered with a protective shield.

Optical correction

One of the major obstacles in children following cataract surgery is optical correction of the induced aphakia.

Contact lenses

Contact lenses remain the standard method of optically correcting infant aphakia (Fig. 37.28). Several different types of contact lenses may be used. Rigid gas-permeable contact lenses are available in a wide range of powers and they are able to correct large astigmatic refractive errors. In addition, they are easily inserted and removed even in uncooperative children.[18] The biggest obstacle for their use is the greater expertise required to fit them. In addition, they must be worn on a daily wear basis. Silicone lenses have the advantage that they can be worn on an extended wear basis, but they are more expensive and are only available in a limited range of powers and sizes. Furthermore, it becomes increasingly difficult to keep proteinaceous deposits from accumulating on the surfaces of these lenses as children become older. Parents are advised to remove the lenses if the eye becomes inflamed or irritated, or if excessive discharge develops. Inadequate care can result in keratitis and corneal scarring. Poor compliance with contact lens wear is most commonly due to poor patient cooperation, rather than complications from their use. Contact lens powers must be changed on a regular basis in young children and they are easily lost. The high cost of purchasing and cleaning contact lenses is a significant deterrent for many families using this method of optical correction. In addition, there are occasions when contact lenses cannot be safely worn (e.g. if a child has a conjunctivitis). For this reason, aphakic children wearing contact lenses should be prescribed a pair of glasses to be worn on a back-up basis.



Fig 37.29 Aphakic spectacles. Aphakic spectacles are safe and the power can be easily changed, but they have optical and cosmetic disadvantages.

Spectacles

Aphakic spectacles are better tolerated than contact lenses by some children with bilateral aphakia, especially between 18 months and 5 years of age. In addition, some parents prefer their ease of use compared to contact lenses. They also have the advantage of magnifying the apparent size of microphthalmic eyes. Their disadvantages include restricting peripheral vision and a poor cosmetic appearance with the high plus powers often required (Fig. 37.29).

Intraocular lenses

IOL use in young children is complicated by the increased number of additional intraocular operations associated with

their use, primarily to remove visual axis opacities, and the difficulty of predicting the optimal IOL power.[19,20] In young children, an IOL power is generally chosen that undercorrects the eye, in anticipation of a myopic shift. Immersion A-scan biometry in an anesthetized young child or optical biometry in an older child are the most accurate means of measuring axial length. No IOL formula has been specifically developed for pediatric eyes. The T2, SRK/T, and Holladay 1 IOL calculation formulas have been shown to be associated with the lowest absolute prediction errors in young children.[21] However, even using these formulas, the mean absolute prediction error is typically much larger in children (e.g. 1.0–1.5 D) than adults. An international panel of pediatric ophthalmologists recently recommended the following age-based undercorrections when implanting IOLs in the eyes of children: age <6 months, +6–10 D; 6–12 months, +4–6 D; 1–2 years; +3–4 D; 3–4 years, +3 D; 4–6 years, +2–3 D; 6–8 years, +1–2 D, >8 years, 0 to +1 D. "In-the-bag" IOL implantation is the preferred procedure when performing primary IOL implantation in a child. IOL implantation in-the-bag may also be achieved as a secondary procedure in many children by opening the Soemmerring ring at the junction of the anterior and posterior lens capsules, aspirating its contents, filling the capsular bag with an ophthalmic viscoelastic device, and then positioning the IOL between the capsular leaflets.[22] It is important to leave a rim of capsule for 360° at the time of the lensectomy to facilitate secondary IOL implantation into the capsular bag later in childhood. If insufficient capsular remnants are available for in-the-bag fixation, the IOL can be implanted into the ciliary sulcus if there is a continuous rim of lens capsule. Implantation of an IOL into the anterior chamber may be required if there is insufficient capsular support for a ciliary sulcus-fixated IOL. Anterior chamber IOLs may be attached to the iris by enclavation or suture fixation or fixated in the angle. IOLs offer the advantage of a constant optical correction. An overcorrection with spectacles or contact lenses is usually necessary to fully focus the eye.

Postoperative care

The frequent administration of topical corticosteroids is critical after pediatric cataract surgery to blunt the exuberant inflammatory response that usually occurs in these eyes. The frequency and duration of their use depends on many variables such as the age of the child, the difficulty of the surgery, and whether an IOL was implanted. A topical cycloplegic agent should also be administered to prevent the pupil from becoming miotic. Because of the increased risk of the eye being rubbed, spectacles or a shield should be worn over the eye during the immediate postoperative period. Broad-spectrum topical antibiotic should also be prescribed.

Postoperative complications

Amblyopia (see Chapter 73)

Amblyopia is nearly universal in children with dense congenital cataracts. It arises as a result of the retina receiving a defocused image when the central visual pathways are forming. Uncorrected aphakia or induced anisometropia can exacerbate amblyopia even after the removal of a cataract. Whatever optical correction is worn, frequent re-examinations are necessary to ensure that the correction is up to date. Each examination should include an assessment of fixation behavior or grating acuity in preverbal children and optotype acuity in verbal children to detect or manage amblyopia. When amblyopia is present, occlusion therapy of the preferred eye should be initiated. The duration of patching each day depends on the severity of the amblyopia. Good visual outcomes can be achieved in children undergoing unilateral congenital cataract surgery by patching the fellow eyes for 30–50% of waking hours.[23] Patching the fellow eye for longer periods of time each day may result in subtle visual deficits in the fellow eye, strabismus, and impaired binocularity. Patching therapy is most important during the critical period of visual development during early childhood. It may be discontinued when children are 7 years of age. Amblyopia can be treated in a child wearing contact lenses to optically correct bilateral aphakia by delaying insertion of the contact lens in the preferred eye for a specified time each day. Occlusion therapy is not usually necessary in older children with bilateral acquired cataracts or unilateral traumatic cataract when treated promptly.

Visual axis opacities

Visual axis opacities may arise from fibrin forming a pupillary membrane, opacification of the residual posterior lens capsule, or lens re-proliferation extending into the visual axis. It is particularly common after IOL implantation during infancy (Fig. 37.30). Because of the almost universal occurrence of posterior capsular opacification in children, a primary posterior capsulotomy and anterior vitrectomy are recommended in children under 5 years of age. In older children, the posterior capsule can be left intact and a YAG laser capsulotomy can be performed later when the posterior capsule opacifies.[24] The procedure should not be delayed after the posterior capsule opacifies because of the increased difficulty of opening a thickened posterior capsule and the risk of developing amblyopia in a child under 7 years

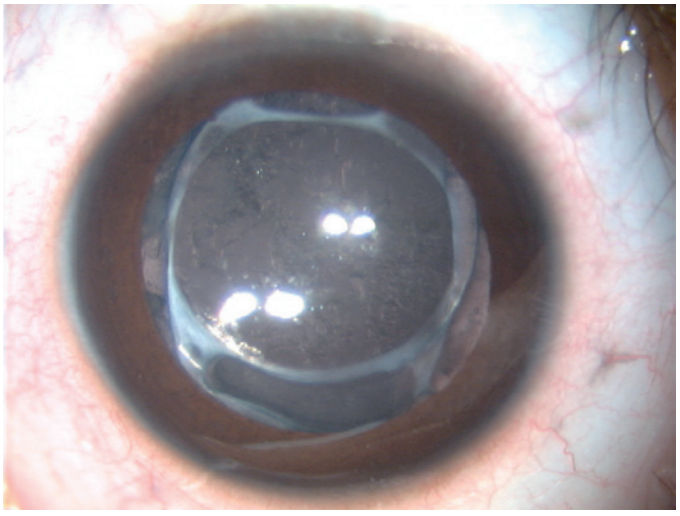


Fig. 37.30 Posterior capsular opacification. The posterior capsule was left intact at the time of cataract surgery and intraocular lens implantation. The posterior capsule was too thickened to open with a YAG laser so a membranectomy was performed.



Fig. 37.31 Anterior capsular phimosis. The capsulorrhexis has undergone progressive phimosis, which makes it difficult to perform retinoscopy.

of age. If the posterior capsule is too dense to open with a YAG laser, a pars plana or limbal membranectomy may be performed with a vitrector. A Soemmerring ring develops in children's eyes after cataract surgery. In most cases, the re-proliferating lens material is confined to the retro-iridial space, but it may extend into the pupil. Re-proliferating lens material commonly extends into the pupillary space after IOL implantation during infancy presumably because the IOL prevents the margins of the anterior and posterior capsular leaflets from fusing together. In these instances, intraocular surgery may be necessary to clear the visual axis. Capsular phimosis may also develop for either the anterior or posterior capsulotomy, making it difficult to refract the child (Fig. 37.31). In some cases, capsulotomies must be enlarged surgically in order to perform refractions and to examine the fundi.

Glaucoma (see Chapter 38)

Glaucoma may arise during the early postoperative period or years later. It is a serious problem and is difficult to manage. Pupillary block glaucoma has a higher incidence in neonates following lensectomy due to vitreous prolapse into the anterior chamber or pupillary membrane formation. This complication can largely be averted by performing an adequate anterior vitrectomy and atropinizing the pupil postoperatively. A prophylactic peripheral iridectomy is generally not performed in a child's eye because of the increased risk of inflammation associated with any manipulation of a child's iris. Affected patients usually have ocular pain, corneal edema, and iris bombé. Open angle glaucoma is one of the most common late complications of pediatric cataract surgery, particularly in children undergoing cataract surgery during early infancy and in eyes with PFV. The risk of glaucoma increases twofold by performing cataract surgery at 1 month compared to 2 months of age.[24] Unlike infantile-onset glaucoma, which is usually associated with readily detectable signs and symptoms such as bupthalmos, corneal edema, and epiphora, juvenile-onset glaucoma is usually more subtle in its onset. Intraocular pressure should be assessed at each outpatient examination after cataract surgery to screen for ocular hypertension. Rebound tonometry is better tolerated by young children than applanation tonometry.[25] Anatomical signs of glaucoma in young children include cupping of the optic disc, an increase in axial length or the corneal diameter, or a rapid myopic shift.

Strabismus

Strabismus is often the presenting sign of a unilateral cataract in a child. Esotropia is more commonly observed in a child with a congenital cataract, while exotropia is more frequently observed in a child with an acquired cataract. A delay in the removal of an acquired cataract or optical correction in an older child can result in diplopia after cataract surgery even after the eyes are surgically aligned due to a disturbance of central fusion.

IOL complications

Posterior chamber IOLs may become subluxated secondary to trauma or if the suture securing a haptic at the pars plana breaks (Fig. 37.32A). In most instances, the IOLs can be re-positioned and re-fixated with one or more prolene sutures (Fig. 37.32B). Eyes with IOLs in the anterior chamber fixated in the angle may develop the UGH syndrome (uveitis, glaucoma, and hyphemas) if the IOL is incorrectly sized. Movement of the IOL may also result in a haptic rotating though a periperhal iridotomy (Fig. 37.33). A large myopic shift may also occur after IOL implantation during early childhood. This may even occur when the eye is undercorrected when the IOL is implanted. In some cases, exchanging the IOL for a lower power IOL may be indicated. Generally the IOL used to replace the original IOL will need to be positioned in the ciliary sulcus.

Irregular pupil

An irregular pupil is a frequent complication of infantile cataract surgery and is most noticeable in children with lightly colored irides. Most commonly it arises secondary to posterior synechaie between the iris and the residual lens capsule. It may also develop secondary to iris trauma occurring intraoperatively. Strands of vitreous extending to the surgical incision site may cause peaking of the pupil. This may be averted by turning off the infusion line before removing the vitrector from the eye, maintaining a low flow of irrigating solution, and minimizing the number of times the vitrector is inserted and removed from the eye. Even when the pupil is round after cataract surgery, it frequently is less reactive to light and pharmacological dilation.

Heterochromia iridis

Cataract surgery during infancy is commonly associated with increased iris pigmentation in the operated eye (Fig. 37.34). This is likely due to the release of prostaglandins following cataract surgery.[26]

Endophthalmitis

Bacterial endophthalmitis is an uncommon, but devastating, complication after cataract surgery. A concurrent nasolacrimal

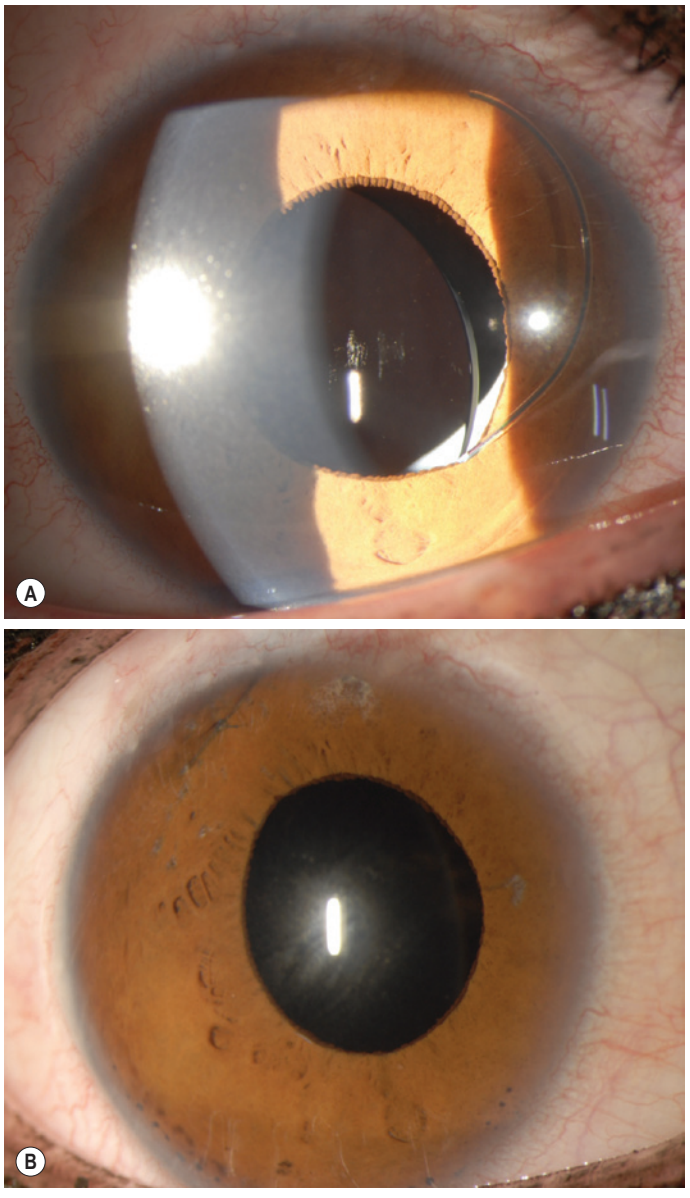


Fig. 37.32 Subluxated ciliary sulcus-fixated intraocular lens (IOL). (A) The IOL spontaneously subluxated in this active teenager 10 years after being implanted in the ciliary sulcus. (B) The inferior haptic was re-positioned over the capsular rim and the superior haptic was sutured to the iris at 11 o'clock using a 10-0 prolene suture.

duct obstruction, upper respiratory infection, or periorbital skin disease increases the risk. The most common organisms causing it in children are *Staphylococcus aureus* and *Streptococcus pneumoniae*.

Even though most cases are diagnosed during the early postoperative period, the visual prognosis is poor. In one series, 65% of affected eyes ended up with no light perception despite aggressive treatment with intravitreal and systemic antibiotics.[27] The incidence of this complication can be minimized by using strict sterile techniques and delaying surgery for children with ocular infections. Intracameral antibiotics at the end of cataract surgery have been shown to reduce the incidence of this complication.[27]

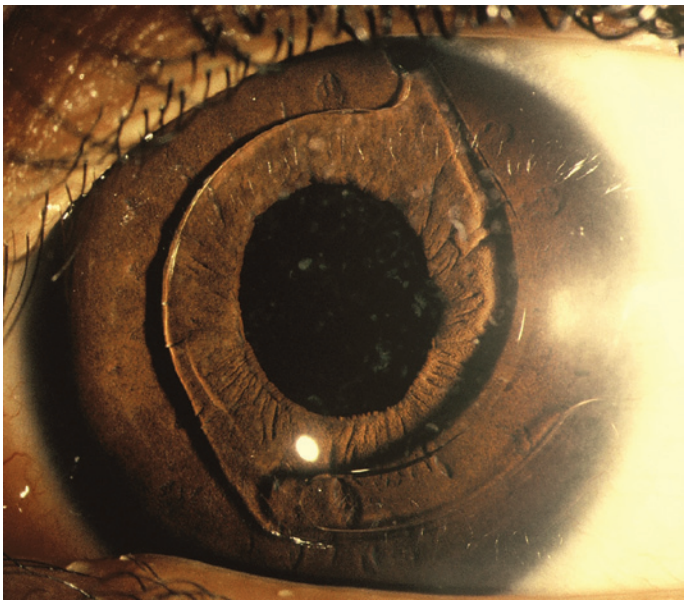


Fig. 37.33 Anterior chamber intraocular lens (IOL). Anterior chamber IOL in an aphakic child. The superior haptic has subluxed through a peripheral iridotomy.

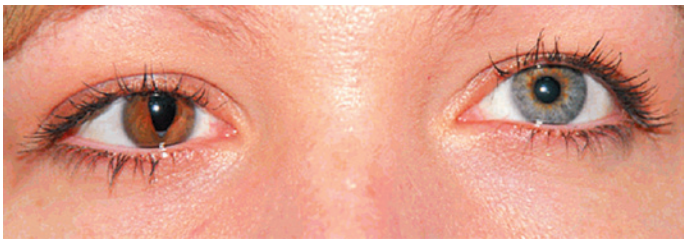


Fig. 37.34 Hetererochromia iridis. This 32-year-old woman underwent a lensectomy in her right eye when 1 year of age. The iris often becomes darker in the operated eye after cataract surgery during infancy.

Retinal hemorrhages and detachments

A hemorrhagic retinopathy develops in some infants after a lensectomy and anterior vitrectomy. In most cases, this consists of flame-shaped hemorrhages in the posterior pole that resolve without sequelae in 1–2 weeks.[28] Occasionally, a hemorrhage may occur in the fovea and result in a severe reduction of vision. In these cases, even after the hemorrhage has resolved, the visual acuity may remain reduced by amblyopia.

Retinal detachments are infrequent and usually occur decades after the removal of a congenital cataract. They are particularly common in developmentally delayed children following cataract surgery due to self-inflicted trauma. Retinal detachments are frequently bilateral, and the visualization of the retinal breaks may be hampered by miotic pupils and Soemmerring rings.

Cystoid macular edema

Cystoid macular edema is rare in children following cataract surgery unless there are other comorbidities such as uveitis.

Corneal edema

Corneal edema may result from excessive corneal trauma after a long cataract surgery or secondary to toxic anterior segment syndrome.[29] Disposable cannulas should be used whenever possible and toxic chemicals such as formaldehyde should not be used to clean instruments for intraocular surgery to avoid toxic anterior segment syndrome. Corneal edema after cataract surgery in children usually resolves in a few days.

Visual outcomes

Many factors influence the visual outcome after cataract surgery including:

1. the age of onset of the cataracts;
2. the laterality of the cataracts;
3. associated ocular and systemic conditions;
4. the age when cataract surgery is performed;
5. compliance with optical and patching therapy.

Children who develop cataracts when 7 years of age or older usually have an excellent visual prognosis. Children with early-onset bilateral cataracts also have an excellent visual prognosis with prompt cataract surgery and optical correction. Children with early-onset unilateral cataracts have the worst visual prognosis. However, it is possible for these children to have an excellent visual outcome with early cataract surgery and good compliance with their optical correction and patching therapy of the fellow eye.[30] The Infant Aphakia Treatment Study showed that in the USA one of the best predictors of a good visual outcome in a child with a unilateral congenital cataract was the parents having private health insurance.[31] This was likely a surrogate for better compliance with optical correction and patching therapy. Concomitant ocular abnormalities such as corneal opacities, glaucoma, retinal abnormalities, and nystagmus worsen the visual prognosis. Binocular vision is uncommon after cataract surgery in children, but it can be achieved even in children with early-onset unilateral cataracts.[32]

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Childhood glaucoma

Maria Papadopoulos and Sir Peng Tee Khaw

Chapter contents

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See online for supporting video for this chapter.

Introduction

Glaucoma in children is a rare, potentially blinding condition characterized by elevated intraocular pressure (IOP)-related damage to the eye and is caused by a diverse group of conditions. Clinical presentation can vary because, depending on the age of onset, elevated IOP can affect the whole eye and not just the optic nerve by characteristic cupping. The goal is to provide a lifetime of vision where possible. Successful control of IOP is crucial in achieving this goal but can be challenging, especially when surgery is necessary. The correction of ametropia and amblyopia therapy is also vital to maximize visual function.

Clinical presentation

A child suspected of having glaucoma can present in many ways: Firstly, they may present with clinical manifestations of elevated IOP as occurs in infancy. Secondly, they may present with a condition that predisposes them to glaucoma, e.g. aphakia. Thirdly, glaucoma may be found during screening when there is a family history of childhood glaucoma. Lastly, they may present after having failed routine school vision testing.

Glaucoma from any cause in a neonate or infant is synonymous with the *classic triad of lacrimation, blepharospasm, and photophobia* due to corneal edema from elevated IOP. These signs are not entirely specific but are very suggestive of glaucoma and may appear before the hazy cornea and characteristic buphthalmos become obvious. *Buphthalmos* (*ox eye*), a descriptive term, refers to the generalized ocular enlargement by elevated IOP from any cause in infancy (Fig. 38.1). It is a unique finding of glaucoma in infancy because the young eye increases in size from increased IOP due to corneal and scleral collagen immaturity. The potential for corneal enlargement usually ceases by the age of 3 years, although the sclera remains deformable until around 10 years of age. As the IOP rises, Descemet membrane eventually ruptures, with one edge usually retracting as a scroll to form a ridge known as *Haab stria* (Fig. 38.2). As the underlying endothelium is torn, localized or diffuse corneal edema results from aqueous influx into the stroma causing a sudden cloudiness (Fig. 38.3). With successful lowering of IOP, corneal clouding typically begins clearing first in the periphery (Figs 38.4 and 38.5). Photophobia may still persist with normalization of IOP due to the Haab striae. Beyond the age of 3 years, children are more likely to present with progressive myopia, strabismus, or after having failed vision testing.

Differential diagnosis

The differential diagnosis of glaucoma in children is broad (Box 38.1). Many conditions mimic glaucoma and must be excluded before labeling a child with glaucoma. The IOP is normal and the signs will usually not be progressive in patients with other diagnoses.

Classification

Childhood glaucoma can simply be classified as: *primary* where there is only a developmental abnormality of the anterior chamber (AC) angle; and *secondary* where aqueous outflow is reduced by non-acquired (congenital) or acquired ocular diseases or systemic disorders[1] (Box 38.2).

Primary childhood glaucoma

Primary congenital glaucoma

Primary congenital glaucoma (*PCG*) is typically bilateral (70–80%) but asymmetric, and usually manifests in the first year of life. Diagnosis is based on the finding of isolated angle anomaly, i.e. *isolated trabeculodysgenesis*. It is subclassified based on the age of onset of signs, which influences the response to angle surgery.

Demographics

PCG is the commonest glaucoma in infancy but has a reported incidence of only about 1 in 10,000–20,000 live births in Western countries.[2] The highest reported incidence is 1:1250



Fig. 38.1 Infant with right buphthalmos.

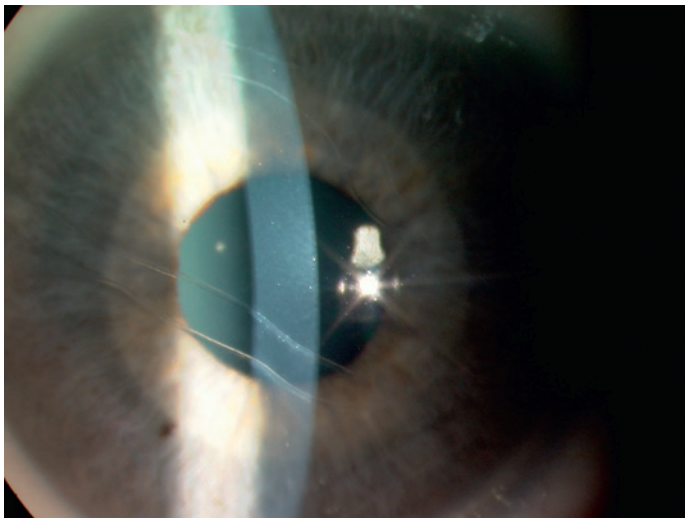


Fig. 38.2 Haab striae, pathognomonic of glaucoma in infancy in the presence of an enlarged cornea.

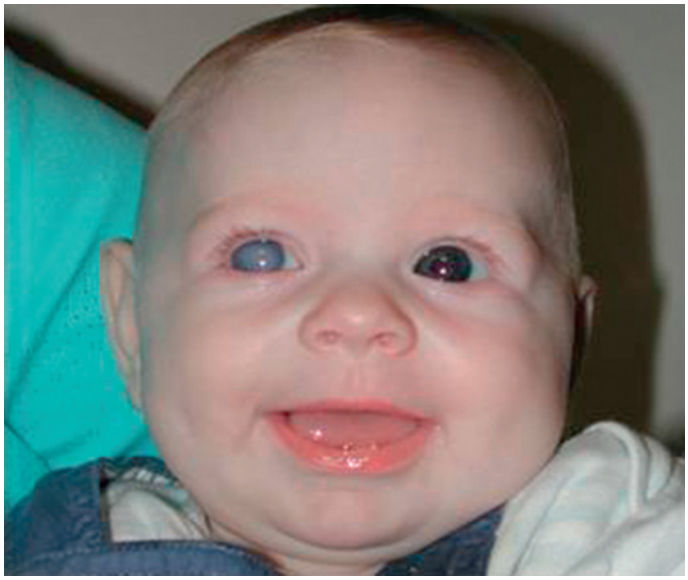


Fig. 38.3 Right stromal edema from ruptured Descemet membrane due to elevated intraocular pressure.

in Slovakian Romani people. Parental consanguinity, especially cousin–cousin marriages, is thought to be responsible for the higher prevalence in certain ethnic groups. PCG occurs more frequently in males than females with a ratio of between 2–2.5 : 1.

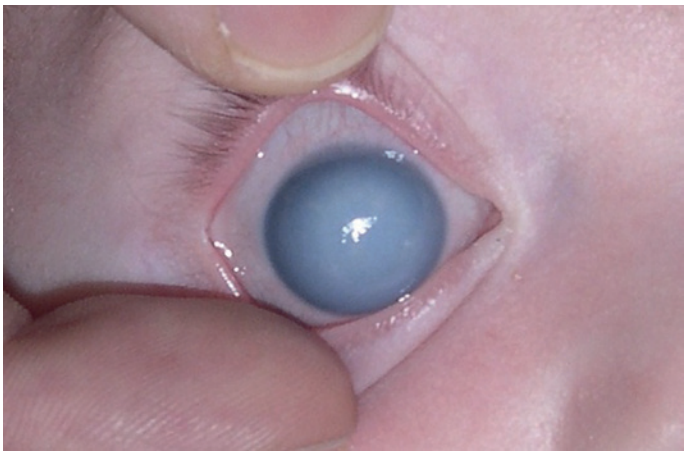


Fig. 38.4 Right corneal stromal edema from uncontrolled intraocular pressure before surgery.

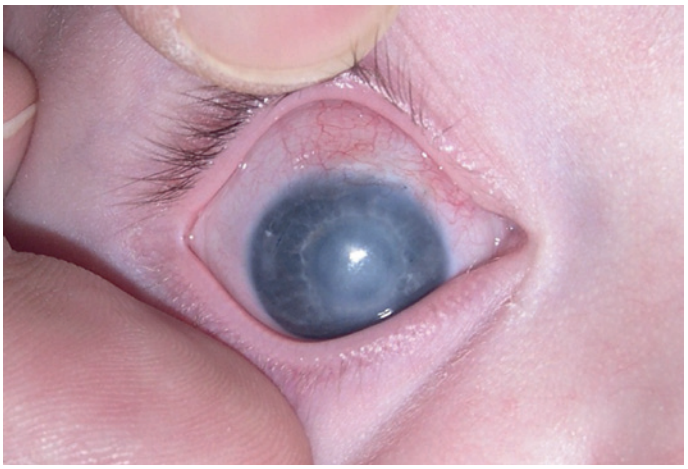


Fig. 38.5 Same eye with clearing of cornea edema following successful lowering of intraocular pressure with trabeculectomy.

Genetics

Most cases of PCG are sporadic. A family history of glaucoma is reported in 10–40% of cases associated with autosomal recessive inheritance and variable penetrance ranging from 40–100%. The GCL3A is the major locus for PCG and has been mapped to the short arm of chromosome 2 (2p21), the GLC3B locus to chromosome 1p36, and GLC3C to chromosome 14q24.3. Other loci are speculated to exist. The majority of cases of PCG relate to mutations of the *CYP1B1* gene associated with the GLC3A locus[3] but its frequency varies according to populations, ranging from 100% in Slovakian Roma to around 20% in the Japanese. It encodes for enzyme cytochrome P4501B1 that is thought to participate in the development and function of the trabecular meshwork (TM). Oxidative stress early in development has been postulated to cause trabecular dysgenesis and result in PCG.[4] *CYP1B1* mutations are associated with variable expressivity. Neonatal presentations of PCG are more likely to have *CYP1B1* mutations, but the same mutations can be associated with less severe PCG or no glaucoma in childhood at all. Attempts at genotype–phenotype correlations have been inconclusive, as have attempts at establishing a relationship between genotype and surgical outcomes.

Box 38.1

Differential diagnosis of childhood glaucoma

Cornea enlargement

(No Descemet membrane splits or corneal edema, symmetrical)

1. X-linked megalocornea (non-progressive, optic disc normal, very deep anterior chamber with shortened vitreous length, follow-up necessary for refractive amblyopia and exclusion of glaucoma)
2. Congenital high myopia (physiological cupping with tilted disc, peripapillary scleral crescent)
3. Connective tissue disorders, e.g. osteogenesis imperfecta, Marfan syndrome
4. *LTBP2* mutations (primary congenital megalocornea, spherophakia, ectopia lentis, and secondary lens-related pupil block glaucoma)

Corneal splits

(No corneal enlargement, normal optic nerve)

1. Trauma (obstetric, non-accidental, history)
2. Hydrops (history)

Corneal edema or opacity

(Usually no corneal enlargement unless associated with glaucoma which is rare)

1. Trauma (obstetric, non-accidental)
2. Congenital corneal dystrophies, e.g. congenital hereditary endothelial dystrophy
3. Metabolic disorders, e.g. mucopolysaccharidoses, mucolipidoses, cystinosis
4. Infection, e.g. congenital rubella, herpes simplex keratitis
5. Sclerocornea

Watering and "red eye"

(No Descemet membrane splits, corneal or ocular enlargement, normal optic nerve and intraocular pressure [IOP])

1. Conjunctivitis (often discharge, red eye)
2. Nasolacrimal duct obstruction (purulent discharge, no photophobia, no "runny nose")
3. Corneal epithelial defect/keratitis (history and examination very important)
4. Ocular inflammation

Congenital optic nerve cupping

(No corneal enlargement or edema, normal IOP)

1. Physiological cupping in large optic nerves
2. Congenital optic nerve pits, colobomata
3. Papillorenal syndrome
4. Optic nerve hypoplasia with periventricular leukomalacia

The risk of PCG in siblings and offspring of Caucasian patients (low parental consanguinity) is low (<5%), but it is prudent to examine the siblings and offspring of patients, especially in the first 6 months of life. However, the risk is higher if there is a history of consanguinity, making screening of siblings essential. If both disease-causing alleles in an affected family member have been identified, it is possible to perform carrier testing for at-risk relatives and prenatal diagnosis.

Pathogenesis

The immature angle appearance is thought to result from the developmental arrest of tissues derived from cranial neural crest cells in the third trimester of gestation. The severity of the abnormality varies according to the stage at which development was arrested. Obstruction to outflow was historically thought to be due to the presence of an impermeable membrane (*Barkan membrane*) but this has never been verified histopathologically. It is now thought that thick, compacted trabecular sheets obstruct outflow and also prevent the normal posterior migration of the uveal tract (iris and ciliary body).[5]

Gonioscopic findings

The characteristic gonioscopic appearance includes a flat iris insertion and the absence of an angle recess. Some of the changes seen are due to the physical stretching of structures from elevated IOP. These include: a thin and hypopigmented iris stroma, peripheral scalloping of the posterior pigmented iris layer, and easily visible, hyperemic iris vessels with circumferential vessels running tortuously in the peripheral iris or on the ciliary body (Fig. 38.6). In unilateral disease, the fellow eye usually shows typical gonioscopic findings with a large corneal diameter and axial length (AL), but the disc is normal and may represent drainage angles that have continued to mature after *spontaneous arrest* of the disease. Hence, the fellow eye of apparently unilateral cases must be followed as closely as the affected eye, as the glaucoma may relapse at any stage.



Fig. 38.6 Classic immature primary congenital glaucoma angle appearance with scalloped posterior iris pigment epithelium.

Treatment

Medical therapy is almost always ineffective for long-term IOP control. Angle surgery, goniotomy and trabeculotomy is typically the procedure of choice but requires an experienced surgeon and often more than one operation to achieve IOP control. There is a similarly high rate of success after multiple attempts in favorable cases, such as those with onset of signs between 3–12 months of age. The recent introduction of circumferential

Box 38.2

Classification of childhood glaucoma

Primary childhood glaucoma

Primary congenital glaucoma (isolated trabeculodysgenesis)
- Neonatal or newborn onset (0–1 month)
- Infantile onset (>1 month to 2 years)
- Late onset or late recognized (>2 years)
- Spontaneously arrested (non-progressive buphthalmos, Haab striae, normal intraocular pressure [IOP] and optic nerves)

Juvenile open angle glaucoma

Secondary childhood glaucoma

Glaucoma associated with non-acquired ocular anomalies

Conditions with predominantly ocular anomalies *present at birth* that may or may not be associated with systemic signs

Axenfeld–Rieger anomaly ("syndrome" if systemic associations)

Peters anomaly ("syndrome" if systemic associations)

Congenital ectropion uveae

Congenital iris hypoplasia

Aniridia

Persistent fetal vasculature (PFV) (if glaucoma present before cataract surgery)

Oculodermal melanocytosis (nevus of Ota)

Microphthalmos/microcornea

Ectopia lentis

Simple ectopia lentis (no systemic associations)

Ectopia lentis et pupillae

Glaucoma associated with non-acquired systemic disease or syndrome

Conditions predominantly with known syndromes, systemic anomalies, or systemic disease *present at birth* that may be associated with ocular signs:

Phacomatoses
- Sturge–Weber syndrome
- Neurofibromatosis (NF-1)
- Klippel–Trenaunay–Weber syndrome

Chromosomal disorders such as trisomy 21 (Down syndrome)

Connective tissue disorders
- Marfan syndrome
- Weill–Marchesani syndrome
- Stickler syndrome

Metabolic disorders
- Homocystinuria
- Lowe syndrome
- Mucopolysaccharidoses

Rubinstein–Taybi

Congenital rubella

Glaucoma associated with acquired condition

Conditions that are not inherited or present at birth but that *develop after birth*:

Uveitis

Trauma (hyphema, angle recession, ectopia lentis)

Steroid induced

Tumors (benign/malignant, ocular/orbital)

Retinopathy of prematurity (ROP)

Post-surgery other than cataract surgery

Glaucoma following cataract surgery

Subdivided into three categories based upon cataract type and there being *no glaucoma prior to cataract surgery*:

Congenital idiopathic cataract

Congenital cataract associated with ocular anomalies/systemic disease or syndrome

Acquired cataract

Adapted from Beck A, Chang TCP, Freedman S. Definition, classification and differential diagnosis. In: Weinreb RN, Grajewski A, Papadopoulos M, et al., editors. Childhood Glaucoma. WGA Consensus Series – 9. Amsterdam: Kugler Publications, 2013: 3–10.

(360°) trabeculotomy with an illuminated microcatheter, for improved safety, has been a significant advance as it potentially incises the whole angle in one operation and minimizes anesthetic exposure.[6] An *ab interno* trabeculotomy approach has also been recently described. The options in children that fail angle surgery are either trabeculectomy with anti-scarring agents or glaucoma drainage device (GDD) surgery.

Juvenile open angle glaucoma (JOAG)

Juvenile open angle glaucoma refers to a distinct group of patients who have no ocular anomalies or systemic features and usually present with glaucoma late in childhood up to the age of 35. Often there is a strong family history of glaucoma with autosomal dominant inheritance. Up to 20% of patients have mutations of the *myocilin/TIGR* (*trabecular meshwork inducible glucocorticoid response*) gene at the GLC1A locus on chromosome 1q23. These patients typically have high pressures (40–50 mmHg), a normal angle appearance and respond well to prostaglandin analogs. If medical treatment fails, a trabeculectomy with anti-scarring agents can be considered.

Secondary childhood glaucoma

With conditions that predispose to secondary glaucoma, it is important to remember the potential lifelong risk of glaucoma. Those at risk need regular IOP review to prevent devastating late presentations of glaucoma that are usually associated with a poor long-term visual prognosis. Consistently elevated IOP should be treated medically. Patients with conditions known to be associated with systemic findings should be referred to a pediatrician for assessment. Family screening and genetic counseling is indicated for inherited conditions. Disorders commonly associated with glaucoma are reviewed below.

Glaucoma associated with non-acquired ocular anomalies

Axenfeld–Rieger anomaly covers a spectrum of disease involving neural crest mesenchyme with overlapping clinical features that was traditionally divided into distinct entities: *Axenfeld anomaly*, defined by posterior embryotoxon (anteriorly displaced, prominent Schwalbe line) with attached iris strands; and Rieger anomaly, these changes in addition to iris changes such as

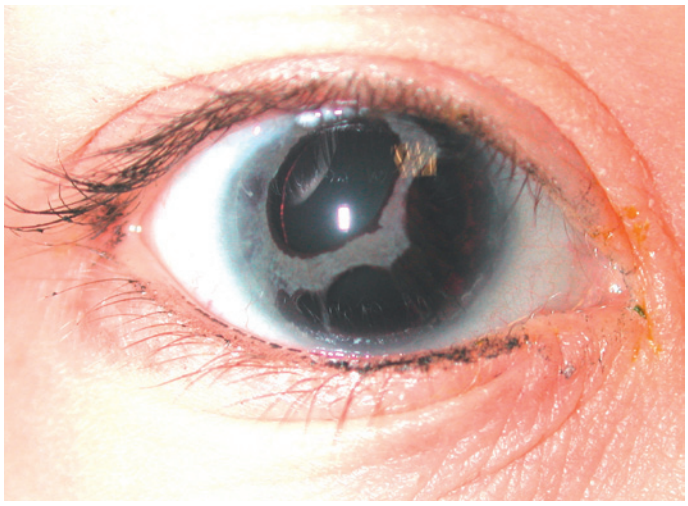


Fig. 38.7 Axenfeld–Rieger anomaly with corectopia and posterior embryotoxon.



Fig. 38.8 Axenfeld–Rieger syndrome with small conical widely spaced teeth.

corectopia or iris stromal thinning (Fig. 38.7). In association with systemic anomalies such as hypertelorism, periumbilical skin tags, dental and cardiac abnormalities, it is referred to as *Axenfeld–Rieger syndrome* (Fig. 38.8). It is usually bilateral, asymmetrical, and autosomal dominantly inherited. Examination of family members, including gonioscopy, is essential to determine both whether the patient is a sporadic or familial case, and to identify undiagnosed cases. Two major genes have been identified, *PITX2* gene at chromosome 4q25 and *FOXC1* at 6p25. Systemic findings are more likely to be associated with *PITX2* defects. The risk of glaucoma is greatest in decreasing order with: *FOXC1* duplication, *PITX2* mutations, and *FOXC1* mutations.[7]

Peters anomaly is characterized by a congenital, central corneal opacity with underlying defects in stroma, Descemet membrane, and endothelium. The opacity can be variable in size and density and clears with time. It may be an isolated finding or be associated with iris and lens involvement. When associated with systemic features it is referred to as *Peters plus syndrome* and carries a higher risk of glaucoma. It is usually bilateral (80%) and sporadic. Peters anomaly may result from abnormalities of the *PITX2*, *FOXC1*, *CYP1B1* and *PAX6* genes.

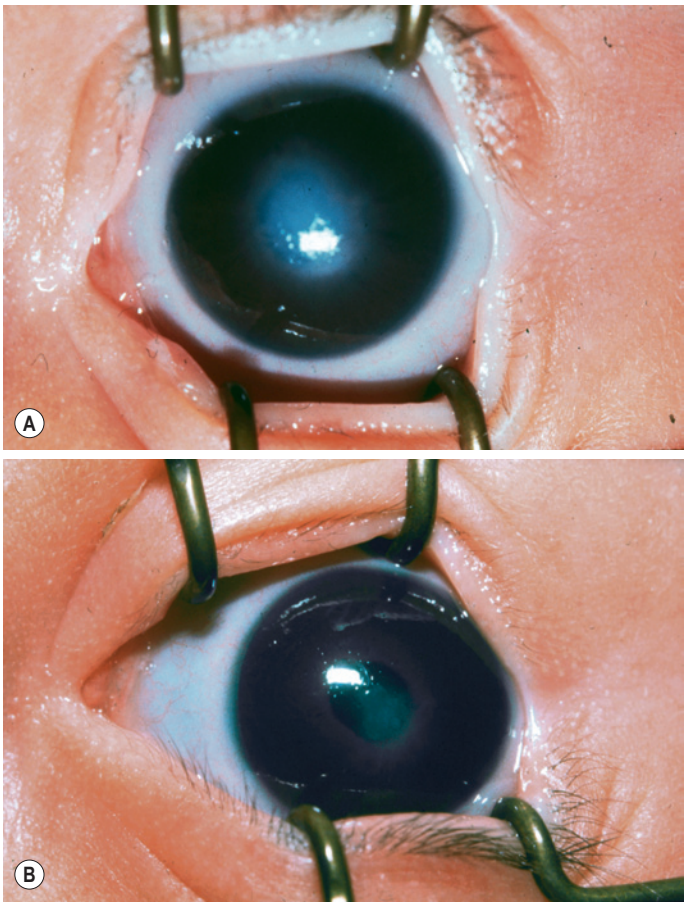


Fig. 38.9 (A) Uncontrolled intraocular pressure (IOP) and dense central corneal opacification before mitomycin C trabeculectomy. (B) Same eye with controlled IOP in low teens and improved corneal clarity after surgery.

The risk of glaucoma with the above conditions is 50%, so lifelong surveillance is indicated. Glaucoma usually occurs in childhood or young adulthood, very rarely in infancy, and is thought to be due to an underlying trabeculodysgenesis from arrested maturation of angle structures. The IOP is often labile. Medical therapy is usually tried first. Angle surgery is potentially more complicated and less successful than in PCG. Often trabeculectomy with anti-scarring agents is necessary to control the IOP. The more disorganized the anterior segment, the greater the risk of failure and the more potent the anti-scarring agent required, i.e. mitomycin C (MMC). MMC is more likely to achieve a low IOP and so significantly reduce corneal opacification in cases of Peters anomaly (Fig. 38.9A,B). Primary GDD surgery may be indicated in the more severe cases.

For dense corneal opacities and when the lens is clear, pupil dilation or a broad optical iridectomy can be performed (via a scleral approach to prevent further corneal scarring) at the site of maximum corneal clarity. Penetrating keratoplasty is associated with disappointing results,[8] especially in infants, but can be considered in at least one eye in the setting of bilateral dense opacities if the child has a dedicated caregiver.

Aniridia is a bilateral condition characterized by a variable congenital absence of iris. It results from abnormal neuroectodermal development secondary to *PAX6* gene mutations at chromosome 11p13. Inheritance is usually autosomal dominant with high penetrance and variable expressivity. Sporadic aniridia is associated in 30% of cases with

nephroblastoma (Wilms tumor), genitourinary abnormalities, and mental retardation (WAGR) related to large deletions of 11p13 (see also Chapters 33 and 11).[9]

Glaucoma occurs in half to two-thirds of cases usually presenting in pre-adolescence or early adulthood. It may be due to progressive angle closure by the iris stump or more commonly can be associated with an open angle. Medical therapy should always be tried first, with preservative-free drops if possible. Goniotomy in cases of documented progression of angle closure both as therapy (with poor results) and prophylaxis has been described, but the latter is not widely practiced due to the potential risk of lens trauma. In the presence of a clear lens, we perform a MMC trabeculectomy. If significant cataract is present or trabeculectomy fails then GDD surgery is indicated.[10] Consider placement of the tube obliquely over the zonules, away from the lens to mimimize tube-related trauma. Hypotony should be avoided at all costs due to the danger of lens–corneal touch, which will cause both cataract and corneal decompensation. Symptomatic relief of photophobia can be achieved with lubricants and tinted spectacles.

Glaucoma associated with non-acquired systemic diseases or syndromes

The commonest phakomatosis associated with glaucoma is *Sturge–Weber syndrome* (encephalotrigeminal angiomatosis), a sporadic, congenital condition characterized by a facial cutaneous vascular malformation (port wine stain) and ocular vascular lesions (episcleral and choroidal hemangioma). It is associated with a somatic mutation in the *GNAQ* gene on chromosome 9q21 (see Chapter 68).

Glaucoma occurs in around 30–50% of cases at any time from birth to adulthood and is thought to arise from elevated episcleral venous pressure (EVP). There may be an element of goniodysgenesis with infantile presentations. Port wine stains involving the ophthalmic division of V1 (especially upper lid and bilateral involvement) and the presence of episcleral vascular malformation or choroidal hemangioma (40%) increase the risk of glaucoma.

When medical treatment fails, surgery is indicated. The surgical plan depends on the age of onset and the mechanism of glaucoma. Congenital or infantile presentations may respond to angle surgery if there is evidence of goniodysgenesis. After failed angle surgery or in older children with increased EVP, either trabeculectomy with anti-scarring agents or a GDD is indicated. In the presence of a choroidal hemangioma, the potential for serious complications is high as it may give rise to expulsive choroidal hemorrhage if rapid decompression of the globe occurs or to choroidal effusions if there is prolonged hypotony. Preoperative radiotherapy should be considered if the hemangioma is very thick (>5 mm). Trabeculectomy or GDD surgery can be considered. All surgery in these patients must be coupled with measures to minimize hypotony. Trabeculectomy should have tight scleral flap closure and GDD a tight tube tunnel into the AC along with an extraluminal occlusive suture (6/0 vicryl) and an intraluminal stent (3/0 supramid) in non-flow-restricted implants. Smaller surface area implants, e.g. Baerveldt 250 mm^2, reduce the risk of hypotony and should be considered especially in infants. An AC maintainer should be used in all cases to avoid intraoperative hypotony. When surgery is planned it is important to take into consideration anticoagulation the child may be taking for stroke-like episodes, which have been reported in these patients.

Other phakomatoses can be associated with glaucoma, although with a lower incidence than Sturge–Weber syndrome: *Klippel–Trenaunay–Weber syndrome*, characterized by a triad of cutaneous vascular malformations and varicosities involving one limb and hypertrophy of bone and soft tissue; and Neurofibromatosis 1, an autosomal dominant condition, which may first present with iris abnormalities, e.g. ectropion uveae and glaucoma, before the systemic disease is apparent.

For rare conditions associated with childhood glaucoma, determining the mechanism of the glaucoma by a thorough history and examination, along with an assessment of risk factors for surgical failure, results in the best treatment plan. For example, *Weill–Marchesani syndrome* and *homocystinuria* may give rise to childhood glaucoma that is usually associated with lens displacement, secondary pupil block, and angle closure. In this context, prophylactic iridectomy and chronic miosis may be required to prevent pupil block glaucoma or dislocation of the lens into the AC.

Glaucoma associated with acquired conditions

Glaucoma may arise following inflammation from any cause but is most commonly seen in juvenile idiopathic arthritis (30%), usually 2–3 years after presentation. *Uveitic glaucoma* is multifactorial due to chronic cellular trabecular obstruction, trabeculitis, peripheral anterior synechiae (PAS), secondary pupil block, lensectomy, and following chronic topical steroid usage. Children with uveitis develop more severe glaucoma than adults. The IOP can potentially rise dramatically and be associated with rapid progression of optic disc cupping with severe visual loss. The principles of management are firstly to aggressively treat the uveitis with topical ± systemic steroids and steroid-sparing therapy (non-biological, e.g. methotrexate, and biological, e.g. infliximab) in association with a pediatrician, and secondly to control the IOP.

This type of glaucoma is characteristically challenging to manage because of its multifactorial etiology; it is often refractory to treatment, especially medical treatment, which is first line. If surgery is planned, perioperative systemic immunosuppression, particularly steroids, is essential to optimize outcome. Angle surgery often requires medical treatment to control IOP. Trabeculectomy with MMC can be considered but recurrent ocular inflammation may compromise long-term success. The authors' preference is for primary GDD surgery, especially if lensectomy is contemplated in the future or if aphakia is present. With any surgery, the risk of postoperative hypotony is high, even in the absence of overdrainage due to compromised aqueous production. We suggest a smaller surface area GDD, e.g. Baerveldt implant 250 mm^2, with measures to restrict flow as previously described, or an Ahmed implant (184 mm^2). Cyclodiode treatment is associated with poor success rates as primary treatment.[11] We avoid cyclodiode treatment as it aims to reduce the function of an already compromised ciliary body from inflammation, potentially leading to chronic hypotony.

Rarely, childhood tumors such as *leukemia* or *retinoblastoma* may cause glaucoma from outflow obstruction by tumor cells or secondary hemorrhage. The diagnosis of these rare conditions is important, as surgery allowing malignant cells to escape into extraocular tissues worsens the prognosis for life. The treatment of glaucoma in these circumstances is generally conservative. The primary disorder is treated, along with topical medical treatment and cyclodestruction.

Glaucoma following cataract surgery

Glaucoma following cataract surgery occurs after pediatric cataract removal of either congenital idiopathic cataract, cataract associated with an ocular or systemic syndrome, and acquired cataract.

Glaucoma following congenital cataract surgery is one of the commonest secondary childhood glaucoma and a serious cause of late visual loss after successful surgery. Removal of the cataract is what places the eye at risk of glaucoma, which can occur at any time, in either aphakic or pseudophakic eyes. Both chemical (inflammatory cells, lens remnants, and vitreous-derived factors) and mechanical (lack of ciliary body tension and TM collapse) theories have been proposed, combined with developmental reasons, i.e. arrest of postnatal angle maturation due to surgical insult. The incidence of glaucoma following childhood cataract surgery varies with duration of follow-up and ranges from 5% with simple aspiration[12] to 17% with lensectomy and ocutome vitrectomy with a least 5 year follow-up.[13] The angle is usually open, but PAS may be present. Acute angle closure from secondary pupil block is rare but usually results in long-term glaucoma despite relief of pupil block with iridectomy/vitrectomy. Risk factors for glaucoma such as microcornea, early surgery (especially less than 4 weeks of age), the need for secondary surgery, and nuclear cataract are well documented. Selection bias is an important confounder in studies showing a protective effect from intraocular lens implantation. The role of posterior capsule integrity is debated. Following meticulous cataract surgery, lifelong surveillance for glaucoma is crucial. The diagnosis can be easily missed as patients are often asymptomatic, the signs may be subtle, and examining these patients is often difficult. It is essential to monitor the optic disc appearance for progressive cupping on a regular basis. Excessive loss of hyperopia may also be a useful sign, as may contact lens intolerance.

Glaucoma following congenital cataract surgery is often refractory to treatment. Medical treatment is first line but only controls IOP in 50% cases. Angle surgery often does not provide good long-term control. Trabeculectomy with MMC not only has a poor success rate[14] but often excludes postoperative contact lens use in the presence of a thin, avascular cystic bleb due to the risk of endophthalmitis. Cyclodiode laser provides temporizing treatment with occasional long-term control after multiple treatments.[15] However, it is difficult to titrate and so marked inflammation and phthisis are possible, especially in microphthalmic eyes, in which case less energy should be considered. Furthermore, it may predispose future surgery to failure and possibly chronic hypotony. GDD surgery probably has the highest chance of long-term success and allows contact lens use.[16] However, aphakic eyes have higher rates of complications, especially suprachoroidal hemorrhage if hypotony occurs. Techniques minimizing the risk of catastrophic hypotony with GDD are mandatory (described above).

Management

Assessment

Any suspicion of glaucoma in a child should always be treated seriously and with urgency to minimize visual impairment. This requires examination in either the clinic, office, or under anesthesia depending on the child's age and ability to cooperate. A neonate who is feeding or an infant asleep can be thoroughly examined in the clinic or office. Examination under anesthesia (EUA) is usually necessary until 4–5 years of age. However, children should be encouraged onto the slit-lamp for more accurate assessment of IOP and the optic disc whenever this is possible.

The initial consultation and assessment is an absolutely vital part of management. It is the beginning of what may potentially be a lifetime relationship between the ophthalmologist, patient, and their parents. The aim of the initial assessment is either to make a diagnosis of glaucoma and determine the type (primary or secondary, which is necessary in determining management) or if glaucoma cannot be ruled out, to establish that enough evidence exists to justify further appropriately timed follow-up or an EUA for a more complete examination and possible surgery.

History

In a neonate or infant, inquire about a history of epiphora, photophobia, blepharospasm, and change in ocular appearance. It is important to determine: the age of clinical onset for prognosis, associated systemic problems for anesthetic risk, problems during pregnancy (rubella) or labor (use of forceps), a family history of pediatric glaucoma, and parental consanguinity. In older children, a history of trauma, ocular inflammation or surgery, and corticosteroid use may be relevant.

Examination

It is important to begin the examination by assessing the patient's overall appearance and visual behavior including the presence or absence or nystagmus or strabismus. Following the determination of visual acuity, the ambient illumination can be reduced to allow the neonate or infant to open their eyes, permitting a more complete examination. When indicated, it is important to examine the patient's parents as the presence of subtle signs of Axenfeld–Rieger anomaly in the parents may change the genetic advice given and alter the management of subsequent siblings.

Intraocular pressure measurement

Measuring IOP in children can be challenging because it can be influenced by many factors, e.g. type of anesthetic, instrumentation, corneal thickness and opacities. The reference standard for measuring IOP is with Goldmann applanation tonometry. In cases of Peters anomaly a Tono-Pen allows you to measure the IOP more accurately in the peripheral cornea than over the central corneal opacity, which may give you a falsely high IOP. However, Tono-Pen, similar to pneumotonometry, is known to overestimate the IOP compared to Perkins, in both normal children and those with glaucoma.[17,18]

More recently, the iCare Pro portable rebound tonometer has become available for IOP measurement without the instillation of topical anesthetic drops in both supine and upright positions. It is well tolerated and thought to have a similar reliability to Tono-Pen with a tendency to overestimate in known or suspected glaucoma cases compared to applanation tonometry.[19,20] The discrepancy between the Goldmann tonometer and the iCare increases with the level of IOP and

with higher central corneal thickness.[20] In light of the above, it is advisable to use the same tonometer for serial examinations. It is important to note that regardless of the instrument used, lid squeezing and crying may falsely elevate the IOP.

The reference standard for tonometry in children undergoing EUA is the Perkins hand-held tonometer with a blue filter after instillation of fluorescein. Avoid the use of a lid speculum and pressure on the eye. Preferably, the eyes should be in the primary position and motionless, as pressure readings may be altered by eye movements. The IOP should always be measured several times in both eyes. As IOP measurement is influenced by the type of anesthetic, tonometry under anesthesia generally provides us only with an approximation of the true tension. *It should never be the sole method by which the presence or control of glaucoma is assessed.* If IOP measurement is out of keeping with other clinical findings, it may be inaccurate and tactile estimation of the IOP may be useful.

Anterior segment examination

The cornea must be examined for the presence of posterior embryotoxon, edema, opacities, and Haab striae. Oblique illumination and magnification are necessary as the signs can sometimes be subtle. During an EUA, a portable slit-lamp should be used if possible. When a deep AC in a neonate or young infant is associated with an enlarged cornea, glaucoma should be strongly suspected. It is important to remember that the presence of *corneal enlargement with splits with or without edema indicates raised IOP at some stage in infancy*. Persistent corneal edema may be a sign of poorly controlled glaucoma. Excluding primary corneal pathology is important, and a useful finding is the absence of corneal or ocular enlargement.

Detecting iris or pupil abnormalities or co-existing lens opacities is important as the latter may require treatment and influence the choice of glaucoma surgery.

Corneal diameter measurement

The normal horizontal neonatal diameter is up to 10.5 mm, increasing by about 1 mm in the first year of life. A corneal diameter greater than 11 mm in a newborn and 12 mm in an infant less than 1 year is very suggestive of raised IOP, but with Haab striae it is diagnostic. A measurement of greater than 13 mm in a child of any age and asymmetrical corneal diameters is abnormal. During EUA, the horizontal corneal diameter is measured with calipers from limbus to limbus and checked with a graduated ruler with estimation to the nearest 0.25 mm. Serial corneal diameter measurements are useful in monitoring glaucoma progression until the age of 3 years. An increasing corneal diameter may indicate inadequate control of IOP requiring further treatment.

Central corneal thickness

Central corneal thickness (CCT) influences the accuracy of tonometry. Patients with PCG and JOAG have thinner corneas and in theory a tendency for under reading the IOP. Conversely, an increase in corneal thickness, as is found in patients with aphakia and aniridia, may lead to an over estimation of IOP. However, children with aphakia and markedly thickened corneas, regardless of the theoretical overestimation of the IOP, do develop glaucomatous cupping and visual field defects.[21] This may be due to altered biomechanical properties in children with glaucoma, the importance of which is yet to be determined.[22] *Therefore, the role of pachymetry in childhood glaucoma is uncertain and standard correction factors cannot be used.* Regardless of corneal thickness, the emphasis remains on the optic disc appearance.

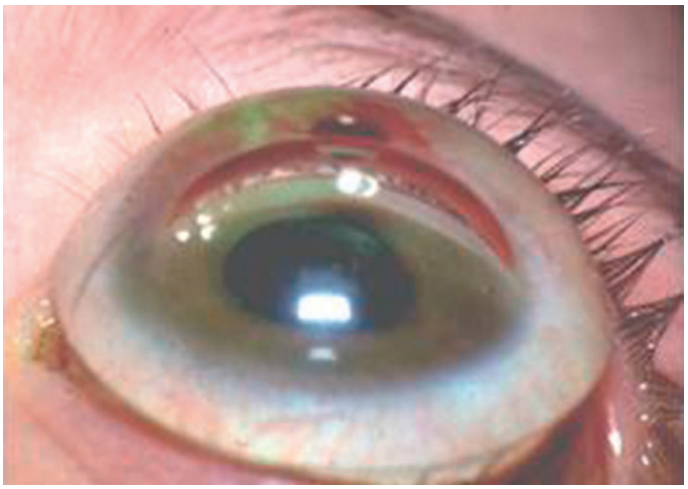


Fig. 38.10 Koeppe lens for direct gonioscopy.

Gonioscopy

Gonioscopy is crucial in making the correct diagnosis, which determines the most appropriate operation and prognosis. It should be performed at least once when possible. In an EUA, direct gonioscopy can be performed with a variety of lenses including a *Koeppe* lens (Fig. 38.10) or a wide-angled goniolens specially modified for angle surgery (Ocular Instruments, Bellevue, WA, USA).

Posterior segment examination

The appearance of the optic disc is by far the most important and sensitive parameter for both diagnosis and progression of glaucoma, as it is influenced neither by anesthesia nor the effect of growth. Richardson noted a cup:disc ratio (CDR) of greater than 0.3 in only 3% of 468 *normal* Caucasian newborn eyes,[23] in contrast to Shaffer who found a CDR of greater than 0.3 in 61% of 85 eyes in infants less than 1 year with *congenital glaucoma*.[24] A CDR *>0.3 in a Caucasian infant less than 1 year or >0.5 in a child and disc asymmetry should greatly increase suspicion of glaucoma.*

The optic disc and the nerve fiber layer should be examined through a dilated pupil and carefully recorded with a drawing and preferably a photograph as a baseline for future comparison. Optic disc photographs can be taken with a Retcam while under EUA. An increase in disc cupping is definite evidence of poorly controlled glaucoma and the need for further treatment, regardless of IOP measurement obtained. Prior to an EUA, the pupil is not dilated as this may alter the angle appearance, spuriously raise IOP, and increase the risk of lens damage if surgery is required. Consider dilating the infant in the office or as an outpatient days before the EUA if angle surgery is contemplated. Examining the optic disc in infants may only be possible after the cornea has cleared. An indirect ophthalmoscope with a small pupil facility can be very useful in obtaining a view of the disc in infants whose pupils dilate poorly.

Disc cupping in children can be reversible if IOP reduction occurs before irreversible nerve atrophy. The younger the child, the greater the potential for disc-cupping reversal (Fig. 38.11A,B). It is thought to represent a "pre-laminar" phenomenon where reversible laminar bowing is associated

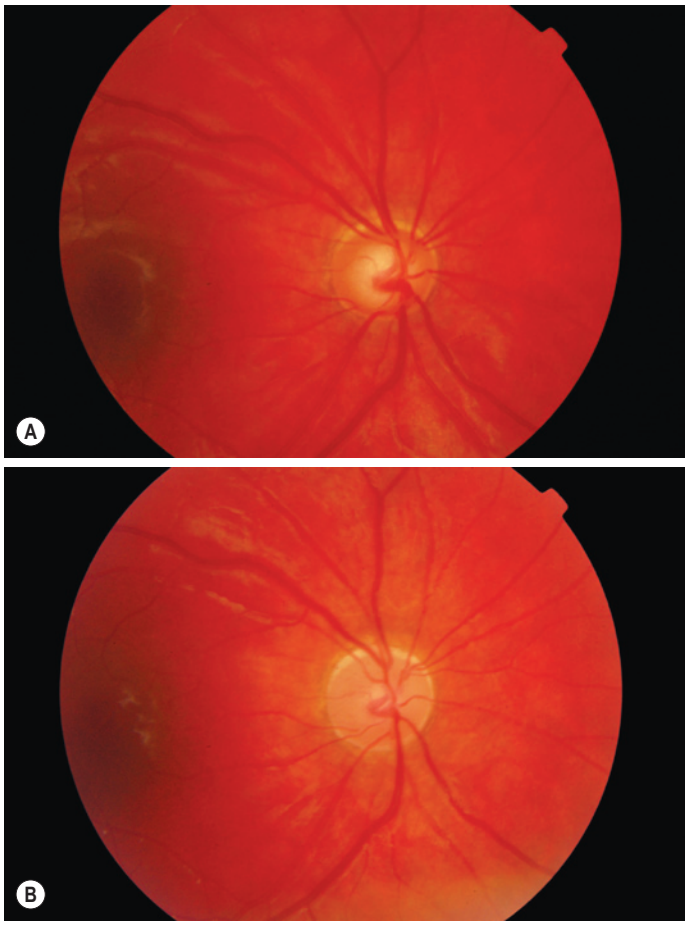


Fig. 38.11 Reversal of optic disc cupping after successful intraocular pressure lowering with surgery. (A) Preoperative disc appearance. (B) Postoperative optic disc appearance.

with compression and stretching of the pre-laminar neural tissue. Once the IOP is normal, the compression is relieved allowing the laminar to move anteriorly, "filling in" the cup. However, despite disc-cupping reversal, retinal nerve fiber layer thinning may persist postoperatively.[25]

The remainder of the fundus should be examined for any associated abnormalities such as foveal hypoplasia associated with aniridia, choroidal hemangiomas in Sturge–Weber syndrome, and pigmentary retinopathy associated with rubella.

Refraction

A significant loss of hypermetropia or the presence of myopia in a neonate or infant is often evidence of glaucoma. Progressive myopia or a myopic shift in aphakic patients suggests inadequate IOP control, especially in the context of progressive increase in axial length.

Examination under anesthesia (EUA)

The decision to examine a child under anesthesia should not be taken lightly and only performed when the information to be acquired will assist in the diagnosis or provide follow-up data important to clinical decision making. To avoid unnecessary anesthesia and delay, preferably the ophthalmologist undertaking the initial EUA should be capable of performing the definitive surgery under the same anesthetic.

As a general rule, all anesthetics lower the IOP with the exceptions of ketamine and chloral hydrate. Inhalation anesthetics, such as sevoflurane, may substantially lower the IOP by 10–30 mmHg; the amount is idiosyncratic and unpredictable. Furthermore, sevoflurane causes progressive lowering of IOP with time from induction. This makes an appropriate anesthetic vital in the assessment of these patients, especially in subtle cases, where it can have a profound impact on the timing of the diagnosis and the visual prognosis. Furthermore, it follows that the finding of a normal IOP with the use of agents known to reduce IOP does not exclude glaucoma. Whichever agent is used, it is important to have a consistent approach using the same agent for serial examinations and to measure the IOP first.

It is the authors' preference to use ketamine hydrochloride, which is believed to result in IOP measurements that are commensurate with those taken in awake infants.[26] It is given intravenously following the use of local anesthetic patches. Children are premedicated with atropine, which reduces bronchial secretions, and oral midazolam, which acts as a sedative and an amnesic. It can cause a transient rise in IOP for a few minutes and so the IOP should be measured several times. Its duration is short, usually lasting 10–15 minutes.

Establishing a routine in recording findings during an EUA is useful to avoid errors. It is important to record IOP (along with anesthetic agent, tonometer), corneal diameters, axial lengths and cup:disc ratio, along with other clinical findings such as corneal clarity at every EUA to assess glaucoma control. While the patient is under anesthesia, a general examination and venesection for laboratory investigation (e.g. screening for infective agents and chromosome studies) can also be performed.

Investigations

Ultrasound

Axial length (AL) measurement is useful for baseline assessment; if it is outside normal limits it is strongly suggestive of glaucoma. Serial AL can be valuable in children for detecting progression when the eye is still distensible. In glaucoma, AL measurements are usually asymmetrical, in contrast to X-linked megalocornea and normal eyes. There usually is a decrease in AL following successful lowering of IOP. In an eye with opaque media, high-resolution B-scan or ultrasound biomicroscopy (UBM) may be a useful to detect the presence of severe cupping or exclude posterior segment pathology such as choroidal hemangioma.

Visual fields

Visual fields are usually possible around the age of 7–8 years, but there is a learning curve. Visual field defects must be reproducible, so defects must be confirmed by repeating the test. Furthermore, the defects must correspond to the optic disc appearance. If this is not the case, and associated with unexplained reduction in visual acuity and color vision, then other causes of visual loss should be considered, especially in children with systemic disease such as Neurofibromatosis 1.

Quantitative optic disc imaging

As in adult studies, differences have been reported between normal and glaucomatous eyes in children using optical coherence tomography (OCT). A prospective, observational study in children with glaucoma revealed retinal nerve fiber layer and macular thickness measurements declined with increasing severity of glaucomatous disc damage as seen in

stereophotographs.[27] All automated optic disc imaging is limited by the lack of a normative pediatric database and the portability of the devices.

Interpretation of findings

The age of glaucoma onset determines the relevant questions to ask during history taking, the clinical findings to elicit, and the investigations to perform. In other words, IOP measurement and optic disc appearance are fundamental features of the examination throughout a child's life with glaucoma, but in an infant whose eye is still vulnerable to the effects of elevated IOP, the physical consequences of elevated IOP (enlarged corneal diameter, increasing axial length, and progressive myopia) need also to be taken into consideration and regularly assessed. So in infants, the diagnosis or progression of glaucoma must be based on the overall clinical findings and investigation results. The most important clinical sign is the optic disc appearance. If the diagnosis is unclear but there is a high risk of glaucoma, then further follow-up (including EUAs) is necessary to confirm pathology before committing the patient to treatment – especially surgery.

As the child grows older, the cornea and sclera become less elastic, so findings such as corneal diameter and AL changes become less useful measurements. With increased cooperation, the IOP can be assessed more accurately on the slit-lamp, as can the optic disc and the nerve fiber layer with greater magnification. Hence, the child should be encouraged onto the slit-lamp for evaluation as soon as possible. Eventually, visual fields become feasible to assess functional vision. This is especially useful in advanced cases.

If glaucoma is confirmed, it is important to explain to the parents the chronic nature of the condition, the possible need for repeat surgery, and definite lifelong follow-up, as glaucoma can relapse at any stage and may develop in the fellow eye of "unilateral" glaucoma.

Treatment

Managing glaucoma in childhood is one of the greatest challenges in the field of glaucoma. Medications play a vital role in management, as they are first-line therapy for most glaucomas; however, sustained efficacy is less likely in neonates and infants, especially those with PCG. Medications are frequently needed to lower the IOP before surgery and are often required as adjunctive therapy after partially successful surgery. Most children with glaucoma will require surgery in their lifetime. However, surgery is challenging, largely because of its greater potential for failure and complications as compared to adults. No treatment is curative, so lifelong follow-up is necessary to ensure IOP control and to detect complications, which can occur at any time, even after years of stability. Furthermore, parents and, later, patients should be warned that minor blunt trauma in buphthalmic eyes may result in severe visual loss. Protective eyewear should be recommended, especially in monocular patients.

Medical therapy

Although drugs used in childhood glaucoma are similar to those in adults, great care must be exercised when prescribing in children as they are at a higher risk of systemic, potentially fatal side effects from topical administration. Warn parents of potential systemic side effects and instruct them on punctal occlusion.[28]

β Blockers

The use of β blockers in premature or newborn infants, children with asthma or any cardiac problems, including arrhythmias, should be avoided. It is important to inquire about asthma symptoms, which may manifest with nocturnal cough in children rather than wheezing. *Timolol 0.1%, timolol gellan 0.25%* are the β blockers of choice as first-line treatment, due to their superior risk profile and efficacy.

Carbonic anhydrase inhibitors

Although *oral acetazolamide* is more potent in reducing IOP than dorzolamide, its use in children is limited by serious systemic side effects such as failure to thrive, disturbed hyperactive behavior, and bed-wetting. Therefore, it should be considered only on a very short-term basis prior to surgery. *Brinzolamide* is less irritating than *dorzolamide* and both are useful as second-line drugs or when β blockers are contraindicated.

Prostaglandin analogues

Latanoprost is the first agent to be approved for use in children.[29] It is thought to be at least as effective as timolol but may be less efficacious in children in combination with other medications. Patients with JOAG may respond particularly well and it should be considered first line in these patients.

Sympathomimetics

Brimonidine crosses the blood–brain barrier and can cause drowsiness to the point of coma and apnea in infants. The authors avoid it in children less than the age of 6 years or less than 20 kg bodyweight. The use of *apraclonidine* in children is theoretically safer as it is less lipophilic.

Parasympathomimetics

Parasympathomimetic agents are useful in the postoperative management of PCG after angle surgery as it may enhance aqueous outflow and prevent anterior synechiae formation. They may be highly effective in some cases of glaucoma following congenital cataract surgery.

Surgical therapy

The principal treatment modality of childhood glaucoma is surgical. The available surgical procedures have varying indications with both advantages and disadvantages and potentially good success rates, especially when performed at referral centers where there is sufficient volume to ensure both skillful surgery and safe anesthesia. Lack of familiarity with buphthalmic eyes can lead to severe complications. The procedure of choice is largely determined by the type of glaucoma and may be further influenced by age of onset, corneal clarity, degree of optic nerve damage, associated ocular disease, history of previous surgery, and the surgeon's experience.

As further surgery is often inevitable, making the right choice initially is paramount as the first operation has the greatest chance of success. In eyes that have undergone multiple procedures, it is important to make the next operation the definitive one, otherwise these eyes are at risk of the downward spiral from repetitive unsuccessful procedures. Once the procedure has been chosen, surgery must be meticulous to minimize complications.

Angle surgery

Goniotomy Although goniotomy is simple in concept and brief in execution, it is a difficult procedure to perform, requiring

considerable experience and rare surgical skills[30] (Box 38.3 and Table 38.1). Adequate *visualization of the angle is the key to successfully performing this procedure* (Fig. 38.12). Epithelial debridement with absolute alcohol provides an adequate view of the angle to allow goniotomy in more than 90% of Caucasian patients.[31]

Goniotomy is an effective operation, with success following multiple goniotomies usually ranging from 70% to 90% with medium term follow-up.[31] Risk factors for failure in PCG include: age of manifestation (onset at or within 3 months of birth), enlarged ocular dimensions (corneal diameter ≥14 mm and AL >24 mm).

Box 38.3

Advantages and disadvantages of diode laser cyclodestruction

Advantages

- Short surgical time and rapid rehabilitation
- Good short-term response rate
- Very useful in high-risk surgery, particularly in only eyes
- Technically less demanding than other procedures

Disadvantages

- Often needs to be repeated in more than 50% of cases due to recovery of ciliary body
- Most patients remain on medical therapy
- Intraocular pressure in the low teens usually not achieved in comparison to filtering surgery
- Potential for significant inflammation and may accelerate cataract formation
- Danger of long-term phthisis with recurrent treatment
- May affect future drainage surgery: hypotony due to hyposecretion and failure due to effect on blood aqueous barrier releasing stimulatory cytokines into aqueous and drainage site

Trabeculotomy Since corneal opacification does not prevent the performance of trabeculotomy, it has greater application than goniotomy but is more invasive, causing conjunctival scarring, an important point considering the potential need for further surgery in the child's lifetime. In light of this, a temporal incision is preferable. *Accurate localization of Schlemm canal (SC) is the key to successful trabeculotomy.*[30] However, abnormally stretched limbal anatomy in buphthalmic eyes makes it difficult to identify and it may not be found at all in 4–20% of patients, especially if the anterior chamber is inadvertently entered before the canal is found. Conventional trabeculotomy with a trabeculotome incises up to one-third of the angle, whereas the use of a blunted 6/0 polypropylene suture[32] or an illuminated microcatheter[33] threaded into SC can potentially incise 360° (circumferential trabeculotomy) in one operation (see Table 38.1). Success is not always possible with

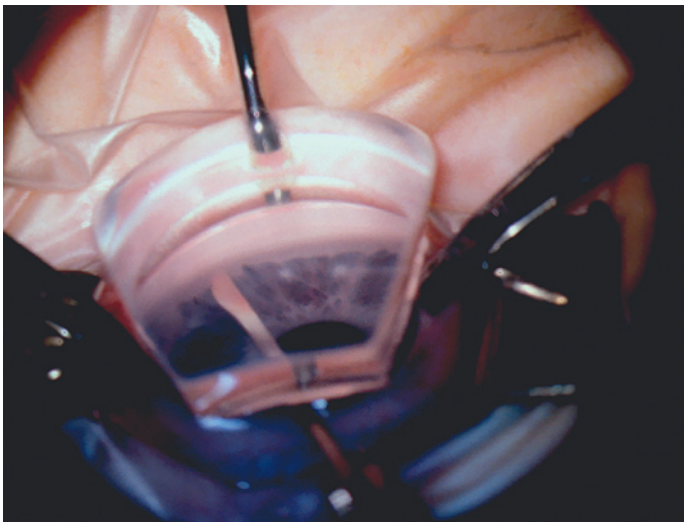


Fig. 38.12 Goniotomy performed in primary congenital glaucoma.

Table 38.1 Comparison of angle surgery techniques

	Goniotomy	Trabeculotomy (probe)	Trabeculotomy (360°)		Trabeculotomy–trabeculectomy
			Suture	Illuminated microcatheter	
Conjunctival incision	–	+	+	+	+
Possible with opaque cornea (angle structures not clearly visible)	–	+	+	+	+
Angle visualization	+	–	– (only with gonio lens)	+	–
Specialized instruments/skills	++	+	+	++	++
Extent of surgical trauma	+	++	++	++	+++
Potential for complications	+	++	++	+	++
Duration of surgery	+	++	++/+++	++/+++	++
Can be repeated	++	++	–	–	+
Bleb related complications	–	–/+	–/+	–/+	+

Adapted from Papadopoulos M, Edmunds B, Fenerty C, et al. Childhood glaucoma in the 21st century. Eye (Lond) 2014; 28: 931–43.

a single incision and severe hypotony along with misdirected (subretinal) sutures have been reported.

Success rates of conventional trabeculotomy and prognostic factors in PCG are similar to those of goniotomy.[34] However, results of circumferential trabeculotomy suggest greater success than goniotomy and combined trabeculotomy–trabeculectomy (CTT) and respectively.[35,36]

Angle surgery is the procedure of choice for PCG, the exact choice being influenced by the corneal clarity, the surgeon's experience and preference. Success rates for secondary childhood glaucomas are generally not as good as for PCG. Russell-Eggitt[31] reported a 20% relapse rate over a 30-year period with no peak age of relapse.

Trabeculotomy combined with trabeculectomy Trabeculotomy has the added advantage of being combined with trabeculectomy to provide, in theory, two major outflow pathways and so improve results. In practice, the clinical benefit is unclear. Some authors have reported greater success than with either procedure performed alone, especially in populations at high risk of failure, such as in East Asia and the Middle East.[37] Others have found no difference in success between the three procedures.[38] Technically, it is a more complex procedure with potentially significant complications, especially with the use of anti-scarring agents.

Trabeculectomy

One of the main indications for trabeculectomy is failed angle surgery. It may be the primary procedure of choice when: the surgeon has no or limited experience with angle surgery; the patient is unlikely to respond sufficiently to angle surgery (very early or late presentations); very low target pressures are required (improved cornea clarity, advanced disc cupping); and for most secondary glaucomas.

Technically it is a more demanding procedure and more likely to fail in children due to a vigorous wound healing response. The propensity to failure necessitates the use of MMC, which is associated with higher complication rates. However, with recent simple modifications to the surgical technique (Moorfields Safer Surgery System)[39] and to the intraoperative application of MMC, trabeculectomy can be associated with more favorable bleb morphology, reduced complications, and satisfactory outcomes in appropriate cases, even infants[40,41] (Fig. 38.13). For a summary of technique, refer to Table 38.2. If significant conjunctival inflammation is present at the drainage site, subconjunctival 5-fluorouracil (5-FU) (0.1–2 ml of 5-FU 50 mg/ml) and steroids such as betamethasone can be injected adjacent to the bleb while under EUA. The advantages and disadvantages of trabeculectomy are summarized in Table 38.3.

With MMC, trabeculectomy cumulative success rates of 59–90% at 2 years reducing to 51% at 5 years have been reported.[42–44] Reported risk factors for failure are: age less than 1 year and aphakia.[14,43,45] The potential for complications after trabeculectomy, especially with MMC, cannot be overstated in children. Early complications relate to hypotony (shallow or flat AC, hypotony maculopathy, choroidal effusion, suprachoroidal hemorrhage) and late complications are associated with thin avascular, cystic blebs prone to leakage and potentially blinding infection. When trabeculectomy fails to control IOP, bleb needling may be attempted with an anti-scarring agent if the bleb architecture allows and the sclerostomy is patent.

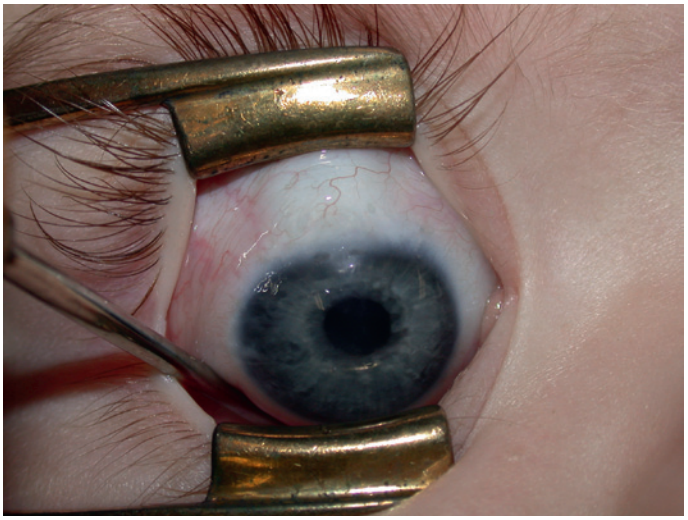


Fig. 38.13 Mitomycin C trabeculectomy in a child with fornix-based conjunctival flap and large antimetabolite treatment area.

Non-penetrating surgery (*deep sclerectomy*) for congenital glaucoma has been performed in an attempt to avoid trabeculectomy-related complications, such as early hypotony. However, it has not been widely adopted because of the technical challenges in bupthalmic eyes with thin sclera. This may also explain the significant rate of conversion to trabeculectomy.[46,47]

Glaucoma drainage devices (GDDs)

Glaucoma drainage devices are an important part of the therapeutic repertoire in childhood glaucoma as they offer the best chance of long-term IOP control in patients whose disease relentlessly progresses despite conventional surgical treatment. As primary surgery, indications include children: with uveitis who are aphakic or pseudophakic; who develop glaucoma following cataract surgery; who have a cataract that will need future imminent removal; and those with very severe disease with onset at birth, as these cases have a very high failure rate, even with MMC trabeculectomy. The prevailing current opinion is that GDDs are best implanted sooner rather than later in the hope of achieving early, definitive IOP control and, in doing so, optimizing long-term visual prognosis. The advantages and disadvantages of GDDs drainage surgery are summarized in Table 38.4.

Success rates of approximately 80% are reported with a mean follow-up of 2 years or less,[48–50] falling to around 50% with longer term follow-up.[51,52] The use of adjunctive MMC has been reported but there are no prospective studies in children to suggest improved outcomes with its use. There is no clear superiority of one GDD over another. Adult studies suggest the Baerveldt implant provides better long-term IOP control than the Ahmed implant.[53] Although the Ahmed implant has fewer complications, it is associated with a 2.6 higher chance of needing further glaucoma surgery (including diode).[53]

Common to all studies, regardless of the implant, is the ongoing decline in success with duration of follow-up and the requirement for adjunctive topical medication to control IOP.[54] Plate encapsulation is a major cause of late failure. Needling or capsule excision may be attempted but

Table 38.2 Important surgical points in pediatric trabeculectomy technique aimed at encouraging posterior flow and formation of diffuse bleb

Surgical steps	Surgical points/rationale
Corneal traction suture (7/0 Mersilk)	Allows adequate exposure Avoids hemorrhage from superior rectus muscle suture
Fornix-based conjunctival flap	Less likely to form a scar limiting posterior flow Allows better visualization of limbal anatomy
Wet field cautery	Hemostasis Avoids scleral shrinkage (important in thin sclera)
Anti-scarring agents	Diffuse large treatment to minimize risk of a focal, avascular bleb
Scleral flap	Consider fashioning scleral flap first before anti-scarring treatment to enable treatment under scleral flap Posterior edge must be well beyond limbus to prevent cheese-wiring of flap Dissection forward into cornea avoids iris, ciliary body and vitreous incarceration Short radial cuts enough to allow reflection of scleral flap for the sclerostomy • Greater the scleral elasticity (incision gap), the smaller the radial cuts • Directs aqueous flow posteriorly to prevent cystic blebs • Valve effect to prevent hypotony Large (5 mm posterior cut) and as thick as possible • Sutures less likely to cheese-wire • Greater resistance to aqueous outflow
Preplaced scleral flap sutures before sclerostomy	Easier to place with formed globe Reduces duration of intraoperative hypotony after sclerostomy and peripheral iridotomy (PI) performed Can be adjusted or removed under anesthetic or slit-lamp without laser Releasables along posterior borders of scleral flap, and fixed sutures at corners if scleral flap gapes, e.g. in infants Releasable loop buried in cornea so suture can be left indefinitely (reduces risk of endophthalmitis)
Paracentesis for AC maintainer	Oblique, peripheral, long tunnel (21G needle) minimizes risk of inadvertent lens damage, avoids wound leak, and stabilizes infusion cannula Allows maintenance of IOP intraoperatively preventing hypotony and potential for choroidal effusions, suprachoroidal hemorrhage, vitreous prolapse with PI Allows anterior chamber (AC) reformation Must turn off when tying scleral flap sutures tight to prevent cheese-wiring Used to gauge flow through sclera flap and ensure adequate flap closure
Sclerostomy	Small sclerostomy punch (500 μm diameter) allows increased control of aqueous outflow both intra- and postoperatively and is quicker to perform As anterior as possible prevents iris, ciliary body, and vitreous incarceration
Scleral flap closure	Tight closure vital with anti-scarring agent use Add additional sutures as required to reduce flow
Fornix-based conjunctival closure	10-0 nylon retains tension longer than dissolvable sutures with minimal inflammation Purse string sutures at peritomy edges, with limbal vertical mattress sutures
Prevention of postoperative hypotony	Short radial cuts create valve effect and minimize leakage from scleral flap sides Tight scleral flap sutures with option to adjust/release at later stage Watertight conjunctival closure Suture paracentesis May leave viscoelastic in AC if flow rate too high despite maximal suturing, or if ciliary body shut down anticipated (uveitic cases) Air bubble in AC

Adapted from Papadopoulos M, Edmunds B, Chiang M, et al. Glaucoma surgery in children. In: Weinreb RN, Grajewski A, Papadopoulos M, et al., editors. Childhood Glaucoma. WGA Consensus Series – 9. Amsterdam: Kugler Publications, 2013: 95–134.

published studies suggest outcomes inferior to additional GDD implantation.[55] Sequential GDD surgery may result in more corneal complications. The authors' preference is for the Baerveldt 350 mm^2 implant with restrictive-flow measures because of its larger surface area. The 250 mm^2 is favored for uveitic eyes, which are prone to aqueous hyposecretion, and microphthalmic eyes, which have smaller anterior chambers that can easily shallow with hypotony. Once failure has occurred, the authors usually prefer diode laser as the next procedure before proceeding with a second GDD.

GDDs have a significant complication profile. Consistently reported more commonly in children compared to adults is tube malposition, with migration anteriorly causing tube corneal touch, or posteriorly leading to retraction (requiring surgical revision in 33% of cases) along with tube erosion and endophthalmitis in up to 10% of cases.[54] Hypotony is another major complication that buphthalmic eyes are especially prone to, and occurs even with the use of valved implants. Modifications to minimize complications are summarized in Table 38.5.

Table 38.3 Advantages and disadvantages of trabeculectomy with mitomycin C (MMC)

ADVANTAGES
"Titration" of postoperative intraocular pressure (IOP) possible with releasable sutures and postoperative subconjunctival 5-fluorouracil (5-FU) and steroid under examination under anesthesia
Lower mean IOP achievable compared to glaucoma drainage device (GDD)
Less dependent on medication for IOP control compared to GDD
Less postoperative surgical revision compared to GDD
May significantly clear cloudy corneas and avoid potential corneal surgery
Many surgeons have experience performing trabeculectomy
DISADVANTAGES
More invasive and higher complications than angle surgery
Significant lifetime risk of endophthalmitis if bleb thin and avascular (more likely with small treatment areas of MMC and limbal based conjunctival flap)
Poor results in aphakic/pseudophakic patients even with MMC
Need close follow-up

Table 38.4 Advantages and disadvantages of glaucoma drainage device (GDD) surgery

ADVANTAGES
Very effective in reducing intraocular pressure (IOP) long term, even if previously failed mitomycin C trabeculectomy
Most likely to survive future intraocular surgery, e.g. penetrating keratoplasty, lensectomy, vitrectomy; therefore best option in these circumstances
Contact lens wear possible in aphakic/pseudophakic patients
DISADVANTAGES
Potentially long surgical time with non-flow-restricted implants
Often dependent on medication for IOP control
High surgical revision rate
Higher risk of corneal decompensation compared to trabeculectomy

Table 38.5 Strategies to minimize glaucoma drainage device (GDD) complications

Complication	Preventative strategies
Anterior tube migration	Secure plate and tube well to sclera to minimize migration Baerveldt plate behind the muscles to prevent migration is preferable
Posterior tube migration	Secure plate and tube well to sclera to minimize migration Avoid very short tube
Corneal decompensation	Aim to place tube away from cornea and as posterior as possible in anterior chamber Avoid long tube
Intra- or postoperative hypotony	Anterior chamber (AC) maintainer (e.g. Lewicky cannula) Relatively long, snug limbal tunnel incision (e.g. 25G needle usually adequate for tube entry as sclera is elastic) Intraluminal stent in non-valved implant (e.g. 3/0 Supramid suture) Extraluminal ligating vicryl suture in non-valved (e.g. 6/0 Vicryl) with venting "Sherwood" slit anterior to suture Viscoelastic or gas in AC at end of surgery if IOP low Two-stage implantation
Tube obstruction	Aphakic cases with AC/sulcus tubes, ensure no vitreous present or likely to prolapse into AC otherwise consider vitrectomy For pars plana tube placement, extensive posterior vitrectomy required Treat inflammation aggressively Avoid short tube in uveitics: reduces risk of iris-related tube obstruction from peripheral anterior synechiae
Tube erosion	Intrascleral tunnel with AC entry at or as posterior to limbus as possible – avoid corneal tunnel, which is more likely to erode Oblique entry into eye rather than 90°, which may produce knuckle of tube at entry point Patch graft along whole of tube length – sclera or cornea, other tissue (e.g. pericardium) Avoid conjunctival tension at limbus with closure Tube entry when inferiorly placed should be covered by lower lid

Adapted from Papadopoulos M, Edmunds B, Chiang M, et al. Glaucoma surgery in children. In: Weinreb RN, Grajewski A, Papadopoulos M, et al., editors. Childhood Glaucoma. WGA Consensus Series – 9. Amsterdam: Kugler Publications, 2013: 95–134.

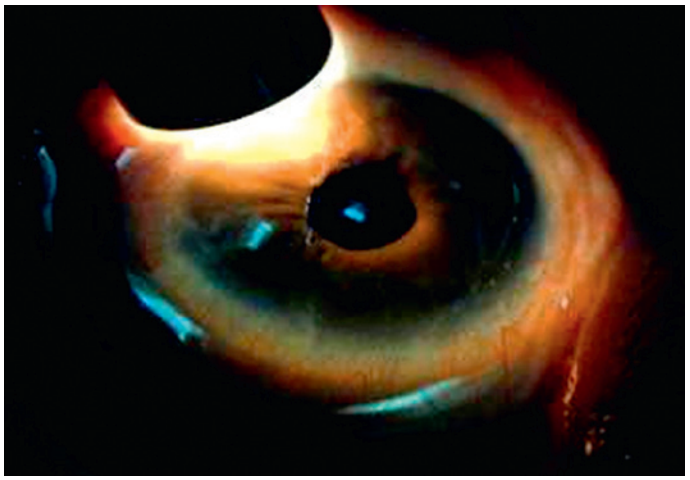


Fig. 38.14 Cyclodiode laser. Transillumination is crucial for correct placement of burns on the ciliary body.



Fig. 38.15 Child with Sturge–Weber syndrome wearing myopic spectacle correction.

Cyclodestruction

The indications for cyclodestruction are: (1) a blind painful eye; (2) poor visual potential; (3) poor surgical prognosis; and (4) surgery is technically impossible or when other treatments have failed. The advantages and disadvantages of diode laser cyclodestruction are summarized in Box 37.3.

Contact transscleral semiconductor diode laser (810 nm) has become increasingly more popular than Nd:YAG laser and cyclocryotherapy as a method of ciliary body ablation because it is better tolerated and associated with fewer complications. As buphthalmic eyes often have distorted anatomical landmarks, transillumination of the eye is essential to ensure accurate placement of the laser burns (Fig. 38.14). Care must be taken to avoid areas of pigmentation, hemorrhage, and scleral thinning, as scleral perforation in a buphthalmic eye has been reported.[56]

Transscleral diode laser has limited long-term success, often requires retreatment, and the continuation of medications.[15,57] Results are similar to those achieved with endoscopic diode with a lower retreatment rate. Overall visual loss rates of up to 18% have been reported, usually in eyes with pre-existing poor vision.[58]

Refractive correction and amblyopia therapy

The ultimate aim of preserving lifelong vision in children with glaucoma is dependent not only on IOP control, but also several inter-related factors such as the treatment of ametropia and amblyopia (Fig. 38.15). All children with glaucoma within the vulnerable age range should be examined regularly for the presence of amblyopia. Refraction should be part of the periodic examination with glasses prescribed as appropriate when the cornea clears and is practical. Occlusion therapy for amblyopia should be attempted in all children in whom there is potential for visual improvement.

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Pediatric iris disorders

Michael O'Keefe

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Anatomy

The iris is the most anterior element of the uveal tract. It divides the anterior segment into anterior and posterior chambers. It is composed of blood vessels, connective tissue, muscles, melanocytes, and pigment cells. Its stroma is made up of pigmented and non-pigmented cells, collagen fibrils, and hyaluronic acid. The stroma contains multiple crypts and is covered by connective tissue cells. Differences in color relate to the amount of pigmentation in the anterior border of the deep stroma; blue irides are lightly pigmented and brown irides have densely pigmented stroma. Blood vessels form the bulk of the iris stroma. They run a radial course arising from the major arterial circle located at the apex of the ciliary body, passing to the center of the pupil. Myelinated and non-myelinated nerve fibers provide sensory and motor functions throughout the stroma.

Embryology

The posterior surface of the iris is densely pigmented and is continuous with the non-pigmented epithelium of the ciliary body. The dilator muscle layer is parallel and anterior to the posterior pigment epithelium. The muscle dilates in response to sympathetic adrenergic stimulation, and parasympathetic stimulation has an inhibitory effect. The sphincter muscle is located near the pupillary rim in the deep stroma. It receives parasympathetic nerve fibers to cause constriction.

The uveal tract develops from the neuroectoderm, neural crest, and mesoderm. The iris sphincter and dilator muscles and posterior iris epithelium develop from the neuroectoderm. Pigment differentiation and migration continue into the second and third trimesters. The smooth muscle of the iris develops from the neural crest. Iris formation starts with the closure of the fetal cleft at 35 days' gestation. The sphincter muscle first appears at the optic margin at 10 weeks' gestation, becoming myofibrils at 10–12 weeks. The smooth muscle of the ciliary body is present at 4 months' gestation before the iris stroma develops. The blood vessels arise from the mesoderm and neural crest. The pupillary membrane regresses shortly before term. The pupil is small at birth but it enlarges as the dilator muscle develops. Pigmentation is complete at one year and the irides get darker in the first year of life.

Signs and symptoms of iris disease

Pain and photophobia are features of iritis. Congenital structural and developmental abnormalities of the pupil include iridodonesis, aniridia, micropupil, polycoria, corectopia, ectropia, coloboma, iris sphincter atrophy, and dilated oval pupils (Boxes 39.1 and 39.2; Figs 39.1 and 39.2).

Acquired abnormalities include trauma (Fig. 39.3), ischemia, hemorrhages, or infiltration of the iris with tumors such as lymphoma, leukemia, juvenile xanthogranuloma, Lisch nodules, and neurofibromas. Anisocoria, a difference in pupil size, occurs in approximately 20% of the normal population. It may be transmitted as an autosomal dominant trait with variable expression.[1]

Congenital idiopathic microcoria is a developmental abnormality of the pupillary membrane. It is usually unilateral with an absent or eccentric pupil. It is autosomal dominant and is associated with myopia and corectopia.[2] Congenital fibrovascular pupillary membranes are likely a variant of persistent fetal vasculature.[3] Bilateral microcoria is associated with microphthalmos and posterior segment anomalies.[4]

Box 39.1

Congenital pupil abnormalities

Aniridia
Ectopia
Micropupil
Coloboma
Polycoria
Microcoria
Corectopia
Anisocoria
Congenital fixed pupil

Box 39.2

Congenital iris abnormalities

Brushfield spots
Iris melanosis
Iris ectropion
Lisch nodules
Iris stromal cyst
Juvenile xanthogranuloma
Heterochromia iridis
Persistent pupillary membrane
Coloboma

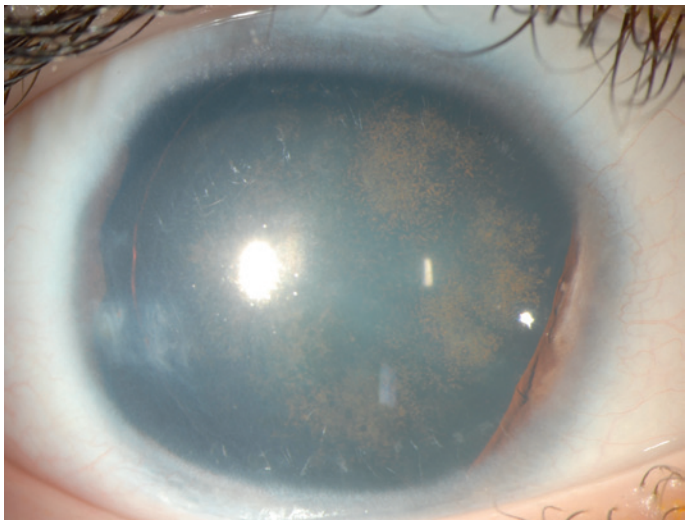


Fig. 39.1 Partial aniridia and pigment dusting of the anterior capsule.

Persistent pupillary membranes

Congenital persistent pupillary membranes result from incomplete involution of the tunica vasculosa lentis during the third trimester. These are often still present in premature infants before complete involution has occurred. These membranes are formed by buds from the annular iris vessels growing centrally to form the anterior vascular envelope of the lens. They may span the entire pupil and can be attached to the anterior capsule of the lens with or without cataract. They may occur in association with microcoria, megalocornea,

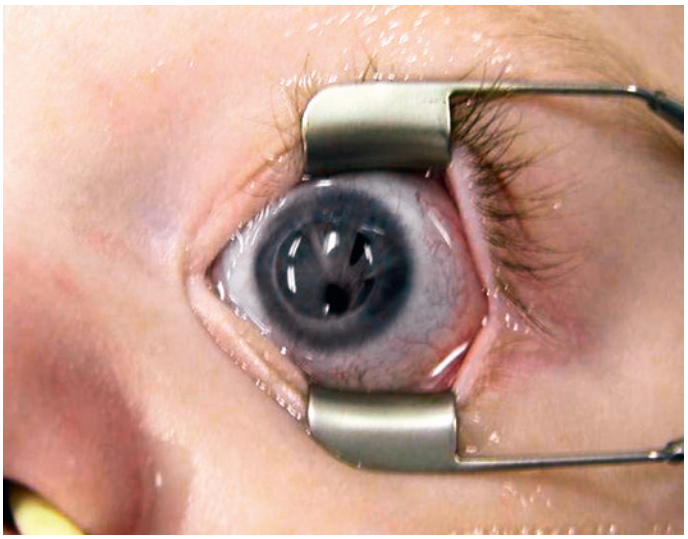


Fig. 39.2 Child with Peters' anomaly showing corectopia through a corneal transplant.

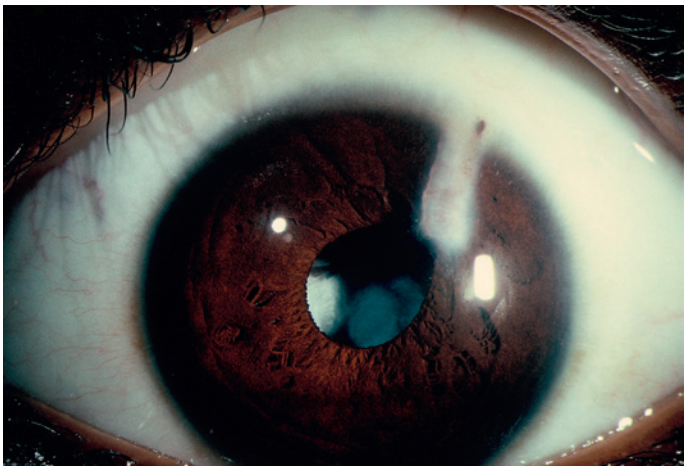


Fig. 39.3 Iris incarceration after a penetrating injury that was never repaired surgically.

microphthalmos, and coloboma. Most are asymptomatic and require no treatment.[5] It is sometimes difficult to assess whether a membrane is amblyogenic. Removal involves surgery with viscoelastics and excision with microscissors or vitrector[6] (Figs 39.4 and 39.5). Complications of surgery include cataracts, sphincter damage, or iridodialysis.[7] Laser lysis uses a Nd:YAG laser to disrupt the adhesions between the strands of the membrane and the normal iris.[8] Complications include pigment dispersion and hyphema and cataract. The visual prognosis is good,[9] but poor initial visual acuity is an indication of a poor outcome. Myopic and hyperopic anisometropia may accompany persistent pupillary membranes.

Congenital iris and stromal crypts

Iris cysts may be congenital resulting from an accumulation of fluid within the epithelial lining. They are found in either the pigment epithelium or stroma and have a squamous epithelial or neuroepithelial lining. Iris pigment cysts are

usually stationary with a transparent wall and vascular lining at the pupillary margin. Stromal cysts are progressive and are located in the anterior surface of the iris. While some advocate a conservative approach, many require surgery. A variety of treatments have been tried, including aspiration with or without cryotherapy applied to the base of the cyst near the limbus, the injection of alcohol or sclerosing agents, surgical excision with sector iridectomy, Nd:YAG or argon laser, or irradiation.[10] The differential diagnosis of congenital iris cysts includes epithelial cell implantation from surgery, trauma, and tumors. Complications include glaucoma, cataract, and spontaneous detachment, when an iris cyst may become free-floating.

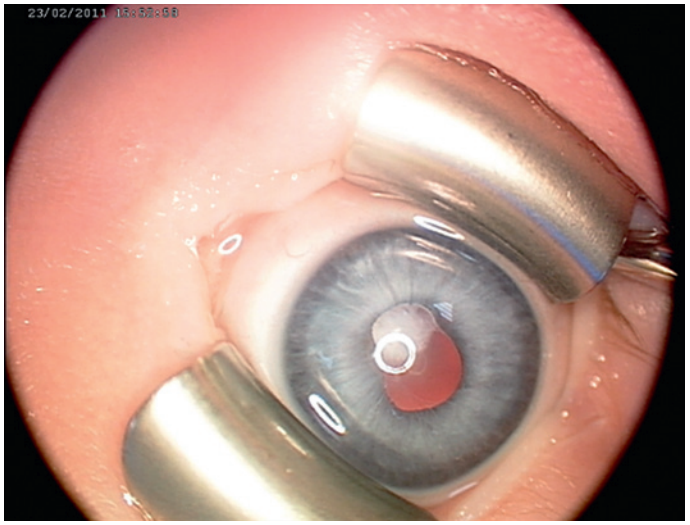


Fig. 39.4 Persistent pupillary membrane. A five-week-old baby presented with a persistent pupillary membrane in the left eye. Our initial treatment was patching and pupil dilation; however, she was intolerant of patching. We removed the membranes through a small corneal incision and using microscissors and viscoelastic. She had a clear visual axis post-operatively. She tolerated patching and now has equal vision in each eye.

Ciliary body cysts are less common; they may be solid or filled with fluid, and may cause astigmatism and amblyopia (Fig. 39.6).

Multisystemic smooth muscle dysfunction syndrome

Multisystemic smooth muscle dysfunction syndrome is a recently described genetic disease characterized by dysfunction of the smooth muscles throughout the body. It manifests as congenital fixed pupils with lack of accommodation. Affected patients may have persistent ductus arteriosus, aortic and cerebrovascular disease, hypotonic bladder, intestinal hypoperistalsis, and pulmonary hypertension.[11] It is thought

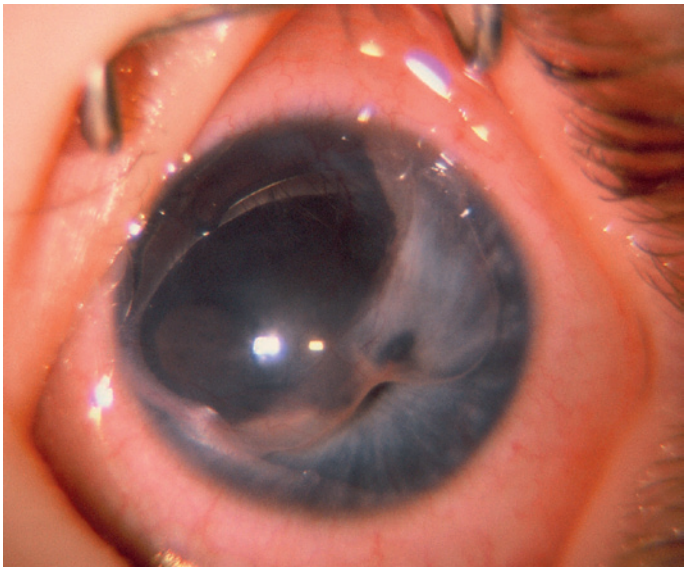


Fig. 39.6 Iris stromal cyst in a 10-month-old child involving the visual axis.

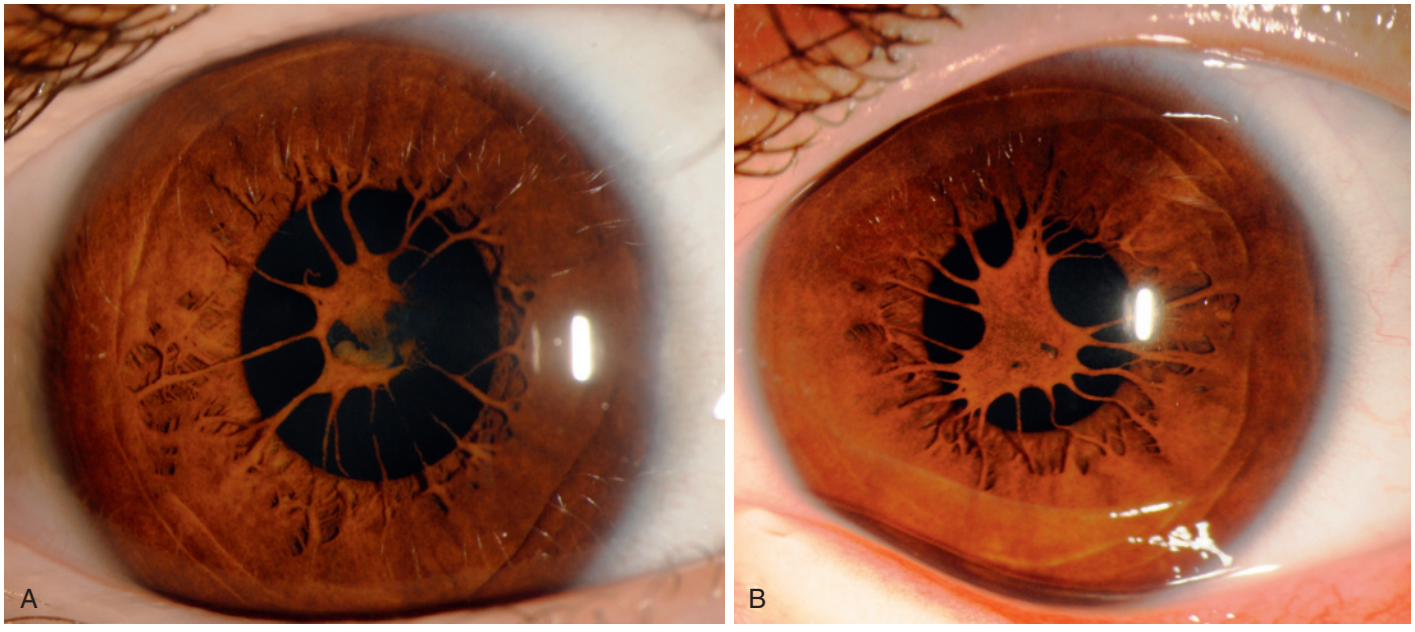


Fig. 39.5 Bilateral persistent pupillary membranes in a 6-year-old child. The visual acuity was 20/20 in the right eye and 20/25 in the left eye. (A) Right eye. (B) Left eye.

to be caused by a *de novo* mutation of the *ACTA2* gene, on chromosome 10 (10q23.3).

Iris ectropion or ectropion uveae

Ectropion uveae (Fig. 39.7) is characterized by extension of the posterior pigment epithelium onto the anterior surface of the iris. It may be congenial or acquired.[12] It can be associated with glaucoma, neurofibromatosis type 1 (NF1), or anterior segment dysgenesis. This should be distinguished from iris flocculi, which are excrescences of the pigment epithelium at the pupil margin. These may be a marker of familial aortic aneurysms.[13]

Heterochromia iridis

A difference in iris color can be congenital or acquired. In congenital heterochromia (Fig. 39.8), the involved iris is darker, an indicator of ocular melanocytosis, oculodermal melanocytosis, or a sector hamartoma syndrome. Congenital Horner syndrome results in ipsilateral hypopigmentation miosis and ptosis (Fig. 39.9). Waardenburg syndrome (WS) is an autosomal dominant condition with sensorineural deafness, white forelock, and heterchromia iridis. Type 1 WS includes lateral displacement of the inner canthi, a prominent root of the nose, and unusual eyebrows, which may meet across the midline (synophrys). It is caused by mutations in the *PAX3* gene.[14] Type 2 WS does not include facial dysmorphism or dystopia canthorum, where telecanthus can result in an abnormal displacement of the inner canthal relative to the globe. Type 3 is similar to type 1 with limb abnormalities. Type 4 is associated with Hirschprung disease. The gene has been localized to 3p–12:p141[15]; however, several genes may be implicated.

Iris sector heterochromia and Hirschprung disease is an autosomal recessive condition due to a neural crest cell lineage abnormality.[16]

In acquired heterochromia the iris may become darker through processes such as nevus formation, melanomatous tumors, and deposits of iron within the iris (siderosis). Hemosiderosis results from iron deposition from a longstanding hyphema.[17] Conversely, the iris may become lighter. Fuchs heterchromic iridocyclitis is the commonest cause, but others such as juvenile xanthogranuloma, metastatic malignancy, and leukemia are differentials. Acquired Horner syndrome infrequently leads to heterochromia; this may only appear after some years. William syndrome is a rare autosomal dominant disorder. Associated systemic features include aortic valve disease, hypercalcemia, elfin facial feature, prominent lips, hyperacusis, and developmental delay.[18] It is associated with a unique stellate appearance of the iris.[19] Other ocular features include strabismus, hyperopia, and retinal vein tortuosity.

Juvenile xanthogranuloma (JXG) is a benign condition of unknown etiology that occurs in infancy and early childhood. There is a proliferation of non-Langerhans histiocytes, plasma cells, and occasional eosinophilic and Touton giant cells.[20] Xanthogranulomas are more common in children with neurofibromatosis 1. The skin is most commonly involved, but lesions may occur in the eye. Children with cutaneous JXG rarely have eye involvement, and eye screening in these children is of little merit.

Risks factors for ocular involvement include an increased number of skin lesions and age under 2 years. Within the eye, the iris is the most common location, but the choroid, orbit, cornea, conjunctiva, and sclera may be involved. Iris lesions may be localized or diffuse and are mostly unilateral.



Fig. 39.7 Ectropion uveae and a cystic drainage bleb. A 2-year-old girl was referred with raised intraocular pressure (IOP) and grossly cupped optic disc. She had unilateral, ectropion uveae glaucoma. After a mitomycin-enhanced trabeculectomy, her IOP was reduced to 8 mmHg. Six years later, her vision is LogMAR 0.48 (Snellen equivalent, 6/15).

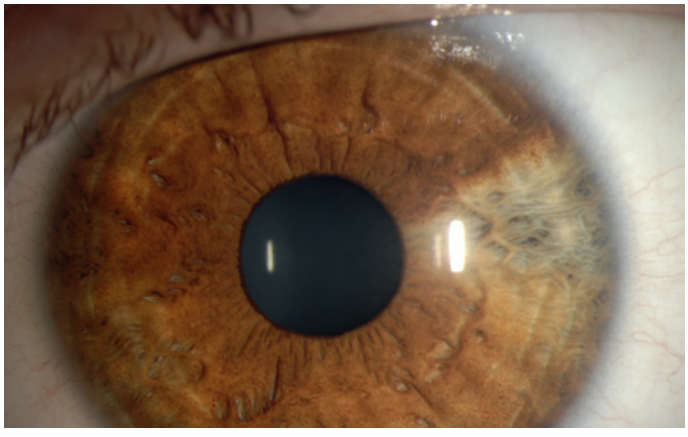


Fig. 39.8 Sectoral heterochromia.



Fig. 39.9 Congenital Horner syndrome with iris heterochromia.

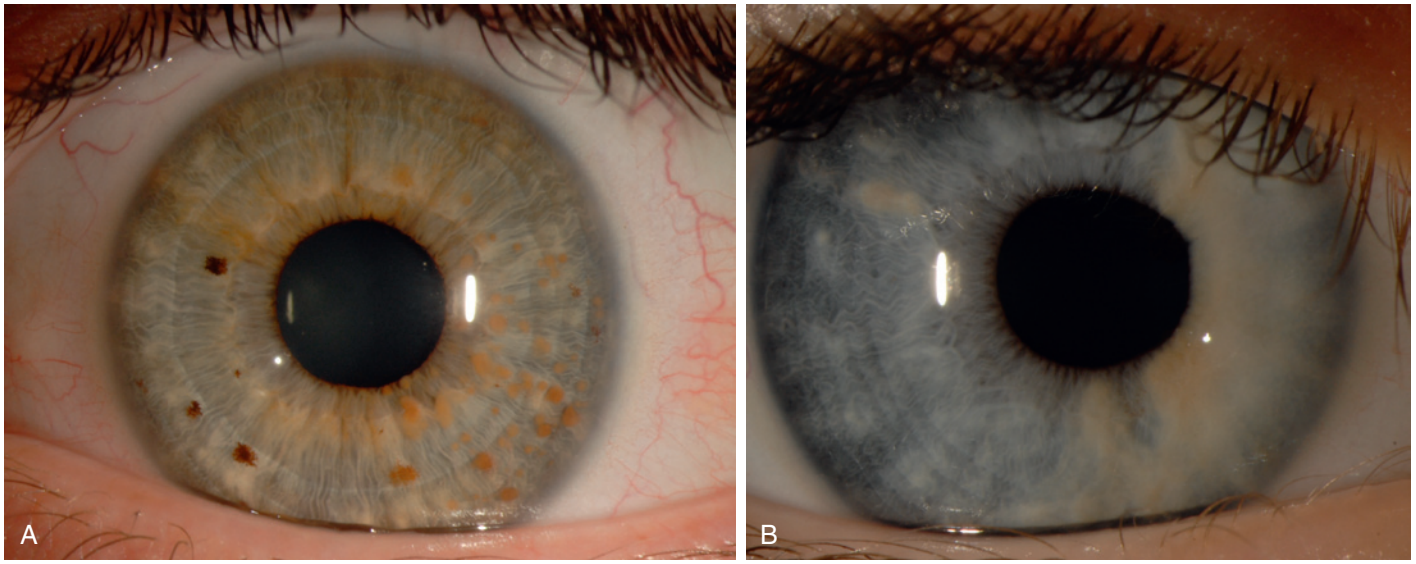


Fig. 39.10 Lisch nodules. (A) The father has multiple Lisch nodules. (B) The son has hypopigmented Lisch nodules and sectoral depigmentation of his iris temporally. Both the father and son have neurofibromatosis type 1.

They are usually highly vascular and frequently bleed spontaneously, resulting in a hyphema, an elevation of the intraocular pressure, and corneal edema. Amblyopia is a significant risk in affected infants. If the child presents with a spontaneous hyphema, the differential diagnoses include juvenile xanthogranuloma, retinoblastoma, fibrosis secondary to persistent fetal vasculature, and iris corneal malformations.

The diagnosis can usually be established by biopsy of a skin lesion. However, in children with only ocular involvement, the diagnosis can be made by performing a paracentesis over an iris lesion and examining the cells in the aspirate histopathologically. Iris biopsy carries a high risk of operative hyphema and it is contraindicated if retinoblastoma is suspected. Treatment options include topical corticosteroids and low-dose radiotherapy.[21]

Lisch nodules

Lisch nodules are dome-shaped lesions on the anterior surface of the iris (Fig. 39.10). They are brown/orange in color, round, and bilateral. In dark irides they appear lighter than the background. Their size varies widely. Histopathologically they are melanocytic hamartomas. In NF1, they are present in one-third of 2-year-olds, 50% of 5-year-olds, 75% of 15-year-olds, and 100% of patients over 21 years of age.[22] Rarely, they can also occur in patients with NF2.

Brushfield spots

Brushfield spots are areas of normal or hypercellular iris tissue with surrounding stromal hypoplasia. They occur in a quarter of normal individuals, where they were initially described, but Thomas Brushfield considered them to be characteristic of Down syndrome, although they are not always present in these children. They differ from iris pigment spots and freckles in that they are more central and numerous.



Fig. 39.11 Iris coloboma of the right eye and severe microphthalmos of the left eye.

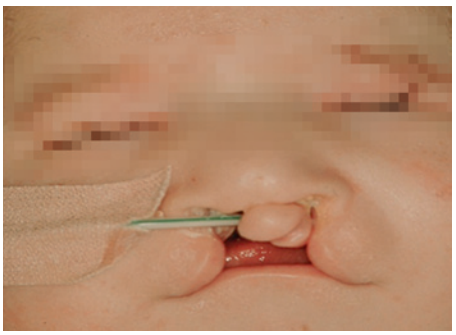


Fig. 39.12 Patau syndrome.

Iris colobomas

Iris colobomas may be typical or atypical, complete or partial. Typical colobomas are caused by a failure of fetal fissure closure at the inferior nasal quadrant and are referred to as "keyhole" pupils (Fig. 39.11). They can involve the iris, ciliary body, retina, and optic nerve. Atypical colobomas are those found anywhere other than the inferior nasal quadrant and are usually restricted to the iris. "Typical" colobomas are part of a continuum that includes microphthalmos and anophthalmos.[23] Autosomal dominant colobomas can be isolated lesions or manifestations of microphthalmia and anophthalmos.[24] Several syndromes (Box 39.3) and chromosomal disorders (Box 39.4 and Fig. 39.12) are associated with ocular colobomas. The most

Box 39.3

Syndromes associated with colobomas

Aircardi syndrome
CHARGE syndrome
Goldenhar syndrome
Goltz syndrome (focal dermal hypoplasia)
Median facial cleft syndrome
Warburg syndrome
Rubinstein–Taybi syndrome
Linear nevus sebaceus syndrome
Meckel syndrome
Klinefelter syndrome
Turner syndrome

Box 39.4

Chromosomal disorders associated with colobomas

Trisomy 13 (Patau syndrome)
Cat-eye syndrome
4p, 119, 139, 189, 18F, 18T
Trisomy 18 (Edwards syndrome)



Fig. 39.13 Iris coloboma in a child following closure with modified McCannel suture technique. (Blackmon DM, Lambert SR. Congenital iris coloboma repair using a modified McCannel suture technique. Am J Ophthalmol 2003; 135: 730-732).

common associated condition is CHARGE syndrome[25] (coloboma associated with heart disease, choroidal atresia, mental retardation, genital hypoplasia, and deafness). There is also an association between uveal colobomas and teratogens such as thalidomide.

Children with coloboma should have a complete eye and medical examination. The family history should be documented and relatives examined. A child with coloboma should be followed for potential amblyopia, anisometropia, and retinal detachment. An iris coloboma can be closed surgically, but is usually not indicated unless it is combined with cataract surgery (Fig. 39.13).

Box 39.5

Tumors of the iris

Iris nevi
Medulloepithelioma
Leiomyoma
Hemangioma
Iris melanoma

Iris melanosis and iris mammillations

Iris melanosis is rare. The iris is hyperpigmented. It is associated with scleral pigmentation and choroidal hyperpigmentation. It is usually autosomal dominant.[26] Heavily pigmented irides commonly have pigmented protuberances called iris mammillations, which are distributed uniformly, often covering much of the anterior surface of the iris. They are associated with iris nevi (Fig. 39.13).[27] There is a risk of glaucoma with both conditions. Cogan–Reese syndrome is a unilateral iris nevus with peripheral anterior synechiae and ocular hypertension.

Iris tumors (Box 39.5)

Iris leiomyomas are rare, benign, slow-growing smooth muscle tumors that are more common in girls. They usually present with pupillary distortion and hyphema, and later may develop glaucoma and cataract. They can be indistinguishable from melanomas.[28] If they enlarge, surgical excision is advised.

Iris hemangiomas are rare. They are most common on the inferior sector of the iris and they may cause spontaneous hyphema. They may be isolated or associated with multiple cutaneous and even visceral hemangiomas.[29] Iris melanomas are rare in childhood. They tend to occur in the inferior iris and can present with a hyphema. Histologically, most are spindle cells with a low risk of metastasis. The differential diagnosis includes juvenile xanthogranuloma, iris rhabdomyosarcoma, and iris foreign body. Medulloepitheliomas (diktyomas) are unilateral solid or cystic tumors occurring in the iris and extending to the non-pigmented ciliary body epithelium. They can appear in infancy or early childhood and are often associated with glaucoma, leukocoria, distorted pupil, or hyphema. Histologically, they are composed of membranes, tubes, and rosettes, and they may undergo malignant transformation. The potential for spread is low. If the tumor is anterior, local resection or cryotherapy is the recommended treatment. When the diagnosis is delayed and there is a risk of extraocular extension, enucleation is the recommended treatment.

Spontaneous hyphemas

Spontaneous hyphemas occur secondary to anomalous iris capillary loops; tumors such as juvenile xanthogranuloma, medulloepithelioma, or retinoblastoma; retinopathy of prematurity; persistent fetal vasculature; and blood dyscrasias. In older children, scarring and iris rubeosis should also be included in the differential diagnosis. Leukemic infiltration

of the iris may cause hyphema and glaucoma and hypopyon. Studies to determine the underlying cause include: ultrasonography, magnetic resonance imaging, and general physical examination. Hematological screening for blood disorders is also necessary.

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Uveitis

Clive Edelsten

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Box 40.1

Differential diagnosis of childhood intraocular inflammation

Unreported trauma or intraocular foreign body
Neoplasia
- Diffuse retinoblastoma
- Juvenile xanthogranuloma
- Relapse of leukemia
- Rosai–Dorfman disease

Photoreceptor dystrophy, especially where retinal pigment epithelium (RPE) changes have not yet developed or where RPE changes resemble choroiditis
Retinochoroidal dysgenesis
Hereditary vitreoretinal degeneration
Retinal vascular abnormalities that leak or bleed: Coats disease, vasoproliferative tumors
Congenital disc abnormalities, especially with secondary vascular complications
Infection, especially in the congenitally or iatrogenically immunodeficient

Introduction

This chapter will discuss endogenous childhood ocular inflammation including uveitis and the vasculitides. There is considerable overlap with conditions causing orbital inflammation and central nervous system (CNS) vasculitis. Infections are a significant differential, precipitating or co-existing diagnosis, but are not the primary focus of this chapter.

The differential diagnosis of autoimmune and auto-inflammatory ocular inflammation in this age group is wide (Box 40.1). Uveitis is a relatively common feature of several localized autoinflammatory diseases that have both unique and shared genetic associations (Table 40.1). There is often a family history of autoimmune and autoinflammatory conditions in pediatric idiopathic uveitis. Despite the various genetic associations, a family history of uveitis is rare, unless caused by a dominant single-gene disorder such as Blau syndrome or a strong family history of HLA-B27-related disease.

Experimental models of uveitis have concentrated upon antigen-specific autoimmune mechanisms of inflammation. Sympathetic ophthalmia and phacoanaphylaxis may be examples of organ-specific autoimmunity, but the majority of childhood uveitis syndromes are secondary to localized or generalized disorders of the control of inflammation. Advances in population immunogenetics and study of the differential response to treatments have led to a continuing re-appraisal of disease classifications and treatment indications.

General considerations

When considering ocular inflammation in childhood one needs to ask:

1. Why has the inflammation started in childhood rather than adulthood?
2. Will the age of onset influence the disease phenotype?
3. Is there a genetic disorder of the control of inflammation?
4. Is there a genetic predisposition to autoimmunity?
5. Does the age influence treatment efficacy?

Table 40.1 Major inflammatory diseases associated with childhood uveitis

SYSTEMIC AUTOINFLAMMATORY DISEASES				
Diagnosis	**Systemic signs**	**Ocular signs**	**Gene**	**Inheritance**
Familial Mediterranean fever	Peritonitis, rash, arthritis	Uveitis	*MEFV*	Recessive
Chronic infantile neurologic cutaneous articular syndrome	Rash, arthritis, hepatosplenomegaly, deafness, chronic meningitis	Disc edema, uveitis, keratitis	*CIAS1*	Dominant
Muckle–Wells syndrome	Rash, arthralgia, deafness	Conjunctivitis, disc edema	*CIAS1*	Dominant
Blau syndrome	Rash, arthritis	Panuveitis, CAU, MFC	*CARD15*	Dominant
LOCALIZED AUTOINFLAMMATORY DISEASES				
Diagnosis	**Systemic signs**	**Type of uveitis**	**HLA Gene associations**	**Ethnicity**
Juvenile idiopathic arthritis	Joint	CAU	DRB*0801, 1101, 1301, DPB1*02	Worldwide
Behçet disease	Mucosal ulceration, follicular rash, vasculitis	Pan	B-51	Eastern Mediterranean to Orientals
Enthesis-related arthritides	Joint	Acute anterior	B-27	N. Europeans
Sarcoidosis	Skin, joints, hepatosplenomegaly, lymphadenopathy, CNS, lung	Pan, CAU, MFC	DRB*04, DQB1*0301, DRB1*1201, DRB1*1101	N. Europeans, Afro-Caribbeans
Ulcerative colitis	Large bowel, joints	Acute anterior, RV	DRB1*150 2, 0103	
Crohn disease	Small bowel, joints	Acute anterior, RV	DRB1*03	
Vogt–Koyanagi–Harada syndrome	Skin, CNS, vitiligo	Pan	DRB1*04	Native Americans, Orientals, Asians
Tubulointerstitial nephritis and uveitis syndrome	Kidney	CAU, MFC	DRB1*0102	
Multiple sclerosis	CNS	IU	DRB1*1501	N. Europeans
Psoriasis	Skin, joints	CAU, IU	Cw6	

CAU, Chronic anterior uveitis; CNS, central nervous system; IU, intermediate uveitis; MFC, multifocal choroiditis.

Consanguinity, familial clustering, or unusual disease patterns suggests rare or novel mutations. The immune system develops through childhood and adolescence when most infections are first encountered. An unusual ocular inflammatory response to a common childhood infection may be the first expression of a congenital systemic immune disorder (Box 40.2).

Organization of service

Childhood uveitis requires an organizational approach:

1. Early therapeutic decisions have to be made; early referral pathways to relevant clinicians are required.
2. Long-term social and educational planning needs to be in place for those with visual loss and/or poor treatment compliance.
3. Multiple surgical and medical specialties may be required simultaneously to form a treatment plan.
4. Transition to adult services may need a multidisciplinary approach.
5. Clinically relevant outcomes may differ from those used in adult ocular inflammatory disease.[1,2]
6. Screening for juvenile idiopathic arthritis (JIA)-uveitis needs public health support as with other screening programs.

Box 40.2

Immunodeficiency diseases associated with uveitis

Cyclic neutropenia
Chronic granulomatous disease of childhood
X-linked lymphoproliferative disease with Epstein–Barr virus (EBV) persistence and hypogammaglobulinemia
EBV viremia with CD27 deficiency or T-cell/NK-cell deficiency
- Common variable immunodeficiency
- Immunoglobulin (Ig)G2 deficiency
- Hyper IgM disease with hypogammaglobulinemia

STAT3 gain of function
- Hypereosinophilic syndrome
- Hypocomplementemic vasculitis

Interleukin (IL)-1 and IL-10 receptor deficiency
Cartilage hair hypoplasia syndrome
Nijmegen breaking

Evaluation for systemic disease

Ocular inflammation may herald systemic disease; subclinical systemic disease may have developed before presentation (see Table 40.1). Symptoms of systemic disease may occur later than ocular disease in juvenile idiopathic arthritis, sarcoidosis,

Behçet disease, psoriasis, inflammatory bowel disease (IBD), multiple sclerosis (MS), and Vogt–Koyanagi–Harada (VKH) syndrome. Since arthritis is the most frequent systemic association of childhood uveitis, pediatric rheumatologists are most commonly involved in the systemic assessment.

Skin changes are frequent in a variety of relevant systemic diseases and the ophthalmologist needs to enquire about these and refer appropriately.

Associated CNS inflammation is difficult to diagnose if it presents with behavioral changes, deafness, retrobulbar optic neuritis, headaches, or movement disorders in preverbal toddlers. Sensorineural hearing loss related to a systemic inflammatory disease may have developed earlier and been diagnosed as congenital in origin: hearing loss may need to be re-evaluated (Table 40.2).

Optic disc edema is frequent in childhood uveitis and scleritis; the diagnosis of optic disc changes (Figs 40.1 and 40.2) may be challenging. Raised intracranial pressure can occur in meningoencephalitis associated with sarcoidosis, systemic lupus erythematosus (SLE), and chronic infantile neurologic cutaneous and arthritis (CINCA) syndrome, as well as secondary to venous sinus thrombosis, idiopathic intracranial hypertension, and systemic steroid withdrawal.

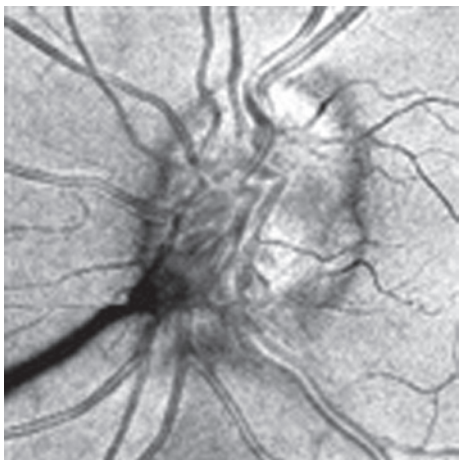


Fig. 40.1 Persistent optic disc edema with anterior inferonasal vitreous band to disc, 1 year after remission of intermediate uveitis.



Fig. 40.2 Optical coherence tomography of persistent optic disc edema 15 years after onset of juvenile idiopathic arthritis-associated uveitis.

Epidemiology of pediatric uveitis

The incidence of uveitis is uncommon at 17–25/100,000; it increases with age and peaks in the fifth decade. In 0- to 4-year-olds, the incidence is 3/100,000; in 10- to 14-year-olds, 6/100 000.[3] Childhood uveitis comprises 5% of most series of uveitis patients. Twenty-six percent of visual loss from all types

Table 40.2 Structural complications of juvenile idiopathic arthritis-associated uveitis (JIA-uveitis) and intermediate uveitis (IU)

JIA-uveitis	Intermediate uveitis
ANTERIOR SEGMENT CHANGES	
AC cells and flare	AC signs only in "anterior and intermediate uveitis"
Band keratopathy	
Extensive posterior synechiae	Rare
Progressive anterior synechiae	
Iris hyperemia and, rarely, neovascularization	
Unexplained hyphema	
Pupillary membrane	
Early irreversible ciliary body damage with chronic hypotony and phthisis	Hypotony rare
High risk glaucoma	Low risk glaucoma
Early cataract formation	Often late developing despite persistent cellular activity
Persistent diffuse vitreous flare and opacities with minimal vitritis	Vitritis necessary for diagnosis
Rarely, minimal snowball formation	Acute IU may cause dense central anterior floaters Chronic opacities tend to be dependent and aggregate – snowballs, snowbanks
Diffuse macular and disc edema and subretinal fluid with minimal vitritis	Disc edema can be marked in absence of macular edema
Disc neovascularization	Disc and peripheral retinal neovascularization
Vitreous hemorrhage	Vitreous hemorrhage
Retinal detachment, rare in phakic patients or without coexisting hypotony	Retinal detachment, pars plana cysts, localized peripheral detachments.
	Retinoschisis
POSTOPERATIVE COMPLICATIONS	
IOL membrane formation	Usually tolerates IOL
Frequent posterior capsular opacification	
Membrane formation following capsulotomy	

Box 40.3

Commonest types of uveitis by age

- 0–6 years: JIA-CAU
- 7–12 years: Idiopathic CAU, IU
- 13–16 years: IU, B27-associated AAU
- Adult: B27-associated AAU

For abbreviations, see text.

of uveitis with severe visual impairment in the Netherlands is due to non-infectious uveitis.[4]

The most common type is idiopathic. The most common pattern in children under 8 years of age is chronic anterior uveitis (CAU); in those aged 8–16 years it is intermediate uveitis (IU). After the age of 16, the pattern is that of adult disease (Box 40.3). Idiopathic painful bilateral CAU, idiopathic IU, and idiopathic panuveitis are also not uncommon in children. Specific uveitis syndromes, such as birdshot retinochoroidopathy and Fuchs heterochromic cyclitis[5] are exceptionally rare in children.[6]

JIA is the most common extraocular disease reported in tertiary referral series followed by those with no systemic disease (idiopathic uveitis), enthesitis-related arthritis (ERA), sarcoidosis, IBD, and Behçet disease. Even in countries with high rates of Behçet disease, Behçet uveitis is uncommon in childhood.[7] Behçet disease and VKH syndrome are 10–100 times more common in some Oriental, Asian, and Mediterranean groups than in Caucasians.

Tubulo-interstitial nephritis and uveitis syndrome (TINU), MS, and sarcoidosis are more common in North Europeans; there are also high rates of sarcoidosis in Afro-Caribbeans and high rates of ERA in Middle America.

Epidemiology of pediatric vasculitis

The commonest type of childhood systemic vasculitis is Henoch–Schonlein purpura in which ocular involvement is very rare; giant cell arteritis is the commonest vasculitis in the elderly and is exceptionally rare in childhood. The incidence of childhood SLE is 0.8/10,000 and juvenile dermatomyositis (JDM) is 0.4/100,000. Childhood polyarteritis nodosa (PAN) is the fourth most common childhood vasculitis and ocular involvement is not uncommon. Granulomatous polyangitis (GPA), Behçet disease, and microscopic polyangiitis (MPA) are very rare – each less than 0.1/100,000.

Takayasu disease (TAK) and Kawasaki (KAW) disease are more common in Asians and Orientals. In Japan, the incidence of KAW in children under 5 years of age is 110/100,000; in the UK it is about a hundred times less frequent.

Clinical types of uveitis

Idiopathic uveitis

Classification is based on the site and course of inflammation: unilateral or bilateral, acute or chronic, painful or painless, and redness present or not (Fig. 40.3). Chronic unilateral uveitis suggests an infective cause but should not preclude a search for systemic disease. Twenty percent of JIA-uveitis remains unilateral.

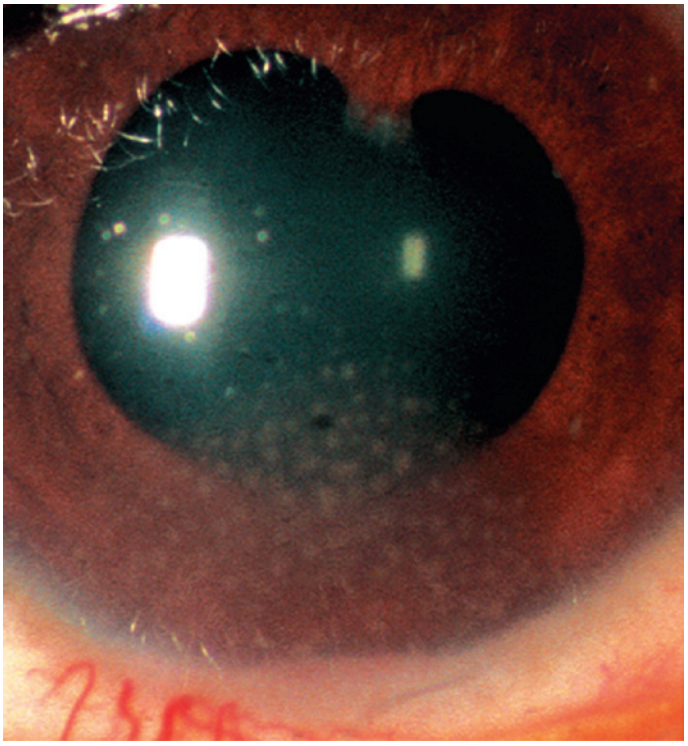


Fig. 40.3 Idiopathic chronic anterior uveitis with granulomatous keratic precipitates and limbal inflammation.

Although "acute" and "chronic-onset" are classifying terms, they rely on a history and are less helpful classifying terms in children. It is more practical to introduce a distinction between red and painful eyes at presentation.

Painful anterior uveitis

Unilateral, painful, acute anterior uveitis (AU) is most frequently associated with HLA-B27-related diseases. They present in later childhood and rarely before 6 years of age; an infective or posterior segment cause is likely in this age group. Bilateral painful AU is the most frequent uveitis type following infection or severe systemic inflammation and is a common pattern of uveitis in otherwise healthy 7- to 14-year-olds where it can persist for a couple of years. This pattern is common in TINU and sarcoid. Complications, other than ocular hypertension, are uncommon in chronic painful AU despite the length of disease when compared to the painless CAU of JIA.

Painless anterior uveitis

Chronic painless AU without systemic disease is common in young children. The arthritis of JIA may develop up to 7 years after the onset of painless CAU (Fig. 40.4). Investigation of renal function for TINU syndrome, sarcoidosis, and possible immunodeficiency is also indicated in this type. Skin rashes are a common manifestation of sarcoid, Blau early-onset sarcoidosis syndrome, and CINCA. Rashes in these conditions are frequently misdiagnosed or ignored prior to the definitive diagnosis: they are easy to biopsy. Fuchs heterochromic cyclitis is very rare.

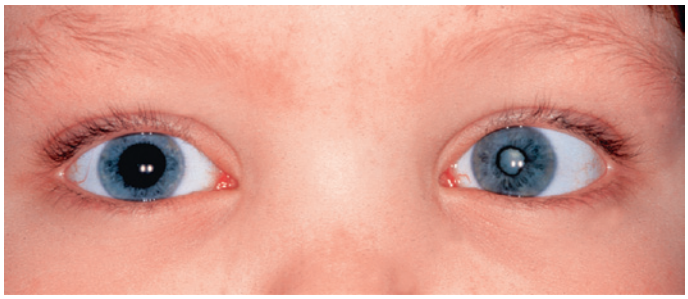


Fig. 40.4 Idiopathic chronic anterior uveitis in white eyes presenting with left cataract in a 4-year-old. Juvenile idiopathic arthritis developed 7 years later.

Intermediate uveitis

This refers to vitritis with a variable-level retinal inflammation and minimal anterior segment inflammation (see Table 40.2). The peak age of onset is 9–13 years.[8–11] Children present late compared to adults, and there may be extensive retinal complications. Children are less likely to develop macular edema but it is more difficult to resolve. Optic disc edema with chronic vitritis is more common than in adults. Peripheral vascular abnormalities are difficult to detect and may only be suspected when they cause hemorrhage. Neovascularization of the optic disc and retina may be caused solely by inflammation and can subside with immunosuppression.

Changing signs in the inferior fundus are useful to monitor disease progression as the level of vitritis is difficult to monitor in children and visual acuity may be maintained despite progressive extramacular damage. Sarcoidosis produces aggregates of white cells in the inferior vitreous ("snowballs") rather than pars planitis ("snow bank"), and multifocal choroiditis is characteristic. IU associated with MS rarely produces significant vitreous opacities. Focal retinal pigment epithelial scars can develop inferiorly at sites of previous retinal inflammation and do not necessarily indicate the development of choroiditis. Retinal vascular leakage and periphlebitis may be marked in acute IU but are not diagnostic of any specific cause.

Posterior uveitis, panuveitis, and multifocal choroiditis

Unifocal, unilateral choroiditis suggests infection such as toxoplasmosis. Multifocal, bilateral disease suggests systemic disease or a white spot syndrome. Both are rare in childhood. Many children with multifocal choroiditis (MFC) and vitritis resemble sarcoidosis or Blau syndrome, with no evidence of extraocular disease. In some children, the patches of choroiditis and retinal pigment epithelium (RPE) atrophy are small and limited to the inferior fundus. A similar human leukocyte antigen (HLA) profile to that found in TINU has been reported in these cases.[12,13] Some infections such as brucellosis, borreliosis, and varicella may also mimic sarcoid choroiditis. Multifocal choroiditis and panuveitis rarely occur in childhood. They can be complicated by severe visual loss from secondary choroidal neovascularization and warrant aggressive control of inflammation (Fig. 40.5). If the fundus cannot be seen in children with AU it must be assumed they have panuveitis. Ultrasound may disclose scleritis, focal infection, or tumor.

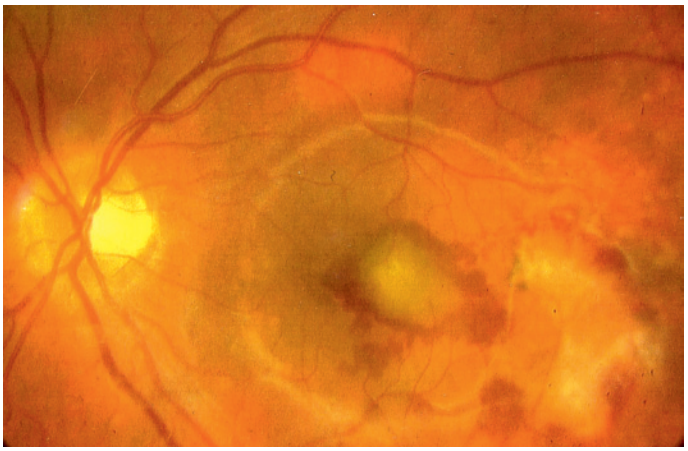


Fig. 40.5 Idiopathic panuveitis and multifocal choroiditis complicated by cataract, glaucoma, and choroidal neovascular membranes.

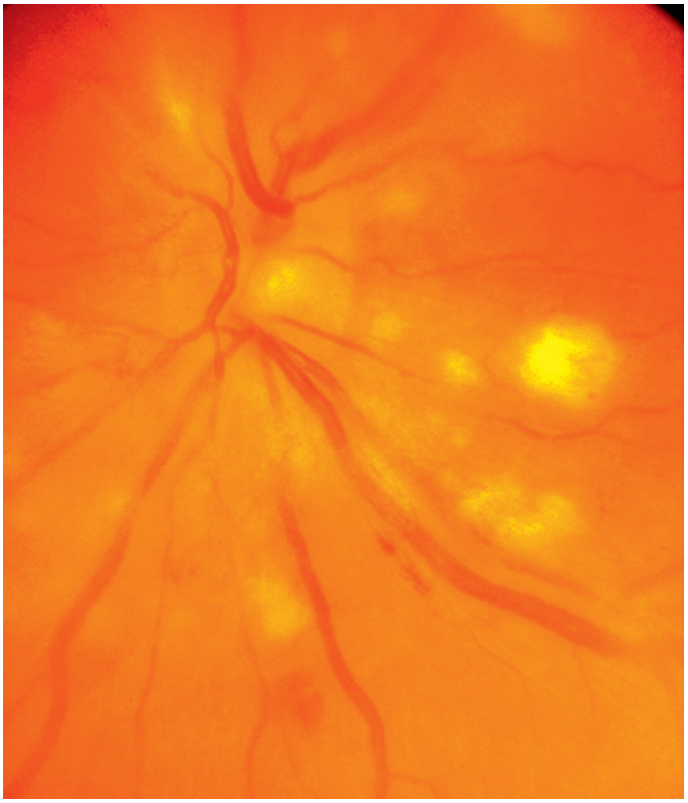


Fig. 40.6 Postviral retinitis with multiple retinal infiltrates and normal acuity.

Retinitis

Focal infiltrates of the inner retina with little overlying vitritis are typical of acute viral infections (Fig. 40.6). They are more discrete and persistent and yellower than cotton-wool spots. Retinal infiltrates in Behçet disease are accompanied by signs of retinal vasculitis.

Frosted branch angiitis

This is a hyperacute extravasation of multiple retinal vessels that may be post-infectious, but can also be the presenting

signs of small vessel vasculitis such as Behçets disease.[14] It may be accompanied by hemorrhage and does not always resolve benignly.[15]

Neuroretinitis

In neuroretinitis, swelling of the neuroretina, maximal at the optic disc, is out of proportion to signs of posterior segment inflammation. Exudates around the fovea form a macular star. Children are more likely to develop edema in response to infections that trigger optic neuritis and neuroretinitis. Cat-scratch disease typically involves the posterior segment in this manner.

Specific uveitis syndromes

Post-traumatic uveitis

Trauma may provoke an autoimmune response to ocular antigens. Children are as prone as adults to these rare conditions.

Sympathetic ophthalmia

There is a bilateral chronic panuveitis with peripheral multifocal choroiditis with many clinical and histologic similarities to VKH and sarcoidosis.[16] Vitritis may be severe. It follows unilateral penetrating trauma, cycloablation, or intraocular surgery. It may co-exist with lens-induced uveitis.

Lens-induced uveitis

This is a granulomatous panuveitis that may occur hours to months after the release of lens material and can complicate severe uveitis from other causes.

Parainfectious uveitis

Childhood is a time when community-acquired pathogens are first encountered and transient ocular inflammation may result. Varicella and streptococcal infections are frequent causes of reactive uveitis. Reported associations may be coincidental and identification of intraocular viruses in specific uveitis types remains rare.[17] Clusters of severe acute panuveitis in children have been reported from Tanzania and Nepal; in the former, the incidence was 540/100,000 in children under 9 years of age. There are no reports of epidemic outbreaks of post-streptococcal uveitis: the causal association between streptococcal infection and uveitis remains weak.

Acute AU can follow varicella, but mild retinal vasculitis, a self-limiting retinitis, and MFC can occur, usually within 4 weeks (see Fig. 40.6). Chronic inflammation and progressive retinitis is an absolute indication for antiviral treatment, but not usually necessary for AAU.

Enteric infections triggering reactive arthritis may cause a reactive uveitis: HLA-B27 positivity is a risk factor. Reactive arthritis with urethritis and uveitis and/or keratitis is very rare but does occur in children.

Localized autoinflammatory diseases: juvenile idiopathic arthritis

JIA describes chronic joint inflammation starting before 16 years of age and lasting more than 6 weeks. Early-onset rheumatoid arthritis, vasculitides, and ERA are rare causes of arthritis under the age of 7 years. A family history of psoriasis and HLA-B27-associated disease are used in the classification of JIA, but not the presence of uveitis.

Box 40.4

Levels of risk in juvenile idiopathic arthritis-associated uveitis, evidence based where possible

1. Baseline risk factors
2. Male gender, non-Caucasian ethnicity, antinuclear antibody positive, complications at presentation
3. Additional levels of risk
   a. No risk: no cells, flare, steroid treatment, or ocular hypertension
   b. Possible risk: any topical steroid treatment, any anterior chamber (AC) cells, persistent activity >3 months
   c. Probable risk: topical steroids more than once daily, persistent AC cells >1+, persistent activity >3 years
   d. Higher risk, one of: topical steroids more than once daily for several months, AC cells >1+, for more than 3 months, any activity >6 years, transient flare, any episode of macular or disc edema
   e. Definite increased risk, any of: continuous topical steroids more than three times daily, persistent AC cells >2+, persistent flare, previous surgery, multiple episodes of macular and disc edema
   f. Extreme risk: multiple risk factors

Epidemiology

The incidence of JIA is 10/100,000 children. Half of these have oligoarticular or polyarticular subtypes. The incidence of JIA-uveitis is 1/100,000, almost entirely in younger patients with these subtypes. Oligoarticular JIA is defined by the involvement of less than five joints at the onset of disease. If more joints become involved later, it is named *extended* oligoarticular JIA. If more than five joints are involved at onset, it is classified as *polyarticular*. The cut-off is artificial, and age at onset of arthritis and antinuclear antibody (ANA) status are as important as the number of joints in defining JIA phenotypes. ANA status and specific age at onset of arthritis are not used in the classification but are major independent risk factors for uveitis.

There are genetic similarities between oligoarticular and polyarticular JIA in the youngest groups. Older children with ANA-negative polyarticular JIA may have a distinct pattern of arthritis and be at a much lower risk of CAU. JIA is found in all races; JIA-uveitis may be more common in Caucasians (Box 40.4).

Several genes are associated with different clinical types of JIA. Oligoarticular-onset JIA is associated with HLA genes common to polyarticular JIA (DRB1*08), psoriatic arthropathy (DRB1*1301), and systemic onset JIA (DRB1*11), as well as unique associations such as DPB1*02. Uveitis is associated with the DRB1*13 haplotype, which is most frequently found in oligoarticular JIA, and DPB1*02. ERA and early-onset rheumatoid arthritis are clinically and genetically distinct from the types of JIA associated with CAU.

Uveitis is primarily associated with oligoarticular JIA, ANA-positivity, and JIA of early onset (less than 6 years); the highest risk groups may have a frequency of uveitis of over 50%. The risk of uveitis is minimal in those whose arthritis starts

after 13 years of age, and the upper age limit for developing uveitis may be earlier in those with polyarticular ANA-negative JIA. ANA status does not change the risk sufficiently to alter screening policy; it is not clear yet whether female gender is an independent risk for developing uveitis.[18]

In those developing uveitis, arthritis typically starts at a mean of 28 months and uveitis 13 months later: 86% have oligoarticular JIA, 75% are female, and 80% are ANA-positive.

Investigation of CAU with arthritis

All children with chronic painless AU require screening for asymptomatic arthritis as well as for other relevant signs of systemic disease. Routine laboratory testing in CAU can be limited to white count, serum angiotensin-converting enzyme (sACE), ANA, immunoglobulins, antistreptolysin (ASO) titers, electrolytes, and C-reactive protein. Other autoantibodies, such as double-stranded DNA, anticardiolipin, and perinuclear antineutrophil cytoplasmic, as well as raised ASO titers, may occur in JIA. Raised sACE, immunoglobulins, and a lymphopenia suggest sarcoid, which may present with arthritis indistinguishable from JIA but have low specificity, and the relevant secondary investigations need to be guided by relevant specialists.

Other JIA types

Systemic-onset JIA involves the eye in only 1–2% of cases; the uveitis usually occurs within months of presentation of extraocular disease.

Psoriasis is associated with ERA, IBD, and Behçet disease. It may also be an independent risk factor for uveitis. Psoriasis present in a family member changes the rheumatologic classification, but the accompanying arthritis may be indistinguishable from oligoarticular JIA; some patients with a personal and/or family history of psoriasis have a distinctive pattern of arthritis – *psoriatic arthritis* with dactylitis and nail changes. Eight percent of children with psoriatic arthritis develop uveitis. The presence of psoriasis with JIA does not alter the need for uveitis screening. Psoriasis may develop years after the onset of JIA and uveitis.

Childhood-onset ERA presents with peripheral arthritis and enthesitis (inflammation of the bony attachments of tendons or ligaments), rather than the sacroiliitis seen in adults. In younger children, the arthritis of ERA may be indistinguishable from oligo/polyarticular JIA and patients need to be screened routinely for uveitis until a definite clinical diagnosis of ERA. A family history of ERA is highly suggestive of the diagnosis but also does not preclude the need for uveitis screening in younger children. The usual form of uveitis is AAU, as in adults, and screening has no role once this has developed. AAU with definite ERA is rare before the age of 10 years.

Early-onset rheumatoid arthritis starts around the age of 11 years and is not associated with uveitis. The presence of a positive rheumatoid factor in children with JIA does not equate to a diagnosis of juvenile rheumatoid arthritis; it should not alter screening in oligo/polyarticular JIA.

IBD and IBD-related arthropathy may also be associated with uveitis. Patients may develop arthritis first and diagnosed with JIA and later develop IBD. Uveitis associated with IBD may be CAU-like JIA but these patients may also suffer AAU, scleritis, and retinal vasculitis.

Screening

The period of risk of developing uveitis largely depends on the age at onset of the arthritis. Those developing arthritis below the age of 3 years remain at risk for 7 years. Those developing arthritis after the age of 6 years are at risk for 3 years. In those regularly screened, the development of uveitis after the age of 13 years is rare. The optimal screening interval is not known. There seems little value in screening at intervals of more than 3 months if the primary purpose is to reduce the risk of structural changes at diagnosis, although this is widely recommended for low-risk subgroups. The UK screening program (2006) can be found at http://www.bspar.org.uk/pages/clinical_guidelines.asp.

Screening involves the exclusion of anterior chamber cells and keratic precipitates by a slit-lamp examination. Younger children require experienced ophthalmologists to perform the initial checks; frequent checks may be needed at the onset until the child is happy to cooperate. When patients are old enough to cooperate, monitoring can be devolved to less specialist practitioners. The age at which this is possible depends on each individual child and local facilities.

Physicians should be encouraged to refer patients for screening as soon as the diagnosis of JIA is being considered and not wait until a definitive diagnosis is made: the speed of the initial screen is the single most important manageable risk factor of subsequent visual loss.

Monitoring

Subclinical and clinical uveitis may develop while on systemic arthritis treatment; uveitis may recur vigorously when systemic immunosuppression is reduced abruptly, and patients should be checked within a few weeks of dose reductions. As systemic treatment for arthritis may also completely suppress uveitis, stopping it may result in uveitis presenting clinically for the first time. Patients in remission and off all treatment may relapse, and monitoring needs to continue for 3 years. Patients on long-term immunosuppression for systemic disease may develop uveitis well beyond the established risk period.

Clinical signs

The course of uveitis has a wide range of aggressiveness, severity, and chronicity (see Table 40.2). Late presentation has a profound effect on the severity and risk of long-term complications. Mild disease is a painless CAU; severe disease may cause a painful AU and IU. A red eye occurring at each relapse, hypopyon, or scleritis in the absence of uveitis, may occur after years of painless CAU. It is not clear whether the patient's age or the longstanding inflammation and treatment alter the pattern of inflammation.

Minimal disease may produce "dusting" of the corneal endothelium only. A severe cellular reaction with 4+ cells, hypopyon, or fibrin is unusual. Band keratopathy accompanying even mild uveitis is characteristic, but not universal. Progression of keratopathy on treatment indicates aggressive disease (Figs 40.7–40.9).

Persistent flare, iris hyperemia, which may be mistaken for rubeosis, and a persistent intraocular pressure (IOP) less than 10 mmHg are signs of severe disease, and may be reversible if treated aggressively. Fibrovascular sheets may cover the pupil and impede a view of the posterior segment despite a clear

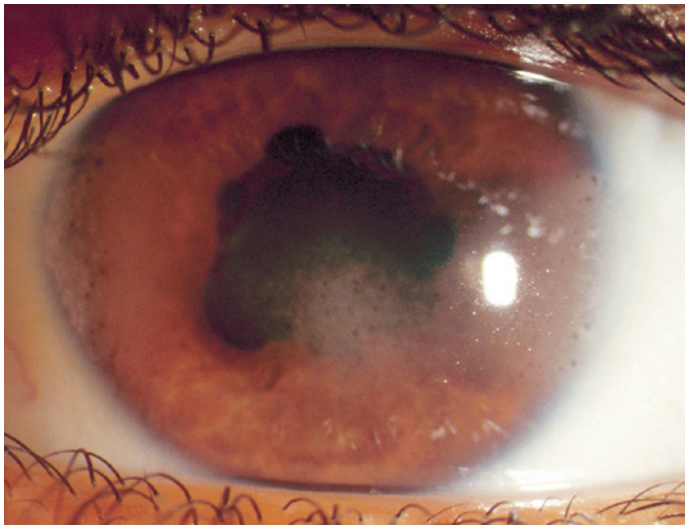


Fig. 40.7 Mild paracentral band keratopathy not affecting acuity.

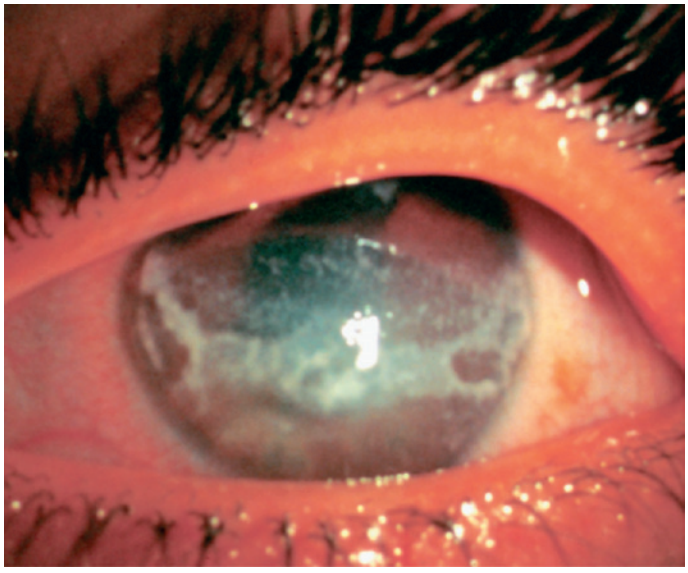


Fig. 40.8 Severe progressive band keratopathy.

lens. Iris bombé is not uncommon. Sometimes posterior synechiae are not obvious without mydriasis if they occur in mid-iris and are not present at the pupil margin.

Anterior chamber (AC) cells rarely "spill over" into the vitreous in significant numbers as with adult AAU, but a dense vitreous haze with fibrin clumps that takes several weeks of systemic steroids to clear, may occur in untreated disease.

Aphakic patients on treatment may experience relapses that largely consist of worsening macular edema, vitreous haze, and low IOP with little accompanying increase in anterior chamber or vitreous cells. Macular edema can be more extensive than in adult uveitis. Disc edema can be profound and persistent, and mimic papilledema. Increased inflammation is associated with reduced IOP. Permanent ciliary body damage is associated with reduced IOP and secondary hypotonous maculopathy – this usually requires an IOP chronically less than 5 mmHg. Only a treatment trial can determine if low IOP is irreversible, or if edema is due to inflammation or hypotony. Hypotony and

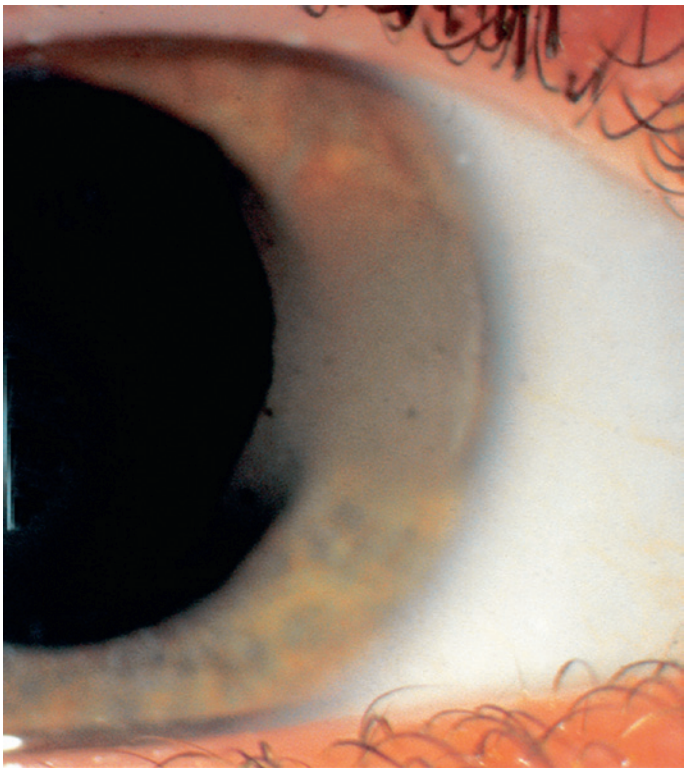


Fig. 40.9 Clear central cornea following excimer laser removal of band keratopathy.

inflammation also accompany retinal detachment, which may be difficult to diagnose if inferior in a poorly visible fundus.

Patients require screening for glaucoma. To reduce the need for examination under anesthetic, children need to be trained to accept tonometry as soon as feasible; rebound tonometry has proved very useful for younger children. Baseline disc appearances and changes must be documented at the initial visit and subsequent changes documented. There should be a low threshold for examination under anesthesia in newly diagnosed cases where IOP measurement is difficult, as inflammatory glaucoma can progress rapidly. Large fluctuations in IOP are typical and disc damage may occur during periods of unrecorded high IOPs and only noted when the IOP has normalized some weeks later.

Course

Patients may take several weeks to develop irreversible complications, even with aggressive disease: the inflammation changes slowly compared to other forms of uveitis. Posterior synechiae are usually the first to develop. Relapses are usually unaccompanied by redness or pain.

The majority of those entering life-long remission will have done so within 7 years of disease onset, but even with contemporary treatment only 30–40% will obtain long-term, complication-free remission. Some patients may develop increasingly severe disease 3 or 4 years after a mild onset. Exacerbations in late teenage years are common in those with longstanding disease; both poor compliance and weakening treatment efficacy may play a role.[19]

The risk and nature of complications change through the course of the disease and the benefits of treatment regimens may alter over time. This is especially true when steroid

treatment is used and where complete remission has not been achieved. Twenty-five percent of complications occur more than 10 years after disease onset in those who have not achieved a significant period of complete remission. The risks of new severe visual loss continue for more than 15 years after disease onset.

Indications for treatment

With such a wide range of outcomes it is important to match treatment risks and costs to the risk of patient-centered quality outcomes such as functional visual loss, surgical interventions, and frequent hospital attendance.[20]

Complete remission is the aim of treatment since it halts the onset of new inflammatory complications. Prolonged periods of low activity may precede complete remission. The threshold of AC activity beyond which complications develop is not clearly defined. Isolated AC cell counts may have limited value as a prognostic indicator. Cataracts form at similar rates in those with a trace of AC cells and those with 2+ cells. AC cell counts are of less importance than AC flare in increasing risk of complications. The presence of activity is more significant than the level of activity. Patients who achieve more than 6 months remission in the first 2 years of disease are highly likely to enter long-term remission. Cataract surgery further increases the risk of additional sight-threatening complications. The reduction of cataract risk should be a secondary aim of treatment. There is a wide range of reported outcomes; incidence of blindness ranges from zero to 25% over 3 years.[21,22]

Without clear descriptions of the risks of patient populations at referral, it is not possible to infer any regional differences in outcome. The range of outcomes is probably due to differences in screening efficacy and referral speed to specialist centers rather than differences in prescribing patterns. More aggressive and earlier therapy of arthritis by rheumatologists and improved glaucoma surgical techniques likely account for the improved outcomes of the past few decades.

Prognostic factors

Structural damage at presentation is the greatest risk factor associated with subsequent visual loss. Complications are more likely in males, non-Caucasians, and those with episodes of macular edema, hypotony, or frequent relapses.

The range of risk is great: females with no complications at diagnosis may have an 80% chance of complete, complication-free remission within 15 years. Males with cataract at presentation may have 50% risk of blindness over 15 years.

Glaucoma

Glaucoma occurs in 10–20% in recent studies, less than earlier reports[23]; the SITE (Systemic Immunosuppressive Therapy for Eye Diseases) study of US referral patients has an incidence of ocular hypertension of 19% per patient year.[21] Steroid-induced ocular hypertension (OHT) and aphakia are major risk factors; inflammatory glaucoma may contribute and usually develops after 2 or 3 years of CAU, not at presentation. Steroid-induced OHT is expected in 5% and is usually evident within a few months. Angle closure glaucoma can occur if the early presentation was complicated by iris bombé but is rarely the sole cause in late-developing glaucoma. The cause of IOP changes is usually complex in severely damaged eyes, as outflow obstruction may be combined with severe ciliary body damage with aqueous hyposecretion.

Hypotony

Childhood CAU has the highest risk of hypotony of all uveitis types.[24] The ciliary body is the initial site of inflammation in JIA-uveitis. Cyclitis causes aqueous hyposecretion and, eventually, atrophy. A vigorous treatment trial with systemic steroids is required to establish whether subnormal IOP is reversible. The IOP at which hypotonous maculopathy or progression to phthisis occur is not clear; a pressure of 5 mmHg is the conventional definition of hypotony. Secondary hypotony from ciliary body detachment, cyclitic membranes, or retinal detachment need to be distinguished from that due to ciliary body atrophy by appropriate examination. As ciliary membranes usually co-exist with ciliary atrophy, it is not clear whether their removal can help reduce the risk of phthisis.

Other localized autoinflammatory diseases

Behçet disease

Systemic features

Recurrent, painful, oropharyngeal and genital ulceration with uveitis are major criteria for the diagnosis. Ulceration may precede the full expression of disease by 2 years. Mild symptoms such as arthralgia, erythema nodosum, gastrointestinal inflammation, and ulceration are non-specific. Acne, folliculitis, epididymitis, and intestinal ulcers are more specific. Spondylitis may occur in one-third of cases.

Diagnosis is clinical. The disease is characterized by episodic severe localized inflammation and there is a strong association with HLA-B51; genetic variations in interleukin (IL)-10 and IL-23 pathways may contribute. Anti-tumor necrosis factor alpha (TNF-α), anti-IL-1, and interferon alpha2 (IFN-α2) biologics have been used where conventional immunosuppressants have not led to disease control.

Vascular thrombosis and CNS disease are the major causes of morbidity. Thrombosis is more common in veins than in arteries. CNS inflammation can be primary, with demyelination, or secondary to thrombosis. Basal ganglia and brainstem are most commonly involved, but there may be a diffuse, acute meningoencephalitis with behavioral changes.

Children may have milder disease and more delay to the complete syndrome: arthritis may be more common and ulceration less common. Neonatal onset has been reported. Childhood neuro-Behçet disease has a mean onset at 11 years of age.[25]

Ocular features

There is a panuveitis with explosive relapses, hypopyon, and sudden small and large retinal vein occlusion with white patches of retinitis. Retinal arteries may be involved; macular edema occurs in a minority. Retinal ischemia frequently leads to neovascularization.

A non-granulomatous CAU may occur, but chronic IU is unusual. Conjunctivitis, episcleritis, or scleritis may occur. Choroidal involvement is rare. The optic nerve may be involved with an inflammatory optic neuropathy, papilledema

from CNS involvement, particularly sinus venous thrombosis. Secondary optic atrophy is common. The natural course of retinal vasculitis and ischemia leads to a high risk of bilateral blindness and a quarter of eyes may eventually lose vision despite immunosuppression.

Sarcoidosis

Systemic features

This chronic granulomatous inflammation can affect any part of the body. Histologically, non-caseating epithelioid cell granulomas are seen, with an accumulation of CD4+ T-lymphocytes. The adult form involves the lung in 90% of cases and is the predominant type after the age of 12. In two-thirds of patients, the disease remits, usually within 2 years, the majority requiring no treatment.[26]

Childhood sarcoidosis rarely involves the lung.[27] Skin, joint, and eye involvement are common; the arthritis can mimic JIA. Biopsy is essential for definitive diagnosis. Skin, synovium, and liver are good sites. Joints can develop tenosynovial hypertrophy with little pain or restriction in the early stages. A delayed diagnosis is common. Skin involvement consists of a follicular or nodular rash. Renal involvement is not uncommon with interstitial nephritis and nephrocalcinosis. Most childhood sarcoid arthritis cases have uveitis. Serum ACE levels are elevated in only one-third of cases and gallium-67 scanning and other imaging may be needed to detect nodal and visceral disease. Meningoencephalitis, which may present with seizures, is more common in childhood sarcoidosis and in those with posterior segment inflammation. Childhood sarcoidosis is more common in Caucasians. Familial sarcoidosis occurs in 4%, and this is distinct from Blau syndrome.

Ocular features

Anterior uveitis may start with pain and redness and become chronic and painless. Iris and angle granulomas may distinguish the CAU from JIA-uveitis; band keratopathy is less common and inflammatory ocular hypertension more common than other types of CAU. Sarcoid may involve the lid margins and cornea more frequently in childhood (Fig. 40.10).

Sarcoid rarely causes chronic IU without other features. Panuveitis can develop with MFC that may be very widespread (Fig. 40.11). Visual loss may result from choroidal neovascularization. Optic disc swelling is frequent, caused by a granulomatous optic neuropathy, raised intracranial pressure, or secondary to uveitis. There may be a necrotizing vasculitis. Unilateral posterior segment or optic nerve disease may occur.

As young children with sarcoid may present with uveitis, disease may be very advanced at presentation. Uveitis frequently requires more prolonged and intensive immunosuppression than extraocular sarcoid to obtain clinical remission.

Inflammatory bowel disease

Crohn disease and ulcerative colitis are associated with ocular inflammation. Both may present with a mild arthritis in childhood, IBD arthropathy, which may be initially misdiagnosed as JIA (see Fig. 40.10).

AAU and episcleritis are the most frequent presentations: rarely, there may be a severe retinal vasculitis or acute hypopyon.

Vogt–Koyanagi–Harada syndrome

Systemic features

There is an acute-onset meningoencephalitis with headache, vitiligo, poliosis, tinnitus, and dysacusia. Stroke may result.[28] The skin may be painful to touch in the acute phase. Childhood cases often present with panuveitis with later vitiligo.

Ocular features

There is a painful, bilateral panuveitis with granulomatous anterior uveitis. Ciliary body edema may result in shallowing of the anterior chamber and increasing or lowering of the IOP. Scleral perforation may occur. Serous retinal detachments occur,

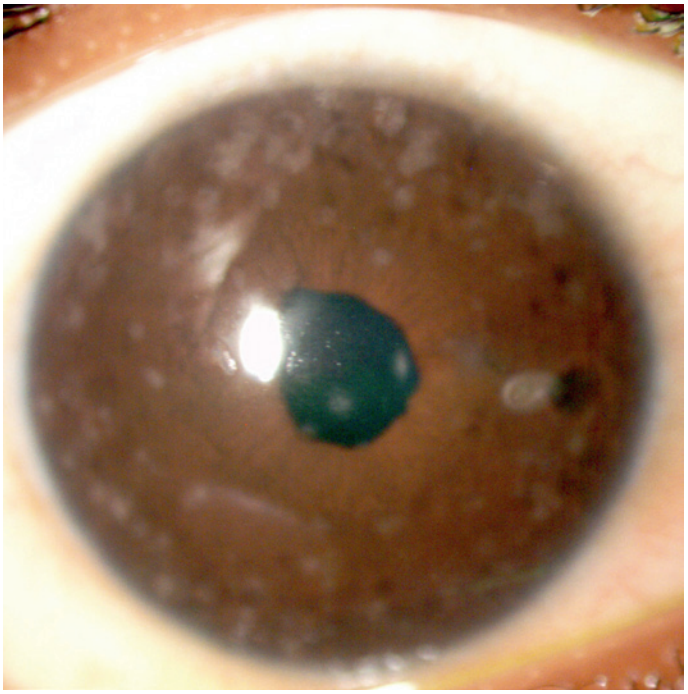


Fig. 40.10 Sarcoid multifocal keratitis.



Fig. 40.11 Sarcoid multifocal choroiditis.

especially inferiorly. Disc edema and peripheral choroiditis are frequent and angiography may demonstrate widespread pinpoint sites of RPE leakage. After repeated inflammation, depigmentation of the RPE and choroid lead to a "sunset glow fundus."

Children are more likely to have worse outcomes; 61% of eyes lose sight compared to 26% in adults.

Tubulointerstitial nephritis and uveitis syndrome

Systemic features

Acute tubulointerstitial nephritis and uveitis (TINU) occur within a few weeks of each other. Screening renal function in newly presenting pediatric uveitis is essential.[29] The commonest symptoms are fever, malaise, and weight loss; one-third have signs of ocular inflammation. Twenty percent present with uveitis up to 2 months before renal involvement. The median age of onset is 15 years; the youngest reported is 9 years. Renal disease consists of an eosinophilic and mononuclear infiltrate, but granulomas can also be found in the lymph nodes and marrow.

Interstitial nephritis is a sign, not a diagnosis, and occurs in other conditions associated with uveitis such as sarcoidosis, Behçet disease, Sjögren syndrome, and postviral syndromes. Uveitis has also been reported with immunoglobulin (Ig)A nephropathy.

Ocular features

There is a painful CAU; there may be granulomatous features.[30–32] Posterior involvement occurs in one-fifth with retinal periphlebitis, hemorrhages, disc edema, and multifocal choroiditis. The mean duration is 2 years and visual outcome is usually good.

Uveitis and non-vasculitic neurological disease

Multiple sclerosis

This is rare in childhood. It can occasionally present with uveitis, usually a mild IU.

Rasmussen syndrome

This is a chronic, unilateral encephalitis associated with an ipsilateral chronic uveitis that may present in childhood. It has been associated with cytomegalovirus infection.[33,34]

Systemic autoinflammatory disorders and familial granulomatous diseases

Several familial disorders present with periodic fevers, urticarial rashes, and joint and ocular inflammation. The most frequent are cryopyrin gene mutations.[35]

Blau syndrome and familial sarcoidosis may present in childhood with fevers, rashes, joint, and eye involvement. Single-gene disorders of inflammation, like some vasculitides, may be associated with very localized disease.

Cryopyrin-associated periodic fever syndromes

These immune disorders have a prevalence of 3 per million. Mutations of the *NLRP3* gene lead to uncontrolled activation of inflammasomes, multimolecular intracellular complexes composed of cryopyrin, leading to increased production of active IL-1β, IL-18, and IFN-γ. There are three clinical groups: familial cold autoinflammatory syndrome (FCA), Muckle–Wells syndrome (MWS), and CINCA.

Severity ranges from transient rashes and fevers to persistent inflammation with renal amyloidosis, deafness, chronic uveitis, and arthropathy. Forty percent of CINCA patients do not have a recognized genetic abnormality; some may be mosaics. There are overlap syndromes within the three groups.

Familial Mediterranean fever is rarely accompanied by uveitis.[12,36]

CINCA syndrome

Systemic

A neonatal urticarial rash occurs on the trunk and limbs as well as a large joint arthritis with endochondral ossification. Chronic meningoencephalitis can lead to developmental delay and papilledema. There is frequent sensorineural deafness from cochlear inflammation. Renal failure may result from amyloidosis. CINCA commonly arises from *de novo* mutations with a severe phenotype whereas milder syndromes are usually familial. Anti-IL-1 biologics are used.[37,38]

Ocular

The chronic meningitis is associated with a cellular cerebrospinal fluid (CSF) and raised intracranial pressure, with chronic disc swelling and optic atrophy. A mild CAU develops around 7 years of age without synechiae formation or redness; band keratopathy may occur.

Familial granulomatous disease

Blau syndrome (familial) and early-onset sarcoidosis (sporadic) are sometimes grouped as "pediatric granulomatous arthritis."

The gene *CARD15* encodes the NOD2 receptor; mutations may lead to inappropriate inflammation in response to bacterial peptidoglycan and result in IL-1 overproduction. The *CARD15* mutations associated with Blau syndrome are separate to those associated with Crohn disease. The type of mutation may influence the severity of ocular involvement in Blau syndrome. Other *CARD15* mutations may be associated with early-onset sarcoidosis and psoriatic arthritis.

Systemic features

Blau syndrome is a familial, early-onset granulomatous disorder; it resembles childhood sarcoidosis.[39–41] There is a transient punctate erythematous rash in the first year evolving into a scaly ichthyosiform rash. The arthritis is a polyarticular granulomatous tenosynovitis, with mean onset at 2 years and commonly involves wrists and fingers. There are also dysplastic joint changes including giant synovial cysts and camptodactyly. Hepatic and renal involvement may occur but not the lung. A vasculopathy may develop involving small and large vessel.[42] There is earlier onset in successive generations and incomplete forms may occur. The genetic mutation may not be clinically expressed. One-third are sporadic cases.

Ocular features

Uveitis occurs in 80%, usually within 2 years of the arthritis at 4 years of age; the youngest recorded is 18 months.[40] A JIA-like

CAU with band keratopathy is the most frequent presentation. Subepithelial corneal opacities and peripapillary atrophy have been reported to be diagnostic but also occur in sarcoidosis. Later IU occurs in 64%; MFC in 18%. The vasculopathy may affect the optic nerve, retina, and cranial nerves. The disease can be severe: half require immunosuppression and 14% develop severe visual loss.[39] Anti IL-1 therapy has been used in addition to conventional immunosuppression.

Other granulomatous diseases include sporadic sarcoidosis, Crohn disease, vasculitides (giant cell arteritis [GCA], Takayasu's arteritis [TAK], granulomatous polyarteritis [GPA], primary angiitis of the CNS (PACNS), cancer-associated chronic granulomatous disease (CGD) and secondary to anti-TNF therapy. Granulomatous infection such as tuberculosis must always be considered in the differential diagnosis.

Vasculitides

Vasculitis is uncommon in childhood and ocular involvement is rare. They can be life-threatening diseases that present with ophthalmic signs and sight-threatening disease. Their treatment may require prolonged immunosuppression, which may result in drug-associated ocular complications (e.g. hydroxychloroquine and steroids) and an increased risk of infection. Some infections may predispose to vasculitis such as streptoccocal and hepatitis B infections. Some congenital immunodeficiencies such as CGD and Blau syndrome may predispose to vasculitis.

Classification

Primary vasculitides are classified by the size of the vessel involved and clinical presentation; there are variable vessels involved and variable presentations in most syndromes.[43] Vasculitic syndromes may be limited in extent but otherwise have identical pathology to more widespread presentations such as orbital GPA. Some conditions are associated with highly specific autoantibodies and their testing methods continually develop (Table 40.3).

Secondary vasculitides may occur with connective tissue disorders, autoinflammatory diseases, and immunodeficiencies. Retinal vasculitis is not included in contemporary systemic vasculitis classifications and mostly describes conditions with secondary vasculitis or variable vessel vasculitis such as Behçet disease, sarcoidosis, and inflammatory bowel disease.[44]

Chronic vasculitis may result in secondary aneurysm formation, e.g. polyarteritis nodosa (PAN), luminal obliteration from endothelial cell proliferation, and secondary thromboembolism seen in antiphospholipid syndrome and Sneddon disease.[45] Small arteriolar occlusion may be transient in inflammatory conditions such as Susac syndrome[46] and in genetic endotheliopathies such as MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes).

As fluorescein angiography and reliable static perimetry is often not possible in small children, previous vascular occlusions may only be detected by signs of focal retinal thinning on optical coherence tomography.

Ocular involvement in vasculitis

There are few diagnostic ocular signs as the pathologic processes may be common to different vasculitis syndromes.

Table 40.3 Classification of vasculitides and diagnostic autoantibodies

Antibody class	Antibodies	Disease	Type of vasculitis
		TAK	Large
		GCA	Large
ANCA	pANCA-MPO rare	PAN	Medium
		KAW	Medium
	C1q	HUV	Small-immune complex
	GBM	anti-GBM	Small-immune complex
		CV	Small-immune complex
		IgA-HSP	Small-immune complex
ANCA	cANCA PR3	GPA	Small-ANCA associated
ANCA	pANCA	EGPA	Small-ANCA associated
ANCA	pANCA-MPO	MPA	Small-ANCA associated
		CS	Variable
		BD	Variable
		PCNSV	Single organ
		Ocular	Single organ
	ACA	APL	With systemic disease
ENA	RF	RA	With systemic disease
ENA	RNP	MCTD	With systemic disease
ENA	Scl-70	Scleroderma	With systemic disease
ENA	Sm	SLE	With systemic disease
ENA	SS-A, Ro and SS-B, La	Sjögrens	With systemic disease
		Sneddon	With systemic disease
		Susac	With systemic disease
		Sarcoid	With systemic disease
		Relapsing polychondritis	With systemic disease
		HVZ vasculitis	With probable etiology

APL, antiphospholipid syndrome; BD, Behçet disease; CS, Cogan syndrome; CV, cutaneous vasculitis; EGPA, eosinophilic granulomatosis with polyangiitis; GBM, glomerular basement membrane; GCA, giant cell arteritis; GPA, granulomatous polyangiitis; HUV, hypocomplementemic urticarial vasculitis; HVZ, herpes varicella zoster; IgA-HSP, IgA vasculitis/Henoch–Shönlein purpura; KAW, Kawasaki disease; MCTD, mixed connective tissue disease; MPA, microscopic polyangiitis; PAN, polyarteritis nodosa; PCNSV, primary central nervous system vasculitis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TAK, Takayasu disease.

Vasculitis occurs in 2% of adults with uveitis and is usually a monoepisodic or recurrent AAU. In adults, prolonged uveitis accompanying vasculitis is most uncommon: ocular involvement secondary to vasculitis is usually an inflammatory or ischemic optic neuropathy, sclerokeratitis, or orbital inflammation.

An acute red eye in children with vasculitis needs full evaluation. Episcleritis is more likely to be accompanied by systemic disease in children than in adults; in contrast, most childhood posterior scleritis is idiopathic.

Types of ocular involvement

1. Bilateral inflammatory signs of severe systemic disturbance: conjunctivitis, episcleritis, scleritis, anterior uveitis, retinopathy, and optic disc edema and papilloedema.
2. Localized ocular vasculitis: varying with vessel size: peripheral ulcerative keratitis, scleritis, episcleritis, retinal vasculitis, choroidopathy (and central serous retinopathy), optic neuropathy, and orbital inflammation.
3. CNS inflammation, which may be diffuse (e.g. lupus encephalopathy) or focal and secondary to cerebral vasculitis (PACNS).
4. Hypertensive retinopathy secondary to renal vasculitis.
5. Acute and chronic ischemic complications within the eye and CNS from medium and large vessels occlusion.

Types of vasculitis

Large vessel

Takayasu disease (TAK)

Systemic This is an inflammation of the aorta and its major branches. It is 100 times more common in East Asia, nine times more common in females and, in one-third, starts before the age of 20. Phases of systemic inflammation may precede chronic occlusive vasculopathy by several years. Cardiac failure may result.[47]

Ocular Ocular symptoms are secondary to chronic carotid and vertebral artery occlusion and collateral formation.[48]

Medium vessel

Polyarteritis nodosa (PAN)

Systemic PAN is a necrotizing segmental vasculitis of small and medium arteries with frequent aneurysm formation. Diagnosis requires tissue biopsy or abdominal angiography when the clinical picture is unclear. Thrombosis of involved arteries is frequent. It can be secondary to infections such as hepatitis and streptococci as well as neoplasia. Disease may be limited to the skin but half of children with PAN present with fever, rashes, musculoskeletal pain, neuropathy, and renal impairment. The main age of onset is 7–11 years.[49] Seizures from CNS involvement are more frequent than peripheral nerve involvement.

Ocular Conjunctivitis, episcleritis and necrotizing scleritis, and peripheral ulcerative keratitis are found in up to 20% of patients. AAU and bilateral panuveitis are rare. Choroidal vasculitis is a common histologic change but is usually asymptomatic; retinal involvement is usually an arteriolitis but veins may also be involved.

Kawasaki disease (KAW)

Systemic There is an acute conjunctivitis, a red tongue and lips, and erythema of the trunk, palms, and soles. It may present with uveitis.[50] There may be marked edema of hands and feet. The skin of the soles and hands desquamate on recovery. Later, 20% develop coronary artery aneurysms, some of which may resolve with treatment, but there may be long-term cardiac sequelae. CNS involvement is uncommon; there may be hearing loss.[51]

Ocular AAU and conjunctivitis occur in the majority in the acute phase and appear to be benign: disc edema and congested retinal vessels may occur.

Small vessel, ANCA-associated vasculitides (AAV)

Granulomatous polyangiitis (GPA, formerly Wegener granulomatosis)

Systemic Diagnosis requires three of six criteria: involvement of kidneys; upper airways; laryngotracheobronchial system; lung parenchyma; positive biopsy; or classic antineutrophil cytoplasmic antibody (cANCA) positivity.[52] The ophthalmologist is usually involved with orbital and CNS cases without renal involvement. The normal age of onset is the sixth decade.

Tissue damage from respiratory tract granulomas can be extensive. Subglottic stenosis and nasal deformity are more common in children.[53,54] Limited forms without cANCA positivity can occur, including cases limited to the CNS.

Ocular Ocular presentation occurs in 10%. Focal, necrotizing scleritis with adjacent keratitis is the most common presentation. Orbital inflammation may be diffuse or from adjacent sinus involvement. A panuveitis or AAU can occur rarely.

Urticarial vasculitis

There is a leukocytoclastic vasculitis that mostly occurs in middle-aged women; half have reduced complement. It has been associated with uveitis, scleritis, and idiopathic intracranial hypertension.

Vasculitis accompanying connective tissue disease

Systemic lupus erythematosus (SLE)

Systemic The vasculopathy involves small arteries, arterioles, and capillaries, resulting in fibrinoid necrosis. A hypersensitivity vasculitis occurs in 28%. Thrombosis is more likely in the presence of anticardiolipin antibodies, and these may also occur as an independent phenomenon in the antiphospholipid syndrome, or precede the development of SLE by several years. CNS disease may be caused by diffuse vasculopathy and localized thrombosis exacerbated by the presence of anticardiolipin antibodies. It may originate from abnormal DNA methylation in T cells leading to autoreactivity.

Ocular Five percent of children with SLE have ocular involvement. The most frequent ocular involvement is dry eye; chronic inflammation is unusual. Lupus retinopathy is a sign of severe systemic vasculopathy and may be complicated by hypertensive changes. AAU, scleritis, episcleritis, and keratitis are uncommon and may indicate uncontrolled systemic disease.

Scleroderma (SSC)

Systemic Limited forms start with skin involvement of the extremities but may progress to the diffuse form with proximal limb and organ involvement (systemic sclerosis). The mean age of onset in childhood is 9 years; most are female. Localized scleroderma is more common in young females and may involve isolated patches of skin (morphea) or a linear patch on the face (*en coup de sabre*).

Ocular Thirteen percent of those with localized scleroderma have eye involvement, and it is not always related to the site of skin disease. Uveitis may occur, especially in scleroderma *en coup de sabre*. Choroidopathy is relatively common, arising from choroidal capillary closure and perivascular mucopolysaccharide deposition. The retinal circulation is usually spared but hypertensive changes may occur.[55,56]

Sjögren syndrome

Very rare in childhood, this usually presents with dry eyes and mouth and is associated with several connective tissue disorders.[57]

IgG4 disease

This may mimic Sjögren involvement of the lacrimal and salivary glands. It can also cause orbital inflammation and uveitis. Infraorbital nerve involvement is characteristic. Histology may resemble GPA.[58–62]

Juvenile dermatomyositis (JDM) and polymyositis

Dermatomyositis is the commonest inflammatory myopathy of childhood presenting with gradual muscle weakness. A purple heliotrope rash on the eyelids commonly precedes the myopathy. Extramuscular features are more common in children, including subcutaneous calcification and vasculitis. A retinal microangiopathy may occur.[63]

Relapsing polychondritis (RPC)

Systemic There is recurrent inflammation of cartilage in the ear, nose, trachea and larynx, and joints with an adjacent dermal vasculitis. One-quarter of patients have other connective tissue disease, particularly rheumatoid arthritis. It is rare in childhood.

Ocular Up to 60% have ocular involvement and 25% present with ocular symptoms. Episcleritis and scleritis are the most frequent patterns, with keratitis, uveitis, and retinal vasculitis occurring rarely. A CNS vasculitis may occur.

Other vasculitides

Cogan syndrome (COG)

Systemic Typically, acute interstitial keratitis, deafness, and systemic vasculitis occur in the third decade. There may be an autoantigen shared between the cornea, large vessels, and the inner ear.[64,65] Acute hearing loss and keratitis can occur in other vasculitides. There is aortitis in classic disease; other vessels are more frequently involved in atypical disease including CNS vasculitis.

Ocular Interstitial keratitis is found in two-thirds of cases. Episcleritis and scleritis are found in 36% and retinal vasculitis in 24%. Uveitis and conjunctivitis may be the sole manifestation in a minority. Keratitis can be severe, leading to corneal perforation and extensive neovascularization (Figs 40.12 and 40.13).

Vasculitis also occurs in conditions covered in the uveitis section such as Behçet disease, IBD, and sarcoidosis.

Pediatric inflammatory brain disease and localized vasculitis

Pediatric inflammatory brain disease may cause focal neurological events such as stroke or diffuse inflammation presenting with encephalitis: there is a large differential diagnosis which includes many conditions causing ocular inflammation and systemic vasculitis. Visual disturbance is more commonly associated with encephalopathic and vasculitic disorders.[66]

There are several ocular inflammatory conditions in which the predominant CNS sign is sensorineural deafness (Table 40.4).

Monophasic CNS and retinal vasculitis may follow infection such as herpes varicella zoster. Other secondary vasculitides

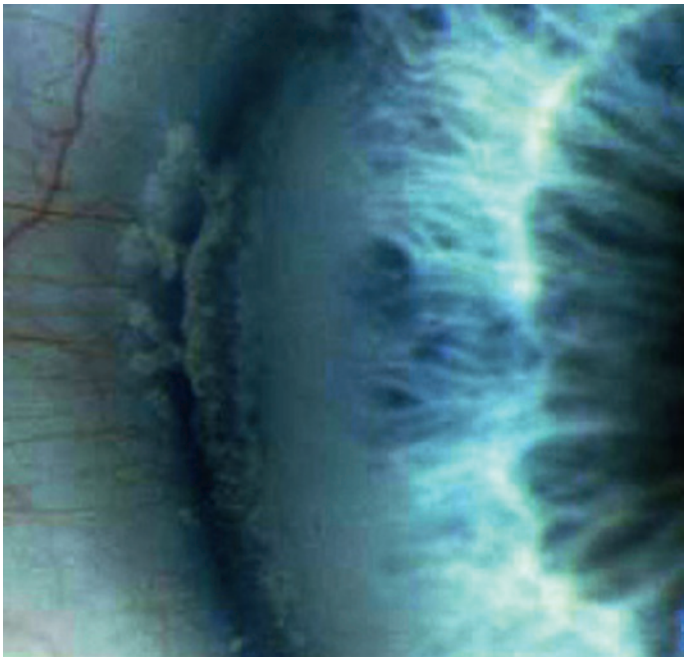


Fig. 40.12 Cogan keratitis. Early limbal deposits.

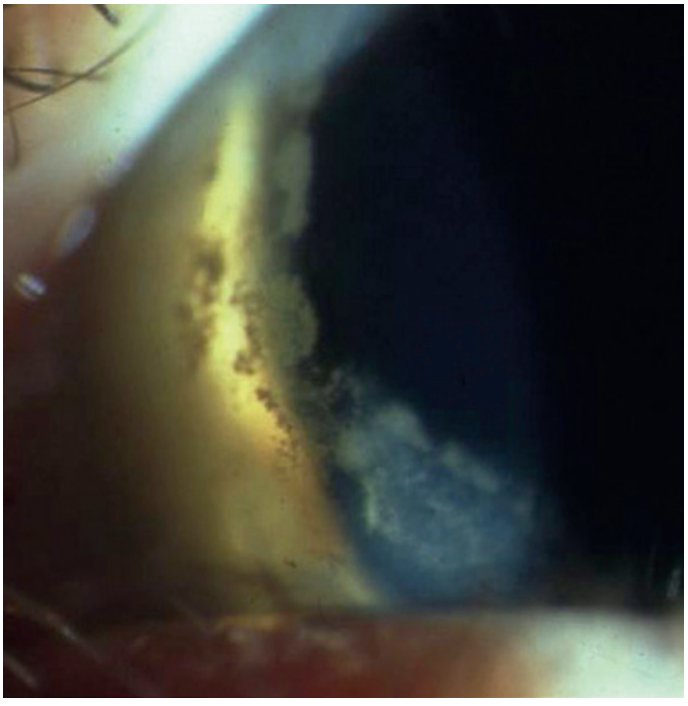


Fig. 40.13 Cogan keratitis. Later paralimbal deposits.

Table 40.4 Associations of uveitis and hearing loss and CNS disease

Type of disease	Type of vaculitis	Diagnosis	Uveitis	Hearing loss	Other CNS
Localized	Secondary	Sarcoid	✓	✓	✓
Localized	Autoinflammatory disease	VKH	✓	✓	✓
Systemic	Autoinflammatory disease	CINCA	✓	✓	✓
Systemic	Autoinflammatory disease	MWS	✓	✓	
Vasculitis	AAV	GPA		✓	
Vasculitis	Other	Susac		✓	✓
Vasculitis	LVV	KAW	✓	✓	
Vasculitis	VVV	Cogan	✓	✓	
Vasculitis	MVV	PAN		✓	✓
Vasculitis	Localized	PACNS			✓
Vasculitis	Seondary	SLE			✓

AAV, ANCA-associated vasculitides; CINCA, chronic infantile neurologic cutaneous and arthritis; Cogan, Cogan syndrome; GPA, granulomatous polyangiitis KAW, Kawasaki disease; LVV, large vessel vasculitis; MVV, medium vessel vasculitis; MWS, Muckle–Wells syndrome; PACNS, primary angiitis of the central nervous system; PAN, polyarteritis nodosa; SLE, systemic lupus erythematosus; Susac, Susac syndrome; VKH, Vogt–Koyanagi–Harada syndrome; VVV, variable vessel vasculitis.

with CNS involvement include SLE, IBD, and human immunodeficiency virus (HIV).

Non-diagnostic multifocal magnetic resonance imaging (MRI) changes and non-specific inflammatory CSF abnormalities are frequent and brain biopsy is sometimes required for diagnosis if angiography is not diagnostic.

Primary angiitis of the CNS diagnosed on angiography is the commonest pediatric inflammatory brain disorder in referral centers. It is a granulomatous and necrotizing vasculitis and there may be paravascular demyelination.

Ocular involvement in demyelinating disorders of childhood primarily present with optic neuritis and rarely progress to relapsing MS.

Medical treatment of ocular inflammation

The initial treatment of most anterior uveitis is topical steroids. There is little evidence that any specific steroid is optimal for both disease control in CAU and reducing the risk of secondary ocular hypertension. There is little evidence for the benefit of the chronic use of non-steroidal anti-inflammatory agents, although their short-term use in severe relapse with AC flare and macular edema may be warranted. Complex, frequent regimens of drops are to be avoided: compliance is greatly reduced particularly at school. It is preferable to use a single steroid and vary its frequency rather than swap between steroid preparations. If needed more than four times a day, then a different route of steroid use is indicated. Some patients with CAU may avoid relapse on regimens of topical steroid as infrequent as twice weekly.

The aim of treatment is to minimize the acute risk of damage at times of high activity, achieve remission, and maintain this for a sufficient length of time to reduce the risk of short-term relapse. AAU in adults commonly has a natural course of a couple of months and rapid reduction of treatment is appropriate. The natural course of most relapses in CAU is of the order of several months and so inappropriately reducing treatment as soon as remission is found simply leads to an early relapse. Maintaining the dose of steroid at which remission is achieved for at least 4–8 weeks and reducing treatment in monthly, rather than weekly, steps will diminish the risk of relapse. In relatively benign forms of CAU, cycles of very frequent steroid followed by rapid tapering may result in unnecessary morbidity.

Systemic treatment: indications

At some point, the risks of cataract and glaucoma with continuous topical steroid treatment are sufficiently high to justify systemic immunosuppression if prolonged remission is never achieved. Topical steroids cannot treat adequately the posterior segment complications even when AC activity is controlled.

The aim of treatment is to achieve a sufficiently long remission that withdrawal of treatment is not followed by an early recurrence. This differs in different types of uveitis but is likely to be of the order of 12–18 months in JIA-uveitis. It may be best to achieve 3 years of remission before tailing off treatment in those who are at most risk.[67,68]

About half of patients given methotrexate (MTX) for JIA arthritis will relapse on withdrawal of treatment. Less than 20% of patients with JIA-uveitis started on immunosupression will enter long-term remission off treatment within 5 years. In contrast, other types of CAU, such as TINU syndrome, and idiopathic IU may only need treatment for 2–4 years and are at low risk of later relapse.[9,69]

Conventional immunosuppressants.

MTX is in widespread use because of trial evidence in the treatment of arthritis in JIA and adult rheumatoid arthritis, and because there is long-term safety data. Its efficacy in uveitis has only been directly compared to mycophenolate mofetil.[70] The

response rate of patients with uveitis to MTX in a meta-analysis was 73%.[71] Serum predictors of relapse may aid decisions about the timing of treatment withdrawal.[72]

The dose of MTX required to control arthritis in JIA is frequently insufficient to control uveitis, and ophthalmologists and rheumatologists have to collaborate closely to optimize dose and timing of treatment changes.

Azathioprine,[73] everolimus,[74] ciclosporin,[75] and tacrolimus[76] have all shown efficacy in childhood and adult uveitis. These immunosuppressive agents are less successful in treating the arthritis of JIA; it is not uncommon for arthritis to present in children taking other immunosuppressants for an apparently idiopathic CAU.

It remains unclear whether dual therapy with conventional immunosuppressives adds benefit, and treatment switching of single agents ought to be considered before using multiple therapies, which greatly increase drug toxicity and complications.[77]

The use of systemic steroids is often vital in the acute control of ocular inflammation; their long-term use in childhood leads to growth retardation, in addition to their well-known side effects in adults, and alternatives are required wherever relapse occurs after an appropriately tapered dose reduction.

Biologics

Biologic agents are monoclonal antibodies that bind specific molecular targets, in contrast to conventional immunosuppressants. Their use in treating inflammatory disease first developed in adult inflammatory arthritis. Inadequate control of arthritis in JIA with MTX usually leads to the addition of an anti-TNF agent, and etanercept was the first trialed in childhood uveitis. A wide range of biologics is now licensed for use in adult inflammatory arthritis and additional classes of biologics in vasculitis, MS, and systemic autoinflammatory disease. Several classes other than anti-TNF agents, are now licensed in arthritis and patients are often prescribed sequences of agents from different classes in order to maintain a clinical response.[78]

Although the use of biologics in uveitis is guided by the efficacy of treating extraocular manifestations of the associated systemic disease, it cannot be guaranteed that uveitis will respond in a similar way.[79,80] Etanarcept appears less efficacious than other anti-TNF agents for treating the uveitis in JIA although it has similar efficacy in treating the arthritis. Most series include patients previously and concomitant treated with multiple conventional and biologic treatments, at different time points in disease and with different ocular comorbidities – usually unspecified. This makes treatment effect difficult to predict.

The use of many biologics has been reported in pediatric uveitis; recent reviews rely on case series only and do not indicate a clearly preferred class specifically more efficacious in the various uveitis types.[81–83] The most effective biologics may have a clinical effect in 70–80%, with a quarter of patients showing relapse over the subsequent 2 years; these effect sizes are similar to those found in trial data of biologics approved for use in inflammatory arthritis. Since response of all treatments is likely to be related to the level of ocular damage at time of treatment initiation, the timing of treatment escalation is critical. Generally, insufficient control within 3–6 months of initiation justifies a treatment switch.[84,85]

Switching between anti-TNF agents may provide benefit in about one-quarter of patients.[86] Etanercept appears to have less effect on uveitis activity compared to other anti-TNF agents; anti-TNF agents other than etanercept are suggested in recent guidelines for JIA-uveitis[87,88] and are the subject of ongoing trials.[89]

Trials in adult uveitis are usually of heterogenous types excluding CAU, but their results are likely to be relevant to pediatric populations. The choice of biologic is likely to be determined largely by cost and regulatory restrictions rather than high-level clinical evidence.

Indications of treatment efficacy

The ocular signs relevant to titrate treatment remain unclear in all forms of uveitis although cell counts and vitreous flare are both central to drug trials.[90] Visual loss is of prime patient concern, and useful in auditing, but has only a distant connection to the short-term measures of clinical activity. There may also be an entirely different set of measures relevant to assessing treatment response in those already under treatment, i.e. markers of disease relapse under treatment as opposed to markers of activity in untreated disease.

As complete remission is associated with no further inflammatory complications, this it is the aim of treatment. Visual loss is associated with surgery for cataract, glaucoma, as well as hypotony, so treatment should be aimed at preventing these conditions. It is not known what level of AC cellular activity leads to complications; AC flare is much less responsive to anti-inflammatory treatment, but may reverse in some patients and have a stronger association than AC cells with future complications.[74,91,92] Cataracts form at statistically similar rates in those with a trace of AC cells and those with 2+ of cells, although the trend increases with increasing cell counts.

Surgical treatment

Cataracts

The indications for cataract surgery are:

1. the prevention of amblyopia;
2. to allow the management of posterior segment disease;
3. to improve visual function with an acceptable risk.

Surgery should not be embarked upon lightly. Children with mild bilateral cataracts and persistent inflammation can undergo a normal education with 6/18 vision and surgery might be deferred for long periods, until disease activity subsides.

Surgery on a unilateral cataract during the first years of life may often result in an aphakic amblyopic eye that adds little to the visual function, but also allows monitoring of posterior segment disease, which, if untreated, may result in an unsightly painful eye. Families need to understand the limited choices available in this situation.

Disease activity must be rigorously controlled, as postoperative inflammation can be unpredictable and severe. When cataract surgery is planned, patients should be started on systemic immunosuppression in order to see whether disease can be completely controlled without topical medication. Treatment should be increased before, at the time of surgery, and for at

least 2 months after. Some patients with preoperative macular edema require 4 or 5 months of systemic steroids as well as second-line immunosuppression before maximum postoperative acuity is achieved. When planning surgery in cases with a short history, one should assume that inflammation may become more difficult to control for some years afterwards. Periocular or intraocular steroids given intraoperatively reduce the need for systemic steroid in the perioperative period but increase the risk of glaucoma.

The surgical view may be compromised by band keratopathy; preoperative excimer laser, or EDTA, may precede intraocular surgery. Posterior synechiae can be more extensive than is apparent on slit-lamp examination and intraoperative iris damage is frequent. Pupillary membranes may be vascularized and bleed intraoperatively but occasionally may be simply peeled off the anterior capsule.

Techniques of lens removal depend on the possibility of capsulorrhexis, visibility, and hardness of the lens. Often the lens can be aspirated even if white. Occasionally, calcified subcapsular plaques and pigment clumps related to posterior synechiae complicate capsulorrhexis.

Posterior capsule opacification is universal and a posterior capsulorrhexis is advisable, especially in a child who would require GA for YAG laser capsulotomy. An anterior vitrectomy may reduce the risk of pupillary and posterior intraocular lens (IOL) membrane formation, but a more extensive vitrectomy may add other risks.

Intraocular lenses are easy to put in but very difficult to take out. JIA-uveitis, especially, has a high rate of IOL "cocooning," synechiae, and membrane formation. It may be prudent to delay IOL implantation until months after lens extraction. The drawbacks of aphakia are trivial compared to the profound visual loss that may result from complications of IOL explantation, so families should be fully informed of the added risk to the visual outcome that IOL implantation provides.[93]

In contrast, IOL implantation in other types of childhood uveitis may have little risk, including late-developing cataract in JIA-uveitis. The outcomes of unilateral cataract surgery in children prone to amblyopia are poor and this is also the case in JIA-uveitis. Patients and their parents should be counseled preoperatively about the need for vigorous patching after surgery.

Treatment of glaucoma

Many glaucoma surgical treatments have been tried including goniotomy and cycloablation. As patients may have compromised aqueous production, despite raised IOP, all procedures need caution when the eye has been severely inflamed due to the great risk of postoperative hypotony.

The use of tube drainage devices has greatly improved the prognosis of aphakic glaucoma. Steroid-induced glaucoma in a quiet eye may respond well to conventional assisted trabeculectomy. Whatever the success of angle surgery and cyclodestructive procedures in the short-term, they may reduce the effectiveness of later drainage procedures.

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Albinism

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Chapter contents

INTRODUCTION
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Introduction

Albinism, derived from the Latin *albus*, meaning white, is an inherited disorder of melanin biosynthesis, which results in absent or reduced melanin production and causes phenotypic heterogeneity. Melanogenesis requires complex interactions of enzymes and proteins within melanosomes to produce eumelanin (brown or black pigment) or pheomelanin (yellow or red pigment), encoded by genes known to cause albinism (Fig. 41.1).[1] Oculocutaneous albinism (OCA) and syndromes associated with OCA are inherited in an autosomal recessive manner, whereas ocular albinism (OA1) is associated with X-linked inheritance. Current terminology is based on the specific gene in which mutations can be found to define a particular type of albinism.[2] Older terms, such as partial, imperfect, incomplete, or complete albinism and tyrosinase-positive or tyrosinase-negative albinism, which were based on results of hair bulb incubation with L-tyrosine, are no longer used. Several laboratories provide panels for genetic testing of individuals with the phenotype of albinism.

Classification of albinism by genes

Non-syndromic oculocutaneous albinism

Although the rate of albinism varies geographically, albinism occurs with a frequency of approximately 1 in 20,000 worldwide, and more than 1% of the population carries a heterozygous mutation in a gene that causes albinism.[3–5] The most common types are OCA1 and OCA2. OCA1 is due to mutations in the tyrosinase (*TYR*) gene, which is essential in the initial and rate-limiting steps of melanin biosynthesis. Children with OCA1A (previously tyrosinase-negative) produce no melanin pigment in their skin, hair, or eyes over their lifetime. Those with OCA1B have some residual enzyme activity so they produce some melanin pigment in their hair, their eyelashes darken, their skin develops a slight tan, and melanin pigment can be detected in the posterior iris epithelium and occasionally in the macular retinal pigment epithelium (RPE) (Fig. 41.2).[6–8] OCA1 includes those diagnosed with minimal pigment or temperature-sensitive albinism, and those previously classified as having yellow albinism.[9–11] Those with OCA2, due to the mutations in the *OCA2* gene, often have blond or red hair at birth (Fig. 41.3).[12–14] Persons with OCA2 can often be difficult to discern from persons with OCA1B due to their pigmenting phenotype. In sub-Saharan Africa, there is a predominance of OCA2 due to a 2.7-kb interstitial deletion in *OCA2*, related to a founder effect.[15] Other types of OCA include OCA3, OCA4, OCA5, OCA6, and OCA7 (Table 41.1).[16–21]

Syndromic albinism

Syndromes associated with oculocutaneous albinism are less common than non-syndromic albinism and include Hermansky–Pudlak syndrome (HPS), in which affected individuals have absent dense bodies (delta granules) in their platelets, which interferes with the secondary phase of irreversible aggregation. Thus, individuals with HPS have easy bruising, epistaxis, and prolonged bleeding after procedures such as dental extraction, childbirth, and surgery.[22–26] Nine types of HPS have been identified and all have autosomal recessive inheritance.[27–35] Some types are associated with pulmonary fibrosis and intestinal accumulation of ceroid, causing granulomatous colitis (see Table 41.1).[36] Whole-mount electron microscopy of platelets without dense bodies can identify those with HPS, but genetic testing identifies the specific type of HPS and the potential for other systemic abnormalities.[37,38] The phenotype for oculocutaneous albinism in HPS is variable and can overlap with non-syndromic types of albinism.[39]

Chédiak–Higashi syndrome (CHS) is also associated with oculocutaneous albinism, inherited as an autosomal recessive disorder.[40,41] Persons with CHS have frequent infections and can progress to a lymphoproliferative phase.[42,44] They are treated with hematopoietic stem cell transplantation, preferably prior to the accelerated phase. If untreated, they will also develop neurological abnormalities and eventually succumb to an overwhelming infection.[45] Although these individuals have the ocular and cutaneous features of albinism, their hair has a

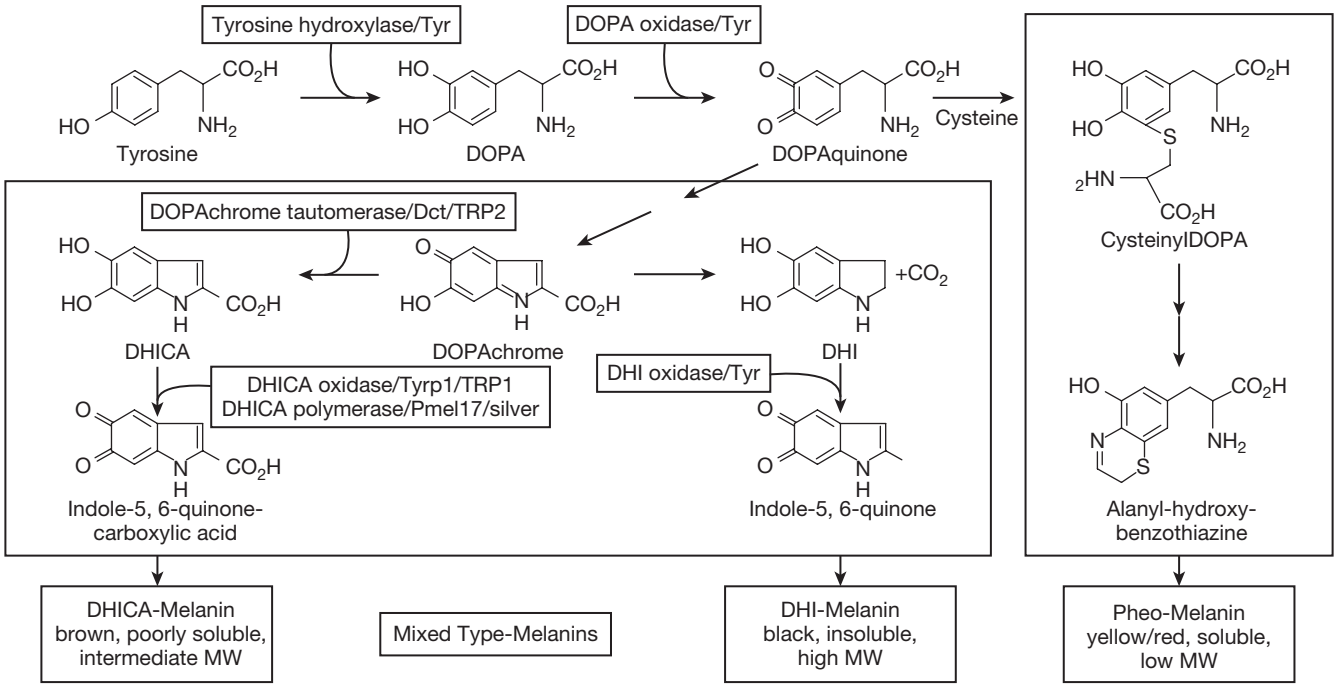


Fig. 41.1 The pathway for normal melanogenesis results in production of eumelanin or pheomelanin. *(Reprinted from Rimoin DL, Connor JM, Pyeritz RE, Korf BR, editors. Emery and Rimoin's Principles and Practice of Medical Genetics, 5th edition, volume 3, King RA, Oetting WS, Summers CG, Creel DJ, and Hearing VJ. Abnormalities of Pigmentation; 3380–427. © 2007, with permission from Churchill Livingstone.)*



Fig. 41.2 Both boys have mutations in *TYR*. The one on the left makes no melanin pigment (OCA1A) whereas the one on the right makes a moderate amount of melanin pigment (OCA1B).

subtle silvery sheen, often prompting investigation to establish the diagnosis. Peripheral blood smear shows giant intracellular granules in neutrophils.[43]

Ocular albinism

In ocular albinism (OA1), which occurs less frequently than OCA,[46–48] there is a mutation in the *GPR143* gene on the X chromosome. Males with OA1 have the typical ocular features of albinism, but their cutaneous and hair pigment is nearly normal.[49–51] Some may have hypopigmented macules; skin biopsy may show macromelanosomes, but they are not pathognomonic.[52,53] Without careful eye examination, these individuals may be identified as having uncomplicated infantile nystagmus syndrome. Mothers of children with OA1 will typically show some iris transillumination and pigmentary mosaicism in the retina (Fig. 41.4), although the obligate carrier is rarely symptomatic.[53–57] Pigmentary mosaicism, noted in 80% to 90%, represents expression of Lyonization with pigmented RPE adjacent to non-pigmented areas, most notable in the mid-periphery of the fundi. Some males and females with almost normal pigmentation have been given a diagnosis of autosomal recessive ocular albinism, but many have been found to have oculocutaneous albinism with genetic testing, most often due to mutations in the *TYR* gene.[58–61] If a deletion in *GPR143* occurs, contiguous genetic disorders may be associated with OA1, e.g. ichthyosis of the skin (*STS*),[62] Kallman syndrome (*KAL1*),[63] and chondrodysplasia punctata (*ARSE*).[64]

Clinical phenotype

Ocular features

The ocular features in albinism vary from one individual to another, within a family, and within a specific type of albinism, due to interaction of heterogeneity in the type of albinism and the constitutional genotypes.[65–67] A clinical diagnosis of albinism is based on a constellation of findings and may be confirmed with genetic testing.

Reduced visual acuity

Many parents report that their infants with albinism close their eyes when exposed to bright light and do not appear to be as visually attentive as their children without albinism were, but most agree that there is evidence of improvement in



Fig. 41.3 This girl with African American heritage has mutations in the *P* gene that causes OCA2.

visual attentiveness by 5 to 6 months of age.[68,69] Vision often continues to improve as the child matures.[69–72] The spectrum of best-corrected visual acuity in persons with albinism ranges from 20/20 to worse than 20/400.[68–70,73–77] A spectrum of visual acuity is noted across and within the different types of albinism, and persons with OCA1A generally have worse visual acuity than persons with other types of albinism. High refractive errors are common in albinism, with large amounts of astigmatism being particularly noted in OCA1A.[73,77,78] Early correction of large refractive errors and careful re-evaluation of the refractive error over time maximizes the visual outcome by reducing ametropic amblyopia and improving binocular alignment.[79,80] Other reasons for reduced visual acuity include foveal hypoplasia, light scattering, nystagmus, and possibly retinostriate misrouting. Certain features associated with relatively better visual outcomes include demonstration of some stereoacuity and the presence of granular melanin pigment in the macula.[74,77,81]

Nystagmus

Most persons with albinism develop nystagmus within the first 2 to 3 months of life. Nystagmus is often horizontal and pendular, but rotary, jerk, and periodic alternating nystagmus have also been reported. In general, the amplitude of nystagmus diminishes as the children age, due, in part, to the development of a head posture as they develop better head control, and their visual attentiveness to smaller targets improves. The head posture damps the nystagmus amplitude and provides the best visual acuity.[74,80,82] The preferred position of the eyes, whether eccentric or in primary gaze, is called the null point of the nystagmus. In some persons with albinism who have better visual acuity, nystagmus may be undetectable, even when the eyes are examined with the slit-lamp biomicroscope or ophthalmoscope.[70,74,77,81,83] Others, particularly adults with albinism, may show only latent nystagmus.

Iris transillumination

Another feature common in albinism is iris transillumination, occasionally noted by parents as pink or translucent irides. Iris transillumination is best detected with retroillumination in a darkened room with a small, bright light of the slit-lamp directed toward the undilated pupil. Iris transillumination varies from complete, indicating that there is no melanin pigment present, as in OCA1A, to scattered punctate areas of iris transillumination, indicating the presence of a marked amount of melanin pigment in the posterior iris epithelium, derived from neuroectoderm (Fig. 41.5).[84] Stromal melanocytes, derived from the neural crest, can also restrict transillumination.

Foveal hypoplasia

At least some degree of foveal immaturity and deficiency of melanin pigment in the retinal pigment epithelium, derived from neuroectoderm, are common in albinism. At times, there is no foveal development and in other patients, typically with better visual acuity, an annular reflex is noted in the macula even though an umbo is not detected.[74,77,81,85] Optical coherence tomography has documented these structural findings and adaptive optics has shown variation in cone packing.[75,77,85–89] In many persons with albinism, the choroidal vessels are easily visualized in the macula, and the retinal vessels do not normally form a wreath around the intended fovea, whereas, in others, choroidal vessels are not seen in the macula even though they are often seen outside the macula (see Fig. 41.5).[75,84,86,88–90] With magnification, some individuals with albinism can be seen to have granular melanin pigment within the macula (Fig. 41.6); this is often associated with relatively better vision and measurable stereoacuity.[74,81] The optic nerve appears mildly hypoplastic in albinism, with a complete or incomplete scleral ring around the optic nerve head, and the disc can appear to be gray with indirect ophthalmoscopy.[91]

Strabismus and positive angle kappa

One finding that is helpful in the more pigmented individual, in whom one questions if albinism is the correct diagnosis, is the presence of a moderately positive angle kappa, determined with the subject fixing monocularly on a small light source.[77,92,93] A moderately positive angle kappa can mask an esotropia that measures 15 prism diopters or more and can make an exotropia appear larger than measured.[92] Both esotropia and exotropia are common in albinism, presumably related to abnormal binocular interaction from retinostriate misrouting.[4,70,76,83] Such a positive angle kappa relates to the

Table 41.1 Genetic classification of albinism

Type of albinism	MIM#	Gene	Locus	Encoding function	Comments
OCA1* OCA1A OCA1B	606933 203100 606952	*TYR*	11q14–21	Tyrosinase, which catalyzes several steps in melanogenesis	OCA1A: no melanin; OCA1B: varying amounts of melanin are present
OCA2	203200	*OCA2* (previously called *P* gene)	15q11.2–12	Melanosomal membrane protein	Common in sub-Saharan Africa due to 2.7–kb deletion; includes Brown OCA
OCA3	203290	*TYRP1*	9p23	Stabilizes tyrosinase and regulates eumelanin production	Previously called red or rufous OCA
OCA4	696574	*SLC45A2* (previously called *MATP* and *AIM1*)	5p13.2	Membrane transport protein	Minimal to near normal melanin; phenotype similar to OCA2; common in Japan
OCA5	615312	Unknown	4q24	Unknown	Described in Pakistani family
OCA6	609802	*SLC24A5*	15q21.1	Melanosome maturation	Described in Chinese family
OCA7	615179	*C10orf11*	10q22.2–q22.3	Melanocyte differentiation	Described in families in Faroe Islands and Denmark
OA1	300500	*GPR143*	Xp22.2–22.3	Regulation of melanosome distribution	Nettleship–Falls OA; pigmentary mosaicism in obligate carrier
HPS-1	203300	*HPS1*	10q23.1–23.3	Transmembrane protein in BLOC-3 within BLOC-4 and BLOC-5	Common in northwestern Puerto Rico due to founder effect; progressive pulmonary fibrosis and colitis
HPS-2	608233	*ADTB3A*, *AP3B1*, *HPS2*	5q14.1	Lysosomal trafficking	Neutropenia and/or immune defects; pulmonary fibrosis, conductive hearing loss, dysplastic hip
HPS-3	614072	*HPS3*	3q24	Vesicle-related protein	Found in central Puerto Rico; mild systemic findings; colitis
HPS-4	614073	*HPS4*	22q11.2–12.2	Involved in BLOC-3 and BLOC-4	Pulmonary fibrosis, colitis
HPS-5	614074	*HPS5*, *RU2*, *KIAA1017*	11p15–p.13	Organelle biogenesis	Hyperlipidemia, elevated creatinine clearance
HPS-6	614075	*HPS6, RU*	10q24.32	Organelle biogenesis	Mild systemic findings
HPS-7	614076	*DTNBP1, HPS7*	6p22.3	Component of BLOC-1	Mild lung disease
HPS-8	614077	*BLOC1S3, HPS8*	19q13.32	Vesicular transport protein	Mild systemic findings
HPS-9	614171	*BLOC1S6, PLDN, PA, HPS9*	15q21.1	Intracellular vesicle trafficking	Few cases described
HPS-10	NA	*AP3D1*	NA	Lysosomal biogenesis	Microcephaly, seizures, immunodeficiency
CHS	214500	*LYST* (previously *CHS1*)	1q42.1–42.2	Lysosomal trafficking regulator protein	Frequent infections due to immunodeficiency; may have bleeding diathesis

*OCA1 includes previously described temperature-sensitive OCA, minimal pigment OCA, and yellow OCA.
AP, Adapter protein; *BLOC*, biogenesis of lysosomal-related organelles complex; CHS, Chédiak–Higashi syndrome; *GPR*, G protein-coupled receptor; HPS, Hermansky–Pudlak syndrome; *LYST*, lysosomal trafficking regulator; MIM, Mendelian inheritance in man; NA, not available; OA, ocular albinism; OCA, oculocutaneous albinism; *PLDN*, pallidin; *SLC*, solute carrier family; *TYRP1*, tyrosine-related protein-1.



Fig. 41.4 Examination of the fundus of the obligate carrier for OA1 typically shows pigmentary mosaicism, with some areas having normal melanin pigment and other areas having no melanin pigment, as a manifestation of Lyonization.



Fig. 41.6 Careful microscopic examination of the fundus may show granular melanin pigment in the macula.

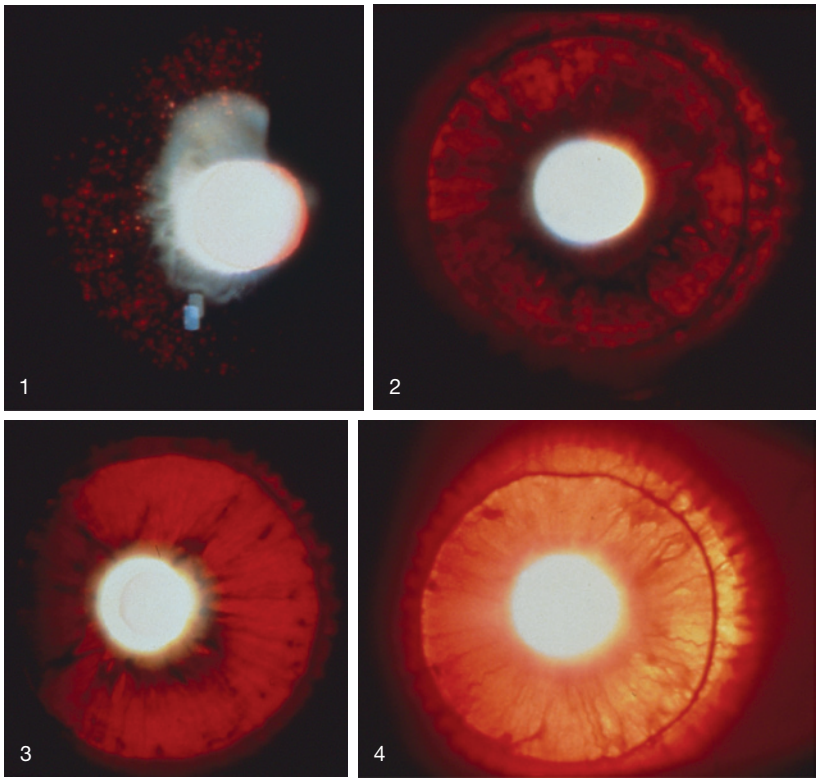


Fig. 41.5 Iris transillumination varies from punctate transillumination (top left, grade 1) to full iris transillumination (bottom right, grade 4) in albinism. *(Reprinted from Summers CG, Knobloch WH, Witkop CJ, Jr, King RA. Hermansky–Pudlak syndrome. Ophthalmic findings. Ophthalmology 1988; 95: 545–554, © 1988 with permission from Elsevier.)*

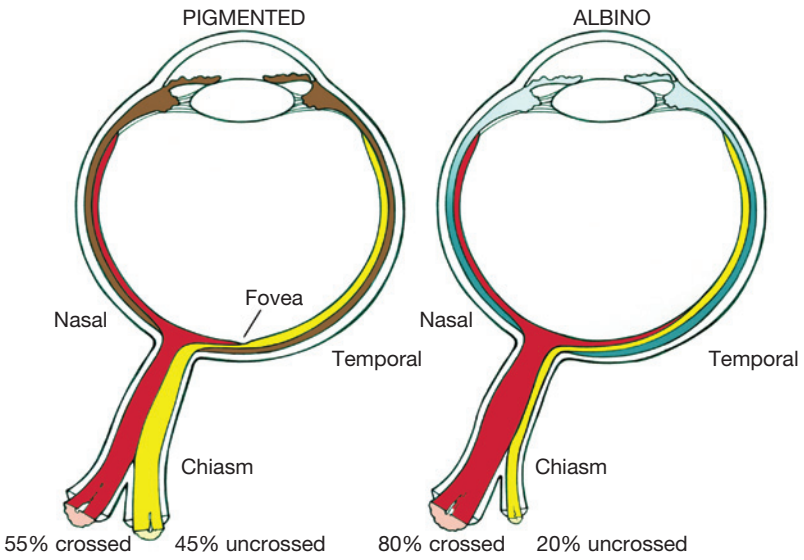


Fig. 41.7 Normal retinostriate routing (left) shifts from contralateral (crossed) to ipsilateral routing (uncrossed) at the fovea, whereas in albinism (right), the point of routing ipsilaterally is temporal to the fovea, resulting in a greater number of retinal ganglion fibers decussating at the chiasm (crossed) and being routed to the contralateral lateral geniculate nucleus. *(Reprinted from Creel DJ, Summers CG, King RA. Visual anomalies associated with albinism. Ophthalmic Paediatr Genet 1990; 11: 193–200. © 1990, with permission from Taylor & Francis.)*

neural fibers temporal to the expected location of the fovea crossing at the chiasm to synapse in the contralateral lateral geniculate nucleus, compared to normal eyes (Fig. 41.7).[94]

Neurophysiological alterations

Albinism is associated with absent or reduced stereoacuity.[74,81,95] This is most likely related to the excessive retinostriate decussation of the nerve fibers at the chiasm in albinism, developing early in embryogenesis (see Fig. 41.7).[94,96] With a reduced number of nerves coursing ipsilaterally, the normal pattern of layering of the lateral geniculate nucleus is disrupted. Although the reason for this misrouting is unknown, it can be detected with a specialized pattern onset or flash visual evoked potentials (VEP) recorded with occipital electrodes.[94,96,97] Misrouting has also been documented with positron emission tomography and functional magnetic resonance imaging.[24,98–103] Abnormal decussation may contribute to strabismus and nystagmus.

Cutaneous features

Males with OA1 typically have hair and cutaneous pigment that is similar to or slightly lighter than others in the family, as the OA1 phenotype involves primarily the eyes. However, all types of non-syndromic and syndromic albinism have at least some degree of skin hypopigmentation that places them at risk for damaging sunburns that can lead to cutaneous malignancies later in life. Hair color depends on the type of OCA, with it being white in OCA1A, blond to brown in pigmenting types of albinism, and silvery brown in Chédiak–Higashi syndrome.[4]

Differential diagnoses

Other disorders with incomplete foveal development include aniridia and achromatopsia.[104,105] Persons with aniridia or achromatopsia also typically have nystagmus. Individuals with congenital stationary night blindness also have nystagmus and when associated with high myopia, it may appear that the fovea is poorly developed.[106] Distinguishing albinism from these disorders can be difficult, particularly if the irides have been dilated prior to slit-lamp biomicroscopy. Examination showing normal color vision, a positive angle kappa, absent stereoacuity, and perhaps a VEP showing misrouting can help to establish a diagnosis of albinism. Cursory examination of the person with a pigmenting type of albinism may lead to the erroneous diagnosis of infantile nystagmus syndrome not associated with albinism, or nystagmus in males due to a *FRMD7* mutation, which has X-linked inheritance.[107] Examination of the obligate carrier of OA1 can help to elucidate the correct diagnosis.[53–57]

Occasionally a child with a retinal dystrophy presents with nystagmus, foveal blunting, and some granular pigment in the macula, similar to some individuals with albinism. Early on, no significant pigment change is noted in the retinal periphery. These children with a retinal dystrophy can be correctly identified by observing paradoxical pupillary constriction when room lights are dimmed and by performing full-field electroretinography, as persons with albinism do not show a paradoxical pupillary response and their electroretinogram is normal or supranormal.[108]

The occasional person with albinism presents with mildly subnormal visual acuity and no nystagmus, and an annular reflex in the macula that might be interpreted as normal. In these individuals, a high index of suspicion for albinism will prompt the astute clinician to look for other signs of albinism and consider a VEP to demonstrate misrouting of the retinostriate fibers.[96,97]

Management

Making the diagnosis

The hair bulb incubation test[109] is not precise for diagnosis and is no longer used. In some persons with suspected albinism, the diagnosis can be established with genetic testing for mutations in a gene known to cause albinism. Panels that evaluate several

genes causing albinism are readily available. Until treatment that requires knowledge of the mutations is available, those with lifelong absence of melanin pigment in their skin, hair, and eyes (OCA1A), and those with only ocular features and the finding of pigmentary mosaicism in the obligate carrier may not need molecular testing, as the phenotype defines the specific type of albinism.

Providing counseling

Counseling by a geneticist or a genetics counselor can be helpful to obtain a pedigree, explain inheritance patterns, and indicate that a negative gene test does not necessarily mean that the person does not have albinism.[60,61,77,110,111] Individuals with autosomal recessive albinism can be counseled that they will not have a child with albinism unless their partner has the same type of albinism or carries a mutation in the same gene. Those with OA1 will pass the mutation to none of their sons and to all their daughters who will be carriers.

Supporting educational needs

Quality of life in persons with albinism has been shown to be impaired, particularly for distance visual acuity.[112] Their refractive error should be corrected for the best visual acuity and evaluation by a low vision specialist should be considered. Although it is rare that persons with albinism need to learn Braille, orientation and mobility training is important for those with severely reduced visual acuity. Current electronic technology to enlarge reading matter has supplemented the use of magnifiers and bifocals. Many will prefer to reverse the black/white setting on computers and other electronic aids to reduce asthenopia due to photosensitivity. Self-advocacy should be encouraged in early education.[113] Additional education and support for families are available, e.g. the National Organization of Albinism and Hypopigmentation in the United States (www.NOAH.org), the Albinism Fellowship of Australia (www.albinismaustralia.org), the Albinism Fellowship of the United Kingdom and Ireland (www.albinism.org.uk) and the Hermansky–Pudlak Syndrome Network (www.hps.network.org).

Children with albinism may require preferential seating and enlargement of print when they start school. Electronic media are used well by children with low vision. A teacher for the visually impaired can help to assure that the child's needs are being met. As children mature, more reading is required and print size in texts becomes smaller. A bifocal can help with near work, and audio books can be used when an electronic version is not available. An increased rate of attention deficit and hyperactivity disorder has been reported in children and adults with albinism, not related to visual acuity.[114]

Social issues

Sensitivity to the social issues surrounding a diagnosis of albinism is essential. Parents with dark pigmentation may have difficulty understanding how they could have a child with oculocutaneous albinism and may have difficulty raising a child in their culture. Persons with albinism are no longer referred to as "albinos." Attempts have been made to eliminate the negative portrayal of persons with albinism in media and the false notion that those with albinism have magical powers. Albinism is not associated with intellectual disability. Health care providers for persons with albinism may be the first to be informed about taunting behavior by peers and should alert the school system so that such behavior is not tolerated.

Follow-up eye care

Children with albinism require periodic updating of glasses prescriptions; filtering lenses and a cap or hat are helpful, especially if the individual is photosensitive. Contact lenses are often used successfully in conjunction with sunglasses. In some cases, extraocular muscle surgery is recommended to restore binocular alignment in those with strabismus and/or to improve a head posture in those with an eccentric null point.[69,76,115–118] Such surgery may produce minimal improvement in visual acuity.

If genetic testing has not identified mutations in a gene known to cause albinism, each examination in a child with OCA should include an inquiry about easy bruising, epistaxis, or other excessive bleeding. When the answer is affirmative, consideration is given to evaluating platelets for absent dense bodies[4]; if dense bodies are absent, genetic testing for HPS is considered, to assess the risk of associated systemic abnormalities. Those with HPS should avoid aspirin and non-steroidal anti-inflammatory agents, and have medical information available for severe trauma or surgery. Desmopressin (1-desamino-8-D-arginine-vasopressin or DDAVP) and a platelet infusion can be administered when hemostasis is needed.

Skin care

Children with OCA should establish regular care with a dermatologist in view of their increased risk of damaging sunburns, later resulting in cutaneous malignancies.[4] Sunscreens with ultraviolet A (UVA) and UVB protection and a sun protection factor (SPF) of at least 30 should be used regularly and liberally, even on cloudy days if outside, and should be re-applied every few hours. Use of hats, caps, UV-protective clothing, sunglasses, and SPF lip protection are recommended. Outdoor exposure in midday sunlight should be avoided. The risk of DNA-altering sunburn is increased near water, snow, concrete, and sand.[1,5] Most individuals obtain enough incidental ultraviolet light to produce vitamin D, but if there is concern about hypovitaminosis D, a vitamin D level can be obtained by the primary care provider.

Treatment

Drug trials have been performed in an attempt to improve the symptoms noted by those with albinism. Oral levodopa has not been shown to improve visual acuity in oculocutaneous albinism.[119] A study of nitisinone, which darkens the coat and iris color in mice,[120] is under way in humans with OCA1B. To date, gene therapy has not been tried in albinism.

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Vitreous

Michel Michaelides and Anthony T Moore

Chapter contents

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VITREORETINAL DYSPLASIA
INHERITED VITREORETINAL DISORDERS
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Introduction

The vitreous, a transparent gelatinous structure that fills the posterior four-fifths of the globe, is firmly attached to the pars plana and loosely to the retina and optic nerve posteriorly. In childhood there is a firm attachment to the lens.

The development of the vitreous body and zonule can be divided into three stages:

1. The *primary* vitreous is formed during the first month of gestation and is a vascularized mesodermal tissue separating the developing lens vesicle and the neuroectoderm of the optic cup. It contains branches of the hyaloid artery that later regress.
2. The *secondary* vitreous starts at 9 weeks and develops throughout embryonic life. It forms the vitreous body, is avascular and transparent, and displaces the primary vitreous, which becomes Cloquet's canal, running from the optic disc to the lens. By the third month, the secondary vitreous fills most of the developing vitreous cavity.
3. The *tertiary* vitreous lies between the ciliary body and lens, separated from the secondary vitreous as well-formed fibrils, which later develop into the zonule.

Developmental anomalies of the vitreous

Persistence of the primary vitreous or part of its structure may give rise to a number of congenital abnormalities.

Persistent hyaloid artery (see Chapter 36)

Persistence of all, or more frequently part, of the hyaloid artery is a common congenital abnormality. Hyaloid artery remnants occur in 3% of full-term infants but are commonly seen in premature infants, with most regressing. Rarely, the whole artery may run from the disc to the lens. Posterior remnants may give rise to a single vessel running from the center of the disc or to an elevated bud of glial tissue – Bergmeister's papilla. Anterior remnants of the hyaloid system may be seen as a small white dot on the posterior lens capsule – Mittendorf's dot. They are non-progressive and do not interfere with vision.

Vitreous cysts

Acquired cysts occur with inflammatory disease and, rarely, with X-linked retinoschisis. Congenital cysts are usually found in otherwise normal eyes. Their origin is unknown but, as blood vessels are sometimes seen within them, they may develop from hyaloid artery remnants.

Cysts may lie in the vitreous immediately behind the lens (Fig. 42.1) or in the posterior vitreous. They may be mobile or attached to the lens or optic disc. Mostly, intervention is not required; occasionally laser treatment (Nd:YAG or argon laser) may be used to collapse the cyst if it is symptomatic. However, repeat Nd:YAG therapy of an anterior pigmented cyst has resulted in a cataract.[1]

Persistent fetal vasculature (persistent hyperplastic primary vitreous) (see Chapter 37)

Persistent fetal vasculature (PFV), also referred to as persistent hyperplastic primary vitreous (PHPV) in the past, is caused by failure of the primary vitreous to regress. Most cases are sporadic and unilateral; there may be minor abnormalities in the fellow eye. Bilateral and familial cases have been reported but these are likely to represent cases of vitreoretinal dysplasia (see below).

For anterior PFV, see Chapter 37. In posterior PFV, the ocular abnormality is confined to the posterior segment, and may present with leukocoria, strabismus, microphthalmia, or nystagmus. The lens is usually clear. There is often a fold of condensed vitreous and retina running from the optic disc to the ora serrata or lens (Fig. 42.2), often associated with a retinal detachment. Ultrasound and computed tomography (CT) imaging help in differentiating PFV from retinoblastoma (see Chapter 43).

Enucleation should be avoided because a prosthesis may be less acceptable cosmetically, and there may be decreased growth of the orbit giving facial asymmetry. A limbal or pars plicata approach may be used to remove the lens and retrolental

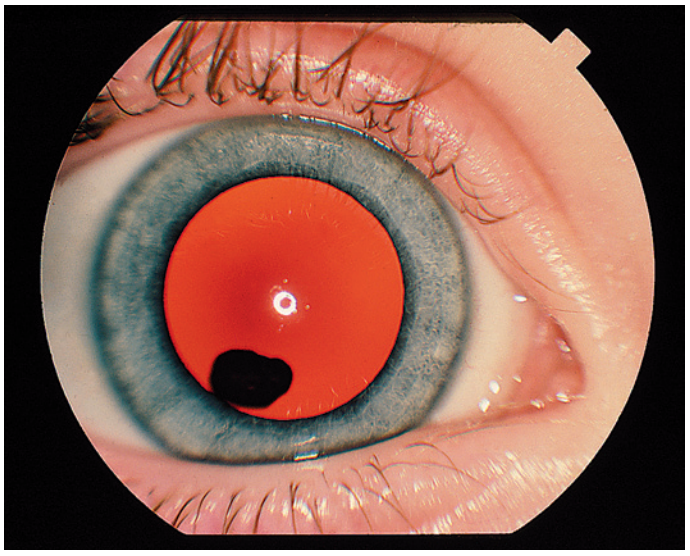


Fig. 42.1 Anterior vitreous cyst seen with retroillumination.



Fig. 42.2 Posterior persistent hyperplastic primary vitreous. A fold of condensed vitreous running from the optic disc can be seen. The left optic disc is normal.

tissue to clear the visual axis, improve cosmesis, deepen the anterior chamber, and prevent angle closure glaucoma caused by anterior chamber shallowing. However, in many cases, surgical intervention is not required.

Vitreoretinal dysplasia

Maldevelopment of the vitreous and retina, vitreoretinal dysplasia, is seen either as an isolated abnormality or associated with systemic abnormalities.[2] Syndromes such as Norrie disease and Warburg syndrome may have bilateral vitreoretinal dysplasia. It also occurs in trisomy 13, trisomy 18, triploidy, and in association with cerebral malformations.

There appears to be no relationship between the histologic findings and the various syndromes in which retinal dysplasia is reported. The dysplastic retina contains rosettes that resemble retinoblastoma rosettes but contain Müller cells with an abnormal relationship between the retina and retinal pigment epithelium (RPE).

Norrie disease

Clinical and histologic findings

Norrie disease is an X-linked recessive disorder; affected males are blind at birth or in early infancy. Twenty-five percent of affected males are developmentally delayed and one-third later develop cochlear deafness, usually starting in late teenage years. A more severe systemic phenotype is seen in patients with large chromosomal deletions encompassing the Norrie gene locus. Ocular findings include bilateral cataracts, bilateral retinal folds, retinal detachment, vitreous hemorrhage, and bilateral vitreoretinal dysplasia (Fig. 42.3). The retinal detachments are usually of early onset and have been observed *in utero* by ultrasonography. Most cases progress to an extensive vitreoretinal mass and bilateral blindness.

Angle closure glaucoma may develop; this is best managed by lensectomy. Late signs include corneal opacification, band keratopathy, and phthisis bulbi (see Fig. 42.3).

Carrier females do not usually show any ocular abnormality and electroretinography (ERG) is normal. An affected female has been reported, born to a carrier mother who had a retrolental mass in the right eye and a retinal fold with a tractional retinal detachment in the left. Molecular genetic testing confirmed that she was a manifesting heterozygote. She showed skewed X-inactivation in her peripheral blood lymphocytes, suggesting non-random inactivation, with inactivation occurring more frequently in the normal rather than the mutant X chromosome. A female with Norrie disease with an X autosome translocation has also been described.[3]

Histopathology of a vitreoretinal biopsy suggested arrest of normal retinal development during the third or fourth month of gestation, but the eyes of an aborted 11-week fetus with Norrie disease showed no evidence of primary neuroectodermal maldevelopment of the retina, suggesting a later disorder of development, probably related to abnormal retinal vascular development (see below).

Molecular genetics and pathogenesis

More than 100 mutations have been identified in the Norrie disease gene *NDP*. The gene is expressed in the neural layers of the retina, throughout the brain, and in the spiral ganglion and stria vascularis of the cochlea. The encoded protein, Norrin, is a component of the Wnt signaling pathway, a key regulator of various stages of ocular development, including retinal field establishment, maintenance of retinal stem cells, vasculogenesis in the retina, formation of the ciliary body, and cornea and lens development.[4] Wnt signaling is important in retinal development: uncontrolled, it may cause other retinal diseases including familial exudative vitroretinopathy, the osteoporosis–pseudoglioma syndrome, and Norrie disease. The association of Norrie disease with peripheral vascular disease affecting the lower limbs is evidence for a role of the Norrin gene in extraocular angiogenesis.

The identification of the Norrie disease gene allows molecular genetic diagnosis of the carrier state and prenatal diagnosis. Norrie disease may be associated with chromosomal deletions involving the *NDP* locus, the adjacent monoamine oxidase genes *MAOA* and *MAOB*, and additional genetic material. Children with such deletions have a more severe ("atypical") phenotype.[5] In addition to the characteristic retinal dysplasia, the "atypical" phenotypes may include: severe

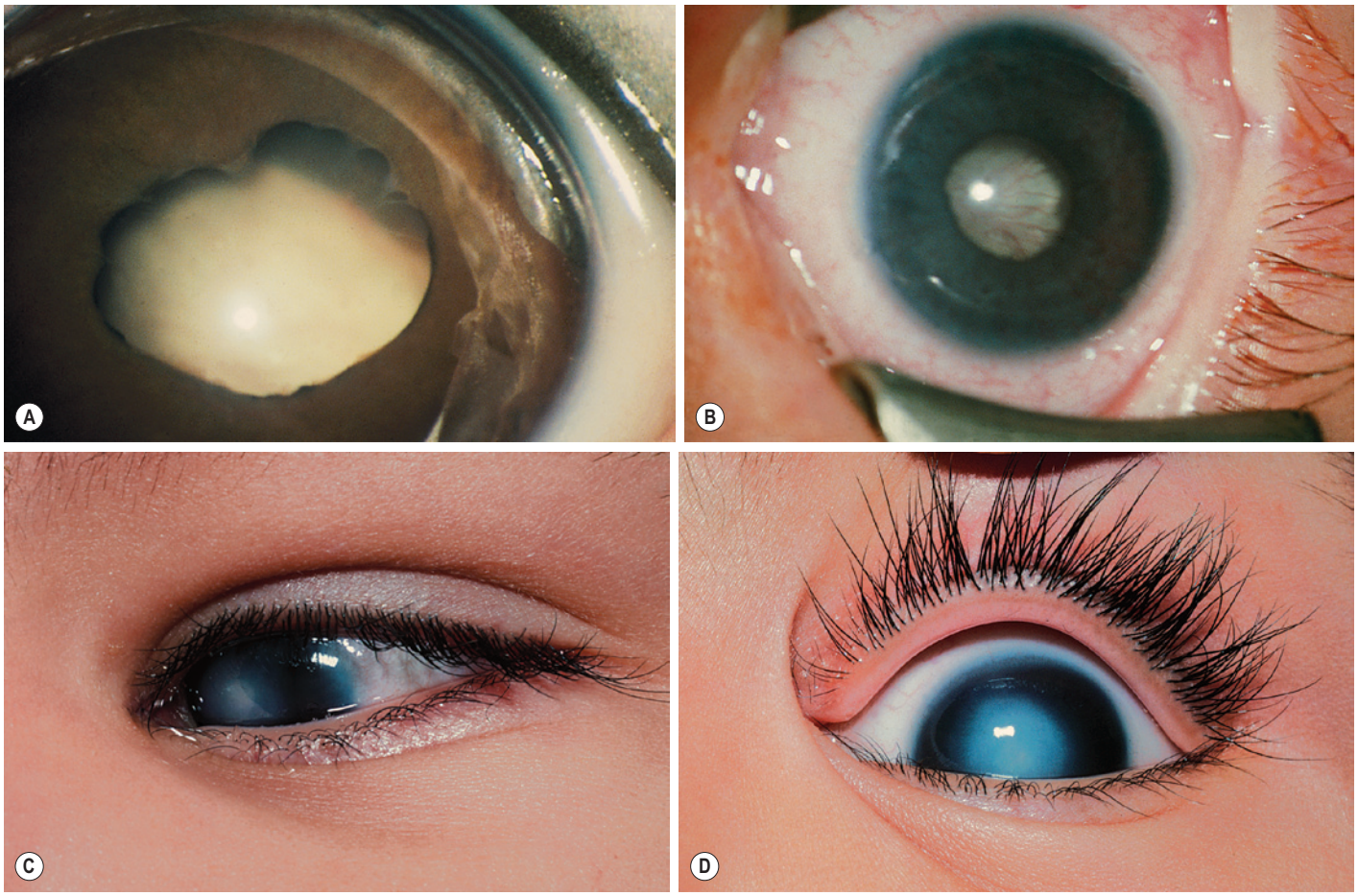


Fig. 42.3 Norrie disease. (A) Posterior synechiae, shallow anterior chamber, and retrolental white mass. (B) Brother of patient in (A) showing vascularized white retrolental mass. (C,D) Flat anterior chambers and lens–cornea adhesions.

learning difficulties, involuntary movements, atonic seizures, hypertensive crises, and hypogonadism.[5]

Mutations of the Norrie disease gene may be responsible for another rare vitreoretinal disorder, X-linked familial exudative vitreoretinopathy (see below).

Coats disease may be caused by somatic mutations in *NDP* only in the retina of affected eyes; the somatic mutations result in deficiency of Norrin with consequent abnormal retinal vascular development, the hallmark of Coats disease.

The role of the *NDP* gene in retinopathy of prematurity (ROP) is controversial. Some case–control studies have suggested that sequence variants in the *NDP* gene may predispose to stage 5 ROP; other studies have been negative.[6,7] The controversy will not be resolved until larger studies have been performed.

NDP knock-out mouse models have a similar ocular phenotype to humans, with fibrous masses in the vitreous cavities, disorganization of retinal ganglion cells, and sporadic degeneration of other retinal cell types. The retinal vasculature is abnormal by postnatal day 9, with abnormal vessels in the inner retina and few vessels in the outer retina. This is further evidence for disordered retinal vascular development being the primary cause of the retinal detachment in Norrie disease. As in humans, these mice have progressive hearing loss leading to profound deafness, with abnormal vasculature and eventual loss of most of the vessels in the stria vascularis (the main vasculature of the cochlea), suggesting a principal function of Norrin in regulating the interaction of the cochlea with its vasculature.

Management

In most cases of Norrie disease, affected males have bilateral total retinal detachment from birth and vitreoretinal surgery is not indicated. Lensectomy may be indicated when there is shallowing of the anterior chamber and a risk of pupil-block glaucoma. It is important that children and their families have good educational and social support and are referred for genetic counseling to discuss the risk of further affected pregnancies. Molecular diagnosis is possible in the majority of cases and prenatal and pre-implantation diagnosis is possible where the causative mutation is known. Recently, early delivery of a fetus known to carry a Norrin mutation followed by anti-vascular endothelial growth factor (VEGF) and laser treatment of the retina was shown to result in a good outcome with normal foveal structure.[8] This suggests that in some families who choose this option, prenatal diagnosis, preterm delivery, and prompt laser treatment may prevent retinal detachment.

Trisomy 13

Clinical and histologic findings

Trisomy 13 (Patau syndrome) is the chromosomal abnormality most consistently associated with severe ocular defects.

Box 42.1

Ocular abnormalities in trisomy 13

- Microphthalmos
- Coloboma of the uveal tract
- Cataract
- Corneal opacities
- Retinal dysplasia
- Persistent hyperplastic primary vitreous
- Dysplastic optic nerves
- Cyclopia

Systemic abnormalities include microcephaly, cleft palate, congenital cardiac defects, polydactyly, skin hemangiomas, umbilical hernia, and malformation of the central nervous system. Most children die within the first few months of life.

Bilateral ocular abnormalities are seen in almost all cases of trisomy 13; the common ocular findings are detailed in Box 42.1. There is total disorganization of the vitreous and retina; extensive retinal dysplasia is evident histologically. Intraocular cartilage, which is frequently present, may be a characteristic feature.

Incontinentia pigmenti (Bloch–Sulzberger syndrome)

Clinical and histologic findings

Incontinentia pigmenti (IP) is an uncommon X-linked dominant disorder affecting the skin, bones, teeth, central nervous system, and eyes, which is usually lethal *in utero* in males, leading to a marked female preponderance. The characteristic skin lesions appear soon after birth with a linear eruption of bullae predominantly affecting the extremities (Fig. 42.4A). The bullae gradually resolve to leave a linear pattern of pigmentation (Fig. 42.4B).

Ocular abnormalities are common including amblyopia, strabismus, nystagmus, optic atrophy, and retinal changes.[9] The retinal changes are the cause of severe visual impairment that may be seen in IP. Corneal abnormalities include whorl-like epithelial keratitis with epithelial microcysts, subepithelial anterior stromal opacities, and mild mid-stromal haze.

The most serious complication is retinal detachment, which may lead to severe visual impairment. Retinovascular abnormalities are common and include retinal vascular tortuosity, capillary closure, and peripheral arteriovenous shunts (Fig. 42.4C–E). These are most marked in the temporal periphery and may be associated with retinal neovascularization. Fluorescein angiography demonstrates areas of non-perfusion in the temporal periphery (Fig. 42.4E). Retinal neovascularization, if left untreated, may lead to tractional retinal detachment.

An ophthalmologist should regularly assess affected females soon after diagnosis and during infancy, in order to detect those cases of retinal vascular non-perfusion requiring treatment, usually occurring in the first 2–3 years of life. In very young infants referred early, an examination in the clinic with a lid speculum may be sufficient to obtain a peripheral fundus examination. If the retinal vessels are normal and extend into zone 3 then an examination under anesthetic can be avoided. If any peripheral retina abnormality is identified, and in those infants where it is not possible to see the periphery well, then a single baseline examination under anesthetic with RetCam photography and fluorescein angiography is indicated. Laser treatment is indicated when there is significant capillary non-perfusion (Fig. 42.4F–H). Careful follow-up in infancy and early childhood is necessary for those infants that have incomplete retinal vascularization. Established retinal detachment is difficult to manage and has a poor visual outcome (Fig. 42.4I). It is rarely bilateral.

Strabismus, refractive errors, and amblyopia are common in patients with IP, and clinic visits for retinal examination are also an opportunity for examination of visual acuity, refraction, ocular alignment, and treatment of amblyopia where necessary.

Molecular genetics and pathogenesis

IP is caused by mutations in the ubiquitously expressed gene *NEMO* (also known as *IKBKG*, NF-κB essential modulator). The NEMO protein is the regulatory component of the IκB kinase (IKK) complex, a central activator of the NF-κB transcriptional signaling pathway.[10] In IP, loss-of-function mutations in *NEMO* lead to a susceptibility to cellular apoptosis in response to tumor necrosis factor (TNF)-α.[8]

A recurrent genomic deletion within *NEMO* accounts for 90% of mutations. This deletion eliminates exons 4–10 (*NEMOΔ4–10*) and abrogates protein function. The remaining mutations are small duplications, substitutions, and deletions. Most *NEMO* mutations cause premature protein truncation, which is predicted to eliminate NEMO function and thereby cause cell death. Expression analysis of human and mouse *NEMO*/*nemo* has shown that the gene becomes active early during embryogenesis and is expressed ubiquitously, suggesting a vital role in embryonic and postnatal development.

Irrespective of the mutation causing IP, X-inactivation is likely to modulate the severity in females and account for some of the phenotypic variation. Some females carry the common deletion but are clinically normal, suggesting that selection against mutant cells commenced very early in prenatal development, as in mouse models, in which surviving $nemo^{+/-}$ female mice show marked skewing of X-inactivation. Although X-inactivation may account for the female phenotypic variation, a role for modifier genes cannot be excluded. In males, X-inactivation is not an issue, and most *NEMO* mutations are lethal because they abolish NF-κB activity, making cells susceptible to TNF-α-induced apoptosis, a finding also demonstrated in *nemo*-null male mice.

Less deleterious mutations can give rise to surviving males and an ectodermal dysplasia-like phenotype with immunodeficiency. Males with skin, dental, and ocular abnormalities typical of those seen in female patients with IP are rare. To date, all carried the common deletion *NEMOΔ4–10*, normally associated with male death *in utero*. Survival in one patient was explained by a 47,XXY karyotype and skewed X-inactivation. The three other patients had a normal 46,XY karyotype, with both wild-type and deleted copies of the *NEMO* gene, and thereby represent somatic mosaics for the common mutation: they acquired the deletion at a post-zygotic stage. There are, therefore, three mechanisms for survival of males carrying a *NEMO* mutation: mild mutations, a 47,XXY karyotype, and somatic mosaicism.

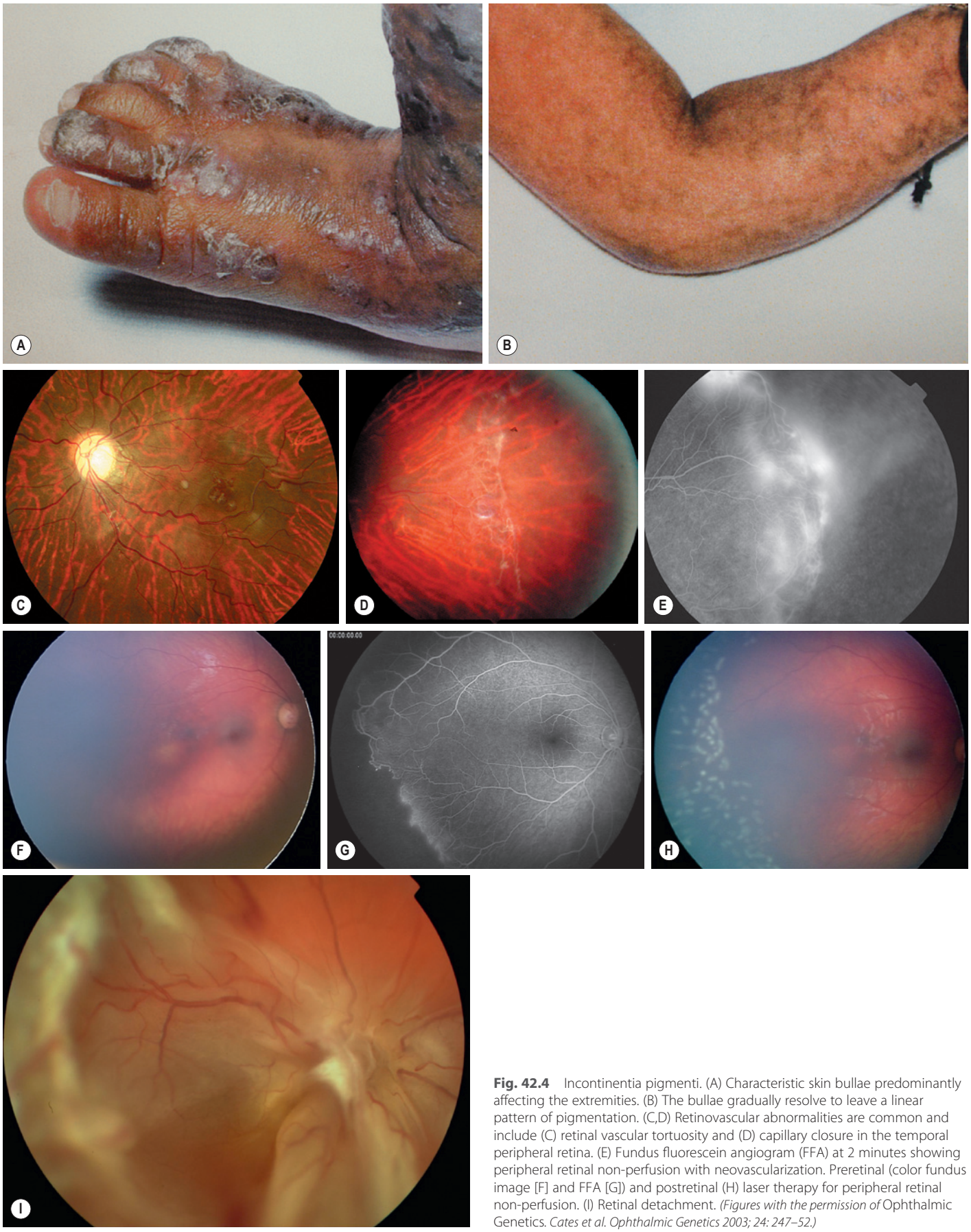


Fig. 42.4 Incontinentia pigmenti. (A) Characteristic skin bullae predominantly affecting the extremities. (B) The bullae gradually resolve to leave a linear pattern of pigmentation. (C,D) Retinovascular abnormalities are common and include (C) retinal vascular tortuosity and (D) capillary closure in the temporal peripheral retina. (E) Fundus fluorescein angiogram (FFA) at 2 minutes showing peripheral retinal non-perfusion with neovascularization. Preretinal (color fundus image [F] and FFA [G]) and postretinal (H) laser therapy for peripheral retinal non-perfusion. (I) Retinal detachment. *(Figures with the permission of* Ophthalmic Genetics. *Cates et al. Ophthalmic Genetics 2003; 24: 247–52.)*

Walker–Warburg syndrome (HARD ± E) and related syndromes

Clinical findings

The acronym "HARD ± E" stands for hydrocephalus, agyria, retinal dysplasia, with or without encephalocele (Fig. 42.5).



Fig. 42.5 Walker–Warburg syndrome. (A) Shallow anterior chamber and a retrolental mass. (B) Computed tomography scan showing hydrocephalus, lissencephaly, and colpocephaly.

This autosomal recessive syndrome is characterized by type II lissencephaly (absence of cortical gyri) (see Chapter 60), retinal dysplasia, cerebellar malformation, and congenital muscular dystrophy. Hydrocephalus is common, which is helpful for prenatal diagnosis by ultrasonography. Other variable features of the Walker–Warburg syndrome (WWS) include Dandy–Walker malformation and encephalocele. Neonatal death is common and survivors are severely developmentally delayed. The ocular features in this disorder are variable and include microphthalmia, Peters' anomaly, cataract, retinal coloboma, and retinal dysplasia.

There are two other rare autosomal recessive disorders characterized by the combination of congenital muscular dystrophy and brain malformations, including a neuronal migration defect: muscle–eye–brain (MEB) disease and Fukuyama congenital muscular dystrophy (FCMD) (see Chapter 60). Ocular abnormalities are a constant feature in MEB and WWS, but not in FCMD.[11] The distinction between MEB and WWS is difficult due to the overlap in their clinical characteristics.[11] Survival past 3 years of age is far more likely in MEB; death in infancy is more usual in WWS. Magnetic resonance imaging findings can also be helpful to differentiate between MEB and WWS: an absent corpus callosum suggests WWS.[11]

Genetic linkage studies have shown that WWS is not allelic to MEB.[11] The molecular genetics of these three disorders are likely to be helpful in distinguishing between them when the clinical diagnosis is unclear.

Molecular genetics and pathogenesis

The causative genes have been identified in MEB and FCMD; the encoded proteins are involved in protein glycosylation. Mutations in the gene *POMT1*, encoding *O*-mannosyltransferase 1, have been identified in WWS. Immunohistochemical analysis of muscle from patients with *POMT1* mutations corroborated the *O*-mannosylation defect, as judged by the absence of glycosylation of α-dystroglycan. The lack of this glycosylation is thought to explain the muscular dystrophy in WWS. The brain and eye phenotypes in WWS may involve defective glycosylation of other proteins. Further genetic heterogeneity in WWS is likely since only 20% of patients with WWS harbor *POMT1* mutations.

Autosomal recessive vitreoretinal dysplasia

Vitreoretinal dysplasia may occur as an isolated abnormality in a healthy child. The inheritance is presumed to be autosomal recessive. In male infants, mutations in the Norrie disease gene (*NDP*) must be excluded. Presentation is with bilateral poor vision in early infancy, a shallow anterior chamber, and white retrolental mass. Progressive shallowing of the anterior chamber can result in pupil-block glaucoma, which may require lensectomy.

Osteoporosis–pseudoglioma syndrome

Clinical findings

This autosomal recessive syndrome is characterized by osteoporosis, severe learning difficulties, and vitreoretinal dysplasia (Fig. 42.6). Multiple fractures, often after minor trauma, are commonplace. Affected children present in infancy

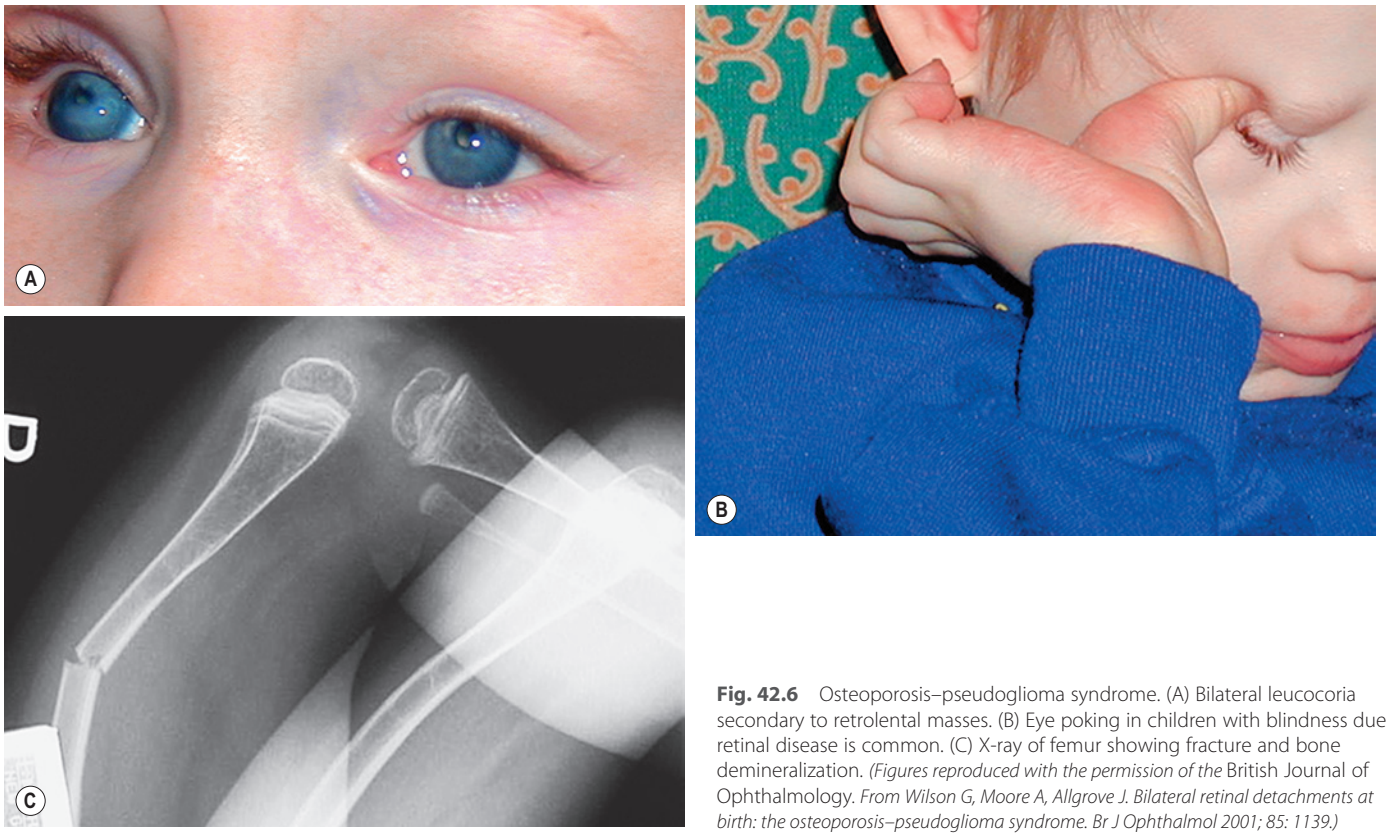


Fig. 42.6 Osteoporosis–pseudoglioma syndrome. (A) Bilateral leucocoria secondary to retrolental masses. (B) Eye poking in children with blindness due to retinal disease is common. (C) X-ray of femur showing fracture and bone demineralization. *(Figures reproduced with the permission of the* British Journal of Ophthalmology. *From Wilson G, Moore A, Allgrove J. Bilateral retinal detachments at birth: the osteoporosis–pseudoglioma syndrome. Br J Ophthalmol 2001; 85: 1139.)*

with bilateral nystagmus and severe visual impairment; the systemic features occur in later infancy and childhood. Ocular features include vitreoretinal dysplasia with retrolental masses, microphthalmia, anterior chamber anomalies, cataract, and phthisis bulbi. Most patients are blind from birth but a few patients have useful vision into their teenage years.

Molecular genetics and pathogenesis

Mutations have been identified in the gene encoding the low-density lipoprotein receptor-related protein 5 (LRP5). Mutations in *LRP5* have also been shown to be associated with both autosomal recessive and autosomal dominant familial exudative vitreoretinopathy (FEVR). These patients have also been shown to have reduced bone mineral density, suggesting that osteoporosis–pseudoglioma syndrome and *LRP5*-associated FEVR are part of a single phenotypic spectrum with both ocular and bone manifestations.[12]

Studies of LRP5 indicate that it affects bone accrual during growth by regulating osteoblastic proliferation. Furthermore, LRP5 is a component of the Wnt signaling pathway, regulating retinal development and angiogenesis. This accounts for the retinopathy resulting from LRP5 mutation.[4,13]

Oculopalatal–cerebral dwarfism

Three siblings of consanguineous parents were described with vitreoretinal dysplasia and systemic abnormalities including microcephaly, developmental delay, cleft palate, and short stature.[14] The ocular abnormalities, similar to those seen in PHPV, were bilateral in one child and unilateral in the others. It is probably autosomal recessive.

Unilateral retinal dysplasia

Lloyd et al. reported a family in which three affected members had unilateral retinal dysplasia without any systemic abnormalities.[15]

Genetic counseling in the vitreoretinal dysplasias

The vitreoretinal dysplasias are genetically heterogeneous disorders that result in a similar ocular abnormality; it is often not possible to subdivide them on the clinical or pathologic ocular findings alone, so the diagnosis depends on the systemic findings or molecular genetics, although the family history may suggest the mode of inheritance.

For the purposes of genetic counseling, families fall into two groups.

Group 1

The diagnosis and hence the mode of inheritance of the affected child is clear. When one child has been born with a trisomy, the risk of a similar affected child in a future pregnancy is 1%, but may be higher if one of the parents has a structural chromosome abnormality or mosaicism.[16] Such parents may be offered prenatal diagnosis.

In children with the systemic features of Walker–Warburg syndrome or the osteoporosis–pseudoglioma syndrome, the inheritance is autosomal recessive.

In Norrie disease there are no detectable clinical abnormalities in the carrier female to aid counseling. When there is another affected male relative, the mother can be assumed to be a carrier. In isolated boys, the status of the mother is uncertain,

but can usually be resolved by molecular genetic testing. If the mutation has been identified in the affected child, the mother and other at-risk female members can be screened for the mutation. Most mothers will be carriers. However, some mothers will not carry the identified Norrie gene mutation: their affected child may have a new mutation. Germline mosaicism is possible but rare. In this situation, the mother will need to be counseled that there is an increased, but low, risk of having a further child with Norrie disease.

Group 2

Counseling a family with an otherwise normal child with bilateral retinal dysplasia is more difficult. Isolated retinal dysplasia is rare so there are insufficient empirical data to aid counseling. If the affected child is female, retinal dysplasia may be autosomal recessive or non-genetic. Autosomal recessive dysplasia is rare; if there is no parental consanguinity, the recurrence risk is likely to be low. In an affected male child, retinal dysplasia may be autosomal recessive, X-linked, or non-genetic. Most affected males will have Norrie disease, which can be confirmed by molecular genetics. In the small minority without identifiable mutations in the *NDP* gene, if there is no parental consanguinity and other multisystem disorders have been excluded, the recurrence risk is probably low. Advances in molecular genetic testing using next-generation sequencing will greatly improve molecular diagnosis and genetic counseling.

Inherited vitreoretinal disorders

Wagner syndrome

Clinical findings

Wagner syndrome is an autosomal dominant vitreoretinal dystrophy with low myopia and vitreous and retinal abnormalities, without systemic abnormalities. The vitreous appears optically empty apart from scattered translucent membranes: there is usually a posterior vitreous detachment with a thickened posterior hyaloid. Peripheral vascular sheathing is common and normally associated with perivascular RPE atrophy and pigment deposition. The electroretinogram (ERG) is subnormal and parallels the chorioretinal pathology and poor night vision. Cataract develops after the second decade and is the usual cause of visual loss. Rhegmatogenous retinal detachment is infrequent, whereas peripheral tractional retinal detachment occurs in most of the elderly affected patients.

Wagner disease and erosive vitreoretinopathy share some clinical features; they both have subnormal ERGs, poor night vision, and field defects, which are not found in *COL2A1*-associated Stickler syndrome. The vitreoretinal phenotype is different, as neither of the recognized vitreous abnormalities in Stickler syndrome are present in Wagner syndrome (see below). In addition, retinal detachment is less common in Wagner syndrome, but occurs in the majority of patients with Stickler syndrome and erosive vitreoretinopathy.

Molecular genetics and pathogenesis

Wagner syndrome and erosive vitreoretinopathy are linked to 5q13–14 and are likely to be allelic disorders, distinct from Stickler syndrome. Heterozygous mutations in the gene encoding chondroitin sulfate proteoglycan-2 (CSPG2), a proteoglycan present in the vitreous body, have been identified in both Wagner syndrome and erosive vitreoretinopathy.

A phenotypically distinct vitreoretinopathy with early-onset retinal detachments and anterior segment developmental abnormalities, without systemic features, has been described, which also maps to 5q13–q14, to a 5-cM region already implicated in both Wagner syndrome and erosive vitreoretinopathy.

Erosive vitreoretinopathy

Clinical findings

Erosive vitreoretinopathy is characterized by autosomal dominant inheritance, night blindness, progressive field loss, vitreous abnormalities, progressive RPE atrophy, and combined tractional and rhegmatogenous retinal detachment.[17] ERG shows widespread rod and cone dysfunction. Peripheral RPE atrophy, field loss, and ERG abnormalities are evident in childhood. The vitreous is syneretic with areas of condensation but without the inflammatory signs seen in autosomal dominant neovascular inflammatory vitreoretinopathy. There are no systemic abnormalities.

Dragged retinal vessels and macular ectopia may occur, with tractional or rhegmatogenous retinal detachment in most affected adults. Twenty percent of affected eyes become blind from retinal detachment.[17]

Molecular genetics and pathogenesis

Heterozygous mutations in the gene encoding chondroitin sulfate proteoglycan-2 (CSPG2) have been identified.

Stickler syndrome (see also Chapter 52)

Clinical findings

In Stickler syndrome, abnormalities of vitreous gel architecture are a pathognomonic feature, usually associated with congenital and non-progressive high myopia. Other eye features include paravascular pigmented lattice degeneration, cataracts, and retinal detachment. Non-ocular features are very variable: deafness, a flat midface with depressed nasal bridge, short nose, anteverted nares, and micrognathia that can become less pronounced with age. Midline clefting, if present, ranges from a submucous cleft to Pierre–Robin sequence, whilst joint hypermobility declines with age. Osteoarthritis may develop after the third decade. Stature and intellect are normal.

Molecular genetics and pathogenesis

Most forms of Stickler syndrome are inherited as an autosomal dominant trait but rare recessive forms have been reported.

Autosomal dominant Stickler syndrome

The *COL2A1* gene encodes type II procollagen, a precursor of components of secondary vitreous and articular cartilage; several mutations occur in families with Stickler and Kniest syndrome. There is phenotypic variability with presence or absence of systemic features and locus heterogeneity with about two-thirds of families showing linkage to *COL2A1*.

Stickler syndrome can be divided into two types by slit-lamp biomicroscopy of the vitreous, facilitating prioritization of molecular screening:

1. type 1: with retrolental vitreous anomaly and is associated with mutations of the *COL2A1* gene;

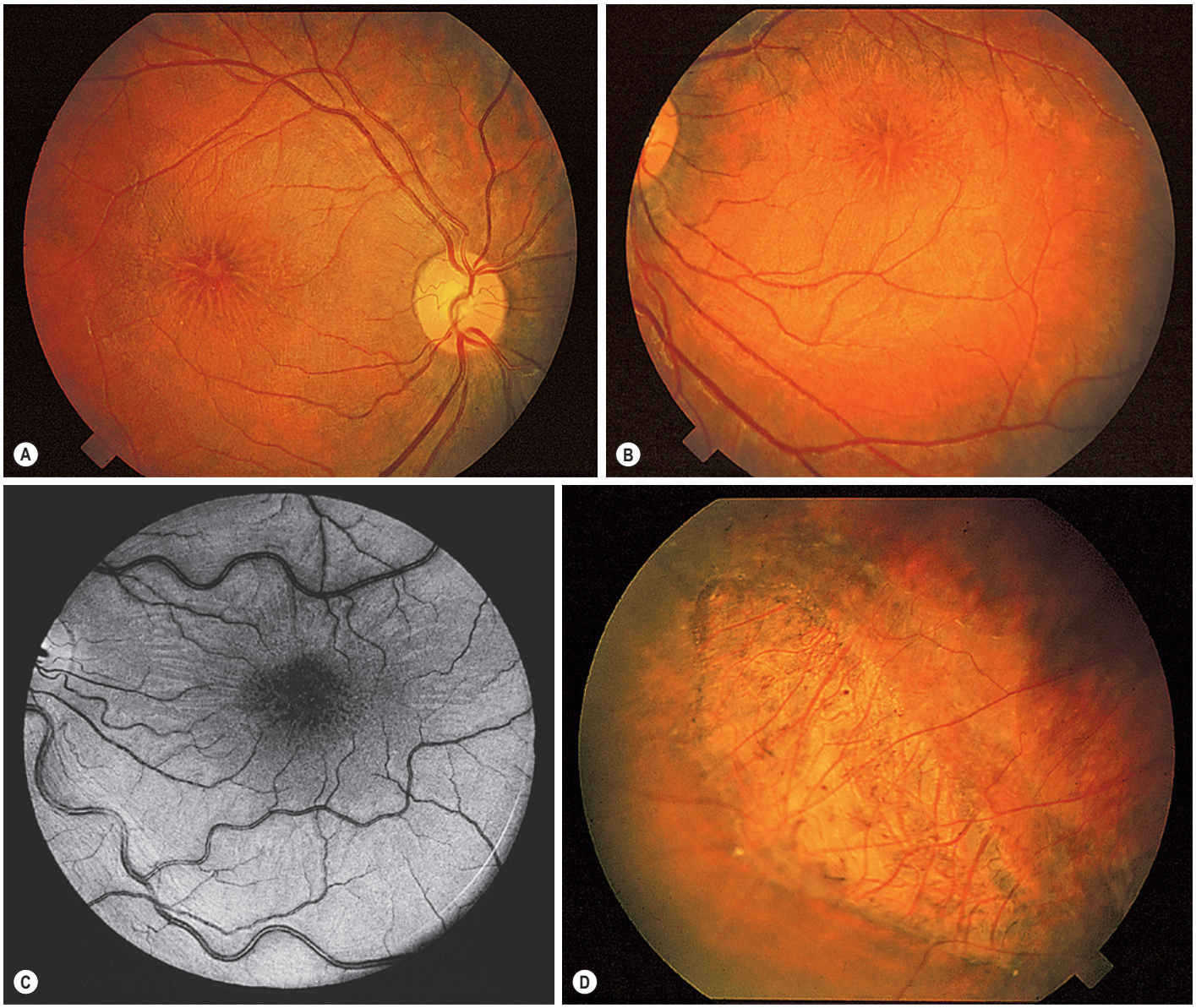


Fig. 42.7 Juvenile X-linked retinoschisis. (A,B) Bilateral foveal schisis. (C) The foveal schisis is best seen with ophthalmoscopy using a red free light. (D) Peripheral pigmentary changes in an area of schisis.

2. type 2: no retrolental vitreous anomaly and does not harbor *COL2A1* variants. Mutations in *COL11A1* (encoding α1 chain of type XI collagen) and *COL11A2* (encoding α2 chain of type XI collagen) have been identified in type 2 families.

Mutations in exon 2 of the *COL2A1* gene may produce a Stickler phenotype with predominantly ocular manifestations.

Autosomal recessive Stickler syndrome

Recessive forms of Stickler syndrome are rare and have been reported in association with mutations in *COL11A1*, *COL9A1*, *COL9A2*, and *COL9A3* genes.

Myelinated nerve fibres, vitreoretinopathy, and skeletal malformations

Severe vitreoretinal degeneration, high myopia, myelinated nerve fibers, and skeletal abnormalities were described in a mother and daughter that were distinct from those seen in Stickler syndrome. Both had severe visual impairment and roving eye movements, and electrophysiologic testing in the mother showed an abnormal scotopic and photopic ERG.

X-linked retinoschisis (see Chapter 51)

Clinical and histologic findings

This X-linked disorder is almost exclusive to males. The characteristic fundus abnormality is a cystic spokewheel-like maculopathy (foveal schisis), present in about two-thirds of males (Fig. 42.7A–C). Fifty percent of affected males show additional peripheral retinal changes (Fig. 42.7D). Foveal retinoschisis may occur in early infancy, but most children present between 5 and 10 years of age, either with reading difficulties or when they fail the school eye test. The visual acuity is 6/12–6/36 at presentation, and strabismus, hypermetropia, and astigmatism are common. If the macular changes are

Box 42.2

Classification of autosomal dominant familial exudative vitreoretinopathy

Stage I

Mild peripheral retinal changes with abnormal vitreous traction but no evidence of retinal vascular or exudative change.

Stage II

Dilated tortuous vessels between the equator and ora serrata with subretinal exudates and localized retinal detachment. Dragging of disc vessels and macular ectopia is often present.

Stage III

Advanced disease with total retinal detachment and extensive vitreoretinal traction. There may be secondary cataract and rubeosis iridis.

subtle, it may be misdiagnosed as strabismic or ametropic amblyopia or functional visual loss (see Chapter 63).

Familial exudative vitreoretinopathy

FEVR describes a group of inherited disorders with abnormal retinal vascularization often associated with exudation, neovascularization, and tractional retinal detachment.[18] In advanced disease there are some clinical similarities to cicatricial ROP. The clinical appearance varies considerably, even within families: severely affected patients are often registered as blind during infancy and mildly affected patients have few or no visual problems.

FEVR can be inherited as an autosomal recessive, autosomal dominant, and X-linked disorder. All the genes identified to date are components of the Wnt signaling pathway.[4,13] There appears to be no correlation between phenotype and mode of inheritance, particular mutations, or mutation types. *LRP5* mutation carriers (autosomal dominant and autosomal recessive FEVR) remain the only subset of FEVR patients that can be clinically distinguished by the presence of low bone-mass density.[4,12,13]

Autosomal dominant familial exudative vitreoretinopathy (AD-FEVR)

Clinical findings

The clinical expression is markedly variable (Box 42.2) with a widespread abnormality of the retinal vasculature, due to the arrest of normal vasculogenesis.[3,10] In the asymptomatic form, fundoscopy and fluorescein angiography reveals peripheral retinovascular abnormalities, particularly temporally, although fundus findings may be subtle (Fig. 42.8). These include vascular dilatation and tortuosity, arteriovenous shunting, capillary closure, and peripheral retinal neovascularization (Fig. 42.9). Optic disc neovascularization is less common. Vitreoretinal adhesions are frequently seen at the border between vascularized and non-vascularized retina, and other peripheral retinal changes include retinal pigmentation and intraretinal white deposits.

More advanced cases show vascular leakage, cicatrization with macular ectopia, tractional retinal detachment, and macular edema (Fig. 42.10). Vitreous hemorrhage and secondary rhegmatogenous retinal detachment are complications. The

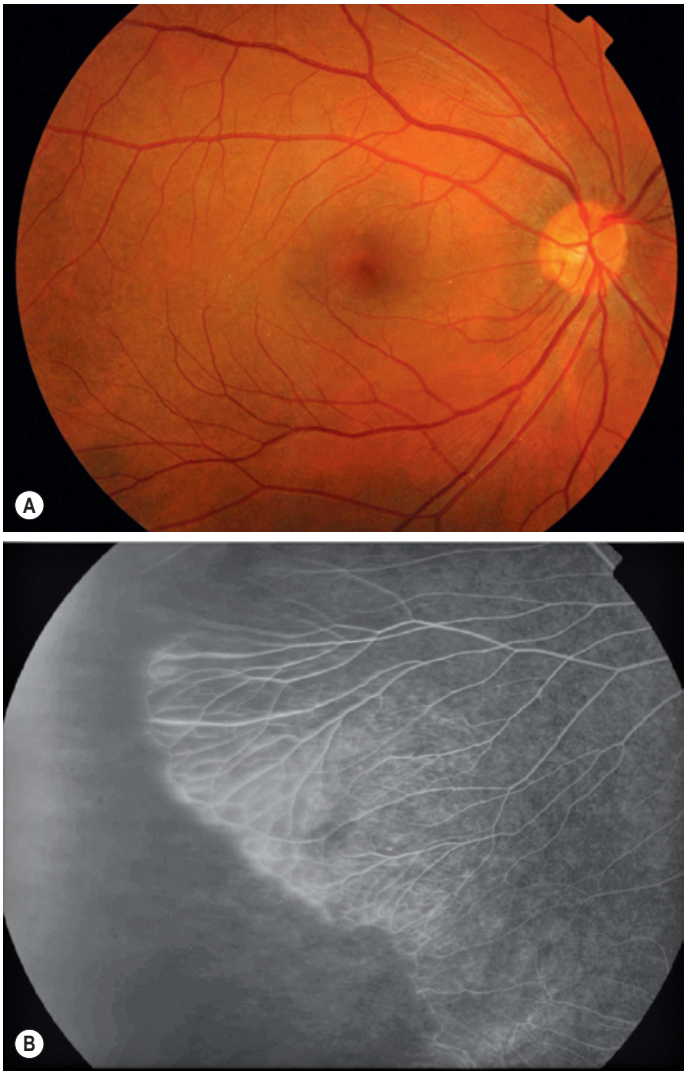


Fig. 42.8 Autosomal dominant familial exudative vitreoretinopathy. (A,B) An asymptomatic carrier with a normal examination of the posterior pole (A). The importance of fundus fluorescein angiography (FFA) can be seen in helping to determine status, with marked temporal retinal capillary closure observed on FFA.



Fig. 42.9 Autosomal dominant familial exudative vitreoretinopathy. Peripheral vascular dilatation, tortuosity, and shunting with some preretinal changes.

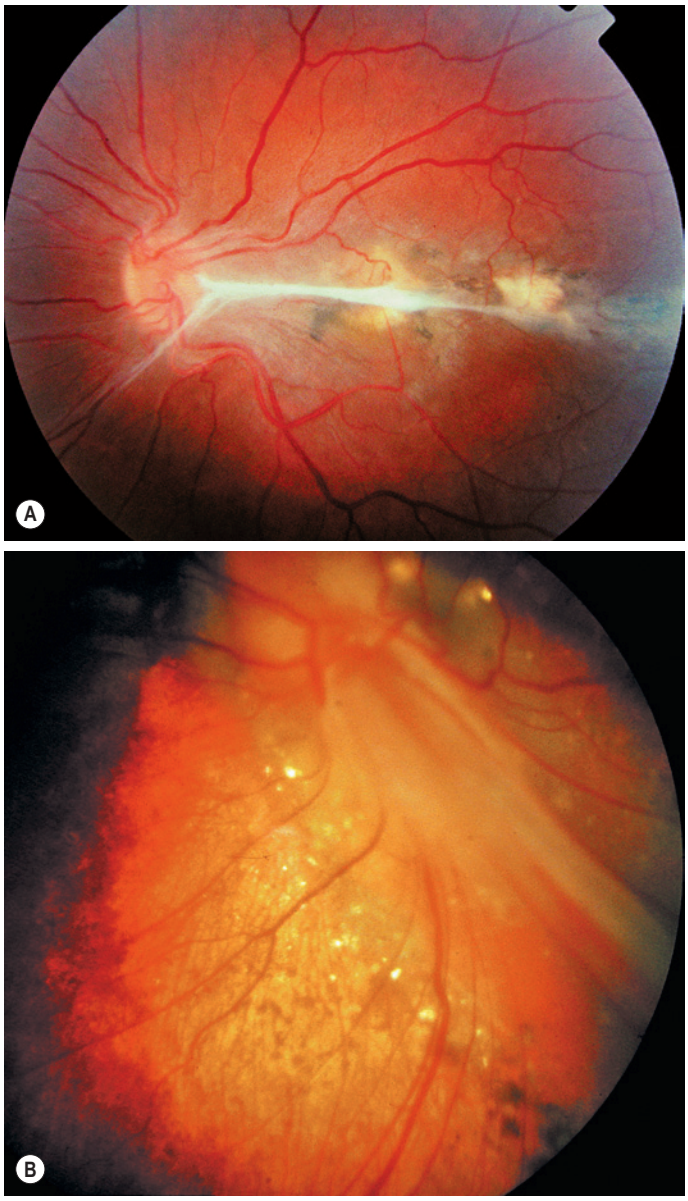


Fig. 42.10 Autosomal dominant familial exudative vitreoretinopathy (FEVR). (A) Cicatrization with macular ectopia. (B) Severe retinal fold secondary to FEVR.

retinal changes may progress throughout childhood, but rarely after the age of 20. In children who show progression from stage I disease (Box 42.2), laser ablation of peripheral ischemic retina may be indicated. In advanced cases, vitreoretinal surgery may be beneficial.

Many FEVR gene carriers are asymptomatic and have only minor retinovascular abnormalities. The gene is highly penetrant. It is important to perform a careful fundoscopic examination, preferably with fluorescein angiography, before excluding carrier status.

Molecular genetics and pathogenesis

Mutations in *FZD4* and *LRP5* have been detected in affected individuals.[4,13] *FZD4* and *LRP5* encode the receptors Frizzled-4 and low-density lipoprotein receptor-related protein-5, respectively, with these two proteins acting as co-receptors for Wnts and Norrin.[4,13] Mutations in *TSPAN12* have also been identified, which encodes a protein that facilitates the binding of Norrin to the aforementioned receptor. Other genes remain to be discovered, as not all cases are accounted for by current known genes. Recently, exome sequencing in Dutch families with FEVR with no known molecular cause has identified a missense variant in the *ZNF408* gene, which is a member of a family of zinc finger transcription factors.[19]

X-linked familial exudative vitreoretinopathy

Clinical findings

The phenotype may be similar to the severe form of dominant exudative vitreoretinopathy and may also resemble congenital falciform retinal folds. Affected males usually have severe early-onset visual impairment. Prominent retinal folds from the disc to the ora serrata are characteristic. Rarely, mildly affected males have been reported in families with X-linked FEVR.

Molecular genetics and pathogenesis

Point mutations in *NDP* have been identified. X-linked FEVR (XL-FEVR) and Norrie disease are thereby allelic disorders (different mutations of the same gene giving rise to a different but well-defined phenotype).

Autosomal recessive familial exudative vitreoretinopathy

Autosomal recessive FEVR (AR-FEVR) is less common than AD- and XL-FEVR. AR-FEVR is usually more severe than the dominant form of the disorder (Fig. 42.11). The management of the disorder follows the same principles as AD-FEVR.

Molecular genetics and pathogenesis

Biallelic mutations in *LRP5* and *TSPAN 12* have been detected in affected individuals.[4,13]

Autosomal dominant vitreoretinochoroidopathy (ADVIRC)

Clinical and histologic findings

This rare dystrophy has abnormal chorioretinal pigmentation in a 360° circumference between the vortex veins and the ora serrata, which is present in childhood and usually progresses. There are areas of hypo- and hyperpigmentation and scattered yellow dots may be seen in the peripheral retina and at the posterior pole. There are usually retinovascular changes with arteriolar narrowing, venous occlusion, and widespread leakage. A demarcation line is seen between the normal and abnormal retina. The vitreous is liquefied with peripheral condensation. Presenile cataract occurs frequently. Fluorescein angiography shows areas of capillary dilatation and diffuse vascular leakage; peripheral neovascularization may develop in a few cases.

Visual symptoms are rare in childhood but may occur in adults from cataract, macular edema, vitreous hemorrhage, and retinal detachment. Nyctalopia is not prominent and the ERG is normal, sometimes becoming abnormal with age. The electrooculogram (EOG) usually suggests a widespread RPE defect but can be normal. There are no consistent systemic abnormalities.

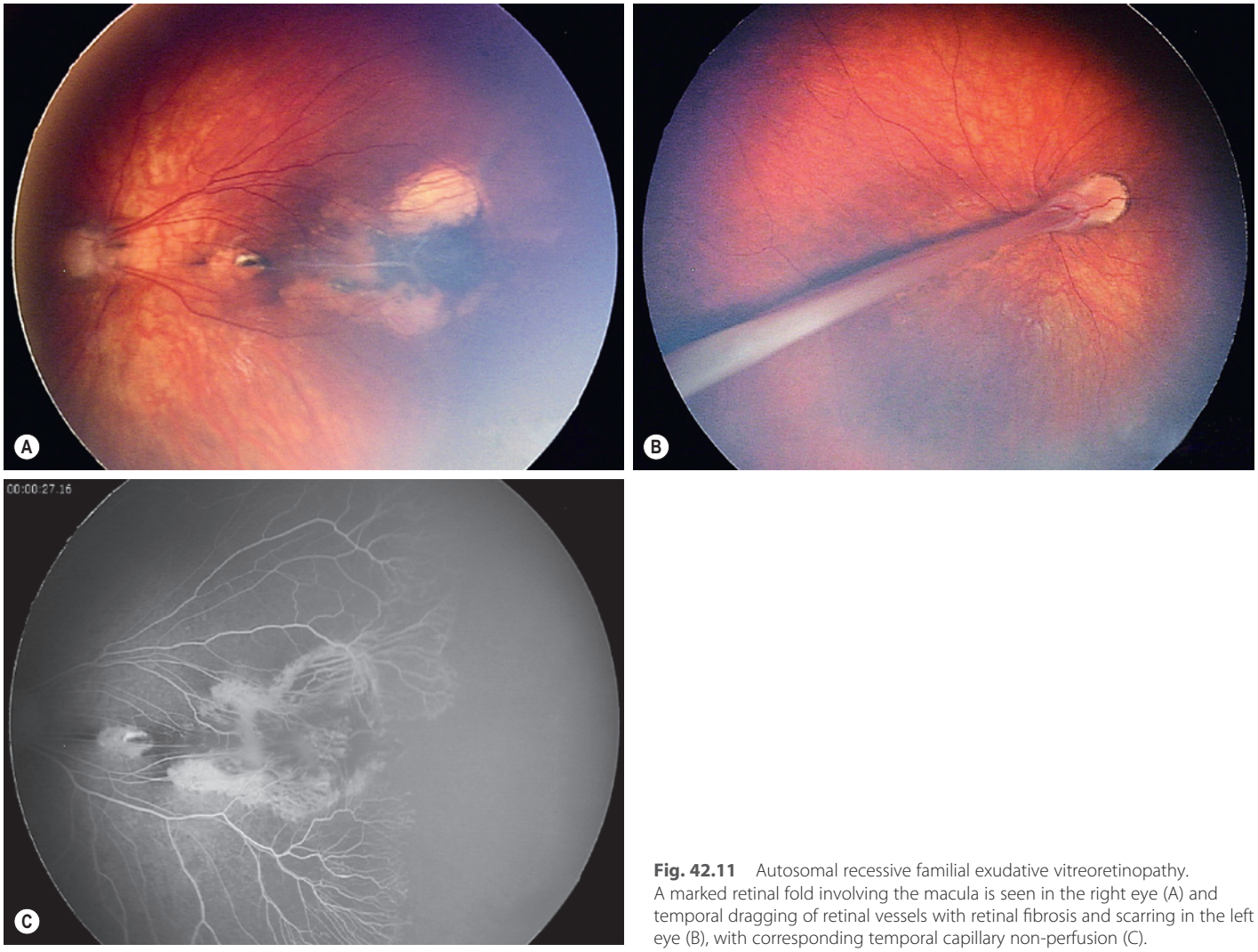


Fig. 42.11 Autosomal recessive familial exudative vitreoretinopathy. A marked retinal fold involving the macula is seen in the right eye (A) and temporal dragging of retinal vessels with retinal fibrosis and scarring in the left eye (B), with corresponding temporal capillary non-perfusion (C).

Light and electron microscopy showed similar findings in a young and an old patient suggesting that ADVIRC is an early-onset peripheral retinal dystrophy with minimal subsequent progression, characterized by a RPE response that includes marked intraretinal migration and extracellular matrix deposition.

Molecular genetics and pathogenesis

Mutations have been found in the bestrophin-1 gene (*BEST1*). Sequence variants have also been identified in *BEST1* in several other retinal phenotypes,[20] including Best disease (see Chapter 48), autosomal recessive bestrophinopathy, adult vitelliform macular dystrophy, MRCS (microcornea, rod–cone dystrophy, cataract, and posterior staphyloma), and retinitis pigmentosa (see Chapter 46).

Autosomal dominant neovascular inflammatory vitreoretinopathy

Clinical findings

This rare autosomal dominant disorder is characterized by panocular inflammation, peripheral retinal pigment deposition, retinal vascular occlusion and neovascularization, vitreous hemorrhage, and tractional retinal detachment. Presenile cataract is common. The single bright white flash ERG shows early selective loss of the b-wave ("negative-ERG"), which differentiates it from the other vitreoretinopathies with vascular closure. Night blindness is a late feature; the ERG may become totally extinguished in advanced disease. There are no reported systemic abnormalities.

The earliest signs are vitreous cells, mild peripheral retinal ischemia, and reduced b-wave amplitudes on ERG. It cannot be reliably detected in childhood.

Molecular genetics

It has been mapped to 11q, with heterozygous missense mutations identified in the gene *CAPN5*.

Autosomal dominant snowflake degeneration

This disorder is characterized by extensive "white-with-pressure" change in the peripheral retina, multiple minute "snowflake" retinal deposits, and sheathing of the peripheral retinal vessels. Later, there may be peripheral vascular occlusion and retinal pigmentation. The vitreous is degenerate and liquefied. Psychophysical studies show abnormal rod and cone function and although ERG may be normal initially, the b-wave amplitude is later reduced. There is an increased risk of retinal tears and detachment. The retinal changes may be

Box 42.3

Some causes of vitreous hemorrhage in children

- Trauma
  - Blunt
  - Penetrating
- X-linked juvenile retinoschisis
- Vitreoretinal dystrophies
  - Familial exudative vitreoretinopathy
  - Autosomal dominant vitreoretinochoroidopathy
  - Autosomal dominant neovascular inflammatory vitreoretinopathy
- Stickler syndrome
- Retinopathy of prematurity
- Persistent hyperplastic primary vitreous
- Retinal dysplasias
- Retinal hemangioblastoma
- Cavernous hemangioma
- Eales disease
- Coats disease
- Pars planitis
- Non-accidental injury/child abuse
- Birth-related hemorrhages
- Hematological disorders
  - Leukemia
  - Thrombocytopenia
  - Hemophilia
  - von Willebrand disease
  - Protein C deficiency

seen in childhood, but more often in the teens or later. There are no systemic abnormalities.

Molecular genetics and pathogenesis

A missense mutation has been identified in *KCNJ13*, which encodes an inwardly rectifying potassium channel. Null mutations in this gene have been implicated in Leber congenital amaurosis (see Chapter 46).

Acquired disorders of the vitreous

Acquired disorders of the vitreous are uncommon in childhood and generally occur when there is vitreous opacification caused by hemorrhage or, less commonly, inflammation. Tumor or infection may involve the vitreous cavity.

Vitreous hemorrhage (Box 42.3)

The management of vitreous hemorrhage is relatively straightforward in children who have reached the age of visual maturity. A conservative approach is preferred, with surgery only indicated if the hemorrhage is persistent or if there is an associated retinal detachment. In infants and young children, vitreous hemorrhage may lead to amblyopia and affect emmetropization. If, after a short period of observation, there is no resolution and if there is no underlying retinal abnormality that may herald a poor prognosis, early lens-sparing vitrectomy may be considered. Occlusion needs to be started as soon as possible.

Inflammatory disease of the vitreous

See Chapter 40.

Vitreous opacity due to tumor

Vitreous seeding may complicate retinoblastoma; clumps of tumor cells float in the vitreous but rarely give rise to diagnostic problems as there is usually a typical retinoblastoma. When there are clumps of cells in the anterior vitreous in an inflamed eye with an opaque vitreous there may be doubt as to whether the underlying etiology is inflammatory or neoplastic. Ultrasound or CT scan usually demonstrates a retinoblastoma, but not in the rare diffuse infiltrating forms.

Tumor cells may be found in the vitreous in leukemia but there is almost always associated retinal infiltration (see Chapter 67). Other intraocular tumors are rare.

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Retinoblastoma

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Chapter contents

PATHOGENESIS OF RETINOBLASTOMA
PRESENTATION
DIAGNOSIS
TREATMENT
PROGNOSIS
LONG-TERM FOLLOW-UP
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FUTURE PERSPECTIVE
REFERENCES

Retinoblastoma is an uncommon malignant ocular tumor of childhood, occurring in 1:18,000 live births.[1] Late diagnosis globally results in up to 70% mortality; where optimal therapy is accessible, more than 95% of children are cured. An integrated team approach of clinical specialists (ophthalmologists, pediatric oncologists and radiotherapists, nurses, geneticists) with imaging specialists, child life (play) specialists, parents, and others is an effective way to manage retinoblastoma. National guidelines can bring the whole health team up to developed country standards and set the stage for audits, studies, and clinical trials to continuously evolve better care and outcomes.[2] Retinoblastoma arises from embryonic retinal cells so the majority of cases occur under the age of 4 years. Primary treatments options include enucleation, or systemic or intra-arterial chemotherapy with laser and cryotherapy, selected with very careful considerations of the wellbeing of the whole child and family in treatment choices. Patients with a constitutional mutation of the *RB1* tumor suppressor gene are at increased lifelong risk of developing other cancers, which is increased with exposure to radiation (Figs 43.1 and 43.2).[3] Therefore, radiation is no longer a primary therapy to save an eye, and screening for extraocular and trilateral retinoblastoma is performed with magnetic resonance imaging (MRI) and ultrasound, not computed tomography (CT) scan.

The study of retinoblastoma has been seminal in the understanding of cancer in general. Studies of retinoblastoma have revealed that hereditary and non-hereditary tumors are initiated by the loss of both alleles of the tumor suppressor gene, *RB1*.[4,5] The existence of specific genes that act to suppress cancer was predicted from clinical studies of retinoblastoma.[6,7] The *RB1* gene was the first tumor suppressor gene to be cloned,[4] and has been found to have a critical role in many types of cancer.

Pathogenesis of retinoblastoma

Heritable and non-heritable retinoblastoma

All children with retinoblastoma tumors in both eyes (bilateral) have an *RB1* gene mutation on one of their chromosome 13s that predisposes them to develop retinal tumors in infancy and other cancers throughout life (see Figs 43.1 and 43.2). All bilaterally affected persons have *heritable* disease, but 90% have no family history of retinoblastoma (*not inherited*). They are the first affected in their family with a *new* germline mutation,[8] and 50% of their offspring will *inherit* the mutant *RB1* gene with 95% risk of developing tumors. Most children without a family history with retinoblastoma in only one eye have normal constitutional *RB1* alleles, but the eye tumor(s) has lost both functional alleles, similar to hereditary retinoblastoma. Fifteen percent of persons who had unilateral retinoblastoma have constitutional *RB1* mutations that can be transmitted to their offspring. Molecular and clinical genetics is an integral part of the management of all families affected by retinoblastoma.

Loss of both *RB1* alleles induces retinoblastoma

The observation that the children with bilateral retinoblastoma tend to be diagnosed at a younger age than those with non-hereditary retinoblastoma led to Knudson's prediction that two mutational events are required to initiate retinoblastoma tumors.[6] His analysis suggested that in the presence of a predisposing constitutional mutation, a single second mutation in one developing retinal cell initiates tumor development (heritable retinoblastoma) (median age of diagnosis 12 months), but both alleles are mutated in the single developing retinal cell in non-heritable unilateral retinoblastoma (median age of diagnosis 24 months). The two events were hypothesized to be mutations of both alleles of a gene that would "suppress" tumor formation in the retina.[7] The chance of losing the second *RB1* allele from developing retinal cells with only one normal *RB1* allele is sufficiently high that multiple tumors are common in hereditary retinoblastoma (see Fig. 43.1). However, it is virtually impossible for children without a constitutional *RB1* mutation to lose both alleles from several retinal cells so they develop only one, unilateral tumor (Fig. 43.3), and tend to

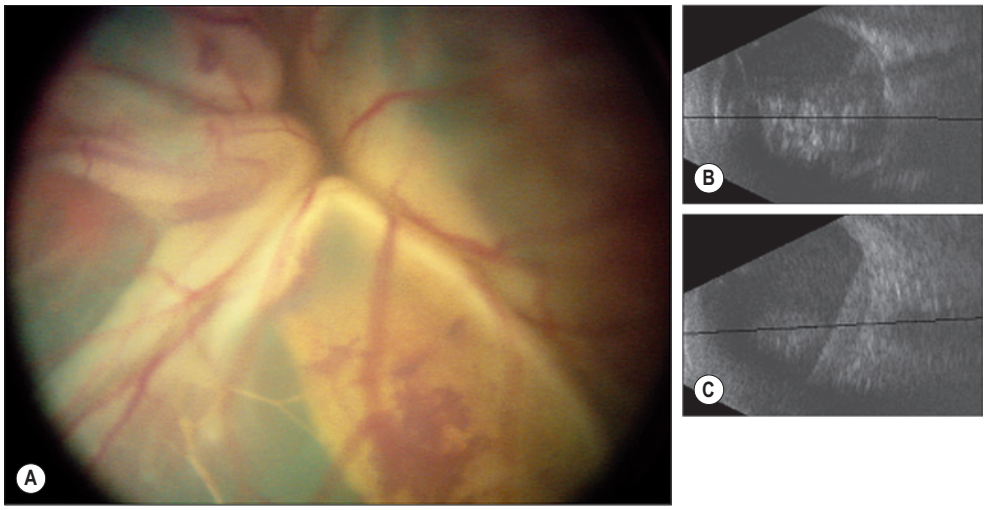


Fig. 43.3 (A) Exophytic retinoblastoma (IIRC[33] Group D) with retinal detachment in a unilaterally affected 3-year-old boy. (B) B-scan ultrasound showing calcification in a single tumor beside the optic nerve. (C) B-scan ultrasound showing subretinal hemorrhage and no tumor involvement of optic nerve. *(Images by Cynthia VandenHoven and Carmelina Trimboli.)*

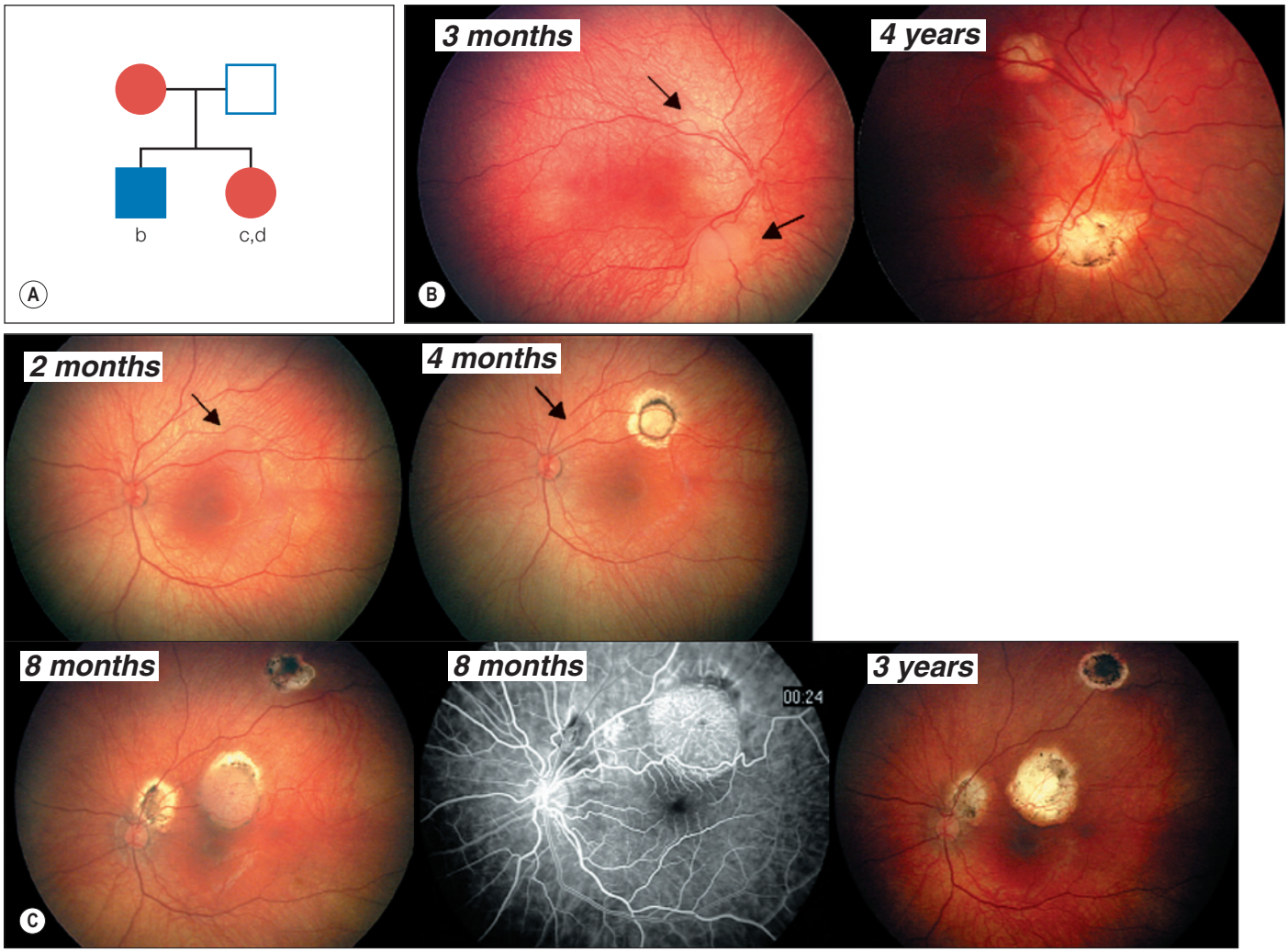


Fig. 43.1 (A) Family tree: Mother was cured of bilateral retinoblastoma by enucleation of one eye and external beam radiation of the other eye. Both children were delivered at 36 weeks' gestation to facilitate early treatment of tumors and developed bilateral tumors. Mother and both children carry a germline *RB1* mutation (M1, deletion of ATTTC starting at bp 778, reading to a STOP, 9 codons away) that results in no product of the RB1 gene (pRB) when the normal *RB1* allele is lost (M2) from a developing retinal cell, initiating a tumor. (B) Wide-angle retinal images: Prior to treatment, right eye (IIRC[33] Group A, more than 1.5 mm from optic disc) of the boy at 3 months, showing two tumors; stable right eye of boy age 4 years after laser, two cycles of CEV (carboplatin, etoposide, and vincristine) with cyclosporin A chemotherapy, and more laser treatments. (C) Wide-angle retinal images: Prior to treatment, left eye (IIRC[33] Group B, tumor less than 3 mm from fovea) of the girl at 2 months; laser scar and new tumor above nerve at 4 months of age; recurrence in original scar extending toward fovea, with tumor vascularization showing on fluorescein angiography; after laser, two cycles of CEV chemotherapy with cyclosporin A to control recurrence threatening vision, flat scars at age 2.5 years. *(Images by Leslie MacKeen, Cynthia VandenHoven, and Carmelina Trimboli.)*

be diagnosed at an older age than children with hereditary retinoblastoma.

Function of the retinoblastoma protein

The product of the *RB1* gene (pRB) is a 110-kDa, phosphoprotein that interacts with many proteins in the regulation of the cell cycle, differentiation, and control of genomic stability.[9] DNA tumor viruses that induce cancer, such as human papilloma virus, do so in part by binding to the "pocket" region of pRB.

Germline mutation of *RB1* leads to a 40,000-fold relative risk (RR) for retinoblastoma, a 500-fold RR for sarcoma that is increased up to 2000-fold by therapeutic radiation, but no increase in the RR for leukemia.[10] Although pRB is key to all cycling cells, its function in development is highly tissue-specific. A subset of developing retinal cells may be uniquely dependent on pRB in order to differentiate terminally into adult, functioning retina. Loss of pRB promotes genomic changes and instability, leading to further mutations in oncogenes and other tumor suppressor genes that result in a retinal tumor.[11,12]

Spectrum of *RB1* mutations

The majority of *RB1* mutations are unique to each family, and are distributed throughout the *RB1* gene with no real hot spots.[8] Sensitive mutation identification requires determination of the copy number of each exon and the gene promoter to reveal large deletions and duplications, sequencing for point mutations, examination of the mRNA to confirm or detect intronic mutations altering exon splicing, and assay for the methylation status of the promoter in tumor samples (Fig. 43.4). Next generation sequencing technologies are rapidly developing with promise to efficiently identify *RB1* mutations,

but do not yet approach the overall sensitivity necessary for full clinical application. Application of multiple techniques, combined with a retinoblastoma-specific focused expertise in interpreting the data, can identify 97% of *RB1* mutations[8,13] (see Figs 43.1, 43.3, 43.4, 43.5).

Oncogene-initiated retinoblastoma

A rare subset (2%) of unilateral, non-heritable retinoblastoma tumors have normal *RB1* and the tumors are initiated instead by high level amplification of the MYCN oncogene.[14] These are aggressive cancers that arise in very young children (median age of diagnosis 4.5 months)

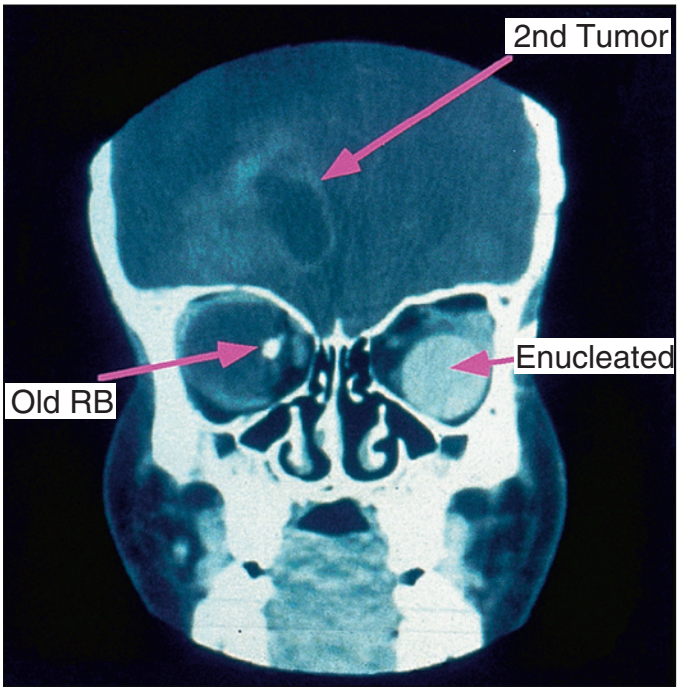


Fig. 43.2 Glioblastoma multiforme arising within the radiation field, 10 years after enucleation of the left eye and irradiation of the right eye for bilateral retinoblastoma (RB).

Other manifestations of *RB1* mutant alleles

Mutation of *RB1* also predisposes to benign retinal tumors, retinoma,[11,15] intracranial midline embryonic tumor (trilateral retinoblastoma),[16] and second non-ocular malignancies.[3]

Retinoma

A retinoma is a non-malignant manifestation of the *RB1* mutation.[15] Three features characterize these non-progressive lesions: an elevated grey retinal mass, calcification, and surrounding retinal pigment epithelium (RPE) proliferation and pigmentation (Fig. 43.5). These features are also seen after radiation treatment for retinoblastoma. If documented in childhood, which is very rare, retinoma is a quiescent tumor that has not progressed to malignancy. Occasionally a retinoma has been observed to later progress to active retinoblastoma. However, retinoma commonly underlies active retinoblastoma and can be discovered on pathologic examination of an enucleated eye with the distinctive features of fleurette formation and absence of proliferative markers.[11] Both *RB1* alleles are mutant in the retinoma and genomic instability is detectable, which progresses in degree and number of genes involved in the adjacent highly proliferative retinoblastoma. Discovery of retinoma on retinal examination of a relative of a patient with retinoblastoma indicates that they share an *RB1* mutant allele (see Fig. 43.5).

Intracranial midline embryonic tumor (trilateral)

Trilateral retinoblastoma is a midline intracranial tumor or a primary pineal tumor associated with heritable retinoblastoma that is not related to a metastasis.[16] The tumors are neuroblastic and resemble a poorly differentiated retinoblastoma. Pineal tumors arise in 5% of children with an *RB1* mutation but should not be confused with pineal cysts which occur in 2% of all children and require no treatment.[17] Affected children may present with raised intracranial pressure leading to diagnosis

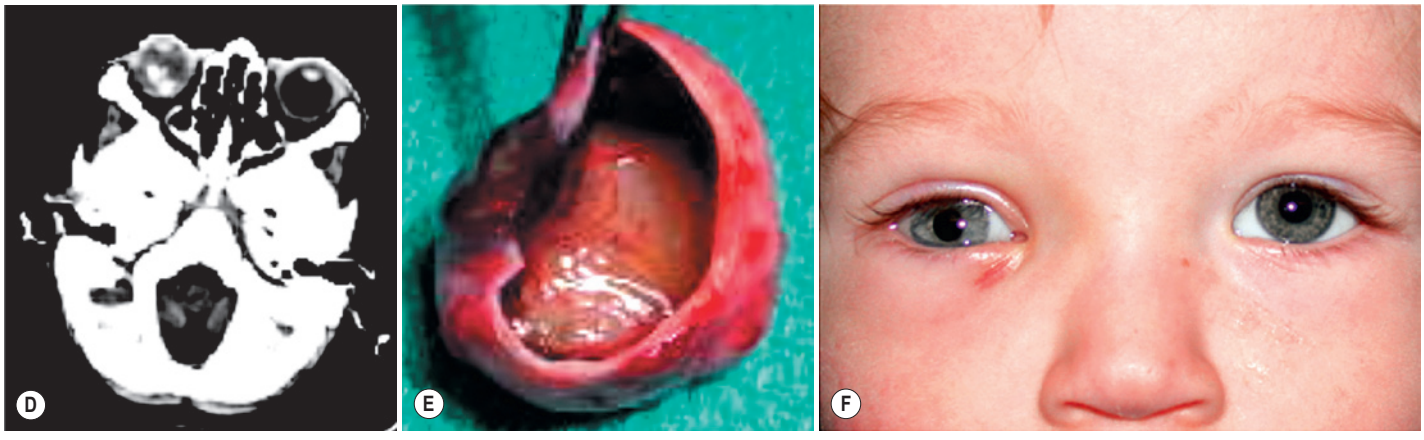


Fig. 43.3 (D) Computed tomography scan showing intraocular calcification, normal sized optic nerve. (E) The eye was opened immediately after enucleation, in order to obtain live tumor cells and the two *RB1* mutations (homozygous exon 16 deletion C-1450, insertion AT) defined. (F) The child 2 days after enucleation, wearing the temporary prosthetic conformer inserted at the time of surgery. The exon 16 *RB1* mutation of the tumor was not detected in blood, indicating high likelihood that the retinoblastoma is not heritable, eliminating risk for siblings. Due to the remaining possibility that the affected child is mosaic for the *RB1* mutation, his future offspring will be tested for this mutation. *(Images by Cynthia VandenHoven and Carmelina Trimboli.)*

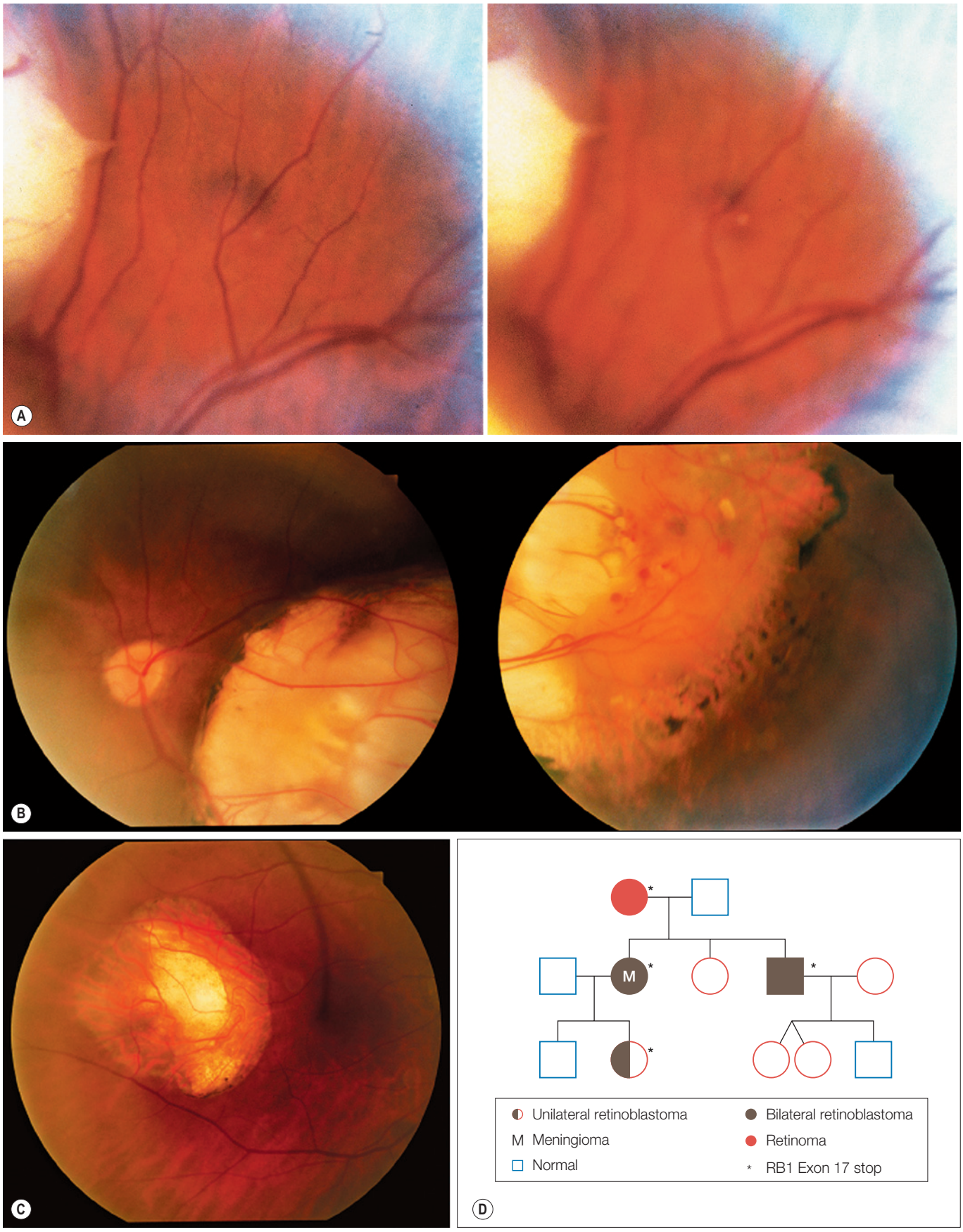


Fig. 43.5 (A) Retinoma with a vitreous seed (stereo images) discovered at age 18, followed for 30 years with no change; daughter had bilateral retinoblastoma. (B,C) Multifocal bilateral retinoma discovered in the grandfather when his granddaughter developed unilateral retinoblastoma. His daughter had bilateral retinoblastoma and meningioma at age 40. (D) All affected members carry a "null" germline *RB1* mutation (heterozygous point mutation in exon 17 resulting in a STOP codon).

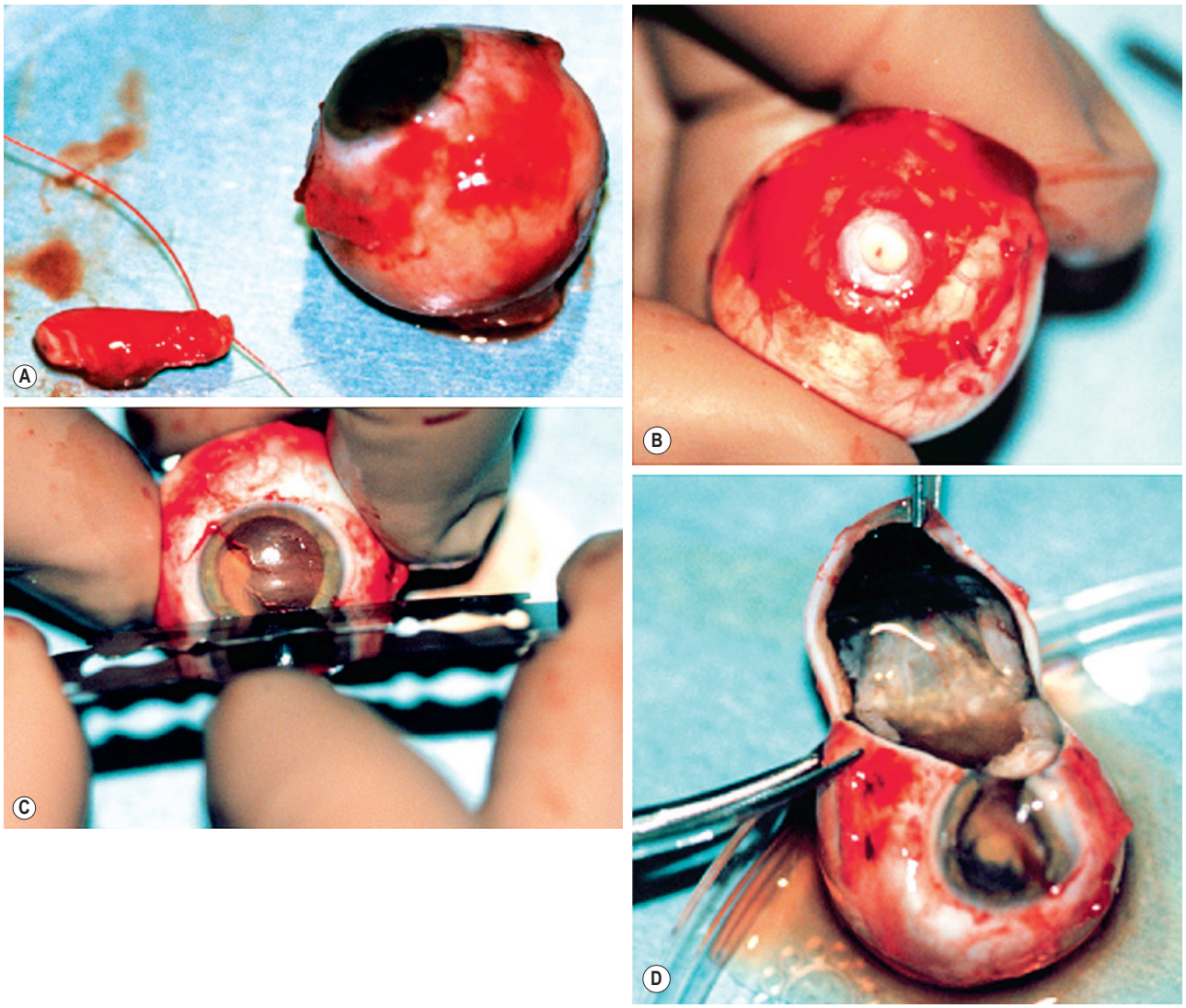


Fig. 43.4 Harvest of fresh tumor for determination of the *RB1* mutant alleles in unilateral tumor. (A) Optic nerve (8–12 mm) is excised from the globe and the distal end marked with a suture. The nerve is submitted as a separate specimen in a separate formalin container so that it is not contaminated by tumor from the opened eye. (B) Optic nerve just beyond the cribriform plate appears normal on gross inspection, to be confirmed microscopically. (C) Globe is opened with a razor incision in a pupillary–optic nerve plane, superior or inferior, at the limbus, in order to access intraocular live tumor. (D) Superior or inferior calotte allows harvest of large amount of intraocular tumor for adequate molecular studies. Optic nerve and choroid are not interfered with, since these are important for pathologic assessment for risk of extraocular spread. Tumor for molecular studies is sent to the lab in sterile tissue culture medium. The *RB1* mutations (M1 and M2) in this unilateral tumor were a heterozygous exon 14 CGA to TGA (R445X) and a heterozygous intron 16 G to A (cDNA 1498+5) causing a splice mutation. Neither M1 nor M2 were detected in blood of the child. *(Images by Cynthia VandenHoven.)*

of a pineal or parasellar mass on MRI.[18] Routine screening by MRI for intracranial tumors may detect pineal tumors at a stage when they can be cured, but formal evidence-based recommendations have not yet been produced.[16]

Multiple different malignancies

Persons with *RB1* gene mutant alleles are at increased risk of developing second non-ocular malignancies[3,19,20], which may occur within or outside the radiation field (see Fig. 43.2). Radiation, particularly of infants under 1 year of age, increases the risk of sarcomas and other cancers within the radiation field. Osteosarcoma is the commonest second primary tumor in persons with *RB1* mutations, but a wide variety of other neoplasms have been reported. Since these radiation-induced tumors are very difficult to treat, in the past more children with *RB1* mutations have died of their second tumor than have died of uncontrolled retinoblastoma. Radiation is now restricted to salvage of the remaining eye in children with retinoblastoma.[21]

Genetic counseling for retinoblastoma

The most accurate way to predict who in a family will develop retinoblastoma is to test them for the precise *RB1* mutant allele found in the proband. In the absence of precise knowledge of the *RB1* mutant alleles in tumor or blood, the empiric risk for the relatives of retinoblastoma patients to be affected can be estimated.[22] Offspring of patients with a family history of retinoblastoma or bilateral tumors have a 50% risk of inheriting the mutant allele and a 45% risk of developing retinoblastoma, due to incomplete penetrance related to "weak" *RB1* mutations. When two affected children are born to apparently normal parents, one parent must be carrying

but not expressing the mutant allele. Many such individuals are now shown to be mosaic for an *RB1* mutation.[13] Hence, there is also a 45% risk that any subsequent child born will develop retinoblastoma. The risk that other relatives have inherited the mutant allele depends on the number of intervening "apparently normal" individuals, each of whom have a 10% chance of carrying but not expressing the mutant allele. The risk falls by a factor of 0.1 for each intervening unaffected generation. Since 15% of patients with unilateral retinoblastoma have a germinal mutation, the offspring of individuals with unilateral retinoblastoma have a 7.5% risk of carrying the abnormal gene. The probability of other relatives developing retinoblastoma falls by a factor of 0.1 for each intervening unaffected generation.[22]

Infants born with a risk of developing retinoblastoma need to be examined immediately after birth and then at regular intervals to detect early tumors that can be treated to obtain the best visual result (see Fig. 43.1). Infants proven to carry the family's *RB1* mutant allele can be delivered at early-term gestational age, to optimize the chance of keeping good vision with minimally invasive therapy. Examination of the retina starts at birth, and continues at frequent intervals depending on the child's risk. Up to 3 months of age, examination may be done without general anesthetic, greatly facilitated by the wide-angle retinal camera on video mode. After 3 months, anesthetic is necessary to get an accurate view of the retina to detect tiny tumors up to the ora serrata. As soon as a tumor is documented, anesthetic is required to initiate treatment.

Timely and sensitive molecular diagnosis of *RB1* mutations has a strong positive effect on quality of outcomes: early treatment of retinoblastoma achieves lower risks and better health outcomes, allows families to make informed family-planning decisions, and costs less than conventional surveillance.[8,23] The savings when at-risk children avoid repeated examinations substantially exceeds the one-time cost of molecular testing. Moreover, health care savings continue to accrue as succeeding generations avoid the unnecessary examinations and often do not need molecular analysis or clinical surveillance, because their parents do not carry the family's mutant allele.

The *RB1* mutations usually result in unstable or absent protein. Such mutations show high penetrance (>95% of offspring affected) and expressivity (average of seven tumors per child). More uncommon *RB1* mutations cause lower penetrance and expressivity[23]: "in frame" deletions or insertions that result in a stable but defective pRB[24]; promoter mutations that result in a reduced amount of otherwise normal protein[23]; and splice mutations that may be additionally altered by unlinked "modifier genes".[25]

When a somatic *RB1* mutation occurs after embryo development has begun, the *RB1* mutation is present in only some cell lines distributed throughout the body. If the germline cells are involved, the mutation can be inherited by the offspring.[13]

Presentation

The majority of children with retinoblastoma without a family history are first noticed because of leukocoria, often detected on a digital image of the child (Table 43.1).[26,27] Parents observe an odd appearance in their child's eye. Too often, primary health care personnel are unaware of the importance of what the parents are saying and diagnosis is delayed. Awareness of the dangers underlying the parent's words will encourage health care professionals to respond to a parent's description of a "cat's eye reflex" by referring the child for full investigation of the eyes (Figs 43.6–43.8).

Table 43.1 Presenting symptoms and signs of retinoblastoma[26]

Sign/symptom	Percentage
White reflex	56%
Strabismus	20%
Glaucoma	7%
Poor vision	5%
Routine examination	3%
Orbital cellulitis	3%
Unilateral mydriasis	2%
Heterochromia iris	1%
Hyphema	1%
Other	2%

From Ellsworth RM. The practical management of retinoblastoma. Trans Am Ophthalmol Soc 1969; 67: 462–534.

Retinoblastoma families and support groups have embarked upon awareness campaigns to educate the lay public on the importance of a "white pupil" (see Fig. 43.6). Digital images of the baby with retinoblastoma frequently show a white pupil, "photoleukocoria," in contrast to the red eye reflex of the flash picture of a normal eye.[27] Although retinoblastoma is the most important and dangerous condition to cause leukocoria, various conditions also show unusual appearance on flash images, such as congenital cataract, toxocariasis, persistent fetal vasculature (PFV), cicatricial retinopathy of prematurity, myelinated nerve fibers, optic nerve coloboma, high myopia, astigmatism, and normal optic nerves when the camera angle is directed at the optic nerve.[28]

The second most common presenting sign of retinoblastoma is strabismus (esotropia or exotropia).[26] The red reflex test should be applied to any child with strabismus or suspected strabismus, with prompt, urgent referral from the primary health level to an ophthalmologist if the red reflex test is abnormal.[2] Other presenting symptoms and signs (see Table 43.1) include a painful red eye (due to glaucoma) (Fig. 43.9), orbital cellulitis secondary to extensive necrosis of the intraocular tumor (Fig. 43.10),[29] unilateral mydriasis, heterochromia, hyphema, hypopyon, uveitis, and "searching" nystagmus (due to blindness from bilateral macular involvement).[26] In countries with limited medical services, many children present with extensive unilateral or bilateral proptosis with orbital extension and/or metastatic disease due to delayed access to care (Fig. 43.11).

Screening of the retina for tumors in babies and children who are relatives of patients with retinoblastoma, before any signs are noted will enable early treatment and better outcomes. Genetic testing for the family's precise mutant *RB1* allele (see Fig. 43.1) can identify those at risk, to initiate treatment early when the tumors are small and curable by laser therapy alone, or with short cycles of local or systemic chemotherapy in order to obtain the best visual outcome. Family members shown to

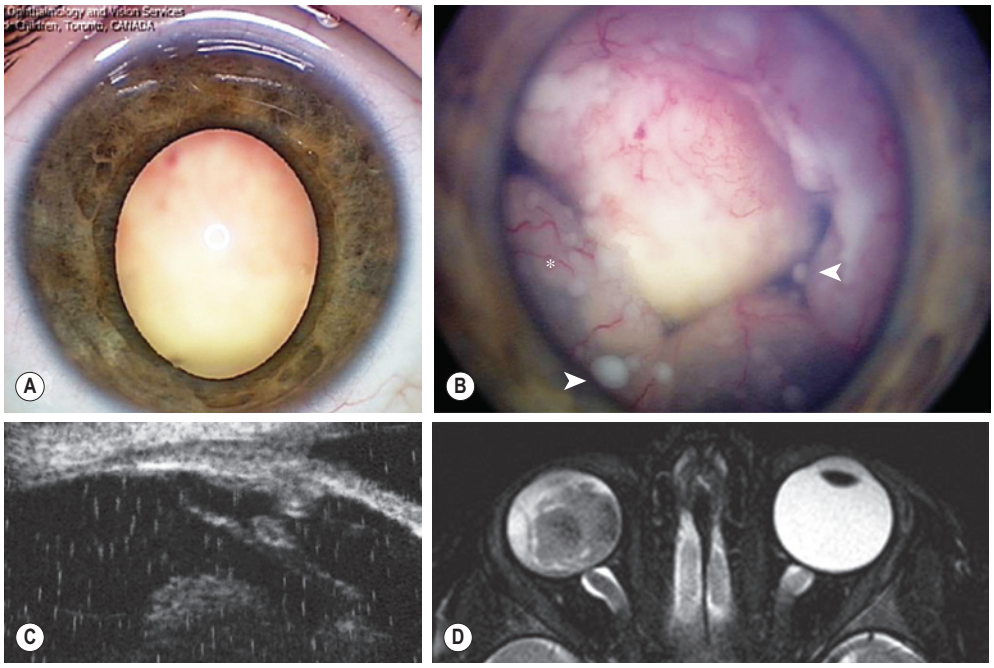


Fig. 43.7 A child with unilateral retinoblastoma IIRC[33] Group E eye. (A) Leukocoria. (B) Large white mass with multiple diffuse vitreous seeds (arrows) and subretinal seeds (*). (C) Ultrasound biomicroscopy (UBM) showing tumor mass invading the anterior hyaloid face. (D) Magnetic resonace imaging showing the intraocular tumor with tumor-free optic nerve and no extraocular spread. *(RetCam images and UBM by Leslie MacKeen.)*

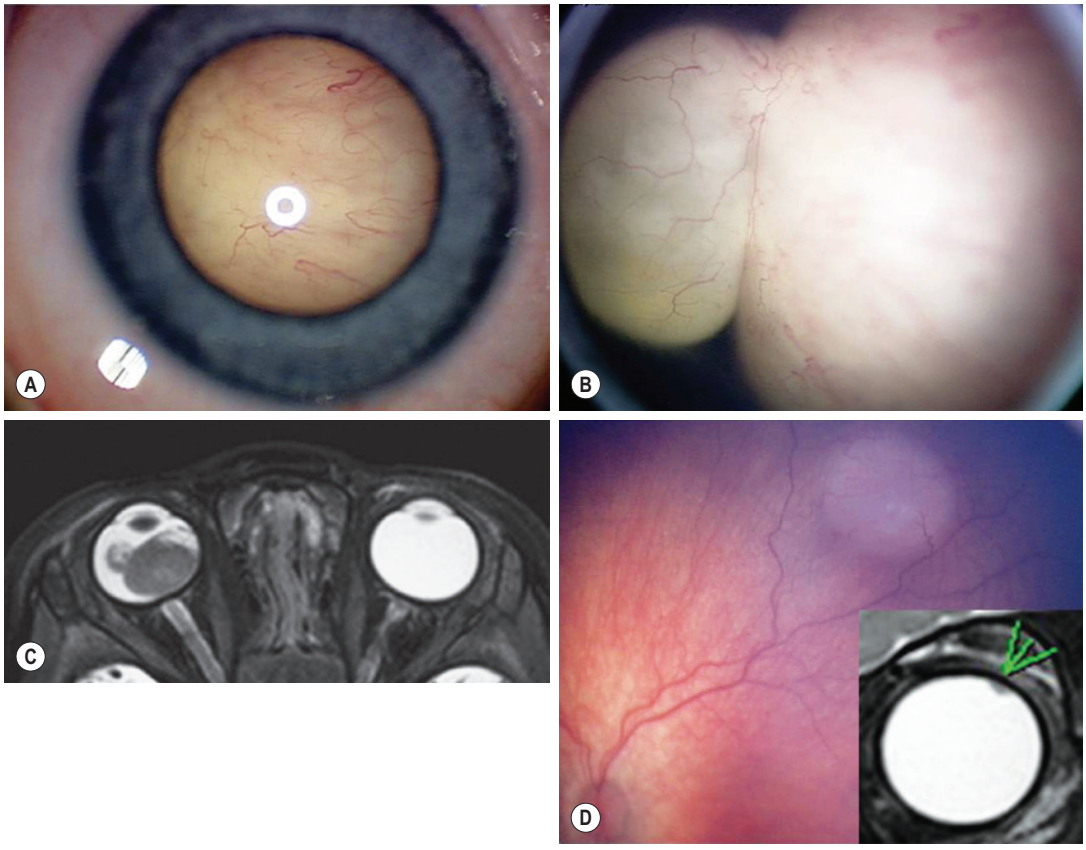


Fig. 43.8 Child with bilateral retinoblastoma. (A) Right eye (IIRC[33] Group D) with leukocoria. (B) Caused by a large multilobular tumor. (C) Magnetic resonance imaging (MRI) showing the configuration of the intraocular tumor, no involvement of the optic nerve, and no extraocular involvement. (D) Left eye showing a small superotemporal tumor (IIRC[33] Group B) documented by MRI (insert, arrow). *(RetCam images by Leslie MacKeen and Cynthia VandenHoven.)*

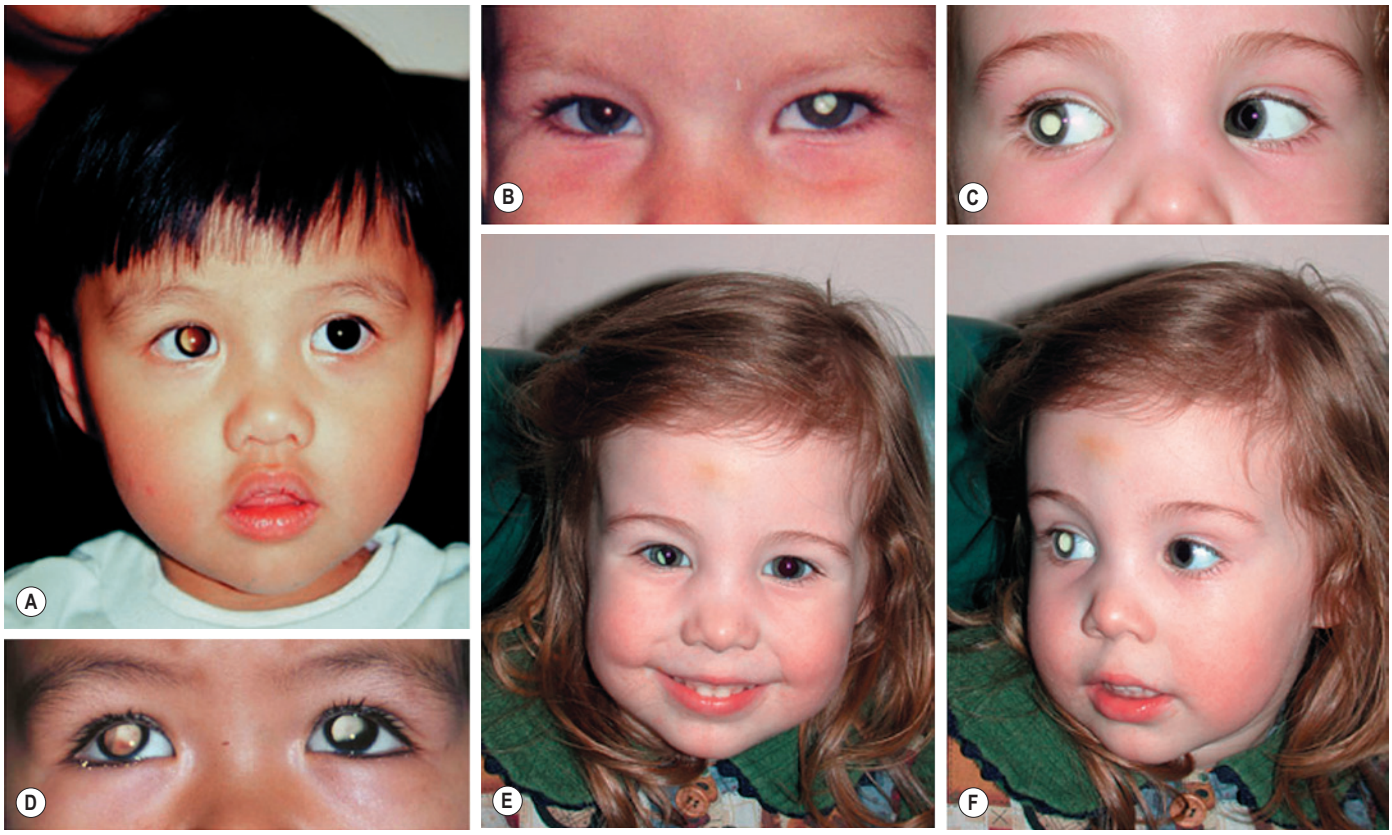


Fig. 43.6 Leukocoria. (A–C) Unilateral leukocoria. (D) Bilateral leukocoria. (E,F) Right unilateral leukocoria, more obvious in right gaze due to the anterior temporal location of tumor. *(Images by Leslie MacKeen.)*

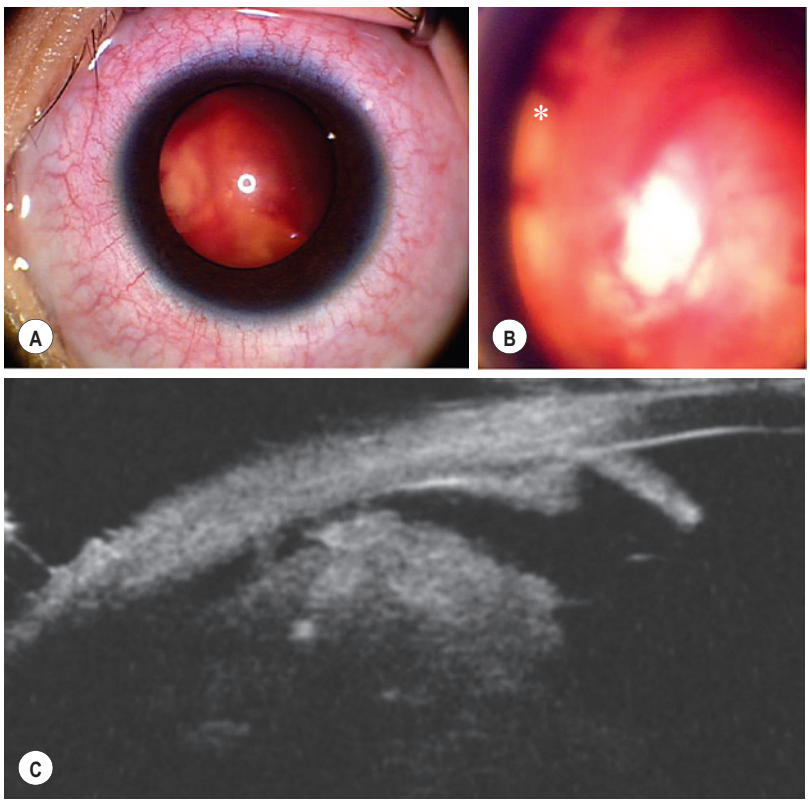


Fig. 43.9 (A) Unilateral retinoblastoma presented with red eye, corneal edema, elevated intraocular pressure, new iris vessels, and leukocoria. (B) A tumor mass (*) is seen very anterior behind the iris with exudative detachment, subretinal seeds, and vitreous hemorrhage. (C) Ultrasound biomicroscopy (UBM) shows tumor anterior to the anterior hyaloid face so this eye was classified as IIRC[33] Group E. *(RetCam images and UBM by Leslie MacKeen.)*

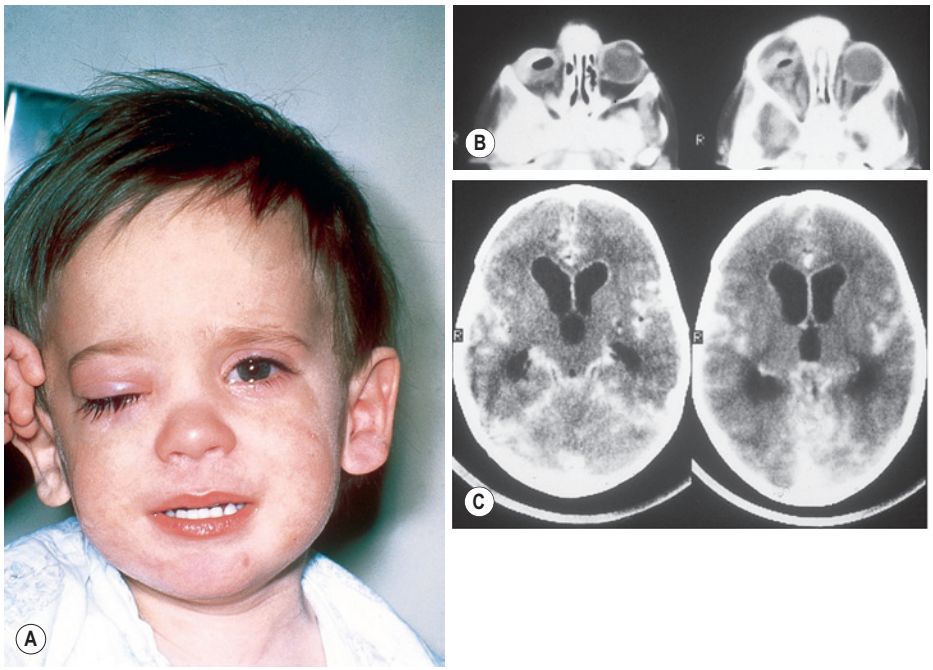


Fig. 43.10 (A) Unilateral retinoblastoma that presented as orbital cellulitis (IIRC[33] Group E, suggestive of extraocular tumor). (B) Extensive intraocular necrosis and replacement of the optic nerve with tumor. (C) Despite therapy, 4 months later the brain was covered with meningeal retinoblastoma and the child died.

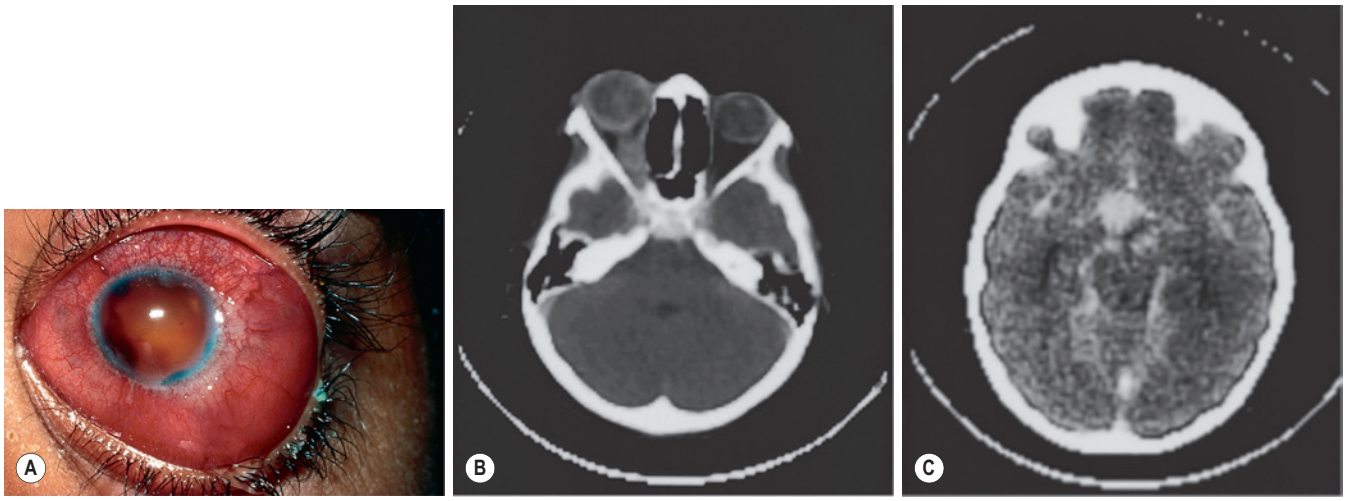


Fig. 43.11 (A) Extraocular retinoblastoma with iris invasion, glaucoma, subconjunctival and orbital extension. (B) Computed tomography (CT) scan showing optic nerve involvement. (C) CT scan showing suprasellar and cerebral extension from optic nerve invasion.

not carry the mutant allele are free of the expense of clinical surveillance.[8]

Diagnosis

The initial examination of the child presenting as possible retinoblastoma will provide a short-list of differential diagnoses, including Coats disease (Fig. 43.12), persistent fetal vasculature, toxocara (Fig. 43.13), medullo-epithelioma (Fig. 43.14), and others (Box 43.1).[26] Referral of a child with possible retinoblastoma is urgent, generally requiring examination within 1 week.[2]

Ultrasound is a readily available tool to confirm the diagnosis, with the demonstration of a calcified mass in the eye with leukocoria, and also to check a "normal" other eye for possible tumor. To rule out trilateral retinoblastoma and evaluate the optic nerve, MRI is now standard. The whole multidisciplinary team should be aware of the patient since each will play a role throughout the course of care.

Examination under anesthesia

Full assessment of the eye with retinoblastoma, including anterior segment examination and complete fundus examination, requires examination under anesthesia (EUA). The pupils must be widely dilated and scleral depression used to visualize the retina to the ora serrata. Retinoblastoma appears as a creamy white mass (Figs 43.15 and 43.16) projecting into the vitreous with large irregular blood vessels running on the surface and penetrating the tumor. Hemorrhage may be present on the tumor surface. Spheres of tumor cells in

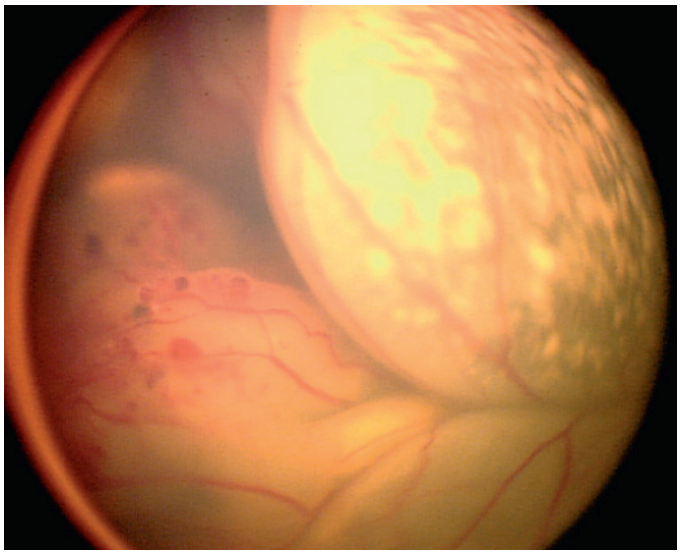


Fig. 43.12 Coats disease. Presenting with leukocoria, with a yellow appearance (xanthocoria), not white like retinoblastoma, total retinal detachment, and the characteristic aneurysmal vascular malformations in the peripheral retina.

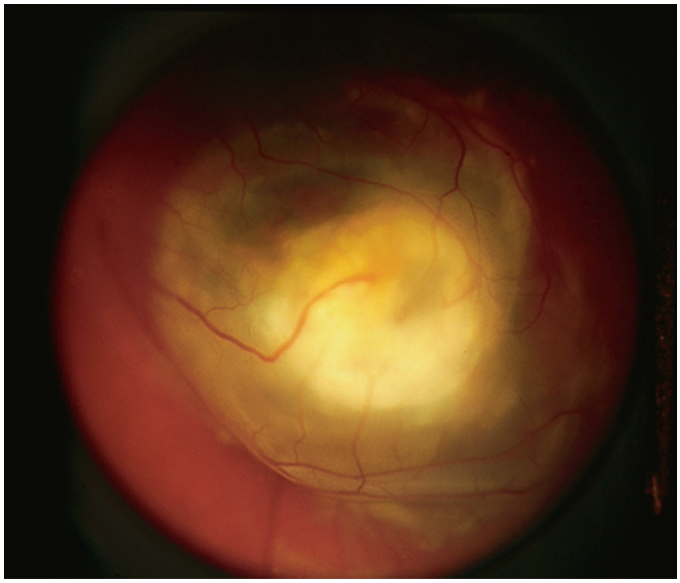


Fig. 43.13 Solitary toxocara granuloma in the macular, with a cilioretinal arteriole, masquerading as a retinoblastoma.

the vitreous ("seeding") are pathognomonic of retinoblastoma (see Figs 43.7 and 43.15). Seeds morphologically can be in the form of dust, spheres, or clouds, and may also lie in the subretinal space, and in advanced cases extend into the anterior chamber.[30] Tumors surrounded by a halo of proliferating retinal pigment epithelium may be slow growing and have a retinoma component.[15] Calcification within retinoblastoma is common and resembles "cottage cheese" (Fig. 43.17). Such tumors leave no doubt as to the diagnosis of retinoblastoma.

Less commonly, retinoblastoma presents as an avascular white mass in the periphery of the retina. The tumor may be obscured by vitreous opacity or extensive retinal detachment (see Fig. 43.3). Calcification of a mass shown on ultrasound, formerly by CT (see Figs 43.3 and 43.10) and MRI (see Figs 43.7 and 43.8), may be critical in establishing the diagnosis of retinoblastoma.

The presence of tumors in the second eye confirms the diagnosis of heritable, bilateral retinoblastoma. If no tumors are seen on clinical exam, the second eye cannot be assured to be normal until examined under anesthetic.

Unusual presentations such as heterochromia, hypopyon (see Fig. 43.11), uveitis, or orbital cellulitis may delay and

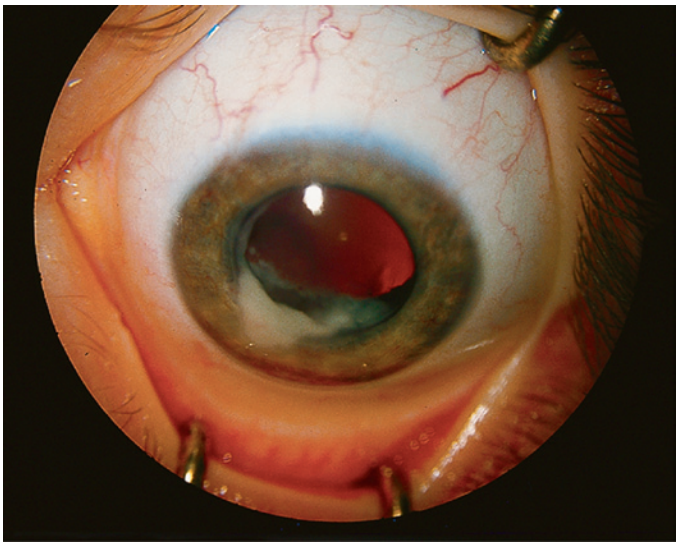


Fig. 43.14 Medulloepithelioma (diktyoma) presenting as a felt-like structure arising in the ciliary body and involving the iris.

Box 43.1

Differential diagnosis of retinoblastoma

Hereditary conditions

Norrie disease
Warburg syndrome
Autosomal recessive retinal dysplasia
Dominant exudative vitreoretinopathy
Juvenile X-linked retinoschisis
Orbital cellulitis

Developmental anomalies

Persistent fetal vasculature
Cataract
Coloboma
Congenital retinal fold
Myelinated nerve fibers
High myopia
Morning glory syndrome

Others

Coats disease
Retinopathy of prematurity
Rhegmatogenous retinal detachment
Vitreous hemorrhage
Leukemic infiltration of the iris

Inflammatory conditions

Toxocariasis
Toxoplasmosis
Metastatic endophthalmitis
Viral retinitis
Vitritis

Tumors

Astrocytic hamartoma
Medulloepithelioma
Choroidal hemangioma
Combined hamartoma of retina and RPE

Modified from Shields JA, Augsburger JJ. Current approaches to diagnosis and management of retinoblastoma. Surv Ophthalmol 1981; 25: 347–72.

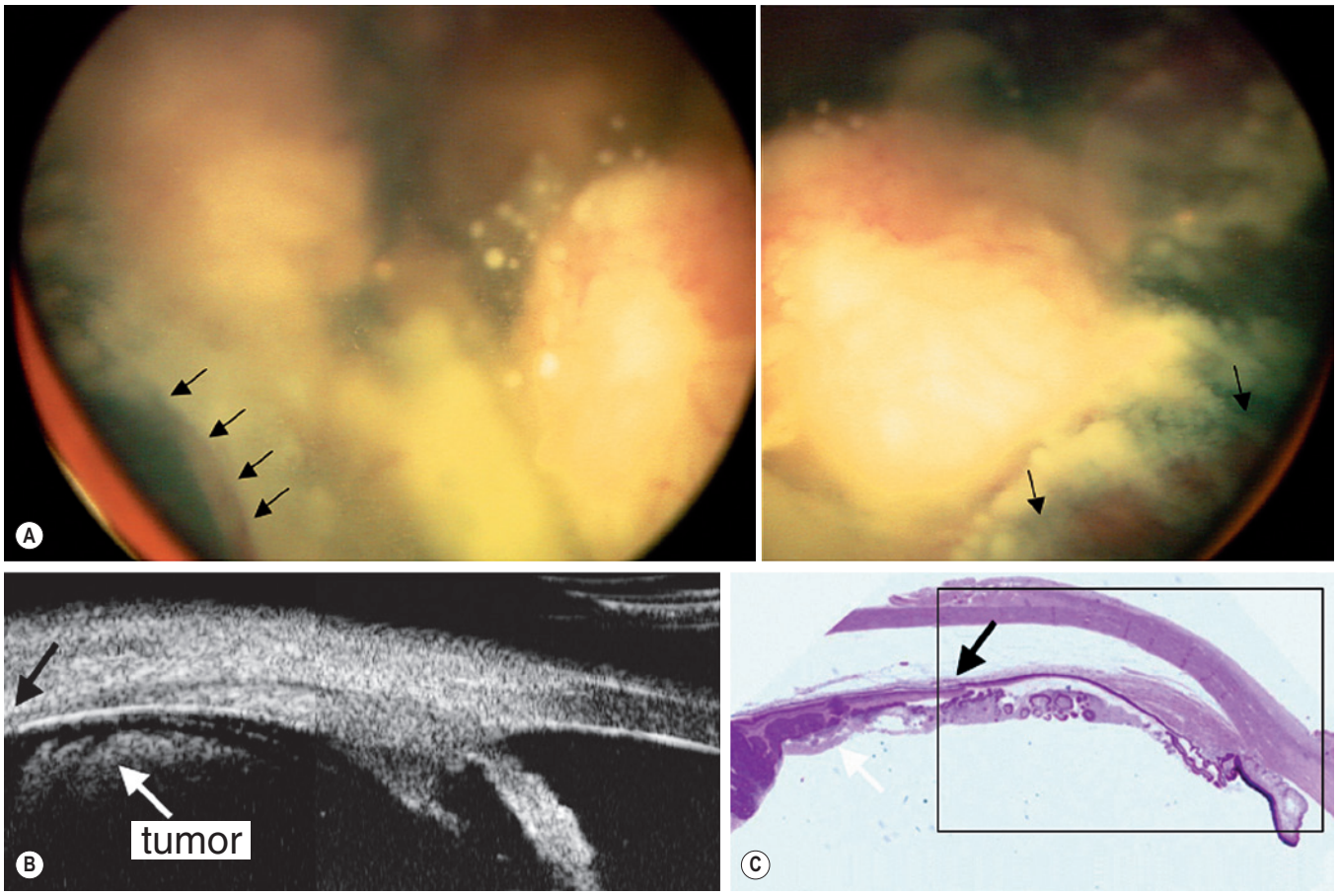


Fig. 43.15 Unilateral endophytic IIRC[33] Group E retinoblastoma. Wide-angle retinal images showing (A) Left, massive vitreous seeding; right, extension of tumor for 180° inferiorly, anterior to the ora serrata (arrows) to lie on the pars plana. (B) Ultrasound biomicroscopy of tumor on pars plana and pars plicata of ciliary body. (C) Hematoxylin and eosin section of ciliary region showing tumor anterior to ora serrata (arrow); box corresponds to area imaged in (B). *([A] RetCam images by Carmelina Trimboli.)*

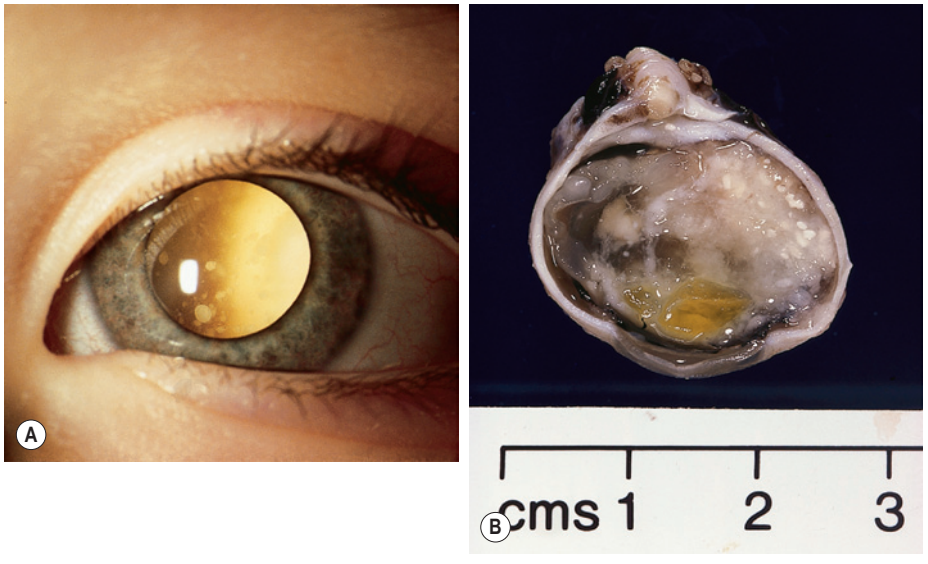


Fig. 43.16 Endophytic retinoblastoma. (A) The tumor has invaded the vitreous and seeds can be seen on the back of the lens (IIRC[33] Group E). (B) Calotte of enucleated eye with tumor filling the eye (same patient).

mask the diagnosis of retinoblastoma. It is important that retinoblastoma is considered an important differential diagnosis, which can be lethal with delay. Diffusely infiltrating retinoblastoma is uncommon, and can masquerade as uveitis. Since there is no solid, calcified tumor mass or retinal detachment, diagnosis is difficult.

When the inner limiting membrane of the retina breaks, "seeds" float in the vitreous cavity, where they are hypoxic, relatively resistant to therapy, and cannot be treated by laser or cryotherapy. When the seeds fall onto the retinal surface, they can attach and grow (see Fig. 43.15). If noticed early they can be successfully treated with laser and cryotherapy.

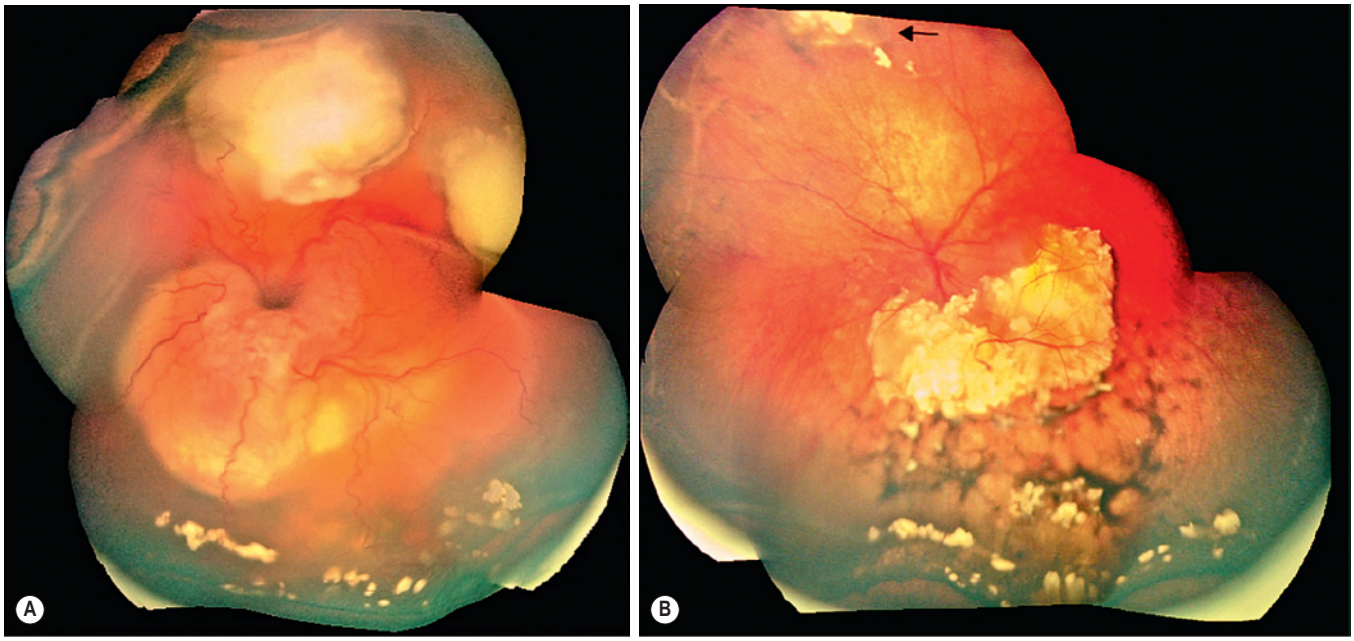


Fig. 43.17 Collage of wide-angle retinal images of the whole retina. The ora serrata is visualized for 360° by scleral depression. (A) Left eye at diagnosis of child with bilateral multifocal exophytic IIRC[33] Group D retinoblastoma, no family history, and a "null" *RB1* mutation (heterozygous deletion of exons 18–23) in blood. (B) Excellent regression after 3 of 7 cycles of CEV (carboplatin, etoposide, and vincristine) with cyclosporin A chemotherapy, with arrow indicating residual tumor treated by laser. Similar appearance of residual tumor and tented retina near the macula was not treated to optimize vision and has not changed over 1 year off treatment. This child had excellent response in both IIRC Group D eyes. *(RetCam images and collage by Cynthia VandenHoven.)*

Bone marrow aspiration and lumbar puncture to screen for metastatic disease are performed only when there is a suggestion of extraocular extension and can be performed later if high-risk pathologic features are discovered on the enucleated eye.

Images[31] for retinoblastoma management

The wide-angle retinal camera provides wide-field imaging of the retina and anterior segment, including the anterior chamber angle (Figs 43.1, 43.7, 43.9, 43.15, 43.17–43.20).[32] Some small retinoblastomas, obscuring the clarity of the choroidal vessels, and vitreous seeds, may be better noted by imaging than with indirect ophthalmoscopy (see Figs 43.1 and 43.20). Sequential images are useful to determine if the tumors are growing or regressing.

Digital fluorescein angiography can assess vascularity, residual tumor activity, and recurrences within laser scars (see Fig. 43.1). Islands of ischemic retina may complicate focal laser and cryotherapy leading to neovascularization that can be clearly distinguished from tumor by fluorescein angiography; prophylactic panretinal photocoagulation can block the stimulus for ischemic angiogenesis, whereas direct early treatment may control tumor recurrence.

Ultrasound biomicroscopy is the only way to detect disease anterior to the ora serrata in the ciliary body, behind iris, and touching lens (see Figs. 43.7 and 43.9). These parts of the eye cannot be viewed by indirect ophthalmoscopy, digital imaging, or conventional ultrasonography. It is critical to detect anterior disease (International Intraocular Retinoblastoma Classification [IIRC][33] Group E), which requires immediate enucleation, since it is not possible to deliver accurate focal therapy to the anterior part of the eye.

Optical coherence tomography (OCT) at the time of EUA may find invisible tumors, or confirm a suspicious retinal spot.[32,34] The smallest tumors appear to emerge in the inner nuclear layer on OCT, in the visually critical posterior pole of the eye in infants at risk (i.e. they carry a mutant *RB1* allele) (Fig. 43.21). OCT is also useful to monitor response to laser therapy, identify edge recurrences (Fig. 43.22), localize precisely sensitive structures such as the fovea for treatment planning, and identify secondary pathologies such as cystoid macular edema that may affect visual prognosis.

The survival of patients is normal if retinoblastoma remains intraocular (96% of cases), but cure of extraocular retinoblastoma is very difficult. Biopsy of retinoblastoma is contraindicated due to the risk for tumor spread outside the eye.

MRI of the brain (see Figs 43.7 and 43.8) and orbits[35] is essential in assessment of every child at presentation to ensure the diagnosis, assess potential optic nerve involvement and the possibility of scleral invasion,[35,36] the extent of suspected extraocular involvement, and to detect possible intracranial tumor (trilateral retinoblastoma).

Treatment

Optimal treatment of retinoblastoma depends on collaboration between all those involved in the care of the child, especially the parents. Specialized centers with inter-professional teams have developed expertise, resources, and equipment, and specific treatment protocols that are gradually gaining an evidence base. Global mapping of centers of excellence in retinoblastoma care now assists parent and caregivers to find expert care (http://www.1rbw.org) (Fig. 43.23). Retinoblastoma

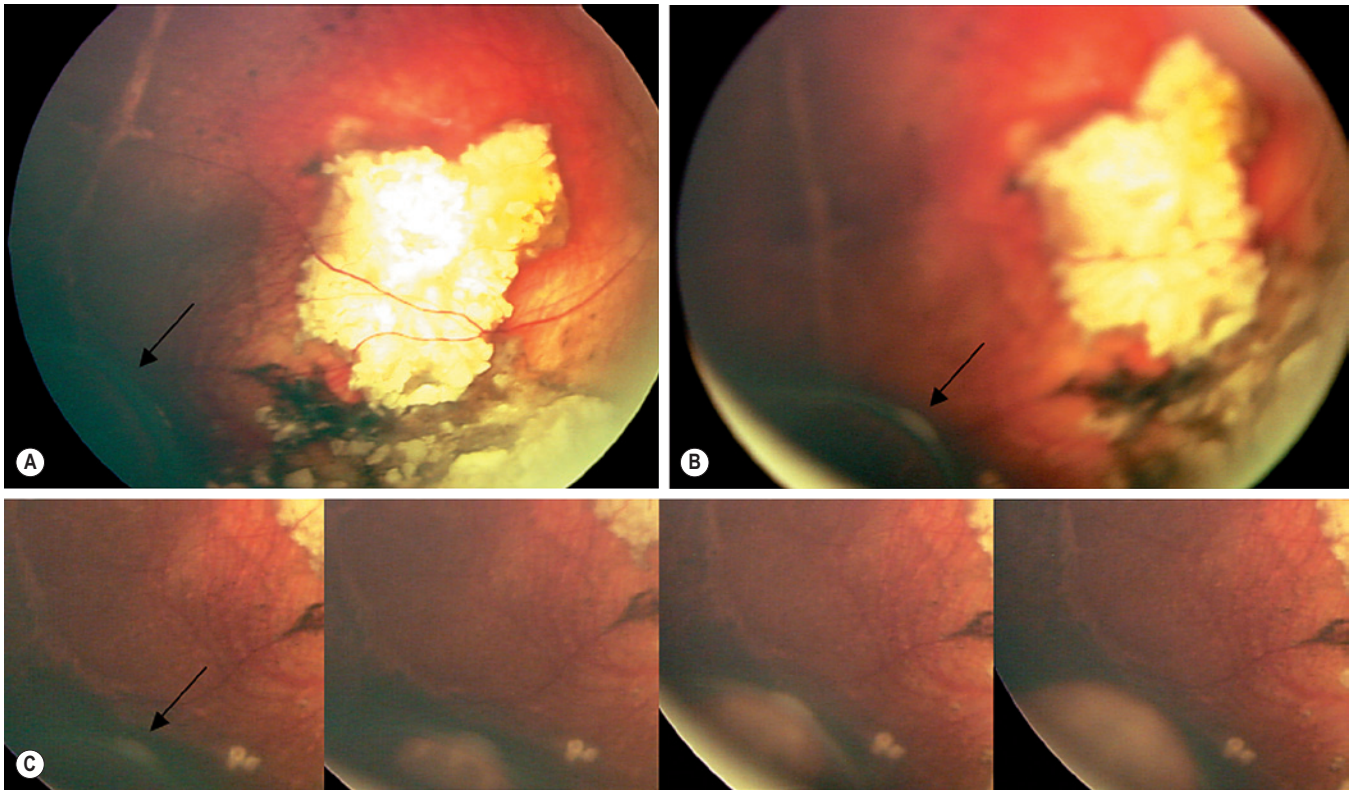


Fig. 43.20 New tumor in a previously treated eye. (A) Arrow indicates no tumor 8 months after initiation of CEV (carboplatin, etoposide, and vincristine) chemotherapy with cyclosporin for IIRC[33] Group D retinoblastoma in the right eye of the child. (B) New peripheral small tumor 2 months later, 10 months after diagnosis. (C) Triple freeze–thaw cryotherapy for the small new tumor, encasing the tumor in ice, thawing for 1 minute, and refreezing. *(RetCam images by Cynthia VandenHoven.)*

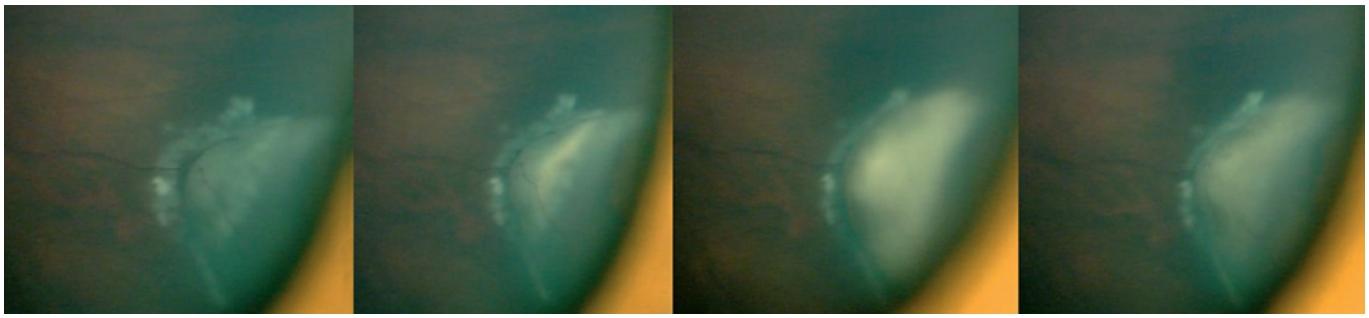
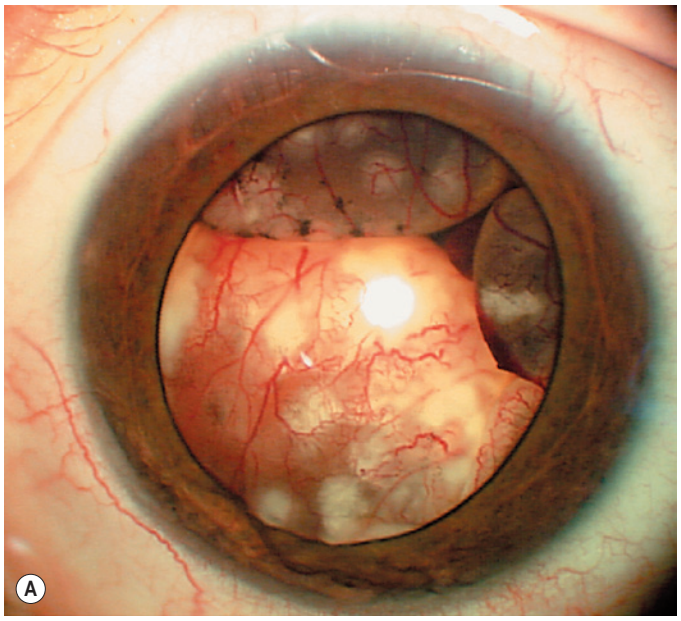


Fig. 43.18 Sequential wide-angle retinal images of the first freeze of triple freeze–thaw cryotherapy applied to a small peripheral retinoblastoma after placement of a 532-nm laser barrier line to limit serous effusion.



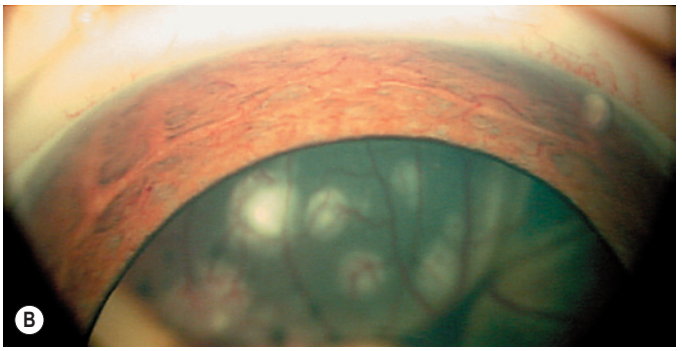


Fig. 43.19 IIRC[33] Group E retinoblastoma prior to enucleation, showing (A) large retinoblastoma, total retinal detachment, large subretinal seeds, neovascular glaucoma, and (B) anterior chamber seeding visualized by wide-angle retinal anterior segment and anterior chamber angle photography through gel. *(RetCam images by Leslie MacKeen.)*

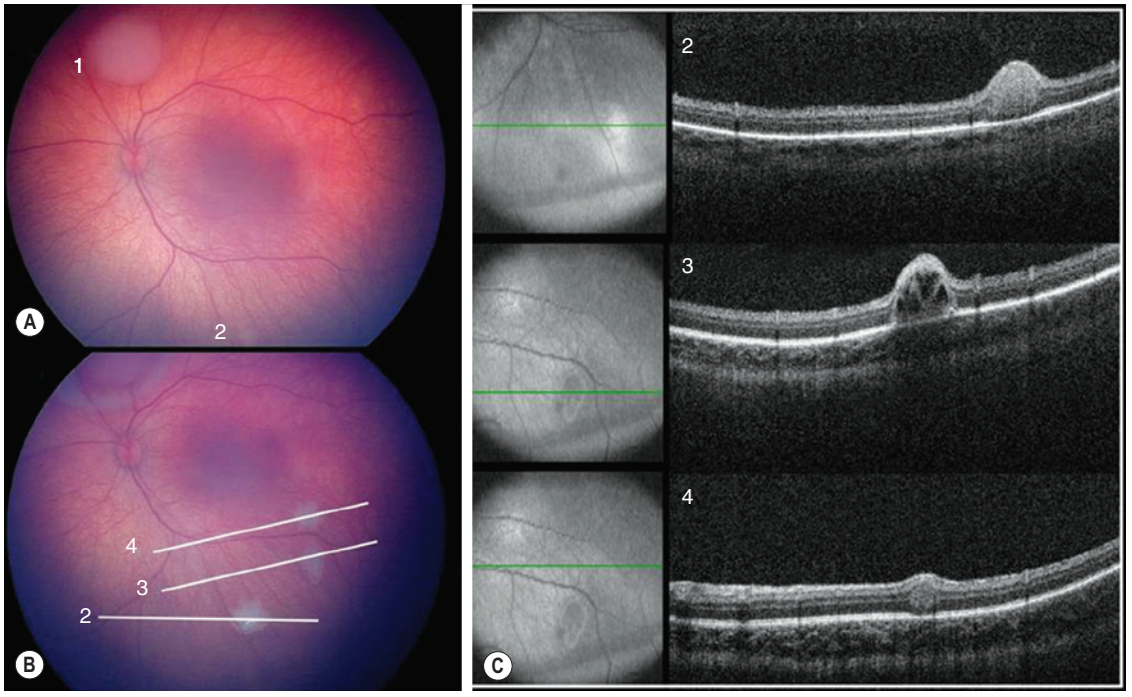


Fig. 43.21 Optical coherence tomography (OCT) imaging of preclinical tumors. (A) Wide-angle retinal image shows tumor 1 and 2 as seen on clinical examination. OCT documented the clinically observed tumors but also found invisible tumors 3 and 4. All tumors were treated with 532-nm laser. (B) Wide-angle retinal image post-laser showing the location of visible and invisible tumors. (C) OCTs on clinically visible tumor 2 pre-laser, invisible tumor 3 post-laser, and invisible tumor 4 pre-laser. *(Retcam images by Leslie MacKeen and Cynthia VandenHoven; OCT images by Cynthia VandenHoven.)*

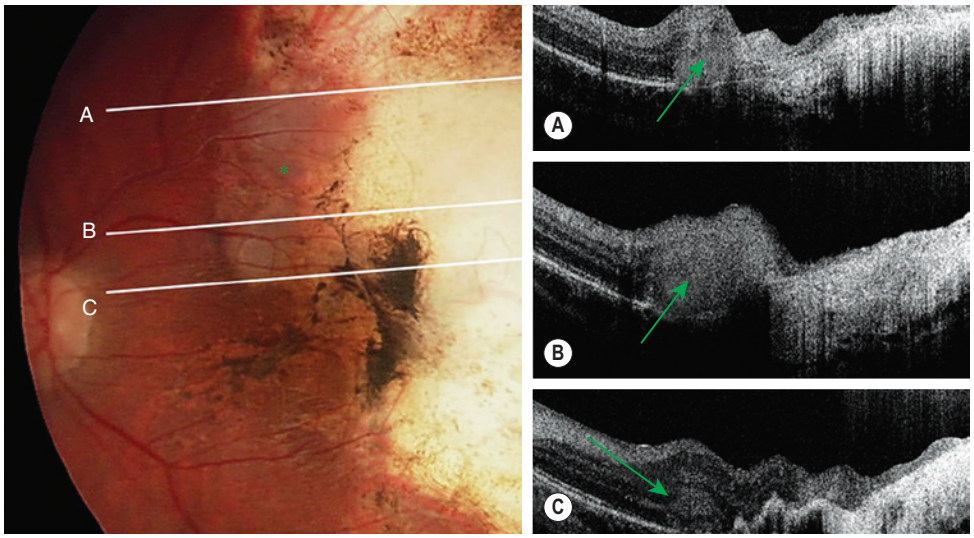


Fig. 43.22 Optical coherence tomography (OCT) detection of tumor recurrence. (Left) Wide-angle retinal image showing a large central scar with a nasal suspicious edge (*) after chemotherapy and laser treatment of retinoblastoma. OCT scans (A,B,C) through the suspicious area reveals active tumor (arrow). *(RetCam and OCT images by Cynthia VandenHoven.)*

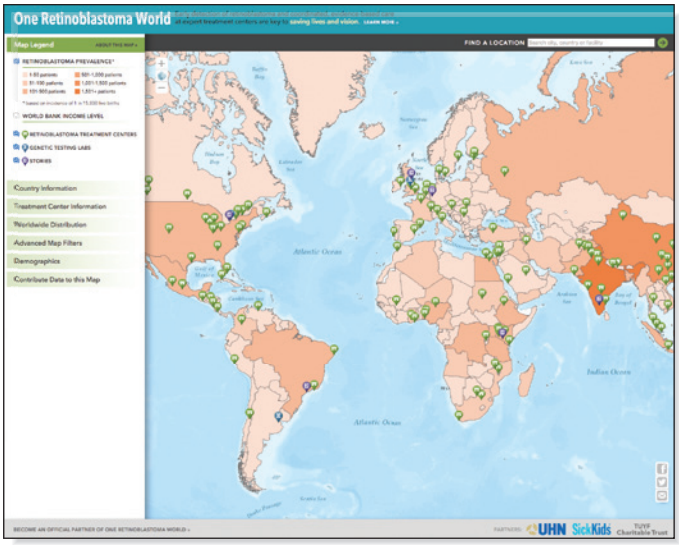


Fig. 43.23 One Retinoblastoma World Map (www.1rbw.org). A tool designed for patients or doctors to facilitate location of centers of excellence in retinoblastoma. The map shows centers of excellence, retinoblastoma prevalence by country (color coded), information regarding available modalities of therapy, and *RB1* genetic testing laboratories.

is too uncommon for busy ophthalmologists and oncologists in non-specialized units to acquire the expertise necessary to optimize outcomes for the children and their families. Overall outcomes will improve over time when each affected child is treated systematically on carefully defined protocols, such that the knowledge gained can be used in the design of more effective future protocols.

Classification

Optimized care and outcome for intraocular retinoblastoma balances the morbidity of treatment with the likelihood to cure the cancer. Classification of cancer severity/extent is the standard way to categorize eyes/patients best suited to particular therapies most likely to succeed, based on current evidence.

The Reese–Ellsworth (R-E) classification was devised to predict prognosis when intraocular retinoblastoma was treated with external beam radiotherapy.[37] Since radiotherapy is no longer a primary treatment for retinoblastoma, due to the high risk of radiation-induced second cancers, the International Intraocular Retinoblastoma Classification (IIRC)[33] (Box 43.2) was developed to predict outcomes from current therapies (predominantly chemotherapy and focal therapy, with radiation as a salvage modality for refractory recurrence) (see Figs 43.1, 43.3, 43.4, 43.7, 43.10, 43.16, 43.17, 43.19, 43.24, and 43.25).[33] However, a second version of this classification[38] results in the safely treatable eyes being indistinguishable from eyes with imminent risk of, or actual, extraocular extension, resulting in un-interpretable data in the literature, and danger to children since the features of any eye appropriate for a specific treatment are not clear.[39] The TNM cancer staging system has been developed for all types of cancer, including retinoblastoma.[40] The two eyes are each scored for clinical intraocular disease (cTNM) (see Box 43.2) and pathology (pTNM). The stage of the worst eye, or extraocular disease, determines the whole patient cTNM stage. At diagnosis, it is valuable to record all three classifications: the R-E and IIRC[33] groups and the TNM stage. Major journals now request the TNM stage for publications.

The eCancerCare^{RETINOBLASTOMA} (eCC^{RB})[41,42] is a retinoblastoma-specific secure, online database in which point-of-care clinical data is recorded and used as a summary of the retinoblastoma-specific clinical care. Demographics, presenting symptoms and signs, medical history, treatments, retinal drawings, and photographic images of tumors are accessed through the Disease-specific ePatient Clinical Timeline (DePICT) (Fig. 43.26). The presenting clinical details are entered into eCC^{RB} at diagnosis, and the IIRC eye classification and TNM staging are automatically generated.

Enucleation

Enucleation is an excellent way to cure retinoblastoma confined to the eye. Immediate enucleation is indicated for all IIRC[33] Group E eyes (see Figs 43.15 and 43.19). A trial of chemotherapy (whether systemic or intra-arterial) prior to enucleation is very dangerous for IIRC[33] Group E since a good intraocular response creates a sense of false security and high-risk pathologic features endangering the child's

Box 43.2

International intraocular retinoblastoma classification[33]

Group A: Small intraretinal tumors away from foveola and disc

- Tumor ≤3 mm in diameter, located >3 mm from the fovea and >1.5 mm from the optic disc

Group B: All remaining discrete tumors confined to the retina

- Tumor >3 mm in diameter, located <3 mm from the fovea and or <1.5 mm from the optic disc with or without subretinal fluid less than 3 mm from the tumor with no subretinal seeding

Group C: Discrete local disease with minimal subretinal or vitreous seeding

- Tumor(s) with local fine vitreous or subretinal seeding, present or past, less than 3 mm (2 DD) from the tumor and or subretinal fluid, present or past, involving up to ¼ retina

Group D: Diffuse disease with significant vitreous or subretinal seeding

- Tumor(s) with diffuse vitreous or subretinal seeding, present or past, more than 3 mm (2 DD) from the tumor and or subretinal fluid, present or past, involving up to total retinal detachment
- Diffuse seeds may include "greasy" vitreous seeds, avascular vitreous tumor masses, subretinal plaques, or tumor nodules

Group E: Presence of any one or more of these poor prognosis features

- Tumor touching the lens
- Neovascular glaucoma
- Tumor anterior to anterior vitreous face involving ciliary body or anterior segment
- Diffuse infiltrating retinoblastoma
- Opaque media from hemorrhage
- Tumor necrosis with aseptic orbital cellulitis
- Phthisis bulbi

life are unrecognized and untreated.[43] When only one eye is involved, or when the other eye is Group A treatable with only focal therapy, a Group D eye may also be enucleated to avoid invasive therapies. On the other hand, unilateral Group C eyes with potential for useful vision may be suggested for curative therapy. A frank discussion with the family is essential as the treatment journey to save an eye with anticipated poor vision and a normal other eye carries significant socioeconomic and psychologic impacts for the families.[44] Enucleation is also indicated for recurrent tumor that has failed other treatment modalities; prolonged treatments risk metastasis and death, when up-front enucleation would have cured the unilaterally affected child.

Bilateral retinoblastoma commonly presents with one eye full of tumor, with smaller tumors in the fellow eye. Both eyes may be primarily treated with chemotherapy for Groups B, C, or D disease (see Figs 43.16 and 43.20).

If both eyes are Group E, bilateral enucleation may be indicated, since attempts to save severely involved Group E eyes puts the child's life in jeopardy from difficult-to-treat, poor-prognosis systemic metastasis.[43] Even if Group E eyes can be cured, vision is very poor in such severely damaged eyes. The short- and long-term morbidities of systemic or intra-arterial chemotherapy or radiation may not be in the best interest of a child with bilateral Group E eyes.

Enucleation should be performed with great care so as not to penetrate the eye and spill tumor. A long optic nerve (8–12 mm) is important to ensure that the surgical margin is tumor-free. For unilaterally affected children, the tumor is important for *RB1* mutation studies, since this is the best way to determine whether the child has heritable or non-heritable retinoblastoma (see Fig. 43.4).

Although expensive porous implants have been widely used to give good movement of the prosthesis, they frequently acquire a deep chronic infection that is challenging to treat. A randomized study showed significantly better movement of the prosthetic eye with less costly polymethyl methacrylate implants and the myoconjunctival technique compared to porous implants with muscle imbrication.[45] In the myoconjunctival technique, the four recti muscles are sutured to the conjunctival fornices rather than in front of the implant, where they act directly on the rims of the prosthesis. Immediately at the time of surgery, a "stock" prosthetic eye can be used as a conformer, so that when the patch is removed 24–48 hours later, the child looks quite normal, a psychological benefit to child and family[46] (see Fig. 43.4).

Histopathology

Retinoblastomas are poorly differentiated malignant neuroblastic tumors, composed of cells with large hyperchromatic nuclei and scanty cytoplasm. Mitotic figures are common. In some tumors, differentiated cells form typical Flexner–Wintersteiner rosettes[47,48] in which columnar cells are uniformly arranged in spheres around a lumen containing hyaluronic acid. Homer–Wright rosettes also occur, characteristic of many neuronal tumors, with centrally located neurofibrils. Benign, non-proliferative retinoma shows the fleurette pattern of partial differentiation,[49] although these premalignant retinomas have already lost both copies of the *RB1* gene.[11]

Retinoblastoma tumors often outgrow their blood supply leading to cell necrosis. True spontaneous regression of retinoblastoma is rare, but is probably due to extensive tumor necrosis and central retinal artery occlusion, resulting in phthisis bulbi.[15,29] Calcification is almost pathognomonic of retinoblastoma, but its etiology is not known.

The most important component of histopathology of eyes enucleated for retinoblastoma is accurate assessment of risk that the tumor has become extraocular and life threatening. The pTNM for retinoblastoma provides this evaluation (see Box 43.2).[40] The most common routes of dissemination are through the optic nerve to brain and hematogenous spread from invasion of choroid and/or sclera, usually to bone marrow. Post-enucleation adjuvant chemotherapy may still cure, if given when high risk is recognized, prior to clinical presentation of extraocular retinoblastoma.[50]

If retinoblastoma metastasizes, it generally becomes evident within 18 months of the last active tumor in the eye, and is rare beyond 3 years without evidence of ongoing tumor activity in the eye.[51] The most common and dangerous route of metastasis of retinoblastoma is direct extension into the optic nerve. The tumor can grow toward the optic chiasm and beyond, or into the subarachnoid space with leptomeningeal involvement (see Fig. 43.8). Direct extension via the choroidal vessels, or spread along the ciliary vessels and nerves into the orbit, may occur in advanced cases (see Fig. 43.11).[52,53] Systemic metastases may occur via the

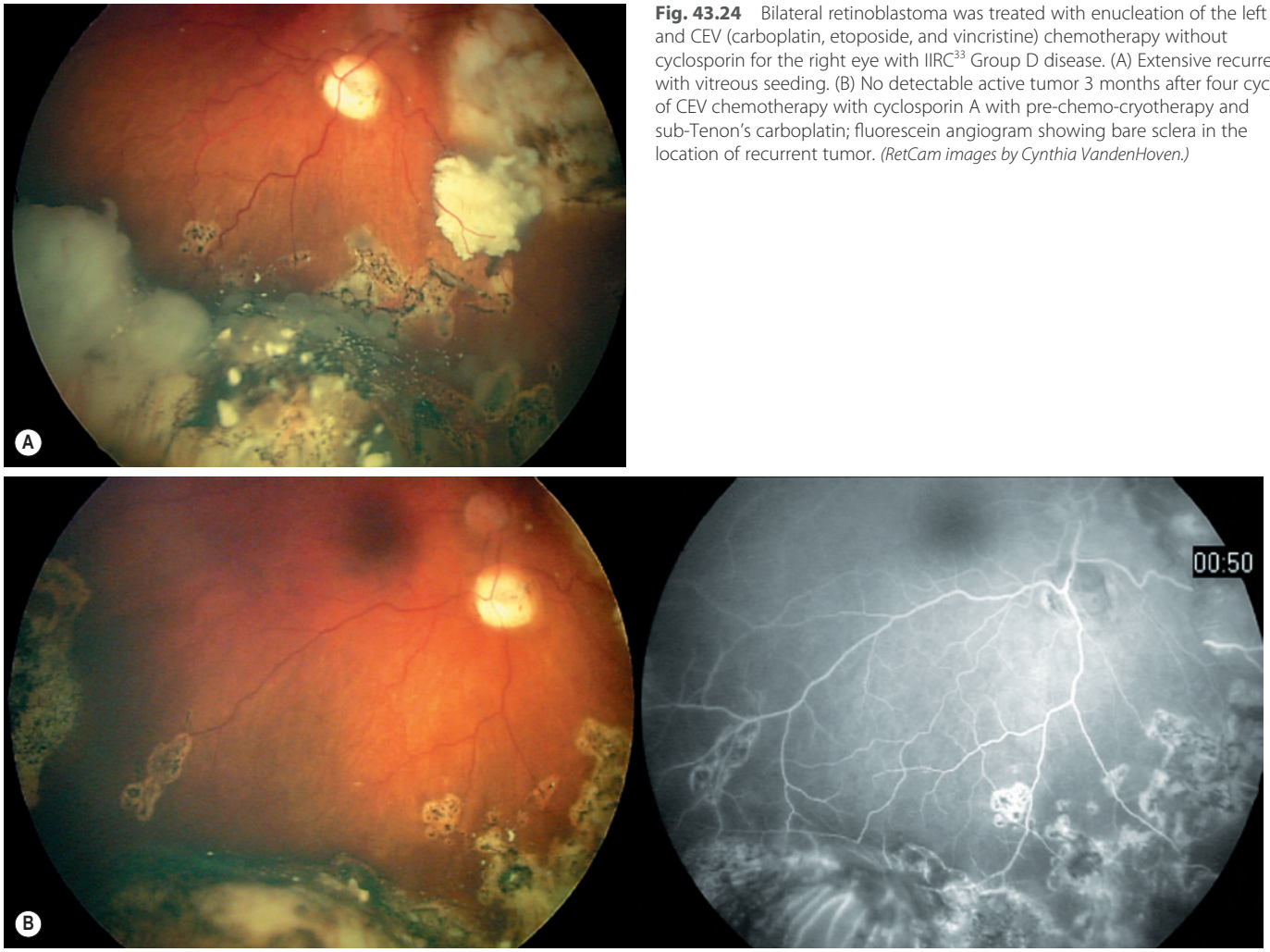


Fig. 43.24 Bilateral retinoblastoma was treated with enucleation of the left eye and CEV (carboplatin, etoposide, and vincristine) chemotherapy without cyclosporin for the right eye with IIRC[33] Group D disease. (A) Extensive recurrence with vitreous seeding. (B) No detectable active tumor 3 months after four cycles of CEV chemotherapy with cyclosporin A with pre-chemo-cryotherapy and sub-Tenon's carboplatin; fluorescein angiogram showing bare sclera in the location of recurrent tumor. *(RetCam images by Cynthia VandenHoven.)*

choroidal circulation or aqueous drainage, particularly if glaucoma is present. Bone marrow is the preferred site for retinoblastoma metastasis, and only terminally are bone, lymph node, and liver involved. Lung metastases are rare and occur late.

Chemotherapy

Systemic chemotherapy became the standard primary treatment for IIRC[33] Groups B, C, and D, after the lethal risk of second radiation-induced cancers became recognized.[19] Following an initial response to the first few cycles of chemotherapy, focal therapy with cryotherapy or laser therapy is initiated to destroy residual or recurrent tumor[54] (see Figs 43.1, 43.18, and 43.24). The most commonly used drugs are carboplatin, etoposide, and vincristine (CEV) given every 3 weeks through a central venous access line.[55]

The Toronto Multicenter Clinical Trial is studying the efficacy and toxicity of short 3-hour infusions of high-dose cyclosporin A (achieving high cyclosporin peak levels of >20,000 ng/ml for a very short time) to block P-glycoprotein that mediates multidrug resistance by acting as a plasma membrane drug-efflux pump, which is commonly overexpressed in retinoblastoma tumors.[56]

Increased intraocular concentrations of the chemotherapy drugs (e.g. carboplatin) was experimentally demonstrated by concurrent high-dose cyclosporin, possibly by inhibiting the P-glycoprotein expressed in the blood–eye barrier, and a single-freeze cryotherapy ("pre-chemo-cryotherapy") in peripheral retina to induce a small serous effusion.[57]

Following a good response to chemotherapy, consolidation is achieved by frequent (≈3–4 weeks) focal cryotherapy and laser therapy to destroy any surviving tumor cells (see Fig. 43.19). With high-dose CEV chemotherapy and focal therapy consolidation achieved 47% salvage of IIRC[33] Group D eyes without using radiation[58] (see Figs 43.3, 43.17, 43.24, and 43.25) and better results with less severely affected eyes. Note that the alternate definition of Group D/E eyes[38] inflates the success rate for treatment so studies cannot be compared.[39]

Unlike radiation, systemic chemotherapy is not associated with long-term cosmetic deformity of the orbit and upper face, radiation-induced cataracts, or ocular complications. Although chemotherapy is used in order to avoid the large risk of induction of a second primary tumor by radiation (estimated to be as high as 51% risk at 50-year follow-up),[59,60] etoposide also carries a small risk of induction of a specific type of acute myelogenous leukemia.[61] The cumulative dosage

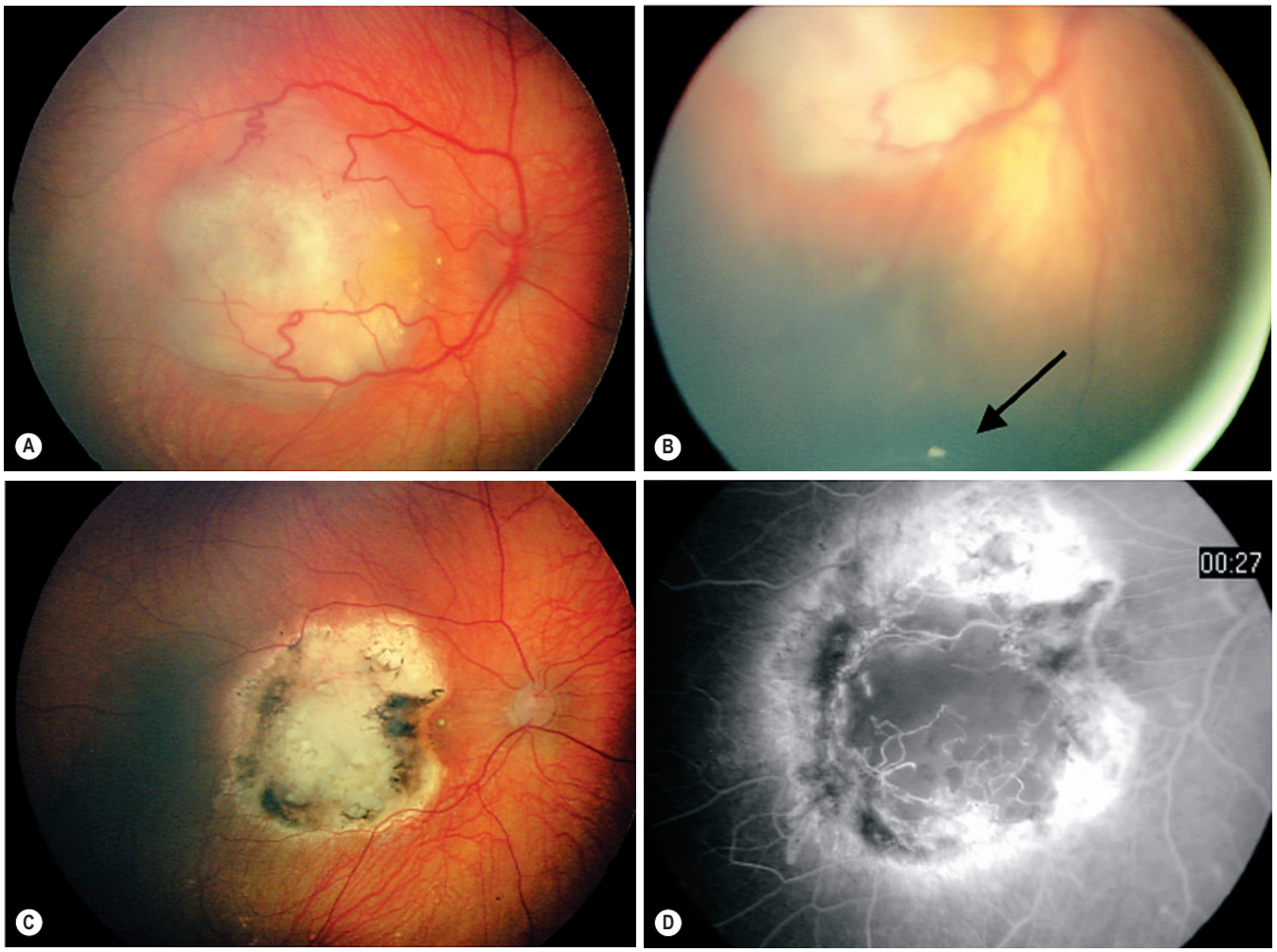


Fig. 43.25 (A) Unilateral retinoblastoma at diagnosis. (B) The subretinal seed (arrow) inferiorly at the 6 o'clock position places this eye in the IIRC[33] Group D (subretinal seeding more than 3 mm from the tumor). (C) Response to chemotherapy (four cycles of CEV [carboplatin, etoposide, and vincristine] with high-dose cyclosporin) and laser and cryotherapy. (D) Fluorescein angiography shows active tumor vessels in the scar, which were successfully ablated by 532-nm and 810-nm laser treatments. *(RetCam® images by Leslie MacKeen and Cynthia VandenHoven.)*

of etoposide used for treating retinoblastoma is less than the doses incurring a 2–3% risk of leukemia.[62]

Paraocular chemotherapy

To avoid systemic chemotherapy, carboplatin and topotecan have been given subconjunctivally to treat retinoblastoma. Instillation of carboplatin into Tenon's space has significant local orbital toxicity.[63] Topotecan given paraocularly in a fibrin clot at the usual systemic dose has no local orbital toxicity and no bone marrow toxicity, but is useful only as an adjunct to other therapies for small tumors.[64]

Cryotherapy

Cryotherapy is used for small anteriorly placed tumors (IIRC[33] Groups A and B eyes), or more posterior tumors when visual damage will not result.[65] Since the tumor cells are killed when they thaw, a triple freeze–thaw technique is used, with a full minute for thawing between the successive freezes (see Figs 43.18 and 43.20). Cryotherapy is repeated at several EUAs 4 weeks apart, until no residual active tumor remains. Cryotherapy may be used as a primary procedure for small tumors, or to treat residual or recurrent tumors. When moderately sized tumors are treated with cryotherapy, a laser barrier placed posterior to the tumor may protect the retina from detachment by the serous exudate of the acute freeze (see Fig. 43.18).

Laser

Laser coagulation is used for small tumors (IIRC[33] Groups A and B eyes) (see Fig. 43.1), for tumors that have been initially shrunk by chemotherapy, or for recurrences following chemotherapy. Small tumors (IIRC[33] Group A eyes) behind the equator are treated by encircling the tumor with a double row of contiguous laser burns. The small avascular tumor can be directly coagulated, starting with power/duration settings that barely blanch or opacify the tumor, and gradually increasing the power to make the tumor turn opaque white. Larger or visually threatening tumors (IIRC[33] Groups B and C eyes) treated first with chemotherapy and recurrent tumors after cessation of chemotherapy are treated with laser coagulation. For IIRC[33] Group D eyes, laser is used only after a good response has occurred with chemotherapy, to eliminate recurrence before the tumor has a chance to regrow (see Fig. 43.17).

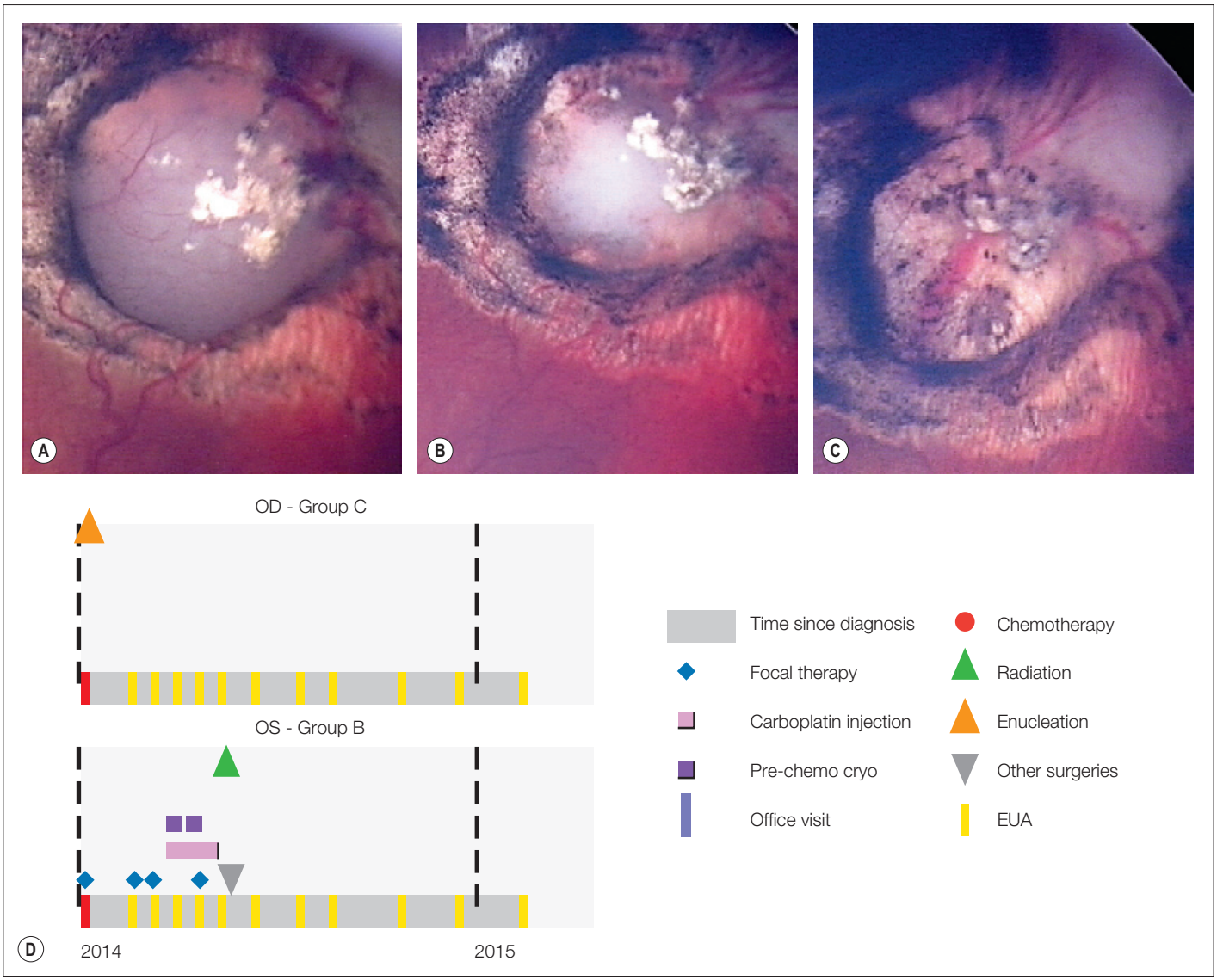


Fig. 43.26 Brachytherapy. (A) Tumor refractory to laser and cryotherapy was treated with a radioactive ^{125}I plaque applied on the sclera to deliver 40 Gy to the tumor apex over 7 days. (B) Tumor responded dramatically by the day of plaque removal. (C) A flat scar 1 month after removal of the plaque, which did not subsequently change. (D) eCancerCare$^{\text{RETINOBLASTOMA}}$ (eCC$^{\text{RB}}$) timeline describing the overall retinoblastoma care of this child. *(RetCam images by Leslie MacKeen and Cynthia VandenHoven.)*

The diode 810-nm laser is most widely available but causes more scarring and traction that may progress than the green frequency-doubled YAG at 532-nm. Thermotherapy has been promoted widely, using a 810-nm laser to gently heat tumors over a long period of time.[66,67] For IIRC[33] Group A small tumors, 532-nm is effective without drifting of the scars. Infrared lasers (diode 810-nm or 1064-nm-long duration YAG) can be applied after chemotherapy to larger, thicker tumors with good effect. With all lasers, it is important *not* to use too much power at any one treatment, and retreat at frequent intervals until only flat scars remain. Fluorescein angiography is useful for identifying early potential spots of recurrences in a laser scar (see Fig. 43.1).

Focal irradiation

Solitary tumors less than 15 mm in diameter that are not adjacent to the disc or macula may be treated with an episcleral radioactive plaque, iodine-125 (^{125}I), or ruthenium-106 (^{106}Ru)[68] (Fig. 43.26). Plaques are useful to treat single recurrences after chemotherapy or whole-eye radiation has failed. Under general anesthesia, the tumor is localized, and the plaque is sutured to the sclera apposed to the tumor and left *in situ* until the prescribed dose of radiation has been delivered to the apex of the tumor. A second course of radiation to the whole eye (external beam radiation) is prohibited because it will lead to severe radiation retinopathy and/or optic neuropathy, and potential increase in the already-high risk of late induced cancers.

External beam irradiation

Radiation was the first approach that cured intraocular retinoblastoma, saving many eyes with useful vision, but with severe consequences of inducing second cancers and severe cosmetic deformities. Most commonly, there is significant

calcification ("cottage cheese-like") or a combination of calcification and translucent residual tumor after radiation. The risk of second primary cancers within the radiation field in children with a germline *RB1* mutation is significant; most children die of these induced cancers[19,69] (see Fig. 43.2). The risk may be greatest when infants are irradiated under 1 year of age.[70] External beam radiotherapy has been used for treatment of recurrences after chemotherapy. However, intra-arterial chemotherapy for treatment of specific recurrent disease is now shown to be more effective with less toxicity than radiation.[71]

Intra-arterial chemotherapy (IAC)

Local treatment of retinoblastoma with chemotherapy is an attractive idea, sparing the child from the complications of systemic drugs. Injection of a chemotherapeutic agent (melphalan) into the carotid artery/ophthalmic artery has been performed for over 20 years in Japan, but the single outcome study is inconclusive about efficacy and safety.[72] Despite lack of clear outcome data, intra-arterial chemotherapy (IAC) has been widely adopted in the last few years because of the predictions that all eyes with retinoblastoma might be saved by this approach. Without formal rigorous follow-up of clinical trials, initial studies were very encouraging. A retrospective study suggests that IAC is most successful as primary therapy for less severely involved eyes.[73] Local side effects, such as third cranial nerve palsy, retinal pigment epithelial changes, and retinal detachment can occur, but external beam radiotherapy or enucleation can be avoided.[74]

However, the use of IA chemotherapy for IIRC[33] Group E retinoblastoma is very dangerous. The IAC results in a sometimes dramatic local shrinking of intraocular tumor, but tumor leaving the eye into the nerve, choroid, and blood remains unacknowledged. As a result, a child may be responding well until an extraocular relapse is identified and the child dies. Such a child might have been cured by enucleation of the IIRC[33] Group E eye with timely adjuvant therapy for high-risk pathologic features. Multiple cases of metastasis following IAC are reported[72,73,75,76] and more are evident on parent blogs that are not yet acknowledged in the medical literature.

Intravitreal chemotherapy

Delivery of the chemotherapy into the vitreous cavity theoretically provides the highest chemotherapeutic drug levels in the vitreous cavity, ideal for treatment of vitreous seeds. The fear of extraocular spread by injection into an eye with active seeds has been set aside by the careful technique for selected eyes with vitreous seeds after control of the source of seeds.[30,77–79] Responses are excellent, potentially solving the most difficult-to-treat problem in eye salvage, vitreous seeds.

Extraocular retinoblastoma

Extraocular retinoblastoma results in a precipitous drop in the prognosis for life (see Fig. 43.11). Until recently, metastatic retinoblastoma was considered fatal. Local orbital recurrence is generally treated with 40–50 Gy orbital radiation and systemic chemotherapy. Metastatic retinoblastoma to bone marrow or other sites may be treated with intensive chemotherapy, with cyclosporin to counter multidrug resistance, and, if remission is attained, supralethal chemotherapy and peripheral stem cell transplantation. Meningeal spread of retinoblastoma is treated additionally with intrathecal and intraventricular chemotherapy via an Ommaya reservoir, with rare cures.[80]

Prophylactic radiation is considered when histopathologic examination of the enucleated globe shows involvement of the cut end of the optic nerve with high risk of orbital recurrence. When marked choroidal invasion and involvement of the optic nerve past the cribriform plate are noted on histopathology (pT3), adjuvant therapy may be advised to treat potential tumor spread beyond the eye. However, tumor into or minimally past the lamina cribrosa may be managed by surveillance with regular MRI, bone marrow, and cerebrospinal fluid examinations, treating only when disease is documented. Otherwise, many children may be treated unnecessarily. Evidence to support these treatment recommendations is pending a multicenter trial of prophylactic treatment for adverse histology.

Children presenting with extensive orbital disease, with proptosis and likely intracranial extension, are now treated first with systemic chemotherapy.[81] After several cycles of chemotherapy, there is often a marked shrinkage of the orbital tumor, and enucleation can be performed. This is generally followed with more chemotherapy and orbit radiation. There is no role today for exenteration in the treatment of retinoblastoma.

Prognosis

With modern methods of diagnosis and treatment, the prognosis for retinoblastoma is excellent. The 3-year survival for both unilateral and bilateral retinoblastoma approaches 96%.[51] More patients with germline *RB1* mutations die of their second primary cancer than from uncontrolled retinoblastoma.[19]

The prognosis for vision is excellent in unilateral retinoblastoma (for the normal eye), but depends on the size and location of the tumors in bilateral cases. Awareness and prompt diagnosis, with good results with chemotherapy and focal therapy, means that bilateral enucleation is now rare. Extra-foveal tumors have a good visual prognosis but, when the macular region is directly involved, the visual results may be poor, despite tumor control. The most important impact on further improving visual outcome for retinoblastoma children lies in the earlier recognition of the presenting signs by the primary caregivers.

Long-term follow-up

Following the initial management and resolution of active tumor, assessment of the response to treatment will require frequent EUAs, especially in the first year following diagnosis with completion of chemotherapy, when recurrence or new tumors are most likely to occur. Regular EUAs will be necessary until the child is old enough to cooperate for a full-dilated eye examination in the clinic, variably at about 3 years of age. Follow-up can then be continued on an outpatient basis. However, children with IIRC[33] Groups C and D eyes may need a much longer follow-up with EUA in order to assess peripheral tumors for recurrence.

Lifelong implications of retinoblastoma

Retinoblastoma patients who carry a mutant *RB1* allele are at risk of other cancers throughout their lives, many years after their initial treatment for retinoblastoma. Anecdotal reports demonstrate that some adults who were treated as children (often by enucleation or radiation) are not aware that they had cancer and have been lost to follow-up. They may, however, present to their local ophthalmologists with ocular and/or orbital problems. It is important that ophthalmologists are aware of the long-term systemic problems associated with retinoblastoma as they may be the only secondary care physician seen by the patient.

Everybody in the Western world has a lifetime risk of approximately 1 in 3 of developing cancer. Patients with an abnormal *RB1* gene reach this risk by the age of about 50 years of age. The non-ocular cancers that have increased incidence include bone and soft tissue sarcomas during adolescence and early adulthood, malignant melanoma, epithelial cancers, bladder, esophagus, and probably breast cancer. These risks are increased significantly by radiation exposure.

All patients with a past history of retinoblastoma should be offered molecular *RB1* gene analysis for counseling with regard to the risk of retinoblastoma in their offspring, and their own increased risk of developing a non-ocular cancer. This is particularly important for the patients with unilateral disease who may carry a mutation of the *RB1* gene and are unaware of this fact. Emphasizing the dangers of known carcinogenic factors such as smoking, radiation, obesity, and excess ultraviolet light is particularly important. As radiation is associated with an increased risk of cancers, routine X-rays and CT scans are not advised.

Likewise, patients who have been treated with chemotherapy and/or radiation will require oncologic follow-up for early detection and appropriate management of possible long-term complications. It is important for retinoblastoma patients to retain contact with their oncologist because of the risk of secondary malignancies, whether sporadic or induced by radiation or chemotherapy. It is also important to ensure that accurate genetic counseling is available to the parents, and to the child when he or she reaches maturity.

Future perspective

Global collaboration and the ability of parents, health care teams, and scientist to communicate through the Internet now sets the stage to optimize care for all children and families who are affected by retinoblastoma. We look to projects such the 1RBW map (http://www.1rbw.org) (see Fig. 43.23) and retinoblastoma registries such as eCancerCare$^{\text{RETINOBLASTOMA}}$ (eCC$^{\text{RB}}$)[41,42] to ultimately perform as a "learning health system" to achieve equity in retinoblastoma management for all children, targeting zero deaths from retinoblastoma by year 2025.

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Fig. 43.3 (A) Exophytic retinoblastoma (IIRC[33] Group D) with retinal detachment in a unilaterally affected 3-year-old boy. (B) B-scan ultrasound showing calcification in a single tumor beside the optic nerve. (C) B-scan ultrasound showing subretinal hemorrhage and no tumor involvement of optic nerve. (D) Computed tomography scan showing intraocular calcification, normal sized optic nerve. (E) The eye was opened immediately after enucleation, in order to obtain live tumor cells and the two *RB1* mutations (homozygous exon 16 deletion C-1450, insertion AT) defined. The mutant RB1 allele was not detected in the child's blood, eliminating risk for his siblings. His future offspring will be checked for the mutant allele of the tumor, since he could still be mosaic. (F) The child 2 days after enucleation, wearing the temporary prosthetic conformer inserted at the time of surgery. The exon 16 *RB1* mutation of the tumor was not detected in blood, indicating high likelihood that the retinoblastoma is not heritable, eliminating risk for siblings. Due to the remaining possibility that the affected child is mosaic for the *RB1* mutation, his future offspring will be tested for this mutation. (Images by Cynthia VandenHoven and Carmelina Trimboli.)

Fig. 43.5 (A) Retinoma with a vitreous seed (stereo images) discovered at age 18, followed for 30 years with no change; daughter had bilateral retinoblastoma. (B,C) Multifocal bilateral retinoma discovered in the grandfather when his granddaughter developed unilateral retinoblastoma. His daughter had bilateral retinoblastoma and meningioma at age 40. (D) All affected members carry a "null" germline *RB1* mutation (heterozygous point mutation in exon 17 resulting in a STOP codon).

Fig. 43.7 A child with unilateral retinoblastoma IIRC[33] Group E eye. (A) Leukocoria. (B) Large white mass with multiple diffuse vitreous seeds (arrows) and subretinal seeds (*). (C) Ultrasound biomicroscopy (UBM) showing tumor mass invading the anterior hyaloid face. (D) Magnetic resonace imaging showing the intraocular tumor with tumor-free optic nerve and no extraocular spread. (RetCam images and UBM by Leslie MacKeen.)

Fig. 43.8 Child with bilateral retinoblastoma. (A) Right eye (IIRC[33] Group D) with leukocoria. (B) caused by a large multilobular tumor. (C) Magnetic resonance imaging (MRI) showing the configuration of the intraocular tumor, no involvement of the optic nerve, and no extraocular involvement. (D) Left eye showing a small superotemporal tumor (IIRC[33] Group B) documented by MRI (insert, arrow). (RetCam images by Leslie MacKeen and Cynthia VandenHoven.)

Fig. 43.20 New tumor in a previously treated eye. (A) Arrow indicates no tumor 8 months after initiation of CEV (carboplatin, etoposide, and vincristine) chemotherapy with cyclosporin for IIRC[33] Group D retinoblastoma in the right eye of the child. (B) New peripheral small tumor 2 months later, 10 months after diagnosis. (C) Triple freeze–thaw cryotherapy for the small new tumor, encasing the tumor in ice, thawing for 1 minute, and refreezing. (RetCam images by Cynthia VandenHoven.)

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Retinopathy of prematurity

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Retinopathy of prematurity (ROP) was first reported by Theodore L. Terry in 1942. This condition, then known as retrolental fibroplasia, is a disorder of the immature retinal vasculature. It was extremely rare before the 1940s. The retinopathy developed after a normal fundus examination at birth. Clinical and experimental evidence supported a toxic effect of oxygen on the immature retinal vasculature, which led to the restriction of oxygen use in preterm neonates.[1] This resulted in a dramatic fall in the incidence of ROP, but even though oxygen plays a central role, many other factors contribute to the pathogenesis. However, despite major advances in our understanding, its identification, and treatment, ROP remains an important disorder as a cause of visual disability, and a consumer of health service resources.

Retinal vascular development

The choroid, which is vascularized by 6 weeks' gestational age (GA) meets the metabolic needs of the retina in early fetal life, but as the retina becomes increasingly complex and metabolically active, this single circulation is insufficient, resulting in a state of physiological retinal hypoxia so generating the stimulation of vascular endothelial growth factor (VEGF) and the development of a retinal circulation. This commences at about 13–14 weeks GA with the centrifugal migration from the optic disc of vascular endothelial cells, microglia, pericytes, and astrocytes. These proliferate, and become aligned into vascular cords that develop lumina and differentiate into capillaries, a process known as vasculogenesis. This is succeeded by angiogenesis in which vessels grow out from existing vessels, remodel, and form a mature retinal vascular network with capillary-free areas. The developing retina responds to excessive or insufficient oxygen by trimming or inducing growth in the microvasculature to match the retina's metabolic requirements.[2]

While oxygen-dependent VEGF plays a critical part in all stages of vascular development, other factors are also involved such as oxygen-independent insulin-like growth factor 1 (IGF-1) and erythropoietin.[3]

Pathogenesis

There are two phases in ROP development and both occur postnatally.

Phase I: decreased retinal vessel growth

Premature birth removes the fetus from a milieu uniquely suited to growth, so not only does it deprive the fetus of maternal nutrition, but also exposes the baby to a harsh environment requiring considerable physiological adaptation and also many potential pathological processes.

The cardiopulmonary adaptations associated with birth and transfer from the fetal environment to room air include PaO_2 rising from <25 mmHg (kPa <3.5) to 80–95 mmHg (kPa 10.5–12.5) within 6 hours. While this has no effect on the fully vascularized retina of the term infant, for the premature infant this so-called physiological hyperoxia causes a VEGF-mediated cessation of retinal vascular development, but may also cause retraction and loss of retinal vessels. Evidence of the former is the location of the ROP lesion. Vasobliteration was observed in the experimental animal over 60 years ago, but not confirmed in the human until very recently; eyes that initially were vascularized into zones II and III exhibited obliteration of formed vessels and regression into zone I following exposure to unblended oxygen.[4]

While the major factor in phase 1 of ROP is oxygen-induced VEGF downregulation and also suppression of hypoxia-induced erythropoietin, also important are deficiencies of several maternal nutrients, which can no longer reach the fetus, now baby.[3] These include growth hormone and IGF-1. IGF-1

controls VEGF activation of the Akt endothelial cell survival pathway and low levels result in reduced survival and growth of vascular endothelial cells – reduced suppression angiogenesis. Another nutrient normally transferred from mother to fetus and consequently deficient following premature birth is ω-3 long chain polyunsaturated fatty acids, which have a role in vascular and neuronal survival and have been shown to prevent ROP in the experimental animal.[3,5]

Phase II: vasoproliferation

In phase I, the retina is rendered hypoxic by hyperoxia-induced VEGF downregulation. The resultant cessation of vessel growth and vessel retraction is replaced in phase II by hypoxia-induced VEGF stimulation for which clinical features are described later.

The postnatal timing of the two ROP phases has attracted some attention and, as discussed below, in general, the timing of the phases is largely determined by postmenstrual age (PMA). However, the abnormal vascularization of phases of ROP occurs within a relatively short timeframe and must be complete for full retinal vascularization within certain confines, as ROP is a postnatal condition and must commence before full vascularization.

Risk or associated factors

The major ROP risk factor is the degree of immaturity as measured by either birth weight or gestational age. ROP may develop in preterm infants who never received oxygen. However, studies have confirmed the relationship between oxygen administration (and transcutaneous levels >80 mmHg) in the first few postnatal weeks and ROP, particularly within the first few weeks after birth.[6,7] A relationship between neonatal hypoxia and ROP has also been suggested.[8] That both hyperoxia and hypoxia may be associated with ROP is not contradictory as both are invoked in its pathogenesis, so explaining the association of recurrent apnea with ROP.

There has been a recent trend to keep babies at lower oxygenation levels. However, recent international randomized controlled trials reported significantly higher mortality and necrotizing enterocolitis in infants targeted to 85–89% SpO_2 compared to those targeted to 91–95% SpO_2, but with more ROP in the latter.[9] This confirms what was understood in the 1970s – that lower oxygen levels reduce the incidence of ROP blindness, but at the expense of reduced survival and higher morbidity. While a safe oxygen level still cannot be precisely given, SpO_2 targets of 85–89% are unsafe in extremely preterm infants. In contrast to oxygen management in the early neonatal period as described above, a meta-analysis concluded that "late" (≥32 weeks PMA) high oxygen was associated with reduced incidence of severe ROP.[10]

Acidosis is a risk factor for ROP, whereas hypercarbia is not; however, the combination of high PCO_2, PaO_2, and low pH in the first 3 days after birth is associated with severe ROP.[11]

It has been reported that mutations in the Wnt signaling pathway,[12] which also encompasses the Norrie's gene and familial exudative vitreoretinopathy, are associated with increased incidence of ROP. However, a recent study does not support this, noting instead an association of severe ROP with low levels of brain-derived neurotrophic factor.[13]

Many factors have been suggested as possible contributors to ROP. Some have been confirmed: male gender, assisted reproductive technology, and White compared to Black race are predictive factors for severe ROP.[14] The following are not independent ROP risk factors: multiple birth, early exposure to light, and hypercarbia. The roles of many other possible factors have not been confirmed or clarified such as: hyperglycemia,[15] inflammation, vitamin E, surfactant, and acidosis. The suggested association between ROP and blood transfusion has not been confirmed.[16]

Recombinant erythropoietin, a cytokine angiogenic factor that regulates fetal erythropoiesis, can be used to treat neonatal anemia, a use that has been reported to increase the risk of ROP; however, this is not borne out by systematic analyses.[17]

Many factors are active simultaneously and differently according to the standard of neonatal care. Thus, the characteristics of babies developing ROP in some countries are different from those in others: larger and more mature infants are at risk in less developed countries, where the unrestricted use of oxygen and sepsis are factors.[18]

Classification

A revision of the 1984 international classification of acute ROP[19] and 1987 expansion to include retinal detachment and sequelae[20] was published in 2005.[21] It maintained four basic parameters to describe ROP morphology including severity, location, extent of disease, and plus disease (Table 44.1), while expanding two concepts: pre-plus disease and aggressive posterior ROP (AP-ROP).

The normal fundus of the extremely premature baby can be difficult to visualize in detail (Figs 44.1 and 44.2). The retinal blood vessels are thin and straight. Later, they increase in caliber and tortuosity, but abnormally so with active ROP.

Severity of disease

The peripheral changes at the leading edge of the developing retinal vessels have been divided into five stages.

Stage 1

A flat gray-white demarcation line separates the vascularized from non-vascularized retina. Often faint, it can be difficult to identify. Retinal vessels run up to the line but do not cross it (Figs 44.3 and 44.4).

Stage 2

The demarcation line has increased in volume and extends out of the plane of the retina (Figs 44.4–44.6). The color of the ridge may be white or pink, and small neovascular tufts may be seen posterior to the ridge. Differentiating stage 1 and early stage 2 is difficult, but usually not prognostically important.

Stage 3

Stage 3 has the features of stage 2, but is characterized by extraretinal neovascularization (Figs 44.6 and 44.7). The new vessels may be continuous with, or disconnected from, the posterior border of the ridge, or extend into the vitreous. The extraretinal neovascularization may extend from the region of the ridge into the vitreous or, typically in more

Table 44.1 International classification of retinopathy of prematurity – revisited (2005)

Severity	
Stage of ROP	Stage 1: demarcation line Stage 2: ridge Stage 3: ridge with extraretinal vascular proliferation Stage 4: subtotal retinal detachment 4A: extrafoveal detachment 4B: foveal detachment Stage 5: total retinal detachment
Aggressive posterior ROP (AP-ROP)	Severe dilation and tortuosity of posterior pole vasculature Innocuous appearance of ROP at junction between vascularized and avascular retina Located in zone I or posterior zone II
Anterior-posterior location	Zone I: retina within a circle centered on the disc with a radius of twice the disc–foveal distance Zone II: a doughnut-shaped area that extends from the edge of zone I to a circle which has a radius of the distance from the disc to the nasal ora serrata Zone III: crescent-shaped retinal area peripheral to zone II
Extent of disease (in clock hours)	30° sectors of ROP along circumference of the vascularized retina
Plus disease	Abnormally dilated and tortuous vessels of the posterior pole (at least two-quadrant involvement required)
Pre-plus disease	Abnormal vascular dilation and tortuosity insufficient for diagnosis of plus disease (at least two-quadrant involvement required)

Adapted from An International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005. 123: 991–9.

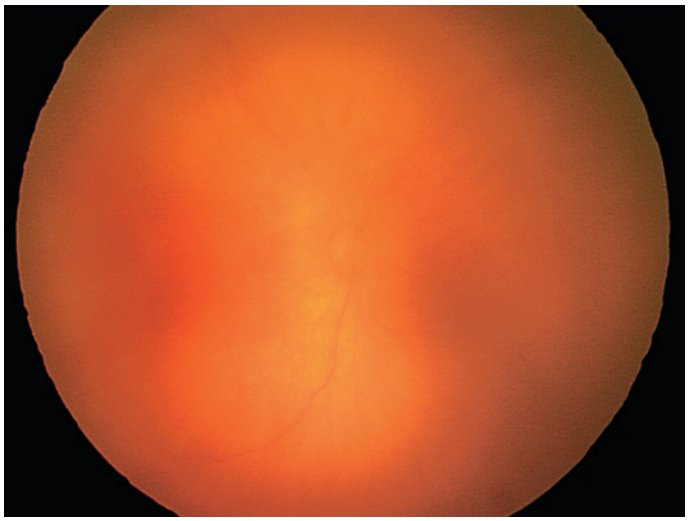


Fig. 44.1 Immature retinal vessels in an extremely immature baby. The view is hazy. Note how thin and straight are the retinal vessels.

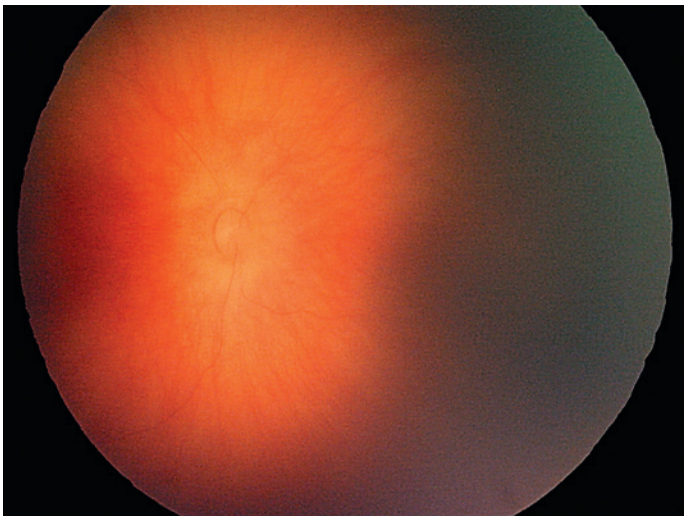


Fig. 44.2 Immature retinal vessels 1 week after image in Fig. 44.1. No retinopathy of prematurity.

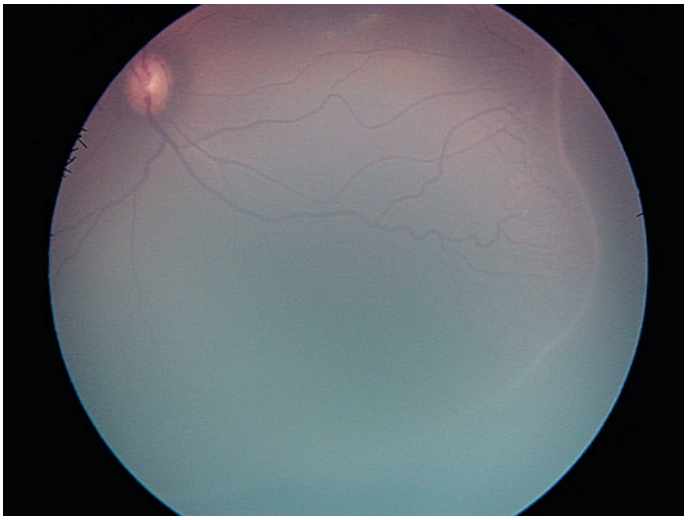


Fig. 44.3 Stage 1 retinopathy of prematurity. Thin line separates vascularized from avascular retinal regions. The bluish tint is due to dark fundus.

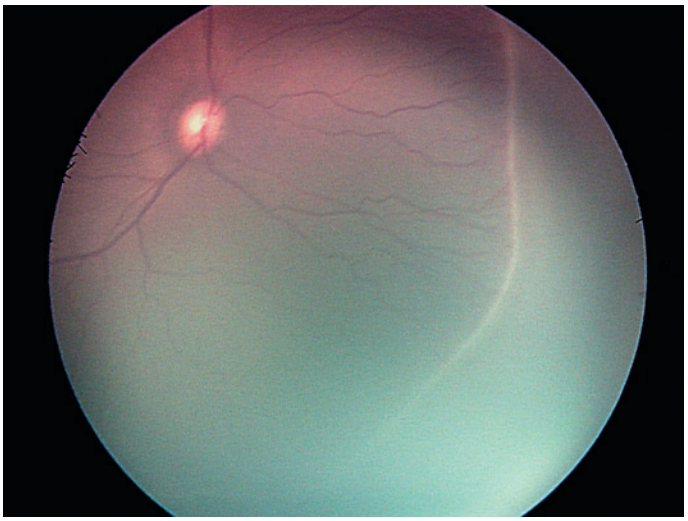


Fig. 44.4 Retinopathy of prematurity stages 1 and 2. Stage 1 in its lower part, but the line becomes thicker (ridge) toward the top of the image. Differentiating stages 1 and 2 is not always easy – or necessarily important.

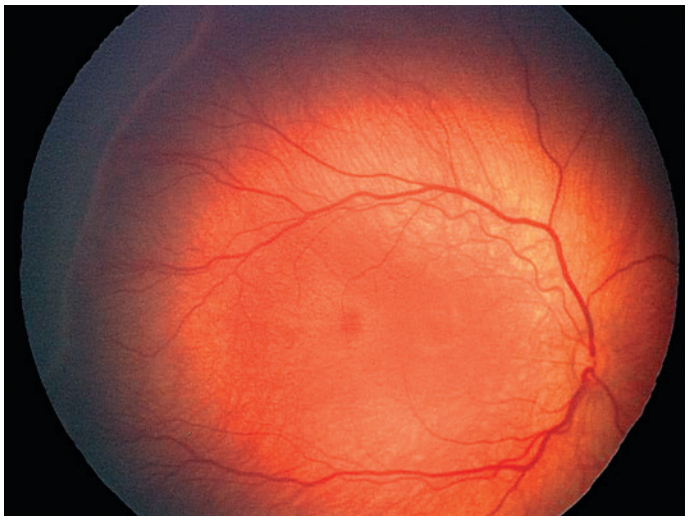


Fig. 44.5 Stage 2 retinopathy of prematurity.

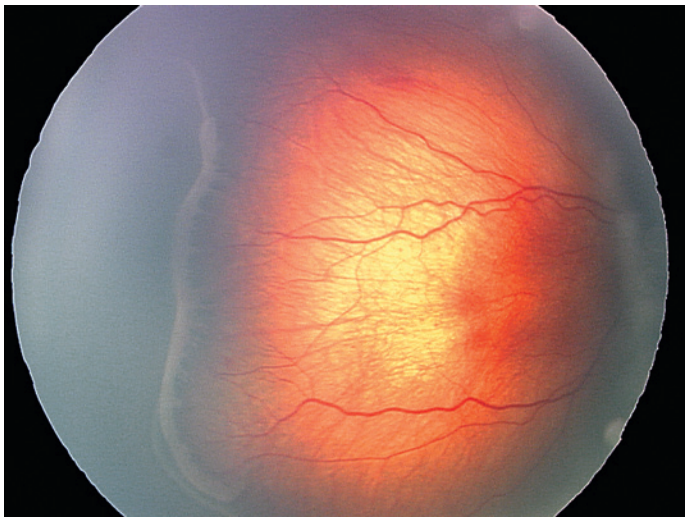


Fig. 44.6 Stage 2 and stage 3 retinopathy of prematurity. Stage 2 at top and bottom of the image with about 1 clock hour of mild stage 3 disease that curls away from the ridge at its lower edge.

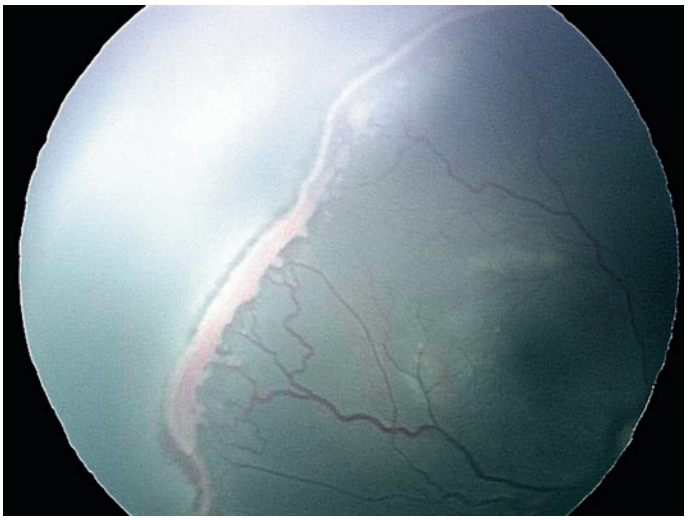


Fig. 44.7 Stage 3 retinopathy of prematurity (ROP) that has developed in the eye with stage 2 disease shown in Fig. 44.5. Note the peripheral tortuosity and dilation as the vessels become close to the ROP lesion (compare with Fig. 44.5). The shadow, just behind the lesion, indicates that the lesion is off the retinal surface.

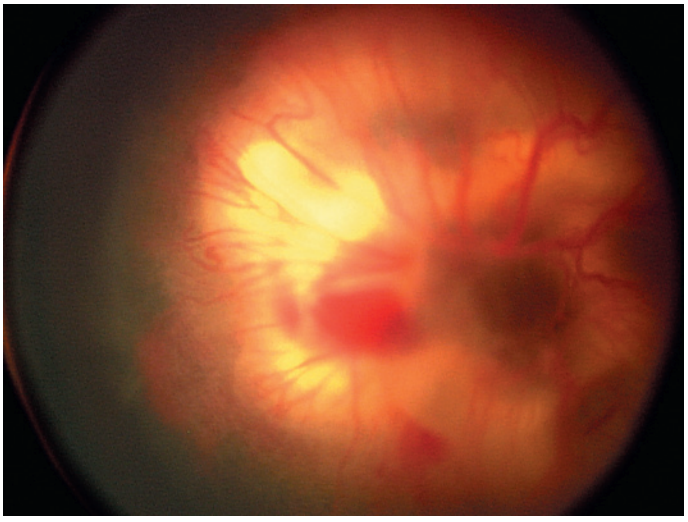


Fig. 44.8 Acute stage 5 funnel retinal detachment.

posterior disease, lies back across the surface of the vascularized retina.

Stage 4

This is characterized by subtotal exudative or tractional retinal detachment, that is extrafoveal (stage 4B), or involves the foveal region (stage 4A).

Stage 5

There is a funnel-shaped total retinal detachment (Fig. 44.8). This stage is further defined according to the anterior and posterior characteristics of the funnel.

Aggressive posterior ROP (AP-ROP)

This severe form of ROP[21] is characterized by a posterior location (zone I or posterior zone II) and a prominence of plus disease out of proportion with the rather innocuous appearance of the vascular abnormality at the vascular/avascular junction. The severity often makes it difficult to distinguish arterioles from venules (Fig. 44.9). Critically, AP-ROP does not show progression from stage 1 to stage 2 and stage 3; the flat network of new vessels can easily be missed.

Plus disease

The cardinal signs of plus disease (Fig. 44.10) are marked increased tortuosity of retinal arterioles and engorgement of venules near the optic disc. Engorgement of the iris vessels and poor pupillary dilatation and vitreous haze are late signs and generally indicate advanced disease. Signs of plus disease may appear at any ROP stage. This clinical diagnosis is made by comparing with a reference photograph in the classification.[21] At least two quadrants must be involved and the peripheral changes of ROP must be present. Plus disease does not refer to vascular changes in the retinal periphery. Plus disease is the current major ROP morphological sign indicating treatment,

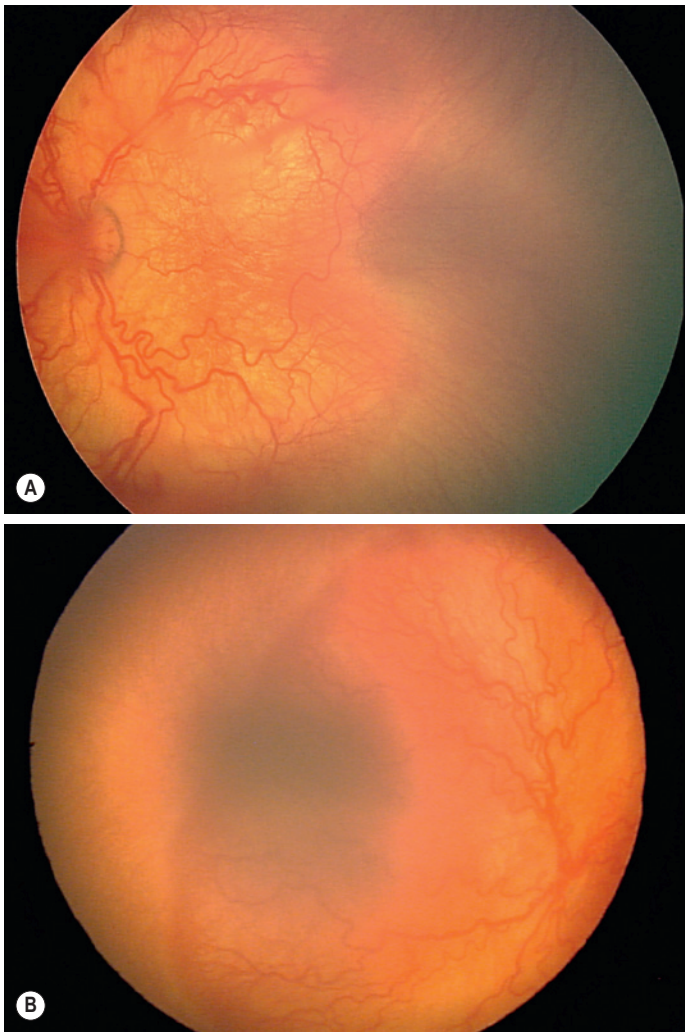


Fig. 44.9 Examples of aggressive posterior retinopathy of prematurity (AP-ROP). (A) View of AP-ROP – note the posterior locations, prominence of plus disease, and the modest appearance of the peripheral retinopathy. (B) AP-ROP image showing plus disease with a brush-like neovascular proliferation at junction between vascular and avascular retina. *(Reproduced with permission from An International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005. 123: 991–9.)*

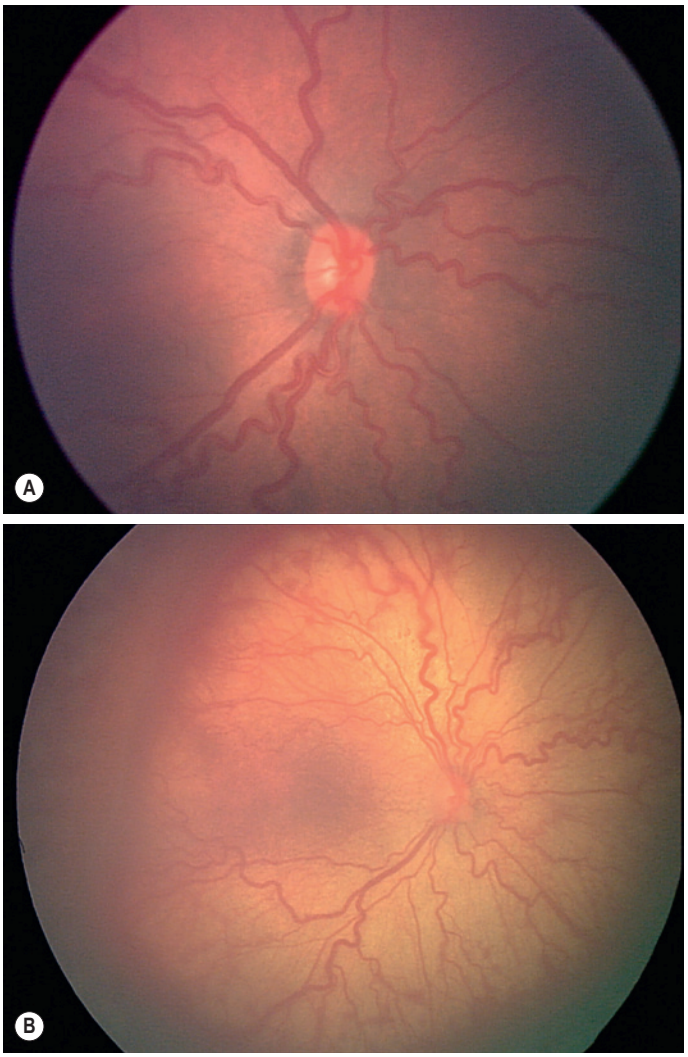


Fig. 44.10 Two examples of plus disease. Note the different appearance with different magnification and field of view between (A) and (B). *(Reproduced with permission from An International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005. 123: 991–9.)*

and is associated with an increased likelihood of poor outcome.[22,23]

Pre-plus disease

The term "pre-plus" disease[21] indicates posterior vascular changes that are as yet insufficient to be termed plus disease (Fig. 44.11). It alerts to the likelihood of peripheral retinopathy.

Location

The retina is divided into three concentric zones centered on the optic disc, with zone I defined as a circle of approximately 30° with a radius twice the disc–foveal distance. Zone II is doughnut shaped, and extends from the edge of zone I with a radius reaching the nasal ora serrata. Zone III includes all retina anterior to zone II. With no anatomic landmarks identifying zone III, only when the direct nasal retina is fully vascularized can it be stated that zone III has been entered.

Extent

The extent of disease along the junction between the vascularized and avascular retina is described in clock hours or by 30° sectors.

Regression and resolution

Resolution of acute phase retinopathy has been less well studied. The first signs of regressing ROP are failure to progress and lessening of posterior pole vascular abnormalities. The ridge thins and breaks up, and retinal vessels grow through the ridge into the peripheral avascular retina. Involution is characterized by vascular remodeling with gradual movement of vessels toward the periphery, although in some eyes, vascularization does not proceed to the ora serrata. Vasoproliferative lesions become fibrotic. In general, stages 1 and 2 ROP completely resolve, while stage 3 may lead to peripheral fibrosis and retinal dragging (Fig. 44.12) or detachment. Residua of acute phase ROP were defined in the 1987 International

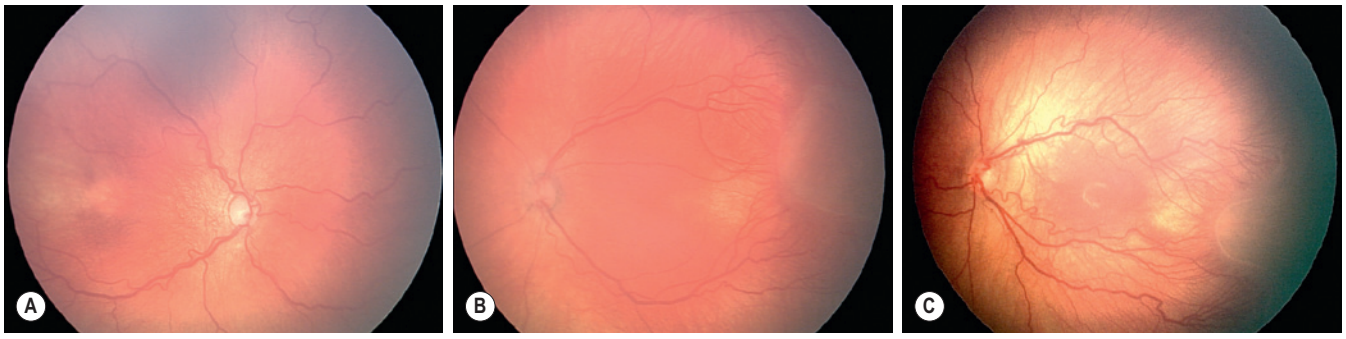


Fig. 44.11 Examples of pre-plus disease showing increased tortuosity and dilation compared to normal, but insufficient to be designated plus disease. *(Reproduced with permission from An International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005. 123: 991–9.)*

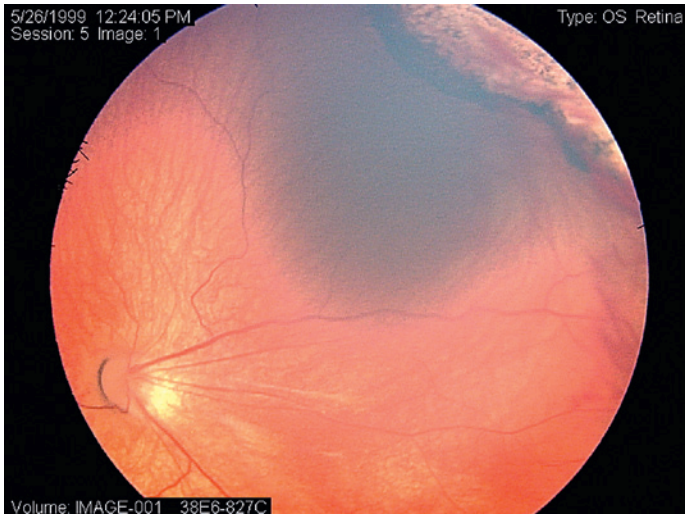


Fig. 44.12 Mild dragging of the retinal vessels. Note response to cryotherapy on upper border of picture.

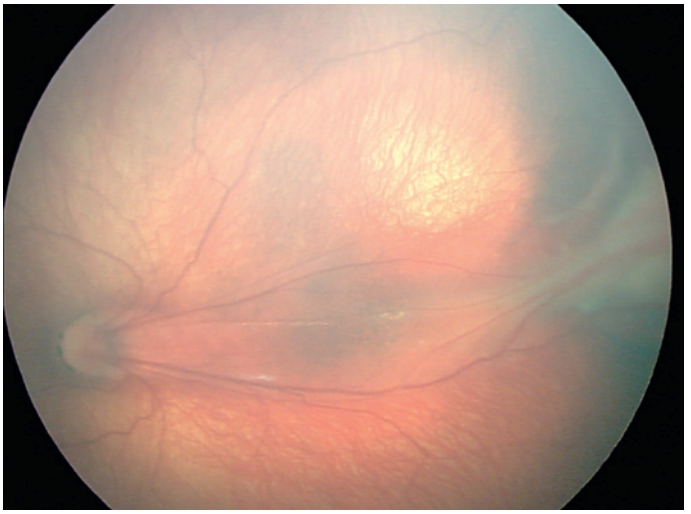


Fig. 44.13 Fundus photograph showing late cicatricial changes including stage 4B retinal detachment with extensive temporal dragging of vessels and macula. *(Reproduced with permission from An International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005. 123: 991–9.)*

Classification of Retinopathy of Prematurity (ICROP) paper in terms of retinal and vascular changes in the peripheral retina such as incomplete vascularization, pigmentary changes, vitreoretinal interface changes, up to and including retinal detachment and posterior changes.[20] Posterior abnormalities resulting from acute phase ROP included vascular tortuosity, straightened temporal vessels, macular heterotopia, retinal fold (Fig. 44.13), and detachment.

The mean time of onset of signs of involution in children with birth weights of less than 1251 g was 38.6 weeks; 74% of all ROP had begun to involute by 40 weeks of PMA, 90% by 44 weeks.[24] Advanced scarring or "cicatricial" changes may shallow the anterior segment, leading to glaucoma and corneal decompensation.

Incidence and prevalence

The incidence of acute phase ROP and ROP blindness that may result from severe disease in an individual region varies with the level of health care provision and socioeconomic development in high-, middle-, or low-income countries.[18,25] There may, however, be diverse health–socioeconomic communities within a single country. In high-income countries, where economics and technology permit generally high-quality health care and neonatal intensive care, ROP-induced disability accounts for 3–8% of childhood vision impairment.[26,27] In middle-income communities, technology permits increased survival of preterm babies, but limited health resources may limit the standard of care.[25] Consequently, babies with higher birth weights and gestational ages are at risk of severe ROP; ROP-induced blindness contributes up to 39% of childhood vision impairment due to increased survival and associated limited resources with suboptimal quality neonatal care.[18,28] In low-income countries, very few preterm babies survive to develop ROP.[18,25]

As shown in Table 44.2, there have been three ROP epidemics.[18,29] The first in the 1940s was due to unrestricted, unmonitored oxygen, and was brought to an end by oxygen restriction. The survival of neonates of <1000 g birth weight was 5–8%, and most of the babies blinded during this period had heavier birth weights. ROP blindness was greatly decreased by advances in neonatal care.[30] In the late 1960s, in countries with well-developed neonatal intensive care services, the increased survival of the very immature neonate who had not previously survived (now around 50–60% <1000 g birth weight) resulted

Table 44.2 Risk factors for retinopathy of prematurity: a historical perspective

		First epidemic (1940–1950s)	Second epidemic (1970–1980s)	Current: Regions with well developed neonatal care systems	Current: Regions with developing neonatal care systems (third epidemic)
Risk factors	Prematurity	+	++	++++	+ to ++++
	Low birth weight	+	++	++++	+ to ++++
	Excessive oxygen supplementation	++++	+++	+	++++
	Illness	+	+	+/–	+/–
BW <1000 g	Survival rate	+	++	++++	+ to +++
	Risk of ROP	+	++	+++	+ to ++++
BW 1000–1500 g	Survival rate	+++	++++	++++	+ to +++
	Risk of ROP	+++	+	+/–	+ to +++
BW >1500 g	Survival rate	++	+++	++++	++ to ++++
	Risk of ROP	+++	+	0	0 to +++
Ocular outcome		Poor	Moderate	Good	Poor to good

BW, Birth weight; ROP, retinopathy of prematurity.
Adapted from Gilbert C. Retinopathy of prematurity: a global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev 2008; 84: 77–82.

in a second epidemic. In retrospect, the first epidemic could be considered largely preventable, whereas the second is not preventable at our current level of neonatal care.[18]

The term "third epidemic" describes the prevalence of ROP-induced visual disability that began to emerge worldwide in the early 1990s, with ROP blindness being an increasing cause for visual impairment in Latin America, South and Southeast Asia, China, Eastern Europe, and Central Asia. Blencowe et al.,[25] based on 2010 data, estimated that there were approximately 15 million premature infants born each year, with about 2.6 million <32 weeks' gestation. Estimated incidence of acute phase ROP in <32 week-gestation infants varied from 21.8% in countries with neonatal mortality rates (NMR) of <5, to 36.5% in countries with NMR ≥5. Overall, an estimated 20,000 (uncertainty range 15,500–27,200) of all premature survivors had severe visual impairment or blindness in 2010, with an additional more than 12,000 infants having mild or moderate visual impairment. As shown in Fig. 44.14,[25] the majority of visually impaired survivors were born in middle-income regions of Latin America, East and South Asia, and Eastern Europe and Central Asia. Since optimal neonatal care and effective ROP detection and treatment programs are still being developed in these regions, there are opportunities for preventive interventions from both neonatal care and ophthalmological perspectives.[18]

Not all premature infants who develop ROP will become visually impaired. In the US-based Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP),[31] more than 4000 children with birth weights of less than 1251 g had serial eye examinations in 1986–87.[32] ROP was observed in one or both eyes of 65.8% of these infants, with ROP observed in 90% of children with birth weights of less than 750 g, in 78% of those with birth weights of 751–1000 g, and in 47% of those with birth weights of 1001–1250 g. These acute phase ROP data have been consistent in later studies[33,34] in the US, despite the increasing number of the smallest, least mature infants.

Natural history

Age at onset and rate of progression

ROP develops over a relatively narrow PMA range in the premature baby and its onset is linked more to the stage of development of the infant than neonatal events such as oxygen therapy or illnesses.[23] Further, the rate of progression to more severe disease is also governed predominantly by the stage of development rather than by postnatal age or neonatal events. As shown in Table 44.3 based on two large US trials conducted about 15 years apart,[32,33] there is a remarkable consistency in onset of various ROP stages and the behavior of ROP, with mean onset of stage 1 occurring at 34.3 weeks PMA in the CRYO-ROP trial and 34.1 weeks PMA in the Early Treatment for Retinopathy of Prematurity Randomized Trial (ETROP). Prethreshold ROP occurred at a mean of 36.1 weeks PMA for both studies, although there are wide 5% and 95% confidence intervals for all events in ROP progression. However, in countries with developing standards of neonatal care systems, sight-threatening disease frequently affects more mature and larger babies at similar rates of progression.[18,35,36]

Zone and site of involvement

The likelihood of developing severe ROP is closely related to the state of retinal vascularization.[32] More than half of the eyes

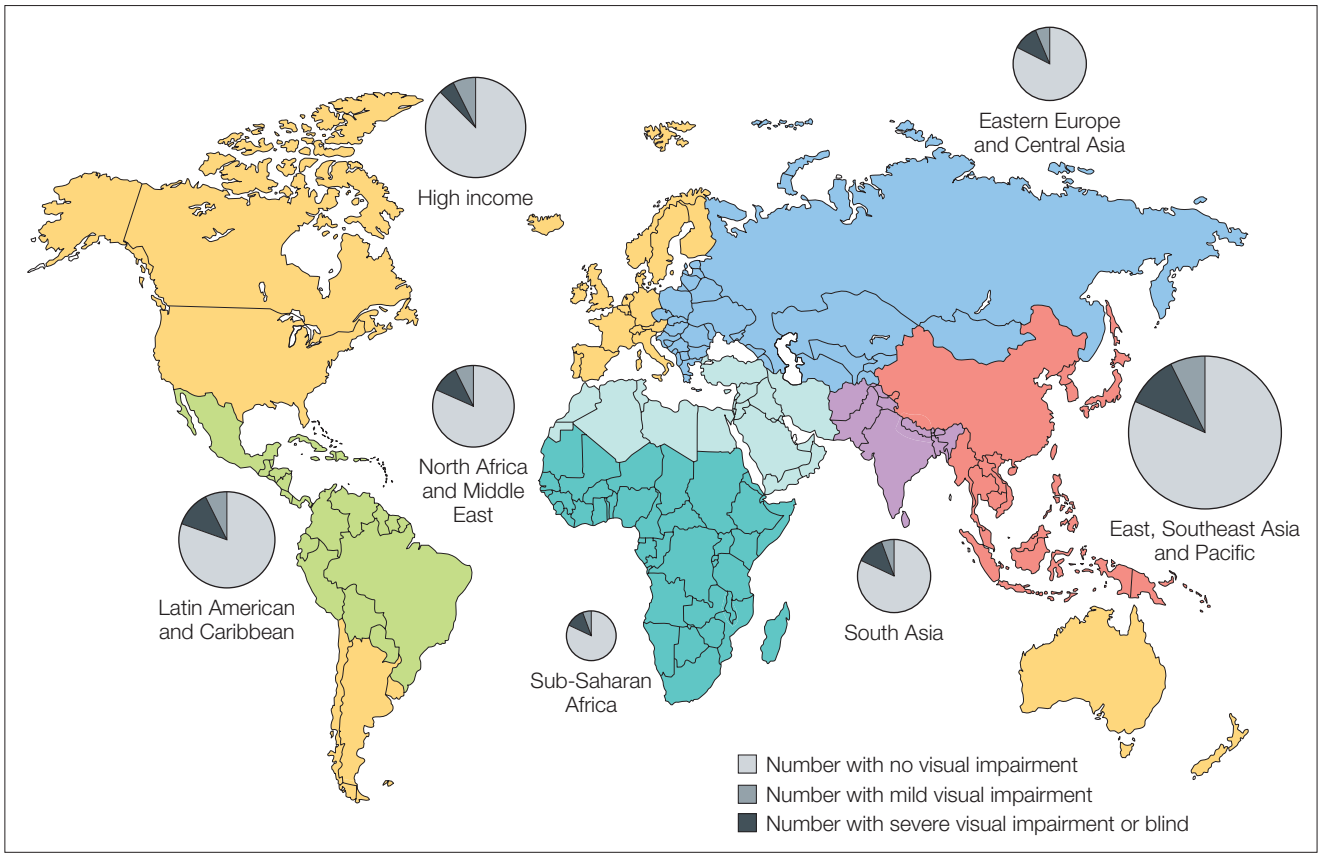


Fig. 44.14 Regional burden of visual impairment from retinopathy of prematurity among preterm babies born in 2010 and surviving the neonatal period. *(From Blencowe H, Lawn JE, Vazquez T, et al. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatr Res 2013; 74 Suppl 1: 35–49.)*

Table 44.3 Onset of different ROP events by postmenstrual age in weeks. Median (5%, 95%)

ROP stage	CRYO-ROP (N=4099)	ETROP (N=6998)
Stage 1 ROP	34.3 (–, 39.1)	34.1 (–, 38.9)
Stage 2 ROP	35.4 (32.0, 40.7)	35.1 (32.4, 40.1)
Stage 3 ROP	36.6 (32.9, 42.4)	36.6 (33.4, 41.6)
Plus disease	36.3 (32.6, 42.9)	36.0 (33.0, 41.4)
Prethreshold ROP	36.1 (32.4, 41.5)	36.1 (32.1, 42.1)

CRYO-ROP; Cryotherapy for Retinopathy of Prematurity trial; ETROP, Early Treatment for Retinopathy of Prematurity study; ROP, retinopathy of prematurity. Adapted from Good WV, Hardy RJ, Dobson V, et al. The incidence and course of retinopathy of prematurity: findings from the early treatment for retinopathy of prematurity study. Pediatrics 2005; 116: 15–23.

with incomplete vascularization in zone I observed at the first ROP examination will require treatment. The risk falls to less than 10% when vascularization has proceeded to zone II, and to near zero when vessels reach zone III.

In the very immature baby, ROP commences preferentially in the nasal retina and later extends to other regions. In the 2005 ICROP revision,[21] the zones of vascular development were recognized as having an elliptical shape, with nasal ROP frequently closer to the optic disc than ROP in the temporal retina. The more premature the neonate, the more likely ROP is to be in a posterior zone and to have a greater potential for progression to severe disease.

Plus disease

Plus disease is a critical, but qualitative, sign of ROP severity and is now the main driver for treatment.[22] Plus disease may be observed at any stage of ROP and is a sign of disease severity.[36] It is relatively easy to distinguish between plus disease and "normal" posterior pole vessels, but since the vascular abnormalities in ROP are along a continuous spectrum, making the call for "plus" when "mild" is the least robust and worrying diagnostic aspect of ROP.

Retinopathy of prematurity detection programs

Severe ROP can usually be successfully treated. Thus the ophthalmologist needs to identify severe, potentially treatable ROP – at present that is type 1 ROP.[22] Also babies with stage 3 ROP have a high risk of developing strabismus, myopia, and various vision deficits and thus merit continued surveillance.

There is no one-size-fits-all guideline for determining which babies should be checked, since birth weight (BW) and GA characteristics of at-risk babies differ between countries and even between neonatal intensive care units within one city.

Nevertheless, there are fundamental principles that apply to all populations and can be applied broadly:

ROP has a clearly described natural history: The timing of its onset and progression are largely determined by PMA and are generally consistent across ethnic groups and settings, with more mature infants having an earlier age at onset and a shorter interval to resolution or progression than more immature babies.

Re-evaluation of inclusion criteria is essential from time to time, with local audit an essential component; the results of this can be used to broaden criteria; making them narrower, especially with a relatively small evidence base, should be undertaken with caution.

High-income countries

There are two approaches for developing guidelines in high-income countries that have a relatively uniform high level of neonatal care. The first, using GA and BW alone, is simple, but requires relatively wide criteria so that all at-risk babies are included. This scheme is used in the UK: all babies <31 weeks GA or <1251 g BW must be screened and a lower level of recommendation, "should" be screened, was made for babies between 31 and 32 weeks GA and 1251–1501 g BW. A second approach is combining sickness criteria with GA and BW. This approach permits screening of fewer babies and is used in many countries including the United States (<31 weeks GA or <1500 g BW), Sweden (<31 weeks GA), and Canada (<31 weeks GA and <1251 g BW). However, outliers can occur, so these countries suggest also the screening of larger, more mature babies if the clinical course is complex and unstable.[37]

Low- and middle-income countries

Compared to high-income countries, in low- and middle-income countries, variations in the standard of neonatal care render larger and more mature babies at risk of developing severe ROP – sometimes >2000 g BW and 34 weeks GA. Inclusion criteria on GA and BW alone would be inappropriate, as many babies would be unnecessarily included and the demand on ophthalmic services would be inordinate. In addition, sometimes the GA is unknown. For those middle-income countries with guidelines, inclusion criteria range from ≤30 weeks GA and <1500 g BW to ≤34 weeks GA and <1750 g BW, with, in most countries, additional sickness criteria to identify the larger and more mature babies falling outside the guideline.[37]

Timing of examinations

Examination timing is based on the principle that the onset and progression of ROP are predominantly determined by PMA. Timing is critical as there is only a narrow window of opportunity for treatment (Table 44.4).[38] Reynolds et al.[38] developed an algorithm, which is now widely accepted, and in Table 44.4 has been adapted to include more mature babies.

After the initial ROP examination, weekly or fortnightly examinations are indicated, but as ROP progresses, more frequent examinations will be required. A weekly visit to the neonatal intensive care unit (NICU) allows examination of those babies likely to be discharged home soon and decreases the need for babies to be recalled, so decreasing the likelihood of missed examinations and potentially disastrous consequences.

Table 44.4 Age for the first screening examination

	Age at first ROP screening examination	
Gestational age (weeks)	**Postnatal age (weeks)**	**Postmenstrual age (weeks)**
22	8	30
23	7	30
24	6	30
25	5	30
26	4	30
27	4	31
28	4	32
29	4	33
30	4	34
31	4	35
32	3	35
33	2	35
34	2	36
35	2	37

ROP, Retinopathy of prematurity.
Adapted from reference Reynolds JD, Dobson V, Quinn GE, et al. Evidence-based screening criteria for retinopathy of prematurity: natural history data from the CRYO-ROP and LIGHT-ROP studies. Arch Ophthalmol 2002; 120: 1470–6.

For the baby transferred to another hospital while still at risk, arrangements must be made for the continuation of ROP examinations.

One of the critical decisions in the screening program is when to stop screening examinations. For the baby who never developed ROP, once retinal vascularization has reached zone III, the risk of a serious adverse outcome is minimal, although accurate identification of the zone is often difficult and the PMA, GA, and BW of the infant must be considered. Whether screening needs to be continued for longer in the larger baby is not known.

The eye with ROP signs of regression should be seen on at least two examinations with regression.

Methods of examination

Eye examinations are stressful for the preterm baby,[39] but this can be reduced by supportive neonatal care. Babies should be handled gently with a trained nurse to help and to monitor the infant's wellbeing. After instilling dilating drops well prior to the examination, indirect ophthalmoscopy should be performed using a 28- or 20-diopter lens and an infant lid speculum as needed with a scleral depressor (for ocular rotation rather than indentation) after anesthetic eye drops. Observing the nasal retina allows the ophthalmologist to determine whether vascularization extends into zone III.

While indirect ophthalmoscopy currently remains the "gold standard," wide-field digital imaging is being increasingly used for routine ROP screening and is particularly useful when ROP is present.[40] However, visualizing zone III is difficult with imaging at present.

Clinical findings

Examination of the anterior segment should include checking for the tunica vasculosa lentis as persistence beyond 34 weeks suggests highly active ROP.[41]

Start the fundus examination with the posterior pole vessels for signs of pre-plus or plus disease. Both of these are powerful indicators that type 1 ROP is present or imminent.

The retinal periphery is white-gray in its non-vascularized regions; the extent of this depends on the degree of immaturity (see Fig. 44.1). The optic disc frequently has a grayish appearance and the macular and foveolar reflexes do not appear until 36 and 42 weeks PMA, respectively.

Retinopathy of prematurity screening in the future

Predicting severe ROP through postnatal weight gain

Both VEGF and IGF-1 are critical for normal retinal vascular development. IGF-1 is a somatic growth factor that is correlated with birth weight and postnatal growth. IGF-1 levels rise during the last trimester of pregnancy, so promoting, through VEGF activation, normal retinovascular development.[42–44] Following preterm birth, IGF-1 levels fall, inhibit retinovascular development, and set the scene for subsequent development of ROP. When IGF-1 increases some time after birth, VEGF is maximally stimulated and ROP results.

Since IGF-1 is a somatic growth factor, birth weight and postnatal growth can to be used as surrogates for retinal vascular development and assessing the potential for ROP. The decrease in IGF-1 levels after preterm birth is manifested by a corresponding decrease in postnatal weight gain and its magnitude indicates the severity of retinal hypoxia. Detection of decreased postnatal weight gain precedes the detection of acute phase ROP by several weeks and might be useful in identifying infants at higher risk early in the postnatal period. WINROP, a computer-based algorithm for ROP screening,[45] compared an individual infant's rate of weight gain to a series of premature infants who did not develop proliferative acute phase ROP (stage 3 or worse). It has been used to trigger an "alarm" to indicate the probable development of severe ROP, usually many weeks before ROP develops. Depending on the setting of the NICU in terms of case mix and country, the sensitivity of WINROP varies from very good (all 28 infants with severe ROP detected)[46] to detecting only 90.5% of infants with proliferative retinopathy.[47]

Other prediction models have been developed based on early weight gain.[48–50] The non-computer-based CHOP-ROP model uses birth weight, gestational age, and daily weight gain to determine if type 1 ROP is likely to develop. In a cohort of 524 at-risk infants in a level III NICU, this model accurately predicted, well in advance, all infants who developed type 1 ROP and, if it had been implemented clinically, would have reduced the number of examinations required by almost 50%.[50] The easy-to-use system is based on a simple logistic regression using a nomogram.

The use of postnatal weight gain algorithms for prediction of severe ROP could reduce the number of infants needing examinations significantly, but larger validation studies need to be conducted in various clinical settings to determine the utility of this approach.[51] Further, how these algorithms will perform in centers with developing NICU systems and larger more mature infants developing ROP remains to be seen.

Telemedicine and ROP

Several features of the epidemiology of ROP make ROP telemedicine an attractive option. For example, the infants who need treatment are usually still in the hospital, the natural history of ROP is well known, and there are guidelines for determining the timing of the evaluations needed. As digital imaging became feasible in the NICU in the 1990s, this technology has been increasingly used in clinical research and routine screening. In 2012, a report from the American Academies of Ophthalmology and Pediatrics and the American Association of Certified Orthoptists noted eight level 1 studies with from 43 to 1257 infants using digital retinal images to detect moderate to severe ROP.[40] Various definitions of moderate to severe ROP were used and sensitivity ranged from 57% to 100%.

In 2014, the largest of these studies, the "Telemedicine approaches for evaluating acute-phase ROP (e-ROP)" study was reported.[52] A multicenter observational study conducted in 13 clinical centers in North America enrolled infants with birth weights <1251 g and was designed to detect in digital retinal images eyes with "referral warranted" (or RW-ROP), which indicated the need for an ophthalmoscopic examination by an ophthalmologist to evaluate for possible treatment. RW-ROP was defined by Ells et al. in 2003 as any stage of ROP in zone I, any stage 3 or worse ROP, or the presence of plus disease.[53]

In the e-ROP study, infants underwent both diagnostic ROP examinations by e-ROP-certified ophthalmologists and imaging sessions undertaken by trained non-physicians using a wide-field camera in the neonatal intensive care nursery. For each eye, an image set, consisting of five retinal images – posterior, superior, inferior, nasal, and temporal and an external eye image, was graded by two trained non-physician readers for the presence of the retinal morphology findings consistent with RW-ROP. The result of the diagnostic examination was compared to the result of image grading and the sensitivity for detecting the RW-ROP in either eye of an infant was 90.0% (95% CI: 85.4–93.5%) with a specificity of 87% (95% CI: 84.0–89.5%) and a negative predictive value of 97.3%. The e-ROP study results provide strong support for the validity of a telemedicine system to detect the presence of potentially serious ROP.[52]

In other regions of the world with developing NICU systems and a limited number of ophthalmologists available, providing a telemedicine system can increase the likelihood of detection and treatment of potentially serious disease. An excellent example of such a system in place is in India under the guidance of A. Vinekar.[54] Technicians are trained to obtain images from at-risk infants and to recognize key signs of serious disease. If detected, those images are sent to the ophthalmologist and treatment given if needed. Such an approach is particularly important in countries with widely dispersed or large populations of at-risk premature babies and a very limited number of ophthalmologists.

Remoteness is relative. The infant with sight-threatening ROP who is only a mile or so from a too-busy ophthalmologist

is as equally remote from care as one many miles away. To have a real and sustainable effect, telemedicine needs not only to work afar, but must also contribute to routine medical care enabling local teams to work better than they do currently.

Large randomized trials of peripheral retinal ablation from 1986 to 2002

Cryotherapy and xenon arc photocoagulation were first used for treatment of acute ROP with argon laser later. However, it was not until 1988 that retinal ablative therapy was proven in large randomized clinical trials to have a beneficial effect on severe retinopathy.[31] The CRYO-ROP set out to determine prospectively whether cryotherapy is effective in the treatment of severe acute ROP and to study its natural history.[31,32] In 1986–87, 291 infants from among the 9751 enrolled at 23 US centers participated in a randomized trial comparing outcome of eyes treated with cryotherapy with those eyes assigned to observation. Treatment "threshold" was defined as five continuous or eight cumulative clock hours of stage 3 in zone I or II with plus disease, as previous studies had shown that without treatment, such eyes had a 50% risk of blindness. Cryotherapy produced a significant reduction in the unfavorable structural outcome of threshold ROP of 49.3% at 3 months[31] and 45.8% at 12 months,[31] as judged by fundus photographs and clinical examination. Visual function assessments were added beginning at the 1-year outcome visit with significantly better grating acuity in the treated eyes. The beneficial effect persisted with a 42.2% reduction in unfavorable structural outcomes and 43.4% reduction in visual acuity outcomes of 20/200 or worse at the final 15-year follow-up study examinations.[55]

The CRYO-ROP study showed that cryotherapy for threshold ROP produced a significant benefit for structural status of the eye and for vision. However, at 15 years, 23% of treated and control eyes had visual acuity of 20/40 or better, showing that retinal ablation did not necessarily result in normal structure or visual acuity.[55]

A second retinal ablation trial examined whether some eyes with ROP of less than threshold severity would benefit from treatment. Using a risk model (RM-ROP2, based on data from the CRYO-ROP study)[56] including patient demographic characteristics, pace of disease, and severity of retinopathy, ETROP[22] was conducted in 26 USA clinical sites to determine whether "high risk" prethreshold eyes (15% or greater likelihood of progression to unfavorable structural outcome) would benefit from earlier treatment. Prethreshold ROP was defined as: zone I ROP less than threshold; zone II, stage 2 with plus disease and stage 3 without plus disease; or stage 3 with plus disease but less than threshold. By this time in 2000, laser photocoagulation was widely available and eyes of 401 infants were randomized to treatment at "high risk" or conventional management consisted of observation with treatment only if threshold ROP developed.

The initial reports showed that early treatment of high-risk prethreshold eyes significantly reduced grating acuity and structural unfavorable outcomes.[22] To simplify the clinical applications of the ETROP findings, a clinical algorithm based on the ROP status of an eye was developed to determine if an eye required treatment (Table 44.5). Two types of prethreshold disease were defined with the recommendation that "type 1" be considered for earlier treatment and "type 2" be followed conservatively and treated if progression to type 1 developed. At the final ETROP 6-year examinations,[57] there continued to be a benefit to ocular structure in early-treated eyes compared to conventionally managed eyes (8.9% vs. 15.2%, $p<0.001$), but there was no statistically significant visual benefit from earlier treatment of high-risk prethreshold eyes. However, when the results at 6 years were classified using the type 1 or type 2 algorithm, visual acuity was significantly better in the group of eyes with type 1 compared to the eyes with type 2 ROP (25.1% vs. 32.8%, $p=0.02$). Furthermore, there was a significant benefit to the extent of visual field, measured using white-sphere double arc perimetry, for the group of eyes with type 1 ROP that received early treatment compared to the group of type 2 eyes.[58]

Table 44.5 Treatment algorithm based on results of the ETROP study

	Zone	Stage of ROP	Plus disease
Type 1 ROP: treatment indicated	Zone I	Any stage ROP	+
	Zone I	Stage 3 ROP	–
	Zone II	Stage 2 or 3	+
Type 2 ROP: observe closely for progression	Zone I	Stage 1 or 2	–
	Zone II	Stage 1	+
	Zone II	Stage 1, 2, or 3	–
Other ROP: observe for progression	Zone III	Any ROP	+/–

ETROP, Early Treatment for Retinopathy of Prematurity study; ROP, retinopathy of prematurity.

Involving parents

The parents of a very preterm infant have much to cope with and they have a right to know what ocular problems may befall their baby; providing sensitive, balanced information is important.

Information should be available at three levels for:

1. The parents of all babies who are to undergo ROP examination: Written information providing a general description of ROP is required, noting that, although ROP is a frequent occurrence, over 90% of cases of acute retinopathy spontaneously resolve. Generally, the ophthalmologist does not personally need to counsel the parents of all babies who have ROP examinations, but should be available to provide information if required.
2. The parents of babies with ROP that is or might become severe: Written information should be provided that emphasizes that treatment is available and may need to be considered. At this juncture, the ophthalmologist should discuss the situation face-to-face with parents.
3. The parents of the baby with end-stage disease: Not all eyes well treated respond satisfactorily to treatment and

blindness still occurs. Ophthalmologists should not lose contact with the family. Most parents accept that treatment sometimes fails, but they cannot accept lack of interest. The ophthalmologist must ensure that the child gains early access to the services for the visually impaired and with certification as blind or partially sighted as appropriate

Outcomes

Premature birth can affect the developing visual system by refractive changes (see Chapter 8), strabismus, neurologic damage (see Chapters 60 and 90), and ROP. Most infants with ROP undergo complete resolution without adverse effects, and mild ROP (stages 1 and 2) has no additional adverse effect on vision.[59,60] Severe ROP may impact acuity[59] and contrast sensitivity.[61] It was the less-than-ideal response following cryotherapy that generated the Early Treatment Study. Color vision does not seem to be affected by preterm birth alone, although the CRYO-ROP study noted an increased prevalence of blue–yellow deficits not related to ROP severity.[62,63] Visual field area measured at 10 or 11 years in children who had significant acute phase ROP was reduced regardless of whether the eyes underwent cryotherapy.[64,65] Both visual acuity and visual field benefited from treatment of type 1 but not type 2.[57,58]

The prevalence of strabismus is increased by preterm birth and by ROP stage (even mild ROP). The incidence of strabismus is raised from around 6% to over 60%, and this increases as acute phase ROP increases.[66–68]

The direct consequences of ROP are more frequent in severe and posterior disease, but occasionally occur in mild acute ROP. Retinal detachment can occur at any time of life, including after peripheral retinal ablation for severe ROP, although this is infrequent. Large punched-out macular lesions are infrequent sequelae of severe ROP. When they develop is unknown, but they have been observed during infancy. Originally thought to be the consequence of cryotherapy, they may occur in eyes that have not been treated. Anterior segment sequelae of severe ROP have been described.[69]

Microcornea/microphthalmos may be the consequence of reduced growth during the acute phase or later shrinkage due to advanced cicatrization. Other changes are due to changes in the anterior vitreous causing anterior displacement of the iris–lens diaphragm, causing shallowing of the anterior chamber[70] and, if severe, corneal opacity and cataract.

Children who were preterm have an increased prevalence of all refractive errors, especially myopia.[62,71,72] Myopia is a consequence of low birth weight even in the absence of ROP. The myopia is low and has the following characteristics: steep corneal curvature, shallow anterior chamber, thick lens, and an axial length shorter than expected for the degree of myopia.[62,72] Myopia is a well-known complication of severe ROP.[71] In contrast to myopia of prematurity, which has its onset in school years, myopia associated with severe ROP has its onset in infancy with progression during the first year after birth but with relative stability thereafter, unlike most forms of myopia not associated with ROP.[72,73] There is no significant difference in myopia between eyes with severe ROP that were treated compared to those that were not.[74]

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Current treatment of retinopathy of prematurity

Joshua Robinson and G Baker Hubbard

Chapter contents

RATIONALE FOR TREATMENT
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See online for supporting video for this chapter.

Rationale for treatment

The neovascular manifestations of acute retinopathy of prematurity (ROP) are managed by reducing the stimulus for vessel growth. Traditionally this has been accomplished by ablating the peripheral avascular retina either with cryotherapy[1] or, more commonly in recent years, laser treatment.[2] Ablation of the peripheral avascular retina has its therapeutic effect by decreasing the production of pathologic vascular endothelial growth factor (VEGF), the dominant stimulus for neovascularization in ROP. In the last few years, anti-VEGF medications have been utilized to pharmacologically achieve this goal.[3] The most severe manifestations of ROP, stage 4 and 5 traction retinal detachments (TRDs), are managed with vitrectomy.[4–7]

Peripheral retinal ablation

The indications for ablative treatment of the avascular retina for acute ROP were initially established by the results of the Multicenter Trial of Cryotherapy for ROP Study (CRYO-ROP) published in 1988.[1] The Early Treatment for ROP Trial (ETROP) updated the indications for treatment in 2003.[2] The ETROP compared outcomes of early treatment to outcomes of treatment performed according to older guidelines established by CRYO-ROP. Results from ETROP demonstrated significant reduction in unfavorable structural outcomes at 9 months from 15.6% in eyes managed according to CRYO-ROP guidelines to 9.1% for eyes managed with early treatment ($p < 0.001$). The study recommended treatment for type 1 ROP and defined type 1 ROP as having any of the following three features:

1. zone I, any stage of ROP with plus disease;
2. zone I, stage 3 ROP with or without plus disease;
3. zone II, stage 2 or 3 ROP with plus disease.

Treatment should be performed within 48 hours of identifying type 1 ROP, and more severe cases should be treated sooner.

As can be seen in the recommended indications for treatment according to ETROP, the presence of plus disease is the main driver in the decision to treat. Controversy exists over the variability in detecting plus disease between observers.[8,9] Efforts have been made to more precisely quantify plus with digital image analysis. This topic was considered in more detail in the previous chapter.

Laser is the preferred method of achieving ablation of the avascular retina and portable laser indirect ophthalmoscopes (LIO) are generally used to deliver the treatment.[10] The pattern of treatment is semi-confluent to confluent and laser spots cover the entire avascular retina from the ridge to the ora serrata for 360° (Fig. 45.1).[11,12] Skip areas in laser treatment are to be avoided as even small skip areas can lead to treatment failure and progression to retinal detachment. Fundus photography after laser may aid in identifying and treating skip areas.[13] Treatment posterior to the ridge has been advocated and there is data from fluorescein angiography analysis showing capillary dropout, and presumably ischemic retina, posterior to the ridge.[14–17] There is no level 1 evidence, however, supporting treatment posterior to the ridge and this modification of standard technique is not recommended by the authors for most cases.

Refinements of the laser procedure to minimize stress on the infant and the ophthalmologist have been reported. Recent work has shown that sedation without endotracheal intubation works well in many cases and may reduce ventilator dependence along with associated ventilator complications and expense.[18–20] The authors' experience has been that laser can be performed without intubation in many cases. LIO can also cause stress on the ophthalmologist's cervical spine. The field of ophthalmology is known to have a high rate of spine-related pain that can be career threatening.[21] We have described an ergonomically superior method of indirect ophthalmoscopy that can be useful in treating ROP with LIO.[22]

Choice of laser wavelength for ROP treatment is important. Cataract can occur after laser and may result from uptake

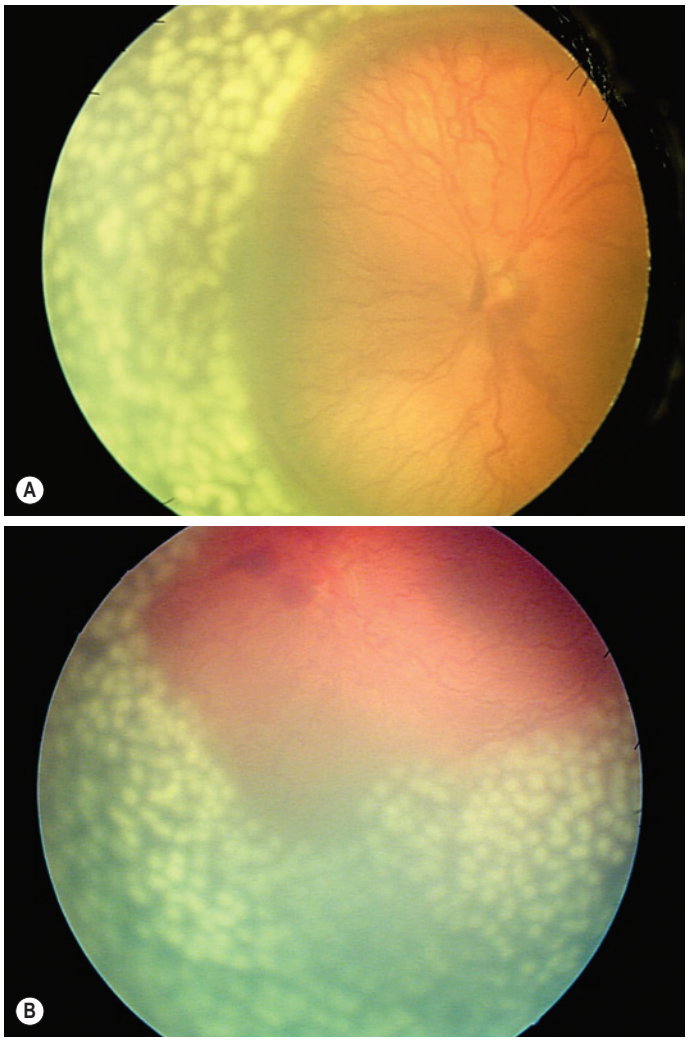


Fig. 45.1 (A) This infant was referred for laser treatment before anti-vascular endothelial growth factor (anti-VEGF) was available. Note the extensive stage 3 in the setting of severe plus disease. Despite the near-confluent laser pattern, this eye later developed stage 4 traction retinal detachment. (B) This infant with aggressive posterior retinopathy of prematurity was also referred for laser before anti-VEGF was available. After laser the retinopathy of prematurity regressed without traction. With 10 years of follow-up, the retina is attached but the child has severe high myopia.

of laser energy by the tunica vasculosa lentis with secondary heating of lens protein. Uptake of energy by the iris may also result in heating of the lens. Studies of cataract formation after laser have shown that 810 nm wavelength laser is less likely to cause cataract compared to argon green wavelengths (510–532 nm).[23] Uptake of energy by vascular structures occurs most efficiently with wavelengths in the yellow range (577 nm) and yellow laser should be avoided due to the presence of perfused tunica vessels around the lens in many cases of ROP. Other complications from laser include corneal edema, hyphema, iris atrophy, angle closure glaucoma, anterior segment ischemia, vitreous hemorrhage, retinal hemorrhage, and exudative retinal detachment.[24–33] In the ETROP study, early treatment was associated with more apnea and bradycardia, and a higher rate of reintubation for mechanical ventilation compared with standard treatment. There was no difference, however, between the groups for ocular complications, mortality, or known permanent morbidity.[2]

Cryotherapy can also be used to ablate the peripheral retina. This was the original modality of treatment in the 1980s and early 1990s.[1] Cryotherapy, however, causes more inflammation and more discomfort for the neonate. In addition, cryo application is less precise than laser and outcomes with laser are at least as good if not better than cryo.[34] With the wide availability of portable 810-nm lasers, cryotherapy is rarely used today.

Anti-vascular endothelial growth factor for retinopathy of prematurity

Pharmacologic modification of intraocular VEGF levels represents a promising approach in the management of acute ROP and this topic has been the subject of excellent recent reviews.[35,36] The BEAT-ROP (Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity) study was the first multicenter randomized trial of anti-VEGF for ROP and it compared the efficacy of intravitreal bevacizumab for stage 3 ROP to standard of care peripheral retinal laser ablation.[3,37] Recurrence of active ROP was the primary outcome and BEAT-ROP demonstrated reduction in recurrence with bevacizumab as compared to laser for zone I disease, but no difference was found for zone II disease. For zone I, the recurrence rate for the bevacizumab cohort was 6% versus 42% for the conventionally treated laser group ($p = 0.003$). Several limitations of BEAT-ROP have been highlighted in commentary.[38–40] One is the relatively short follow-up in the study with infants followed until 54 weeks postmenstrual age (PMA). Other reports on bevacizumab note that late recurrences of ROP may occur beyond 54 weeks PMA.[41] In addition, the reported laser failure rate of 42% is well above previously published reports for zone I disease (which are generally 18–22%).[42–44] Despite these limitations, BEAT-ROP established two important points about intravitreal bevacizumab: it is effective at stopping progression of neovascular ROP; and, unlike with laser ablation, avascular retina is not destroyed and may become at least partially vascularized with time. Long-term follow-up is lacking for anti-VEGF treatment of ROP, but emerging data suggest that visual results after bevacizumab are not significantly impaired compared to laser and that treatment with anti-VEGF results in less myopia.[45–48] The relatively low cost of bevacizumab and the ease of intravitreal injection technique compared to indirect laser have resulted in extensive worldwide use of bevacizumab for ROP; over 50 reports on its use for ROP have been published since 2007.

Systemic safety of intravitreal anti-VEGF remains a major concern for infants with ROP. VEGF is a key growth factor in the development and maintenance of nearly every human organ system.[49] Bevacizumab has been shown to reduce serum VEGF concentrations in human infants with ROP for at least 2 months following a single intravitreal injection.[50–52] It would logically follow that systemic suppression of this physiologic growth factor may have potential for harm when administered to developing preterm neonates, but the long-term clinical impact remains to be elucidated. The dose of bevacizumab used in BEAT-ROP and other studies was half the adult dose, or 0.625 mg. Lower doses may be as effective with reduced potential for systemic effects. Lower dosing of bevacizumab is currently under study (NCT02390531). The pharmacokinetics of ranibizumab seem more favorable than

bevacizumab for infants with ROP. Ranibizumab has a shorter half-life and is cleared from the systemic circulation faster than bevacizumab. A prospective multicenter trial of ranibizumab for ROP is underway in Germany (CARE-ROP NCT02134457) and planned for the US (RAINBOW NCT02375971). In assessing available information regarding systemic safety of bevacizumab, one finds limited data from case series emerging over the last few years.[46,53–58] No major systemic safety issues have become apparent. However, there have been no trials to date that have been powered to study systemic safety over a long course of follow-up. Such safety data is imperative before anti-VEGF can become standard therapy for ROP. The authors reserve intravitreal anti-VEGF for cases with the following features: posterior zone I disease, media opacity, poor pupillary dilation, or persistent vascular activity after laser ablation.

The technique for intravitreal injection is relatively straightforward for ophthalmologists. Anesthesia is achieved with topical proparacaine or tetracaine, and may be supplemented with light sedation. A neonatal eyelid speculum in inserted and topical povidone–iodine is applied to the ocular surface and lid margins. The injection should be administered 0.5–1 mm posterior to the corneoscleral limbus through the pars plicata. Injection sites located more posteriorly run the risk of penetrating avascular retina. The needle trajectory should parallel the visual axis to avoid injuring the disproportionately large infantile lens.

Post-laser and post-injection management

After treating acute phase ROP with laser ablation, initial postoperative management consists of treating inflammation with topical steroids. For anti-VEGF treatment, topical antibiotics may be used for a few days after the intravitreal injection but antibiotics are likely unnecessary. The role of topical antibiotics after intravitreal injection has been the subject of much attention in the adult literature and consensus has emerged that topical antibiotics are not necessary after routine intravitreal anti-VEGF injections.[59] At the authors' center topical antibiotics are no longer used after intravitreal injections in adults or neonates.

Improvements in plus disease and neovascularization occur more quickly after anti-VEGF injection than after laser ablation (Fig. 45.2). After laser, there can be initial worsening of vascular engorgement and exudation, presumably due to the inflammatory effects of the ablative procedure.[30,33] Generally,

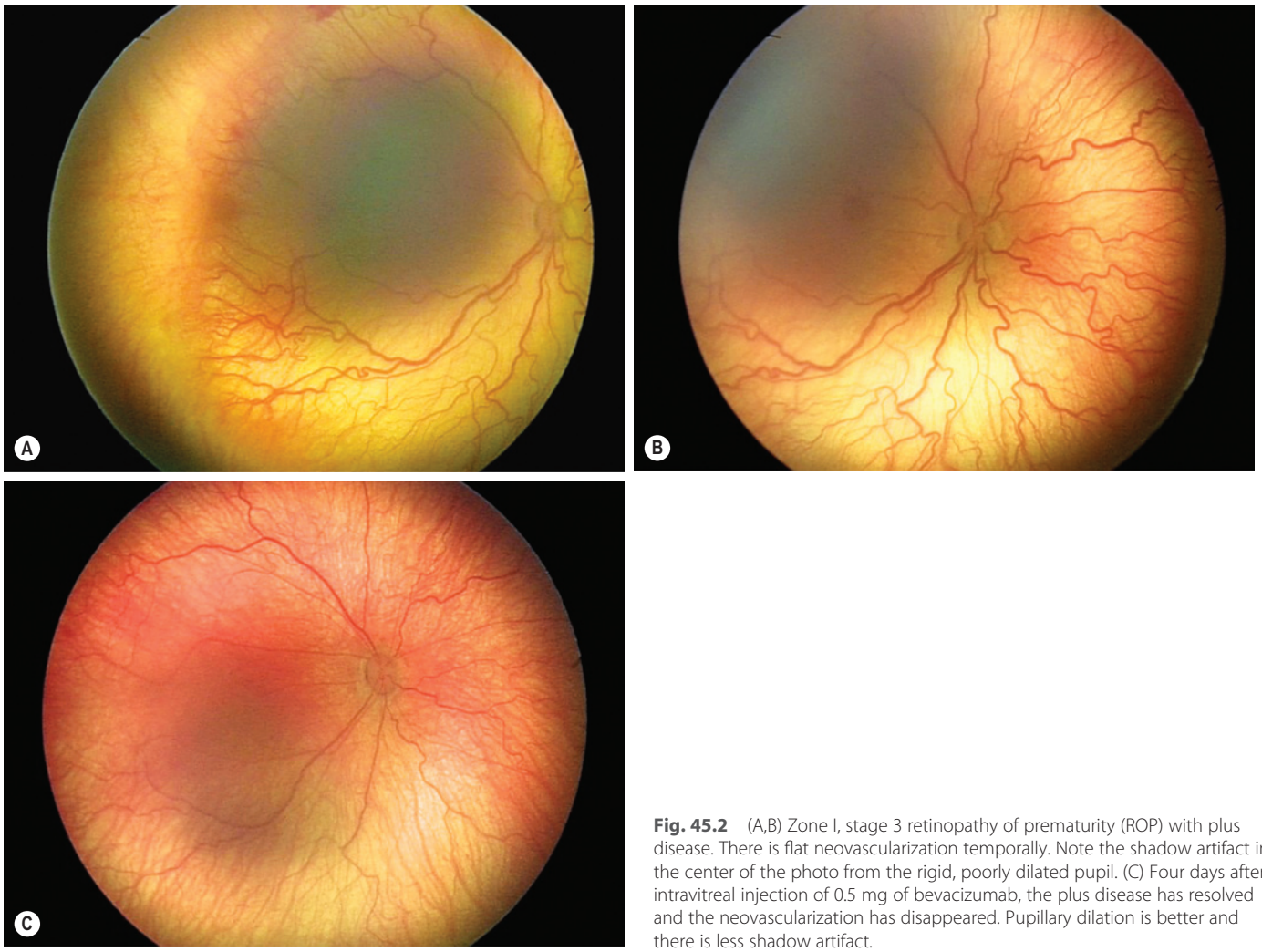


Fig. 45.2 (A,B) Zone I, stage 3 retinopathy of prematurity (ROP) with plus disease. There is flat neovascularization temporally. Note the shadow artifact in the center of the photo from the rigid, poorly dilated pupil. (C) Four days after intravitreal injection of 0.5 mg of bevacizumab, the plus disease has resolved and the neovascularization has disappeared. Pupillary dilation is better and there is less shadow artifact.

the vascular engorgement and exudation begin to improve 7–10 days after treatment. By 2 weeks, plus is nearly or completely resolved and neovascular tissue has become involuted and often almost completely disappears. The improved appearance is similar, but occurs more quickly, after anti-VEGF therapy.

While laser ablation is technically more difficult and time consuming to perform compared to anti-VEGF injection, the postoperative management is generally easier with laser. Once plus disease and neovascularization resolve, recurrence is unusual.[2] If there is no fibrosis, traction, or blood at 3–4 weeks after laser, then the authors generally follow monthly for two more visits and then discharge from acute ROP care, with follow-up in 6 months by a pediatric ophthalmologist.

Treatment failure after laser ablation for ROP does occur even with timely and thorough treatment. The clinical features of failing treatment have been well described.[60–62] Vitreous blood, along with organization of sheets and strands of condensed vitreous, are hallmarks of treatment failure. The persistence of plus or engorgement of vessel on or around the ridge with thickening of the ridge also may precede progressive traction and retinal detachment.[32] If these clinical features begin to appear, the treated avascular retina should be carefully inspected to look for skip areas or places where more laser can be applied. The authors generally examine patients 7–10 days after laser. Earlier exams reveal the exudative response to treatment-related inflammation. After 10 days, persistence of vascular engorgement is significant and may indicate that more treatment is needed. Proliferation and vascular engorgement may continue in any meridian where there is inadequate laser (Fig. 45.3). If the laser pattern is complete, and neovascular activity with plus disease are still present, intravitreal anti-VEGF can be considered. Contraction of membranes after anti-VEGF with worsening traction retinal detachment has been described.[63]

Primary treatment of ROP with anti-VEGF is easier initially but much more demanding in terms of follow-up.[64] Recurrence of ROP may be seen after the effects of the anti-VEGF injection have worn off.[41,65,66] Many cases continue to have substantial areas of persistent avascular peripheral retina for an indefinite amount of time after treatment and some will likely have permanent, large avascular zones. The clinical implications of this persistent avascular retina are not well understood but there are reports of recurrent neovascularization and plus with progressive traction and retinal detachment up to 35 weeks (69 weeks PMA) after intravitreal bevacizumab.[41] There are no established guidelines for follow-up after intravitreal anti-VEGF for ROP, but a sensible approach is to follow every 1–2 weeks until retinal vessels grow into zone III or until 60 weeks PMA. If avascular retina persists in zone I or zone II at 60 weeks PMA, consideration can be given to scatter laser treatment of residual avascular retina. The importance of follow-up must be stressed for parents and caregivers, as any loss of follow-up may have severe consequences in the event of late recurrence.

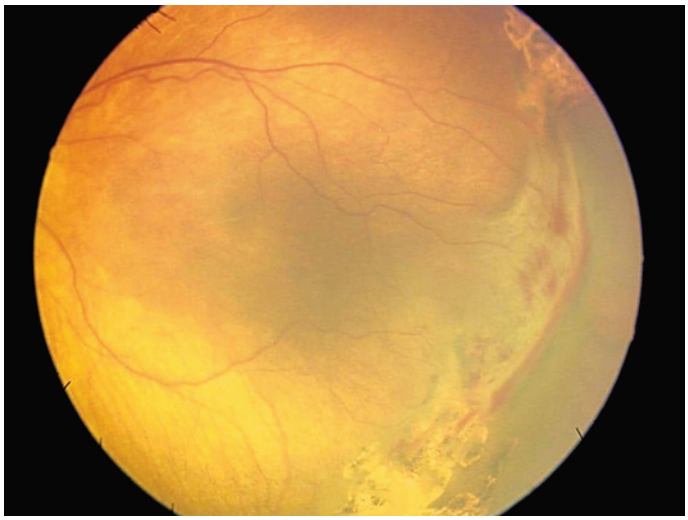


Fig. 45.3 This patient underwent laser treatment at an outside facility and was referred with persistent vascular activity after laser. Note the large skip area temporally with active stage 3 in the same meridians as the skip area.

Treatment of retinal detachment

Retinal detachment will occur in some cases of ROP even when the neovascular phase of the disease is managed with the best available treatment. For example, despite timely and thorough laser as performed in the ETROP study, almost one in 10 infants developed unfavorable structural outcomes.[2] Some eyes with retinal detachment in ETROP were treated with vitreoretinal surgery, but outcomes of this intervention were generally poor with attached macula present at 6 years in only 31% of stage 4A (5 of 16), 60% of stage 4B (6 of 10), and 0% of stage 5 (0 of 10) eyes.[67] These results contrast with results of other published studies of vitrectomy for stage 4 ROP in which re-attachment rates have been in the range of 80–90%.[4–7,68]

One key to successful outcome is to operate after the neovascular activity and plus disease have completely or almost completely resolved (Fig. 45.4).[69] Performing vitrectomy before resolution of this vascular activity may result in bleeding, increased exudation, or continued proliferation and contraction after vitrectomy. In some instances, however, detachment may progress rapidly after laser ablation before the plus disease and neovascular activity have a chance to resolve. This is more likely to be the case for more posterior ROP. For cases of aggressive posterior retinopathy of prematurity (APROP), early vitrectomy has been advocated before complete resolution of vascular activity and before onset of TRD.[70–72] Intravitreal anti-VEGF injection can facilitate vitrectomy before complete resolution of vascular activity and may result in better anatomic outcomes.[73,74] In general, eyes that fail despite early laser treatment are those that are inherently more severe and more likely to progress to total, stage 5, retinal detachment before the neovascular activity and plus resolve.

Successful repair of stage 5 ROP is very difficult because vitrectomy performed after laser-induced resolution of plus and neovascular activity usually is taking place in an eye that has massive proliferation. Success rate in this setting is in the range of 0–50%.[67,75–78] With the addition of triamcinolone or anti-VEGF agents, results may be better.[79,80] Visual function for successfully re-attached stage 5 eyes is generally poor, but any visual function can nevertheless be highly valuable for patients relative to complete blindness.[81–85]

The operative technique most commonly utilized for stage 4 ROP is lens-sparing, 2- or 3-port vitrectomy. Small, 23- and 25-gauge, instruments are now used commonly and are advantageous in small infant eyes.[86,87] Sclerotomies are created 0.5–1 mm posterior to the limbus and the blade or

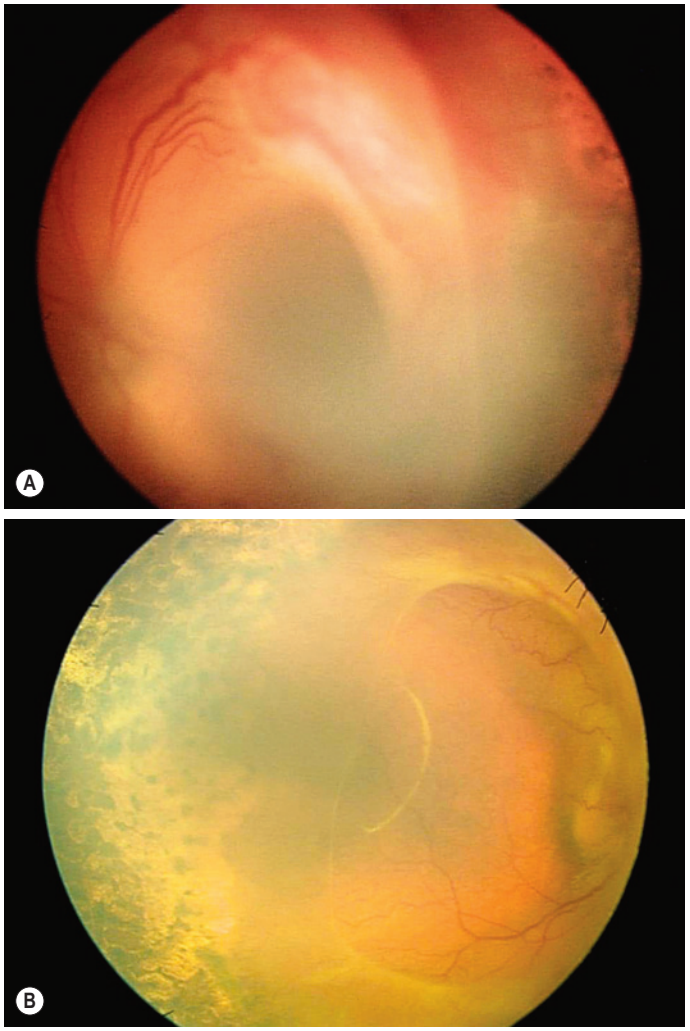


Fig. 45.4 (A) This eye has combined tractional and exudative stage 4B retinopathy of prematurity (ROP). Note the vitreous haze, vascular engorgement, and extensive proliferation. (B) This eye has tractional stage 4A ROP in the setting of almost completely regressed vascular activity. If traction progresses and threatens the macula, vitrectomy in this setting has an excellent anatomic prognosis.

trocar is oriented parallel to the visual axis during insertion to avoid the lens. Scleral buckling (SB) has been used in the past but vitrectomy is generally considered superior to SB. Vitrectomy combined with SB does not seem to be better than vitrectomy alone.[88] For stage 5 ROP, lensectomy in addition to vitrectomy is often required due to the presence of proliferative tissue in contact with the lens.

Long-term outcomes

Over the last 30 years, tremendous strides have been made in the management of ROP. Rigorous screening and treatment of ROP substantially reduces the societal burden of blindness and associated costs.[89–91] Despite the advances, however, long-term outcomes from the perspective of parents can seem rather modest, and counseling is important so that parents know what to expect. Data from ETROP and CRYO-ROP show that a large proportion of patients do not achieve reading vision and many are legally blind.[92,93] In addition, high myopia is common and peripheral vision is reduced after treatment with laser or cryotherapy.[94] It is important for parents to understand that reduction of peripheral vision is a function of the disease and not necessarily the treatment. Pathologic myopia is also a function of severe ROP but it may be exacerbated by treatment with peripheral ablation. Eyes treated successfully with peripheral ablation continue to have lifelong increased risk for strabismus, amblyopia, cataract, glaucoma, vitreous hemorrhage, and retinal detachment.[92,95] Whether treatment of ROP with anti-VEGF agents will result in better long-term outcomes is unknown, as no long-term data for ROP treatment with anti-VEGF exist. Limited data are available regarding long-term outcomes after repair of retinal detachment in ROP.[76,77,85,96,97] When treated with lens-sparing vitrectomy, eyes tend to retain a clear lens.[98] After successful repair of TRD, eyes continue to be at risk for recurrent detachment and other problems indefinitely. Patients and families should be educated about the ongoing lifetime risks of ocular complications after treatment of ROP, and the importance of lifetime surveillance should be emphasized.

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Inherited retinal disorders

Michel Michaelides, Graham E Holder, and Anthony T Moore

Chapter contents

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PROGRESSIVE RETINAL DYSTROPHIES
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Introduction

The inherited retinal disorders are a clinically and genetically heterogeneous group of conditions. Many become symptomatic in childhood. They are usually an isolated abnormality in an otherwise healthy child but, in syndromic form, they may be associated with systemic abnormalities (see Chapter 47). Many of the genes causing childhood-onset retinal disorders have been identified. There is considerable genetic heterogeneity for individual clinical disorders, and mutations in a single gene may give rise to several different phenotypes. Despite this, these disorders can be usefully divided clinically according to whether they:

1. are stationary or progressive;
2. have generalized retinal or localized macular dysfunction; and
3. if the former, exhibit predominantly rod or cone involvement.

Stationary disorders usually present at birth or in the early months of life and are best referred to as dysfunction syndromes, as most do not show significant progression. Progressive conditions, which typically present later, are termed dystrophies.

Stationary retinal dysfunction syndromes

These include the forms of stationary night blindness and the cone dysfunction syndromes.

Stationary night blindness

There are three main forms of stationary night blindness: (i) congenital stationary night blindness (CSNB) in which the fundus is normal or shows myopic changes; (ii) fundus albipunctatus; and (iii) Oguchi disease. Both (ii) and (iii) have a distinctive fundus appearance.

Congenital stationary night blindness

Clinical findings

CSNB is characterized by night blindness, variable visual loss, and a largely normal fundus. It may be inherited as an autosomal dominant (AD), autosomal recessive (AR), or X-linked (XL) disorder.

The visual acuity is usually normal or mildly reduced in the AD form, whereas mild-to-moderate central visual loss is common in the AR and XL subtypes. Other features of XL and AR CSNB include moderate-to-high myopia, nystagmus, strabismus, and paradoxical pupil responses. Fundus examination is usually normal but some patients have myopic fundi and pale or tilted optic discs (Fig. 46.1). Patients with AD CSNB usually present with symptomatic night blindness, but patients with XL or AR CSNB may present in infancy with nystagmus, strabismus, and reduced vision. Nystagmus is not invariable and some patients are not diagnosed until late childhood or adulthood. The diagnosis is easily missed without electroretinography (ERG). XL and AR CSNB may be further subdivided into *complete* and *incomplete* forms. This differentiation, originally proposed in XL disease using electrophysiological and psychophysical criteria, was subsequently shown to reflect genetically distinct disorders.

Electrophysiology

International Society for Clinical Electrophysiology of Vision (ISCEV) standard ERGs should be performed, but this may not be possible in infants, for whom a simplified protocol is more appropriate (see Chapter 9). Four main responses are defined by the adaptive state of the eye (DA: dark adapted; LA: light adapted) and the flash strength in cd.s.m^2: a rod-specific ERG (DA 0.01) and a bright flash response (DA 10.0) performed under scotopic conditions, and two measures of cone function, a 30 Hz flicker ERG (LA 30 Hz) and a single flash photopic ERG (LA 3.0). Both complete and incomplete CSNB show a "negative ERG": the largely photoreceptor-derived a-wave in the bright flash response is normal, but there is selective reduction in the inner nuclear-derived b-wave, so that it is smaller than the a-wave, indicating predominantly inner retinal dysfunction. There is no detectable DA 0.01 ERG in

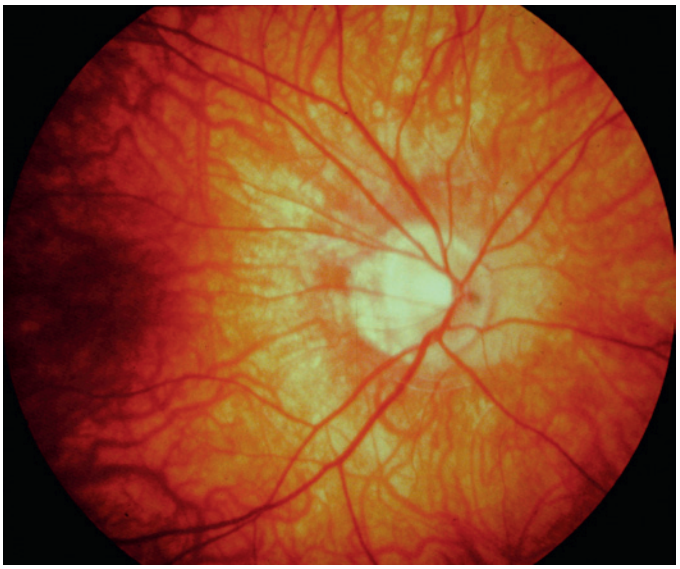


Fig. 46.1 X-linked congenital stationary night blindness. Tilted optic disc with myopic fundus.

complete CSNB and a profoundly negative DA 10.0 response. Cone ERGs show subtle abnormalities reflecting ON- bipolar cell dysfunction (Fig. 46.2). There is a detectable rod-specific ERG in incomplete CSNB, and a profoundly negative bright flash response. Cone ERGs are much more abnormal than in complete CSNB, reflecting involvement of both ON- and OFF- bipolar pathways. They show a characteristic triphasic appearance in the 30 Hz flicker response (see Fig. 46.2).

ERG evidence of inner retinal rod system dysfunction may also occur in AD CSNB but in association with normal ISCEV cone ERGs. In other cases of AD CSNB, ERG rod responses are attenuated with normal cone responses, but the standard bright flash response does not have a negative waveform.

Molecular genetics and pathogenesis

Autosomal dominant CSNB Mutations in the genes encoding three components of rod-specific phototransduction have been reported in AD CSNB: rhodopsin (*RHO*), the α-subunit of rod transducin (*GNAT1*), and the rod cyclic guanosine monophosphate (cGMP) phosphodiesterase β-subunit (*PDE6β*).

X-linked CSNB Two causative genes (*CACNA1F* and *NYX*) have been identified, accounting for most families with XL CSNB. *Incomplete* CSNB is associated with mutation in *CACNA1F*, which encodes the retina-specific α_{1F}-subunit of the voltage-gated L-type calcium channel. The expression of *CACNA1F* appears limited to photoreceptors and is prominent in the synaptic terminals. Most mutations are inactivating truncation sequence variants. The loss of functional channels impairs the calcium flux into rod and cone photoreceptors required to sustain tonic neurotransmitter release from presynaptic terminals. This results in the inability to maintain the normal transmembrane potential of bipolar cells, so the retina remains in a partially light-stimulated state, unable to respond to changes in light levels.

Complete CSNB is associated with mutation in *NYX*, the gene encoding the leucine-rich proteoglycan nyctalopin. Leucine-rich repeats are believed to be important for protein interactions, with many of the mutations identified within these repeats. Nyctalopin is expressed in photoreceptor inner segments, outer and inner nuclear layers, and ganglion cells. Nyctalopin may guide and promote the formation and function of the retinal ON- pathway.

Several genotype–phenotype studies have been performed in individuals with either *CACNA1F* or *NYX* mutations. There is considerable inter- and intra-familial phenotypic variability associated with *CACNA1F* mutations, even with an identical sequence variant,[1] suggesting that other genetic or environmental factors modify the phenotype. Although most patients with XL CSNB have non-progressive disease, Nakamura et al. reported two brothers with a *CACNA1F* mutation and progressive decline in vision, with eventually undetectable rod and cone ERGs.[2] We have also infrequently observed slow progression in patients with XL CSNB. Patients with complete XL CSNB (*NYX* mutations) are invariably myopic and have more pronounced night blindness.[3]

Autosomal recessive CSNB Mutations in *GRM6*, *TRPM1*, or *GPR179* lead to complete CSNB. *GRM6* encodes a metabotropic glutamate receptor (mGluR6) located on the dendrites of rod and cone ON- bipolar cells, mediating the sign inversion that occurs at the first synapse, such that glutamate release in the dark by photoreceptors causes hyperpolarization of the ON bipolar cell membrane. TRPM1, a transient receptor potential cation channel, subfamily M, member 1, is probably involved in effecting the membrane voltage change in ON- bipolar cells in response to glutamate. *GPR179* encodes a G protein-coupled receptor expressed in bipolar cells.

Mutations in *CABP4* have been associated with incomplete CSNB. CABP4, a member of the calcium-binding protein (CABP) family, is specifically located in photoreceptor synaptic terminals, where it is directly associated with the *C*-terminal domain of CACNA1F.

Sequence variants have been identified in *SLC24A1*, in patients with AR CSNB without a negative ERG; in the standard scotopic bright flash response, both the a- and b-waves are equally reduced.[4] SLC24A1 is a member of the solute carrier protein superfamily located in inner segments, outer and inner nuclear layers, and ganglion cells.

Åland Island eye disease

Åland Island eye disease (AIED) is an X-linked recessive disorder similar to incomplete CSNB, characterized by reduced visual acuity, nystagmus, nyctalopia, mild red–green dyschromatopsia, and myopia. Affected males may show iris translucency, foveal hypoplasia, and decreased fundus pigmentation. The clinical appearance may resemble X-linked ocular albinism (XLOA) but in XLOA color vision is usually normal and patients with AIED do not show the typical intracranial visual pathway misrouting associated with albinism.[5]

The symptoms of night blindness and the psychophysical and ERG changes seen in AIED are similar to those in the incomplete form of the XL CSNB. The disorders are allelic, with disease-causing variants now identified in *CACNA1F* in AIED.

Other related phenotypes

Patients with a contiguous gene syndrome (which includes glycerol kinase deficiency, congenital adrenal hypoplasia, Duchenne muscular dystrophy [DMD], and ocular abnormalities known as Oregon eye disease), with a deletion of Xp21, have

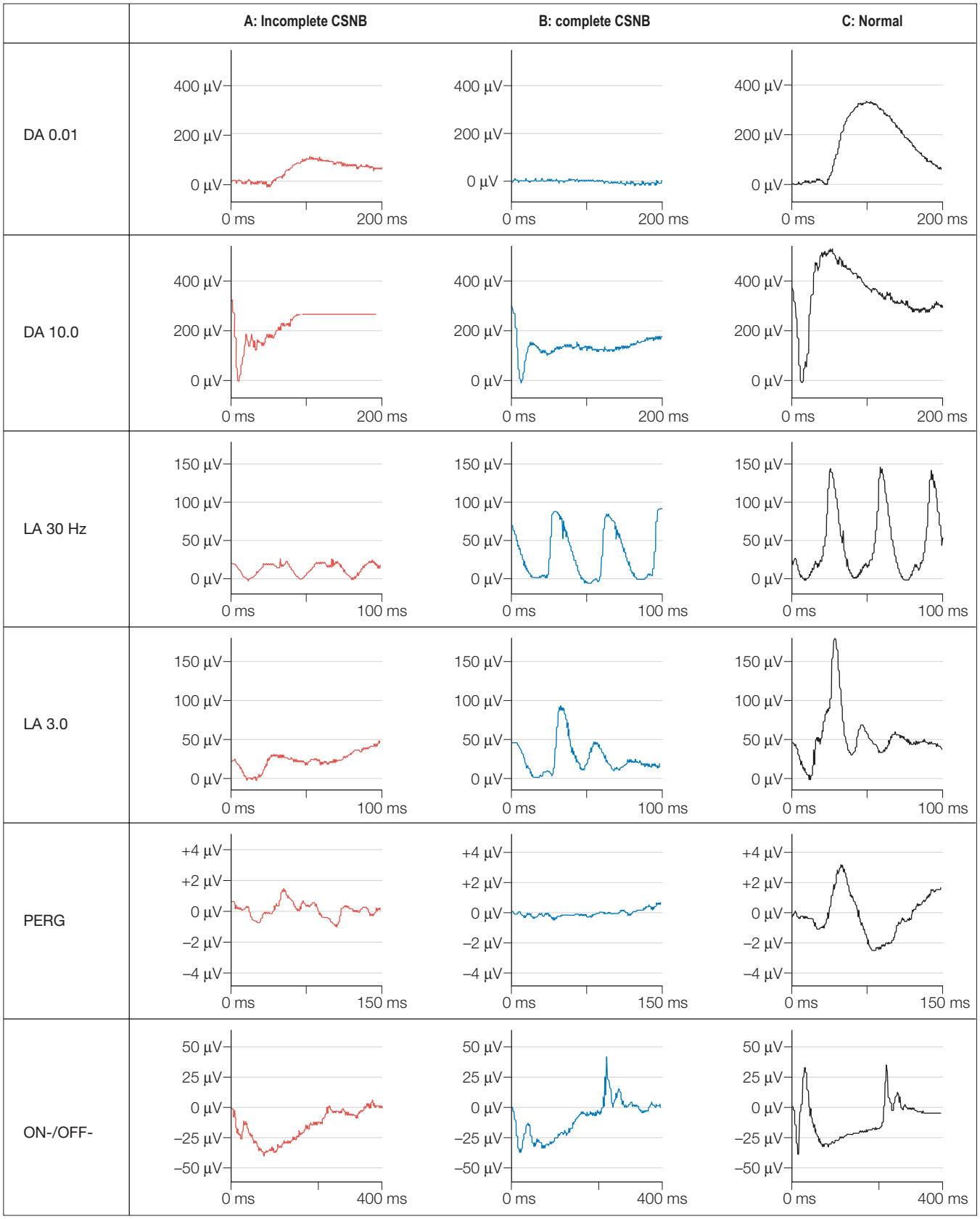


Fig. 46.2 Congenital stationary night blindness. The left-hand column traces (A) show data from a patient with "incomplete" CSNB (iCSNB); the center traces (B) are from a patient with "complete" CSNB (cCSNB); the right-hand column traces (C) are from a representative normal subject. In iCSNB the rod ERG (DA 0.01) is mildly subnormal. The bright flash response (DA 10.0) is electronegative, with a normal a-wave confirming normal photoreceptor function, but a profoundly reduced b-wave. The 30 Hz flicker ERG (LA 30 Hz) is markedly subnormal and clearly shows the delayed double peak characteristically seen in iCSNB. The photopic single flash ERG (LA 3.0) shows marked reduction in the b:a ratio with simplification of the waveform and loss of the photopic oscillatory potentials, shown on ON-/OFF-response recording (200 ms orange stimulus on a green background) to reflect involvement of both ON- (depolarizing) and OFF- (hyperpolarizing) cone bipolar cell pathways. The pattern electroretinogram (PERG) is mildly subnormal in keeping with mild macular dysfunction. In cCSNB there is no detectable DA 0.01 response and the profoundly electronegative DA 10.0 ERG confirms the site of the dysfunction to be post-phototransduction. The LA 3.0 response shows a distinctive broadened a-wave and a sharply rising b-wave with a reduced b:a ratio and lack of photopic oscillatory potentials. This appearance indicates marked dysfunction of cone ON-bipolar cell pathways but preservation of the OFF- pathways. The profoundly negative ON- response, with preservation of the ON- a-wave and loss of the ON-b-wave, accompanied by a normal OFF- response is confirmatory. The broadened trough of the 30 Hz flicker ERG with a sharply rising peak is a manifestation of the same phenomenon. The PERG is almost undetectable. Overall, the findings in cCSNB are those of loss of ON- pathway function in both rod and cone systems.

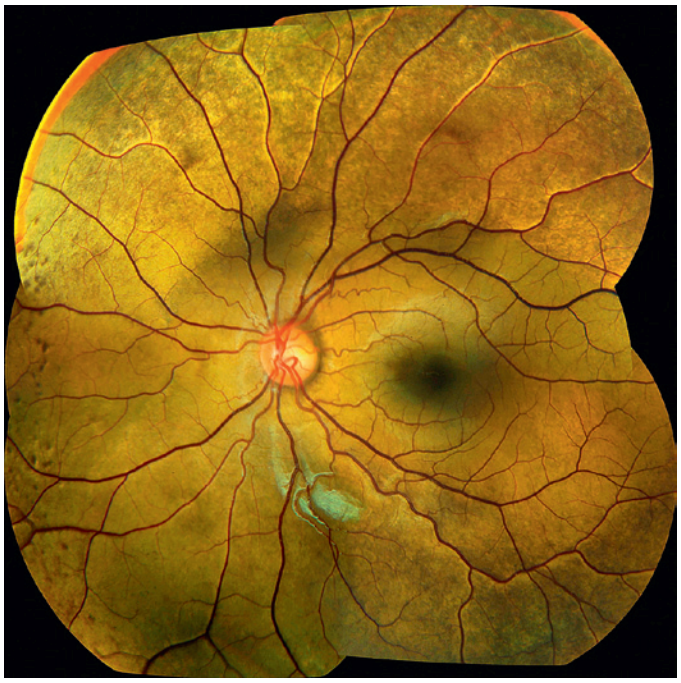


Fig. 46.3 Oguchi disease. Greyish or green-yellow discoloration of the fundus, which reverts to normal on prolonged dark adaptation (Mizuo phenomenon).

ocular features in common with affected males with AIED and have similar predominantly inner retinal ERG abnormalities. Furthermore, some males with isolated DMD (mutations of the dystrophin gene at Xp21) have ERG abnormalities similar to those of CSNB; the ERG phenotype is determined by the site of the mutation within the dystrophin gene. These multisystem disorders have a non-progressive form of predominantly rod system dysfunction.

Oguchi disease

Clinical findings

Oguchi disease is a rare autosomal recessive stationary night blindness with a greyish or green-yellow discoloration of the fundus at the posterior pole or extending beyond the arcades, which reverts to normal on prolonged dark adaptation (Mizuo phenomenon) (Fig. 46.3). Exposure to light then usually leads to the gradual reappearance of the abnormal discoloration in 10–20 minutes.

Most patients present with poor night vision. Visual acuity is normal or mildly reduced and photopic visual fields and color vision are normal. Most cases are from Japan, but it can occur in other races.

Electrophysiology and psychophysics

There are two types of Oguchi disease depending on the dark adaptation findings:

Type 1: rod adaptation is markedly slowed; full recovery of sensitivity takes several hours and the absolute threshold is normal or only minimally elevated.

Type 2: there is no recognizable rod adaptation; the abnormal retinal appearance is less marked and the Mizuo phenomenon may be absent.

Most patients with Oguchi disease have a "negative" bright flash ERG, confirming the site of dysfunction to be post-phototransduction, as in AR and XL CSNB. In contrast to fundus albipunctatus (see below), the ERG remains abnormal even after prolonged dark adaptation.

Molecular genetics and pathogenesis

Oguchi disease in some patients is a consequence of a truncating deletion in *SAG*, encoding arrestin. Reduced activity of arrestin is likely to result in prolonged activation of transducin and rod phosphodiesterase following light exposure. cGMP levels would thereby be maintained at a low level in even dim light exposure and the outer segment cation channels would remain closed resulting in prolonged rod hyperpolarization. The rods would behave as if they were light adapted and would be unresponsive to light at low levels of illumination, explaining the psychophysical abnormalities.

Null mutations in *GRK1*, encoding a second component of the rod phototransduction pathway, rhodopsin kinase (RK), have also been identified in Oguchi disease. The key function, of both RK and arrestin, in the normal deactivation and recovery of the photoreceptor after exposure to light, explains the delayed recovery in Oguchi disease. The consequences of these reported RK mutations have been assessed by expression studies in COS7 cells of wild-type and human mutant RK. The markedly reduced mutant RK activity supports their pathogenicity.[6]

Evidence from knockout mice models suggests that patients with *SAG* or *GRK1* mutations may be more susceptible to light-induced retinal damage; it may therefore be advisable for affected patients to wear tinted spectacles.[7,8]

Fundus albipunctatus

Clinical findings

This autosomal recessive form of stationary night blindness, most commonly related to mutation in *RDH5*, usually has a characteristic fundus appearance with multiple white dots throughout the retina; however, a normal fundus appearance has also been reported with molecular confirmation and the typical functional changes. Patients either present with night blindness or an abnormal retinal appearance on routine fundoscopy. The visual acuity is usually normal and the condition non-progressive.

The deposits are discrete dull-white lesions at the level of the retinal pigment epithelium (RPE). They are most numerous in the mid-periphery and are usually absent at the macula; the optic discs and retinal vessels are normal. Fluorescein angiography shows multiple areas of hyperfluorescence, which may not directly correlate to the deposits seen clinically. In some patients there is good correlation between the white dots and increased autofluorescence on fundus autofluorescence imaging, but not in others. The differential diagnosis is from other causes of flecked retina (see Chapter 50).

Electrophysiology and psychophysics

Dark adaptation is severely delayed in fundus albipunctatus (FA), reflecting abnormal regeneration of rhodopsin. The rod–cone break is delayed and full rod adaptation may take many hours. Rod ERGs are markedly abnormal, with the rod-specific ERG (DA 0.01) usually being undetectable under standard conditions, but normalizing following prolonged dark adaptation (Fig. 46.4). The dark-adapted bright flash ERG (DA 10.0), which after a standard period of dark adaptation arises in dark-adapted cones, can have a low b:a ratio; a red

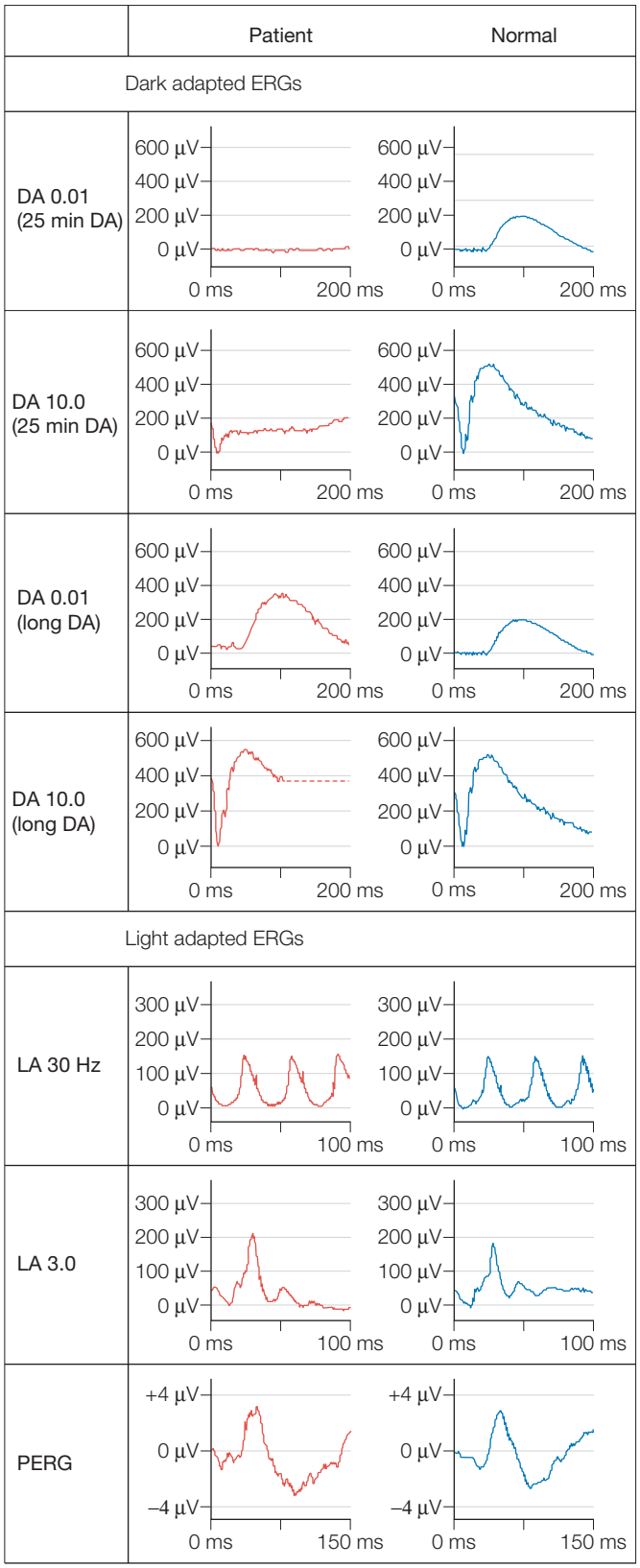


Fig. 46.4 Fundus albipunctatus. The DA 0.01 electroretinogram (ERG) is undetectable following a standard period of dark adaptation and the DA 10.0 response is reduced with additional reduction in the b:a ratio, in keeping with an origin in dark-adapted cones. Following an extended period of dark adaptation, both DA 0.01 and DA 10.0 responses are completely normal in keeping with delayed restoration of normal levels of rhodopsin.

flash stimulus under dark adaptation shows a normal cone component but an undetectable rod component and prevents confusion with CSNB associated with a negative ERG. It is necessary to considerably exceed the ISCEV ERG standard recommendations for dark adaptation to confirm the diagnosis of FA. Most but not all patients with *RDH5* mutations show full recovery of rod function with extended dark adaptation. This contrasts with the findings in retinitis punctata albescens (see below), related to mutation in *RLBP1*, and usually helps to distinguish between the two disorders.

There are two forms of FA, one in which cone ERGs are normal, and a rarer form described as fundus albipunctatus with cone dystrophy and negative ERG.[9–11]

Molecular genetics and pathogenesis

Mutations in three genes (*RDH5*, *RLBP1*, and *RPE65*), encoding components of the visual cycle, have been identified to date. The gene *RDH5* encodes 11-*cis*-retinol dehydrogenase. Recombinant mutant 11-*cis*-retinol dehydrogenases have reduced activity compared with recombinant enzyme with wild-type sequence.[10] The function of the protein product of *RDH5* is consistent with the delay in the regeneration of photopigments characteristic of the disorder.

Mutations have also been reported in *RLBP1*, encoding the cytosolic cellular retinaldehyde binding protein (CRALBP). *RLBP1* mutations usually cause retinitis punctata albescens (see below). CRALBP has been localized to the RPE, Müller cells, and ciliary epithelium. It can select 11-*cis*-retinaldehyde from a mixture of retinoids and protect it from photoisomerization, suggesting a possible role in the generation of 11-*cis*-retinoids in the visual cycle and in keeping with the phenotypic features of FA.

Sequence variants in *RPE65* have also been identified in patients with a retinal appearance similar to FA.[12] Reduced fundus autofluorescence has been observed in patients with *RPE65* and *RDH5* mutations,[11,12] supporting the concept that disruption of retinoid recycling in the RPE is essential for the development of FA.

Stationary cone disorders (cone dysfunction syndromes)

The cone dysfunction syndromes include congenital color vision disorders where there is normal visual acuity but defective color vision, and the various forms of cone dysfunction associated with reduced central vision and often nystagmus and photophobia (Table 46.1).[13]

Disorders of color vision with normal visual acuity

Color vision in humans is trichromatic; there are three classes of cone photoreceptor that contain visual pigments maximally sensitive at 560 nm (L-cones [red]), 535 nm (M-cones [green]), and 440 nm (S-cones [blue]). The genes for the protein component (opsin) of the L- and M-cone pigments are on the long arm of the X chromosome, and the S-cone opsin gene on chromosome 7. About 8% of men and 0.5% of women have a red–green color vision defect, which is associated with abnormalities of the red and green cone opsin genes. Tritanopia is an uncommon autosomal dominant disorder in which there is a specific deficiency of S-cone sensitivity associated with mutations of the S-cone opsin gene.

Table 46.1 Summary of the cone dysfunction syndromes

Cone dysfunction syndrome	Alternative names	Mode of inheritance	Visual acuity	Refractive error	Nystagmus	Color vision	Fundi	Mutated gene(s) or chromosome locus
Complete achromatopsia	Rod monochromatism Typical achromatopsia	Autosomal recessive	6/36–6/60	Often hypermetropia	Present	Absent	Usually normal	*CNGA3* *CNGB3* *GNAT2* *PDE6C* *PDE6H* *ATF6*
Incomplete achromatopsia	Atypical achromatopsia	Autosomal recessive	6/24–6/60	Often hypermetropia	Present	Residual	Usually normal	*CNGA3* *PDE6C*
Oligocone trichromacy	Oligocone syndrome	Autosomal recessive	6/12–6/24	Equal incidence of myopia and hypermetropia	Often absent	Normal	Normal	–
RGS9/R9AP retinopathy	Bradyopsia	Autosomal recessive	6/12–6/24	Equal incidence of myopia and hypermetropia	Often absent	Normal	Normal	*RGS9* *R9AP*
Cone monochromatism	–	Uncertain	6/6	–	Absent	Absent or markedly reduced	Normal	–
Blue cone monochromatism	X-linked atypical achromatopsia X-linked incomplete achromatopsia	X-linked	6/24–6/60	Often myopia	Present	Residual tritan discrimination	Usually normal or myopic	(i) Deletion of the locus control region (ii) Single inactivated L/M hybrid gene
Bornholm eye disease	–	X-linked	6/9–6/18	Moderate-to-high myopia with astigmatism	Absent	Deuteranopia Protanopia	Myopic	L/M opsin array

This group of disorders, their clinical characteristics, and the molecular pathology are reviewed elsewhere.[14]

Achromatopsia

Achromatopsia is genetically heterogeneous and characterized by an absence of functioning cones in the retina.[13] It may occur in complete (typical) and incomplete (atypical) forms.

Complete achromatopsia (rod monochromatism)

Clinical and histopathologic findings

The usual presentation is with reduced vision, nystagmus, and marked photophobia at birth or early infancy. The incidence is approximately 1 in 30,000. Parents often comment that vision is much better in dim illumination. Pupil reactions are sluggish or may show paradoxical constriction in the dark. High hyperopic refractive errors may be present and the fundi are normal. The nystagmus and photophobia, marked in infancy, may improve with age. The visual acuity is usually 6/60 and there is complete color blindness. Peripheral visual fields are normal but a central scotoma can often be detected. Achromatopsia is generally a stationary disorder but slow deterioration and macular atrophy may occur.[15,16]

Histopathologic studies have demonstrated cone-like structures in the retina,[17,18] which have also been observed *in vivo* using adaptive optics imaging, albeit to a variable degree.[16] Thus, cone function could potentially be rescued with gene replacement therapy.

Electrophysiology and psychophysics

The dark adaptation curve is monophasic with no evidence of a cone contribution. Spectral sensitivity studies show that rods mediate threshold under both photopic and scotopic conditions; there is no evidence of a Purkinje shift. Electroretinography (Fig. 46.5) shows normal rod-derived ERGs but no detectable cone-derived responses.

Molecular genetics and pathogenesis

Achromatopsia is recessively inherited and genetically heterogeneous. Five genes have been identified, *CNGA3*, *CNGB3*, *GNAT2*, *PDE6C*, and PDE6H, all encoding components of cone phototransduction.

CNGA3 and *CNGB3* code for the α- and β-subunits of the cGMP-gated (CNG) cation channel in cone cells, respectively. In the dark, cGMP levels are high in cone photoreceptors, enabling cGMP to bind to the α- and β-subunits of CNG channels. This results in them adopting an open conformation and permitting influx of cations, with consequent cone depolarization. When light is applied, activated photopigment interacts with transducin, a three-subunit guanine nucleotide binding protein, stimulating the exchange of bound guanosine diphosphate (GDP) for guanosine triphosphate (GTP). The

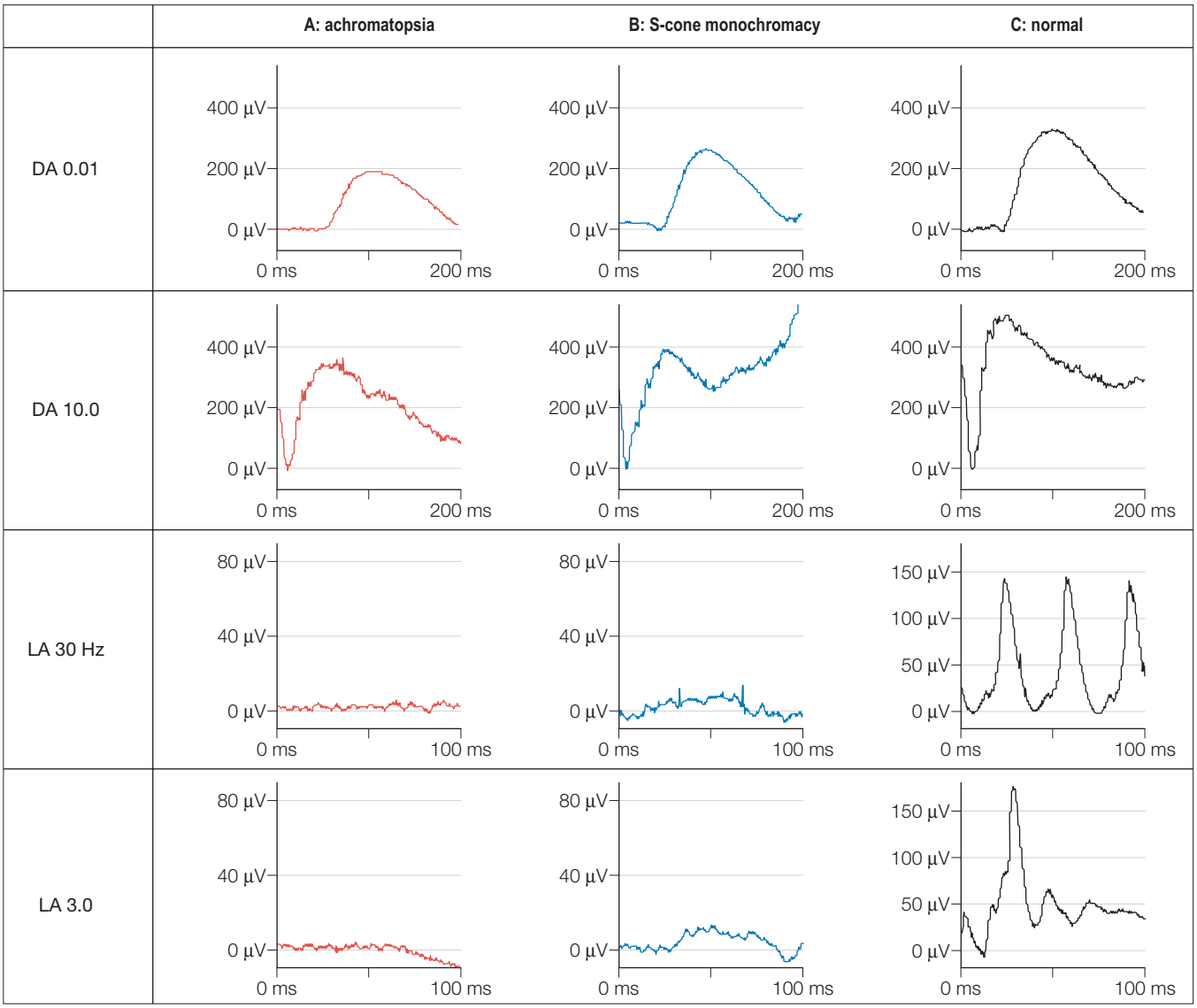


Fig. 46.5 Electroretinograms (ERGs) from a patient with achromatopsia (A), a patient with S-cone monochromacy (B), and a representative normal (C). The rod-specific (DA 0.01) and bright flash ERGs (DA 10.0) show no definite abnormality in either of these cone dysfunction syndromes. The 30 Hz flicker ERG (LA 30 Hz) is undetectable in both, but the single flash photopic ERG (LA 3.0) is small and late, typical of S-cone origins. Note that the scale for the photopic ERGs in the two patients differs from that in the normal subject better to illustrate the low amplitude LA 3.0 response in the S-cone monochromat.

cone α-transducin subunit (encoded by *GNAT2*), which is bound to GTP, is then released from its β- and γ-subunits and activates cGMP-phosphodiesterase by removing the inhibitory γ-subunits (encoded by *PDE6H*) from the active site of this enzyme, which is formed by two α-subunits (encoded by *PDE6C*). cGMP-phosphodiesterase lowers the concentration of cGMP in the photoreceptor, which results in closure of cGMP-gated cation channels.

More than 80 disease-causing mutations in *CNGA3* have been identified in patients with achromatopsia. Four mutations (Arg277Cys, Arg283Trp, Arg436Trp, and Phe547Leu) account for approximately 40% of all mutant *CNGA3* alleles.[19] Far fewer mutations have been identified in *CNGB3*. The 1 base pair frameshift deletion, 1148delC (Thr383fs), accounts for up to 80% of *CNGB3* mutant disease chromosomes.[20,21] The majority of *CNGA3* mutations identified to date are missense mutations, indicating that there is little tolerance for substitutions with respect to functional and structural integrity of the channel polypeptide. In contrast, the majority of *CNGB3* alterations are nonsense mutations.

About 70–80% of achromatopsia results from mutations of *CNGA3* and *CNGB3*, with *GNAT2*, *PDE6C*, *PDE6H*, and *ATF6* each accounting for less than 1–2%[19–21]; further causative genes remain to be discovered.

Incomplete achromatopsia

Clinical findings

The presentation and clinical findings in infancy are similar to the complete form of achromatopsia; however, visual acuity is slightly better (6/24–6/36) with some residual color perception. This form is also inherited as an autosomal recessive trait.

Molecular genetics and pathogenesis

As in the complete form, mutations in *CNGA3* have been identified in individuals with incomplete achromatopsia.[19] The identified mutations are all missense, located throughout

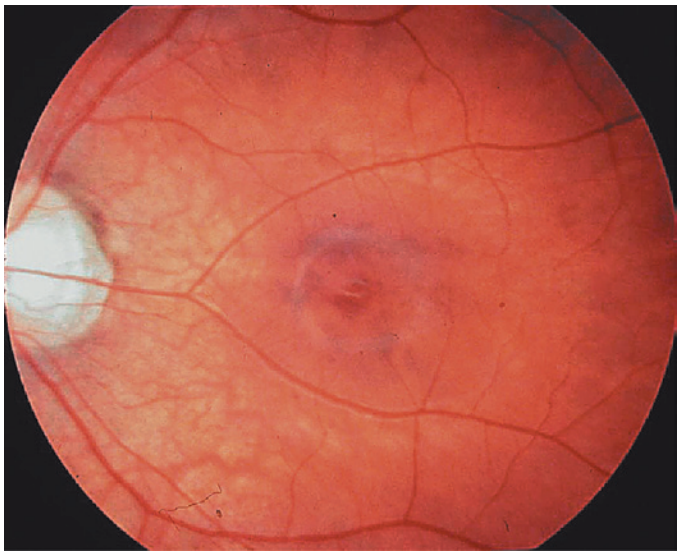


Fig. 46.6 Blue cone monochromatism. Pale tilted optic disc with myopic fundus.

the channel polypeptide including the transmembrane domains, ion pore, and cGMP-binding region. Only three of these, Arg427Cys, Arg563His, and Thr565Met, are exclusively found in patients with incomplete achromatopsia.[19] Therefore, in the majority of cases of incomplete achromatopsia, other factors may influence the phenotype such as modifier genes or environmental factors. The missense variants identified in incomplete achromatopsia must be compatible with residual channel function since the phenotype is milder than in complete achromatopsia. Mutations in *PDE6C*,[22] *GNAT2*, and *CNGB3* have also been identified in incomplete achromatopsia.

S-cone monochromatism (blue cone monochromatism)

Clinical findings

Blue cone monochromatism (BCM; also known as S-cone monochromacy) is an X-linked recessive disorder, affecting approximately 1 in 100,000 individuals, in which affected males have normal rod and S-cone function but lack L- and M-cone function. The clinical features are similar to complete achromatopsia but less severe. Affected infants have photophobia and nystagmus from early infancy. They are usually myopic, in contrast to achromatopsia (Fig. 46.6). The nystagmus often reduces with time.

BCM is generally accepted to be a stationary disorder but deterioration with macular atrophy may occur over time.[23–26]

Electrophysiology and psychophysics

Achromatopsia and BCM may be differentiated by the mode of inheritance, findings on psychophysical testing, and electrophysiology. There is some preservation of the single flash photopic ERG (LA 3.0) in BCM (see Fig. 46.5), and specialized spectral ERG techniques to measure S-cone ERGs can also be used (see Fig. 46.5). Female carriers of X-linked BCM may have abnormal cone ERGs and mild anomalies of color vision.

Color vision tests that probe the tritan color axis, such as the Hardy, Rand, and Rittler (HRR) plates, are necessary in order to distinguish between achromatopsia and BCM, with relative preservation of tritan discrimination in BCM. Blue cone monochromats display fewer errors along the vertical axis in the Farnsworth 100-hue test (fewer tritan errors), and may display protan-like patterns on the Farnsworth D-15.

Molecular genetics and pathogenesis

Mutation analyses have established the molecular basis for BCM.[24] The mutations in the L- and M-opsin gene array causing BCM fall into two main classes:

1. A normal L- (*OPN1LW*) and M- (*OPN1MW*) pigment gene array is inactivated by a deletion in the locus control region (LCR), located upstream of the L-pigment gene. A deletion here abolishes transcription of all genes in the pigment gene array and therefore inactivates both L- and M-cones.
2. The LCR is preserved but changes within the L- and M-pigment gene array lead to loss of functional pigment production. The most common genotype in this class consists of a single inactivated L/M hybrid gene. The first step in this second mechanism is unequal crossing over reducing the number of genes in the array to one, followed in the second step by a mutation that inactivates the remaining gene. The most frequent inactivating mutation that has been described is a thymine-to-cytosine transition at nucleotide 648, which results in a cysteine-to-arginine substitution at codon 203 (Cys203Arg), a mutation known to disrupt the folding of cone opsin molecules.

The data suggest that 40% of BCM results from the one-step mutational pathway (deletions in the LCR). The remaining 60% of BCM is predominantly secondary to the aforementioned two-step pathway. Other less common mutational mechanisms include the deletion of an entire exon in a single opsin array gene or gene conversion transferring a mutation between *OPN1LW* and *OPN1MW*.

Oligocone trichromacy

Oligocone trichromacy is characterized by reduced visual acuity (6/12 to 6/24), mild photophobia, normal fundi, reduced cone ERGs with normal rod responses, and normal color vision.[13] Patients have been described both with and without nystagmus. These patients have a reduced number of normal functioning cones (oligocone) with preservation of the three cone types in the normal proportions, thereby permitting trichromacy, supported by high-resolution quantitative retinal imaging.[27]

Color vision testing either reveals normal or slightly elevated color discrimination thresholds. Slightly elevated discrimination thresholds are compatible with a reduction in cone numbers.

Oligocone trichromacy is inherited as an autosomal recessive trait; the condition is likely to be genetically heterogeneous and some patients have been reported with variants in *CNGB3* and *CNGA3*. Patients with either *RGS9*/*R9AP* mutations ("bradyopsia", see below) or oligocone trichromacy have similar clinical phenotypes, characterized by stationary cone dysfunction with normal color vision[28] but the electrophysiologic features associated with *RGS9* and *R9AP* are distinctive.

RGS9/R9AP retinopathy ("Bradyopsia")

Clinical findings

Bradyopsia is a stationary cone dysfunction syndrome with onset in early childhood; it is characterized by mild photophobia, delayed dark and light adaptation, moderately reduced visual acuity, normal color vision, and normal fundi. Some patients report difficulty seeing moving objects. It is not possible clinically to distinguish bradyopsia from oligocone trichromacy; however, there are pathognomonic findings on extended electrophysiologic assessment.[28]

Electrophysiology

The rod-specific ERG (DA 0.01), the red flash ERG under dark adaptation (which has both a cone and rod component), and the single bright white flash (DA 10.0) with inter-stimulus interval (ISI) of 2 minutes are normal. The usual DA 10.0 ERGs, with an ISCEV standard ISI of 20 seconds show amplitude reduction and waveform change, which becomes progressively less severe with increasing ISI, consistent with delayed recovery following the flash. The pattern electroretinogram (PERG) and standard 30 Hz flicker ERG (LA 30 Hz) are usually undetectable. A residual low amplitude standard photopic single flash ERG (LA 3.0) is usually recorded.

The ISCEV ERG standard protocol in *RGS9/R9AP* mutation shows normal dark-adapted responses, an undetectable 30 Hz flicker ERG, and a severely reduced LA 3.0 ERG, suggesting incomplete achromatopsia. However, ERGs to a red flash under dark adaptation, which in a normal subject gives an early cone system-derived response and a later rod system-derived response, show that dark-adapted cones retain good function and rule out achromatopsia.

Molecular genetics and pathogenesis

Mutations in both *RGS9* and *R9AP* have been associated with bradyopsia, with no sequence variants in either of these genes identified in subjects with oligocone trichromacy.[28]

Each of the activated phototransduction molecules has to be deactivated to turn off the visual response; α-transducin and cGMP-phosphodiesterase are simultaneously deactivated by the hydrolysis of the α-transducin-bound GTP to GDP. This GTPase activity is substantially accelerated by RGS9, a GTPase-activating protein that binds to the Gβ5 subunit, and to R9AP, a membrane anchor protein. RGS9 and R9AP have a critical role in the recovery phase of visual transduction. RGS9 is anchored to photoreceptor outer segment disc membranes by R9AP; R9AP is required for the correct targeting and localization of RGS9 in photoreceptors and enhances RGS9 activity up to 70-fold.

Bornholm eye disease

Clinical findings

Bornholm eye disease (BED) is an X-linked disorder with myopia and astigmatism, impaired visual acuity, moderate optic nerve hypoplasia, thinning of the RPE in the posterior pole with visible choroidal vasculature, and abnormal cone ERGs.[29] Affected members in this single family were all deuteranopes, with a stationary natural history; a similar phenotype has however also been published in association with protanopia.[30,31] This disorder is therefore best described as an X-linked cone dysfunction syndrome with myopia and dichromacy.

Molecular genetics and pathogenesis

The condition was mapped by linkage analysis in the original Danish family to Xq28, in the same chromosomal region as the L/M opsin gene array. Subsequent genetic interrogation has shown that rare haplotypes ("L/M interchange haplotypes") at polymorphic positions in exon 3 of the opsin genes, which result from intermixing between L and M opsin genes, are the principal underlying genetic basis of BED. Some of these interchange haplotypes have been shown to result in aberrant splicing of the opsin genes and a variable degree of exon 3 skipping.

Progressive retinal dystrophies

Rod–cone dystrophies

The rod–cone dystrophies (retinitis pigmentosa [RP]) are a clinically and genetically heterogeneous group of disorders with progressive loss of rod and later cone photoreceptor function leading to severe visual impairment. RP usually occurs as an isolated retinal abnormality, but it may also be syndromic with other systemic abnormalities (see Chapter 47).

Leber congenital amaurosis

Clinical findings

Leber congenital amaurosis (LCA) is a severe congenital or early infant-onset non-syndromic retinal blindness first described by Theodore Leber in 1869. He characterized the disorder by a searching nystagmus, abnormal pupil responses, minimal, if any, vision beyond infancy, and an initially normal fundus appearance followed by the development of pigmentary changes. He later described a milder form of the same disease, which has had several names, including early-onset severe retinal dystrophy (EOSRD), severe early childhood-onset retinal dystrophy (SECORD), and early-onset retinitis pigmentosa. Whereas LCA is congenital or presents within the first few months of life, EOSRD is defined as a severe retinal dystrophy presenting before the age of 5 years. LCA/EOSRD is the most common inherited cause of severe visual impairment in children, accounting for 10–18% of children in institutions for the blind.

LCA is associated with severe visual impairment from birth or the first few months of life accompanied by roving eye movements or nystagmus and poor pupillary light responses. Eye-poking, the "oculodigital" sign, is common (Fig. 46.7). Fundus examination may be normal but a variety of abnormal fundus appearances may be present such as disc pallor, vessel attenuation, or mild peripheral pigmentary retinopathy. There may also be disc drusen, optic disc edema or pseudopapilledema (Fig. 46.8), a flecked retina, maculopathy, or nummular pigmentation. Affected infants often have high hyperopia or, less commonly, high myopia, suggesting impaired emmetropization.

Although most patients have normal fundi in infancy, signs of a pigmentary retinopathy appear in later childhood with optic disc pallor and retinal arteriolar narrowing. Other late signs, which may be related to eye-poking, include enophthalmos, keratoconus, and cataract. Eventual vision is in the region of 3/60 to perception of light. Some cases show no evidence of progression over time.



Fig. 46.7 Leber congenital amaurosis. Eye-poking, the "oculodigital sign," is very common but of unknown cause; it results in atrophy of orbital fat and enophthalmos.



Fig. 46.8 Leber congenital amaurosis. High hypermetropia and pseudopapilledema.



Fig. 46.9 Leber congenital amaurosis. *RDH12*-associated disease characterized by bone spicule pigmentation and maculopathy.

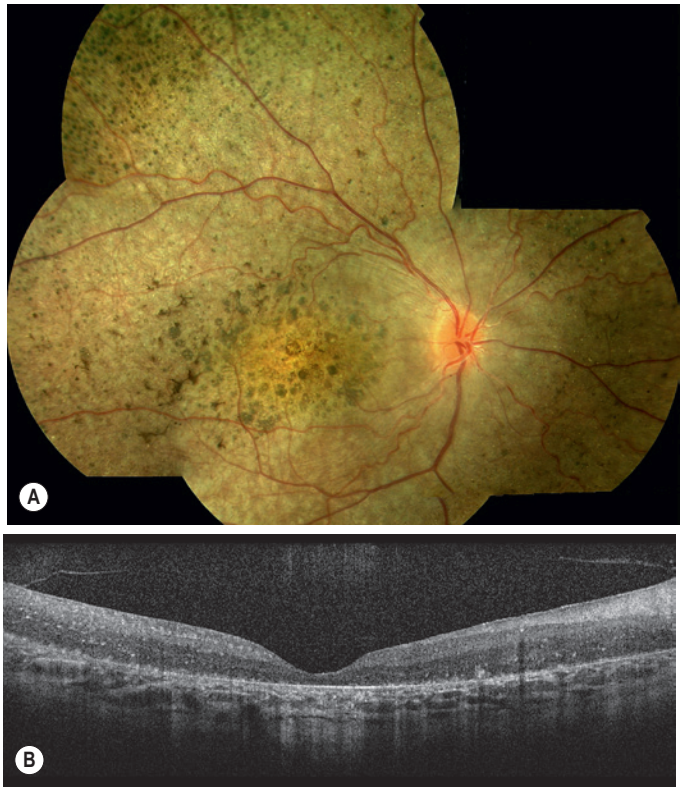


Fig. 46.10 Leber congenital amaurosis. *CRB1*-associated disease which is characterized by (A) nummular pigmentation, maculopathy, relative preservation of para-arteriolar retinal pigment epithelium (RPE), with (B) retinal thickening and loss of lamination observed on optical coherence tomography.

Following the discovery of many disease-causing genes (see below) it has sometimes been possible to identify characteristic associated phenotypes (Figs 46.9–46.12): *RDH12*-associated disease is characterized by bone spicule pigmentation and maculopathy (see Fig. 46.9) and *CRB1*-associated disease has nummular pigmentation, maculopathy, relative preservation of para-arteriolar RPE, with retinal thickening, and loss of lamination on optical coherence tomography (see Figs 46.10 and 46.11). *TULP1*, *AIPL1*, and *NMNAT1*-associated LCA are also characterized by maculopathy.

Electrophysiology

The ERG is undetectable or severely abnormal in infants with LCA. It is important to distinguish LCA from CSNB and achromatopsia, which may also present in infancy with nystagmus and poor vision. The visual evoked potential (VEP) is often undetectable, but VEP preservation, despite an undetectable ERG, is associated with a better visual prognosis.



Fig. 46.11 Leber congenital amaurosis. *CRB1*-associated disease can be complicated by a Coats-like exudative retinopathy.

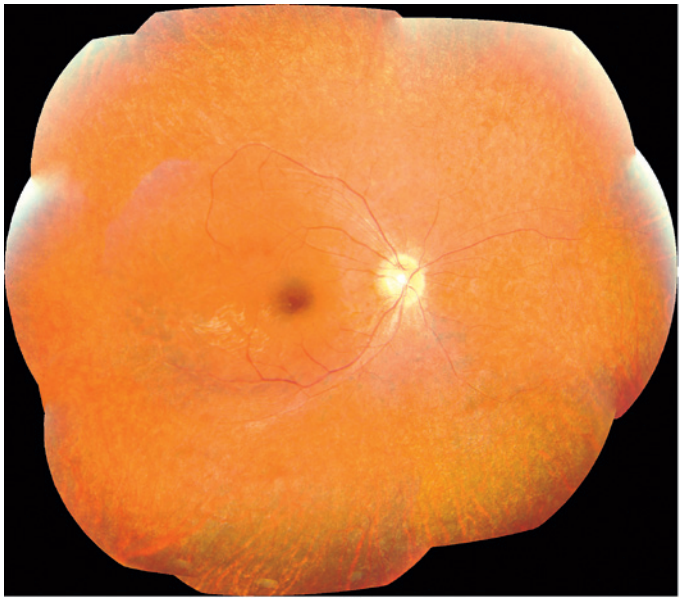


Fig. 46.12 Leber congenital amaurosis. *RPE65*-associated disease often characterized by mild peripheral retinal pigment epithelium (RPE) mottling and white dots at the level of the RPE, usually with relatively normal vessel caliber and optic disc.

Non-ocular features

Most cases of LCA occur in otherwise normal infants and any non-ocular symptoms or signs should be investigated for syndromic retinal dystrophies or neurometabolic disease, usually in conjunction with a pediatrician (see Chapters 47 and 65).

Molecular genetics and pathogenesis

LCA and EOSRD are extremely genetically heterogeneous, being caused by more than 18 genes (including *AIPL1*, *CEP290*, *CRX*, *CRB1*, *GUCY2D*, *IMPDH1*, *LCA5*, *LRAT*, *MERTK*, *RD3*, *RDH12*, *RPGRIP1*, *RPE65*, *SPATA7*, *KCNJ13*, *ICQB1*, *NMNAT1*, and *TULP1*).[32] All exhibit autosomal recessive inheritance except *CRX*, where certain *de novo* mutations result in an autosomal dominant trait.[32] These genes are usually expressed preferentially in the retina or the RPE. Their putative functions are quite diverse and include retinal photoreceptor development (*CRX*), photoreceptor cell structure (*CRB1*), phototransduction (*GUCY2D*), protein trafficking (*AIPL1*, *RPGRIP1*), and visual cycle function (*RPE65*, *LRAT*).

Molecular genetic testing can now refine the diagnosis in approximately 60–70% of patients, facilitating prognostic counseling. For example, patients with *RPE65* mutations have a better visual outcome than those with *GUCY2D* mutations.[32] Identification of disease-causing mutations in LCA patients allows improved genetic counseling, the potential for prenatal diagnosis, and selection of patients for gene-specific therapies.

Therapeutic intervention

Animal models of retinal blindness from deficiency of *RPE65* have either been engineered via targeted disruption of the gene in the mouse, or are available due to a natural mutation in the Briard dog. Pharmacologic bypass of the metabolic block, using synthetic retinoids, has resulted in rapid restoration of visual pigment and function in the mouse. Gene replacement, using a normal copy of the gene in an adeno-associated virus (AAV) vector administered subretinally, has successfully restored ERGs and retinal function in both the murine and the canine models, resulting in substantial, durable recovery of vision as determined by ERGs, pupillary responses, and behavioral measures. This success has led to human clinical trials in the USA and UK involving a subretinal injection of AAV-vector delivering a wild-type copy of *RPE65*. These have all reported good safety with varying degrees of efficacy, which waned over time.[33–35]

Further forms of LCA/EOSRD are now subject to ongoing gene replacement clinical trials, with more anticipated (www.clinicaltrials.gov).

Retinitis pigmentosa

Retinitis pigmentosa (RP) is a term used for a genetically heterogeneous group of disorders characterized initially by night blindness and visual field loss. ERGs may be undetectable or, more frequently, show the rod system to be more severely affected than the cone system, at the level of the photoreceptor. Dysfunction confined to the rod system is unusual but can occur early in the course of the disorder. Onset is often in childhood and inheritance can be autosomal recessive, autosomal dominant and X-linked. The disease may be confined to the eye or it may be part of a more widespread systemic disorder (see Chapter 47).

Clinical findings

Children with RP most commonly present with night blindness, but can also present with symptoms associated with peripheral field loss or central retinal involvement. The age of onset is extremely variable. In some, there may be no symptomatic night blindness and the child is referred after routine fundoscopy. When a close relative has RP, children may be referred early for investigation to exclude the disease.

In most cases, the visual acuity is initially normal; later, visual loss may occur from posterior subcapsular cataract, macular edema, or macular involvement. Early visual field changes are small scotomata in the mid-periphery, commonly in the upper visual field. These gradually coalesce to give

the classical peripheral ring scotoma. Visual fields become concentrically constricted over time, often leaving an island of preserved field in the far temporal periphery until late in the disease. In sector RP, which commonly involves the lower nasal quadrant, bilateral upper temporal field loss may lead to unnecessary investigation to exclude a chiasmal lesion – it should be noted that the temporal field defect in RP does not respect the midline.

The appearance of the fundus in the early stages of RP is variable and, in young children, subtle. The earliest change may be mild pigment epithelial disturbance in the mid-periphery, often with small white dots at the level of the RPE (Fig. 46.13). Later, pigment deposition is seen and there may be arteriolar narrowing and optic disc pallor. Abnormal pigment may be lacking in some children and, less commonly, there may be multiple white deposits throughout the retina (similar to retinitis punctata albescens). The classical fundus appearance of optic disc pallor, retinal arteriolar attenuation, and peripheral pigment epithelial atrophy and intra-retinal "bone corpuscle" pigmentation is present in late disease (Fig. 46.14). Other findings may include vitreous cells, posterior subcapsular cataract, optic disc drusen, and macular edema. Occasionally, retinovascular changes similar to Coats disease are seen.

The retinal phenotype is similar in most forms of RP although there may be marked variation in severity between affected individuals. There are, however, some gene-specific phenotypes. AD sector RP is usually associated with mutations in the rhodopsin gene, and the uncommon AR form of RP (RP12) with preserved para-arteriolar RPE, is associated with *CRB1* mutations. Two early-onset forms of AR RP caused by mutations in the *RLBP1* gene are associated with multiple white deposits at the level of the RPE (Newfoundland rod–cone dystrophy and Bothnia dystrophy).[36,37]

Electrophysiology and psychophysics

The ERG in RP shows a rod–cone pattern of dysfunction; the rod-derived responses are more affected than the cone-derived responses. There is marked variation in severity, partly related to the nature of the mutation, the inheritance pattern, and the subject's age. The ERG may be undetectable in the late stages of RP, or small residual cone responses may be found. There is reduction in the amplitude of the rod a- and b-waves in mild disease or early RP and the rod-mediated b-wave peak-time may be prolonged. The 30 Hz cone flicker ERG is usually both delayed and reduced, in keeping with generalized cone system dysfunction.

The macula may be spared and central retinal function tests, such as the PERG or multifocal ERG, may show minimal involvement despite almost complete loss of the full-field ERG. PERG may also be helpful in demonstrating central retinal involvement prior to the development of visible abnormalities. The electro-oculogram (EOG) provides little relevant information in RP and can be difficult to perform in young children.

Sector retinitis pigmentosa

The term "sector RP" should be reserved for those forms of RP (usually AD) where functional testing suggests restricted loss of function; pigmentary abnormalities are usually confined to the inferior retina (Fig. 46.15). A similar sectorial involvement may occasionally be seen in the female carriers of X-linked RP or as an early stage in generalized RP. The ERG in true sector RP usually shows amplitude reduction but no peak-time changes; the presence of marked peak-time shift suggests generalized dysfunction even though the pigmentary changes may be restricted. It is important in isolated cases to examine other family members, as the disorder is often asymptomatic. Dominant sector RP is often associated with mutations of the rhodopsin gene. Children with sector RP are usually asymptomatic and are referred when an abnormal fundus appearance is noted on routine fundoscopy or they are ascertained during family surveys.

Field loss on Goldmann perimetry is confined to the sector corresponding to the clinically involved retina. However, dark-adapted perimetry may show mild rod and cone threshold elevation in the apparently uninvolved retina indicating dysfunction outside the clinically evident region. Rod dark

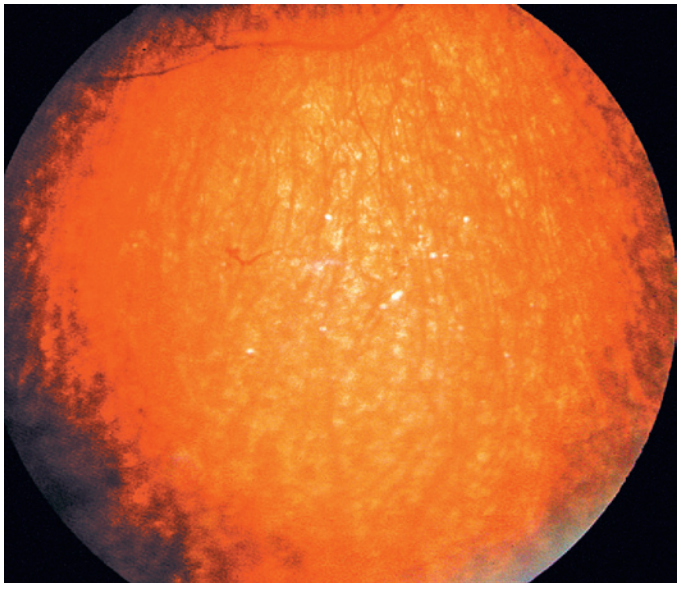


Fig. 46.13 Retinitis pigmentosa. Pigment epithelial atrophy in the mid-periphery with small white dots at the level of the retinal pigment epithelium.

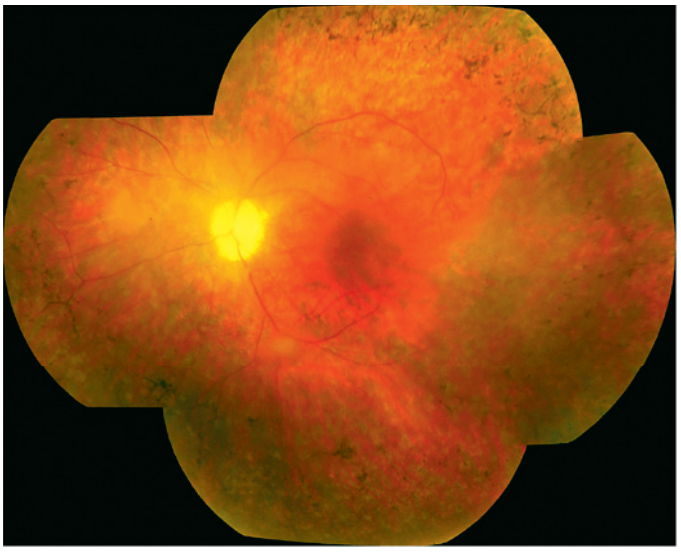


Fig. 46.14 Retinitis pigmentosa. "Bone spicule" formation, arteriolar narrowing, and optic nerve pallor.



Fig. 46.15 Sector retinitis pigmentosa. Retinal pigmentary changes confined to the lower quadrants.

adaptation may be extremely delayed. The ERG is usually relatively well preserved with mild or moderate reductions in both rod and cone amplitudes. Disease progression is slow and usually confined to the clinically involved sector. The visual prognosis is good.

Autosomal dominant retinitis pigmentosa with incomplete penetrance

Variability of expression is common in autosomal dominant RP, but true non-penetrance is unusual. However, incomplete penetrance is notable and common in many families. There is genetic heterogeneity in autosomal dominant RP with incomplete penetrance; mutations have been identified in several genes including *RP9*, *RP1*, *PRPF8*, and *PRPF31*.

Genetic counseling in families showing incomplete penetrance may be problematic because of the high incidence of asymptomatic gene carriers, but molecular genetic diagnosis is now possible in many families.

X-linked retinitis pigmentosa

X-linked RP is severe with onset of night blindness usually by 10 years and progression to blindness by the third to fourth decade. Those affected are often myopic and show fundus abnormalities and ERG changes early (Fig. 46.16). If there is a family history of other affected males, the diagnosis is usually straightforward. Examination of close female relatives is helpful in the absence of a family history, as the recognition of the XL carrier state confirms the diagnosis.

The carrier state for XL RP can be diagnosed with certainty in females who have affected sons or fathers and are therefore obligate gene carriers, or where they can be shown by molecular genetic testing to carry the causative mutation. In other female family members, carrier detection depends upon recognition of the heterozygote's abnormal fundus appearance or on the results of autofluorescence imaging, and electrophysiologic or psychophysical testing.

Fundus abnormalities are common in XL heterozygotes: a prominent "tapetal" reflex may be seen at the posterior pole (Fig. 46.17) or a mild pigment epithelial thinning and pigmentation. The ERG is usually abnormal and asymmetric in heterozygotes (see Fig. 46.16). Delay in the 30 Hz flicker response is probably the most frequent abnormality, but reduced rod amplitude may also occur. XL carriers can be identified in most cases using a combination of fundoscopy, autofluorescence imaging, and electrophysiology. Molecular genetic diagnosis is possible in many families and is increasingly the method of choice for identification of heterozygotes.

The retinal dysfunction in some XL carriers can be progressive, as older carriers may report symptoms of night blindness, have detectable field loss, and more extensive retinal pigmentation. Some carrier females may be severely affected at a relatively young age; however, there is considerable intra- and interfamilial variability. Skewed X inactivation, with the X chromosome having the mutant allele active in most cells, may account for severely affected females.

Unilateral "retinitis pigmentosa"

Fundus changes of unilateral pigmentary retinopathy have been described but only one genetically confirmed case from an extended family with RP. The patient with unilateral RP in that family[38] harbored a common nonsense mutation in *RP1*, a common cause of AD RP. Thus, a somatic mutation might have occurred in a progenitor cell during the development of the unaffected retinal tissue that ameliorates the effect of the *RP1* mutation.[38]

Most other cases are probably not genetically determined and may be post-inflammatory, post-traumatic, or follow retinal ischemia. A minority of individuals with RP have an asymmetric fundus appearance at presentation so that one eye appears clinically unaffected, but psychophysical testing and ERG demonstrate abnormal function bilaterally.

Differential diagnosis of retinitis pigmentosa

Other disorders may be confused with RP either because there is symptomatic night blindness or because of a similar fundus appearance (Table 46.2 and Fig. 46.18). Other inherited retinal dystrophies can usually be differentiated from RP by the clinical findings and electrophysiology. Although history and examination may exclude many of the acquired causes of pigmentary retinopathy, it is likely that some cases of apparently sporadic RP are due to acquired retinal or pigment epithelial disease.

Genetics of retinitis pigmentosa

RP may be inherited as an autosomal dominant, autosomal recessive, or X-linked recessive disorder. There is genetic heterogeneity within these subtypes. The relative frequency of the different modes of inheritance differs widely in different series, but 50% of patients have no family history of RP or parental consanguinity. It is unlikely that all such cases have AR disease. Some males may have XL disease transmitted via asymptomatic female carriers; other cases may represent new AD mutations or AD disease in a family with reduced penetrance. Some sporadic patients may not have genetic disease. Similar retinal dystrophies may be seen in association with mutations of mitochondrial DNA but there are usually other systemic abnormalities (see Chapters 47 and 65).

XL and AR RP tend to have an earlier onset and are more severe than dominant disease. The clinical findings should be taken into account, particularly when counseling those patients with apparently sporadic disease. A severely affected female is more likely to have AR disease, whereas a severely affected male may have XL or AR disease. A significant number of patients with sporadic RP, however, have mild disease and

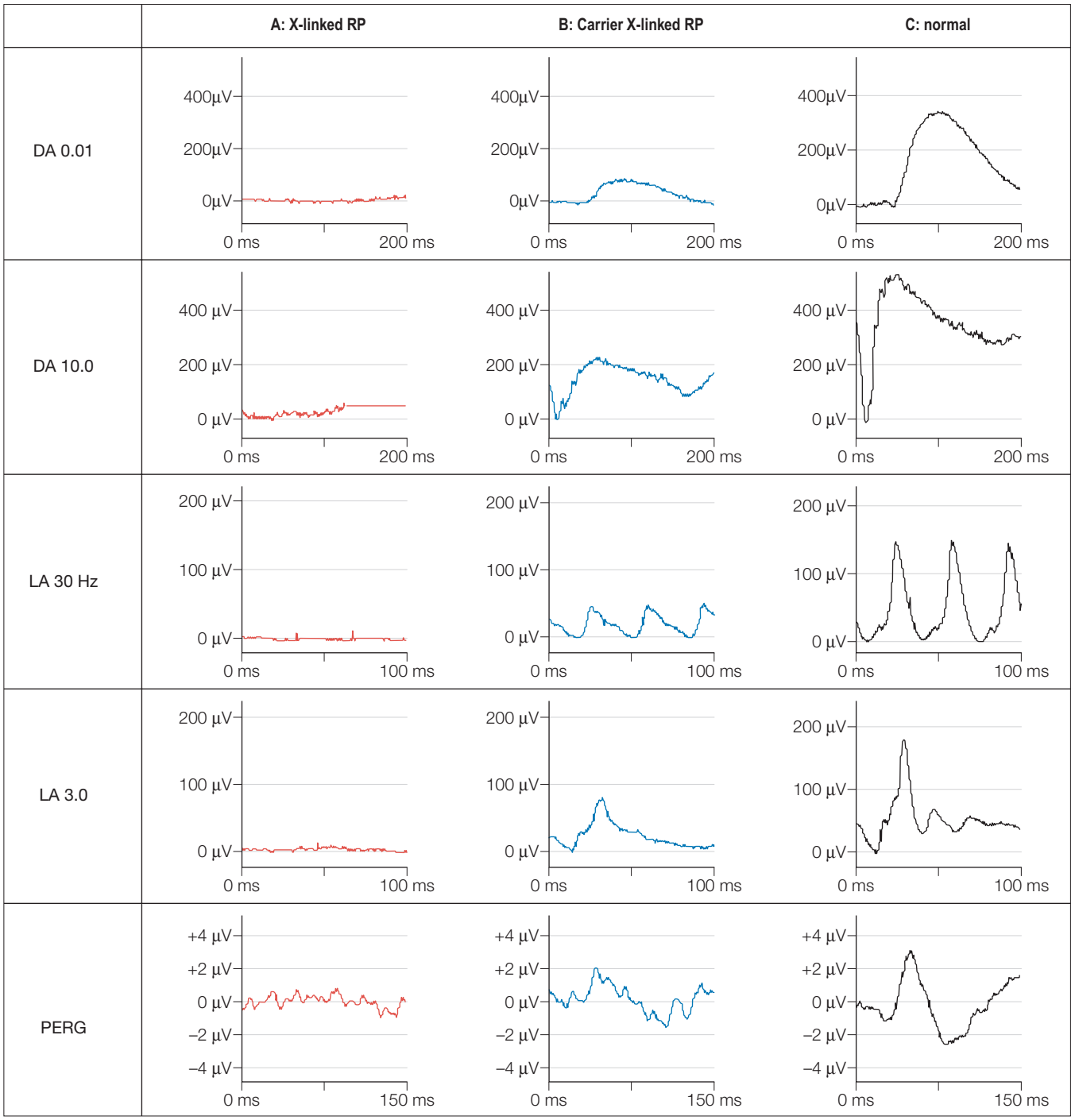


Fig. 46.16 X-linked retinitis pigmentosa (RP). Electroretinograms (ERGs) from a young affected patient (A), his heterozygote mother (B), and a representative normal subject (C). There is only residual ERG activity detectable in the patient. The ERGs in his mother are mildly subnormal under all stimulus conditions, the subnormal a-wave of the bright flash response (DA 10.0) confirming the abnormality to be at the level of the photoreceptor. ERG abnormalities are usually present in heterozygotes, and can vary from mild to severe.

some of these probably have new AD mutations. Prior to counseling, it is important to examine other family members, especially the mothers of severely affected males who may show the fundus/imaging or electrophysiologic abnormalities of an X-linked heterozygote.

Accurate genetic counseling depends upon identification of the causative mutation. Much progress has been made in identifying the causative genes, and molecular genetic diagnosis is now possible in many forms of RP. More than 60 genes have been identified in non-syndromic RP, encoding proteins of the phototransduction cascade, proteins involved in vitamin A metabolism and cell–cell interaction, photoreceptor structural proteins and transcription factors, intracellular transport proteins, and splicing factors.[39–41] The advent of exome and whole-genome sequencing, and their use in clinical practice, will greatly improve the efficiency of molecular diagnosis and will allow the causative mutation to be identified in most patients with RP.

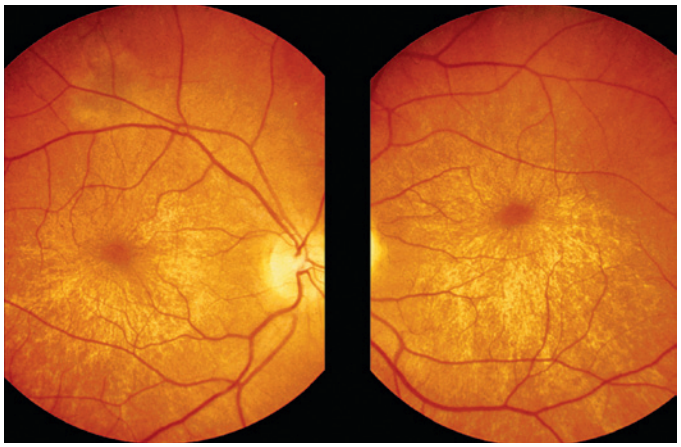


Fig. 46.17 X-linked retinitis pigmentosa carrier female showing the "tapetal reflex."



Fig. 46.18 Rubella retinopathy showing retinal pigment mottling. Retinal function is usually good and the electroretinogram (ERG) normal, whereas most retinal dystrophies with deafness have severely abnormal ERGs.

Table 46.2 Differential diagnoses of retinitis pigmentosa

Pigmentary retinopathy	Night blindness
Blunt trauma	**Genetic disorders**
Retained intraocular foreign body	Congenital stationary night blindness
Congenital infection	Oguchi disease
Rubella	Fundus albipunctatus
Varicella	Choroideraemia
Herpes simplex	Gyrate atrophy
Syphilis	Progressive cone–rod dystrophy
Acquired infection	Enhanced S-cone syndrome
Measles	**Acquired**
Onchocerciasis	Vitamin A deficiency
Metabolic	Desferrioxamine toxicity
Cystinosis	
Oxalosis	
Drugs	
Phenothiazines	
Chloroquine	
Desferrioxamine	
Resolved retinal detachment	
Ophthalmic artery occlusion	
Other retinal dystrophies	
Cone–rod dystrophy	
Inherited vitreoretinal dystrophies	
Enhanced S-cone syndrome	
Unknown etiology	
Pigmented paravenous chorioretinal atrophy	

Molecular genetics

Autosomal dominant retinitis pigmentosa There is considerable genetic heterogeneity within AD RP. Mutations in more than 25 genes have been identified, accounting for approximately 60–70% of patients with AD RP; mutations in the rhodopsin gene (*RHO*) are the most common. Sequence variants in *RP1* and *PRPF31* are the next most common causes of AD RP.

Mutations of the rhodopsin gene account for about 25% of patients with AD RP; more than 100 different mutations have been identified. There is considerable variation in the ocular phenotype seen with the different mutations, which has also been reported in dominant forms of CSNB and AR RP. The phenotypic variability is even more marked with mutations of the gene *PRPH2* (formerly *RDS/peripherin*), where the clinical picture may resemble RP, cone–rod dystrophy, cone dystrophy, a fleck retina syndrome, or macular dystrophy (see Chapters 48 and 50). *PRPH2* mutations account for about 5–10% of cases of AD RP.[39–41]

In an unusual form of RP showing digenic inheritance, mutations of both the *PRPH2* and *ROM1* (rod outer segment protein 1) genes are present within the same family. Individuals with a mutation of one gene but not the other are clinically unaffected. Affected individuals are double heterozygotes with mutations of both *ROM1* and *PRPH2*. Peripherin is located in rod and cone outer segment discs, whereas ROM1 is only found in rods. Interaction of the two proteins is important for the maintenance of structure in the rod outer segment; some mutations in the *PRPH2* gene may be insufficient to cause significant photoreceptor disease unless accompanied by a defective ROM1 protein.

Splice factors have increasingly been identified as being associated with AD RP, including mutations in *PRPF31*, *PRPF3*, *PRPF6*, and *PRPF8*.[39,40] An insufficiency in splicing function may be disease-causing only under conditions of elevated splicing demand. With the need to replenish disc proteins daily, such conditions exist in rod photoreceptors, which may explain the paradox of isolated retinal disease caused by ubiquitously expressed splice-factor genes.

See references 39, 40, and 41 for AD RP phenotype–genotype correlations.

Autosomal recessive retinitis pigmentosa Mutations in more than 35 genes have been identified to date in AR RP, accounting for approximately 50% of patients with AR RP, the most common being *USH2A* (10–15% of AR RP), with more severe

mutations causing Usher syndrome type 2 (see Chapters 47 and 99).[39–41]

Mutations in genes encoding many components of the rod phototransduction cascade have been identified[39–41] including:

1. the rhodopsin gene;
2. the genes coding for the α-subunit and the β-subunit of the rod cGMP-phosphodiesterase;
3. the genes for the α- and β-subunits of rod cGMP-gated cation channels;
4. S-antigen gene (arrestin);
5. genes coding for components of the visual cycle involved in recycling vitamin A which have been implicated in AR RP, including *RPE65*, *ABCA4*, *LRAT*, and *RLBP1*.

X-linked retinitis pigmentosa Mutations in three genes have been identified in X-linked RP, *RPGR* (RP3), *RP2* (RP2), and *OFD1* (RP23). Sequence variants in *RPGR* cause approximately 75% of all XL RP.[39–41] Two other loci have been reported: Xp21.3–p21.2 (RP6) and Xq26–27 (RP24).

RPGR mutations are usually associated with typical rod–cone degeneration, but in a few patients, retinal dystrophy, deafness, and abnormalities in respiratory cilia have been noted.[42] The majority of mutations may result in premature termination of translation. Exon ORF15 is a "hot spot" for mutations, responsible for 80% of cases of XL RP.[43] RPGR may act as a regulator of a specific type of membrane transport or trafficking that is particularly active in the retina or RPE.

Mutations in *RP2* account for up to 15% of XL RP.[39–41] RP2 is a protein of uncertain function, which is targeted to the plasma membrane by dual *N*-terminal acyl-modification. Dual-acylated proteins are targeted to lipid rafts, suggesting a potential role for the protein in signal transduction.

Management of retinitis pigmentosa

Most forms of RP are not amenable to specific treatment, but the deterioration may be slowed by dietary modification in some rare disorders where the biochemical basis of the disorder is better elucidated (see Chapters 47 and 65).

There was a small effect on the rate of decline of the cone flicker ERG in one randomized controlled trial of vitamin A supplementation in RP; the effect was, however, marginal and no beneficial effect was found on visual acuity or visual field loss.[44] This form of treatment has not gained widespread acceptance.

Despite the lack of effective treatment for RP, the ophthalmologist has an important role to play in the management of both the child and the family. Once the diagnosis is established, it is important that the parents and the child (if old enough) are given a full and sympathetic explanation; they can be reassured that most children complete their education at a normal school as central vision is preserved until later.

Parents are often concerned that other children may be at risk of developing the disease; they should be offered genetic counseling and it may be appropriate to examine other family members. It is also helpful to have available the contact details of patient self-help groups such as their national RP association.

Practical help can also be given when there are visual difficulties. Many patients with RP have poor vision in bright sunlight and have problems in adapting from bright to dim illumination; tinted lenses may be helpful. Significant refractive errors should be corrected. A trial of oral acetazolamide, topical dorzolamide, orbital floor or intravitreal steroids, or intravitreal anti-VEGF agents should be considered if there is macular edema. Low vision aids may be helpful in established edema or macular atrophy. Visual loss may also develop secondary to posterior subcapsular cataract and, although cataract surgery is often successfully performed in adults with RP, it is rarely necessary in childhood.

Research is being conducted to investigate multiple treatment avenues for retinal dystrophies including gene therapy, stem cell therapy, neuroprotective agents, and artificial vision – with clinical trials ongoing or planned in all of these areas. Some of the research is aimed at treating specific genetic mutations, whereas other research efforts are studying potential therapies that can be used in a broader range or potentially all RP types. It is possible that these novel therapies may be more valuable in combination, for example, by combining gene therapy or stem cell therapy with neuroprotective growth factors. These interventions may be applied sequentially, for example, pharmacological approaches may be beneficial early in the disease and stem cell therapies at later stages. Further detailed information on these research avenues can be obtained from the websites of Retinitis Pigmentosa Fighting Blindness (http://www.rpfightingblindness.org.uk/index.php?tln=research) or the Foundation Fighting Blindness (http://www.blindness.org/news-and-research).

Prognosis

The prognosis in RP varies according to the type of disease and the causative mutation. Ideally, prognosis should be inferred by the identification of the specific genetic mutation. Advice on prognosis can also be aided by deep phenotyping and a full family history to establish the mode of inheritance. However intrafamilial variability of disease expression commonly occurs: the visual outcome of older affected family members is not necessarily a good guide to the likely prognosis in younger children.

Affected males with XL RP are night blind in early childhood, usually show extensive field loss by their teens, and central visual loss in their twenties. By the fourth decade, most have visual acuity reduced to less than count fingers. AR RP is such a heterogeneous condition that accurate prognosis is difficult. The disease is often of early onset and severe. Most patients have a severely constricted visual field by their teens and may have marked central visual loss by their late twenties. Some with recessive disease follow a more benign course.

The prognosis is better in AD RP. Although night blindness and field loss may develop in childhood, central vision may remain normal throughout life. Many patients maintain reasonable visual acuity until the fifth or sixth decade, although they may have extremely constricted visual fields. There is, however, wide variation even in RP caused by mutations at the same locus.[39–41] Severe, early onset forms are unusual.

True sector RP has the best prognosis of any form of the disease. Although there may be marked altitudinal upper visual field loss, severe involvement of the macula is uncommon.

Pigmented paravenous chorioretinal atrophy (PPCRA)

This is a rare chorioretinal atrophy in which there is paravenous RPE atrophy and pigment clumping (Fig. 46.19). It is more common in males, most cases are sporadic, and it is usually diagnosed on routine examination in asymptomatic



Fig. 46.19 Pigmented paravenous atrophy. The veins are surrounded by a band of retinal pigment atrophy and clumping.

patients. The ERG shows a spectrum of abnormalities and, in contrast to most retinal dystrophies, often shows marked interocular asymmetry. This asymmetry is also often seen on fundoscopy, autofluorescence imaging, and visual field testing. Retinal function may be relatively stable, or may show slow deterioration.

It is uncertain whether this disorder may have a genetic basis, with only one report of a heterozygous *CRB1* mutation of uncertain significance identified in a family with dominantly inherited PPCRA with variable expressivity.[45] In one report, the monozygotic twin of an affected adult was unaffected, suggesting that at least some cases are non-genetic.[46]

Acquired rod–cone dysfunction

Vitamin A deficiency

Worldwide, vitamin A deficiency remains an important cause of blindness in childhood. In developing countries it is usually caused by a combination of malnutrition and malabsorption associated with frequent gastrointestinal infection. In developed countries, vitamin A deficiency is rare and usually seen in association with liver disease or malabsorption; rarely an unusual diet may be the cause.

Vitamin A is an essential component of rhodopsin and cone opsins; night blindness is an early symptom of deficiency. In early deficiency, there is slowing of rod dark adaptation and, later, rod and cone thresholds are elevated. Peripheral fields may be constricted and in some patients white dots at the level of the RPE are seen throughout the periphery. Rod ERGs are undetectable with cone responses usually being well preserved. Bright flash dark-adapted ERGs (DA 10.0) may show a pseudo-negative ERG, with the b-wave amplitude lower than that of the a-wave, reflecting origins in dark-adapted cones (as seen in the patient with fundus albipunctatus in Fig. 46.4).

The ocular abnormalities are reversible with vitamin A supplementation if this is started before the disease is too advanced.[47] The recovery of retinal function is extremely rapid and accurate early diagnosis is important, since vitamin A deficiency is a treatable cause of night blindness.

Vitamin A and vitamin E supplementation may be curative in abetalipoproteinemia (Bassen–Kornzweig disease), a malabsorption diarrhea syndrome of infancy (see Chapter 65).

Desferrioxamine toxicity

Desferrioxamine is a chelating agent used in the treatment of iron storage disorders such as transfusion siderosis. Ocular side effects include cataract, optic neuropathy, and retinal degeneration.[48] Patients with retinal toxicity develop night blindness, peripheral field loss, and a peripheral pigmentary retinopathy; dark adaptation is abnormal and both rod and cone ERGs can show abnormalities.[48] Some improvement occurs on stopping the drug. Histologically, the RPE is predominantly affected.

Isotretinoin toxicity

Isotretinoin (13-*cis*-retinoic acid) is a treatment for acne vulgaris, which has several potential severe adverse effects including liver toxicity and dysregulation of lipid metabolism, necessitating regular blood testing whilst on therapy. Ocular side effects include photophobia, meibomian gland dysfunction, blepharoconjunctivitis, corneal opacities, keratitis, and reversible decreased night vision.[49]

Inherited chorioretinal dystrophies

Choroideremia

Clinical and histopathologic findings

Choroideremia is an X-linked recessive disorder characterized by progressive atrophy of the RPE and choriocapillaris. Affected males usually present in early childhood with night blindness and progressive field loss, but central vision is usually preserved until late in the disease. A longitudinal study reported a slow rate of visual acuity loss and good retention of central vision until the seventh decade.[50] There is a wide variation in clinical expression.[51] Female carriers, usually asymptomatic, have a widespread fine peripheral RPE atrophy and granular pigment deposition (Figs 46.20 and 46.21). Cases with deafness, hypopituitarism, and developmental delay probably represent a contiguous gene defect.

Affected males usually present between the ages of 5 and 10 years with night blindness and mild myopia. The earliest fundus signs are fine pigment epithelial atrophy and pigmentation in the peripheral retina; the clinical appearance may then be confused with RP. Focal areas of atrophy of the RPE and choriocapillaris, well demonstrated on fluorescein angiography or autofluorescence imaging (Figs 46.22 and 46.23), develop as the disease progresses. These coalesce to give a widespread atrophic appearance throughout the equatorial retina, spreading to involve the peripheral and more posterior retina; the macula is spared until late in the disease.

Visual fields initially show small mid-peripheral scotomata corresponding to areas of atrophy. Marked constriction of the visual field develops with disease progression, often with a preserved island of field in the far periphery.

Histologic examination of eyes with early disease[52] showed marked degeneration of the outer retina with loss of RPE, Bruch's membrane, and choriocapillaris. Biochemical studies showed reduced levels of interphotoreceptor retinal binding protein (IRBP) and increased levels of cAMP in the RPE and choroid.

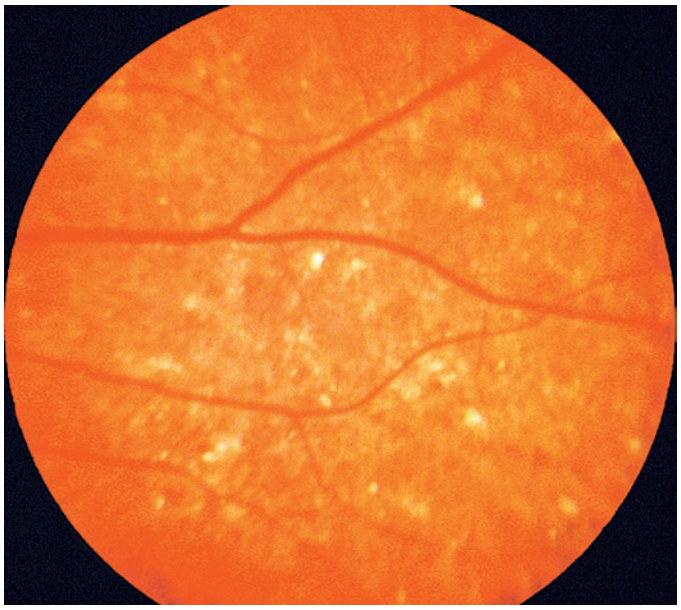


Fig. 46.20 Choroideremia carrier. Granular pigmented and depigmented areas in the peripheral retina.



Fig. 46.21 Choroideremia carrier. Peripheral retinal pigmentation.

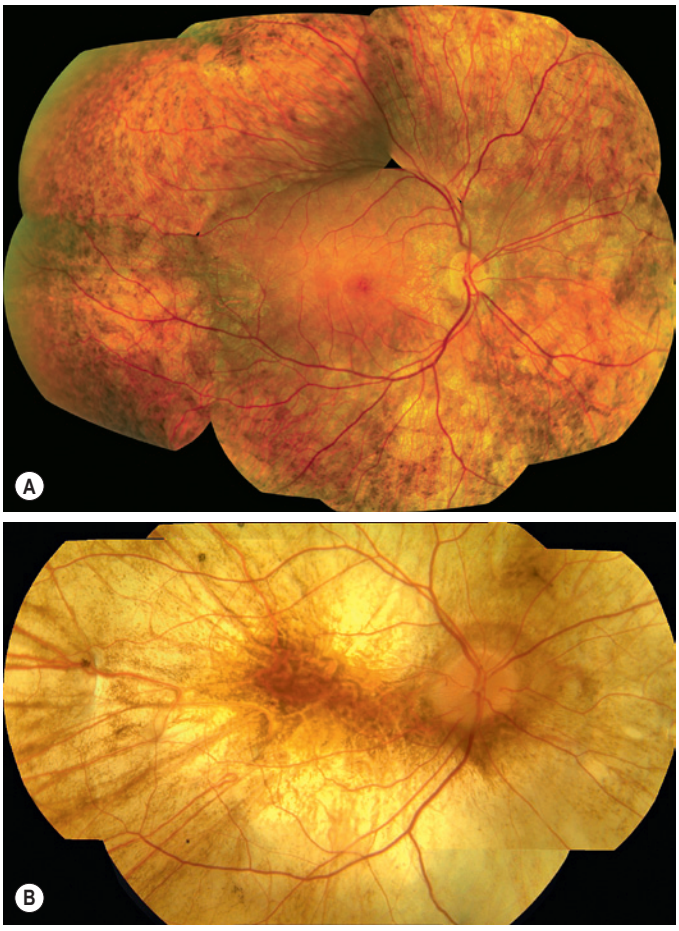


Fig. 46.22 Choroideremia. Chorioretinal changes with scalloped edges: (A) early disease; (B) advanced.

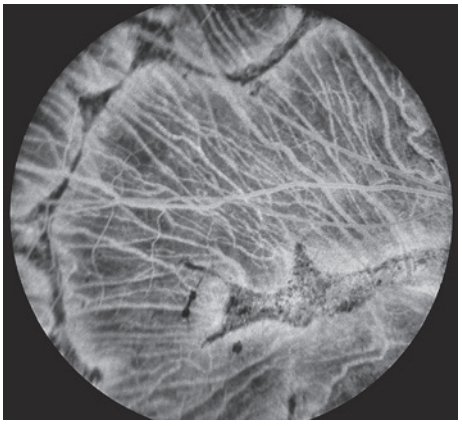


Fig. 46.23 Choroideremia. Fluorescein angiogram showing characteristic scalloped appearance given by the surviving retinal pigment epithelium and loss of the choriocapillaries.

Electrophysiology

The ERG is markedly abnormal at an early stage and may be undetectable. Rod and cone amplitudes are reduced in those with ERG preservation. Peak-time changes are less prominent, but may be present later in the disease process.

Female heterozygotes

Most female carriers are asymptomatic but the fundus appearance is characteristic (see Figs 46.20 and 46.21). The EOG and ERG are usually normal. Some elderly heterozygotes may develop nyctalopia and show more extensive RPE atrophy with an abnormal ERG and elevated rod thresholds on psychophysical testing. Molecular genetic diagnosis is now possible.

Molecular genetics and pathogenesis

The choroideremia gene (*CHM*) has been mapped to Xq21, with many mutations in *CHM* identified. An intronic mutation remote from the exon–intron junctions has been reported in *CHM*, creating a strong acceptor splice site and leading to the inclusion of a cryptic exon into the *CHM* mRNA. Intronic sequence is often not screened in inherited retinal dystrophy mutation investigations, which suggests that a significant proportion of disease-causing variants are being missed.

CHM is widely expressed and the product of this gene, Rab escort protein (REP)-1, is involved in the post-translational

lipid modification and subsequent membrane targeting of Rab proteins, small GTPases that play a key role in intracellular trafficking. It is thought that REP-2 compensates for the loss of REP-1 function elsewhere in the body but is insufficient to compensate in the retina.

Gene replacement therapy is a potential treatment for choroideremia and Edwards et al have recently reported encouraging results of gene replacement therapy, using an AAV vector in patients with choroideremia.[53] Longer term follow up in larger numbers of subjects will however be needed before the effectiveness of treatment can be confirmed.

Gyrate atrophy of the choroid and retina

Clinical and histopathologic findings

Gyrate atrophy of the choroid and retina is a rare autosomal recessive disorder with progressive chorioretinal loss, hyperornithinemia, and a deficiency of the mitochondrial enzyme ornithine aminotransferase (OAT). The level of OAT activity in obligate carriers of the gene is about 50% of normal.

Children may present with night blindness, progressive myopia, or field loss, but the diagnosis of gyrate atrophy may be made in early infancy when a raised level of plasma ornithine is found in a child with a family history. The earliest fundus changes are small discrete areas of choroidal and RPE atrophy in the mid- and far-peripheral fundus. The adjacent fundus may show diffuse depigmentation of the RPE and atrophic areas. The atrophic areas coalesce and enlarge toward the posterior pole with a characteristic scalloped leading edge.

Most patients have moderate-to-high myopia and posterior subcapsular cataracts develop in early-adult life. Some develop visual loss secondary to macular edema or atrophy. Most patients maintain a reasonable level of visual acuity until their forties or fifties, although with a constricted field. There are early small mid-peripheral scotomata, but progression leads to marked peripheral constriction.

Light and electron microscopy (EM) from a patient with a pyridoxine-sensitive form of gyrate atrophy showed focal areas of photoreceptor and RPE atrophy at the posterior pole; in the mid-periphery, there were areas of abrupt transition from near-normal to atrophic areas of retina.[54] EM showed abnormal mitochondria in the cornea, ciliary epithelium, ciliary muscle, and in the photoreceptors. Similar mitochondrial abnormalities in other tissues of patients with gyrate atrophy are likely to be a secondary effect of the biochemical disturbance.

Electrophysiology and psychophysics

The ERG relates to the severity of disease: early in the course of the disorder, rod and cone amplitudes are reduced; later, the ERG becomes undetectable. EOG reduction parallels the reduction in the rod ERG. Dark adaptation shows markedly elevated rod thresholds in areas of field corresponding to involved retina.

Non-ocular features

Although patients with gyrate atrophy show no muscle weakness, muscle biopsy shows atrophy of type 2 fibers with accumulation of tubular aggregates. Other reported abnormalities include structural abnormalities of the hair, electroencephalographic abnormalities, mild developmental delay, peripheral neuropathy, and mitochondrial abnormalities in a variety of tissues.

Molecular genetics and pathogenesis

A large number of mutations in the *OAT* gene have been identified in patients with gyrate atrophy including some in which the OAT is pyridoxine-responsive. Expression studies have demonstrated reduced mutant OAT activity.

Chronic reduction of ornithine may prevent the retinal degeneration of gyrate atrophy; using an arginine-restricted diet in a mouse model of OAT deficiency ($oat^{-/-}$),[55] plasma ornithine levels were substantially reduced and completely prevented retinal degeneration in $oat^{-/-}$, suggesting that ornithine accumulation is important in the pathophysiology of the retinal degeneration and that restoration of OAT activity in the retina may not be required for effective treatment.

Biochemical findings and treatment

Patients with gyrate atrophy have a deficiency of the pyridoxal phosphate-dependent mitochondrial enzyme OAT, which is responsible for the conversion of ornithine to glutamic acid. The major dietary source of ornithine is arginine, which may be converted to ornithine by the arginase reaction of the urea cycle or by the glycine transamidase reaction. Ornithine, an intermediary in the urea cycle, is necessary for the production of polyamines and in the synthesis of proline and glutamate.

It is not clear whether high levels of ornithine or the reduced levels of proline and glutamate that accompany OAT deficiency cause the retinal abnormalities. Not all patients with raised ornithine levels develop gyrate atrophy and one patient with gyrate atrophy has been reported who had normal ornithine levels and low plasma proline levels, suggesting that reduced availability of proline may be a contributory factor.[56]

Three different approaches to treatment have been used:

1. A few patients are responsive to pyridoxine (B_6) supplements and show reduced plasma ornithine levels and improvement in the ERG. Vitamin B_6 should be used initially in all patients and continued in those who show a positive response.
2. In non-responders, adhering to an arginine-restricted diet may reduce plasma ornithine levels.
3. Proline supplementation may slow the progress of retinal degeneration in some patients.[56,57]

Children with gyrate atrophy need to be managed in collaboration with a metabolic physician. Although present treatment regimens are promising, more long-term studies are needed to assess whether such treatments prevent retinal deterioration.

Cone and cone–rod dystrophies

The inherited cone dystrophies are a heterogeneous group of progressive disorders characterized by photophobia, reduced central vision, abnormal color vision, and abnormal cone ERGs.[58] Autosomal recessive, autosomal dominant, and X-linked recessive inheritance has been reported and there is heterogeneity even amongst these subtypes.[58]

The functional deficit is confined to the cone system in some forms of cone dystrophy, but in many there is later evidence of rod dysfunction (cone–rod dystrophy). The distinction between cone and cone–rod dystrophies may be difficult, particularly during childhood, and is dependent upon good electrophysiology. Most forms of cone and cone–rod dystrophy are seen in otherwise normal individuals; those associated with systemic abnormalities are discussed in Chapter 47.

Progressive cone dystrophy

Clinical findings

In contrast to the stationary cone disorders, which present in early infancy, the progressive cone dystrophies are not usually symptomatic until later childhood or early-adult life.[58] The age of onset of visual loss and the rate of progression show wide variability but eventually visual acuity usually deteriorates to the level of 6/60 or to count fingers only. Photophobia is a prominent early symptom, with progressive loss of visual acuity and color vision. Since all three classes of cone photoreceptor can be affected, the color vision defects are along all three color axes, often progressing to complete loss of color vision. Some cases have a predominant early involvement of L-cones leading to a protan color vision phenotype.[59,60] AD cone dystrophy pedigrees with early tritan color vision defects have also been reported.[61,62] Nystagmus may be present. A small central scotoma is frequently detected on visual field testing; peripheral fields may be normal in the early stages but constrict later.

Fundus examination may show a typical "bull's eye" maculopathy (Figs 46.24 and 46.25, and Box 46.1). In some cases, there may only be minor macular RPE atrophy. The optic discs show variable temporal pallor. The retinal periphery is usually normal although, rarely, white flecks may be seen. Fluorescein angiography shows typical "window" defects at the macula in the majority of cases and the so-called dark choroid sign (see Chapter 48) may be seen.

Electrophysiology and psychophysics

Electroretinography shows normal rod responses but substantially abnormal cone responses (Fig. 46.26). The 30 Hz flicker ERG is usually of increased peak-time but, rarely, such as in the cone dystrophy related to *GUCA1A* mutation,[58] the peak-time is normal and amplitude reduction is the only abnormality. A small subgroup of patients with cone dystrophy may show supernormal rod responses or rod responses within the normal range but with distinctive and specific abnormal characteristics[58] (see below).

Dark adaptation studies show either a monophasic curve with no recognizable cone component, or a biphasic curve with elevated cone thresholds; rod-mediated thresholds are normal. Spectral sensitivity studies show variable abnormalities of the photopic responses. In some families, there is generalized depression of sensitivity across all wavelengths tested, whereas others show more specific functional deficits in the early stages of the disease. A typical rod sensitivity curve may be seen under both scotopic and photopic conditions in advanced disease.

Obligate carriers of X-linked cone dystrophy may show evidence of cone dysfunction on electrophysiologic or psychophysical testing.



Fig. 46.24 Progressive cone dystrophy with bull's eye maculopathy.

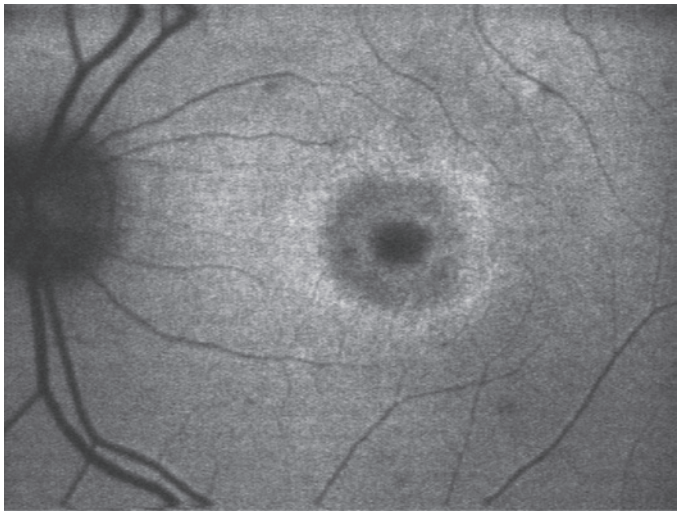


Fig. 46.25 Progressive cone dystrophy. Autofluorescence (AF) images of bull's eye maculopathy.

Box 46.1

Bull's eye maculopathy in childhood

Stargardt disease
Progressive cone dystrophy
Cone–rod dystrophy
Batten disease
Hallervorden–Spatz disease
Bardet–Biedl syndrome
Mucolipidosis IV
Fucosidosis
Drug toxicity (e.g. chloroquine)
Benign concentric macular dystrophy
Fenestrated sheen dystrophy

Cone dystrophy with supernormal rod ERG (KCNV2 retinopathy)

Clinical findings

An unusual AR disorder has been described with abnormal photopic responses associated with supernormal and delayed rod ERG b-waves.[58] Patients have generalized loss of cone vision, clinical evidence of progression, and often have nyctalopia.[63] The ERG findings are diagnostic. Cone ERGs are reduced and delayed, typical of a cone dystrophy. However, with a bright flash under dark adaptation the dark-adapted b-wave is of high amplitude (and may be supernormal), but at low stimulus strengths the rod b-wave is subnormal and profoundly delayed.[63] Some cases have supernormal rod ERGs without nyctalopia, suggestive of reasonable rod function despite an abnormal scotopic ERG.[64]

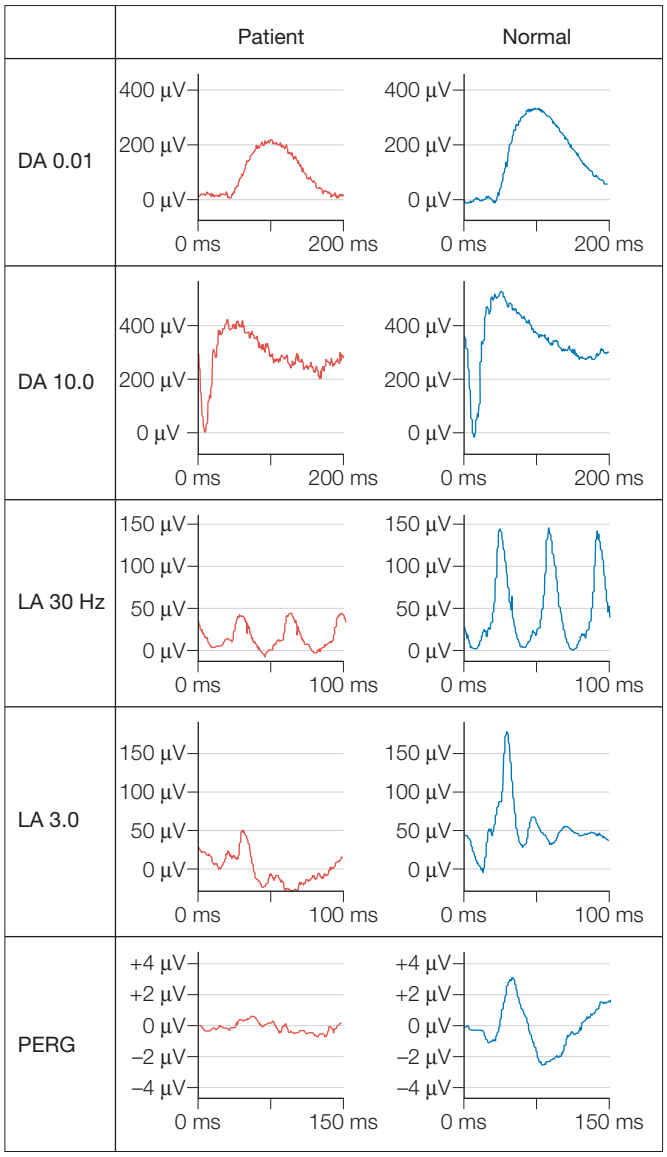


Fig. 46.26 The rod-specific (DA 0.01) and bright flash dark-adapted electroretinograms (ERGs) (DA 10.0) fall within the normal range. The 30 Hz flicker ERG (LA 30 Hz) is both delayed and reduced, typically present in most cone dystrophies. The photopic single flash ERG (LA 3.0) is markedly subnormal with particular reduction in the b-wave. The pattern ERG is profoundly subnormal in keeping with marked macular involvement.

Several clinical features may suggest the diagnosis.[58] Onset of symptoms of reduced central vision and photophobia is in the first and second decades of life. Patients are usually myopic and often have severely reduced red–green color discrimination with relative preservation of tritan color vision. Onset of nyctalopia and presence of nystagmus is variable.

There is often RPE disturbance at the macula with a normal retinal periphery. Autofluorescence (AF) imaging reveals a perifoveal ring of increased AF; in older subjects, an area of increased AF may be seen centrally. By the fifth decade, there is usually marked central atrophy.

Electrophysiology

The PERG is often absent, indicative of marked macular dysfunction. Rod ERG amplitudes are subnormal at the lowest flash energies, but a characteristic abnormality seen in all published cases is a profound and rapid increase in the amplitude of a delayed b-wave despite only a relatively small increase in stimulus intensity. At higher flash strengths under dark adaptation, the b-wave may exceed the upper limit of normal (supernormal). The initial phase of the bright flash dark-adapted ERG a-wave to a flash strength greater than the routine ISCEV standard flash is well formed, suggesting that the kinetics of phototransduction are within normal limits. The shape of the ERG is then characteristic. The normally commencing a-wave then plateaus, shows a small dip, and is then followed by a very sharply rising b-wave, which may be supernormal in some patients. Cone ERGs are reduced and delayed, typical of a cone dystrophy. Some cases have supernormal rod ERGs without nyctalopia, suggestive of reasonable rod function despite an abnormal scotopic ERG.

Molecular genetics and pathogenesis

Recessive mutations have been identified in *KCNV2*, encoding a voltage-gated potassium channel subunit.[65] *In situ* hybridization has demonstrated KCNV2 expression in human rod and cone photoreceptors.[65] *KCNV2* mutations might perturb or abrogate the potassium current within vertebrate photoreceptor inner segments shown previously to set their resting potential and voltage response.[65]

Progressive cone–rod dystrophy

Clinical findings

In this disorder, affected patients develop the typical findings of a cone dystrophy in early life but later develop rod involvement with night blindness. Most present in the first two decades of life, with the retinal dystrophy either being isolated or associated with systemic abnormalities. AD, AR, or XL inheritance has been reported.

Fundus examination shows macular atrophy in the early stages of the disease, with peripheral RPE atrophy, retinal pigmentation, arteriolar attenuation, and optic disc pallor in the late stages (Figs 46.27 and 46.28). A bull's eye maculopathy may also be seen.

Electrophysiology and psychophysics

Both rod and cone thresholds are elevated on psychophysical testing. Generalized abnormalities of rod and cone ERGs are present, with the cone ERGs being more abnormal than the rod ERGs. The 30 Hz cone flicker ERG peak-time is usually delayed. The bright flash dark-adapted ERG (DA 10.0) a-wave is subnormal, in keeping with rod photoreceptor involvement.

Molecular genetics of cone and cone–rod dystrophies

Most cases of progressive cone and cone–rod dystrophy are sporadic, with the majority of these probably representing AR inheritance, but some may represent new AD mutations, and, in severely affected males, X-linked disease.

Several loci and causative genes have been identified in the progressive cone dystrophies.[58] Mutations in *ABCA4*, *CNGA3*, *CNGB3*, and *PDE6C* have been identified in AR cone dystrophies, *GUCA1A* mutations have been reported in AD pedigrees, and *RPGR* and *OPN1LW*/*OPN1MW* sequence variants in XL disease.[22,58]

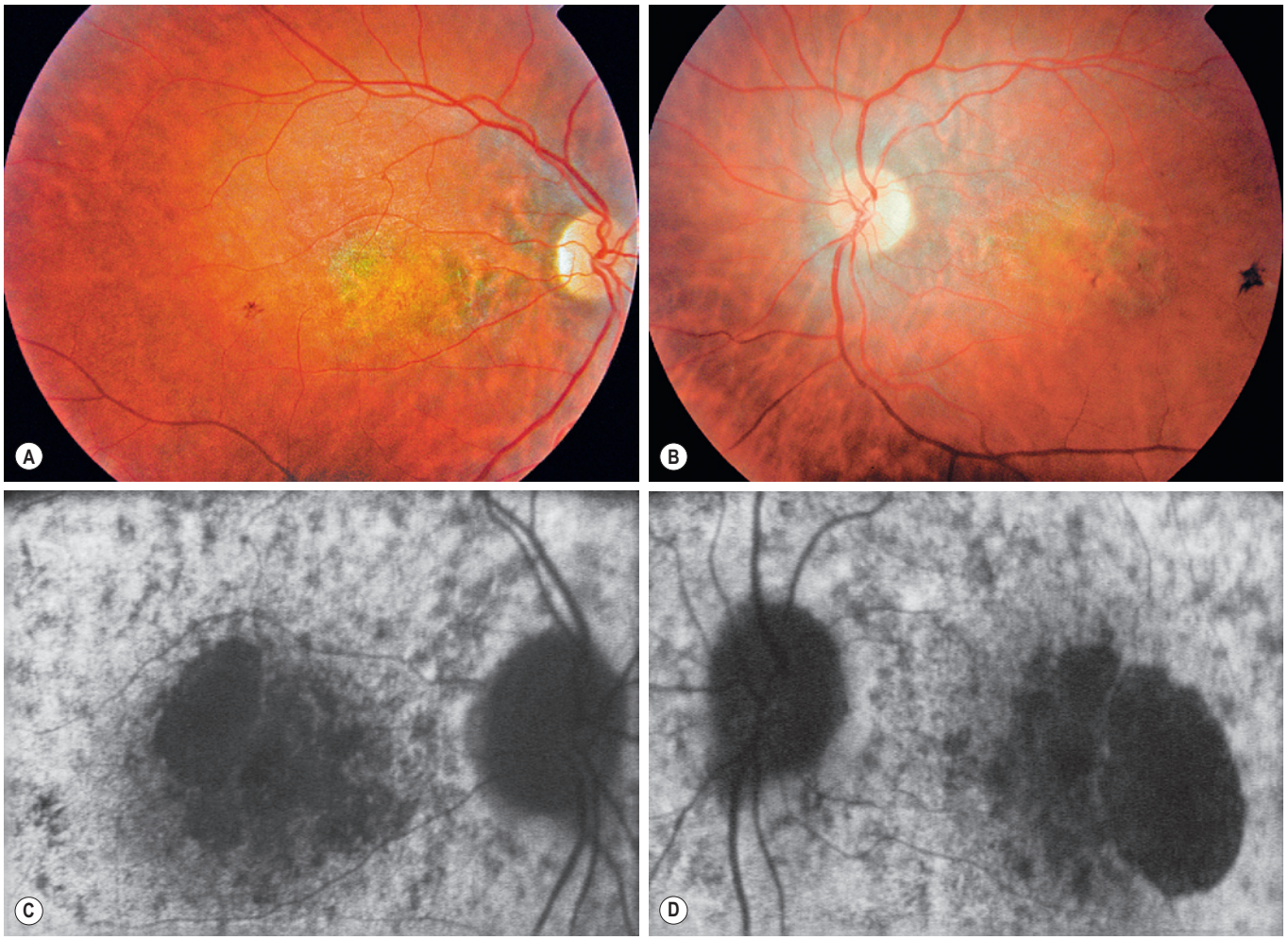


Fig. 46.27 Cone–rod dystrophy. (A,B) Bilateral macular atrophy. (C,D) Autofluorescence (AF) images showing decreased AF at the maculae corresponding to the atrophy seen ophthalmoscopically with an abnormal mottled appearance of the surrounding retina, with areas of relative increased and decreased AF.

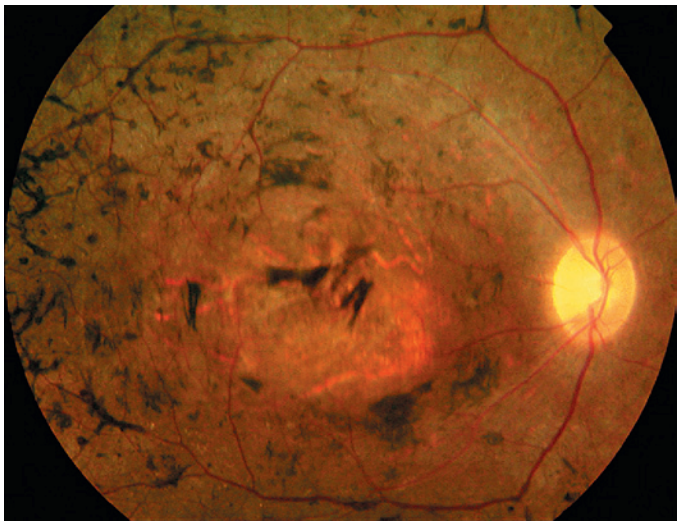


Fig. 46.28 Cone–rod dystrophy. End-stage disease with marked macular atrophy, retinal pigmentation, and arteriolar narrowing.

More than 10 genes have been associated with AD cone–rod dystrophy,[58] including *CRX*, *GUCY2D*, *RIMS1*, *PRPH2*, *GUCA1A*, *PROM1*, and *AIPL1*. Twelve genes have been associated with AR disease,[58] including *ABCA4*, *CNGA3*, *CNGB3*, *ADAM9*, *PCDH21*, and *RPGRIP1*. Mutations in *ABCA4* have been shown to be the commonest cause of AR cone–rod dystrophy.[58] Mutations in *RPGR*, the gene encoding the protein that interacts with RPGRIP1, have been associated with XL childhood-onset retinal dystrophy families.[58]

Goldmann–Favre syndrome and enhanced S-cone syndrome

Clinical findings and electrophysiology

Goldmann–Favre is a rare AR disorder characterized by gradual visual loss or night blindness with liquefaction of the vitreous, macular retinoschisis, and peripheral RPE atrophy and pigmentation. Peripheral retinoschisis and cataract may also occur. The retinal dystrophy is progressive, resulting in extensive visual field loss and variable central visual loss. Fluorescein angiography may show evidence of peripheral capillary closure and vascular leakage. ERG is markedly abnormal or undetectable. Studies of patients with the Goldmann–Favre

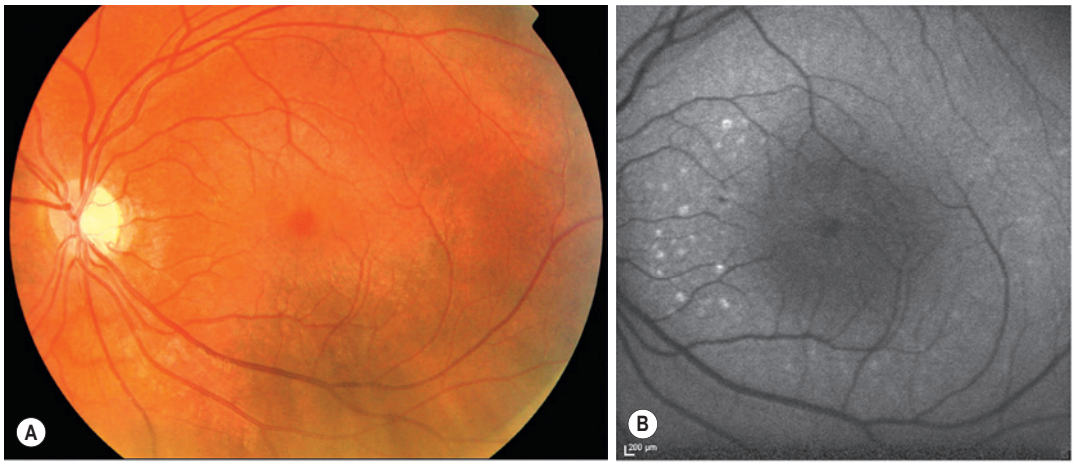


Fig. 46.29 Enhanced S-cone syndrome. (A) White dots are seen at the level of the retinal pigment epithelium in early disease, which are more readily seen on autofluorescence imaging (B).

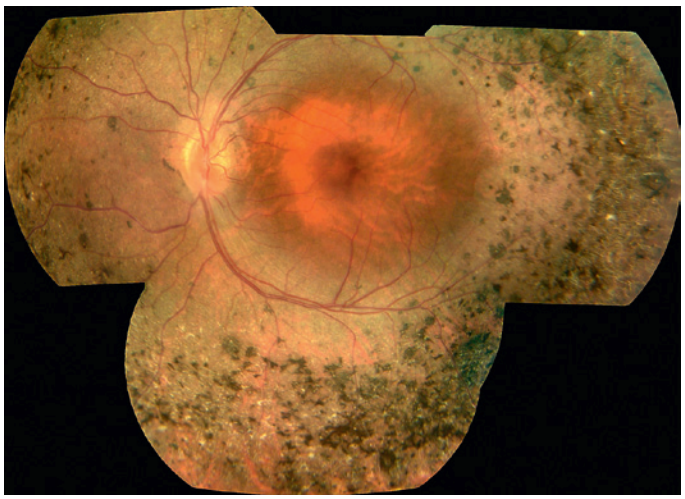


Fig. 46.30 Enhanced S-cone syndrome. Typical pigment clumps (including nummular pigmentation) seen at the posterior pole and macular atrophy (advanced disease).

syndrome using spectral ERG have demonstrated that S-cones are less affected than the mid-spectral cones.

There is overlap between Goldmann–Favre syndrome and enhanced S-cone syndrome (ESCS) where there are no rods but increased numbers of cones, mostly short wavelength sensitive. Patients usually present with nyctalopia and are found to have foveal schisis/cysts. Since mutations have been identified in *NR2E3* in both disorders, Goldmann–Favre syndrome may represent severe ESCS. Although the macular appearance may be similar, the vitreous changes, peripheral retinopathy, ERG abnormalities, and mode of inheritance help differentiate this condition from X-linked retinoschisis and inherited forms of isolated foveal schisis (see Chapter 51).

The characteristic pigmentary deposition in ESCS is at the level of the RPE rather than intraretinal, has a nummular appearance, and tends to be around the arcades (see Figs 46.29 and 46.30). Despite this typical appearance, patients are often diagnosed with RP due to the night blindness and pigmentary changes. The ERG in ESCS is diagnostic (Fig. 46.31). The rod-specific ERG to a dim flash under dark adaptation (DA 0.01) is undetectable. The responses to the same flash strength under photopic (LA 3.0) and scotopic conditions (DA 3.0) are of similar waveform, being simplified and very delayed. The flicker ERG is markedly delayed and, in addition, the amplitude of the 30 Hz flicker ERG, which in a normal subject falls between that of the LA 3.0 response a- and b-waves, is usually of lower amplitude than the photopic a-wave. PERGs, when detectable, can show profound delay.

Molecular genetics and pathogenesis

Mutations in *NR2E3* (encoding a transcription factor and thus believed to play a role in determining cone cell fate) have been identified both in ESCS and Goldmann–Favre syndrome.[66] There is evidence in ESCS of a greater than normal number of S-cones, with mutation in *NR2E3* thought to cause disordered cell differentiation, possibly by encouraging default to the S-cone pathway and thereby altering the relative ratio of cone subtypes. A small number of cones co-express L-/M- and S-opsins.[66] There are no rods.

Management

There is currently no specific treatment for the vast majority of these inherited retinal disorders. Nevertheless, it is important that the correct diagnosis is established early to enable accurate prognostic information and informed genetic counseling. A molecular diagnosis facilitates this process.

The provision of appropriate spectacle correction, low vision aids, and educational support is also important. Photophobia may be a prominent symptom, especially in the cone dysfunction syndromes, and tinted spectacles or contact lenses may be beneficial both to improved comfort and to vision. Macular edema or foveal schisis may be amenable to treatment with topical or oral carbonic anhydrase inhibitors.

Conclusions

Inherited retinal disorders are a common cause of childhood blindness and most are not currently amenable to specific forms of treatment. Advances in molecular biology have led to the identification of many causative genetic mutations and it is likely, given the advances in genetic analysis, that the

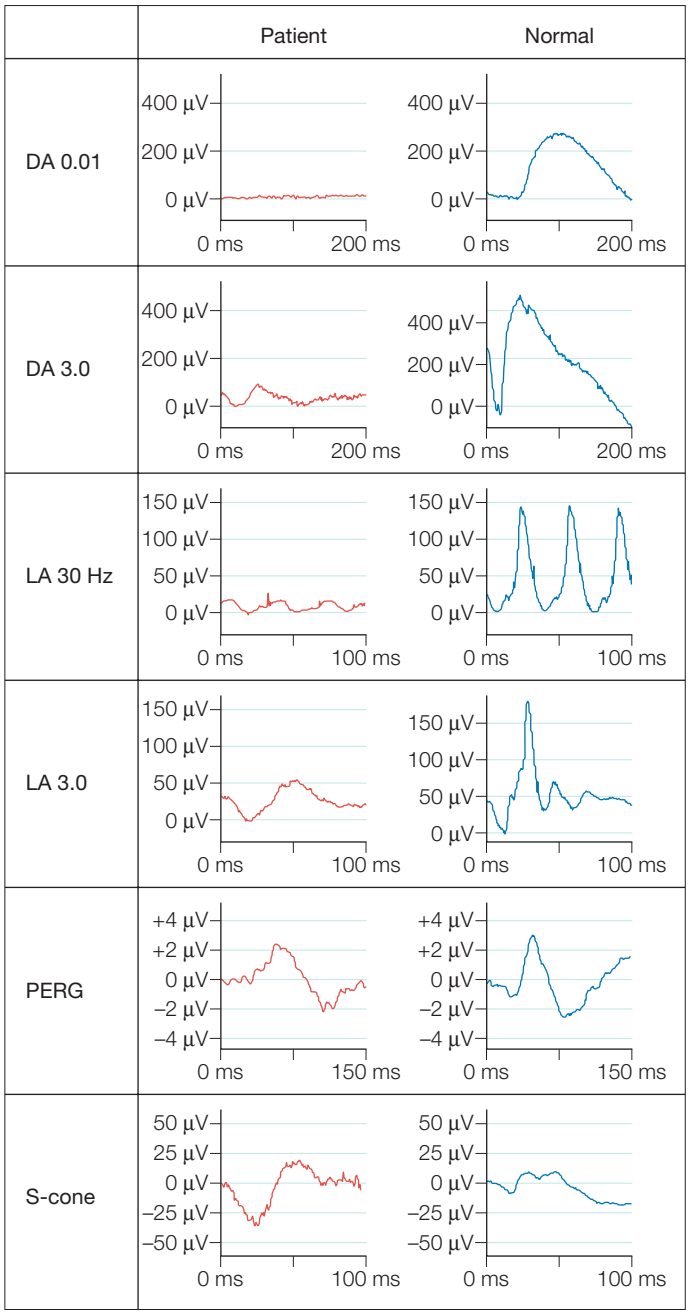


Fig. 46.31 Enhanced S-cone syndrome (ESCS). The rod-specific electroretinogram (ERG) (DA 0.01) is undetectable in keeping with the known absence of rods in this disorder. However, there are two main additional diagnostic features: firstly, there is a similar waveform between the photopic (LA 3.0) and scotopic (DA 3.0) ERGs to the same stimulus, both of which show a simplified, grossly delayed waveform. Secondly, the amplitude of the grossly delayed 30 Hz flicker ERG is lower than that of the photopic a-wave. In a normal subject, the 30 Hz flicker ERG amplitude always falls between that of the photopic a-wave and the photopic b-wave. Note the profoundly delayed pattern ERG (PERG), often present when the PERG is detectable in this disorder, and the increased sensitivity to short wavelength stimulation revealed by specific S-cone ERG recording (5 ms blue stimulus on a bright orange background). In a normal subject, the S-cone ERG consists of two components: a late S-cone specific component at ~50 ms and an L-/M-cone component at ~30 ms. The earlier component is not present in the patient, and the later component is enhanced.

molecular pathology of most disorders will be established in the near future. This is the first stage in understanding the pathophysiological mechanisms that lead to photoreceptor cell dysfunction and/or death.

Treatment strategies aimed at prolonging photoreceptor survival or improving function are currently being investigated in animal models and, increasingly, in human clinical trials (www.clinicaltrials.gov). They include the use of exogenous growth factors, pharmacologic intervention, gene therapy, and stem cell based therapies.[33–35,67–70] Another approach for more advanced disease is the development of retinal implants, which are also being investigated in clinical trials.[71]

There is cautious optimism that these multiple avenues of research will yield meaningful treatments for various forms of genetic retinal disease in the future.

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Retinal dystrophies with systemic associations and the retinal ciliopathies

Hélène Dollfus

Chapter contents

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Children affected by retinal degeneration associated with extraocular manifestations *define* the inherited systemic retinitis pigmentosa (RP) syndromes (retinal dystrophies related to inborn errors of metabolism are covered in Chapter 65) (Tables 47.1 and 47.2). The gene or the group of genes involved in the syndrome belong to a specific biologic network whose mutations lead to retinal degeneration associated with manifestations in other organs defined by the specific biologic role of the protein. Retinal degeneration occurs in these syndromes by virtue of the biologic complexity of the retina. The photoreceptor cell is remarkably sensitive to alterations in many biologic pathways but the clinical presentation is often indistinguishable between syndromes with the classical features of retinal degeneration: night blindness, visual field constriction, and reduced visual acuity. In the early phases of the retinal degeneration, the fundus may appear normal although the electroretinogram (ERG) is altered. Later, the fundus will acquire the usual aspects observed in retinal degeneration: pigment mottling, pigment migration with spicules, optic disc pallor, narrowed vessels, and macular changes that are prominent and early in the cone–rod dystrophies.

All the conditions are rare inherited diseases; the most frequent syndromes are Usher syndrome (USH) and Bardet–Biedl syndrome (BBS).

Over the last two decades, many of the genes responsible for these conditions have been identified. This field will continue to greatly benefit from new genome exploration especially high-throughput sequencing with next-generation sequencing (NGS) technologies (targeted, exome or genome sequencing).[1–5] Molecular diagnosis and genetic counseling are constantly improving, especially for the syndromes which are highly heterogeneous. The classical syndromes illustrating this group of diseases are described, but a growing number of overlapping phenotypes have become evident as molecular investigations improve. Moreover, different mutations in the same gene may lead to different syndromes on the same clinical spectrum (see section "The ciliopathies"). Major clinical variability in each syndrome has been described. For some genes, specific mutations may lead to isolated features such as isolated RP (e.g. Usher syndrome gene *USH2A* or Bardet–Biedl genes *BBS8* and *BBS3*).[6–8]

A child with RP should be systematically evaluated for extraocular associated features (unless he/she is proven to be affected by a non-syndromic mutation). These conditions require multidisciplinary follow-up and management.

Usher syndrome: a deaf child who loses vision

In Usher syndrome, sensorineural deafness is associated with progressive retinal degeneration. USH occurs in 1 of every 10 deaf children (5% of all cases of congenital deafness). It is the most frequently inherited syndrome with deafness and is the most common syndrome among the deaf–blind.[9–11] The syndrome is subdivided into three groups: Usher type 1 (USH1), type 2 (USH2), and type 3 (USH3). USH1 and 2 are usually diagnosed in early or late childhood, respectively, but may be diagnosed later in life as the visual impairment may be overlooked in a deaf child. Vestibular dysfunction is classically associated with USH1. Each type of Usher syndrome is autosomal recessive but genetically heterogeneous. For each type, a number of genes have been identified[12–16] (see Table 47.1). Molecular studies have shown clinical overlap between the classical types USH1 and USH2.[17] Some Usher genes can be involved in either isolated deafness or isolated RP (USH2A).[6,18]

Cochlear implantation is highly recommended for these children (especially in USH1).[19,20] No therapy is yet available for the retinal degeneration (Fig. 47.1A–C).

Usher syndrome type 1: the most severe form

The child with USH1 is affected with congenital severe to profound sensorineural hearing loss associated with delayed

Table 47.1 Main extraocular features found and the corresponding systemic retinitis pigmentosa (RP) syndrome

Extraocular clinical feature associated with RP in a child		Key feature found in systemic syndrome
Stature	Dwarfism	Cockayne syndrome (cachectic), spondylometaphyseal dysplasia or spondyloepiphyseal dysplasia associated with cone dystrophy
	Obesity	Bardet–Biedl syndrome (BBS), Alström syndrome, Cohen syndrome (truncal), MORM (mental retardation, truncal obesity, retinal dystrophy, and micropenis) syndrome
Skeletal abnormality	Polydactyly	BBS, Joubert syndrome, Jeune syndrome
	Short ribs with abnormal thorax	Jeune syndrome
	Various abnormal skeletal development	Spondylometaphyseal dysplasia or spondyloepiphyseal dysplasia
Deafness		Usher syndrome (variable severity according to types), Alström syndrome (progressive starting in childhood)
CNS malformations	Cerebellar vermis agenesis (molar tooth)	Joubert syndrome
Kidney dysfunction	Polyuria-polydypsia Kidney failure	BBS, Alström syndrome, Jeune syndrome, Senior–Loken syndrome, Joubert syndrome
Endocrine dysfunction	Type 2 juvenile diabetes	Alström syndrome
	Pituitary deficiency	Oliver–McFarlane syndrome
Cardiomyopathy		Alström syndrome
Cognitive impairment		Classical: Cohen syndrome, Joubert syndrome Occasional: BBS, Alström
Teeth	Amelogenesis imperfecta	Jalili syndrome
	Prominent incisors	Cohen syndrome
Skin/hair	Ultraviolet sensitivity	Cockayne syndrome
	Alopecia – early hair loss	Hypotrichosis with juvenile macular dystrophy; EEM (ectodermal dysplasia, ectrodactyly, macular dystrophy) syndrome
	Long eyelashes	Oliver–McFarlane syndrome

sitting and walking due to abnormal vestibular function. Retinal degeneration occurs early in childhood. As early as 2 or 3 years old, the ERG can confirm the diagnosis of retinal degeneration although the fundus appears to be normal.[21,22] Five causative genes are known and mutated in various proportions according to the studied population: *MYO7A* (recognized to be the main USH1 gene mutated in half of the cases and also responsible for non-syndromic deafness), *USH1C*, *CDH23*, *PCDH15*, *USH1G* and *CIB2*.[14,16,17] Although always severe, the course of disease may vary according to the type of mutation.[23]

Usher syndrome type 2: later onset retinal degeneration in a deaf child

Congenital mild to severe sensorineural stable hearing loss with major impairment in high frequencies and normal vestibular function are the main characteristics of USH2. The retinal degeneration occurs later than in USH1, usually during puberty or after. USH2 and USH3 are not usually symptomatic in the first decade and initially have a normal fundus appearance. Many patients retain good visual acuity in spite of constricted visual fields. The ERG may initially be normal; however, ERG changes may be detected in presymptomatic young children. During the second decade, night blindness and loss of peripheral vision become evident and inexorably progress (Fig. 47.1D). Four genes have been identified: *USH2A* (Usherin found also mutated in isolated RP), *GPR98*, *WHRN and PDZD7*.[14,16]

Usher syndrome type 3: the later onset, variable form

The onset of RP in USH3 is variable and is often recognized after the second decade of life, but can be confused with the two other types. Sensory hearing loss is postlingual, after the acquisition of speech (as opposed to the prelingual loss in USH1 and USH2), but it evolves progressively to profound deafness. Vestibular dysfunction of variable intensity occurs in half of the patients.

The USH3A gene (*CLRN1*) has been identified in particular in Askenazi Jews and Finns. USH3 has also been found mutated in patients with USH1 and USH2.[14,16]

Pathogenesis of Usher syndromes

Progress has been made in understanding the pathogenesis of this disease affecting the inner ear stereocilia and photoreceptor cells of the retina.[24] The USH1 gene products form a network, the Usher interactome, which plays a key role in the early hair bundle development.[25–26] They are also key components of the mechanoelectrical transduction machinery necessary for

Table 47.2 Main systemic retinitis pigmentosa syndromes

Name of the syndrome with retinal degeneration	Main diagnostic extraocular signs	Identified gene(s)	Pathogenesis
Usher syndrome type 1	Deafness: congenital and profound Vestibular dysfunction	MYO7A, cadherin-23 (*CDH23*), Harmonin, protocadherin-15 (*PCDH15*), *SANS*, *CIB2*	Stereocilia and photoreceptor development and function. Network of Usher proteins
Usher syndrome type 2	Deafness: congenital, moderate to severe No vestibular deficit	*GPR98*, *Ush2A*, *WHRN*, *PDZD7*	Stereocilia and photoreceptor development and function. Network of Usher proteins
Usher syndrome type 3	Late-onset rod–cone dystrophy Late-onset progressive deafness	*USH3A* (*CLRN1*),	Stereocilia and photoreceptor development and function. Network of Usher proteins
Bardet–Biedl syndrome	Polydactyly Obesity Intellectual disability Kidney dysfunction Urogenital malformation	*BBS1* to *BBS19*	Ciliopathy
Alström syndrome	Obesity Type 2 diabetes mellitus Deafness Cardiomyopathy Kidney dysfunction Liver dysfunction Growth and endocrine deficiency Occasional intellectual disability	*ALSM1*	Ciliopathy
MORM	Mental retardation Truncal obesity Micropenis	*INPP5E*	Ciliopathy
Senior–Loken syndrome	Nephronophthisis	*NPHP1* to *6*, *SDCCAG8*	Ciliopathy
Mainzer–Saldino syndrome	Renal dysplasia Cerebellar ataxia Skeletal dysplasia Cone-shaped epiphyses	*IFT140*	Ciliopathy
Joubert syndrome	Cerebellar vermis hypoplasia Ataxia Cognitive impairment Tachypnea Abnormal eye movements Kidney dysfunction Polydactyly	*TMEM216*, *AHI1*, *NPHP1*, *NPHP6* (*CEP290*), *TMEM67*, *RPGRIP1L*, *ARL13B*, *CC2D2A*, *CXORF5* gene (X linked), *TTC21B*, *KIF7*, *TCTN1*, *TMEM237*, *TMEM138*, *C5ORF42*, *TCTN3*, *ZNF423*, *TMEM231*, *CSPP1*, *PDE6D*	Ciliopathy
Jeune syndrome	Severe constricted thorax Chondrodysplasia with short bones Kidney dysfunction Liver fibrosis	*ATD*, *IFT80*, *DYNC2H1*, *TTC21B*, *WDR34*, *CSPP1*	Ciliopathy
Cohen syndrome	Myopia Facial gestalt Truncal obesity Prominent upper incisors Intermittent granulocytopenia Long tapered fingers Joint laxity Mental retardation	*VPS13B*	Presumed vesicular transport
Cockayne syndrome	Cachectic darwfism Deafness Optic atrophy Cataract UV sensitivity Neurodegeneration	CSA (*ERCC8*), CSB (*ERCC6*)	Transcription factor related

Continued

Table 47.2 Main systemic retinitis pigmentosa syndromes—cont'd

Name of the syndrome with retinal degeneration	Main diagnostic extraocular signs	Identified gene(s)	Pathogenesis
Jalili syndrome	Amelogenesis imperfecta	*CNNM4*	Metal transport protein
Hypotrichosis with juvenile macular dystrophy	Early hair loss	*CDH3*	Cadherin family
Ectodermal dysplasia, ectrodactyly, macular dystrophy (EEM) syndrome	Early hair loss Lobster-claw hands	*CDH3*	Cadherin family
Oliver–McFarlane syndrome	Long eyelashes Early hair loss Short stature – pituitary deficiency Developmental and neurologic impairment	*PNPLA6*	
Boucher–Neuhauser syndrome	Spinocerebellar ataxia Hypogonadotropic hypogonadism	*PNPLA6*	
Spondylometaphyseal dysplasia or spondyloepiphyseal dysplasia associated to cone dystrophy	Short stature Limb abnormalities	*PCYT1A*	

hearing. In the retina, the Usher interactome acts at the level of the ciliary/periciliary region of the connecting cilia of the photoreceptor cells. It is important in the transport of proteins between the outer and the inner segments.[27–30] Alteration of the USH proteins leads to early dysfunction of the inner ear and of the retina simultaneously (Fig. 47.1E).

The ciliopathies: a novel systemic retinal dystrophies group

A single non-motile cilium ("primary cilium") is present in almost every vertebrate cell; motile cilia are present only in specific organs such as in the respiratory or the reproductive systems (for review see Brown et al.[31]) (Fig. 47.2A). The primary cilium is the central "antenna" of the cell, allowing transduction of sensorial information from the extracellular environment to the cell. The photoreceptor cell has a connecting cilium and is, therefore, a ciliated cell.

Ciliopathies are rare genetic disorders characterized by primary cilium dysfunction, frequently affecting photoreceptors and causing retinal degeneration either as an isolated condition (e.g. Leber congenital amaurosis with *CEP290* mutations) or as a ciliopathy syndrome affecting more than one organ system.[32–34] Ciliopathies involve many target organs that have in common an important role of the primary cilia. Overlapping phenotypes have been reported, as well as high clinical variability on the number of affected organs among patients with the same syndrome. The most common ciliopathies are schematically represented in Figure 47.2B.

Molecular investigations have revealed major genetic heterogeneity for each syndrome and also allelic variability (different mutations in the same gene may lead to different syndromes). For instance, *CEP290-NPHP6* truncating mutations have been identified in Joubert syndrome and hypomorphic mutations in Leber congenital amaurosis (LCA). Moreover, CEP290-*NPHP6* is mutated in several distinct disorders (nephronophthisis, Senior–Loken syndrome, Joubert syndrome, BBS and the lethal Meckel syndrome).[35]

Supplementary genetic factors such as a third mutated allele in a BBS gene (known as oligogenism – a third mutation occurring in addition to the two main mutations found in recessive inheritance) or other genetic modifiers can influence the phenotype.[36,37]

A yearly multidisciplinary follow-up is recommended for these children with special attention given to kidney function and prevention of obesity.

Bardet–Biedl syndrome

The cardinal features of the BBS syndrome are early-onset retinal degeneration, obesity, polydactyly, renal failure, hypogonadism, and intellectual disability (Fig. 47.3A–D). Secondary features may include anosmia, diabetes, cardiac anomalies, hepatic fibrosis, brachydactyly, and Hirschprung disease.[38,39] The retinal dystrophy is early in onset, leading to severe visual handicap before adulthood. Profound ERG abnormalities can be detected as early as 3 years of age. Legal blindness usually results before the second decade of life.[40–46] Retinal dystrophies in BBS are mainly a rod–cone dystrophy or a cone–rod dystrophy,[46] usually classified as a global retinal degeneration because both rods and cones are affected[44] (Fig. 47.3E).

Obesity is the second major feature, present in 72–96% of BBS patients, usually beginning in early childhood and worsening with age. The origin of obesity is both central (hypothalamic eating control) and peripheral (adipose tissue).[47–49]

Limb anomalies are found in almost 95% of BBS patients, usually a postaxial polydactyly (69%). Other limb malformations such as brachydactyly or syndactyly are frequently reported for both hands and feet and have a diagnostic value. Abnormalities of the genitalia can occur: hypogonadism in males or vaginal atresia in females. Rarely, there is hydrometrocolpos, a neonatal vaginal malformation leading to a massive abdominal tumor.[50,51] Renal dysfunction can occur in late childhood and may lead to kidney failure.[52] Neuropsychiatric symptoms can include developmental delay, intellectual disability, learning difficulties, speech deficit, and

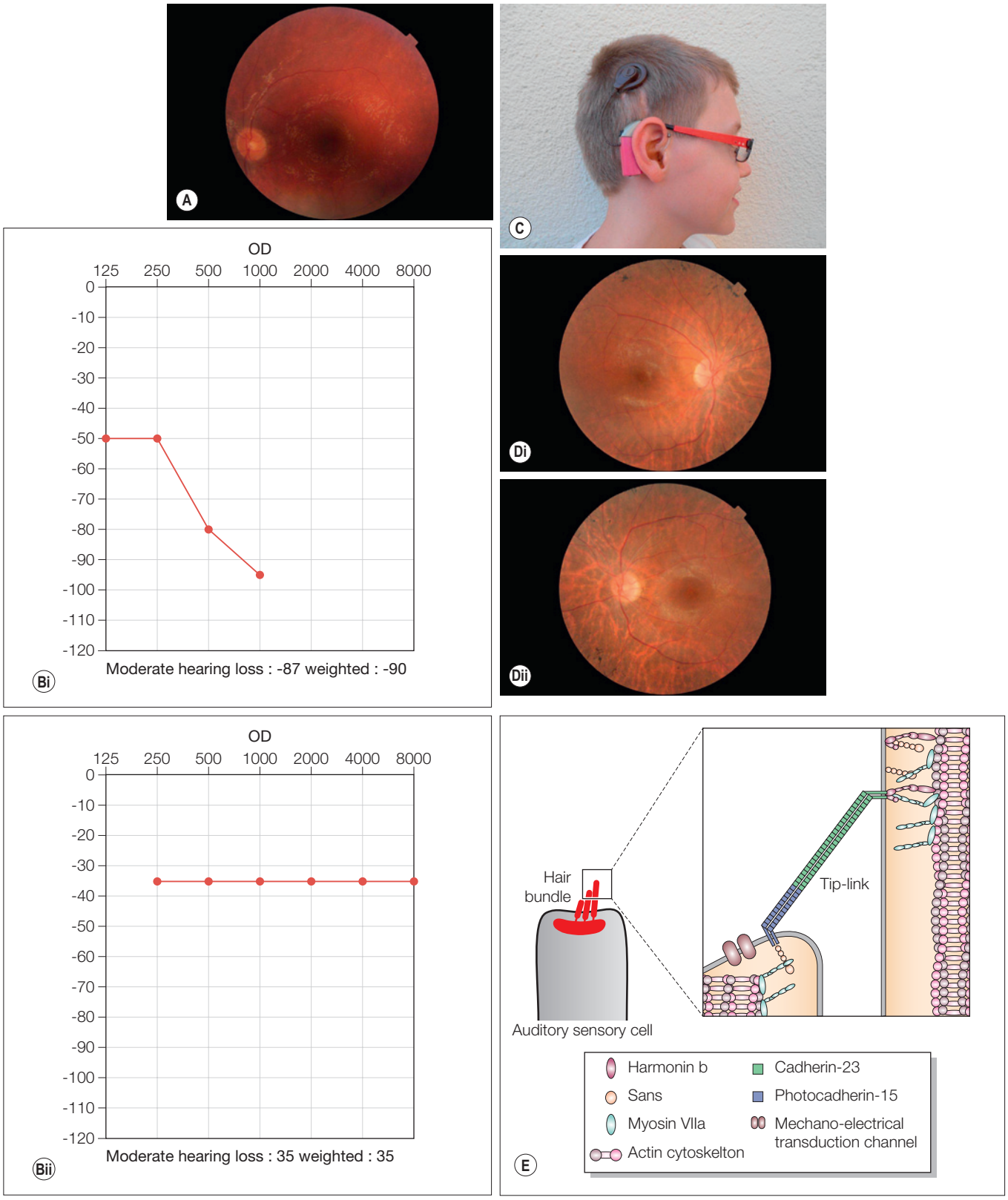


Fig. 47.1 Usher syndrome. (A) Fundus photograph of a 5-year-old patient with Usher syndrome type 1 due to MYO7A mutation. The patient walked at age 24 months. The fundus shows very mild pigment epithelium irregularity and the electroretinogram is extinguished. (Bi) Audiogram of the same patient before implantation showing profound deafness. (Bii) Audiogram after cochlear implantation showing dramatic hearing improvement. (C) Photograph of the patient showing the cochlear implantation device. (Di) Fundus photograph of the right eye of a patient affected by Usher syndrome type 2 C (mutations in VLGR1G). (Dii) Fundus photograph of the left eye of the same patient showing retinitis pigmentosa. (E) Schematic representation of an auditory sensory cell and of the tip link molecular complex. *([E] Courtesy of Professor Christine Petit, Institut Pasteur, Inserm, UPMC, Collège de France, Paris, France.)*

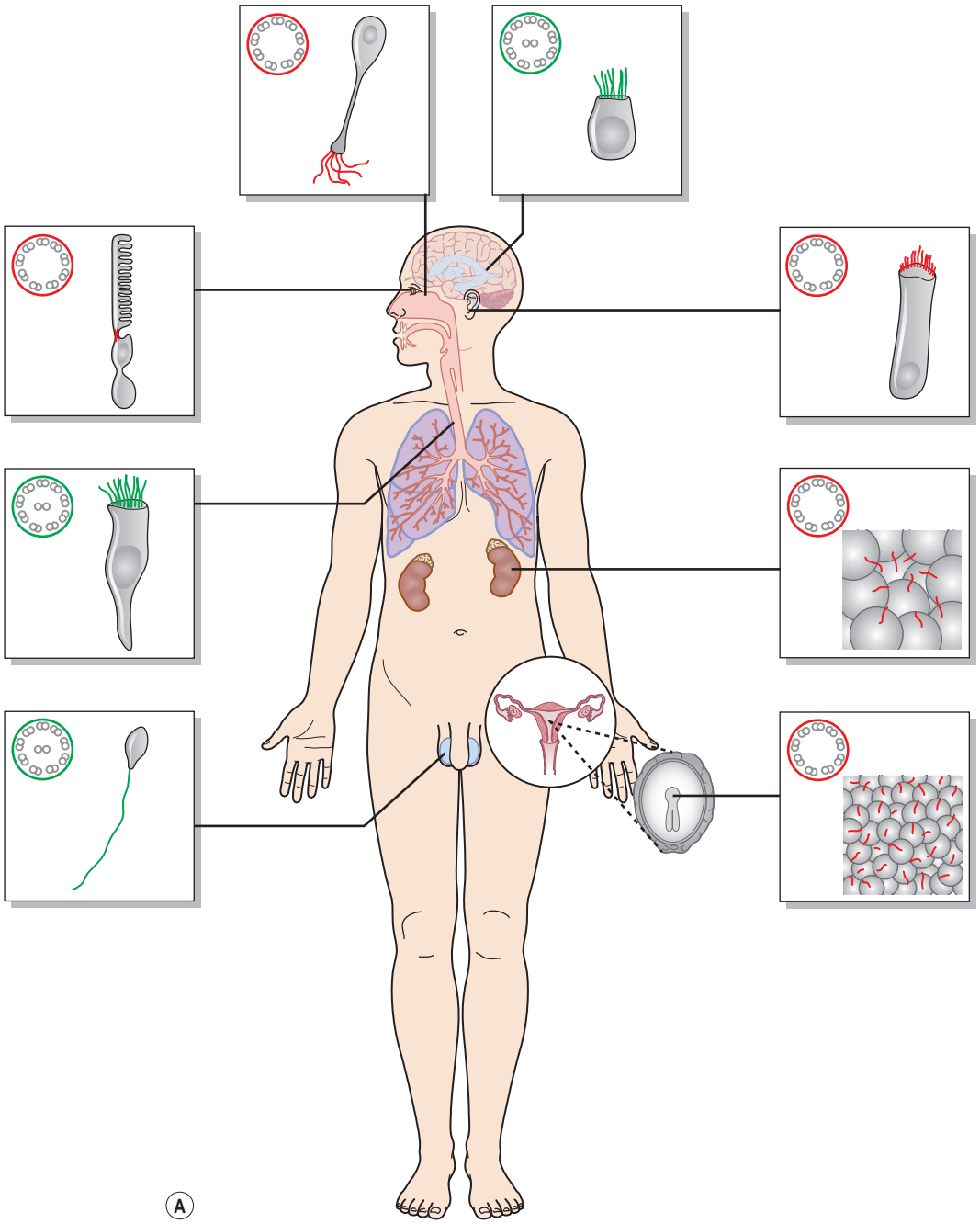


Fig. 47.2 Ciliopathies. (A) Schematic representation of cilia in various cells in the human. In green: motile cilia; in red: primary cilia.

Continued

behavioral problems.[38] Intellectual function ranges from severe mental retardation (29%) through weak intelligence and average intelligence (29%). Slow ideation and hyperemotive status are common.

BBS is an autosomal recessive heterogeneous condition; more than 19 genes have been identified, accounting for about 85% of cases.[53] All the genes have been related to cilium biogenesis and/or function. *BBS1* and *BBS10* are the two most common, each accounting for about 20% of the cases. Implication of the other BBS genes ranges from a unique family to a few percent of mutated families. The classical autosomal recessive inheritance model has been challenged by molecular and functional investigations with the oligogenic model and the effect of additional genetic modulators on the phenotype.[37]

Alström syndrome

Alström syndrome (ALMS) manifestations include RP in early childhood, hearing impairment, and metabolic defects leading to hyperinsulinemia, type 2 diabetes mellitus and obesity in childhood. Polydactyly does not occur. Dilated cardiomyopathy can occur in infancy or later in life and renal dysfunction is reported in half of ALMS cases.[54] Developmental or motor delays occur, but most children have normal intelligence.

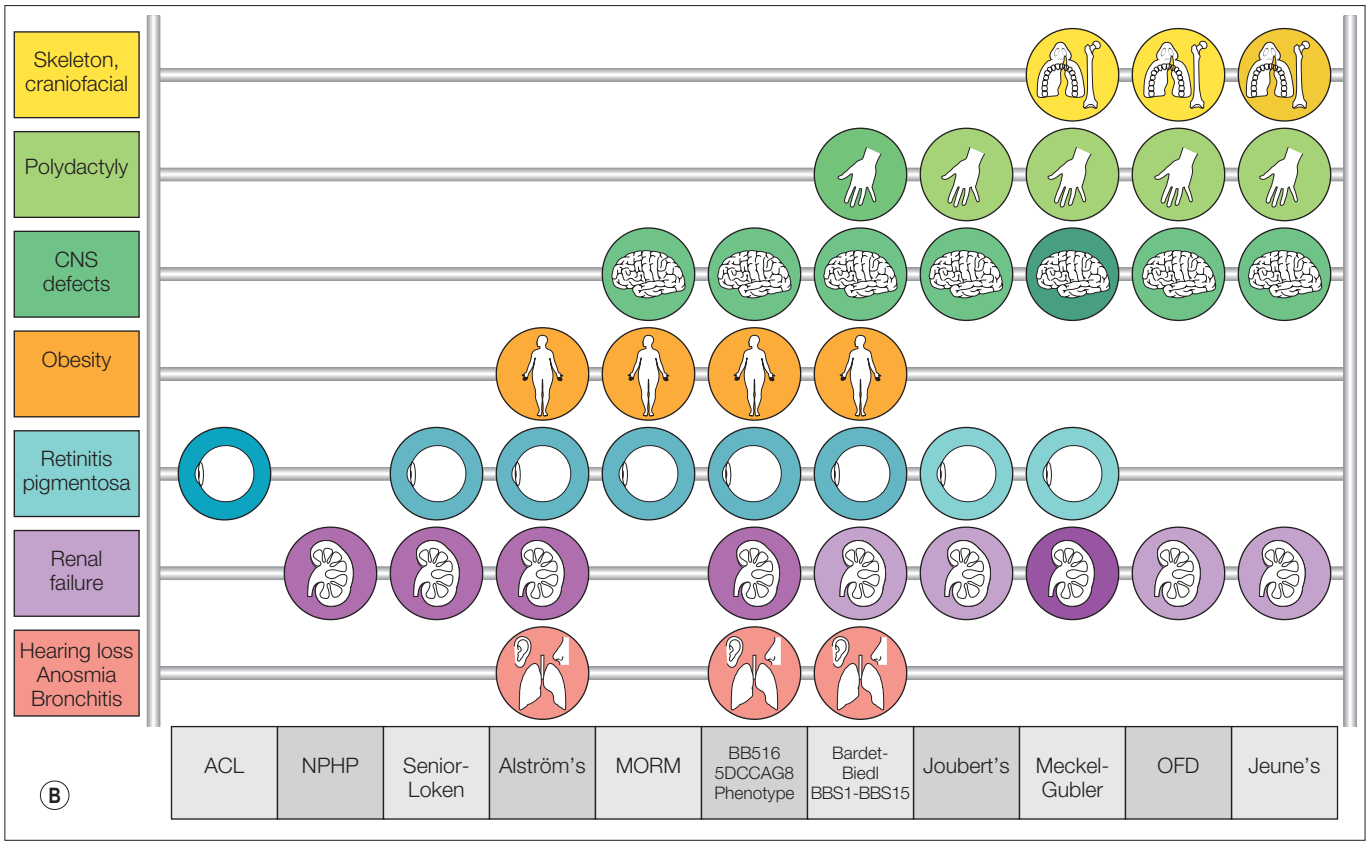


Fig. 47.2, cont'd (B) Schematic representation as an abacus (adding various target organs) of syndromes recognized as ciliopathies.

The first manifestation of ALMS is severe early-onset cone–rod retinal dystrophy, sometimes mimicking Leber congenital amaurosis with very early visual impairment, photophobia, and nystagmus (Fig. 47.4). Children usually become truncally obese during their first year. Sensorineural hearing loss presents in the first decade in up to 70%; it may progress to the moderately severe range (40–70 dB) by the end of the first to second decade. Insulin resistant type 2 diabetes mellitus often presents in the second decade and is accompanied by acanthosis nigricans (pigmentation mostly in body folds). Other endocrine and metabolic abnormalities include hypothyroidism, diabetes insipidus, growth hormone deficiency, hyperuricemia, hyperlipidemia, hypothyroidism, and hypogonadotrophic hypogonadism. Hepatic and renal dysfunction can be present in the second decade. This syndrome requires a multidisciplinary follow-up to detect complications once the diagnosis is confirmed.[54,55]

A single gene is involved in all the cases, *ALMS1*.[56,57] ALMS1 protein has been found to be located at the base of cilia.[58]

MORM syndrome

MORM syndrome (**m**ental retardation, truncal **o**besity, **r**etinal dystrophy, and **m**icropenis) is very rare.[59] A congenital non-progressive retinal dystrophy with poor night vision occurs within the first year of life with reduced visual acuity by 3 years of age that remains stable thereafter. The identified gene, *INPP5E* (inositol polyphosphate-5-phosphatase), classifies this syndrome as a ciliopathy. It is related to Joubert syndrome.[60]

Senior–Loken syndrome and Mainzer–Saldino syndrome

Senior–Loken syndrome (SLS) combines nephronophthisis (NPH) and retinal degeneration. NPH, the most common cause of inherited renal failure in childhood, is characterized by initial normal kidney size that will eventually shrink, tubulo-interstitial nephritis, and a loss of corticomedullary differentiation leading to cyst formation.[34,61–64] The first symptoms are polyuria and polydipsia caused by a urinary concentration defect. The end-stage of the renal failure is variable – infantile, juvenile, or adolescent. The occurrence of the retinal dystrophy is higher in the juvenile form of NPH. The early retinal dystrophy usually occurs years before the kidney involvement is detected. The retinal dystrophy may be very early, mimicking isolated LCA or may have a later onset. Thus, clinical diagnosis of LCA should lead to clinical and molecular testing for LCA-SLS associated genes and, according to the results, annual kidney follow-up may be indicated.

SLS is a ciliopathy and the kidney involvement is explained by the role of the *NPHP* proteins at the level of the tubular epithelial renal cells. Each of these has a primary cilium in contact with the urinary flow.

Nineteen (*NPHP1* to *NPHP19*) genes are known to be involved in NPH, and for many of them cases of SLS associated with RP have been reported.[34,65,66] Mutations in *NPHP5*[67] and *NPHP6*[68] are more often linked to severe and early RP. The Mainzer–Saldino syndrome is closely related. Kidney disease, retinal dystrophy, and skeletal features including the typical

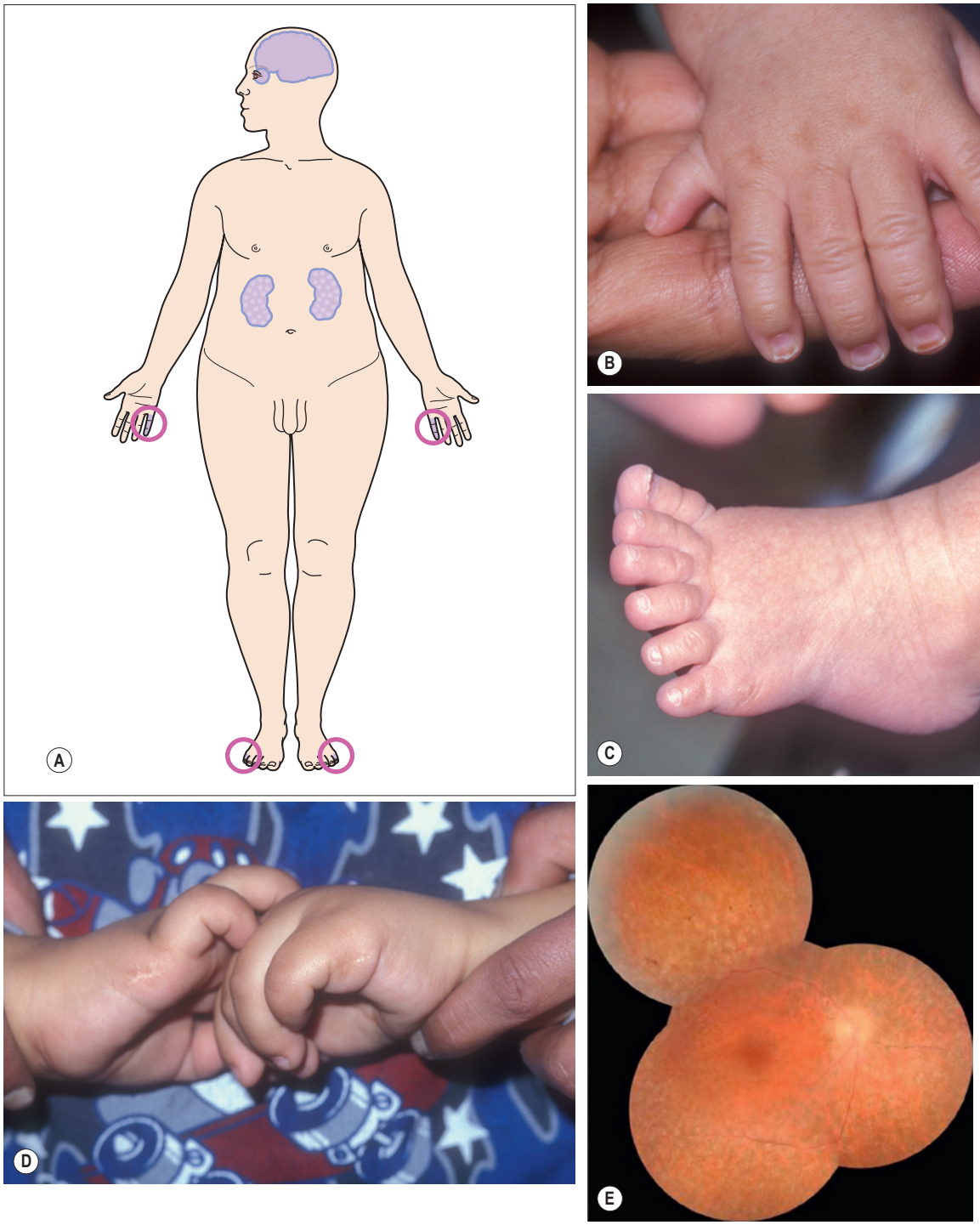


Fig. 47.3 Bardet–Biedl syndrome (BBS). (A) Schematic representation of the BBS with five major manifestations: obesity, polydactyly, renal dysfunction, retinitis pigmentosa, and cognitive impairment. (B) Polydactyly of the hand of a patient aged 6 months old with mutations in the *BBS1* gene. (C) Polydactyly of the foot of a patient aged 6 months old with mutations in the *BBS1* gene. (D) Bilateral scarring resulting from the surgical removal of the extra digits in the brother of the previous case. (E) Fundus photograph of a teenager patient carrying mutations in the *BBS16* gene showing widespread retinal degeneration.

cone-shaped epiphyses occur. It was recently shown to be associated to *IFT140* mutations [69,70]

Joubert syndrome

Joubert syndrome may be autosomal recessive or X-linked.[71,72] This syndrome is a combination of cognitive impairment, ataxia, tachypnea, eye movement abnormalities, with frequent retinal degeneration and kidney manifestations. Cerebellar vermis hypoplasia is a pathognomonic finding on magnetic resonance imaging (MRI) where it is evident as the "molar tooth" sign (Fig. 47.5).[73,74] Multiple other features can be associated with this midbrain–hindbrain malformation leading to the designation: Joubert syndrome and associated disorders

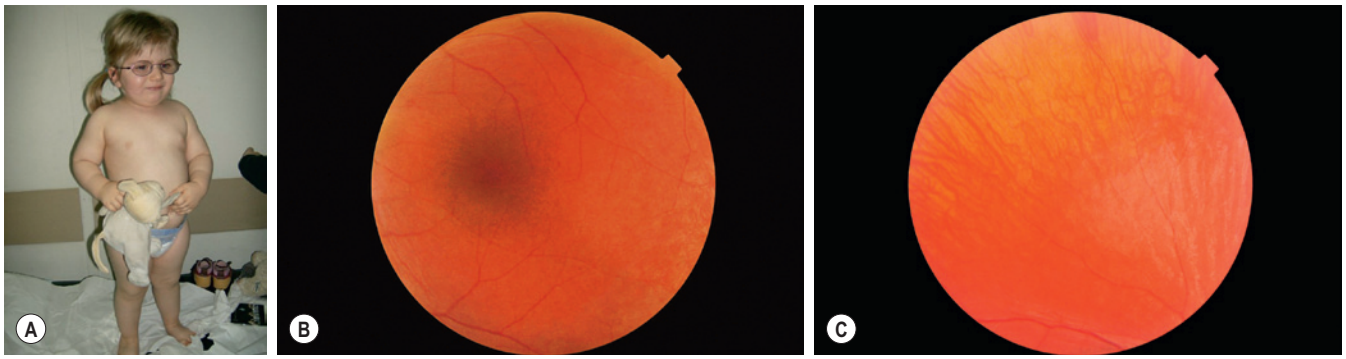


Fig. 47.4 Alström syndrome. (A) This 26-month-old girl was noted to be photophobic and overweight. She has mutations in the ALS gene. (B) Fundus photograph of the patient's macular region showing marked irregularity of the macula. Electroretinogram shows severe photopic reduction and a lesser degree of scotopic impairment. (C) Photograph of the peripheral retina; it is thinned with patchy pigmentation.

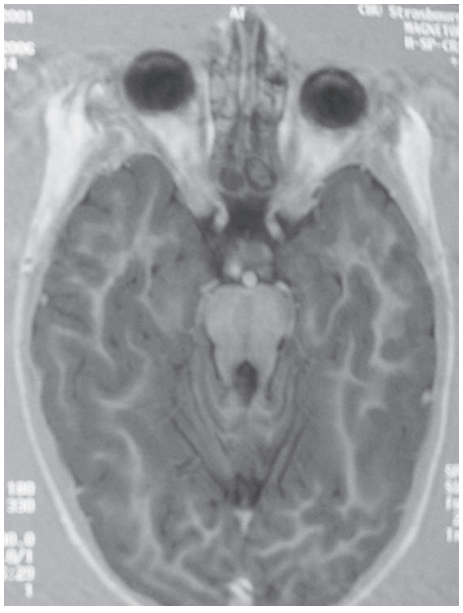


Fig. 47.5 Joubert syndrome. Molar tooth sign on the MRI of a child with Joubert syndrome carrying mutations in the *CEP290-NPHP6* gene.

(JSAD). In the kidneys, there may be a cystic dysplasia, caused by multiple cysts of different sizes, or NPH. More than 30% of patients with Joubert develop renal failure. Hepatic fibrosis occurs in 10% of patients. Skeletal findings are rarer and include polydactyly and cone-shaped epiphyses. The ocular phenotype is broad and may include abnormal motility, nystagmus, and ocular motor apraxia (saccade initiation failure; see Chapter 90). Coloboma has been reported rarely. RP occurs in a third of patients with either very early onset (mimicking LCA) or later-onset night blindness.[75] Twenty genes have been identified to be mutated in Joubert-related syndromes: *TMEM216*, *AHI1*, *NPHP1*, *NPHP6* (*CEP290*), *TMEM67*, *RPGRIP1L*, *ARL13B*, *CC2D2A*, *CXORF5* gene (X linked), *TTC21B*, *KIF7*, *TCTN1*, *TMEM237*, *TMEM138*, *C5ORF42*, *TCTN3*, *ZNF423*, *TMEM231*, *CSPP1*, and *PDE6D*.

The RP phenotype varies with the mutated gene and is not constant depending on the affected gene. Eighty percent of *AHI1*-mutated patients present with a retinal dystrophy and NPH-related renal disorder but no hepatic defects. RP has been observed in one family out of two mutated in *ARL13B*.[76] *CC2D2A* is found mutated in JSAD patients with or without RP.[77] The same mutation in *TMEM216* was identified in eight JSAD-related families presenting psychomotor retardation and frequent retinopathy.[78]

Jeune syndrome

Jeune asphyxiating dystrophy or Jeune syndrome is an autosomal recessive chondrodysplasia. The phenotype is highly variable and can lead to death in early infancy because of a severely constricted thoracic cage and respiratory insufficiency.[79,80] Patients present with a long narrow thorax due to short ribs (Fig. 47.6), shortened long bones, and sometimes polydactyly. Kidney cysts, hepatic fibrosis, and RP may occur as early as 5 years of age. Five genes are now reported for Jeune syndrome, but for each of them the risk of developing retinal degeneration remains unclear.[81–85]

Pathogenesis of the ciliopathies

The retinal degeneration in ciliopathies is related to dysfunction of the connecting cilium, a major site of transport and transit for proteins synthesized in the inner segment and necessary for phototransduction in the outer segment[86] (Fig. 47.7). The ciliary-specific transport machinery is known as the intraflagellar transport (IFT) machinery and is composed of molecular motors linked to IFT protein complexes that organize anterograde and retrograde transport. IFT gene mutations have been found in Jeune and Mainzer–Saldino syndromes. To regulate cargo delivery to the cilium, two main regulatory pathways occur: vesicular sorting from the Golgi to the ciliary base and selective transport along the cilium. BBS proteins (the BBSome complex) are involved in these regulatory processes.[86–87]

The extraocular manifestations are linked to specific roles of ciliary proteins involved in the development or function of many organs. As an example, the kidney epithelial cells' primary cilia are mechanosensors.[88] Primary cilia are implicated in major developmental processes and especially in planar cell polarity, body asymmetry, or limb development.[89]

The ciliopathies are a growing family of syndromes with overlapping features due to target organ manifestations that should be systematically sought when assessing any child with pigmentary retinopathy.

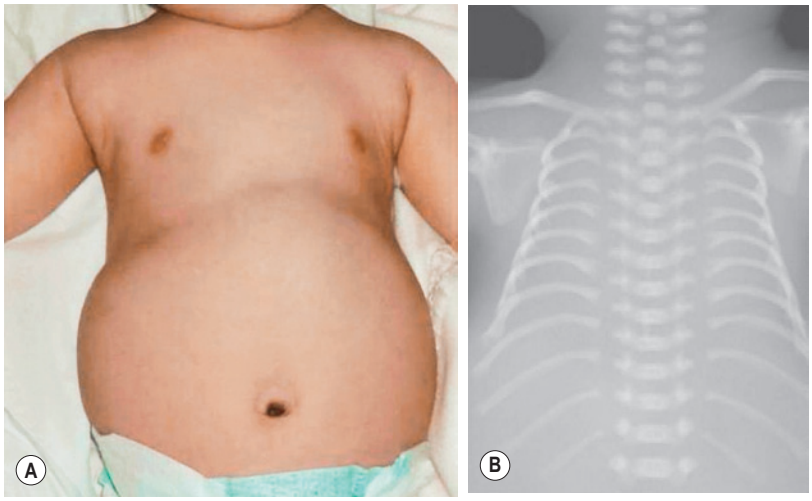


Fig. 47.6 Jeune syndrome. (A) Photograph of the narrow thorax of a young patient with Jeune syndrome. (B) X-ray of a patient with Jeune syndrome showing short ribs. *(Courtesy of Professor Valerie Cormier-Daire, Medical Genetics Department, IMAGINE Foundation, Hôpital Necker-Enfants Malades, Paris, France.)*

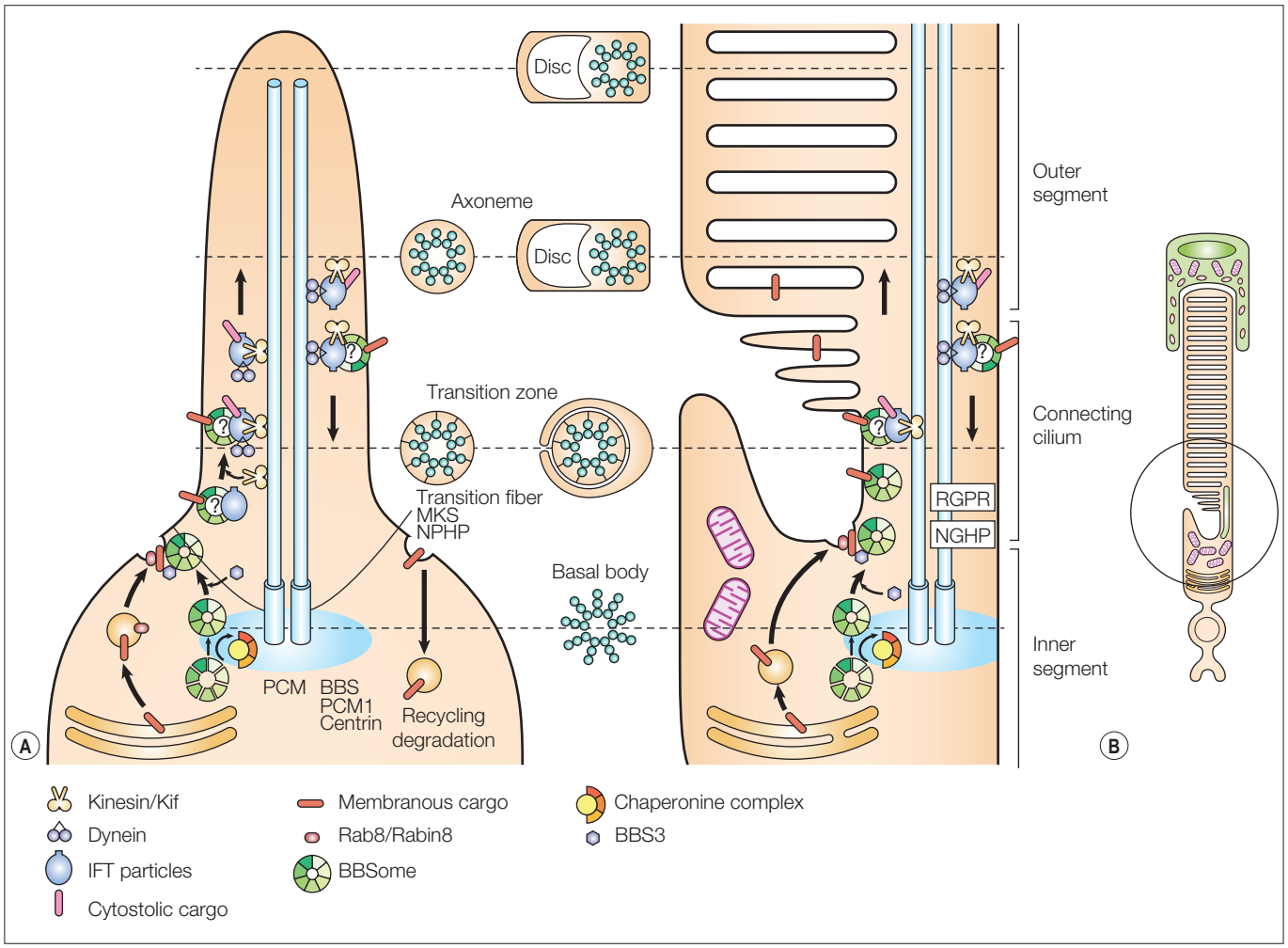


Fig. 47.7 Ciliary structure. The photoreceptor connecting cilium is structurally very similar to the classical primary cilium, which are compared in the picture. Schematic representation of the ciliary protein complexes especially the Bardet–Biedl syndrome (BBS) proteins and noticeably the BBSome. *(From Mockel A, Perdomo Y, Stutzmann F, et al. Retinal dystrophy in Bardet–Biedl syndrome and related syndromic ciliopathies. Prog Retin Eye Res 2011; 30: 258–74.)*

Other rare syndromes with retinal dystrophy

The following syndromes with retinal degeneration may result from a disorder of a well-defined biologic system (e.g. Cockayne syndrome and DNA repair); others are still under investigation (e.g. Cohen syndrome).

Cohen syndrome

Cohen syndrome is a rare worldwide autosomal recessive disorder, common in Finland where the phenotype is well defined, with clinical variability.[90–93] It is characterized by mental retardation, postnatal microcephaly, intermittent granulocytopenia, and facial dysmorphism with downslanting and wave-shaped palpebral fissures, short philtrum, heavy eyebrows, and a prominent nasal base (Fig. 47.8A,B). Long tapered fingers and joint laxity are common as well as prominent upper central incisors (Fig. 47.8C,D).[91,94] There may be a history of neonatal hypotonia with poor feeding and delay in motor milestones with speech delay, and stridor secondary to laryngomalacia. Truncal obesity is common, but not invariable, by 5 years of age. Early-onset retinal dystrophy with myopia is classical.[95] The onset of myopia is usually under 5 years of age and exceeds 7 diopters by the second decade. The macula may develop a "bull's eye" appearance (Fig. 47.8E) in the first decade evolving toward a cone–rod dystrophy. The first symptoms are of myopia and night blindness followed by reduced acuity, and reduced visual field, generalized pigmentary retinopathy with bone spicules or lacunar RPE atrophy in the mid-periphery by the second decade.

One gene (*COH1*) has been identified which encodes for VPS13B. This could have a role in vesicle-mediated sorting and transport of proteins within the cell.[96] Many mutations and intragenic deletions have been reported.[97,98]

Cockayne syndrome and DNA repair

Cockayne syndrome is a DNA repair disorder due to a dysfunction of the transcription-coupled DNA repair genes.[99,100] All the cells are hypersensitive to effects of ultraviolet (UV) light, which is used as the basis for the diagnostic cellular tests of cultured fibroblasts from a skin biopsy.

The main characteristics of the disease are UV skin sensitivity and severe physical and mental retardation (cachectic dwarfism) with progressive neurologic deterioration, sensorineural deafness, and retinal degeneration[101,102] (Fig. 47.9Ai–Aiii). The retinal dystrophy is characterized by a "salt and pepper" pigmentation with optic disc pallor and progressive deterioration in the rod and cone ERG.[103,104] The progression is usually rapid. Cataracts may be present from birth and are often associated with poorly developed iris dilator muscle (the children are difficult to dilate and examine). Corneal changes may occur associated with lagophthalmos as well as chronic blepharitis that can make aphakic contact lens wear difficult[105] (Fig. 47.9Aii). Cachexia may lead to massive orbital fat atrophy.

Early death can occur especially if early-onset cataracts are observed.[106] However, a spectrum of severity has been reported ranging from an early-onset severe form, the cerebro-ocular-facial syndrome (COFS),[107,108] to severe, moderate, and mild forms diagnosed in adulthood as UV sensitivity only[109] (Fig. 47.9Bi–Biv). Mutations in two genes have been identified: CSA (group 8 excision-repair cross-complementing protein; *ERCC8*) and CSB (group 6 excision-repair cross-complementing protein; *ERCC6*).[110–112] The latter is more frequently mutated (60–80%).[113]

Pediatric syndromes with retinal degeneration and features of the ectodermal spectrum (hair, skin, teeth)

Retinal degeneration observed in children with abnormalities related to the ectodermal dysplasia spectrum (affecting hair, skin, nails, or sweat glands or teeth) is rare.

Hypotrichosis with juvenile macular dystrophy

Congenital hypotrichosis associated with juvenile macular dystrophy (HJMD, OMIM 601553) is an autosomal recessive condition with early hair loss and juvenile macular degeneration in the first decade that can show phenotypic variability.[114–116] The retinal involvement becomes widespread and is a cone–rod dystrophy.[117] Mutations have been identified in a P-cadherin gene, *CDH3*, that encodes an integral membrane glycoprotein responsible for calcium-dependent cell–cell desmosomal adhesion.[118]

Ectodermal dysplasia, ectrodactyly, macular dystrophy syndrome

The ectodermal dysplasia, ectrodactyly, macular dystrophy (EEM) syndrome inherited as an autosomal recessive entity is a specific ectodermal entity because of the unusual associated retinal features.[119,120] The retinal involvement has a typical severe macular onset with geographic atrophy that has a peripheral progression. The patients are characterized by hypotrichosis with sparse and short hair, eyebrows and eyelashes, partial anodontia, and limb defects with syndactyly or "lobster-claw" hands.[120] The syndrome shares features with the HJMD syndrome and the *CHD3* gene is mutated, showing allelic variability.[121]

Interestingly, cadherins constitute a superfamily of genes found mutated in various genetic disorders including USH1. For the latter, there is a crucial role of transient fibrous links formed by cadherin 23 and protocadherin 15 in the cohesion of the developing hair bundle as well as the involvement of these cadherins in the formation of the tip link, a key component of the mechanoelectrical transduction machinery.[122] This illustrates that proteins of the same superfamily may have different roles in inherited systemic retinal degenerative syndromes.

Uncombable hair with retinal pigmentary dystrophy, brachydactyly, and dental anomalies

This is a very rare ectodermal dysplasia with RP and is reported to be autosomal dominant.[123,124]

Oliver–McFarlane syndrome, trichomegaly, and chorioretinopathy with pituitary dysfunction (Fig 47.10)

The Oliver–McFarlane syndrome is autosomal recessive, and most often reported as sporadic cases with long eyelashes, hair abnormalities such as early alopecia, and short stature due to pituitary deficiency. Developmental and neurologic

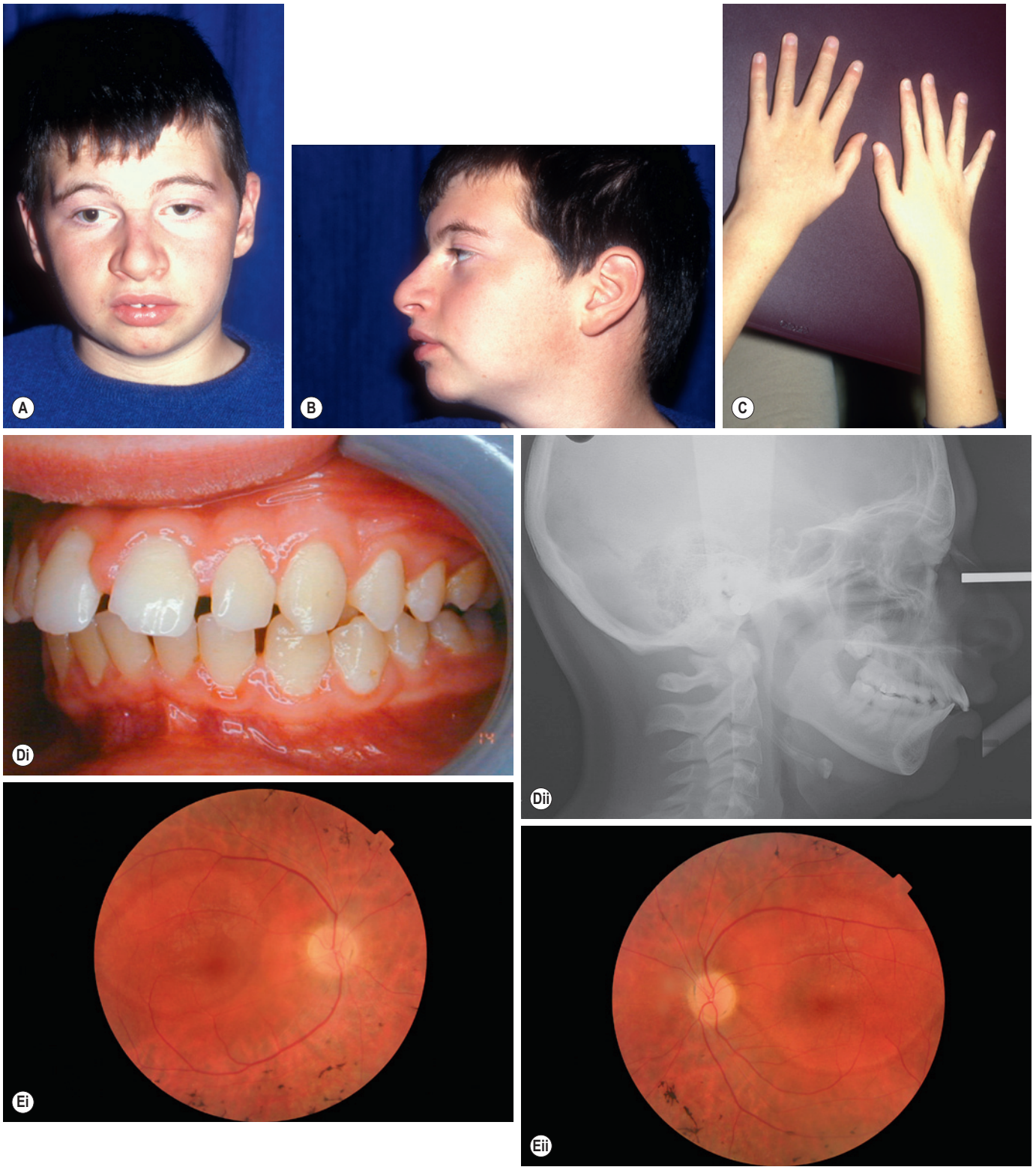


Fig. 47.8 Cohen syndrome. (A) Photograph of the face of a patient with Cohen syndrome carrying mutations in the *COCH* gene. (B) Profile photograph of the same patient. (C) Hands of the patient showing long tapered fingers. (Di) Prominent upper incisors seen on clinical dental photograph; (Dii) on X-ray. (Ei,Eii) Fundus photographs of the patient showing retinal degeneration and a bull's eye appearance. *([D] Courtesy Dr Y. Bollender, Strasbourg, France.)*



Fig. 47.9 Cockayne syndrome. (Ai) Patient with severe Cockayne syndrome with a *CSB* mutation showing cachetic dwarfism and ultraviolet sensitivity after a very short sun exposure coming into the clinic. (Aii) Close-up photograph of the same patient a couple of years later with atrophy of the periocular fat and sunken eye appearance. Both pupils are miotic; he has chronic blepharitis and corneal involvement. (Aiii) Profile picture of the sunken eye appearance. (Bi) Patient with moderate Cockayne syndrome with growth delay, carrying mutations in the *CSB* gene. (Bii) Facial close-up. The pupils are miotic. (Biii) Profile close-up showing sunken eye appearance. (Biv,Bv) Fundus photographs showing retinal dystrophy and optic atrophy.

impairment with cerebellar ataxia may occur.[125–127] The retinal degeneration occurs as early as 5 years of age with night blindness and rapid panretinal dysfunction. Vision is very reduced and there is extensive atrophy of the retinal pigment epithelium and choriocapillaris with an undetectable ERG.[128]

This syndrome has been found to be allelic with spastic paraplegia type 39, Boucher–Neuhauser syndrome, Laurence–Moon syndrome and Gordon Holmes syndromes as mutations in the *PNPLA6* gene have been discovered in these syndromes that share spastic paraplegia with various characteristic features trichomegaly/retinal degeneration/congenital hypopituitarism being specific for Oliver–Mcfarlane.[129,130]

Retinal dystrophy and dental abnormalities: Jalili syndrome

Jalili syndrome is a very rare autosomal recessive condition with early onset cone–rod dystrophy and *amelogenesis imperfecta* (abnormal tooth biomineralization). The *CNNM4* gene has been implicated. It encodes for a metal transport protein important for the retina and teeth[131] (Fig. 47.11).

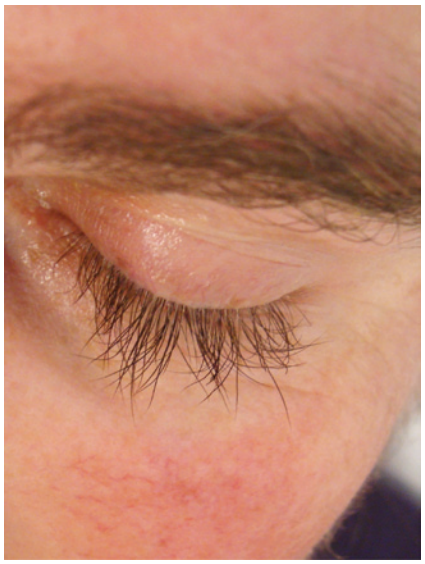


Fig 47.10 Oliver–McFarlane syndrome. Trichomegaly with long eyelashes. *(Courtesy of Dr Klaus Dieterich, Grenoble University Hospital, Grenoble, France.)*

RP syndrome with prominent skeletal involvement

Retinal degeneration may rarely be associated with inherited skeletal dysplasias. A child with spondylometaphyseal/epiphyseal dysplasia should undergo systematic ocular examinations. Genes and pathogenesis remain unknown although theories linking them to ciliopathies have been suggested.[132,133]

Spondylometaphyseal dysplasia short stature with cone dystrophy

This autosomal recessive condition has postnatal growth deficiency, profound short stature, platyspondyly (flattened vertebral bodies) and rhizomelic foreshortening of the limbs, and early bowing of the long bones of the legs with shortening of all the tubular bones.[133] The retinal degeneration occurs in early childhood. It initially involves the macula with a cone–rod evolution. Mutations in the *PCYT1A* gene inducing a deregulation of the phosphatidylcholine pathway has been reported.[134–135] A phenotypically less severe skeletal axial spondylometaphyseal dysplasia with features of retinal dystrophy has been reported.[136–137]

Spondyloepiphyseal dysplasia with cone–rod dystrophy

Another skeletal dysplasia with short stature characterized by spondyloepiphyseal dysplasia has been described with cone–rod dystrophy[138,139] and associated with growth hormone deficiency.[140–141]

Conclusion

Retinitis pigmentosa can be part of a syndrome, particularly when it presents in childhood. Extraocular manifestations may appear later or can already be present at the time of diagnosis. Follow-up of a child affected with syndromic RP is multidisciplinary. The molecular diagnosis of these conditions is continuously improving, facilitating diagnosis and genetic counseling. The understanding of the pathogenesis is important and opens avenues for specific treatment for the retinal degeneration, such as gene therapy or pharmacologic approaches.



Fig. 47.11 Jalili syndrome. (A) Amelogenesis imperfecta (abnormal enamel development) observed in the upper jaw of a patient carrying mutations in Jalili syndrome gene. (Bi,Bii) Fundus photographs of both eyes of the patient showing macular changes related to the cone dystrophy manifestations. *([A]Courtesy of Professor A. Bloch Zupan, Center for Rare Dental Diseases, Strasbourg, France.)*

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Inherited macular dystrophies

Michel Michaelides and Anthony T Moore

Chapter contents

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Introduction

The inherited macular dystrophies are characterized by bilateral central visual loss and symmetrical macular abnormalities. Most present in the first two decades of life with a wide range of clinical, electrophysiological, psychophysical, and histological findings. The molecular basis of inherited macular disease is now well understood, providing insights into the pathogenesis (Table 48.1).

We review pediatric macular dystrophies and not those that present later, such as Sorsby fundus dystrophy, dominant drusen, and adult vitelliform macular dystrophy. Systemic disorders with macular dystrophy will be discussed in Chapters 47 and 65.

Autosomal recessive inheritance

Stargardt disease and fundus flavimaculatus

Clinical and histological findings

Stargardt macular dystrophy (Stargardt disease, STGD) is the most common inherited macular dystrophy with a prevalence of 1 in 10,000; it is inherited as an autosomal recessive (AR) trait. Most cases present with central visual loss in early teens. There is typically macular atrophy with yellow-white flecks at the level of the retinal pigment epithelium (RPE) at the posterior pole (Fig. 48.1). The flecks may be "fish-shaped" (pisciform), round, oval, or semilunar. The oval area of macular atrophy may, in the early stages, have a "beaten bronze" appearance (see Fig. 48.1). However, there may be no evidence of flecks at presentation, the only abnormality being macular atrophy, but in these patients, flecks usually develop over time. The term "fundus flavimaculatus" (FFM) is used to describe the phenotype of retinal flecks occurring without macular atrophy. STGD and FFM are caused by mutations in the same gene; both patterns may be seen in the same family. Most patients who present with FFM develop macular atrophy.

Table 48.1 Chromosomal loci and causative genes in inherited macular dystrophies

Macular dystrophy; OMIM number	Mode of inheritance	Chromosome locus	Mutated gene
Stargardt disease/fundus flavimaculatus; 248200	Autosomal recessive	1p21–p22 (STGD1)	*ABCA4*
Macular dystrophy with central cone involvement; 616170	Autosomal recessive	4q28.2	*MFSD8*
Autosomal recessive bestrophinopathy; 611809	Autosomal recessive	11q13	*BEST1*
Autosomal recessive (atypical) vitelliform dystrophy; 616151	Autosomal recessive	6q14.1	*IMPG1*
Stargardt-like macular dystrophy; 600110	Autosomal dominant	6q14 (STGD3)	*ELOVL4*
Stargardt-like macular dystrophy; 603786	Autosomal dominant	4p (STGD4)	*PROM1*
Autosomal dominant bull's eye macular dystrophy; 608051	Autosomal dominant	4p (MCDR2)	*PROM1*
Autosomal dominant (atypical) vitelliform dystrophy; 616151	Autosomal dominant	6q14.1	*IMPG1*
Best macular dystrophy; 153700	Autosomal dominant	11q13	*BEST1*
Pattern dystrophy; 169150	Autosomal dominant	6p21.2-cen	*PRPH2*
Doyne honeycomb retinal dystrophy; 126600	Autosomal dominant	2p16	*EFEMP1*

Table 48.1 Chromosomal loci and causative genes in inherited macular dystrophies—cont'd

Macular dystrophy; OMIM number	Mode of inheritance	Chromosome locus	Mutated gene
North Carolina macular dystrophy; 136550	Autosomal dominant	6q14–q16.2 (MCDR1)	Not identified
Autosomal dominant macular dystrophy resembling MCDR1; 608850	Autosomal dominant	5p15.33–p13.1 (MCDR3)	Not identified
North Carolina-like macular dystrophy associated with deafness	Autosomal dominant	14q (MCDR4)	Not identified
Progressive bifocal chorioretinal atrophy; 600790	Autosomal dominant	6q14–q16.2	Not identified
Sorsby fundus dystrophy; 136900	Autosomal dominant	22q12.1–q13.2	*TIMP3*
Central areolar choroidal dystrophy; 215500	Autosomal dominant	6p21.2-cen; 17p13	*PRPH2* *GUCY2D*
Adult-onset macular dystrophy; 602225	Autosomal dominant	19q13.33	*CRX*
Juvenile retinoschisis; 312700	X-linked	Xp22.2	*RS1*
X-linked recessive atrophic macular degeneration	X-linked	Xp11.4	*RPGR*

OMIM, Online Mendelian Inheritance in Man.



Fig. 48.1 Stargardt disease. Yellow-white flecks at the level of the retinal pigment epithelium at the posterior pole. There is early macular atrophy.

In both STGD and FFM, fluorescein angiography classically reveals a dark or masked choroid (Fig. 48.2) in the early phase. This is due to excess lipofuscin accumulation in the RPE, which obscures fluorescence from choroidal capillaries. The retinal flecks appear hypofluorescent on fundus fluorescein angiography (FFA) early in their evolution, but later they appear hyperfluorescent due to RPE atrophy. Autofluorescence (AF) imaging, using the intrinsic fluorescence from lipofuscin in the RPE, has superseded FFA in confirming the diagnosis. The abnormal accumulation of lipofuscin, the presence of active and resorbed flecks, and RPE atrophy are characteristic on fundus AF imaging[1] (Fig. 48.3). In children with normal fundoscopy and visual loss from macular dysfunction, FFA may be helpful; a subtle window defect in the central macula or a dark choroid helps confirm the diagnosis. However, this has now been generally superseded by high-resolution optical coherence tomography (OCT), which shows abnormal foveal structure at very early stages of disease. In more established disease, OCT reveals loss, or marked disruption, of central outer retinal macular architecture with relative preservation of peripheral macular structure (Fig. 48.4).

Electrophysiology

Electrophysiological abnormalities in STGD are variable. An abnormal electro-oculogram (EOG), suggestive of generalized RPE dysfunction, is common. The pattern electroretinogram (PERG) and focal electroretinogram (ERG) are usually abolished or markedly reduced, suggesting macular dysfunction. The full-field ERG may be normal at diagnosis (group 1) or suggest widespread retinal dysfunction (group 2 or 3)[1]:

group 1: severe pattern ERG abnormality with normal full-field ERG;
group 2: additional generalized cone dysfunction;
group 3: generalized cone and rod dysfunction.

These groups are not explained by differences in age of onset or duration of disease and electrophysiological classification at onset of disease may be helpful in informing prognosis. Patients in group 1 have the best visual prognosis, with those in group 3 the worst.[1]

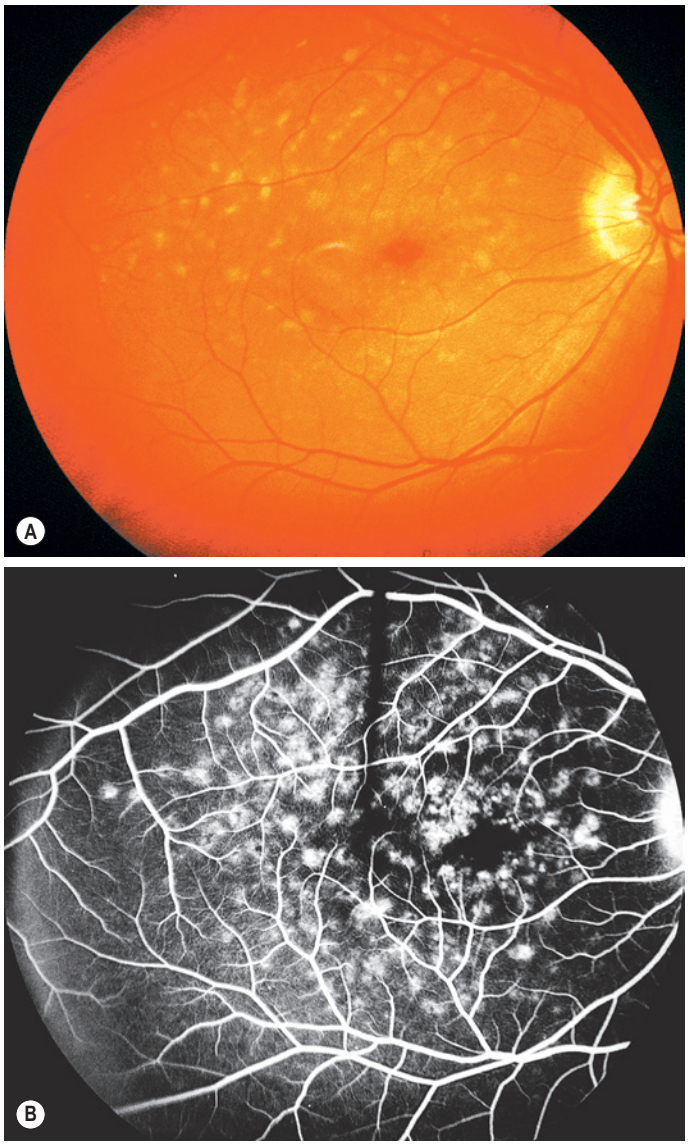


Fig. 48.2 Stargardt disease. Fluorescein angiogram (B) showing "dark choroid" and transmission defects with a color fundus photograph above (A) for comparison.

Molecular genetics and pathogenesis

Mutations in the gene *ABCA4* underlie STGD/FFM, and have also been implicated in retinitis pigmentosa (RP) and cone–rod dystrophy. *ABCA4* encodes a transmembrane rim protein in the outer segment discs of rod and cone photoreceptors involved in transport of retinoids from photoreceptor to RPE. Failure of this transport results in deposition of a lipofuscin fluorophore, A2E (*N*-retinylidene-*N*-retinylethanolamine), in the RPE,[2] which is deleterious to the RPE and leads to secondary photoreceptor degeneration.

More than 800 sequence variations in *ABCA4* have been reported, demonstrating the high allelic heterogeneity and highlighting the difficulties in assigning disease-causing status to sequence variants detected when screening such a large (50 exons) and polymorphic gene. Nonsense mutations with a major effect on the encoded protein can be confidently predicted to be disease causing. A major problem occurs with missense mutations since sequence variants are common in controls; therefore, establishing pathogenicity may be problematic. Direct evidence of pathogenicity can only be established by functional analysis of the encoded mutant protein.

Correlation between the type and combination of *ABCA4* mutations with the severity of the phenotype is often possible.[3] For example, biallelic null mutations usually lead to an early-onset cone–rod dystrophy phenotype rather than STGD. Variable retinal phenotypes within families may be explained by different combinations of *ABCA4* mutations segregating within a single family, but it is likely that other modifier genes or environmental factors may also influence intrafamilial variability.

Accumulation of lipofuscin-related products in the RPE, such as A2E, occurs in STGD and in *ABCA4* knockout mice (*abca4*$^{-/-}$), resulting in free radical generation, release of pro-apoptotic mitochondrial proteins, and lysosomal dysfunction.[2] This leads to RPE dysfunction and cell death and subsequent photoreceptor cell loss.

A2E synthesis can be reduced by raising *abca4*$^{-/-}$ mice in total darkness, and is increased by feeding the mice supplemental vitamin A. It seems reasonable to advise STGD patients to avoid vitamin A supplementation and to wear ultraviolet light-blocking sunglasses. We also recommend an antioxidant-rich diet, which slows photoreceptor cell death in animal models of retinal dystrophies. Affected children may be helped by low vision aids and educational support. Families should also be offered genetic counseling. STGD is inherited as an AR trait and thus younger siblings of an affected child have a 1 in 4 risk of developing the disorder. Older siblings are at a lower risk, as the age of onset is usually similar between affected siblings. The carrier frequency of STGD is 1 in 50; thus there is a 1 in 50 chance that an asymptomatic partner of an affected individual carries a disease-causing sequence change in *ABCA4*. Therefore, there is a 1% risk of an affected individual having an affected child (higher if the partner is a close relative).

Future therapies

New therapeutic interventions for STGD include drugs that target the adenosine triphosphate (ATP)-dependent transport mechanism, thereby augmenting ABCA4-related retinoid transport, or slow the visual cycle, reducing the production of A2E. Directly inhibiting the toxic effects of A2E may prove more effective. Pharmacological agents aimed at these three targets have been developed and are likely to progress to a human clinical trial in the near future.[2,4] Such agents may also be helpful in other macular degenerations associated with lipofuscin accumulation, such as Best disease.

Other interventions including gene-replacement therapy and stem cell-based transplantation are currently in clinical trial (http://www.clinicaltrials.gov).

Autosomal dominant inheritance

Autosomal dominant Stargardt-like macular dystrophy

Clinical and histological findings

Compared to the recessive disorder, individuals with autosomal dominant (AD) STGD-like dystrophy have a milder phenotype

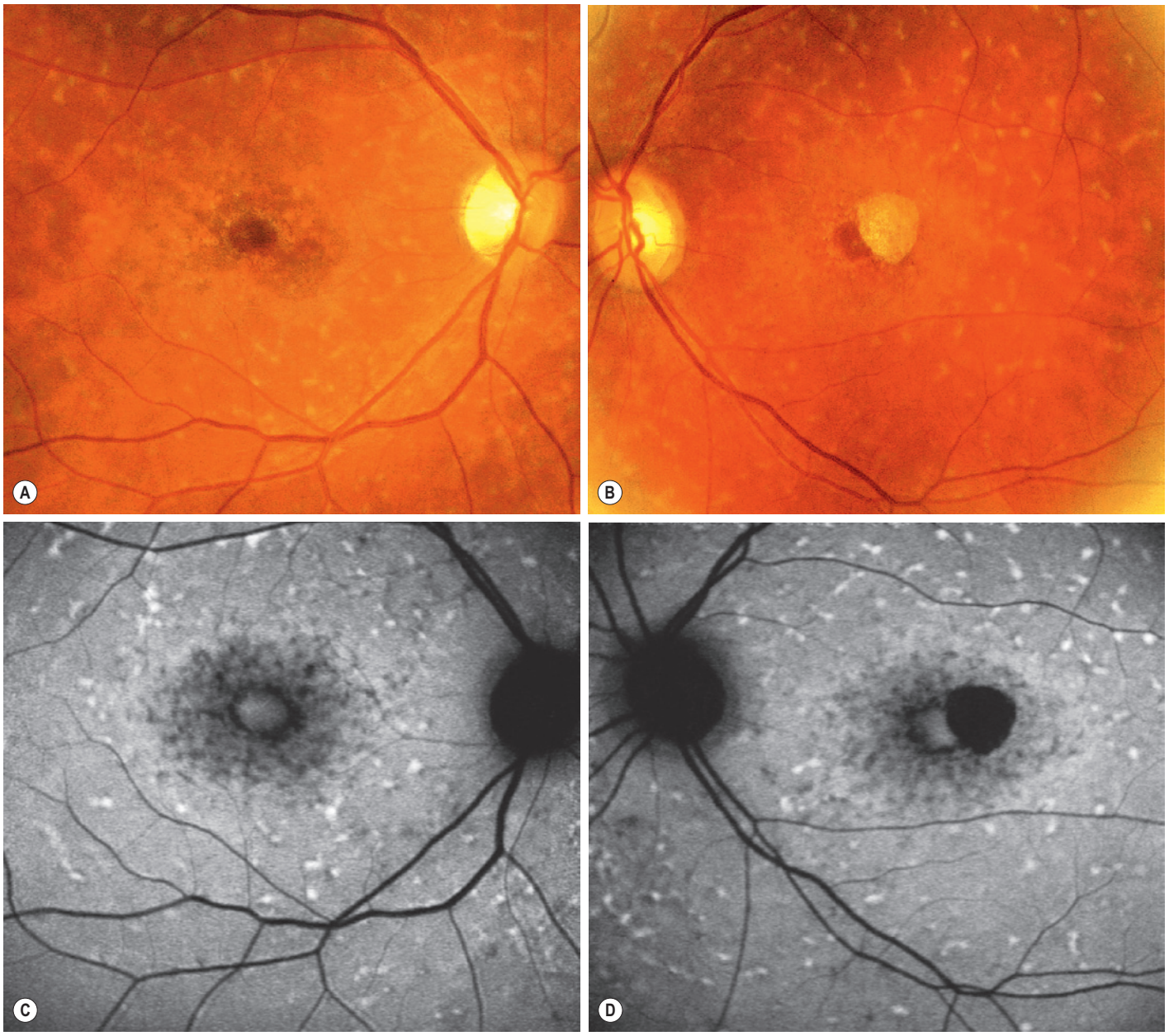


Fig. 48.3 Stargardt disease. Characteristic appearance on fundus autofluorescence imaging (C,D) showing abnormal accumulation of lipofuscin, the presence of active and resorbed flecks, and RPE atrophy. Color fundus photographs (A,B) are shown for comparison.

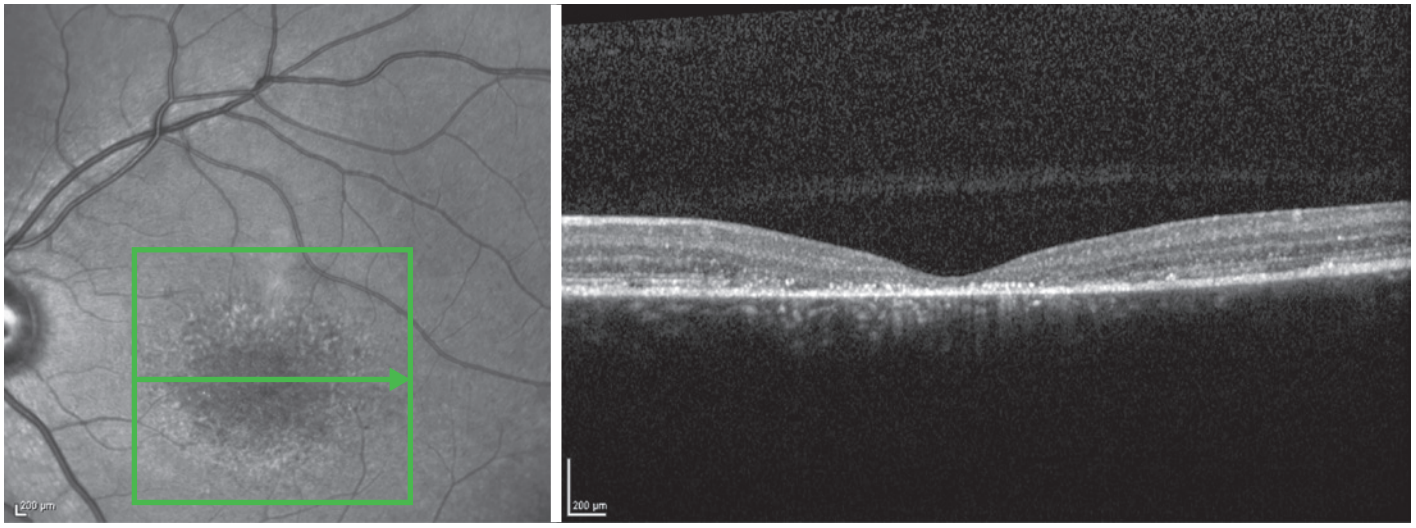


Fig. 48.4 Stargardt disease. Spectral domain optical coherence tomography (SD-OCT) showing loss of central outer retinal macular architecture with relative preservation of peripheral macular structure. Outer retinal debris can be seen at the fovea.

with good vision and minimal color vision defects. Individuals usually present in the first or second decades with visual loss, which may precede retinal changes. Temporal optic disc pallor may precede retinal findings. The "dark choroid" sign on fluorescein angiography is uncommon in the dominant form. Histopathological findings are similar to AR STGD, with widespread accumulation of lipofuscin throughout the RPE.

Electrophysiology

Individuals with AD STGD-like dystrophy often have no significant EOG or ERG abnormalities.

Molecular genetics and pathogenesis

Inheritance patterns may distinguish the two forms of STGD but pseudodominance is a confounding factor – the carrier frequency of AR STGD is sufficiently common (1 in 50) for an affected individual to have an asymptomatic partner carrying a disease-associated sequence change in *ABCA4*. Pseudodominance is also common in consanguineous families.

Two chromosomal loci have been identified: 6q14 (STGD3) and 4p (STGD4). Two mutations, a 5-base pair (bp) deletion and two 1-bp deletions separated by four nucleotides, in the gene *ELOVL4* have been associated with STGD3 and other macular dystrophies, including pattern dystrophy. *ELOVL4* is expressed in rod and cone photoreceptor inner segments and may be involved in retinal fatty acid metabolism.

A missense mutation, p.Arg373Cys, in *PROM1* co-segregates with disease in STGD4. *PROM1* encodes human prominin 1, which has a role in outer segment disc formation and maintenance. The same *PROM1* missense mutation, p.Arg373Cys, occurs in patients with an early-onset autosomal dominant "bull's eye" macular dystrophy (MCDR2).

Autosomal dominant "bull's eye" macular dystrophy (MCDR2)

Clinical and histological findings

Onset is from the end of the first to the sixth decade, with most presenting with reading difficulties.[5] RPE mottling in younger subjects progresses to a bull's eye maculopathy (BEM) and, later, macular atrophy. Some patients have typical features of RP (see Chapter 46). Patients have a mild to moderate reduction in visual acuity, except when associated with RP, where markedly reduced central vision is common.

Electrophysiology

Electrophysiological findings range from isolated macular dysfunction without generalized photoreceptor dysfunction, to a very severe rod–cone dysfunction.

Molecular genetics and pathogenesis

A distinct missense mutation, p.Arg373Cys, in *PROM1* has been identified.[5] Recessive nonsense mutations have also been reported in *PROM1* that cause a severe form of autosomal recessive RP, not associated with BEM.

Best disease (vitelliform macular dystrophy)

Clinical and histological findings

Best disease (BD) is an autosomal dominantly inherited macular dystrophy with a round or oval yellow subretinal macular deposit that is highly autofluorescent on AF imaging (Fig. 48.5). Although most gene carriers show a reduced light rise on EOG, the retinal phenotype is variable. Some gene carriers have a completely normal fundus. The phenotype is classified into five stages (Table 48.2):

stage 0: pre-vitelliform – a normal fundus in an asymptomatic gene carrier with an abnormal EOG;
stage I: minor RPE changes;
stage II: classical "egg yolk" macular lesion (Fig. 48.6A). FFA shows a corresponding area of blocked choroidal fluorescence (Fig. 48.6B). This appearance is usually seen during the first or second decades, often with near-normal visual acuity;
stage IIa: the "egg yolk" begins to break up secondary to resorption of the yellow material lying between the RPE and sensory retina, usually associated with noticeable visual impairment (Fig. 48.7);
stage III: pseudohypopyon – part of the lesion is resorbed leaving the appearance of a "fluid level" at the macula;
stage IVa: the yellow material is completely resorbed, leaving RPE atrophy;
stage IVb: subretinal fibrosis;
stage IVc: choroidal neovascularization (Fig. 48.6C,D).

Histopathology shows accumulation of lipofuscin throughout the RPE. Although the ophthalmoscopic abnormality is usually in the macular region, more widespread retinal involvement is present.

The visual prognosis is good; most patients retain reading vision beyond the fifth decade. Carriers who have minimal macular abnormality or a normal fundus appearance (but abnormal EOG) in early-adult life usually retain good visual acuity.

Electrophysiology

Full-field ERG is normal; the EOG shows a reduced or absent light rise, indicating widespread RPE dysfunction. Most individuals carrying mutations in the gene associated with BD, *BEST1*, have an abnormal EOG, but the macular appearance may be normal. True non-penetrance is rare.

Molecular genetics and pathogenesis

Best disease is caused by mutations in *BEST1*, encoding the protein bestrophin, localized to the basolateral plasma membrane of the RPE. It forms a calcium-activated chloride channel that maintains chloride conductance and regulates fluid transport across the RPE. OCT studies suggest that impaired fluid transport in the RPE secondary to abnormal chloride conductance leads to accumulation of fluid and/or debris between RPE and photoreceptors and between RPE and Bruch's membrane, leading to detachment and secondary photoreceptor degeneration.[6] The variable expression of BD remains unexplained: additional genes and/or environmental influences may play a role in the wide range of clinical expression.

Recessive mutations have been identified in *BEST1* in a condition associated with multiple vitelliform retinal deposits and maculopathy: autosomal recessive bestrophinopathy (ARB).[7] Hyperopia is common and there is an increased incidence of angle closure glaucoma. In childhood, the retinopathy is characterized by bilateral multifocal subretinal

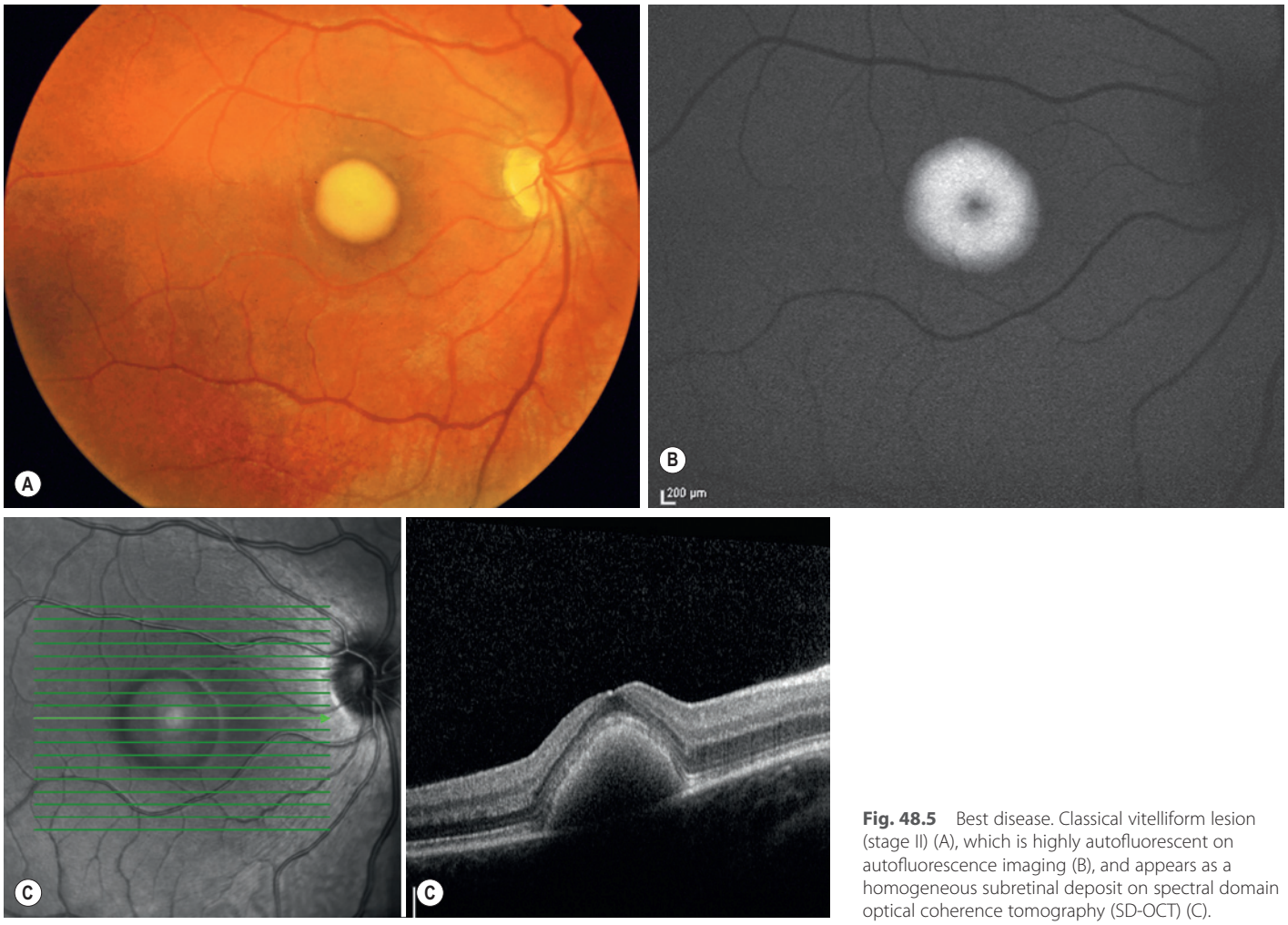


Fig. 48.5 Best disease. Classical vitelliform lesion (stage II) (A), which is highly autofluorescent on autofluorescence imaging (B), and appears as a homogeneous subretinal deposit on spectral domain optical coherence tomography (SD-OCT) (C).

Table 48.2 Classification of vitelliform dystrophy

Stage	Macular appearance
0	Normal fundus (abnormal EOG)
I	Minor retinal pigment epithelial changes
II	Typical vitelliform lesion
IIa	"Scrambled egg" appearance
III	Pseudohypopyon phase
IVa	Atrophic retinal pigment epithelium
IVb	Fibrous scar tissue
IVc	Choroidal neovascularization

EOG, electro-oculogram.
Modified from Mohler CW, Fine SL. Long-term evaluation of patients with Best's vitelliform dystrophy. Ophthalmology 1981; 88: 688–92.

yellow deposits seen most clearly on AF imaging. Retinal edema and subretinal fluid may be observed clinically and on OCT (Fig. 48.8). The EOG light rise is absent or severely reduced. In contrast to the dominant form, the parents of patients with ARB have a normal EOG. Adults with ARB have an abnormal EOG and reduced rod and cone responses on full-field ERG. In children with ARB, the ERG is usually normal. The prognosis for central vision is worse than in BD.

AD and AR mutations in *IMPG1* and *IMPG2* have been reported in families with AD and AR atypical vitelliform dystrophy.[8] The vitelliform lesions may be confined to the macula or be multifocal. This condition can be distinguished from BD by the later age of onset, drusen-like deposition, and by the fact that in patients with mutations in *IMPG1* and *IMPG2* the EOG light rise is normal or only mildly subnormal.

Future therapies

Future interventions may include gene-based therapies or therapeutic agents that either improve the function of the calcium-activated chloride channel and fluid exchange across the RPE, slow the visual cycle to reduce the accumulation of lipofuscin, or directly inhibit the toxic end-product, A2E, as has been described for STGD.[4]

Pattern dystrophies

Clinical and histological findings

Pattern dystrophies are usually dominantly inherited disorders of the RPE, with bilateral symmetrical yellow-orange deposits at the macula in various distributions, including butterfly or reticular patterns. There is increased AF (Fig. 48.9). On FFA,

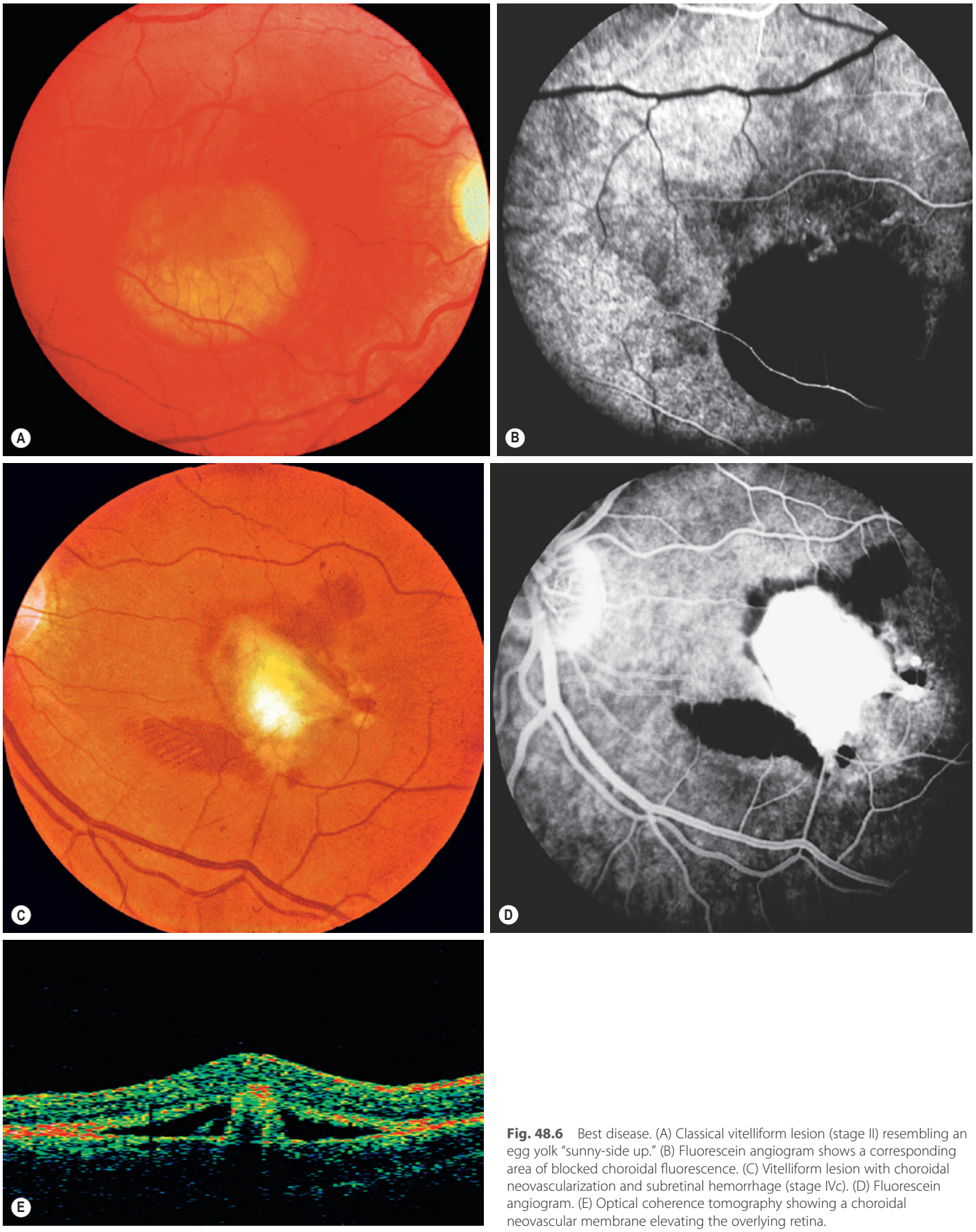


Fig. 48.6 Best disease. (A) Classical vitelliform lesion (stage II) resembling an egg yolk "sunny-side up." (B) Fluorescein angiogram shows a corresponding area of blocked choroidal fluorescence. (C) Vitelliform lesion with choroidal neovascularization and subretinal hemorrhage (stage IVc). (D) Fluorescein angiogram. (E) Optical coherence tomography showing a choroidal neovascular membrane elevating the overlying retina.

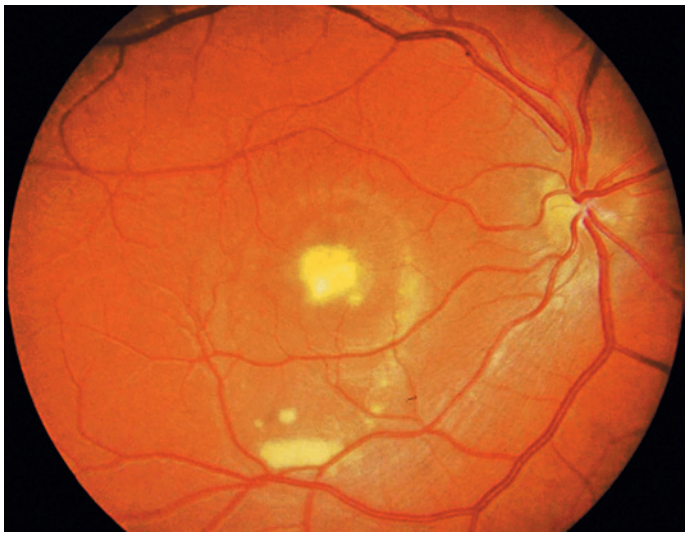


Fig. 48.7 Best disease. A partially resorbed yellow subretinal macular deposit (stage IIa).

the macular deposits appear hypofluorescent secondary to blockade of underlying choroidal fluorescence. The macular deposits represent the accumulation of lipofuscin in RPE cells and within the sub-RPE space, seen histopathologically. However, the RPE accumulation is not restricted to the macular region.

The macular changes are often associated with good vision, although a slowly progressive loss of central vision may occur with atrophic macular changes. The age at presentation is between the second to fifth decades: it is rarely symptomatic in childhood. Examination of at-risk young family members may show mild macular changes.

Three main pattern dystrophy phenotypes have been described: butterfly-shaped dystrophy, reticular dystrophy, and fundus pulverulentus:

Butterfly-shaped dystrophy is inherited as an autosomal dominant trait, first evident in late childhood, characterized by normal or mildly reduced visual acuity, and normal color vision, peripheral visual fields, and dark adaptation.

Reticular dystrophy is inherited as an autosomal dominant or recessive trait, first appearing in early childhood. First, there is an accumulation of pigment granules at the fovea; later a typical reticular pattern extends to the periphery. Visual acuity is usually normal.

Fundus pulverulentus is a rare non-progressive disorder characterized by normal visual acuity and a symmetrical granular mottled pigmentation at the posterior pole (Fig. 48.10).

Electrophysiology

Usually, the pattern ERG and the EOG are abnormal, with variable full-field ERG ranging from normal to generalized cone and rod system dysfunction, suggesting widespread RPE–photoreceptor dysfunction.

Molecular genetics and pathogenesis

Mutations in the gene *PRPH2* (previously *peripherin/RDS*) have been described. Further genes remain to be identified.

The *PRPH2* gene was identified in mice with a photoreceptor degeneration known as "retinal degeneration, slow" (rds). Subsequently, the orthologous human *PRPH2* gene was shown to cause autosomal dominant RP. Mutation in codon 172 of *PRPH2* has been implicated in autosomal dominant macular dystrophy. Weleber et al. described a 3-bp deletion in *PRPH2* that resulted in retinitis pigmentosa, pattern dystrophy, and FFM in different individuals.[9]

The PRPH2 protein is a membrane-associated glycoprotein restricted to photoreceptor outer segment discs in a complex with ROM1. It may function as an adhesion molecule involved in the stabilization and maintenance of a compact arrangement of outer segment discs. It interacts with the GARP domain (glutamic acid- and proline-rich region) of the beta-subunit of rod cyclic guanosine monophosphate (cGMP)-gated channels, in a complex including the Na^+/Ca^{2+}–K^+ exchanger. This interaction may anchor the channel–exchanger complex in the rod outer segment plasma membrane. The rds mouse (homozygous for a null mutation in *PRPH2*) fails to develop photoreceptor discs and outer segments with downregulation of rod opsin expression, resulting in apoptotic loss of photoreceptor cells. Subretinal injection of recombinant adeno-associated virus encoding a *PRPH2* transgene in these mice resulted in the generation of outer segment structures and formation of new stacks of discs containing both PRPH2 and rhodopsin with electrophysiological function preserved.[10] Ultrastructural improvement depended on the age at treatment, but a single injection may be longlasting. Thus, gene therapy in patients with photoreceptor defects may need early intervention and accurate control of transgene expression.

North Carolina macular dystrophy

Clinical and histological findings

North Carolina macular dystrophy (MCDR1) is a non-progressive autosomal dominant disorder with complete penetrance and a variable macular phenotype. Presentation is usually during the first or second decade. The disorder is a failure of normal macular development.[11] Bilaterally symmetrical fundus appearances in MCDR1 range from a few small (less than 50 μm) yellow drusen-like lesions in the central macula (grade 1) (Fig. 48.11) to larger confluent lesions (grade 2), and well-demarcated macular chorioretinal atrophy (grade 3) (Fig. 48.12). Peripheral retinal drusen-like deposits have been described. The severity of visual loss is grade dependent; vision is poorest with grade 3 lesions. Color vision is usually normal. Occasionally MCDR1 is complicated by choroidal neovascular membrane formation (CNVM).

Histopathology shows accumulation of lipofuscin in the RPE within the atrophic macular lesion.

Electrophysiology

EOG and ERG are normal.

Molecular genetics and pathogenesis

MCDR1 is linked to a locus on chromosome 6q16, but the causative gene has yet to identified.[11] The identification of the gene may improve our understanding of macular development in man.

A dominantly inherited macular dystrophy has been mapped to chromosome 6q14, adjacent to but probably distinct from

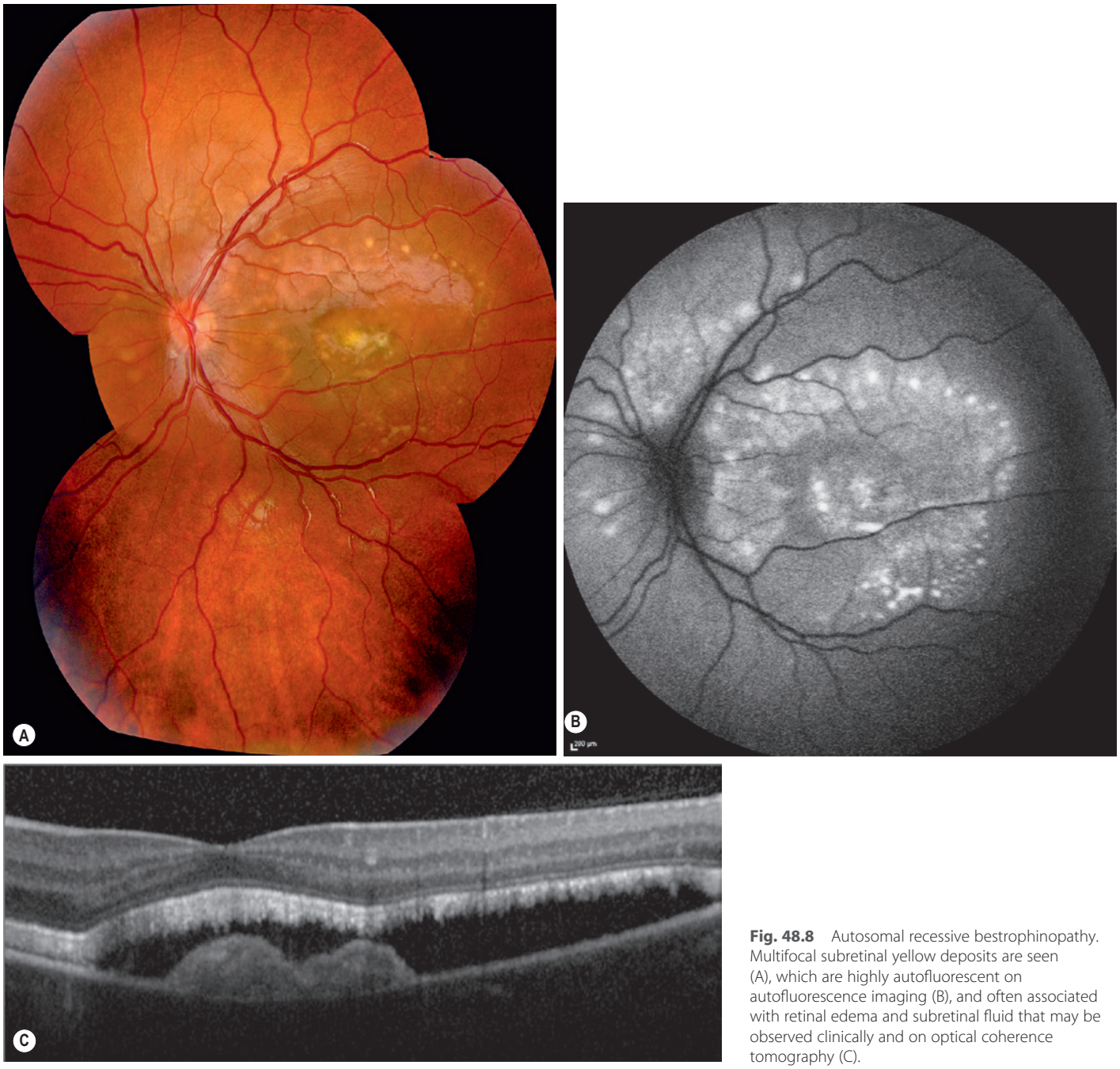


Fig. 48.8 Autosomal recessive bestrophinopathy. Multifocal subretinal yellow deposits are seen (A), which are highly autofluorescent on autofluorescence imaging (B), and often associated with retinal edema and subretinal fluid that may be observed clinically and on optical coherence tomography (C).

the MCDR1 locus.[12] It has a highly variable phenotype; an autosomal dominant drusen disorder with macular degeneration (DD). A study by Griesinger et al. showed that most young adults had fine macular drusen and good vision.[12] Patients who were symptomatic from infancy or early childhood had poorer vision with an atrophic maculopathy and drusen. There was also evidence of progression in late adulthood. The DD disease interval overlaps with that of STGD3 and an autosomal dominant atrophic macular degeneration (adMD),[13] suggesting an allelic disorder. However, the phenotype of DD differs from that of STGD3 and adMD. Macular drusen are a hallmark of DD, whilst RPE atrophy and subretinal flecks are prominent features of STGD3 and adMD.

North Carolina macular dystrophy-like phenotypes

Three North Carolina macular dystrophy-like phenotypes map to different genetic loci than MCDR1, suggesting further genetic heterogeneity in the MCDR1 phenotype.[11]

Autosomal dominant macular dystrophy (MCDR3) resembling North Carolina macular dystrophy

Clinical and electrophysiological findings

A pedigree has been described with an early-onset autosomal dominant macular dystrophy (MCDR3).[14] Visual acuity ranged from 6/5 to 6/60. The retinal changes, confined to



Fig. 48.9 Pattern dystrophy.

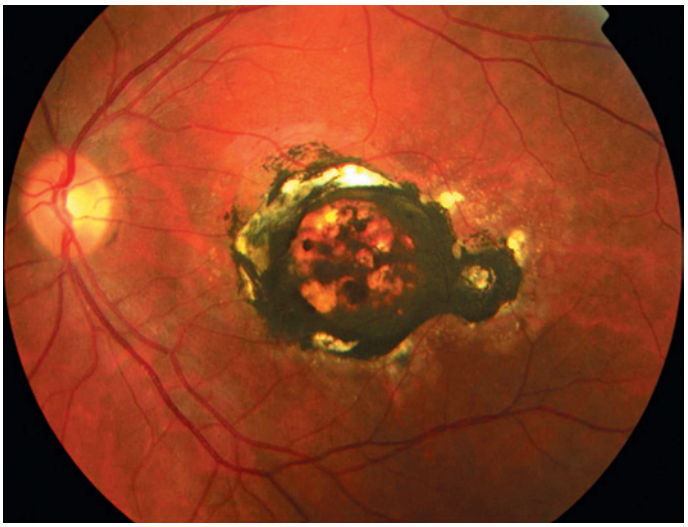


Fig. 48.12 North Carolina macular dystrophy (MCDR1). Macular atrophy and hyperpigmentation with surrounding drusen-like deposits (grade 3).

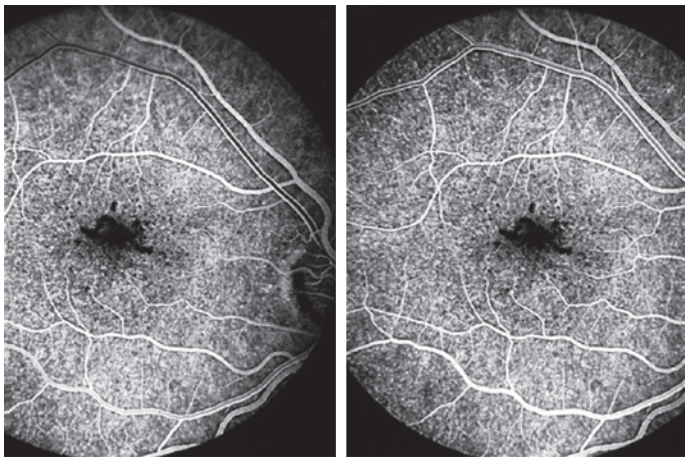


Fig. 48.10 Fundus pulverulentus. Fluorescein angiogram showing mottled and clumped pigment epithelium at the posterior pole. *(Courtesy of Professor A.C. Bird.)*

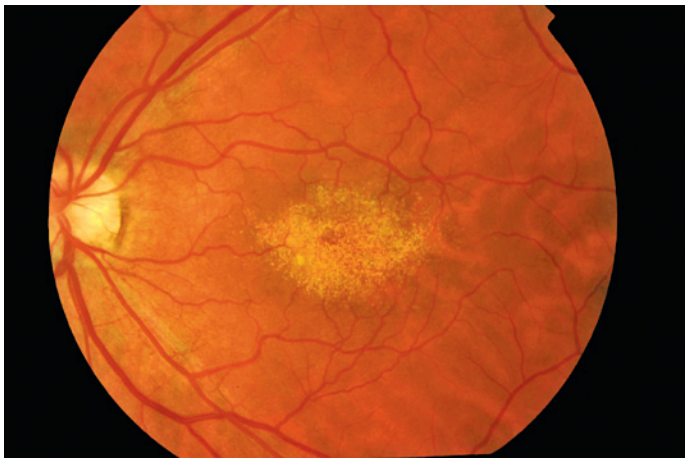


Fig. 48.11 North Carolina macular dystrophy (MCDR1). Small yellow drusen-like lesions at the central macula (grade 1).

the macular region, varied from mild RPE pigmentary change to atrophy. Drusen-like deposits were present to varying degrees and were characteristic of the phenotype (Fig. 48.13). Choroidal neovascular membrane formation is an uncommon complication. The only significant differences between this phenotype and MCDR1 is that in MCDR3 color vision is abnormal in the majority of affected individuals and there was evidence of disease progression in a single case.

A phenotype similar to MCDR3 mapping to the same locus has been reported.[15]

Molecular genetics

Linkage to chromosome 5p13.1–p15.33, but excluding the MCDR1 locus,[14,15] has been reported. The gene is unidentified.

North Carolina-like macular dystrophy and progressive sensorineural hearing loss

Clinical and electrophysiological findings

A non-progressive MCDR1-like macular dystrophy in association with progressive sensorineural hearing loss has been reported (MCDR4).[16] Visual acuity ranged from 6/9 to hand movements. The EOG and full-field ERG were normal. Progressive sensorineural deafness was present in all adult-affected individuals.

Molecular genetics

Genotyping excluded linkage to the MCDR1 locus and established linkage to chromosome 14q.

North Carolina-like macular dystrophy and digital anomalies (Sorsby syndrome)

Clinical findings

A dominantly inherited condition with bilateral macular dysplasia and apical dystrophy or brachydactyly has been reported (Fig. 48.14).[17,18] Visual acuity ranged from 6/12 to 4/60. The maculopathy was non-progressive and variable in severity, ranging from mild RPE pigmentary changes to excavated chorioretinal atrophic lesions. There was no generalized retinal dysfunction.

Molecular genetics

The MCDR1, MCDR3, and MCDR4 loci have all been excluded, providing evidence of further genetic heterogeneity associated with the North Carolina macular dystrophy-like phenotype.[11,19] This is in keeping with the established heterogeneity in the genetic mechanisms underlying split-hand and split-foot malformations (microdeletions being common) and the developmental macular dystrophies.

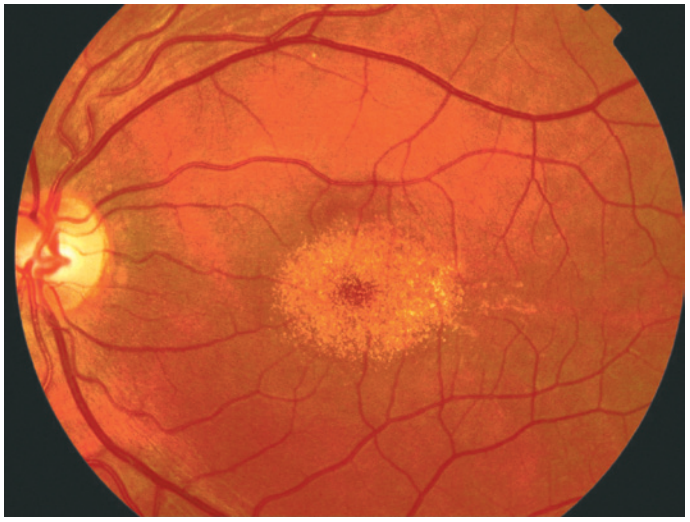


Fig. 48.13 Autosomal dominant macular dystrophy (MCDR3) resembling North Carolina macular dystrophy. Characteristic drusen-like deposits at the macula.

Progressive bifocal chorioretinal atrophy

Clinical findings

Progressive bifocal chorioretinal atrophy (PBCRA) is an early-onset autosomal dominant disorder characterized by infantile onset nystagmus, myopia, poor vision, and slow progression.[20] A large atrophic macular lesion and nasal subretinal deposits present soon after birth. An atrophic area nasal to the optic disc appears in the second decade and enlarges progressively (Fig. 48.15). Marked photopsia in early/middle age and retinal detachment extending from the posterior pole are complications. FFA and indocyanine green angiography (IGA) demonstrate a large circumscribed area of macular choroidal atrophy with staining of deposits in the peripheral retina.

Electrophysiology

Unlike MCDR1, both ERG and EOG are abnormal, reflecting widespread abnormality of photoreceptors and RPE.

Molecular genetics and pathogenesis

PBCRA has been linked to 6q14–q16.2; the disease locus overlaps with the established MCDR1 interval. These two

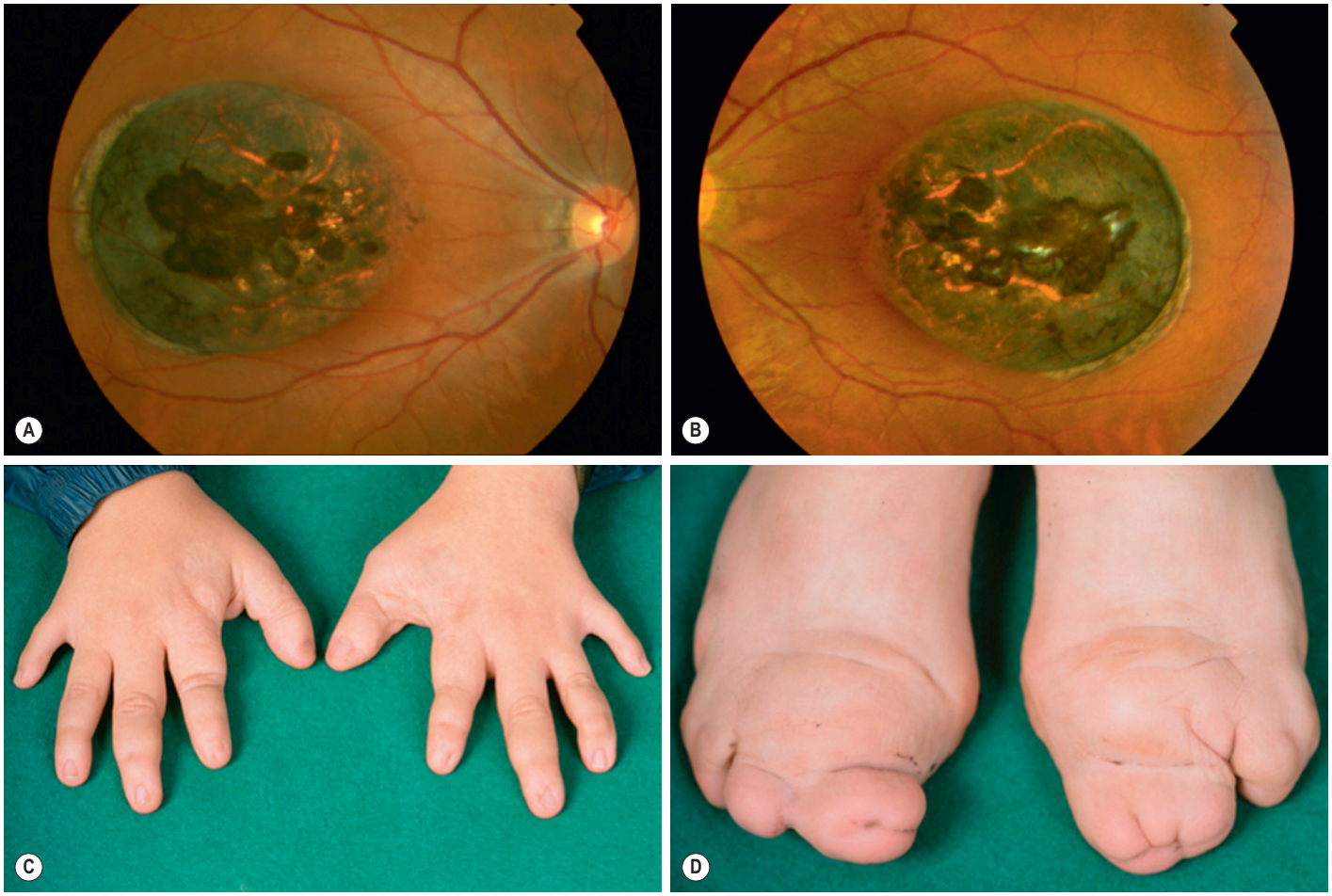


Fig. 48.14 North Carolina-like macular dystrophy and digital anomalies (Sorsby syndrome). (A,B) Color fundus photographs showing the typical bilateral macular dysplasia. (C,D) In this individual there is shortening and deformity of the fingers and toes due to aplasia and hypoplasia of middle and terminal phalanges. There is skin syndactyly in association with bifurcation of the terminal phalanx of the hallux causing severe deformity of the foot.

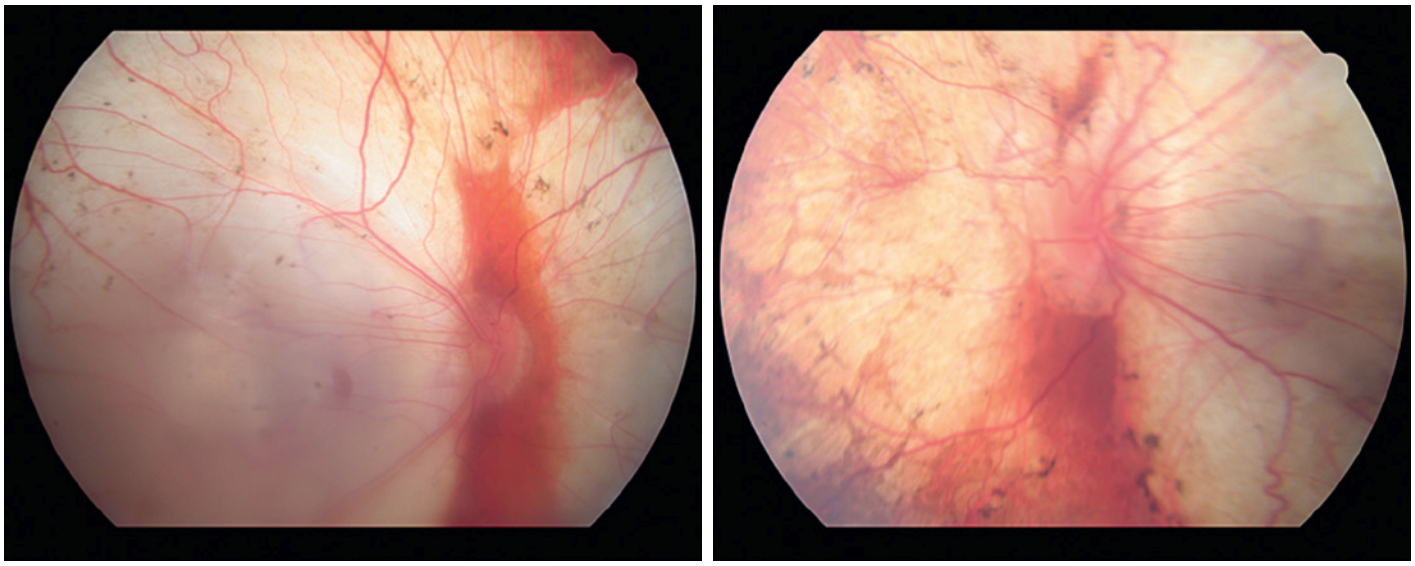


Fig. 48.15 Progressive bifocal chorioretinal atrophy. Color fundus photographs showing bilateral extensive macular atrophy and atrophy nasal to the optic nerve head.

autosomal dominant macular dystrophies have some phenotypic similarities; both result from a failure of normal macular development.[11] PBCRA differs significantly from MCDR1 in several important respects, including slow progression, abnormal color vision, extensive nasal as well as macular atrophy, and abnormal ERG and EOG. If allelic, it is likely that different mutations are involved in their etiology. An alternative explanation is that PBCRA and MCDR1 are caused by mutations in two different adjacent developmental genes.

Central areolar choroidal dystrophy

Clinical and histological findings

Central areolar choroidal dystrophy (CACD) is characterized by bilateral, symmetrical, subtle mottling of the RPE at the macula in the second decade, which progresses to atrophy of the RPE and choriocapillaris. The round or oval macular lesion is well demarcated. CACD has been divided into four stages[21]:

stage I: slight parafoveal changes of the RPE;

stage II: RPE mottling encircling the fovea;

stage III: additional atrophy of the choriocapillaris without central involvement;

stage IV: stage III plus central involvement.

Color vision is abnormal and central scotomata are present with normal peripheral visual fields. FFA and IGA reveal RPE atrophy and various degrees of choriocapillaris loss.

Electrophysiology

Full-field ERGs are normal in the early stages, but may become abnormal in advanced stages.

Molecular genetics and pathogenesis

A p.Arg142Trp mutation in *PRPH2* has been implicated as one cause of this rare autosomal dominant macular dystrophy. Sporadic cases of CACD have been described but no mutations have been found in *PRPH2* suggestive of further genetic heterogeneity. A locus at 17p13 has also been identified, with a novel mutation in *GUCY2D* reported.

X-linked inheritance

X-linked juvenile retinoschisis (XLRS)

See Chapter 51.

Foveal hypoplasia

Clinical findings

This presents in infancy with reduced vision, nystagmus, and a poorly developed fovea; there is no recognized foveal pit or luteal pigment, and blood vessels may cross the presumed foveal region. These changes can be demonstrated using OCT and AF imaging (Fig. 48.16). Foveal hypoplasia may be an isolated abnormality or associated with aniridia or albinism (see Chapter 41).

Molecular genetics

Isolated foveal hypoplasia is most commonly sporadic, but two dominant pedigrees have been reported, with a *PAX6* missense mutation identified in one of these families.[21,22] The mutation occurred in the C-terminal part of the paired domain.[21] However, *PAX6* has been screened in some reported isolated cases, with no mutations identified.[23] Autosomal recessive forms of foveal hypoplasia are also seen and recently mutations in a glutamine transporter gene *SLC38A8* have been reported in a rare recessive disorder with foveal hypoplasia associated with chiasmal misrouting.[24]

Bull's eye maculopathy

The term "Bull's eye" maculopathy (BEM) first described the characteristic appearance of chloroquine retinopathy. Bull's eye lesions have since been reported in cone dystrophy, cone–rod dystrophy, rod–cone dystrophy, *ABCA4*-retinopathy and in

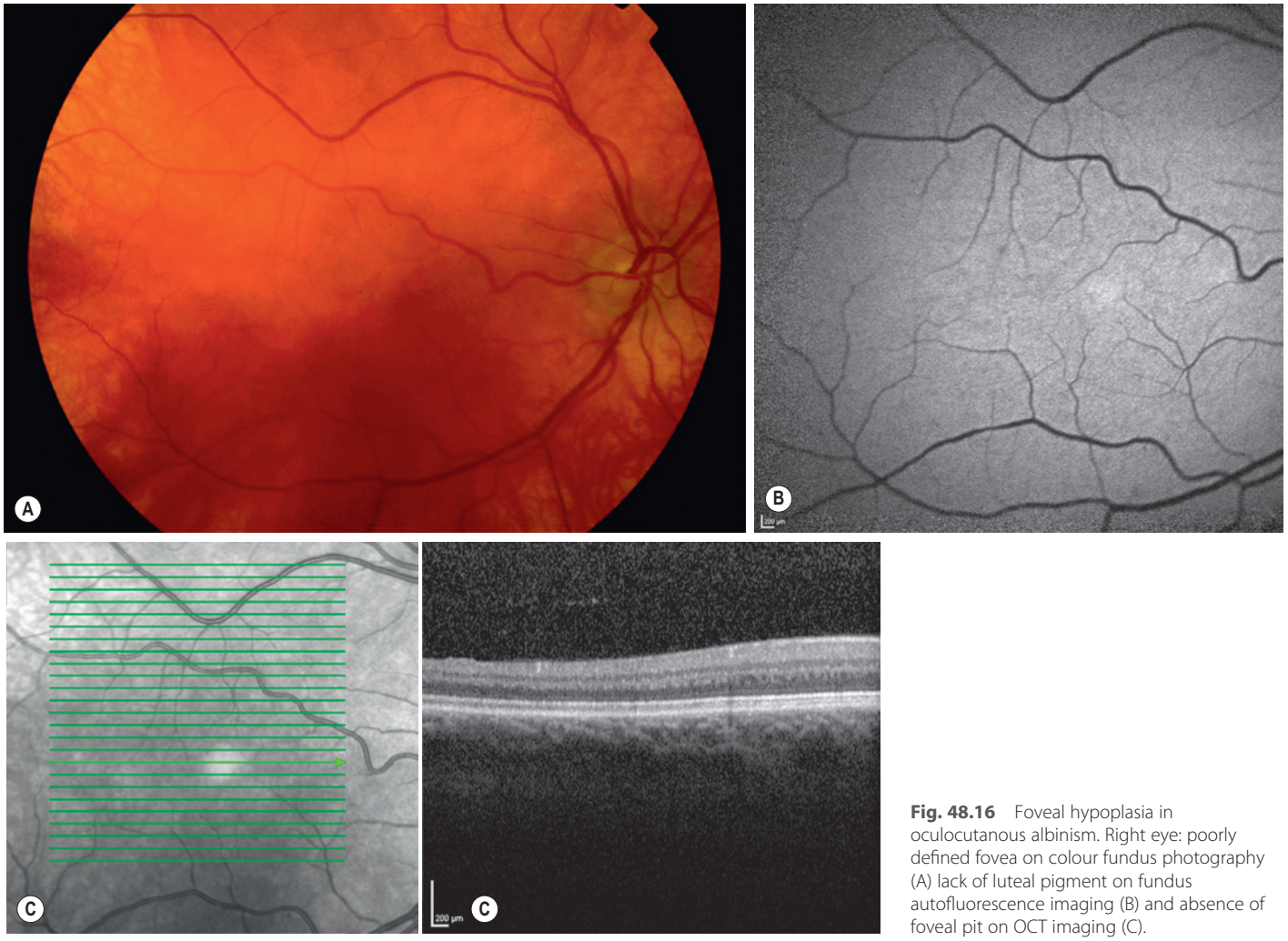


Fig. 48.16 Foveal hypoplasia in oculocutanous albinism. Right eye: poorly defined fovea on colour fundus photography (A) lack of luteal pigment on fundus autofluorescence imaging (B) and absence of foveal pit on OCT imaging (C).

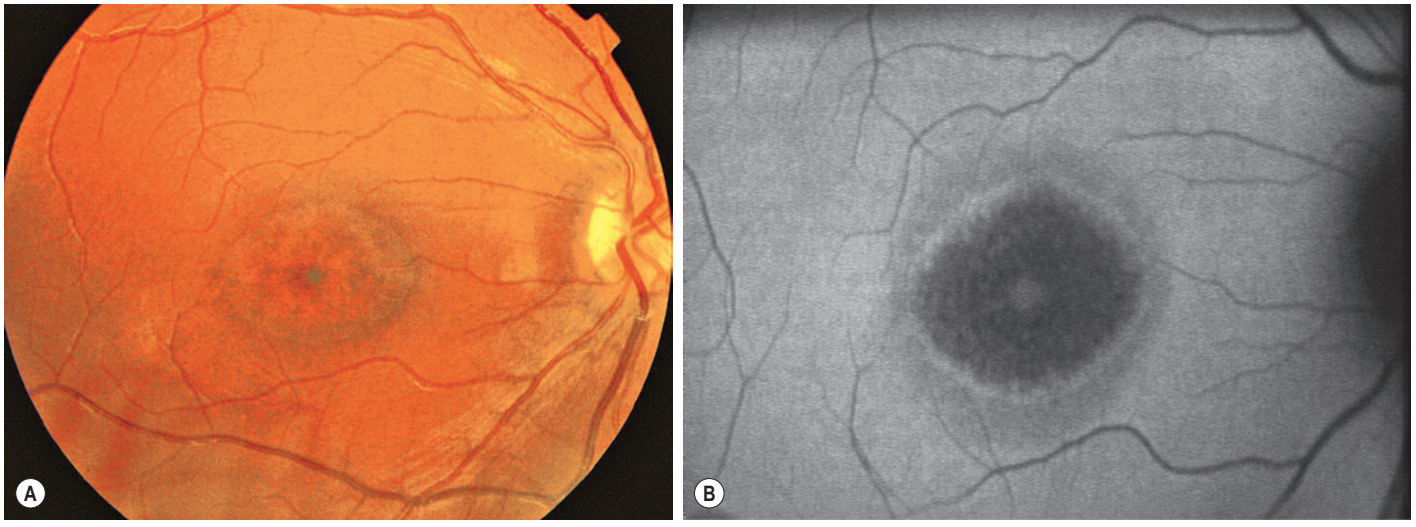


Fig. 48.17 Bull's eye maculopathy (BEM). (A) Characteristic ophthalmoscopic appearance in which there is annular retinal pigment epithelium atrophy and central sparing. (B) Typical autofluorescence image of BEM.

some dominantly inherited macular dystrophies, including benign concentric annular dystrophy, fenestrated sheen macular dystrophy and in association with the p.Arg373Cys *PROM1* variant.[5,25] BEM is a frequent finding in neurodegenerative disorders, especially Batten disease, Hallervorden–Spatz disease, and olivopontocerebellar atrophy (see Chapters 47 and 65).

The pathogenesis of BEM is poorly understood. The annular RPE atrophy and central sparing may correspond to the pattern of lipofuscin accumulation in the RPE, which in healthy individuals is highest at the posterior pole and shows a depression at the fovea (Fig. 48.17). The initially spared center usually becomes involved as the disease advances. BEM is not a discrete macular disorder but describes a retinal phenotype that may be seen in a wide variety of macular dystrophies at an early stage of their evolution.

Conclusions

The inherited macular dystrophies are clinically and genetically heterogeneous with well-characterized phenotypes; many causative genes have been identified. Although in some inherited macular dystrophies the disease is confined to the macula, in the majority there is electrophysiological, psychophysical or histological evidence of widespread retinal dysfunction.

There is no established treatment, but treatment trials have begun for STGD; others are anticipated over the next decade. Making the correct diagnosis is important in order to provide accurate information on prognosis and to offer informed genetic counseling. Prenatal and preimplantation diagnosis is possible when the mutation(s) causing disease in the family is known.

Although there is no specific treatment available for these disorders, research is resulting in clinical trials. We are cautiously optimistic that effective interventions will be available in the near future. The provision of best refractive correction, appropriate low vision aids and educational support is very important. Photophobia may be prominent and tinted spectacles or contact lenses and a sunhat may improve comfort and vision.

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Congenital pigmentary and vascular abnormalities of the retina

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Congenital hypertrophy of the retinal pigment epithelium (CHRPE)

- Flat or slightly raised, round or oval, pigmented lesions of the retinal pigment epithelium (RPE).
- Located predominantly at the mid-periphery; less commonly at the posterior pole (Fig. 49.1).
- Pigmented and non-pigmented halo surround lesions.
- Multiple intralesional depigmented lacunae corresponding to areas of RPE loss.[1]
- Depigmented CHRPEs are less common.
- Intensely pigmented RPE cells that are 1.5–2 times the height of normal RPE cells.[2]

Investigations

- Optical coherence tomography (OCT): photoreceptors and outer retinal layers absent directly overlying the lesion.[2,3]
- Autofluorescence (AF): absence of autofluorescence within the lesion is consistent with a lack of lipofuscin with punctuated areas of isoautofluorescence within the lesion.[4]
- Fluorescein angiography (FFA): demonstrates choroidal masking.[4]

Prevalence

CHRPE has a prevalence of between 1.2% and 4.4% in the general population.[5,6] Age at presentation ranges from infancy to 80 years.

Associations

- Vessel sheathing, attenuation, and microangiopathy.
- Crusen.
- Adjacent white-without-pressure and depigmented linear RPE streaks.

Eighty-three percent of lesions enlarged at a median rate of 2 µm per millimeter lesion base per month due to flattening and shifting of cells to accommodate normal attrition of the surrounding RPE.[2]

In adults, 1.5% of lesions may contain a nodular component associated with remote macular edema or malignant transformation within lesions.[7,8]

CHRPE associated with adenomatosis polyposis of the colon (APC)

Multiple (more than three) bilateral, mixed pigmented and depigmented CHRPE are a highly specific and sensitive marker of adenomatous polyposis of the colon (APC) or familial adenomatous polyposis (FAP) and are highly penetrant. APC-associated CHRPEs are:

- Ovoid, pisciform or irregular in shape, surrounded by a pale-gray halo or adjacent depigmented linear streaks (Fig. 49.2).
- Variable sizes and location, from dot-like lesions to multiple disc diameters[9].
- Present at birth and do not grow throughout life.

Diffuse abnormalities of the RPE are also present, including enlargement of RPE cells outside the lesional area containing



Fig. 49.1 Congenital hypertrophy of the retinal pigment epithelium (CHRPE). Slightly raised jet-black lesion in the mid-periphery with an associated small visual field defect. *(Professor A.C. Bird's patient.)*

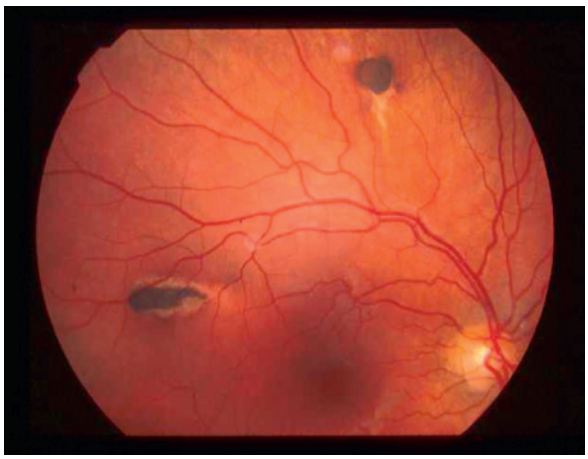


Fig. 49.2 CHRPE lesions in a patient with familial adenomatous polyposis.

enlarged, round melanin granules rather than the smaller, oval granules associated with normal RPE.[10]

Genetics of APC

- Autosomal dominant (AD) with an incidence of 1 in 8300.
- Accounts for ~1% of all colorectal cancers.[11]
- Associated with mutations of APC gene and cause:
  - Gardner syndrome – APC with extra-colonic manifestations such as osteoma and desmoid tumors (10%).
  - Turcot syndrome APC with primary brain medulloblastoma.
  - Also found in APC families without such extra-colonic manifestations.[11]
- APC gene:
  - A tumor suppressor gene on chromosome 5q21-22.[12] CHRPEs suggest the presence of a mutation between codons 148 and 2043.

Multiple adenomatous colorectal polyps (>100) appear between the second and fourth decades.[13] Malignant transformation is seen in over 90% by age 50 years. Colonoscopy is recommended from 12 years and may lead to elective colectomy. Polyps may exist in the upper gastrointestinal (GI) tract including stomach, small bowel, and duodenum, the latter being associated with a significant risk of malignant transformation. Mandibular osteomas and dental anomalies such as missing or supernumerary teeth are also common.

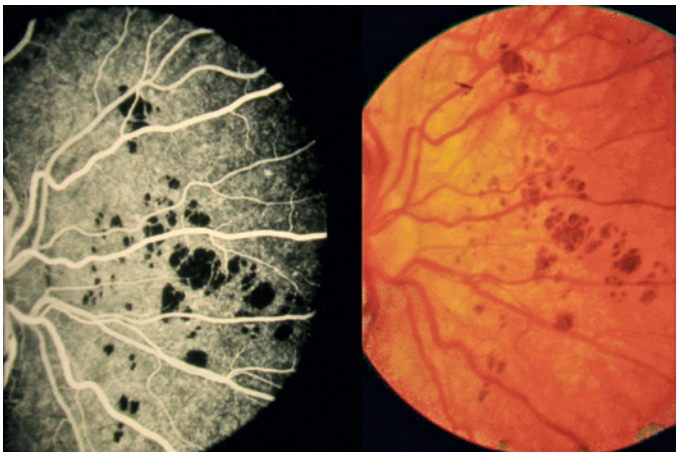


Fig. 49.3 Congenital grouped pigmentation ("bear track"). Unilateral, multiple brown patches in the retinal pigment epithelium of no functional significance. Fluorescein angiography shows masking of the underlying choroidal fluorescence. *(Professor A.C. Bird's patient.)*

Congenital grouped pigmentation of the RPE

- Small, darkly pigmented, flat, circumscribed lesions at the level of the RPE (also known as "bear tracks").
- Increasing in size as they approach the retinal periphery (Fig. 49.3).
- Unilateral and sectorial. Occasionally involving the entire fundus.[14]
- Normal visual function.
- Depigmented variant, "polar bear tracks."[15]
- Pigmented and depigmented lesions may co-exist within the same patient.[16]

Prevalence

The prevalence is 0.12% in the ophthalmic clinic population.[17]

Associations

Usually isolated but possible chance associations include:

- Retinoblastoma.
- Café-au-lait spots and hairy nevus.
- Persistent fetal vasculature.
- Microcephaly.
- Rieger anomaly.
- Macular coloboma.

Congenital simple hamartoma of the retina (CSHRPE)

- Rare, located within the macula region close to the fovea.
- Circumscribed, nodular, and heavily pigmented.

- Arise from RPE, project through the full thickness of the retina into vitreous.
- A feeder arteriole and venule are usually present.
- Subtle surrounding retinal traction may reduce visual acuity.

Investigations

- Ultrasound: nodular, echogenic mass with moderate-to-high internal reflectivity.
- Fluorescein angiography: demonstrates a non-fluorescent lesion with a variable surrounding ring of late hyperfluorescence.[18]
- Indocyanin green angiography: completely blocks choroidal fluorescence.
- OCT: elevation of the inner retina with enhanced reflectivity of its vitreal face and marked optical shadowing at the level of the outer retina and choroid, with normal retina immediately adjacent to lesion.[19,20]

The lesions are congenital, stable, and asymptomatic but can show adjacent intraretinal hemorrhage and exudation.[18]

Torpedo maculopathy

- An ovoid, sharply defined, non-pigmented lesion in the temporal region of the macula, centered on the horizontal raphé (see Fig. 49.3).
- Lesions are longer horizontally (2–3 mm) than vertically (1 mm) and point toward the fovea with either a frayed, pigmented tail or rounded margin located temporally (Fig. 49.4).
- Usually unilateral and unifocal, although satellite lesions have been described.
- The margins have a hyperpigmented border.

Investigations

- OCT: absence of RPE, overlying outer retinal disorganization and thinning, irregular, and degenerate photoreceptor outer segments, interruption of the ellipsoid layer, and clefting corresponding to a loss of the RPE and outer retinal layers.[21,22]
- Autofluorescence: variable hypoautofluorescence with most showing greatest absence in the temporal aspect of the lesion, confirming either non-functional or absent RPE.[23]

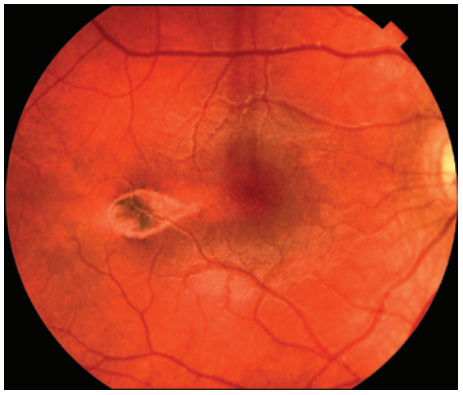


Fig. 49.4 "Torpedo" maculopathy. Sharply defined, non-pigmented lesion in the temporal region of the macula with a characteristic point aimed toward the fovea.

The fovea usually retains normal architecture preserving normal visual acuity but cases have been described with foveal involvement.[24]

Prevalence

A rare congenital abnormality and unknown prevalence.

Associations

Usually isolated but can co-exist with kidney disease, blepharophimosis, situs inversus, ipsilateral choroidal nevus, and ametropia.

Retinal astrocytic hamartoma (RAH)

- Benign glial tumors of the retinal nerve fiber layer.
- Present in 44% of patients with tuberous sclerosis (TSC).[25]
- Less frequently associated with neurofibromatosis.
- Flat or slightly elevated, semi-translucent or opaque lesions (type 1) with poorly defined borders within the nerve fiber layer, 0.5–5 mm in diameter.
- Occasionally nodular lesions (type 2), "mulberry tumors," containing calcospherites, which autofluoresce. Can be confused with retinoblastoma, although RAH is present in older children.[26] Rarely, lesions progress from a flat to a nodular appearance.

Investigations

- OCT: tumors originate from the nerve fiber layer as a thickened, hyperreflective mass with intact outer retinal layers and RPE.[27,28] Calcium-containing lesions have a "moth-eaten," cavitated appearance.

Acquired RAH are more aggressive, resulting in retinal exudation, vitreous hemorrhage, retinal detachment, retinochoroiditis, neovascular glaucoma, vitreous seeding,[29] and even globe perforation.[30] They are typically isolated and located at the posterior pole. Multiple RAH associated with systemic disease appear at both the posterior pole and peripheral retina.

Histopathology

Astrocytomas contain elongated fibrous astrocytes with interlacing cytoplasmic processes. Aggressive tumors are composed of larger, plump pleomorphic cells with abundant eosinophilic cytoplasm.[30]

Genetics

TSC is a disease associated with two tumor suppressor genes: hamartin (*TSC1*) and tuberin (*TSC2*), which control cell growth and survival via the mTOR signaling pathway.[31]

Management

TSC-associated RAH can be observed. Aggressive lesions associated with retinal neovascularization, vitreous hemorrhage, or macular edema have been treated with systemic or intravitreal bevacizumab, alone or in combination with vitrectomy or intravitreal triamcinolone.[32,33] More recently, inhibition of the

mTOR pathway using sirolimus to shrink retinal astrocytoma has been considered.[34]

Retinal capillary hemangioblastoma (RCH)

- Circumscribed, orange-red, round vascular tumors with a prominent feeding and draining vessel.
- Sporadic, usually unilateral and unifocal.
- RCH are frequently associated with von Hippel–Lindau syndrome (VHL), a multisystem, autosomal dominant, familial cancer-predisposition syndrome.
- VHL RCHs are more likely to be bilateral and multifocal.[35]

Investigations

- Fluorescein angiography: shows early hyperfluorescence with late leakage, identifies and distinguishes feeder vessels from draining venules, and highlights small peripheral RCHs.[36]
- Ultrasound: b-scan is used to measure basal dimension/vertical height as well as detecting subretinal fluid. Lesions have medium-to-high internal reflectivity.[37]
- OCT: used to monitor response to treatment.[38]

Most (85–90%) RCHs are located in the peripheral retina, anterior to the equator in the superior temporal quadrant followed, in order of frequency, by the superior-nasal, inferior-temporal then inferior-nasal quadrants.[39] They gradually increase in size with glial proliferation on their surface, with resulting tractional changes. Visual loss occurs through chronic leakage and exudation, leading to cystoid macular edema and exudative and tractional retinal detachment.[40] Neovascular glaucoma or cataract occurs less commonly.

Between 10% and 15% of lesions are found in the juxtapapillary region with sessile, endophytic (most common), or exophytic growth patterns.[41] They remain stable for prolonged periods. Many advocate observational management unless the macula becomes involved.[41]

Genetics

- VHL is autosomal dominant. Approximately 20% of VHL patients have no family history.
- Estimated prevalence of 1 in 39,000–53,000.
- The gene, located on the short arm of chromosome 3, encodes two proteins that regulate the degradation of α-subunits of hypoxia-inducible factors, HIF-1α and HIF-2α.[42]
- VHL is diagnosed in the presence of a positive family history or two typical tumors.
- Viscera affected include pancreas, kidney, liver, adrenal glands, inner ear, and epididymis.
- Typical lesions include central nervous sytem hemangioblastomas, multiple abdominal organ cysts, renal clear cell carcinoma, and phaeochromocytoma.

In VHL, hemangioblastomas occur in 45–60% of affected individuals, starting around the age of 4 years, and the probability increases with age. They begin to cause visual symptoms by the beginning of the second decade. Annual screening is recommended from 10 years. All RCHs will have appeared by the age of 30 years, so adults with normal retinal examination by this age are unlikely to develop RCH for the remainder of their life.[40,43]

Management

Severe visual loss may be seen in up to 25% of cases of RCH.[40] Prognosis may be worse with larger tumors or worse presenting visual acuity.[44] Treatment for RCH includes laser photocoagulation, photodynamic therapy (PDT), transpupillary thermotherapy (TTT), cryotherapy, plaque radiotherapy/brachytherapy, trans-scleral penetrating diathermy, vitreoretinal surgery, and systemic or intravitreal bevacizumab.

For small (<1.5 mm in diameter), posteriorly located lesions, laser photocoagulation applied directly to the RCH and to the feeder vessels has been shown to be highly effective.[45] Anterior lesions and those with subretinal fluid (SRF) may be best treated with cryotherapy.[45] PDT has been used in both peripheral and juxtapapillary RCHs.[46] PDT shows a relatively better outcome in juxtapapillary RCHs but may be associated with worsening of epiretinal membranes (ERMs).[46] Larger tumors are less responsive due to lack of penetration,[47] but TTT has deeper penetration.[44]

Anti-vascular endothelial growth factor (anti-VEGF) treatments given systemically or as intravitreal injection have mixed results, with some evidence of a transient reduction in retinal edema but no significant reduction in tumor size or new tumor development.[48,49] Combined anti-VEGF therapy, PDT, and/or vitreoretinal surgery has demonstrated some benefit, although not complication free.[50,51] Therapeutically targeting overexpression of HIF-2α may be a better alternative strategy.[52]

Retinal cavernous hemangioma

- A rare congenital vascular hamartoma of the retina.
- Usually sporadic, unilateral, and unifocal and are present within the inner retina.
- Occasional autosomal dominant inheritance with incomplete penetrance associated with intracranial and cutaneous cavernous hemangiomas.[53]
- Appear as a cluster of saccular aneurysms following the course of a retinal vein, frequently located in the mid-peripheral retina, but occasionally at the macula, optic disc, and peripapilllary area (Fig. 49.5).

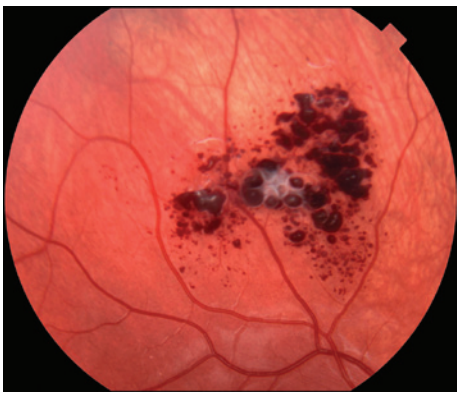


Fig. 49.5 Cavernous hemangioma of the retina showing the "grape-like" clusters of saccular aneurysms.

Visual loss occurs due to recurrent vitreous hemorrhage or macula involvement. Those located at the optic disc may cause nerve fiber compression.[54] Fluorescein angiography demonstrates delayed filling with hyperfluorescent capping of the saccules. Swept-source OCT demonstrates the intraretinal location of the saccular aneurysms.[55] No leakage or exudation occurs and vessel composition is identical to that of normal retinal vessels.[56]

Genetics

It is recommended to examine first-degree relatives. The co-existence of retinal cavernous hemangioma with cerebral cavernous malformations (CCM) may be associated with mutations of the *KRIT1* (CCM1), *MGC4607* (CCM2), and *PDCD10* (CCM3) involved in the regulation of endothelial cell morphogenesis, and blood vessel stability.[57]

Management

Mostly observational; neuroimaging is recommended where there is a positive family history of cavernous hemangiomas, associated cutaneous cavernous hemangiomas or multiple or bilateral retinal cavernous hemangioma or choroidal cavernous hemangiomas.[58] Lesions are non-progressive and frequently have an overlying pre-retinal glial membrane. Pre-retinal membrane traction may cause spontaneous vitreous hemorrhage[59] that may require vitrectomy. Occasionally, photocoagulation and cryotherapy have been used to treat these lesions and, recently, regression with intravenous infliximab has been reported.[60]

Combined hamartoma of the retina and retinal pigment epithelium (CHRRPE)

- Rare, benign, solitary lesions.
- Usually unilateral, but bilateral cases are described.
- Located at the posterior pole in the peripapillary or macular region or in the peripheral retina.[61]
- Likely to be congenital; cases described in infants as young as 2 weeks of age.[62]
- Mostly non-progressive.
- A small proportion of affected individuals may be asymptomatic; the majority present with reduced vision, metamorphopsia, or strabismus, particularly if there is macular involvement.[62]

Lesions are elevated with variable pigmentation (Fig. 49.6). Retinal vascular tortuosity and an overlying epiretinal membrane are typical. Lesions have been classified as melanocytic, vascular, or glial. Glial subtypes, associated with epiretinal membrane (ERM), are associated with progressive retinal traction resulting in visual loss. These may be most amenable to surgery.[63]

Investigations

- Fluorescein angiography: hypofluorescence of background choroid during arterial phase, underlying retinal vascular tortuosity, capillary dilation within the lesion, and intralesional vascular leakage.

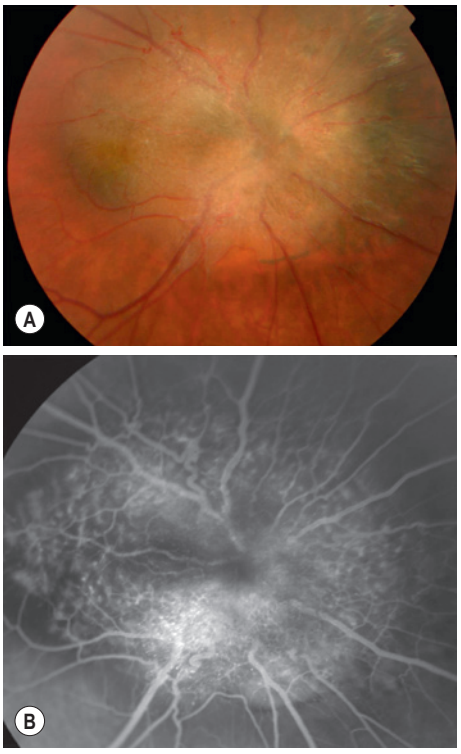


Fig. 49.6 Combined hamartoma of the retina and retinal pigment epithelium (CHRRPE). (A) Elevated, very slowly progressive right optic disc lesion presenting in a 6-year-old child with visual loss to 0.7 LogMAR at 11 years of age. Note the pigmentation, aneurysmal vessels, and pale "glial" tissue. (B) Fluorescein angiogram showing widespread telangiectatic vessels.

- OCT: hyperreflective epiretinal membrane with variable underlying retinal folds involving inner retina. In severe cases, folds extend to outer retina with retinal thickening and disorganization and underlying choroid thinning.[64,65]

Histopathology

- Thickened, disorganized retina and, if involved, optic nerve.
- Abundant hyperplastic and dysplastic glial cells.
- Reduplicated sheets and cords of proliferating RPE infiltrating the overlying tissue.
- Capillary hyperplasia and fibrous tissue proliferation overlying the lesion folding the anterior lesion surface.[66]

Associations

Notable associations include:

- Neurofibromatosis 1 and 2.
- Gorlin syndrome.
- Tuberous sclerosis.

A range of rare associations has been described:

- Poland anomaly.
- Branchio-oculofacial syndrome.
- Branchio-oto-renal syndrome.
- Juvenile nasopharyngeal angiofibroma.
- Incontinentia pigmenti.
- Juvenile retinoschisis.
- Optic disc coloboma and optic nerve head drusen.

Management

Progressive ERM traction may require intervention where loss of vision can be demonstrated due to extension of ERM

onto macula.[67,68] Complications include retinal and vitreous hemorrhages, retinal and choroidal neovascularization, retinoschisis, retinal detachment (usually exudative), and macular edema.[62]

Coats disease

An idiopathic retinal telangiectasia with intraretinal and/or subretinal exudation without appreciable retinal or vitreous traction.[69]

- Vascular telangiectasia (Fig. 49.7).
- Aneurysmal dilation of the retinal vessels ("light-bulbs"; Fig. 49.8).
- Retinal capillary microaneurysms.
- Subretinal and intraretinal, yellow-white patchy exudation located at the posterior pole and beneath the retinal vessels.
- Sheathing of retinal vessels with cholesterol deposits.

The equatorial and peripheral retina is usually affected with a predilection for the temporal side. The disorder generally progresses to retinal detachment (Fig. 49.9), glaucoma, cataract, and phthisis bulbi. Preschool-age children usually present with strabismus or leukocoria; older children, with subjective visual loss or on routine vision screening.[70] Cholesterolosis bulbi has been described rarely. Poor vision is present in over 50% as a result of exudative retinal detachment or macular involvement.[70,71] Macular pathologies include telangiectasia, exudation, edema, macular fibrosis, or full-thickness hole.[72]

The staging of Coats disease is listed in Table 49.1.[73] Most eyes present at stage 2 or 3, rarely at stage 1 or 5, with younger patients tending to present at stage 3.

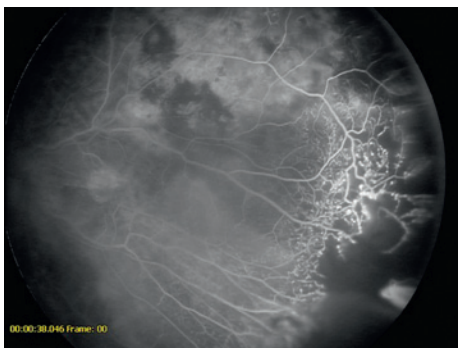


Fig. 49.7 Coats disease. The "hallmark" is vascular telangiectasia, shown in this peripheral fluorescein angiogram, and aneurysmal dilation of the retinal vessels.

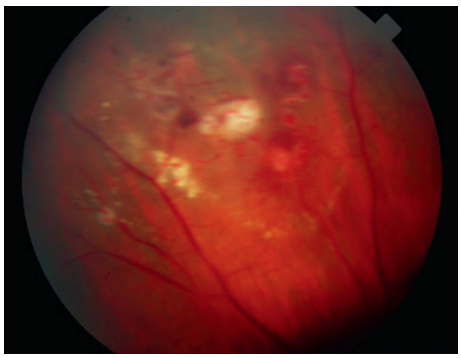


Fig. 49.8 Coats disease. Aneurysmal dilation of retinal vessels, exudates – few in this case – and microaneurysms.

Incidence

- Commoner in males (ratio of 17:3).
- Estimated population incidence of 0.09 per 100,000.
- Median age at presentation is 8 years, with the majority of patients presenting in the first 15 years of life, peaking between 5 and 10 years.

The earliest described presentation was in a 3-week-old baby.[74] Earlier-onset disease tends to have a more rapid progression.[70] Although classically described as unilateral, some bilateral cases have been documented.[71] Wide-field FFA demonstrates peripheral avascular retina in 61% of fellow eyes with classic, unilateral Coats disease.[75]

Histopathology

- Thickening and hyalinization of blood vessels.
- Thinning and loss of endothelial elements and plasma leakage into vessel walls.
- Vessel wall necrosis, formation of vessel dilation, and telangiectasias.
- Subretinal exudates, hemorrhage, cysts, edema, lymphocytic infiltration, and deposition of fibrin.
- The neural retina undergoes secondary degeneration.

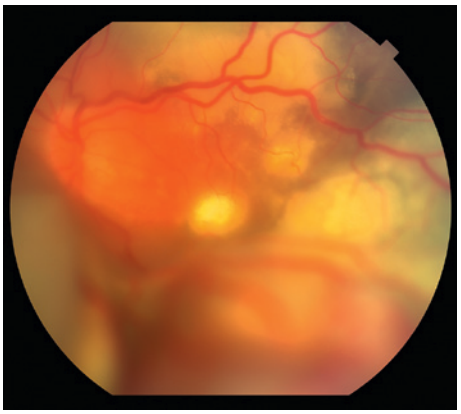


Fig. 49.9 Coats disease. Serous retinal detachment with massive subretinal cholesterol accumulation.

Table 49.1 The staging of Coats disease

Stage	Description
0	Regressed; no telangiectasia/exudation
1	Retinal telangiectasia only
2	Telangiectasia and exudation
2A	Extrafoveal exudation
2B	Foveal exudation
3	Exudative retinal detachment
3A1	Extrafoveal detachment only
3A2	Foveal detachment
3B	Total retinal detachment
4	Total retinal detachment with glaucoma
5	End-stage disease (phthisis bulbi)

- RPE cells phagocytose lipid, transforming them into lipid-laden "ghost cells."[76,77]

Genetics

Most cases of Coats disease appear to be sporadic although somatic mutations in the *NDP* gene (associated with Norrie disease) within a segment of the retina at an early stage of development has been described.[78]

Coats-like changes are seen in:

- Retinal dystrophies associated with *CRB1* and *CEP290* genes[79,80].
- Coats-plus disease (intracerebral calcification, cerebral microangiopathy, sparse hair, dystrophic nails, intrauterine growth retardation, bone marrow involvement, and postnatal growth failure); it is caused by mutations in the *CTC1* gene[81,82].
- Facioscapulohumeral muscular dystrophy.
- Plasminogen deficiency type 1.
- Cornelia de Lange syndrome.
- Hallerman–Streiff syndrome.
- Senior–Loken syndrome.
- Multiple glomus tumors.[83–88]

Management

An important differential diagnosis is retinoblastoma, in particular rare diffuse infiltrating tumors that are flat and ill defined, and present at an older mean age (around 4 years). Eyes with Coats disease are occasionally enucleated because of the inability to exclude retinoblastoma.[89] Other differential diagnoses include persistent fetal vasculature, vitreoretinal dysplasia, retinopathy of prematurity, pars planitis, idiopathic retinal vasculitis and neuroretinitis (IRVAN), X-linked retinoschisis, toxocariasis, and von Hippel–Lindau disease.

Slow progression to retinal detachment is seen in 64% of patients over a 5-year period. Progression appears more likely in patients 4 years or younger. Poor prognostic features include: postequatorial involvement, diffuse and superior retinal location, retinal macrocysts, failed resolution of fluid after treatment, and retinal detachment at presentation.[71,89] Enucleation is rare and performed due to concerns that retinoblastoma might be present in an otherwise blind, glaucomatous eye.[89,90] Most cases will stabilize or improve with treatment (98% in a British Ophthalmological Surveillance Unit [BOSU] study).[91] In milder cases, the goal is to preserve vision. In more advanced cases, the goal is preservation of ocular comfort and cosmesis.

Ablation of peripheral telangiectasia and aneurysms is more effective for stage 2 disease. Treatment includes cryotherapy, argon green or diode laser (532 nm).[92] Treatment complications include cataract, retinal detachment, and proliferative vitreoretinopathy.

In cases of retinal detachment, surgical correction by drainage of subretinal fluid and/or vitrectomy combined with laser or cryotherapy has been described,[93] although in many cases the visual outcome is limited due to the presence of a macular fibrotic scar, which may represent a retinal angiomatous proliferation associated with a chorioretinal anastamosis and pigment epithelium detachment.[94]

Adjunctive treatment with intravitreal anti-VEGF antibody has been used for stage 3a and b disease. However, tractional retinal detachment has been documented and there is lack of long-term safety and efficacy data.[95] Intravitreal steroid injections with triamcinolone or slow-release implants risk development of cataract and glaucoma.

Familial retinal arteriolar tortuosity (fRAT)

- Rare; autosomal dominant.
- Progressive tortuosity of second- and third-order retinal arterioles associated with retinal hemorrhages most obvious around the macular region.[96]
- The venules and major arterioles and capillaries are normal with no aneurysms or abnormal anastomoses.
- Fluorescein angiography shows no leakage from vessels.

Also seen are:

- Telangiectasia of the bulbar conjunctival vessels.
- Malformations of the Kieselbach nasal septum.
- Spinal cord vascular mass.
- Internal carotid artery aneurysm.

Retinal hemorrhages cause transient visual disturbance or loss when involving the central macular area and can arise following exertion or Valsalva maneuvre.[96]

Genetics

fRAT is caused by mutations in *COL4a1*,[97] also associated with hereditary angiopathy with nephropathy, aneurysm, and cramps (HANAC syndrome),[98] autosomal dominant infantile hemiparesis and porencephaly associated with leukoencephalopathy,[99] and diffuse small vessel disease of the brain accompanied by Axenfeld–Rieger anomaly.[100]

Inherited retinal venous beading

- A rare, autosomal dominant disorder of unknown etiology.
- Prominent sausage-like retinal venous beading of the retina.
- Retinal arterioles may show narrow caliber.
- Saccular, aneurysmal changes of the conjunctival vessels.
- Episodes of acute vascular decompensation characterized by neovascularization and vitreous hemorrhage.
- Intraretinal lipid
- Fluorescein angiography shows areas of capillary nonperfusion, leakage of fluorescein, and intraretinal microvascular changes including microaneurysms and telangiectasias.
- Families have been described with nephritis, neutropenia, and deafness.[101]

Congenital retinal macrovessel

- A large vessel crossing over the central macula with large tributaries extending on both sides of the horizontal raphé.
- Visual acuity is not normally affected.[102,103]
- Occasionally the macrovessel is an artery or combined artery and vein.[104]

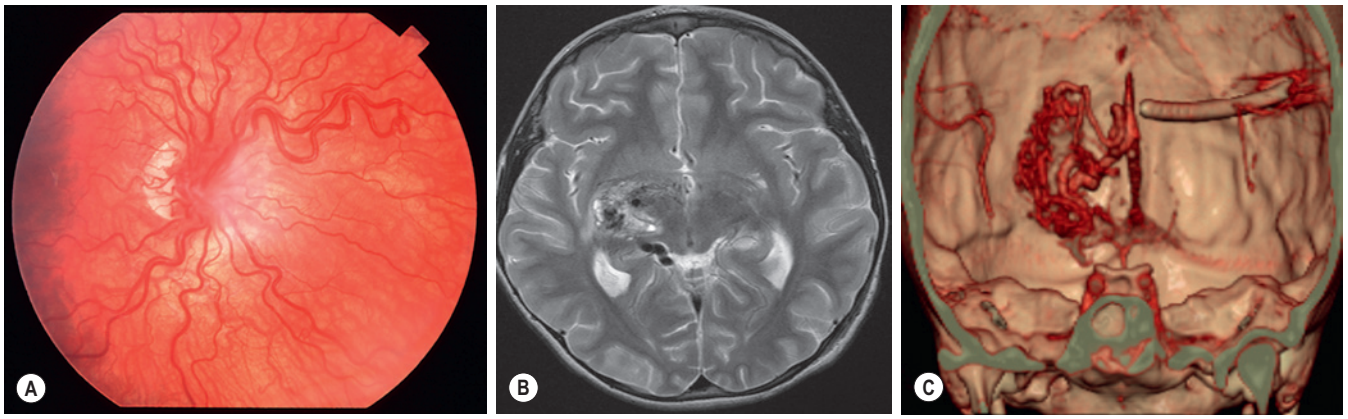


Fig. 49.10 (A) Racemose hemangioma. Large loop vein in upper nasal quadrant of the right eye. Normal visual acuity. (B) Magnetic resonance (MR) imaging showing right-sided vascular malformation from which a sudden hemorrhage occurred at 10 years of age causing obtundation (from which the child recovered) and a left homonymous hemianopia (which did not recover). (C) MR angiogram reconstruction showing anteroposterior view with a right-sided vascular malformation and a shunt on the left.

- Prevalence: rare; in a series of 3506 eyes, seven eyes of six patients had branches coming off the inferotemporal artery, with none having a branch of the superotemporal artery or vein.[105]
- Arteriovenous communications are frequently observed.

Investigations

- Fluorescein angiography: early filling of venous component, areas of capillary non-perfusion in the perifoveal or perivenular region, and disturbance of the foveal capillary microangioarchitecture with poorly defined, enlarged avascular zones and microaneurysms. During the late phase angiogram, the retinal macrovessel remains preferentially hyperfluorescent compared to other retinal vessels.
- Communication between a cilioretinal artery and macrovessel has been described and retinal macrovessels are classed as a mild arteriovenous anastamosis.[106,107]
- OCT imaging of the retina demonstrates macular thickening.[108]
- Complications include serous retinal detachment that may spontaneously resolve[109]; serous exudation, Valsalva retinopathy,[106] and intraretinal cyst.[103]

Racemose retinal hemangioma

These rare, unilateral congenital vascular malformations can be associated with brain vascular malformations that can cause strokes (Fig. 49.10). Usually discovered at routine examination or when the patient has presented with a neurological episode, they require no treatment.

Familial retinal arterial macroaneurysms (FRAM)

- Autosomal recessive disorder.
- Multiple, bilateral retinal arterial macroaneurysms and beading affecting first-order arterioles and progressing to second- and peripheral third-order vessels.[110]
- Retinal changes occur as early as 3 months.
- Macroaneurysms arise from areas of retinal arterial beading.
- Intraretinal and subretinal exudation gives a Coats-like appearance.
- Reactive changes at the level of the RPE leaves subretinal scarring, atrophy, and vascular sheathing.[110]
- Complications include recurrent sub-ILM hemorrhages, leakage from the macroaneurysms, and areas of exudative retinal detachment.
- Treatment: argon green laser photocoagulation.[110]

Genetics

FRAM is associated with mutations in the insulin-like growth factor binding protein 7 (IGFBP7).[111]

Associations

Cardiac abnormalities, including supravalvular pulmonary stenosis and congestive hepatopathy.[111]

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Retinal flecks, dots and crystals

Panagiotis I Sergouniotis and Anthony T Moore

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Introduction

A number of conditions, inherited or acquired, can present with multiple yellow-white retinal lesions. These lesions may look like flecks, dots/drusen, or crystals and can be associated with a variable degree of retinal dysfunction.[1–3] This chapter reviews the differential diagnosis of yellow-white spots in the pediatric retina; some disorders predominantly seen in adults are also included.

Clinical evaluation

It is important to inquire about visual symptoms such as blurred vision, night blindness, or light hypersensitivity and to obtain a family history. Examination of relatives can be helpful, as other affected family members may remain asymptomatic. Current or previous systemic drug administration and dietary habits should be inquired after. Careful note should be taken of any other medical disorders particularly those associated with malabsorption (e.g. cystic fibrosis[4]).

When examining the child, the distribution of retinal deposits, their depth in the retina, and whether they are crystalline in nature should be noted. Investigations that may assist in the differential diagnosis include optical coherent tomography (OCT), fundus autofluorescence (FAF) imaging and, in some cases, psychophysical and electrophysiologic (electroretinogram [ERG] and electro-oculogram [EOG]) testing. Molecular diagnostic testing can often prove useful to confirm the diagnosis.

Yellow-white retinal lesions in primary ocular disease

Stargardt disease and fundus flavimaculatus (see also Chapter 48)

Stargardt disease is a common retinal dystrophy, typically associated with autosomal recessive mutations in the *ABCA4* gene.[5] Pseudodominant inheritance can be observed, particularly in consanguineous families.[6] In such cases, it is important for counseling to distinguish *ABCA4*-related disease from phenotypically similar autosomal dominant disorders due to mutations in *ELOVL4*[7] or *PRPH2/RDS*.[8]

Stargardt disease is characterized by the presence of yellow-white flecks that are located in the deep retinal layers and are scattered throughout the posterior pole (Fig. 50.1). These classical flecks are not always present at diagnosis, but can appear later in the course of disease.[9,10] Macular atrophy is common, and affected individuals typically present with reduced visual acuity in the second decade of life; night blindness and light hypersensitivity may also be present.[11] Some patients have good central vision with minimal or no macular involvement at presentation, and may be diagnosed with fundus flavimaculatus (i.e. retinal flecks without macular atrophy).[12] Stargardt disease and fundus flavimaculatus are parts of the phenotypic spectrum of the same genetic disorder.

FAF imaging is a useful monitoring tool and allows detection of the abnormal phenotype even when it is not otherwise evident (including children with unexplained visual loss).[10] Abnormalities in the form of a speckled hyper- and hypoautofluorescence pattern and/or focal areas of increased signal spatially correlating with the retinal flecks may be observed.[13,14] Quantitative FAF imaging, a modality measuring FAF intensities in a standardized way, can provide further insights including distinguishing *ABCA4* mutation-positive from *ABCA4* mutation-negative individuals.[15] OCT, in particular the degree of preservation of the hyper-reflective line corresponding to the inner segment ellipsoid zone, allows accurate assessment of disease severity.[16] A "dark choroid" has been classically described on fluorescein angiography, although this is now not a commonly used diagnostic tool for Stargardt disease.[17]

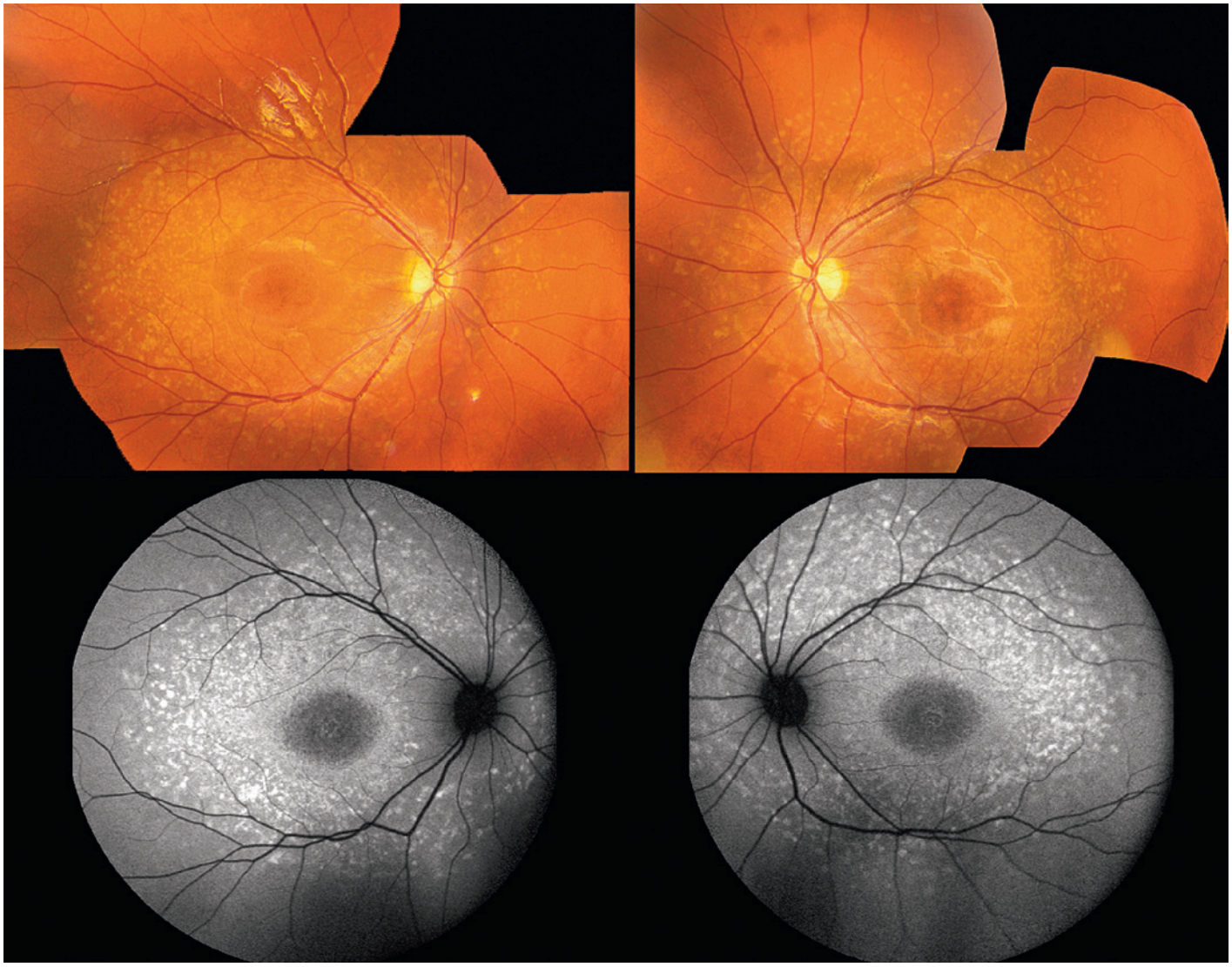


Fig. 50.1 Stargardt disease. Fundus photograph of the left and right eyes of a 9-year-old individual with Stargardt disease (top row). Fundus autofluoresence imaging (bottom row) revealed hyperautofluorescent lesions corresponding to the flecks and abnormal autofluorescence at the foveal region.

Electrophysiologic testing reveals attenuated central macular responses on the multifocal ERG and an abnormal pattern ERG. Full-field ERGs can be variable but may be prognostically useful, since individuals with early evidence of generalized rod and/or cone system dysfunction are likely to develop rapidly progressive disease.[18,19] Notably, generalized retinal dysfunction is more common in childhood-onset than in adult-onset disease, in keeping with a more severe phenotype.[9]

Benign fleck retina

Benign fleck retina is an autosomal recessive condition associated with a distinctive retinal appearance and no apparent visual or electrophysiological deficits.[20] Affected individuals are asymptomatic, but fundus examination reveals a striking pattern of diffuse, yellow-white flecks extending to the far periphery but sparing the foveal region (Fig. 50.2).[21–24] The flecks are located in the deep retinal layers and can be present in early infancy.

FAF imaging reveals multiple hyperautofluorescent lesions corresponding in location with the flecks. On OCT, there is discrete deposit accumulation located posterior to the inner segment ellipsoid zone.[24] Normal full-field and pattern ERGs confirm the diagnosis[22]; multifocal ERG may be slightly subnormal in some isopters.[23]

Recessive mutations in the gene encoding group V phospholipase A_2 (*PLA2G5*) and mildly elevated serum cholesterol levels have been described in some individuals with benign fleck retina.[24,25]

Benign fleck retina should not be confused with a condition described by Kandori in 1972.[26] This disorder, named "fleck retina of Kandori", has been associated with large white lesions, possibly atrophic changes, and night blindness.[26] It is not clear if "fleck retina of Kandori" is a genetic condition or even an independent clinical entity.

Fundus albipunctatus

Fundus albipunctatus is an autosomal recessive disorder associated with night blindness and multiple widespread yellow-white punctate lesions (Fig. 50.3); the spots spare the foveal region, are located at the deep retinal layers, and are

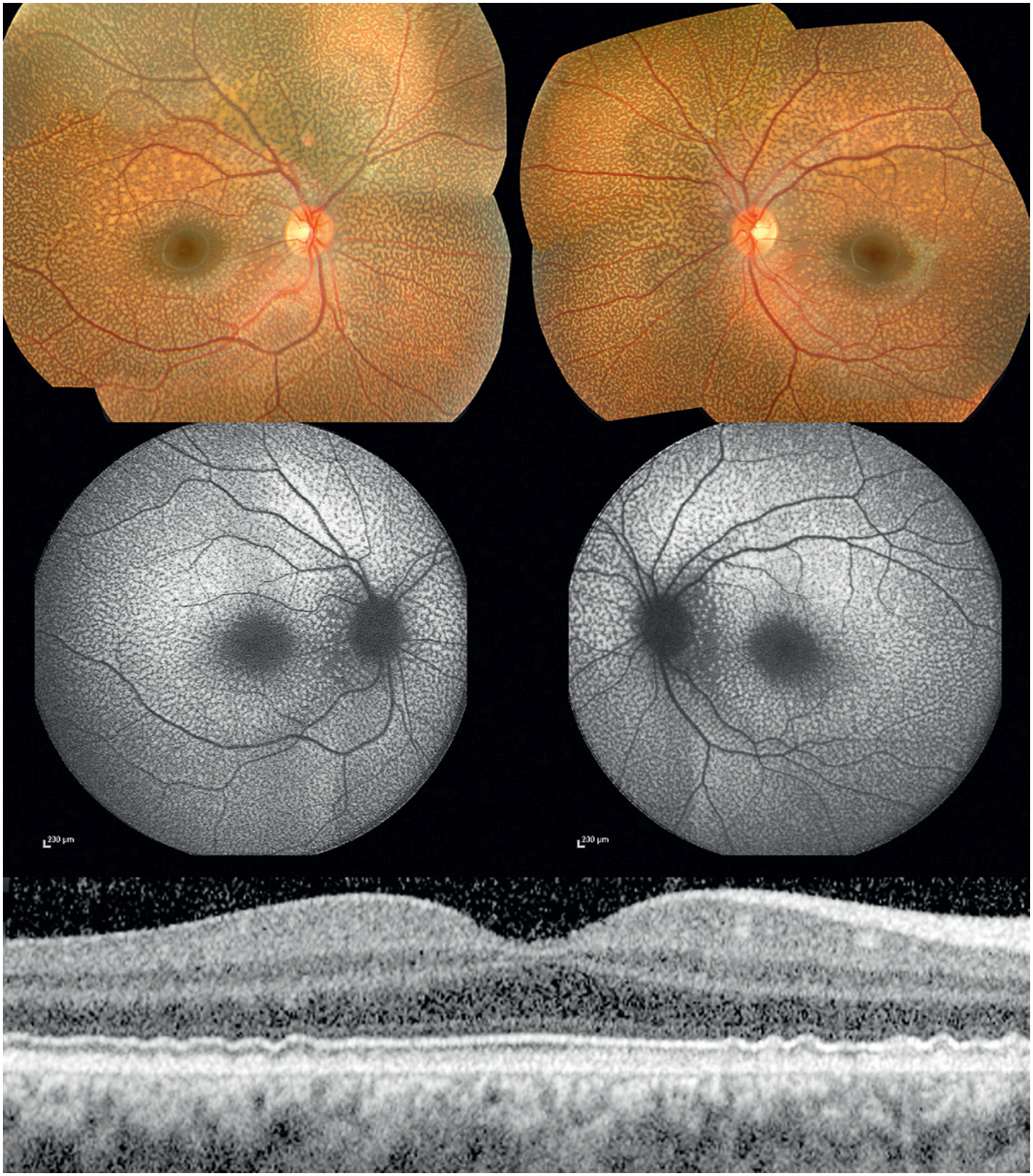


Fig. 50.2 Benign fleck retina. Fundus photograph of the left and right eyes of a 10-year-old individual with benign fleck retina (top row). Fundus autofluorescence (middle row) and optical coherence tomography (horizontal, centered on the fovea, linear scan of the right eye; bottom row) revealed endogenously fluorescent lesions at the level of the retinal pigment epithelium. These do not disrupt the inner segment ellipsoid zone.

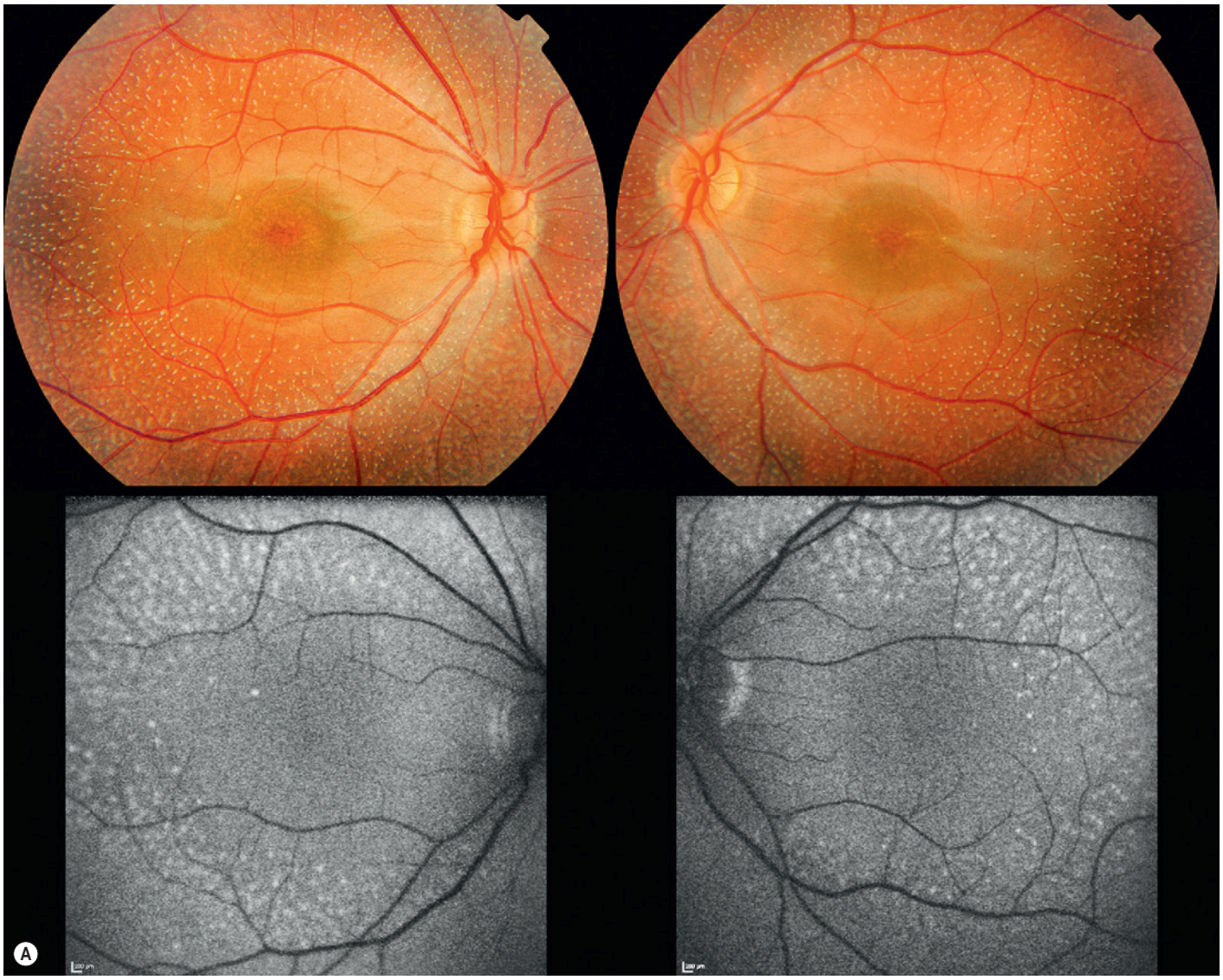


Fig. 50.3 Fundus albipunctatus. (A) Fundus photograph of the left and right eyes of an 18-year-old *RDH5* mutation-positive individual (top row). Fundus autofluorescence imaging (bottom row) revealed hyperautofluorescent lesions; these are unlikely to represent lipofuscin accumulation.

typically present in the first decades of life.[27,28] Patients are either noted to have an abnormal retinal appearance on a routine eye test or present with problems in dim illumination. On direct questioning, affected individuals often describe night blindness from birth and delay in dark adaptation after exposure to bright light.[27] Visual acuities and visual fields are usually normal.

FAF imaging reveals a low autofluorescent signal; digital enhancement artefacts such as autofluorescence from the optic disc and large vessels may be observed.[29,30] In young subjects, high-density foci partially associating with the yellow-white dots on fundoscopy can be seen (see Fig. 50.3A).[27,30] Hyper-reflective lesions extending from the retinal pigment epithelium (RPE) to the outer nuclear layer are detected on OCT (see Fig. 50.3B).[28,31,32]

Characteristic abnormalities on electrophysiology and dark adaptometry facilitate the diagnosis (see Chapter 46). Notably, scotopic ERG responses are subnormal following conventional dark adaptation, but partially recover or normalize following extended dark adaptation.[27,33] Photopic ERGs and pattern ERGs can be normal or abnormal[27,34,35] and adaptive optics imaging reveals an irregular macular cone mosaic.[30,31]

Molecular testing can be useful: fundus albipunctatus is commonly associated with recessive mutations in *RDH5*, a gene encoding an enzyme with 11-*cis*-retinol-dehydrogenase activity.[36] This enzyme catalyzes the oxidizing of 11-*cis*-retinol to 11-*cis*-retinaldehyde, the universal vertebrate chromophore of visual pigments in human RPE.[37,38] Mutations in *RPE65*[39] and *RLBP1*[40,41] have also been described in patients with some features of fundus albipunctatus.

Retinitis punctata albescens, Bothnia, and Newfoundland retinal dystrophies

Retinitits punctata albescens is a variant of recessive retinitis pigmentosa characterized by multiple retinal yellow-white dots rather than pigment deposition.[42] Affected individuals present with night blindness and/or peripheral vision problems; early

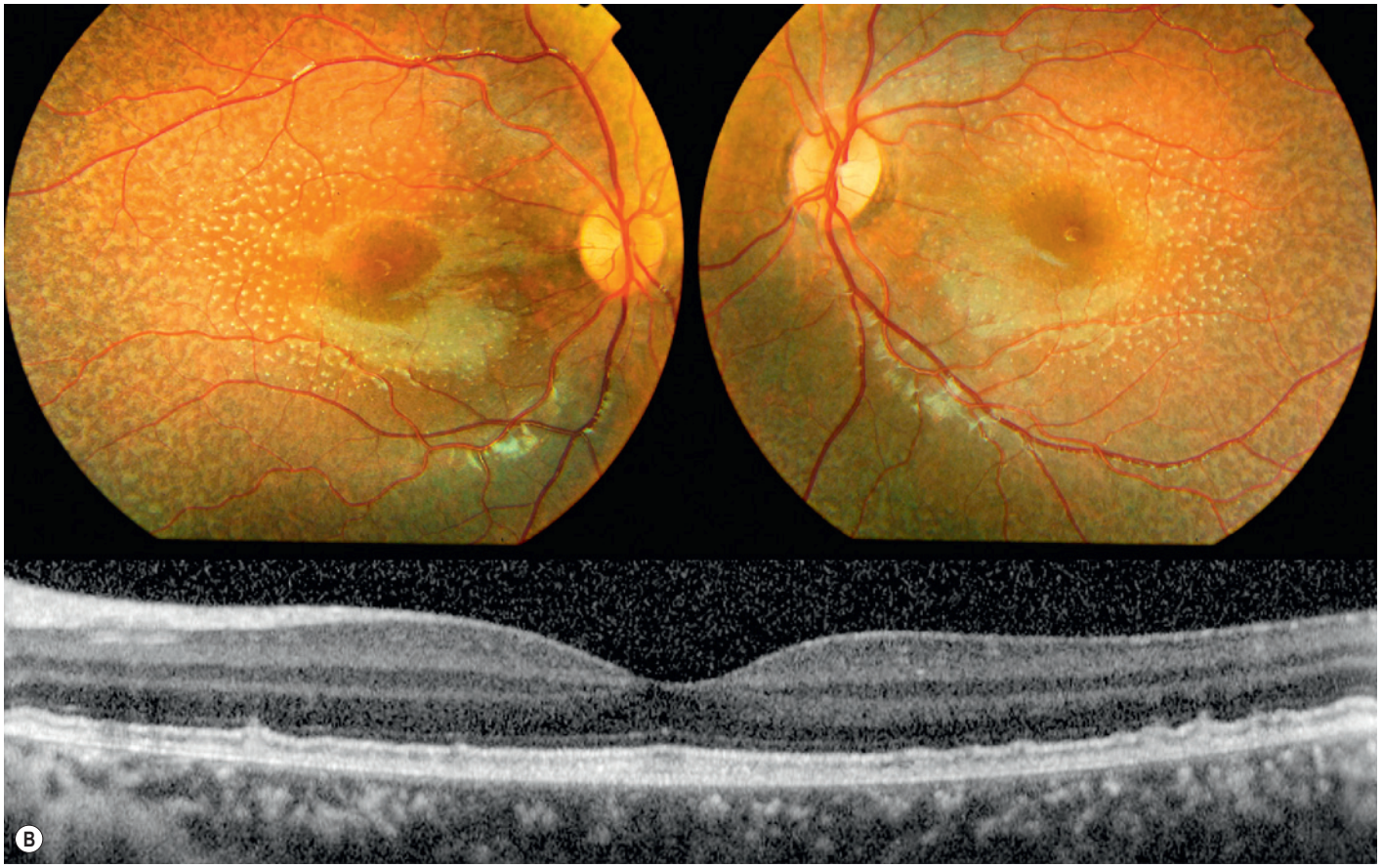


Fig. 50.3, cont'd (B) Fundus photographs of the left and right eyes of a 10-year-old, *RDH5* mutation-positive individual (top row). Optical coherence tomography (horizontal, centered on the fovea, linear scan of the left eye; bottom row) revealed hyper-reflective lesions extending from the retinal pigment epithelium to the outer nuclear layer.

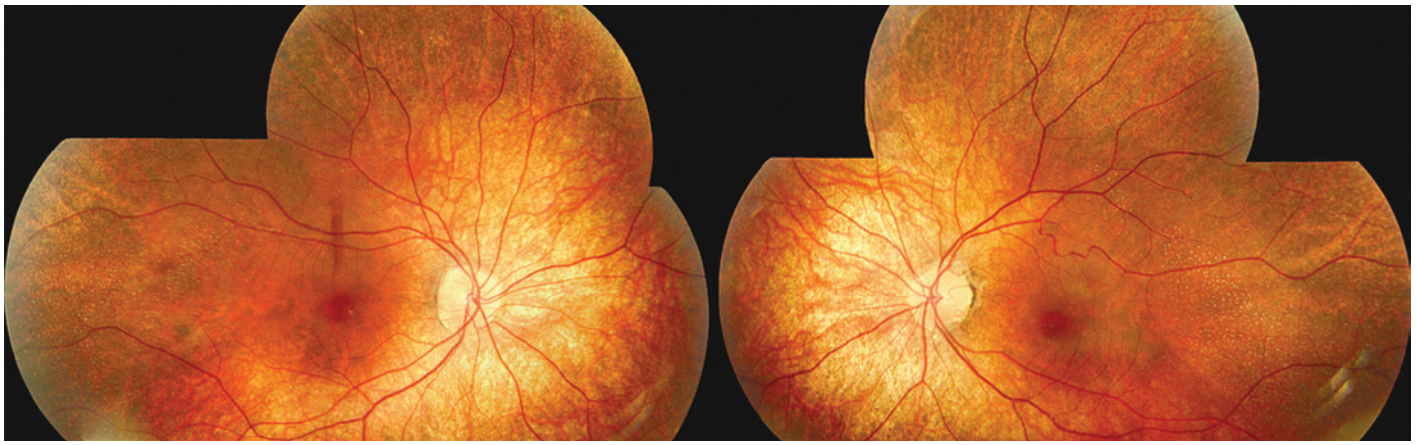


Fig. 50.4 Retinitis punctata albescens. Fundus photograph of the left and right eyes of a 15-year-old *RLBP1* mutation-positive individual.

macular involvement resulting in visual acuity loss may also be a feature of the disorder.[43,44] On fundoscopy, yellow-white spots similar to the ones seen in fundus albipunctatus are observed (Fig. 50.4). These spots spare the fovea and may evolve to give rise to a more classical pigmentary retinopathy.[45] It is important to differentiate early retinitis punctata albescens from fundus albipunctatus: the prognosis for daytime vision is considerably better in the latter and the former features more severe and progressive retinal degeneration. Vascular attenuation, visual field loss, retinal thinning on OCT and a more severe electrophysiological phenotype are key distinguishing features (see Chapter 46).[41,46]

Retinitis punctata albescens is primarily associated with recessive mutations in *RLBP1*[47]; this gene encodes a key component of the retinal visual cycle with a role in maintaining normal cone-driven vision and in accelerating cone dark adaptation.[48] Recessive mutations in *LRAT*[49] and dominant mutations in *PRPH2/RDS*[50] and rhodopsin[51] have also been described in a small number of retinitis punctata albescens cases.

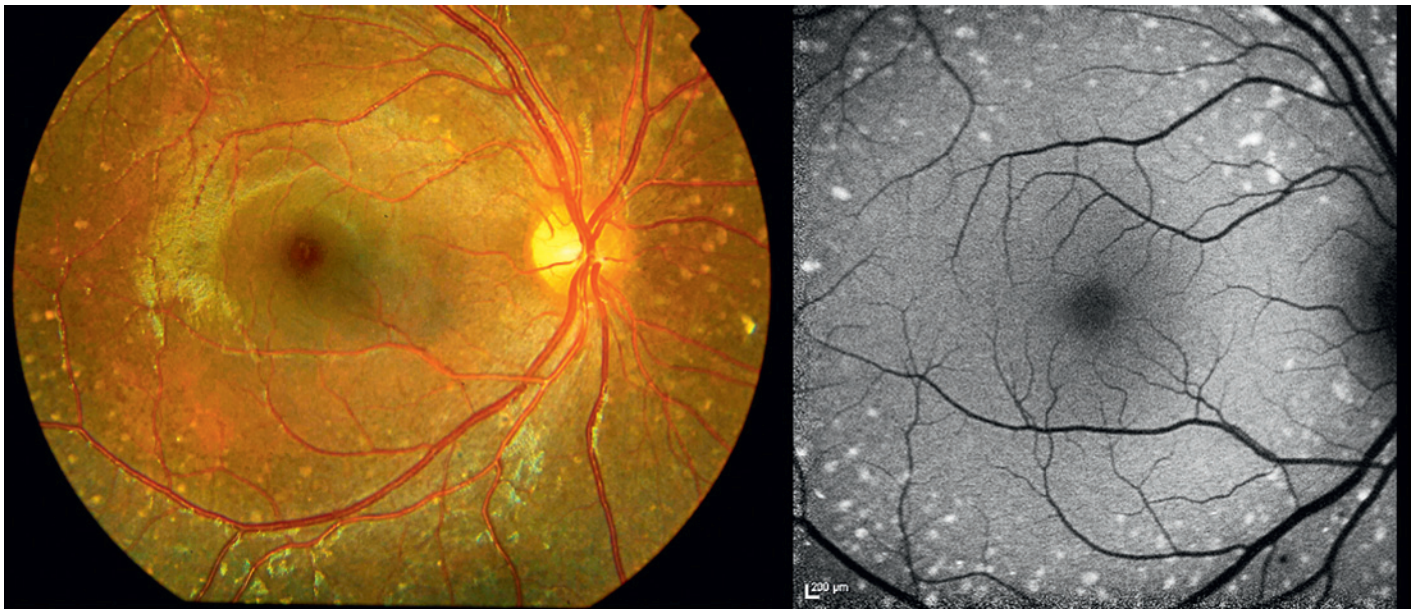


Fig. 50.5 Enhanced S-cone syndrome. Fundus photograph and fundus autofluorescence imaging of the left eye of a 13-year-old affected individual.

Newfoundland rod–cone dystrophy[52] and Bothnia dystrophy[45] are two early-onset forms of retinal disease that have high prevalence in the genetically isolated populations of northeastern Canada and northern Sweden, respectively. Both share genetic etiology (*RLBP1* mutations) and key phenotypic features with recessive retinitis punctata albescens and should be considered parts of the phenotypic spectrum of the same disorder.[41]

Enhanced S-cone syndrome and Goldmann–Favre syndrome

Yellow-white flecks at the deep retinal layers can be an early feature of "enhanced S-cone syndrome" (ESCS), an autosomal recessive progressive retinopathy.[53,54] Patients typically present with night blindness and/or visual acuity loss in the first or second decade of life; a hypermetropic refraction is often noted.[55] Various fundoscopic features have been described; a sequence of change from a normal fundus appearance, followed by RPE mottling along the vascular arcades, and then the development of yellow-white spots (primarily along the arcades; Fig. 50.5), followed by deep nummular pigmentary deposition has been suggested. Macular retinoschisis can also be a feature of the disorder[54,56] and visual field loss can occur in later adulthood.[57,58]

FAF imaging is a useful monitoring tool that typically reveals abnormal signal, in particular beyond the vascular arcades; midperipheral hyperautofluorescent spots only partially corresponding to the flecks are often observed in young subjects.[54,58] A hyperautofluorescent ring may also be present.[55,59] Intraretinal cysts that may involve the fovea (resulting in reduced vision), outer retinal rosette-like structures and, in some cases, a disorganized retinal architecture, can be observed on OCT.[54,58,60,61]

ESCS is unique among retinal dystrophies as there is both retinal degeneration resulting in visual loss and increased function in a subset of photoreceptors, the S-cones.[62–64] Consequently, a distinctive electophysiological phenotype is observed[65,66] (see Chapter 46). ESCS is associated with recessive mutations in *NR2E3*, a gene encoding a transcription factor with a role in activating rod development and repressing cone development.[64,67,68]

Goldmann–Favre syndrome was initially described as an autosomal recessive vitreoretinopathy characterized by night blindness, pigmentary degeneration, macular and peripheral retinoschisis, cataract, and degenerative vitreous changes.[69,70] Many of these features are shared with ESCS and appropriate electrophysiological and genetic testing revealed that they are not distinct entities but simply two identifiable phenotypes in a wide spectrum of clinical expression of the same retinal degeneration.[57,70,71]

Miscellaneous reports of retinal flecks associated with inherited retinal disease

Small yellow-white lesions have been also reported in association with a number of other retinal disorders, including juvenile retinoschisis[72,73] and early-onset retinal dystrophy due to *RPE65*, *LRAT*, *LCA5*, or *CEP290* mutations.[74–76] In these subtypes of early-onset retinal dystrophy, the flecks/dots tend to be more fine and peripheral; in juvenile retinoschisis, they are usually within the posterior pole. Additionally, autosomal recessive bestrophinopathy, a condition associated with biallelic *BEST1* mutations, may present in childhood with yellow-white hyperautofluorescent subretinal deposits in the fovea and around the vascular arcades (see Chapter 48).[77,78]

Drusen-like deposits in inherited retinal disease, including North Carolina macular dystrophy

Drusen deposition at the macula is the hallmark of age-related maculopathy. Similar lesions may also be seen in young adults affected with Sorsby fundus dystrophy (mutation in

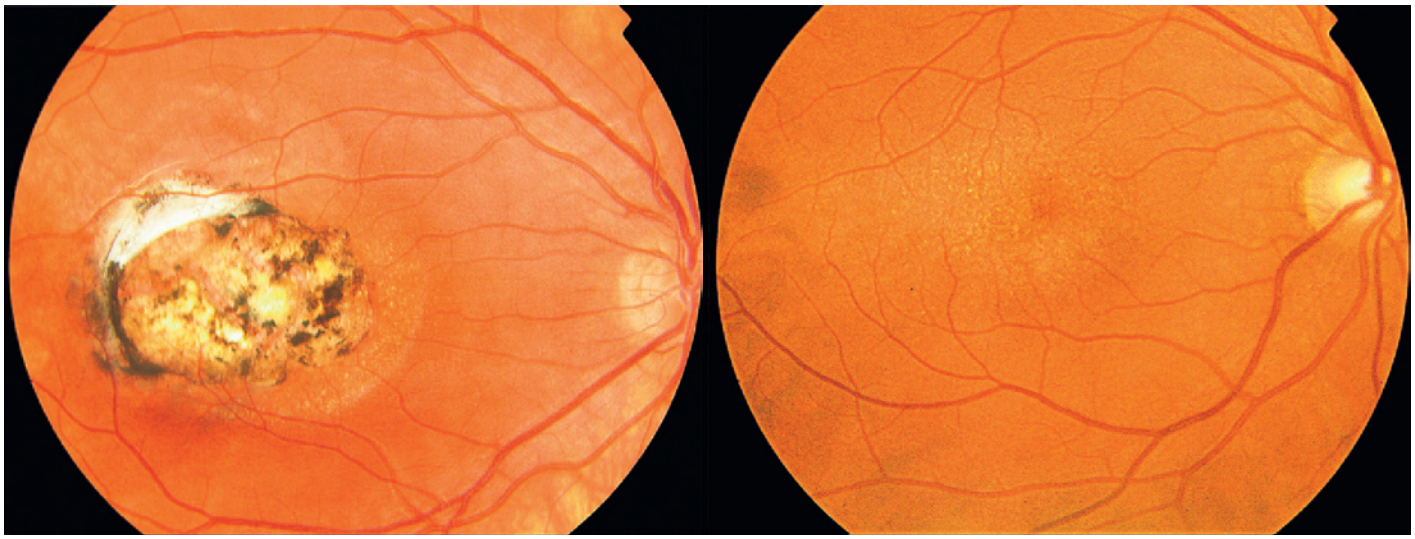


Fig. 50.6 North Carolina macular dystrophy. Fundus photograph of the right eyes of a 12-year-old boy (left panel) and his 40-year-old father (right panel). Both are affected with North Carolina macular dystrophy.

the *TIMP3* gene[79–81]) or autosomal dominant drusen (also known as Doyne honeycomb retinal dystrophy[82] or malattia leventinese[83]; mutation in the *EFEMP1* gene[84]), two dominantly inherited maculopathies. Rarely, dots or drusen-like lesions are seen in asymptomatic children as an incidental finding.[1,85]

Drusen-like deposits in pediatric patients can be observed in children with North Carolina macular dystrophy. This autosomal dominant condition is characterized by macular drusen that are present from birth.[86,87] Fundoscopic findings are highly variable (Fig. 50.6) and tend to be more dramatic than one would predict from visual acuity measurements. Affected individuals may have only a few drusen in the fovea (grade I), confluent drusen with or without RPE changes (grade II), or central macular chorioretinal atrophy with hypertrophic fibrous tissue (grade III)[86,88] (see Chapter 48). Importantly, the condition rarely progresses and the grading does not reflect successive stages of progression.[88–90] Visual acuity is stable and generally well preserved, except in those with central atrophic lesions. Development of choroidal neovascularization is uncommon, but can result in late visual loss.[86,90]

Mutations in the long arm of chromosome 6 causing dysregulation of PRDM13, a retinal transcription factor, have been described in 12 affected families. [91,92] Notably, a number of macular dystrophies that do not map to chromosome 6 but share features with North Carolina macular dystrophy (including macular drusen) have also been described[93–95] (see Chapter 48).

Bietti crystalline corneoretinal dystrophy

Bietti crystalline dystrophy is an autosomal recessive progressive chorioretinal degeneration characterized by night blindness, reduced visual acuity, visual field constriction and multiple yellow-white crystalline deposits at the retina, in circulating lymphocytes and, occasionally, in the anterior stroma of the peripheral cornea.[96–98] Retinal crystals are observed predominantly at the posterior pole (Fig. 50.7); they are often associated with multiple, sharply demarcated areas of RPE atrophy and tend to disappear as the disease advances.[98,99] Affected individuals typically become symptomatic after the second decade of life.[98–100] However, some pediatric cases have been described.[101,102]

On FAF imaging, lesions partially corresponding to the crystals may or may not be evident.[103,104] OCT reveals hyperreflective lesions in all retinal layers; many of these lesions do not spatially associate with the retinal crystals.[105–108] Intraretinal rosette-like structures and reduced subfoveal choroidal thickness are other common OCT features.[103,108–109] Full-field ERGs range from normal to undetectable, with most affected individuals having generalized cone and rod system involvement, even in the early stages of disease.[98,101,110,111]

Bietti corneoretinal dystrophy is associated with defects in *CYP4V2*,[97] a gene encoding an enzyme with a role in fatty acid metabolism.[112,113] A high heterozygous carrier frequency for *CYP4V2* mutations and, therefore, relatively high prevalence of the condition have been reported in East Asia, especially in Chinese and Japanese populations.[100]

Yellow-white retinal lesions in acquired disease

Vitamin A deficiency

Deficiency of the fat-soluble vitamin A limits growth, weakens innate and acquired host defenses, and increases the risks of infectious morbidity.[114–116] Ocular manifestations of hypovitaminosis A are an important health problem worldwide and a common cause of pediatric blindness, typically as a result of corneal scarring (xerophthalmia; see Chapter 34).[117,118] Vitamin A deficiency can be due to malnutrition, malabsorption, or impaired metabolism of vitamin A associated with liver disease, Crohn disease, or cystic fibrosis.[119]

Chronic vitamin A deficiency may lead to visual symptoms as a result of reduced photoreceptor visual pigment formation.[120] Night blindness is a common complication and an early symptom of the disorder; visual field loss, abnormal color vision, and visual acuity loss may occur in advanced



Fig. 50.7 Bietti crystalline corneoretinal dystrophy. Fundus photograph of the left and right eyes of a 16-year-old *CYP4V2* mutation-positive individual showing crystalline deposits.

disease. Fundus examination often reveals multiple gray-white punctate spots scattered in the peripheral retina.[121,122] OCT changes associated with these lesions are observed in the deep retinal layers; these are remarkably similar to the ones seen in *RDH5* or *RLBP1* retinopathy (see Fig. 50.3B).[28,44,122] Atrophic and pigmentary changes may occur with disease progression. Dark adaptometry demonstrates elevated rod and cone thresholds, with rods more severely affected.[123] Electrophysiology reveals reduced or undetectable scotopic ERGs and reduced amplitude cone-flicker ERGs of normal implicit time.[121,123] The flecked retinopathy, visual field, psychophysical and electrophysiological abnormalities usually resolve upon prompt vitamin A supplementation (see Chapter 46).[124,125]

Inflammatory chorioretinopathies

A heterogeneous group of rare inflammatory chorioretinopathies can be associated with multiple yellow-white macular lesions of various sizes. These conditions are more commonly seen in adults and are broadly termed "white dot syndromes."[126–128]

Drug-induced crystalline retinopathies

Acquired yellow-white retinal lesions that are crystalline in nature[3] may be due to medication side effects or associated with West African crystalline maculopathy.[129] Drug-related causes include methoxyflurane anesthesia, tamoxifen therapy, canthaxantine therapy, and talc retinopathy.[130–132] These are generally seen in adults rather than children.

Inherited causes of crystalline retinopathy in children include Bietti crystalline dystrophy (described above), primary hyperoxaluria type I and Sjogren–Larsson syndrome (discussed later in this chapter).

Yellow-white retinal lesions in systemic disease

Abetalipoproteinemia

Abetalipoproteinemia is a rare metabolic disorder that affects absorption of cholesterol, dietary fats and fat-soluble vitamins from the small intestine.[133–136] It is associated with recessive mutations in the *MTTP* (microsomal triglyceride transfer protein) gene and typically presents with failure to thrive and diarrhea in infancy.[134,135,137] A number of multisystem manifestations including abnormally shaped red blood cells (acanthocytosis) and ataxic neuropathy have also been described (see Chapter 65).[138]

Ophthalmic involvement in abetalipoproteinemia is variable and a wide range of signs has been reported. These include ophthalmoplegia, ptosis, nystagmus, anisocoria, cataract, angioid streaks, and a progressive retinal dystrophy characterized by pigmentary changes and yellow-white mid-peripheral dots located at the deep retinal layers.[139–141] Treatment with vitamins A and E has been reported to slow the course of disease or prevent the development of retinal degeneration.[142,143]

Pseudoxanthoma elasticum

Pseudoxanthoma elasticum (PXE) is a connective tissue disorder causing abnormal mineralization and fragmentation of elastin fibers.[144,145] Characteristic skin findings include lax, redundant, and relatively inelastic skin in flexural areas. Cardiovascular abnormalities (occlusive peripheral vascular disease) and retinal complications are also observed.[146,147] Recessive mutations in *ABCC6* are identified in the majority of affected individuals.[148–150] Pseudodominance is relatively common due

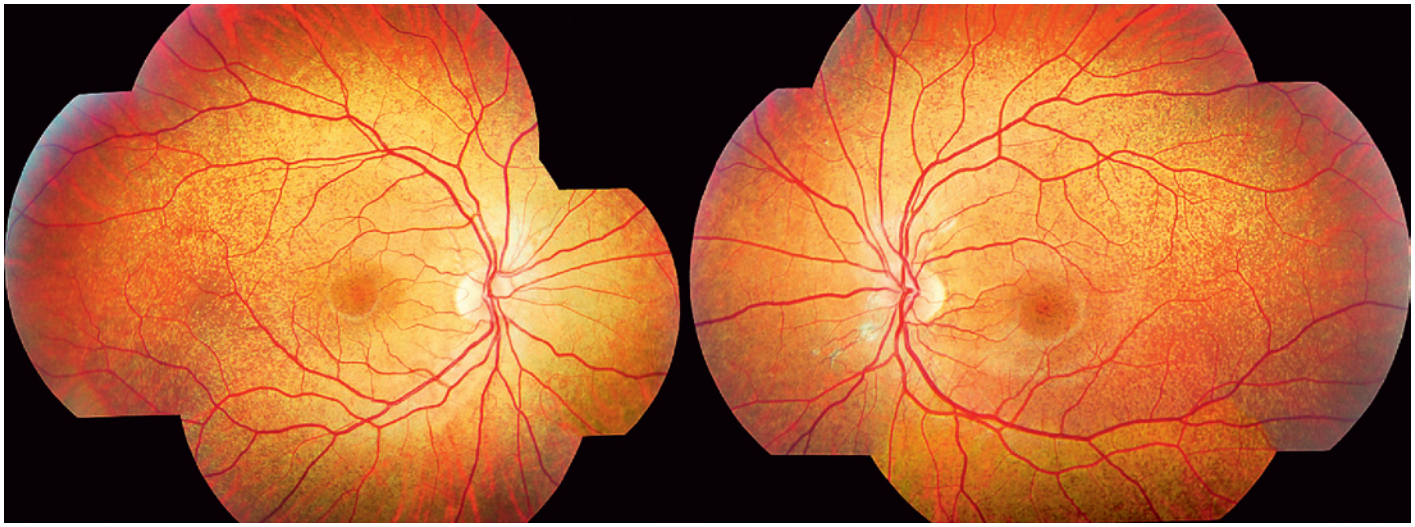


Fig. 50.8 Pseudoxanthoma elasticum. Fundus photograph of the left and right eyes of a 16-year-old individual affected with pseudoxanthoma elasticum.

to an unexpectedly high prevalence of heterozygous carriers in the population.[151]

The most frequent retinal abnormalities in PXE are a characteristic fundal sheen, primarily in the temporal macula (peau d'orange), and jagged cracks radiating around and away from the optic disc (angioid streaks).[152] The former is associated with subconfluent calcification of Bruch's membrane.[153] The latter develop in more heavily calcified portions of Bruch's membrane and are present in almost all PXE patients; they often lead to choroidal neovascularization, fibrovascular scarring of the posterior pole, and visual loss.[153–155] The peau d'orange appearance seems to precede angioid streaks and can be observed in younger patients as fine, yellow-white lesions in the temporal posterior or midperipheral fundus (Fig. 50.8).[152,156] FAF imaging is useful in assessing individuals with PXE, as it reveals the extent of RPE alterations.[157,158] OCT reveals increased reflectivity from the outer border of the RPE/Bruch's membrane complex.[153,158,159] Early recognition of the PXE phenotype is important, alerting the ophthalmologist and prompting a referral to a dermatologist and cardiologist.

Alport syndrome

Alport syndrome is a rare, genetically heterogeneous disorder caused by mutations in collagen biosynthesis genes (*COL4A3*, *COL4A4*, and *COL4A5*); these result in defective production or assembly of the type IV collagen network.[160–163] X-linked semidominant (~85% of cases; *COL4A5* gene), autosomal recessive (~15% of cases; *COL4A3* and *COL4A4* genes), autosomal dominant (rare; *COL4A3* gene), and digenic inheritance have been described.[164–166]

This disorder of the basement membrane results in progressive renal failure, high-tone sensorineural hearing loss, and variable ocular abnormalities including cataract, anterior lenticonus, corneal posterior polymorphous dystrophy, macular hole, and a dot-and-fleck retinopathy.[167–170] Retinal changes in the latter, typically occurring in adulthood, comprise numerous yellow-white perimacular flecks and/or dots (Fig. 50.9). These spare the fovea, and may extend to or solely affect the retinal periphery; an associated dull macular reflex has been described in some cases.[170] FAF imaging may show irregular signal in the retinal periphery and OCT often reveals temporal perifoveal thinning.[171–175] In a small number of cases, larger, central, vitelliform-like lesions have been described.[172] Though there are exceptions, visual function and electrophysiological testing are generally normal.[171]

Dense deposit disease

Dense deposit disease (a C3 glomerulopathy previously known as membranoproliferative glomerulonephritis type II) is a rare renal disorder manifesting in childhood or young adulthood. It is characterized by the presence of complement deposits within the glomerular capillary basement membrane; deposits of similar composition and structure are also found along the Bruch's membrane/RPE interface of affected individuals.[176–178] These drusen-like lesions ("cuticular drusen"[179]) are bilateral, symmetrical, and typically detectable in the second decade of life. They are most easily visualized on fluorescein angiography where they can exhibit a "stars-in-the-sky" pattern (marked hyperfluorescence in early arteriovenous phase).[179] In terms of distribution, they can be only peripheral or only macular at early stages, but they tend to increase in number and eventually affect the entire fundus.[180–183] Although initially they have little impact on vision, they can sometimes lead to vision loss due to choroidal neovascularization or RPE atrophy.[178,184–188] Therefore, ophthalmic screening in individuals with dense deposit disease is recommended. Notably, the extent of ocular involvement does not appear to be related to the severity of renal involvement.[180]

Primary hyperoxaluria

Primary hyperoxaluria is a rare inborn error of oxalate metabolism resulting in increased serum and urinary levels of oxalate.[189,190] As serum levels rise, calcium precipitates with oxalate to form insoluble crystals that are then deposited in various organ systems (mainly bone, blood vessel wall, and

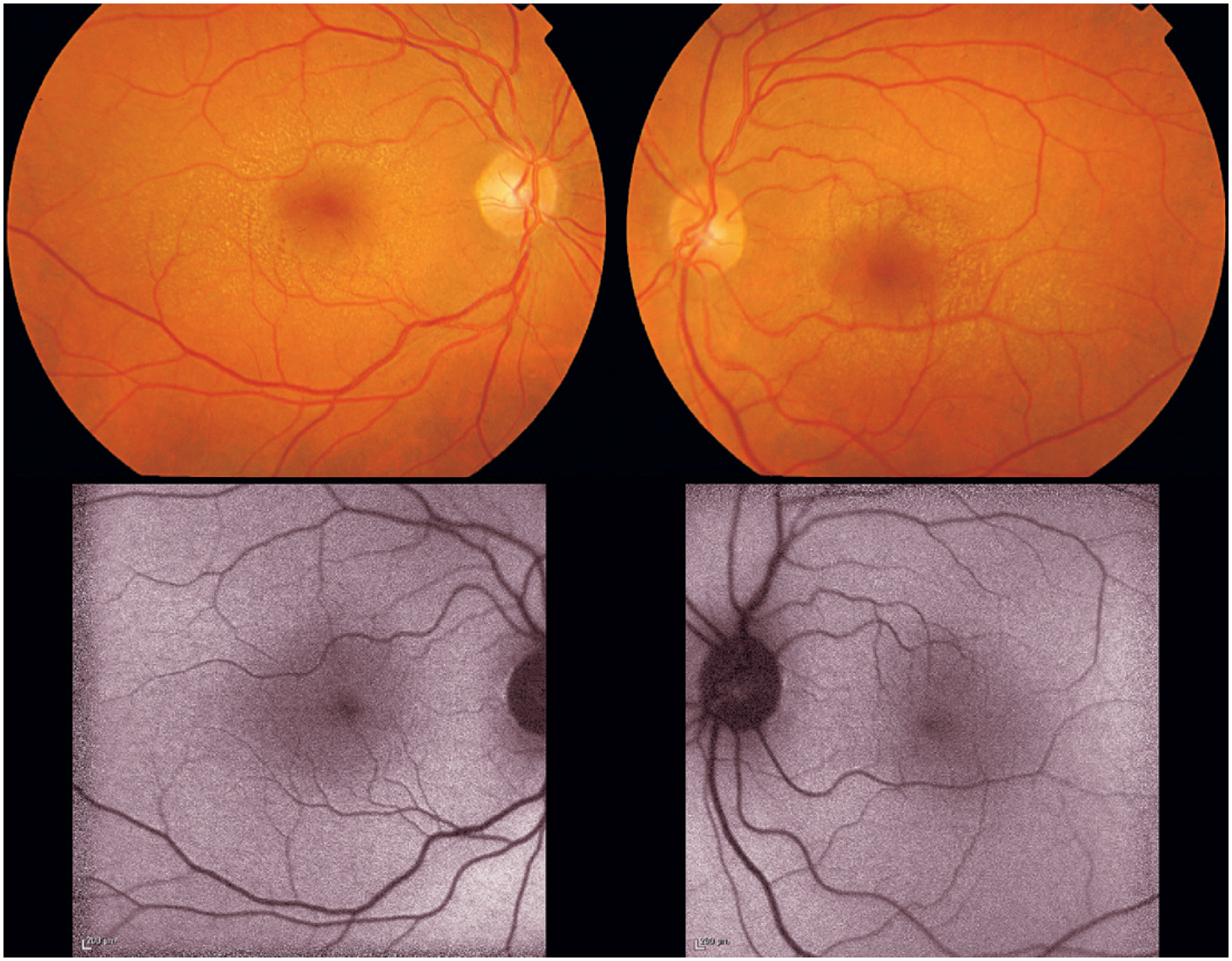


Fig. 50.9 Alport syndrome. Fundus photograph of the left and right eyes of a 28-year-old individual with Alport syndrome (top panel); fundus autofluorescence imaging (bottom panel) was normal. *(Courtesy of Professor Andrew R. Webster.)*

kidney).[191] Primary hyperoxaluria usually presents in early childhood but can occur at almost any age; it often leads to end-stage renal disease and is associated with significant morbidity and mortality.[192] A high index of suspicion and timely diagnosis are key, especially because renal transplantation alone cannot correct the abnormality (the primary metabolic defect is in the liver).[190,193]

Three different types have been described.[191] Type I hyperoxaluria, the most common and severe form, is caused by deficiency of the liver-specific peroxisomal enzyme alanine: glyoxylate aminotransferase (AGT) and has been associated with ocular abnormalities.[194,195] The main ophthalmic feature is the presence of multiple crystals deposited in the deep retinal layers. These are more numerous at the posterior pole and along the vascular arcades (Fig. 50.10).[196–199] Abnormalities of the retinal vasculature and optic disc pallor have been described in a few cases.[200,201] Over time, atrophic macular lesions may develop and patches of pigment may be observed.[201,202] Choroidal neovascularization can also be a feature of the disorder.[203]

Sjogren–Larsson syndrome

Sjogren–Larsson syndrome is an autosomal recessive neurocutaneous disorder of childhood caused by deficiency of the microsomal enzyme fatty aldehyde dehydrogenase (FALDH).[204] Clinical features include congenital ichthyosis, spastic paresis (legs more than arms), and moderate cognitive impairment.[205,206] Most affected individuals are born preterm and exhibit a characteristic crystalline, childhood-onset maculopathy; this can be accompanied by photophobia and visual acuity loss. Yellow-white glistening macular deposits (Fig. 50.11) corresponding to intraretinal spots of increased reflectivity on OCT (mainly in the perimacular ganglion cell layer and inner plexiform layer) are observed.[207] Inner retinal microcystoid spaces ("pseudocysts") at the fovea and/or parafovea may also be seen.[207–211] On FAF imaging there is increased foveal autofluorescent signal surrounded by an irregular pattern of hypoautofluorescence; this appearance is associated with a characteristic widespread congenital loss

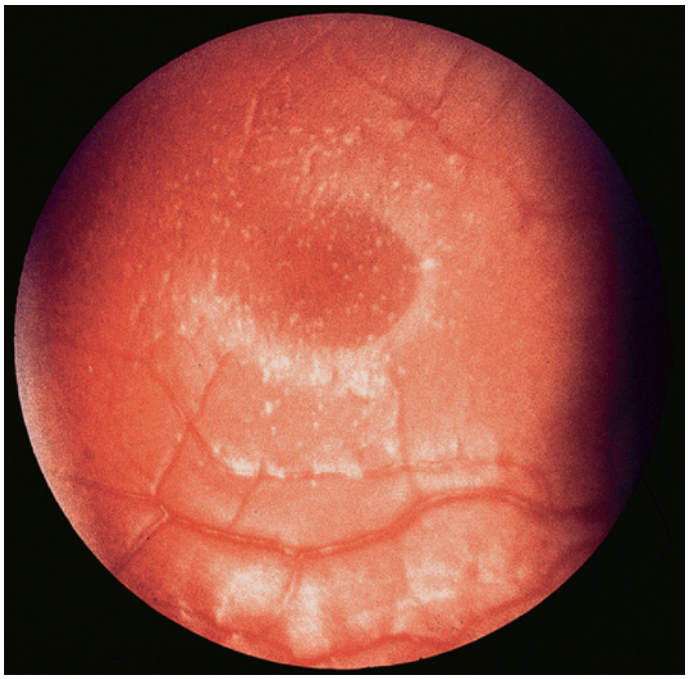


Fig. 50.10 Primary hyperoxaluria type I. Fundus photograph of the right eye of an affected individual. *(Courtesy of Professor Alistair Fielder.)*

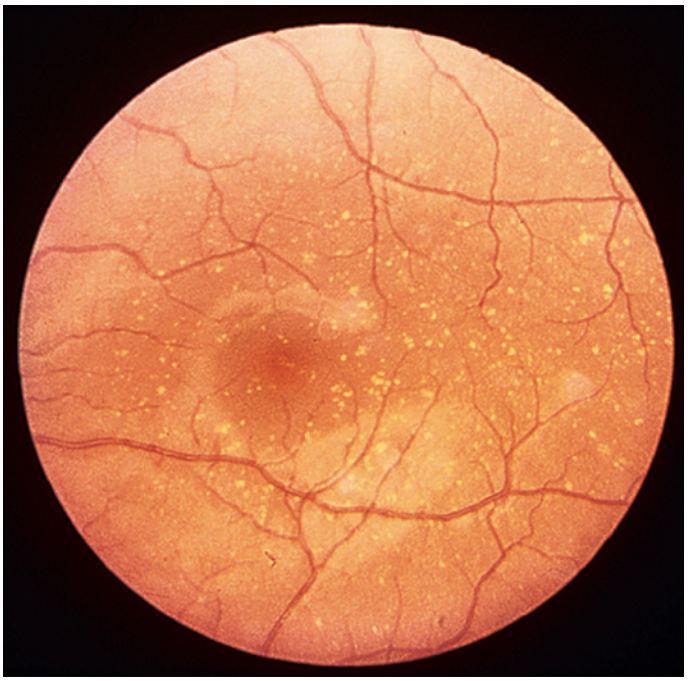


Fig. 50.12 Flecked retina syndrome and ring chromosome 17. Fundus photograph of the left eye of a child with ring chromosome 17.

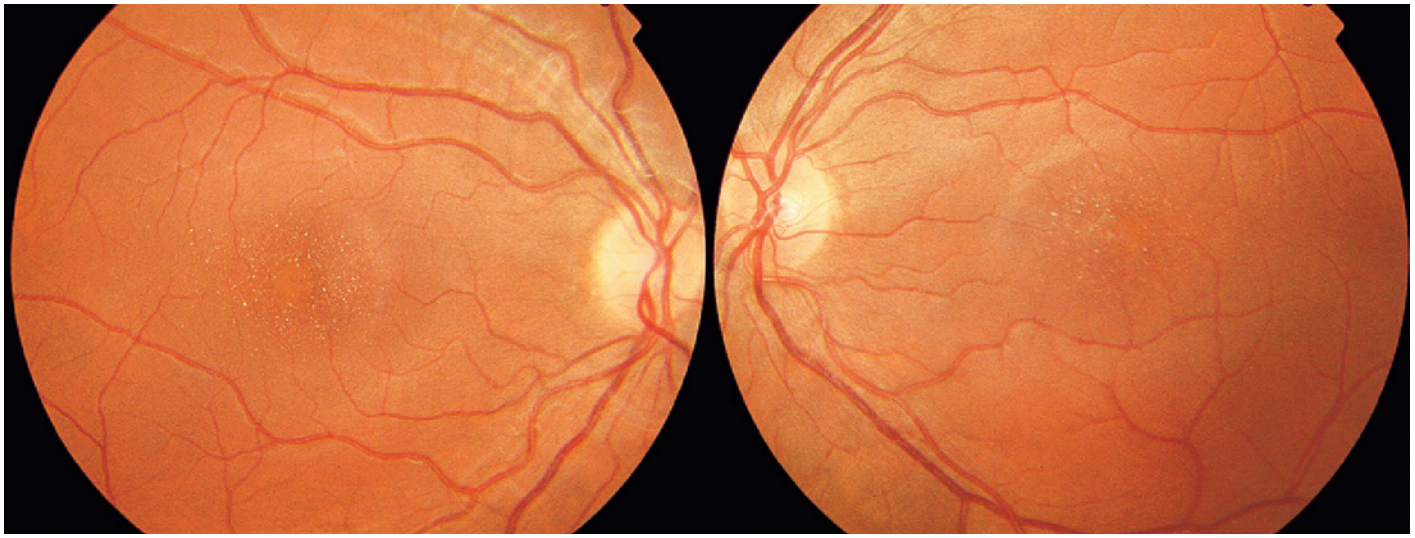


Fig. 50.11 Sjogren–Larsson syndrome. Fundus photograph of the left and right eyes of a 22-year-old affected individual. *(Courtesy of Professor Andrew R. Webster.)*

of macular pigment.[207,212] Generalized retinal function is preserved.[213–215]

Miscellaneous reports of retinal flecks associated with syndromic eye disease

A number of other systemic disorders can give rise to yellow-white retinal lesions. They include:

1. Kjellin syndrome (recessive mutations in *SPG11* or *SPG15*)[216–219];
2. sensorineural hearing loss, dental abnormalities, and flecked retina[220];
3. flecked retina syndrome and ring chromosome 17 (Fig. 50.12)[221–223];
4. peroxisomal bifunctional enzyme complex deficiency.[224–226]

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Acquired and other retinal diseases (including juvenile X-linked retinoschisis)

Mary J van Schooneveld and Jan EE Keunen

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REFERENCES

Diabetic retinopathy

Diabetic retinopathy (Fig. 51.1) is uncommon in children and is strongly correlated with the duration of diabetes mellitus and the overall long-term metabolic control (mean glycosylated hemoglobin A1c). Therefore, children and young adults with diabetes should be cared for by a multidisciplinary team including a diabetologist, pediatrician, and ophthalmologist.[1]

At this time, no definite genetic associations with diabetic retinopathy have been consistently reported. However, a genetic susceptibility to proliferative diabetic retinopathy has been suggested.[1,2]

The 25-year cumulative rate of progression of diabetic retinopathy and incidence of proliferative diabetic retinopathy was reported to be 83% and 42%, respectively, in a major study.[3] In this study, however, a lower prevalence of proliferative diabetic retinopathy was observed in more recently diagnosed persons, reflecting improvement in diabetes care. The prevalence of diabetic retinopathy seems to be decreasing; in a recent study, diabetic retinopathy was found in approximately 50% of adolescents with type 1 diabetes mellitus after a median duration of 9 years in the early 1990s, compared with only 12% in recent years.[4] This is likely due to more intensive therapy for patients with type 1 diabetes, as a result of the findings of the American Diabetes Control and Complications Trial in 2000.[5]

Longitudinal studies demonstrate clinically significant macular edema after 7 years of systemic disease, with a linear yearly cumulative risk as high as 6.7% between 10 and 20 years of duration.[6] Older age at onset of type 1 diabetes is a risk factor for macular edema.[2] The onset of puberty does not affect this significantly.[7]

Until recently, pediatric diabetes was almost exclusively the type 1 insulin-dependent form. With increasing obesity in the pediatric population, particularly in higher income countries, type 2 diabetes and insulin resistance in children and adolescents is an emerging epidemic, comprising 8–45% of all juvenile diabetes.[8] Impaired glucose tolerance was noted in 21% of obese children aged 11–18 years and 25% of obese children aged 4–10 years.[9] As the prevalence of childhood-onset type 2 diabetes increases, the number of children with diabetic retinopathy will also increase.

The majority of guidelines recommend that the first fundus examination occurs after puberty in children and adolescents with type 1 diabetes.[10] The American Diabetes Association and the American Academy of Pediatrics guidelines recommend annual eye exams for children with type 1 diabetes who are older than 10 years, starting 3–5 years after diagnosis.[11] The feasibility of using a non-mydriatic fundus camera to screen children as young as 2 years for changes related to diabetic eye disease was recently demonstrated.[12]

Sickle cell retinopathy

Hemoglobinopathies are inherited disorders characterized by hemoglobin abnormalities and diagnosed by hemoglobin electrophoresis. Sickle cell retinopathy is the most important hemoglobinopathy in children. Sickle cell disease, leads to a variety of occlusive vascular changes, both proliferative and non-proliferative, in the anterior and posterior segments of the eye.[13] Proliferative sickle cell retinopathy is characterized by the development of peripheral retinal neovascularization, eventually giving rise to a "sea fan" proliferative retinopathy (Fig. 51.2). Vitreous hemorrhage and tractional or rhegmatogenous retinal detachments may also occur.[14] Natural history studies demonstrate a high rate of autoinfarction of neovascular

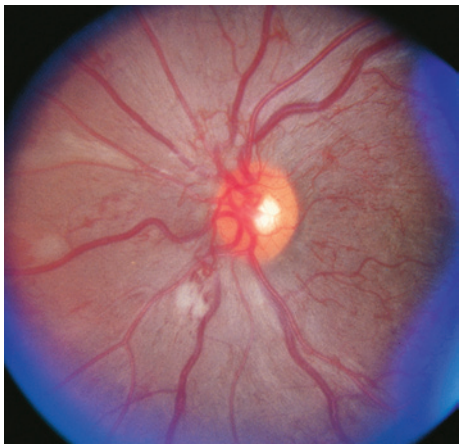


Fig. 51.1 Diabetic retinopathy. Proliferative diabetic retinopathy in a young adult. Neovascularization of the disc is present, in addition to multiple cotton-wool spots and intraretinal hemorrhages.

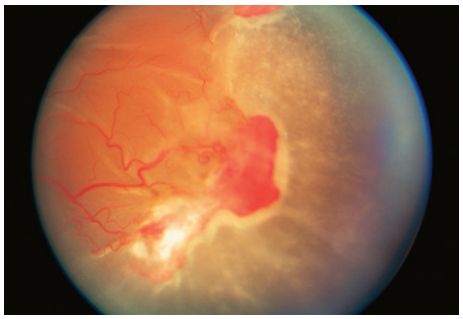


Fig. 51.2 Sickle cell retinopathy. Proliferative SC retinopathy in a young male with hemoglobin SC disease. The patient subsequently developed a tractional retinal detachment.

complexes in the absence of treatment, but selected cases require vitreoretinal surgical management to improve or stabilize vision.[15]

Suggested mechanisms for autoinfarction include feeder arteriolar occlusion, capillary occlusion, or hemodynamic alterations induced by vitreous traction.[16] Peripheral scatter photocoagulation may induce regression and reduce the risk of vitreous hemorrhage.[17]

Wide-field imaging detected peripheral vascular changes in sickle cell retinopathy that were missed on the seven-standard field photographs. Wide-field fluorescein angiography and color photography enhance the clinician's ability to visualize peripheral vascular remodeling in sickle cell disease, and to identify high-risk characteristics for proliferative sickle cell retinopathy.[18]

SC hemoglobinopathies in children with traumatic hyphema increase the risk of complications, including raised intraocular pressure as a result of aqueous outflow obstruction by sickled erythrocytes.[19] Additionally, there is an increased risk of re-bleeding in pediatric SC patients after the initial hyphema.[20]

Central retinal artery occlusion is a rare and potentially devastating complication of sickle cell disease.[21,22]

Radiation retinopathy

Radiation retinopathy in children is a delayed-onset complication of radiation exposure secondary to focal plaque (brachytherapy) or external beam treatment for retinoblastoma, orbital tumors, and, rarely, uveal melanoma.[23] Radiation retinopathy most commonly develops between 6 months and 3 years following treatment; however, retinal changes have been observed as early as 1 month following both plaque and external beam.[24] It may be progressive. Radiation induces a cascade of changes in the retinal vascular architecture, predominantly in the macula, which lead to vascular non-perfusion, leakage, and proliferation. Histologic studies demonstrate a preferential loss of vascular endothelial cells with relative sparing of the pericytes (which is a distinct contrast to the early loss of pericytes in diabetic retinopathy).[24] Besides retinopathy, radiation may lead to maculopathy, cataract, neovascular glaucoma, optic neuropathy, persistent exudative retinal detachment, and scleral necrosis.

Various host and radiation parameters determine the risk of developing radiation retinopathy. The major modifiable risk factor is the total dose of radiation.[23] More severe and extensive radiation retinopathy is associated with diabetes mellitus and the administration of chemotherapeutic agents.[25]

Focal laser photocoagulation and photodynamic therapy have been the primary treatment options; more recently anti-vascular endothelial growth factor agents and periocular or intravitreal steroids (during radiotherapy and/or postoperatively) have been shown to have some efficacy.[23,26]



Fig. 51.3 Bone marrow transplant retinopathy. Multiple cotton-wool spots and a small perifoveal hemorrhage occurring 3 months after bone marrow transplant.

Bone marrow transplant retinopathy

An ischemic retinopathy, similar to that observed with radiotherapy, is seen following bone marrow transplantation (BMT) for hematologic malignancies and aplastic anemia. The retinopathy is decreasing in prevalence as better chemotherapy makes BMT less necessary and stem cell transplants reduce immunologic complications. Retinal manifestations include capillary non-perfusion, cotton-wool spots, and intraretinal hemorrhages (Fig. 51.3).[27] The vasculopathy generally develops within 6 months of BMT, with histologic changes resembling those of early radiation retinopathy.[28] While the most common ocular complications associated with BMT are cataract and dry eye, the incidence of ischemic retinopathy and disc swelling ranges from 6.9% to 13.5%.[29,30] In a study of children undergoing bone marrow transplantation, 95.7% of eyes retained visual acuity of 20/40 or better, with poor visual outcomes associated with cytomegalovirus retinitis, a presumed sub-

macular *Nocardia* abscess, corneal ulcers secondary to dry eye syndrome, and cataracts.[30]

The pathogenesis of the retinopathy in BMT patients remains unclear, confounded by the conditioning regimens administered prior to transplantation, which typically involve total body radiation and chemotherapy, as well as agents following transplantation designed to suppress graft-versus-host disease. The chemotherapeutic agents may be directly toxic to the retinal vasculature, potentially increasing the susceptibility to retinopathy, since retinopathy develops with relatively low doses of total radiation as well as in its absence.[30,31] Atypical cases of bone marrow transplant retinopathy were recently reported.[32,33]

Retinal vasculitis

Retinal vasculitis (Fig. 51.4) in children is very rare and usually occurs in the setting of intermediate uveitis, posterior uveitis, or panuveitis.[34] The causes are: (1) infectious (e.g. toxoplasmosis, viral [human immunodeficiency virus – HIV, human T-cell lymphotropic virus type-1,[35] H1N1-influenza[36]], Candida); (2) non-infectious (e.g. collagen vascular disorders, Behçet disease,[37] multiple sclerosis,[38] idiopathic retinal vasculitis, aneurysms and neuroretinitis [IRVAN],[39] systemic lupus erythematosus, Susac syndrome[40]); and (3) isolated idiopathic (Eales disease). The diagnosis of Eales disease is made by exclusion. Although usually seen in adult males, Eales disease may occur in children.[41] It is sometimes difficult to differentiate between vasculitis and vascular occlusion. Fluorescein angiography is very helpful to show vascular leakage, cystoid macular edema, or optic disc leakage as possible signs of inflammation. However, fluorescein angiography may be difficult to perform in children. An alternative is to perform an oral angiogram, by having a child swallow pure fluorescein dye with some sweetener and taking fundus photographs 20 minutes later. The time needed for the dye to appear in the fundus after passing the gastrointestinal system is variable.

The treatment will depend on the cause and the extent of the condition; often, laser photocoagulation will be necessary to prevent bleeding from proliferative retinopathy.

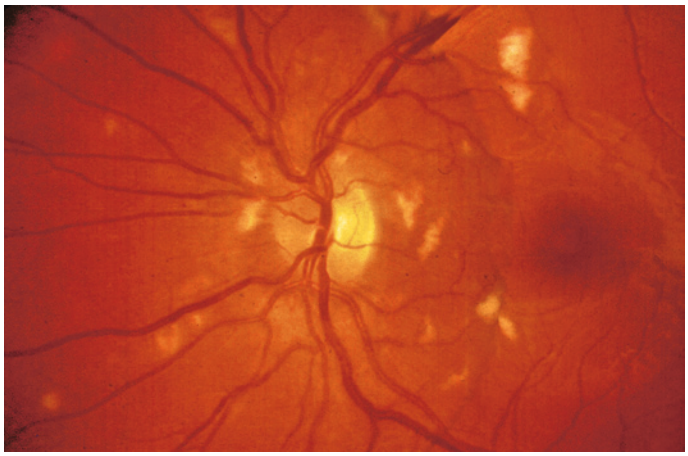


Fig. 51.4 Retinal vasculitis in a child with systemic lupus erythematosus. Shows multiple cotton-wool spots.

Frosted branch angiitis

Frosted branch angiitis is not a true diagnosis but a term that describes a form of panuveitis or posterior uveitis with retinal vasculitis and extensive perivascular exudates, causing vessels to appear white. Fluorescein angiography shows leakage from the affected vessels without occlusive vasculopathy. Venous involvement is more common than arteritis. It may be associated with a variety of causes, but in spite of an extensive work-up many cases remain "idiopathic." These idiopathic cases are often seen in healthy children or adults, especially in Japan.[42] The preceding flu-like illness may suggest a viral cause.

It may also be associated with a variety of conditions,[42] including cytomegalovirus, herpes simplex, Epstein–Barr virus, syphilis, HIV, Behçet disease,[43] immune reconstitution syndrome with Langerhans' cell histiocytosis,[44] and even after blunt trauma.[45]

In spite of the often-dramatic fundus picture (Fig. 51.5), the prognosis is said to be usually favorable with a good response to systemic steroid therapy. Intravitreal triamcinolone has been reported to successfully treat persistent macular edema after idiopathic frosted branch angiitis in an 11-month-old boy.[46]

Angioid streaks

Angioid streaks are dark or light broad lines radiating from the optic disc that have the appearance of retinal vessels, hence the name "angioid streaks." They represent cracks in a fragile and calcified Bruchs' membrane and are typically associated with pseudoxanthoma elasticum[47] (PXE; also see Chapter 50). Angioid streaks usually appear in the third decade of life and are rarely seen in teenagers (Figs 51.6 and 51.7; also see Fig. 50.8). However, angioid streaks have been reported in a 5-year-old girl with generalized arterial calcification of infancy (GACI).[48] This rare condition is caused by biallelic mutations in the *ENPP1* gene, leading to arterial stenosis from calcification of the internal elastic lamina and fibrotic myointimal proliferation of muscular arteries. The prognosis used to be poor because of severe congestive heart failure and ischemia during the neonatal period, but the outcome has improved as a result of treatment with bisphosphonates.

Other systemic conditions associated with angioid streaks in children are sickle cell disease and thalassemia. A family with optic disc drusen, mottled fundus appearance, and angioid streaks not associated with PXE has also been described.[49]

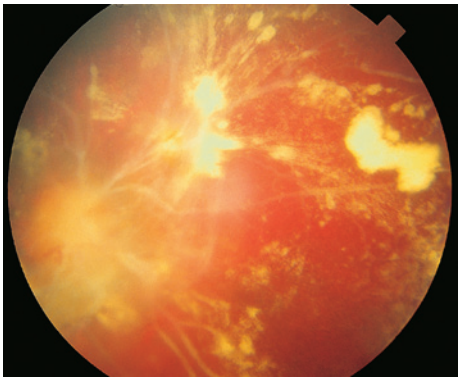


Fig. 51.5 Frosted branch angiitis. Unilateral frosted branch angiitis in a 10-year-old girl, of no known cause. Sheathed retinal vessels and subretinal exudates.

Angioid streaks are visible using fundoscopy (see Fig. 51.6), but stand out more clearly with near-infrared reflectance, fundus autofluorescence, fluorescein angiography, and the late phase of indocyanine green angiography (ICG). The streaks may be either hypo- or hyperfluorescent in the late phase of ICG. They radiate from the optic disc, sometimes with circumferential connections, and tend to increase with age. The pattern is believed to result from traction forces exerted by the extraocular muscles.

The importance of recognizing angioid streaks lies in discovering a systemic illness like PXE, but also in ophthalmological care: early detection and treatment of choroidal neovascularization (CNV) and counseling about wearing protective eyewear during contact sports (polycarbonate safety glasses). Their presence infers an increased risk of serious retinal hemorrhage from minor (blunt) trauma.[50]

The streaks, like lacquer cracks in myopia, traumatic choroidal ruptures, and peripapillary atrophy in presumed ocular histoplasmosis syndrome are believed to be a "low resistance pathway" (locus minoris resistentiae) for ingrowth of new vessels in the subretinal space. Sooner or later CNVs will occur, but fortunately the results of treatment have improved.

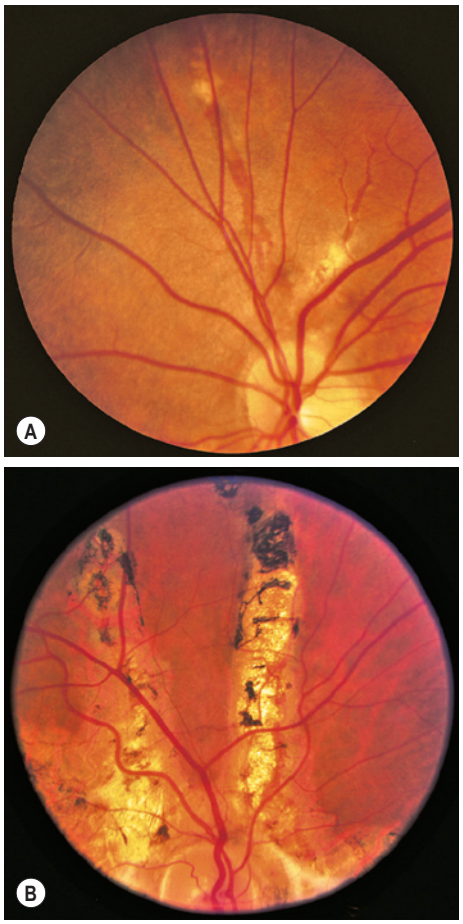


Fig. 51.6 Angioid streaks. (A) Angioid streak above the left optic disc in a 10-year-old girl with abetalipoproteinemia. (B) Marked angioid streaks in an adult with pseudoxanthoma elasticum. They taper away from the optic disc where they have formed a confluent ring around the disc. Neovascularization and hemorrhage occur at the margins of the streaks.

Idiopathic epiretinal membrane

Unlike in adults, idiopathic epiretinal membranes (Fig. 51.8) are rare in children and adolescents.[51] Epiretinal membrane formation (macular pucker, premacular gliosis, premacular fibrosis, cellophane maculopathy) diagnosed in young adults is often associated with an underlying etiology such as retinopathy of prematurity,[52] ocular trauma,[53] posterior segment inflammation,[54] combined hamartoma of the retinal pigment epithelium (RPE) and retina,[55] Coats disease,[56] and neurofibromatosis type 2.[57]

In children, an idiopathic epiretinal membrane may be secondary to vitreous hemorrhage or retinal hemorrhages.[58,59] Histopathologic studies demonstrate that epiretinal membranes consist of glial and RPE cells, with a greater proportion of myofibroblasts and collagen formation observed in the epiretinal membranes of adolescents than in the elderly.[60]

The etiology of idiopathic epiretinal formation in children and young adults remains unknown, with cases of epiretinal membranes occuring both with and without a posterior vitreous detachment.[60,61] The congenital persistence of primary vitreous has been proposed, supported by reports of epiretinal membranes in young patients with both a Mittendorf dot and a Bergmeister papilla.[62] In contrast, epiretinal membrane formation in young adults may be an acquired abnormality, with reported cases of epiretinal membrane in eyes with previous normal funduscopic examinations.[63] Optical coherence tomography (OCT) is helpful in evaluating idiopathic epiretinal membrane in children.[52,64]

Many young adults with epiretinal membranes can be followed conservatively without surgical intervention.[63,65,66] Epiretinal

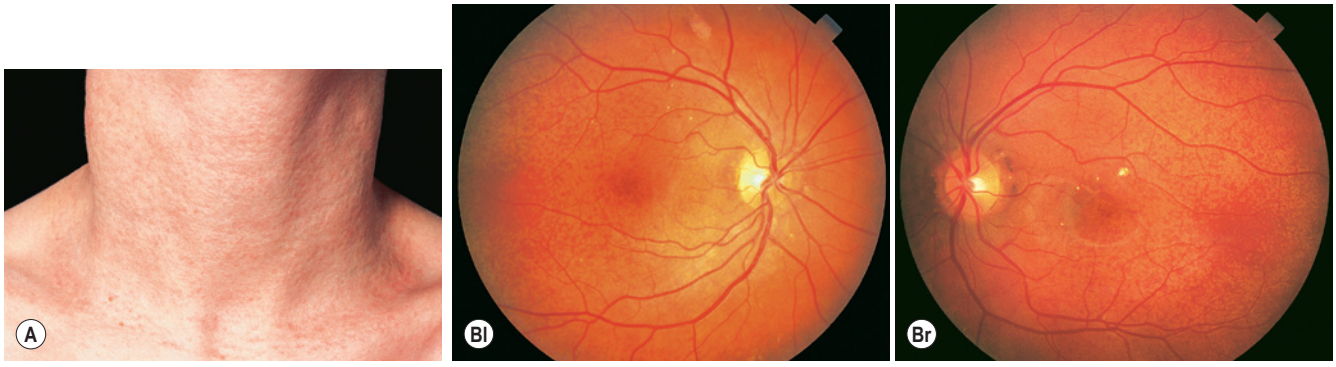


Fig. 51.7 Pseudoxanthoma elasticum (PXE). (A) The skin lesions of PXE consist of small, yellowish bumps in rows or a lacy pattern, which may join to make large patches. The skin is soft, lax, and slightly wrinkled or pebbly in appearance, which has been described as cobblestoned. The neck is often affected. (B) A 14-year-old child with PXE. "Peau d'orange" pigment speckling in the retinal pigment epithelium (RPE) at the posterior pole, yellow deposits in the RPE in both eyes, and angioid streaks at 12 and 6 o'clock in the right eye (Br) and 3 o'clock in the left (Bl).

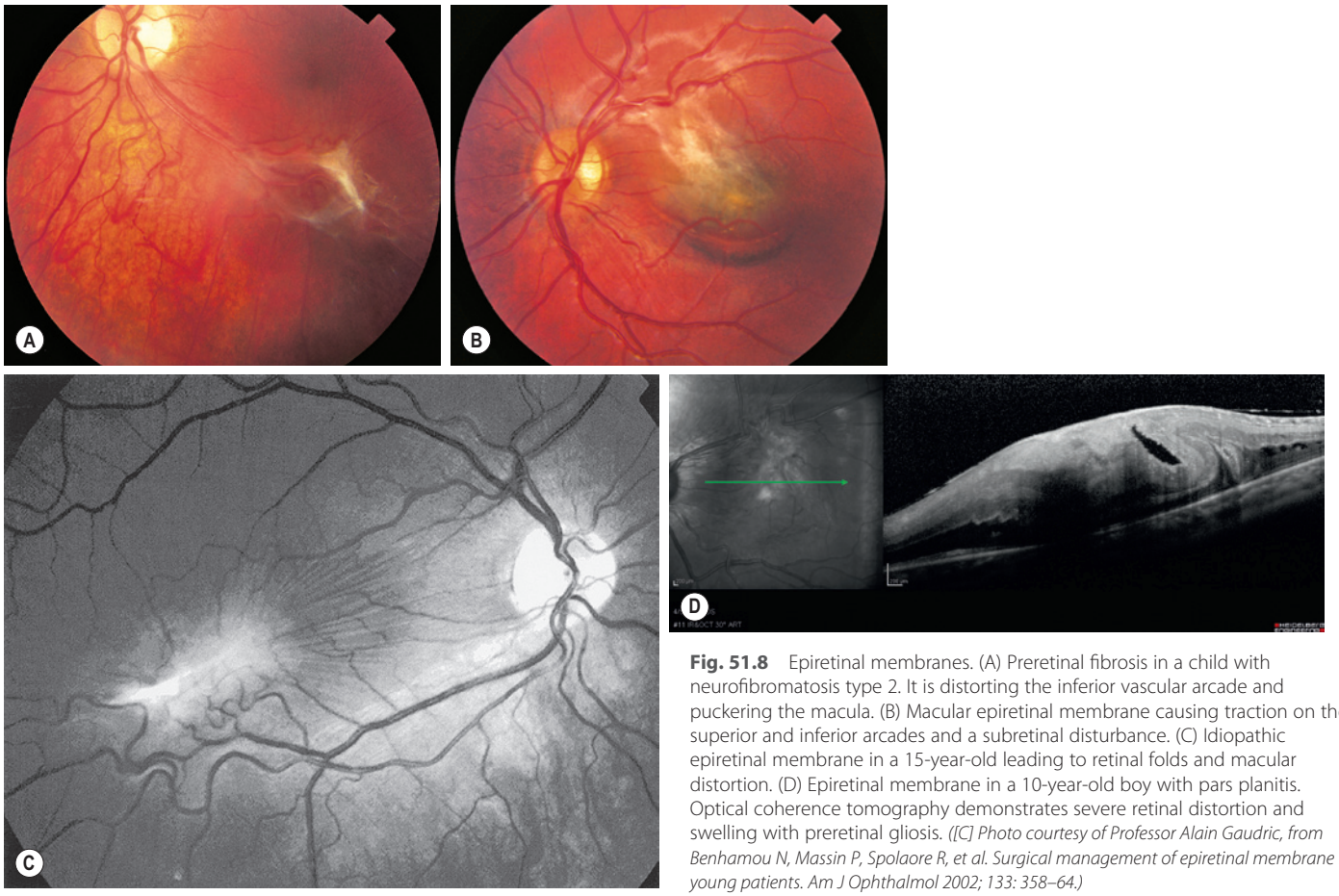


Fig. 51.8 Epiretinal membranes. (A) Preretinal fibrosis in a child with neurofibromatosis type 2. It is distorting the inferior vascular arcade and puckering the macula. (B) Macular epiretinal membrane causing traction on the superior and inferior arcades and a subretinal disturbance. (C) Idiopathic epiretinal membrane in a 15-year-old leading to retinal folds and macular distortion. (D) Epiretinal membrane in a 10-year-old boy with pars planitis. Optical coherence tomography demonstrates severe retinal distortion and swelling with preretinal gliosis. *([C] Photo courtesy of Professor Alain Gaudric, from Benhamou N, Massin P, Spolaore R, et al. Surgical management of epiretinal membrane in young patients. Am J Ophthalmol 2002; 133: 358–64.)*

membranes in young adults tend to be thicker, whiter, more adherent, and associated with a higher recurrence rate than in adults, particularly when overlying retinal blood vessels.[67] Spontaneous separation of idiopathic epiretinal membrane in young patients, even in the absence of a posterior vitreous detachment, has been reported.[58,68,69] When the contracting forces of the immature idiopathic epiretinal membrane are stronger than its adhesions to the retina, the membrane may separate spontaneously. Banach et al.[70] reported that patients with a visual acuity of 20/50 or better have favorable outcomes with observation alone, while patients with 20/60 or worse vision had significant improvement following vitrectomy and membrane peeling. In cases in which spontaneous peeling occurs, long-term follow-up is warranted until posterior vitreous detachment is complete, as delayed cases of macular hole have been reported.[71]

Lipemia retinalis

Lipemia retinalis – white retinal vessels filled with a creamy content (Fig. 51.9) – is an impressive but extremely rare ocular manifestation of hypertriglyceridemia. It is quite unusual in children, but may occur even in neonates[72] as a result of primary hypertriglyceridemia (not hypercholesterolemia!) in patients with lipoprotein lipase (LPL) deficiency. A transient LPL deficiency has been described in a premature male infant with extremely low birth weight.[73] Secondary hyperlipidemia has

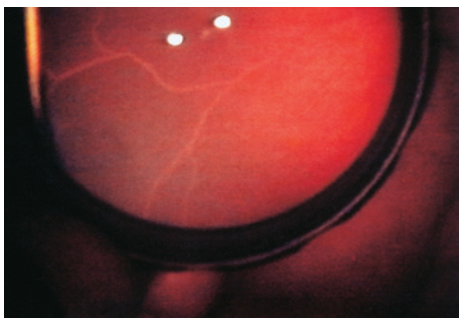


Fig. 51.9 Lipemia retinalis. Indirect ophthalmoscopic view of the retinal vessels, which stand out pale against the background, in a child with hyperchylomicronemia.

been associated with diabetes mellitus,[74,75] biliary obstruction, nephrotic syndrome, pancreatitis, hypothyroidism, alcoholism, medications (estrogens, beta-blockers, protease inhibitors), and in a patient with acquired immunodeficiency syndrome treated with protease inhibitors.[76]

With serum triglyceride levels above 2500 mg/dl (normal <200 mg/dl), the peripheral retinal vessels appear creamy and thin, and above 5000 mg/dl the fundus becomes salmon colored with creamy arteries and veins in the posterior pole.

The visual acuity usually remains unaffected, but electrophysiological abnormalities (reduced scotopic and photopic amplitudes, reduced Arden ratio with electro-oculography)

have been observed in an 11-year-old girl with diabetes.[75] Treatment of the underlying condition is mandatory, of course, and results in normalization of the fundus picture and the electroretinogram (ERG).

Cystoid macular edema

Macular cystoid structures may be seen in 39% of neonates undergoing screening for retinopathy of prematurity (ROP).[77] Cystoid macular edema (CME) has been reported to be common in premature infants independent of ROP. It may serve as an indicator of neurodevelopmental health for very preterm infants.[78,79] CME may occur in children with chronic ocular inflammation, retinitis pigmentosa, diabetes, radiation, Coats disease, X-linked retinoschisis, and autosomal dominantly inherited cystoid macular edema. In X-linked juvenile retinoschisis and enhanced S-cone syndrome it is not true CME, but rather foveal schisis without leakage on fluorescein angiography. CME is a common complication in children with uveitis and can be present even with good visual acuity.[80]

Serial spectral-domain OCT before and up to 12 months after cataract surgery demonstrated no cystoid macular edema in a pediatric patients cohort of 3 years and older.[81] Explanations for the lower incidence of postoperative CME in children than adults include a healthier vitreous body and vasculature, a lack of systemic disease, and possible differences in prostaglandin physiology.[82]

Choroidal neovascularization

CNV (Fig. 51.10) is quite rare in children and adolescents. It may be associated with a range of conditions as outlined in Box 51.1, including (1) scars of intraocular inflammation and infection[83]; (2) dystrophies (like Best disease or, very rarely, hyperoxaluria); or (3) weak anatomic spots between the retina and choroid (the so-called locus minoris resistentiae [see above], e.g. choroidal ruptures, dysplastic optic discs and optic disc drusen, angioid streaks, choroidal osteoma and choroidal coloboma). Often, no cause is found and the CNV is said to be idiopathic.[83,84] Later on, signs of presumed ocular histoplasmosis syndrome (POHS) may subsequently develop.



Fig. 51.10 Choroidal neovascularization. This 7-year-old with congenital rubella had a congenital cataract in the left eye and noted a reduction in the vision in the right eye. Background pigment mottling is present as well as serous detachment and a disciform lesion. The acuity fell to 6/60 but recovered to 6/12 over 4 months.

Children may complain of metamorphopsia and blurred vision, but often they do not inform their caretakers of any trouble. Fundus findings may include a dark gray membrane, subretinal or intraretinal hemorrhage, hard exudates, and pigmentary changes, most commonly in the macula or peripapillary region.

CNV in children has a more favorable prognosis than in adults with age-related macular degeneration. Goshorn et al.[83] reported spontaneous involution of CNV in 11 of 19 (58%) untreated eyes in children; nine patients achieved visual acuity better than or equal to 20/50. Laser photocoagulation, photodynamic therapy with verteporfin,[85] and submacular surgery[86] have been employed successfully. However, anti-vascular endothelial growth factor (anti-VEGF) agents[87,88] intravitreal injections, with or without corticosteroids, are the preferred treatment option, although the long-term effects of suppressing VEGF in children is uncertain.[89]

Chronic granulomatous disease

Chronic granulomatous disease (CGD) is a hereditary immunodeficiency disorder caused by a defect in the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme complex that causes dysfunction of phagocytes, making these patients more prone to severe infections including sepsis. Uncontrolled inflammation may also occur in various organs including the gastrointestinal tract, the bladder, the skin, and the eye.[90] The condition is very rare, with an incidence between 1 : 200,000 and 1 : 250,000 and occurs as an X-linked form (mutation in *CYBB* gene) in about two-thirds of cases and several autosomal recessive forms in the remainder. Several therapeutic strategies are under investigation including: anti-tumor necrosis alpha (anti-TNF-α) agents, hematopoietic stem cell transplants, and gene therapy. Eye involvement may consist of blepharitis, conjunctivitis, and chorioretinitis in

Box 51.1

Associations with choroidal neovascularization in children and adolescents

Inflammatory/infectious
- Presumed ocular histoplasmosis syndrome
- *Toxocara canis*
- Toxoplasmosis
- Rubella retinopathy

Inherited retinal disorders
- Best's vitelliform macular dystrophy
- Choroideremia

Miscellaneous
- Choroidal rupture
- Congenital optic pits
- Optic nerve head drusen
- Angioid streaks
- Myopia
- Choroidal osteoma
- Combined retinal pigment epithelium: retinal hamartomas
- Photocoagulation
- Idiopathic

about one-third of patients.[91,92] Severe atrophic scarring may ensue as can be seen in Figure 51.11. Bad outcome may occur secondary to complications like retinal ischemia, neovascular membranes, subretinal fibrosis, and macular edema.[91,92]

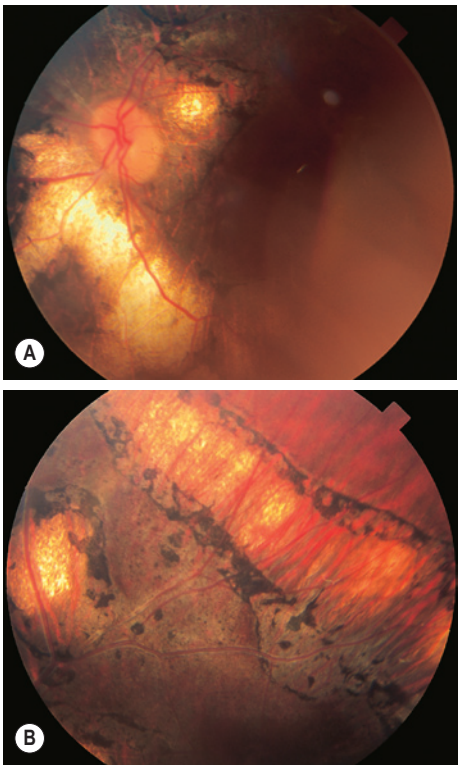


Fig. 51.11 Chronic granulomatous disease. (A) Chorioretinal atrophy and pigment clumping in the retinal arcades. (B) Linear peripheral chorioretinal atrophy and pigment clumping.

Juvenile X-linked retinoschisis

Juvenile retinoschisis (XLRS) is an X-linked condition without any symptoms in female carriers. The presentation can be quite characteristic, almost pathognomonic, with low vision in a young male due to foveal schisis (Fig. 51.12), with additionally peripheral retinoschisis (present in about half of the cases), golden reflexes seen with fundoscopy in the periphery, an electronegative ERG, often associated with a visually handicapped maternal uncle or grandfather. The diagnosis is confirmed with DNA investigation and the finding of a causative mutation in the *RS1* gene on the short arm of the X-chromosome. The gene product, retinoschisin, is implicated in cell adhesion and the development of the inner retina, but the function is still not precisely understood.[93] About 200 different mutations have been described with no clear genotype–phenotype correlation.[94] The condition is almost as frequent as Stargardt disease with a prevalence of 1 : 15,000 males.[95] However, misdiagnoses often occur, as the presentation may be quite variable (Fig. 51.13), with falciform folds, toxoplasmosis-like scars, ectopic maculae, gliotic maculopathy in adult or elderly males, a

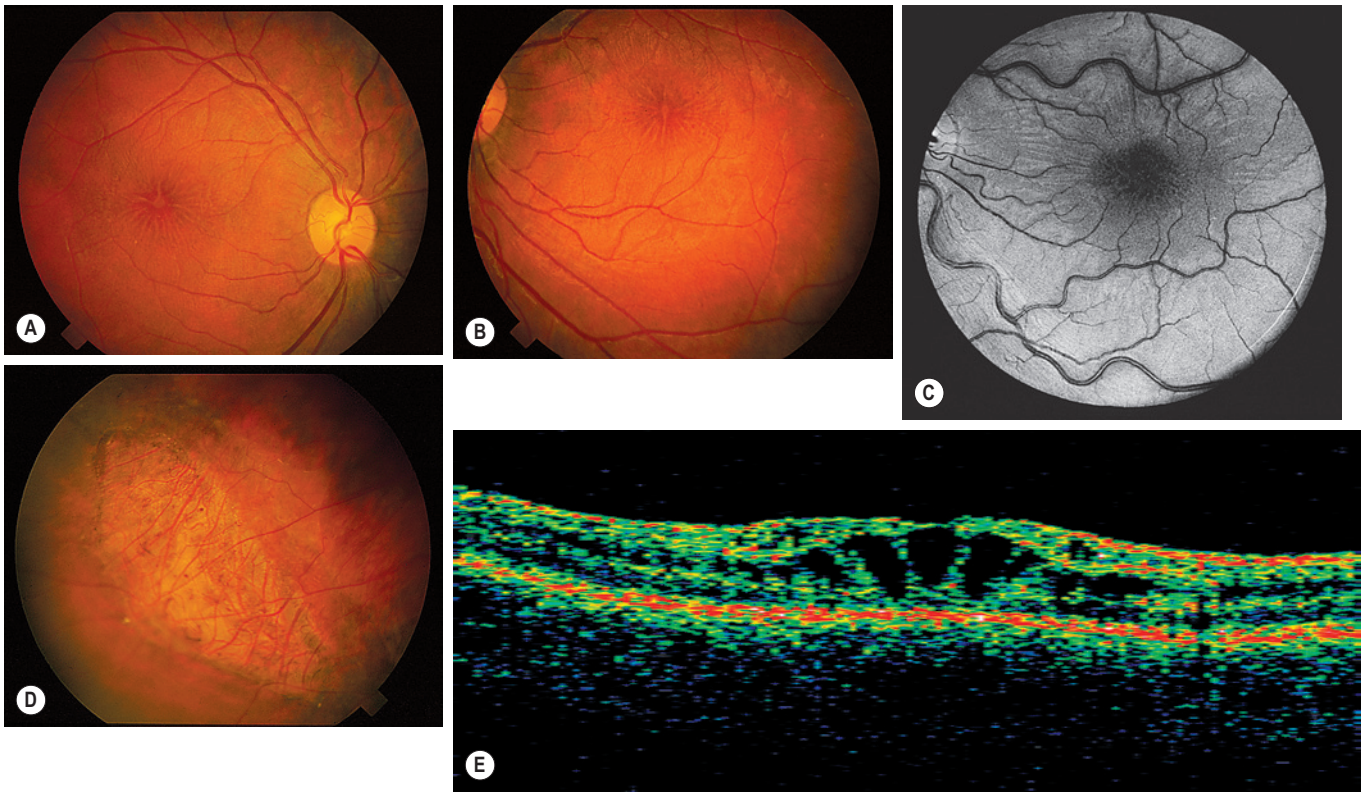


Fig. 51.12 Juvenile X-linked retinoschisis. (A,B) Bilateral foveal schisis. (C) The foveal schisis is best seen with ophthalmoscopy using a red free light. (D) Peripheral pigmentary changes in an area of schisis. (E) Optical coherence tomography study of retinoschisis demonstrating the optically empty spaces in the macula. *(Image courtesy of Dr Dorothy Thompson.)*

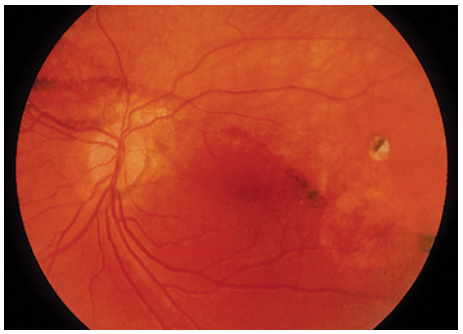


Fig. 51.13 Juvenile X-linked retinoschisis. Fundus appearance after a bullous retinoschisis cyst involving the macula has resolved, leaving a flat retina with a pigment demarcation line.

fundus albipunctatus-like appearance, widespread pigmentations similar to retinitis pigmentosa, exudative Coats-like abnormalities, and even atypical glaucoma or buphthalmus. Hyperopia, strabismus, nystagmus and (additional) amblyopia are often present.

Vitreous hemorrhage often occurs, especially when peripheral schisis is present and the retinal vessels lack support. This may lead to deprivation amblyopia in young children in whom surgical intervention may result in cataract formation. Retinal detachment, although feared, is relatively uncommon. Nonetheless, it is important to warn the parents about the vulnerability of these eyes and advise protective eyewear during sports and outside activities.

With the new imaging techniques, especially OCT, the cystic maculopathy is less easily missed. However, OCT has also shown that the typical maculopathy may be absent even in DNA-proven cases[96]!

Treatment with dorzolamide drops may reduce foveal cysts in some patients but the effect on visual acuity seems to be modest.[97] Proof of principle of gene therapy in a mouse model of XRS has been established,[93] and gene therapy in humans is now being performed at two sites in the USA (see NCT02416622 and NCT02317887 at www.ClinicalTrials.gov).

Laser pointer maculopathy

In the late 1990s, concerns about retinal damage from laser pointers were raised in the media but there was no convincing evidence of retinal damage.[98,99] Case reports of visual disturbances, without maculopathy, were reported due to afterimage or psychogenic effects. Although the American laser classification differs from that in Europe, laser pointers emitting visible radiation with an upper power limit of 5 mW are designated as class 1 or 2 and are regarded as safe if used properly as a pointing device.

However, the introduction of more powerful laser pointers and the easy availability of these on the Internet has led to renewed concerns about possible retinal damage. A recent PubMed literature search of proven laser pointer maculopathy (Fig. 51.14) revealed 15 cases.[100] These were more commonly caused by green rather than red laser pointers and mainly affected teenagers who used the laser pointer inappropriately as a toy.[100,101] In one case, the output of the involved laser pointer could be measured and was reported to be unsafe due to a high output (150 mW).[101] Laser pointers are not designed to be children's toys, popping balloons as a party trick. Neither should they be used to annoy people in a crowd as hooligans did during the 2015 Union of European Football Associations

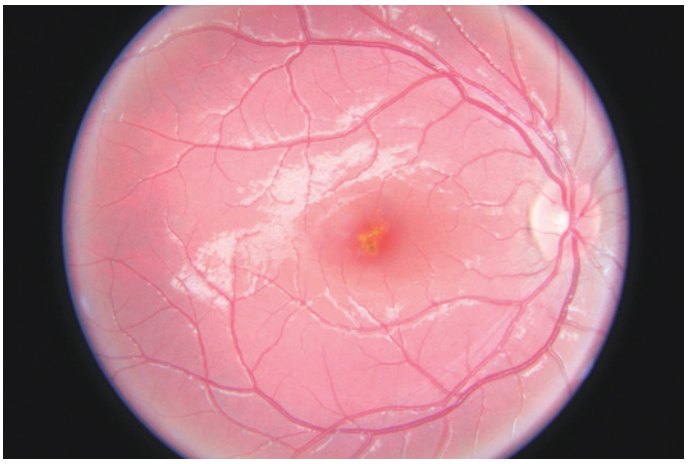


Fig. 51.14 Laser pointer maculopathy. Fundus of the right eye with a scar in the center of the macula.

(UEFA) Champions League. A drastic increase in instances of laser pointers aimed at aircrafts was reported in 2011 by the Federal Aviation Administration's Civil Aerospace Medical Institute, distracting pilots during their flight.[102] Unfortunately, the regulation and control of laser pointer sales do not fully apply in many countries. Green laser pointers of up to 1200 mW, which are very likely to be harmful to the retina if misused, can be easily ordered through on the Internet. Only very attentive custom declaration officers might stop the illegal import of such dangerous devices. The widespread availability of unsafe laser pointers, and consequently increased laser pointer-induced visual loss and increased risk for aviation incidents, raises an important social issue for health authorities and government officials.

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Retinal detachment in childhood

Martin P Snead

Chapter contents

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Rhegmatogenous retinal detachment (RRD) is uncommon in childhood but the prognosis is often poor due to aggressive proliferative vitreoretinopathy (PVR) and late presentation with or without second eye involvement at the time of diagnosis. The majority of cases of RRD in childhood are associated with inherited vitreoretinopathies and developmental abnormalities, with trauma making up the remainder.

Rhegmatogenous retinal detachment associated with trauma

Traumatic retinal detachment is seen mostly in older children, usually caused by blunt trauma where retinal tears may be found in 2–5%.[1] Penetrating injuries and retained intraocular foreign bodies are less common causes[2,3] but are frequently associated with severe PVR.

Blunt ocular trauma

Retinal dialysis

Retinal detachment due to blunt trauma is usually caused by a disinsertion at the ora serrata in older children. Sudden anteroposterior compression of the globe with a violent coronal expansion leads to retinal avulsion (Fig. 52.1A) characterized by a festoon of non-pigmented pars planar epithelium in the vitreous cavity. This is the hallmark of traumatic retinal dialysis. There may be signs of related orbital injury (Fig. 52.2) or, more frequently, subtle signs of collateral trauma to the iris, lens, or drainage angle. Superior quadrant involvement (Fig. 52.3) is more frequent than the lower temporal quadrant involvement seen in non-traumatic dialysis (Fig. 52.1B). Although the disinsertion may exceed 90° and resemble a giant retinal tear, the vitreous characteristically remains attached to the posterior flap so that independent mobility is not a feature. Dialyses, therefore, respond very well to conventional scleral buckling techniques. Further distinguishing features are the absence of radial extensions, which frequently occur at the apices of "true" giant retinal tears (GRTs) (Fig. 52.4) and the normal compact healthy vitreous architecture. Subretinal fluid recruitment in dialyses is typically slow, so that unless the ora serrata is routinely inspected after blunt trauma, the diagnosis may be delayed by weeks or months until macular involvement.[3]

Ragged impact necrosis breaks account for about one-fifth of the retinal breaks in blunt trauma.[3] Retinal vessel and retinal pigment epithelial (RPE) disruption may be confirmed on fundus fluorescein angiography, and retinal detachment usually presents within 6 weeks.[3] These breaks are often large, post-equatorial, and irregular, making closure by external buckling problematic. An internal approach is frequently required.

Giant retinal tears

True GRTs account for a minority of retinal breaks due to blunt trauma.[4] They are best managed with vitrectomy and internal tamponade (see below), although the visual prognosis may be limited by associated collateral ocular trauma.[5]

Penetrating ocular trauma

Penetrating injury is an uncommon cause of retinal detachment in childhood and may rarely follow inadvertent perforation of the globe at strabismus surgery. Intraocular foreign bodies are rarely seen in very young children, although penetrating injuries from air-gun pellets may be seen in older children and adolescents, usually with a poor prognosis because of the associated damage and aggressive PVR. Retinal perforation or incarceration from penetrating trauma rarely causes acute rhegmatogenous retinal detachment. The corneoscleral wound provides access for extrinsic fibroblasts, often leading to late tractional and rhegmatogenous retinal detachment.[5]

Non-traumatic retinal dialysis

Non-traumatic retinal dialysis accounts for approximately 10% of all juvenile retinal detachments[2,4] and in 97% affects the inferotemporal quadrant (Table 52.1 and see Fig. 52.1B). Examination of the entire retinal periphery may reveal two or

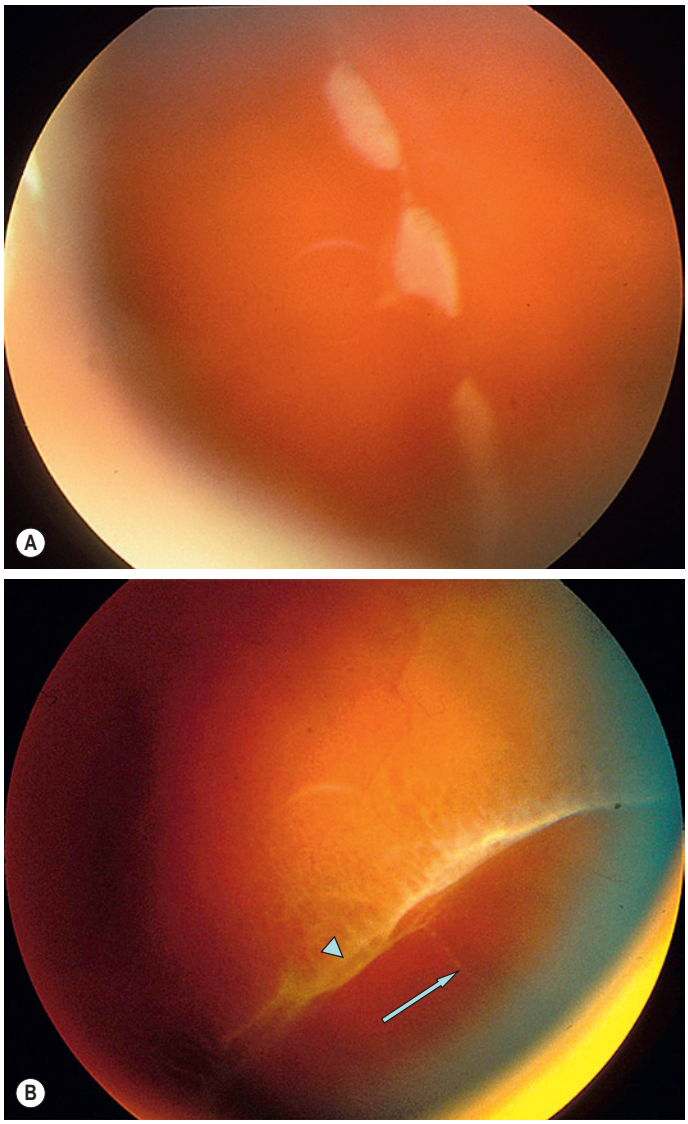


Fig. 52.1 Retinal dialysis. (A) Traumatic 180° "bucket handle" avulsion non-pigmented pars planar epithelium from patient in Fig. 52.2. (B) Non-traumatic retinal dialysis. Note characteristic associated cystic oral frill (arrowhead) and trans-dialysis tissue bridges (arrow).



Fig. 52.2 Blunt injury with associated traumatic retinal dialysis. Vision 6/6 unaided. Note also enophthalmos from associated blow-out fracture. Fundus findings illustrated in Fig. 52.1A.

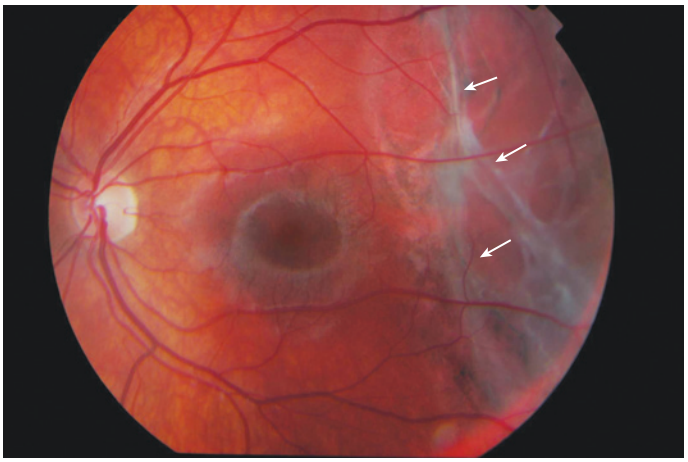


Fig. 52.3 Traumatic retinal dialysis associated with chronic retinal detachment in an 11-year-old girl. Bands of subretinal fibrosis (arrows) rarely require removal via an internal approach and the retina was re-attached with a 3-mm circumferential sponge.

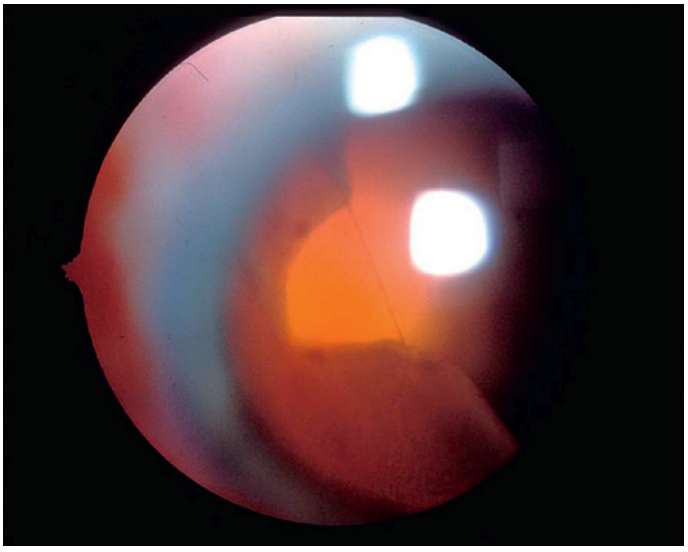


Fig. 52.4 Gravity-induced radial extension at the apex of a giant retinal tear.

Table 52.1 Cambridge guide to characteristic retinal break types in rhegmatogenous retinal detachment

The more common pediatric subgroups are highlighted in yellow.

Break type	Sex	PHM	Refractive error	Fellow eye pathology
Horseshoe tear	M=F	OFF	Myopic	15%
Round hole	F>M	ON	Myopic	50%
Dialysis	M>F	ON	Hypermetropic	15%
Giant retinal tear	M=F	OFF	Myopic	Up to 80%
Macular hole	M=F	OFF	Highly myopic	Rare
XLRS	M	ON	Hyperopic	100%

PHM, Posterior hyaloid membrane; XLRS, X-linked retinoschisis.

more separate dialyses in the same eye. There is a 2:3 male preponderance. The majority of patients are hypermetropic or emmetropic.[6,7] Detachments associated with dialyses progress slowly and often present either as an incidental finding or when the macula becomes detached. They are routinely managed with conventional buckling. Although the anatomic success rate of surgery is high, visual acuity may remain poor if there has been chronic macular involvement. Familial dialyses are rare, but consideration should be given to sibling examination because: (1) the patients are asymptomatic and (2) visual recovery once macular involvement has occurred may be poor. Examination of the fellow eye under anesthesia is important as retinal dialysis may be bilateral and abnormalities of the ora serrata, in the form of a "frill" or flat dialysis, are found in the fellow eye in up to 15% (see Table 52.1). In such cases, prophylactic retinopexy can be applied to the fellow eye to avert detachment with potential macular involvement requiring formal repair.

Rhegmatogenous retinal detachment associated with developmental abnormality

Ocular coloboma

Eyes with colobomas are at increased risk of detachment and account for approximately 0.5% of pediatric retinal detachments,[8,9] forming part of the spectrum of wider systemic developmental abnormality (Fig. 52.5). GRTs are seen with lens colobomas.[10] Rhegmatogenous detachment may develop in eyes with choroidal coloboma, when small retinal breaks develop in the hypoplastic retina overlying the coloboma. Assessment of vision can be difficult and the diagnosis of detachment can be further impaired by restricted pupil dilation, nystagmus, microphthalmos, and cataract (Fig. 52.6). The intercalary membrane stretched across the coloboma cavity can simulate a retinal detachment on ultrasound examination. The clinician should be alert to this and assess the retinal mobility on dynamic examination before surgery. The intercalary membrane consists of hypoplastic inner retina with reversal and duplication of outer neuroblastic layers at the coloboma margin.[11] Since both retinal pigment epithelium and Müller cells are vestigial or absent within the coloboma, effective retinopexy may be impossible unless applied outside the margin.

When retinal breaks occur away from the coloboma, they may be managed by conventional buckling provided the sclera is of sufficient quality and the break can be adequately closed. More usually, the retinal break lies within the coloboma (Fig. 52.7) so that identification and closure with retinopexy may be impossible without an internal approach. Retinal breaks over a coloboma are often small, multiple, and difficult to localize against the pale scleral background, but may be confirmed intraoperatively by the visualization of proteinaceous "schlieren" during internal drainage. Laser may be applied around the border of the colobomatous area. If this includes the papillomacular bundle it may be applied prior to retinal re-attachment to minimize the risk of thermal damage to the nerve fiber layer. Maintenance of tamponade whilst the retinopexy matures to full strength can be compromised by the abnormal configuration of the colobomatous globe and recurrent detachment occurs in up to 30%,[12] which may then require permanent internal tamponade.



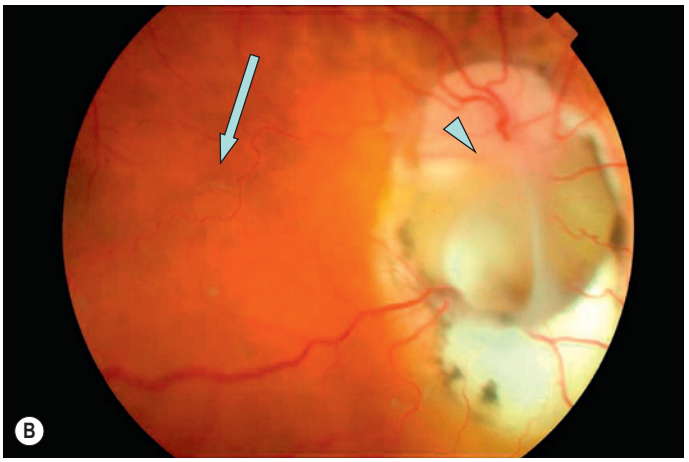


Fig. 52.5 Optic disc coloboma (arrowhead) associated with macula-off retinal detachment (arrow) in CHARGE syndrome. *(© Addenbrooke's Hospital.)*

Optic disc pits and macular detachment

The association of serous macular detachment and optic disc pits and coloboma is well recognized, and similar findings with the morning glory disc abnormality suggest that these conditions are variations of the same abnormality (Fig. 52.8A–D). The vitreous is characteristically attached. It has been suggested that up to 45% of optic disc pits may be complicated by serous retinal detachment.[13–15]

Although natural history studies have shown eventual spontaneous re-attachment in 25% of cases,[14] the combination of vitrectomy, laser photocoagulation, and gas tamponade may offer a greater chance of visual improvement, albeit with a risk of operative morbidity.[13,15]

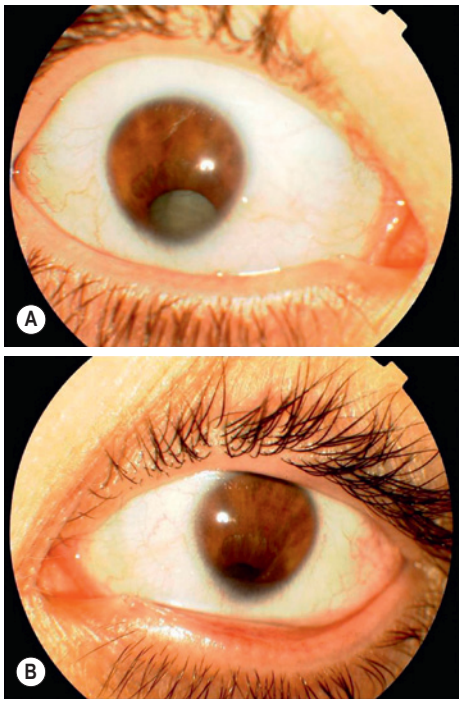


Fig. 52.6 Bilateral coloboma associated with microphthalmos, nystagmus, and cataract. Intercalary membrane simulating retinal detachment on B-scan ultrasonography (not shown).

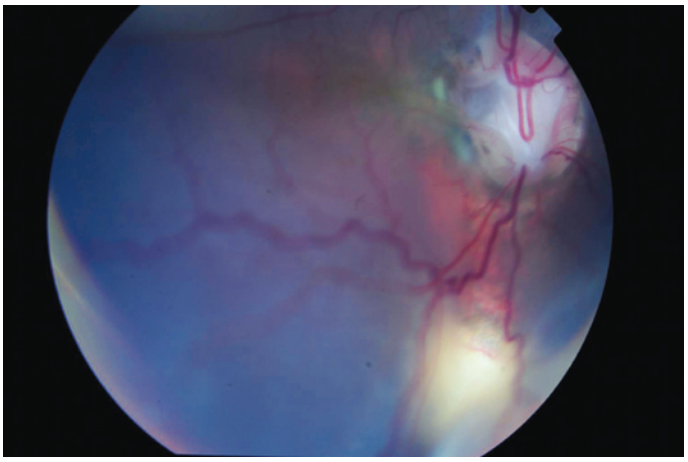


Fig. 52.7 Rhegmatogenous retinal detachment complicating coloboma in a 9-year-old boy. Retinal breaks may be difficult to identify preoperatively, but visualization of schlieren during vitrectomy can assist localization.

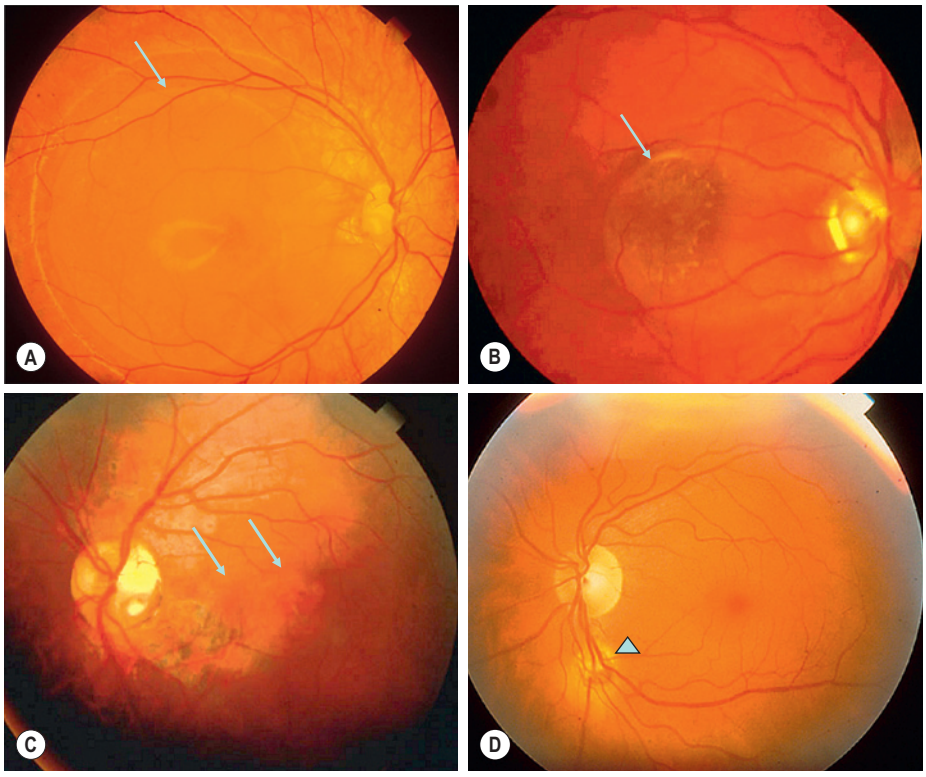


Fig. 52.8 (A,B) Two examples of optic disc colobomas associated with macular detachment (arrows). (C,D) child [optic disc pit with serous macular detachment (arrows)] and parent [choroidal coloboma (arrowhead)], respectively, illustrating inherited etiology in some cases.

Rhegmatogenous retinal detachment associated with inherited vitreoretinopathies

Inherited vitreoretinopathies are the basis for the majority of rhegmatogenous retinal detachments in childhood and may be classified as follows[16]:

1. vitreoretinopathies with skeletal abnormalities;
2. vitreoretinopathies with progressive retinal dysfunction;
3. vitreoretinopathies with abnormal retinal vasculature;
4. vitreoretinopathy with corneal changes.

The detachments are often complex and frequently associated with GRTs.

Vitreoretinopathies with skeletal abnormalities

Vitreoretinopathies associated with skeletal abnormalities are the largest subgroup (Table 52.2). The various forms of the Stickler syndromes account for the majority of these.

Table 52.2 Vitreoretinopathies associated with skeletal abnormalities

Syndrome	Gene	Distinguishing features	MIM #
STICKLER SYNDROME			
Type 1	*COL2A1*	Membranous congenital vitreous anomaly, congenital megalophthalmos, deafness, arthropathy, cleft palate	108300
Ocular only	*COL2A1*	Membranous congenital vitreous anomaly (usually), congenital megalophthalmos. No systemic features	609508
Type 2	*COL11A1*	Beaded congenital vitreous anomaly, congenital megalophthalmos, deafness, arthropathy, cleft palate	604841
Type 2 recessive	*COL11A1*	Autosomal recessive; beaded congenital vitreous anomaly, congenital megalophthalmos, cleft palate, profound severe congenital deafness	TBC
Type 3	*COL11A2*	Normal vitreous and ocular phenotype, deafness, arthropathy, cleft palate	184840
Type 4	*COL9A1*	Recessive inheritance; sensorineural deafness, myopia, vitreoretinopathy, epiphyseal dysplasia	614134
Type 5	*COL9A2*	Recessive inheritance; sensorineural deafness, myopia, vitreoretinopathy, epiphyseal dysplasia	614284
Type 6	*COL9A3*	Recessive inheritance; sensorineural deafness, myopia, vitreoretinopathy, epiphyseal dysplasia	TBC
Other	Unknown	Hypoplastic vitreous, deafness, arthropathy, cleft palate	Not assigned
KNEIST DYSPLASIA			
	COL2A1	Congenital vitreous anomaly, severe arthropathy, short stature, phalangeal dysplasia	156550
SEDC			
	COL2A1	Congenital vitreous anomaly, severe short stature, rhizomelic limb shortening, barrel chest	183900
V-PED			
	COL2A1	Congenital vitreous anomaly, vitreoretinopathy associated with severe phalangeal dysplasia	Not assigned
MARSHALL SYNDROME			
	COL11A1	Sparse hair, reduced sweating, congenital/juvenile cataract	154780
KNOBLOCH SYNDROME			
	COL18A1	Occipital encephalocele, renal abnormalities, abnormal palmar creases	267750
MARFAN SYNDROME			
	FBN1	Cornea plana, ectopia lentis, arachnodactyly, aortic root dilatation	154700

SEDC, Spondyloepiphyseal dysplasia congenita; V-PED, vitreoretinopathy with phalangeal epiphyseal dysplasia.

The Stickler syndromes

The Stickler syndromes form part of the spectrum of type II/IX/XI collagenopathies, which include Kniest dysplasia (MIM #156550) and spondyloepiphyseal dysplasia congenita (SEDC, MIM #183900). So far, at least eight clinically different subgroups have been identified (see Table 52.2) and further genetic heterogeneity remains to be resolved.

The majority of cases are type 1 Stickler syndrome, inherited in an autosomal dominant fashion. However, a significant minority results from *de novo* mutations with no family history. Furthermore, there are "ocular-only" variants, which have few, if any, systemic features to suggest the possible diagnosis.[17] The clinician should be alert to this possibility and the need to consider and/or exclude the diagnosis in all cases of pediatric giant retinal tear detachment.

Diagnosis

Before routine molecular genetic analysis, diagnosis was wholly reliant on the combination of major and minor clinical criteria.[18] The assignment of clinical phenotype still assists substantially in directing molecular genetic analysis (Fig. 52.9).[17,19–26]

Clinical features

Ocular features The fundamental feature of Stickler syndrome is a congenital abnormality in vitreous development, which manifests as an abnormal architecture visible on slit-lamp examination (see Fig. 52.9). This pathognomonic feature is especially important for the clinical diagnosis of the ocular-only subgroups, which have no systemic features to suggest the diagnosis.[17] The majority of patients presenting to an ophthalmologist will have either type 1 or type 2 Stickler syndrome and are frequently myopic.[16] Autosomal recessive Stickler syndrome due to mutations in type IX collagen is rare (see Table 52.2).

There is usually high myopia, which is congenital and often associated with significant astigmatism (Fig. 52.10). However, in some series, almost a quarter of patients have no significant refractive error. The association with congenital cataract is well recognized, and some patients exhibit a characteristic quadrantic lamellar cortical lens opacity, which can be a very useful diagnostic sign (Fig. 52.11). It does not, however, differentiate between subgroups, being present in both type 1 and type 2 Stickler syndrome.

In the UK and USA, over 50% of patients with a clinical diagnosis of one of the Stickler syndromes will develop retinal

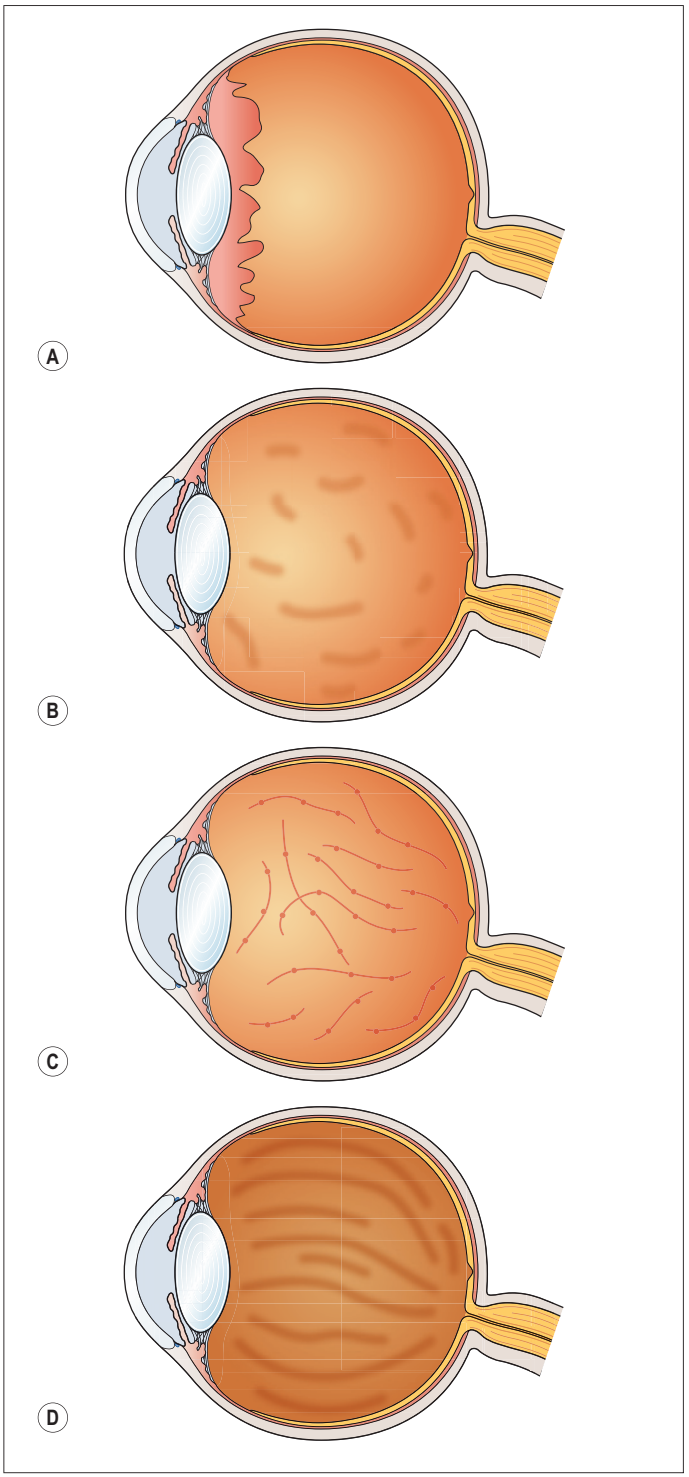


Fig. 52.9 Schematic illustration of vitreous phenotypes in Stickler syndrome. (A) Membranous congenital vitreous anomaly (haploinsufficiency mutations of *COL2A1*). (B) Hypoplastic congenital vitreous anomaly (*COL2A1* splicing mutations). (C) Beaded congenital vitreous anomaly (*COL11A1*-dominant negative mutations). (D) Normal vitreous architecture: compact lamellar array (*COL11A2* mutations).

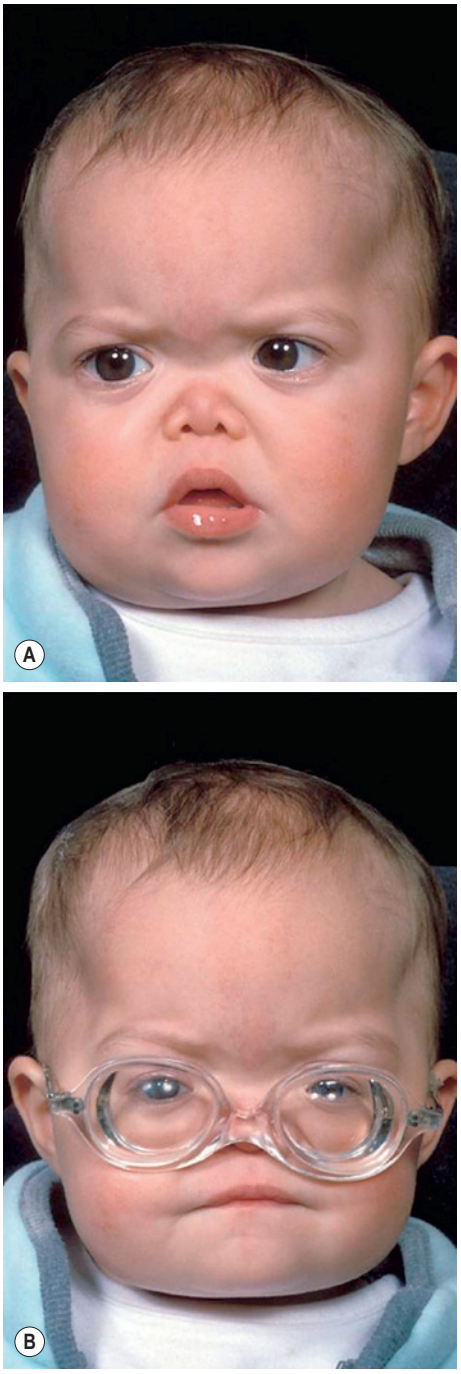


Fig. 52.10 Stickler syndrome. Marked nasal hypoplasia (A) and congenital high myopia (B) revealed under cycloplegic refraction.

detachment.[27] However, in the genetically confirmed high-risk subgroup, this figure rises to over 70%.[28,29] In a recent study, the median interval between retinal detachment in the first eye and retinal detachment in the second eye was 4 years[29] and, although rare before 1½ years of age, the youngest child with bilateral retinal detachment was 6 weeks of age, with a further case of bilateral total retinal detachment before 1 year of age. The risk of retinal detachment in type 2 Stickler syndrome appears to be slightly lower but remains to be quantified; surveys suggest that between 40% to 50% of patients had suffered retinal detachment. In the non-ocular subgroup (type 3), the risk appears to be no greater than the average population.

Systemic features All subgroups of Stickler syndrome may exhibit abnormalities of the hard or soft palate that are frequently associated with eustachian tube dysfunction and

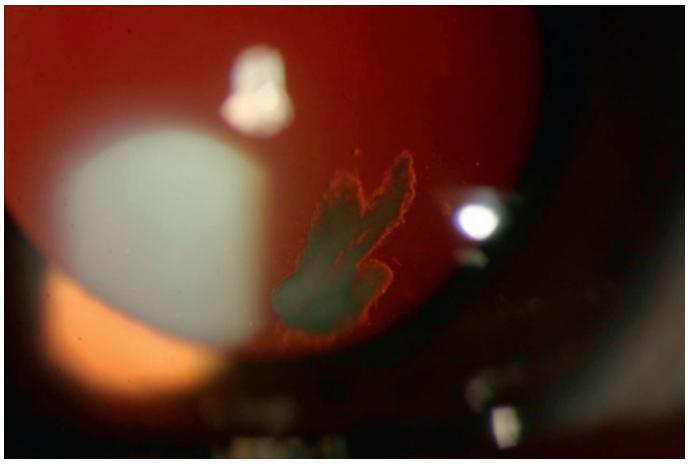


Fig. 52.11 Classic quadrantic lamellar cataract found in both type 1 and type 2 subgroups of Stickler syndrome.

middle ear impairment. In those patients without a history of palate repair, direct examination and palpation will help identify those with subclinical clefts – an easily overlooked diagnostic sign. In addition to conductive hearing impairment, many patients also exhibit a subtle, subclinical high-tone sensorineural hearing defect due to cochlear abnormalities.

Over 80% of children with Stickler syndrome report musculoskeletal symptoms, and joint hypermobility is common (Fig. 52.12). Patients are occasionally given an erroneous diagnosis of Perthe's disease, as the appearances can be similar radiologically. It is also common for adolescent Stickler syndrome patients to receive a diagnosis of Osgood–Schlatter disease, but since this is a clinical rather than a radiologic diagnosis, the true nature of this association remains to be clarified.

Kniest dysplasia (MIM #156550)

Kniest dysplasia is an autosomal dominant disorder that shares many similarities with Stickler syndrome and the same genetic locus. Mutations are found in the same gene as for type 1 Stickler syndrome (*COL2A1*), but result in dominant-negative effects rather than haploinsufficiency, resulting in more severe arthropathy.[30] It typically presents at birth with shortened trunk and limbs, congenital megalophthalmos, and flattened nasal bridge (Fig. 52.13A,B). The joints are often large at birth and the fingers long and knobbly. Motor milestones can be delayed by joint deformities, and disuse muscle atrophy may result. Both conductive and sensorineural hearing loss may be present, as with the Stickler syndromes. The intellect is normal. Myopia, retinal detachment, and GRT are the major ophthalmic complications.

Spondyloepiphyseal dysplasia congenita (MIM #183900)

Spondyloepiphyseal dysplasia congenita (SEDC) presents at birth with shortening of the trunk and, to a lesser extent, the extremities (rhizomelic limb shortening) (Fig. 52.14). It is an autosomal dominant disorder and characteristically results from dominant-negative mutations in the gene for type II collagen (*COL2A1*). In common with other type II collagenopathies, patients exhibit congenital abnormalities of vitreous development, retinal detachment, hearing loss, and cleft palate. Odontoid hypoplasia may be present, predisposing to cervicomedullary instability. Imaging of the cervical spine should therefore be considered prior to general anesthesia.

Knobloch syndrome (MIM #267750)

Knobloch syndrome is an automosomal recessive vitreoretinopathy. There is high myopia, nystagmus, featureless iris, cataract, ectopia lentis, retinal detachment, severe RPE atrophy resulting in prominent choroidal vasculature, congenital occipital encephalocele, unusual palmar creases, nail hypoplasia, and dental caries (Fig. 52.15). In instances where the occipital encephalocele is subclinical, computed tomography or magnetic resonance imaging may be required to support the clinical diagnosis. Molecular genetic analysis most commonly implicates homozygous splice site changes in the gene encoding the α1 chain of type XVIII collagen (*COL18A1*), although compound heterozygotes have also been identified.

Marfan syndrome (MIM #154700)

Marfan syndrome is an autosomal dominant connective tissue disorder associated with an abnormal vitreous architecture, myopic astigmatism, and characteristic skeletal features, including increased height with disproportionately long limbs and digits, scoliosis, lumbar lordosis, joint laxity, a crowded, high-arched (but not cleft) palate, and anterior chest deformity. It is a disorder of fibrillin, a high molecular weight extracellular glycoprotein. Mutations in the fibrillin gene on chromosome 15 (*FBN1*) cause both Marfan syndrome and dominant ectopia lentis. Other ocular features include retinal detachment, myopia, megalophthalmos, cornea plana, hypoplastic iris, glaucoma, and early nuclear sclerotic cataract.

An association with rhegmatogenous retinal detachment has been reported in 8–50% of cases; approximately 75% of these occur before 20 years of age. The myopia is characteristically developmental: in one large series, no case of myopia was found under 3 years of age. This contrasts with the congenital non-progressive myopia found in type 1 Stickler syndrome. In Marfan syndrome, the pupils dilate poorly because of a structural iris abnormality. This, combined with lens subluxation and weak scleral architecture, can make retinal detachment repair a formidable surgical challenge. Pars plana lensectomy and internal tamponade are often required.

Cardiovascular associations include mitral valve prolapse, mitral regurgitation, dilation of the aortic root, and aortic regurgitation. Aortic aneurysm and dissection are the most significant life-threatening complications.

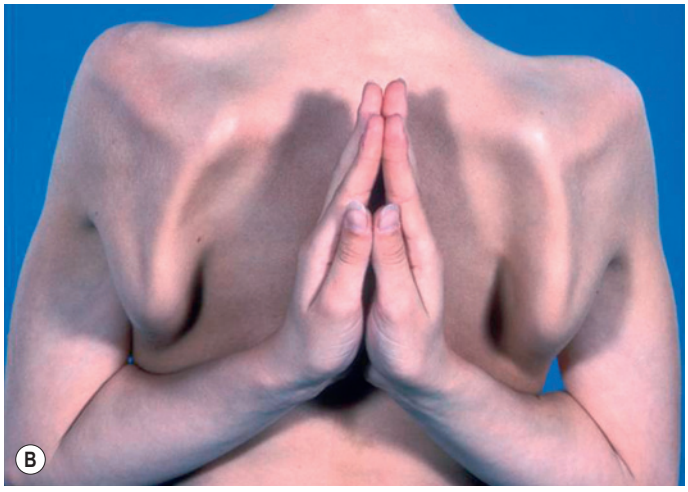
Vitreoretinopathies associated with progressive retinal dysfunction

Wagner vitreoretinopathy (MIM #143200) (see also Chapter 42)

Wagner syndrome features autosomal dominant inheritance, low myopia (−3.00 diopters or less), fluid vitreous, cortical cataract, inconstant and variably affected dark adaptation, and retinal detachment. The cardinal features are absence of the normal vitreous architecture and thickening and incomplete separation of the posterior hyaloid membrane, which tends to occur in a circular band. A large range of chorioretinal abnormalities has been described, including the typical chorioretinal atrophy with pigment migration into







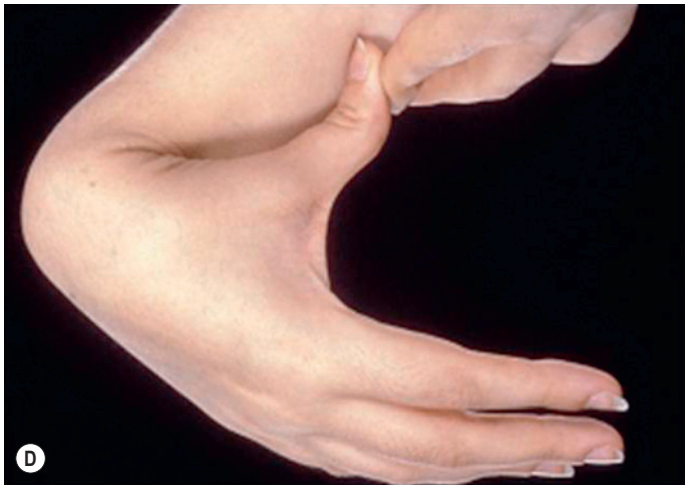


Fig. 52.12 Stickler syndrome. (A–D) Joint hypermobility can be assessed in a variety of ways.





Fig. 52.13 Kniest dysplasia. Note high myopia and severe arthropathy, particularly spine, knees, elbows, and phalangeal dysplasia.
(© Addenbrookes Hospital.)



Fig. 52.14 Spondyloepiphyseal dysplasia congenita. Note short stature, barrel chest, and rhizomelic (proximal) limb shortening. Patients typically exhibit the membranous congenital vitreous anomaly. *(Reproduced with permission from Snead MP, Richards AJ. Hereditary vitreoretinopathies. In: Sebag J, editor. The Vitreous in Health and Disease. New York, NY: Springer, 2014: 21–40.)*

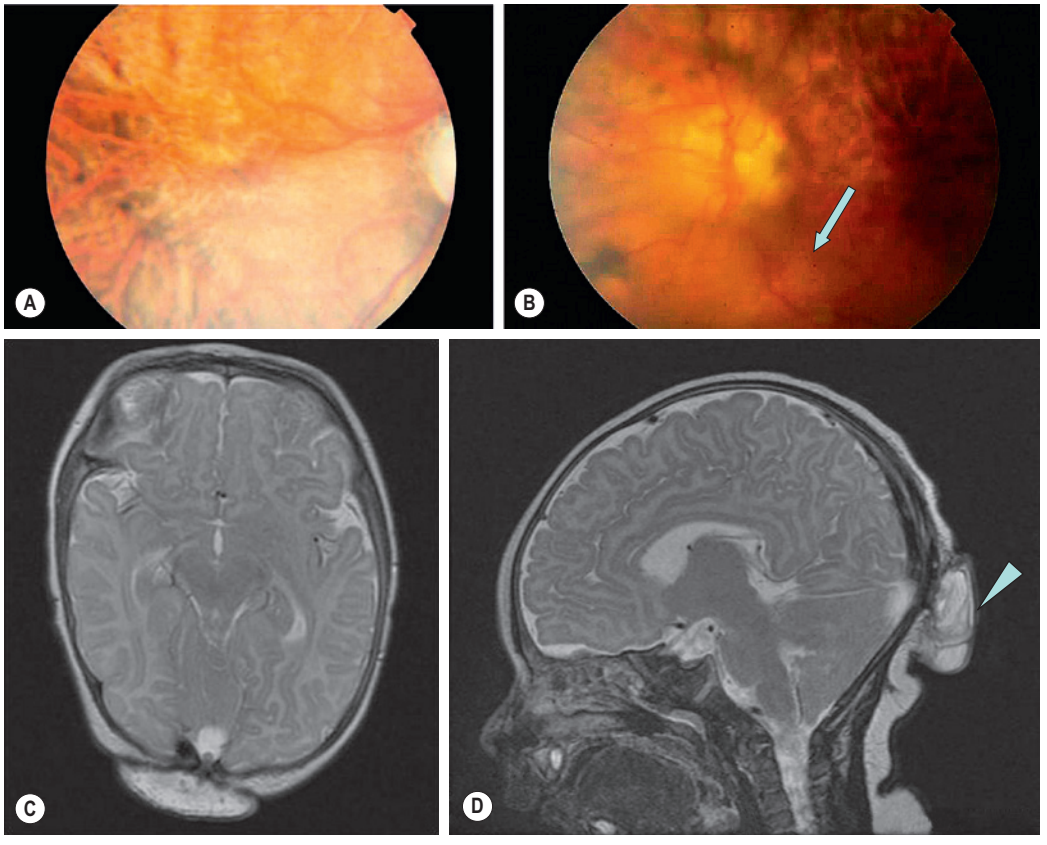


Fig. 52.15 Knobloch syndrome. Macula-off detachment left eye (arrow) associated with high myopia and occipital encephalocele (arrowhead).

the retina (Fig. 52.16). There is gradual progressive visual loss even without retinal detachment. Electroretinographic responses are progressively reduced, and visual-field testing demonstrates ring scotomas with eventual loss of central visual acuity. The phenotype at the end-stage is referred to as erosive vitreoretinopathy. The lenses typically develop anterior and posterior cortical opacities in puberty, with rapid progression during the fourth decade. The anterior lens capsule is tough and elastic, which can make capsulorrhexis difficult. Rhegmatogenous retinal detachment and glaucoma

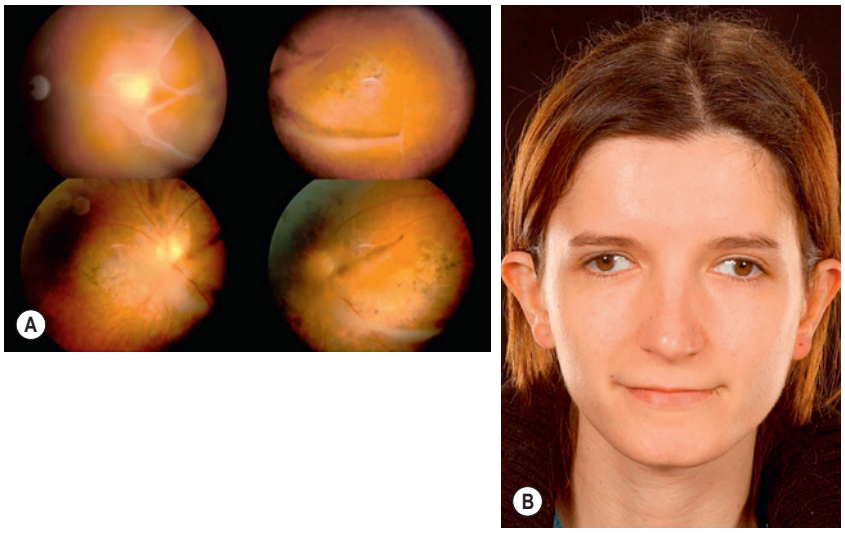


Fig. 52.16 Wagner vitreoretinopathy. Note thickening and incomplete separation of the posterior hyaloid membrane (A) and marked pseudo-exotropia (B). *(Reproduced from Meredith SP, Richards AJ, Flanagan DW, et al. Clinical characterisation and molecular analysis of Wagner syndrome. Br J Ophthalmol 2007; 91: 655–9.)*

were not reported by Wagner, but are now recognized. Wagner syndrome is also associated with large angle kappas indicative of an ectopic fovea (Fig. 52.16). The prognosis is poor, with progressive visual loss. The risk of rhegmatogenous retinal detachment, although higher than normal, is not as high as in the Stickler syndromes. The term "Jansen syndrome" has been used to describe a hereditary vitreoretinopathy with clinical features consistent with Wagner syndrome. It shows linkage to the same genetic locus.

Goldmann–Favre syndrome/enhanced S-cone dystrophy (MIM #268100)

Patients with Goldmann–Favre syndrome have liquefaction and fibrillar changes of the vitreous, night blindness, equatorial chorioretinal atrophy, and pigment clumping. There is also peripheral and macular schisis, cortical lens opacities, rod–cone dysfunction, and diffuse vascular leakage on fluorescein angiography. Goldmann–Favre syndrome is inherited as an autosomal recessive disorder, and is caused by a mutation in the same gene (the *NR2E3* gene) that causes enhanced S-cone syndrome (ESCS). ESCS is the only inherited retinal disease that exhibits a gain in photoreceptor function. Patients show enhanced sensitivity to blue (short-wavelength) light, night blindness, and loss of sensitivity to long and medium wavelengths. The electroretinogram (ERG) findings in this group demonstrate undetectable rod-isolated responses and reduced combined rod–cone responses.

Vitreoretinopathies associated with abnormal retinal vasculature

Familial exudative vitreoretinopathy (MIM #133780, #601813, #305390) (see also Chapter 42)

Familial exudative vitreoretinopathy is believed to be a premature arrest of retinal angiogenesis and vascular differentiation resulting in incomplete vascularization of the peripheral retina. The failure to fully vascularize the retina may be asymptomatic, but secondary changes can include neovascularization, retinal exudate, peripheral snowflake vitreous changes, and tractional or combined tractional and rhegmatogenous retinal detachment. Epiretinal membranes can cause severe retinal distortion and macular ectopia, which may be the presenting feature of poor vision in children (Fig. 52.17). The prognosis is highly variable, with some individuals blind by 10 years of age and others asymptomatic throughout adult life. Vascular abnormalities in individuals with milder phenotypes may only be evident on fluorescein angiography. It is an autosomal dominant condition.

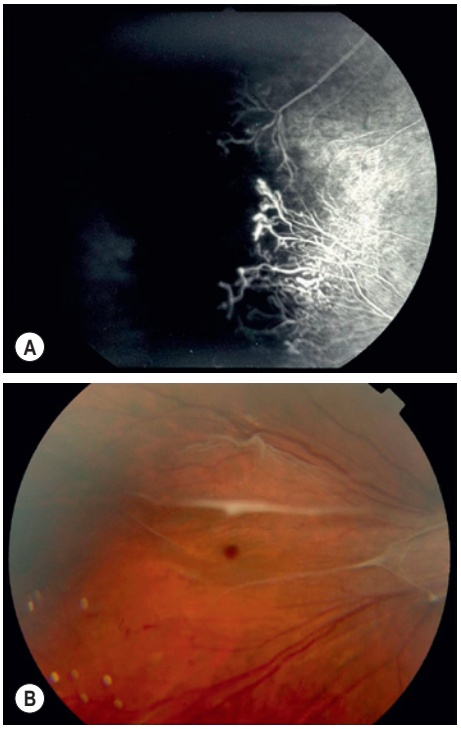


Fig. 52.17 Familial exudative vitreoretinopathy (A). Epiretinal surface membrane can cause severe retinal distortion and macular ectopia (B).

Autosomal dominant vitreochoroidopathy (MIM #193220)

Autosomal dominant vitreochoroidopathy is characterized by vitreous syneresis with or without peripheral vitreous changes.

Peripheral pigmentary changes typically occur at the equatorial region with a discrete posterior boundary (Fig. 52.18) associated with diffuse retinal vascular leakage, cystoid macular edema, and early-onset cataract. The peripheral pigmented band extends from the ora serrata to the equator through 360° of the retina. Other features are rhegmatogenous retinal detachment, punctate retinal opacities, choroidal atrophy, and early nuclear sclerosis. The ERG responses are normal, although the electro-oculogram is abnormal.

Vitreoretinopathy associated with corneal changes

Snowflake vitreoretinal degeneration (MIM #193230) (see also Chapter 42)

The pathognomonic feature of snowflake vitreoretinal degeneration is the association with corneal guttata, and disc pallor, which is not a feature of any of the other hereditary vitreoretinopathies. The vitreous has a fibrillar appearance, and small snowflake-like opacities in the retina may not be immediately obvious. Minor vascular abnormalities of small retinal vessels have been reported.

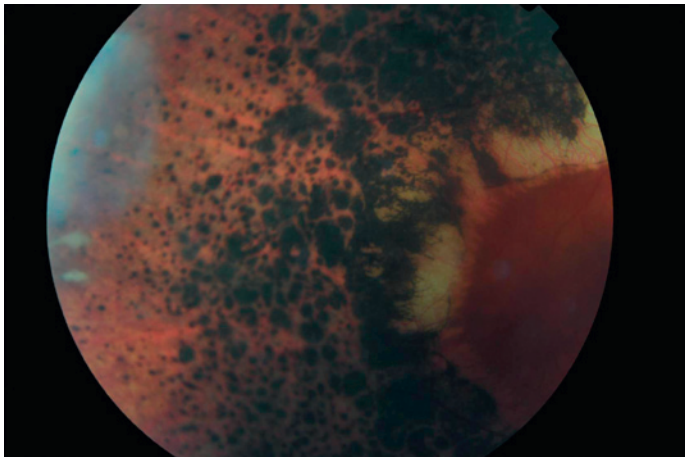


Fig. 52.18 Autosomal dominant vitreochoroidopathy. Peripheral pigmentary changes typically occur at the pre-equatorial region with a characteristically sharp posterior boundary.

X-linked retinoschisis (MIM #312700) (see also Chapter 42)

X-linked retinoschisis is an uncommon cause of retinal detachment in childhood, accounting for 2.5–5% of all pediatric retinal detachments. The incidence of retinal detachment varies in the different series, but it may occur in up to 16% of affected patients. Vitreous hemorrhage is another cause of visual loss (Fig. 52.19). Peripheral retinoschisis is found in approximately 50% of cases, and can be complicated by retinal detachment by various mechanisms. A full-thickness retinal break occurring *de novo*, or a communication between outer and inner leaf defects in the schisis wall, may lead to rhegmatogenous retinal detachment. Full-thickness breaks may be managed by scleral buckling procedures, provided complete break closure can be achieved. Where communication exists between inner and outer leaf breaks, an internal approach may be required.

Occasionally, X-linked retinoschisis can be complicated by cyst formation, hemorrhage into the cavity, or even be so bullous as to obscure the visual axis. Spontaneous resolution can occur, but prolonged delay may compromise the visual prognosis, so some advocate surgical drainage and internal de-roofing of the cyst.

Surgical considerations in pediatric rhegmatogenous retinal detachment

Prophylaxis

For the most common cause of RRD in childhood (Stickler syndrome), the risk of retinal detachment in childhood and blindness can be substantially reduced by accurate genotyping and prophylaxis. Patients with type 1 Stickler syndrome are the subgroup at highest risk of developing retinal detachment, typically as a result of a GRT – that is to say a circumferential break at the pars plana junction caused by a separation of the posterior hyaloid membrane much more anteriorly than would normally be the case (Fig. 52.20A–E). Prophylactic retinopexy, deployed and specifically positioned to prevent GRT progression, has been shown to substantially reduce the risk of retinal detachment and blindness from this type of break in type 1 Stickler syndrome (Fig. 52.21A). In a cohort analysis of 487 patients with type 1 Stickler syndrome, those

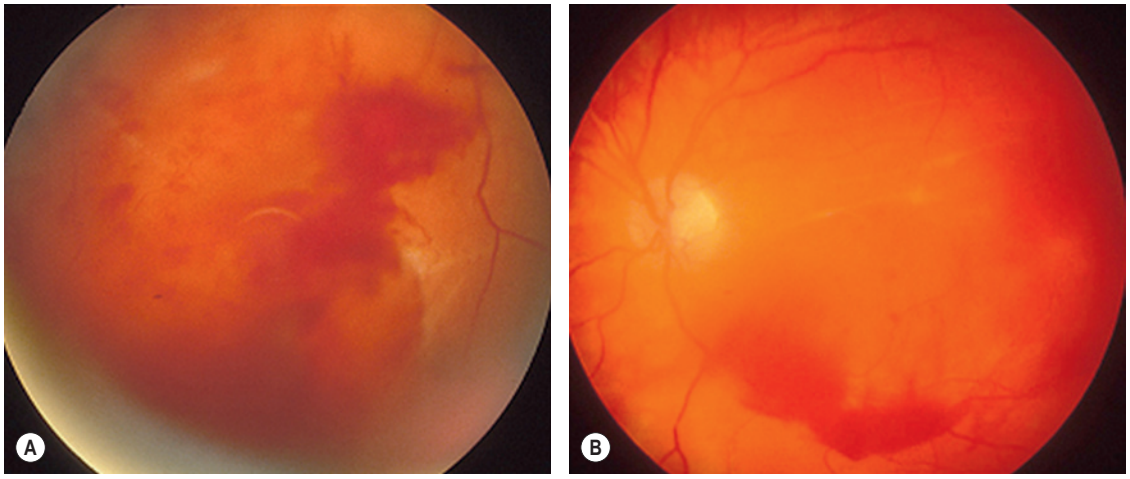


Fig. 52.19 Non-accidental injury was initially queried in this 10-year-old boy with X-linked retinoschisis with bilateral vitreous hemorrhage (A) Right eye; (B) left eye.

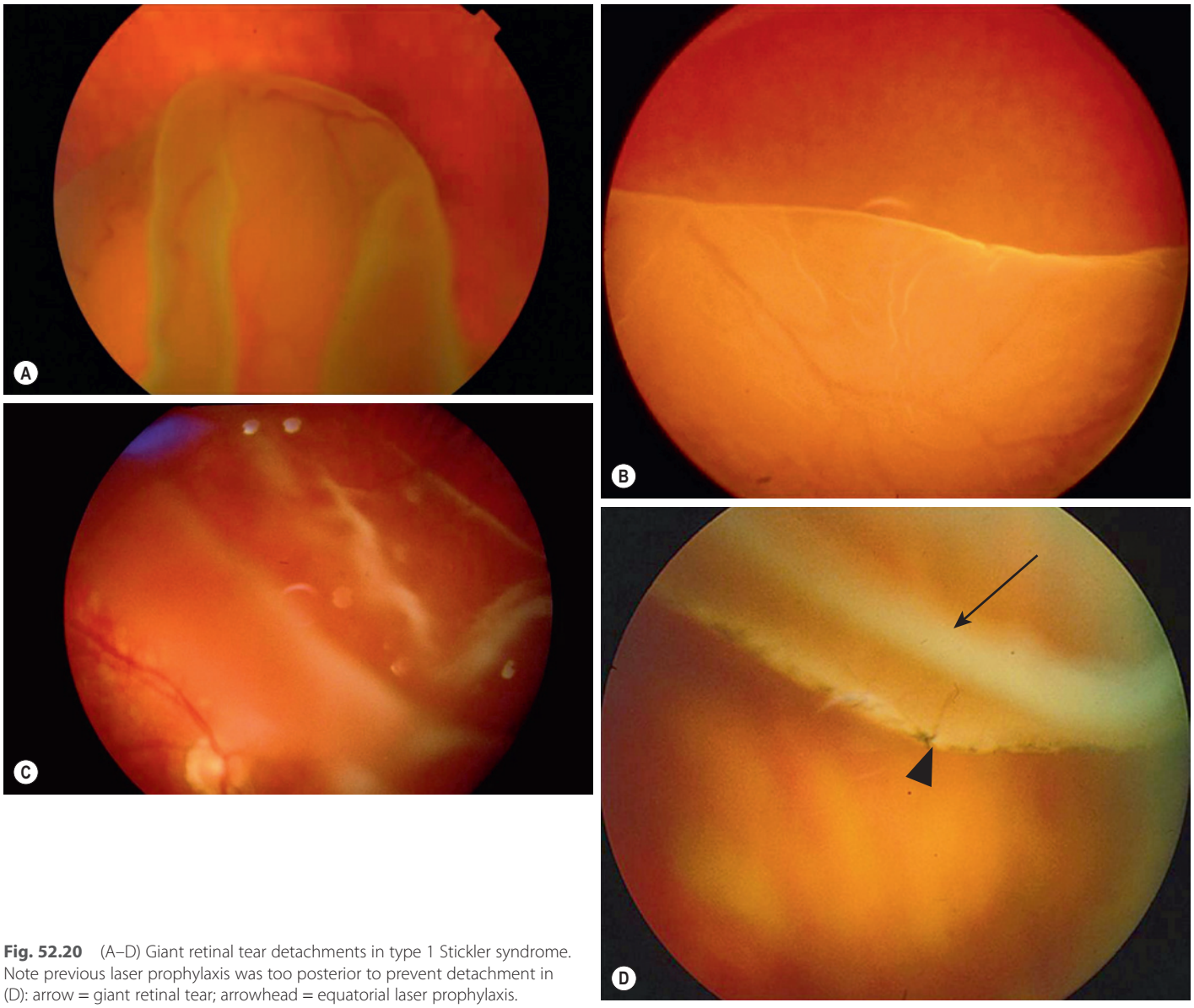


Fig. 52.20 (A–D) Giant retinal tear detachments in type 1 Stickler syndrome. Note previous laser prophylaxis was too posterior to prevent detachment in (D): arrow = giant retinal tear; arrowhead = equatorial laser prophylaxis.

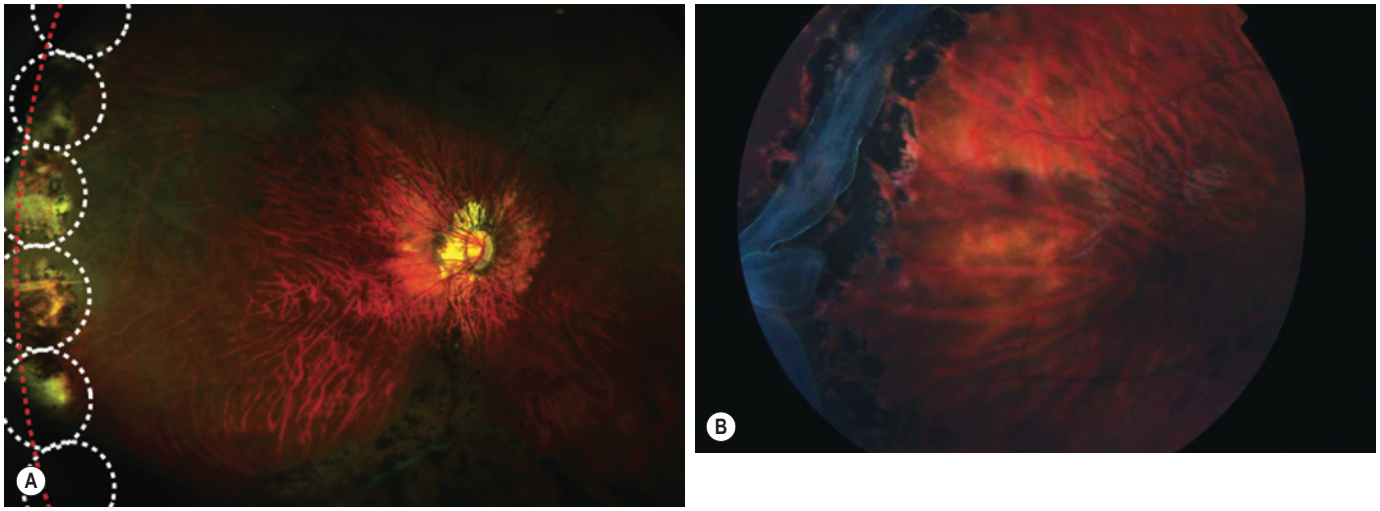


Fig. 52.21 (A) Prophylactic 360° cryoretinopexy in type 1 Stickler syndrome according to Cambridge Prophylactic Cryotherapy Protocol.[29] (B) Laser retinopexy to arrest progression of a giant retinal tear in type 1 Stickler syndrome (no prophylaxis).

patients who were untreated had a greater than seven-fold increased risk of detachment compared to those who received prophylaxis.[29] Detachment due to retinal breaks at other more posterior locations can occur, but are impossible to predict in terms of position, making effective prophylaxis in all cases impractical.

Surgical approaches and considerations in pediatric rhegmatogenous retinal detachment repair

General considerations and principles of repair

The prime goal in all cases should be to achieve successful and permanent re-attachment of the retina, with the minimum number of procedures (ideally one), and with the minimum risk of collateral or secondary damage. Some complex situations may need to be approached in two stages (with a second procedure to remove cataract and/or internal tamponade). Primary repair is now successful with a single operation in well over 90% of cases. Children (much more than their adult counterparts) develop particularly rapid and aggressive PVR with failed surgery. Even if re-attachment is achieved after surgery for recurrent retinal detachment, macular and binocular function may still be severely compromised.

Examination under anesthesia (EUA)

Children with retinal detachment may be difficult to assess in clinic; indirect ophthalmoscopy with scleral depression is frequently impossible. Examination under anesthesia allows the assessment of the type, number, and extent of retinal breaks, together with a risk assessment/prophylaxis to the fellow eye (see Prophylaxis above, Table 52.1 and Vitrectomy and internal approaches below).

Scleral buckling: when, why, and how?

Although there has been a pronounced shift in recent years towards vitrectomy and internal approaches for all types of RRD repair, scleral buckling remains a valuable procedure. In correctly selected cases, it is a quick, extraocular, and highly effective technique for RRD repair. Indeed, in two common varieties of pediatric RRD where the vitreous remains attached (see Table 52.1), the primary success for buckling far exceeds anything achieved by internal approaches, where the risk of PVR with failed surgery is high, and firm vitreous attachment may impair internal drainage.[31] External buckling also reduces the need for simultaneous or subsequent removal of the crystalline lens, an important amblyogenic factor, especially in unilateral retinal detachment. Scleral buckling may also be required in combination with vitrectomy for complex cases and those associated with advanced PVR. The main indications favoring an external approach are cases where the vitreous remains attached (round hole and dialyses), or in cases of PVD where breaks are single or small, and anterior, with shallow, non-bullous detachment. Key steps in a safe, successful procedure include the absence of any associated scleromalacia (Fig. 52.22), accurate identification and application of retinopexy to all retinal breaks, and precise selection and localization of scleral buckle. Accurate break and buckle localization also allows smaller explants to be used, with consequently reduced risks of extrusion, drainage requirements, hemorrhage, incarceration, and extraocular motility problems (Fig. 52.23). In

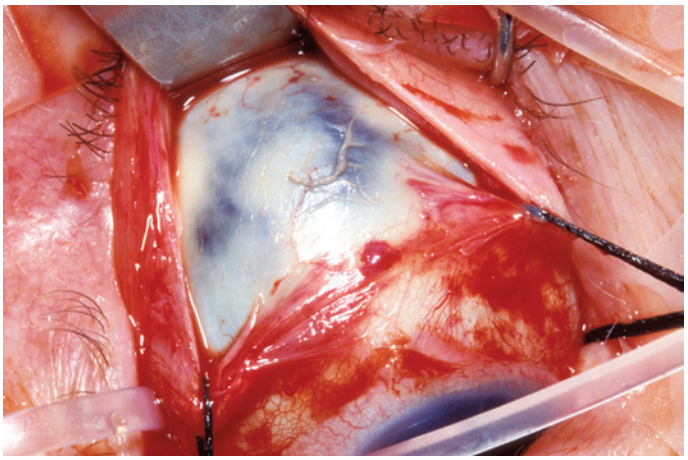


Fig. 52.22 Severe scleromalacia in a patient with type 2 Stickler syndrome. Scleral buckling attempts in such cases are hazardous and an internal approach will be required.

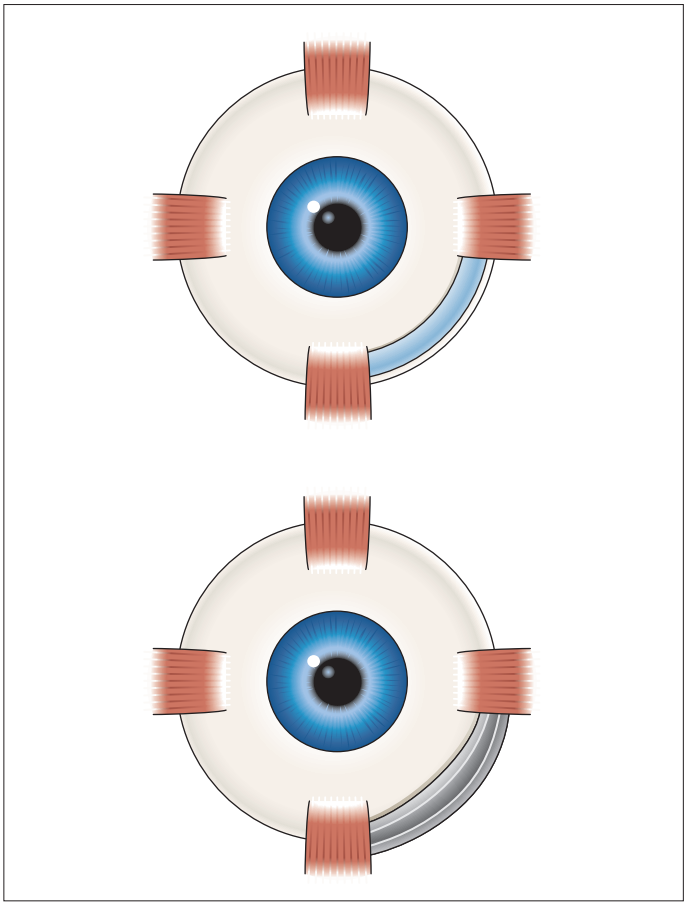


Fig. 52.23 Scleral buckling for repair of retinal dialysis. Accurate localization and break closure with a narrow gauge sponge (top) substantially reduces problems with drainage, intraocular pressure, ocular motility, and extrusion, all of which may occur after wide solid explants (below). The latter are virtually never required.

situations where a radial explant is required to close a break that is equatorial or posterior, it is often safer to use two backhand sutures (both in an anteroposterior direction), which circumvents the need to attempt one with a posterior-to-anterior path and its attendant high risk of inadvertent

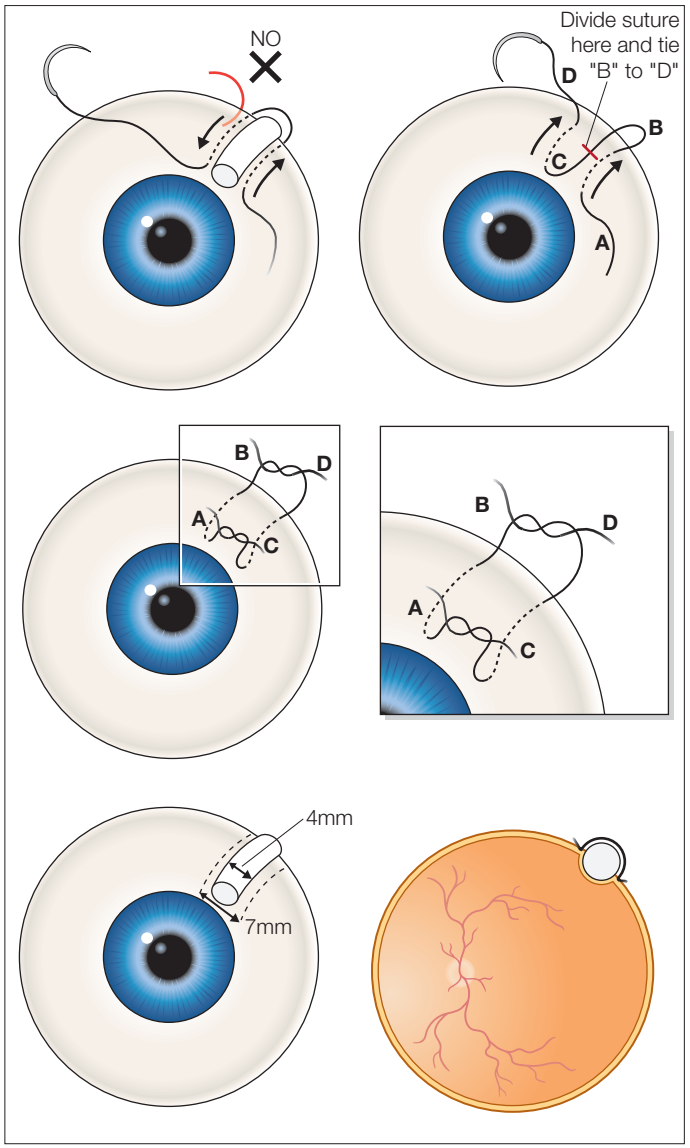


Fig. 52.24 Technique for applying radial buckle. A single modified radial mattress suture is produced by deploying two backhand sutures (both in an anterior-to-posterior direction, bottom left and right), which circumvents the need to attempt one with a posterior-to-anterior path (top left) and its attendant high risk of inadvertent perforation and incarceration on the forward passage from deep behind the globe.

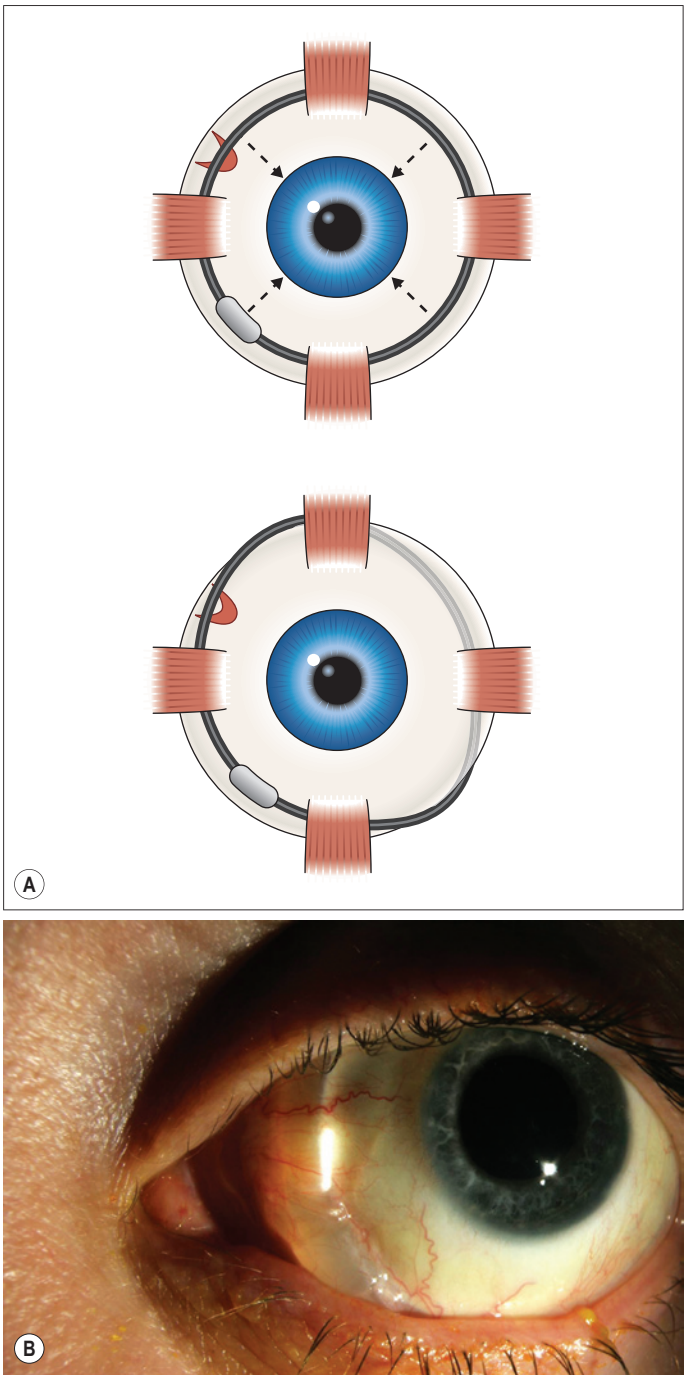


Fig. 52.25 Encircling buckle. After accurate break localization and closure, care should be taken to ensure the remainder of the buckle continues on a "great circle" of the globe (A, bottom) thereby avoiding the risk of secondary anterior migration (A, top) – an inevitable but unwanted sequel to encircling elements sutured anterior to the equator in their entirety (B).

perforation and incarceration on the forward passage from deep behind the globe (Fig. 52.24).

In some cases with multiple breaks (particularly with round atrophic holes), an encircling buckle is often very effective,[31] but if the breaks being buckled are anterior to the equator, care should be taken to localize the reciprocal extent of the buckle an equal distance posterior to the equator, so that the entire extent of explant remains on a "great circle" of the globe (Fig. 52.25). This will avoid the risk of subsequent slippage of the buckle anteriorly (Fig. 52.26) – an inevitable but unwanted sequel to encircling elements mistakenly sutured anteriorly to the equator in their entirety.

Vitrectomy and internal approaches

Cases complicated by large and/or multiple breaks, GRTs, media opacity, PVR, penetrating trauma, and developmental anomalies will usually require an internal approach. This is distinct from "giant" dialyses, which may also extend circumferentially over 90°. As discussed above, these latter cases are most safely and easily managed with an external approach, even when chronic and associated with subretinal fibrosis (see Fig. 52.3).

Cases of PVR and penetrating trauma will have additional tractional components that can only be divided by vitrectomy; cases in which shortening is very severe may need to be stabilized

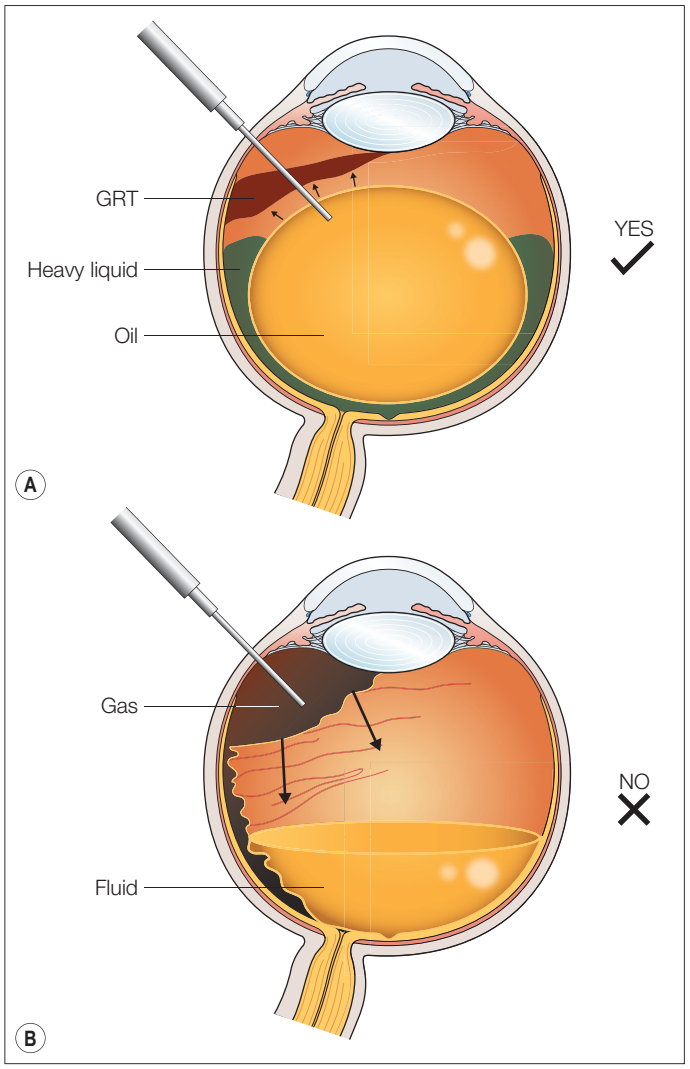


Fig. 52.26 Perfluorocarbon liquids (PFCLs) and a giant retinal tear repair. Slippage of the posterior flap can be avoided by direct PFCL/oil exchange (A), avoiding the intermediary gas exchange phase (B) when the risk of slippage is exacerbated.

by a tailored combination of buckling with vitrectomy and retinectomy.

Fellow eye considerations

General anesthetic surgical repair of retinal detachment allows assessment of the fellow eye for prophylaxis (see above) or treatment of undiagnosed tears. The incidence of bilateral pathology varies between break types and is summarized in Table 52.1.

Giant retinal tear approaches

Giant retinal tears are the most common cause of retinal detachment in Stickler syndrome, and present their own individual surgical challenges. Extensive separation of the posterior hyaloid membrane anteriorly to the pars plana, in combination with the rapid and massive circumferential extension of the retinal break, leads to an independent mobility and collapse of the retina under gravity to the posterior pole (see Fig. 52.20A). Perfluorocarbon liquids (PFCLs) have greatly simplified the perioperative repositioning of the retina, but have a high rate of emulsification and uveitis if left *in situ*. Slippage of the posterior flap may occur during the PFCL exchange, which can be avoided by direct PFCL/oil exchange (avoiding the intermediary gas exchange phase when the risk of slippage is exacerbated) (Fig. 52.26). GRTs of less than 360° are frequently associated with small, non-contiguous satellite tears, and it is vital that these are also identified and treated to avoid risk of recurrent detachment at stage II surgery (silicone oil removal).

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Congenital anomalies of the optic discs

David S Taylor

Chapter contents

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Introduction

Overview

1. Children with bilateral optic disc anomalies present in infancy with poor vision and nystagmus; unilateral cases present during preschool years with sensory esotropia, occasionally nystagmus.
2. Any structural ocular abnormality that reduces visual acuity in infancy may also lead to amblyopia.[1]
3. Malformed optic discs are often associated with central nervous system (CNS) malformations.
4. Small discs are associated with malformations involving the cerebral hemispheres, pituitary infundibulum, and midline structures. Large anomalous discs may be associated with a trans-sphenoidal encephalocele.
5. Many optic discs that are congenitally anomalous do not fit into any category. Rather than put them conveniently into a diagnostic category, it is preferable to label them as an optic disc dysplasia (Fig. 53.1).

Epidemiology (see Chapter 2)

Four or more of every 10,000 children born in the UK will be diagnosed as severely visually impaired or blind (SVI/BL) by their first birthday, increasing to nearly 6 per 10,000 by the age of 16 years.[2]

Congenital optic nerve defects now account for a significant number of cases of visual impairment (VI),[3] about 15% of SVI/BL patients in the UK. Optic nerve hypoplasia alone accounts for over 10%,[2] and the incidence may be increasing.[4,5] In the early literature, developmental abnormalities such as optic nerve hypoplasia were unusual.[6] The early ophthalmoscopists were able to see retinal minutiae, some, which are rarely recognized by today's practitioners with technologically advanced kit, so it seems likely that it was overlooked as a diagnosis much more than it is today because it was not commonly known. After all, "you see what you know." Thus, optic nerve hypoplasia is now probably more common, but, more significantly, it is better recognized than a few decades ago.

As developmental abnormalities of the anterior visual pathways are often associated with brain, endocrine, and other systemic problems and syndromes, they may have far greater significance than to vision alone and some may be hereditary.

Normal and abnormal retinal ganglion cell (RGC) development

RGCs are the first retinal cells to appear, at about 4 weeks' gestation from progenitor (stem) cells, from posterior to anterior. Guided by a complex series of time-linked guidance molecules and molecular gradients, axonal growth cones guide them almost unerringly towards the optic disc, through it, and on across the chiasm. There, they make binary decisions as to whether they decussate and project to the contralateral lateral geniculate body (LGB), or whether they remain ipsilateral. They grow to the LGB, guided by attractant, repellent, and fasciculant molecules. Their number increases to over 3.5 million in each eye, only to decrease by apoptosis to about 1.2 million at around term birth. This fascinating programmed cell birth and death probably ensures a complete connection of retinal elements to the LGB to achieve a retinotopic projection.

Optic nerve hypoplasia (ONH) may result from primary failure of retinal ganglion cells at 4–6 weeks of gestation, or failure secondary to other disease processes at any site from the eye to the visual cortex, and maybe from other brain areas in young preterm infants. ONH may also occur from failure of a proper concert of guidance molecules anywhere along the path. In prenatal and very early postnatal life, retrograde trans-synaptic degeneration may result in some forms of ONH.

Retinal ganglion cell developmental disorders

Optic nerve aplasia

Imagine the wonderment of Dr W. Newman in 1864, using the newly invented ophthalmoscope, when he looked into the

recently visible depths of the eye to find no optic nerve and no retinal vessels[7]!

Optic nerve aplasia is rare enough to contribute nothing to the epidemiology of childhood blindness. Diagnosed in a blind eye, there is no optic disc nor retinal vessels visible, but the occurrence of partial cases, with a few retinal blood vessels or an area in the fundus that corresponds to an optic disc, makes it difficult to be dogmatic about inclusion.[8]

From the cases of the author[8] and from the literature there may be three groups:

1. A grossly normal choroid but absent retinal vessels and no ophthalmoscopically visible optic disc. The electroretinogram (ERG) may be present, but abnormal.
2. A severely abnormal hyper/hypopigmented fundus (Fig. 53.2), abnormal choroid, absent retinal blood vessels and absent optic disc. The ERG is absent. Choroidal neovascularization is an occasional finding.
3. Cases that have signs of fetal fissure closure defects (colobomas) but with no visible disc (Fig. 53.3) or an extremely abnormal disc. Retinal vessels may be present but arise and are distributed abnormally. An ERG is present (Table 53.1).

There are no unifying hypotheses on etiology and pathogenesis, as one might expect for such a diverse condition. It may be due to ganglion cell development problems, although some cases (group 3) seem to be related to abnormalities of the

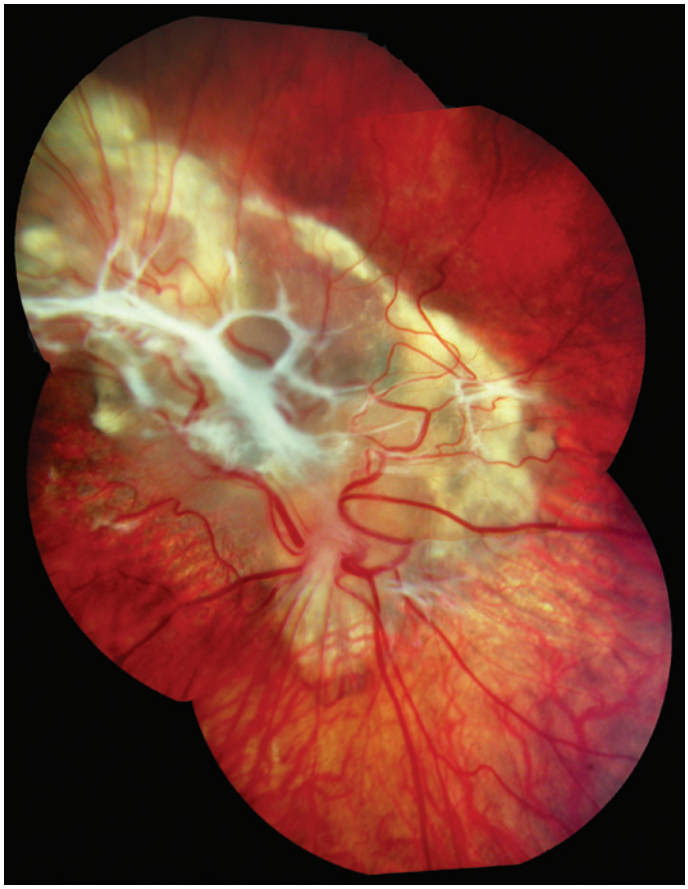


Fig. 53.1 Collage of the optic disc of a healthy infant with bilateral optic disc anomalies. It does not fit in any category and is best designated "optic disc dysplasia (category unknown)."

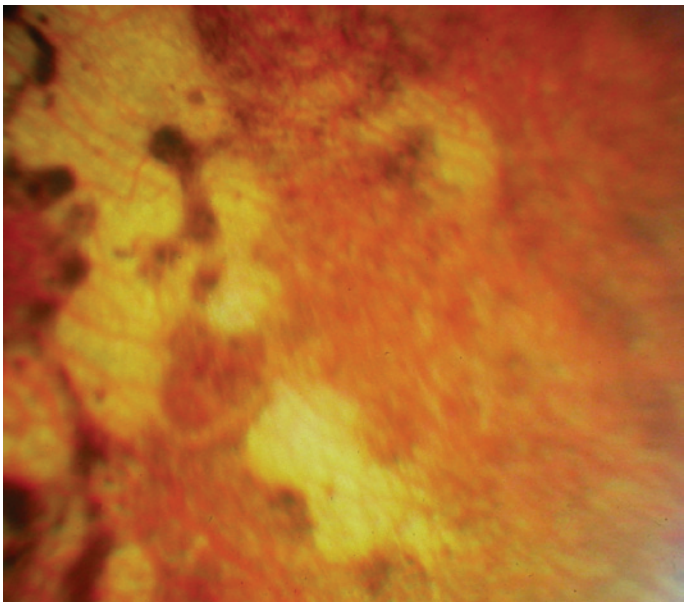


Fig. 53.2 Bilateral optic nerve aplasia, group 2. This child shows gross retinal and choroidal pigment disturbance and absence of retinal vessels.

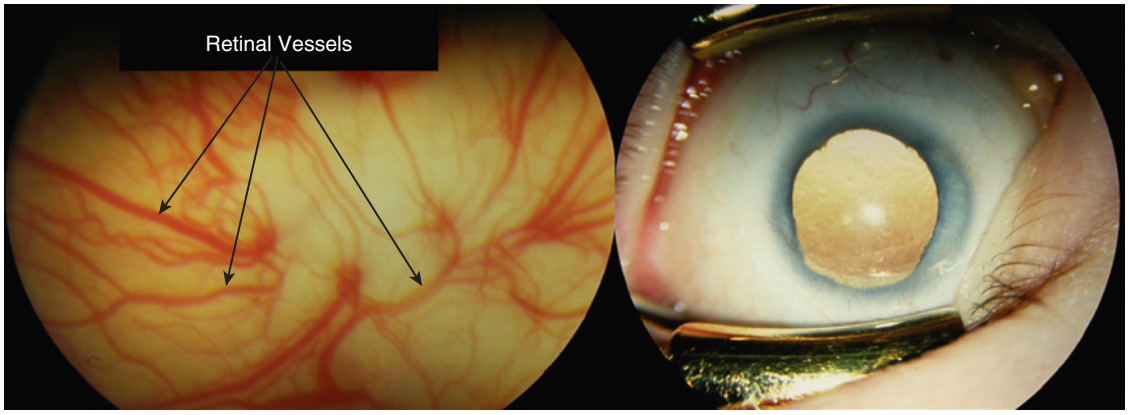


Fig. 53.3 This male child with a left iris coloboma (right) has no visible optic disc but retinal vessels emerging through the sclera. There was a rudimentary electroretinogram and no visually evoked potential responses from the affected eye.

Table 53.1 Optic nerve aplasia

	Optic disc	Retinal vessels	Choroid	ERG	VEP	Coloboma
Group 1	Not visible	Absent	Grossly normal	Present, abnormal	Absent	No
Group 2	Not visible	Absent	**Severely abnormal**	Absent	Absent	No
Group 3	Not or barely visible	Some present	Grossly normal	Present +/– normal	Severely abnormal	**Present in one or both eyes**

ERG, Electroretinogram; VEP, visually evoked potential.

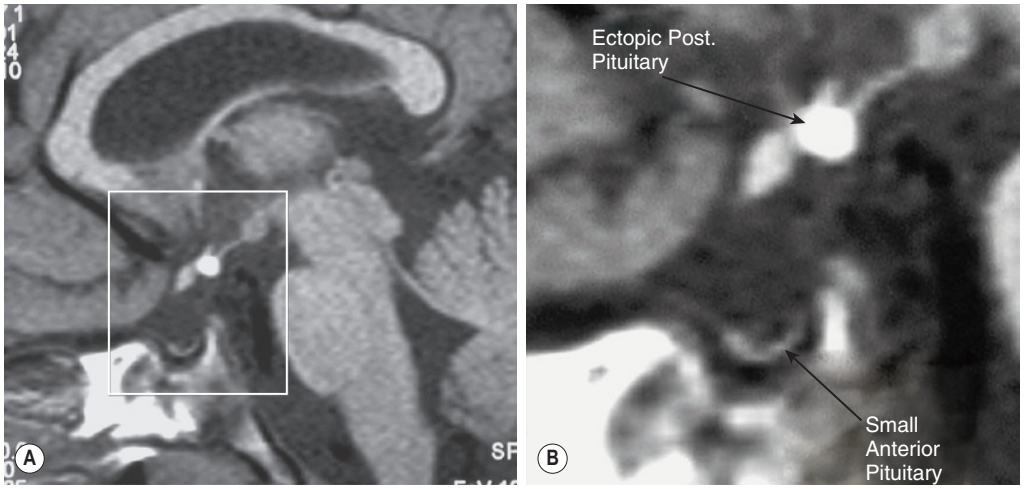


Fig. 53.4 Septo-optic dysplasia. Infant with bilateral optic nerve hypoplasia without clinically apparent growth or endocrine disturbances. The corpus callosum is hypoplastic and the anterior pituitary is small and there is no posterior pituitary bright spot in the pituitary fossa – it is sited ectopically, a high T1 signal nodule posterior to the tuber cinereum.

development of the fetal fissure or mesenchyme around the optic stalk.

A general rule of developmental disorders is that if there is one developmental anomaly, there may well be another. While unilateral cases are usually otherwise normal, bilateral cases may have associated brain, cardiac, and other abnormalities. There are 10 associated syndromes in the "GENEEYE" database (www.lmdatabases.com). For cases without a family history or a history of consanguinity, the recurrence risk seems low. Since this is based on little data, expert advice is necessary.

Optic nerve hypoplasia

ONH is an abnormality of the optic disc that occurs before the full development of the optic nerve. There is a reduced population of retinal ganglion cell axons. It is the cause of over 10% of SVI in childhood.[2] The genetic and molecular events leading to the successful development of the hypothalamic–pituitary axis and related structures during embryogenesis are complex.[9] It is not surprising that ONH is related to midline developmental abnormalities (Fig. 53.4). A significant proportion of patients with ONH have associated brain abnormalities, mostly involving midline structures – usually the septum pellucidum, and accompanying hypothalamic–pituitary abnormalities (Fig. 53.5). This constellation is graced with the term septo-optic dysplasia (SOD), but the presence or absence of the septum does not alter their management.

Presentation

Bilateral, severe, ONH presents as blindness in early infancy with roving eye movements and sluggish or absent pupil reactions to light. Lesser degrees of bilateral ONH may cause lesser visual defects, strabismus, or nystagmus. Unilateral or highly asymmetrical cases may present with nystagmus,

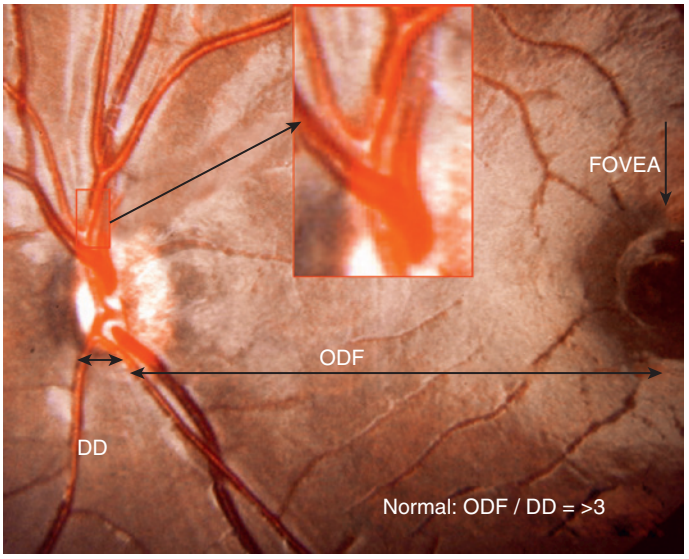


Fig. 53.5 Optic nerve hypoplasia. If the ratio of the distance of the optic disc edge to the fovea (ODF) to the average (vertical + horizontal divided by 2) disc diameter (DD) is greater than 3, optic nerve hypoplasia is a possibility. The inset shows how a main branch retinal vessel diameter can also be used to estimate the size of the optic disc. Optical coherence tomography studies are also very helpful (see Chapter 10).

sometimes "manifest latent nystagmus" (MLN, see Chapters 89 and 90), and strabismus. ONH may also be found at a routine test. Amblyopia may contribute to the poor vision and the vision may improve with patching.[1] Astigmatism may be more frequent than in the population as a whole, and all children with ONH, regardless of severity, should be refracted. Affected patients may also present because of a variety of endocrine disorders or brain defects, neonatal jaundice, or hypoglycemia.

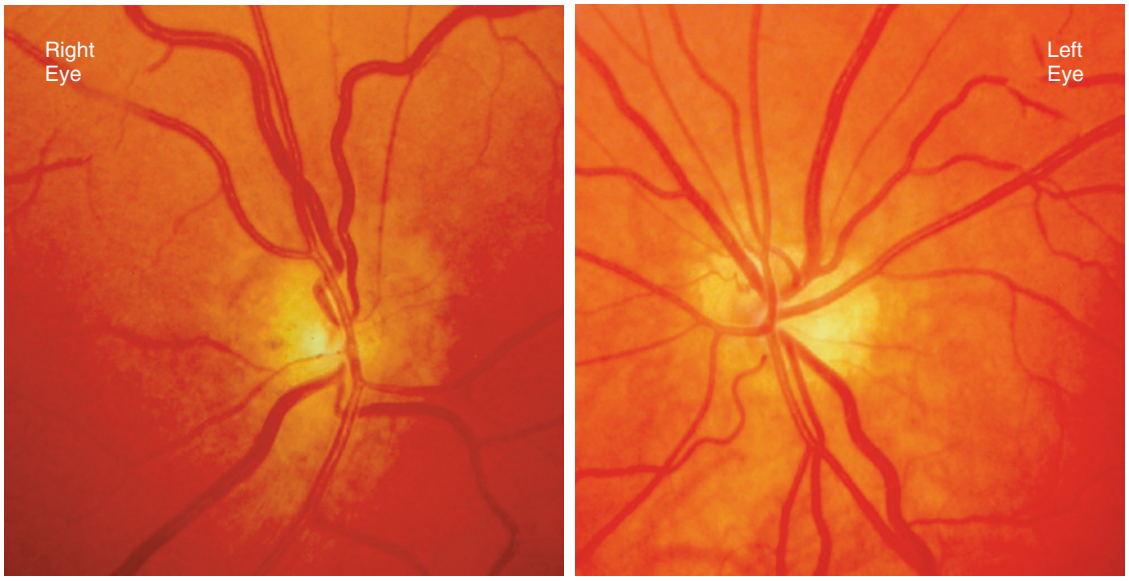


Fig. 53.6 Bilateral optic nerve hypoplasia. The right eye has "counting fingers" vision. The left eye has 0.0 LogMAR acuity (6.6, 20/20, 1.0) but the visual field is restricted enough to preclude driving.

Demographics

Hypoplastic nerves occur more frequently in males than females, and probably without racial predilection. The parents of children with ONH tend to be young and may be from certain ethnic groups,[10] but this is likely to result from overlapping with adverse socioeconomic environments and unemployment.[11]

Clinical assessment

The diagnosis of optic nerve hypoplasia is not made on size of the optic nerve alone: it is made on a combination of size, shape, an estimate of the number of axons, a small or absent cup, an increase in the tortuosity of the retinal vessels – with fewer than normal branching points – and the presence of peripapillary abnormalities. Some objectivity can be introduced by comparing ratios of vessel size and optic disc size or the disc–macula to disc diameter ratio (see Fig. 53.5). This ratio does not change with time.[12] Using volumetric, heavily T2-weighted magnetic resonance imaging (MRI) orbital sequences[13] of ONH patients compared with controls, it has been possible to provide a useful formula to more objectively determine the significance of the size of the optic nerve. Optical coherence tomography can usefully define the nerve fiber pattern around the optic disc[14] and improve objective disc measurement. Ultrasound and photogrammetry may also be helpful.

Ophthalmoscopy

There is a very wide variation in the appearance and effects of hypoplastic optic discs (Fig. 53.6), all of which are best seen with high magnification, using a direct ophthalmoscope. The baby can usually be kept quiet for a few moments by allowing feeding after the pupils have been dilated. The area of the optic disc (outer ring) is composed of bare sclera or cribriform plate; this is variably larger than the circular area (inner ring), which contains any retinal nerve fibers (the optic disc "substance"). The difference between the two gives rise to the "double ring" appearance (see Fig. 53.5). Histopathologically, retinal ganglion cell axons are reduced in number with normal mesodermal elements and glial supporting tissue. Between the inner and outer ring there is dysplastic retina and pigment epithelium. The double ring sign is, however, not pathognomonic of ONH, especially in milder degrees.

There is a spectrum between the normal, atrophic and hypoplastic disc that depends on how severe the causative event was and at which time or times it occurred. The optic disc substance may be a normal color if the fibers that survived the journey from RGCs to the LGB are healthy and relatively numerous; equally, it may be pale (see Fig. 53.6), suggesting atrophy of the remaining fibers after the event that caused the hypoplasia.[15]

Visual effects

The visual effects vary from good visual acuity (often with a field defect) to blindness. Visual acuity is determined largely by the size of the papillomacular bundle, not by the overall size of the disc (Fig. 53.7). The eventual visual acuity may be predicted from assessment of the optic disc size (and distribution of RGC axons), the initial acuity card assessment, and visually evoked potentials (VEPs).[16] Associated delayed visual maturation (see Chapter 5) is not uncommon, but it is best not to be too pessimistic after examinations in infants. Refraction, visual acuity, color vision, and visual fields are mandatory studies in older children, as are flash and pattern VEPs at all ages.

Timing and site of causative agents

The timing of any "insult" is likely to be after the retinal ganglion cell precursors appear and suggests that the defect, when severe, occurs early in prenatal development. The development of the optic disc continues after birth, albeit at a greatly reduced rate, and some cases occur from an insult in late in pregnancy and even postnatally. Very hypoplastic discs may be the result of an early insult, whereas subtle degrees of hypoplasia, where the optic disc size is overall roughly normal, are due to a later insult.

Specific patterns of optic nerve hypoplasia

These result from local defects throughout the central nervous system[17]; the site of the "insult" in optic nerve hypoplasia is reflected in the pattern of disc hypoplasia (Fig. 53.8). Optic

disc hypoplasia results from an early injury at any site in the developing visual system.

Homonymous hemi-optic hypoplasia

Retro-geniculate lesions in primates[18] may give rise to a pattern of ONH by trans-synaptic degeneration across the lateral geniculate body. In humans these were first described[19] in a case in which trans-synaptic degeneration from a cerebral lesion gave rise to a pattern of optic disc hypoplasia and retinal nerve fiber defects that reflected the field defect that the lesion caused. The ipsilateral optic tract may be shown to be hypoplastic on MRI scanning. It may be mixed with direct damage to the developing visual system occurring with trans-synaptic degeneration.

Optic tract hypoplasia

Isolated damage to the optic tract may occasionally occur (Fig. 53.9[20]) in patients with an incongruous hemianopia from a developmental lesion. Many more cases are associated with more widespread damage to other brain structures.

Chiasmal hypoplasia and achiasmia

When the optic nerves are hypoplastic, the chiasm is hypoplastic in most cases and the crossed and uncrossed fibers are reduced proportionally. If the chiasm is not just hypoplastic but crossing fibers are either absent or reduced, this is known as achiasmia. In achiasmia, some cases may have a hemianopia, often reflected in the optic disc morphology (Fig. 53.10), but in many the retinotopic projections have compensated in early development and there is no visual field defect, and the optic discs may also be normal

Segmental hypoplasia

The occurrence of specific patterns of hypoplasia (see Fig. 53.8) may result from localized defects throughout the central nervous system[17]; the site of the "insult" in ONH is reflected in the pattern of disc hypoplasia. For instance, the appearance of segmental optic disc hypoplasia related to a macular coloboma means that the site of the injury is in the eye, while optic disc

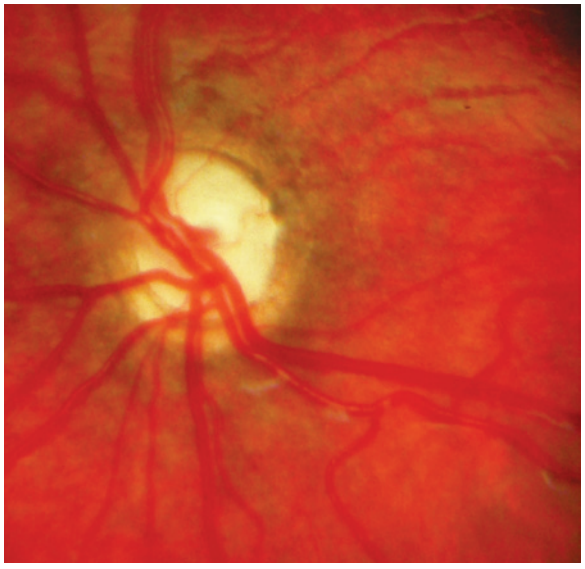


Fig. 53.7 The optic disc is small with a double ring sign, suggesting that the causative factor was early in gestation. The hypoplastic disc itself is atrophic and pale, suggesting continuing damage to retinal ganglion cells and axons.



Fig. 53.8 Unilateral temporal segmental hypoplasia of the left optic disc of unknown cause.

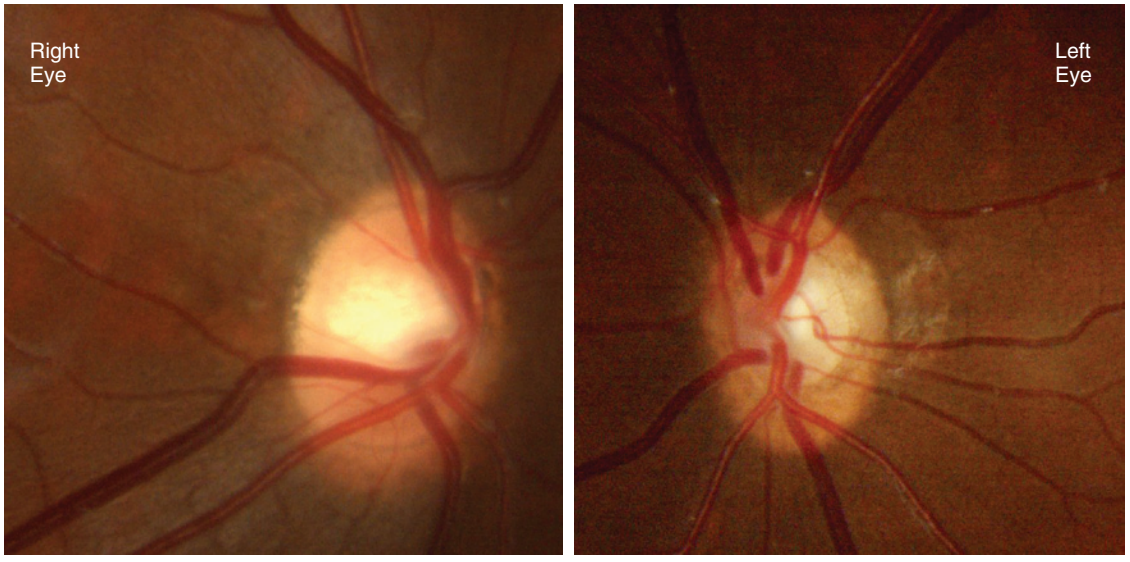


Fig. 53.9 This healthy 19-year-old male had a longstanding incongruous hemianopia secondary to right optic tract hypoplasia of unknown cause. The left optic disc is hypoplastic with LogMAR acuity of 0.4 (6/15, 20/50, 0.4). The right visual acuity was 1.0 LogMAR (6/6, 20/20, 1.0) and the optic disc shows hypoplasia of the central horizontal band. *(From Hatsukawa Y, Fujio T, Nishikawa M, et al. Congenital optic tract hypoplasia. J AAPOS 2015; 19: 383–5.)*

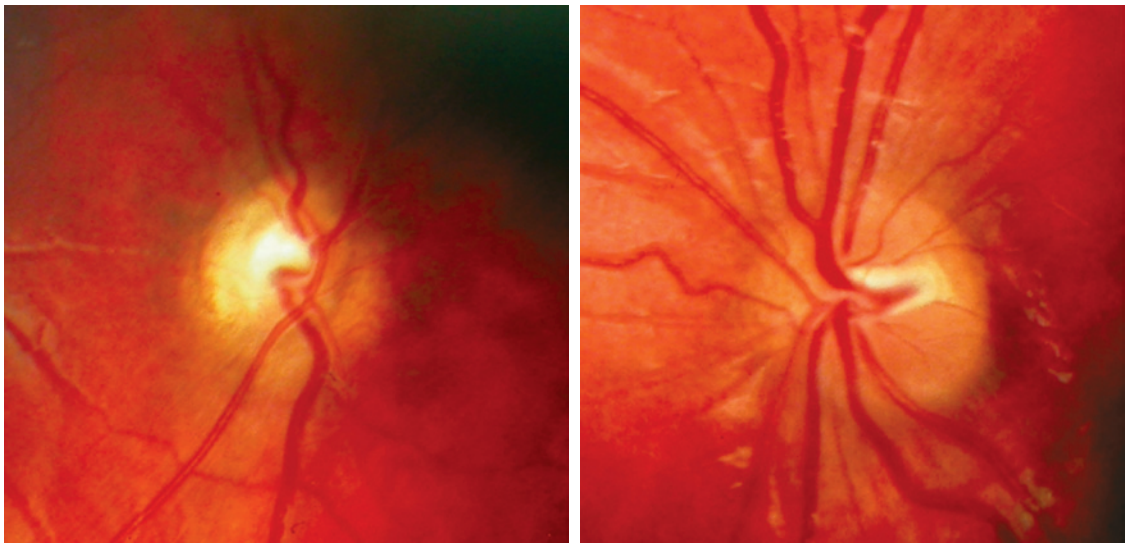


Fig. 53.10 This child, who has radiologically and electrophysiologically proven achiasmia, has a markedly hypoplastic right optic disc and horizontal band hypoplasia of the left disc.



Fig. 53.11 Right optic disc of a child with a congenital tumor, presumed optic glioma, of the optic chiasm.[24] The disc is hypoplastic and has a "figure of eight" shape, presumably due to the early prenatal shaping of the disc with early loss of the crossing retinal ganglion cell axons.

hypoplasia of a "figure of eight" shape (Fig. 53.11) in patients with a suprasellar tumor suggests a chiasmal site. Segmental optic disc hypoplasia therefore results from an early injury at any site in the developing visual system.

Superior segmental hypoplasia

Babies of diabetic mothers may have neurological anomalies, including optic disc hypoplasia. In these cases, the superior half of the disc may be most affected, the so-called superior segmental ONH[21] (SSONH), or "topless" optic discs (Fig. 53.12). The visual defect may be relatively mild and the signs subtle. About 10% of children of diabetic mothers are at risk for this condition. Female gender, short gestation time, low birth weight, and poor maternal diabetes control are additional risk factors. It is not pathognomonic: it may occur without maternal diabetes. SSONH has been described in identical twins, but there are no pathogenetic clues other than the fact that certain RGC axon guidance proteins (i.e. EphB) are found in the superior (dorsal) retina; their absence in mice lets the developing axons stray away from their normally tightly fasciculated paths to the optic disc.[22]

Causes and associations

Drugs and alcohol

Causative agents include quinine, anticonvulsants, serotonin re-uptake inhibitors, LSD and crack cocaine, and, particularly, maternal alcohol ingestion.

Family history and genetics

Familial cases are rare and not all necessarily genetic; in the absence of a recurrent environmental cause (such as drugs or alcohol) or a family history or consanguinity, a very low recurrence risk can be given. *HESX1* mutations, amongst others, have been recorded but seem quite unusual.

Optic nerve hypoplasia with early-onset tumors

Optic nerve hypoplasia or tilted discs may rarely be associated with a developmental tumor (see Fig. 53.11), particularly an optic glioma, in the region of the chiasm.[24]

Optic nerve hypoplasia in children with brain abnormalities

There is a causal association with a wide variety of brain malformations, probably of common origin. Premature babies with periventricular leukomalacia (PVL, see Chapter 60) may have optic discs that are of normal overall size but may fall within a broad definition of hypoplasia[23] by trans-synaptic degeneration causing cupping (Fig. 53.13). Acuity may be normal despite quite large cups, and field defects may cause concern about glaucoma. However, the history of prematurity, the non-glaucomatous fields (when field studies are possible), the round cup displaced temporally or superotemporally, and the normal intraocular pressure should be enough to distinguish PVL-associated cupping from glaucoma.

Septo-optic dysplasia

Although the term septo-optic dysplasia implies absence of the septum pellucidum and optic nerve hypoplasia only, the syndrome encompasses a wide variety of structural abnormalities of the cerebral hemispheres and commissures, hypothalamus, visual system, the pituitary body and stalk. Hemispheric abnormalities occur in nearly half of patients with optic nerve hypoplasia, including migration anomalies

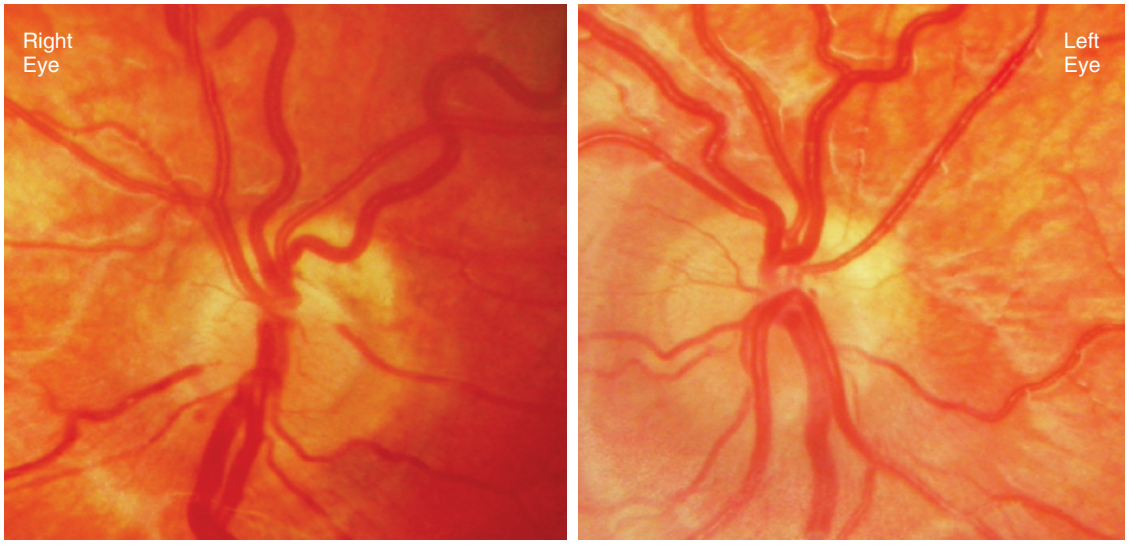


Fig. 53.12 Bilateral superior segmental hypoplasia in the child of a type 1 diabetic mother. The upper halves of the optic discs are virtually absent and the lower halves are small. There was an irregular inferior visual field defect but the visual acuity was LogMAR 0.40 (6/15, 20/50, 0.40) in each eye.

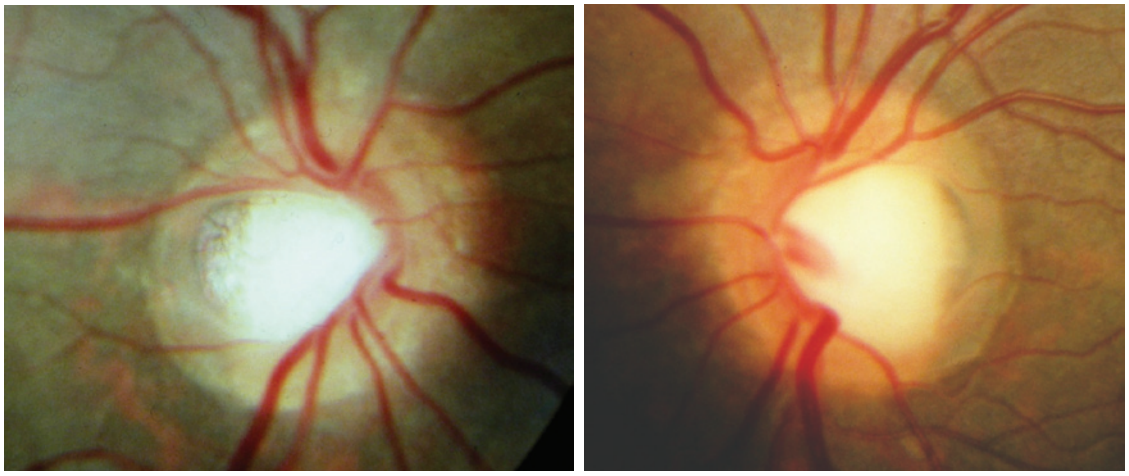


Fig. 53.13 The optic discs of a 6-year-old child who was born prematurely and developed periventricular leukomalacia (PVL).The discs have an irregular margin and are somewhat pale with large cups. There is an ill-defined inferior visual field defect. The intraocular pressures were normal.

(polymicrogyria, schizencephaly, and heterotopia), intrauterine or perinatal hemispheric injury (PVL, encephalomalacia). In holoprosencephaly, a variable midline facial defect is associated with a single cerebral ventricle, and absence of the corpus callosum and septum pellucidum.

Normally, the posterior pituitary gland appears bright on T1-weighted images, but in posterior pituitary ectopia, there is absence of the normal posterior pituitary and its infundibulum. Instead there is an ectopic posterior pituitary bright spot at the tuber cinereum (see Fig. 53.4). This suggests anterior pituitary hormone deficiency, whereas the cerebral hemispheric abnormalities and thinning or agenesis of the corpus callosum suggest neurodevelopmental deficits in both bilateral and unilateral cases: Absence of the septum pellucidum alone is not endocrinologically significant, and if the septum pellucidum and the hypothalamic–pituitary axis are both normal, it is unlikely that there will be any endocrine disturbance.

A variety of hormonal defects have been described ranging from isolated growth hormone, adrenocorticotrophic, or antidiuretic hormone deficiency to panhypopituitarism. Hypothyroidism may be the most common significant abnormality, but there is wide variation and the possibility of minimal abnormalities in multiple hormones should be remembered. Growth hormone defects may present later in childhood, as growth can be stimulated by prolactin. Whether or not MRI or endocrine abnormalities are found, weight and height must be monitored annually, usually under the care of an endocrinologist or pediatrician.

Children with septo-optic dysplasia are at risk of sudden death from the combination of reduced anterior and posterior pituitary hormones and hypothalamic defects when exposed to stress, especially in the form of hyperthermia or infection (Fig. 53.14). Parents must be warned to avoid exposure of an affected child to such stresses.

Management of children with optic nerve hypoplasia

All cases should, wherever possible at diagnosis, have a full clinical ophthalmology and endocrinology assessment and neuroimaging: MRI looking especially at the hypothalamus and pituitary. Patients with any abnormalities will need expert monitoring and possibly treatment for life. If they are found to be normal, their height, weight, and development should still be monitored at least yearly until fully grown. The management of the visual defect is discussed in Chapters 5 and 61.

Tilted optic discs

The tilted disc, in which the optic disc is D-shaped (Fig. 53.15), is accompanied by a defect in the retinal nerve fiber layer adjacent to the flat arm of the "D," usually inferiorly.[25] Peripapillary fundus ectasia or staphyloma are sometimes associated (Fig. 53.16). Although most are myopic and astigmatic, nearly half of the patients have non-refractive visual abnormalities associated with the defect, suggesting it may represent a form of segmental hypoplasia. The visual field defects are frequently superotemporal but, unlike chiasmal compression, do not follow the midline and should be repeated with refractive correction appropriate to the ectatic area. Tilted optic discs may also be mistaken for mild papilledema. Myopia and tilted optic discs commonly occur together in X-linked congenital stationary night blindness.

Situs inversus

Situs inversus is a more widespread defect in which the vessels emerging from the often-small optic disc are so distorted that, together with the appearance resulting from the tilt *per se*, the disc appears to be rotated through approximately 180° (Fig. 53.17). Although the anomaly was thought to be related to coloboma, in reality the cause is unknown. When these occur bilaterally, superior bitemporal relative visual field defects may occur, which also cross the midline. There may be an

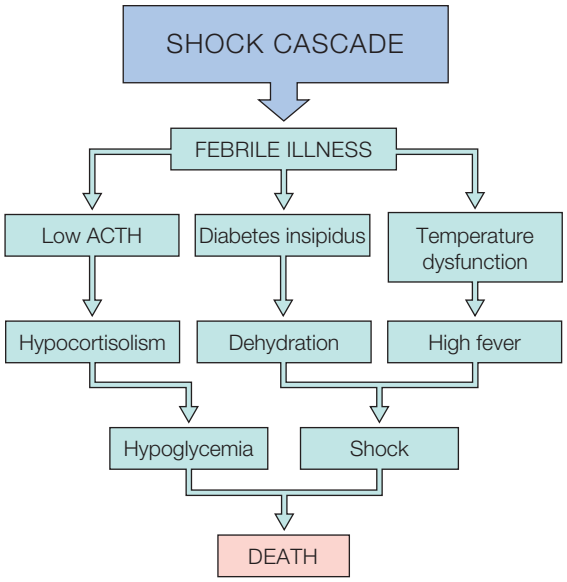


Fig. 53.14 Children with septo-optic dysplasia may die as a result of their brain defects or because they are more susceptible to death from various causes due to their brain and endocrine defects. A prominent and preventable cause of early death is a combination of low adrenocorticotropic hormone (ACTH), hypothalamic dysfunction, and diabetes insipidus (DI). When the child has a fever or is in an unaccustomed hot climate, a cascade occurs which may result in death.

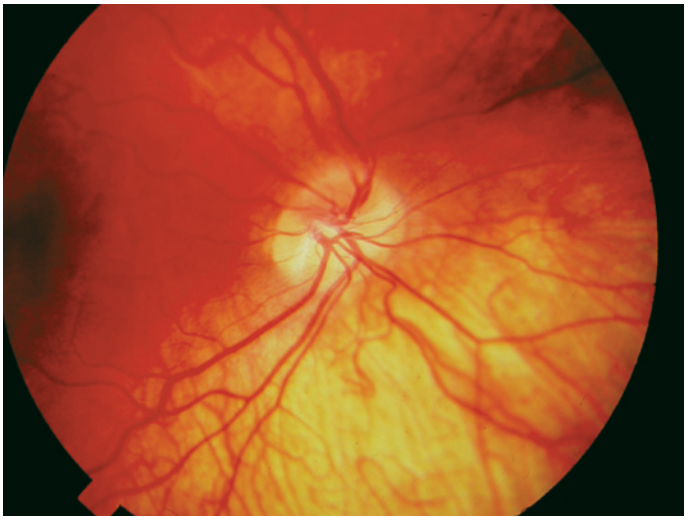


Fig. 53.16 Right eye with the macula visible. Inferonasal to the tilted optic disc is a pale area that represents a staphyloma. There is marked myopic astigmatism.

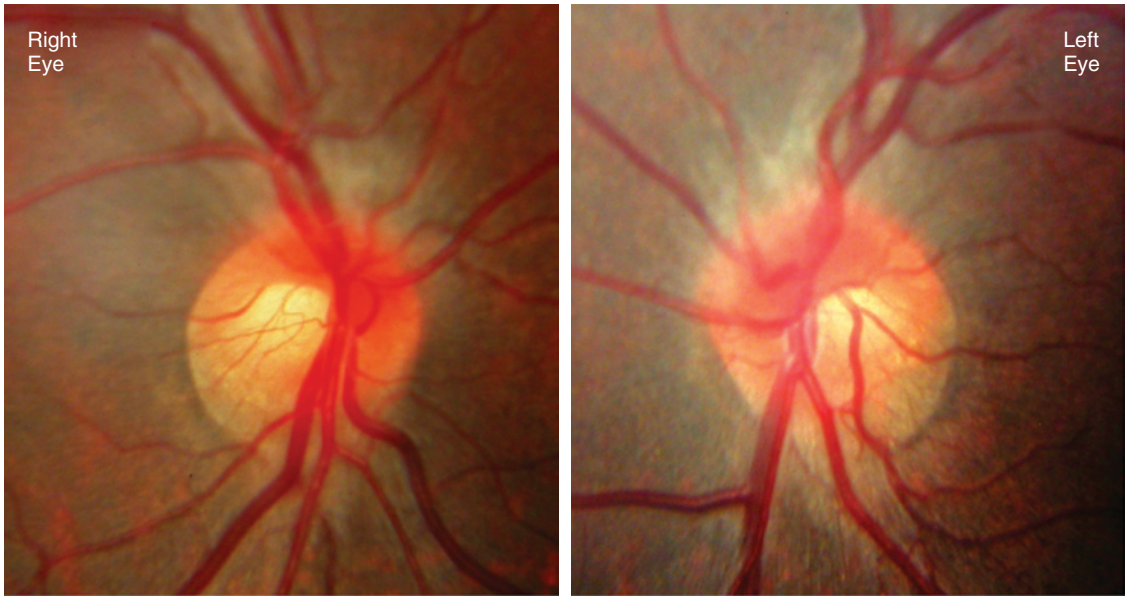


Fig. 53.15 Bilateral "tilted" optic discs in a myopic and astigmatic child.

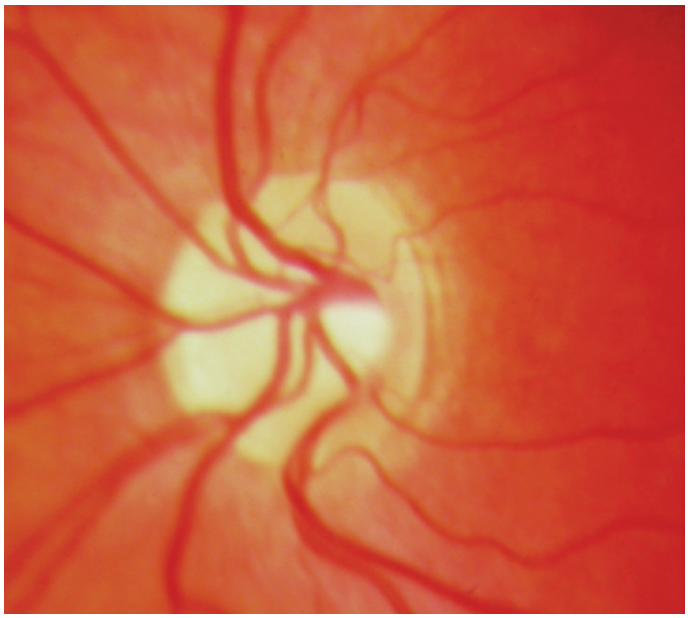


Fig. 53.17 Unilateral situs inversus in an astigmatic man. The corrected acuity was LogMAR 0.18 (20/30, 6/9, 0.67).

associated posterior staphyloma below the disc. In many cases, the apparent field defect disappears with appropriate optical correction of the myopia caused by the staphyloma.

Fetal fissure-related optic disc abnormalities

Coloboma

Developmental aspects

A coloboma is a defect that results from an abnormality of the closure of the fetal fissure in the inferonasal quadrant of the developing optic cup. Closure starts at the equator and extends anteriorly and posteriorly. Incomplete closure creates a defect of any size from the margin of the pupil to the optic disc. Some are quite subtle. Microphthalmos and clinical anophthalmos may represent extreme manifestations of the same disorder.

Presentation

Children with colobomas present either as a result of the appearance of microphthalmos, abnormally shaped pupil, or, if bilateral, because of poor vision. If unilateral with poor vision, they may present with a squint or manifest latent nystagmus. If a fundus coloboma is extensive, the parent may notice an abnormal red reflex on flash photography or a mother may notice it when feeding the baby with the light coming from behind her. Sometimes the systemic associations of colobomas are the presenting features, or the coloboma may only be discovered on routine examination.

Clinical features

Typically, optic disc colobomas are inferonasal and range from a subtle change in the retinal pigment epithelium (RPE) (Fig. 53.18) to a hugely excavated disc (Figs 53.19 and 53.20). Colobomas of the disc may be associated with subtle manifestations of choroioretinal colobomas, iris or, rarely, inferonasal lens defects. Very rarely, neoplasms may occur along the line of closure of the fetal fissure: these include glioneuromas and medulloepitheliomas.



Fig. 53.18 Right eye: there is an inferonasal retinal pigment epithelial defect extending from a cupped anomalous optic disc with normal intraocular pressure. Although this has no functional consequences, its diagnostic significance is as great as any other coloboma.

Colobomas of the choroid result in scotomas in proportion to their size. Optic nerve colobomas cause varying visual defects, depending on their size and the degree of macular involvement. Amblyopia is often a significant factor, related to associated myopic astigmatism.

Various intraocular abnormalities may occur in association with colobomas. These may include a preserved hyaloid vascular system, an anomalous Cloquet's canal, lens notches, vitreous striae, cataract, and glial tissue with dysplastic retina near the optic disc. Heterotopic intraocular tissues, including lacrimal, cartilage with or without ossification, adipose, and smooth muscle sometimes occur. Smooth muscle, when present, may be the basis for periodic contraction of some colobomatous defects. The scleral canal can be large and the central nerve head is occupied by loose vascular connective tissue and the peripapillary retina "bunched-up" and folded (Fig. 53.21).

Other eye malformations may be associated, in particular to glaucoma resulting from an anterior chamber anomaly, which may also cause disc excavation. Retinal detachment, subretinal neovascularization, and disciform degeneration may all occur as complications of colobomas of the choroid. Their prevalence is unknown but they are more frequent in severe colobomas.

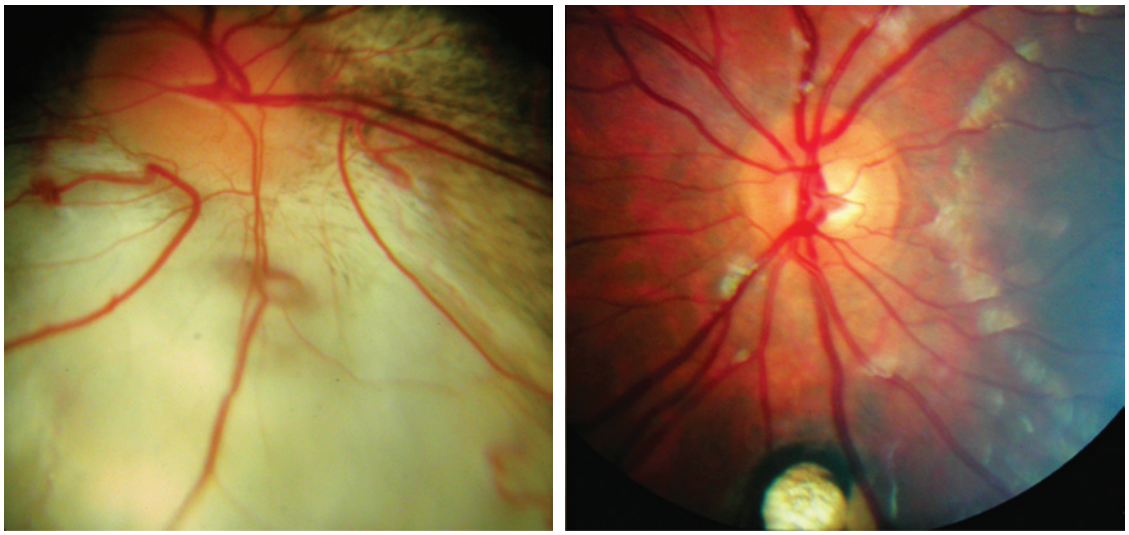


Fig. 53.19 This infant with the CHARGE syndrome (see text) presented with a white reflex from the right pupil when feeding. An iris coloboma extended back to the optic disc but the optic disc itself was quite healthy and there was a macula present. The baby was able to fix with this eye but required patching and astigmatic spectacles. The left eye had a normal optic disc and good vision, but a small, colobomatous defect inferiorly.

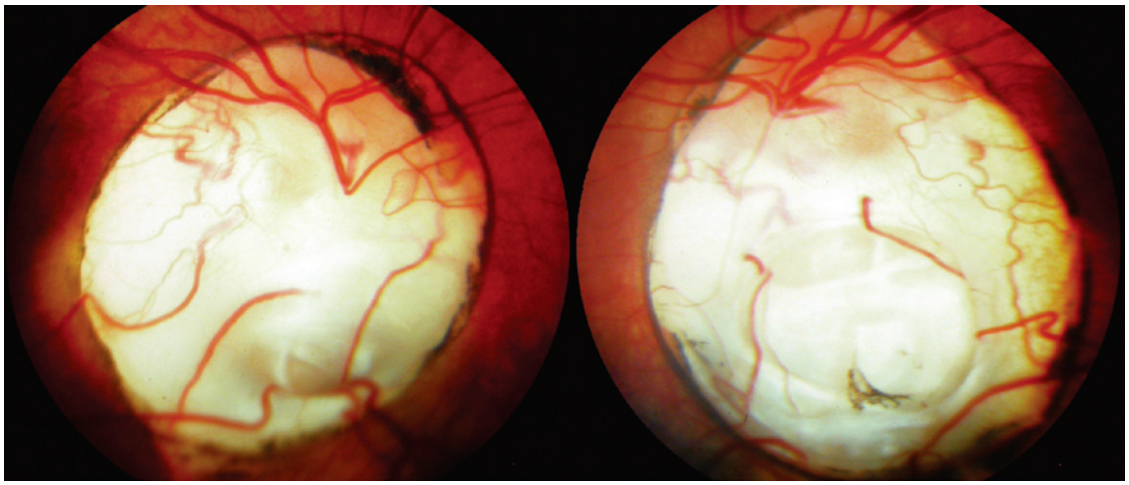


Fig. 53.20 Deeply excavated bilateral large colobomas in a child with the CHARGE syndrome.

The retinal detachments are usually reported by retina units; incidence studies are difficult to conduct.

Coloboma with cyst

Colobomas may be associated with developmental cysts that are related fetal fissure closure defects. Orbital cysts with colobomas or colobomatous microphthalmos are unusual. Affected infants usually present because of the ocular abnormality, and the cyst becomes evident as it subsequently enlarges. Occasionally, it can be large at birth (Fig. 53.22). The cysts appear as a bluish swelling in the lower lid, which enlarges on crying, or as a thin-walled cyst adjacent to the globe; it may cause a gradual proptosis and orbital enlargement. The cyst may communicate with the microphthalmic eye or even be fused with it. Surgical decompression of the cyst may cause decompression of the eye and, if functionless, the microphthalmic eye may need to be removed. The benefit of leaving the cyst, if possible, is that it allows better orbital growth. Needle aspiration of the cyst can cause a useful reduction in the size, which can be permanent.[26] These cysts contain cerebrospinal fluid and the wall may contain neuroglial tissue. The inheritance is similar to other colobomas.

Double optic discs

"Double" optic discs are usually a form of coloboma. The second optic disc usually lies below the "main" disc and has its own set of retinal vessels; it is often joined to the main disc by an arteriolar and venular connection and a bridge of the coloboma (Fig. 53.23).

Family history

Many cases of coloboma without systemic associations are sporadic or dominantly inherited with variable expressivity. The subtle phenotypic expressions have the same diagnostic and genetic implications as gross manifestations and it is very important to examine both parents and any siblings in detail (see Fig. 53.22). Autosomal recessive inheritance is less frequent.

Systemic associations of colobomas

Colobomas may occur either as part of a chromosomal syndrome or other systemic disease. One database (www.lmdatabases.com) lists 80 syndromes associated with optic

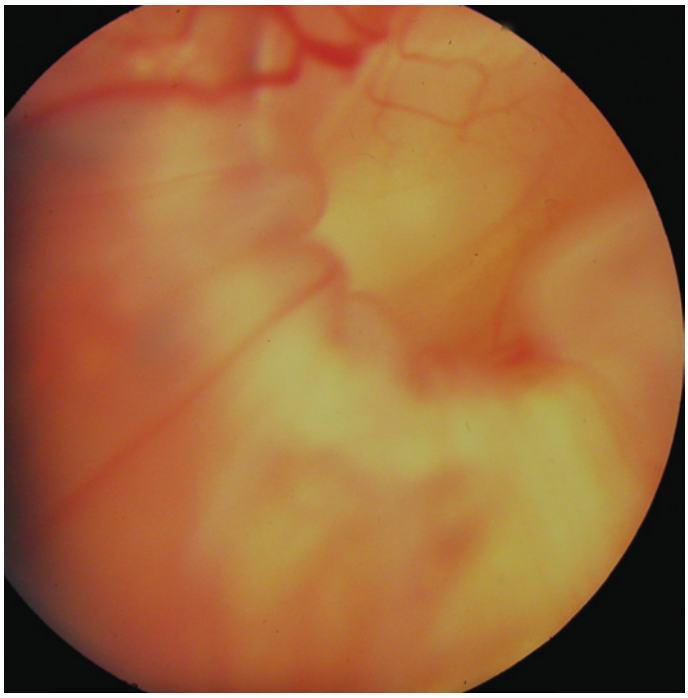


Fig. 53.21 Large colobomatous disc with overlay of the peripapillary retina.

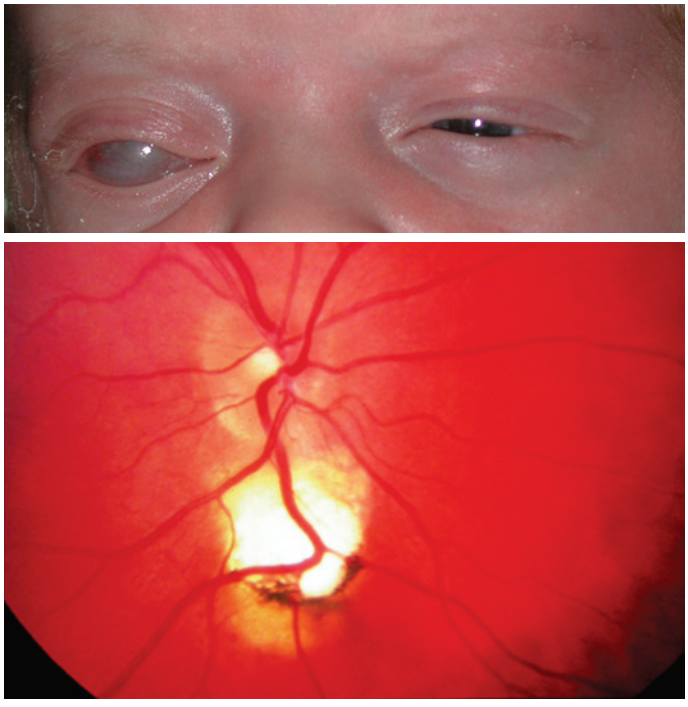


Fig. 53.22 The neonate in the top of the figure was born with a large cyst in the right orbit. The left eye was normal. The diagnosis was suggested by the finding of a coloboma in the mother's right eye (below). The cyst responded partially to repeated aspiration.[26]

disc coloboma and 104 with iris coloboma, many overlapping. Such databases are helpful for the systemic diagnosis and management of patients with colobomas, as the systemic associations are too diverse for all to be included in this chapter!

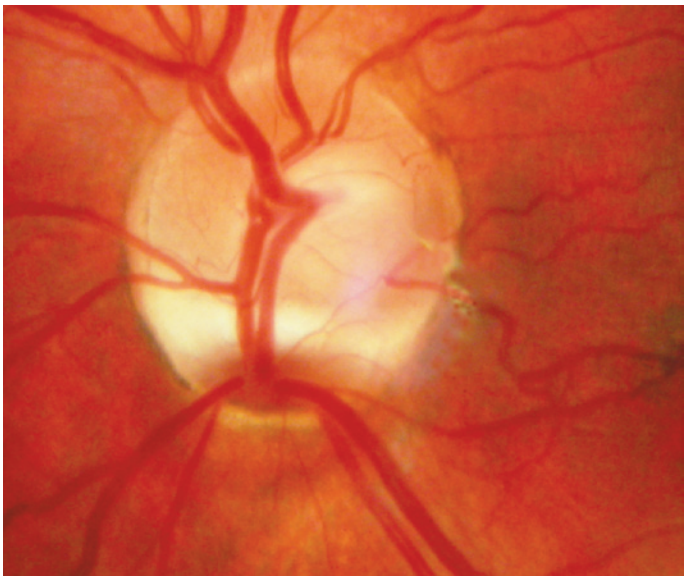


Fig. 53.23 A "double" optic disc. The inferior disc is joined to the superior one by a set of vessels.

Box 53.1

Chromosomal syndromes frequently associated with coloboma

Trisomy 13 (Patau syndrome)
Cat eye syndrome (tri- or tetrasomy 22pter)
4p- syndrome (Wolf–Hirschhorn syndrome)
Triploidy

Chromosomal syndromes uncommonly associated with coloboma

Trisomy 18 (Edwards syndrome)
Monosomy 9
11q- , 13q- trisomy 4p and trisomy 22

The occurrence of colobomas with a systemic defect thus warrants chromosome studies.

Coloboma with chromosomal syndromes (Box 53.1)

Coloboma as a part of a multisystem disorder

CHARGE syndrome CHARGE is an mnemonic for **c**oloboma, **h**eart defect, **a**tresia choanae, **r**etarded growth and development, **g**enital anomalies, and **e**ar anomalies and deafness. A patient needs four of these major findings to fit the diagnosis. Other anomalies may include facial palsy, micrognathia, cleft palate and pharyngeal incompetence, tracheo-oesophageal fistula, and renal anomalies. Many cases are associated with a CHD7 mutation. Colobomas, some atypical, occur in most cases of the CHARGE association: they range from subtle (Figs 53.19 and 53.20) to microphthalmos.

Lenz microphthalmia syndrome This is an X-linked condition with microphthalmos, microcephaly, vertebral, dental, renal, and urogenital anomalies, congenital heart disease, protruding simple ears, and finger defects. The colobomas or colobomatous microphthalmos are variable. Affected males rarely reproduce, reducing familial recurrences. *BCOR* and *NAA10* genes are sometimes implicated. If the mother is a carrier, the chance of

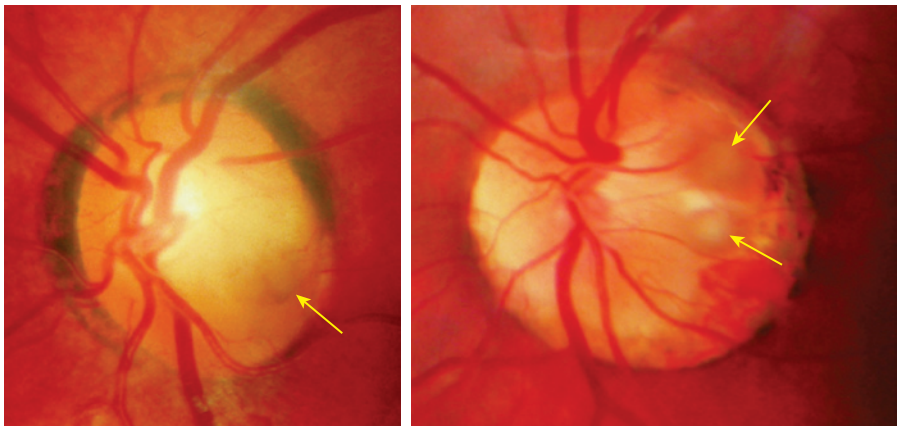


Fig. 53.24 Optic disc pits in the left eyes of two unrelated children. The yellow arrows point to the pits.

transmitting the pathogenic variant is 50% in each pregnancy: males affected, females carriers.

Focal dermal hypoplasia (Goltz syndrome) Affected children, mostly female, are born with focal dermal hypoplasia. Bony defects, "keratocystic" odontogenic tumors and mental retardation occur. Coloboma occurs with or without microphthalmos. The skin findings are striking, with pink atrophic macular areas, pinkish-brown nodules of fat herniation through the dermis, and "raspberry" papillomas at skin–mucous membrane junctions, including the lids. It is thought to be X-linked dominant, lethal in males.

Meckel–Gruber syndrome This is a severe disorder of presumed autosomal recessive inheritance. Affected infants usually have a very short lifespan. Findings include, in order of decreasing frequency, abnormal kidneys, occipital encephalocele, polydactyly, cleft palate and micrognathia, abnormal urinary tract, microphthalmia or coloboma, and congenital heart disease. It is a ciliopathy.

Joubert syndrome (see Chapter 47) These children often present in the first days of life with apnea or tachypnea, rhythmic tongue protrusions, and developmental delay. They have a retinal ciliopathy, a saccade initiation failure ("oculomotor apraxia") associated with hypoplasia of the cerebellar vermis. Up to a quarter have colobomas.

Branchio-oculo-facial syndrome The branchio-oculo-facial syndrome is an autosomal dominant syndrome with variable expression associated with mutations in the transcription factor TFAP2A. Patients have hypertrophy of the lateral pillars of the philtrum, vertical ridges between the lip and the nose, and aplastic or hemangiomatous cervical skin lesions, which may contain thymic tissue, with or without branchial sinuses. Malformed ears, cleft lip and palate, and colobomas with or without microphthalmos occur.

Basal cell nevus (Gorlin) syndrome These children present with macrocephaly, frontal and temporoparietal bossing, prominent supraorbital ridges, prognathism, and telecanthus or hypertelorism. Multiple odontogenic keratocysts of the jaw develop during the first decade of life. These and multiple nevoid basal cell carcinomas occur from late childhood, especially on the face and trunk. Colobomas may occur and myelinated retinal nerve fibers have been associated (see Figs 53.34 and 53.37). Inheritance is autosomal dominant with high penetrance and variable expression.

Linear nevus sebaceous syndrome Also known as the epidermal nevus, Jadassohn syndrome, Soloman syndrome, or Fuerstein–Mims syndrome; affected children have a non-dermatomal linear pigmented nevus, a variety of other skin defects, skeletal anomalies, and usually severe developmental delay. Eye abnormalities include ptosis, epibulbar dermoids, and lid colobomas. Fundus abnormalities have been described, including colobomas, anomalous discs, peripapillary staphyloma, Coats disease, pseudopapilledema, osseous choristoma of the choroid, and optic nerve hypoplasia.

Optic disc pits

These are grayish pits of variable size that usually occur temporally near the temporal margin of the disc, sometimes elsewhere (Fig. 53.24). They can be multiple and may be bilateral. They may be associated with visual field defects, a large blind spot with a paracentral arcuate scotoma.

Optic disc pits may be of a similar pathogenesis to colobomas, but they may occupy a site unlikely to result from an abnormal closure of the fetal fissure, although they occasionally occur with an optic disc coloboma either in the same eye or in the other eye. There are no regularly occurring systemic associations and they are rarely inherited.

Up to 60% of patients will develop central serous retinopathy with visual symptoms from the third decade of life, especially if the pit lies by the rim of the optic disc. The origin of subretinal fluid in humans with central serous retinopathy associated with a pit is still uncertain, but cerebrospinal fluid seems the most likely source. Although often following a benign course, subretinal neovascularization and other complications may occur, and some authors advocate aggressive treatment in selected cases such as pars plana vitrectomy with or without internal limiting membrane peeling, with or without endolaser photocoagulation and C3F8 gas tamponade.[27]

Other optic disc anomalies

Morning glory optic disc anomaly

This is an unusual defect that should be diagnosed specifically because of its significant associations. The disc may be large and

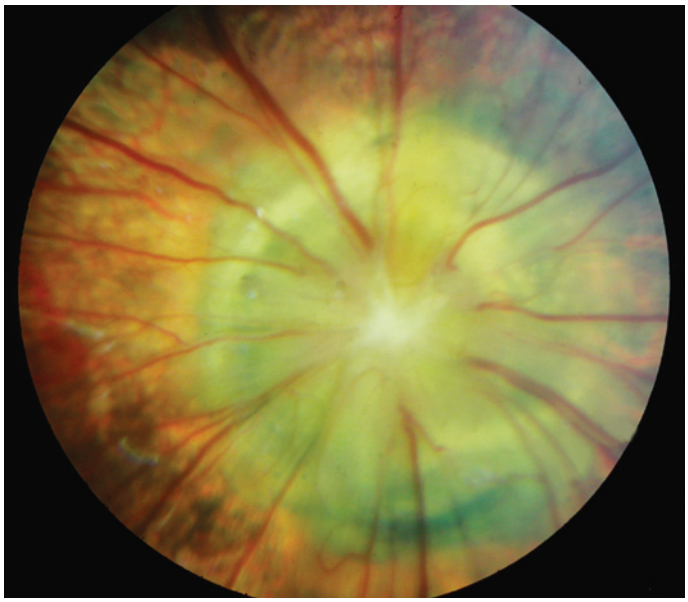


Fig. 53.25 Morning glory disc anomaly. This child presented with strabismus and poor vision at 5 years of age. Occlusion was abandoned, as the child was unable to navigate with the occlusive patch.

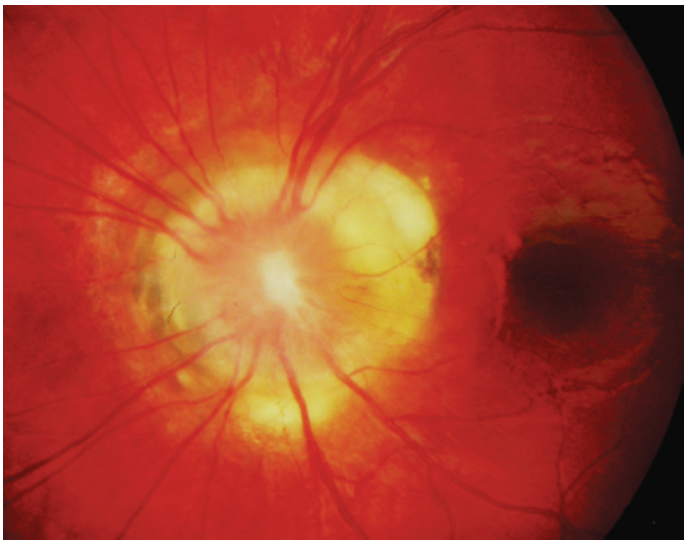


Fig. 53.26 Morning glory disc anomaly. The macula is present and the visual acuity is LogMAR 0.48 (20/60, 6/18, 0.33).

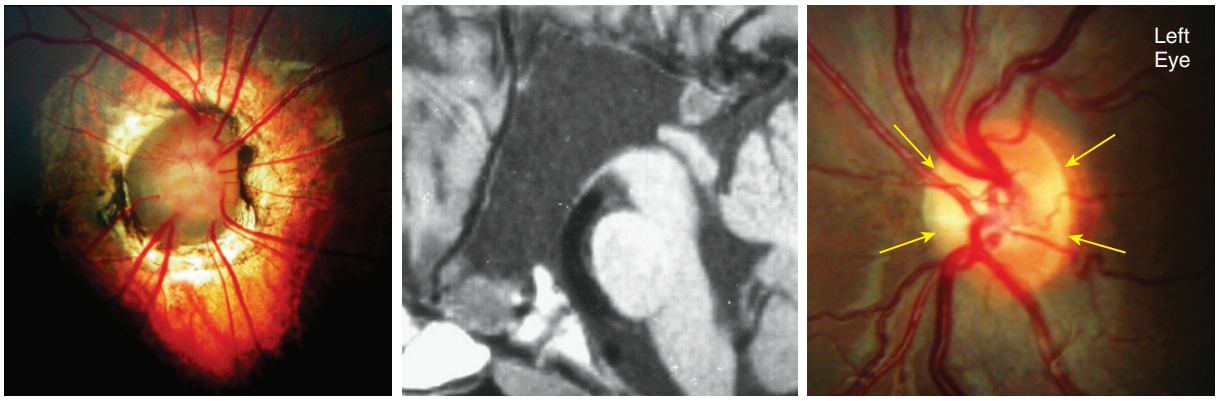


Fig. 53.27 The central part of this figure shows a coronal magnetic resonance imaging of an encephalocele. The patient's right eye has a morning glory disc anomaly with low vision and the left has horizontal band atrophy (arrows) and a temporal visual field defect. Electrophysiology showed crossed asymmetry (see Chapter 9).

the peripapillary area is variably elevated with an associated annulus of pigment, and there is a central glial tuft containing abnormal tissue on MRI studies, extending anteriorly to a variable extent. The vessels, which originate from near the disc edge, radiate outwards (Fig. 53.25); it is often difficult to determine whether they are arterioles or venules, sometimes with A–V communications adjacent to or distant from the disc.

The vision in the affected eye is usually, but not invariably (Fig. 53.26), poor and may be worsened by amblyopia from myopic astigmatism.

Similar to some colobomatous and other optic disc defects, they may show slow contractile movements.

There are three main systemic associations:

Basal encephaloceles Basal encephaloceles are associated with a variety of dysplastic discs, including typical morning glory anomaly (Fig. 53.27); mostly, they are dysplastic, sometimes with features of colobomas, notably an inferior V-shaped chorioretinal pigment anomaly. The encephalocele may present with difficulty feeding, mouth breathing, or snoring because of nasal obstruction, hypertelorism, or because of a midline notch in the upper lip or a cleft lip or palate.

Moyamoya disease The morning glory anomaly may be associated with (usually ipsilateral) cerebral vascular narrowing or closure; some may be associated with moyamoya disease. Affected patients may present with strokes, transient ischemic attacks (TIAs or mini-strokes), or epilepsy. Revascularization surgery may be successful in children. Spontaneous improvement may occur.[28]

PHACES syndrome A morning glory disc anomaly (MGDA) may, mostly in girls, be associated with **p**osterior fossa malformations, **h**emangiomas, **a**rterial anomalies, **c**ardiac defects, **e**ye abnormalities, **s**ternal cleft, and supra-umbilical raphe syndrome (PHACES syndrome; Fig. 53.28). The MGDA is usually ipsilateral to the hemangioma. The visual prognosis is usually, but not necessarily, poor for the affected eye, which may also be amblyopic.

Other associations include microtia (small pinna of the ear), Duane retraction syndrome, Brown syndrome, cleft lip and palate, hypertelorism, agenesis of the corpus callosum, endocrine and central nervous system anomalies, and a variety of ocular defects. Not infrequently there is a widespread non-rhegmatogenous or rhegmatogenous retinal detachment, often early in life, which may settle spontaneously or with treatment.

MGDA is usually unilateral and non-genetic: its nosology and relationship to typical coloboma are uncertain. The association with moyamoya disease and PHACES syndrome and the vascular features of the optic disc anomaly, both suggest an abnormality of vasculogenesis, but the presence of an inferior tongue of depigmentation suggests a fetal fissure-related pathogenesis (see Fig. 53.27).

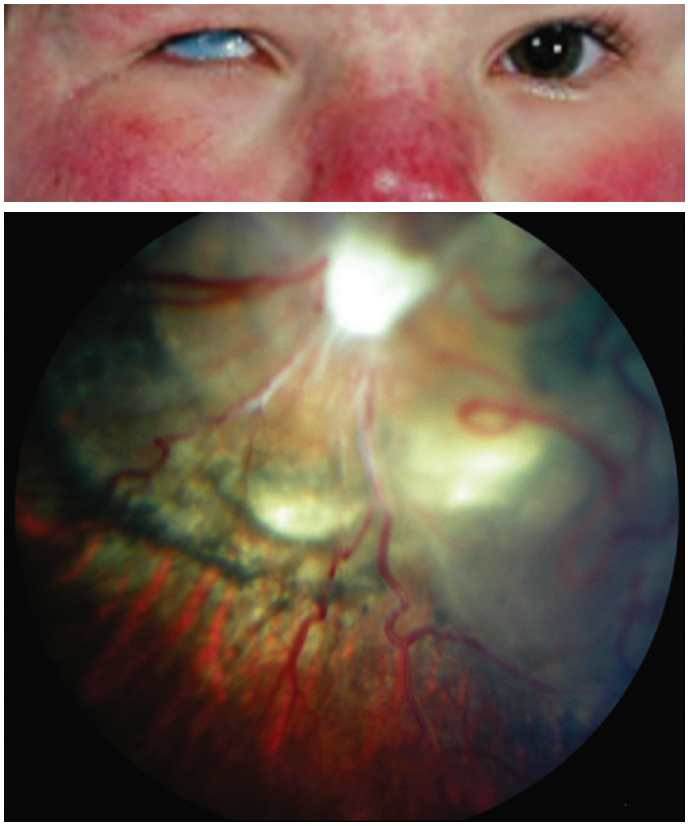


Fig. 53.28 This infant with the PHACES syndrome has an opaque right cornea and a morning glory disc-like anomaly in the left eye.

Renal-coloboma (papillorenal) syndrome

In this autosomal dominant syndrome, there may be some central optic disc excavation, with multiple cilioretinal vessels exiting the optic disc radially. Not all patients have renal disease and not all patients with the associated renal disease, or even with a family history, have the disc anomaly. Doppler ultrasound of the optic discs may show reduced central retinal artery flow. Because there are no normal central vessels, the disc may be excavated or "vacant" (Fig. 53.29), the central part having few vessels.

Patients with the syndrome may develop serous retinal detachments, perhaps associated with a pit, and they may have thin peripheral retinas.

Renal disease is variable and usually progressive, often necessitating renal transplantation for chronic renal failure in young adulthood. The diagnosis is usually made only when there is frank renal disease or a family history. The optic disc findings, although characteristic, are not pathognomonic but the appearance demands renal investigation. About a half of patients with the syndrome have a *PAX2* mutation.

Megalopapilla

Megalopapilla is a generic term used to describe large optic discs without other significant abnormalities. The optic disc may also be large in, for instance, morning glory syndrome and peripapillary staphyloma or congenital glaucoma, but in those instances the primary diagnosis is used. Many represent the extreme end of the normal range of optic disc size.

There seem to be two main phenotypes:

1. A usually bilateral form with a basically normal configuration but an overall diameter of over 2.1 mm, a large round or horizontally oval cup associated with a normal rim volume and area without notches, a normal visual field (but large blind spots), a normal intraocular pressure, and normal retinal nerve fiber layer thickness.[29] They may appear pale, as the axons are spread over a larger area of cribriform plate.
2. A large dysplastic disc (Fig. 53.30) not fitting into a clear diagnostic category, often with an excavation that is

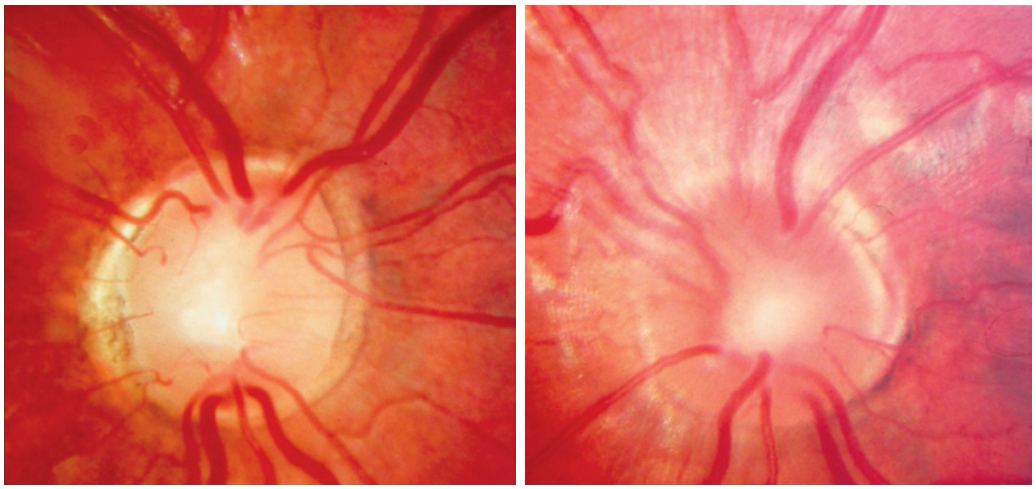


Fig. 53.29 The optic discs of a child with the renal-coloboma (papillorenal) syndrome. The vessels appear like cilioretinal vessels and radiate out from the periphery of the cupped optic discs.

non-colobomatous (does not occur in the inferonasal quadrant). Cilioretinal arteries are common. Associated midline facial abnormalities, midline clefts or pits, etc., require neuroimaging.

Peripapillary staphyloma and posterior staphyloma

Peripapillary staphyloma is a non-hereditary congenital optic disc anomaly in which a fundus excavation surrounds, locally, a relatively normal-appearing optic disc. It is generally unilateral and is also associated with poor vision, including amblyopia.

"Posterior staphyloma" is a term used to describe the very variable ectasia of the posterior pole (see Fig. 53.16), usually centered on the macula (Fig. 53.31), which is usually bilateral. It is not usually congenital and is very strongly associated with progressive myopia.

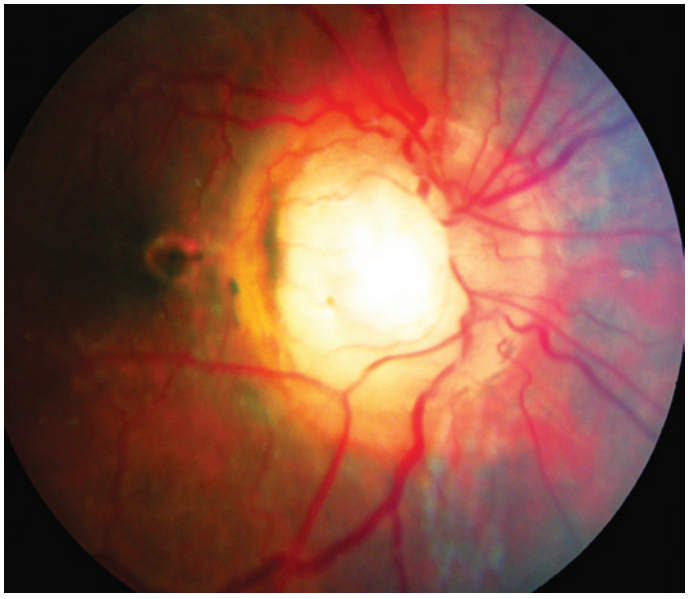


Fig. 53.30 Megalopapilla: a large dysplastic optic disc.

In peripapillary staphyloma, the area of the sclera around the optic disc is ectatic and thus relatively myopic (Fig. 53.32A). There is often a certain amount of glial tissue in the disc, and the vessels radiate out from the edge of the disc. Occasionally a serous detachment of the retina occurs around the disc. Retinal detachment, choroidal neovascular membranes and hemorrhages are not uncommon. Intermittent contraction suggests that some are associated with midline encephaloceles (see morning glory syndrome, above). Some cases are deeply excavated behind the staphyloma (Fig. 53.32B,C). The pathogenesis of these cases is unknown, but their relationship to fetal fissure closure problems is attested to by thinning of the choroid, usually inferior to the disc as in Figure 53.32A, and the often inferior site of the staphyloma. Not all cases are below the disc, however, suggesting multiple etiologies.

Congenital optic disc pigmentation and grayness

True congenital optic disc pigmentation is extremely rare, but it has been described in a child with an interstitial deletion of chromosome 17 and in Aicardi syndrome, in congenital varicella syndrome and, very rarely, in an otherwise normal eye. In itself, it is compatible with good visual acuity, but may be associated with co-existent optic disc anomalies that decrease vision. It is very frequently found as clumps of black pigment in colobomatous defects.

Gray optic discs are sometimes seen in premature, albino, or just young infants and were once thought to suggest that a slow myelination of the optic nerves might be an underlying mechanism for delayed visual maturation (DVM; see Chapter 5). Since they more commonly occur in otherwise-normal children who develop normal vision, their significance is not certain.

Aicardi syndrome

Aicardi syndrome[30] is a disorder of unknown cause that occurs in people with two X chromosomes (XX or XXY). The main features are agenesis of the corpus callosum, intractable seizures with a hypsarrhythmic electroencephalogram, profound

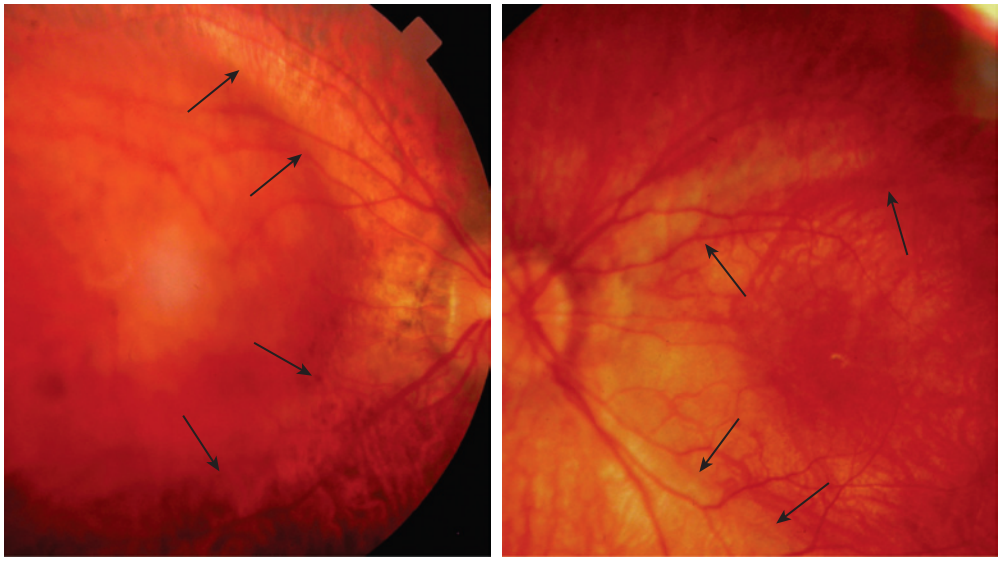


Fig. 53.31 Bilateral posterior staphylomas in a highly myopic teenager. The arrows delineate the margins of the staphyloma.

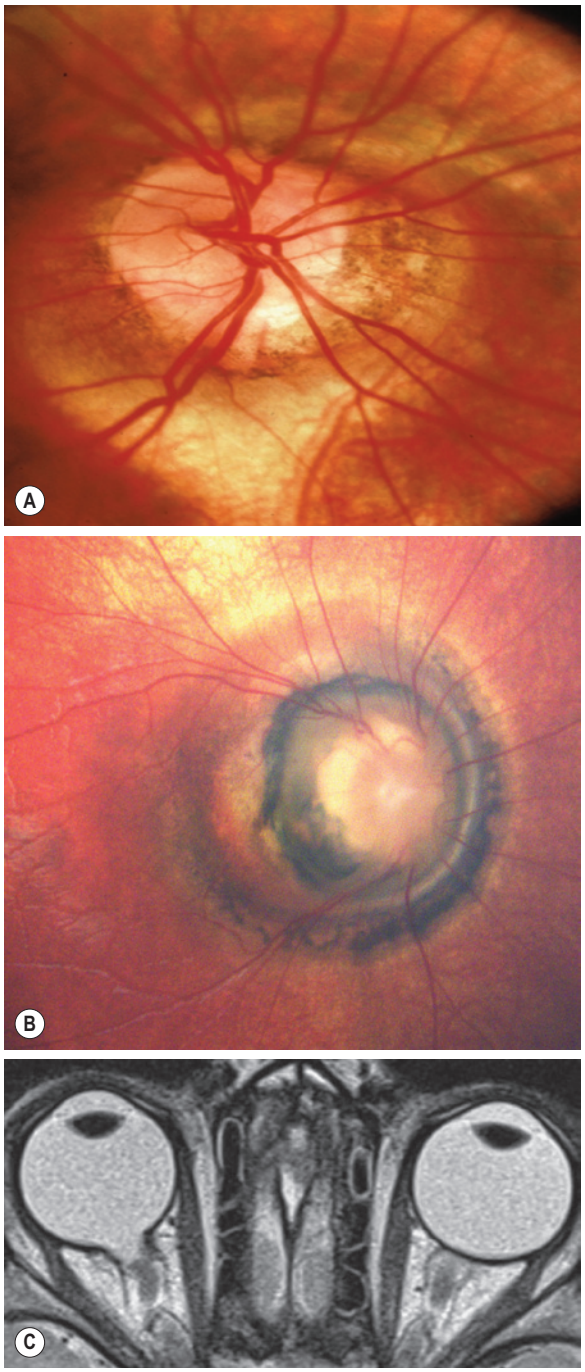


Fig. 53.32 Peripapillary staphyloma. (A) The optic disc is recessed on a circumpapillary ectatic area with inferior extension in this man with a congenital basal encephalocele. (B) There is an optic disc seen eccentrically inside an elevated partly pigmented ring, which surrounds the area; its apex shows as a sickle-shaped light gray line. The disc itself, inside the elevated ring, is surrounded by a black-pigmented circle. There are radial vessels except temporally and some "glial" tissue anterior to the center of the optic disc. There are some similarities to the morning glory disc anomaly, the significance of which is not clear. Such patients should be managed with both conditions in mind. (C) The cavitary defect in the anterior optic nerve on the right side (left of image) is well shown. *([A] Courtesy of Dr William F. Hoyt. [B,C] Courtesy of Ms Tamsin Sleep, FRCOphth.)*

developmental delay, and chorioretinal lacunae mostly distributed around the optic disc (Fig. 53.33). The chorioretinal lacunae are full-thickness defects of the RPE and choroid and abnormal retina. Even a small lacuna can be of diagnostic significance.

Other ocular abnormalities include optic disc and iris colobomas, optic nerve hypoplasia, optic disc pigmentation and dysplasia, microphthalmos, retrobulbar cyst, pseudoglioma, retinal detachment, macular scars, cataract, and pupillary membranes.

Fused vertebrae, scoliosis, spina bifida and rib malformations, muscular hypotonia, microcephaly, and auricular anomalies also occur. Severe mental retardation is almost invariable. CNS anomalies in Aicardi syndrome include agenesis of the corpus callosum, cortical migration anomalies (pachygyria, polymicrogyria, ectopic gray matter) and structural CNS malformations. The inheritance of Aicardi syndrome is probably X-linked dominant with lethality in the hemizygous male. All cases would, on this hypothesis, be new mutations.

Other optic disc dysplasias

It is easy for us to fall for the Procrustean crime of squeezing uncertain findings into a definite diagnosis. The term "dysplastic" might best be applied to any optic disc that is congenital anomalous but does not fall within one of the clearly defined anomalies (coloboma, hypoplasia, etc.). It is better, for instance, to call the anomalous optic disc of the papillo-renal syndrome "dysplastic" than "colobomatous," since the latter implies a fetal fissure-related anomaly, which is likely not the case. Many abnormalities are given the euphonic name "morning glory" discs when they do not fall strictly into that description.

Myelinated nerve fibers

Myelination of the optic nerve begins posteriorly from the lateral geniculate body at about 5 months of gestation, reaching the lamina cribrosa at around term. Myelinated (also termed medullated) retinal nerve fibers are found in up to 1% of humans. They appear as white striated "feathered" patches at the poles and at the optic discs (Fig. 53.34). They are not uniform and there may be areas of normal retina (Fig. 53.35). They may simulate papilledema (Fig. 53.36). They are frequently bilateral. The pathogenesis is unknown but may be due to anomalies of the cribriform plate allowing access for oligodendrocytes to the retina, allowing myelination of retinal ganglion cell axons.

Extensive unilateral (or, less commonly, bilateral) myelination of nerve fibers, often all around the optic disc, can be associated with high myopia and often profound amblyopia. The macula is usually unmyelinated, but may appear abnormal with a dull reflex and pigment dispersion.

Myelinated nerve fibers may be inherited as an autosomal dominant trait and occur in association with Gorlin basal cell nevus syndrome (see above and Figs 53.34 and 53.37), or in association with epiretinal membrane, vascular abnormalities,[31] and retinal and vitreous hemorrhages.

Rarely, areas of myelinated nerve fibers may be acquired after infancy and even in adulthood associated with trauma, surgery, or optic nerve glioma, and they may disappear as a result of demyelination, ischemia, inflammation, or glaucoma.

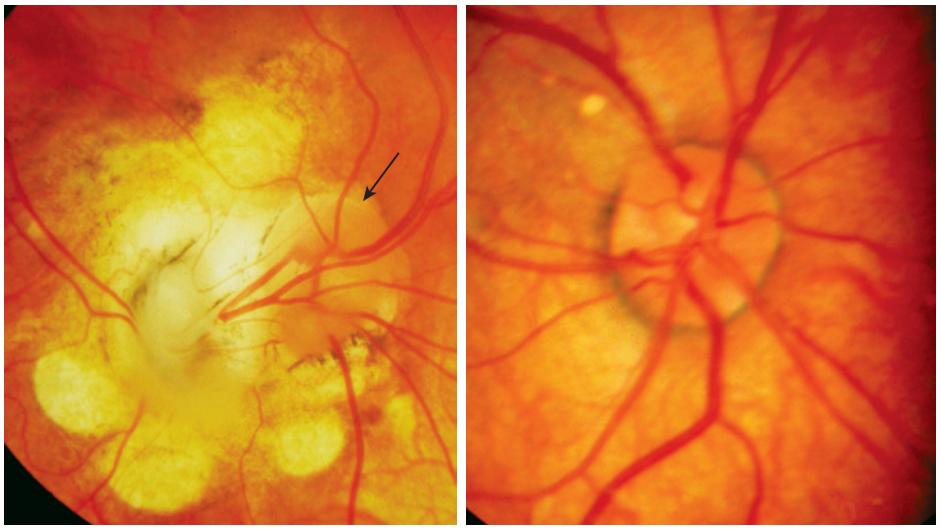


Fig. 53.33 Both these fundi are of girls with Aicardi syndrome. The very dysplastic right posterior fundus on the left of the figure shows multiple retinal pigment epithelium lacunae, a relatively normal optic disc (arrowed) and a vascular anomaly at the posterior pole. The fundus on the right belongs to a girl with severe Aicardi syndrome but the only ocular indication is the small lacunae: these, though small, have great diagnostic significance.

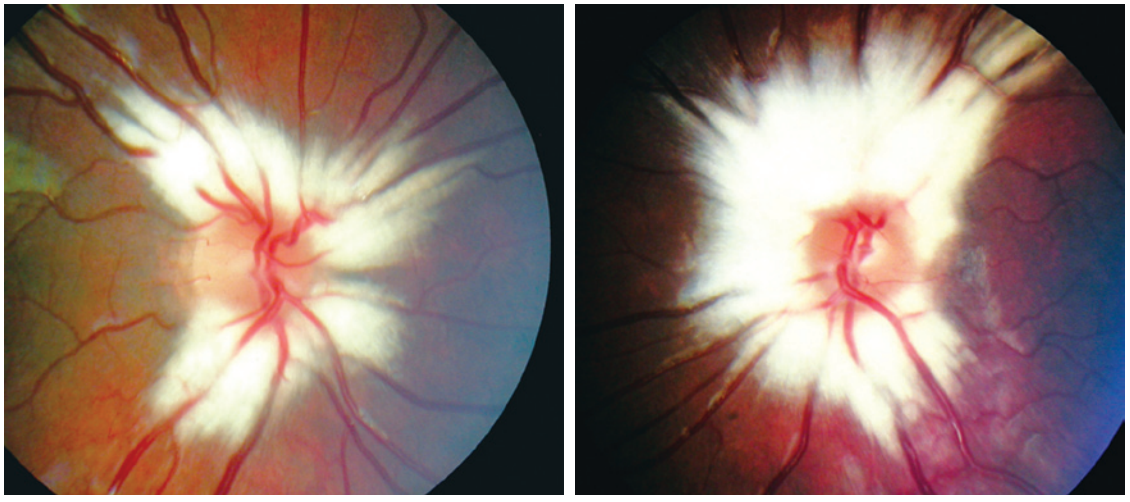


Fig. 53.34 Bilateral myelinated nerve fibers in a child with Gorlin syndrome.

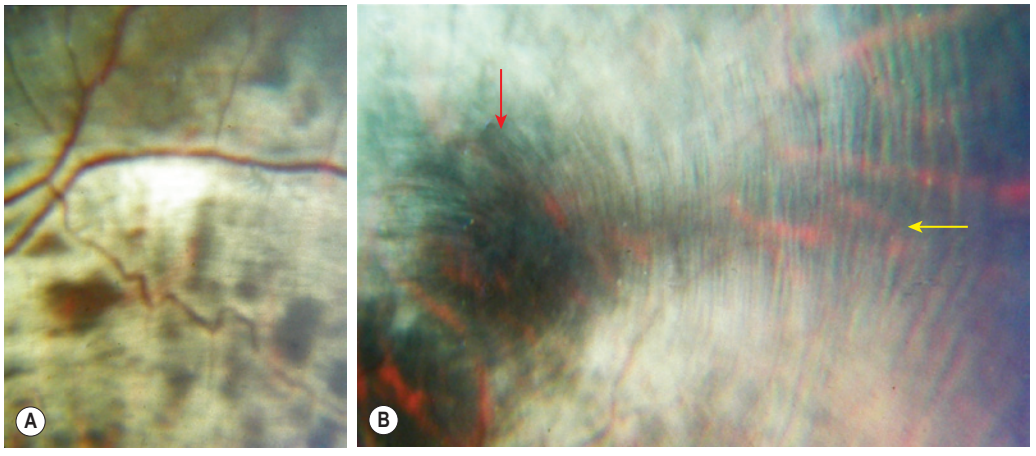


Fig. 53.35 Myelinated nerve fibers showing (A) areas without myelination and (B) the unmyelinated foveal area (red arrow) and interdigitation at the median raphe (yellow arrow).

The optic disc in albinism and aniridia

See Chapters 39 and 41.

Vascular anomalies and prepapillary looped vessels

A persistent hyaloid artery results from failure of regression and is seen as a small vascular or avascular thread coming from the optic disc anteriorly through Cloquet's canal in the vitreous towards the posterior lens capsule. It is commonly associated with persistent hyperplastic primary vitreous (PHPV or persistent fetal vasculature; Fig. 53.38), and is usually asymptomatic. It can bleed after trauma or posterior vitreous detachment.

A congenital retinal macrovessel may extend to the optic disc, and retinal arteriovenous malformations often extend to the optic disc (see Chapter 49). Optociliary shunt vessels (between the retinal and ciliary vessels) are almost exclusively seen with large optic nerve tumors, central vein obstruction, or other causes of raised ciliary venous pressure, but may rarely be mimicked as a congenital anomaly.

Looped or coiled peripapillary retinal vessels are rare congenital anomalies. They can be unilateral or occasionally bilateral.[32] Often asymptomatic (Fig. 53.39), they may present with floaters from preretinal or vitreous hemorrhage. Occasionally, usually in older children or adults, they may obstruct, resulting in infarction of the retinal zone supplied.



Fig. 53.36 Myelinated nerve fibers in a child with raised intracranial pressure. The patient was known to have myelinated nerve fibers before she had a shunt blockage. The myelinated nerve fibers are obvious but the thickened nerve fibers are visible near the black arrow.

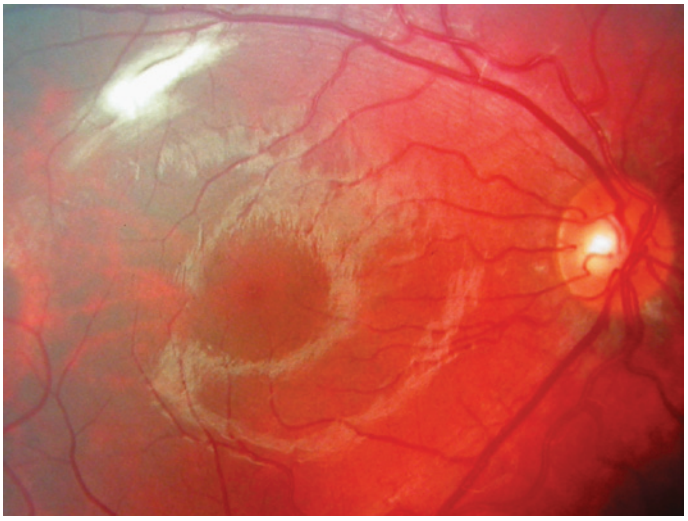


Fig. 53.37 A small patch of nerve fibers near the temporal arcade in a child with Gorlin nevoid basal cell carinoma syndrome.

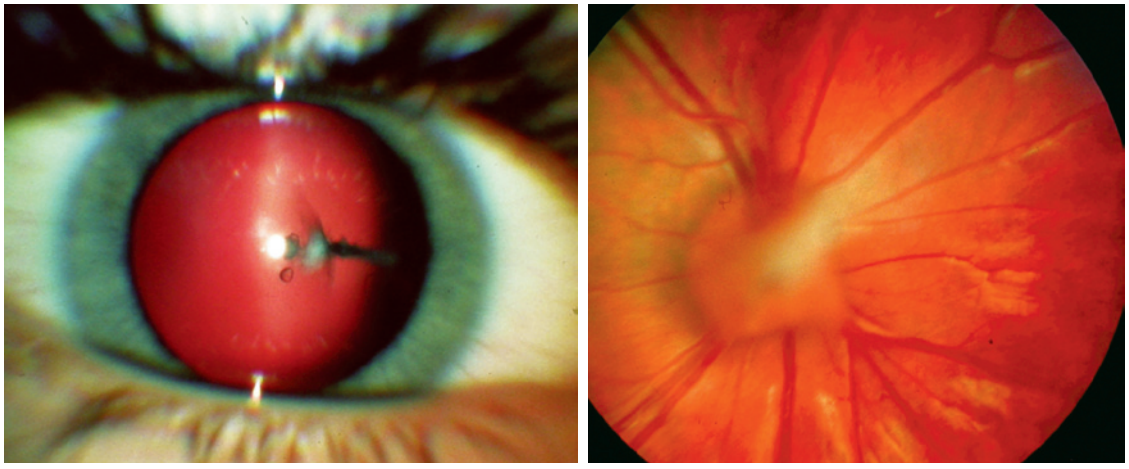


Fig. 53.38 A persistent fetal vasculature with a persistent hyaloid artery passing forward from the optic disc (right) to the back of the lens where there is a small cataract (left).



Fig. 53.39 Small looped vessel (arrow) at the optic disc.

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Hereditary optic neuropathies

Jason H Peragallo, Valérie Biousse, and Nancy J Newman

Chapter contents

MONOSYMPTOMATIC HEREDITARY OPTIC NEUROPATHIES
HEREDITARY OPTIC ATROPHY WITH OTHER NEUROLOGIC OR SYSTEMIC SIGNS
OPTIC NEUROPATHY AS A MANIFESTATION OF HEREDITARY DEGENERATIVE OR DEVELOPMENTAL DISEASES
REFERENCES

The hereditary optic neuropathies comprise a group of disorders in which the cause of optic nerve dysfunction appears to be hereditary, based on familial expression or genetic analysis. Clinical variability, both within and among families with the same disease, often makes recognition and classification difficult.[1–3] Inherited optic neuropathies are often classified by pattern of transmission, most commonly autosomal dominant, autosomal recessive, and maternal (via mitochondrial DNA [mtDNA]). The same genetic defect may not be responsible for all pedigrees with optic neuropathy inherited in a similar fashion. Similarly, different genetic defects may cause identical or similar phenotypes – some inherited in the same manner, others not. Alternatively, the same genetic defect may result in different clinical expression, although the pattern of inheritance should be consistent. Single cases are often presumed or proven to be caused by inherited genetic defects, making the pattern of familial transmission unavailable as an aid to classification.

The inherited optic neuropathies typically manifest as symmetric, bilateral, painless, central visual loss. In many of these disorders, the papillomacular nerve fiber bundle is affected, with resultant central or cecocentral scotomas. The exact location of initial pathology along the ganglion cell and its axon, and the pathophysiologic mechanisms of optic nerve injury, remain unknown, but mitochondrial dysfunction plays a central role in the pathogenesis of most, if not all, of the inherited optic neuropathies.[2,3] Optic nerve damage is usually permanent and may be progressive. Once optic atrophy is observed, substantial nerve injury has already occurred.

In some of the hereditary optic neuropathies, optic nerve dysfunction is isolated. In others, various neurologic and systemic abnormalities are regularly observed and inherited diseases with primarily neurologic or systemic manifestations, such as the multisystem degenerations, can include optic atrophy. In this chapter, the hereditary optic neuropathies are classified into three major groups[1]:

1. Those that occur primarily without associated neurologic or systemic signs.
2. Those that frequently have associated neurologic or systemic signs.
3. Those in which optic neuropathy is usually recognized as secondary in the disease process.

As more specific genetic defects are discovered, our concept of the phenotypes of these disorders will likely change, as will our classification.

Monosymptomatic hereditary optic neuropathies

Leber hereditary optic neuropathy

Leber hereditary optic neuropathy (LHON) is one of the first diseases to be etiologically linked to specific mtDNA defects.[1–3] It has a minimum point prevalence of 1 in 31,000 in the northeast of England, 1 in 39,000 in the Netherlands, and 1 in 50,000 in Finland.[3] Age of onset is typically between 15 and 35 years, but may range from 1 to 87 years. LHON is expressed predominantly in males, a feature not expected from mtDNA inheritance. Between 25% and 50% of male and 5% and 10% of female LHON carriers will have vision loss during their lifetime. Visual loss is bilateral, painless, central, and usually abrupt in onset. In about 50% of cases, the vision loss is recognized as occurring sequentially, with one eye affected weeks to months before the second eye. Within 1 year, both eyes are invariably affected. Over weeks or months, vision worsens in each eye to acuities of 20/200 or worse. Color vision is affected early and severely, and visual fields typically show central or cecocentral defects. Funduscopic abnormalities may be seen in patients with LHON and in their asymptomatic maternal relatives. Especially during the acute phase of visual loss, there may be hyperemia of the optic nerve head (pseudo-edema), dilation and tortuosity of vessels, and circumpapillary telangiectatic microangiopathy (Fig. 54.1). Eventually, there is optic atrophy with nerve fiber layer dropout, especially in the papillomacular bundle, sometimes with non-glaucomatous cupping of the disc. In most LHON patients, visual loss is the only manifestation of the disease. Some pedigrees have family members with associated cardiac conduction abnormalities,

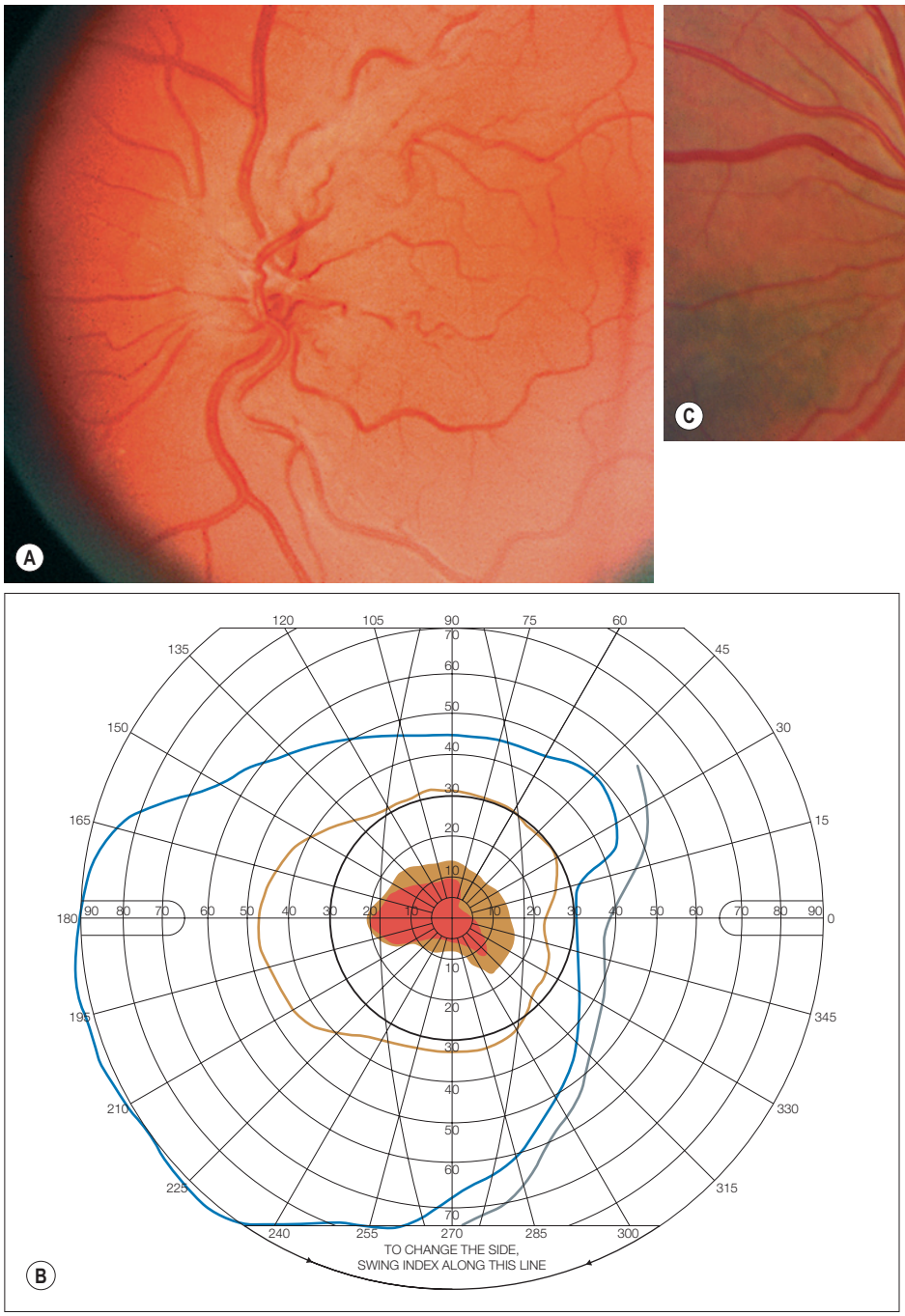


Fig. 54.1 Leber hereditary optic neuropathy. (A) Left fundus at the time of visual loss showing mild hyperemia of the optic disc with peripapillary telangiectasias. (B) Goldmann visual field demonstrating a central scotoma in the left eye. (C) Left optic disc pallor with cupping 5 months after visual loss in a patient with Leber hereditary optic neuropathy.

especially pre-excitation syndromes, minor neurologic and skeletal abnormalities, and even multiple sclerosis-like disease.

Ancillary tests in LHON are of limited clinical value. Fluorescein angiography may help distinguish the LHON optic disc from true disc edema. Electrocardiograms may show cardiac conduction abnormalities. Optical coherence tomography has demonstrated initial thickening of the peripapillary nerve fiber layer, followed by thinning as optic atrophy ensues. Visual evoked responses are predictably abnormal when there is visual loss. Standard flash electroretinograms, electroencephalograms, cerebrospinal fluid (CSF), and brain computed tomography (CT) and magnetic resonance imaging (MRI) are generally normal. Rarely, MRIs show anterior visual pathway enhancement acutely in affected LHON patients and bright T2 lesions in the late phases.

LHON pedigrees follow a maternal inheritance pattern, and the disease has been linked to point mutations in the mtDNA[1–4] (Fig. 54.2). Three point mutations in the mtDNA, known as the "primary LHON mutations," cause about 90% of cases of LHON worldwide. They are located at mtDNA nucleotide positions 11778 (69% of cases), 3460 (13% of cases), and 14484 (14% of cases) (see Fig. 54.2). Other point mutations have been found with a greater frequency in LHON patients than controls. Some of these mutations may

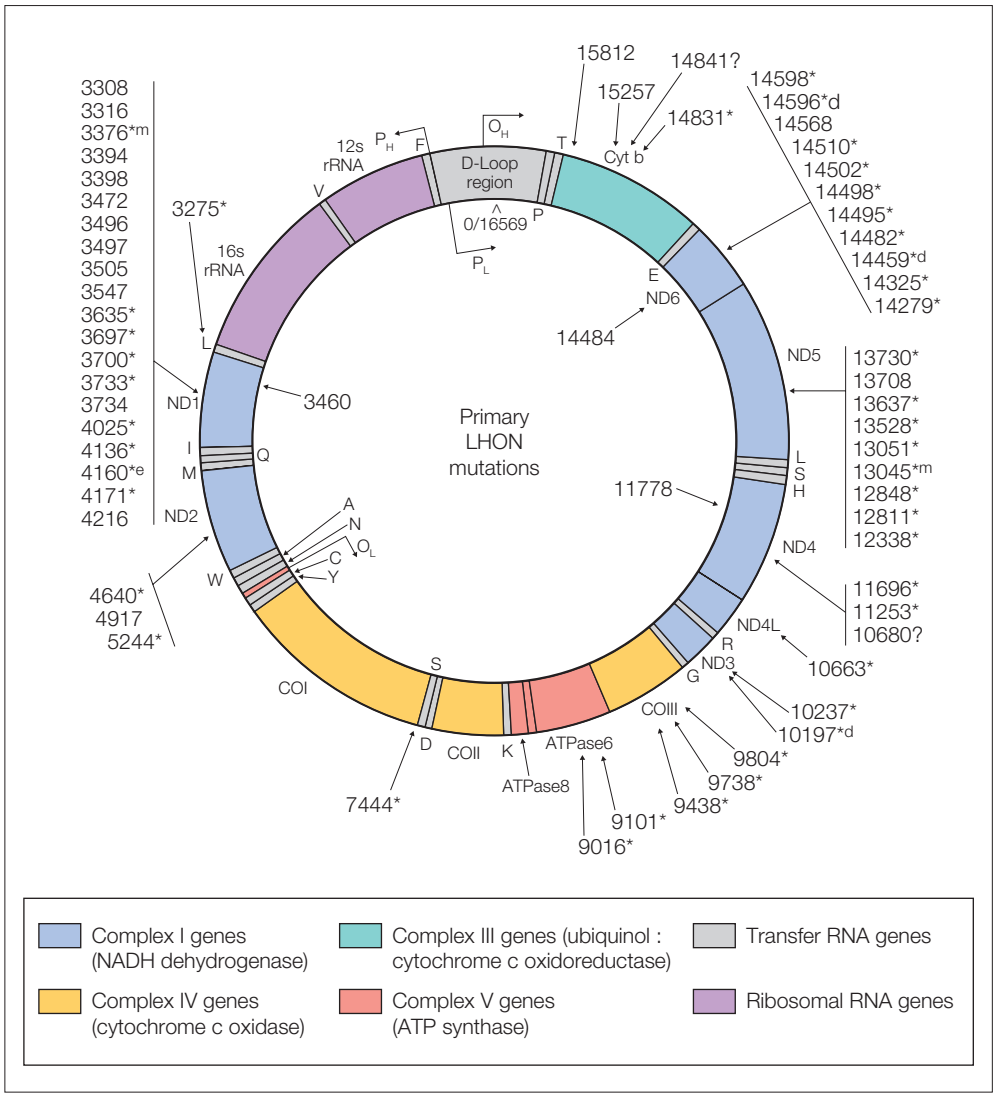


Fig. 54.2 Mitochondrial genome showing the point mutations associated with Leber hereditary optic neuropathy (LHON). Over 90% of all cases of LHON are associated with the three primary mutations located inside the genome (circle), and the other mutations are shown outside the genome. These other mutations vary markedly in their prevalence, degree of evolutionary conservation of the encoded amino acids altered, and frequency among controls. Mutations marked * may be primary, but they each account for only one or a few pedigrees worldwide. Mutations marked *d are primary mutations associated with LHON and dystonia. Mutations marked *m are primary mutations associated with MELAS. Mutations marked *e are primary mutations associated with LHON and encephalopathy. *(Adapted and updated from Newman NJ. Hereditary optic neuropathies. In: Miller NR, Newman NJ, Biousse V, et al. editors. Walsh and Hoyt's Clinical Neuro-Ophthalmology, Vol I, 6th ed. Baltimore, MD: Williams & Wilkins; 2005: 465–501.)*

be true primary mutations in a few pedigrees. Others are of unknown significance. Screening for LHON in a patient with visual loss should begin with the three primary mutations. In those primary mutation-negative patients in whom suspicion remains high, mitochondrial genome sequencing can be considered, but should be interpreted by someone familiar with the complexities of mitochondrial genetics.

Among the primary mutations, the LHON clinical phenotype is remarkably similar. The only consistent differentiating feature is the better prognosis for visual outcome in those patients with the 14484 mutation.[1] Up to 70% of patients with the 14484 mutation will have some degree of visual improvement compared to only 18% of patients with the 11778 mutation. Patients with the 3460 mutation may have a better chance of visual recovery than those with the 11778 mutation, but the numbers of patients are too small for meaningful analysis. Patients with an age of onset of visual loss of less than 20 years, especially less than 10 years, have a much better visual prognosis.[2,3]

The genetic defects, however, cannot fully explain the determinants of expression in this disease. The presence of a mtDNA mutation is necessary for phenotypic expression, but it is not sufficient.[1–3] The presence of heteroplasmy (the co-existence of both mutant and normal mtDNA) may be a factor in expression. Other mitochondrial or nuclear DNA factors may modify expression of the disease, including X-linkage as an explanation for the prominence of male expression. Various environmental triggers for the development of visual loss in LHON have been suggested. Systemic illnesses, nutritional deficiencies, and medications or toxins that stress the organism's mitochondrial energy production might be detrimental to those individuals already genetically at risk for

mitochondrial energy deficiency. Smoking, probably through its deleterious effect on mitochondrial function, has been associated with a higher expression of visual loss among carriers of the LHON primary mutation; only heavy alcohol intake has been similarly associated.[5]

The pathophysiology of LHON remains unknown.[2–4] It may involve abnormal oxidative phosphorylation and deficient generation of adenosine triphosphate (ATP), either directly or indirectly related to free radical production, resulting in irreversible damage to the ganglion cells and their axons. The reason these mechanisms result in selective damage to the optic nerve remains uncertain. Histochemical studies of the optic nerve in animals have shown a high degree of mitochondrial respiratory activity within the unmyelinated, prelaminar portion of the optic nerve, suggesting a particularly high requirement for mitochondrial function in this region. Of great interest is the recent identification of genetically induced rodent models of complex I deficiency that show histopathological features of optic nerve degeneration similar to those seen in LHON patients.[4]

Therapies tried in the treatment of LHON include coenzyme Q10, idebenone, L-carnitine, succinate, dichloroacetate, vitamin K_1, vitamin K_3, vitamin C, thiamine, vitamin B_2, and vitamin E.[1–4,6] A randomized, controlled study of idebenone in the treatment of LHON patients within 5 years of visual loss suggested that patients with a disparity in their visual function between the two eyes (i.e. those likely earlier in the course of their disease) may have a better visual outcome with treatment.[7] Treatment effect persisted following cessation of therapy at 30 month follow-up.[8] However, irreversible damage makes optic atrophy an unlikely candidate for a good response to any therapy. Avoiding agents that might stress mitochondrial energy production is a non-specific recommendation with no proven benefit. However, we suggest that LHON patients and maternal relatives at risk avoid tobacco, excessive alcohol, and environmental toxins. Symptomatic therapies include pacemakers in those patients with serious cardiac conduction defects and low-vision aids for the patient with severe visual loss. As the specific genetic and biochemical abnormalities become better defined, more directed therapies may be created to replace or bypass the genetic or metabolic deficiencies in patients with the disease and in their relatives at risk. Rodent models of induced LHON with the G11778A mutation have been phenotypically rescued by allotopically expressed wild-type ND4, paving the way for phase I clinical trials in humans.[9] This form of gene therapy known as allotypic expression may play a future role in the therapy of LHON and other mitochondrial diseases.[4,6] Genetic counseling regarding maternal inheritance among family members is essential.

Dominant optic atrophy

Autosomal dominant ("Kjer type") optic atrophy (DOA) is the most common of the autosomal hereditary optic neuropathies, with an estimated disease prevalence in the northeast of England of 1 in 35,000 individuals, and as high as 1 in 12,000 in Denmark.[1–3]

Although it is difficult for patients to identify a precise onset of reduced vision, the majority of affected patients date the onset of visual symptoms between 4 and 10 years of age, with 58–84% of patients reporting visual impairment by age 11 years. Rarely, severely affected individuals have visual difficulties and sensory nystagmus prior to schooling. Many patients are unaware of a visual problem and are discovered to have optic atrophy as a direct consequence of examination of other affected family members.[1,2] Visual acuity is usually reduced to the same mild extent in both eyes. Acuities range from 20/20 to 20/800. Only about 15% of patients have vision of 20/200 or worse. Hand motion or light perception vision is extremely rare. There is considerable interfamilial and intrafamilial variation in acuities. Although not as rapid and devastating as LHON, DOA results in visual impairment severe enough to preclude driving in about 50% of affected adults. Blue–yellow color defects are classic in patients with dominant optic atrophy, but a mixed color deficit is most common. Visual fields in patients with dominant optic atrophy characteristically show central, paracentral, or cecocentral scotomas. A bitemporal depression may mimic chiasmal compression. The optic atrophy in patients with dominantly inherited optic neuropathy may be subtle, temporal only, or involve the entire disc (Fig. 54.3). The most characteristic change is a striking triangular excavation of the temporal portion of the disc, sometimes leading to the erroneous diagnosis of glaucoma. Insidious progressive decline in visual function occurs in about 50–75% of patients.[10]

Dominant optic atrophy is believed to be a primary degeneration of the retinal ganglion cells. The majority of cases of DOA (50–60%) are the result of mutations in the *OPA1* gene, located on the long arm of chromosome 3 (3q28–q29).[1–3] This nuclear gene is widely expressed in mitochondria and encodes a dynamin-related protein anchored to the inner membrane of mitochondrial cristae, abundantly represented in the retina. More than 300 pathogenic mutations in the *OPA1* gene have been identified, including missense, nonsense, deletion/insertion, and splicing mutations. However, the monosymptomatic DOA phenotype is genetically heterogeneous, and other genetic loci have been implicated. In a single family of German descent with DOA, the causative *OPA4* locus was mapped to chromosome 18 (18q12.2–12.3), and in two unrelated French families the *OPA5* locus was mapped to chromosome 22 (22q12.1–13.1).[2,3] Interestingly, linkage analysis of patients with normal-tension glaucoma has shown an association with polymorphisms of the *OPA1* gene.[2]

Classically, DOA presents with monosymptomatic optic atrophy and no other neurologic or systemic manifestations. However, it has long been known that some pedigrees with individuals manifesting classic DOA, have also included affected family members with other clinical features such as sensorineural hearing loss and even chronic progressive external ophthalmoplegia, ataxia, myopathy, peripheral neuropathy, and, rarely, phenotypes suggestive of hereditary spastic paraplegia. Most of these families are not genetically distinct from pedigrees with monosymptomatic DOA, and, indeed, *OPA1* gene mutations have been confirmed as the causative genetic defects in many of these syndromic forms of DOA, so-called "DOA plus."[11] Some patients with monosymptomatic DOA have been found to have subclinical features of DOA plus.[12] In these patients, a severely dysfunctional OPA1 protein may result in aberrant replication of mtDNA and multiple large-scale deletions of the mtDNA, and hence a more dramatic phenotype suggestive of mitochondrial disease.[13,14] While these new observations emphasize the common final pathway of mitochondrial dysfunction in the hereditary optic neuropathies, they also blur the classic classification distinctions of

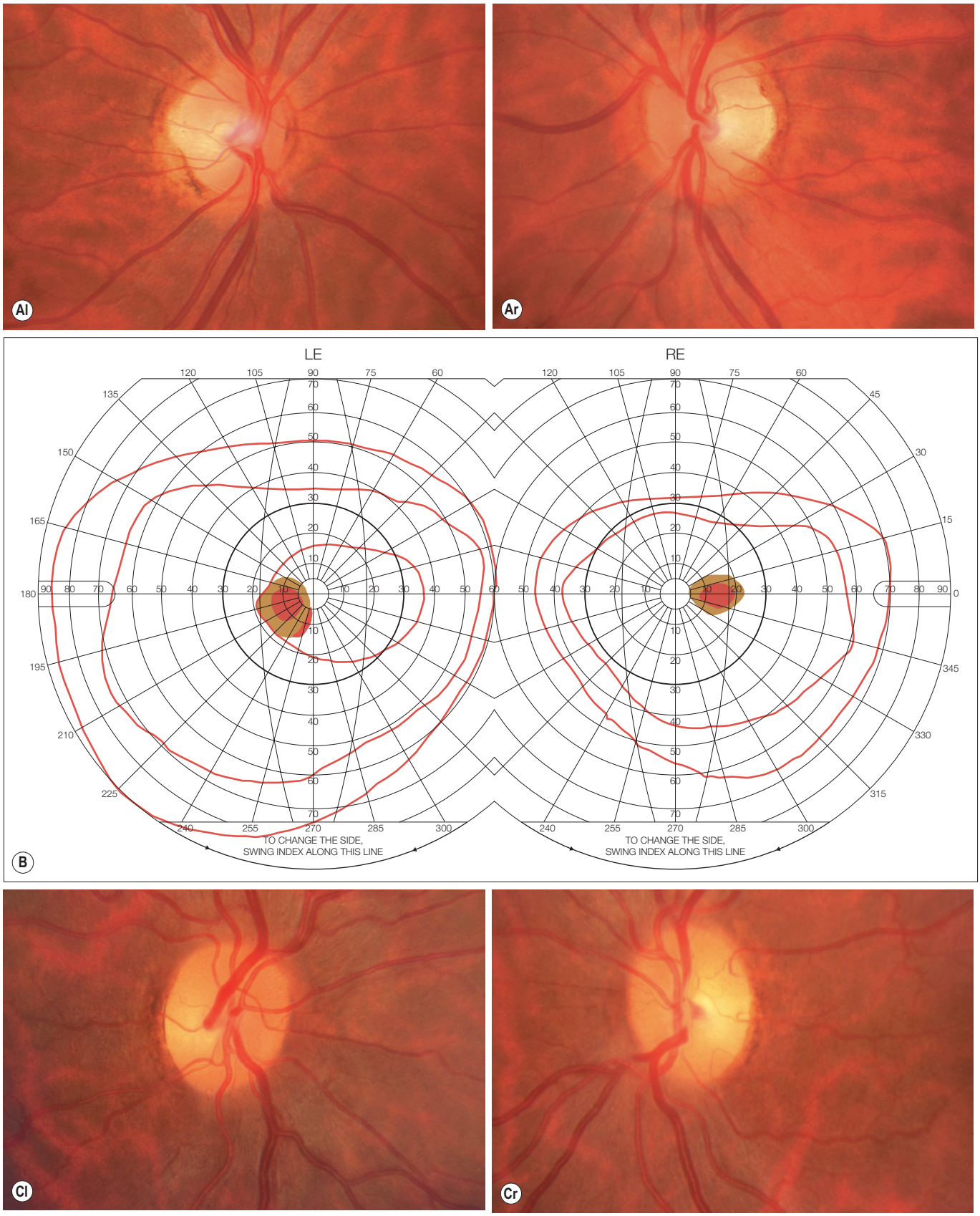


Fig. 54.3 Dominant optic atrophy. (A) Funduscopy showing bilateral temporal pallor with excavated appearance. (B) Goldmann visual field showing bilateral cecocentral scotomas (depression). (C) Funduscopy of the above patient's mother who is asymptomatic. Note the temporal pallor of both optic discs.

the non-syndromic from the syndromic forms of hereditary optic neuropathy.

Autosomal recessive optic atrophy

This form of optic atrophy is present at birth or develops at an early age and is usually discovered before the patient is 3 or 4 years old.[1] It is presumed to have autosomal recessive transmission and there is often consanguinity between parents. The visual acuity is so severely affected that the patient may be blind, with sensory nystagmus. The optic discs are completely atrophic and often deeply cupped. By funduscopy alone, it is difficult to differentiate this entity from infantile retinal degeneration, making electroretinography essential. In one consanguineous family of French origin, isolated autosomal recessive optic atrophy was linked to chromosome 8 (8q21–q22),[15] and the gene was designated *OPA6*. In a number of consanguineous North African families with autosomal recessive optic atrophy, both with and without mild (often asymptomatic) sensorineural hearing loss, defects were found in a gene designated *OPA7* on chromosome 11 (11q14.1–q21), which codes for a transmembrane mitochondrial protein.[16]

X-linked optic atrophy

Pedigrees with optic atrophy inherited in a documented sex-linked fashion are extremely rare, especially with the primary manifestation of only monosymptomatic optic atrophy. In two families, linkage to the X chromosome at the same locus (Xp11.4–Xp11.2) has been established and the gene designated *OPA2*.[17] Other families with presumed X-linked optic atrophy more consistently have other neurologic and systemic signs.

Hereditary optic atrophy with other neurologic or systemic signs

Autosomal dominant optic atrophy and sensorineural hearing loss

Several pedigrees with DOA and hearing loss have been described. In many of these pedigrees, there are no other systemic or neurologic abnormalities. Some, but not all, of these pedigrees have now been shown to harbor *OPA1* mutations that in other pedigrees cause only optic neuropathy.[1–3] In one Italian family, a new locus on chromosome 16 (16q21–q22) was designated *OPA8*, and preliminary studies suggest its pathogenesis may also be via mitochondrial dysfunction.[18]

In a Dutch pedigree with DOA and deafness, *OPA1* mutations were excluded, but a novel missense mutation was found in the *WFS1* gene on chromosome 4 (4p16.1), a common locus for mutations typically causing the autosomal recessive DIDMOAD or Wolfram syndrome (see below).[19] Similarly, in another DOA pedigree with hearing impairment and impaired glucose regulation, mutation analysis excluded mutations within the *OPA1*, *OPA3*, *OPA4*, and *OPA5* genes, but identified a novel missense mutation in the *WFS1* (Wolfram) gene.[20]

In other pedigrees with DOA and deafness, there may be associated ataxia, limb weakness, or polyneuropathy. The hearing loss in these pedigrees may be severe at birth with poor speech development, or may be only moderate and slowly progressive. The acronym CAPOS (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural deafness) has been suggested, but is as yet genetically undefined.[1] "DOA plus" with *OPA1* mutations may ultimately account for many of these more complicated syndromic pedigrees, but clearly the syndromic combination of DOA and hearing loss is genetically heterogeneous.

Autosomal dominant optic atrophy, deafness, ophthalmoplegia, and myopathy

The combination of autosomal dominant optic atrophy, deafness, ptosis, ophthalmoplegia, dystaxia, and myopathy should raise suspicion for "DOA plus" and prompt testing for mutations in the *OPA1* gene on chromosome 3.[11] Visual loss usually occurs in the first decade and progresses to the 20/30 to 20/400 range. Hearing loss is sensorineural and progressive, with onset in the first or second decade. Ophthalmoplegia and myopathy occur in midlife. This disorder likely represents mitochondrial disease secondary to nuclear genetic abnormalities (see above under DOA).

Autosomal dominant optic atrophy with premature cataracts

Two French families manifest optic atrophy and premature cataract in an autosomal dominant mode of inheritance. Mutations in the *OPA1* gene were excluded and pathogenic mutations were found in the *OPA3* gene on chromosome 19 (19q13.2–q13.3), a locus for mutations that typically cause Costeff syndrome (see below). Screening for *OPA3* mutations as a cause of monosymptomatic DOA cases in multiple other pedigrees has failed to identify any pathogenic OPA3 variants, suggesting that *OPA3* mutations as a cause of DOA are likely very rare.[21]

Autosomal recessive optic atrophy with progressive neurodegeneration and type III 3-methylglutaconic aciduria (Costeff syndrome)

In this autosomal recessive syndrome, most commonly seen in Iraqi Jewish pedigrees, severe optic atrophy is associated with extrapyramidal signs, cognitive impairment, increased urinary levels of 3-methylglutaconic acid, and elevated plasma levels of 3-methylglutaric acid. The causative gene is located on chromosome 19 (19q13.2–q13.3), and has been designated *OPA3*.[2,3]

Autosomal recessive optic atrophy with juvenile diabetes mellitus, diabetes insipidus, and hearing loss (Wolfram syndrome)

This syndrome consists of juvenile diabetes mellitus and progressive visual loss with optic atrophy, almost always associated with diabetes insipidus, neurosensory hearing loss, or both (hence, the acronym DIDMOAD for diabetes insipidus, diabetes mellitus, optic atrophy, and deafness).[3,22] Diabetes mellitus develops within the first or second decade of life and usually precedes the development of optic atrophy. In several cases, however, visual loss with optic atrophy is the first sign of the syndrome. In later stages, visual loss usually becomes severe. Visual fields have shown both generalized



Fig. 54.4 DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). The optic disc is atrophic and there is retinal hemorrhage associated with the diabetes mellitus.

constriction and central scotomas. Optic atrophy is uniformly severe (Fig. 54.4), and there may be mild-to-moderate cupping of the disc. Both hearing loss and diabetes insipidus begin in the first or second decade of life and may be quite severe. Atonia of the efferent urinary tract is present in half of patients and is associated with recurrent urinary tract infections, neurogenic incontinence, and even fatal complications. Other systemic and neurologic abnormalities include ataxia, axial rigidity, seizures, startle myoclonus, tremor, gastrointestinal dysmotility, vestibular malfunction, central apnea, neurogenic upper airway collapse, ptosis, cataracts, pigmentary retinopathy, iritis, lacrimal hyposecretion, Adie's pupil, ophthalmoplegia, convergence insufficiency, vertical gaze palsy, nystagmus, mental retardation, psychiatric abnormalities, short stature, primary gonadal atrophy, other endocrine abnormalities, anosmia, megaloblastic and sideroblastic anemia, abnormal electroretinography, and elevated CSF protein. Neuroimaging and pathology in some patients reveal widespread atrophic changes and malformations of cortical development, and suggest a diffuse neurodegenerative disorder, with particular involvement of the midbrain and pons. When the syndrome is accompanied by anemia, treatment with thiamine may ameliorate the anemia and decrease the insulin requirement.

Linkage analysis in several families has shown localization of a Wolfram gene to chromosome 4 (4p16.1). The gene responsible at this locus has been designated *WFS1*, in which multiple point mutations and deletions have been identified. The gene product, wolframin, is an endoplasmic reticulum protein, which plays a role in the regulation of intracellular calcium. A second causative Wolfram gene on the other arm of chromosome 4 (4q22–24) has been identified and designated *CISD2*; it is associated with bleeding tendency and peptic ulcers. Knockout of the *CISD2* gene in mice results in a Wolfram-type syndrome associated with mitochondrially mediated premature aging. Indeed, many of the associated abnormalities reported in Wolfram syndrome are commonly encountered in patients with presumed mitochondrial diseases, especially those patients with the chronic progressive external ophthalmoplegia syndromes. This has led to speculation that the Wolfram phenotype may be non-specific, reflecting a variety of underlying nuclear or mitochondrial genetic defects with a final common pathway of mitochondrial dysfunction.[2,3] Indeed, most cases of Wolfram have been classified as sporadic or recessively inherited, the latter usually concluded from sibling expression (which is now known to also be consistent with maternal transmission).

Spastic paraplegia, optic atrophy, and neuropathy (SPOAN syndrome)

An autosomal recessive neurodegenerative disorder was clinically defined by: non-progressive congenital optic atrophy; infantile-onset spastic paraplegia; childhood-onset of progressive motor and sensory axonal neuropathy; dysarthria starting in the third decade of life; exaggerated acoustic startle response; and progressive joint contractures and spine deformities.[23] Linkage is to chromosome 11q13.[23]

Congenital cerebellar ataxia, mental retardation, optic atrophy, and skin abnormalities (CAMOS)

Non-progressive autosomal recessive congenital ataxia associated with optic atrophy, severe mental retardation, and structural skin abnormalities is caused by a mutation in *ZNF592*, which encodes for a zinc finger protein thought to be involved in a complex developmental pathway.[24]

Deafness, dystonia, and optic neuropathy (DDON, Mohr–Tranebjaerg syndrome)

In this X-linked disorder, sensorineural deafness, dystonia, and ataxia present in late childhood, followed by optic atrophy by the age of 20, and cognitive decline and psychiatric manifestations before the age of 50.[2] The visual prognosis is poor; most patients are blind by the age of 40. The disorder is caused by mutations in the *TIMM8A* gene on the X chromosome (Xq22), whose gene product localizes to the mitochondrial intermembrane space.

Complicated hereditary infantile optic atrophy (Behr syndrome)

The designation of Behr syndrome reflects optic atrophy beginning in early childhood, associated with variable pyramidal tract signs, ataxia, mental retardation, urinary incontinence, and pes cavus. Both sexes are affected, and the syndrome is usually inherited as an autosomal recessive trait. Visual loss usually manifests before age 10 years, is moderate to severe, and is frequently accompanied by nystagmus. In most cases, the abnormalities do not progress after childhood. Neuroimaging may demonstrate diffuse symmetric white matter abnormalities. Clinical findings in some patients with Behr syndrome may be similar to those in cases of the hereditary ataxias. Behr syndrome is likely heterogeneous, reflecting different etiologic and genetic factors.[1]

Progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy (PEHO syndrome)

A progressive encephalopathy with onset in the first 6 months of life, followed by severe hypotonia, convulsions with hypsarrhythmia, profound mental deterioration, hyperreflexia,

transient or persistent facial and body edema, and optic atrophy has been described. Optic atrophy is usually noted by the first or second year of life, and nystagmus is common. A metabolic defect has yet to be determined and an autosomal recessive mode of inheritance is likely.[1] This could be considered a form of Behr syndrome, which likely represents a heterogeneous group of disorders (see above).

Optic neuropathy as a manifestation of hereditary degenerative or developmental diseases

Optic neuropathy may be associated with a variety of hereditary degenerative or developmental systemic disorders. Table 54.1 and Box 54.1 summarize the important findings in the more common such disorders.

Hereditary ataxias

The hereditary ataxias comprise a group of chronic progressive neurodegenerative conditions involving the cerebellum and its connections, and are sometimes associated with optic atrophy. A genomic classification by chromosomal location is available for many of these disorders, and the abnormal gene products involved are under investigation, many of them localized to the mitochondria.[1–3,25,26]

Friedreich ataxia is inherited in an autosomal recessive manner, and the gene defect has been localized to the proximal long arm of chromosome 9 (9q13–q21). The majority of cases are homozygous for a GAA trinucleotide expansion in a gene designated *FRDA/X25* that codes for a protein called frataxin, which regulates iron levels in the mitochondria.[1,26] The disease usually begins during the second decade of life and includes progressive ataxia, dysarthria, loss of joint position and vibratory sensation, absent lower extremity tendon reflexes, and extensor plantar responses. Scoliosis, foot deformity (pes cavus), diabetes mellitus, and cardiac disease are common. Other manifestations include distal wasting, deafness, nystagmus, eye movement abnormalities consistent with abnormal cerebellar function, and optic atrophy. The course is progressive, with most patients unable to walk within 15 years of onset, and death from infectious or cardiac causes usually in the fourth or fifth decade. Although optic atrophy is a common feature of Friedreich ataxia, most patients are visually asymptomatic, and severe visual loss occurs rarely,[27] sometimes resembling LHON.

The spinocerebellar ataxias (SCAs), previously called olivopontocerebellar atrophy or autosomal dominant cerebellar ataxia, include a group of dominantly inherited ataxic disorders in which the ataxia is related more to degeneration of the cerebellum rather than the spinal cord.[1,25,26] In 2015, there were at least 37 different genetic loci for the SCAs (SCA1 through SCA39). The combination of SCA1 (chromosome 6p), SCA2 (chromosome 12q), SCA3 (chromosome 14q), SCA6 (chromosome 19p), and SCA7 (chromosome 3p) comprises approximately 80% of the autosomal dominant ataxias. Most of the SCAs are caused by mutations involving the expansion of a CAG trinucleotide repeat in the protein-coding sequences of specific genes. As with other diseases with abnormal repeats, the expanded regions can become larger with each generation, resulting in a younger age of onset in each, so-called anticipation. Clinically, the SCAs have signs and symptoms of cerebellar degeneration, and sometimes other neurologic dysfunction secondary to neuronal loss. Loss of vision is usually mild but may be prominent, occurring with constricted visual fields and diffuse optic atrophy. However, it is not clear in some cases whether the primary process is retinal with secondary optic atrophy or primarily involving the optic nerve. SCA7 is specifically associated with retinal degeneration, whereas optic neuropathy is usually associated with SCA1 or SCA3.[25]

Hereditary polyneuropathies

Charcot–Marie–Tooth disease (CMT) encompasses a group of heredofamilial disorders characterized by progressive muscular weakness and atrophy that begins during the first two decades of life.[1–3] This group of hereditary polyneuropathies accounts for 90% of all hereditary neuropathies, with a prevalence of at least one in 2500 individuals. Most forms of CMT begin between the ages of 2 and 15 years, and the first signs may be pes cavus and other foot deformities, or scoliosis. There is slowly progressive weakness and wasting, first of the feet and legs, and then of the hands. Motor symptoms predominate over sensory abnormalities. At the time of writing, causative mutations for the hereditary peripheral neuropathies have been identified in more than 80 different genes.[28] Numerous patients with CMT and optic atrophy have been reported. Taking into account both electrophysiologic and clinical data, up to 75% of patients with CMT have some afferent

Box 54.1

Familial storage diseases and cerebral degenerations of childhood associated with optic neuropathies

Mucopolysaccharidoses (MPS IH, IS, IHS, IIA, IIB, IIIA, IIIB, IV, VI)
Lipidoses (infantile and juvenile GM1-1 and GM1-2, GM2, infantile Niemann–Pick disease)
Metachromatic leukodystrophy
Krabbe disease
Adrenoleukodystrophy
Zellweger syndrome
Pelizaeus–Merzbacher disease
Infantile neuroaxonal dystrophy
Hallervorden–Spatz disease
Menkes syndrome
Canavan disease
Cockayne syndrome
COFS
Allgrove syndrome ("4A")
Smith–Lemli–Opitz syndrome
GAPO syndrome
Blepharophimosis–mental retardation syndromes
Cerebral palsy

"4A", Alacrima, achalasia, autonomic disturbance, and ACTH insensitivity; COFS, cerebro-oculo-facio-skeletal syndrome; GAPO, growth retardation, alopecia, pseudoanodontia, and optic atrophy; GM1-1 and GM1-2, GM1-gangliosidoses; GM2, GM2-gangliosidoses: Tay–Sachs disease, Sandhoff disease, late infantile, juvenile and adult GM2-gangliosidoses; MPS HIS, Hurler–Sheie syndrome; MPS IH, Hurler syndrome; MPS IIA and IIB, Hunter syndrome; MPS IIIA and IIIB, Sanfilippo syndrome; MPS IS, Sheie syndrome; MPS IV, Morquio syndrome; MPS VI, Maroteaux–Lamy syndrome.

Table 54.1 Optic neuropathy as a manifestation of hereditary degenerative or developmental diseases

Condition name	Onset	Locus, gene, product, inheritance	Clinical course	References
HEREDITARY ATAXIAS				
Friedreich ataxia	2nd decade	9q13–q21 *FRDA/x25* Frataxin AR	Ataxia, dysarthria, scoliosis, diabetes mellitus, cardiac disease, pes cavus, cerebellar abnormality Progressive to death in 5th decade Optic neuropathy very common but usually asymptomatic	1, 26, 27
Spinocerebellar ataxias	Varies	37+ varieties SCA1→ SCA39 AD	Signs and symptoms of cerebellar degeneration and neurologic dysfunction Optic neuropathy variable Some have retinal degeneration	1, 25, 26
HEREDITARY POLYNEUROPATHIES				
Charcot–Marie–Tooth disease	1st and 2nd decades	80+ mutations AD or AR	Commonest hereditary neuropathy Pes cavus, progressive peripheral motor weakness and wasting 75% have optic neuropathy, often subclinical, some severe but a few recover	1–3, 28
Familial dysautonomia (Riley–Day syndrome)	Birth	Ch 9 *IKBKAP* AR	Optic atrophy very common, usually mild, after 1st decade 50% die by 30 years	1
HEREDITARY SPASTIC PARAPLEGIAS				
Hereditary spastic paraplegias (Strümpell–Lorrain)	3rd decade	72 mapped loci AD, AR, X-LR	Progressive spasticity of lower limbs AR form with prominent optic atrophy	2, 3, 30
HEREDITARY MUSCULAR DYSTROPHIES				
Myotonic dystrophy	20+ years	DM1 *DMPK* Ch 9 DM2 *ZNF9* Ch 3 AD	Progressive myopathy, ptosis, cataracts, cardiomyopathy with conduction defects, frontal balding, bifacial weakness, and diabetes mellitus External ophthalmoplegia, pigmentary retinopathy, and optic atrophy	1, 26
STORAGE DISEASES AND CEREBRAL DEGENERATIONS (see Chapter 65 and Box 54.1)				
MITOCHONDRIAL DISORDERS				
Leigh disease (subacute necrotizing encephalomyopathy)	2 months to 6 years	Complex disorders of mitochondrial metabolism AR, X-LR, maternal	Progressive deterioration of brainstem functions, ataxia, seizures, peripheral neuropathy, intellectual deterioration, impaired hearing, and poor vision Optic atrophy + retinal degeneration	Chapter 65 1–3
MELAS	Variable 20+ years	Mitochondrial tRNA gene *MT-TL1* Maternal	Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes Retinal degeneration Optic atrophy	Chapter 65 1–3
MERFF	Childhood	tRNA gene MT-TK Maternal	Myoclonic epilepsy and ragged red fibers Cardiac disease, retinal degeneration Optic atrophy	Chapter 65 1–3
Kearns–Sayre	<20 years	mtDNA rearrangements Maternal	Retinal degeneration and cardiac conduction abnormalities	Chapter 65 1–3

AD, Autosomal dominant; AR, autosomal recessive; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MERRF, myoclonic epilepsy and ragged red fibers; mtDNA, mitochondrial DNA; tRNA, transfer RNA; X-LR, X-linked recessive.

visual pathway dysfunction, demonstrating that subclinical optic neuropathy occurs in a high proportion of patients with CMT. A subtype of CMT, hereditary motor and sensory neuropathy type VI (HMSN VI), is defined by the combination of axonal peripheral neuropathy and optic atrophy, and has both autosomal dominant and autosomal recessive forms of inheritance.[1–3] The optic atrophy typically develops in late adolescence, a decade or more after the peripheral neuropathy, with a subacute visual decline, usually to below 20/400. As in LHON, a subset may recover vision years after the onset of optic neuropathy. The autosomal dominant form of HMSN VI is caused by a mutation in the nuclear mitofusin-2 gene, and constitutes a subclass of CMT2A, the most common autosomal dominant form of axonal CMT. The mitofusin-2 protein is a

GTPase localized to the mitochondrial outer membrane, and shares many structural and functional similarities with the OPA1 protein in DOA.[2,3]

Familial dysautonomia (Riley–Day syndrome) is an autosomal recessive disease that almost exclusively affects Ashkenazi Jews. Abnormalities of the peripheral nervous system cause the clinical manifestations of sensory and autonomic dysfunction. Optic atrophy is very common in patients with familial dysautonomia, with involvement of the papillomacular bundle similar to the other hereditary optic neuropathies, suggesting familial dysautonomia may affect mitochondrial function.[29] However, in most cases, early mortality from the disease probably precludes the later development of optic atrophy.[1] Other ophthalmic features of familial dysautonomia include dysmetric saccades, saccadic intrusions, abnormal smooth pursuit, and corneal opacities.

Hereditary spastic paraplegias

The hereditary spastic paraplegias (Strümpell–Lorrain disease) are inherited disorders characterized by progressive spasticity of the lower limbs with degeneration of the corticospinal system. The prevalence of these disorders is about 3–10 per 100,000. As of 2015, there were at least 72 mapped loci for the hereditary spastic paraplegias, and 55 identified genes.[30] Hereditary spastic paraplegia is classified as "pure" if spasticity is the only manifestation, or as "complicated" if other features, such as optic atrophy, are present. Complicated hereditary spastic paraplegia with optic atrophy may result from several different nuclear DNA mutations. The *SPG7* gene, found on chromosome 16 (16q24.3), encodes for a mitochondrial metalloproteinase, paraplegin. Mutations in the *SPG7* gene have been identified in an autosomal recessive form of hereditary spastic paraplegia in which some patients have bilateral optic atrophy as a prominent manifestation of their disorder.[2,3]

Hereditary muscular dystrophies

Myotonic dystrophy is a relatively common autosomal dominant disorder with a prevalence of 1 in 20,000, characterized by progressive myopathy, ptosis, cataracts, cardiomyopathy with conduction defects, frontal balding, bifacial weakness, and diabetes mellitus. Less common ophthalmic manifestations include external ophthalmoplegia, pigmentary retinopathy, and optic atrophy.[1,26] Most have an expansion of a CTG repeat in a protein kinase gene on chromosome 19q13.3.

Storage diseases and cerebral degenerations of childhood

Over 100 inherited metabolic and degenerative diseases with ocular manifestations have been described, some detailed in Chapter 65 (see also Table 54.1).

Mitochondrial disorders

The subacute necrotizing encephalomyelopathy of Leigh results from multiple different biochemical defects that impair cerebral oxidative metabolism.[1–3] This disorder may be inherited in an autosomal recessive, X-linked, or maternal pattern, depending on the genetic defect. The onset of symptoms is typically between the ages of 2 months and 6 years, and consists of progressive deterioration of brainstem functions, ataxia, seizures, peripheral neuropathy, intellectual deterioration, impaired hearing, and poor vision. Visual loss may be secondary to optic atrophy or retinal degeneration. Leigh syndrome is likely a non-specific phenotypic response to certain abnormalities of mitochondrial energy production.

Other presumed mitochondrial disorders of both nuclear and mitochondrial genomic origins may manifest optic atrophy as a secondary clinical feature, often a variable manifestation of the disease.[1–3] Examples include cases of MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes), DCMA (dilated cardiomyopathy with ataxia), MERRF (myoclonic epilepsy and ragged red fibers), MNGIE (mitochondrial neurogastrointestinal encephalomyopathy), and chronic progressive external ophthalmoplegia, both with and without the full Kearns–Sayre phenotype. The other, more constant, phenotypic characteristics of all of these mitochondrial disorders distinguishes them from diseases such as LHON in which visual loss from optic nerve dysfunction is the primary manifestation of the disorder.[1–3]

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Other acquired optic disc abnormalities in children

Stacy Pineles

Chapter contents

INTRODUCTION
PSEUDOPAPILLEDEMA AND OPTIC DISC DRUSEN
TUMORS
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Introduction

Acquired optic disc abnormalities in children can range from benign incidental findings to harbingers of serious systemic diseases. It is important for ophthalmologists to understand the various findings that one might detect when examining the optic disc of a child, and to recognize when a systemic evaluation is required. Acquired optic disc abnormalities discussed in this chapter include pseudopapilledema and optic disc drusen, intrinsic optic disc tumors, and optic disc atrophy secondary to nutritional, toxic, and hypoxic/ischemic etiologies. Other causes of acquired optic disc abnormalities will be covered in Chapters 23 and 57 (optic nerve and chiasmal tumors), 56 (inflammatory, infectious, and infiltrative optic neuropathies), and 59 (papilledema).

Pseudopapilledema and optic disc drusen

Optic disc elevation may be due to causes other than increased intracranial pressure or intrinsic optic neuropathies. The term "papilledema" refers strictly to disc swelling secondary to raised intracranial pressure. In cases where the disc appears edematous (either due to disc elevation or blurring of the disc margin) but the intracranial pressure is normal, the term "pseudopapilledema" can be applied. Optic disc drusen is the most common cause of pseudopapilledema; however, there are several other causes. For example, children with high hyperopia often have small, crowded and elevated discs, suggesting possible optic disc edema. Myelinated nerve fibers, papillary glial tissue, or persistent hyaloid vasculature may obscure the disc margin, causing the appearance of optic disc edema. In such cases, a high index of suspicion will lead the clinician to recognize pseudopapilledema and avoid further diagnostic testing.

Optic disc drusen

Unlike the etiologies described above, optic disc drusen may be buried deep in the optic disc, preventing easy recognition. Co-existent disc hemorrhages and visual field defects can also complicate the clinical picture and lead to unnecessary diagnostic studies to rule out increased intracranial pressure.[1] Optic disc drusen are present in approximately 2% of the population.[2] They may be inherited in an autosomal dominant fashion with incomplete penetrance.[3] They are less common in black patients, possibly due to larger cup-to-disc ratio or a lack of a genetic predisposition.[4] They are acellular hyaline concretions located in the prelaminar portion of the optic nerve head, and can be present on the surface of the optic disc ("surface drusen") or buried deeper in the disc and not readily visible ("buried drusen"). In contrast to adults, drusen in children are often buried and more difficult to see; however, as children grow older, the drusen often emerge to become visible on the surface of the disc.[5] Superficial drusen may be seen in less than 20% of children with drusen who are under 15 years of age.[6]

The pathogenesis of optic disc drusen is poorly understood; however, anatomical predisposition appears to play a role. Whether a small scleral canal or congenitally abnormal disc vasculature are the underlying etiologies is unclear, but it is hypothesized that one or more of these anatomical predisposing factors leads to axoplasmic stasis and degeneration, leading to extrusion of mitochondria and eventual calcification.[7]

Clinical findings

Surface drusen (Fig. 55.1) protrude from the disc and are most prominent at the nasal aspect, giving the margin of the disc a "lumpy-bumpy" appearance. They appear as globular yellow formations that may accumulate in conglomerations. Conversely, buried drusen (Fig. 55.2) often cause the appearance of elevation of the optic disc with associated blurring of the disc margins.[8] In cases of buried drusen, the elevated disc may be gray or yellow-white. Indirect illumination of the disc can often cause a diffraction of light from buried drusen. With time, the border of the disc becomes more scalloped due to early protrusion of the buried drusen. Optic disc drusen are often accompanied by anomalous retinal vessels, with increased looping, branching, and tortuosity.[8]

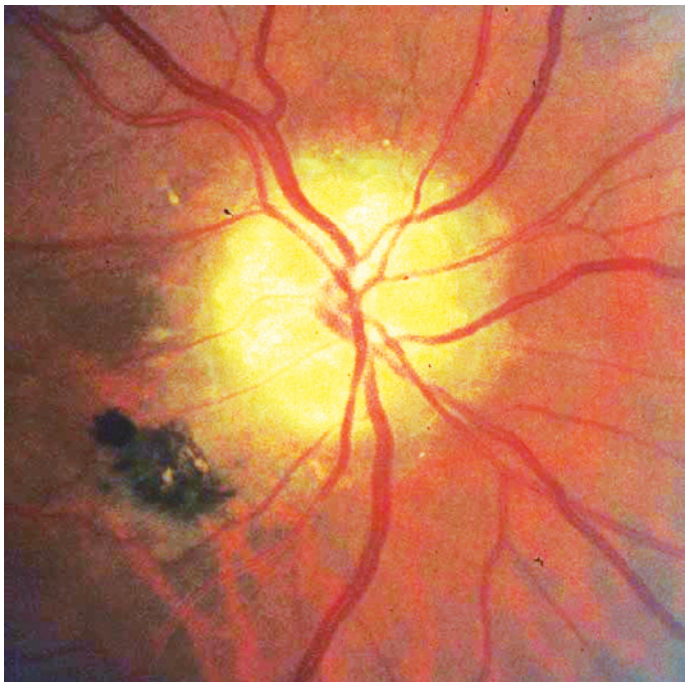


Fig. 55.1 Surface optic disc drusen demonstrating the typical appearance of a "lumpy-bumpy" disc surface with visible irregular deposits on the surface of the optic disc. *(Courtesy of Anthony C. Arnold, MD.)*

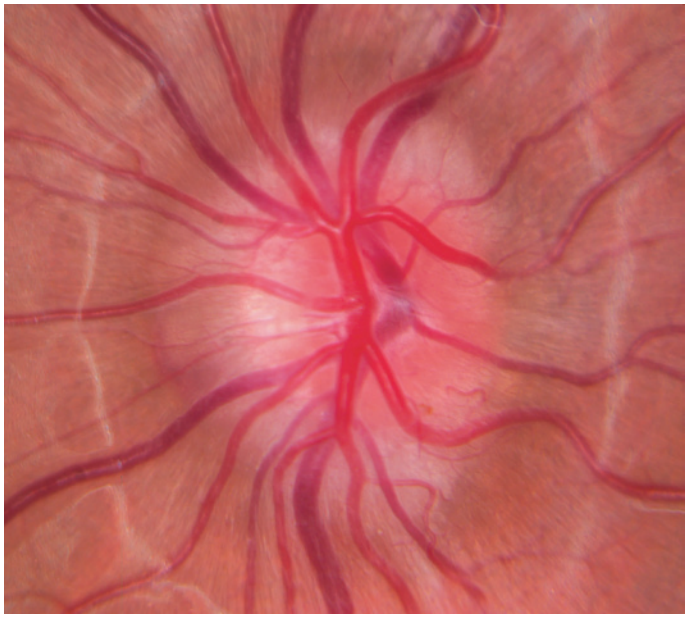


Fig. 55.2 Buried optic disc drusen cause optic nerve elevation and blurring of the optic disc margins.

While visual acuity loss is extremely rare in patients with optic disc drusen, visual field defects occur frequently. The prevalence of visual field defects in children with buried drusen ranges from 11% to 51%[6,9]; however, the prevalence of visual field defects seems to increase by adulthood to up to 87%.[3] Studies comparing the prevalence of visual field defects in patients with surface versus buried drusen have shown a much greater incidence of visual field defects with surface drusen (73%) compared to buried drusen (36%).[8] The most common visual field defects are nerve fiber bundle defects, followed by generalized constriction, and enlarged blind spot.[8] Visual field defects are typically asymptomatic and, when asymmetric, are often associated with an afferent pupillary defect.[6]

Differentiating optic disc drusen from optic disc edema: diagnostic testing (Table 55.1)

Fundus examination

Optic disc drusen can often be differentiated from true optic disc edema by a lack of other findings, including a lack of hyperemia, hemorrhages, and exudates (Table 55.2). Obscuration of the blood vessels as they exit the optic disc can be an indicator of true edema, as opposed to the blood vessels coursing over a disc harboring drusen, which are never obscured by nerve fiber layer edema. Also, spontaneous venous pulsations, when observed, can indicate a lack of true edema. Patients with drusen have also been shown to have larger arterial diameter and more secondary venous branching than patients with true papilledema.[10]

Autofluorescence

A variety of ancillary tests can be performed to help differentiate drusen from papilledema. Optic disc drusen are known to autofluoresce when photographed using angiography filters.[11] Autofluorescence has been found to be a somewhat sensitive test in adults with optic disc drusen, with sensitivity nearing 80%[11,12]; however, it is not clear whether autofluorescence is equally sensitive in children with buried drusen since adults with buried drusen have been found to have a much lower rate of autofluorescence.[13] One study found a sensitivity of 94% despite most of their children harboring buried drusen, but this study was small and has yet to be reproduced.[11]

Ultrasound

B-scan ultrasound has also been used as a diagnostic tool to detect calcified drusen.[14] Even in uncooperative children, deep calcified drusen can be seen as a highly reflective round structure with acoustic shadowing in the medium-gain scan. They can also be seen in low-gain scans due to their calcium content (Fig. 55.3).[7] In a study of adults, B-scan was approximately 50% sensitive in detecting optic disc drusen.[13] Given the higher likelihood of children harboring buried and non-calcified drusen, B-scan ultrasound is a useful test, but a negative result does not completely rule out the presence of optic disc drusen.

Fluorescein angiography

Fluorescein angiography has also proven to be a useful diagnostic tool in patients who are cooperative.[15] Although the youngest patients may not cooperate for angiography, children older than 5 years are often capable of doing so. In a large study of adults with optic disc drusen, fluorescein angiography correctly differentiated true optic nerve edema from pseudoedema based upon a lack of dye leakage from the disc. In addition, several angiographic characteristics have been defined to aid diagnosing optic disc drusen.[15] Surface drusen can often be seen due to their autofluorescence on pre-injection photos as described above. Additionally, they are usually associated with early and late nodular staining of the disc. Buried drusen can be differentiated from true disc edema based on a lack of dye leakage and the presence of late nodular or peripapillary circumferential staining (Fig. 55.4).

Table 55.1 Different imaging modalities to diagnosis optic disc drusen

Modality	Advantages	Disadvantages
Fundus examination	Simple, inexpensive; most useful in cases with surface drusen	Often insufficient for differentiating buried drusen from true edema
Autofluorescence	Does not require injection; most useful in cases with surface drusen; highly specific	Often does not detect deep buried drusen; lacks sensitivity
Fluorescein angiogram	Easily differentiates true edema from pseudoedema based on dye leakage	Requires high degree of cooperation from patient
Computed tomography (CT) scan	Detects calcified drusen	Radiation exposure, expense, and low sensitivity for non-calcified drusen
B-scan ultrasound	Simple, inexpensive and non-invasive; does not require high level of cooperation to detect calcified drusen	Often does not detect deep buried drusen; poor resolution; lacks sensitivity
Optical coherence tomography	May be useful in detecting both superficial and buried drusen. Patterns of reflectivity and internal contour may aid in differentiating true edema from drusen; able to produce retinal nerve fiber layer thickness	Sensitivity and specificity still under investigation; requires cooperation

Table 55.2 Fundus findings in pseudopapilledema from optic disc drusen and true optic disc edema

Feature	True optic disc edema	Optic disc drusen
Disc contour	Smooth, elevated	Lumpy, elevated
Disc color	Hyperemic	Normal or yellow-white
Disc vasculature	Normal configuration with venous congestion	Increased branching and number of major vessels
Disc vasculature obscuration by edematous nerve fiber layer	Common	Not seen
Nerve fiber layer	Grayish, thickening extends beyond disc	Normal color with thickening abruptly ending at disc margin
Hemorrhages	Splinter hemorrhages common	Splinter and deeper hemorrhages rare
Exudates	Common	Rare

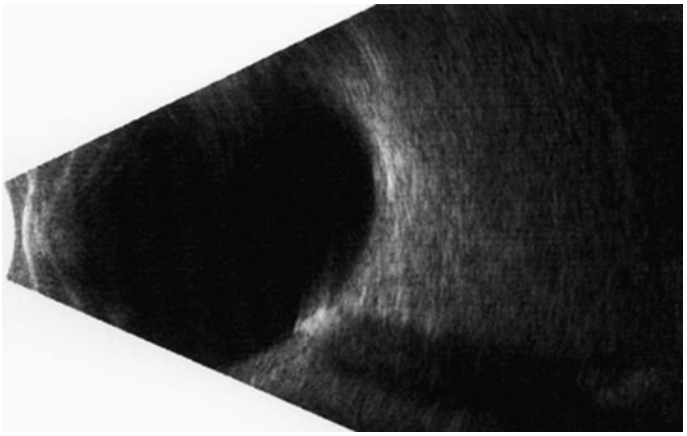


Fig. 55.3 B-scan ultrasound revealing a highly reflective round structure with acoustic shadowing at the medium-gain scan that persists on the low-gain scan due to its calcium content.

Optical coherence tomography (OCT)

The ability of OCT to determine *in vivo* measurements of retinal nerve fiber layer thickness, optic disc volume, and anatomical information may help clinicians to diagnose buried optic disc drusen. Early studies using spectral-domain OCT demonstrated a significant difference in nerve fiber layer thickness between patients with drusen and those with true chronic papilledema.[16] In a study comparing patients with true papilledema to patients with drusen, OCT characteristically revealed a "lumpy-bumpy internal contour" in the eyes with drusen, and a "smooth internal contour" in eyes with true edema (Fig. 55.5).[17] Spectral domain OCT has been shown to reveal a hyperreflective or hyporeflective mass within the optic nerve head in some drusen cases.[18,19] Additionally, as resolution improves with new techniques such as enhanced depth imaging OCT and swept source OCT, drusen can be directly imaged, appearing either as poor signal intensity regions surrounded by hyperreflective bands or as isolated hyperreflective bands without the associated poor signal area in the center.[20] Furthermore, these newer imaging techniques allow for delineation of the posterior extent and shape of each individual druse.[20] Unfortunately, studies of all diagnostic modalities, including OCT, are limited by the lack of a gold standard in diagnosing buried optic disc drusen.

Prognosis and treatment

There is no known treatment for optic disc drusen. Typically, they do not impact central visual acuity and the visual field defects are often not progressive. However, some physicians will recommend lowering the intraocular pressure in cases where the visual field defect is progressing. Superficial flame-shaped and deep peripapillary hemorrhages can also be seen, but these do not typically cause visual symptoms. Rarely, choroidal neovascular membranes can occur, and reported treatment modalities include laser photocoagulation, photodynamic therapy, and intravitreal anti-vascular endothelial growth factor agents.[21–23] Finally, ischemic events such as ischemic optic neuropathy and retinal vascular occlusions have all been reported in children with optic disc drusen.[24–26]

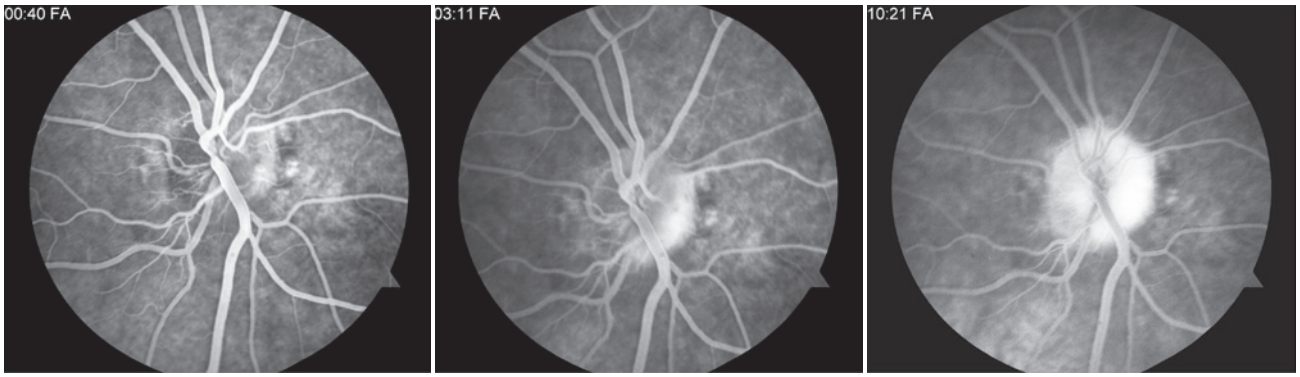


Fig. 55.4 Fluorescein angiography of optic disc drusen demonstrates early and late nodular staining of the disc without leakage of dye.

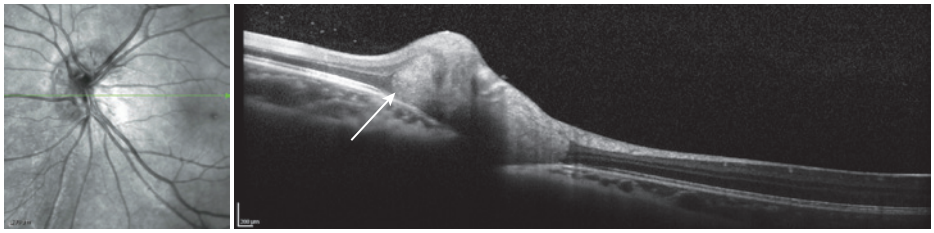


Fig. 55.5 Optical coherence tomography of optic disc drusen reveals a "lumpy-bumpy" internal contour (arrow) that is not seen in eyes with true optic disc edema.

Systemic associations

Optic disc drusen can be seen in association with several systemic diseases. The incidence of pseudoxanthoma elasticum in patients with drusen is much higher than that of the general population (1–3% vs. 1 in 160,000).[7] Additionally, optic disc drusen appear to be more common in children with retinitis pigmentosa.[27]

Tumors

Acquired tumors that directly affect the optic nerve and chiasm will be discussed in Chapters 23 and 57. However, the following section will briefly discuss the optic nerve appearance in cases of intrinsic optic disc tumors.

Intrinsic optic disc tumors

Intrinsic optic nerve tumors are rare and include optic disc gliomas, optic disc hemangiomas, simple optic disc hamartomas, and combined hamartomas of the retina and retinal pigment epithelium (CHRPE). Many of these tumors are often seen in association with a systemic condition. For example, optic disc hemangiomas are often seen in patients with von Hippel–Lindau disease. Astrocytic hamartomas of the optic disc are most commonly seen in patients with tuberous sclerosis, and appear as an elevated protrusion of the optic disc that is translucent in early childhood and progresses to be a yellow, opaque mulberry lesion over time. Both optic disc gliomas and CHRPEs are seen most commonly in neurofibromatosis type-2.[28,29]

Acquired optic atrophy in childhood

The differential diagnosis of acquired optic atrophy in childhood is wide and includes hereditary, nutritional, toxic, metabolic, hypoxic, compressive, traumatic, metabolic, and neurodegenerative conditions. This chapter will focus on nutritional, toxic, hypoxic, and traumatic etiologies of optic atrophy in children.

Nutritional optic neuropathies in children

Several vitamin deficiencies can cause clinical syndromes that include optic neuropathy. Reported etiologies of nutritional optic neuropathy in children include vitamin A deficiency,[30] vitamin B_{12} deficiency,[31] thiamine deficiency,[32] and folate deficiency.[33] Although vitamin deficiencies are rare in children residing in developed countries, several scenarios should raise a clinician's index of suspicion. For example, children with autism often assume highly stereotyped diets and refuse all foods except those of a certain color or texture. For this reason, they may present with a wide range of vitamin deficiencies, some of which have been reported to result in optic atrophy, including vitamin A and vitamin B_{12}.[30,31] In addition, children with gastrointestinal diseases such as celiac disease may also present with nutritional deficits. Children on severely limited diets due to anorexia nervosa, ketogenic diet for seizure control, or fad diets should also be evaluated for a nutritional etiology when presenting with vision loss. Increasingly, gastric bypass surgery is being performed for the treatment of childhood obesity. This procedure has often been linked to vitamin deficiency optic neuropathy secondary to malabsorption.[34] Finally, in developing countries, optic neuropathy secondary to malnutrition has been reported in children as young as 12 years.[33]

Nutritional optic neuropathies commonly present with a gradual, insidious vision loss related to central scotomata, and diminished color vision. Clinicians should ask about a diagnosis of autism, gastrointestinal disease or surgery, or strict dietary limitations. Clinical examination typically reveals diminished central visual acuity and color vision, with visual field defects including central scotoma, cecocentral scotoma, or

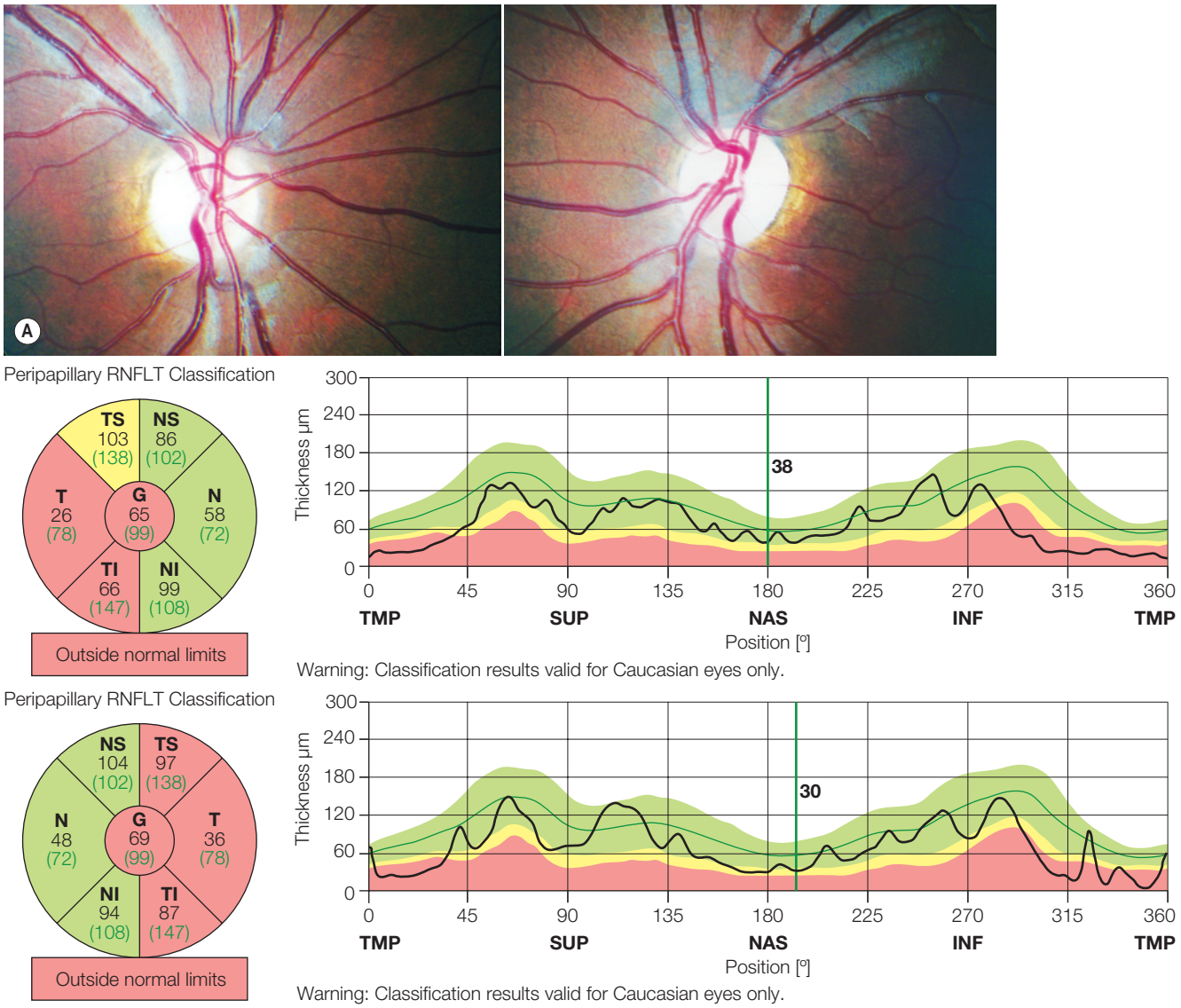


Fig. 55.6 Child with vitamin B_{12} deficiency optic neuropathy. (A) Fundus photograph reveals temporal optic nerve pallor. (B) Optical coherence tomography demonstrates temporal thinning of the retinal nerve fiber layer.

arcuate defects. The optic nerve in these cases typically reveals temporal pallor and nerve fiber layer dropout throughout the papillomacular bundle (Fig. 55.6). OCT has been shown to reveal significantly decreased retinal nerve fiber layer thickness in the superior and temporal peripapillary region (see Fig. 55.6).[35]

Toxic optic neuropathies in children

Anti-tuberculous agents

Streptomycin, isoniazid and, more frequently, ethambutol are implicated in optic nerve toxicity (Fig. 55.7). Age, duration of treatment, and dose are correlated with toxicity. In addition, ethambutol has been reported to trigger or accelerate visual loss in patients harboring mutations associated with Leber hereditary optic neuropathy and autosomal dominant optic atrophy.[36]

Antibiotics

Systemic administration of chloramphenicol is associated with an optic neuropathy.[37] This is characterized by mild disc swelling and central/cecocentral scotomas, with partial resolution on discontinuing treatment. Chloramphenicol results in depletion of mitochondrial DNA, implicating a mitochondrial toxic effect as a cause of the optic neuropathy. Linezolid is a synthetic antibiotic used in the treatment of serious gram-positive infections. Prolonged treatment is associated with a reversible optic neuropathy and usually with a peripheral neuropathy that has been linked to mitochondrial toxicity.[38]

Immunomodulatory agents

Infliximab is an anti-tumor necrosis factor alpha antagonist. Optic nerve toxicity has been reported following its use in the treatment of Crohn disease, ulcerative colitis, and psoriatic arthropathy.[39]

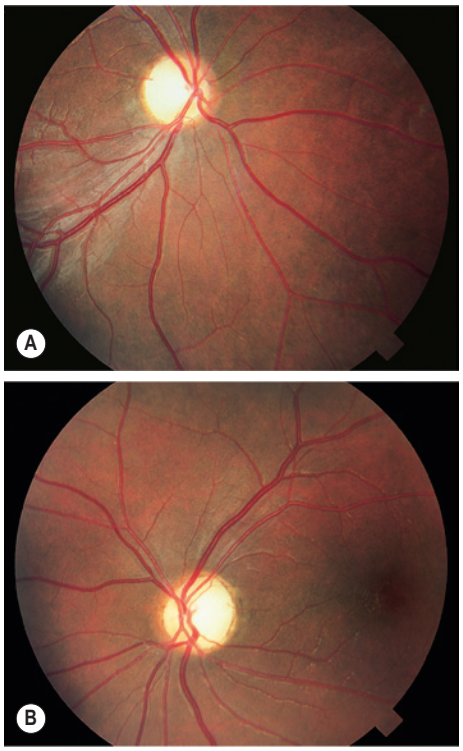


Fig. 55.7 A patient with tuberculous meningitis. Bilateral optic neuropathy was presumed secondary to ethambutol toxicity.

Anti-neoplastic agents

Vincristine disrupts neurofilament organization, resulting in a reversible optic neuropathy.[40]

Hypoxic/ischemic optic neuropathies in children

The typical adult presentation of anterior ischemic optic neuropathy on waking, presumably linked to nocturnal blood pressure reduction, is not seen in children. Anterior ischemic optic neuropathy in children is usually associated with more severe dips in blood pressure, for example with hemodialysis, peritoneal dialysis, or overly aggressive treatment of severe hypertension.[40] In these settings, uremia, hypotension, and diabetes may also be contributory.[41] Finally, ischemic optic neuropathy has also been reported in children with congenital heart disease or pulmonary hypertension taking sildenafil.[42]

Traumatic optic neuropathy in children

Traumatic optic neuropathy is classified according to the site of injury (optic nerve head, intraorbital, intracanalicular, and intracranial), or according to the mode of injury (direct and indirect). It is an uncommon cause of visual loss with a reported incidence of 0.7–2.5% following blunt or penetrating head trauma, and a prevalence of about 1 in 1,000,000 in the general population.[43] Bilateral optic nerve involvement is rare (5%). Although most patients are young adult males, 20% occur during childhood. In children, the most common causes of traumatic optic neuropathy are falls, road traffic crashes, and sporting injuries.[44]

A diagnosis of traumatic optic neuropathy is based on the clinical history and corroborative examination findings. The assessment can be difficult when the patient's mental status is impaired due to severe trauma. It is essential to exclude other reversible causes of visual loss, such as a retrobulbar hemorrhage. Traumatic optic neuropathy frequently results in profound loss of central vision, with 50–60% of patients presenting with visual acuities of light perception or worse. The optic disc usually looks normal in the acute phase, but with injuries anterior to the entry point of the central retinal vessels, edema of the optic nerve head and retinal hemorrhages can be observed. In cases of optic nerve avulsion, the optic disc is absent and there is a surrounding ring of hemorrhage. The visual outcome in traumatic optic neuropathy is largely dictated by the patient's initial visual acuities. Little or no visual recovery can be expected for patients with light perception or worse at baseline. Other poor prognostic factors include loss of consciousness, no improvement in vision after 48 hours, and the absence of visual evoked responses. Optic canal fractures have been associated with a worse visual prognosis in some case series.

The management of traumatic optic neuropathy remains controversial. Some clinicians favor observation alone, while others treat with systemic steroids (in various doses, duration, and mode of administration), surgical decompression of the optic canal, or both. An optic canal fracture with a bone fragment impinging on the optic nerve is an indication to some clinicians for prompt surgical intervention. The evidence base for these treatments is weak. Recent reviews have not supported the routine use of high-dose steroids or surgery in traumatic optic neuropathy.[45,46] There is a high rate of spontaneous visual recovery (40–60%) among patients managed conservatively, and the adverse effects of intervention need to be carefully considered. It is essential to be vigilant about the possibility of delayed visual loss in traumatic optic neuropathy. If this is secondary to the development of an optic nerve sheath hematoma, urgent decompression with sheath fenestration is indicated.

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Demyelinating, inflammatory, infectious, and infiltrative optic neuropathies

Gena Heidary

Chapter contents

PEDIATRIC OPTIC NEURITIS
INFECTIOUS OPTIC NEUROPATHY
INFILTRATIVE OPTIC NEUROPATHY
REFERENCES

Pediatric optic neuritis

Optic neuritis is an inflammatory process involving the optic nerve. It presents with a painful, acute/subacute vision loss with corroborating evidence of an optic neuropathy on examination. This may include a relative afferent pupillary defect, visual field dysfunction, dyschromatopsia, and optic nerve edema. Optic neuritis may occur as a clinically isolated syndrome or in association with neurologic/systemic disease. This section examines pediatric optic neuritis in the context of demyelinating and inflammatory disease processes in children. When possible, a careful understanding of the underlying etiology of optic neuritis is critical in order to target the appropriate treatment to protect the child from irreversible vision loss, and to address neurologic or systemic disease. Therefore, a multidisciplinary approach involving both ophthalmology and neurology is essential to assess visual function and to manage systemic therapy when relevant.[1]

Optic neuritis associated with demyelinating disease

The prevalence of pediatric optic neuritis is unknown. In one retrospective study of all patients presenting with optic neuritis in Minnesota, USA, pediatric optic neuritis accounted for fewer than 5% of cases, with a higher prevalence in adolescents compared with children.[2] The clinical presentation differs from adult optic neuritis: nearly half the pediatric cases of optic neuritis were bilateral. Also, the anterior optic nerve was more commonly involved (Fig. 56.1).[3-6] In a meta-analysis of 223 published cases, bilateral optic nerve involvement was associated with younger age at presentation, with 72% of children <10 years experiencing bilateral disease and 70% of children ≥10 years with unilateral involvement.[4] Further, pain with eye movements is not a universal presenting symptom in pediatric optic neuritis.[3,5] Multiple retrospective studies have reported on the variable levels of vision loss at presentation, which range from minimal to severe, with excellent visual recovery of high-contrast acuity.[3,5] In one retrospective study of a large pediatric cohort with their first episode of optic neuritis, the primary risk factor for a poor high-contrast acuity at 1 year of <20/40 was lack of recovery to 20/20 vision at 3 months after the initial presentation.[3] Recent work has emphasized that low-contrast acuity highlights the persistent visual disability occurring after optic neuritis even when there is good recovery of high-contrast visual function.[7] Vision loss may be accompanied by visual field defects including, but not limited to, central or paracentral scotomata (Fig. 56.2). Optical coherence tomography (OCT) demonstrates damage to the retinal nerve fiber layer (rNFL) as well as the ganglion cell layer (GCL) after an episode of optic neuritis. These changes correlate well with visual function as measured by low-contrast acuity.[7,8] In the future, OCT changes may therefore become a useful metric in clinical studies of optic neuritis and demyelinating disease.

The diagnosis may be made in the context of the clinical symptoms and signs coupled with findings on magnetic resonance imaging (MRI). Contrast enhancement of the optic nerve is seen on T1-weighted MRI images, and hyperintensity of the optic nerve is evident on T2-weighted images (Fig. 56.3).

The treatment of pediatric optic neuritis is institution-dependent but typically involves intravenous (IV) methylprednisolone followed by an oral prednisone taper.[1,3,9] This strategy was derived from the corticosteroid regimen used in the landmark adult Optic Neuritis Treatment Trial, in which IV methylprednisolone followed by an oral prednisone taper was shown to hasten visual recovery.[10] This consideration is particularly helpful in pediatric patients when bilateral disease is present. Nevertheless, prospective data on the efficacy of corticosteroid treatment in pediatric optic neuritis are lacking. In patients with refractory vision loss, a multimodal approach including plasma exchange (PLEX) or administration of intravenous immune globulin (IVIg) is often used.[3] Since optic neuritis often occurs in the context of demyelinating disease, and indeed may be the initial presenting sign of a demyelinating condition, its management must involve both ophthalmology and neurology. Three primary considerations arise in children: multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), and neuromyelitis optica (NMO; also known as Devic disease). The reported incidence of an acquired demyelinating condition of the central nervous system (CNS) (including transverse myelitis) in children is

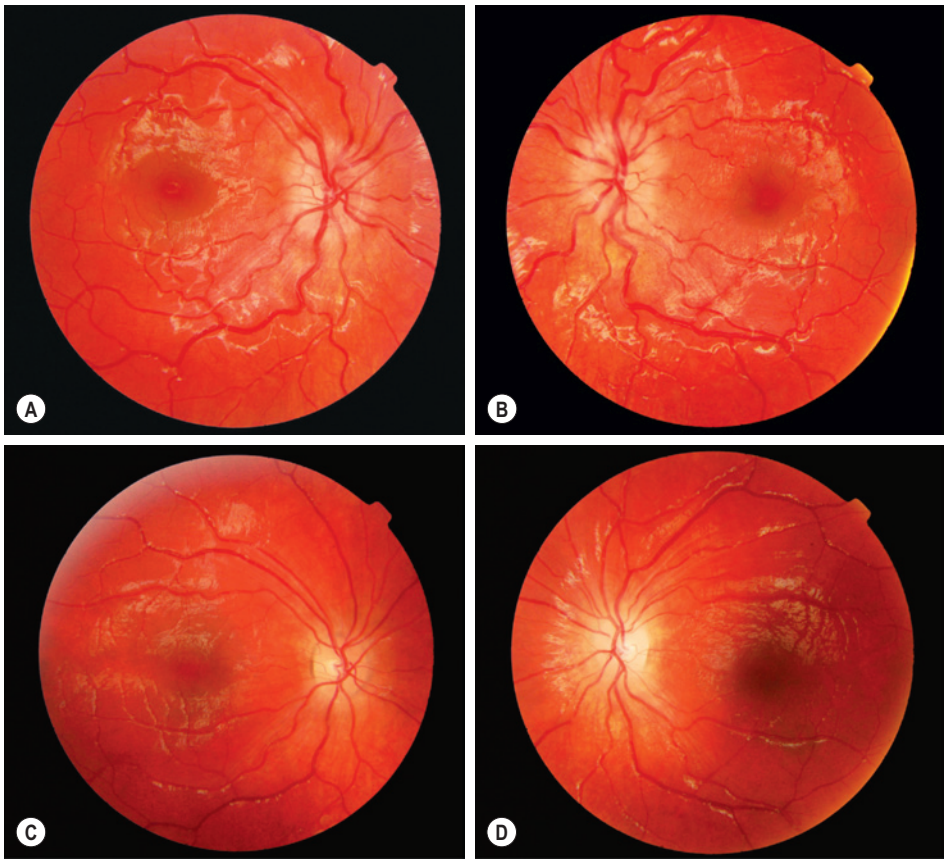
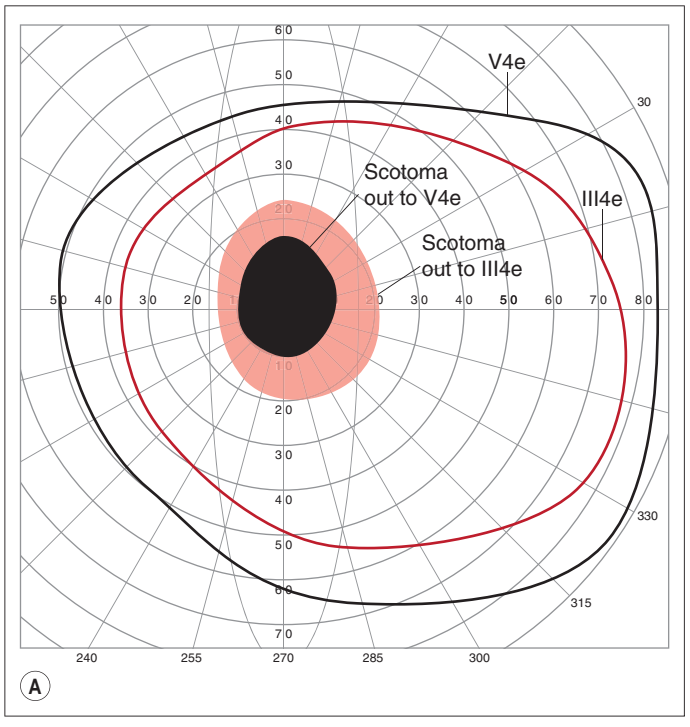


Fig. 56.1 Bilateral optic neuritis. Fundus photography revealing swollen right optic nerve (A) and left optic nerve (B) of a 7-year-old girl with bilateral optic neuritis. When she presented, she was legally blind with acuities of 20/400 right eye and light perception left eye. Three weeks following the initial presentation and after corticosteroid treatment, visual acuities recovered to 20/20 right eye and 20/25 left eye with resolution of optic nerve edema in both the right (C) and left (D) eyes.



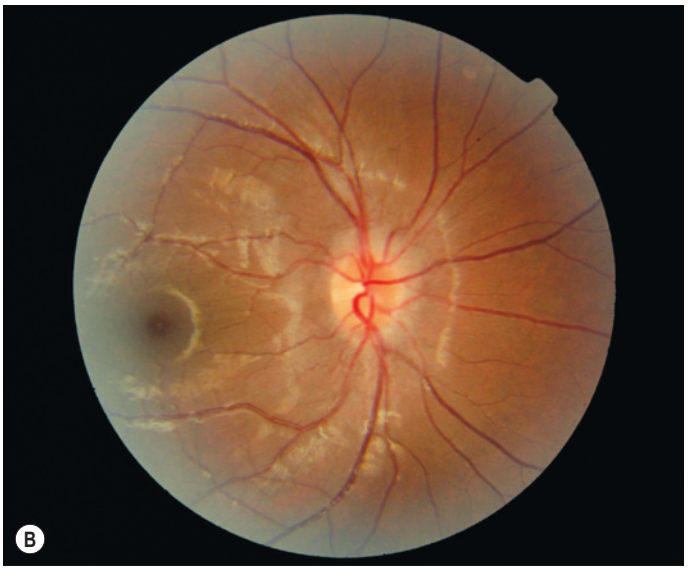


Fig. 56.2 Optic neuritis in a 16-year-old girl. Goldmann visual fields showing central scotoma right eye (A) and optic nerve edema right eye (B) in the setting of subacute vision loss to 20/80 right eye, dyschromatopsia, and a relative afferent pupillary defect right eye.

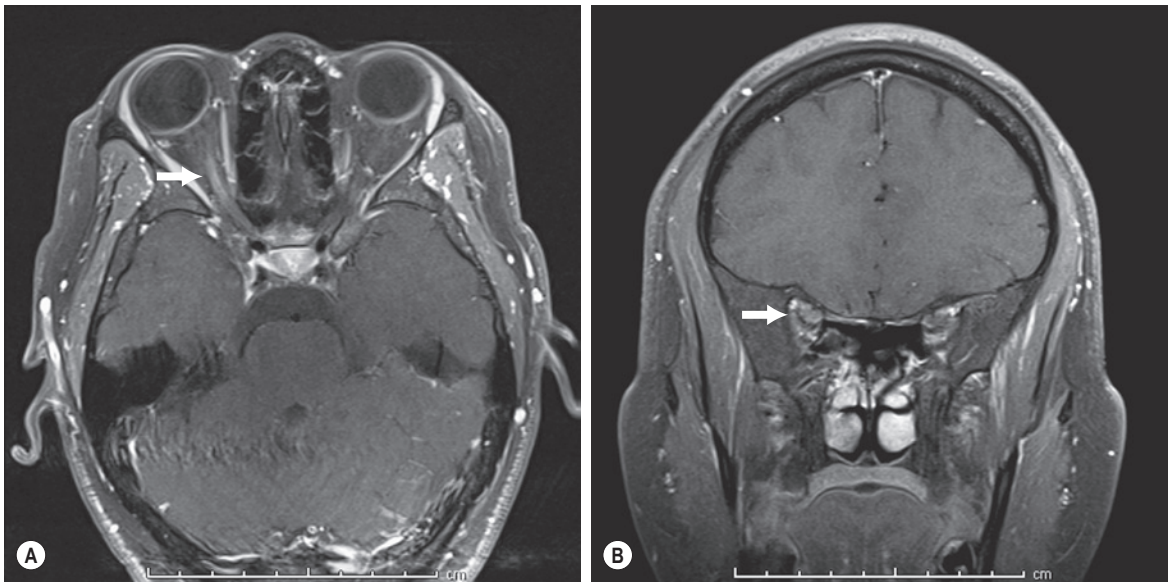


Fig. 56.3 Magnetic resonance imaging (MRI) findings in unilateral optic neuritis. T1-weighted post gadolinium MRI axial (A) and coronal (B) images revealing contrast enhancement of the right optic nerve (arrows) in the patient in Figure 56.2.

0.9 per 100,000 person-years in Canada and 1.66 per 100,000 person-years in a multi-ethnic California-based cohort.[11,12] Each condition is associated with a unique prognosis and treatment plan and therefore a careful evaluation for these conditions is essential in a child with optic neuritis.

The incidence of MS specifically in US children has been reported at 0.51 per 100,000 person-years with the relapsing-remitting form of MS. This form is far more common than the primary progressive form in pediatric patients.[12,13] In addition to optic neuritis, children presenting with MS may have accompanying ataxia, brainstem involvement, and encephalopathy, making it difficult to distinguish MS from other acquired demyelinating syndromes such as ADEM.[13] Many important studies have evaluated the risk of conversion to MS in children who present with first time optic neuritis. The conversion rate to MS in children has not been prospectively evaluated. However, as with adults, T2 lesions on MRI scan outside the visual system at presentation are associated with an increased risk of developing MS.[1,4,14,15] In addition, older age at presentation of optic neuritis has been found to be an independent risk factor for conversion to MS.[4]

Demyelination in ADEM is multifocal and may include optic neuritis, encephalopathy unrelated to fever, and irregular, large MRI lesions involving the white matter and potentially deep gray matter. ADEM is considered classically to be a monophasic condition, although multiphasic ADEM has been described.[16] Distinguishing ADEM from other demyelinating syndromes may be difficult at presentation. Recent studies have demonstrated a high proportion of children with ADEM to be positive for antibodies to myelin oligodendrocyte glycoprotein (MOG), which become undetectable at follow-up.[17] Presence of MOG-Ig antibodies may be associated with a better prognosis.[18]

NMO or Devic disease is a central nervous system inflammatory disorder affecting predominantly the optic nerves and spinal cord. The pathogenesis of NMO is distinct from MS, and in about 70% of cases it is associated with an NMO-IgG autoantibody, which targets aquaporin-4 water channels (AQP4) expressed in astrocytes.[19] The NMO-IgG antibody is not present in patients with MS.

Box 56.1

Diagnostic criteria for definite neuromyelitis optica[16]

Acute myelitis
Optic neuritis
Two of three additional supporting criteria:
- Aquaporin-4 immunoglobulin G seropositivity
- Non multiple sclerosis brain magnetic resonance imaging findings
- Longitudinally extensive transverse myelitis involving three or more vertebral segments

NMO appears to affect predominantly female patients and NMO-optic neuritis is associated with more profound, irreversible vision loss.[20] OCT reveals more severe rNFL thinning and evidence of microcystic macular edema in NMO-optic neuritis compared with MS-optic neuritis.[21] NMO should be considered in any case with severe bilateral optic neuropathy, particularly with evidence of transverse myelitis, although optic neuritis may precede the onset of transverse myelitis. The term "NMO spectrum disorder" is used for patients with some, but not all, of the disease-defining features. The diagnostic criteria for pediatric NMO are shown in Box 56.1.

On MRI, NMO-optic neuritis may involve longer segments of the optic nerve that extend more posteriorly towards the optic chiasm compared with MS-optic neuritis. Importantly, brain findings may be present in NMO, including large tumefactive lesions, but the periventricular white matter lesions seen in typical MS are generally not present.[22] Spinal cord involvement is classically characterized by longitudinally extensive transverse myelitis involving three or more vertebral segments (Fig. 56.4).[22]

Standard corticosteroid treatment may not be effective, and plasma exchange or IVIg may be required for an acute attack. Long-term immunosuppression to prevent relapse is the goal

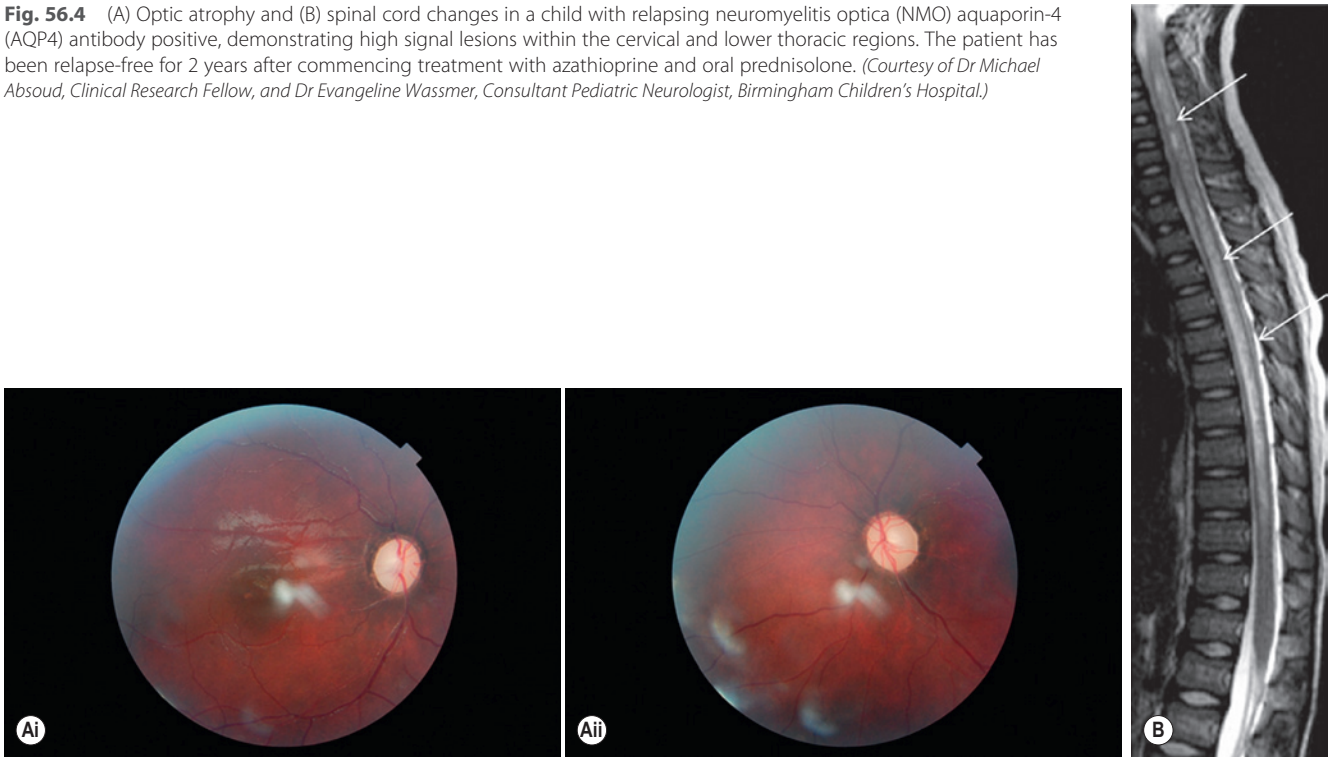


Fig. 56.4 (A) Optic atrophy and (B) spinal cord changes in a child with relapsing neuromyelitis optica (NMO) aquaporin-4 (AQP4) antibody positive, demonstrating high signal lesions within the cervical and lower thoracic regions. The patient has been relapse-free for 2 years after commencing treatment with azathioprine and oral prednisolone. *(Courtesy of Dr Michael Absoud, Clinical Research Fellow, and Dr Evangeline Wassmer, Consultant Pediatric Neurologist, Birmingham Children's Hospital.)*

of therapy using agents such as rituximab, mycophenolate mofetil, and azathioprine, and avoiding MS treatments thought to exacerbate NMO such as fingolimod.[23]

Para-infectious optic neuritis

Para-infectious optic neuritis following a febrile illness occurs in both children and in adults. In children, clinical symptoms of optic neuritis generally present 1–2 weeks after the febrile illness, with either unilateral or bilateral disease and optic nerve swelling.[24] Cases of para-infectious optic neuritis have been reported in association with *Mycoplasma pneumoniae*,[24] varicella,[25] rubeola,[25] mononucleosis,[25] and influenza B infection.[26] This form of optic neuritis is often responsive to corticosteroid treatment; an autoimmune process is thought to be implicated rather than primary infection of the optic nerves. Although the visual outcome is favorable, many children will have residual optic atrophy after an episode.[24,25]

Post-immunization optic neuritis

A link between optic neuritis and inoculation with a number of different vaccines including measles, rubella,[27,28] rabies,[29] meningococcus,[30] and influenza has been reported, based on vaccine administration a few days prior to the onset of optic neuritis. There is no conclusive evidence of an epidemiologic association between routine childhood immunization and optic neuritis.[31]

Chronic relapsing inflammatory optic neuropathy

Chronic relapsing inflammatory optic neuropathy (CRION) is a poorly understood inflammatory optic neuropathy characterized by recurrent optic neuritis that is highly sensitive to corticosteroid treatment. Kidd and colleagues first codified this entity and proposed the nomenclature of "CRION" in 2003 in their series of 15 patients with relapsing, isolated optic neuritis.[32] Since 2003, approximately 122 cases of CRION have been reported in the literature with an age range of 14–69 years.[33]

The characteristic features of CRION include pain with subacute vision loss, prompt response to corticosteroid treatment, and relapse upon cessation of corticosteroid treatment. The interval between episodes ranges from less than 1 year to years,[34] and the number of relapses has been reported to range from 2 up to 18 episodes of optic neuritis.[33] Involvement may be unilateral or bilateral, with simultaneous or sequential involvement of the optic nerves.[32,33] Commonly, vision loss is profound to the level of "counting fingers" or worse, with anterior optic nerve involvement.[32] Visual field changes are similar to those seen in demyelinating optic neuropathy, including central or paracentral scotomata or altitudinal visual field loss.[32] Visual outcome data are heterogeneous and limited. In one review of all published cases of CRION from 2003 to 2013, approximately 30% of affected patients had vision less than LogMAR 0.5 (Snellen 20/60) compared with 2% of adults with optic neuritis in the Optic Neuritis Treatment Trial.[33,35]

The diagnosis is one of exclusion and is established after careful assessment for underlying neurologic or systemic causes of optic neuritis that may include neuroimaging, lumbar puncture, and serologic testing. On MRI, contrast enhancement of the optic nerves should be seen in the acute phase. Otherwise, neuroimaging should essentially be negative, with the exception of non-diagnostic and non-specific T2 changes, which have been reported in patients with CRION.[32] In the acute phase of an episode of optic neuritis, IV methylprednisolone followed by an oral corticosteroid taper is used with or without adjunctive IVIg or plasma exchange.

With respect to chronic immunosuppression, a variety of agents have been tried including IVIg, mycophenolate mofetil, azathioprine, and methotrexate.[32,36] Importantly, in contrast to the demyelinating optic neuritis associated with MS, vision loss associated with CRION may be progressive without appropriate chronic immunosuppressive therapy.[33]

Infectious optic neuropathy

Neuroretinitis

Neuroretinitis is an inflammatory disorder characterized by optic nerve edema and the subsequent development of a macular star. Most commonly, unilateral involvement is seen, although bilateral cases have been reported (Fig. 56.5). The formation of the macular findings is thought to occur because of increased permeability of the optic disc vasculature with leakage of fluid into the peripapillary retina.[37] Fluorescein angiography shows an arteriolar vasculitis on the optic disc. The macular star has a characteristic perifoveal appearance.

An underlying infectious cause is common; the most frequent etiologies are *Bartonella henselae* (cat scratch disease) or *Borrelia burgdorferi* (Lyme disease). Neuroretinitis has been reported in association with syphilis, tuberculosis, leptospirosis, and toxoplasmosis.[38] Therefore, serologic testing should be performed to assess etiology. Although spontaneous recovery may ensue, many ophthalmologists will treat neuroretinitis before an underlying etiology can be confirmed. Specifically in the setting of cat scratch disease, doxycycline, azithromycin, and rifampin have all been used.[39]

Other infectious optic neuropathy

Many infectious agents have been associated with the development of an optic neuropathy. Spirochetes associated with optic neuropathy include *Borrelia burgdorferi*, causing Lyme disease, and *Treponema pallidum*. A fungal optic neuropathy may occur in immunosuppressed patients, most commonly due to *Cryptococcus neoformans*. Although cytomegalovirus optic neuropathy is usually associated with juxtapapillary retinitis, cases with optic neuropathy in the absence of retinitis have been described,[40] presumably due to direct invasion of the retrolaminar optic nerve. Optic neuropathy may occur primarily due to human immunodeficiency virus type 1 (HIV-1) infection rather than secondary to opportunistic infections.[25]

Infiltrative optic neuropathy

Leukemic infiltration (see Chapter 67)

Leukemic optic disc infiltration tends to be associated with central nervous system relapses, and it may be the presenting feature of relapses among patients in prolonged remission. The affected nerves appear swollen and may have surface hemorrhages. However, no disc appearance is diagnostic. Optic nerve involvement may be seen in association with leukemic retinopathy, which is characterized by tortuous vessels, dilated veins, retinal hemorrhages, and cotton-wool spots. MRI may show perioptic nerve infiltration.[41] About 90% of the cases of optic nerve involvement occur in the acute forms of leukemia.

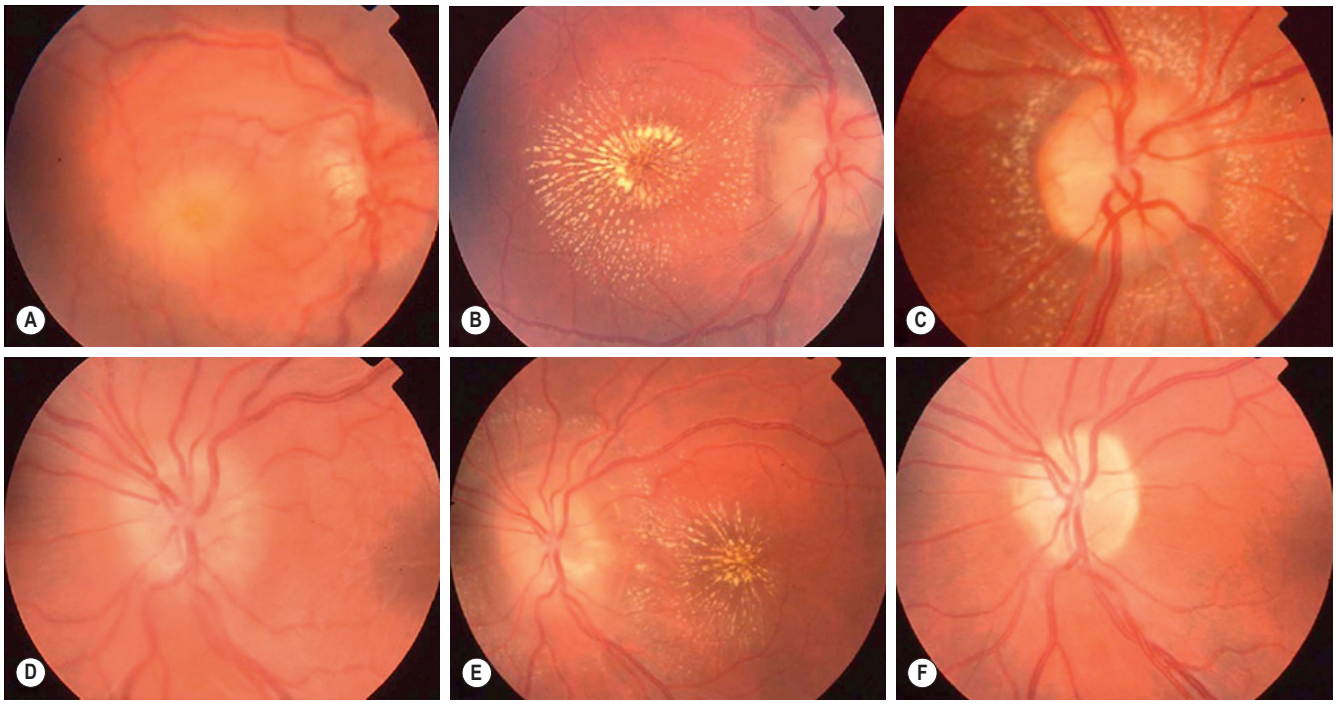


Fig. 56.5 Stages of evolution of fundus changes in neuroretinitis. (A) At presentation the optic disc is swollen and the macula has an opaque appearance. (B) Three weeks later, there is a well-formed macular star. (C) Further resolution leading later to optic atrophy. (D–F) Neuroretinitis in the left with resultant optic atrophy in the fellow eye. *(Reproduced with permission of Dr Valerie Purvin, Midwest Eye Institute, USA; from Purvin V, Sundaram S, Kawasaki A. Neuroretinitis: review of the literature and new observations. J Neuro-ophthalmol 2011; 31: 58–68.)*

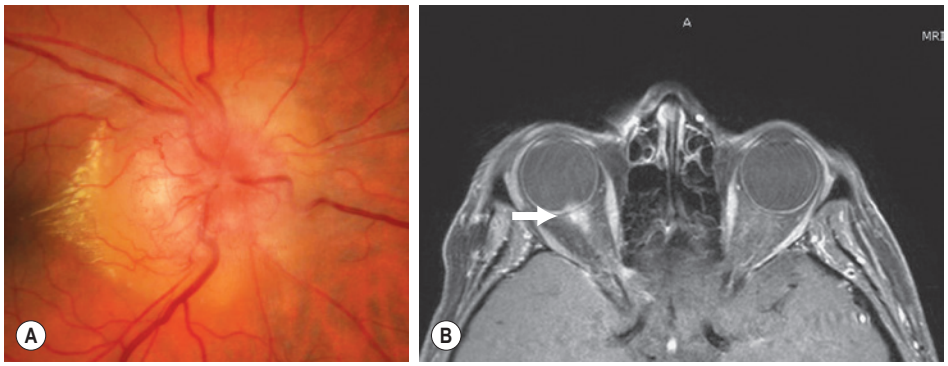


Fig. 56.6 Sarcoid granuloma of the optic nerve. (A) Optic nerve head edema secondary to infiltration from sarcoidosis. (B) Axial, enhanced T1- weighted magnetic resonance image showing contrast enhancement at the neuro-ocular junction and of the right optic nerve head (arrow). *(Courtesy of Dr Joseph Rizzo, Director Neuro-ophthalmology Service, and Dr Katherine Boudreault, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA.)*

Optic nerve involvement in leukemia is an emergency. Without prompt diagnosis and treatment, permanent and catastrophic loss of vision may occur. The optic nerve and meninges are pharmacologic sanctuary sites where leukemic cells are resistant to systemic chemotherapy. Intrathecal chemotherapy doses of primary treatment may be inadequate to destroy leukemic cells in the optic nerve, hence the propensity for recurrence at this site. Urgent low-dose radiotherapy to the orbital apex may be sight-saving in this context.[42,43]

Sarcoid-related optic neuropathy

Sarcoidosis is a multisystem inflammatory condition characterized by the development of non-caseating granulomas with predilection for the lungs. Neurosarcoidosis is the term used to describe sarcoidosis that involves the CNS, and is a rare manifestation of the disease. Data are limited regarding neurosarcoidosis and include few large case series and many smaller case reports.[44-46] In neurosarcoidosis, cranial neuropathy, may occur with the development of optic nerve granulomas. In one study of 54 predominantly adult patients, optic neuropathy both unilateral and bilateral, was the most commonly observed presentation, affecting 35% of patients. Bilateral involvement was associated with a poorer visual recovery: 7/13 bilateral patients in this series had an acuity of <20/200 in one eye at follow-up.[45] Although the clinical presentation in children is thought to be similar to adults, increasingly studies have demonstrated that in addition to cranial neuropathy, many children may present with seizures.[44,46] Although uncommon in children, sarcoid granuloma of the optic nerve should be included in the differential diagnosis of an inflammatory optic neuropathy, particularly if there is indication of both optic neuritis and/or perineuritis on neuroimaging (Fig. 56.6). Corticosteroid treatment is the mainstay of initial therapy.

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The optic chiasm

Michael C Brodsky

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Introduction

The chiasm is so named because it is shaped like the Greek letter chi.[1] Over 2 million nerve fibers pass through it: most are visual, but some non-visual fibers project from the optic chiasm to hypothalamic nuclei, forming the retinohypothalamic tract subserving circadian rhythms.[2] The ratio of crossed to uncrossed fibers in the human chiasm is about 53:47.[3]

Evolutionary considerations

The chiasm provides the major route for the juxtaposition of corresponding parts of the visual field in each eye. It is important for binocular vision. To establish fusion, it is necessary to have overlapping visual fields, congruence of corresponding retinal elements, and for the extraocular muscles to maintain alignment of the visual axes.[4] In lateral-eyed animals, optic fibers from each eye decussate entirely to the contralateral hemisphere. The percentage of uncrossed fibers increases as the orbits rotate anteriorly and the frontal field of single binocular vision increases.[5] The reason that our visual system is crossed is controversial[5,6] (Fig. 57.1).

In humans, there is more retina nasal to the fovea than temporally, so the right eye covers more right visual field than left visual field. The primordial nasal retinas are concerned with a phylogenetically older "panoramic" function. The temporal retinas have entered into a phylogenetically younger "binocular" function.

Our foveas are placed where nasal (panoramic) and temporal (binocularity-providing) retinas intersect.[6] This allows vision to subserve its elemental functions, namely:

- Exploration (mobility)
- Detail (foveas)
- Stereopsis (binocularity).[6]

Exploration of the surround is a primordial panoramic function of the nasal retinas, while binocular vision, stereopsis, and convergence concern the temporal retinas.

Anatomy

The optic nerves, chiasm, and optic tracts extend posteriorly and upward 45° from the optic canals in adults and children.[7] The chiasm lies in the suprasellar cistern several millimeters above the diaphragma sellae. The anterior cerebral arteries and the anterior communicating arteries lie anteriorly and above the chiasm and optic nerves. The carotid arteries lie laterally, with the posterior communicating artery passing underneath the optic tracts. The chiasm lies in the floor of the anterior end of the third ventricle. Expansion of the third ventricle may cause chiasmal compression. Posteriorly lie the hypothalamus and the pituitary stalk, the tuber cinereum, and the mamillary bodies. The optic nerves emerge from the optic canals. The length of the intracranial optic nerve varies, so the position of the chiasm in relation to other structures also varies. When the optic nerves are short, the chiasm is "prefixed," when long it is "postfixed." Von Willebrand's knee is an artefact.[8]

Embryology

The chiasm appears in the first month of life,[9] arising from a thickening of the floor of the forebrain. Retinal ganglion cells (RGCs) grow down the optic stalks and enter the floor of the third ventricle where they decussate to form the optic chiasm.

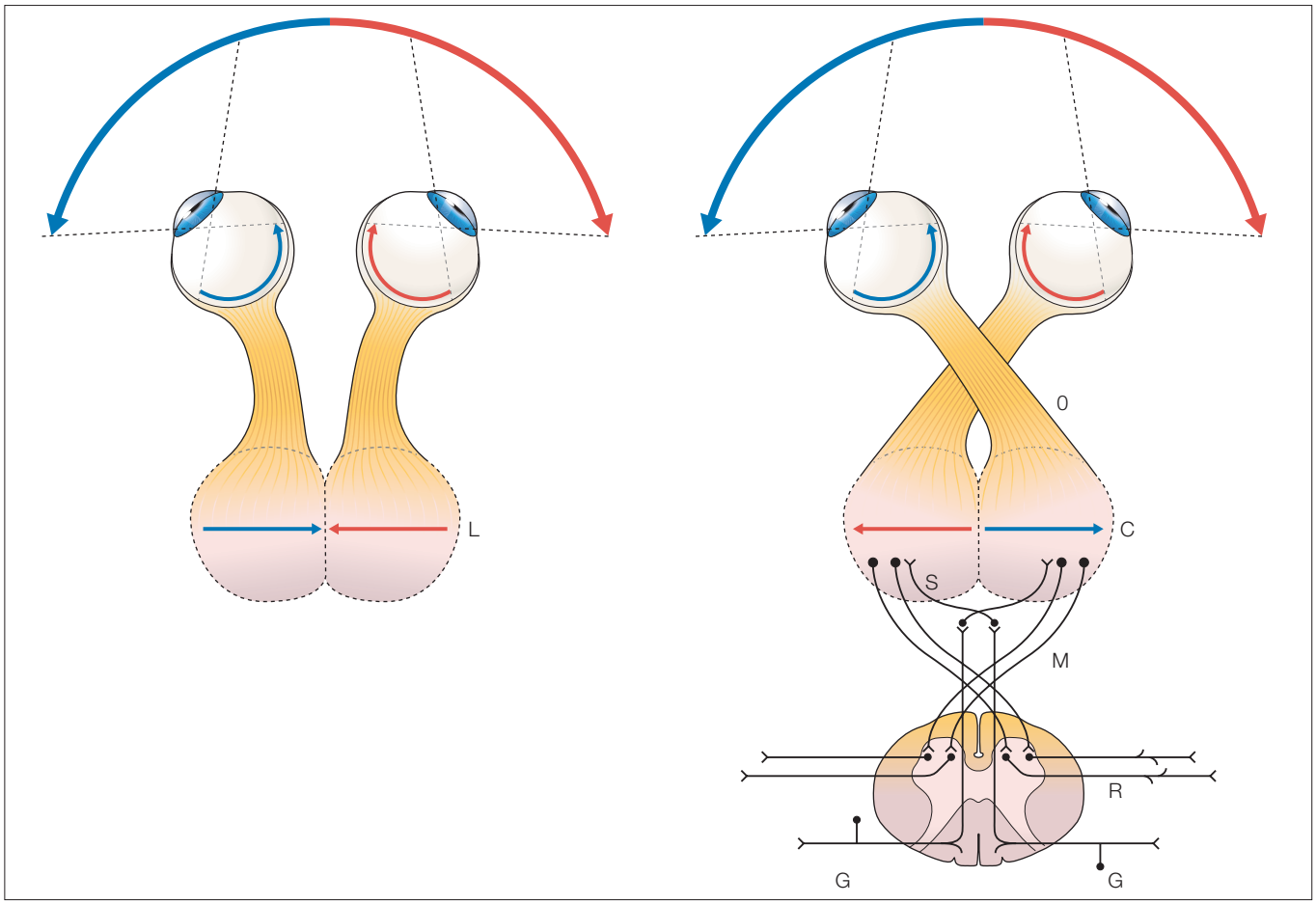


Fig. 57.1 Ramón y Cajal's original diagram of the hypothetical uncrossed chiasm (left). On the right is the completely crossed chiasm in lateral-eyed animals. *(With permission from Polyak S. In: Kluver H, editor. The Vertebrate Visual System. Chicago, IL: University of Chicago Press, 1957.)*

The pattern of axon crossing occurs in two phases.[10] The first retinal axons meet in the midline at the ventral diencephalon, forming an X-shaped chiasm; subsequent axons grow into either the ipsilateral or contralateral optic tract.[11]

A morphological specialization of the axon called a growth cone allows the axon to sense and respond to signals in the embryonic brain environment.[12] Neuronal and glial cells provide guidance information to ingrowing RGC axon. Histologic evidence suggests that uncrossed axons are confined within the lateral portion of the optic nerve and do not approach the chiasmal midline.[13] Neurons and radial glial cells in the ventral diencephalon serve a role in RGC axon guidance during chiasm formation. Growth-associated proteins in retinal growth cones enable RGC axons to progress and perform path-finding tasks. In the mouse, neurons at the site of the future chiasm are required for its formation by retinal ganglion cell axons. A growth-associated protein essential for chiasm formation has been identified.[14] There is substantial overproduction of neurons which later die back by apoptosis.[15] The chiasm reaches its definitive form by the fourth month of gestation.

Transcription factors that pattern the developing chiasm have been identified.[16–19] Foxd1 expressed in the developing temporal retina and its downstream effectors (tyrosine kinase membrane proteins) are involved in patterning of the optic chiasm in chicks and mammals.[17,18] Foxd1 imprints axons ipsilaterally. Foxd1 is expressed in progenitors of Zic2-positive retina ganglion cells and is the determinant of temporal retinal identity.[17,18] Neuropilin molecules, transmembrane proteins, serve as receptors for axonal guidance to regulate axon divergence at the chiasm in mammals.[19] Neuropilin 1 (NRP1) is expressed at the chiasm midline, and acts on contralateral retinal ganglion cells to provide growth-promoting and chemo-attractive signals for commissural axon crossing at the chiasm.[19] Ventral anterior homeobox 1 (Vax1) has also been found to possess retinal ganglion cell growth factor activity that is necessary for chiasmal development in the mammalian binocular visual system.[20]

Signs and symptoms

Developmental defects and suprasellar tumors are common in children (Box 57.1). Most chiasmal syndromes result from neoplastic disorders, developmental derangements, radiation injury, inflammation, infection, demyelination, infarction, transection, or hypoplasia.[21] Dominant optic atrophy may present with a bitemporal hemianopia simulating a chiasmal disorder.[21]

In young children, chiasmal disease often presents late because the child compensates and is not suspected of having poor vision until there is substantial bilateral visual loss.

Box 57.1

Signs and symptoms of chiasmal disease

Symptoms

Loss of stereopsis
Postfixational blindness
Loss of motor fusion
Hemifield slide
Bitemporal hemianopia
Bagolini striated lenses "mountain" pattern
Worth Four Dot (selective loss of temporal green dot as viewed through green lens)

Signs

Large pupils/sluggish pupillary responses/light near dissociation
Small optic discs (for congenital tumors)
Bilateral band atrophy (for acquired lesions)
"Spasmus nutans" in infancy
See-saw nystagmus
Monocular temporonasal optokinetic asymmetry

The hallmark of chiasmal disease is a bitemporal hemianopia. Some form of visual field testing is essential. Inferior lesions have to grow large before signs of chiasmal compression appear. They compress the lower nasal fibers first and tend to give an upper bitemporal field defect. Lesions from above tend to cause an inferior defect. By the time a compressive lesion has caused defects, there is usually thinning of the chiasm and the pattern of the field defect is not always clear-cut.

There is often an acuity defect. Chiasm-splitting lesions, such as trauma, do not affect acuity greatly because the nasal field and the nasal half of the fovea is not affected, but involvement of the optic nerve or widespread involvement of both crossed and uncrossed fibers in the chiasm give rise to an acuity defect. Frequently, one eye has a very severe acuity defect and the other is relatively spared, except for a field defect. In chronic lesions, there is often preservation of a high level of acuity despite funduscopic evidence of a profound loss of neurons.

With optic nerve involvement, there is significant color vision defect. Some patients notice postfixational blindness (e.g. noticing that the road disappears when looking at the front windshield glass from the inside of the car). When there is chiasmal compression, the pupils may be large and sluggishly reactive to light, resulting in light-near dissociation. Stereoacuity tests and Bagolini striated lens are useful tests in patients with suspected chiasmal compression.[4] Decreased stereoacuity is common with chiasmal lesions, even when no visual field abnormalities are detectable.[4] However, stereopsis can be elicited with complete chiasmal transection by haploscopic stimulation of the intact temporal retinas.[22] This shows the sensory capacity for stereopsis is retained in chiasmal transection, but the absence of motor fusion precludes stereopsis.[23] A valuable and underutilized diagnostic test involves testing Titmus stereoacuity with the book held upright, then turning the Titmus book upside-down and repeating the test. Viewing the Titmus stereoacuity book upside-down normally causes the circles to appear retruded into the page, because the figures are monocularly displaced onto each nasal retina and defective temporal field. In chiasmal disease, this stereoscopic retrusion cannot be readily appreciated, because of the bitemporal hemianopia. Thus, the finding of an "inverse Titmus stereoacuity" that is lower than the upright Titmus stereoacuity should signal chiasmal disease. In chiasmal disease, the upside-down Titmus test furnishes figures that are monocularly displaced onto each nasal retina and defective temporal field, resulting in a more severe stereoacuity deficit relative to the upright Titmus test. Bagolini striated lens testing reveals a binocular "mountain" pattern in chiasmal lesions.[24] Children with early-onset chiasmal disease may present with nystagmus. The classic form is a spasmus nutans-like nystagmus with variable head titubation, but isolated see-saw nystagmus can also occur (see Chapter 89). Loss of chiasmal crossing fibers also causes loss of monocular nasalward horizontal optokinetic responses in each eye. In young children in whom reliable visual fields are not easily obtained, we have found this monocular temporonasal optokinetic asymmetry to be a useful clinical clue to the presence of chiasmal disease.[25]

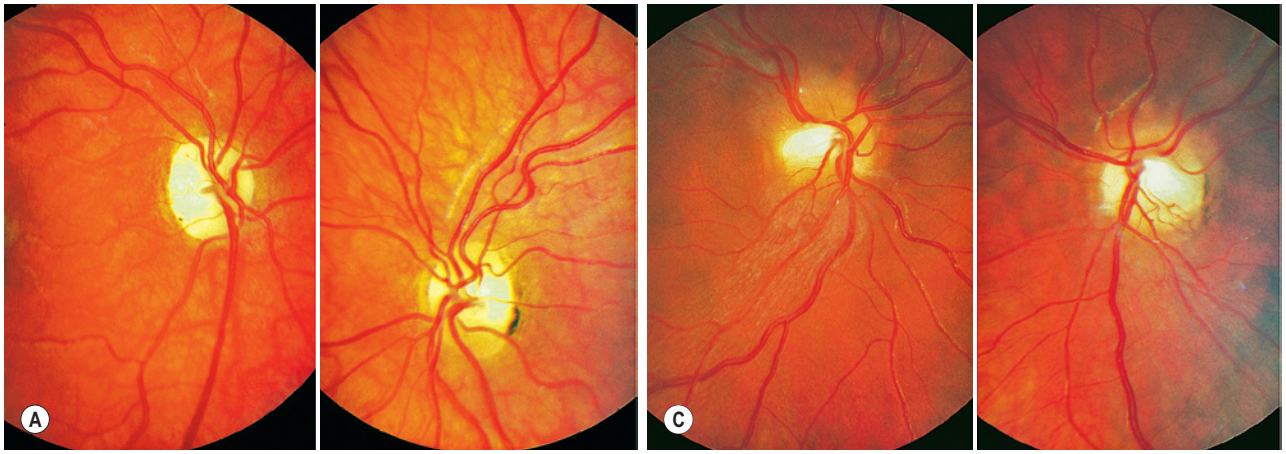
Optic atrophy frequently occurs in chiasmal disease. There may be a generalized loss of neurons, or a pattern of band atrophy due to the loss of fibers subserving the temporal fields and the preservation of fibers subserving the intact nasal field (Fig. 57.2). In developmental chiasmal defects and tumors, there are often optic disc anomalies (Figs 57.3 and 57.4).[26,27] Congenital suprasellar tumors can produce horizontal "bow-tie" cupping with selective loss of the nasal and temporal nerve fiber layer.[28] Papilledema in these optic discs occurs predominantly in the superior and inferior poles (see Fig. 57.2C).

Because of the proximity of the hypothalamus and pituitary gland, endocrine and growth defects may occur. Infants with hypothalamus-involving tumors may develop Russell diencephalic syndrome: emaciation with loss of subcutaneous fat (Fig. 57.5), accelerated growth in length relative to weight (Fig. 57.6), and personality changes with euphoria and hyperactivity. One must examine and measure the infant's body habitus and inquire about weight gain.

In bitemporal hemianopia, the hemifield slide phenomenon may occur (Fig. 57.7). Since only the nasal portion of each visual field is functioning fully, corresponding retinal points between the two eyes no longer exist. Sensory fusion becomes impossible, and motor fusion cannot maintain alignment. A previous heterophoria becomes a manifest deviation. Esodeviations lead to letters or words appearing deleted. Exodeviations produce letters or words appearing duplicated. A vertical hemifield slide causes the child to lose track of which line of text they are reading. These children do not complain of diplopia but rather a duplication of the middle of words or objects. The hemifield slide phenomenon does not require a complete bitemporal hemianopia, and can occur as the initial symptom.[29] Signs and symptoms of chiasmal disease are summarized in Table 57.1. Rarely, chiasmal tumors can produce photophobia as their presenting symptom.[30]

Further investigations

Further investigations consist of endocrine studies, neurophysiological evaluation (see Chapter 9), and neuroimaging. Optical coherence tomography of the macular ganglion cell layer is highly sensitive to binasal retinal nerve fiber layer thinning resulting from congenital or acquired chiasmopathies. Neurophysiological studies may detect a crossover defect (particularly in a preverbal child) and quantitatively



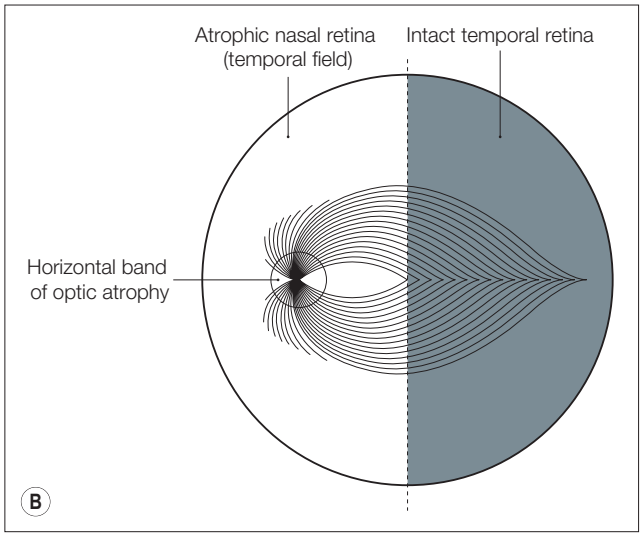


Fig. 57.2 Craniopharyngioma. (A) The right eye has bare perception of hand movements. The left eye has an absolute temporal hemianopia, normal color vision, and a visual acuity of –0.1 LogMAR (6/4.8, 20/16, 1.25). The left optic disc shows band atrophy: there is loss of the nerve fibers that subserve the temporal visual field but preservation of those that subserve the nasal field, which are inserted into the upper and lower segments of the disc. (B) The origin of the band of atrophy is due to the fact that the horizontal band or bow-tie area is the visible area of atrophy where temporal field fibers alone are inserted into the disc. (C) Craniopharyngioma showing "bi-lobed" papilledema during a period of raised intracranial pressure. Since papilledema occurs only when the retinal ganglion cell axons are swollen and only the superior and inferior (nasal field) axons survive in chiasmal compression, the papilledema occurs only in the upper and lower poles giving bi-lobed or "twin peaks" papilledema.

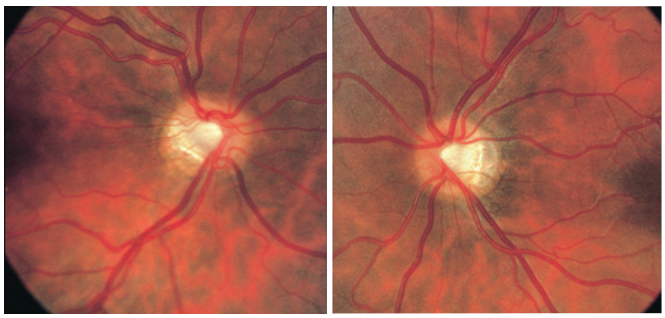


Fig. 57.3 Craniopharyngioma. Bilateral segmental hypoplasia or "tilted" optic disc. Bitemporal hemianopia with a visual acuity of –0.1 LogMAR (6/4.8, 20/16, 1.25) right eye (refraction: –4.0 D) and –0.22 (6/3.6. 20/12, 1.67) left eye (–4.50 D).

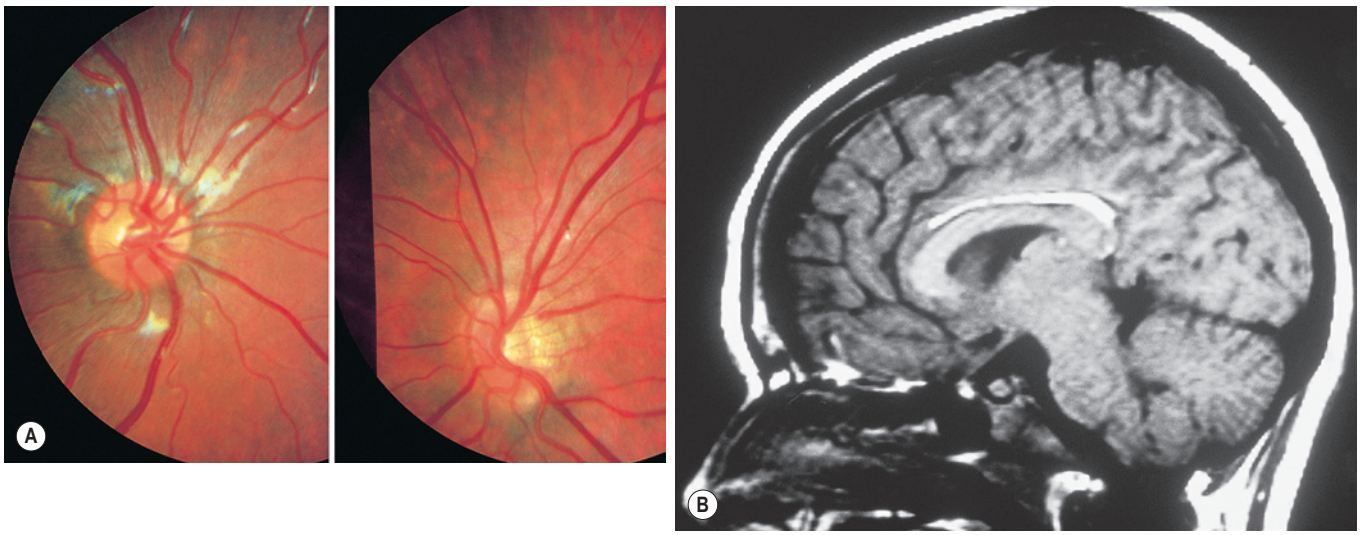


Fig. 57.4 Midline facial defect. (A) Dysplastic tilted left optic disc in a patient with a midline facial defect. (B) Magnetic resonance imaging of corpus callosum lipoma in a patient with a midline facial defect.

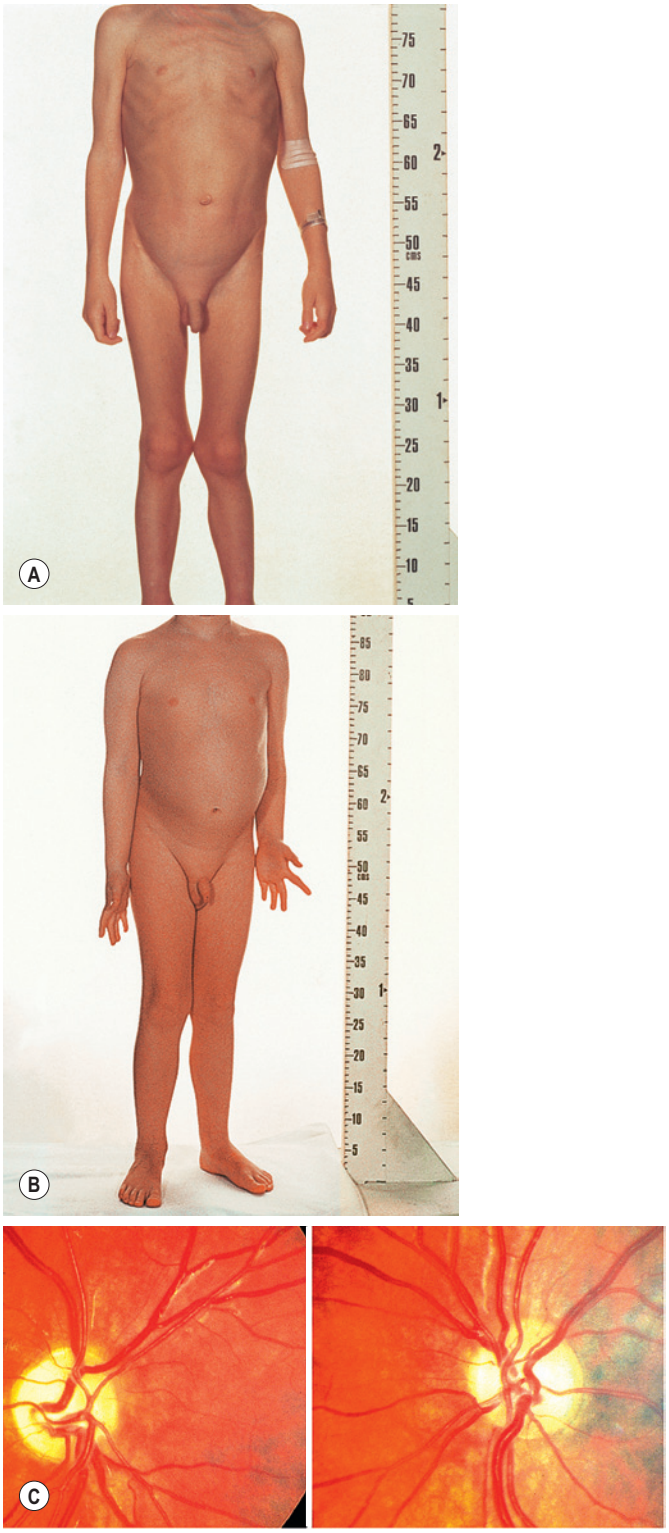


Fig. 57.5 Chiasmal glioma. (A) This boy presented with poor vision and recent weight loss – photograph on 12 February 1973. (B) Photograph on 31 January 1974 showing rapid growth in weight and height. Weight and growth rate fluctuation are common in chiasmal glioma. (C) Bilateral band atrophy (same patient).

and qualitatively assess the visual defect. Magnetic resonance imaging (MRI)[31,32] provides neuro-anatomical detail of the chiasm and surrounding structures. Computed tomography (CT) scanning may provide important information about bony changes involving the parasellar area.

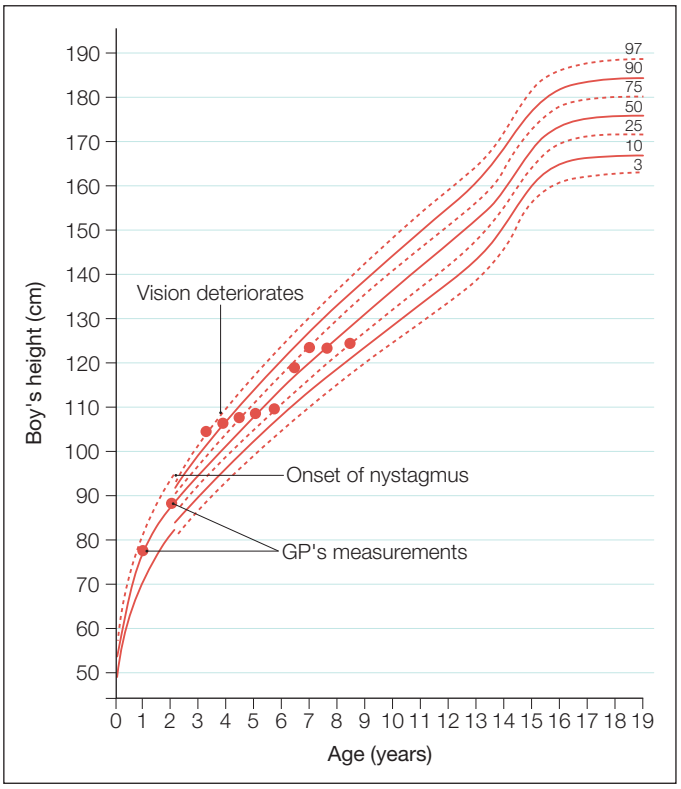


Fig. 57.6 Height growth record of a child with chiasmal glioma showing height growth rate fluctuation. Pediatric ophthalmology clinics need to have these charts available.

Developmental defects

Developmental derangements of the optic chiasm include:

- Albinism
- Achiasmia
- Aplasia
- Anophthalmia

Albinism (see Chapter 41)

Anomalous decussation of chiasmal projections occurs in persons with albinism.[24] Retinogeniculate axons arising from ganglion cells in the portion of the temporal retina within 20° of the vertical meridian decussate abnormally in the optic chiasm to synapse in the contralateral lateral geniculate nucleus.[33–35] The human optic chiasm has a predominance of crossed fibers. Albinism is associated with smaller optic nerves, chiasm, and tracts and a wider angle between the optic nerves and tracts.[36] The crossed predominance can be diagnosed electrophysiologically by finding asymmetrical hemispheric visual evoked potentials[37,38] (Fig. 57.8; see Chapters 9 and 41). Pigment around the optic disc plays an important role in axonal guidance, suggesting that loss of retinal epithelial pigment could be the source of chiasmal misrouting in albinism.[39] Recently, the role of the transcription factor Zic2 has been implicated in the chiasmal misrouting in albinism.[40]

Achiasmia

Belgian sheep dogs with achiasmia have congenital and see-saw nystagmus.[41,42] Two unrelated girls with achiasmia had normal

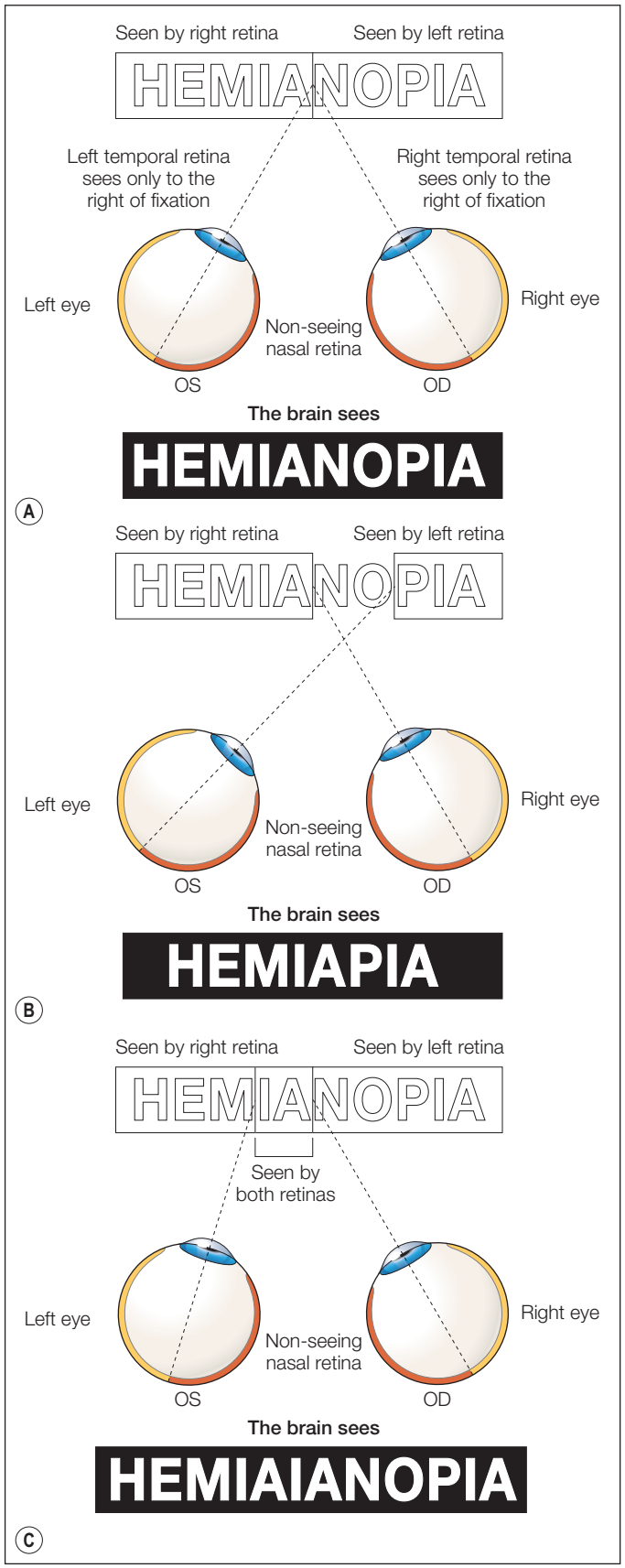


Fig. 57.7 Hemifield slide phenomenon. *(From Fritz KJ, Brodsky MC. Elusive neuro-ophthalmic reading impairment. American Orthoptic Journal 1992; 42: 159–164. Reprinted by permission of The University of Wisconsin Press.)*

Table 57.1 Chiasmal diseases in children

Category	Disease/disorder
Developmental defects	Albinism Achiasmia Aplasia Anophthalmia
Tumors	Chiasmal glioma Craniopharyngioma Pituitary adenoma Dysgerminoma Retinoblastoma ("trilateral")
Trauma	Transection Hematoma Contusion Traction
Infiltration	Langerhans cell histiocytosis Sarcoidosis Juvenile xanthogranuloma
Chiasmal neuritis	Postviral Postimmunization Multiple sclerosis
Optochiasmatic arachnoiditis	Tuberculosis Neurosyphilis Fungal Cysticercosis
Vascular anomalies	Arteriovenous malformation Cavernous angioma
Radiation	Acute visual loss months to years after radiation
Empty sella	Third ventricular distension secondary to aqueductal stenosis Downward traction on chiasm secondary to surgical scarring on pituitary apoplexy

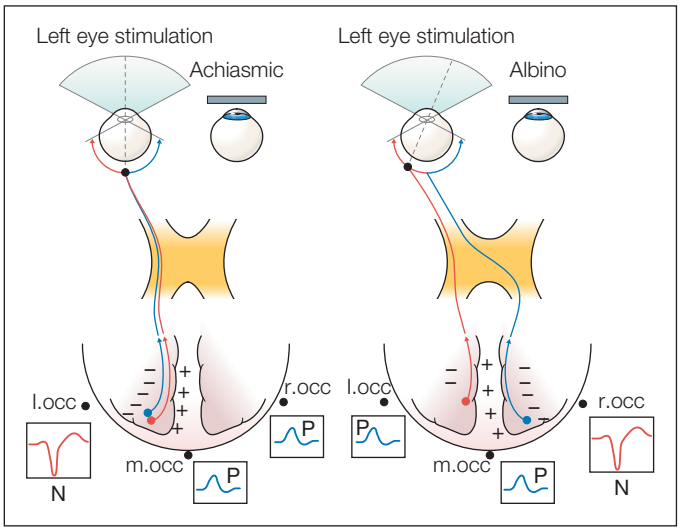


Fig. 57.8 Schematic comparing the visual pathway and visual evoked potential (VEP) distribution in albino and achiasmic patients for flash stimulation of the left eye. Stimulation of the right eye produces the mirror image distribution for either condition. In the achiasmic subject, all the visual fibers from the left eye project to the left occipital cortex, and at 80–100 ms a positivity is recorded over the right scalp and a negativity over the left. In contrast, most of the fibers from one eye cross at the chiasm in albinism, and the VEP distribution is the opposite, with a positivity recorded over the left scalp, and negativity over the right. *(Courtesy of Dr Dorothy Thompson.)*



Fig. 57.9 Achiasmia in a child who presented with a cleft lip and palate: see-saw nystagmus. (A) Coronal magnetic resonance imaging (MRI) and (B) sagittal MRI showing a large encephalocele completely dividing the chiasm. (C) The encephalocele protruding through the hard palate. *([A,B] Photographs courtesy of Dr Dorothy Thompson.)*

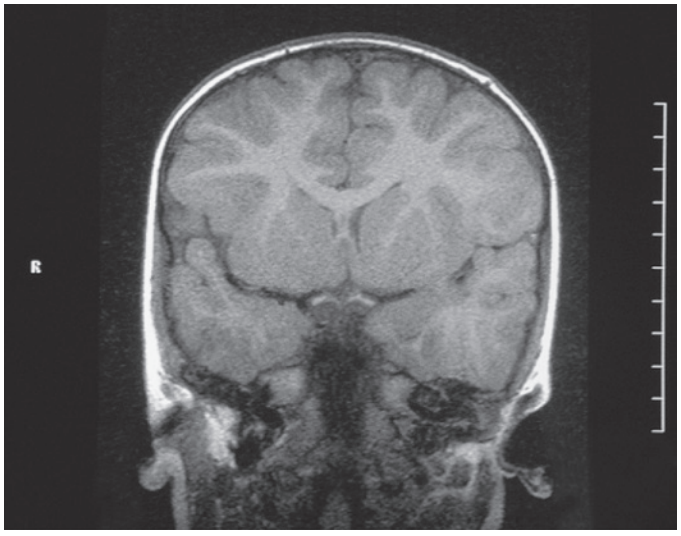


Fig. 57.10 Chiasmal hypoplasia. The chiasm is divided into two halves that are joined by a fragment of tissue. Electrophysiologically the patient was achiasmic. *(Photograph courtesy of Dr Dorothy Thompson.)*

visual fields and no stereoacuity.[43] Eye movement recordings showed congenital nystagmus in the horizontal plane and see-saw nystagmus in the vertical and torsional planes. MRI showed absence of the chiasm, with each optic nerve projecting entirely to the ipsilateral hemisphere. The polarity of the visual evoked potential (VEP) distribution across the occiput was the reverse of the crossed asymmetry that has been described in albinism (see Fig. 57.8).[44] Altered expression of transcription factors such as NRP1, which promotes contralateral axon projection in mammals, may be found to produce achiasmia.[18]

Achiasmia may be complete (Fig. 57.9) or partial (Fig. 57.10). Patients with bilateral optic nerve hypoplasia invariably have chiasmal hypoplasia; those with unilateral optic nerve hypoplasia have selective hypoplasia of the ipsilateral side of the chiasm.[45] Patients with isolated chiasmal hypoplasia may have segmental optic nerve hypoplasia confined to the nasal and temporal sectors of the optic discs.[46,47] Chiasmal anomalies have been described in patients with midline defects in the brain, midfacial defects, and basal encephaloceles.[48–50]

Aplasia and anophthalmia

Unilateral anophthalmos or optic nerve aplasia produces an asymmetrical chiasm.[51] Bilateral anophthalmia or optic nerve aplasia is usually associated with absence of optic nerves, chiasm, and lateral geniculate bodies,[52–54] although some show remnants of the optic nerves and chiasm.[55] In mice, prenatal removal of one eye produces a preponderance in crossed fibers from the other eye, whereas postnatal removal of one eye produces an increase in the surviving uncrossed component.[35] Patients with unilateral optic nerve aplasia may show crossed hemispheric VEP asymmetry.[51] Loss-of-function mutations in *ALDH1A3* can cause anophthalmia/microphthalmia with hypoplasia of the optic nerve and chiasm by reducing retinoic acid synthesis, which is critical for normal ocular morphogenesis and downstream signaling.[56]

Trauma

Following closed head trauma, a child may develop an absolute bitemporal hemianopia and poor acuity and color vision if there is also damage to the non-crossing fibers or optic nerve.[57] Damage to surrounding structures may lead to diabetes insipidus, anosmia, cerebrospinal fluid rhinorrhea, growth defects, and mood changes. Traumatic enucleations can produce tractional injury to the optic chiasm and a temporal hemianopic defect in the other eye.[58]

Tumors

The peculiar geometry of the optic chiasm may render its midportion more vulnerable to deformation stress exerted from below. Despite its anatomic vulnerability to compression by suprasellar tumors, the optic chiasm is surprisingly resistant to compression.[59] Frisén and Jensen found an elevation of 6 mm is necessary to produce visual field defect in 50% of patients, and an additional elevation of 5 mm to produce visual field defects in 90% of patients.[60]

Chiasmal glioma

Chiasmal, optic nerve, and hypothalamic gliomas are closely related; they may show common histopathological features and clinical behavior. All occur with increased frequency in neurofibromatosis (NF).[61] It may occur in Beckwith–Wiedemann syndrome – macrosomia, macroglossia, encephalocele, hemihypertrophy, hepatomegaly, and advanced bone age.[62]

Infants with large chiasmal–hypothalamic glioma can present with Russell diencephalic syndrome. The main features are emaciation despite a normal or only slightly diminished caloric intake, alert appearance, hyperkinesis or increased vigor, euphoria, skin pallor, irritability, and normal or accelerated linear growth (see Fig. 57.5). These infants usually have large chiasmal gliomas. Radiation therapy can induce dramatic tumor shrinkage and long-term regression of clinical abnormalities.[63,64]

Small children often present with a compound nystagmus, typically see-saw in nature (see Chapter 89). Any child with a compound nystagmus with rotary, vertical, and horizontal elements should be suspected of having a chiasmal lesion.[65] Visual loss is often profound before it is noticed, but in older children the visual defect may be noticed by the child or detected by school visual testing. Some large optic gliomas may have no gross visual defect.[66] Chiasmal gliomas may affect growth and development. An unusual presentation is the "bobble-headed doll syndrome." This is usually an indication of hydrocephalus.

The diagnosis can be suggested by visual field testing or multifocal visual evoked cortical potential testing. Plain X-rays are seldom used, but the classical finding is an expanded and pear-shaped sella turcica (Fig. 57.11) with chronic bone changes without calcification. One or both optic foramina may be enlarged, especially if there is an optic nerve component to the tumor. CT scanning shows three diagnostic patterns (Fig. 57.12)[67]:

1. A tube-like thickening of optic nerve and chiasm.
2. A suprasellar tumor with contiguous optic nerve expansion.
3. A suprasellar tumor with optic tract involvement.

Cystic or "globular" suprasellar tumors are not characteristic and may require histological confirmation.[54] MRI scanning better delineates the extent and nature of the tumor.[68] CT and MRI scanning will both diagnose hydrocephalus. Tumors may evolve in areas thought to be normal on initial CT and even MRI scans.[69]



Fig. 57.11 Expanded pituitary fossa shown on plain X-ray with some calcification due to a craniopharyngioma.

The histopathology of optic gliomas has long been the subject of discussion because it is relevant to treatment decisions. Optic gliomas are benign tumors that often behave similarly to hamartomas.[70] They undergo enlargement by an accumulation of mucosubstance, local invasion, induction of hyperplasia in adjacent glial cells, or growth of cell "rests" present in adjacent optic nerve or chiasm.[71] Malignant gliomas rarely occur and mainly in adults. Meningeal spread in children, however, is not unknown[72,73] and spread through a ventriculoperitoneal shunt has been recorded.[74]

The clinical course of 36 optic gliomas (29 chiasmal) were reviewed[70]: some were reviewed in 1971,[75] others in 1986.[61] The 1971 follow-up showed a very stable course, but the later follow-up showed that 57% of the 29 patients with chiasmal gliomas were dead, although only 18% from the direct effects of the glioma. The patients were more at risk from other tumors associated with neurofibromatosis type 1 (NF1). Twelve survivors had not had radiation therapy, whereas 11 of 16 patients who died had.[61]

Early studies reported that NF had no influence on the prognosis of optic pathway gliomas. It now appears that NF acts as a protective factor, both visually and neurologically.[76–78] In one study, the most common site of visual pathway involvement in NF was the orbital optic nerve (66%), followed by the chiasm (62%). This contrasted to patients without NF, in which the chiasm was the most common site of involvement (91%), and the orbital optic nerves were involved in only 32%. Extension beyond the optic pathway at diagnosis was uncommon in the NF group (2%), but frequent in the non-NF group (68%). In the NF group, the tumor was smaller and the original shape of the optic pathways was preserved (91% vs. 27% in the non-NF group). The presence of a cystic tumor was significantly more common in non-NF patients (66% vs. 9% in the NF group). The tumors in half the NF patients remained stable, in contrast to 5% of the non-NF group. Hydrocephalus as a presenting symptom was found only in the non-NF group.

In children with NF and optic pathway gliomas, the likelihood of visual loss is dependent on the extent and location of the tumor and is particularly associated with involvement of postchiasmal structures.[79] Complete spontaneous regression can occur in both NF- and non-NF-associated gliomas.[80] Spontaneous visual improvement can also take place in the absence of MRI changes.[81] Many authors have reported a reasonable long-term prognosis that does not seem to be improved by treatment.[61,82,83] Radiotherapy may decrease the size of tumors[54] and may improve vision,[84–88] but its use should be avoided, except in the Russell diencephalic syndrome, because of its serious side effects, especially in young children.[89–91] Chemotherapy[72,92,93] is as yet of uncertain benefit. Newer agents are promising, and may allow deferment of damaging radiotherapy in the young child.[93]

Surgery is not indicated except to treat obstructive hydrocephalus in large chiasmal/hypothalamic gliomas,[94] in rare cases of optochiasmatic apoplexy,[95] or if there is a cystic tumor with doubts about its pathology. A biopsy and cyst aspiration may be indicated.

Follow-up usually involves periodic review of the visual fields, acuity, color vision and optic discs, neurophysiological studies, where available, and CT or MRI scanning.

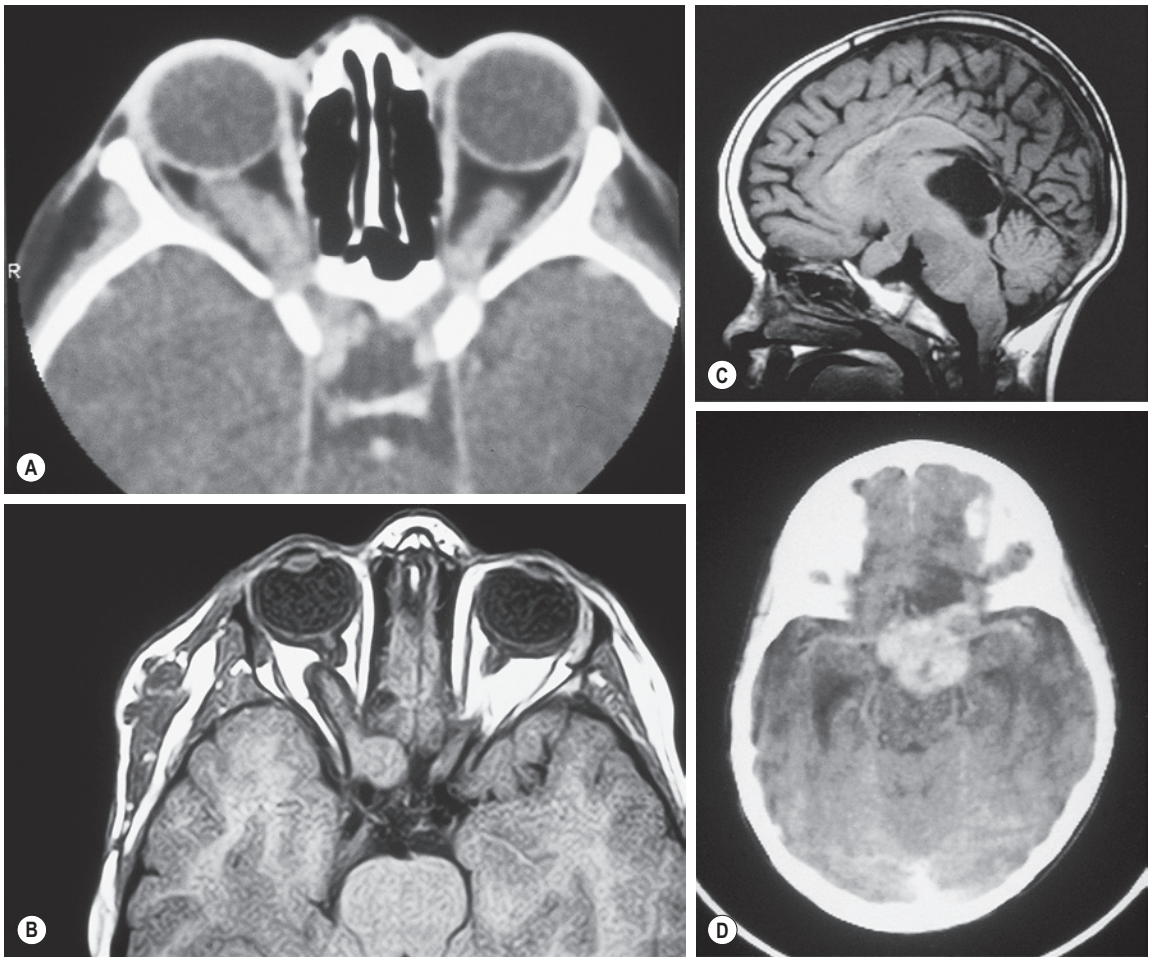


Fig. 57.12 Chiasmal glioma. (A) Computed tomography (CT) scan of bilateral optic nerve gliomas extending to the chiasm. (B) Magnetic resonance imaging (MRI) scan of left optic nerve glioma extending to the chiasm and kinking the intraorbital optic nerve. (C) Sagittal MRI of an optic nerve and chiasmal glioma. (D) CT scan with contrast of a cystic chiasmal glioma. *([A,B] Courtesy of Dr Kling Chong, Great Ormond Street Hospital, London, and Dr Bob Zimmerman of the Children's Hospital, Philadelphia.)*

Craniopharyngioma

These cystic tumors grow slowly and do not usually present until after 3 or 4 years of age. They may present even in old age. Their origin is from the pituitary stalk and they compress the chiasm, classically from behind and above. Hypothalamic disturbances are frequent, and loss of vision may be profound. Young children tend to develop hypothalamic disturbances or hydrocephalus, while older children (first decade) are more likely to present with visual disturbance, strabismus, or nystagmus (see Figs 57.11 and 57.13). The diagnosis is made by CT or MRI scanning (see Fig. 57.13). Calcification occurs in virtually every case in childhood and the tumors are often cystic. Endocrine assessment and management is essential. The tumors are usually treated by surgery with or without radiotherapy; total removal is sometimes possible.

Pituitary adenomas

Pituitary tumors are relatively uncommon in childhood, but can occur in adolescence.[7] In the pubertal period, they are more likely to show extrasellar extension and hemorrhage.[96,97] Children with macroadenomas may develop pituitary apoplexy, characterized by sudden headache, visual deterioration, ophthalmoplegia, and depressed consciousness consequent to hemorrhage into the tumor.[98,99]

Dysgerminoma

Diabetes insipidus is a common symptom of dysgerminomas together with chiasmal defects, including acuity and visual field loss and hypothalamic or pituitary disturbances.[100,101] They are often not large[102] and occur in older children or young adults.[103]

Other chiasmal tumors

Trilateral retinoblastoma is the association of bilateral retinoblastomas and ectopic intracranial primitive neuroectodermal tumor. These midline intracranial tumors most commonly occur in the pineal region, but can occur in the suprasellar area involving the chiasm.[104] The suprasellar tumors can present before the diagnosis of ocular retinoblastoma.[105] Other rare tumors, such as metastatic neuroblastoma, arachnoid cysts, choristomas,[106] ependymomas, epidermoid tumors, leukemic deposits, ectopic pinealomas, and teratomas, can occur.[107]

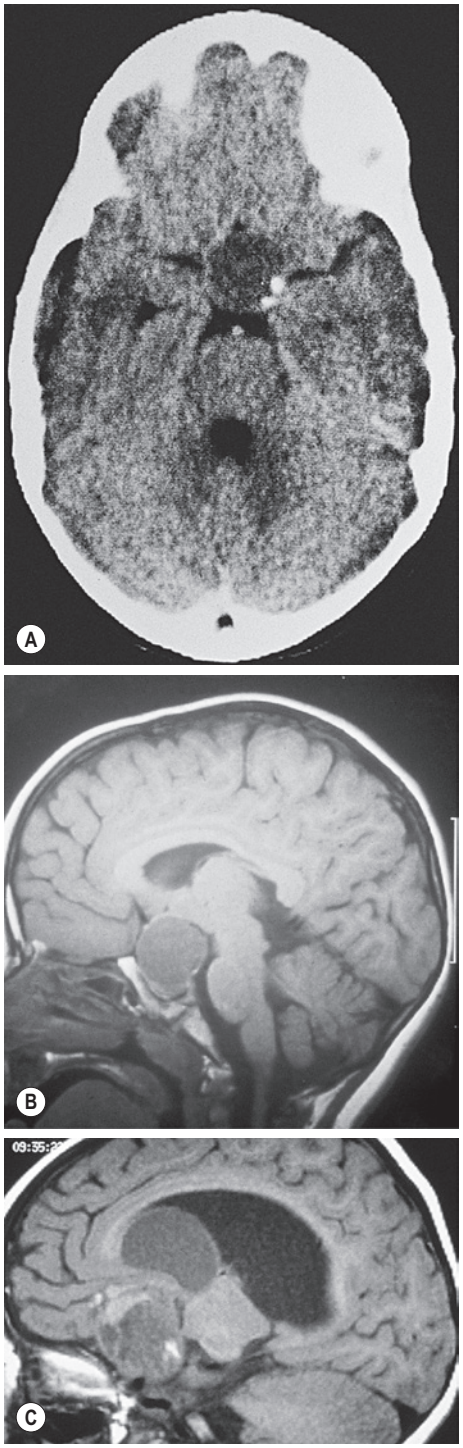


Fig. 57.13 Craniopharyngioma. (A) Computed tomography scan of a small cystic craniopharyngioma with calcification in its wall. (B) Sagittal magnetic resonance imaging (MRI) of small craniopharyngioma. (C) MRI scan of a large cystic craniopharyngioma with calcification in its wall. There is hydrocephalus.

Granulomas and chronic inflammatory disorders

The chiasm and surrounding structures may be involved in abnormalities of the skull base, such as Langerhans cell histiocytosis (see Chapter 27). A variant of this condition tends to present with diabetes insipidus and visual defects. Sarcoidosis, juvenile xanthogranulomas, and pseudotumors may also affect the chiasmal area.

Sphenoid sinus disease

A chiasmal syndrome, or even rapid blindness, may result from the formation and expansion of a mucocele,[108] even in the absence of symptomatic sinus disease.[109]

Chiasmal neuritis

Chiasmal neuritis is characterized by visual loss and bitemporal hemianopia.[98] Most cases are associated with demyelinating disease,[110] although Purvin et al. described a boy with infectious mononucleosis and chiasmal neuritis.[111] MRI shows swelling and enhancement of the chiasm.[110,112]

Optochiasmatic arachnoiditis

Optochiasmatic arachnoiditis with localized thickening of the arachnoid at the base of the brain may surround and compress the optic nerves and chiasm. Tuberculous meningitis, hydatid disease, cysticercosis, and fungal disorders (especially in debilitated, immune deficient children) may affect the suprasellar cistern with damage to the chiasm and surrounding structures.[113–115] Although the diagnosis has come to imply that surgical lysis of intracranial adhesions may be necessary to restore vision, the efficacy of surgical treatment remains unproven. Corticosteroids and cytotoxic agents are reportedly effective in some instances.[116] Modern neuroimaging seems to have rendered the diagnosis of optochiasmatic arachnoiditis an anachronism.

Third ventricle distension

In hydrocephalus, distension of the third ventricle may cause chiasmal damage with visual field defects[117] and profound vision loss due to stretching or compression of the optic nerves and chiasm. Unilateral visual loss from compression of one optic nerve against the internal carotid artery has been reported.[118]

Vascular malformations

Aneurysm is an extremely rare cause of chiasmal defects in children.[119,120] In children, intracranial aneurysms may be large and associated with polycystic kidneys, coarctation of the aorta, and Marfan and Ehlers–Danlos syndromes. Multiple aneurysms (usually small) may also occur in "mycotic" aneurysms with subacute bacterial endocarditis and moyamoya disease.[121–123]

Arteriovenous or cavernous malformations localized to the chiasm may hemorrhage to produce a sudden-onset chiasmal visual deficit accompanied by headache (termed "chiasmal apoplexy").[124]

Radionecrosis

Radiation injury to the optic chiasm is an uncommon, but serious, complication of radiation treatment. When vision becomes impaired, enhancement of the chiasm after gadolinium

injection is a consistent finding. Chiasmal enlargement may also be present. These neuroimaging abnormalities may antedate visual loss by several months.[125] The pathogenesis involves damage to the capillary beds. The risk of radionecrosis appears to be increased by the concomitant use of chemotherapy.

Empty sella syndrome

In empty sella syndrome, the subarachnoid space extends into the sella turcica, and the pituitary gland is flattened against the sellar floor or walls.[126,127] Chiasmal visual field defects occasionally occur.[127,128] Chiasmal prolapse can be caused by a distended third ventricle pushing the chiasm down into the sella, or by scarring and contracture pulling the chiasm into the sella. Aqueductal stenosis is particularly prone to produce ballooning of the third ventricle with downward herniation of the chiasm.[129] Pituitary apoplexy or sellar surgery can produce adhesions and cause downward traction of the chiasm into the sella.[128] Although pseudotumor cerebri is the most common cause of empty sella,[127] it does not seem to be associated with chiasmal prolapse into the empty sella.[128]

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Headache in children

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Introduction

Headache is a common symptom in children. A landmark epidemiology survey of 6000 school children found a complaint of generalized headache in 37–51% of 7-year-olds, and this proportion gradually increased to 57–82% by adolescence.[1] Accompanying eye or vision signs and symptoms may lead these children for an eye exam. Since serious neurologic morbidity and mortality can be heralded by head pain, it is important for pediatric ophthalmologists to understand the causes of headache in children as well as recognize headache syndromes to help guide the diagnostic work-up and management.

Classification and etiology

Headaches in children can be classified as primary or secondary. The International Classification of Headache Disorders (ICHD-3 beta)[2] defines the headache syndromes, and pediatric criteria were first included in 2004. In adults and children, the most common type of primary headache is migraine with and without aura, and less common syndromes include new persistent daily headache (NPDH), trigeminal autonomic cephalalgia (TAC), and tension-type headache (TTH).[3,4] Medication-overuse headache can often complicate a primary headache syndrome or be a secondary headache unassociated with a headache syndrome. Other primary headaches are listed in Box 58.1.

Migraine

Migraine is common in children; its frequency increases throughout childhood and peaks in adolescence, with a prevalence of 1.2–3.2% in 3–7-year-olds, 4–11% in 7–11-year-olds, and 8–23% by age 15.[5] Migraine is typically more common in boys in the prepubertal ages, but the gender predominance shifts towards girls in the adolescent years. There are three main groups of pediatric migraine: migraine without aura (formerly common migraine); migraine with aura (formerly classic migraine); and childhood periodic syndromes that may be associated with headaches.

Migraine without aura is the most frequent form of migraine in children and adolescents, and accounts for 60–85% of migraine in children.[5] Migraine is defined by recurrent episodes of intense disabling headache separated by symptom-free intervals. The ICHD-3 beta criteria are included in Box 58.2, and typical characteristics in children are bilaterality, a pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with autonomic symptoms such as nausea and/or photophobia and/or phonophobia (may need to be inferred from behavior, as in retreating to a quiet dark room). Migraine in children is different than in adults (Table 58.1). For instance, in children, migraine headache is usually frontotemporal, whereas, occipital headache in migraine is rare and should be a diagnosis of exclusion. The prevalence of cranial autonomic symptoms such as aural fullness, facial flushing/sweating, lacrimation, conjunctival injection, ptosis, gritty eye symptoms, nasal congestion/rhinorrhea, and periorbital edema have been well described in children. These symptoms are more frequent than in adults, with at least one cranial autonomic symptom noted in 62% of pediatric migraineurs.[6] Aural fullness was found to be the most common symptom.

Migraine without aura variants

Typically, migraine in children is episodic with symptom-free intervals; however, when the migraine symptom frequency increases to 15 or more days per month for 3 months, chronic migraine is diagnosed. Status migrainosus occurs when there is a debilitating unremitting headache lasting for more than 72 hours.

Box 58.1

Causes of primary headaches in children

Migraine without aura
Migraine with aura
Tension-type headache
Trigeminal autonomic cephalalgia
Primary stabbing headache
Primary cough/exercise/cold-stimulus/hypnic headache
New daily persistent headache

Box 58.2

Proposed criteria for pediatric migraine without aura

Diagnostic criteria:

A. At least five attacks fulfilling criteria B through D
B. Headache attacks lasting 2–72 hours (untreated or unsuccessfully treated). Sleep is considered part of the headache duration
C. Headache has at least two of the following characteristics:
   1. Bifrontal/bitemporal or unilateral location (adults unilateral head pain)
   2. Pulsating/throbbing quality (which may need inference from child behavior)
   3. Moderate or severe pain intensity (numerical or FACES scale)
   4. Aggravation by or causing avoidance of routine physical activity
D. During headache at least one of the following:
   1. Nausea and/or vomiting
   2. Photophobia or phonophobia (may need inference from child behavior)
E. Not better accounted for by another disorder

Source: The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013; 33: 629–808.

Table 58.1 Differences between adult and childhood migraine

Feature	Childhood	Adult
Laterality	Bilateral (but may start unilaterally)	Unilateral
Expanding "C" fortification spectrum	Rare	Common
Duration of headache	>2 hours	>4 hours
Systemic symptoms	Variable but often few	Common
Positive family history	Common	Common
Non-visual aura	Common	Infrequent
Visual aura without headache	Very rare	Common

Red flags of migraine without aura

The risks of radiation exposure from computerized tomography (CT) imaging and the risk of anesthesia and sedation needed for magnetic resonance imaging (MRI) can often discourage neuroimaging a child with headache. However, the red flag signs and symptoms of a first or isolated headache listed in Box 58.3 should prompt consideration of urgent imaging of a child with headache. In a child with recurrent headaches, the findings of an abnormal neurologic exam should also prompt imaging the brain. A study of 1562 children with recurrent headaches presenting to nine pediatric neurology clinics in tertiary hospitals found that 77% of these children had brain imaging, but only 9.3% had abnormal findings on the scans. In those with an abnormal neurologic exam, however, 50% of the scans identified a cause.[7] A new-onset headache during pregnancy in an adolescent female is a red flag symptom, given increased risk for an underlying etiology such as cerebral venous thrombosis. Emergent and urgent imaging in children or adolescents with headache is often with a CT scan of the head, but a brain MRI in a child is more ideal if promptly available because of the superior neuroanatomic detail and lack of radiation.

Box 58.3

Red flags of pediatric headache

Focal neurological signs
Seizures (focal or generalized)
Alteration of consciousness/confusion
Papilledema
Fever and/or meningeal signs
Change or deterioration of personality/behavior
Age under 4 (especially with increasing head circumference)
Headaches that are always unilateral (rare in pediatric migraine)
Headaches that wake from sleep or upon wakening
Headaches with coughing, straining, or changing position

Migraine with aura

In 30% of patients with migraine, the migraine attacks are preceded or accompanied by an "aura" characterized by transient focal neurologic symptoms.[8] Migraine with aura (Box 58.4) is defined by recurrent (≥2) attacks, lasting 5–60 minutes, with fully reversible visual, sensory, or other central nervous system symptoms. The aura usually develops gradually over minutes and is followed by associated migraine symptoms and headache. It typically starts before the pain phase begins. However, the aura may begin after the pain starts or continue into the pain phase. If a child meets criteria for typical aura, but has no subsequent headache, the child is diagnosed with typical aura without headache, previously referred to as "acephalgic migraine" or "ocular migraine."

Visual aura is the most common aura in adults and children, although it is less often present in children (see Chapter 100). Positive visual symptoms are most often described as an arc of colored or white zig-zag, jagged, or serrated lines moving to the periphery; however, flashes of light or shapes are also described.[9] The visual symptoms usually disappear after 15–20 minutes. Atypical visual complaints in migraine, but not aura *per se*, such as complex hallucinations, visual snow, and Alice in Wonderland syndrome, are well described in children.

Other non-visual auras

Sensory disturbance is the next most common aura and is usually described as pins and needles or numbness that slowly spreads (seconds to minutes) away from a point of

Box 58.4

Proposed criteria for pediatric migraine with aura

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms
   1. Visual
   2. Sensory
   3. Speech and/or language
   4. Motor
   5. Brainstem
   6. Retinal
C. At least one of the following four characteristics:
   1. At least one aura symptom spreads gradually over ≥ 5 minutes, and/or two or more symptoms occur in succession
   2. Each aura symptoms lasts 5-60 minutes (multiple aura symptoms have cumulative time, i.e. 3 symptoms is allotted 3 x 60 minutes for resolution)
   3. At least one aura symptom is unilateral
   4. The aura is accompanied, or followed within 60 minutes by headache
D. Not better accounted for by another ICHD-3 or other neurologic diagnosis

Source: The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013; 33: 629–808.

origin. Migraine with brainstem aura, previously known as basilar migraine, must include at least two brainstem features (dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, or decreased consciousness). Hemiplegic migraine has an aura that includes motor weakness. If there is a first- or second-degree relative with migraine aura involving motor weakness, then familial hemiplegic migraine from causative gene mutations *CACNA1A*, *SCN1A*, or *ATP1A2* should be considered.

Migraine visual aura complications

The visual aura typically lasts less than 1 hour (although motor aura can last weeks) and is fully reversible; however, on rare occasions an aura can persist for more than 1 week and last for months. If there is no ischemia found on neuroimaging, persistent aura without infarction is diagnosed. Persistent positive visual phenomena differs from persistent aura without infarction in that the visual phenomena are usually continuous, full-field without vision loss, and not visually disabling.[10] Another rare complication of aura is migrainous infarction, defined as a migraine aura lasting more than 1 hour and associated with infarction in the appropriate territory on neuroimaging. In a recent study, however, no increase in hemorrhagic or ischemic stroke risk in children with migraine was found.[11]

Red flags of migraine with aura

Neuroimaging should be considered if there are negative visual symptoms (i.e. hemianopia, black curtain in vision, darkening or graying of vision), symptoms lasting longer than 60 minutes for each of the aura symptoms, and/or other associated neurologic features not associated with typical aura.

Other visual conditions related to migraine

Retinal migraine involves monocular and negative visual symptoms with no other associated aura features. At the time of the attack, there can be constriction of the retinal arterioles and venules.[12] Ophthalmoplegic "migraine" (see Chapter 84) is a rare disorder in children, with typical migraine that occurs before the age of 10, with onset of episodes of ophthalmoplegia preceding a headache by several days. This may be a secondary headache rather than a primary headache disorder.[13] The work-up includes a brain MRI, and a short course of oral prednisone is often tried.

Childhood periodic syndromes

Childhood periodic syndromes may represent early-life expression of genes that later in life manifest as migraine headache, and the phenotype changes as the nervous system develops. These syndromes include abdominal migraine, cyclic vomiting syndrome, infant colic, and benign paroxysmal vertigo of childhood. The children are healthy in between attacks, and there is typically a family history of migraine.[14,15] Childhood periodic syndromes are a risk factor for migraine later in life.

Management of pediatric migraine

Imaging

If the history is suggestive of migraine and the examination is normal, then imaging can be deferred with close follow-up.[16,17] The presence of any red flags (Box 58.3) mandates imaging.

Bio-behavioral strategies

Children suffer less from migraines if they sleep well and eat healthy food regularly. Regular exercise also helps, as does maintaining a healthy weight. Dietary triggers are less common in children but, once identified, should be avoided. Caffeine may aggravate migraines by disrupting sleep and changing mood. Behavior modification education is crucial to all migraine management, and cognitive behavioral therapy has recently been found to be effective in headache reduction.[18]

Acute therapies

Abortive medication is most effective when taken within 30 minutes of onset of the migraine. The non-steroidal anti-inflammatory medications are first-line therapy for most mild-to-moderate migraines.[19,20]

As in adults, there have been many studies showing the efficacy and safety of triptans in children with moderate-to-severe migraines. The Food and Drug Administration (FDA)-approved medications for the pediatric age group include almotriptan maleate and rizatriptan; however, sumatriptan and others are frequently used off-label.[21] Triptans should not be used for hemiplegic migraine or when hypertension or cardiac disease is present. For nausea, chlorpromazine and prochlorperazine (administered with diphenhydramine to prevent akathisia) are effective. Pediatric headache experts have adopted the American Academy of Neurology practice parameters for adult migraine treatment, which recommends against using opioids as first-line treatment, given the concern for medication-overuse headache and medication dependence.[22,23] For chronic migraine, greater occipital nerve injections, and/or a course of intravenous dihydroergotamine are treatment options.

Preventive therapies

If a child or adolescent suffers more than 15 days per month of migraine, preventive measures should be considered. A high rate of placebo effect and small open-label studies in pediatric migraine has created insufficient evidence for efficacy in preventive medications; however, amitriptyline/nortriptyline, propranolol, flunarizine (outside of the United States),[24] and topiramate are most commonly used by headache experts.[25] In children less than 10 years old and of normal weight, cyproheptadine has been used.[26] The supplement riboflavin has been tried in all ages.[27] A minimum of 6–12 weeks is necessary to assess efficacy for all preventive medications.

Etiology of migraine

Previous theories regarding migraine mechanisms that attributed a cascade of events starting with cerebral vasodilation are less favored today.[28] The more contemporary trigeminal–vascular theory suggests that migraine results from a dysfunction of brainstem nuclei involved in nociceptive and other sensory modulation of craniovascular afferents.[29,30] The pain of migraine may have its origin in inflammation of meningeal vessels and "sensitization" of peripheral and central trigeminal afferents. The main structures involved are the cerebral cortex, brainstem nuclei (median raphe, periaqueductal gray matter, locus ceruleus, superior salivatory nucleus, trigeminal nucleus caudalis), and trigeminal nerves that communicate via hormones/neuropeptides (substance P, neurokinin A, calcitonin gene-related peptide) released at these sites. A lower threshold for initial excitation or sensitization may be genetic, possibly causing hyperexcitation from otherwise common internal (i.e. hunger, sleep deprivation, stress) and external (i.e. red wine, riding in a car or boat) events. The genetic influence may cause ion channel dysfunction within the brainstem nuclei as highlighted by the known missense mutation in familial hemiplegic migraine, which leads to a dysfunctional subunit of the voltage-gated calcium channel.[31]

Migraine aura is no longer thought to be caused by vasoconstriction *per se*.[32] Rather, migraine aura is likely neurally driven and caused by cortical spreading depression – a slowly propagating wave of depolarization followed by depression of brain activity from changes in neural and vascular function.[33] There is a short phase of increased regional cerebral blood flow (hyperemia) followed by a decrease (oligemia).[34,35] Flashing and jagged lights in the visual aura may be representative of the hyperemia phase.[36] Although the aura typically precedes the headache, the mechanisms causing the aura and pain phases may even be independent and not sequential. The premonitory nausea has been found to originate from central structures of the dorsal medulla (nucleus tractus solitarius, dorsal motor nucleus of vagus, and nucleus ambiguus) and the periaqueductal gray areas on positron-emission tomography imaging.[37]

Other headache disorders

Tension-type headache (TTH)

These are different from migraine, and are featureless with lack of nausea or vomiting. TTHs are typically episodes of bilateral head pain with a pressing or tightening quality, without worsening from routine physical activity. The pain is of mild-to-moderate intensity and can be associated with photophobia or phonophobia. Teeth grinding has been associated with TTH in 50% of affected children.[38] Bio-behavioral strategies using relaxation techniques and coping skills are most effective.

Trigeminal autonomic cephalalgia (TAC)

This class of cranial autonomic disorders is rare in children. The eye findings and symptoms associated with these may bring patients to the ophthalmology clinic. The cranial autonomic signs include conjuctival injection and/or lacrimation, nasal congestion, eyelid edema, forehead and facial sweating/flushing, aural fullness, miosis, and/or ptosis. TACs all include severe unilateral orbital or supraorbital pain with cranial autonomic signs. Each disorder is defined by a different frequency, length of pain, and treatment response. Cluster headaches are groups of attacks lasting 15–180 minutes. The exquisitely indomethacin-responsive disorders include paroxysmal hemicrania (multiple clusters of daily attacks lasting 2–30 minutes) and hemicrania continua (persistent unilateral head pain persistent, >3 months). Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) attacks last 1–600 seconds, occur multiple time per day, are stab-like, and are typically unresponsive to indomethacin.

Medication-overuse headaches

It is common for children and adolescents to take multiple medications for acute pain, a process that can then lead to a chronic problem of medication overuse. This complication increases the frequency of the primary headache and reduces the effectiveness of acute and preventive medications. Overuse of opioids, ergotamines, triptans, acetaminophen, and barbiturates may even transform a migraine from episodic to chronic. There is no exact recommendation by the headache experts but, in general, these medications should be used less than 10 days per month. The non-steroidal anti-inflammatory medications can actually be protective, and these are preferred acute medications.[39]

Secondary headaches

Box 58.5 sets out the important secondary intracranial causes for headache.

Ophthalmic and dental

Headaches in children are occasionally due to eye conditions. The most common ophthalmic causes of headache include refractive error, eyestrain from convergence insufficiency, glaucoma, dry eyes, uveitis, and optic neuritis. Dental problems such as dental malocclusion, cavities, gingival infection, temporomandibular joint disease, and bruxism can also cause "head pain" in children.

Epilepsy

Headache in patients with epilepsy is common and preictal, ictal, and postictal headaches are often mistaken for migraine.

Box 58.5

Secondary intracranial causes for headache in children

- Dental conditions
- Ophthalmic conditions (infectious, inflammatory)
- Epilepsy (pre-, per- and postictal)
- Raised intracranial pressure and pseudotumor cerebri syndrome
- Brain tumors
- Infections
  - Acute viral illness
  - Meningitis
  - Encephalitis
- Structural brain abnormalities
  - Arachnoid cyst
  - Arnold–Chiari malformation
- Vascular abnormalities
  - Intracranial hemorrhage and arteriovenous malformations
  - Cerebral venous sinus thrombosis
- Acute disseminated encephalomyelitis and multiple sclerosis
- Trauma

In children and adolescents with seizures, preictal headaches have been observed in about 30% and postictal headaches in about 60%.[40] The headache is described as a moderately severe, and throbbing pain 24 hours before a seizure is typical; in general, it is more abrupt (over seconds) in onset than migraine, typically lasting minutes to hours. There can be an aura, which is rapid in onset, brief, and sometimes associated with unusual symptoms, such as a rising abdominal sensation followed by a déjà vu illusion or a visual hallucination that can be associated with nausea and fear. Postictal headaches, in particular, can mimic migraine and respond well to triptan therapy.[41]

Raised intracranial pressure and pseudotumor cerebri syndrome

Raised intracranial pressure (ICP) can cause progressive headaches that may wake a child from sleep and are made worse by exertion or a Valsalva maneuver. Associated findings are nausea, vomiting, lethargy, and personality changes. Tumors, aqueductal stenosis (Fig. 58.1), hydrocephalus, meningitis, edema from stroke, and subarachnoid hemorrhage can increase intracranial pressure, with stretching of the meninges contributing to headache.

Pseudotumor cerebri syndrome (PTCS) (see Chapter 59) refers to the primary and secondary disorders that cause symptomatic intracranial hypertension in patients with normal brain parenchyma and normal spinal fluid constituents, typically presenting with papilledema. Idiopathic intracranial hypertension (IIH) is the primary form of PTCS that occurs most commonly in obese adolescent females; however, in prepubertal children, the prevalence is similar in girls and boys, and they are more often thin.[42] Headaches are a common symptom in adolescents with PTCS, but many of the younger children with PTCS do not have headache. Generalized and focal features of head pain are described and cannot be distinguished from migraine or tension-type headache based solely on the pain characteristics.

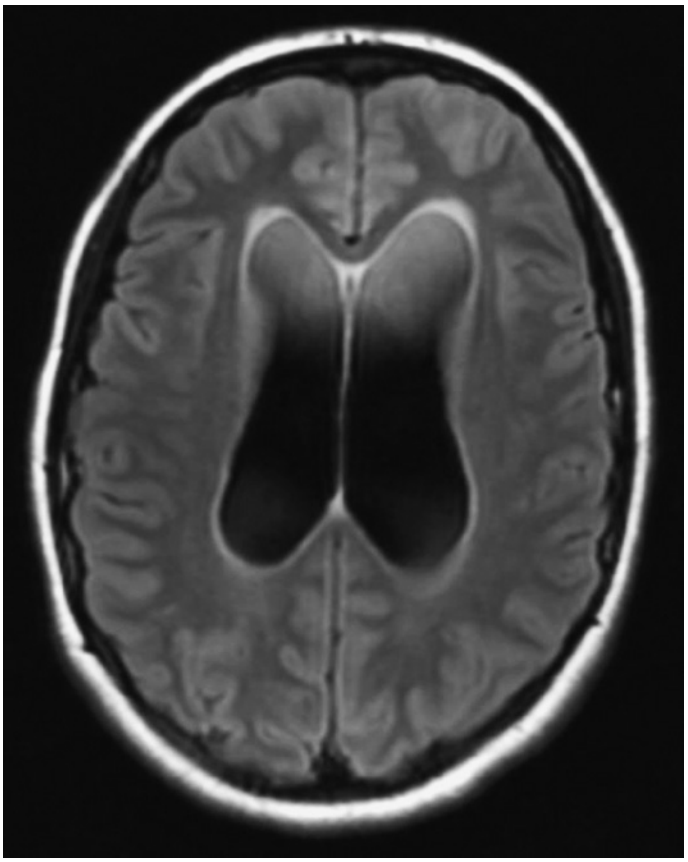


Fig. 58.1 Axial fluid-attenuation inversion recovery (FLAIR) brain magnetic resonance imaging demonstrating non-communicating hydrocephalus due to aqueductal stenosis in a thin 14-year-old girl who presented with headaches and bilateral papilledema.

Brain tumor

This is the diagnosis parents and children worry most about, so it is important to give reassurance that headaches in children are common, and brain tumors (Fig. 58.2) are rare (5.4 per 100,000 person years).[43] Headaches that awake the child from sleep, cause confusion and vomiting, localize to the occiput, are worsened by Valsalva maneuver, are accompanied by new weakness or gait changes, and/or exist in patients with no family or personal history of migraine-like symptoms are worrisome and should be further investigated.

Infections

An acute viral illness is the most common reason that a child will present with a headache to an emergency department. Serious infections such as meningitis and encephalitis account for 5–9% of children with an acute headache presenting as an emergency.[44] As opposed to adults, true "sinus" headaches in children are rare. The dull periorbital, pressure-like pain associated with nasal congestion that adults complain of, rarely gets better when "sinusitis" is treated in children. Instead this is usually an atypical form of one of the primary headaches discussed above.

Structural abnormalities

Arachnoid cysts are collections of cerebrospinal fluid contained in a sac of arachnoid membranes, and are found on imaging

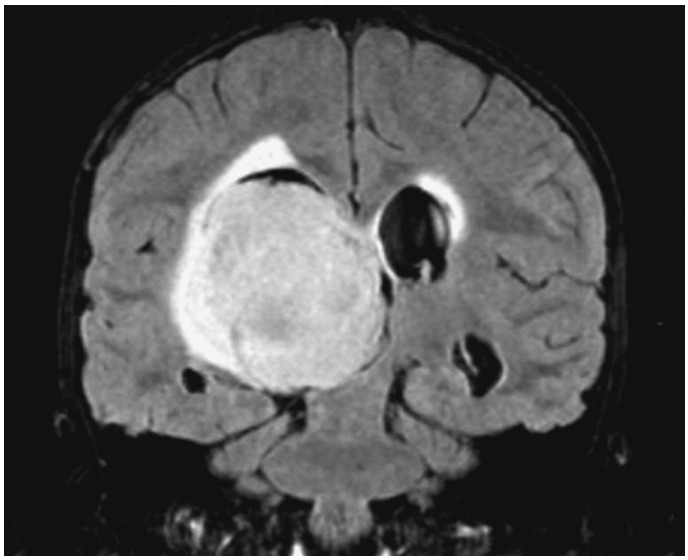


Fig. 58.2 Coronal fluid-attenuation inversion recovery (FLAIR) brain magnetic resonance imaging showing a right thalamic mass in a 9-year-old boy who presented with headache and fatigue. On exam he had a left homonymous field defect and bilateral papilledema.

in about 4% of pediatric patients.[45] They can be congenital or secondary to trauma. Arachnoid cysts are usually incidental, and studies have found 18–41% of children with arachnoid cysts to be symptomatic with headache.[46] The symptomatic cysts are typically those that rupture or hemorrhage, and surgical treatment can include fenestration or shunt insertion.

A Chiari I malformation is the herniation of cerebellar tonsils more than 5 mm below the foramen magnum. Symptoms include headaches, sensory disturbance, neck pain, vertigo and ataxia. 50% to 90% of patients with a Chiari I malformation will be symptomatic with a headache that is similar to migraine; however, there may be a higher incidence of occipital pain that worsens with Valsalva maneuvers.[47,48] Surgical decompression of the posterior fossa is often successful.

Vascular abnormalities

Pediatric hemorrhagic stroke occurs in about 1 per 100,000 children per year.[49] In one study, 77% of children with hemorrhagic stroke complained of headache (mostly sudden onset), and 91% had neurologic symptoms in addition to headache. In these children, 50% were found to have a causative arteriovenous malformation (Fig. 58.3) and 18% had an aneurysm.[50] Other vascular abnormalities include cerebral venous sinus thrombosis in which seizures, coma, and motor weakness are the most common presentations. However, headache occurs in 18% of these children.[51]

Summary

An understanding of the presentation, management, and treatment of primary headaches, as well as a careful history and thorough ophthalmic and systemic neurologic examination, can help identify the children with potentially catastrophic secondary causes. Similarly, this can prevent unnecessary investigations in children with benign headaches.



Fig. 58.3 Non-contrast axial computed tomography scan of the brain demonstrating a right temporoparietal hemorrhage secondary to a ruptured arteriovenous malformation in a 14-year-old girl with sudden-onset headache and a left homonymous hemianopsia.

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Raised intracranial pressure

Robert A Avery

Chapter contents

INTRODUCTION
SIGNS AND SYMPTOMS OF RAISED INTRACRANIAL PRESSURE
OPHTHALMOLOGIC MONITORING
EVALUATION OF RAISED INTRACRANIAL PRESSURE
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Introduction

Raised intracranial pressure (RICP) and its potential for causing permanent vision loss requires close monitoring by the eye physician. Pseudotumor cerebri syndrome (PTCS, also known as idiopathic intracranial hypertension), brain tumors, structural brain abnormalities, and acquired infectious/inflammatory conditions are the most frequent causes of RICP in children seen in the ambulatory setting. Understanding the proper ophthalmologic assessment, monitoring, and treatment is essential for optimizing visual outcomes.

Signs and symptoms of raised intracranial pressure

The spectrum of symptoms and their severity can range widely in children with RICP. Children can be relatively asymptomatic when signs of RICP are discovered. The complaint of headache, especially unremitting headache that may worsen while lying flat, reach peak severity in the morning, and/or is relieved by vomiting, should produce a high suspicion of RICP. When caring for infants and toddlers, it is essential to communicate with their primary care physician to determine if there are concerns about an enlarging head circumference or change in developmental trajectory. The presence of other ophthalmologic and non-ophthalmologic symptoms such as transient visual obscurations, pulsatile tinnitus, failure to thrive, cognitive regression, lethargy, or prolonged alteration in mood/personality should prompt the clinician to perform an exhaustive exam investigating for other RICP risk factors and signs. While children with newly diagnosed brain tumors frequently present with headache, an overwhelming majority (>85%) will also demonstrate other neurologic deficits such as a cranial nerve palsy, ataxia, or weakness.

Objective ophthalmologic signs such as elevated optic nerves, vertical gaze palsy, and cranial nerve VI palsy are frequent indicators of RICP. The term "papilledema" should be reserved for elevated optic nerves due to increased intracranial pressure. The presence of additional cranial nerve palsies, bulging anterior fontanel, or/and other neurologic signs requires prompt referral to a neurologist or neurosurgeon, along with the consideration of imaging.

Ophthalmologic monitoring

The afferent vision examination is essential to evaluating a child with suspected or confirmed RICP. Visual field testing, preferably with a quantitative automated or kinetic perimeter, is essential as an enlarged blind spot will be the first sign of RICP. The visual field deficits can expand most commonly to inferonasal loss and generalized constriction. A decline in visual acuity occurs after significant visual field loss as a sign of severe optic nerve dysfunction. Indirect ophthalmoscopy is mandatory, along with photographs to assess longitudinal changes. It is important to recognize that the appearance of the optic nerve, especially in cases of moderate-to-severe swelling, may be incongruous with the functional deficit (Fig. 59.1). Therefore, functional measures of the afferent examination are the most important metric in caring for children with RICP.

Evaluation of the optic nerve sheath diameter and 30° test are two orbital ultrasonography techniques that have been utilized to differentiate between papilledema and pseudopapilledema.[1] While the combination of these two tests have a high sensitivity to detect papilledema, they have lower specificity and require an experienced user to perform and interpret the results. Studies using optical coherence tomography (OCT) to differentiate between papilledema and pseudopapilledema in cases of suspected RICP have demonstrated mixed results.[2,3] In cases of confirmed papilledema, OCT has been suggested as an objective quantitative metric to monitor changes in optic nerve elevation.[4] The use of volumetric OCT imaging in children experiencing relatively small changes in optic nerve elevation over a long time may offer an advantage over fundus photographs and indirect ophthalmoscopy (Fig. 59.2).

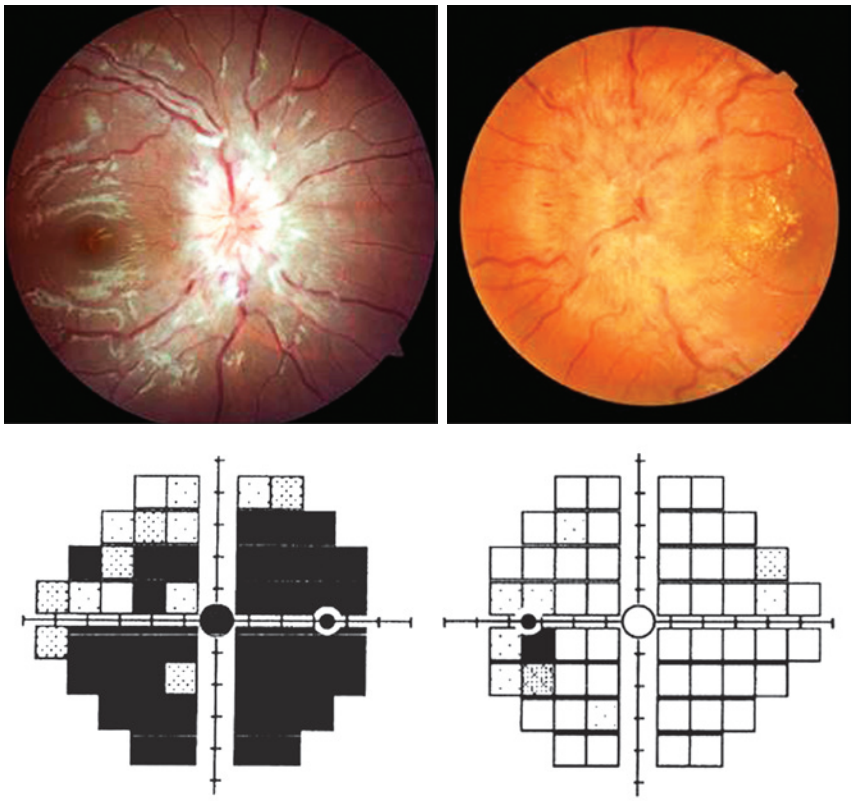


Fig. 59.1 Optic nerve swelling secondary to raised intracranial pressure. (Left panel) Marked swelling, in the setting of 20/30 acuity and severe visual field loss. (Right panel) Marked swelling, hemorrhages, and macular lipid in the setting of 20/20 acuity and very mild blind spot enlargement.

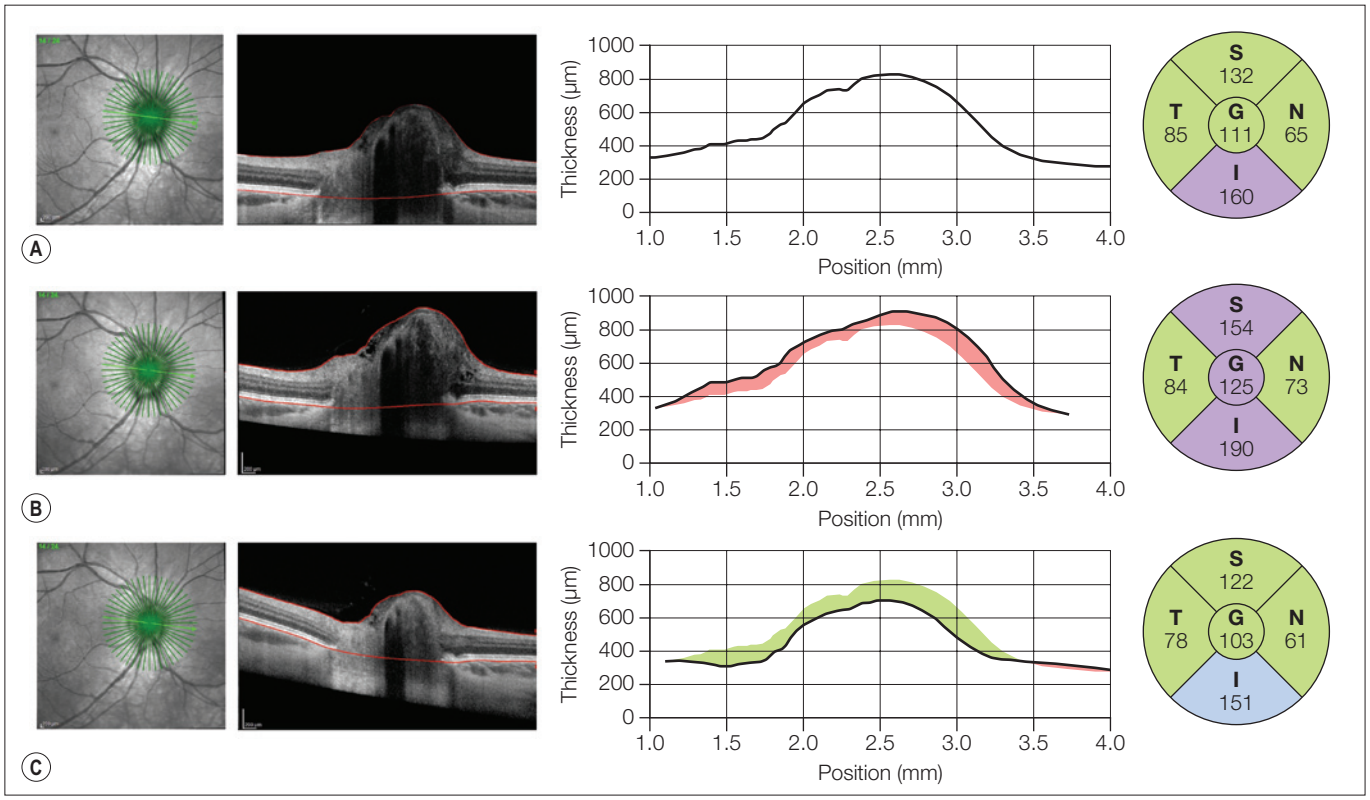


Fig. 59.2 Progressive optic nerve swelling in an asymptomatic child with stable hydrocephalus. (A) A slightly elevated optic nerve and normal retinal nerve fiber layer (RNFL) thickness for all quadrants except the inferior. (B) Visualization of the increasing optic nerve height (red height) along with progressive elevation in the superior and inferior quadrants. After placement of a ventriculoperitoneal shunt, the optic nerve swelling and RNFL thickness declined (C).

Evaluation of raised intracranial pressure

All children with an examination suggestive of RICP should undergo magnetic resonance imaging (MRI) before more invasive intracranial pressure (ICP) monitoring (i.e. lumbar puncture or intracranial monitoring). Magnetic resonance (MR)-venography and MR-angiography sequences can be added if a vascular cause is suspected. Computed tomography (CT) imaging of the brain can be used in emergent cases, although this exposure to radiation should be avoided, if possible. Numerous MRI findings have been reported to be suggestive of RICP including an empty sella turcica (Fig. 59.3), transependymal cerebrospinal fluid flow, flattening of the posterior globe, optic nerve protrusion into the globe (Fig. 59.4), distended optic nerve sheath (see Fig. 59.4), hypoplastic venous sinus, and diffusion restriction of the optic nerve. Some of these MRI features, especially occurring as an isolated finding in a child without neurologic or ophthalmologic signs or symptoms, should not be used to make a diagnosis of RICP.

The cerebrospinal fluid opening pressure measured during a lumbar puncture is the most accessible and least invasive assessment of ICP. Current research suggests an opening pressure below 28 cmH_2O should be considered normal in most children.[5] Depth of sedation and obesity do influence the opening pressure measurement, while patient age and leg position do not have a significant impact.[6] Children with papilledema have an average opening pressure around 41 cmH_2O, although rarely it can be below 30 cmH_2O.[7] An opening pressure above 28 cmH_2O should raise suspicion for RICP, but does not guarantee that the child has RICP, as this indirect measurement of ICP can be influenced by a number of patient and technical factors. Similar to MRI findings, an opening pressure above 28 cmH_2O should not be the sole metric to make the diagnosis of RICP, but instead be interpreted in the context of the clinical history and examination findings. Invasive intracranial monitoring is the most accurate and reliable method to measure ICP as it can vary widely throughout the day.

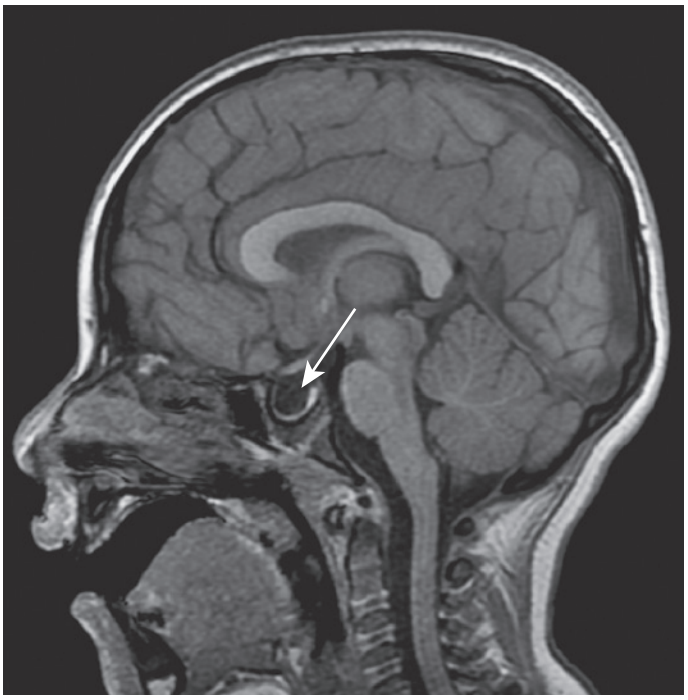


Fig. 59.3 Sagittal T1-weighted magnetic resonance image of an empty sella turcica in a child with raised intracranial pressure.



Fig. 59.4 Axial T1-weighted magnetic resonance image of distended optic nerve sheaths and mild protrusion of the optic nerve in a child with raised intracranial pressure.

Causes of raised intracranial pressure

Impairment of the normal axoplasmic flow throughout the optic nerve from RICP produces swelling of the axons – ultimately resulting in papilledema. Interestingly, not all children with RICP will demonstrate papilledema. Anatomic studies suggest that the subarachnoid space surrounding the optic nerves is a different compartment than the rest of the intracranial subarachnoid space.[8] These separate compartments may explain why not all children with RICP develop papilledema, as well as why papilledema may persist even in the setting of a functional ventriculoperitoneal shunt.

A large number of acquired, structural and congenital problems can disrupt the normal pattern of cerebroshinal fluid (CSF) production, circulation, and absorption. The management and treatment differ according to etiology.

Brain tumors

Brain tumors from any number of locations (i.e. supratentorial or infratentorial) can disrupt the normal flow of CSF, although tumors obstructing the third and fourth ventricles most commonly result in RICP. Not infrequently, tumors without significant cerebral edema and that are located in regions not expected to alter CSF circulation (e.g. frontal lobe) can result in RICP.

Treatment of RICP secondary to brain tumors can be accomplished by surgical resection, although it is not uncommon

for some tumor types to require a ventriculoperitoneal shunt. Tumors that cannot be resected may also require permanent CSF diversion. Due the frequency of ventriculoperitoneal shunt malfunction, pediatric ophthalmologists are frequently asked to evaluate children for signs of RICP. The lack of papilledema or imaging features suggestive of RICP does not exclude the possibility of shunt malfunction. In children with proven shunt malfunction and RICP, only 14% manifest papilledema.[9]

Hydrocephalus

Enlarging ventricle size is frequently due to obstruction of CSF flow from a structural cause (e.g. tumor). In the absence of a structural cause, communicating hydrocephalus is believed to be caused by abnormal reabsorption of CSF. The absence of ventricular enlargement, especially in children with prior central nervous system insults, does not eliminate the possibility of RICP. For infants and young toddlers, the ophthalmologic signs of RICP, such as papilledema, may not be present.

The treatment of hydrocephalus is typically initiated for current or anticipated functional deficits. In the absence of signs or symptoms of RICP, treatment may be deferred for some children with hydrocephalus. Ventriculoperitoneal shunts and endoscopic third ventriculostomy are the most common treatments for hydrocephalus.

Structural abnormalities

Congenital and progressive structural abnormalities can cause RICP, but typically at a lower incidence than brain tumors or other etiologies. Although frequently asymptomatic and benign, arachnoid cysts that are static in size can cause RICP.[10] The descent of the cerebellar tonsils (i.e. Chiari malformation), along with Dandy–Walker malformations and cerebral aqueductal stenosis, are other potential infratentorial structural causes of RICP. Monitoring for signs and symptoms of RICP in children with craniosynostosis and genetic craniofacial syndromes can be challenging due to the young age of presentation and frequency of anomalous optic nerves.

The treatment approach to structural causes of RICP varies depending on the etiology. Surgical correction of the craniosynostosis, bony abnormalities, and obstructive lesions frequently treats the RICP.

Vascular

Although aneurysms and large vascular anomalies (i.e. vein of Galen malformations) can disrupt CSF flow in children, they are relatively rare. The most common vascular problem causing RICP is a cerebral sinovenous thrombosis. Children with acute or chronic mastoiditis are at risk for developing unilateral thrombosis in the transverse/sigmoid venous sinus (Fig. 59.5). Dehydration, infections, head trauma, chronic medical conditions, and prothrombotic conditions are other frequent causes of cerebral sinovenous thrombosis in children. Aggressive intravenous hydration and, when indicated, anti-coagulation are the standard treatments for cerebral sinovenous thrombosis. The use of carbonic anhydrase inhibitors are typically avoided in these cases as they may cause dehydration.

Infectious and inflammatory

Numerous infectious and inflammatory conditions of the central nervous system have been reported to cause RICP, including Lyme disease and demyelinating conditions such as Guillain–Barré syndrome and Miller–Fisher syndrome. The underlying mechanism of RICP in these cases is not well understood, but most respond well to treating the specific etiology. In children with Lyme meningitis, the signs of RICP (i.e. papilledema or sixth nerve palsy) frequently improve with antibiotic treatment. Progressive and severe cases of papilledema have been reported in children being treated for Lyme meningitis; therefore, close monitoring of visual function is required, and treatment with carbonic anhydrase inhibitors should be considered until the papilledema has resolved. Papilledema secondary to demyelinating conditions may also benefit from treatment with carbonic anhydrase inhibitors.



Fig. 59.5 Reconstructed magnetic resonance venogram demonstrating a thrombus that has occluded the left transverse sinus. The thrombus developed after prolonged left-sided mastoiditis resulting in raised intracranial pressure that produced papilledema and bilateral abducen nerve palsies.

Pseudotumor cerebri syndrome/idiopathic intracranial hypertension

RICP in the setting of essentially normal brain imaging and normal CSF composition without infection or malignancy is commonly referred to as either pseudotumor cerebri syndrome (PTCS) or idiopathic intracranial hypertension (IIH). Using the recently updated diagnostic criteria, this condition is best described using the term "PTCS."[11]

PTCS is classified as primary when no medication, vascular abnormality, or medical condition is believed to be causing the RICP. Primary PTCS is typically diagnosed in patients with recent weight gain, obesity, polycystic ovary syndrome, during the peripartum period, or in non-obese children. Secondary PTCS has been attributed to numerous cerebral venous abnormalities, medications, and medical conditions. The most common causes of secondary PTCS in children are listed in Table 59.1, although many rare and weakly associated causes of secondary PTCS can be found in comprehensive reviews.[12]

Table 59.1 Common causes of secondary pseudotumor cerebri syndrome in children

Cerebral venous abnormalities	Medications	Medical conditions
Sinus venous thrombosis	Minocycline	Down syndrome
Superior vena cava syndrome	Isoretinoin	Renal failure
Jugular vein thrombosis	Growth hormone	Anemia
Abnormal CSF circulation/ absorption secondary to previous central nervous system infection or insult	Withdrawal from corticosteroids Vitamin A All-transretinoic acid	Obstructive sleep apnea

As with all cases of RICP, preservation of vision is the treatment goal for both primary and secondary PTCS. When believed to be secondary to obesity or weight gain, treatment of primary PTCS must include weight loss with a goal of 3–5% weight reduction. The addition of acetazolamide to a weight loss plan in cases with mild papilledema demonstrated a greater improvement in the perimetric mean deviation compared to those only on a weight loss plan.[13] A history of allergy to sulfa-based medications does not preclude treatment with acetazolamide.[14] Loop diuretics and medications with carbonic anhydrase activity have been used when acetazolamide cannot be tolerated.

Children may have decreased papilledema after a single lumbar puncture, even before treatment with a carbonic anhydrase inhibitor has begun. Repeated lumbar punctures should not be used as a chronic therapy for PTCS, but instead reserved for those refractory to first-line therapy who are experiencing a rapid decline in visual function and are awaiting more aggressive therapy. In cases of rapid and moderate-to-severe visual loss, high-dose intravenous corticosteroids can be considered as a potential temporizing measure, although the efficacy of this treatment has not been firmly established.

When weight loss and medical therapy fails to resolve or control progressive visual loss, CSF-diversion techniques may be indicated. Optic nerve sheath fenestration has been successfully used in children, and in some centers it is preferred over ventriculoperitoneal shunting, since it does not carry the lifelong risk of infection and obstruction. Cerebral venous stenting has been used in adults, but this treatment has rarely been used in children.

Acknowledgments

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The brain and cerebral visual impairment

Creig S Hoyt

Chapter contents

DEVELOPMENTAL DEFECTS
PERINATAL INSULTS
VISUAL RECOVERY IN BRAIN DISORDERS
REFERENCES

Numerous congenital and acquired disorders of the central nervous system affect children's vision and many directly affect vital visual structures with varying disability. Others do not, but are associated with structural eye defects. In many parts of the world, especially in more developed countries, the prevalence of visual impairment in children due to brain disorders equals or exceeds that related to purely ocular disease. Many children with visual impairment due to brain disorders are multi-handicapped and their long-term potential for successful rehabilitation, education, employment, and independent living is limited. Nevertheless, it is essential that their visual deficits and potential be carefully assessed so that appropriate medical, rehabilitation, and educational services may be provided.

Developmental defects

Embryological errors

Cephalocele (encephalocele)

During the first month of embryogenesis, a neural plate is formed which invaginates into the neural groove and then fuses into a neural tube. Cephaloceles (defects in the skull and dura mater with extracranial extension of intracranial structures) are probably the result of a disturbance in the closure of the neural groove. Fortification of staple foods with folic acid and the use of folic acid supplements by women of childbearing age have greatly reduced the incidence of this type of encephalocele in most countries. Alternatively, they may occur as a postneurulation event with brain tissue herniating through the mesenchyme that will give rise to the cranium and dura. Three of the four major types of cephaloceles are of interest to ophthalmologists.

1. *Occipital cephaloceles.* In these, portions of the occipital cortex and the occipital horn of the lateral ventricle herniate into the defect. Severe visual defects are associated both with the anomaly and the results of any surgical correction. Knobloch syndrome is characterized by high myopia, vitreoretinal degeneration with retinal detachment, macular abnormalities, and occipital encephalocele (see Chapters 42 and 52).
2. *Frontal ethmoidal cephaloceles.* These have a geographical predilection for Southeast Asia. They do not usually impinge on any visual structures, but they may be associated with ipsilateral optic nerve dysplasia.
3. *Nasal pharyngeal cephaloceles.* These are uncommon, but visual function is almost always affected. The optic nerves and chiasm may be compromised as they are stretched when they extend into the sac of the defect. Optic nerve hypoplasia and retinal dysplasia and coloboma are frequent associations.

Holoprosencephaly

During the second month of gestation, the forebrain (prosencephalon) is cleaved transversely into the telencephalon and diencephalon and sagittally into the cerebral hemispheres and lateral ventricles. Failure of differentiation and cleavage of the prosencephalon results in a group of disorders referred to as the "holoprosencephalies." The Hedgehog (Hh) signaling pathway mediates spatiotemporally specific aspects of face and brain development. Genetic and teratogenic disruptions of this pathway may produce holoprosencephaly, although mutations in other genetic pathways may also be causative. Maternal diabetes is the most commonly recognized teratogen. Holoprosencephaly can be seen in a number of syndromes including Patau syndrome (trisomy 13), Edwards syndrome (trisomy 18), and de Morsier syndrome. Facial dysmorphism (hypotelorism and midline clefts) and numerous central nervous system anomalies are frequently associated (Fig. 60.1). Surviving children may show visual responses via ectopic striate cortex. Corpus callosum dysgenesis is common, as is optic nerve hypoplasia (see Chapter 53). Indeed, a significant subset of patients with septo-optic dysplasia may have a mild form of lobar holoprosencephaly.

Malformations of cortical development

Between the second and fourth gestational months, the neurons in the ventricular and subventricular zones of the lateral ventricles proliferate and migrate to the cortical plates. This area of cell proliferation is known as the germinal

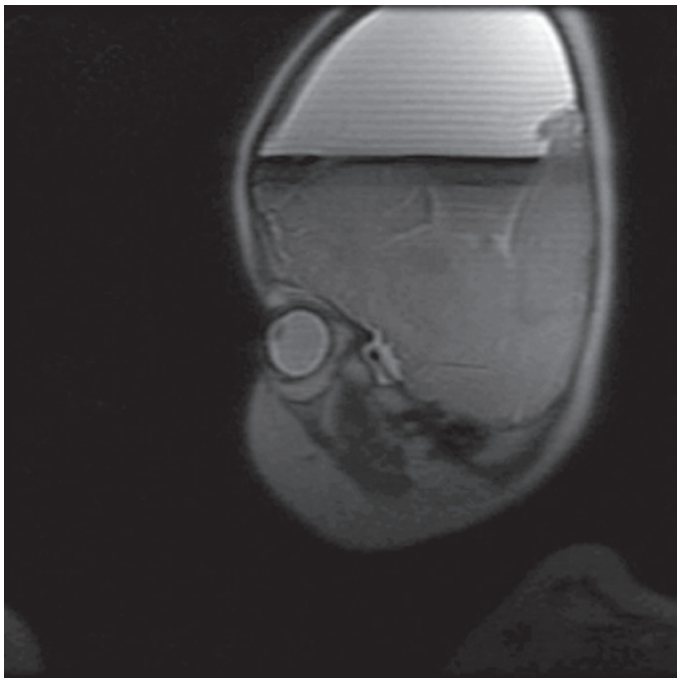


Fig. 60.1 Complex brain anomaly in a 3-year-old girl born at 35 weeks gestational age. She has global developmental delays, intractable seizures, quadraparesis, severe visual impairment, nystagmus, and optic nerve hypoplasia. Magnetic resonance imaging reveals holoprosencephaly, absence of the corpus callosum, interhemispheric cyst, and anomalous ventricular system. *(Courtesy of Dr Alejandra de Alba Campomanes.)*

matrix; here, stem cells give rise to the neurons and glial cells that will form the mature brain. Neurons in early embryogenesis migrate relatively short distances; neurons later in development migrate long distances across the intermediate zones. Neurons arriving first in the cortical mantle assume the deepest locations, while later-arriving neurons assume a more superficial location. Migration is facilitated by radial glial cells acting as guidelines. After arriving in the cortex, neurons form discrete lamina and begin to establish synaptic connection with local and distant neurons. Aberrations in this normal migration and development process result in important neural abnormalities.[1] In general, the resulting malformations can be divided into three categories – those due to:

1. abnormal neuronal and glial proliferation, or apoptosis;
2. abnormal neuronal migration;
3. abnormal cortical organization.

Lissencephaly (smooth brain) is characterized by a paucity of normal gyri and sulci. There are two types: classical and cobblestone. Classical lissencephaly is caused by an arrest of neuronal migration; cobblestone results from over-migration. Over 90% of children with lissencephaly have seizures. Cobblestone lissencephaly occurs in at least three muscular dystrophy syndromes with important ocular features. Mutations in the fukutin-related protein gene account for these three disorders (as well as a broad spectrum of other muscular dystrophies):

- Fukuyama-type congenital muscular dystrophy: affected children develop high myopia and a retinal degeneration (Fig. 60.2A,B);
- the muscle–brain–eye syndrome: this is associated with myopia and early-onset glaucoma and cataracts;

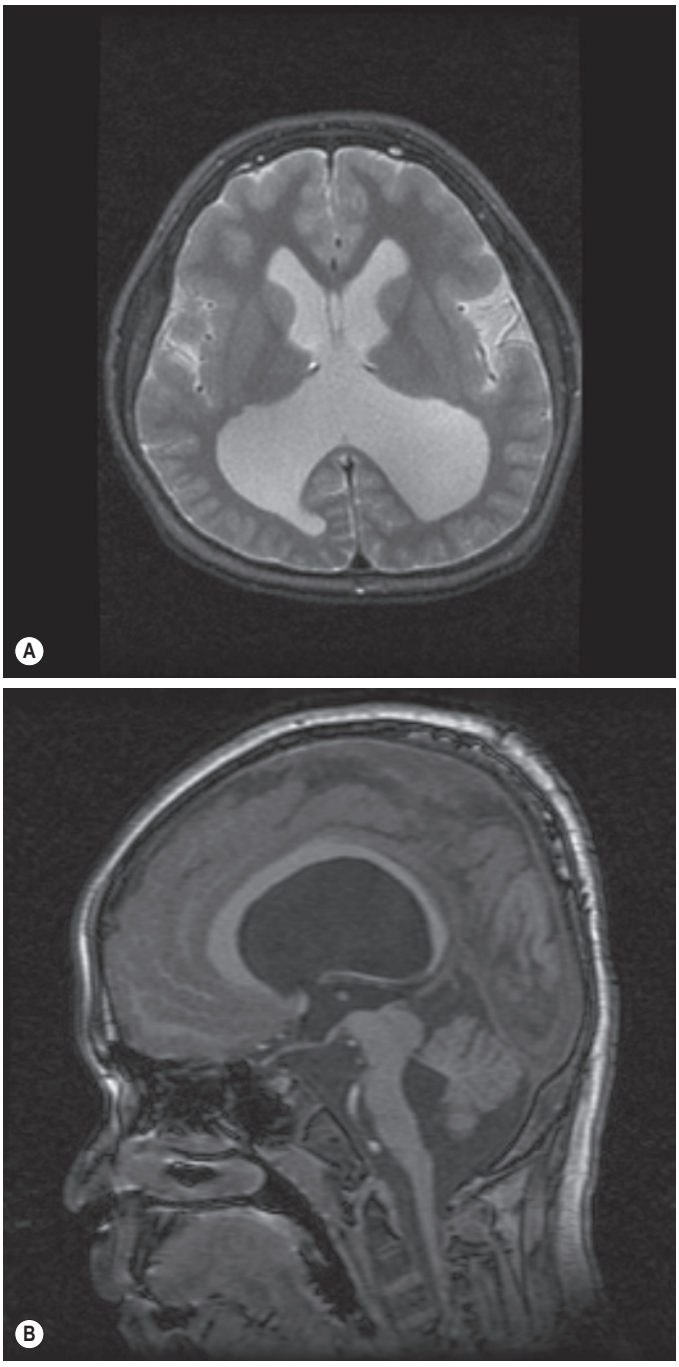


Fig. 60.2 A 10-year-old Vietnamese girl with severe developmental delays and hypotonia presents with bilateral cataracts, glaucoma, retinal detachments, and vitreous hemorrhages. (A) Axial magnetic resonance imaging (MRI) reveals dilated ventricles and pachygyria of the frontal cortex. (B) Sagittal MRI reveals pachygyria and polymicrogyria of frontal cortex, partial agenesis of the septum pellucidum, and hypoplasia of the brainstem. A diagnosis of Fukuyama disease was made. *(Courtesy of Dr. Alejandra de Alba Campomanes.)*

- the Walker–Warburg syndrome (also known as Chemke or HARD syndrome): this comprises microphthalmos, glaucoma, optic nerve anomalies, and retinal dysplasia and non-attachment.

Pachygyria is related to lissencephaly, but occurs at a later stage resulting in reduced numbers of gyri that are thick and underpopulated with neurons (Fig. 60.3). Pachygyria of the

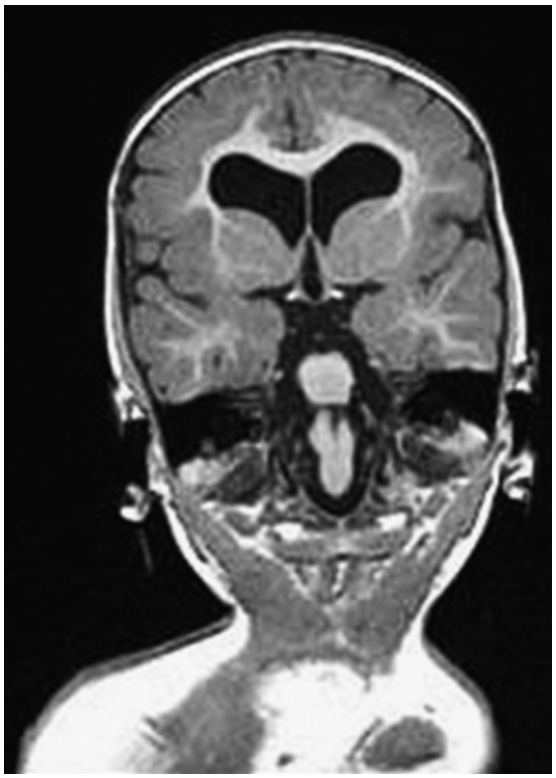


Fig. 60.3 Axial magnetic resonance imaging demonstrating diffuse bilateral pachygyria.

occipital cortex may be associated with congenital hemianopia (see below). Pachygyria of the perirolandic and occipital areas is a prominent feature of Zellweger syndrome. Pachygyria and ocular colobomas are prominent features of Baraitser–Winter syndrome.

Polymicrogyria is the most common malformation of cortical development. It occurs as the result of the interruption of the late stages of neuron migration during the stages of cortical organization. The neurons reach the cortical mantle, but the deep layers are distributed, which results in disorganized, multiple, and small gyri. A disturbance in the formation of the leptomeninges is also an important contributor to this cortical malformation.[2] Its effect on neurological function is less severe than the proliferation and migration anomalies. It may occur as an isolated focal anomaly of little consequence. The most common forms are bilateral perisylvian or frontoparietal. However, it may also occur as a diffuse disorder affecting the entire brain. As an isolated and focal disorder it has been associated with congenital hemianopia (occipital cortex) and dyslexia (left frontal and temporal cortex). It is an important feature of several genetic syndromes including Aicardi syndrome, Joubert syndrome, Zellweger spectrum, Sturge–Weber syndrome, X-linked hydrocephalus, and 22q11.2 deletion syndrome. It is also associated with numerous metabolic disorders and infections, especially cytomegalovirus.

Schizencephaly (agenetic porencephaly) is characterized by full-thickness clefts spanning the wall of the cerebral hemispheres that are lined by gray matter and often surrounded by polymicrogyric cortex. The pathogenesis is incompletely understood although it is thought to represent an *in utero* injury to the germinal matrix during the second trimester before the hemispheres form. The causes of schizencephaly are heterogeneous; they include teratogens, prenatal infections, young maternal age, alcohol use, and *EMX2* mutations.[3] The clefts may be unilateral or bilateral; the lips of the clefts may be open or closed. Seizures, hemiplegia, and mental retardation are the most common symptoms. Involvement of the occipital cortex is unusual but, when it occurs, especially when the cleft's lips are fused, a homonymous hemianopia may occur. In contrast, patients with bilateral clefts are more likely to be severely retarded, severely limited by motor problems and blindness. The blindness is not usually cortical in origin, but due to optic nerve hypoplasia, a frequent accompanying anomaly in all forms of schizencephaly.

Congenital hemianopia

Children with congenital hemianopia show little evidence of visual dysfunction; the visual field defect is often discovered later in life on a routine eye examination. There may be a history of bicycle or auto accidents, but many patients are largely unaffected.

Although the history may not raise suspicions of congenital hemianopia, certain associated ophthalmologic and systemic findings should suggest this diagnosis. Most children with a congenital hemianopia or one acquired early in life, turn their face toward the defective field when fixing on a target straight ahead of them (see Chapter 102).[4] It is not clear how this compensates for the field defect, although the intact field is "centered" on the body by this maneuver. However, a persistent face turn in a child without incomitant strabismus or nystagmus (the common ocular causes of such a turn) should prompt an evaluation of the visual fields. In some cases, the face turn is accompanied by a constant, non-alternating exotropia[5]; the exotropic eye is ipsilateral to the field defect (see Chapter 80). Theoretically, a large-angle exotropia might significantly expand the binocular visual field with the appropriate sensory adaptation (harmonious anomalous retinal correspondence); strabismus with normal retinal correspondence will not be compensatory for a hemianopic visual field defect and may present with diplopia/visual confusion.[5]

In addition to the visual field defect, face turn, and possible exodeviation, the most prominent ophthalmological finding in these children is localized changes in the optic disc and nerve fiber layer – "homonymous hemioptic atrophy" (hypoplasia). There is loss of retinal nerve fibers in the retinal sectors nasal and temporal to the disc in the eye contralateral to the field defect; in the ipsilateral eye, the loss is superior and inferior. This subtle pattern of nerve fiber loss can be seen ophthalmoscopically or with optical coherence tomography (OCT).[6] Examination of the optic discs will reveal a band-shaped atrophy of the contralateral disc and temporal atrophy of the ipsilateral disc. Since the lesions causing congenital hemianopia are almost always posterior to the lateral geniculate body, this points to trans-synaptic degeneration of the retinogeniculate striate pathways. This had been thought to only occur with prenatal or perinatal insults, but recent experiments in non-human primates and OCT and neuroimaging studies (of the optic tract) in patients with acquired hemianopias suggest that this is not the case.[7]

Isolated congenital hemianopias are typically caused by developmental anomalies of the occipital cortex.[8] These include:

- occipital lobe dysplasia: abnormality of neuronal/glial proliferation;

- occipital lobe pachygyria: abnormality of neuronal migration;
- occipital lobe polymicrogyria: abnormality of cortical organization;
- porencephaly with or without polymicrogyria;
- gangliogliomas: neoplastic abnormality of neuronal/glial proliferation;
- cerebral hemiatrophy;
- vascular malformations.

The more extensive the cortical anomaly, the more likely it is that there will be other neurological disorders including hemiplegia, seizures, and developmental delays. The majority of patients with congenital hemiplegias will have an accompanying hemianopia. Hemianopia accompanies congenital occipital cortex lesions in several syndromes including Sturge–Weber and retinocephalic vascular malformation (Wyburn–Mason) syndromes, as well as familial porencephaly.

Asymmetric injury to the periventricular ventricular white matter (periventricular leukomalacia [PVL]) can present as an isolated congenital hemianopia or, more commonly, with hemiparesis. The vast majority of cases of PVL present with bilateral involvement (see below). Rarely, congenital hemianopia associated with absence of the optic tract has been reported. It is uncertain whether these cases occurred as the result of an isolated injury to the optic tract or, more likely, injury to the visual cortex or radiations with severe trans-synaptic degeneration.[7]

Patients with congenital hemianopia are less visually disabled than those with acquired hemianopia. Our understanding of their adaptations and compensations accounting for their minimal disability is incomplete. The possibility that a face turn and/or exotropia could be compensatory has been cited above. A unique saccadic strategy limited to patients with congenital hemianopia allows them to search the blind field. This is distinctly more efficient than the multiple hypometric saccades made by the patient with an acquired hemianopia, but it can occur in congenital lesions. Moreover, in children with acquired hemianopias, the reaction time to initiate a saccade to explore the blind field is prolonged; this is not the case in congenital hemianopia.[9] Some have suggested that the extra-geniculostriate pathways may be playing a compensatory role; others have theorized that re-wiring of the uninjured brain allows it to assume the functions of the injured portion. Mechanisms facilitating visual recovery in children with brain injuries will be discussed in a later section.

Patients with isolated congenital hemianopias, in contrast to those with similar acquired defects, require very little in the way of special ophthalmologic care except to communicate with schools, employers, and government agencies (especially the driving authorities) to reassure them that many of these children are little affected by their visual field defect. If the child has a constant, non-alternating exotropia, strabismus surgery is probably contraindicated.[5]

Acquired hemianopia

Children with acquired hemianopia present in a similar fashion to adults with comparable acquired lesions. The visual acuity is usually normal, but the field defect is easily detected and the disability associated with it declared in the history. Trauma and tumor are the most important causes of acquired hemianopia in children. In contrast to congenital hemianopia, where the lesion is usually cortical, the most common site of injury is the optic radiations. A significant number of children with acquired hemianopias show some spontaneous improvement in the visual field.[10]

Perinatal insults

There are many causes of perinatal brain injury but the vast majority of them are metabolic. They may occur as the result of inherited defects in metabolic pathways, hypoglycemia, or from transient ischemia–reperfusion events. The latter account for most of the visual disability related to brain disorders in infancy. Hypoxic–ischemic brain injury in the newborn results from a simple imbalance between the brain's demand for energy and its supply during the perinatal period. In contrast, the cellular mechanisms accompanying neuronal death are complex, multifactorial, and incompletely defined.[11] The pattern of brain injury and the nature of the resulting visual deficits are determined largely by the age of the infant at the time of the insult, as well as the duration and severity of the hypoperfusion event.

The premature infant

Several types of brain injury may occur in premature infants due to a mild-to-moderate episode of hypoxia and hypoperfusion. These include PVL, periventricular hemorrhagic infarct, germinal matrix hemorrhage, intraventricular hemorrhage, and cerebellar infarction. PVL is the predominant form of brain injury and the leading cause of cerebral palsy and cognitive defects in premature infants.

Periventricular leukomalacia

Advances in neonatology have improved the long-term survival of premature infants and simultaneously reduced the overall incidence and severity of white matter injury in surviving preterm infants, especially those with a birth weight of more than 1500 g. Nevertheless, PVL remains the major brain pathology in preterm infants. It has significant visual consequences and is a major cause of visual disability in many parts of the world.

The pathogenesis of PVL is complex, but most likely involves ischemia–reperfusion in a critically ill premature infant with impaired regulation of cerebral blood flow. The lack of auto-regulation of cerebral blood flow in premature neonates and the high incidence of lung immaturity contribute to the hypoxic perfusion difficulties. In light of these pathogenetic events, the frequent co-existence of PVL and retinopathy of prematurity (see Chapter 44) should not be surprising. The association of maternal infection with PVL suggests that inflammatory mechanisms play an important secondary role in this type of brain injury. The primary cells vulnerable to hypoxic–ischemic injury in the immature brain are the premyelinating oligodendrocytes, oligodendrocyte progenitor cells, and subplate neurons. The resulting myelination disturbances are primarily the result of aberrant regeneration and repair responses of the oligodendrocyte progenitors.[12] Subplate neurons only appear transiently during brain development, but they are essential to the formation of the connections between the thalamus and visual cortex. As a result, the pathology of PVL consists of periventricular necrosis and diffuse gliosis in the cerebral white

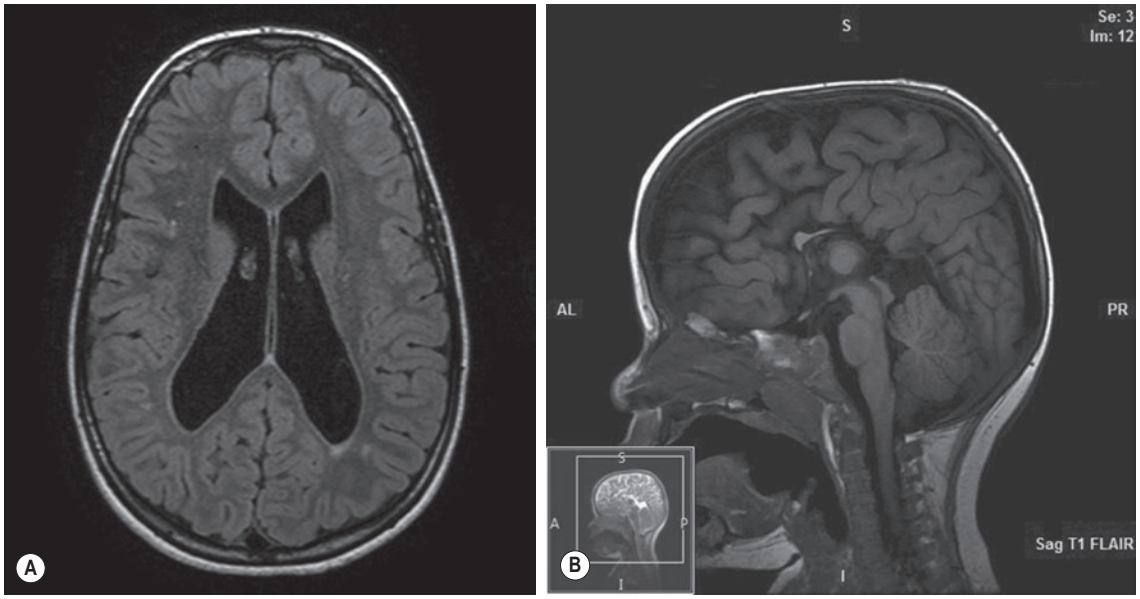


Fig. 60.4 (A) Periventricular leukomalacia in a 9-year-old child born at 25 weeks gestational age. Axial magnetic resonance imaging (MRI) reveals multiple small foci of high fluid-attenuated inversion recovery (FLAIR) signal seen in the periventricular and subcortical white matter representing ischemic changes or gliosis. The ventricles are markedly enlarged with adjacent white matter loss. (B) Sagittal MRI of a different child born at 26 weeks gestational age with periventricular leukomalacia and severe posterior corpus callosum atrophy. *([A] Courtesy of Dr Stacy Pineles. [B] Courtesy of Dr Michael Brodsky.)*

matter and neuronal loss in the thalamus, corpus callosum, and globus pallidus.[13] In long-term survivors with PVL, neuroimaging studies may show reduced cerebral white matter volume, impaired myelination, ventriculomegaly, and reduced volume in the corpus callosum (especially the posterior portion) and thalamus (Fig. 60.4A,B). Although PVL is primarily a disorder of ill, preterm babies, it does occur in near-term infants. With improved neonatal care, the pattern of white matter injury in preterm infants is evolving from cystic necrotic lesions to milder forms.[14]

The motor and visual pathways course through the periventricular white matter that is affected. As a result, motor (commonly "spastic diplegia") and visual impairment are the most common neurologic findings in PVL. The motor fibers serving the lower extremities pass more medially than those of the upper extremity and thus are more likely to be injured by the periventricular injury. The consequences for the motor system may range from a mild spastic diplegia to a severe quadraparesis. Other neurologic symptoms may include athetosis, seizures, cognitive and attention disorders.

Visual impairment is equally variable in its severity, ranging from near-blindness to minor field defects. In many patients, a selective lesion in the superior posterior periventricular white matter is correlated with inferior field loss; in other cases with more extensive damage to the optic radiations, a generalized depression of the visual field results.[15] A normal-sized optic nerve with an enlarged optic cup ("pseudoglaucomatous") is seen in many patients. It is probable that this anomalous optic nerve is not an independent contributing factor to the visual disability, but simply a "marker" for optic radiation damage. This implies that trans-synaptic degeneration has occurred, similar to the case of congenital hemianopia described above. However, the importance of recognizing that a large optic cup in a premature infant is far more likely to indicate PVL than glaucoma cannot be overemphasized. Infantile nystagmus, manifest-latent, or latent nystagmus may occur in children with PVL; most of the children with nystagmus will also have strabismus. As in all cases of cerebral palsy, reduced accommodative facility may occur in PVL. It should be specifically sought and, if found, corrected with glasses.

The long-term visual disability of children with PVL is frequently underestimated by analyzing only the visual field deficits. Visual-perceptual impairment related to PVL may go unrecognized. Dorsal stream (linked to the posterior parietal cortex) dysfunction occurs in PVL and results in a specific pattern of disability.[16] It consists of a deficit in eye–hand coordination, constructional dyspraxia, and impairment of motion perception. Less well studied, but perhaps more important, is the question concerning the visual consequences of the thalamic damage resulting from the injury to the subplate neurons. Injury to two specific subnuclei of the thalamus is found in many children with PVL. The mediodorsal nucleus through its reciprocal connections with the prefrontal lobe plays an essential role in working memory. The mediodorsal nucleus in consort with several cortical centers is vital for attention mechanisms, especially visual attention. Further studies are needed to understand the full range of visual disabilities in PVL.

There is no known treatment for PVL. The role of the ophthalmologist is to assess the visual deficits as fully as possible and counsel the child's parents, other physicians, rehabilitation specialists, and teachers about them. Refractive errors and poor accommodation, if present, should be corrected, even in severely handicapped children. Strabismus surgery may be indicated if the child's general health would not be compromised by an anesthetic and strabismus is not compensatory for a visual field defect.

Many trials are underway to see whether PVL can be prevented or lessened in its severity. Premyelinating oligodendroglia are highly vulnerable to death caused by glutamate, free radicals, and pro-inflammatory cytokines. Pharmacological agents such as memantine that block ischemia-induced glutamate

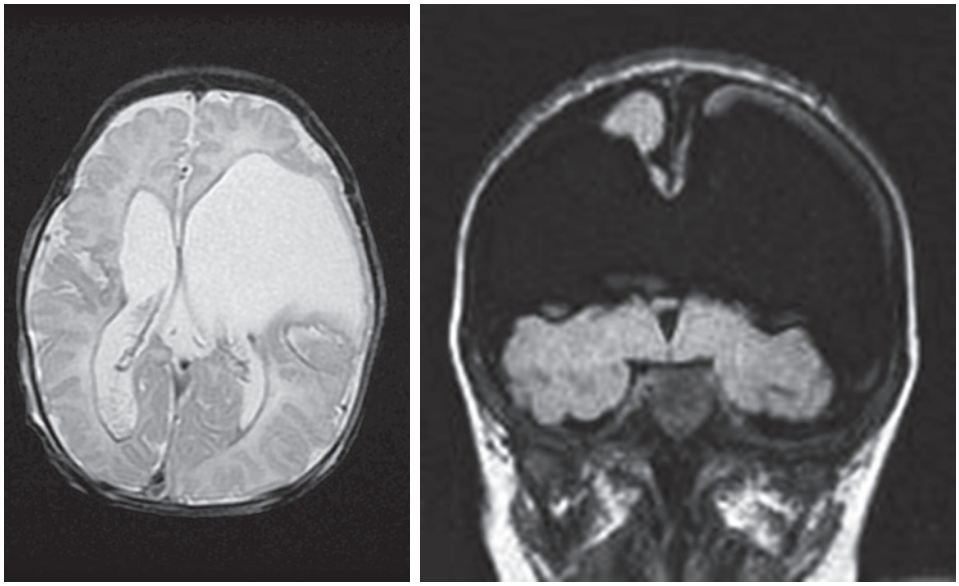


Fig. 60.5 (A) Bilateral hemorrhagic porencephaly seen on magnetic resonance imaging (MRI) in a term infant. The patient has bilateral horizontal gaze palsies and quadraparesis. (B) MRI of an infant with extensive bilateral porencephalic cyst due to perinatal cerebral hemorrhage. This was associated with a *COL4A1* mutation. *(Courtesy of Dr Michael Brodsky.)*

signal transduction may be useful in diminishing the severity of PVL. Other strategies under study include treatment with UDP-glucose and/or glial cell line-derived neurotropic factor (GDNF) that may promote endogenous self-repair by stimulating proliferation of glial cells.[17]

Periventricular and intraventricular hemorrhage

Despite advances in neonatal care, intraventricular hemorrhage remains a major complication of prematurity. It characteristically originates from the periventricular germinal matrix, a highly vascular site where glial and neuronal precursor cells are located at the head of the caudate nucleus beneath the ventricular ependyma. The vessels within the germinal matrix have very thin walls and are especially sensitive to changes in blood flow and pressure. Most intraventricular hemorrhages are an extension of a germinal matrix hemorrhage, which usually occurs within the first 48 hours after birth.[18] Periventricular and intraventricular hemorrhages in premature babies have been divided into four grades:

- grade I: germinal matrix hemorrhage with little or no intraventricular hemorrhage;
- grade II: germinal matrix hemorrhage with extension into the ventricle, but normal ventricle size;
- grade III: intraventricular hemorrhage with ventricular enlargement;
- grade IV: periventricular hemorrhagic infarction.

Grade I and II hemorrhages have a good prognosis for survival and good neurological outcome. Grade III and IV hemorrhages have a significant risk of early death or significant neurological sequelae in the survivors. The neurological complications with important visual consequences include post-hemorrhagic hydrocephalus (see Chapter 55) and infarction, and porencephalic cyst formation in the areas of the occipital-parietal cortex. Significant visual loss may occur even in vigorously treated hydrocephalic neonates as a result of direct damage to the visual cortex and secondary optic atrophy (see Chapter 59).[19] Periventricular hemorrhagic infarctions are associated with significant brain damage and more than 50% of the neonates affected have serious neurological sequelae. In many of these neonates, porencephalic cysts will develop in the area of infarction.

Porencephalic cysts are focal cavities within the cortex that have smooth walls and minimal surrounding glial reaction (Fig. 60.5A). They are the result of focal brain destruction from any cause prior to the 26th week of gestation, after which the potential for glial reactivity is minimal. A familial form of porencephaly (inherited as an autosomal dominant disorder) is associated with mutations in the *COL4A1* gene (Fig. 60.5B). Porencephalic cysts associated with periventricular hemorrhagic infarction commonly involve the optic radiations and occipital cortex and result in homonymous hemianopia and homonymous hemioptic atrophy (hypoplasia) (see above).

The term infant

Neonatal encephalopathy

Neonatal encephalopathy is a serious medical problem; it occurs relatively commonly (1 in 1000 live term births in the United States) with serious neurodevelopmental consequences. The terms "neonatal encephalopathy," "hypoxic–ischemic encephalopathy," and "birth asphyxia" are often used interchangeably. This is unfortunate. Although hypoxia and ischemia are a major factor in most cases of neonatal encephalopathy, intrauterine inflammation increasingly is recognized as a critical contributor to both normal development and injury outcome. Inflammation appears to modulate vulnerability to, and development of, brain injury.[20] Moreover, antepartum risk factors (maternal hypotension, infertility treatment, and thyroid disease) have been identified. However, even if antepartum risk factors are present, prospective magnetic resonance imaging (MRI) studies suggest that at least 80% of term infants who develop neonatal encephalopathy sustain a causative acute brain injury in the perinatal period.

The regions of the brain susceptible to injury due to hypoxia and ischemia change depending on the gestational age of the

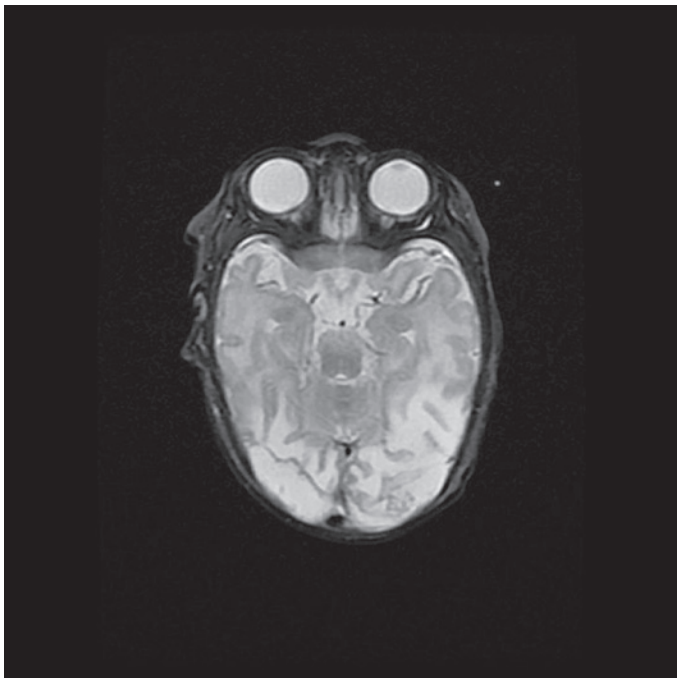


Fig. 60.6 A T2-weighted magnetic resonance imaging scan of a term infant with severe hypoxic–ischemic encephalopathy primarily involving the visual cortex.

infant at the time of injury. Unlike immature oligodendrocytes and oligodendrocyte progenitor cells, mature oligodendrocytes are resistant to hypoxic–ischemic damage. Thus, isolated deep white matter injury is not the primary feature of neonatal encephalopathy in the term infant. Instead, the main site of damage in the term infant is in the cerebral cortex intervascular boundary zones ("watershed areas"). These are the areas between the anterior and middle cerebral arteries and those between the middle and posterior cerebral arteries. The deep gray nuclei and perirolandic cortex are most likely to be damaged. As a result, the most common consequence of mild-to-moderate hypotensive events in the term infant is discrete infarctions in the frontal and parieto-occipital regions of the brain. Watershed cortical damage is the primary site of pathology but, in extensive infarcts, the underlying white matter may be affected. MRI studies may reveal (Fig. 60.6):

1. wedge-shaped infarctions in the watershed zones;
2. cortical thinning and diminution of the underlying white matter in the area of infarction;
3. *ex vacuo* dilation of the lateral ventricles;
4. the development of ulegyria (narrow and distorted gyri, a secondary gyrial anomaly) resulting from the cortical shrinkage.

A different pattern of injury is seen in neonates who suffer profound hypotension or cardio-circulatory arrest. They show injury primarily in the lateral thalami, posterior putamen, hippocampi, and corticospinal pathways, regions of the brain most active metabolically and with the highest degree of synaptic construction at birth. Some of the children develop damage in the lateral geniculate nucleus and optic radiations. Many of these infants die in infancy, but if they survive they will manifest a severe seizure disorder, quadriparesis, mental retardation, microcephaly, and blindness.

It is difficult to predict during the neonatal period which infants with signs of encephalopathy will suffer permanent neurological disability, although the use of amplitude-integrated electroencephalography and diffusion-weighted MRI appear to be promising.[21] Thirty percent of neonates with moderate encephalopathy have clinically normal outcomes. The most common neurological sequelae of neonatal encephalopathy are motor impairment, developmental delays, mental retardation, seizures, and visual impairment. The motor impairment is often a mixture of spasticity, ataxia, weakness, and athetosis. Neonatal seizures occur in the majority of infants with neonatal encephalopathy. Although they are difficult to treat and a poor prognostic sign, they are a persistent problem in only a minority. Cognitive disability occurs infrequently in moderate encephalopathy, but is a common feature in children with severe encephalopathy. Neuropsychological testing identifies memory and attention/executive disabilities as the most common cognitive consequences of neonatal injury.

Infarction of the occipital cortex may result in a wide range of visual disability depending on the location and size of the infarct. The degree of visual impairment may range from "apparent blindness" to barely detectable isolated visual field defects. The majority of these children have detectable residual vision. However, they all have variable and inconsistent visual performance. They function better when well rested and in familiar surroundings. Color perception is frequently superior to perception of form. Detection of motion may be the only consistently documented visual function. The ability to recognize a human face is frequently impaired; this is especially distressing to parents. When reaching for objects, they frequently turn their face away from the object to apparently use their peripheral vision. They may be able to read isolated letters of varying sizes on an acuity test, but unable to read whole words of a similar size.

Examination of the anterior visual pathways is usually normal. Although there is OCT evidence that trans-synaptic degeneration of the geniculostriate pathways does occur with postnatal injuries to the occipital cortex,[6,7] only in a minority of cases of neonatal encephalopathy is mild optic atrophy seen on ophthalmoscopy.[22] Optic atrophy is not a major determinant of visual disability in most cases where it is found. The pupil responses are normal. In contrast to PVL, nystagmus rarely occurs. In a minority of cases, exotropia may occur, but large angle esotropias are rarely seen. Supranuclear ocular motor abnormalities that may occur in children with neonatal encephalopathy include horizontal conjugate gaze deviations, horizontal gaze palsies, and difficulties in ocular pursuit movements. These may contribute to the child's visual disability. Accommodation should be specifically evaluated and, if found to be abnormal, treated with spectacles.

The diagnosis of neonatal encephalopathy with visual loss can usually be established on the basis of the history and other neurologic findings. Neuroimaging studies can be helpful in subtle cases with subtle vision loss and minimal neurologic abnormalities (Fig. 60.7A,B). They are also useful to document the anatomic site(s) and extent of brain damage, but they correlate poorly with functional disability. Magnetic resonance spectroscopy, diffusion-weighted imaging, and diffusion tensor imaging are advanced MRI techniques that go beyond documenting the lesion and its location (Fig. 60.8). They provide useful information on brain metabolism, microstructure, and connectivity, and so may provide quantitative biomarkers

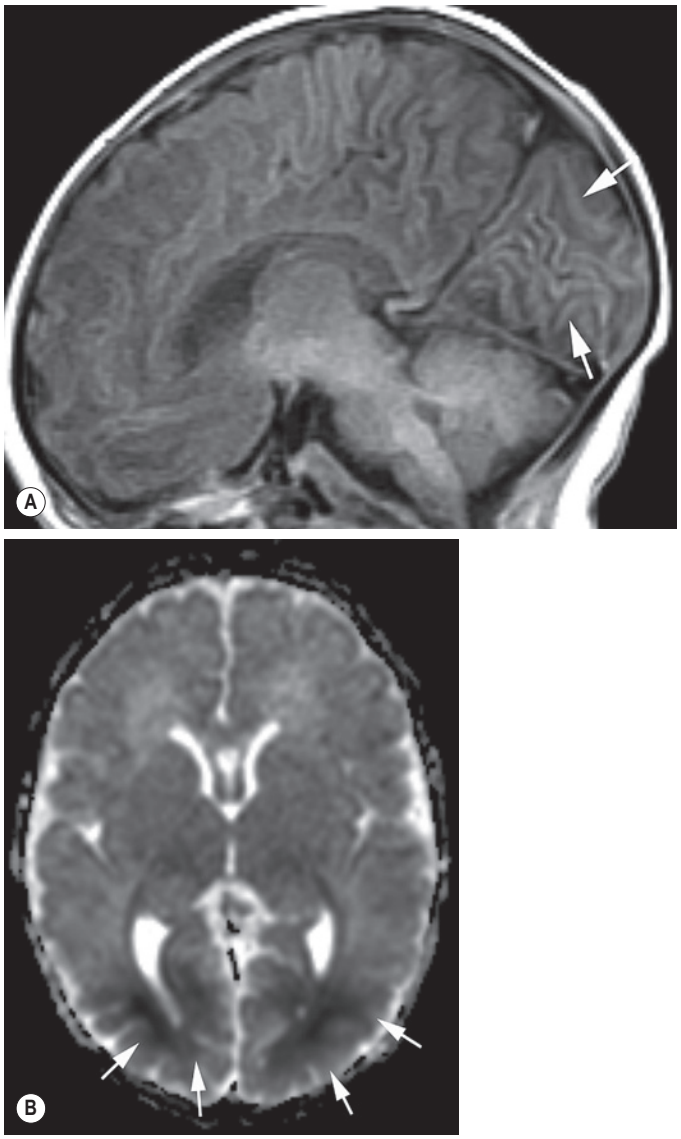


Fig. 60.7 An 8-day-old infant with seizures and profound hypoglycemia. (A) The sagittal T1-weighted image shows abnormal high signal intensity of the occipital cortex. (B) The axial diffusivity map (ADC map) shows markedly reduced diffusion in both occipital lobes (arrows on figures). The child has cortical visual impairment. *(Courtesy of Dr Jim Barkovich.)*

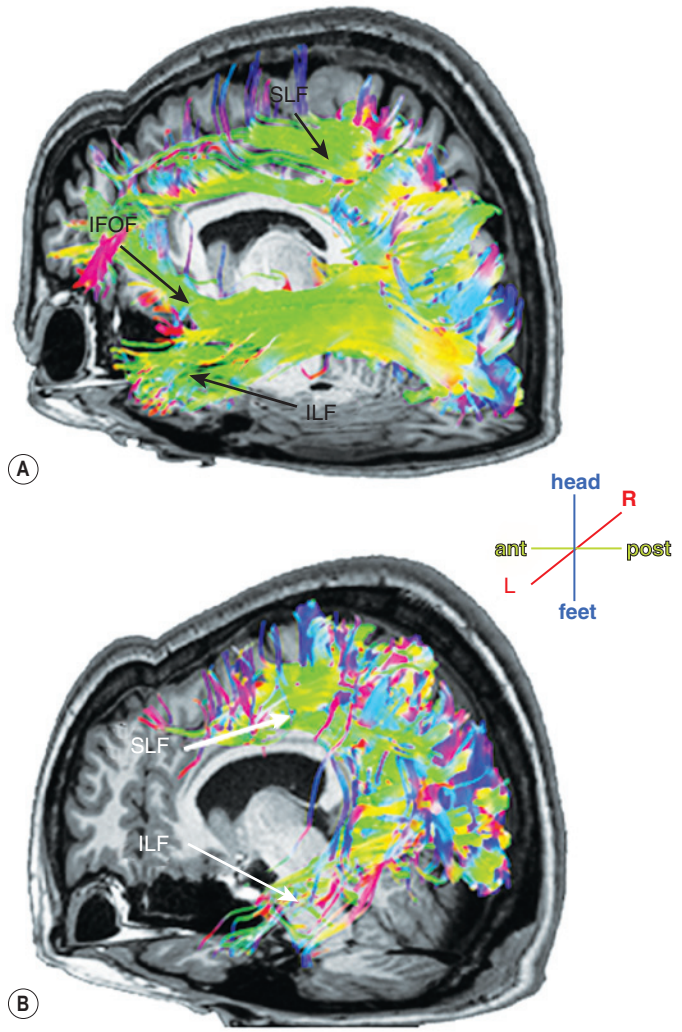


Fig. 60.8 High angular resolution diffusion-weighted imaging (HARDI) of a patient with cortical visual impairment.

for prognostication.[23] Pattern visual evoked potential (VEP) studies can be helpful in diagnosing visual cortex damage, but they are imprecise when quantitatively evaluating visual function in these children. Sweep and step VEPs may be more reliable in quantitative assessments. Vernier acuity VEPs may prove to be the most sensitive electrophysiological technique for quantitative assessment of these injuries.[24]

In caring for the child with neonatal encephalopathy and visual disability, the ophthalmologist's role is two-fold:

1. Periodic assessment of the visual disability and residual visual function.
2. Treatment of any co-existing eye disorder.

Clinical assessment of these children is difficult and time consuming, but vital as a part of the habilitation and education programs for them. Behavioral assessment techniques have been developed to assist ophthalmologists in counseling those caring for these children. The vast majority of affected children show some improvement over time, so re-evaluation is essential. There are no reliable predictors of long-term visual outcome for any specific child. Parents, educators, and other therapists should be encouraged to keep an open mind about the ultimate visual outcome, especially in early infancy when often little or no purposeful visual function can be appreciated. Intensive visual stimulation programs appear to enhance the visual recovery in these children.[25]

Until recently, no treatment was available for the brain damage that occurs in neonatal encephalopathy. However, techniques for neuroprotection of neonates have been developed. External cooling of the head or whole body in the first 6 hours after a hypoxic–ischemic insult is the only treatment currently in clinical use, and only in term infants. Cerebral hypothermia reduces the risk of death and severity of subsequent neurologic disability.[26] There is some evidence that lowering brain temperatures to lower levels than those currently recommended might provide better neuroprotection but the safety of doing so has not been established.[27] Several neuroprotective agents are being evaluated and have shown promise in preclinical and clinical trials. These

include erythropoietin, topiramate, xenon, melatonin, and allopurinol.[11]

Older children

When hypoxia, ischemia, or circulatory arrest occurs in older children, the pattern of brain injury differs from that of neonates. The physiological and biochemical differences that account for this are not yet defined. The differences are relatively minor in injuries from mild-to-moderate hypotension, although the older child is less likely to develop deep white matter injury. With profound hypotension, the older child will show basal ganglia involvement (with sparing of the thalamus) and severe diffuse cortical involvement. The relatively modest injuries suffered by many children as the result of near-drowning events probably are due to the protective effect of hypothermia and the mammalian diving reflex. The mammalian diving reflex is a physiological response to immersion in cold water that shifts blood from the extremities to the central organs. It is especially robust in children less than 6 months old.

Visual recovery in brain disorders

There is considerable evidence to suggest that the capacity of the child's visual system to recover from cerebral injury exceeds that of the adult.[25,28,29] There are several reasons that might explain this superior capacity. First, the child may develop strategies to utilize the remaining visual function. Examples of this include the large single saccade and preserved visual search capacity in cases of congenital hemianopia.[9] A second factor may be that the young brain is endowed with greater endogenous neuroprotection and repair and regeneration capacities than the adult brain.[30] A third possibility is that the child can expand the visual functions normally subserved in uninjured cortical areas outside the primary visual cortex. This has been well documented in experimental animals.[22] This might account for why motion detection (Riddoch phenomenon) is preferentially preserved in so many children with neonatal encephalopathy. There is evidence that the retina–pulvinar–MT cortex pathway that usually regresses during normal development is preserved in children who suffer post-geniculate visual injuries early in life and could, therefore, contribute to visual preservation.[31] Fourth, it is now apparent that the extent of neurological deficit after a focal brain injury cannot be accounted for by the dysfunction attributable just to it. Rather, it is determined by the functional impairment of the connected neural systems that are structurally intact.[32] Diaschisis (inhibition of function in distant portions of the brain anatomically connected to injured brain) is a major factor in determining this, but deactivation, hyperactivity, and hemispheric imbalance also play a role. Children may be more capable of recalibrating these uninjured connected systems.[32] Finally, the possibility that the extra-geniculostriate system might be capable of processing vision even in the absence of the visual cortex (blindsight) seems real. There is some evidence that it plays a role in visual recovery in children with visual impairment due to brain injury. Further defining these recovery mechanisms would be extremely useful in designing habilitation and education programs for these children.

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Delivering bad news

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"We must ask who it is the blindness confronts and what forms this confrontation will take. The parent of a symptomatic mature teenager with a consistent and extensive family history of blindness attributable to retinitis pigmentosa who is surrounded by supportive experience in coping with the disorder, well connected to low-vision and support-group resources, and deeply spiritual in their acceptance of their child's condition will be approached far differently than the socially isolated single parent of an infant newly diagnosed with optic nerve hypoplasia who has overwhelming anxiety, no experience with the disorder, an absence of spiritual connection, anger, low self-esteem, and a life of financial poverty. Rather than simply wait for the blindness to come, we must proactively address the parent's inner needs and concerns to help her or him with more than just a medical prognosis. To do otherwise would only demonstrate our own lack of vision."[1]

Introduction

Pediatric ophthalmologists are faced with the frequent challenge of discussing varying degrees of vision loss. Sometimes decreased vision in children or diplopia in adults may be reversible, while at other times it is permanent. Growing evidence indicates that quality verbal communication between physicians and patients contributes significantly to achieving better health outcomes.[2–6] Therefore, knowing how to deliver bad news effectively and constructively is essential, particularly given the time constraints of the modern medical encounter.[2,5] Furthermore, a patient's overall perception of their care is often based on the conversation surrounding the delivery of bad news.[7–13]

Historically, medical information deemed potentially injurious to a patient was withheld.[14–16] These days in North America, physicians are responsible for disclosing all information a patient wants to learn about their diagnosis and treatment.[14,17] Conveying such "bad news" has been defined as delivering any information that adversely affects a person's outlook about his or her present or future.[18] The negative impact of such news arises from the discord between a patient's expectations of the future and the actual medical situation.[19] In the field of pediatric ophthalmology, this definition might be extended to include any information that unfavorably impacts parental expectations for their child.

Varying levels of bad news exist. Universally bad news, such as informing parents that their child is blind, can be contrasted with news of a more equivocal nature in which the information conveyed leads to undesirable consequences.[20] For example, trabeculotomies might be recommended for a child with primary congenital glaucoma but the treatment and follow-up will require significant family resources while also necessitating a parent's absence from work. Although more diagnostic and treatment options are available than ever before, there are now different and more complex types of bad news to convey, such as positive genetic test results.[14]

How a patient or family receives any information, however, depends upon the life context of that individual patient/family and the unique set of experiences and beliefs they bring to the discussion.[14,18,20] Changing the phrase "breaking bad news" to "sharing life-altering information" was recently proposed to address the subjective nature of how such information is received.[21] In other words, a patient and/or a patient's family are best suited to determine the import of the news delivered in the context of their lives.[21,22] For example, it may be a relief to a family to have a child's blind, painful eye enucleated. We, as caregivers, should not make assumptions about the way the information we provide will be received.

Most of the earlier literature on delivering bad news arose from oncology and palliative care settings and centered on defining bad news, emphasizing the importance of knowing how to deliver bad news, and establishing guidelines for how to break bad news.[14,18,19] Later studies have examined barriers to delivering bad news and outcomes of different strategies for training caregivers to share life-altering information in a variety of settings.[7,20,21,23–25] Current evidence supports a need for physicians to move beyond simply supplying biomedical information into a more patient-centered approach,[2] exploring and addressing psychosocial needs in order to better care for the whole patient.[1,26,27]

Importance of knowing how to deliver bad news

Impact on patients, families, and physicians

The way bad news is delivered affects a patient or family's ability to understand[14,23,28–33] and cope[10,14,20,23,34–42] with the information given, future outlook,[20,41,42] and satisfaction with care.[7,14,23,43–47] Because delivering bad news can be complicated, miscommunication can result.[14] A patient may not understand treatment goals, or take away unrealistic expectations.[14] Quality and coordination of care can suffer as a result of poor communication, and patients' trust in their physician may be diminished.[7–13] Poorly delivered bad news can increase a patient's and/or family's distress at an already difficult time,[20] resulting in anger and increased risk of litigation.[20] On the other hand, well-broken bad news may positively impact care and even outcome.[23,29–33] Well-delivered information can help patients and families to make appropriate quality-of-life decisions,[14] such as whether to subject a child to the risks of general anesthesia or another eye surgery in spite of a limited prognosis for improvement.

In pediatric settings, the parent–child relationship can be re-shaped by how parents are informed of a child's disability.[20,48] Levin has equated news delivered to parents about childhood blindness to a "loss of personhood," as parents must adjust psychologically to adapt their expectations for themselves and their child based on the news delivered.[27] The quality of the initial discussion of a positive newborn screening result for cystic fibrosis has been described as critical to the successful follow up of these children.[49]

Not only can the delivery of bad news be hard on patients, it can also take a toll on doctors.[20] In one review, the difficulties encountered by physicians at many levels of training in various fields included: struggles with telling the truth, emotional stress experienced as a result of giving bad news – including sadness, guilt, feelings of failure – and inadequate training.[20] Anxiety, lack of confidence, fear of compounding a patient or family's suffering, and the desire to avoid a patient's emotional response may cause doctors to defer such encounters or shift responsibility for the conversation to someone else.[7,14,18,20,50–51] Physicians may be tempted to provide an overly optimistic outlook or even consider futile therapies in response to a patient's or family's emotional response to unfavorable news.[14,18,51–52] Physician inexperience,[23] young patient age,[53] poor prognosis, and/or a dearth of treatment options may also lead to heightened anxiety about delivering bad news.[14]

How to deliver bad news

Delivering bad news reflects general communication skills

Good communication "often requires greater thought and planning than a drug prescription, and unfortunately, is commonly administered in subtherapeutic doses."[19] Skills essential for effectively delivering bad news exist as a distillation of the more general set of communication skills that physicians need in order to interact well with patients.[19] Good communication in health care has been shown to increase satisfaction of both physicians and patients.[52] Higher patient satisfaction may correlate more with good communication and family involvement than with medical outcome.[23,54,55] Similarly, the humanistic aspects of the breaking bad news conversation may outweigh the information that is delivered.[52] Overall, physicians must determine an appropriate way to tell the truth, support the patient, and substantiate realistic hopes.[19]

Specific strategies for delivering bad news

While many have recognized the importance of being able to effectively deliver bad news, studies have shown that those who perform the task regularly do not feel well prepared.[14,41] The need for a specific set of communication skills – that are easy to learn and recall – has given rise to multiple paradigms to facilitate these conversations.[14,21,56–58] Such guidelines may provide a strategy to increase physicians' confidence in delivering such news, ease the flow of information, and lessen parental stress.[14] Common to all of these frameworks are techniques that help to determine an individual patient's or family's values and wishes. This information is used to respond appropriately to a patient's emotional response, promoting their active participation in treatment decisions.[14]

Some of the communication strategies established for delivering bad news are the SEGUE,[56] PACE,[57] SPIKES,[14] "The 6 E's,"[58] and SLAI.[21] SEGUE is a framework for teaching and assessing communication skills among US and Canadian medical students that includes: **S**etting the stage, **E**liciting the information, **G**iving information, **U**nderstanding the recipient's perspective, and **E**nding the encounter.[56] PACE was developed as a way to help families learn about their child's chronic condition and includes: **P**lanning the setting, **A**ssessing the recipient's knowledge/needs, **C**hoosing appropriate strategies, and **E**valuating understanding.[57] SPIKES was developed as a six-step protocol for breaking bad news to cancer patients and describes: **S**etting up the interview, assessing the recipient's **P**erception of the situation, obtaining an **I**nvitation to proceed, giving **K**nowledge, **E**mpathizing and addressing patient emotions, and **S**ummarizing the encounter.[14] "The 6 E's" system was established for the pediatric oncology setting and detailed: **E**stablishing agreement about open communication, **E**ngaging the patient, **E**xploring their knowledge, **E**xplaining the news, **E**mpathizing with their emotion, and **E**ncouraging/supporting the patient and family.[58] The SLAI guidelines for "sharing life-altering information" was developed by a multidisciplinary team who modified the SPIKES protocol for a pediatric setting based on recent literature, the consensus of a task force, and experiences of videotaped parents.[21] Changes were made based on the belief that a specialized skill set is needed to effectively deliver bad news in pediatric settings.[21,53]

The well-established SPIKES[14] and pediatric-focused SLAI[21] protocols will be described in more detail here (Table 61.1). When **S**etting up the interview, it is important to determine who will be present. In pediatric ophthalmology, this would include the question of whether or not the child should be present and, if so, how much information the parents want to share with the child.[21] If the child is old enough, he or she should be included in the conversation.[21] To promote establishing a connection with patient and family, interruptions should be minimized and the physician should sit down. Everyone present should be introduced, including his or her role. With regards to assessing a patient or family's **P**erception,

Table 61.1 Recommendations for sharing life-altering information in pediatric settings[14,21]

	Recommendations	Sample questions/ statements
Setting	Minimize interruptions Sit down Introduce everyone in room	Who will participate? To what extent should the child be involved?
Perception	Ask before telling Use open-ended questions Correct misinformation	What is your understanding of your child's condition?
Invitation/ involvement	Repeat some/all of what patient says to show you have been listening	How many details would you like to know?
Knowledge	Warning shot Convey key points at an appropriate level Avoid jargon Cultural sensitivity Check family's understanding	I'm afraid I have some hard news to share.
Emotions/ empathy	Empathize Explore patient's emotions Validate	I know you were not expecting this. Tell me more about that. What do you mean? I can see how you would feel that way.
Strategy/ summary	Treatment recommendations and timeline Teach-back method to verify understanding Provide resources	We will be here to support you.

Adapted from: Baile WF, Buckman R, Lenzi R, et al. SPIKES – A six step protocol for delivering bad news: application to the patient with cancer. Oncologist 2000; 5: 302–11; Wolfe AD, Frierdich SA, Wish J, et al. Sharing life-altering information: development of pediatric hospital guidelines and team training. J Palliat Med 2014; 17: 1011–18.

the importance of asking before telling has been stressed.[14] Physicians should use open-ended questions to determine a patient or family's understanding of the current situation.[14] Inquiring first allows: (1) correction of any misinformation, (2) packaging of information to be delivered according to a patient's ability to understand, and (3) unveiling of unrealistic expectations on the part of the patient or family.[14] For example, is a parent mainly concerned about their junior high school baseball player returning to play immediately following the diagnosis of a hyphema?

Next, it is critical to determine how much information a patient or family would like to know by **I**nviting them to share their desires about this and **I**nvolving them in the care.[14,21] Repeating what a patient or family member has said may facilitate the conversation by showing that the physician has been listening.[19] When delivering **K**nowledge, it is critical to fire a "warning shot" followed by a pause to let a patient or family quickly prepare for the bad news that is coming. Such statements are best preceded by phrases such as, "I am so sorry to tell you that …" Use of the phrase, "There is nothing more we can do for you" should be avoided[14] as, for example, some patients may be helped considerably by low vision evaluation. It is helpful for a physician to be aware of a patient or family's cultural beliefs.[21,59] In general, physicians should deliver information in appropriate amounts,[21] avoiding the use of technical terms and conveying information at a level the patient or patient's family can understand, periodically checking comprehension, or asking the patient to repeat or summarize what they have heard.[14,21]

This recommendation is particularly important in light of recent research in health literacy. This has shown that aspects of the health care setting aside from standard reading skills impact patients' health comprehension and outcomes.[2,60–63] While half of American adults struggle with standard print literacy,[2,64–67] other factors that may limit patients' understanding include the level or complexity of any visual aids, handouts, or videos provided; the demands and assumptions of health care organizations; and the communication skills of health care workers.[2,60–63] Most patients prefer to receive health information in a face-to-face encounter with their clinical providers, but a discrepancy between patient and provider of oral/aural literacy levels creates a barrier to patient learning and is associated with poor health outcomes.[2] Therefore, tailoring the discussion and providing appropriate level educational materials are imperative for effective delivery of life-altering information.

Many physicians find addressing a patient's **E**motions to be the most challenging aspect of delivering bad news.[14,68–69] Responding appropriately requires several steps, including observing and identifying the emotion, seeking the origin of the emotion, and connecting the response with its origin. An empathetic statement might be, "I know you were not expecting this," or, "I was hoping for a different result." Physicians should be willing to ask exploratory questions to determine the root of a patient's response to the news, if it is not clear, for example, "Tell me more about that," or "What do you mean?" It is also important to validate a patient's response using phrases such as, "It is no wonder that you feel that way." A combination of empathy, exploration, and validation can be used to support the patient as the conversation moves into the mutual development of a treatment plan, or **S**trategy.[14] Assisting a patient to develop a clear plan, including treatment recommendations and a timeline, may minimize their anxiety and uncertainty moving forward. Summarizing the conversation should incorporate a "teach-back" method,[2,70] allowing a physician to verify that a patient or family has understood the discussion and plan. Providing information about support services can be helpful at this time.

Training in the delivery of bad news

A 2010 study of 253 pediatric residents, fellows, and attending physicians (consultants) surveyed at one major United States academic center found that half to two-thirds of fellows and attending physicians did not feel "sufficiently knowledgeable" to deliver bad news.[23] Participants cited time limitations, neglect of the subject, absence of positive modeling by instructors, and lack of awareness regarding relevant resources as educational barriers.[23]

Training modules in delivering bad news have been developed for pediatric medical settings. Vail et al. videotaped hospital consultants (attending physicians) from a range of

specialties in the United Kingdom delivering bad news to simulated patients.[26] These conversations, coded using the Roter Interaction Analysis System, revealed that hospital consultants focused mainly on relaying biomedical information and did not actively involve patients in the consultation.[26] Tobler et al. evaluated the impact of a simulation-enhanced breaking bad news workshop in pediatrics and found that teaching these skills in a systematic fashion can be effective.[24] Wolfe et al. introduced the SLAI guidelines with a short didactic session that integrated videotaped parent recollections and group critique of videotaped role-play scenarios demonstrating SLAI encounters.[21] Reed et al. studied pediatric residents and found improvement in the videotaped delivery of bad news during standardized patient encounters immediately and 3 months after the "GRIEV_ING Death Notification Protocol" was reviewed.[25]

Because conversations surrounding the delivery of life-altering information are dynamic,[71] viewing successful demonstration of such skills in real clinical situations and practicing the skills are critical [20–21,23,25] for determining how guidelines can be adapted to each unique clinical encounter.[72] Whether or not such interventions lead to long-term improvements in delivering bad news, however, remains to be seen.[20,73] Awareness of such protocols may not lead to their utilization.[23] Outcomes of many studies to date have relied on participants' self-assessments. Furthermore, while having protocols in place for delivering bad news may lessen stress for those responsible for delivering such news,[20,74,75] it is difficult to evaluate whether or not these guidelines have increased patient satisfaction.

Conclusion

Re-focusing on patient-centered care

The communication skills involved in the delivery of bad news can be taught and learned just like any other clinical skill.[19,76] The essential elements, though, may be "courage, brains, and heart": the ability of a physician to calm his or her own anxiety, convey clinical knowledge and accumulated experience in a user-friendly way, and express real emotion while acknowledging patient emotions and encouraging discussion.[77] *How* a message is conveyed may be even more important than the information that is conveyed,[78] and these difficult conversations must center on the psychosocial needs of the patient. Nothing can change the fact there will always be bad news to communicate, but the way in which life-altering information is shared will heavily influence patient and family perceptions and remembrances of their overall care.[7,8,11,79,80]

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Common issues arising in children with visual impairment

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Introduction

Visual impairment (VI), defined as a reduction of visual acuity and/or visual field loss, is diagnosed from the combination of history, physical examination, electrodiagnostic testing, genetic evaluation, and neuroimaging. Following counseling of the family regarding the diagnosis, the professional needs to provide support for vision habilitation.

Promotion of vision development

Vision develops as the child matures. However, children with visual impairment in the first year of life have different vision and developmental trajectories. For the majority of these children, vision will improve but, in order to do so, the child requires opportunities to view and identify.

Normally, this process is spontaneous, but infants with VI must be encouraged to use their sight. In addition to limitations in vision, visual interaction can be reduced by defective eye movements, marked developmental delay, or visual attention disorders. Although visual learning continues throughout life, the rate of acquisition of visual skills is greatest during infancy. The development and structuring of the visual brain is influenced by visual input. Ideally, the visual environment should be rewarding, meaningful, and increasingly complex – otherwise, there is a loss of opportunity to fully develop the visual potential. Vision stimulation can improve visual potential.[1] It should start immediately after diagnosis. Professionals working with VI infants must understand the visual abilities. It is important to avoid repetitive visual stimuli, such as flashing lights, and to make interactions increasingly meaningful for learning. The facilitation of visual development can be carried out by family members throughout the day when the infant is alert.

The majority of children with significant congenital visual loss appear to have little or no vision during early infancy, but most develop useful sight later. There are two reasons for this:

1. Visual acuity, fields, eye movements, accommodation, perception, and cognitive factors rapidly improve after birth.
2. The vision may be so severely reduced by the combination of physiologic, ocular, or neurologic factors that they cannot use their vision spontaneously and experience delayed visual development.

Because the maturation of the brain and visual system is stimulus dependent, encouraging these infants to use their sight is critical.

Early interventions

The habilitation (or rehabilitation) of children with visual impairment results from their physical, emotional, and intellectual growth responding to skilled, early intervention.[2] The effect of visual loss and other disabilities on development is complex. A multidisciplinary approach is an effective way to deal with VI children. The team may include ophthalmologists, pediatricians, geneticists, nurses, psychologists, speech–language pathologists, audiologists, physiotherapists, and orientation and mobility specialists. Close co-operation between the professionals dealing with the visually impaired child is important. When the parents are included as part of the team, they become more effective in the management of their children. The parents should receive copies of reports related to their child. In addition, the team should advocate for blind people, educate the community, and participate in research.

The multidisciplinary team will consider many areas of child development. This, in turn, will allow the individual with visual impairment to be better able to participate in activities in the home, school, and community. In addition, these groups are often linked to several community organizations, which help to integrate individuals into varying activities, including sports and social events.

Development in the child with visual impairment

Conceptual development

Visual impairment has a noticeable effect on cognition. Reduced vision results in fragmented processing of information, as only a part of the object can be seen or felt at one time. The relationships to other objects may be lost. In addition, children with visual limitations often are less influenced by the environment. This may lead to limited interaction and exploration, particularly with objects outside their reach. The attention span in VI children is usually shorter than for sighted children.

Given these features, these children may become passive and understimulated if experiences are not brought to them. Therefore, difficulties arise when they are assessed about their knowledge of their environment. They may have challenges in organization and verification of information. There are many other features that may affect concept development. These features include, but are not limited to, object permanence, causal relationship, patterning, classification, and relative sizes. As a result, more time may be needed to establish these concepts. This does not necessarily indicate poor cognitive ability, but insufficient opportunity to acquire the skills and information that would be normal for a sighted child. The development of visual motor skills, arrangement of objects in space, and constructive play are also affected. VI children often avoid activities such as construction toys, puzzles, and drawing. Making experiences available and encouraging them to use their residual vision is essential.

Motor development

VI children who are raised in a rewarding, stimulating environment provided by loving, informed parents who are supported by professionals, develop motor skills faster than those who are understimulated.[3] Even infants with severe visual loss, reared under ideal circumstances, may experience motor delays. Often, there is early delay in hand utilization. Crawling and independent walking may begin late, whereas unsupported sitting and standing may be age-appropriate. Understimulated congenitally blind infants frequently develop generalized hypotonia with poor posture, delayed motor skills and poor coordination, and walk with a gait disturbance. It is the self-initiated mobility that tends to be problematic. When intervention is not started early, these problems become permanent. Moreover, physical fitness in older VI children is often poor from habitually reduced physical activity.[4]

Blind infants without brain damage are usually quiet, passive, and require encouragement to be mobile. They may not acquire skills through "incidental" learning, as do the sighted. Motor tasks such as sitting, pushing, pulling, jumping, and early aspects of orientation and mobility must be taught. Partially sighted children usually learn to move about normally and cannot be distinguished from the sighted, unless they are required to carry out balance activities.

Language development

In order for VI infants to learn from hearing, their environment needs to be optimized by reducing background noise and encouraging the child to listen to meaningful sounds. They learn to recognize voices and anticipate events through sound, smell, and touch. Early language in children with visual impairment tends to parallel their exposure to language.

Without the full range of sensory information, language concepts, and words and phrases retained from overheard conversations are based on auditory memory, not direct observation experience. Language skills become stilted, more self-oriented, and word meanings are limited.[5] Often, children with visual impairment have limited initiation in conversation. There may be a lack of descriptors. Limited vision leads to a lack of language experiences. Children with these types of language difficulties sometimes use sophisticated sentences, without fully understanding their meaning. Intervention services minimize this problem. Self-awareness within the environment may be limited, leading to difficulties in personal pronoun usage.

Social and emotional development

Most young VI infants have poor vision, which may improve with maturation. However, the parents miss the rewarding experiences of mutual gaze and smiling, an important part of bonding. Although these infants smile and respond to voices and touch, the responses are subtle. If not addressed, a child may become less interested in interactions with others. The early intervention specialist must interpret the infant's signals to the parents and encourage them to keep their babies nearby, talking to them often.

Older children with visual impairment have difficulty in sensing their effect on their peers because they may not see "body language" or facial expression. They may not be able to see who is available for play, leading to isolation and persistent egocentric behavior. There may be difficulties in initiating play with peers. Because VI children need more structure and predictability in their environments, they are often resistant to change; their behavior may appear rigid. The introduction of activities of daily living may be challenging. Many independent living skills are introduced by watching. When a visual impairment is present, feeding, self-care, and toileting may be delayed.

Education

Visual disorders have a major impact on education: normally, learning requires good vision. The education of the blind is a specialized field. Educators are important in the lives of VI children. The teachers who plan the curricula and teach the students require special training and experience. In addition to the usual subjects adopted from the sighted curriculum, the education includes concept formation; orientation and mobility; daily living skills; and non-visual communication in reading, writing, speaking, listening, and the use of technical aids. To succeed, educators must understand the ocular or neurologic visual disorders, the cognitive abilities, and the health issues facing their students. This requires good parent–teacher relationships and access to information from treating ophthalmologists.

The distance acuity determines where the students should sit in the classroom and how much board work is required.

Those with homonymous hemianopia must be seated so that their functioning visual field is directed toward the teacher and the class. Children with severe peripheral field loss, but intact acuity, function better if they are further away from the blackboard. Students with photosensitivity (as in aniridia, cone dystrophy, or albinism) must not be placed next to a window where the light is most intense. Appropriate lighting, individually adjusted, is critical. Impaired accommodation, contrast sensitivity, color perception, or eye movements can adversely affect learning. It is helpful for educators to understand the reasons for a head turn or movements associated with nystagmus. When the visual disorder is progressive, the rate of deterioration determines the timing of introduction of Braille and assistive devices. Visual aids are more effective when the educators are involved in the transition and instructions.

Since many VI children have neurodevelopmental disabilities, educators require detailed information about them. Teachers for the visually impaired often accompany students to appointments with ophthalmologists and other physicians; it is helpful when they receive copies of the medical reports. Educators should participate in the multidisciplinary team.

It is important to recognize that a child with visual impairment may not have had the same developmental exposures prior to school entry. Many skills require opportunity and experience. Commonly, there is a greater focus on academic-based activities. Assessment of visual function is important for learning. Visual acuity can offer some information as to the amount of power needed to identify at near.

Children with visual impairment may have difficulties with:

- copying from the board;
- written output;
- reading comprehension (confusing similar words; failure to read full sentence due to restricted fields, skipping lines, losing place when reading);
- performance activities – puzzles, word finding, misalignment in math problems, visual concepts, conservation of size.

There are multiple strategies to assist in academic activities. The first is visual acuity optimization with the use of glasses. Other strategies include:

- environmental conditions (lighting, positioning, access to a slant board to improve posture);
- adaptations (optimizing contrast);
- physical enlargements;
- reading window;
- magnification (low magnification for reading; higher for distant details);
- electronic equipment with application software (text to speech);
- Braille.

In considering strategies, the professional must consider each individual child. Many children with visual impairment may enter school with fragmented skills. This not only includes school-based skills such as written output and coloring, but also other dexterity tasks such as opening containers. Although introduction of low vision aids (magnification) can help with identification, children may have difficulty in effectively using the equipment initially. These difficulties will be compounded on multifaceted activities such as copying information from a distance. Often, the easiest strategy will be to enlarge the material.

The education of children with cortical visual impairment (CVI) and ocular visual loss is different.[6] With purely ocular disorders, visual input may be reduced, but neural processing is normal. Thus, visual enrichment and training to scan efficiently are useful. For children with CVI, this approach does not work: visual input must be controlled, to avoid "overloading." Images should be simple and presented in isolation. In their training, teachers for the visually impaired should be exposed to the management of the neurologically and visually impaired child, since this combination of disabilities is increasingly common.

Previously, severely VI students were educated in segregated schools, but now, in many regions of the world, they are "integrated" into classrooms. This has benefits and disadvantages.[7,8] Full integration may lead to underestimation of the disability and is often detrimental to the multi-disabled visually impaired, who learn best in a carefully controlled classroom.

Orientation and mobility

Orientation is the understanding of one's location; mobility is movement from one area to another. Orientation and mobility (O&M) teaches concepts and skills to children with visual impairment regarding how to travel safely and efficiently in different environments. O&M specialists need to know about the visual disorders, the cognitive and neurodevelopmental disabilities, and the emotional issues of each VI child. They are members of the multidisciplinary team. Successful O&M starts early when basic sensory awareness of the environment is formed. It is much more than just training to use a white stick or cane.

O&M cannot be taught by words or by models. It must be experienced in the real world. While it begins in infancy, instruction continues in preschool years. The most common methods of O&M are sighted guides, cane, mobility devices, guide dogs, electronic and ultrasonic travel aids, and computer-generated alternative training.[9]

Assistive technology

Technology has helped the visually impaired.[10] Assistive or adoptive technology has improved the way they are educated or trained and has increased employment opportunities. When assistive technology is offered, the child's visual and intellectual abilities should be evaluated. This should include the individual's ability to use, adjust, and maintain the device in varying environments. When considering a device, the professional needs to consider the main tasks that the child with visual impairment needs to accomplish. For an exclusive reading-based activity, this may be done with magnification and the use of a reading window. For comprehension of a subject, this may be more effectively managed from an auditory device or computer software.

There are a number of devices listed on the Web, ranging from simple magnifiers to computer screen magnification (or other electronic devices), Windows-based tutorials, Braille translation of software, portable note takers, Braille writing equipment, scanners, voice simulation programs, to a variety of video magnifiers or closed-circuit televisions. It should be

noted that many electronic devices can be used to modify or optimize contrast, color, and lighting. Some devices will enlarge but provide a space for the child to perform dexterity tasks. When possible, distant material should be presented at near. A SMART Board can present information shown at distance directly onto a computer screen (SMART Technologies Inc., Calgary, Canada).

One should remember that there is a wide array of different optical devices to assist in activities outside reading/magnification. These include adaptive strategies such as large print checks or enlarged buttons on phones. There are varying audio devices such as talking calculators, clocks, and label readers. There are accessories to handheld devices, such as global positioning system (GPS) navigators and screen readers. In addition, there are multiple pieces of adaptive equipment for food preparation, to assist in appliance use, and home safety.

The use of adaptive equipment should be co-ordinated with other therapies to optimize their use. Assistive technology is a basic tool, like pencil and paper for sighted students and, as they grow, assistive technology use is a continuous process. It is beneficial to introduce these services before school age, so that young VI children may have a chance to learn with them: early referral is important.

Neurodevelopmental issues and the child with visual impairment

Neurodevelopmental disabilities are associated with a number of ocular disorders. They are seen in most children with cortical visual impairment.[11] Many VI children have additional disabilities, which make habilitation more complex.[12] For intervention specialists, it is suboptimal to have experience only with visual disorders.

As previously mentioned, there are multiple domains of child development that are associated with children with visual impairment. Cognition is frequently affected in VI children.[13] The diagnosis of intellectual deficit is difficult and best made by skilled persons such as child psychologists. Children with severe visual impairment can memorize words and phrases, but without experience, they have less understanding of their meaning. The psychologist must distinguish understimulation from intellectual deficit. Cognitive deficits are even more evident in children with cortical visual impairment.[14]

In addition to developmental disabilities, there are a host of common health conditions. Epilepsy is more common among the visually impaired than in the general population. Uncontrolled seizures may result in visual unresponsiveness, which is temporary if the seizures can be controlled. Sedative anticonvulsant drugs should be avoided since they impair attention and learning. In addition, structural brain anomalies are also more common. Given these features, it is important that patients are assessed for the presence of these conditions, as the optimization of health often can lead to improved visual function.

Hearing loss can also be present in the context of visual impairment. In some genetic conditions, hearing loss is part of the condition, such as Norrie disease, Usher syndrome, and CHARGE association. Some children, such as those born prematurely, are also at risk for hearing loss and visual impairment. Given their greater reliance on hearing and the higher prevalence of hearing problems, Hearing tests are particularly important for this group. When hearing loss is present, children need referral to appropriate services. The development and management of the deafblind child is unique (see Chapter 99).

It should be evident to the ophthalmologist when a child has more than one etiological cause for their visual impairment. In the presence of structural eye or optic nerve disease, there may be a structural anomaly within the brain. For example, children with optic nerve hypoplasia can have several structural brain anomalies, such as a schizencephaly, which may cause a cortical visual impairment. Therefore, when functional vision is not in keeping with a diagnosis, additional investigations may be appropriate.

Blind mannerisms

Many children with severe visual impairment exhibit stereotyped behaviors – body rocking, repetitive handling of objects, hand and finger movements, lying face downwards, and jumping.[15] Blind mannerisms need to be carefully analyzed and appropriately managed. They should not be confused with autism or Tourette syndrome.[16]

Stereotyped behavior involving the visual system includes eye rubbing, pressing, poking, gazing compulsively at light, staring at hands, flicking fingers in front of the eyes against a light source, pulling on eyelids, tapping or hitting their globes, repeatedly blinking, or rolling the eyes. Rubbing, pressing, and poking the eyes are grouped together as "oculodigital phenomena."

Eye rubbing is observed in normal or disabled, fatigued children. Eye pressing occurs with severe bilateral, but usually not total, congenital visual loss, usually of retinal cause. The cause of eye pressing is unknown: it may be stimulatory, requiring functioning retinal ganglion cells. This type of stimulation occurs when the vision cannot provide well-formed, sustained images. It occurs when the child is bored, anxious, or during various activities, such as listening to music. It tends to be prolonged and persistent but is not painful. Orbital fat atrophy may result causing enophthalmos. In order to reduce eye pressing parents should continually keep the child's hands busy and remove them from their eyes during the first years of life, when eye pressing is most intense. Later, the urge to eye press diminishes. Eye poking is deliberate and harmful. Usually, eye poking causes pain and it is not unusual for the child to scream afterwards. Eye poking occurs in severely multi-disabled or emotionally disturbed children, who are not necessarily visually impaired. It can cause corneal scarring, infection, retinal detachment, intraocular bleeding, and cataracts; it may lead to blindness.

Compulsive light gazing is one of the signs of cortical visual impairment. VI children who flicker their fingers in front of their eyes against a light source are also light gazers. Mannerisms in children with visual impairment are often influenced by the underlying diagnosis, the presence of comorbid developmental impairments, and level of visual impairment. In most conditions, as the child ages, the mannerisms tend to decrease in frequency.[17]

Behavioral problems

Professionals who are not familiar with VI children may draw the wrong conclusions from their mannerisms, speech,

posture, facial expressions, and psychological test results. These children may be misdiagnosed as emotionally disturbed or unintelligent. Patients with visual impairment are more prone to social isolation. So, behavioral disorders are more common among the visually impaired than among the sighted, especially with additional disabilities.

The assessment of behavioral deviations may require multiple visits. The cause is often simple, but when more complex, the treatment needs to be directed to the family. The psychologist or psychiatrist needs to be familiar with visual impairment and should preferably be part of the multidisciplinary team.

Sleep

Sleep disturbances are increasingly common in Western societies due to changing lifestyles. In healthy children, these sleep difficulties tend to be transient and respond well to sleep hygiene techniques. In contrast, in children with neurodevelopmental disabilities including visual impairment, they tend to be more frequent, persistent, and severe and may not respond to sleep hygiene interventions.[18] The prevalence has been reported greater than 80% in children with intellectual disability and visual impairment.[19] Circadian rhythm sleep disorders (CRSD) are by far the most common,[20] followed by sleep disordered breathing,[21] parasomnias,[22] and restless leg syndrome.[23] Most of these sleep disorders present differently to those seen in adults.

Adverse consequences of impaired sleep

Sleep is a vital restorative neurological function. It is not surprising that severe, persistent sleep deprivation can lead to gradual loss of neurons in various areas of the brain, but more so in the frontal lobes where executive cognitive functions are generated. The behavioral manifestations of inadequate sleep include inattentiveness, aggressiveness, hyperactivity, impulsivity, and mood changes. Cognitive manifestations are impaired comprehension, deficits in reasoning, and memory formation. School failure is common. Health disturbances are also frequent such as impaired immunologic defenses resulting in more frequent infections and even cancer, cardiovascular difficulties, obesity and endocrine disturbances, tendency to accidents, and increased suicide rates among teenagers.[20]

Causes of sleep disturbances

Excessive or inappropriately timed light exposure, leading to CRSD, is the most common cause of sleep difficulties today, which suggests that increasing attention should be paid to environmental light pollution. Light inhibits pineal melatonin production, while the absence of light promotes it. Visually impaired children can have a special type of CRSD resulting from their ocular visual loss. Total absence of light input into the hypothalamus results in free-running sleep/wake rhythm. This is rare in children because total blindness is infrequent. In the absence of light, the suprachiasmatic nuclei begin to promote rhythmicity according to their own endogenous neuronal rhythms. These are usually longer than 24 hours. Therefore, the pineal melatonin production is progressively delayed every day and with it the sleep/wake patterns. The only treatment that can stop this persistent shifting is timed melatonin administration given at bedtime.[24] Children with cortical visual impairments do not exhibit free-running sleep/wake rhythms because the environmental light input via the retina into the hypothalamus is preserved.

Cognitive processes via the cerebral cortex and the thalamus also have strong regulatory inputs into the suprachiasmatic nuclei and pineal melatonin production. The perception of environmental changes and responses to it very much influence human sleep patterns. When the brain functions are disturbed, the prevalence of sleep difficulties may be as high as 80–100%. These sleep disturbances may present as difficulties falling asleep, frequent nocturnal waking lasting from minutes to hours, early morning awakenings, day/night reversals, or advanced sleep onset.

Management of sleep difficulties

When persistent or recurring sleep difficulties are noted, it is essential to identify the underlying cause. In this way, appropriate treatments can be chosen. Family physicians and a number of different specialists can deal with the management of many sleep problems, but increasingly multidisciplinary sleep clinics are becoming established for children. A detailed sleep history and a physical examination are necessary. The caregivers are often asked to document their child's sleep in a diary for 7–10 days. Most sleep clinics use wrist actigraphs that record limb movements and, therefore, more objectively identify periods of sleep (inactivity) and wakefulness (activity) than parental logs. Polysomnography, nocturnal video recordings, and neurologic and metabolic tests are occasionally needed to secure a diagnosis of CRSD and other sleep difficulties.

Sleep disturbances are not an inevitable part of neurodevelopmental disabilities (including visual impairment), and in most instances they can be treated. They must never be ignored. Behavioral, educational, and other types of interventions are ineffective without correcting severe sleep disturbances. Many physicians have received inadequate training in sleep medicine and they tend to overprescribe hypnotics. Persistent use of hypnotics is not recommended for children because of the high frequency of adverse events and because their benefits are usually short lived.

The treatment of CRSD usually starts with the introduction of sleep promotion techniques.[25] For children who do not have significant neurodevelopmental disabilities, modification of sleep environment and sleep habits usually work very well. For the disabled, the sleep hygiene interventions must be individually tailored to their cognitive strengths and weaknesses. However, with increasing loss of cognition, sleep hygiene is harder to enforce, less effective, and may even be ineffective. Melatonin-replacement therapy is now recommended by the American Academy of Sleep Medicine for the treatment of CRSD. It is simple and highly effective, lacks adverse effects, and acts quickly.[26] Melatonin is not addictive, does not conflict with other medications, and tolerance does not develop.[20] However, the therapeutic evidence for melatonin use in children with visual impairment is limited, as this population is rare, heterogeneous, and fraught with many comorbid conditions.[27–29] In patients with no light perception without neurodevelopmental disabilities, a small dose of 2 mg at night often suffices. In patients with visual impairment and a neurodevelopmental disability, a larger dose may be needed.

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Visual conversion disorders: fabricated or exaggerated symptoms in children

David S Taylor and Luis Amaya

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Features and definitions of visual conversion disorder

Many terms used are useful (Table 63.1) but none perfectly encapsulates what we refer to as visual conversion disorder (VCD). Children commonly present to ophthalmologists not only with symptoms that do not fit in with known ophthalmic diseases but that also must be *proved* to have characteristics that *definitely cannot be caused by organic disease*. VCD is not just a diagnosis of exclusion but one that is made by positive identification of signs that cannot be due to disease. It is safer to assign those without positive diagnosis to an "unknown cause – to be reviewed" category than to assign them an incorrect diagnosis for any reason.

Many symptoms that children describe are not understandable but they are not necessarily fabricated. A child's naïve description of a normal phenomenon is easily, falsely, taken as an abnormal or fabricated one. The child's interpretation is not usually a conscious deception.[1]

The major characteristics of VCD are as follows (modified from the Diagnostic and Statistical Manual, Fourth Edition [DSM-IV] of the American Psychiatric Association[2]):

- One or more symptoms or deficits are present that affect voluntary motor or sensory function suggesting a neurologic or other medical condition.
- Psychologic factors are associated with the symptom or deficit because conflicts or other stressing events precede the initiation or exacerbation of the symptom or deficit by a variable time. It is often difficult or impossible to find any clearly abnormal stressing event.

The **symptom or deficit** is not *intentionally* produced or feigned (as it is in factitious disorder or malingering[3]):

- After appropriate investigation, it cannot be explained fully by a medical condition, the effects of a substance, or as a culturally sanctioned behavior.
- It causes significant distress or impairment in social, educational, or other important areas of functioning or warrants medical evaluation.
- It is not limited to pain or, in older children, to sexual dysfunction and is not better accounted for by another mental disorder.

Conversion disorder

Conversion disorder was described as a loss or distortion of neurological function not fully explained by organic disease. The patient has an internal conflict, of which they are unaware, which becomes converted into a symptom as a means of expression after dissociation, a mental mechanism whereby underlying feelings and the symptoms are separated. Conversion disorder can be distinguished from other psychiatric disorders mimicking organic loss by its absence of conscious or intentional desire to trick the doctor (or parent). The child with the ocular manifestations of a VCD develops visual loss due to unconscious problems or mental disturbances outside their awareness. Often such children have a history of previous conversion reactions, not necessarily involving the visual system.

Table 63.1 Alternative terminologies used for children with fabricated or exaggerated symptoms

Terminology	Advantages/disadvantages
Conversion disorder (visual conversion disorder, VCD)	The preferred term of the American Psychiatric Association but it implies certain knowledge of the underlying mechanism
Psychogenic blindness	Terms that are still used and can be helpful
Hysterical blindness/ amblyopia	Incorrectly implies instability or "madness" but it is still commonly used
Stress-related visual disorder	Many cases are not apparently stressed by any definition
Conversion neurosis	Implies a certain knowledge of the underlying mechanism and instability
Medically unexplained visual loss	Obscures the meaning from parents and patients and poses a question that must be answered
Amblyopic schoolgirl syndrome	A sexist and pejorative term
Functional visual loss	Meaningless term designed to obscure the meaning from parents and patients
Malingering	A term correctly used for someone who deliberately feigns a symptom for some form of gain – compensation, avoidance of work, military service, etc.[2] This is usually seen in adults
Factitious disorder	A term correctly used for a person acting as if they have an illness by deliberately producing, feigning, or exaggerating symptoms to gain attention or sympathy. Was known as Munchausen syndrome
Factitious disorder by proxy	Used to be known as Munchausen syndrome by proxy. Symptoms or signs produced in a child by a carer to elicit sympathy, etc., for the carer
Non-organic visual loss	Many parents do not understand what "organic" means in this context but it can be useful when explained.

Clinical presentation and symptoms

The child with VCD is typically between 6 and 16 years, most frequently 10 years old, mostly girls. There may be a family history of illness or of eye disease.[4] The symptoms come on gradually in most cases, often following a marginal failure at an eye test. Subsequent examinations reveal varying degrees of acuity and visual field loss, often worsening as time goes on but rarely to the extent that the child becomes bilaterally blind. Most children are little inconvenienced even by an apparently marked visual loss. Repeated objective examinations, neurophysiology, and radiology, are all normal. The condition is usually bilateral, with the most common complaints being "just not seeing," blurred vision,[5] or distorted or small images. Occasionally visual field defects are described, commonly "tunnel vision"; hemianopias are occasionally encountered. Central scotomas are rare and should make one think of associated organic disease. Non-visual defects occasionally also occur,[6] including spasm of the near reflex, headaches, voluntary nystagmus, and eye movement tics, contraversive eye deviation, and accommodation paralysis.

The symptoms of VCD have some of the following characteristics[7,8]:

1. They conform to the child's concept of a symptom or a disorder.
2. They are definable, if somatic, in terms of positive evidence and, if psychologic, by techniques of clinical examination.
3. They are related to emotional conflict.
4. Despite being profound, the symptoms often cause little concern to the affected child.
5. There is usually only one symptom. It is unusual for this to present with multiple symptoms especially in more than one organ system.
6. Conversion disorders are rare under 6 years old, and the gender ratio is equal up to 10 years, then females outnumber males by 3 : 1.
7. In children, both visual fields and acuity are affected; adults tend to be monosymptomatic.[8]
8. Family disharmony is common and abusive or incestuous relationships should be borne in mind as an underlying cause.[9]
9. Patients tend to have equal difficulty with both large and small letters and read down the letter chart very slowly from the top to the lowest they can achieve, often getting further down the chart if cajoled or if the test is done competitively. They read the near vision test excruciatingly slowly, often only to a much worse level than that achieved at distance.
10. A few children have a history of previous psychiatric or psychologic disease,[6] but it is often difficult to elicit the history. Most are normal children.

Depression

Some children develop somatic complaints in response to depression. Therefore, questions that can elicit signs of depression should be raised when depression is suspected. Depressed children may have sleep and eating disturbances, and may have suicidal thoughts. Their peer relationships may have suffered in the preceding months, and they may appear irritable. These need to be addressed, with help from a pediatrician or psychiatrist.

Association with organic disease

Non-organic symptoms are common among referrals to a pediatric ophthalmology service.[10] Prompt, correct diagnosis with appropriate management saves the doctor, the child, and the parents much heartache and time and saves the discomfort and risk of unnecessary investigations.

The fear of missing organic disease makes doctors more cautious about diagnosing non-organic disorders. In VCD, misdiagnoses occur particularly with macular disease and hereditary optic neuropathy in children, but no disease is exempt!

Organic disease may be associated with non-organic disease; the classic situation is the occurrence of pseudoseizures in

epileptics. The same may happen with VCD but, *in childhood*, the symptoms usually occur free of both organic and psychiatric disease.[6]

Psychological background

Inquiry into the background, looking for the underlying stress that produces the symptoms, should center on two main areas:

1. *The home and family.* Conflict between children, sibling rivalry, the child who needs more attention, an unhappy marriage, overcrowding, sexual abuse,[11] harassment or bullying by relatives or others, or conflict with neighbors and their children may be predisposing factors.
2. *The school*. In the school it is often the slow child who is being "overstretched" or the bright child who is being "understretched" who may produce visual symptoms. Unsympathetic or aggressive teachers, teasing or bullying, sexual or other harassment, or abuse[11] all predispose to VCD.

Enlist the help of the parents, tell them explicitly of the possible underlying problems so that they can best help their own child, because relieving underlying factors is the best treatment.

Detection of functional ocular disorders in children

The diagnosis is made positively, with the clear demonstration of signs that are far outside the bounds of physiological possibility. A detailed history, even if time consuming, is often vital to making the correct diagnosis. Certain clinical situations are particularly suggestive of a non-organic disorder as outlined in Box 63.1.

Box 63.1

Presentations and progressions suggestive of visual conversion disorders

1. A severe functional defect in the presence of a normal physical examination, especially when there is a severe unilateral defect with normal pupil reactions and no refractive error.
2. The sudden onset of a disorder related to an emotionally significant event or situation.
3. A step-like deterioration, with the patient's acuity becoming one or two lines worse on each examination but with no objective abnormalities.
4. The ability of a patient to achieve a better acuity or better visual fields with coaxing or cajoling.
5. A monotonous and excessively slow reading of all the letters on a letter chart, regardless of whether they are large or small.
6. A single symptom is most frequent in VCD whereas psychoneurotic patients will tend to have numerous symptoms. Children rarely have substantial ocular complaints.
7. A previous history of ocular or non-ocular VCD, is a recognized predisposing factor to further disorders.
8. The occurrence of visual problems in other members of the family, especially if serious.

Clinical examination in visual conversion disorders

Total blindness

Bilateral

Although unusual, this severe disturbance is usually easy to detect as being non-organic.

1. Direct threat or throwing a ball on a string at the patient while the eyes are open invariably produces a blink (Fig. 63.1). The string can be concealed before the ball is thrown.
2. When facing a mirror, patients involuntarily move their eyes when the mirror is rotated about a vertical axis. The velocity of the eye movement is proportional to the velocity of rotation of the mirror. The only way in which the patient can inhibit the eye movement is by "looking through" the mirror, usually easily detected by a change in convergence and an associated pupil reaction (Fig. 63.2).
3. An optokinetic drum or tape, subtending a large angle at the eye, can be held in front of the patient and the drum rotated to elicit visual evoked movement (Fig. 63.3). It is possible for the patient to look through the tape or drum giving the impression that he/she is not seeing it.
4. A 5- or 25-diopter prism placed base out in front of a seeing eye will normally induce an appropriate, and totally involuntary, fusional movement (Fig. 63.4). This will not occur in severe visual defects.
5. A blind person can easily touch finger tips, one hand to the other, whereas people with VCD sometimes exhibit great difficulty.[12]

Unilateral

The above tests can be used by covering the unaffected eye. In addition:

1. The "confusion–refraction" test (Fig. 63.5). Polaroid lenses or Polaroid projection devices can also be used to trick the patient into reading with the affected eye.
2. Worth's 4 dots and the Frisby or other stereotest (see Chapter 75), appropriately used, will detect if a child is able to use both eyes together even if the responses may be bizarre. With Worth's test, if the patient sees more than three green or two red he/she must be using both eyes. Seeing the Frisby shapes requires a high degree of binocular vision.
3. Either a horizontal prism, as described in the previous section, or a vertical prism may be placed in front of the apparently defective eye. The vertical prism, if over 5 diopters in power, usually involves diplopia and the patient may report this or terminate the examination.
4. It is in this group that pupil reactions are most useful; if one eye is blind and the other is normal there is always a relative afferent pupil defect.
5. Bar reading is a commonly used technique in orthoptics (Chapter 75). To read with a bar placed in an appropriate position between the reading matter and the patient's eyes requires both eyes to work simultaneously to read a complete line.

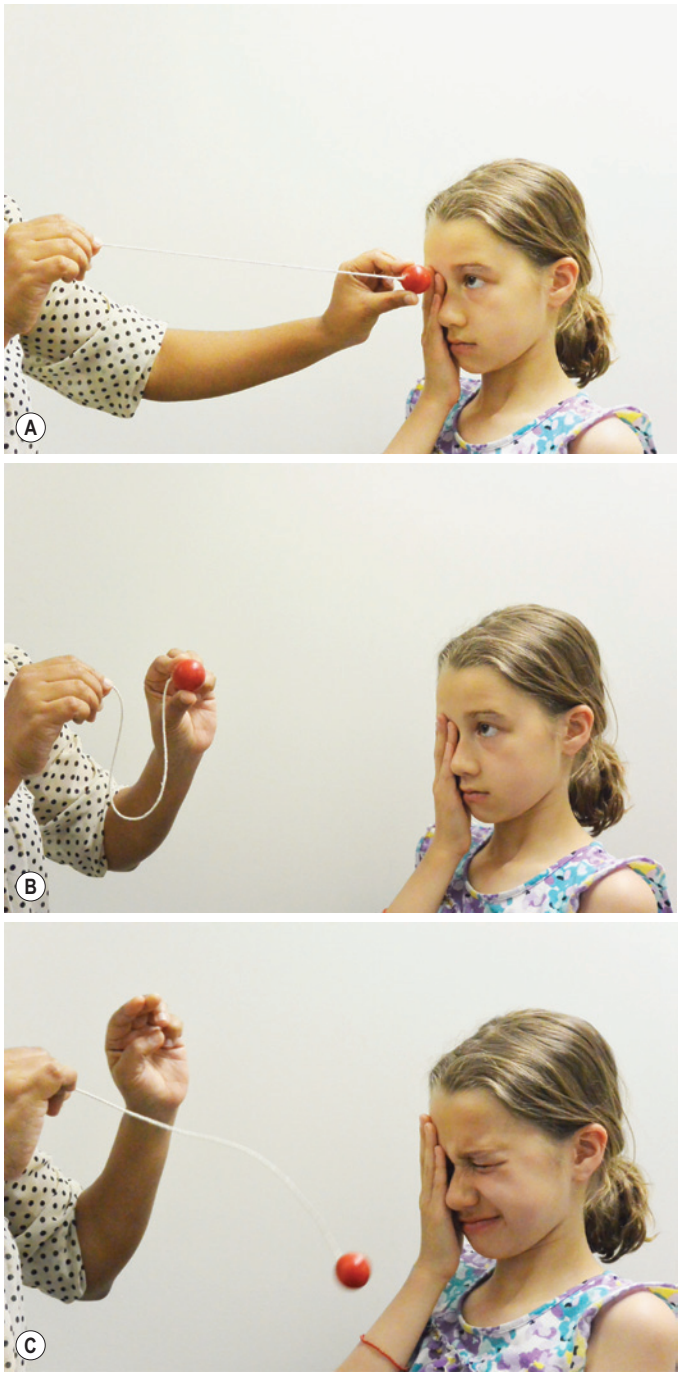


Fig. 63.1 Bilateral non-organic blindness. The ball on a string is measured for distance (A), withdrawn (B), and then thrown at the child, eliciting a blink if they are indeed sighted (C). The first two steps are better performed with the eyes closed. This test needs to be performed meticulously after explanation to the parents the reasons for doing it. It is only really helpful in the unusual instances of complete blindness. *(Image courtesy of Dr CJ Lyons and his completely normal collaborator.)*

Partial acuity loss

If the acuity loss is only partial, it is essential to accept only the most clearly non-organic signs as being true; for instance, a small difference between near and distance acuity is not necessarily non-organic and should not be the basis by itself for such a diagnosis.

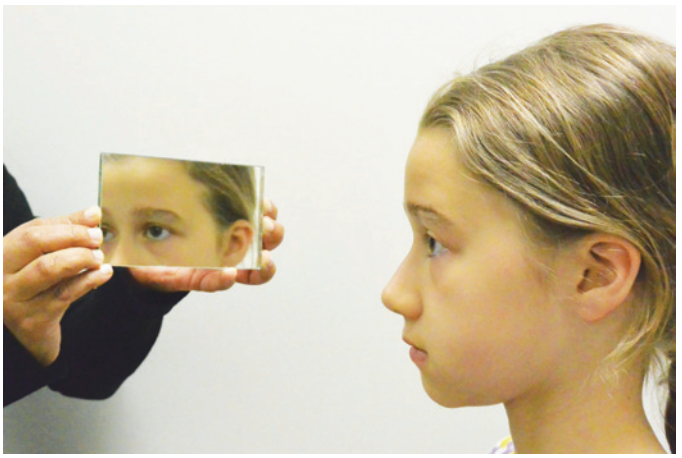


Fig. 63.2 When a blind person looks at a mirror, no movement takes place when the mirror is rotated. The sighted person's eyes will move as the mirror rotates although they believe they are looking straight ahead. *(Image courtesy of Dr CJ Lyons and his completely normal collaborator.)*



Fig. 63.3 Bilateral non-organic blindness. As long as the patient does not "look through" the optokinetic (OKN) tape, the patient's eyes will move with the OKN tape. *(Image courtesy of Dr CJ Lyons and his completely normal collaborator.)*

Unilateral

In this group, the same tests that are used for unilateral complete visual loss are applicable but less easy to interpret. Pupil reactions are rarely helpful. Since there are no clear norms for the correlation between acuity and stereoacuity, these tests are difficult to interpret. The confusion–refraction test is very useful (see Fig. 63.5).

Bilateral

This group is the most difficult to diagnose as non-organic but they nearly always have associated functional field defects that can establish the diagnosis.

1. The finding of an acuity that greatly varies in terms of the angle subtended at different distances is an indicator of VCD. By the use of a second chart with different sized figures or a mirror placed so as to hide the increased distance between the patient and the chart, the patient may be induced to read letters of a size that they were not previously able to read. Similarly, near vision testers,

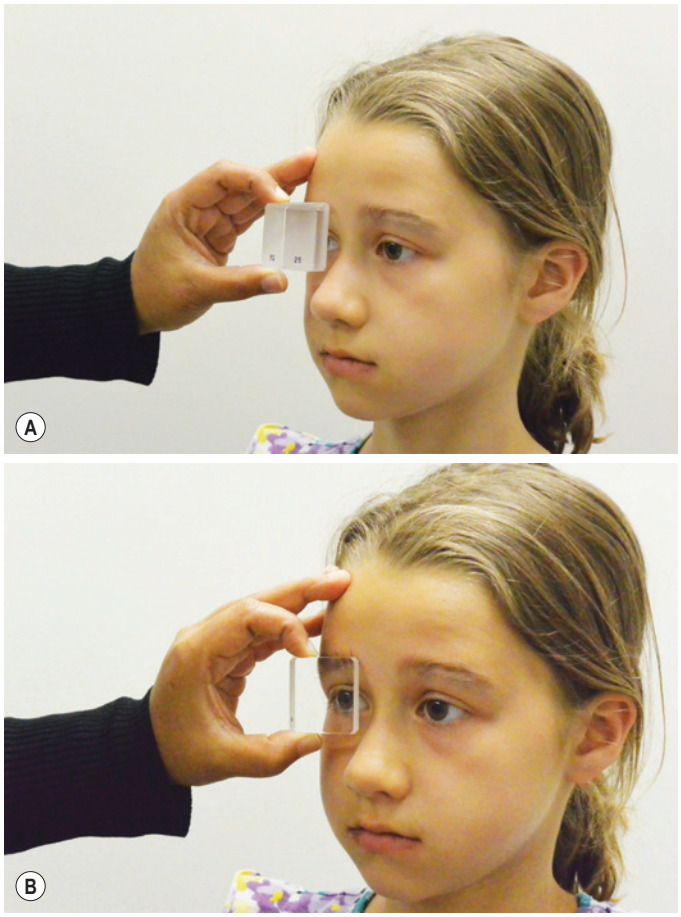


Fig. 63.4 Prism testing. A 25-diopter prism (A) elicits a movement even with only peripheral vision. A 4-diopter prism (B) requires central vision to elicit a movement. *(Image courtesy of Dr CJ Lyons and his completely normal collaborator.)*

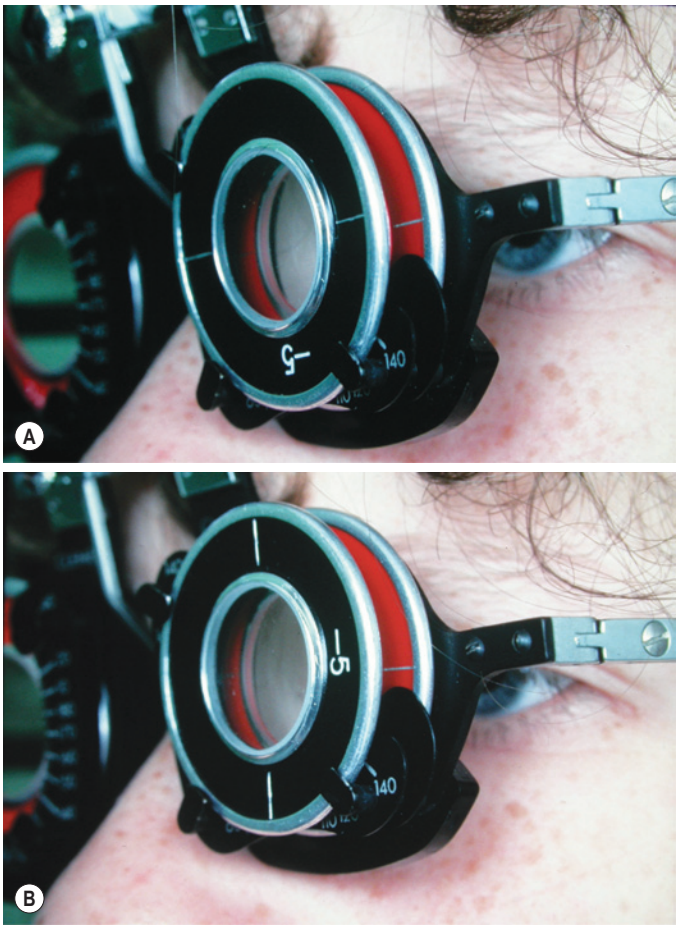


Fig. 63.5 The "confusion–refraction" test. The right eye is suspected of seeing better than the patient indicates. The ophthalmologist puts two canceling 5-diopter cylinders at the same axis in front of the left eye (A), obscures the patient's view of the test type by moving across him, switches the lenses to add to each other (B) and occlude the left eye. As the tester moves away, the patient is urged to read quickly. The left eye is obscured by the lens combination and the right is forced to be used; the patient does not usually detect the change to being forced to use the right eye.

using Snellen near equivalent letters, may show a disparity.

2. Severe bilateral loss of acuity due to organic disease is incompatible with good stereoacuity but a partial loss may be.
3. It is unusual for a patient to make a fusional movement when a 5-diopter prism is placed, base out in front of the other eye, if that eye has organically reduced acuity.

Visual field defects

Children often have fine vision (acuity) symptoms rather than peripheral vision (visual field) symptoms. When testing the visual fields, even normal children may perform in a non-organic manner if the examination is not carefully conducted. Abnormal fields are often associated with an apparently reduced acuity in functional visual loss, or sometimes with other symptoms including reading disability. The presence of a central scotoma should alert the clinician to the co-existence of pathology.[13]

Visual field testing is best done with a tangent screen. Tunnel vision is the most common of the non-organic visual field defects. In tunnel vision, the size of the field is the same at all distances; usually the field is also small. Conversely, purely constricted fields, as in retinitis pigmentosa, are conical, becoming larger as the patient moves away from the testing screen. The defect is always gross; there is an apparently dense defect involving the whole visual field only a few degrees away from the fixation point and this is the same size whether tested at 1, 2 or more meters away from the screen.

The defect, characterized by the "piling" of isopters (isopters all at or near the same eccentricity), is usually "sharp edged" so that both large and small targets are perceived at the same eccentricity, which is often remarkably constant. This "piling" of the isopters may occur even in the face of gross changes in the contrast between the brightness of the background and the target – a distinctly non-physiologic effect!

The absolute nature of the defect makes it easier to detect as being functional. Only clearly abnormal findings should be accepted as indicating a non-organic disorder.

1. In a confrontation technique, the patient alternates fixation between the examiner's eye and a fixation point on a stick held by the examiner, and at a time when he/she is fixing the examiner's eye, the fixation point is moved (Fig. 63.6). If the patient has organic disease with

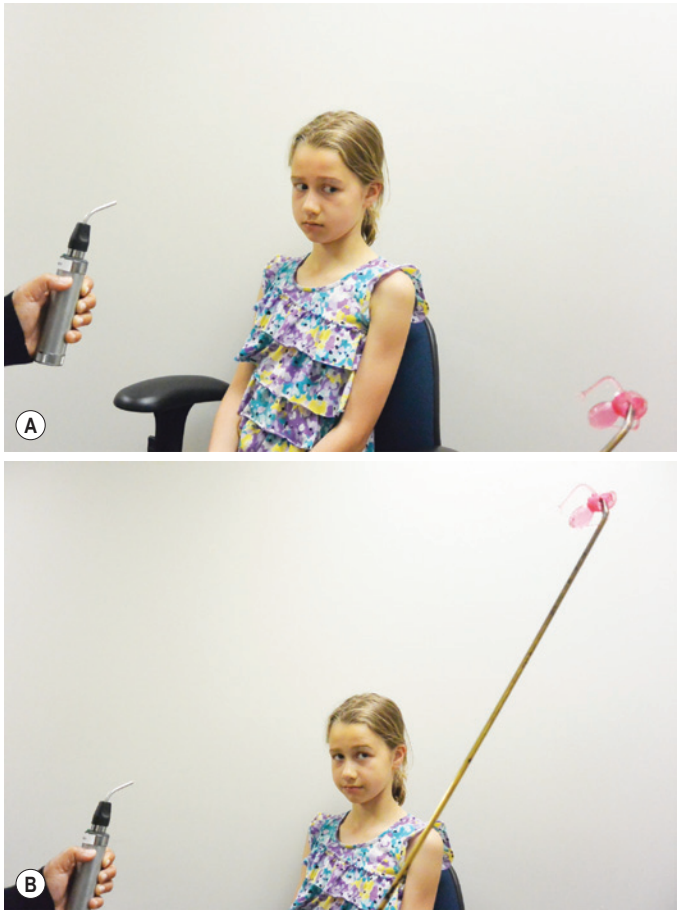


Fig. 63.6 A patient with very constricted visual fields is asked to look at the light (A), then at the figure on a stick, which is kept still. After doing this a few times, when the patient is looking at the light, the figure is moved to another part of the apparently blind part of the visual field (B). If this is done accurately, it is proof that there is a disparity between the tested and the actual visual field, and VCD is a likely diagnosis. *(Image by courtesy of Dr CJ Lyons and his completely normal collaborator.)*

constricted fields, he/she will have difficulty in relocating the spot, whereas a child with VCD finds it accurately.

2. On parting, the examiner fixes the patient in the eye and, without speaking, raises his/her hand from the elbow as though to shake hands. Given the variations of social and cultural backgrounds, most patients with organically constricted fields do not see the examiner's hand, while the child with VCD will.

Using large targets, one may obtain a square visual field, the target when moved inward from one direction being detected in areas previously blind. On successive testing the field may become smaller. If the target is moved inwards as though around a clock-face the target becomes detectable at an ever-decreasing distance from fixation giving rise to "spiraling." This also occurs in patients with organic disease so caution is necessary.

Hemifield defects are rare. A binasal field defect may be a non-organic phenomenon. Functional binasal defects are usually clear-cut; organic ones are not.

In the very rare, true complete bitemporal hemianopic visual field defect, convergence induces a postfixation scotoma, i.e. a wedge of blindness that extends behind the point of fixation. For example, if the patient fixes a point, such as the tip of a pencil held between the examiner's nose and himself/herself, the central features of the examiner's face disappear in the scotoma. This does not occur in a child with VCD.

Blue visual field testing targets are normally detected more peripherally than the red targets of identical size and brightness; the reverse is normal in VCD field testing.

It must be emphasized that an examiner skilled in testing for functional loss should not allow enthusiasm for testing make him/her either overlook co-existing organic disease or encourage the patient to give apparently non-organic results when none are normally present: 9% of 193 normal asymptomatic schoolchildren demonstrated non-organic fields.[14]

Confirmatory studies

VCD tends to be diagnosed late and over-investigated.[15] Once the clinician has made a *positive* diagnosis of non-organic visual loss and has excluded any disease clinically and by selective further investigations, there remains little to do for diagnosis. The more one investigates the child, the more stress one creates and the more one reinforces any underlying problem. If there is any doubt in the mind of the doctor, parent, or the older child about the possibility of organic disease, detailed neurophysiologic studies, including high-quality electroretinograms (ERG): pattern visually evoked potentials (Chapter 9), and fundus imaging studies (optical coherence tomography, autofluorescence, scanning laser ophthalmoscopy, etc., see Chapter 10) may be very reassuring and may inspire sufficient confidence to base the treatment only on reassurance. Non-organic symptoms may also occur in brain disorders, such as Batten disease or adrenoleukodystrophy, many of which, however, are accompanied by detectable neurophysiological changes.

Even with the best neurophysiological studies, it is possible to overlook organic disease, but choosing the optimal test helps avoid this pitfall. For instance, in someone with acuity loss and nothing to find clinically, standard ERGs may be normal but a pattern ERG will detect a commonly missed diagnosis – Stargardt disease. These are useful confirmatory studies in many cases and are risk-free.

Further investigations such as computed tomography or magnetic resonance imaging are not completely risk-free in children, especially if an anesthetic is needed, but they are indicated if the neurophysiological tests are abnormal or if there is real doubt in the doctor's mind.

Management

The exclusion of underlying pathology is the first priority and then the confirmation of the non-organic nature.[16] It is possible to find the underlying psychological cause in some cases; appropriate and sensitive modification of these underlying predisposing factors will abolish the symptom. It is useful to demonstrate the non-organic nature of the defect to the parents and to reassure them strongly that it is such a common problem that it could be regarded as a "normal stress reaction." It is very important to discuss the condition in full with both child and parents, in language appropriate to both.

Most cases can be managed by the ophthalmologist alone. It is important to maintain some contact or follow-up in case the problem does not improve or evolves outside the normal template of non-organic disorders.

The contributions of a psychiatrist or psychologist may be helpful in refractory cases but it is preferable to avoid involvement with too many professionals, because this may reinforce the problem.

The ophthalmologist should maintain a dispassionate approach to the patient. Doctors' emotional reactions to patients can be complex; anger at the patient for "wasting the doctor's time" or frustration are common reactions.

Prognosis

The prognosis is good[14,17] and strong reassurance with minimal follow-up is usually indicated. Psychiatric help may be useful in certain cases and it is likely that "integrative" and family therapy may improve the prognosis.[6] Good prognostic factors are: younger age, treatment compliance, early intervention, healthy family functioning, lack of psychopathology, insight, and acceptance by the family of the psychological nature of the illness.[15] If there is any indication of an underlying psychiatric or psychosocial disorder,[18] or of a more widespread psychoneurosis, for instance, if the patient has recurrent episodes especially affecting more than one system, the psychiatrist's help is mandatory.

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Dyslexia

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Introduction

Pediatric ophthalmologists are often asked to evaluate children who are experiencing difficulties learning to read. Difficulty learning to read occurs in nearly 40% of students in the United States. A number of different factors can cause problems for early readers including deficits in spoken language skills, lack of general knowledge, inadequate instruction, insufficient reading practice, and dyslexia – a learning disability that affects reading.

Although we now know that dyslexia is a language-based learning disorder, historically, dyslexia was thought to be a vision-based disorder. This led to the development of many vision treatments including colored lenses/overlays and vision therapy that are widely promoted to the public today. Pediatric ophthalmologists can detect and treat vision problems, dispel myths, give the family proper information, and help the family find local specialists for educational evaluations and treatments.

Reading

Reading is the complex process of extracting meaning from written symbols. It is the major foundational skill for learning. While speaking is a natural process, reading and writing are neither natural nor easy for many students.[1–3] Strong oral language development is a prerequisite for successful reading.

Currently, the most accepted model for developing the ability to read is the *phonological model*. *Phonological awareness* is the ability to hear and manipulate individual speech sounds.[1–3] It is the main predictor of reading in every language.

Phonemes are the smallest units of sound that are used to form words. When strung together, they form words. Phonemes are not separated in speech; they are co-articulated (spoken together quickly with 8–10 phonemes per second) merging the individual sounds.

Phonics is the understanding of the relationship between the letters and the sounds that they make. Using phonics enables beginning readers to decode new written words by sounding them out and use that skill in reverse to spell or encode words.[1–3] Early readers use phonics to sound out words, but as readers become more fluent, they do not use phonics routinely.

Fluent readers are able to read connected text rapidly, smoothly, effortlessly, with little conscious attention to decoding.

Comprehension is an active complex process that requires automatic decoding and strong higher-order language skills, vocabulary, attention, working memory, inferential thinking, and general knowledge.[1–4]

In 2000 in the USA, the National Reading Panel found that phonemic awareness, systematic phonics, guided oral reading, vocabulary, and comprehension strategies must be taught explicitly in order to promote reading.[4]

Visual functions necessary to read

Reading requires visual acuity, accommodation, convergence, and a series of fixations and saccades. Not used in reading are the vestibular, optokinetic, and smooth pursuit ("tracking") systems.

A visual acuity of 20/20 is not necessary for reading. Accommodation is the ability to focus accurately at near and is necessary for near reading. Accommodative amplitudes are maximal in childhood and decrease naturally with age. The average amplitude of accommodation in children younger than 10 years is 14 diopters, corresponding with a near point of accommodation of 2–3 inches. Seven diopters, or 50%, is available for sustained near activity; thus, young children typically can read comfortably at 6 inches for a prolonged time. Convergence is the inward turning of the eyes used to obtain single binocular vision at near.

Reading uses saccadic eye movements that are of short duration and high velocity. Reading uses both forward

(rightward in English) saccades (85% of saccades) and backward or regression (leftward in English) saccades (15% of saccades). Scanning a line of text requires both right and left saccades.

The saccade length is dependent on the ability to recognize letters, the length of the word before the saccade, and how well the text was understood.[5] Backward saccades are used for verification and comprehension. They increase with the difficulty of the text and are also used to jump to the next line. Visual perception is suppressed during the saccade. Visual information is perceived during foveal fixations, which constitute 90% of our reading time. The duration of a fixation varies with the difficulty of the text.

Dyslexia – reading disability

Definition of dyslexia

The term *dyslexia*, or reading disability, is derived from Greek meaning "difficulty with reading words." The International Dyslexia Association and the USA National Institute of Child Health and Human Development (NICHD) definition of dyslexia[6] is:

> *A specific learning disability that is neurobiological in origin. It is characterized by difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities. These difficulties typically result from a deficit in the phonological component of language that is often unexpected in relation to other cognitive abilities and the provision of effective classroom instruction. Secondary consequences may include problems in reading comprehension and reduced reading experience that can impede growth of vocabulary and background knowledge.*

Epidemiology of dyslexia

Dyslexia is the most common learning disability and has a prevalence in school-aged children in the United States of approximately 15% to 20%. Reading disability affects males slightly more than females, although schools identify boys at least twice as often as girls. Dyslexia occurs at all levels of intelligence. Children with speech and language delays or impairment often become poor readers. Dyslexia represents the lower portion of a normal distribution of reading ability. Dyslexia, itself, varies in degrees of severity; the majority of children with reading disabilities have relatively mild difficulties, with a smaller number having more severe reading disabilities. It is a lifelong condition, and does not represent a transient developmental lag. Untreated, a poor reader in first grade will, almost invariably, stay a poor reader. Adults with dyslexia continue to read slowly throughout life.[3,7]

Etiology of dyslexia

Dyslexia has a strong genetic basis; family history is one of the most important risk factors. Approximately 40% of siblings, children, or parents of an affected individual will have dyslexia.[3,7,8] Recent genetic linkage studies have identified many loci at which dyslexia-related genes are encoded. The candidate genes are implicated in neural migration and brain development. These brain changes seem to cause phonological and auditory processing abnormalities.

Neurobiology of dyslexia

Recent research using functional magnetic resonance imaging (fMRI) brain scanning has provided extensive scientific evidence that the brains of people with dyslexia are "wired" differently. For typical students, reading takes place predominantly in the left hemisphere. Sites include the inferior frontal (Broca) area, (articulation, naming, and silent reading), areas in the posterior brain, the parietal temporal region (word analysis), the occipitotemporal area (word-form and fluency), and the posterior inferior temporal cortex (word retrieval). People with dyslexia demonstrate a dysfunction in the left hemisphere posterior reading areas and show compensatory use of the bilateral inferior frontal gyri and the right occipitotemporal area.[9] The dyslexia-specific brain activation profile has been shown to improve following successful evidence-based phonologic remedial intervention.[10] In people with dyslexia, the white matter connections between the different brain areas used for reading may be weak and slow functioning. (Fig. 64.1).

Dyslexia is a language-based learning disorder

Most people with dyslexia have a phonologic deficit leading to difficulties identifying the individual sounds that make up words, and/or connecting letters to those sounds. Weak phonological skills make it difficult to decode and identify words causing problems with fluency, comprehension, spelling, and writing.[1–3,7,8] Children with more severe forms of dyslexia may have additional language problems such as deficits in rapid automatized naming, speech perception, verbal short-term working memory, sight word recognition, vocabulary, and comprehension, or have problems with attention.

Children with dyslexia often have trouble with *reading comprehension* because of slow and inaccurate decoding,[1–3,7] while most have average comprehension when listening.

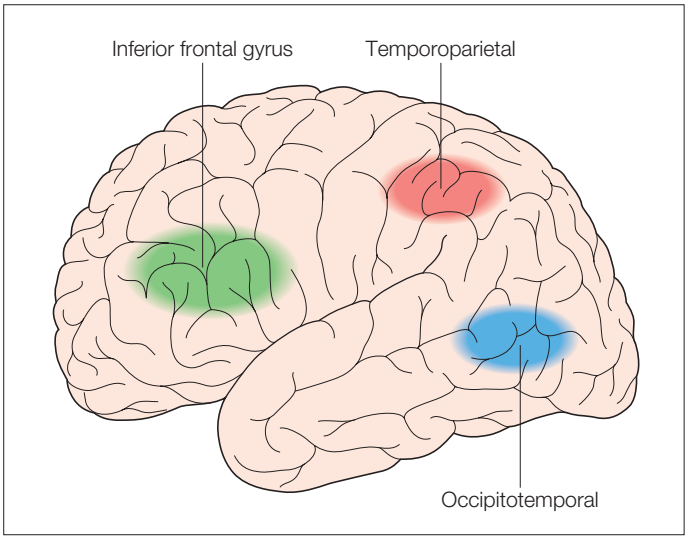


Fig. 64.1 Neural systems used for reading. The three important systems used for reading are in the left hemisphere: (1) Anterior system in the interior frontal region; (2) dorsal temporoparietal system involving the angular gyrus, supramarginal gyrus, and posterior portions of the superior temporal gyrus; (3) ventral occipitotemporal system involving portions of the middle temporal gyrus and middle occipital gyrus. *(Adapted with permission from Shaywitz SE, Shaywitz BA. The science of reading and dyslexia. J AAPOS 2003; 7: 158–66.)*

Approximately 10% of children with reading disabilities show decreased comprehension in the absence of decoding or word recognition problems.

A controversial vision theory of dyslexia – the magnocellular deficit theory

As some children with dyslexia report headaches or visual symptoms,[8] some authors have implicated a deficit in the magnocellular visual system as the cause of dyslexia in this subset of patients. The visual system is composed of two parallel systems: the *magnocellular (large-celled) (transient) system* and the *parvocellular (small-celled) (sustained) system*. The magnocellular system suppresses the parvocellular system at the time of each saccade. This suppression of the parvocellular system prevents activity elicited during one fixation from spilling over into the next. The magnocellular deficit theory of dyslexia proposes that this suppression is lacking, causing confusion and blur.[11]

Most of the evidence supporting the magnocellular deficit theory comes from contrast sensitivity and fMRI studies on visual movement processing. The research evidence in support of the magnocellular theory is equivocal at best. Researchers have calculated that more individuals without dyslexia have magnocellular deficits than those with dyslexia, challenging the view that dyslexia is the result of a magnocellular deficit.

Most investigators reviewing the data have concluded that magnocellular system deficits and associated visual trace persistence are not significant causes of dyslexia.[12–16]

Dyslexia is not a vision-based learning disorder

Vision problems are not more common in children with reading impairment.[17] Eye and vision problems including: high refractive errors, poor vision, nystagmus, saccadic dysfunction, difficulties with "crossing the midline" of the visual field, convergence insufficiency (CI), accommodative insufficiency (AI), strabismus, amblyopia, reduced stereopsis, binocular instability, a magnocellular deficit, or visual perceptual problems do not cause dyslexia and are not more common in dyslexic students.

People with dyslexia do not see things backwards. Difficulty maintaining proper directionality has been demonstrated to be a symptom, not a cause of reading disorders. Contrary to popular belief, the primary sign of dyslexia is *not* reversing letters; rather it is a difficulty sounding out words and also poor spelling.

A child who skips words or lines, or who has choppy reading, may be thought to have a "tracking problem." But *reading tracking* (fluent reading) has nothing to do with *eye tracking*. Both early readers and dyslexic readers use shorter forward saccades, more backward saccades, and fixate for longer periods of time. The saccadic pattern progresses toward the adult pattern as typical readers or dyslexic readers improve their reading skills.

Children reverse words, skip words and lines, or lose their place while reading because of language processing difficulties, not visual or perceptual disorders. Problems with language processing, memory, or attention cause them to struggle to decode a letter or word combination and have poor reading comprehension. Difficulties with fluent reading are the result of dyslexia and not the cause of the reading problem.

Box 64.1

Risk factors for dyslexia

Family history
Prematurity or low birth weight
Fetal exposure to drugs or alcohol
Hearing, speech, or language problems
Developmental delay
Neurological problems
Other chronic health problems

Box 64.2

Possible signs of dyslexia

Difficulty with rhymes
Difficulty learning the names of letters
Trouble connecting letters to their sounds
Difficulty sounding out words
Difficulty with sight word recognition
Slow reading
Poor or erratic spelling

Risk factors for dyslexia

A child should be observed for early indications of dyslexia if he or she has a family history of reading disabilities or has a history of other factors that may be predictive of reading disabilities (Box 64.1).

Possible signs of dyslexia

The signs and symptoms of dyslexia, found in Box 64.2, are indicators, not proof, of dyslexia. Comprehensive testing is necessary to diagnose dyslexia.

Other conditions associated with dyslexia

The comorbidity of *attention-deficit/hyperactivity disorder* (*ADHD*), especially the inattentive type, and dyslexia is common. Approximately 20% to 40% of people with dyslexia also have ADHD and vice versa.[18] Treatment of ADHD may contribute to improvement in the child's reading and overall performance in school.

Dyslexia often co-exists with other learning disabilities, most commonly *dysgraphia* (writing disability), *dyscalculia* (math disability), and dyspraxia (motor skill and coordination difficulties). Students with dyslexia also frequently encounter difficulties learning a foreign language and with organization.

Untreated or inadequately treated dyslexia may lead to frustration, poor self-esteem, and the development of anxiety or depression. Additionally, dyslexic children might be teased or bullied by others.

The importance of early detection of dyslexia

Reading screening tests should be performed on all students in the early elementary grades. Children who are found to be "at risk" for reading difficulties can be given immediate extra assistance in the USA pull-out program called *Response to Intervention* (*RTI*), which can lead to improved reading performance.

Early intervention is often very successful. Students whose dyslexia is identified and addressed in kindergarten or first grade have an approximately 90% chance of improving to grade level. Children identified after third grade have a 74% chance of continuing to struggle through high school. Ideally, it is important to identify and treat children before they leave third grade to have the best chance at academic success, but it is never too late.[19]

Diagnosis of dyslexia

The diagnosis and treatment of a child who has dyslexia depends on the ongoing, coordinated collaboration of a multidisciplinary team that may consist of educators, educational remediation specialists, special services, psychologists, and physicians.

Dyslexia is a clinical diagnosis that requires formal testing. The United States federal law called the *Individuals with Disabilities Education Act* allows parents to request evaluation for a "*Specific Learning Disability*" at their local public school (even if their child attends private school); alternatively, the testing can be conducted privately outside of school. Testing should be used to make the correct diagnosis of the specific type of learning disability and comorbid conditions in order to prescribe the proper therapeutic regimen. Comprehensive evaluation of the causes of a child's reading difficulty can be performed by clinical or educational psychologists, neuropsychologists, or developmental pediatricians, assuming that the clinician conducting the evaluation is properly trained in dyslexia and its assessment. These clinicians can also determine whether there are comorbid conditions, such as ADHD or other psychological issues, which might also interfere with a child's reading. Assessment limited to answering the question of whether the child has dyslexia can be performed by many reading/dyslexia specialists, educational therapists, or speech–language pathologists, again assuming they are properly trained in dyslexia and its assessment.

Family, medical, and school histories are important components in the evaluation. The diagnosis of dyslexia requires a knowledgeable synthesis of clinical history and multiple tests, as there is no single standardized test to identify dyslexia. On testing, most children with dyslexia demonstrate evidence of a phonologic deficit, rapid naming deficits, and/or other language problems.[20]

Treatment of dyslexia

Knowledgeable and skilled teachers are essential for the instruction of children with dyslexia.[2,20–23] Until recently, most elementary education teacher preparation college programs received minimal instruction in language structure, reading theory, reading development, signs of dyslexia, and methods of teaching students with dyslexia.[2,21,23] In 2010, the International Dyslexia Association developed a guide to prepare and certify the professional development of those who teach reading called *The Knowledge and Practice Standards for Teachers of Reading*.[23]

Educational therapists or educators who have been specially trained in reading disabilities can develop and implement intervention plans for children with dyslexia. In public schools, a team determines eligibility for special education and develops an *Individualized Educational Program* (*IEP*) for the student. Severe dyslexia will typically qualify a child for special education, but many children with milder dyslexia may never be properly diagnosed or treated and may "fall through the cracks."

Children with dyslexia learn best in small groups of others who are at the same level. The remediation needs to be tailored to address individual student skill deficits that were detected on the educational evaluation while utilizing their strengths. Practice in oral reading, not silent reading, improves reading fluency.[4] Unfortunately, struggling readers tend to avoid practice, when actually they need to practice much more. Remediation programs must continue long enough, usually 2 years or more, to have a lasting positive effect.

Since dyslexia is a language-based disorder, the educational treatment should target language development. Unfortunately, most schools do not teach reading in a way that is effective for children with dyslexia. Children with dyslexia need reading skills and the structure of language explicitly explained in patterns that are logical, systematic, and multisensory (Boxes 64.3 and 64.4). Multisensory techniques involve the use of visual, auditory, kinesthetic, and tactile pathways simultaneously to enhance learning. The International Dyslexia Association calls multisensory evidence-based reading programs the *Structured Literacy Approach*.[24]

For early elementary school children with dyslexia, *remediations* are very important, while *accommodations* become increasingly important for students in middle school and beyond. Because people with dyslexia continue to read slower throughout life, accommodations can help allow access to higher-level thinking and reasoning skills (Box 64.5).

Children with dyslexia are not one homogeneous group, so there is no single preferred approach to meeting their educational and behavioral challenges. The overall prognosis for a child with dyslexia depends on the severity of dyslexia, patterns of strengths and weaknesses, early diagnosis, and the appropriateness, amount, intensity, and timing of the intervention.

Box 64.3

Explicit teaching of reading skills

Phonemic awareness
Intensive systematic phonics
Fluency training (guided oral reading)
Memorization of sight words
Vocabulary building
Comprehension techniques
Spelling and spelling rules
Writing

Box 64.4

Explicit teaching of the structure of language

Syllable instruction
Morphology (analysis of word parts)
Grammar
Syntax (sentence structure)
Semantics (analysis of meaning)
Pragmatics (interpretation of language in social contexts)

Box 64.5

Important accommodations for people with dyslexia

Extra time
Computers or other technology
Recorded books
Text-reading software
Note-takers
Spell-checkers
Testing alternatives (i.e. verbal testing)
Special quiet room for testing
Preferential seating

Parental involvement is crucial to their child's academic success. Parents need to learn about dyslexia and become their child's advocate. Children with dyslexia need positive emotional support from their teachers and family. Encouragement and positive reinforcement are nearly as important as the instruction itself. It is important to discover the social, athletic, and academic abilities and strengths of children with dyslexia, to encourage, and expand them, because we all succeed on our strengths. Working together, children and parents, in partnership with members of the medical and educational communities, can formulate and oversee a prescription for success.

Controversial treatments

A treatment is controversial if it is sold commercially prior to research, before preliminary research has been replicated, or if the treatment goes beyond what the research data supports.[25]

Colored/tinted lenses and overlays

In 1983, Irlen first proposed using tinted lenses for a specific group of adults with reading problems, which she originally called the *scotopic sensitivity syndrome* (SSS),[26] now also called the *Irlen syndrome* or the *Meares–Irlen syndrome*, or *visual stress*. The initial claims of Irlen were based on observations, students' anecdotal accounts, and no formal experimentation. Supporters contend that the syndrome affects 12% to 15% of the general population and 45% of those with learning problems.

People with this syndrome are thought to suffer from "perceptual dysfunctions" from sensitivities to particular wavelengths of light causing visual distortion, light sensitivity, and "visual stress." This is postulated to interfere with attention and reading, creating symptoms similar to dyslexia. Currently, the magnocellular deficit and cortical excitability theories are considered to be possible causes.

It is important to understand that SSS is *not* a recognized medical syndrome and there are no clearly established criteria for making the diagnosis; the only defining characteristic is the reported benefit of the colored filters themselves.

The Irlen method uses colored lenses or overlays in an attempt to reduce the offending wavelengths to correct "perceptual dysfunctions." Irlen claimed that tinted glasses resulted in instantaneous improvement in reading performance and comprehension. Irlen later clarified that tinted lenses do not treat language deficiencies, dyslexia, specific learning disabilities, or ADHD.

Many studies of the use of colored lenses with good methodology show negative results.[27–29] Others, cited as proof of Irlen lens efficiency, have been found to be inconclusive or invalid upon deeper analysis. Reviews of the literature found little evidence of benefit.[30–33] In spite of the lack of valid supporting evidence that SSS exists or that treatment is effective, Irlen, Wilkins, and Chromagen lenses and overlays are promoted to teachers and directly to the public. Additionally, many children who have worn colored glasses have been teased or bullied, further damaging their self-confidence.

Behavioral optometry

Skeffington was the Director of Education of the Optometric Extension Program from 1928 to 1976. His clinical experience led to the unproven *near-point stress theory*. Skeffington's "near-point stress theory" suggested that the reading demands of our culture are not consistent with the evolutionary development of the visual system, and that such tasks provoke a "biological stress response." The model proposed that binocular anomalies and refractive errors are not primary conditions but products of underlying "near-point stress." Behavioral optometrists believe that this model predicts a group of clinical findings that are not easily explained by other clinical models.[34]

More recently, Scheiman proposed dividing the behavioral optometric evaluation and treatment into three categories: (1) visual acuity, refraction, and eye health disorders; (2) visual efficiency skills of accommodation, binocularity, and ocular motility; (3) visual information processing skills of visual discrimination, visual closure, visual memory, visualization, visual motor integration, and figure-ground perception.[35] (Note: some optometrists include visual acuity and refraction in the category of visual efficiency.)

The optometric literature has implicated problems with "visual efficiency" and "visual information processing skills" as being linked with reading disorders. Optometrists call these problems *learning-related vision problems*. Behavioral optometrists who advocate vision therapy claim that more than 60% of problem learners have undiagnosed vision problems contributing to their difficulties.[36] In opposition, the majority of studies have shown that eye and visual problems do not cause or increase the severity of dyslexia, and, that children with dyslexia have the same visual function and ocular health as typical readers.[17]

Vision therapy

A task force representing the College of Optometrists in Vision Development, the American Optometric Association, and the American Academy of Optometry formulated the following policy statement on "learning related vision problems"[37]:

> *Optometric intervention for people with learning-related vision problems consists of lenses, prisms, and vision therapy. Vision therapy does not directly treat learning disabilities or dyslexia. Vision therapy is a treatment to improve visual efficiency and visual processing, thereby allowing the person to be more responsive to educational instruction.*

Optometrists divide vision therapy into two broad categories: classic orthoptic techniques, to improve "visual efficiency," and "behavioral or perceptual vision therapy," to improve

"visual processing." Behavioral optometrists believe that vision therapy and "training glasses" will make reading more "efficient."

An optometric vision therapy program consists of supervised in-office and reinforcing at-home exercises performed over weeks to months. In addition to "eye exercises," "training glasses," prisms, filters, patches, electronic targets, specialized instruments, balance boards, metronomes, and computer programs may be used.

Vision therapy programs are extremely varied and may include occupational therapy and educational therapy techniques.

Optometrists use various methods to evaluate saccadic eye patterns to detect "inefficient readers." However, there is no basis for testing the saccadic pattern because it is driven by the cognitive needs of reading itself and not from an oculomotor dysfunction. Also, there is no evidence that demonstrates that saccadic training benefits reading. Treating symptomatic CI and/or AI will allow children to read for longer periods of time but will not treat dyslexia. Since no consistent relationship has been demonstrated between visual perception and academic performance or reading ability, there is also no basis for training visual processing.

"Training glasses"

"Training glasses" or "developmental lenses" are low-plus power glasses (+0.25 D to +1.00 D) with or without bifocals or prisms, that behavioral optometrists recommend to help the visual system "develop" and "mature normally," and to relieve reading "stress." They are frequently used with vision training.

In 2000, Jennings reviewed the behavioral optometric literature for the United Kingdom College of Optometrists. This revealed no convincing experimental evidence of any benefits from a low-plus prescription.[38]

Vision therapy and colored/tinted lenses and overlays do not help dyslexia

The optometric literature has been thoroughly reviewed repeatedly over the years,[30,39,40] including several thorough reviews by optometrists[30,38,41]; there is no valid evidence that "training glasses" or vision therapy prevent the development of visual disorders, allow children to be more responsive to educational instruction, or are an effective primary or adjuvant treatment for dyslexia or other learning disabilities. The purported benefits of vision therapy often can be explained by the placebo effect, increased time and individualized attention, maturation changes, or the educational remedial techniques with which they usually are combined.

Because, dyslexia is not a vision problem, methods designed to improve visual function by "training" using "eye tracking exercises," behavioral vision therapy, or colored lenses/overlays have not been found to help children with dyslexia learn to read or improve their long-term educational performance.

The use of these methods contradicts all of the evidence that demonstrates that reading skills depend on language-based processes, such as phonological awareness.

Despite the lack of corroborating research findings with statistical validity, vision therapy and tinted lenses/filters are widely available and directly marketed to parents, teachers, and educational and occupational therapists. These methods rely on anecdotal evidence, instead of scientific evidence, to convince the public and behavioral optometrists often overstate the therapy's effectiveness and the types of problems they may address.

Since using ineffective methods of treatment may give parents and teachers a false sense of security that a child's reading difficulties are being addressed and may delay proper evaluation and treatment, parents and teachers should be advised to evaluate these therapies and become wise consumers.

If vision therapy or colored lenses/overlays have been prescribed, it is recommended that the patient get another opinion by a pediatric ophthalmologist.

The role of the pediatric ophthalmologist

As the first step in reading involves being able to see the printed word, some parents and teachers may understandably suspect that eye problems are the cause of the reading problem. Because routine pediatric vision screening is not designed to detect problems with near vision, children with suspected or diagnosed learning disabilities should undergo a comprehensive eye examination by a pediatric ophthalmologist.

As pediatric ophthalmologists, we are often the first professional evaluating the child, which places us in a unique position to evaluate and treat the child, dispel the myths, give the family proper information, and help them get on the right track. Thus, it is important that pediatric ophthalmologists are well informed on the subject of dyslexia and serve on the dyslexia evaluation team.

Treatable vision problems can occur in addition to a primary learning problem or can masquerade as ADHD or a learning difficulty. Vision problems occur in 5–10% of early elementary students and up to 25% of high school students. Although vision and eye problems may cause trouble seeing the printed word, they rarely result in difficulty learning to read.

Treatable conditions include refractive errors, strabismus, amblyopia, CI, AI, dry eyes, blepharitis, allergic conjunctivitis, and others. Many of these conditions can be treated with corrective eyeglasses and generally will show benefit very quickly. Glasses, however, do not treat reading disorders or dyslexia.

Ophthalmic history and examination

Pediatric ophthalmologists are often asked to evaluate children who are experiencing difficulties learning to read, and this may or may not be the chief complaint. The medical history of school-age children should ask how they are doing in school. You should determine whether there are any difficulties with school, reading, sounding out words, concentration, or attention. The past history should include prior evaluations, diagnoses, and/or treatments for learning disorders, ADHD, or chronic health problems that may have caused school absences. It is important to determine whether there is a family history of dyslexia/reading difficulties or other risk factors for reading difficulties such as premature birth, speech or motor developmental delay, or other neurological problems. The answers to these questions will help guide you as to whether to recommend a dyslexia evaluation for this child.

The ocular history should include any eye or vision complaints, such as blurry vision at distance or near,

diplopia, words that move on the page, headaches, fatigue, or eye itching, burning or tearing. Children with dyslexia whose eyes are normal may present with symptoms such as these. In addition, it is important for the ophthalmologist to recognize that healthy children often have visual complaints from normal visual phenomena, such as physiologic diplopia and relaxation of accommodation.[42] Also, be aware that most children complaining of eyestrain and headaches have a normal eye examination, whereas most children with refractive error, amblyopia, or strabismus have been found to be free of eyestrain, making these complaints a poor marker of eye conditions.[43] Also, ask about the child's use of computers, laptops, hand-held devices, and video games. Be sure to determine if the child experiences similar problems while using these devices. It is unlikely that a near vision abnormality is significant if the child plays on these devices for many hours.

The ophthalmologist should perform a complete dilated eye examination, including cycloplegic refraction. Emphasis should be placed on the evaluation of visual acuity at the distance and near, refractive errors, ocular alignment, amblyopia, versions and ductions, binocular function, stereopsis, accommodation, and convergence. In addition, the child should read out loud a few sentences at their reading level. Even though it is not up to you to diagnose dyslexia, this will give you an indication of the patient's ability to sound out words, and degree of sight word recognition and general fluency. An assessment of the child's activity level, attention span, alertness, cooperation, and ability to communicate should be noted. To obtain correct information in all portions of the examination, it is important to engage the child to obtain his or her full effort. Also, care needs to be exercised to avoid spurious findings.

Visual acuity testing at distance and near with non-letter symbols may be necessary for testing children with dyslexia or other learning disabilities. A child with a significant refractive error may have difficulty seeing the board or reading small print. Refraction using cyclopentolate should be performed to accurately assess refractive errors. The average young school-aged child is mildly hyperopic, averaging between +1.00 D and +2.00 D. Glasses should be considered if the child is greater than or equal to +4.50 D or +3.00 if symptomatic.

The monocular near point of accommodation can be measured by conventional push-up technique using a ruler, the Royal Air Force Rule, or Prince Rule. Before cycloplegia, dynamic retinoscopy can provide a rapid assessment of accommodative function and may be helpful in evaluating a child with high hyperopia, accommodative lag, or AI. The accommodative amplitude can be assessed by using increasing minus lenses in the phoropter while reading at near. Symptomatic AI, an exceedingly uncommon condition in children, can cause blurring and discomfort at near. It is typically associated with uncorrected high hyperopia, occasionally secondary to medications or anxiety, or rarely a primary condition. It can be treated with correction of the hyperopia or with bifocals when indicated. Importantly, children with developmental delay or Down syndrome often hypo-accommodate and may benefit from spectacle correction at lower thresholds of hyperopia.

Accommodative facility can be assessed by alternately applying −1.50 D and +1.50 D lenses in the phoropter (using the 3.00 D coarse adjustment) while the child reads at near.

The near point of convergence should be tested using an accommodative target and measured with a ruler. Distance and near convergence amplitudes can be measured by using a base-out horizontal prism bar or rotary prism while the child is reading.

CI is often asymptomatic. Symptomatic CI can cause discomfort, eyestrain, blurry vision, jumpy vision, diplopia, and headache. It can interfere with a child's ability to concentrate on print and occasionally lead to limited fluency. Because of this behavior in the classroom, CI may be confused with ADHD or dyslexia. Therefore, it is important that ophthalmologists be familiar with CI and its testing to make the correct diagnosis. Depending on the definition chosen, the prevalence of CI varies greatly. It is uncommon in early elementary school children, and patients typically present as teenagers or young adults during extended periods of studying.

Symptomatic CI can be treated with home, computer or office-based orthoptic exercises. Alternatively, for other patients, reading glasses with base-in prism or occlusion during reading can be used to treat the symptoms of diplopia but not the underlying CI.

The treatment of asthenopic symptoms, accommodative difficulties, or symptomatic CI can help reading become more comfortable and may allow reading for longer periods of time, but this approach does not directly improve decoding or comprehension and will not treat dyslexia or ADHD, if present.

A careful external ocular examination should be performed to determine whether the child has problems causing eye irritation that could secondarily interfere with the ability to concentrate and learn. These problems include dry eyes, blepharitis, or ocular allergies. Finally, a dilated retinal evaluation should be performed to detect retinal or optic nerve problems.

Recommendations

The pediatric ophthalmologist on the dyslexia management team should identify and treat any significant vision problem according to standard principles of treatment. The need for additional medical, psychological, educational, or other appropriate evaluations and evidence-based treatments should be discussed with the parents. You should communicate your findings and recommended ophthalmic treatment to the primary care physician and school, and also inform them that you are recommending educational evaluation and remediation as opposed to vision therapy.

Controversial therapies are frequently featured and aggressively promoted by the media, convincing parents to try them. As advocates for patients, ophthalmologists can inform families that dyslexia is a language processing problem, not a vision problem, and that struggling readers need educational evaluation and remediation, not vision-oriented remedies such as eye exercises or colored lenses. Pediatric ophthalmologists should discourage parents from enrolling their children in unproven programs, saving their valuable time and resources for evidence-based educational therapies.

It is *not* enough to reassure the parents that the child's eyes are fine, and that the eyes are not causing the reading problem. The ophthalmologist should give *specific* guidance on how to obtain a reliable diagnosis of the cause of the reading difficulty, and how to obtain evidence-based remediation. If you do not, the parent, who just wants to help their child, may seek help from practitioners offering unvalidated therapies.

Table 64.1 Informational websites

Organization	URL
American Academy of Pediatrics (AAP)	www.aap.org
American Association for Pediatric Ophthalmology and Strabismus (AAPOS)	www.aapos.org
American Association of Educational Therapists (AET)	www.aetonline.org
Children's Dyslexia Centers (free tutoring)	www.childrensdyslexiacenters.org
Dyslexia Help – University of Michigan	www.dyslexiahelp.umich.edu
International Dyslexia Association	www.dyslexiads.org
Learning Disabilities Association of America	www.ldaamerica.org
Learning Disabilities OnLine	www.ldonline.org
National Center for Learning Disabilities	www.ncld.org
Nemours Reading Bright Start	www.readingbrightstart.org
Institute of Multi-Sensory Education	www.orton-gillingham.com
Reading Rockets	www.readingrockets.org
Wrightslaw Special Education Law and Advocacy	www.wrightslaw.com
Yale Center for Dyslexia and Creativity	www.dyslexia.yale.edu

To this end, the ophthalmologist should compile a personalized list of local specialists for evaluation and treatment, so that if dyslexia is suspected, you can assist families in finding resources that are available in the community. Ophthalmologists should also help families become educated by giving parents handout information and recommendations for websites, books, and articles (Table 64.1). The American Association for Pediatric Ophthalmology and Strabismus (AAPOS) and the American Academy of Pediatrics (AAP) have patient education brochures on learning disabilities, dyslexia, and ADHD that can assist families.

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Neurometabolic disease and the eye

Jane L Ashworth and Andrew A M Morris

Chapter contents

LYSOSOMAL DISORDERS
MITOCHONDRIAL DISORDERS
PEROXISOMAL DISEASES
CONGENITAL DEFECTS OF GLYCOSYLATION
INBORN ERRORS OF CARBOHYDRATE METABOLISM
INBORN ERRORS OF AMINO ACID METABOLISM
DISORDERS OF FATTY ACID AND FATTY ALCOHOL METABOLISM
DISORDERS OF STEROL METABOLISM
LIPOPROTEIN DISORDERS
COPPER TRANSPORT DISORDERS
REFERENCES

Many neurometabolic diseases present in childhood with ophthalmic manifestations. In some conditions, the characteristic ophthalmic features may lead toward an early diagnosis. In others, the ophthalmic complications present later in the course of the disease but can have significant visual effects for the patient. Findings such as vertical or horizontal gaze palsy, characteristic corneal changes, cherry-red spot, retinopathy, or optic atrophy, particularly in the presence of progressive systemic or neurologic disorders, should alert the ophthalmologist to the possibility of a neurometabolic disorder.[1]

Although most of the diseases described here are rare, many are now treatable; it is important that the pediatric ophthalmologist is aware of them.

Lysosomal disorders

Lysosomal storage disorders (LSDs) arise as a result of defects in lysosomal enzymes, receptor targets, activator proteins, membrane proteins, or transporters, causing accumulation of specific substrates within lysosomes. This leads to impairment of cellular and tissue function.[2] Most LSDs have central nervous system (CNS) and systemic defects; untreated, many result in death in infancy or childhood. While each type of LSD is rare, their total incidence is 1 per 7000–8000 live births. There are characteristic ocular features in some of the LSDs (Box 65.1), which should alert the ophthalmologist to their possibility, particularly when seen in a child with suggestive systemic features such as organomegaly, skeletal abnormalities or joint stiffness, coarse facial features, progressive neurologic deterioration, or unexplained pain. The pediatric ophthalmologist has an important role in facilitating early diagnosis so appropriate treatment can be started, as well as in monitoring and managing the ophthalmic complications.

All LSDs have autosomal recessive inheritance except for Danon disease, Fabry disease, and Hunter disease (mucopolysaccharidosis type II), which are X-linked. Some disorders are more prevalent in a particular geographic area or in certain populations, such as Gaucher, Tay–Sachs, Niemann–Pick type A, and mucolipidosis IV, which are 50–60 times more prevalent in the Ashkenazi Jewish population.[2] There is often a wide variation in phenotype, including severity of symptoms, systems affected, and presence of CNS manifestations. In many disorders such as Gaucher and Tay–Sachs, there are infantile, juvenile, and adult forms. Diagnosis of an LSD is usually made using biochemical assay of blood, urine, or skin fibroblasts, and confirmed by molecular genetic testing.

There have been major advances in the treatment for many LSDs. Enzyme replacement therapy (ERT) provides an exogenous source of enzyme by repeated intravenous infusions but it does not cross the blood–brain barrier. Hematopoietic stem cell transplantation (HSCT) provides donor stem cells to produce the deficient enzymes; these cells can enter the brain and ameliorate the neurological problems in some disorders. Trials of intrathecal ERT and gene therapy are being undertaken in some disorders. The drug, miglustat, uses a different approach, reducing production of the substrate for the missing enzyme in Gaucher disease and Niemann–Pick disease type C. Despite these advances, there are many systemic and neurologic complications, requiring medical and surgical management and a multidisciplinary approach.

Mucopolysaccharidoses

The mucopolysaccharidoses (MPSs) are a heterogeneous group of multisystem disorders resulting from accumulation of glycosaminoglycans within ocular and systemic tissues. They are classified according to phenotype, and result from deficiency of different lysosomal enzymes (Table 65.1). They are all inherited in an autosomal recessive manner apart from MPS II, which is X-linked. Visual impairment is common, and can be due to corneal opacification, optic neuropathy, retinopathy, or cerebral visual impairment.[3]

Box 65.1

Ocular manifestations of lysosomal storage disorders

Cornea – diffuse corneal clouding
Corneal verticillata
Lens – characteristic cataract
Macula – cherry-red spot
Bull's eye maculopathy
Vasculature – retinal and conjunctival vascular tortuosity
Optic neuropathy
Ocular motor apraxia (saccadic initiation failure)

Table 65.1 Mucopolysaccharidoses and underlying enzyme deficiencies

Type	Eponym	Stored material	Enzyme deficiency
MPS IH	Hurler	DS, HS	Iduronidase
MPS IS	Scheie	DS, HS	Iduronidase
MPS IH/S	Hurler–Scheie	DS, HS	Iduronidase
MPS II	Hunter	DS, HS	Iduronidase sulfatase
MPS IIIA	Sanfillipo A	HS	Heparan *N*-sulfatase
MPS IIIB	Sanfillipo B	HS	*N*-Acetylglucosaminidase
MPS IIIC	Sanfillipo C	HS	Acetyl-CoA-glucosaminidase-acetyltransferase
MPS IIID	Sanfillipo D	HS	*N*-Acetylglucosamine-6-sulfatase
MPS IVA	Morquio A		Galactosamine-6-sulfatase
MPS IVB	Morquio B		α-Galactosidase
MPS VI	Maroteaux–Lamy	DS	*N*-Acetylgalactosamine-4-sulfatase
MPS VII	Sly	HS, CS, DS	α-Glucuronidase
MPS IX	Natowicz	Hyaluronic acid	Hyaluronidase

CS, Chondroitin 6-sulfate or chondroitin 4,6-sulfate; DS, dermatan sulfate; HS, heparan sulfate; MPS, mucopolysaccharidosis.

Systemic manifestations in MPS

Patients with MPS often present in infancy with recurrent ear infections, inguinal or umbilical hernias. Over the first 2 years, many patients develop coarse facial features, with a flat nasal bridge, thickened skin, and hypertrichosis. Skeletal problems include joint stiffness and kyphoscoliosis (Fig. 65.1); conversely, MPS IV patients have joint laxity and very short stature. Developmental regression and difficult behavior are the main feature in MPS III; learning difficulties are also present in severe cases of MPS I, II, and VII. Valvular heart disease, deafness, and obstructive sleep apnea are also common.

Corneal clouding in MPS

Corneal clouding is a characteristic feature of several of the MPS disorders (MPS I, MPS IV, MPS VI, and MPS VII), and may be present from infancy. Deposition of glycosaminoglycans (GAGs) within the corneal stroma leads to progressive diffuse corneal opacification, described as having a "ground-glass" appearance (Fig. 65.2). Corneal opacification is milder in the less severely affected MPS I phenotype, and is not a feature of MPS II or III. Patients with MPS may have coarsening of facial features with pseudoexophthalmos (Figs 65.3 and 65.4), which can result in corneal exposure and subsequent vascularization.

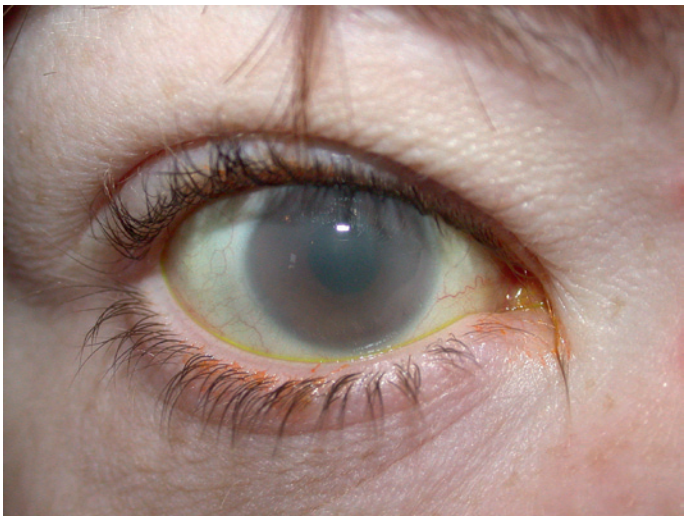


Fig. 65.2 Corneal clouding in a patient with mucopolysaccharidosis I.



Fig. 65.3 Pseudoexophthalmos due to shallow orbits in a 17-year-old patient with mucopolysaccharidosis VI.

A patient with mild corneal clouding may be asymptomatic, but photophobia and reduced vision occur as the opacification worsens. GAG deposition can increase corneal thickness[4,5] and affect corneal hysteresis,[6] thus affecting the accuracy of intraocular pressure measurements. Corneal transplantation (penetrating keratoplasty or deep lamellar keratoplasty) may result in improvement in vision when severe corneal opacification causes visual loss[7,8] with no re-opacification of the graft in up to 11 years follow-up.[7] However, an assessment of potential benefits of corneal transplantation must consider the presence of coexistent retinopathy, optic nerve dysfunction, and cerebral visual impairment, as well as the significant anesthetic risks.

Hypermetropia and strabismus in MPS

The majority of patients with MPS are hypermetropic due to changes in corneal refraction and reduced axial length.[3,9] Strabismus and amblyopia are common.[3]

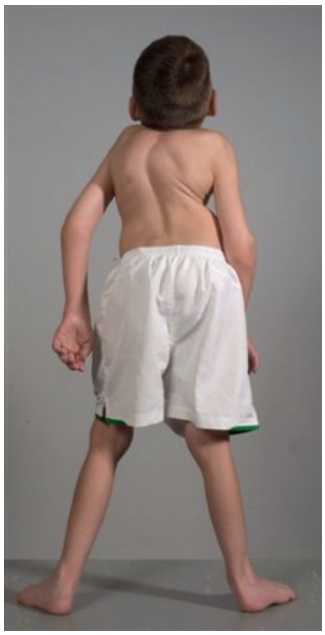


Fig. 65.1 Kyphoscoliosis in mucopolysaccharidosis I.

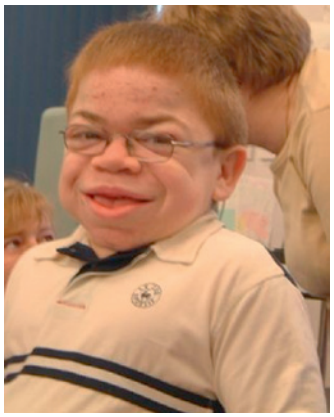


Fig. 65.4 Coarsening of facial features in a 16-year-old patient with mucopolysaccharidosis II.

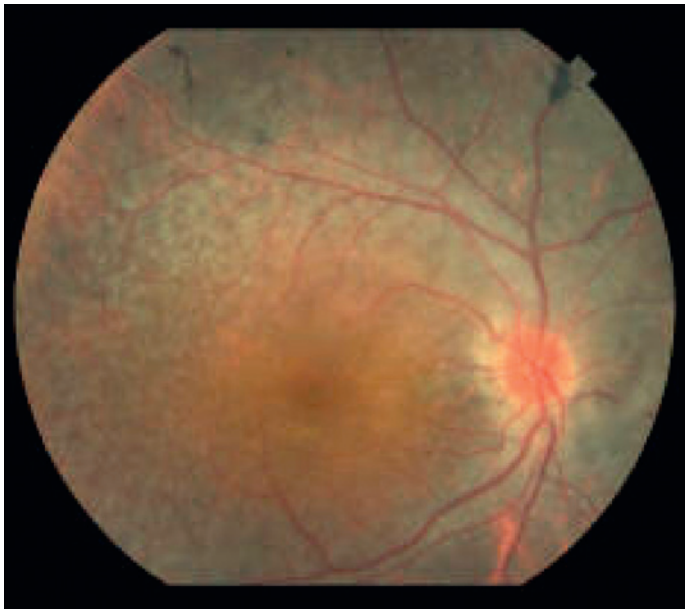


Fig. 65.5 Retinal pigment epithelial changes in a patient with mucopolysaccharidosis I. Vision was 6/60 despite minimal corneal clouding.

Retinopathy in MPS

Progressive retinopathy occurs in MPS I, II, and III, but is not usually a feature of MPS IV or VI.[10] The patient may experience night blindness and problems with peripheral vision, but this may go unnoticed due to the visual loss associated with corneal opacity. Signs of retinopathy include retinal pigment epithelial (RPE) atrophy and pigment clumping (Fig. 65.5), arteriolar narrowing, optic disc pallor, and macula changes. Serial electroretinography (ERG) may show initial deterioration of rod-mediated responses, followed by involvement of cones. Maculopathy and choroidal folds have been described in MPS II associated with a ring scotoma; optical coherence tomography demonstrated extrafoveal photoreceptor loss and cystoid spaces within retinal layers.[11]

Optic disc swelling and atrophy

The optic nerve often has a "full" appearance in patients with MPS (Fig. 65.6A,B). GAG deposition occurs in the ganglion cells and within surrounding sclera causing an enlargement of the nerve and thickening of the sclera[12] (Fig. 65.6C,D). In addition, patients with MPS may develop raised intracranial pressure and the resultant optic nerve compromise may lead to profound visual loss. Visual evoked potential may be useful in monitoring optic nerve function prior to consideration of corneal transplant.

Glaucoma

Glaucoma may arise in MPS due to accumulations of GAGs within the anterior segment resulting in a narrow angle, and within the trabecular cells leading to open angle glaucoma as a result of outflow obstruction. It has been described in MPS I, II, IV, and VI.[10,13] Difficulties in diagnosis and assessment of glaucoma arise in patients with MPS due to inaccuracy of intraocular pressure measurements, corneal clouding hampering assessment of the angle and disc, the presence of coexistent disc pathology, and difficulties with visual field assessment.[13]

Punctate lens opacities occur in MPS IV.

Treatment and prognosis for MPS

The prognosis in MPS is variable depending on the phenotype; some children die before their second decade and others survive into their fifth or sixth decade. ERT is available for MPS I (laronidase), MPS II (elaprase), MPS IV (elosulfase alfa) and MPS VI (galsulfase), but it does not enter the brain and has limited effect on skeletal problems. Early hematopoietic stem cell transplantation (before the age of 2 years) using either matched bone marrow or umbilical cord blood cells is the best treatment for patients with severe MPS I (Hurler).

Management is multidisciplinary, coordinated by a pediatrician with input from many other disciplines, including regular assessment by a pediatric ophthalmologist.

Anesthesia should be undertaken in a department with expertise in the MPS disorders. Children with MPS are difficult to intubate, due to MPS deposition around the airway and vulnerable cervical spinal cords (especially in MPS IV).

Glycoprotein disorders

α-Mannosidosis (α-mannosidase deficiency)

α-Mannosidosis is associated with mild facial coarsening (Fig. 65.7), skeletal abnormalities, a variable degree of learning difficulty, and deafness. A severe form (type I) results in early death from CNS manifestations and recurrent infections. In the attenuated form (type II), hearing loss and skeletal abnormalities become evident usually before the age of 10 years, following which ataxia and mental retardation become manifest. In a multicenter study of 45 patients aged 1–42 years, two had mild corneal clouding, two had cataracts and two had poor vision due to pigmentary retinal degeneration.[14] Other ophthalmologic features include hypermetropia, amblyopia, cataracts, and strabismus.[15] The lens opacities are posterior cortical with multiple discrete clear round vacuoles lying at different depths in the lens, best seen by slit-lamp retroillumination.[16] ERT is being developed for this disorder.

Fucosidosis

Fucosidosis is a progressive neurodegenerative disease with seizures, mild coarsening of the facies, skeletal dysplasia, and angiokeratomas. Affected children have conjunctival and retinal vascular tortuosity. Central "lobulated" corneal opacities may occur at an early age, and later a bull's eye maculopathy.[17] HSCT may improve the neurological outcome if undertaken in the early stages.



Fig. 65.7 A child with mannosidosis showing the mild coarsening of the features. When older, there was an increase in the facial coarsening.

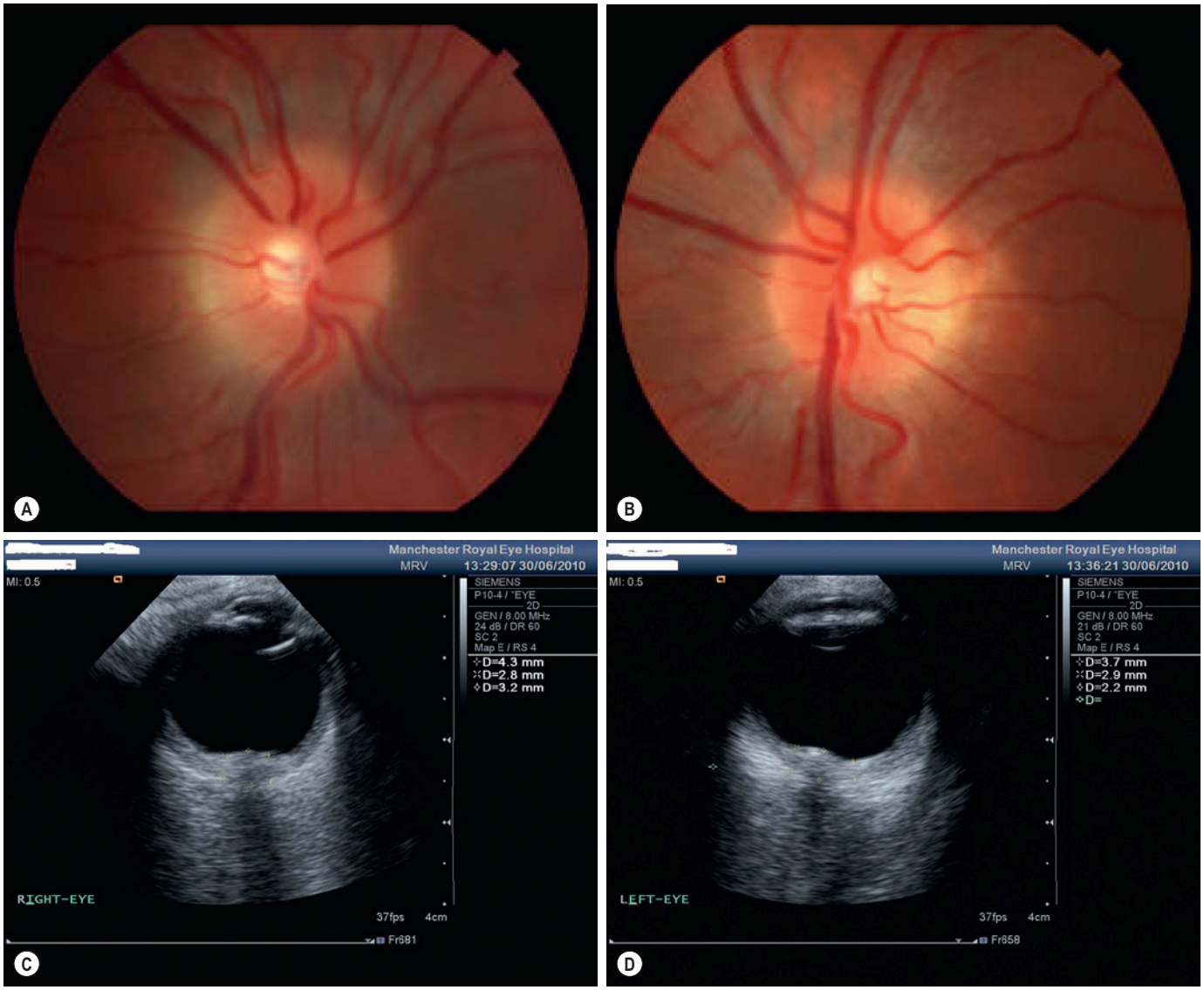


Fig. 65.6 (A,B) "Full" optic discs in a 14-year-old patient with mucopolysaccharidosis II. (C,D) Ultrasound of the same optic nerves as in (A) and (B), showing thickening of sclera and increase in diameter of the optic nerve. *(Courtesy of Mr Vishwanath, MREH.)*

Sialidosis (mucolipidosis type I)

Sialidosis is a result of α-*N*-acetylneuraminidase deficiency; patients excrete sialyloligosaccharide in the urine.

Type 1 sialidosis "cherry-red spot myoclonus syndrome" presents in late childhood with visual loss, myoclonic epilepsy, and ataxia. A cherry-red spot occurs (Fig. 65.8), associated with thickening of the paracentral nerve fiber layer on spectral optical coherence tomography (OCT).[18,19] Type 2 sialidosis has an earlier onset with coarse facies, developmental delay, hepatomegaly, and dysostosis multiplex (Fig. 65.9). In addition to cherry-red spots, patients with sialidoses may have nystagmus, punctate lens opacities, optic atrophy, corneal clouding, and visual field defects.[20–22]

Sialic acid storage diseases

These result from a block in lysosomal efflux of sialic acid as a result of mutations in *SLC17A5*, encoding the lysosomal protein sialin. They range in severity from infantile sialic acid storage disease (ISSD) with coarse facial features and fair complexion, severe developmental delay, hepatosplenomegaly and cardiomegaly, and death in early childhood, to Salla disease with slowly progressive mental retardation, ataxia, spasticity, and epilepsy. In ISSD, children may have albinoid fundi.[23] In Salla disease, strabismus, nystagmus, and optic atrophy may occur.

Mucolipidoses

Mucolipidosis (ML) II and III are autosomal recessive disorders caused by deficiency of *N*-acetylglucosamine-1-phosphotransferase, which phosphorylates carbohydrate residues on *N*-linked glycoproteins. This prevents lysosomal enzymes from entering the organelle.

ML II or "I cell" disease presents at an early age with neurologic degeneration, joint stiffening, facial coarsening, and kyphoscoliosis (Fig. 65.10). Death occurs in childhood. There is retinal degeneration and corneal clouding.

ML III is milder, with a slowly progressive course and survival to adulthood. Ophthalmic features include corneal clouding,

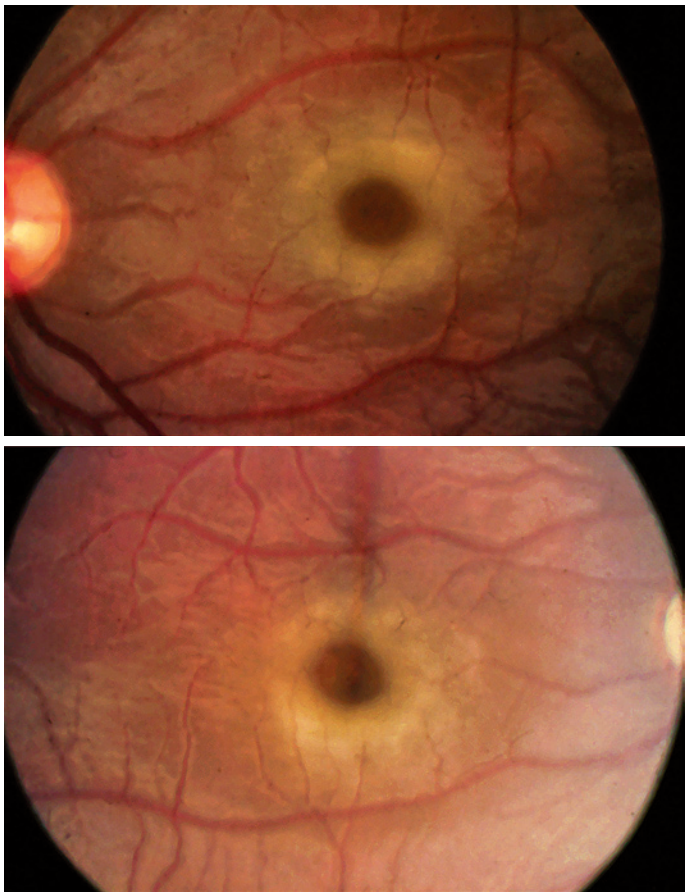


Fig. 65.8 Cherry-red spot in a patient with sialidosis type 1. *(Mr M.D. Sander's patient.)*

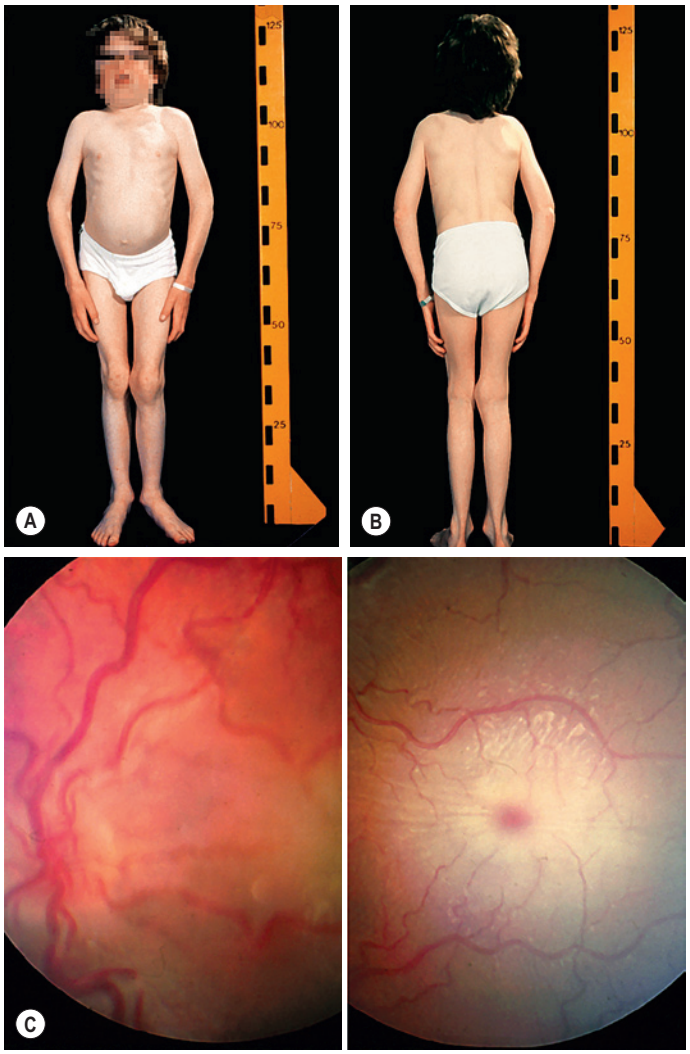


Fig. 65.9 (A,B) Patient with sialidosis type 2. He has kyphoscoliosis and joint changes. (C) Same patient as in (A) and (B), showing a cherry-red spot. The picture is hazy because of corneal clouding.



Fig. 65.10 Mucolipidosis II showing the facial features and the joint stiffening that prevents the patient from fully lifting her arms.

hypermetropic astigmatism, optic disc swelling, retinal vascular tortuosity, and maculopathy.[24] The ERG is normal.

ML IV is an autosomal recessive disorder resulting from mutations in the *MCOLN1* gene, which encodes mucolipin-1. It is seen mainly in Ashkenazi Jews. Clinical features include progressive mental retardation and hypotonia. ML IV patients have corneal epithelial haze, retinopathy with optic nerve pallor, vascular attenuation, and RPE change with electronegative ERG.[25,26] Other ophthalmic features include strabismus, corneal erosion and episodic pain, cataract, and ptosis.[27,28] Mild phenotypes have been described with only ocular manifestations of corneal clouding and retinopathy.[28,29]

Sphingolipidoses

Sphingolipidoses are caused by abnormalities of catabolism of sphingolipids, which form an integral part of cerebral membranes. All show autosomal recessive inheritance except Fabry disease, which is X-linked. The sphingolipidoses have a wide range of presentations and severity, but progressive neurodegeneration and cherry-red spots are characteristic features.

GM2 gangliosidosis

- *Tay–Sachs disease:* hexosaminidase A deficiency, most common in the Ashkenazi Jewish population.
- *Sandhoff disease:* hexosaminidase A and B deficiency.

These are clinically indistinguishable neurodegenerative disorders, with infantile, juvenile, and adult forms. A cherry-red spot is the typical eye finding.[30] There is no effective treatment.

Most patients present in infancy with weakness and an exaggerated startle response, followed by loss of vision, feeding difficulties, seizures, and spasticity. Macrocephaly is common and death usually occurs by 2–4 years.

A cherry-red spot is apparent at an early stage, due to GM2 ganglioside accumulation in the retinal ganglion cells. As the ganglion cells die, the cherry-red spot fades and optic atrophy becomes apparent.[31] The ERG is normal, but the visual evoked potential extinguished.[32]

The juvenile and adult forms usually present with motor symptoms, such as ataxia, followed by dementia. Cherry-red spots are less common in the late-onset forms (Table 65.2) but adults may have saccadic abnormalities.[33]

Metachromatic leukodystrophy (arylsulfatase deficiency)

Metachromatic leukodystrophy usually presents at 1–2 years of age with deteriorating gait, spasticity, and loss of reflexes due to neuropathy. Later, there are speech and feeding problems. Optic atrophy leads to blindness and occasionally there is a cherry-red spot.[30] Juvenile and adult-onset forms may present with deteriorating gait or with behavior problems. HSCT probably slows progression in the late-onset forms[34] and gene therapy is being developed.

Krabbe disease (galactocerebrosidase deficiency)

This is a severe neurodegenerative disorder with infantile, childhood, and late-onset forms. The early-onset form develops symptoms in the first few months with irritability and poor feeding, and progresses quickly to spasticity and a vegetative state. Visual impairment is common in the late stages due to optic atrophy or cortical blindness. There is no treatment

Table 65.2 Cherry-red spot in neurometabolic disorders[1]

Disease	Disease frequency of cherry-red spot
Niemann–Pick type A	Occasional
Niemann–Pick type B	Occasional
GM2 gangliosidosis (Tay–Sachs and Sandhoff)	Frequent
GM1 gangliosidosis, infantile	Occasional
Galactosialidosis	Frequent
Farber lipogranulomatosis	Occasional
Sialidosis type 1	All
Sialidosis type 2	Frequent
Metachromatic leukodystrophy	Occasional

for the infantile form but HSCT may halt progression of the late-onset form.

GM1 gangliosidosis

GM1 gangliosidosis is caused by a deficiency of β-galactosidase resulting in the accumulation of GM1 gangliosides in the brain. Infantile GM1 gangliosidosis causes hypotonia from birth. By 6 months, patients have a coarse appearance with puffy skin, maxillary hypoplasia, hypertrophied gums, and macroglossia. Affected children have hepatosplenomegaly and dysostosis multiplex. Ocular motor apraxia (saccadic initiation failure),[35] a cherry-red spot, optic atrophy, tortuous retinal vessels, retinal hemorrhages, and corneal clouding may occur. Rapid neurologic deterioration is usual, with seizures and swallowing difficulties and death by 2 years. Juvenile and adult forms occur, in which there is neurologic deterioration and dysostosis but no dysmorphism or ophthalmological abnormalities. There is no effective treatment.

Niemann–Pick disease

Disorders in which there is storage of sphingomyelin are called Niemann–Pick disease. Types A and B are due to sphingomyelinase deficiency. Type C is a completely different condition, where ganglioside and sphingomyelin accumulation is due to a disorder of cholesterol transport within the cell.

Niemann–Pick disease types A and B (sphingomyelinase deficiency)

Niemann–Pick type A, the severe part of the spectrum, is commoner in Ashkenazi Jews. Patients present in infancy with failure to thrive and feeding difficulties. Hepatomegaly (Fig. 65.11) is prominent and is more marked than splenomegaly, in contrast to Gaucher disease. Neurologic regression starts at 5–10 months with hypotonia. From around 18 months, there is loss of vision associated with a cherry-red spot (Fig. 65.12) and later optic atrophy. There may be a brown discoloration of the anterior lens capsule, but minimal corneal opacification.[36] There is no treatment and most patients die by 3 years.

Niemann–Pick disease type B is less severe and presents later in childhood with hepatosplenomegaly. Usually there are no neurologic symptoms; some patients may have ataxia but are usually of normal intelligence. Massive splenic enlargement, cirrhosis of the liver, and pulmonary infiltration may occur



Fig. 65.11 An infant with Niemann–Pick type A showing the hepatomegaly and spastic posture.

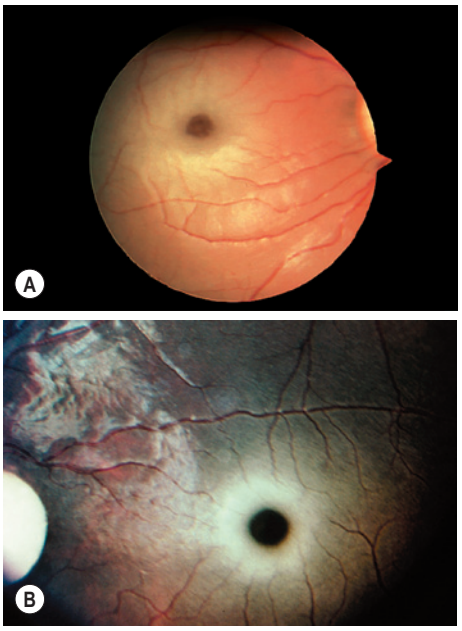


Fig. 65.12 (A) Cherry-red spot in a patient with Niemann–Pick type A: the spot is brownish because of dark pigmentation. (B) Cherry-red spot in a black infant with Niemann–Pick type A. *(Professor C.S. Hoyt's patient.)*

(Fig. 65.13). Eye abnormalities include periorbital fullness, macular granular deposits, and cherry-red spot.[37] ERT is being developed for type B patients.

Niemann–Pick disease type C

Niemann–Pick type C is due to impaired intracellular trafficking of cholesterol as a result of mutations in either the *NPC1* or *NPC2* genes. NPC is pan-ethnic.

Type C has variable presentations including neonatal liver disease, chronic splenomegaly, or neurologic deterioration in children or adults. Neurological features include ataxia,

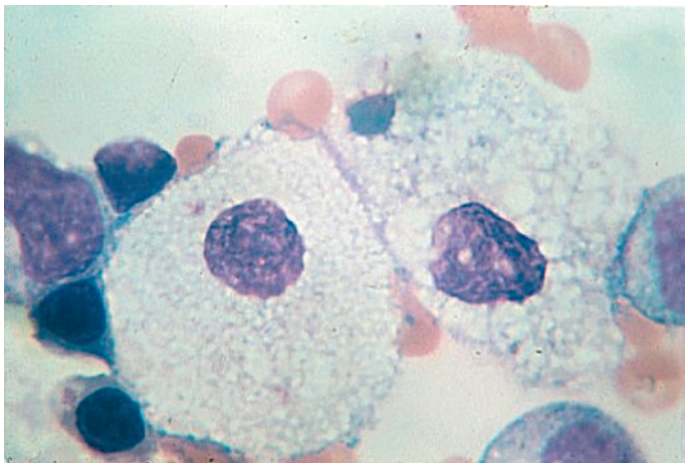


Fig. 65.13 Foam cells. Lipid laden histiocytes seen on bone marrow biopsy in Niemann–Pick disease type B.

cataplexy, seizures, psychoses, and dementia. A vertical supranuclear gaze palsy (Fig. 65.14) is characteristic of this disorder, and may be the presenting feature. There may be horizontal supranuclear eye movement defects or a supranuclear disorder of convergence. A faint cherry-red spot may be seen. Miglustat (an inhibitor of glucosylceramide synthase, which catalyzes the first step of glycosphingolipid synthesis) may slow progression of the neurologic disease.[38]

Fabry disease (α-galactosidase deficiency)

Fabry disease is an X-linked recessive lysosomal storage disease caused by a deficiency of α-galactosidase A. Males with Fabry disease usually present in late childhood or adolescence with pain in the extremities (acroparesthesia) provoked by exertion or change in temperature. Characteristic skin lesions (angiokeratoma corporis diffusum; Fig. 65.15A) are present, with dark red angiectases in the "bathing trunk area" (lower abdomen, buttocks, and scrotum). Later symptoms include a chronic progressive neuropathy (Fig. 65.15B), progressive renal dysfunction, heart disease (hypertrophic cardiomyopathy), and strokes. Heterozygous females may be asymptomatic or suffer the same problems as men, with a later onset and slower progression; the extent of manifestations is determined by X-chromosome inactivation. Fabry disease is treated with ERT, with intravenous infusions of recombinant α-galactosidase, agalsidase alfa, or agalsidase beta.[39]

Corneal verticillata (whorl-like lines radiating from a single vortex; Fig. 65.15C) occur in both males and females with Fabry disease. They do not affect vision but may facilitate diagnosis. Corneal involvement includes corneal haze and fine subepithelial brown lines.[40–42] Conjunctival tortuosity and microaneurysms occur (Fig. 65.15D) and chronic chemosis may occur in affected adults.[43,44] Characteristic lens opacities occur less commonly than corneal and vascular changes: a granular, wedge-shaped, subcapsular cataract, and lines of discrete opacities radiating from the posterior pole of the lens along the sutures (Fig. 65.15E). Retinal vascular tortuosity, particularly of veins, occurs in the second decade. The vessels become beaded, with sheathing, and may develop arteriovenous anastomoses and thromboses. Vascular tortuosity is more frequently observed in patients with greater impairment of renal and cardiac function.[45] Retinal vascular occlusion may be the initial symptom. Optic disc edema or myelinated nerve fibers may occur. Neuro-ophthalmologic problems include nystagmus, third nerve palsy, and strabismus. Optic atrophy and internuclear ophthalmoplegia occur rarely.

Farber disease

This autosomal recessive disease is characterized by the onset in infancy of multiple subcutaneous nodules, lymphadenopathy, a hoarse cry, and variable involvement of lung, heart, and liver. The course is variable with death between 1 and 18 years. Severely affected children may have a cherry-red spot, nodular corneal opacity, or a pingueculum-like conjunctival lesion. There is no treatment.

Gaucher disease (glucocerebrosidase deficiency)

Gaucher disease is an autosomal recessive disease that arises from mutations in the glucocerebrosidase (*GBA*) gene. Gaucher disease is classified according to severity and neurologic involvement into types 1, 2, and 3.

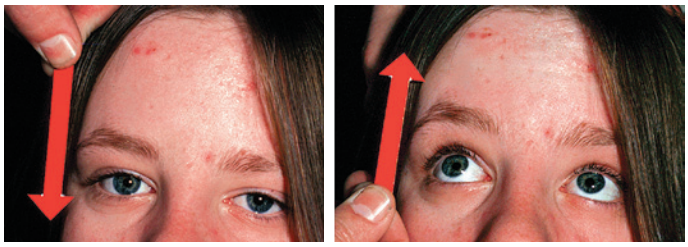


Fig. 65.14 Downgaze palsy in a child with Niemann–Pick type C. The arrow denotes the direction that the child is being told to look. Horizontal and upgaze were normal. *(Mr M.D. Sander's patient.)*

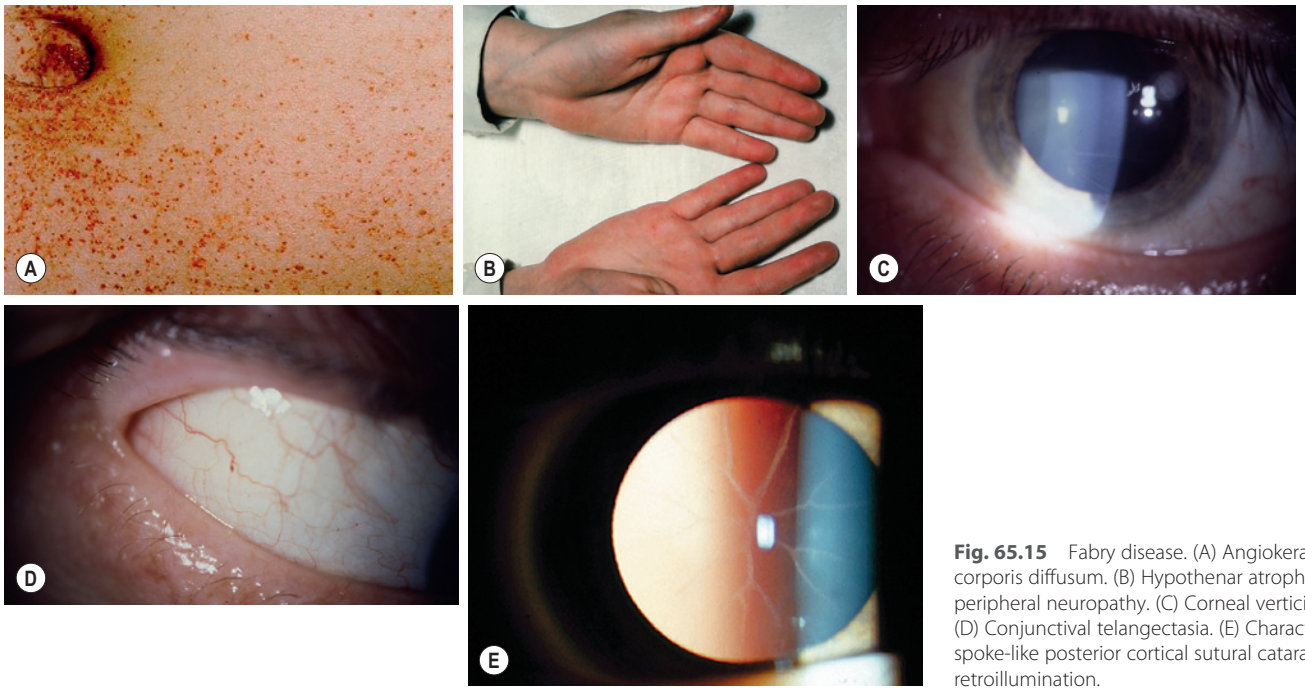


Fig. 65.15 Fabry disease. (A) Angiokeratoma corporis diffusum. (B) Hypothenar atrophy from peripheral neuropathy. (C) Corneal verticillata. (D) Conjunctival telangectasia. (E) Characteristic spoke-like posterior cortical sutural cataract on retroillumination.

Table 65.3 Classification of the neuronal ceroid lipofuscinoses

Age at onset	Designation	Chromosome location	Deficient protein
Congenital or later	CLN10	11p15	Cathepsin D
Infantile or later	CLN1	1p32	Palmitoyl protein thioesterase 1
Late infantile or later	CLN2	11p15	Tripeptidylpeptidase 1
	CLN5	13q22	Partially soluble protein
	CLN6	15q21	Membrane protein
	CLN7	4q28	Membrane protein
	CLN8	8p23	Membrane protein
Juvenile	CLN3	16p12	Membrane protein
	CLN9		
Adult	CLN4		

Source: Kohlschütter A, Schulz A. Towards understanding the neuronal ceroid lipofuscinosis. Brain Dev 2009; 31: 499–502.

Gaucher type 1 (non-neuronopathic)

This is more common in Ashkenazi Jews, and can present in children or adults with hepatosplenomegaly, anemia, thrombocytopenia, and leukopenia. There may be painful splenic and bony infarctions. Osteopenia may lead to pathological fractures and the distal ends of the femur may develop a typical Erlenmeyer's deformity (so named because it resembles a conical flask). Dark brown-yellow pingueculae occur in the nasal bulbar conjunctivae, which are characterized by numerous Gaucher cells on histologic examination. Macular change, choroidal neovascularization, and peripheral retinal vessel leakage occur.[46–48] ERT with recombinant glucocerebrosidase is very effective, correcting the hematological abnormalities and organomegaly and ameliorating the bone disease. Substrate reduction therapy (miglustat and eligustat) may now be used for maintenance treatment in adults, as an oral alternative to ERT.

Gaucher type 2 (infantile)

This presents within the first 6 months of life with severe feeding problems, spasticity, strabismus, neurologic regression, and hepatosplenomegaly. ERT is ineffective and affected infants die within the first few years.

Gaucher type 3 (chronic neuronopathic)

Type 3 usually presents in childhood with failure to thrive and hepatosplenomegaly (Fig. 65.16). Skeletal problems include osteopenia and progressive kyphosis. Oculomotor apraxia (saccadic initiation failure) may be the first sign of neurologic involvement.[49,50] Intermittent strabismus and vertical gaze palsies may also occur. Retinal, preretinal and vitreous white deposits, and epiretinal membranes have been described.[51,52] Though ERT does not cross the blood–brain barrier, it ameliorates the systemic symptoms and allows many patients to survive into adult life.

Cystinosis

See Chapter 34.

Neuronal ceroid lipofuscinosis

The neuronal ceroid lipofuscinoses (NCLs; or ceroid lipofuscinoses, neuronal [CLN]) are autosomal recessive conditions characterized by progressive neurologic deterioration in children or young adults, epilepsy, and visual deterioration due to retinopathy. All the NCLs are associated with accumulation of an autofluorescent material, ceroid lipofuscin, and degeneration of neuronal cells.[53] There are at least 10 genetically distinct NCLs (Table 65.3). The term "Batten disease" refers to the juvenile-onset form of NCL and occurs most commonly as a result of mutations in *CLN3*, on chromosome 16p21.

Juvenile NCL must be considered when a child presents with rapidly deteriorating visual function, particularly when associated with behavioral changes, neurologic deterioration, or seizures. The ophthalmologist plays a crucial role in early diagnosis of the condition.

NCLs are diagnosed increasingly often by molecular genetic testing, but electron microscopy of skin or leukocyte preparations are still helpful, showing characteristic inclusions. Vacuolated lymphocytes can be seen in blood films from patients with CLN3 and enzyme deficiencies can be demonstrated in leukocytes in CLN1 and CLN2. There are no specific treatments available for the NCLs, but there has been a trial of intrathecal enzyme replacement for late-infantile NCL.

Infantile neuronal ceroid lipofuscinosis (CLN1, Haltia–Santavuori disease)

This manifests as rapidly progressive neurologic deterioration from approximately 6 months of age with seizures and brain atrophy, leading to a vegetative state by about 4 years. There is visual loss with retinopathy and optic atrophy but this is less prominent that other features.

Classical late-infantile neuronal ceroid lipofuscinosis (CLN2, Jansky–Bielschowsky disease)

This presents around the third year of life with epilepsy and developmental regression. Visual loss occurs from retinal degeneration but is relatively late.

Juvenile neuronal ceroid lipofuscinosis (CLN3, Batten disease)

Children with juvenile NCL present with rapid deterioration of vision between 4 and 10 years. Other manifestations such as behavioral problems, cognitive decline, and motor deterioration manifest before or after the onset of visual loss.[53–55] Although neurological manifestations occur early, often predating the visual deterioration, they are often quite subtle. Night blindness



Fig. 65.16 Hepatosplenomegaly in Gaucher type 3.

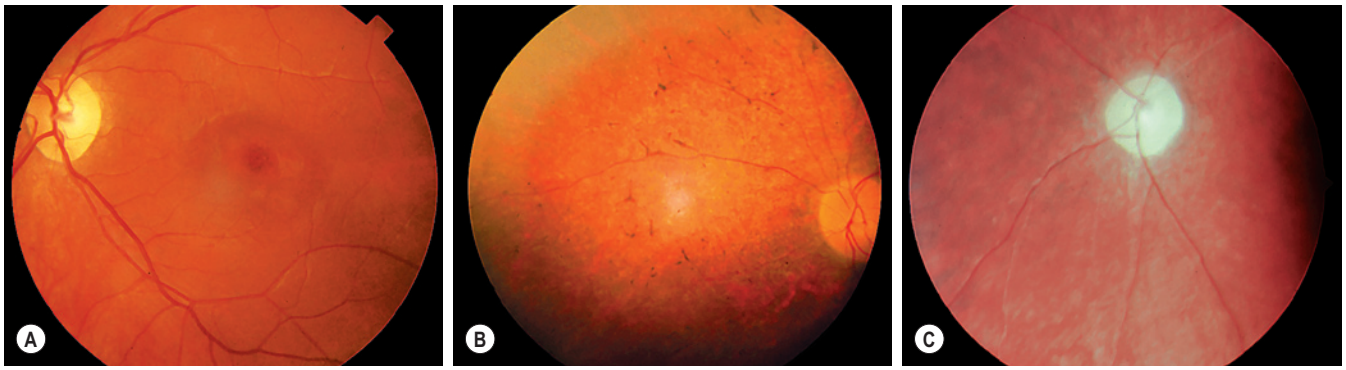


Fig. 65.17 Juvenile Batten disease. (A) Optic atrophy, arteriolar thinning and bull's eye maculopathy. (B) Bone-spicule pigmentation, optic atrophy, and arteriolar narrowing. (C) Late retinal changes, including depigmentation, optic atrophy, and extreme arteriolar narrowing.

and photophobia may be present in addition to visual loss. Eccentric viewing or "overlooking" is often a feature, where children hold their eyes in a raised position while attempting to fixate on a target, presumed due to the relative preservation of the superior peripheral retina.[54,55] Misdiagnosis as macular or retinal dystrophy or even functional visual loss may occur in the early stages.[54] At presentation, the fundus may be normal or show pigmentary maculopathy, atrophic changes, or bull's eye maculopathy. Later there is a widespread retinal degeneration (Fig. 65.17), with sparse bone-spicule pigmentation in the periphery, thinned arterioles and disc atrophy (Fig. 65.17B,C), and the retina eventually becomes avascular. ERG may show an electronegative waveform in early cases with a markedly reduced b : a ratio in the single flash photopic ERG, consistent with inner retinal dysfunction.[53,56] Fluorescein angiography shows diffuse RPE atrophy with stippled hyperfluorescence.[57,58]

The children are usually blind within 3 years, and the disease follows a slow downward path with the onset of seizures between 7 and 16 years of age, dementia in the teens, and death sometimes in the second or third decade.

Mitochondrial disorders

Mitochondrial disorders arise as a result of dysfunction of the mitochondrial respiratory chain. They can present at any age and frequently have ocular manifestations such as ptosis, external ophthalmoplegia, optic atrophy, pigmentary retinopathy, cataracts, and cerebral visual impairment.[59–61] Some mitochondrial disorders have only ocular manifestations (e.g. Leber hereditary optic neuropathy; LHON), but many involve multiple organ systems such as muscle (proximal myopathy), heart (cardiomyopathy), peripheral and central nervous systems (encephalopathy, seizures, dementia, migraine, stroke-like episodes, ataxia, and spasticity), inner ear (sensorineural deafness), and endocrine systems (diabetes mellitus). Several syndromes are described but there is overlap between them and many patients have an atypical pattern.

Mitochondrial disorders can be caused by mutations of nuclear genes (with Mendelian inheritance) or mitochondrial DNA (mtDNA, which is inherited exclusively from the mother). Many copies of mtDNA are present in each cell. In LHON, mutations affect all copies (homoplasmy). In other conditions, mutant mtDNA usually coexists with wild-type mtDNA (heteroplasmy) and the clinical severity depends on the proportion that is mutated; the proportion varies among members of a pedigree, leading to different symptoms and ages of presentation. If the clinical picture is characteristic of a disorder associated with specific genetic abnormalities (e.g. LHON, NARP, MELAS, or Alpers syndromes) then the diagnosis can be confirmed by molecular genetic testing. MtDNA point mutations can be detected in blood or urine but this is not always true for mtDNA deletions. Other tests include measurement of blood or cerebrospinal fluid (CSF) lactate, and biochemical or histochemical studies of the mitochondrial respiratory chain on a muscle biopsy.

Leber hereditary optic neuropathy

See Chapter 54.

Progressive external ophthalmoplegia and Kearns–Sayre syndrome

Progressive external ophthalmoplegia (PEO) occurs in a number of different mitochondrial disorders. The ophthalmoplegia is characterized by ptosis and progressive loss of eye movements; most patients have exotropia but diplopia is rare due to the gradual onset. PEO may be isolated (chronic progressive external ophthalmoplegia) or associated with various additional symptoms.[62] PEO may be sporadic or show autosomal recessive, autosomal dominant, or maternal patterns of inheritance.[63]

Kearns–Sayre syndrome is defined as PEO and pigmentary retinopathy with onset before 20 years of age and at least one of: heart block, cerebellar syndrome, or CSF protein above 1 g/L. Other features may include hearing loss, dementia, cardiomyopathy, and endocrine disorders. The fundus has a "salt and pepper" appearance but visual acuity is seldom severely impaired. Involvement of the orbicularis oculi muscles can lead to exposure keratitis and corneal perforation.[62] Kearns–Sayre syndrome is associated with mtDNA "rearrangements" (large deletions or duplications) but it is sporadic rather than inherited.

MELAS syndrome

MELAS syndrome is characterized by:

M = mitochondrial myopathy
E = encephalopathy
LA = lactic acidosis
S = stroke-like episodes

The stroke-like episodes can start at any age, most commonly between 5 and 15 years, and may cause visual field defects or cortical blindness and hemiplegia; sometimes the symptoms resolve rapidly. Headaches and vomiting may precede the stroke-like episodes and maternal relatives may have a history of severe migraine. Other ocular manifestations may include PEO, "salt and pepper" pigmentary retinopathy and macular RPE atrophy, optic neuropathy, and non-ischemic central retinal vein occlusion.[64,65] The m.3243A>G mtDNA mutation is present in 80% of patients with MELAS syndrome; the remaining patients usually have another mtDNA mutation. MELAS syndrome only occurs if the mutation affects most copies of mtDNA; if it is present at a lower level, patients may have milder problems, such as diabetes and deafness.

NARP syndrome

This is characterized by:

N = neurogenic weakness

A = ataxia

RP = retinitis pigmentosa

It is caused by the m.8993T>G or m.8993T>C mutations. The fundus may have a "salt and pepper" or a "bone-spicule" appearance; some patients develop optic atrophy or maculopathy with severe visual loss.

Leigh syndrome (subacute necrotizing encephalomyopathy)

Leigh syndrome is a severe early-onset neurodegenerative disorder primarily affecting the brainstem and basal ganglia. Problems include dystonia and dysphagia, and death is often due to impaired ventilatory drive. Brainstem involvement can cause ptosis, nystagmus, and strabismus and there may also be optic atrophy.[66]

Alpers syndrome

This neurodegenerative disorder presents with an explosive onset of seizures and developmental regression in early childhood. Involvement of the occipital cortex is common, leading to cortical visual impairment. Terminally, patients often develop liver failure. The condition is caused by autosomal recessive mutations in *POLG1*, which is a nuclear gene involved in mtDNA replication.

Sengers syndrome

Sengers syndrome is characterized by congenital cataracts, hypertrophic cardiomyopathy, skeletal myopathy, and lactic acidosis.[67] The cardiomyopathy may cause early death or the disease may be milder, in which case patients can survive into their second or third decades. It shows autosomal recessive inheritance and is caused by mutations in the gene for acylglycerol kinase (AGK).[68]

Autosomal dominant optic atrophy

See Chapter 54.

Peroxisomal disorders

Peroxisomes are organelles involved in the synthesis of plasmalogens (crucial for myelin), bile acids and isoprenoids, and the oxidation of very long chain and branched chain fatty acids (e.g. phytanic acid).

Peroxisomal biogenesis disorders

In these autosomal recessive disorders, peroxisomes cannot be made properly due to mutations in the *PEX* genes. Peroxisomal biogenesis disorders are classified into the Zellweger spectrum and rhizomelic chondrodysplasia punctata.

Zellweger spectrum (Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum disease)

These disorders vary in severity, with overlap between phenotypes, but with poor vision as a common feature. Zellweger syndrome is the severe end of the spectrum; patients die within a few months of birth. They are dysmorphic with a large anterior fontanelle, high forehead, shallow supraorbital ridges, and epicanthic folds. Hypotonia, seizures, poor feeding, liver disease, impaired hearing, and ocular abnormalities occur (Fig. 65.18). Neonatal adrenoleukodystrophy is a slightly milder phenotype; some patients survive to mid-childhood, although they become deaf, blind, and profoundly retarded. Infantile Refsum disease is the "mild" end of the spectrum; patients have little or no dysmorphism but they still have mental retardation, deafness, and pigmentary retinopathy. Diagnosis is made by demonstrating raised plasma concentrations of very long chain fatty acids (VLCFA) followed by molecular genetic studies.

Retinal dystrophy is almost universal[69] (Fig. 65.19). Patients with neonatal adrenoleukodystrophy and infantile Refsum disease develop macular depigmentation and peripheral leopard spot pigment clumping[70] with loss of peripheral vision that often progresses to complete blindness. Patients with Zellweger syndrome have retinal hypopigmentation and



Fig. 65.18 20-month-old child with a peroxisomal biogenesis disorder. The child presented with hypotonia, deafness, poor vision, and nystagmus and had a pale fundus and extinguished electroretinogram.

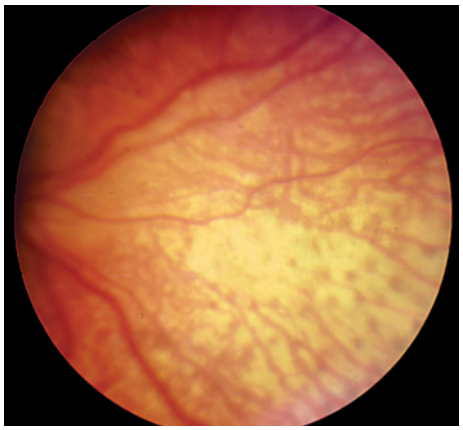


Fig. 65.19 Zellweger syndrome. Retinal dystrophy with mottled retinal pigment epithelium.

a severely abnormal or absent ERG. They may have corneal clouding, congenital cataracts, and glaucoma. Nystagmus and strabismus are common.

Rhizomelic chondrodysplasia punctata

In rhizomelic chondrodysplasia punctata (RCDP), there is severe shortening of the humeri and femora and stippled epiphyses. Most patients have facial dysmorphism and severe neurologic abnormalities: few survive beyond 2 years. Cataracts are very common and are usually congenital (Fig. 65.20) though they may appear at a few months of age. Patients with RCDP have normal plasma VLCFA concentrations but erythrocyte plasmalogen levels are abnormally low.

Refsum disease

Refsum disease is caused by autosomal recessive deficiency of the peroxisomal enzyme phytanoyl-CoA hydroxylase, leading to accumulation of phytanic acid in blood and tissues. Features of Refsum disease include cerebellar ataxia, peripheral neuropathy, and retinitis pigmentosa and cataracts. If started early enough, dietary restriction of phytanic acid can prevent these problems.

X-linked adrenoleukodystrophy

In this X-linked recessive disorder, mutations in the *ABCD1* gene lead to the accumulation of VLCFAs in blood and tissues. There are two main phenotypes, which may occur in the same pedigree. The childhood cerebral form presents at 4–12 years of age with behavioral, cognitive, and neurologic problems, usually leading to a vegetative state within 3 years. Strabismus, visual field defects, and decreased visual acuity are early symptoms. Later, these patients become blind due to optic atrophy and cortical visual loss[71] (Fig. 65.21). The second phenotype, adrenomyeloneuropathy, presents with paraparesis in adults. Adrenal failure occurs in both phenotypes, either before or after the onset of neurologic problems.

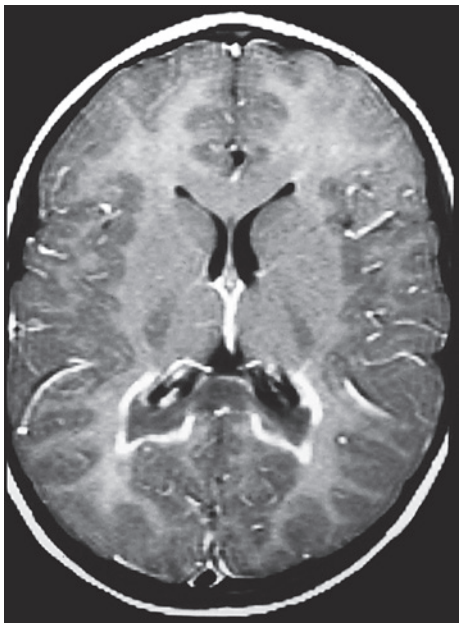


Fig. 65.21 Adrenoleukodystrophy. MRI scan showing characteristically predominant early involvement of the occipital lobes and visual pathway with high signal from the periventricular white matter.

Lorenzo's oil combined with a low-fat diet can normalize plasma VLCFA concentrations and *may* reduce the risk of childhood cerebral disease but it does not alter the clinical course once symptoms have started. HSCT can prevent progression of the childhood cerebral disease if undertaken soon after the onset of problems.

Primary hyperoxaluria type I

See Chapter 50.

Congenital defects of glycosylation

Most extracellular and cell surface proteins and some intracellular proteins are glycoproteins. The oligosaccharide may be attached to the amino acid asparagine in the protein (*N*-linked glycosylation) or to a serine or a threonine (*O*-linked glycosylation). Defects of *O*-linked glycosylation cause various disorders including Walker–Warburg syndrome and muscle–eye–brain disease (see Chapters 42 and 60).

Disorders of *N*-linked glycosylation

Phosphomannomutase-2 deficiency is the commonest congenital defect of glycosylation (PMM2-CDG; previously known as carbohydrate-deficient glycoprotein syndrome [CDG] Ia). Patients present at birth with hypotonia, esotropia, and dysmorphism – long fingers and toes (Fig. 65.22), inverted nipples, and fat pads over the buttocks. Death may occur in infancy from sepsis, pericardial effusions, nephrotic syndrome, or liver failure. Those surviving, or presenting later, show delayed development and ataxia, rarely walking without support. Most patients have esotropia, which is usually present from birth; ocular motor apraxia and nystagmus are common. Pigmentary retinopathy appears after 8 years of age but the ERG may be abnormal much earlier.[72] Other problems include delayed visual maturation, visual field loss, and progressive myopia.[73,74]

The other *N*-glycosylation defects are rarer and the ophthalmologic features are less well defined. Strabismus occurs in a number of disorders and nystagmus, poor acuity, optic neuropathy, congenital cataracts, congenital glaucoma, and colobomas of the iris or retina have been reported.

Inborn errors of carbohydrate metabolism

Galactosemia and galactokinase deficiency

Galactosemia is an autosomal recessive disorder caused by a deficiency of the enzyme galactose-1-phosphate uridyltransferase. It presents in neonates with poor feeding, jaundice, and sometimes sepsis and is treated with a minimal-galactose diet.[75] Cataract formation occurs due to the accumulation of galactitol within the lens, and can be prevented with early diagnosis and implementation of a galactose-restricted diet.[76,77] "Oil-droplet" cataracts occur at an early stage due to refractive change within the lens nucleus (Fig. 65.23). These may

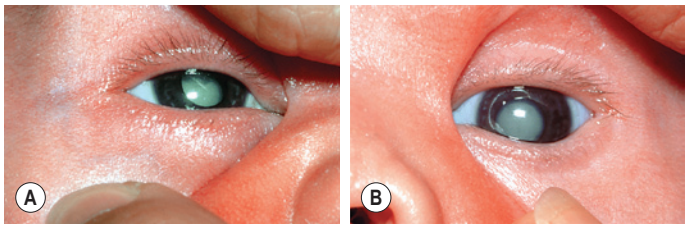


Fig. 65.20 Rhizomelic chondrodysplasia punctata. Bilateral total congenital cataract.



Fig. 65.22 Phosphomannomutase-2 deficiency (carbohydrate-deficient glycoprotein syndrome Ia). (A) Showing long fingers. (B) Showing long toes. (C) 6-year-old boy with esotropia and phosphomannomutase-2 deficiency.

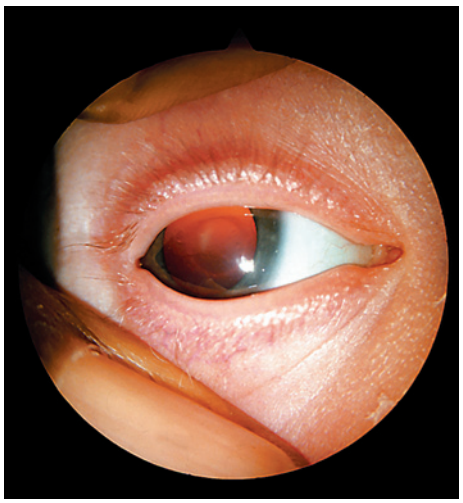


Fig. 65.23 Oil-droplet cataract in galactosemia.

progress to lamellar cataracts in the presence of poor dietary and biochemical control.

Galactokinase deficiency causes early-onset juvenile cataracts, which may stabilize or regress with dietary control; mental retardation has been reported in a few patients.[78] Reducing substances are present in the urine in both untreated galactosemia and galactokinase deficiency. The diagnosis is established by enzyme assays in erythrocytes and molecular genetic studies.

Inborn errors of amino acid metabolism

Homocystinuria

See Chapter 36.

Propionic and methylmalonic acidemias

These autosomal recessive conditions result from defects in the catabolism of branched chain amino acids. Neonates or young children present with vomiting, drowsiness, acidosis, and hyperammonemia. Treatment includes carnitine, dietary protein restriction, and prevention of catabolism; some cases of methylmalonic acidemia respond to vitamin B_{12}. Progressive optic neuropathy (Fig. 65.24) may occur in childhood and may be severe, with central scotomas and optic nerve pallor.[79–81] Visual loss may be exacerbated by episodes of metabolic decompensation.

CblC (cobalamin C) disease

This autosomal recessive disorder of vitamin B_{12} metabolism leads to methylmalonic aciduria and homocystinuria. It may present in infancy with failure to thrive, hypotonia, microcephaly, seizures, and nystagmus. A milder form presents later with neurologic deterioration. Visual loss may occur in childhood due to cone–rod retinal degeneration with an early maculopathy[82] and optic atrophy.[83]

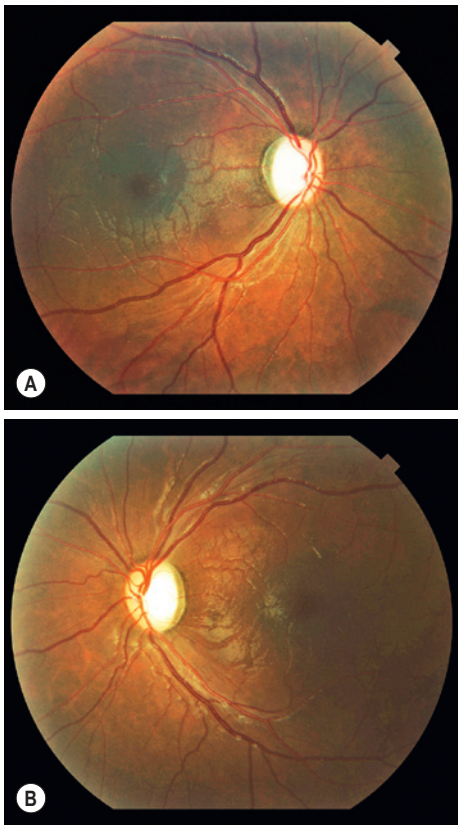


Fig. 65.24 Optic neuropathy in an 11-year-old girl with propionic acidemia. The patient noticed an acute onset of reduced vision in her right eye, and was found to have visions of only counting fingers in the right eye and 1.1 LogMAR in the left, with sluggish pupils, a right relative afferent pupil defect, and bilateral optic nerve pallor.

Maple syrup urine disease

In this autosomal recessive disorder, branched chain amino acids accumulate and are neurotoxic. Most cases present with encephalopathy in the first 2 weeks of life. Patients can be treated acutely by hemofiltration and subsequently with dietary management. Ophthalmoplegia may be a prominent feature of the neonatal encephalopathy.[84] In older children, ataxia is an early feature of encephalopathy and may be accompanied by nystagmus.

Molybdenum cofactor deficiency and isolated sulfite oxidase deficiency

These two autosomal recessive disorders have similar clinical features, with spherophakia and ectopia lentis being common findings. Nystagmus, cortical blindness, enophthalmos, and colobomas may be present.[85] Most patients present in the newborn period with intractable seizures. Subsequently, they develop microcephaly, severe psychomotor retardation, and spastic tetraplegia with early death. Neuroimaging demonstrates multicystic encephalopathy and atrophy. A few patients run a milder course with prolonged survival. Treatment is now available for one form of molybdenum cofactor deficiency but it needs to be started within a few days of birth.[86]

Gyrate atrophy

Gyrate atrophy is an autosomal recessive disorder caused by deficiency of the enzyme ornithine δ-aminotransferase, leading to raised plasma ornithine levels, chorioretinal degeneration, macular edema and progressive loss of vision (Fig. 65.25).[87] Myopia and early cataracts may occur.[88] An arginine-restricted diet may slow the rate of deterioration of the chorioretinal degeneration.[89,90]

Tyrosinemia type 2 (Richner–Hanhart syndrome)

This autosomal recessive disorder is caused by deficiency of tyrosine aminotransferase. It may present with ocular signs and symptoms as the initial manifestation in the first years of life with photophobia, pain, and conjunctival injection. There is a bilateral pseudodendritic keratitis, which may lead to neovascularization and corneal scarring.[91] Patients may have painful erosions and hyperkeratosis of the palms and soles, and cognitive impairment. Plasma tyrosine concentrations are extremely high, and the eye and skin lesions probably result from the intracellular precipitation of tyrosine crystals. Dietary restriction of tyrosine and phenylalanine leads to resolution of these lesions.[92]

Tyrosine concentrations are lower in tyrosinemia types 1 and 3. Type 1 patients treated with nitisinone sometimes complain of sore eyes.

Oculocutaneous albinism

See Chapter 41.

Aromatic L-amino acid decarboxylase deficiency

Eye movement abnormalities are prominent in this rare autosomal recessive disorder, in which the synthesis of catecholamines and serotonin neurotransmitters is impaired. Patients present in infancy with oculogyric crises, hypotonia, and autonomic dysfunction. Convergence spasm, ptosis, and miosis may occur.[93]

Canavan disease

This is an autosomal recessive disorder prevalent in Ashkenazi Jews. Aspartoacylase deficiency leads to the accumulation of *N*-acetyl-aspartic acid. Patients with Canavan disease usually present aged 2–4 months with macrocephaly, hypotonia, and developmental delay. White matter degeneration is seen on neuroimaging. Cortical visual loss, optic atrophy, and nystagmus are common. Most patients die by 3 years of age.[94]

Disorders of fatty acid and fatty alcohol metabolism

Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency

The enzyme long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) participates in mitochondrial fatty acid β-oxidation, and the autosomal recessive condition, LCHAD deficiency, may present in infancy with hypoglycemia, liver disease, cardiomyopathy and hypotonia.[95] Treatment is with dietary restriction of long chain fatty acids, avoidance of fasting and a regular intake of glucose during illness. LCHAD deficiency

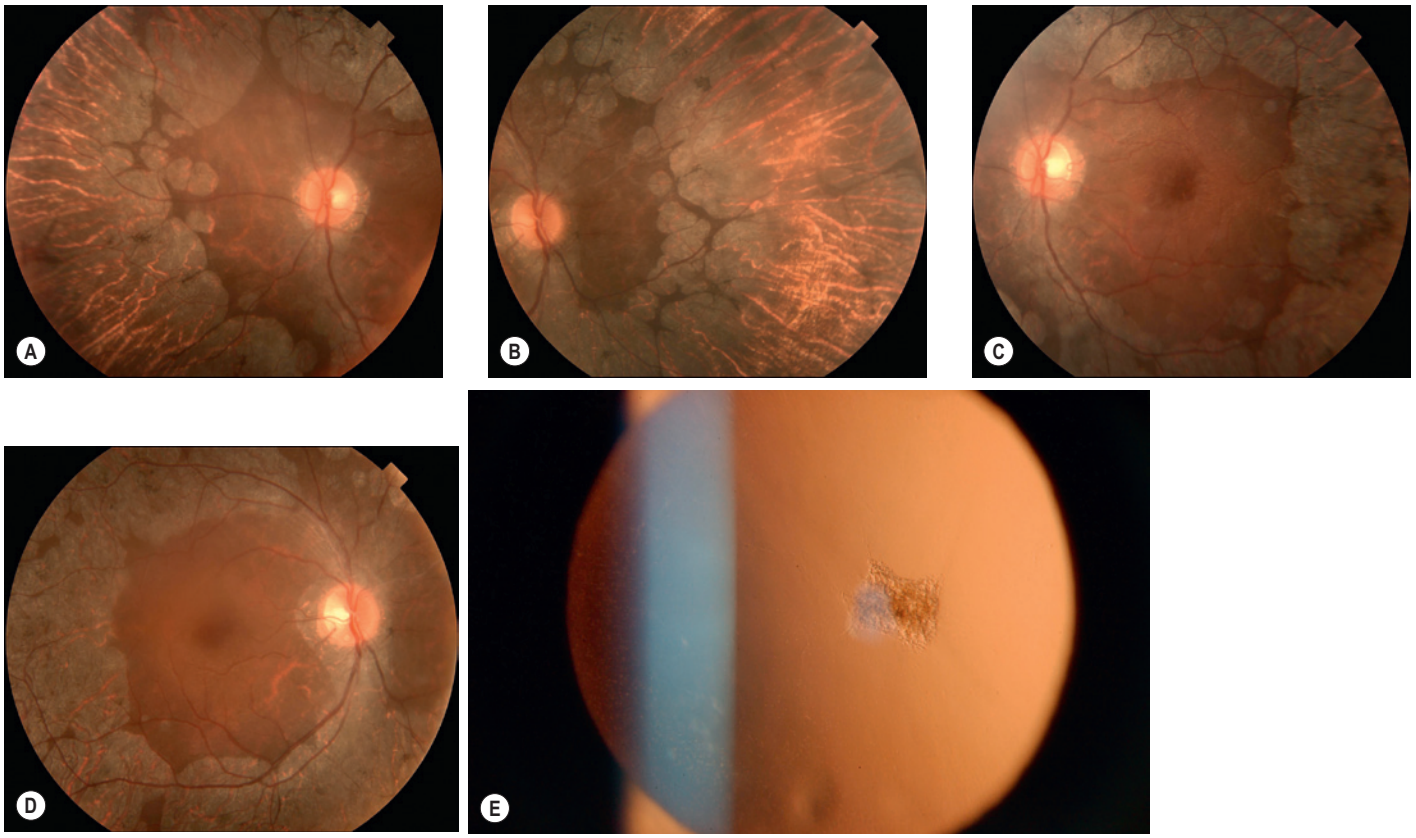


Fig. 65.25 Gyrate atrophy. (A,B) Characteristic sharply demarcated areas of chorioretinal degeneration in the mid-periphery of a myopic patient age 26, with relative sparing of the macula (C,D). The patient had poor dietary control, suffered from significant nyctalopia, and had acuities of 6/24 right and 6/36 left. (E) The patient also had bilateral cataract. *(Courtesy of Mr I.C. Lloyd, Manchester Royal Eye Hospital.)*

causes variable severity of chorioretinal degeneration with visual loss and progressive myopia[96] (Fig. 65.26). Progressive lens opacities may occur.[97] Optimal dietary control may delay the progression of the chorioretinopathy.[98]

Sjögren–Larsson syndrome

See Chapter 50.

Disorders of sterol metabolism

Early-onset cataracts are seen in several disorders of sterol metabolism, including defects of cholesterol synthesis and of bile acid synthesis.

Smith–Lemli–Opitz syndrome

Smith–Lemli–Opitz syndrome is caused by deficiency of 7-dehydrocholesterol reductase, which catalyzes the final step in cholesterol synthesis, resulting in reduced cholesterol and raised 7-dehydrocholesterol levels. It has a spectrum of phenotypic severity with mental retardation and congenital malformations: microcephaly; ptosis; small upturned nose; micrognathia (Fig. 65.27); polydactyly; syndactyly; genital, cardiac, and intestinal abnormalities.[99] One-fifth of patients have cataracts (usually congenital). Other ophthalmologic abnormalities, in addition to ptosis, include strabismus, optic atrophy, and optic nerve hypoplasia. Treatment with cholesterol does not improve intelligence.

Mevalonic aciduria

Mevalonic aciduria is a rare autosomal recessive inflammatory metabolic disorder caused by deficiency of mevalonate kinase, which catalyzes an early step in cholesterol synthesis. Patients present in infancy with dysmorphic features (dolichocephaly, down-slanting eyes, and low-set ears), mental retardation, failure to thrive, cerebellar ataxia, and visual impairment. They have recurrent febrile episodes that are accompanied by hepatosplenomegaly, lymphadenopathy, vomiting and diarrhea, arthralgia, and skin rashes. One-third of patients have cataracts. Uveitis and pigmentary retinopathy occur.[100,101] Many patients die in the first few years.

X-linked dominant chondrodysplasia punctata 2 (CDPX2, Conradi–Hünermann syndrome)

This is an X-linked dominant condition, lethal in males, in which mutations in the emopamil binding protein (EBP) gene lead to deficiency of 3β-hydroxysteroid Δ8,Δ7-isomerase. The main features are skeletal dysplasia, stippled epiphyses, neonatal ichthyosis with subsequent atrophic skin changes in a mosaic pattern, and cataracts, which may be congenital or developmental (Fig. 65.28). Microphthalmos, anterior

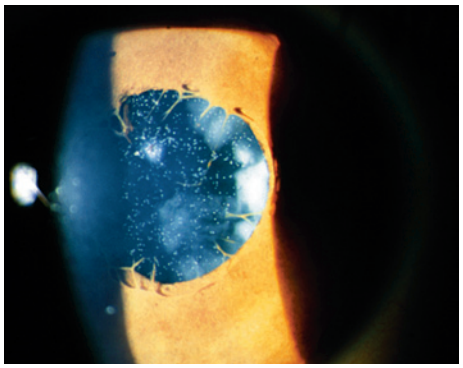


Fig. 65.28 Cataract in a girl with Conradi–Hünermann syndrome.

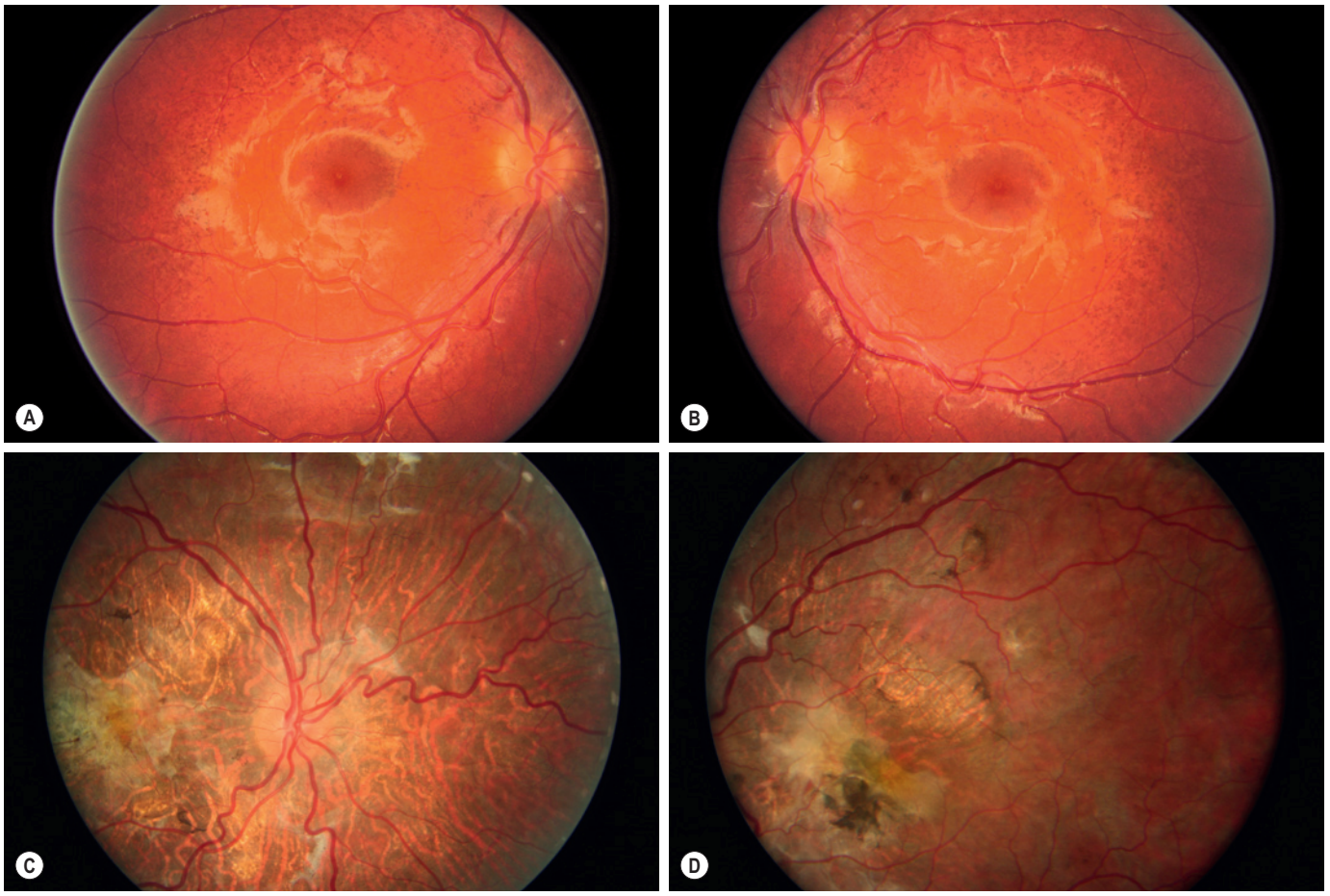


Fig. 65.26 (A,B) Peripapillary and perimacular granular pigmentary changes in an 11-year-old girl with long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency diagnosed neonatally during the first days of life. The acuity was 0.1 LogMAR right and left eye with correction for a slight myopia and astigmatism. Electroretinogram was of subnormal amplitude. (C,D) Bilateral areolar chorioretinopathy in a 21-year-old woman with LCHAD deficiency diagnosed at 8 months of age. Bilateral pigmentary retinopathy, exotropia, and bilateral myopia had been present since age 3 years, and by early adulthood the vision deteriorated due to chorioretinal fibrosis. The visual acuity was <1.0 LogMAR with myopic glasses. *(Courtesy of Kristina Teär Fahnehjelm, St. Erik Eye Hospital, Stockholm.)*



Fig. 65.27 19-year-old with Smith–Lemli–Opitz syndrome, showing facial features including ptosis.

segment dysgenesis, vitreoretinal abnormalities, and optic atrophy occur.[102,103]

Cerebrotendinous xanthomatosis

Cerebrotendinous xanthomatosis (CTX) is caused by mutations in the sterol 27-hydroxylase gene (*CYP27A1*) leading to the accumulation of cholestanol and cholesterol. Infantile-onset diarrhea may be the earliest clinical manifestation of CTX, followed by juvenile cataracts and neurologic problems (spasticity, ataxia, psychiatric disturbances, dementia, and seizures).[104] Adults develop tendon xanthomas and premature atherosclerosis. Optic neuropathy may occur in addition to cataracts. Treatment with chenodeoxycholic acid prevents deterioration and can reverse some neurologic symptoms.

X-linked ichthyosis (steroid sulfatase deficiency)

X-linked ichthyosis is caused by a deficiency of steroid sulfatase, and results in ichthyosis, usually within the first few months of life, in affected males. Characteristic corneal opacities (fine punctate diffuse opacities in posterior stroma adjacent to Descemet's membrane, or subepithelial granular opacities with epithelial irregularity) are present in 25% of

affected males and also in heterozygous females; they have no effect on vision.[105,106]

Lipoprotein disorders

Abetalipoproteinemia (Bassen–Kornzweig syndrome)

This autosomal recessive disorder occurs due to deficiency of microsomal trigylceride transfer protein (MTP), needed for the production of lipoproteins, resulting in malabsorption of fat and fat-soluble vitamins. It presents with failure to thrive, developmental delay, and steatorrhea in infancy. If untreated, spinocerebellar degeneration develops. It is associated with a progressive retinal dystrophy, which may be mistaken for retinitis pigmentosa; it may be stabilized by a low-fat diet and combined vitamin A and E supplementation.[107]

Lecithin-cholesterol acyltransferase (LCAT) deficiency and "fish eye" disease (partial LCAT deficiency)

Lecithin-cholesterol acyltransferase (LCAT) catalyzes the formation of cholesterol esters in high-density lipoproteins. Complete LCAT deficiency causes adult-onset renal failure, anemia, and corneal opacities. Partial LCAT deficiency ("fish eye" disease) causes no problems except progressive corneal clouding. This is due to extracellular lipid deposition in the corneal stroma. Opacities can be detected in children, although they are often asymptomatic. Some adults require corneal transplantation.

Apo A-I deficiency

Corneal clouding has been reported in a few children with Apo A-I deficiency. Other features of this condition are premature atherosclerosis and xanthomas.

Copper transport disorders

Wilson disease

Wilson disease is an autosomal recessive disorder resulting from mutations in ATP7B, which transports copper into the Golgi apparatus of hepatocytes. Impaired biliary excretion causes copper accumulation in liver, kidney, cornea, and brain. It usually presents with liver disease at 5–20 years of age, or with neurologic problems, typically between 20 and 40 years, but sometimes during childhood. Hepatic manifestations include chronic active hepatitis, cirrhosis, and fulminant hepatic failure. Common neurologic features are dystonia, dysarthria, dysphagia, tremor, and parkinsonism, and psychiatric problems. Rarer problems include hemolysis, arthritis, and Fanconi syndrome.

Deposition of copper in peripheral Descemet's membrane leads to golden-brown pigmentation: the Kayser–Fleischer ring (Fig. 65.29). Slit-lamp examination reveals these rings in 95% of patients with neurologic presentations but they are seldom present in asymptomatic patients and often absent in children presenting with liver disease.[108] Kayser–Fleischer rings may occur with chronic cholestasis from other causes. Retinopathy may occur as a result of dysregulation of photoreceptor copper levels.

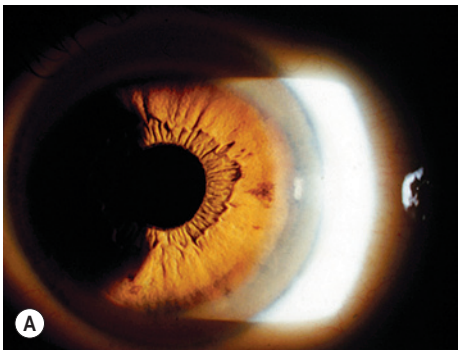


Fig. 65.29 (A) Kayser–Fleischer ring in a child with the neurologic presentation of Wilson disease. A brownish haze can be seen in the peripheral cornea. (B) Continued online.

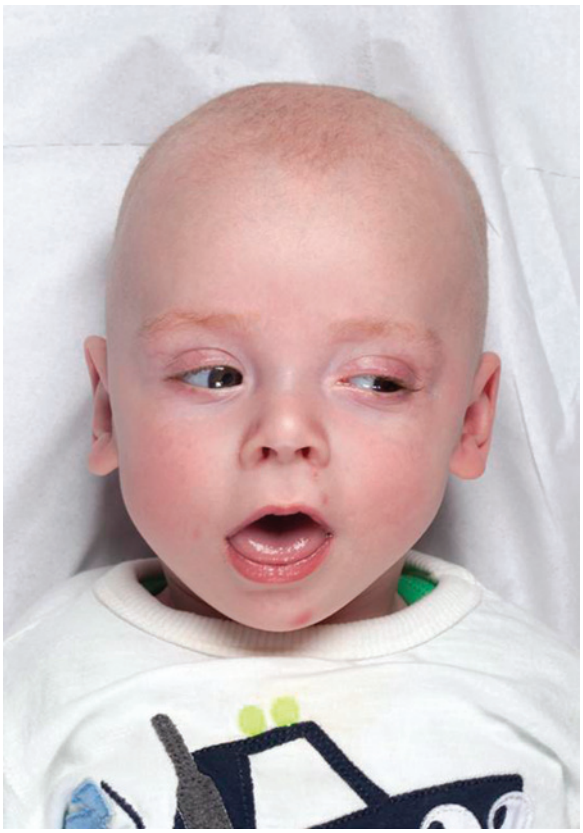


Fig. 65.30 Infant with Menkes disease. *(Courtesy of Dr Chakrapani, Birmingham Children's Hospital; reproduced from Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, editors. Rook's Textbook of Dermatology, 9th edition. Oxford: Wiley-Blackwell, 2015.)*

Treatment with copper chelators (D-penicillamine, trientine) or zinc results in symptomatic improvement and normal life expectancy. Liver transplantation is occasionally required.

Menkes disease

Defects in the copper transporter ATP7A cause this X-linked disease. The main features are infantile-onset neurodegeneration, connective tissue disturbances, and characteristic "kinky" hair (Fig. 65.30). Affected boys present with hypotonia and seizures at 2–3 months of age. They have "pudgy" cheeks, occipital bossing, and sparse, brittle, white hair. Poor visual

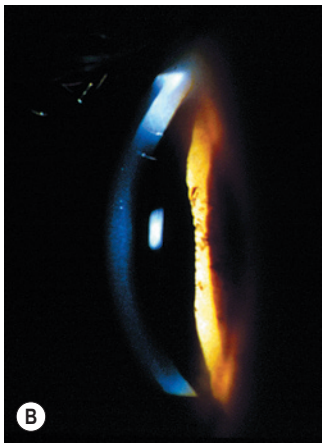


Fig. 65.29 (B) The Kayser-Fleischer ring can be seen in the posterior cornea on slit-lamp examination.

acuity is common with progressive visual loss due to retinal degeneration and optic atrophy. Early-onset myopia, strabismus, blue irides and iris stromal hypoplasia, and aberrant lashes may occur.[109] Patients deteriorate rapidly, with developmental regression, spasticity, and lethargy; most die by 3 years of age. Early treatment with parenteral copper-histidine may improve the neurologic prognosis and enhance survival.

Bonus e-book content online

Fig. 65.1 Kyphoscoliosis in mucopolysaccharidosis I.

Fig. 65.7 A child with mannosidosis showing the mild coarsening of the features. When older, there was an increase in the facial coarsening.

Fig. 65.8 Cherry-red spot in a patient with sialidosis type 1. (Mr M.D. Sander's patient.)

Fig. 65.13 Foam cells. Lipid laden histiocytes seen on bone marrow biopsy in Niemann–Pick disease type B.

Fig. 65.16 Hepatosplenomegaly in Gaucher type 3.

Fig. 65.19 Zellweger syndrome. Retinal dystrophy with mottled retinal pigment epithelium.

Fig. 65.20 Rhizomelic chondrodysplasia punctata. Bilateral total congenital cataract.

Fig. 65.28 Cataract in a girl with Conradi–Hünermann syndrome.

Fig. 65.29 (B) The Kayser-Fleischer ring can be seen in the posterior cornea on slit-lamp examination (arrow).

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Pupil anomalies and reactions

Andrew G Lee

Chapter contents

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The anatomy (Fig. 66.1), physiology, and pathophysiology of the pupillary pathways are important to the pediatric ophthalmologist but they are dealt with so excellently elsewhere that only aspects relevant to children will be discussed here.

Development (see Chapter 3)

The pupillary light response is absent in infants of 29 gestational weeks or less, but is usually present by 31 or 32 weeks.[1] At birth, the pupil is small. It enlarges in the first months and is probably largest at the end of the first decade, gradually becoming more miotic with age. The pupil reactions of term or premature infants are often small in amplitude and, because of their small resting size, may be difficult to elicit clinically, especially with brown irides. The failure of the pupil grating response in infants under 1 month of age is further evidence of the immaturity of the pupil responses in infancy.[2] Topical cocaine and hydroxyamphetamine are less potent in infants, suggesting that decreased sympathetic tone underlies miosis of the newborn.[3] In very premature babies, the pupil may not have fully formed; during the seventh month of gestation, the vascular pupillary membrane atrophies, and the pupil appears. Before 32 weeks' gestation, mydriasis does not necessarily indicate a central nervous system lesion, nor does an unresponsive pupil necessarily indicate an afferent defect.[3]

Dynamic retinoscopy indicates that infants from 6 days to 1 month of age have no accommodation, but that normal function is achieved by 3–4 months.[4] As a result, higher spatial frequencies are defocused, and younger infants cannot discriminate them. However, photorefraction studies have demonstrated accommodation of over 1 diopter in the neonate, and this ability increases rapidly in the first month and to a lesser extent in the first few years of life, with high amplitudes from 4 years until presbyopia develops.

The near synkinesis

The near reflex is activated when looking from a distant to a near target. It comprises a triad of convergence of the eyes, accommodation of the lenses, and miosis of the pupils; these components are separate in origin, but linked as a synkinetic response. The afferent pathway of the near reflex is probably more ventrally located than the pretectal afferent pathway of the light reflex. Both reflexes share the final efferent pathways of, the oculomotor nerve, ciliary ganglion, and the short posterior ciliary nerves.

In uncooperative children, testing of the near pupil response is more difficult than the light response. A suitable fixation target, for example a small internally lit toy for an infant, a mobile toy with sufficient detail to stimulate convergence, or letters or numbers for a literate child, is the most important factor in testing.

Congenital and structural abnormalities

Congenital, structural, and developmental anomalies of the pupil include the following (many are found in Chapters 33 and 39):

- aniridia;
- micropupil (congenital idiopathic microcoria);
- polycoria and corectopia;
- coloboma;
- peninsula pupil (an inherited partial iris sphincter atrophy with dilated oval pupils);
- persistent pupillary membrane;
- congenital mydriasis and miosis;
- irregular pupils;
- abnormalities of iris color (heterochromia iridis);
- unequal size (anisocoria).

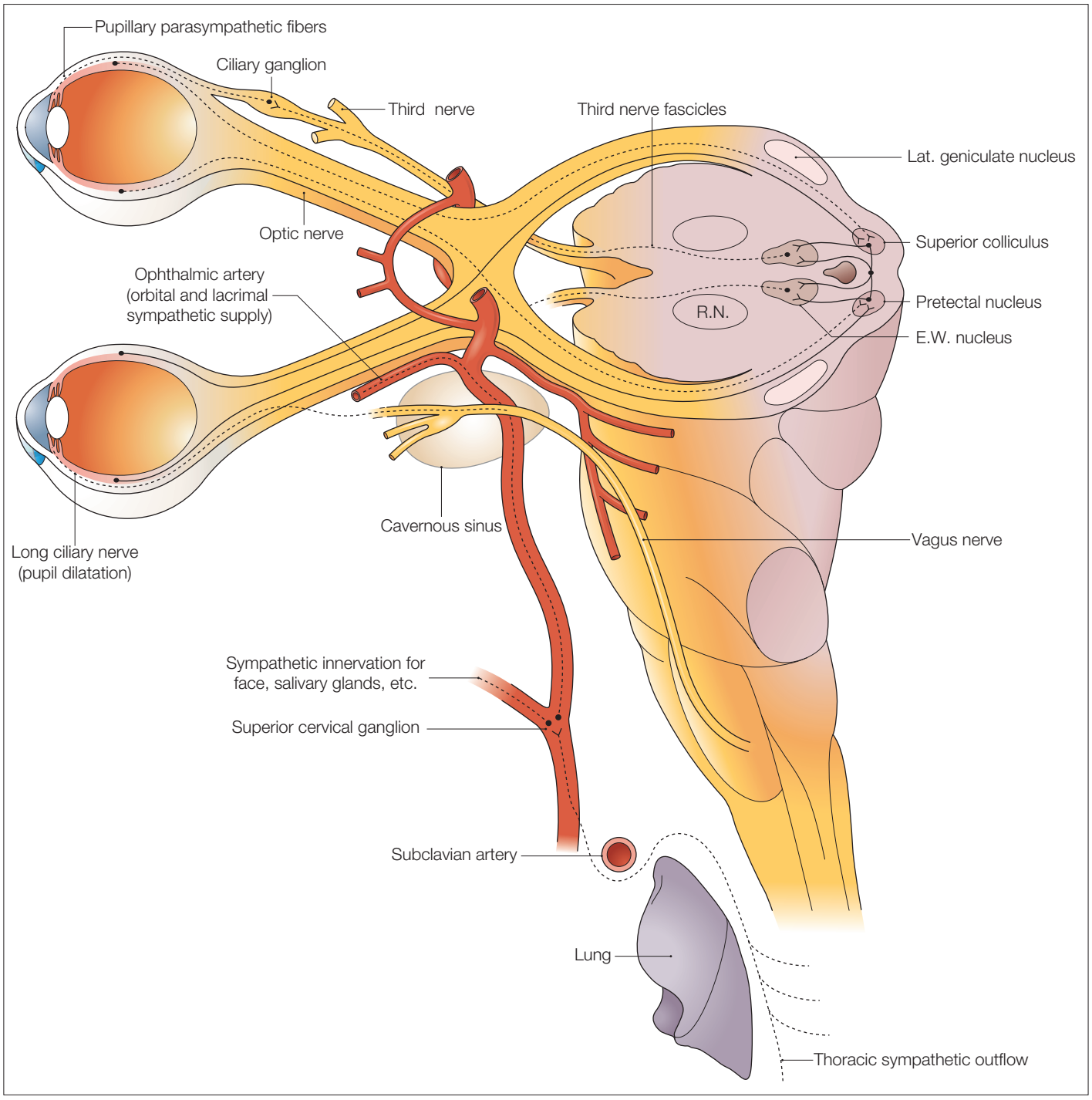


Fig. 66.1 Schematic representation of the efferent and afferent pathways involved in pupillary reactions. Red = blood vessels and parasympathetic; blue = afferent visual pathways; green = sympathetic pathway. E.W. nucleus, Edinger–Westphal nucleus; R.N., red nucleus.

Afferent and efferent abnormalities of pupil reactivity

Afferent pupil defects

Amaurotic pupils

A totally blind ("amaurotic") eye resulting from ocular disease usually has no pupil reaction to a light shone in it (amaurotic pupil), but a normal near reaction if the efferent system is intact. In monocular blindness, the affected eye has no direct pupil reaction but has consensual response to light shone into the unaffected eye (amaurotic pupil reaction). In binocular blindness from anterior visual pathway or retinal disease, both pupils are usually dilated, although they may be nearly normal size in longstanding blindness. If the efferent pupil pathway is intact, then the pupils will still react to near stimuli (light–near dissociation).

Relative afferent pupil defect

When one afferent pathway is affected or if bilateral afferent pathways are affected asymmetrically, the relative afferent pupil defect (RAPD) in the afferent pupil pathway can be detected clinically with the "swinging flashlight" test.[5]

The RAPD is the clinical sign used to detect a defect in the afferent pupillary pathway (i.e. an afferent pupil defect [APD]). The RAPD and the APD should not be used interchangeably; the RAPD is the clinical sign of an APD. Patients with only one eye can still have an APD without an RAPD.

Testing for a RAPD

In dim lighting, the observer shines a bright light into each eye individually. The child should fixate at distance to relax the accommodative pupil response. The light is swung between the two eyes (i.e. "the swinging flashlight test") with one second on each eye. If the afferent pupil pathway of one eye has a defect, the direct response will be less than the consensual reaction driven by the fellow eye, and the pupil of the affected eye will dilate as the light swings from the unaffected to the affected eye (i.e. a relative afferent pupillary defect). The RAPD can be graded subjectively from I through IV, with IV being an amaurotic pupil. Magnification provided by a slit-lamp may help detect a minimal defect in an older, more cooperative child. In situations with a known unilateral efferent pupillary defect or opacity precluding evaluation of one pupil, testing for the RAPD can still be performed. In this setting, a second light is held below the normal pupil. As the light swings from the affected eye to the unaffected eye, the normal pupil constricts, and when the light swings to the affected eye, the normal pupil will dilate. The RAPD is usually attributed to Robert Marcus Gunn who described sequential pupillary assessment with a bright light; the swinging light test is much more sensitive in detecting mild-to-moderate afferent defects.

An RAPD is objective evidence for an asymmetric lesion of the afferent pathway anywhere from the retina to the intercalated neurons of the midbrain pretectal nuclei. Thus, rarely a patient may have an RAPD (tectal RAPD) from a pretectal lesion without any visual loss (i.e. normal visual acuity, normal visual field, and normal fundus exam) because the afferent pupil fibers to the pretectal nuclei exit the optic tract distinctly from the visual pathway to the lateral geniculate nucleus. Although uncommon, a small RAPD may occur in deeply amblyopic eyes.[6] In older children, a useful subjective addition to testing for the RAPD is asking the child in which eye the light is brighter. The child may be asked a question, "If the light in the good eye is worth 1 dollar/pound, how much is the other one worth?" which may give a rough subjective quantification of an RAPD.

Light–near dissociation

Light–near dissociation is present when the pupil reacts better to a near than to a light stimulus. Defects in either the afferent or efferent pupillary pathway can produce light–near dissociation. In patients with symmetrical bilateral afferent disease, an APD might be difficult or impossible to detect. In these situations, it is especially important to look for light–near dissociation as potential evidence of afferent disease helping to localize the lesion.

Efferent pupillomotor defects

Argyll Robertson pupils

In 1869, Douglas Argyll Robertson described a type of light–near dissociation classically seen with tertiary syphilis. The pupils are small, irregular, and constrict more fully and more briskly to a near stimulus than to light (the pupils go from "small to pinpoint"). The iris is often found to be slightly atrophic on slit-lamp examination. The lesion in the Argyll Robertson pupil is presumed to be located in the dorsal midbrain,[7] and patients with such pupils should undergo serologic testing for syphilis.

Sylvian aqueduct syndrome (Parinaud dorsal midbrain syndrome)

Expanding lesions dorsal to the Sylvian aqueduct in children include pinealomas, ependymomas, "trilateral" retinoblastoma, granulomas, hydrocephalus, cystic and other lesions. Compression of the dorsal midbrain produces light–near dissociation that may include a vertical gaze palsy (typically upgaze palsy), lid retraction (Collier sign), accommodation defects, and convergence–retraction nystagmus. The resting size of the pupils is usually larger than normal. Sometimes, probably in more rapidly enlarging tumors, the pupils may be large and poorly reactive to light or near stimuli.

Adie syndrome (tonic pupil syndrome)

Adie syndrome, unusual in young children, is typically idiopathic, but may occur with chickenpox or other viral infections,[8] ophthalmoplegic migraine, and measles vaccination.[9,10] It is more frequent in young women.[11] It is usually unilateral, but many cases become bilateral.[11] Children rarely have symptoms related to the onset, but they may fail a school near vision test or complain of blurred near or, if they are hyperopic, distant vision or photophobia. They may develop anisometropic amblyopia. Many patients are asymptomatic, and parents may be the first to notice.

The acutely affected pupil is usually larger than that of the uninvolved eye (Fig. 66.2), but over time the Adie pupil tends to become miotic ("little old Adie"). There is typically a segmental paralysis of the iris sphincter, which might be extensive or diffuse. Once constricted, the pupil remains constricted longer (the "tonic" pupil). There may also be a transient defect in accommodation, which is often marked at first, but gradually improves over 2 or more years.[11] Corneal sensation may be reduced when tested with an esthesiometer or with a wisp of cotton.

This finding is probably due to damage to the trigeminal fibers that also pass through the ciliary ganglion. Patients with Adie pupil may also have hyporeflexia or areflexia in their extremities, but other neurologic findings are typically absent. Although the Adie pupil is a clinical diagnosis, denervation hypersensitivity of the pupil may be demonstrated by observing pupillary constriction compared to the fellow eye 20 minutes after bilateral instillation of pilocarpine 0.0625%. However, pharmacological denervation hypersensitivity may occur with post- and pre-ciliary ganglionic lesions (Fig. 66.3), and should not be used in isolation to differentiate the etiology for anisocoria (e.g. Adie pupil vs. third nerve palsy).

Loewenfeld and Thompson proposed that the ciliary ganglion is the site of the lesion of the tonic pupil and that

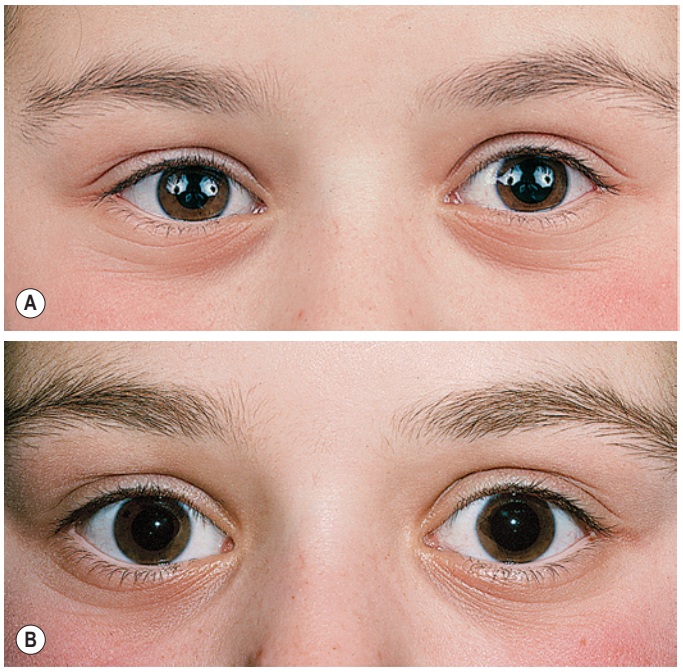


Fig. 66.2 Left Adie pupil. (A) In light; (B) in dark. The pupil size difference is less in the dark.

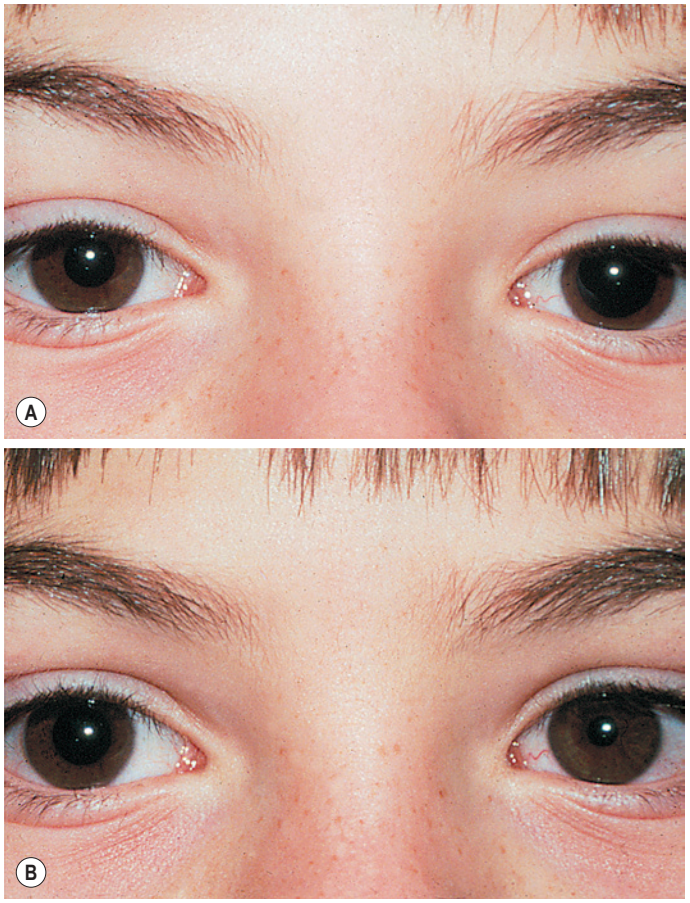


Fig. 66.3 Left Adie pupil (A) before and (B) after instillation of 0.1% pilocarpine. The right pupil is unchanged while the left constricts due to denervation hypersensitivity.

many of its features result from aberrant regeneration.[12] The cause is unknown, but it may be a neurotropic virus. Most patients do not require treatment, but pilocarpine (0.1% three times daily) or another dilute miotic may help with photophobia and occasionally with symptoms secondary to accommodation paresis. In distinction to adult patients, young children with Adie or other tonic pupils should have the unaffected or better eye occluded for a short period each day to avoid amblyopia. Spectacle correction of hyperopia in the affected eye may be necessary to prevent anisometropic amblyopia.

Other causes of tonic pupils

Although Adie syndrome is the classic idiopathic tonic pupil, other etiologies of ciliary ganglion damage cause a similar syndrome. Congenital or acquired tonic pupils have been described in infants with: orbital tumors; traumatic, infectious, or inflammatory diseases; or as part of a variety of widespread neuropathies including syphilis, diabetes, Guillain–Barré syndrome, Miller Fisher syndrome, pandysautonomia, hereditary sensory neuropathy, Charcot–Marie–Tooth disease, and trilene poisoning. Autonomic neuropathy secondary to paraneoplastic disease has also caused tonic pupils.

Iris abnormalities

Damage to the iris by trauma, irradiation, uveitis, ischemia or hemorrhage, or involvement with a tumor such as lymphoma, leukemia, juvenile xanthogranuloma, leiomyoma, or neurofibroma, may all give rise to anisocoria, corectopia, and/or impaired pupil reactions (Fig. 66.4). Slit-lamp examination of the iris can demonstrate the disruption of the iris architecture from the underlying cause.

Benign episodic unilateral mydriasis ("springing pupil")

The syndrome of idiopathic episodic mydriasis is likely a heterogeneous group of conditions that result in parasympathetic insufficiency of the iris sphincter or sympathetic hyperactivity of the iris dilator.[13] In either case, anisocoria usually lasts for several hours and then resolves spontaneously. Other signs of oculomotor or sympathetic nerve dysfunction are absent, but the syndrome is frequently accompanied by headache or orbital pain.[13] Although it affects primarily young women, it has been reported in both genders and many ages.

Midbrain corectopia

Damage to some midbrain pupillary fibers may lead to unequal upward and inward distortion of the pupil and an unequal sinuous pupil reaction to light and near stimuli. The patients described were often, but not always, comatose.

Third nerve palsy (see Chapter 83)

In complete third nerve palsy, the pupil is unreactive (Fig. 66.5), but in partial or recovering third nerve palsy, the ipsilateral pupil reaction may be sluggish or uneven. Patients with a poorly reactive pupil or anisocoria should have motility and lid evaluation to exclude third nerve palsy.

Abnormal pupillary contractions can occur in aberrant regeneration (Fig. 66.6) following third nerve palsy.[14] The

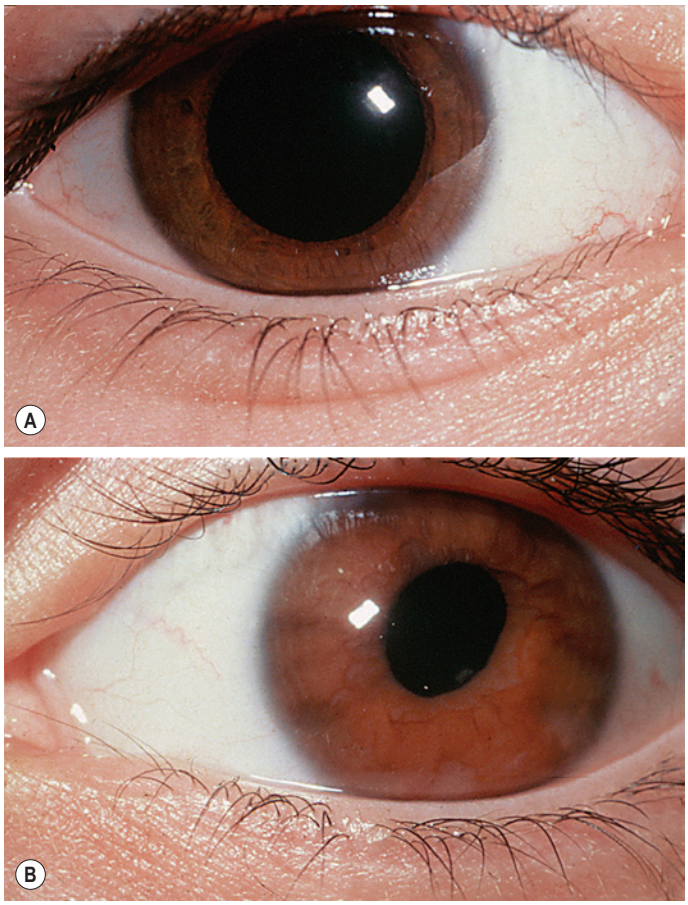


Fig. 66.4 Normal right eye (A) and left iris abnormality with sluggish reactions and small pupil due to leukemic infiltration (B).

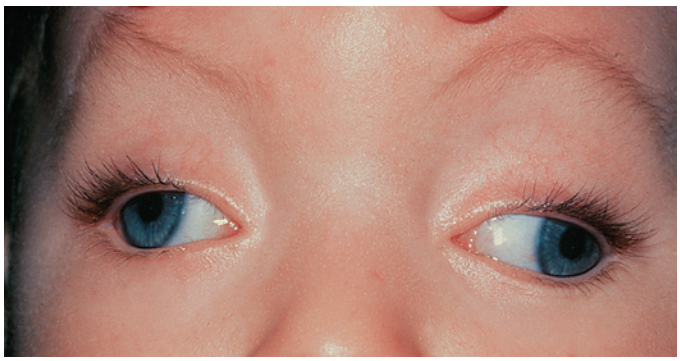


Fig. 66.5 Bilateral congenital third nerve palsy with fixed and unreactive pupils.

pupil may constrict with activation of extraocular muscles or may be smaller on the ipsilateral side (Fig. 66.7).

Riley–Day syndrome

In the Riley–Day syndrome (familial dysautonomia; see Chapters 34 and 54), there is a hypersensitivity to dilute parasympathomimetic agents (i.e. pilocarpine 0.1%).

Iris sphincter or dilator muscle spasms

Spasm of the iris dilator can give rise to "tadpole-shaped" pupils, which usually occurs in otherwise healthy young

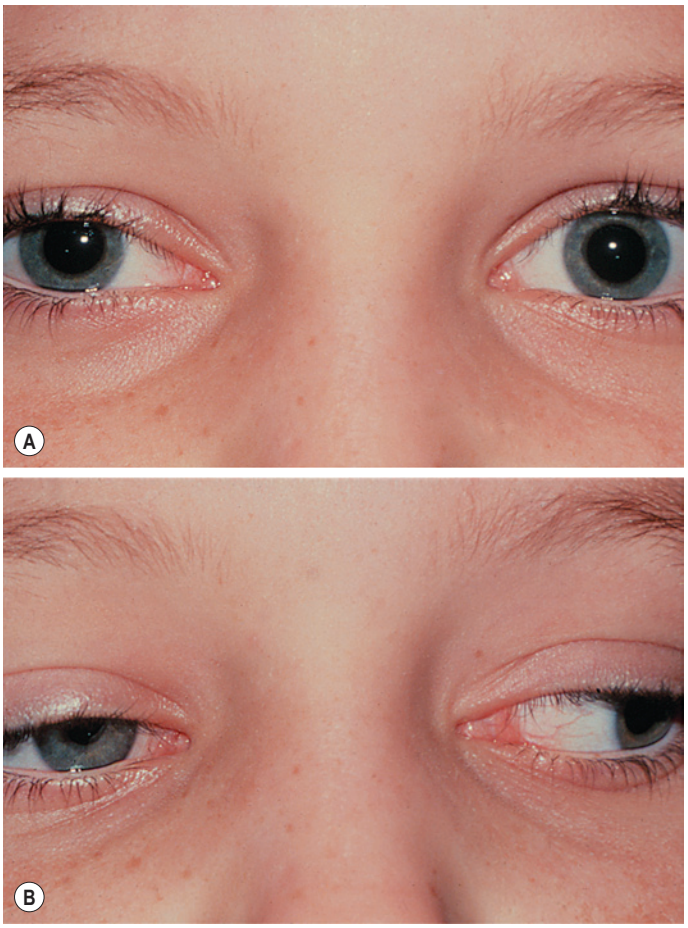


Fig. 66.6 Aberrant regeneration following partial recovery from right traumatic third nerve palsy. The right pupil constricts on attempted adduction.



Fig. 66.7 Left congenital third nerve palsy. In longstanding cases the pupil may be small.

adults.[15] The pupils are peaked in one direction for a few minutes, which may occur on several, separate occasions. This phenomenon may represent a subset of patients with springing pupil.

Paradoxical pupils

In some people with retinal disease, a curious phenomenon occurs in which the pupil size is larger in light than in dark, despite otherwise normal responses.[16] The parents occasionally may remark on it, but it is usually a sign that must be elicited.

When present, it is extremely helpful as it is associated with retinal diseases, typically congenital stationary night blindness (see Chapter 46), but also with cone dysfunction syndromes, such as achromatopsia.[17] It has also been described in Leber amaurosis, dominant optic atrophy (see Chapter 54), optic neuritis, and amblyopia (see Chapter 73).[18] The pupillary responses are brisker in patients with lower acuity and Ishihara scores.[17]

Paradoxical pupils can be recorded using photographs in a fully lit room and in a nearly fully darkened room. The child must be left in the dark for at least a minute; the pupils can be observed using a flashlight for a moment or with an infrared viewing device or videography. In a child with nystagmus, paradoxical pupils suggest obtaining an electroretinogram. The mechanism has not been explained adequately, but it is interesting that dark-rearing normal chicks to maturity causes them to have paradoxically constricted pupils in the dark.

Horner syndrome

Ocular sympathetic denervation (i.e. Horner syndrome [HS]) in childhood is not uncommon, may be congenital or acquired, and may be due to benign or malignant etiologies.

Clinical characteristics

Miosis

The pupils are unequal, with the difference greater in the dark due to the failure of the sympathetically innervated dilator pupillae muscle (Fig. 66.8). The difference depends on the completeness of the lesion, the child's alertness and the ambient lighting conditions. A drowsy child is more likely to have a low resting pupillary tone, and the inequality will be less obvious. There is also a lag in the ipsilateral dilatation, which results in a greater anisocoria at 5 seconds than at 15 seconds after darkening the room. It is best measured by photographs. Pupil reactions to light and near are unaffected.

Ptosis

A 1–2 mm ptosis of the upper lid (due to weakness of Müller's muscle) is typically present in HS, but it may be so slight and variable that it escapes notice or may be absent (Fig. 66.9). Some children present with miosis without ptosis.[19] Parents should watch for the delayed development of ptosis as the onset can be asynchronous. Ptosis can also be present without miosis.[19] The lower lid may also be affected ("reverse ptosis"), giving rise to a more obvious narrowing in the palpebral fissure and a false appearance of enophthalmos (i.e. "apparent enophthalmos").

Ipsilateral anhidrosis

Lesions proximal to the superior cervical ganglion, where the sweat and piloerector fibers branch to travel with the external carotid artery, will damage these fibers and cause ipsilateral facial and conjunctival flushing and nasal stuffiness in acute lesions. In longer-standing lesions, the defect of sweating results in a dry, warm side of the face while the unaffected side is cool and sweaty. In chronic lesions, the affected side may be pale due to denervation hypersensitivity to circulating catecholamines. Most children do not complain of anhidrosis, but parents may describe that one side of the face does not flush, particularly with crying.

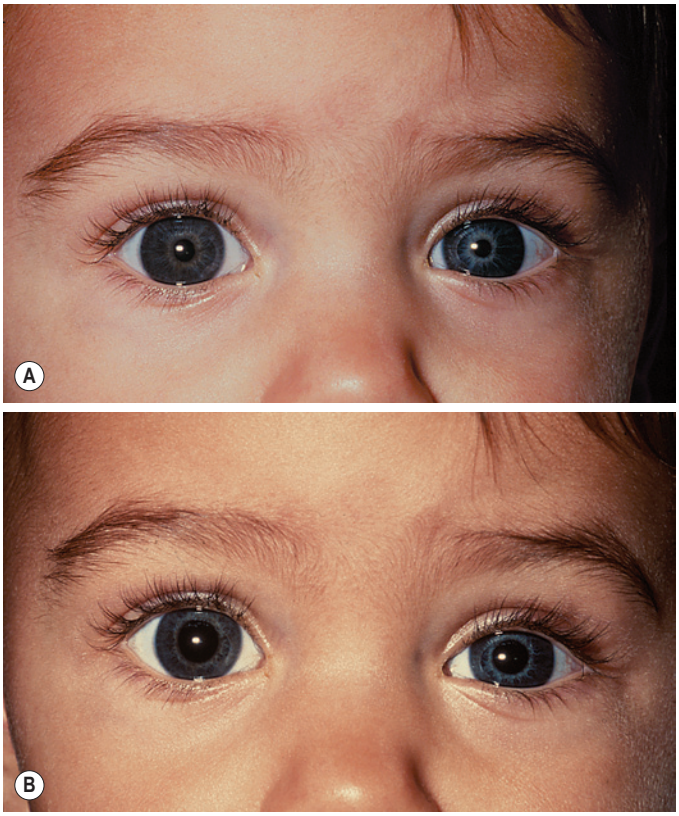


Fig. 66.8 Left Horner syndrome with mild upper and lower lid ptosis. (A) Photograph taken in the light. (B) Same patient 5 seconds after lights turned out showing dilation lag.

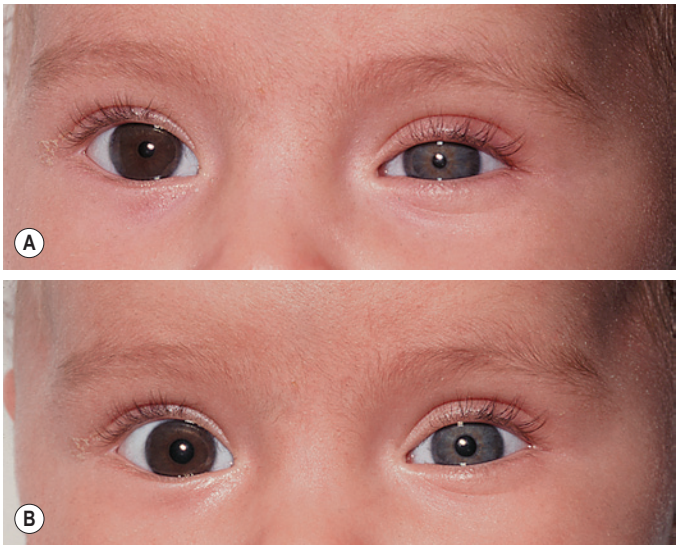


Fig. 66.9 Left congenital Horner syndrome showing upper and lower lid ptosis and an iris heterochromia with the lighter eye being the affected eye. (A) In bright light; (B) in the dark.

Heterochromia

In congenital HS, because iris pigmentation is partially dependent on sympathetic innervation, heterochromia may occur with the lighter iris on the affected side, especially with

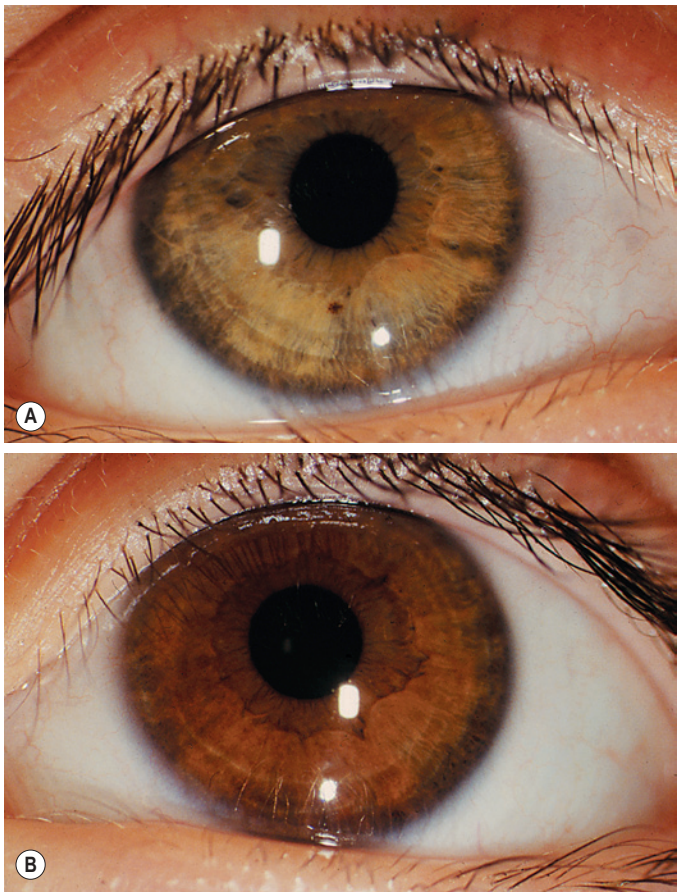


Fig. 66.10 Right congenital Horner syndrome in a teenager. (A) The right iris was noticed to develop a lighter color at the age of 2 years although the ptosis and pupil size were noticed at a few weeks of age. (B) The normal left eye.

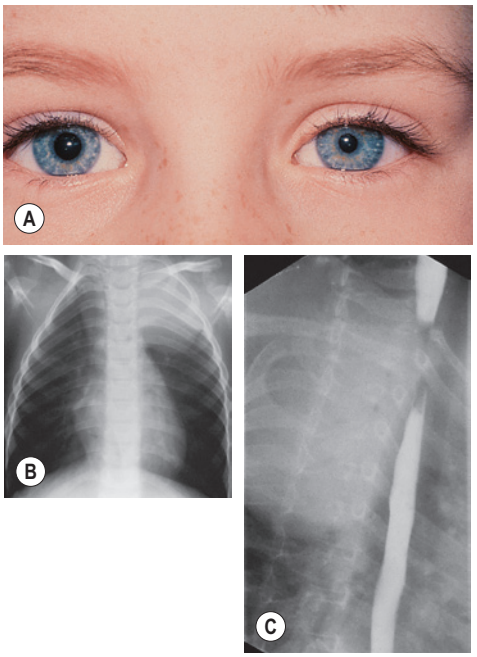


Fig. 66.11 Congenital Horner syndrome. (A) Left Horner syndrome. This child presented with the complaint of a sudden-onset ptosis and small pupil. (B) Chest X-ray showing left apical mass. (C) Barium swallow showing constriction of the esophagus. The cause was a large benign ganglioneuroma.

brown irides (Fig. 66.10). Although believed to be a sign of congenital HS, iris heterochromia occasionally has been described in acquired cases in children[20] and adults.[21] Thus, the presence of heterochromia alone should not be used clinically to define the potential etiology for the HS as benign, especially if the iris heterochromia is progressing rather than static. In addition, heterochromia is not invariably present in congenital HS, especially in already light-colored irides or if insufficient time has elapsed (Fig. 66.11). Histopathologically, in one case, the iris pigment epithelium was normal, there were no iris sympathetic fibers, and the stromal melanocytes were reduced in number, but contained normal melanosomes.[22] The anterior border cells were depleted.

Pharmacological responses

Topical cocaine 10% blocks reuptake of norepinephrine by sympathetic nerve endings, causing dilation of normally innervated pupils. The iris dilator tone depends on an intact oculosympathetic pathway. Lesions of any one of the three oculosympathetic pathway neurons results in decreased norepinephrine release by the postganglionic neuron, so the pupil in the HS fails to dilate as well as the fellow normal pupil, if at all. Topical cocaine can distinguish between normal or physiological anisocoria and anisocoria due to HS.

Hydroxyamphetamine 1% causes release of noradrenaline from presynaptic nerve terminal stores; it should be instilled into the conjunctival sac of both eyes at least 24 hours after the use of cocaine. Where the postganglionic neuron is intact, norepinephrine is present and the pupil dilates; but if the postganglionic neuron is damaged, it contains less norepinephrine and does not dilate as well. Hydroxyamphetamine takes effect in about 40 minutes. However, trans-synaptic degeneration in children limits the sensitivity and specificity of hydroxyamphetamine for localization purposes, and it is not available in many countries.

Low-dose adrenaline (epinephrine) 0.1% (1 : 1000) normally does not dilate the pupil, but in postganglionic HS, the pupil dilates secondary to denervation hypersensitivity. Adrenaline 0.1% has the advantage of being more readily available and is not a proscribed drug.

Apraclonidine 0.5% may be useful in establishing a diagnosis of HS; it causes reversal of anisocoria under both dark and light conditions. Topical apraclonidine is readily available and inexpensive. It is an alpha agonist that normally affects alpha-2 receptors more strongly than alpha-1 receptors. The differential effect on alpha-1 and alpha-2 receptors produces dilation in the smaller pupil and constriction in the normal, larger pupil. Apraclonidine's major site of pharmacologic action is postjunctional alpha-2 receptors in the ciliary body that produces lowered intraocular pressure. Upregulation of alpha receptors that occurs with sympathetic denervation in the HS unmasks the alpha-1 effect, and the smaller pupil dilates. In a recent series of HS in children, apraclonidine 0.5% demonstrated excellent sensitivity and specificity, with the best observation results under light conditions.[23] However, it should be used with caution, if at all, in infants because of possible central nervous system depression.

Pharmacologic testing is usually not necessary to confirm the HS, but because physiological anisocoria presents sometimes with lid abnormalities, and ptosis and miosis can present

asynchronously or in isolation, it may be helpful. Atypical presentations of HS in children can include miosis only, ptosis only, or even intermittent miosis and ptosis.[19] In these cases, pharmacologic testing may aid in the diagnosis.

In children, the main diagnostic difficulty is measuring the inequality and changes in light and dark; it may be aided by photographs. The use of topical testing to differentiate physiologic anisocoria from HS is reasonable for equivocal cases, but most authors believe that children with an unexplained HS should undergo imaging and other testing (e.g. catecholamine testing) of the ocular sympathetic pathway to exclude treatable and potentially life-threatening causes (e.g. neuroblastoma).

Other characteristics

There have been various reports of ipsilateral accommodative increase or decrease, but the difference does not seem to be reliably present or easy to measure in children. The ipsilateral central cornea may be thicker on the affected side.

Congenital Horner syndrome (see Fig. 66.10)

Weinstein et al. divided congenital HS into three causal types[24]:

- Those who suffered obstetric trauma, usually by forceps, to the internal carotid artery and its sympathetic nerve plexus and had a postganglionic HS on drug testing: they did not dilate with 1% hydroxyamphetamine. They had no facial anhidrosis.
- Those who suffered surgical or obstetric trauma to the preganglionic sympathetic pathway including patients with brachial plexus injury (Klumpke palsy). Cardiothoracic surgery is another common cause in children.
- Those without a history of birth trauma but with a Horner syndrome and evidence of a lesion at, or peripheral to, the superior cervical ganglion and anhidrosis. Congenital or early-onset HS with a preganglionic lesion and anhidrosis occurs in patients with neuroblastoma.[25,26]

Congenital HS may also be found with hemifacial atrophy, cervical vertebral anomalies, congenital tumors, arachnoid cysts and holoprosencephaly, and congenital varicella syndrome. Despite the above list of causes, most children with congenital HS have no other abnormalities.[27]

Postnatally acquired Horner syndrome

In contrast to congenital HS, any unexplained acquired HS in children is more significant and usually serious. It may occur in the following:

- "Central" preganglionic lesions due to brainstem trauma, tumors, or vascular malformations, infarcts and hemorrhages, and syringomyelia. Other neurologic dysfunction is usually evident in these cases.
- "Preganglionic" lesions, i.e. of the second neuron between the spinal cord and the superior cervical ganglion, due to neck trauma, neuroblastoma, and other tumors (see Fig. 66.11).
- "Postganglionic" lesions, i.e. of the final neuron after the superior cervical ganglion, due to cavernous sinus lesions (tumors, aneurysms, or inflammatory disease), neuroblastoma, and trauma.

Management

Congenital Horner syndrome

Since birth trauma and early cardiothoracic surgery are the most frequent causes of HS, further investigations are usually unnecessary.[26] However, the albeit rare occurrence of tumors in children with congenital Horner syndrome of no obvious cause may still warrant imaging of the oculosympathetic pathway and a 24-hour catecholamine assay. Several children with unexplained HS were found to have neuroblastoma on imaging, but normal urinary catecholamines[25]; this discrepancy may be due to lower sensitivity of spot urine catecholamine testing as opposed to 24-hour assays. Normal urine studies do not necessarily exclude neuroblastoma. The gravity of this diagnosis may demand both imaging and catecholamine assays as initial investigations. However, given the relatively low incidence of neuroblastoma in children with unexplained HS, performing catecholamine assays and a careful physical examination while reserving imaging studies for children with elevated catecholamines or suggestive examination findings or changes in clinical findings may be an equally suitable approach.[26]

Acquired Horner syndrome

Where there is no obvious cause, such as trauma or surgery, a child with acquired Horner syndrome should be investigated in conjunction with a neurologist, and investigations include imaging of the ocular sympathetic pathway and a 24-hour catecholamine assay (see Fig. 66.9).

Pupil changes from high sympathetic "tone"

Cases have been described in which an intermittent dilated pupil, with or without widening of the palpebral fissure, occurs associated with a cervicomedullary syrinx, post spinal cord injury, lung tumors, seizures, or migraine. In seizures and migraine, there may well be a simultaneous lowering of parasympathetic tone, but sympathetic-induced spasm is suggested by pallor and sweating.

Pupil changes from damage to the parasympathetic system (see Chapter 83)

Internal ophthalmoplegia (paralysis of the sphincter pupillae and accommodation) is occasionally seen without external ophthalmoplegia from nuclear lesions. It is bilateral and often associated with other oculomotor palsies.

Damage to the third nerve in the interpeduncular fossa, where the pupillomotor fibers are confined to the superomedial aspect of the nerve, may occur from aneurysm or tumor and is usually associated with external ophthalmoplegia, but meningitic lesions can cause an isolated internal ophthalmoplegia.

Pharmacological agents

Numerous pharmacological agents affect pupil size and reactivity. Systemic agents usually affect the pupils symmetrically

while topical agents are often instilled into only one eye, causing asymmetry.

Pupil-dilating agents

Parasympatholytic agents

Atropine 0.5–1%, homatropine 2%, cyclopentolate 0.5–1%, and tropicamide 1% are all commonly used agents to dilate the pupil and induce cycloplegia. Homatropine and atropine have prolonged action and are not often indicated diagnostically or therapeutically unless their long action is desirable, as in the case of penalization therapy for amblyopia. Hyoscine 0.5% has an action similar to that of atropine but is shorter acting. These agents may cause respiratory failure in children with congenital central hypoventilation. Inadvertent exposure to topical mydriatrics can produce pharmacologic dilation in children, and parents should be specifically questioned about these agents. In addition, contact with certain garden or wild plants (e.g. belladonna alkaloids, jimson weed) containing parasympatholytic agents can produce mydriasis.

Sympathomimetics

Adrenaline (epinephrine) 0.1–1% or phenylephrine 2.5–10% may be used to dilate the pupil in association with a parasympatholytic. They have no action on accommodation and are not sufficiently effective to produce good dilation. They must be used with great care, and at lowest dilution, if at all, in premature babies, those with cardiac or vascular disease, or those with hypertension.

Pupil-constricting agents

Cholinergic drugs

Pilocarpine 1–4% is commonly used to constrict the pupil. It is now used occasionally in the treatment of glaucoma and has little effect on infantile glaucoma. Some pet flea and tick treatments and collars contain cholinergic agents that produce miosis.

Anticholinesterases

Phospholine iodide (echothiophate) 0.03–0.125% and eserine 0.5% are infrequently used for the treatment of glaucoma. Phospholine iodide is used to cause peripheral accommodation and "unlink" the association between accommodative convergence and accommodation in some cases of high AC:A ratio strabismus. It rarely may cause cataracts and occasionally reversible iris cysts. It interacts with some muscle relaxants used in anesthesia.

Sympatholytic agents

Guanethidine 5% (Ismelin) can be used to counter lid retraction in hyperthyroidism. Thymoxamine 1% may also cause pupil constriction. These drugs are rarely, if ever, used currently in practice.

Systemic agents

Atropine, scopolamine, and benzatropine (benztropine) can cause pupil dilatation and paralysis of accommodation. The seeds of jimson weed, the berries of deadly nightshade, and henbane have all been known to cause a serious or fatal poisoning. The symptoms have been described as "hot as a hare, blind as a bat, dry as a bone, red as a beet, mad as a hatter." Mydriasis from topical atropine or atropine-like drugs is not counteracted by pilocarpine 1%, but in systemic poisoning it may be. Antihistamines and some antidepressants produce mydriasis. Heroin, morphine and other opiates, marijuana, and some other psychotropic drugs cause bilateral pupil constriction.

Abnormalities of the near reflex

Congenital absence

Children may be born with a defect in the near reflex. They have absent accommodation, poor convergence, and the pupil fails to constrict to a near stimulus but constricts to light.[28]

Familial cases of accommodation defect occur.[29] The cause is unknown, but it may be peripheral in origin.

Acquired defects

Sylvian aqueduct (Parinaud) syndrome

Premature presbyopia is one of the signs of tumors encroaching on the dorsal midbrain. Other more classic signs include convergence–retraction nystagmus, vertical gaze defects, eyelid retraction, convergence defect, and pupil light–near dissociation.

Systemic disease

Botulism, diphtheria, diabetes, and head and neck trauma may give rise to accommodation defects either isolated or associated with eye movement and vergence defects. Wilson disease has been shown to be associated with a defect in the near response in some cases.

Pharmacological agents

See above.

Eye disease

Defective accommodation can occur in children with severe iridocyclitis (see Chapter 40), dislocated lenses (see Chapter 36), large colobomas (see Chapter 33), buphthalmos (see Chapter 38), very high myopia, and direct eye trauma including retinal detachment surgery.

Other neurological causes

Adie tonic pupil syndrome and third nerve paralysis may cause defective accommodation. Other orbital diseases, presumably by affecting the short ciliary nerves, may cause cycloplegia and accommodation defect.

Accommodation in school children

A school-aged child normally has a high amplitude of accommodation irrespective of refractive error. It has been suggested that there is a causal relationship between a defective near response and some cases of dyslexia. It is important, however, to distinguish clearly between reading difficulties due to a defective near response, which can be improved by exercises, and dyslexia, which is a defect in the perceptual process involved with reading and writing that cannot be remedied by simple exercises.[30]

Spasm of the near reflex consists of episodes of:

- accommodation-induced pseudomyopia;
- convergence of the eyes (intermittent esotropia);
- miosis.

The symptoms are usually blurred and double vision and ocular pain or headache. These cases are rarely due to organic disease, although closed head trauma is recognized in a number of cases. Upper brainstem pathology is often suspected, but rarely found. In two cases with closed head trauma, magnetic resonance studies revealed no abnormalities in the midbrain, but both had lesions in the left temporal lobe.[31]

In most cases, no organic disease can be found, and it is assumed to be psychogenic. The episodes have a sudden onset and can last many hours and may be variable. There is blurred vision and photophobia. The eyes are crossed and may mimic a bilateral sixth nerve paresis. The essential finding is increasing pupillary constriction as the deviation increases. Pupils that become constricted on attempted lateral gaze are also a clue to the functional nature of the complaint. It is unusual in childhood. Occasionally, symptoms may be recurrent over several years.

The treatment is reassurance of the child and parents. Some patients are helped by miotics, but more often by a combination of cycloplegia and bifocal glasses. Unless there are any neurological signs, no investigations are required, and the prognosis is good.

Acknowledgment

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Leukemia

Richard J C Bowman and Jack Bartram

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer in childhood, accounting for more than 30% of cases, with 400–500 new children diagnosed annually in the UK. Acute myeloid leukemia (AML) accounts for 5% of children's cancers, with 60–70 new cases in children in the UK each year. Combination chemotherapy for acute leukemia in children is highly effective; thus, serious ocular involvement is much less common than it was, and routine ophthalmic surveillance is usually unnecessary. Five-year survival rates of over 85% are usual for ALL and up to 60% for AML. The majority of treatment failures are due to recurrent leukemia, and treatment-related deaths have become less common with improved supportive care.

Several clinical and biologic criteria adversely affect ALL prognosis and treatment regimens: age (infants under 1 year and children over 10 years suffer higher relapse rates), high presenting white blood cell count, slow response to initial therapy, and chromosomal changes within the leukemic cells. The following approach has closed the gap in treatment success rates originally identified between the subgroups of patients.

It is now clear that for children receiving optimal contemporary therapy, leukemia cytogenetics and response to treatment as measured by minimal residual disease are the strongest prognostic indicators. Almost all children are treated with 2–3 years of chemotherapy; bone marrow transplantation (BMT) is reserved for the approximately 10% of children with initial very poor prognosis, or following relapse. AML treatment is very intensive over 5 or 6 months, chemotherapy is increasingly effective, and BMT has become less common. Outcome of therapy correlates with chromosomal changes in the leukemic cells and response to initial treatment, which are used to divide children into subgroups in a manner similar to those for ALL.

Common sites of disease at presentation are bone marrow, blood, lymph nodes, liver, and spleen. The eye is the only site where the leukemic involvement of nerves and blood vessels can be directly observed and it may act as a "sanctuary" for leukemic cells against chemotherapy. Eye complications may occasionally be the major residual disability[1] but serious eye involvement is unusual.[2] Ophthalmic manifestations may be dramatic, requiring prompt diagnosis and treatment, and are more a feature of relapse than of initial presentation. The ocular manifestations of acute leukemia are divided into direct (infiltration of the anterior segment, the orbit, or the central nervous system [CNS]) and indirect (secondary to hematologic changes such as hyperviscosity, anemia, thrombocytopenia, and immunosuppression).[3] Ocular manifestations are more common in AML than ALL and the presence of specific orbital or ocular lesions is associated with a higher frequency of bone marrow relapses and CNS involvement.[4]

Orbital leukemia is a small, but significant, cause of proptosis in children.[5] It can be the presenting feature of leukemia[5]; however, it is more likely to be found in uncontrolled disease, in the first decade, and with AML. It is associated with higher mortality. Orbital presentation may occur without eye involvement and it may be the only manifestation, especially in AML. Myeloid leukemia may present as an isolated solid tumor mass (granulocytic sarcoma) at various sites, including the orbit (Fig. 67.1). A greenish tinge to the tissue mass led to the term chloroma: this appearance may be due to myeloperoxidase or altered blood products.

Orbital involvement in leukemia may be due to bone or soft tissue infiltration, tumor formation, or hemorrhage; the lacrimal gland or lacrimal drainage apparatus may be primarily involved, with a more benign diagnosis. Children with orbital involvement present with proptosis, chemosis, and, rarely, extraocular muscle involvement; these may occur early in the disease. Exposure keratitis may occur. It may be difficult to differentiate between primary leukemic infiltration and



Fig. 67.1 "Chloroma" due to myeloid leukemia.

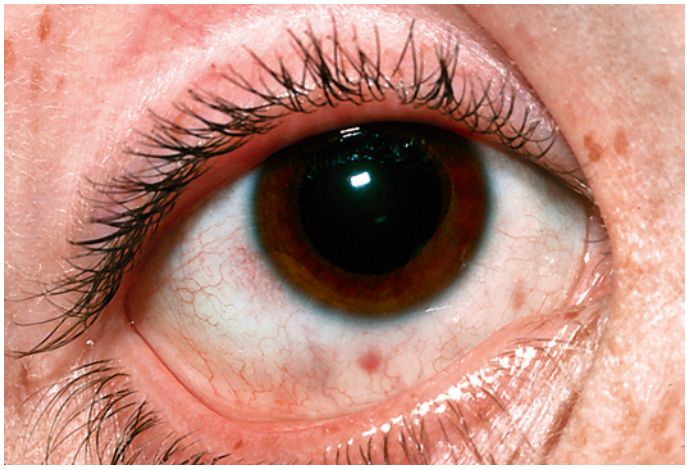


Fig. 67.2 Conjunctival hemorrhages and infiltration in acute lymphoblastic leukemia.

complications such as hemorrhage or opportunistic infection; a biopsy may be necessary.[6] The biopsy should be taken from the center of the abnormal area, not from the periphery where secondary inflammatory changes may occur. Review of the blood count and blood film by a pediatric hematologist, and a thorough clinical assessment prior to biopsy, together with a bone marrow examination at the time of biopsy, are important.

Lids

The lids are usually only involved as a part of orbital infiltration, but lid involvement can occasionally be due to direct leukemic infiltration.[7]

Conjunctiva

The conjunctiva may be involved by hemorrhage (Fig. 67.2), infiltration (Fig. 67.3), or hyperviscosity, when the vessels are tortuous or comma-shaped. Conjunctival mass formation, although rare, can be the presenting sign in acute leukemia.[3]

Cornea and sclera

Being avascular, the cornea is not often involved in the leukemias, but herpes simplex or zoster may occur in the immune-compromised child. Corneal ulcers may be the presenting sign of acute leukemia[8] and perilimbal infiltrates have been described in acute monocytic leukemia.[9]

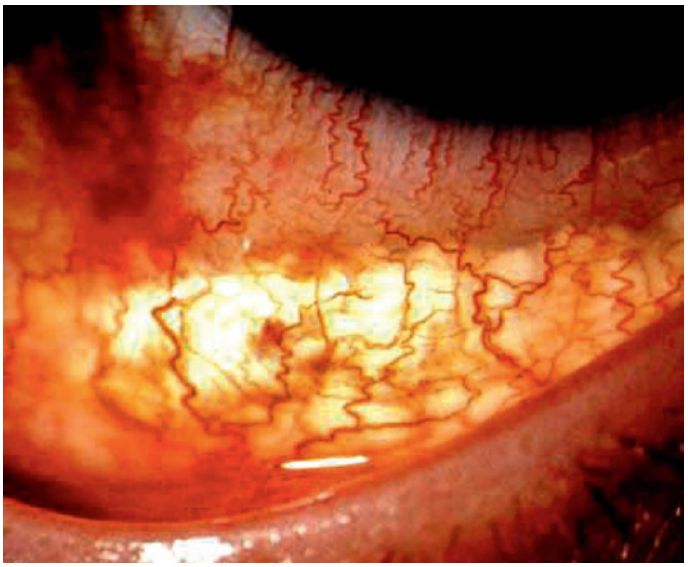


Fig. 67.3 Conjunctival infiltration with leukemic cells (acute lymphoblastic leukemia).

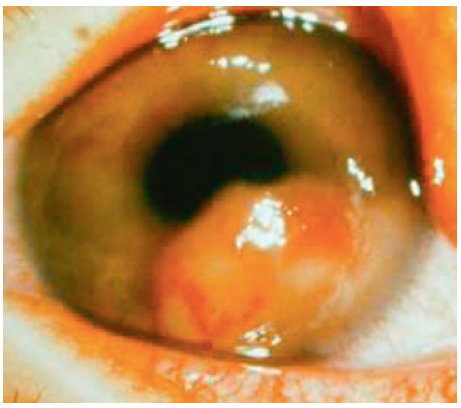


Fig. 67.4 Anterior chamber relapse (acute lymphoblastic leukemia).

Lens

Cataracts develop frequently in patients who have had total body irradiation. Their occurrence is related to the total dose and to the rate and fractionation of administration.[10] The use of steroids to treat graft-versus-host disease may cause or exacerbate cataracts.

Anterior chamber, iris, and intraocular pressure

Most reported cases have been of relapse in ALL (Fig. 67.4) but, rarely, children present with a leukemic hyphema or hypopyon. In ALL, anterior segment relapse accounts for up to 2% of all relapses; it is very rare in AML.[7,11]

The infiltration is most likely to be blood-borne rather than CNS related[10] and the relatively frequent occurrence of isolated anterior segment relapse supports the concept of the eye as a sanctuary site.[12] Because of the blood–eye barrier, chemotherapeutic agents do not penetrate the eye as well as at

many other tissues, allowing leukemic cells to survive, causing recurrence after chemotherapy has stopped. Symptoms include redness, watering, photophobia, pain, and visual loss. The parents may notice changes in the shape or reactions of the pupil or in the color and appearance of the iris (Fig. 67.5). Leukemia accounts for 5% of pediatric uveitis[3] and should always be considered as a possible cause of uveitis in a child with a previous history of leukemia.

Clinical findings are variable; iritis and hypopyon are the most common. Ciliary injection, keratic precipitates, anterior chamber cells, and flare are frequent. Posterior synechiae are unusual, but a grayish hypopyon streaked with blood is common. Secondary glaucoma is common and is associated with corneal edema, pain, and redness.

The iris may be thickened diffusely (Fig. 67.6) or by one or more nodules, or a mass of variable size; the thickening of the iris obliterates the iris crypts resulting in a rather featureless iris. The iris may also be thinned with loss of pigment (Fig. 67.7). The iris color may change, usually by a brownish discoloration. Rubeosis may occur. It is often the failure of standard treatment for uveitis that draws the ophthalmologist's attention to the underlying leukemia. If in diagnostic doubt, anterior chamber paracentesis and iridectomy are helpful diagnostic procedures[11]; a paracentesis alone may not be sufficient to give an accurate diagnosis. Pathologic studies show leukemic infiltration of the iris and trabecular meshwork,[7] and the hypopyon consists of leukemic cells, necrotic tissue, and proteinaceous exudate. Leukemic cells may be difficult to find. Patients with glaucoma have leukemic obstruction of the outflow channels and episcleral vessels.



Fig. 67.5 Anisocoria and mild heterochromia (acute lymphoblastic leukemia).

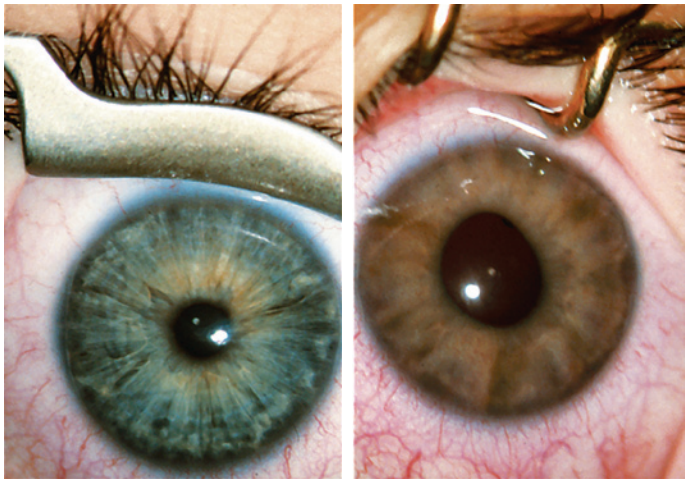


Fig. 67.6 Iris relapse with heterochromia, infiltrated left iris, and sluggish pupil reactions.

Because children with an apparently localized relapse generally have submicroscopic bone marrow disease, retreatment requires full systemic therapy plus local ocular radiotherapy (at least 2000 cGy) and topical steroid treatment. With this approach, long-term survival and likely cure has been achieved in a substantial proportion of patients.[13]

Choroid

The choroid may be the part of the eye most frequently involved in all types of leukemia,[7,14] but it is only rarely clinically apparent. The clinical manifestations are the result of serous retinal detachment or retinal detachment associated with a subretinal mass (Fig. 67.8). Fluorescein angiography demonstrates myriads of diffuse leakage points at the level of the retinal pigment epithelium.[15] Similar fluorescein patterns are seen in serous detachments with melanoma, metastatic tumor, Vogt–Koyanagi–Harada disease, and posterior scleritis. Leukemic choroidopathy can be detected by ultrasound.

Retina and vitreous

The retina, because of its ready visibility, is the part of the eye most frequently found to be involved clinically. Funduscopy is part of the routine follow-up examination of leukemic patients.

Hyperviscosity changes

Hyperviscosity of the blood occurs in many cases of leukemia with very high blood cell counts, especially in monocytic AML. Fluorescein angiography and trypsin digests[3] show capillary saccular and fusiform microaneurysms. Neovascularization, probably related to hyperviscosity,[16] has been seen in chronic myeloid leukemia (Fig. 67.9).

Retinal hemorrhages

Hemorrhages occur as a result of hyperviscosity, coagulation defects, infiltration, damage to retinal vessel walls, and vascular

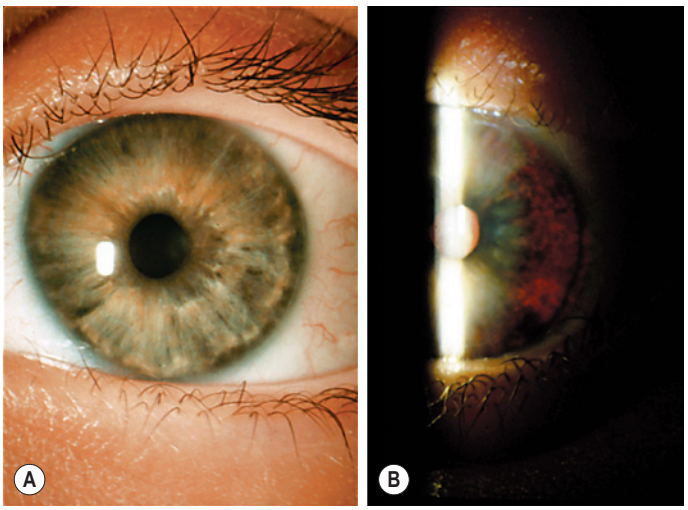


Fig. 67.7 Same patient as in Figure 67.6. After treatment with 2500 cGy there is iris transilluminance. The right eye had become affected.

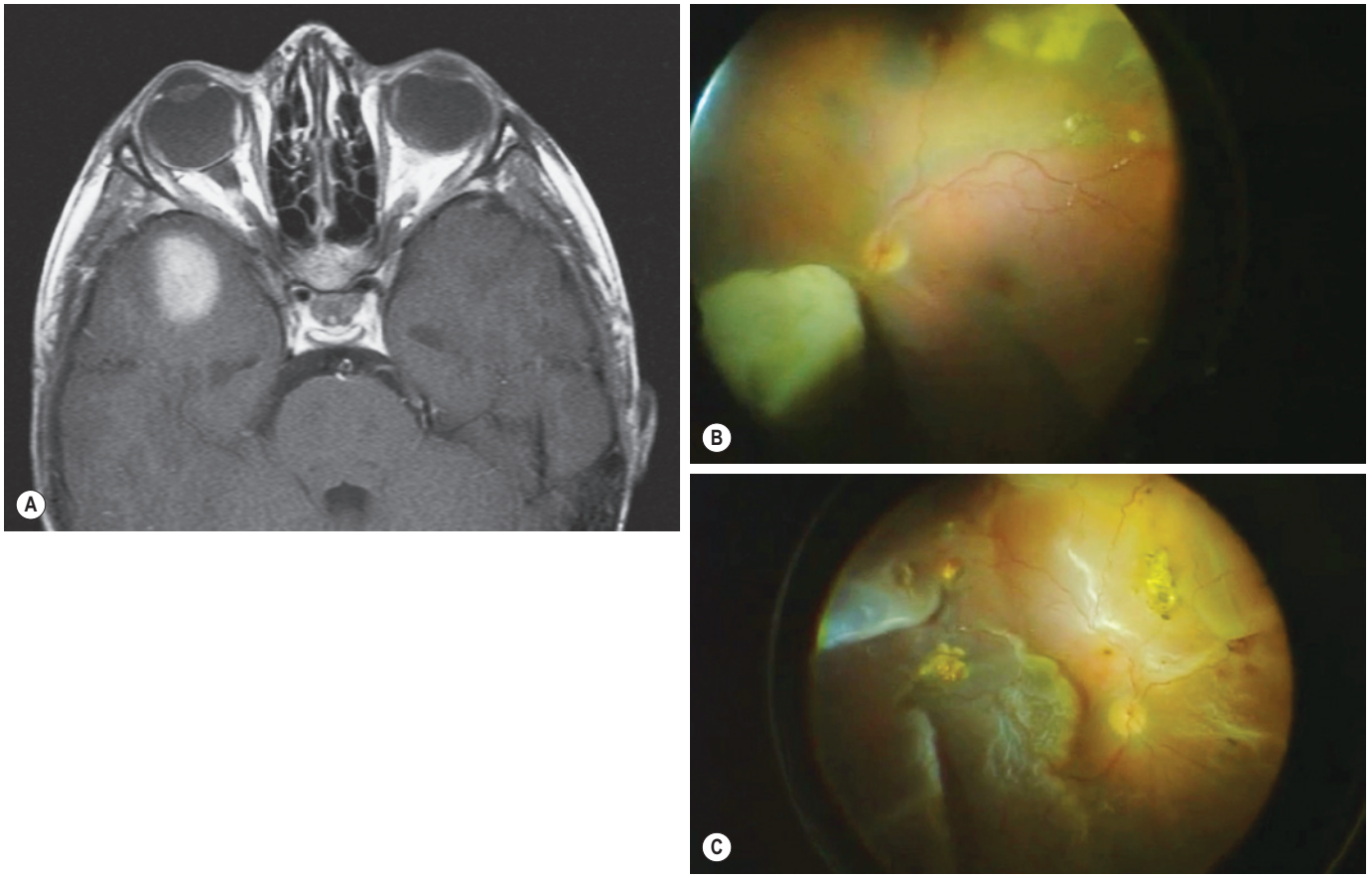


Fig. 67.8 (A) Axial T1-weighted image, after intravenous contrast agent administration, showing enhancing mass lesions on the retina of both globes and in the right temporal lobe. This patient with T-cell acute lymphoblastic leukemia (T-ALL) presented with primary central nervous system and eye involvement. (B) Same patient: intraoperative fundus image of the left eye that shows a large inferior endophytic lesion comprising old blood and inactive leukemia cells. A shallow macula-on retinal detachment is present with subretinal leukemic deposits seen superiorly. (C) Same patient: intraoperative image of right eye. The child had a previous vitrectomy for fundus obscuring vitreous hemorrhage. Subsequent contraction of treated intraretinal leukemic deposits led to macula-off rhegmatogenous retinal detachment. *([A] Mr R Henderson's patient, courtesy of Dr K. Chong.)*

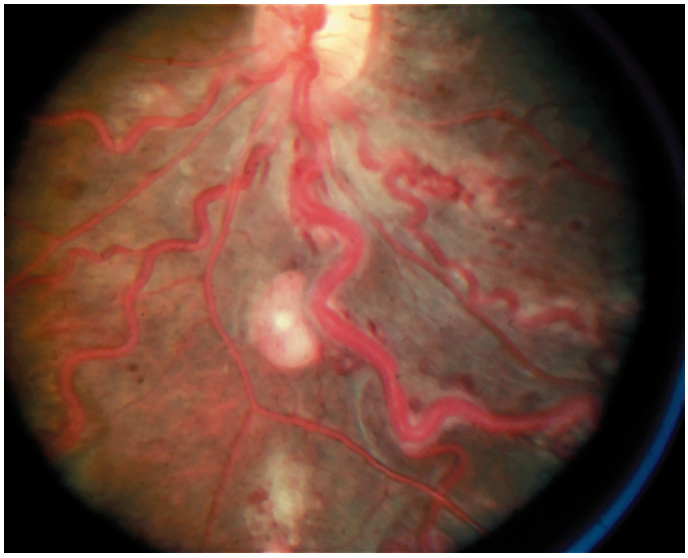


Fig. 67.9 Hyperviscosity changes in chronic myeloid leukemia in a 20-year-old. *(Dr S. Day's patient.)*

occlusion.[17] Sometimes massive, they occur throughout the retina and may involve the vitreous.

Nerve fiber layer hemorrhages are bright red and "flame-shaped." Deeper hemorrhages are less red and usually more rounded. Subhyaloid hemorrhages have sharply defined margins and can form a fluid level with a layer of white cells (Fig. 67.10).

Some hemorrhages are white centered; this should not be confused with the pinpoint white light reflex from the apex of a hemorrhage, or with hemorrhage around a leukemic deposit. The white area consists of platelet and fibrin deposits that occlude the vessel, or septic emboli. The hemorrhage occurs because of infarction and weakening of the vessel wall, which can also be damaged by leukemic deposits, giving the picture of mixed hemorrhage and infiltration (Fig. 67.11).

Retinal infiltrates and white patches

White areas in the retinas of leukemic children may be caused by the following:

1. Vessel sheathing.
2. Retinal infiltrates: these are leukemic deposits (Fig. 67.12), which, before the era of modern chemotherapy, were commonly seen, often with

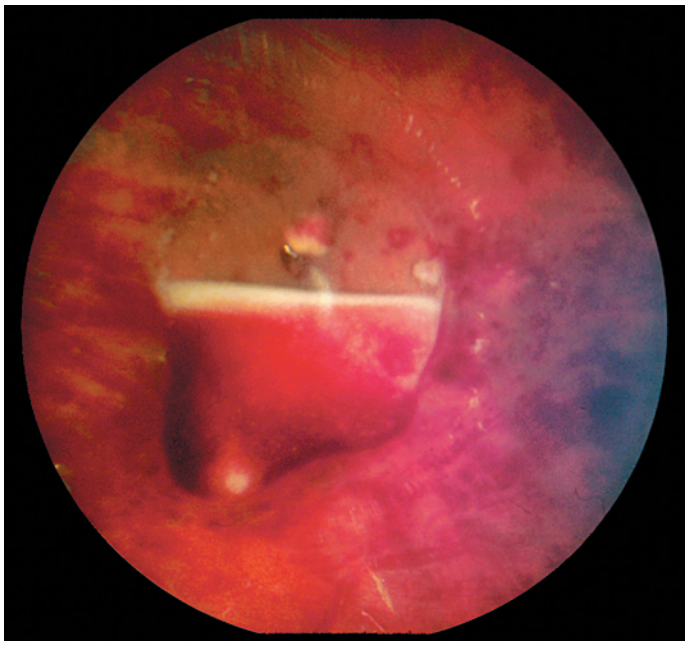


Fig. 67.10 Subhyaloid hemorrhage with a gross leukemic cell content.

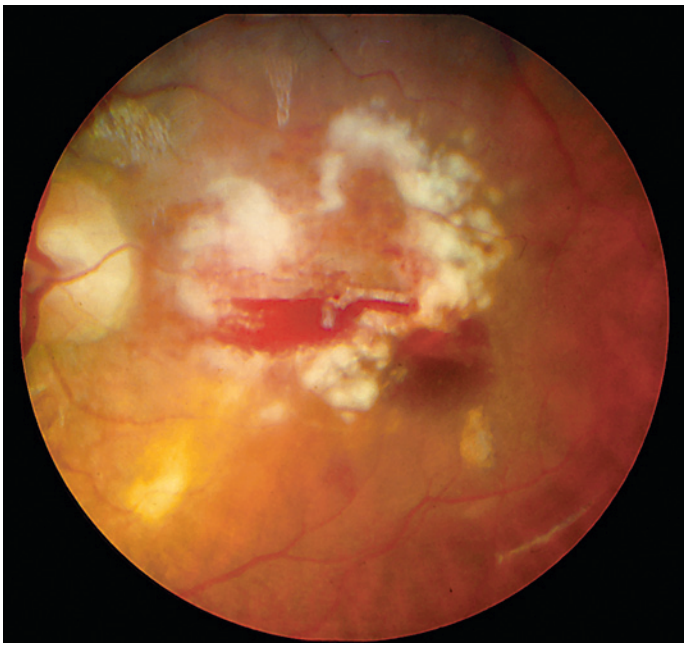


Fig. 67.12 Retinal infiltrates in acute lymphoblastic leukemia.

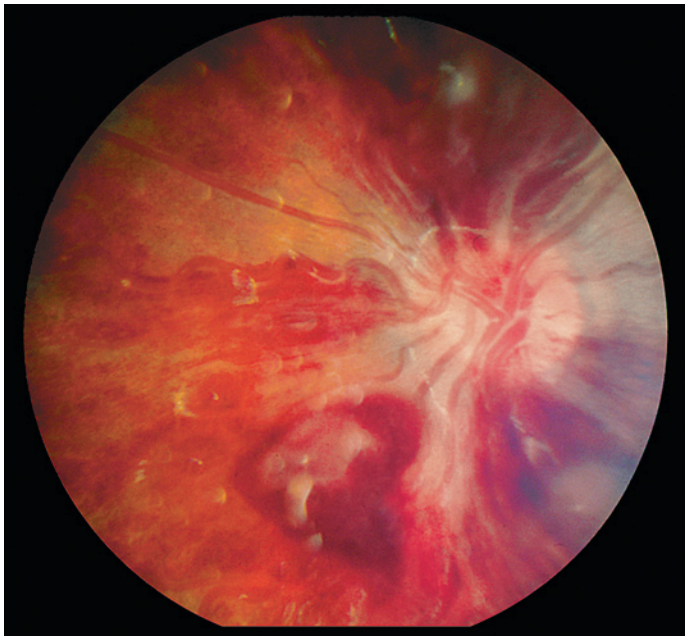


Fig. 67.11 Retinal hemorrhages and infiltrates in acute lymphoblastic leukemia.

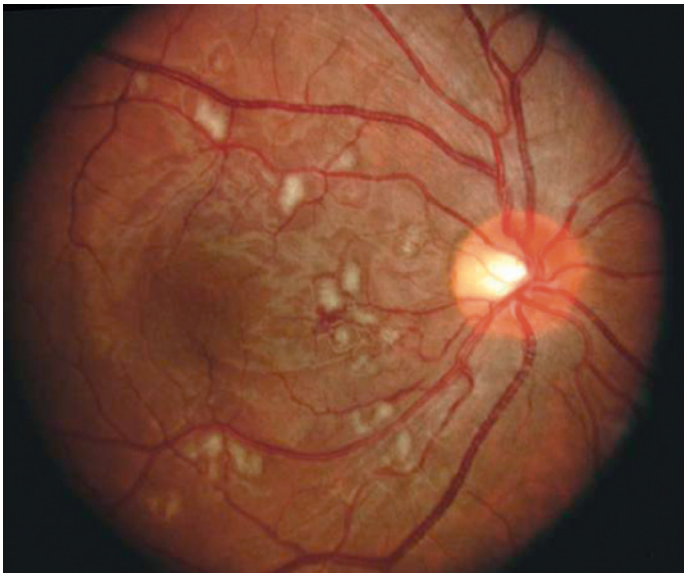


Fig. 67.13 Transient multiple cotton-wool spots after bone marrow transplant.

hemorrhage; they can usually be distinguished from infections by clinical and hematological examination.[18]

3. Cotton-wool spots: these are retinal nerve fiber layer infarcts (Fig. 67.13); they occur frequently in acute leukemia[4] and transiently after bone marrow transplantation. They result from retinal vascular occlusion in patients who have recently received bone marrow transplants, whether or not they have been treated with cyclosporin. They can recover spontaneously and are associated with retinal vascular endotheliopathy.[19]
4. Hard exudates: these small yellowish lesions are seen in relation to vessels that are chronically leaking non-cellular blood elements and are most frequently seen in chronic leukemias with hyperviscosity.
5. Opportunistic infections with cytomegalovirus or fungus in the immunosuppressed.
6. Retinal infarction in the acute stage: this gives rise to large areas of cloudy swelling of the retinal nerve fibers and ganglion cell layer.

Retinal infarction

Occlusion of larger retinal arterioles or of the ophthalmic artery (Fig. 67.14) occasionally occurs as a preterminal event.[1]

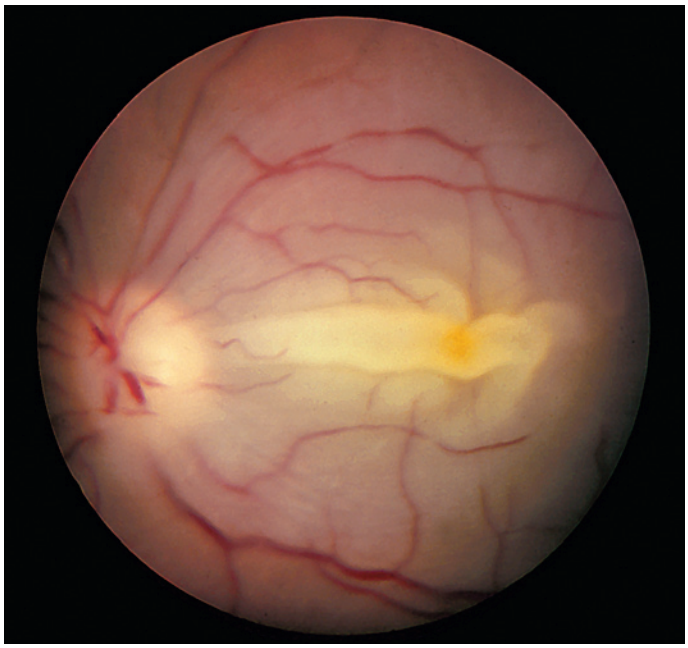


Fig. 67.14 Ophthalmic artery occlusion as a preterminal event.

Vitreous cells

Vitreous involvement with leukemic or blood cells is usually secondary to retinal or choroidal infiltration or hemorrhage.[7] Occasionally, vitreous aspiration may be needed for diagnosis, especially if the patient is apparently in remission and there is a possibility of an opportunistic infection. Vitreous organization is an unusual, but serious, sequela to widespread retinal or optic nerve infiltration.

Other retinal manifestations

Serous retinopathy[15] and retinal pigment clumping occur as manifestations of choroidal ischemia.

Optic nerve

Optic nerve involvement is noted in nearly one-fifth of acute or chronic leukemias postmortem,[4] although in clinical series it is more frequently seen in ALL.[20] Optic nerve involvement, which used to presage death, is now less frequently seen, presumably due to aggressive chemotherapy.[21]

Leukemic optic neuropathy may cause only minimal visual symptoms despite massive involvement, but, often, marked loss of central vision is observed, especially with infiltration behind the lamina cribrosa.[21] With prelaminar infiltration (Fig. 67.15) there is ophthalmoscopically visible fluffy white infiltration with hemorrhage. Occasionally, especially when bilateral, this can be difficult to differentiate from papilledema (which could be caused by idiopathic intracranial hypertension secondary to steroids or steroid withdrawal or CNS infiltration or infection); infectious disease must also be remembered. The response to irradiation at 2000 cGy may be dramatic[22]; whatever the treatment, optic atrophy is a frequent sequel. Optic neuropathy may also be caused by vincristine treatment[23] or by radiotherapy.

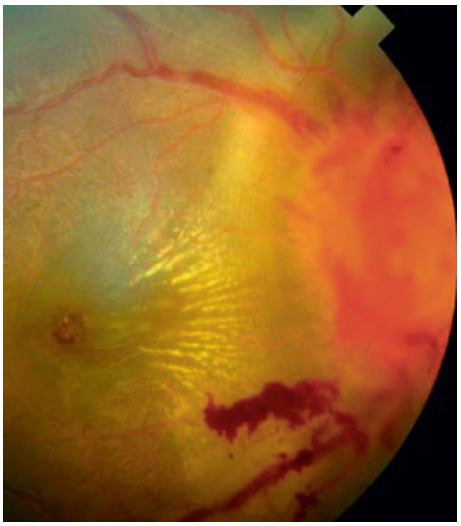


Fig. 67.15 Prelaminar optic nerve infiltration (acute myeloid leukemia) with additional retinal nerve involvement.

Other neuro-ophthalmic involvement

CNS involvement with leukemia manifests as meningeal irritation, with headaches and vomiting, or cranial nerve involvement. Vessel occlusion gives rise to defects ranging from transient deafness to a hypoxic–ischemic encephalopathy. It is usually a feature of leukemia with a very high white blood cell count and hyperviscosity. Communicating hydrocephalus, chiasmal infiltration, and sixth nerve palsies may occur.

In addition to the disease, many of the drugs and radiotherapy used may have CNS side effects, both short and long term, including fits. Rarely, children may develop a leukoencephalopathy due to methotrexate and cranial radiation.

With refinements in therapy, neurologic complications of leukemia and its treatment are now less common. Better supportive care has reduced the incidence of hemorrhage, and improved therapy has reduced leukoencephalopathy. Infection by measles, varicella, or mumps is less common since the introduction of vaccination programs and immunoglobulin prophylaxis in children with proven contacts. Bacterial infections of the CNS are rare.

Complications of treatment

Drugs

Vincristine and related drugs may cause corneal hypoesthesia, ptosis, third, sixth, and seventh nerve palsies, and optic neuropathy, which are reversible if the treatment is stopped early. The neuropathy is dose related and usually starts as a peripheral neuropathy with abnormal deep tendon reflexes. Seizures also occur.

L-Asparaginase may idiosyncratically be associated with a severe, sometimes fatal, encephalopathy. Cytarabine may cause blurred vision from keratoconjunctivitis (prophylaxis with topical steroids has been tried), corneal epithelial opacities, and microcysts. Methotrexate is a significant cause of neurologic problems including arachnoiditis from intrathecal administration, seizures, depression, and leukoencephalopathy with ataxia and

dementia. Steroids may cause posterior subcapsular cataracts; these are often of little visual significance[24] but have a good surgical prognosis, if cataract surgery is necessary. Posterior leukoencephalopathy syndrome has been described as a reversible side effect of immunosuppressants such as cyclosporin, usually presenting with seizures, headache, and cortical blindness.[3] Rapid withdrawal of steroid therapy may cause idiopathic intracranial hypertension (pseudotumor cerebri) (Fig. 67.16).

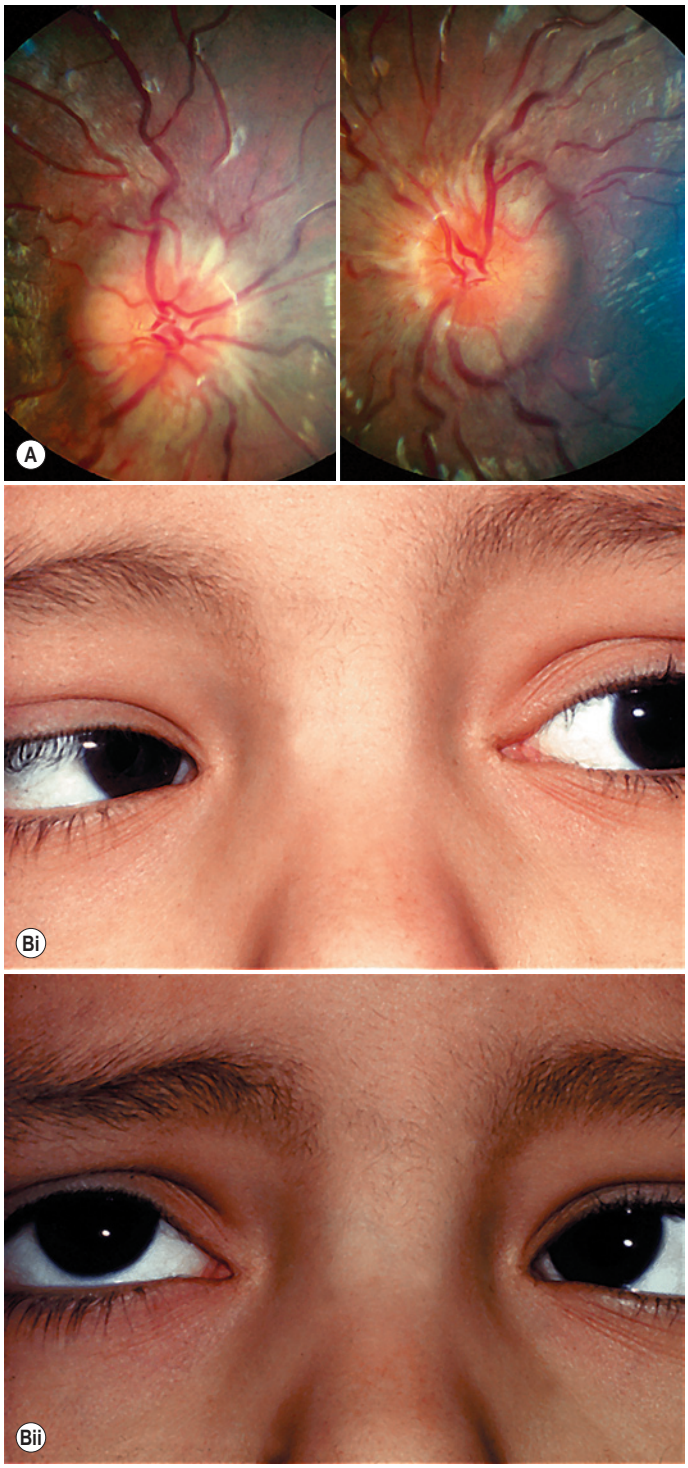


Fig. 67.16 (A) Papilledema and (B) right sixth nerve paresis from idiopathic intracranial hypertension in a patient on withdrawal of steroids in acute lymphoblastic leukemia.

Chemotherapy, steroids, and radiotherapy contribute to immune suppression, which allows infection by opportunistic bacteria, viruses, fungi, or protozoa, some of which do not usually cause significant infection in humans. These complications are related to the intensity of immune suppression and are most likely following bone marrow transplantation. As broad-spectrum antibiotics are now used aggressively for unexplained fever in neutropenic children, uncontrolled bacterial infections have become less frequent, but viruses and fungi have increased. Clinical manifestations may include keratitis, retinitis, endophthalmitis, orbital cellulitis (differentiate from Sweet syndrome/febrile neutrophilic dermatosis[3]), and neuro-ophthalmologic manifestations of CNS infection.

Herpes simplex and zoster affect the cornea (Fig. 67.17), conjunctiva, and lids. Herpes simplex and cytomegalovirus, which have an affinity for neural tissue, may cause a severe necrotizing retinochoroiditis (Fig. 67.18) that may be difficult to differentiate from leukemic infiltrates, a distinction that can be helped by chorioretinal biopsy but can usually be made by culture of urine or saliva.

Yeast and fungal infections are important complications of neutropenia; biopsy is necessary to establish the diagnosis and to plan appropriate treatment. Other infections include mucormycosis, toxoplasmosis, cytomegalovirus, and aspergillosis.

Stem cell transplantation

Bone marrow transplants are sometimes necessary in the treatment of childhood leukemia, but as chemotherapy has become increasingly effective, the number of transplants has fallen. Few children now receive BMT as a first-choice therapy, but it is often considered in relapsed disease.

In recent years, the early hemopoietic progenitor cells required for BMT have been obtained from blood or cord blood collections, and the term "stem cell transplant" (SCT) has supplanted BMT. There are two main types of SCT:

1. allogeneic, when related or unrelated donor stem cells matched by HLA typing are infused;
2. autologous, when the patient's own stored stem cells are used.



Fig. 67.17 Herpes zoster affecting trigeminal division of the fifth cranial nerve (acute lymphoblastic leukemia).

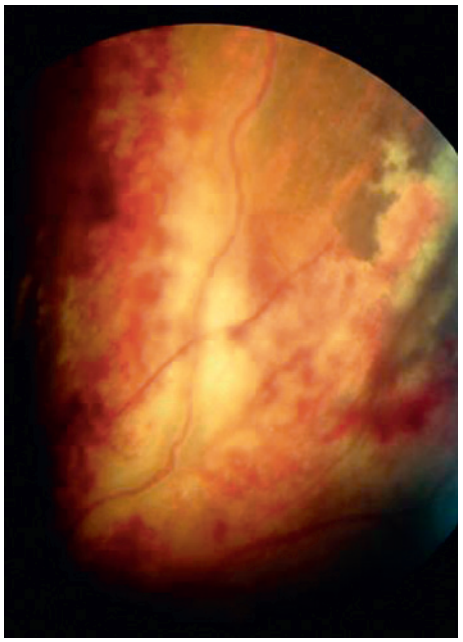


Fig. 67.18 Cytomegalovirus infection in a child with leukemia.

Prior to the SCT, children receive chemotherapy alone or combined with total body irradiation (TBI) as both antileukemia and immune suppressive therapy, to avoid graft rejection. As the marrow regenerates with new transplanted stem cells, all blood cell lineages are donor derived. Ocular changes were found in 50% of children treated with BMT for hematologic disorders.[25] The most frequent findings were dry eye (12%), cataracts (23%), and posterior segment complications (13%). These changes did not seriously compromise vision. Another study[26] identified ocular abnormalities in 82% of children, usually in the anterior segment, usually dry eye.

The incidence of eye complications depends on the treatment regimen, especially the use of TBI, the degree of immune suppression with risk of opportunistic infections, and the occurrence of graft-versus-host disease (GvHD). In one series,[27] cataracts were found in 95% of children given TBI, compared with 23% of children on chemotherapy alone. Low dose rates and fractionated rather than single-dose radiotherapy are associated with a lower incidence of cataracts.[28] It is possible these differences reflect alterations in the latent period before diagnosis, rather than a true reduction in eventual prevalence.

Because of failure to recognize the transplant recipient as "self," the transplanted T lymphocytes may attack the recipient and cause GvHD. Acute GvHD is characterized by the occurrence – within 4 months of the transplant – of any combination of fever, rash, diarrhea, and liver dysfunction. If the disorder occurs or persists after this period, it is termed chronic GvHD (cGvHD). Ocular manifestations are common in cGvHD and include dry eye, cicatricial lagophthalmos, sterile conjunctivitis, and uveitis. The eye problems are frequently severe and their management is demanding. At autopsy, the whole eye is affected including the lacrimal gland. About 10% of patients undergoing BMT develop conjunctival involvement with GvHD.[29] Pseudomembranous conjunctivitis is the most frequent manifestation of conjunctival GvHD and carries a poor prognosis for life. The mainstay of treatment has been topical steroids and lubrication. Topical tacrolimus has recently been reported as an alternative to steroids in children.[30]

Opportunistic infections are a major risk of BMT, especially in mismatched transplants where depletion of T lymphocytes from the marrow graft in order to minimize GvHD results in delayed immune reconstitution.

An interesting occurrence is the transient appearance of multiple white cotton-wool spots in BMT recipients.[31] Retinal complications including retinal or vitreous hemorrhage, cotton-wool spots, optic disc edema, retinitis, lymphoma, and serous retinal detachments occurred in 12.8% of 397 patients after BMT.[32]

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Phakomatoses (including the neurofibromatoses)

John R B Grigg and Robyn V Jamieson

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TUBEROUS SCLEROSIS
VON HIPPEL–LINDAU DISEASE
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Definition

The phakomatoses are a group of systemic disorders with neurologic, ophthalmic, and cutaneous manifestations resulting from disorders in cell regulation. No precise definition exists for including a condition in this group. A common feature is the development of multiorgan hamartomas. The most important of these conditions are neurofibromatosis, tuberous sclerosis, Sturge–Weber syndrome and von Hippel–Lindau syndrome. Others include Klippel–Trénaunay–Weber syndrome, Wyburn–Mason syndrome, ataxia telangiectasia, diffuse congenital hemangiomatosis, linear nevus sebaceous syndrome, Osler–Weber–Rendu syndrome and blue rubber bleb nevus syndrome. With improved understanding of the genetic, molecular, and cellular biology underlying the phakomatoses, clinical trials with biologic agents have been initiated.

Neurofibromatoses

The neurofibromatoses (NF) are a diverse group of genetic conditions that share a predisposition for tumor development with a predilection for the visual pathways. The two main types are neurofibromatosis type 1 (NF1) and neurofibromatosis type 2 (NF2).

Neurofibromatosis type 1

NF1 is a progressive disease with extremely variable manifestations. Individuals are prone to develop benign and malignant tumors of the central nervous system (CNS) and peripheral nervous system as well as other tumors.[1] Diagnostic criteria have been developed by The National Institutes of Health (NIH) (Table 68.1).[2,3]

Genetics and pathophysiology

NF1 occurs in approximately 1 in 3000 people. Inheritance is autosomal dominant with 100% penetrance, but highly variable expressivity. Up to 42% of cases are due to spontaneous mutations caused by a germline mutation in the *NF1* tumor-suppressor gene.[4] The NF1 protein (neurofibromin) downregulates the rat sarcoma viral oncogene homologue (RAS)–mitogen activated protein kinase (MEK) pathway. This reduces growth of astrocytes. Unopposed RAS activity leads to unopposed cell growth as well as activation of several important downstream signaling intermediates, including the mammalian target of rapamycin (mTOR) protein.[5] The genetic mechanism through which *NF1* mutations give rise to malignant tumors is consistent with the two hit hypothesis.

Clinical presentation

Ocular findings are an important component of the NF1 diagnostic criteria (see Table 68.1).[2] They include Lisch nodules, plexiform neurofibroma, sphenoid wing dysplasia, and optic nerve glioma.

Lisch nodules

Lisch nodules are dome-shaped, discrete lesions occurring anywhere on the surface of the iris or in the angle. They are orange-brown (Fig. 68.1), appearing darker on blue irides but paler on brown irides (Fig. 68.2). Their size varies from pinpoint to involvement of a segment of iris. Histologically, they are melanocytic hamartomas. They are present in one-third of 2½-year-olds, half of 5-year-olds, three-quarters of 15-year-olds and almost all adults over 30 who have the *NF1* mutation.[6] They occur earlier than neurofibromas in children. It is important for ophthalmologists to recognize them, and be able to distinguish them from iris nevi.

Anterior segment and uvea

Congenital glaucoma with buphthalmos is well recognized but rare in NF1. Congenital ectropion uveae, iris heterochromia, angle abnormalities, and posterior embryotoxon may predispose to later-onset glaucoma. Cataract is not a feature of NF1. Pigmentary hamartomas (choroidal nevi) may also involve the posterior uveal tract in up to 35%. Choroidal abnormalities appearing as bright, patchy nodules detected by near infrared imaging frequently occur (82%) in NF1 (Fig. 68.3).[7]

Table 68.1 National Institutes of Health diagnostic criteria for neurofibromatosis type 1 (NF1)

The diagnostic criteria are met if two or more of the following are found:

1. Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Freckling in the axillary or inguinal regions
4. Optic glioma
5. Two or more Lisch nodules (iris hamartomas)
6. A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex
7. A first-degree relative with NF1 by the above criteria

Cutaneous and extracutaneous signs to consider in addition to the "classical" diagnostic criteria when evaluating patients with NF1:

Genetic analysis	Cutaneous signs	Extracutaneous
Molecular analysis of the *NF1* gene	Anemic nevus	Choroidal hamartomas
	Juvenile xanthogranuloma	Large head circumference and hypertelorism
	Mixed vascular hamartomas and cherry angiomas	Unidentified bright objects on neuroimaging
	Hypochromic macules	A peculiar neuropsychological pattern (learning, speech, and behavioral disabilities)
	"Soft-touch" skin	Headache and seizures
	Hyperpigmentation	Neoplasms

Adapted from Szudek J, Evans D, Friedman J. Patterns of associations of clinical features in neurofibromatosis 1 (NF1). Hum Genet 2003; 112: 289–97; and Tadini G, Milani D, Menni F, et al. Is it time to change the neurofibromatosis 1 diagnostic criteria? Eur J Intern Med 2014; 25: 506–10.



Fig. 68.1 Multiple Lisch nodules in neurofibromatosis.

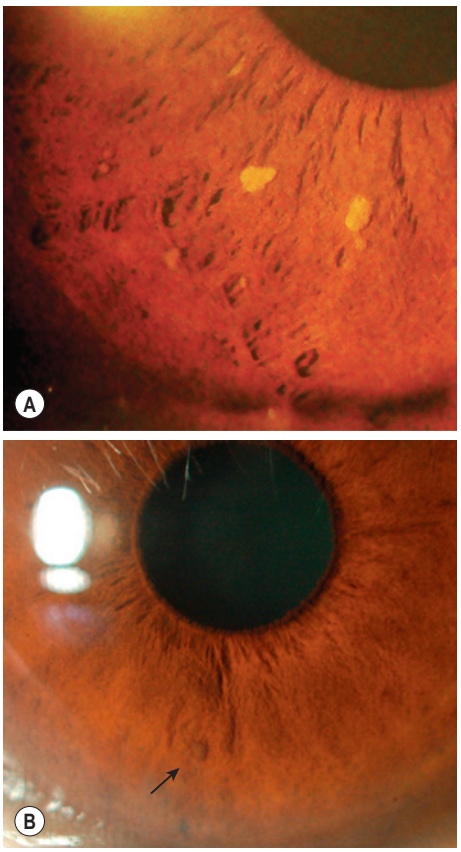


Fig. 68.2 (A) In brown irides Lisch nodules appear light brown. (B) Lisch nodules may be difficult to see in brown irides. *([A] Patient of Dr Shabana Chaudhry.)*

Skin, lids and orbits

Café-au-lait spots are hyperpigmented macular skin lesions. They are often present at birth, and usually appear before the age of 2 years[1]; they tend to enlarge at puberty and are particularly common on the trunk. They are absent from the scalp and eyebrows as well as the palms and soles (Fig. 68.4). Histologically, there is melanocytic hyperplasia with increased pigmentation in the basal layer of epidermis.

Neurofibromas are present in 30–50% of NF1 patients.[8] They are benign Schwann cell tumors.[1] Four types of neurofibroma are recognized (Table 68.2). The presence and growth pattern of neurofibromas is age related. In infancy and early childhood, diffuse plexiform neurofibromas are most active and give rise to cosmetic and visual problems within the orbit (Fig. 68.5). There is a lifelong risk of malignant transformation. In that event, the prognosis for 5-year survival is poor.[9]

Standard chemotherapy is not effective, so surgery has been the treatment option for plexiform neurofibromas. Since complete resection is difficult, surgery is often limited to debulking (Fig. 68.6). Regrowth is common after subtotal resection. Clinical trials with biologic agents including mTOR and MEK inhibitors are underway in these patients.[10,11]

Skeletal anomalies

Sphenoid bone defects occur in association with plexiform neurofibromas, such as hypoplasia of the greater and lesser wings, and widening of the superior orbital fissure (Fig. 68.7). Other osseous abnormalities include abnormal vertebrae, scoliosis, pseudoarthrosis of long bones, and subperiosteal changes.

Optic pathway tumors

Optic pathway gliomas (OPGs) occur in 15–20% of children with NF1; up to half become symptomatic.[12] They are a significant cause of visual morbidity.[13] Nystagmus or strabismus may be the presenting sign of optic nerve or pathway gliomas (Fig. 68.8). The optic disc may be pale or swollen depending on

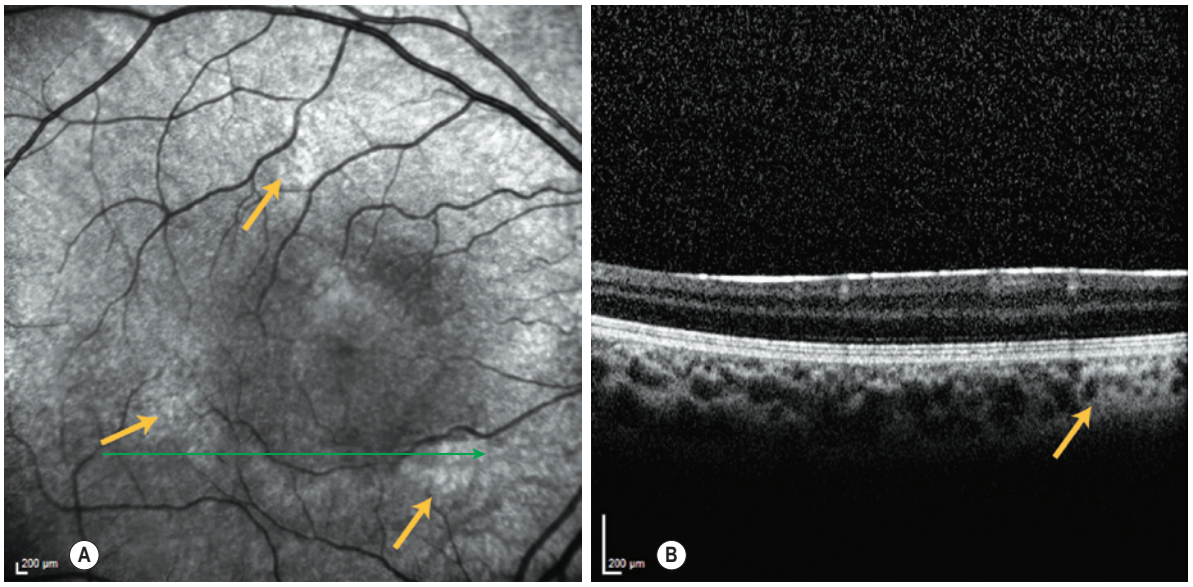


Fig. 68.3 Choroidal nodules detected by near-infrared reflectance (NIR) and ocular coherence tomography (OCT). (A) NIR of the right eye shows bright choroidal nodules. The OCT cross-sectional image obtained along the green line. (B) The corresponding OCT scan shows that these lesions are located within the choroidal tissue.



Fig. 68.4 Café-au-lait patches as well as multiple axillary freckles in a 14-year-old boy.

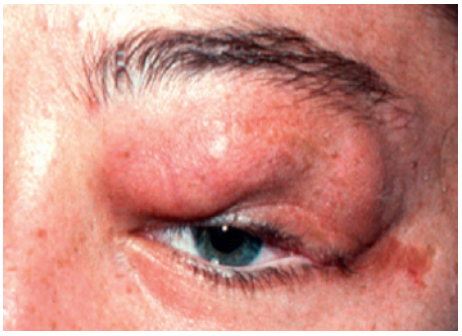


Fig. 68.5 Upper lid plexiform neurofibroma. *(Patient of the University of Sydney.)*

Table 68.2 Neurofibroma clinical features

Neurofibroma types	Location	Clinical signs
Discrete cutaneous	Epidermis and dermis	Moves with skin, blueish tinge
Subcutaneous	Deep to dermis	Skin moves over, firm and rounded feel, located along peripheral nerves
Nodular plexiform	Localized interdigitation with normal tissues	"Bag of worms" feel (see Figs 68.5 and 68.6)
Diffuse plexiform	Infiltrate widely and deeply	Smooth slightly irregular skin thickening

From Demestre M, Herzberg J, Holtkamp N, et al. Imatinib mesylate (Glivec) inhibits Schwann cell viability and reduces the size of human plexiform neurofibroma in a xenograft model. J Neurooncol 2010; 98: 11–9.

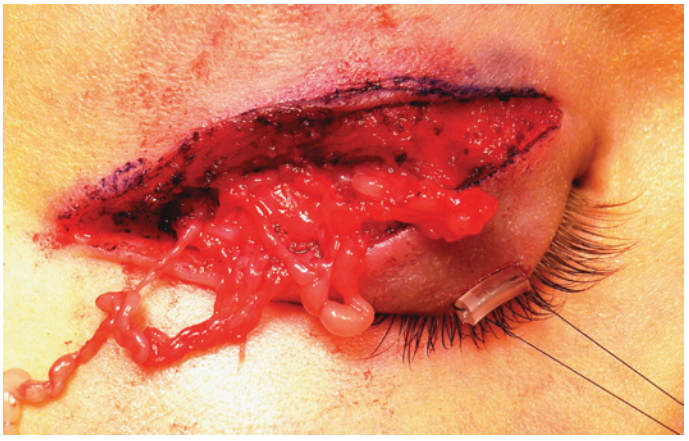


Fig. 68.6 At surgery, the worm-like consistency of an orbital plexiform neurofibroma is evident. *(Patient of Dr Brett O'Donnel, Royal North Shore Hospital, Sydney.)*

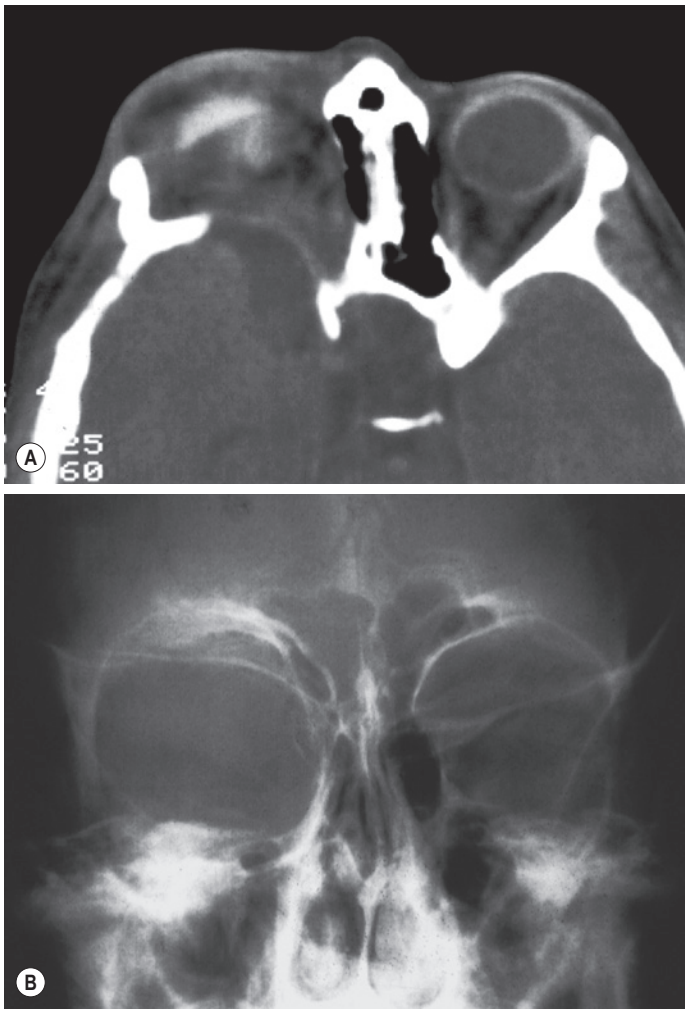


Fig. 68.7 Sphenoid bone dysplasia. (A) Axial computed tomography scan showing absence of greater wing of sphenoid. (B) Plain skull X-ray showing loss of right sphenoid.

disease stage. Optic nerve and chiasmal gliomas are discussed in detail in the section on neurogenic tumors (see Chapter 23).

Screening for optic pathway tumors: Visual acuity measurement is the most useful means of detecting changes in OPG that may require treatment[14] (Table 68.3).[15,16]

Central nervous system

The commonest consequence of NF1 in childhood and often the major concern for parents is cognitive impairment. The children are not usually mentally retarded but may have a wide range of learning disabilities manifesting as academic underachievement, and behavioral problems.

Other systems

Tumors of the spinal cord, sympathetic nerves, and adrenals (pheochromocytoma) may occur in patients with neurofibromatosis.

Neurofibromatosis type 2

NF2 affects 1 in 33,000 live births and is characterized by bilateral vestibular schwannomas (VS), multiple CNS tumors, cataracts, and retinal abnormalities.[17] The diagnostic criteria for NF2 are listed in Box 68.1. Two patterns of presentation exist: mild disease presents late (>25 years), with few tumors other than bilateral VS, and slow progression. Those with severe disease have onset before age 25, multiple CNS tumors (at least two of one type), and rapid progression causing severe handicap or death before reproductive age.

Genetics and pathophysiology

NF2 is an autosomal dominant condition with approximately 50% *de novo* mutations (no family history). *NF2* mutations can either be germline (70%) or somatic mosaic (30%) (mutation takes place after conception, resulting in two separate cell lineages).[18] NF2-associated tumors include schwannomas, meningiomas, and ependymomas.[19] There is correlation between nonsense and frameshift mutations and the severe early NF2 phenotype.

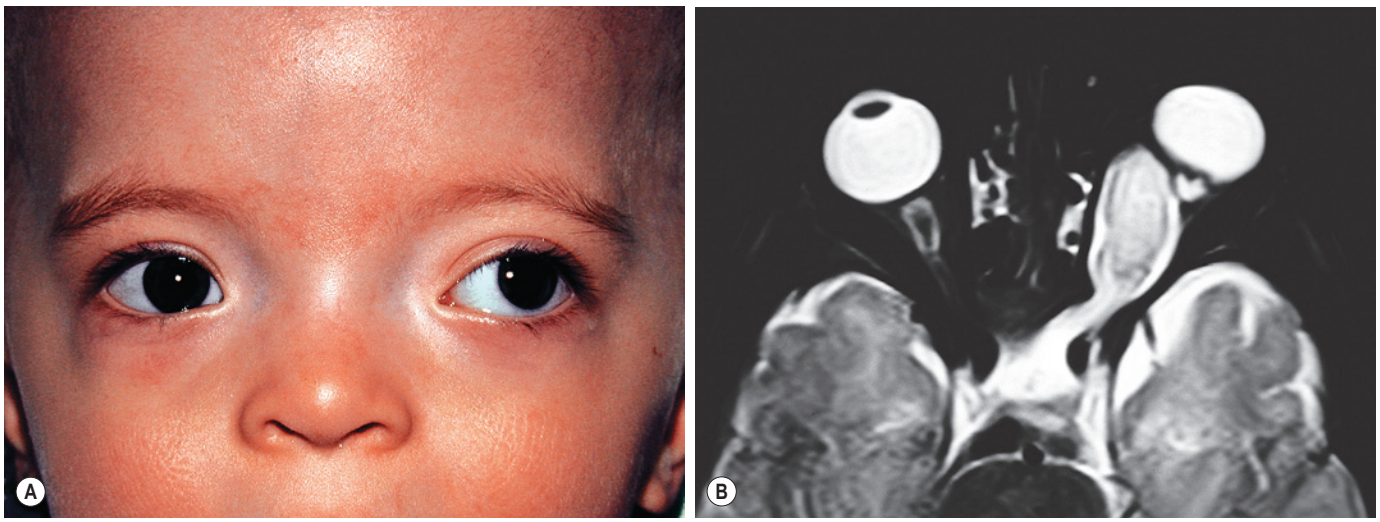


Fig. 68.8 Optic nerve glioma. (A) This 13-month-old girl presented with a history of intermittent exotropia since age 6 months, increasing numbers of café-au-lait spots and increasing proptosis on the left side. She appeared to be blind on the left. (B) A T2-weighted magnetic resonance imaging scan showed a fusiform tumor of the optic nerve extending up to and involving the chiasm.

Table 68.3 Screening for optic pathway tumors in neurofibromatosis type 1 (NF1)

Age and group	Review frequency	Ophthalmology	Neuroimaging
ASYMPTOMATIC CHILDREN WITH NF1 FOR OPG			
Baseline	–	Yes*	No
0–8 years	Annual	Yes*	No**
8–18 years	2 yearly	Yes*	No
Adult	No screening required	Routine eye care	No
EVALUATION OF CHILDREN WITH SUSPECTED OPG			
Ophthalmological abnormality identified: initial assessment	–	OCT if available	Yes***
Follow-up: first year****	3 monthly	Yes* + OCT if available	Yes***
Ongoing follow-up	≥3 monthly	Yes* + OCT if available	Yes***
CHILDREN BEING TREATED FOR NF1-OPG			
Follow-up on chemotherapy	≥3 monthly	Yes* + OCT if available	Yes***
Post-chemotherapy follow-up	3–6 monthly with increasing intervals when evidence of stability or regression	Yes* + OCT if available	Yes***

OCT, Ocular coherence tomography; OPG, optic pathway glioma.
*Ophthalmologic assessment should include age appropriate assessment of visual acuity, confrontation visual field evaluation, color vision testing, and assessment of pupils, eyelids, ocular motility, irises, and fundi.
**In those uncommon situations where reliable eye examinations cannot be obtained, there may be a role for neuroimaging.
***Magnetic resonance imaging of the brain with dedicated views of the orbits.
****Follow-up and management of children with NF1-asociated OPG is complex, they all should be cared for in centers that have significant experience in the treatment of NF1 and childhood cancer.
No universal agreement has been reached on what constitutes "progressive disease" (e.g. radiographic evidence of tumor growth, decreasing visual acuity, or a combination of the two): treatment of symptomatic NF1-associated OPG should be instituted only when there is clear evidence of progressive disease.
Pattern visual evoked potentials (PVEP) are performed in some centers at the same frequency as neuroimaging. PVEP provides additional objective evidence for visual pathway dysfunction when performed in laboratories experienced with visual electrophysiology in children.
Adapted from Listernick R, Ferner R, Liu G. Optic pathway gliomas in neurofibromatosis-1: controversies and recommendations. Ann Neurol 2007; 61: 189–98; and Cassiman C, Legius E, Spileers W, et al. Ophthalmological assessment of children with neurofibromatosis type 1. Eur J Pediatr 2013; 172: 1327–33.

Box 68.1

Revised diagnostic criteria (Manchester) for neurofibromatosis type 2 (NF2)*

NF2 may be diagnosed in any one of the following situations:

A. Bilateral vestibular schwannomas
B. First-degree family relative with NF2 and either unilateral vestibular schwannoma or any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities
C. Unilateral vestibular schwannoma and any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lens opacities
D. Multiple meningiomas (two or more) and unilateral vestibular schwannoma or any two of: schwannoma, glioma, neurofibroma, cataract

*In the Manchester criteria, "any two of" refers to two individual tumors (not different types) or cataract.
From Lloyd SK, Evans DG. Neurofibromatosis type 2 (NF2): diagnosis and management. Handb. 2013; 115: 957–67.

The *NF2* tumor-suppressor gene encodes merlin, which normally regulates downstream mitogenic signaling pathways. Drugs targeting these pathways (i.e. lapatinib and protein kinase inhibitors) are under evaluation.[20,21] The loss of functional merlin, also unmasks vascular endothelial growth factor (VEGF)-induced angiogenesis. Thus, bevacizumab may be effective in limiting tumor progression for these patients.[22]

Systemic findings

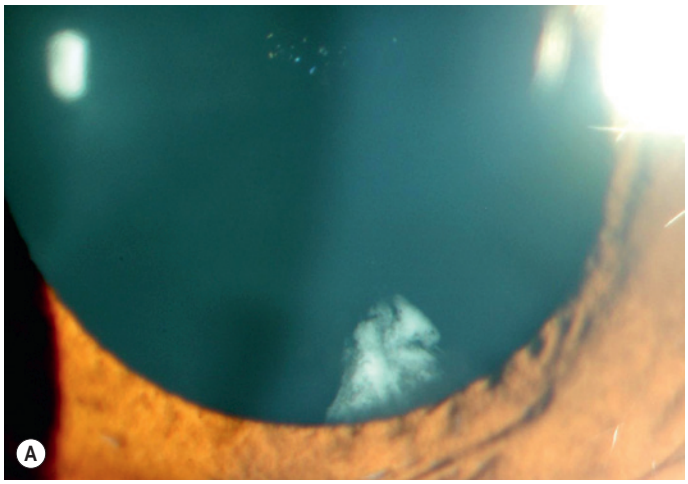
The hallmark of NF2 is bilateral vestibular schwannomas ("acoustic neuromas"), which may only be identified on gadolinium-enhanced magnetic resonance imaging (MRI) (see Fig. 68.10C). The origin of the trigeminal nerve is another frequent intracranial site for schwannomas. They may be found on several cranial nerves in affected patients.

Ocular findings

Most of the ophthalmic findings in NF2 (see Box 68.1) are congenital but may become apparent over time.[23] Visual loss is particularly significant for these children since progressive bilateral hearing loss is so common in this condition.

Anterior segment

The ocular changes of NF2 are early markers of the disease. Between 60% and 81% of patients have presenile central



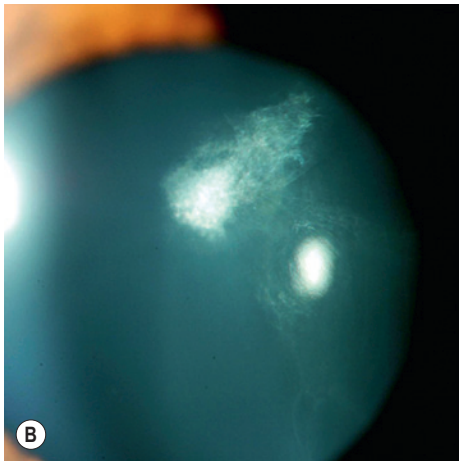
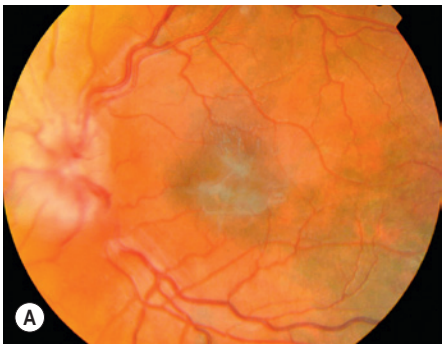


Fig. 68.9
(A) Cortical cataract in a 12-year-old. (B) Posterior subcapsular plaque in a 12-year-old.



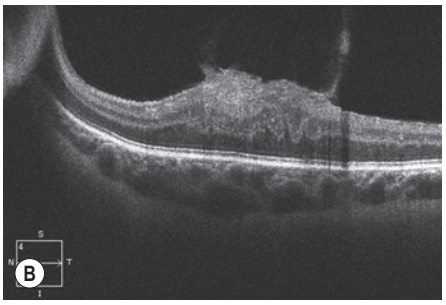




Fig. 68.10
(A) Epiretinal membrane in a 14-year-old neurofibromatosis 2 patient. Note also swollen disc secondary to optic sheath meningioma. (B) Ocular coherence tomography (OCT) scan of epiretinal membrane. Note loss of internal limiting membrane. (C) Bilateral vestibular schwannomas as well as bilateral optic sheath meningiomas in same patient as (A) and (B). *(MRI scan courtesy of Dr Mark Dexter, neurosurgeon, Sydney.)*

posterior subcapsular lens opacities. These mostly have little effect on vision so other causes for visual loss need to be evaluated first (Fig. 68.9). Corneal hypoesthesia from trigeminal nerve schwannoma, and decreased tear production, reduced blinking, and lagophthalmos from facial nerve palsy may adversely affect the outcome of cataract extraction in patients requiring surgery.

Posterior segment

Epiretinal membranes are seen in 1% of patients. They are translucent or whitish-gray membranes with prominent whitish edges demarcating their borders. They do not usually cause visual loss (Fig. 68.10). Combined retinal and pigment epithelial hamartomas (CRPEH) occur in 6–22% of patients. They are slightly raised masses most frequently identified in the posterior pole (Fig. 68.11). They commonly cause a reduction in visual acuity. Optic nerve sheath meningiomas (see Fig. 68.10C), which may be bilateral, are a significant cause of visual loss. These are described in the chapter on neurogenic tumors (Chapter 23).

Prognosis

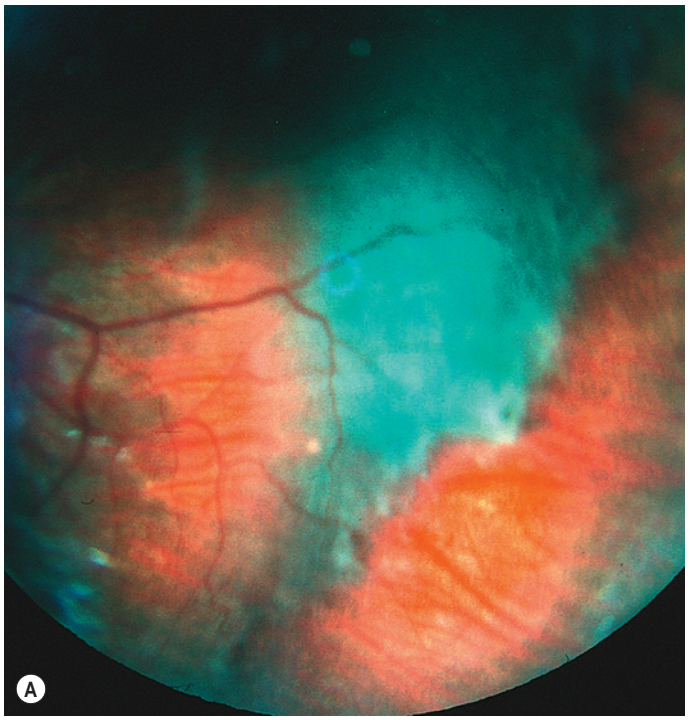
Optimum treatment is multidisciplinary because of the complexities associated with management of the multiple and progressive lesions.[24] Screening is essential (Box 68.2).

Box 68.2

Recommended intervals for screening for neurofibromatosis type 2 (NF2) in children of an affected parent

- Ophthalmological examination yearly from infancy
- Neurological examination yearly from infancy
- Audiology with auditory brainstem evoked potentials yearly from infancy
- Presymptomatic genetic testing: one test from 10 years of age*
- Cranial magnetic resonance imaging (MRI) at 10–12 years of age*
- Spinal MRI at 10–12 years of age* (every 2–3 years)

*Earlier than age 10 years in severely affected families and families in which early detection of disease would aid family preparation for future events related to NF2. From Asthagiri A, Parry D, Butman J, et al. Neurofibromatosis type 2. Lancet 2009; 373: 1974–86.



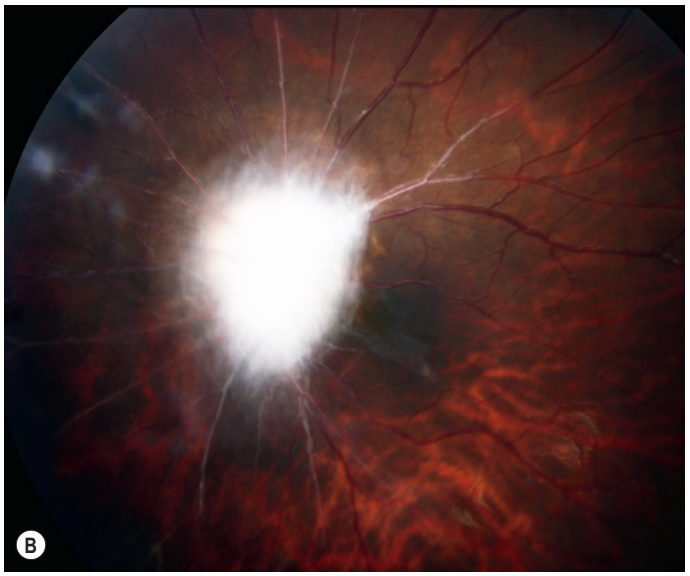


Fig. 68.11 (A) Combined retinal and pigment epithelial hamartoma of peripheral retina. (B) Combined hamartoma of the retina and retinal pigment epithelium optic disc involvement.

Table 68.4 Diagnostic criteria for tuberous sclerosis complex (TSC)

A. Genetic diagnostic criteria		
Identification of either a *TSC1* or *TSC2* pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of tuberous sclerosis complex		
B. Clinical diagnostic criteria		
Major features		**Age at onset**
1	Hypomelanotic macules (≥3, at least 5 mm diameter)	Infancy to childhood
2	Angiofibromas (≥3) or fibrous cephalic plaque	Infancy to adulthood
3	Ungual fibromas (≥2)	Adolescence to adulthood
4	Shagreen patch	Childhood
5	Multiple retinal hamartomas	Infancy
6	Cortical dysplasias*	Fetal life
7	Subependymal nodule	Childhood to adolescence
8	Subependymal giant cell astrocytoma	Childhood to adolescence
9	Cardiac rhabdomyoma	Infancy
10	Lymphangioleiomyomatosis (LAM)**	Adolescence to adulthood
11	Angiomyolipomas (≥2)**	Adolescence to adulthood
Minor features		
1	"Confetti" skin lesions (very small white macules)	
2	Dental enamel pits (>3)	
3	Intraoral fibromas (≥2)	
4	Retinal achromic patch	
5	Multiple renal cysts	
6	Non-renal hamartomas	

*Includes tubers and cerebral white matter radial migration lines.
**A combination of the two major clinical features (LAM and angiomyolipomas) without other features does not meet criteria for a definite diagnosis.
From Northrup H, Krueger DA, International Tuberous Sclerosis Complex Consensus Group. Tuberous sclerosis complex diagnostic criteria update: recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference. Pediatr Neurol 2013; 49: 243–54.

Tuberous sclerosis

Tuberous sclerosis complex (TSC) is a multisystem disease characterized by hamartomatous growths that most commonly affect the brain, skin, kidneys, eyes, and heart, but may affect almost any organ. Malignant tumors are rare and occur predominantly in the kidney. Incidence of TSC is estimated to be 1 in 6000.[25]

Diagnostic criteria

The clinical features are classified into major and minor features (Table 68.4).[26] The presence of two major features or one major plus two minor features constitutes a definitive diagnosis of TSC. One major plus one minor feature indicates a probable diagnosis of TSC, whereas either one major or two or more minor features suggests possible TSC. It is recommended that the diagnosis should be suspected in patients with epilepsy, developmental delay, or a learning disability in the absence of other known etiologies.[25] Ideal management is for patients to be followed in specialized TSC clinics to enable the comprehensive evaluation of the multisystem complications (Table 68.5).

Genetics and pathophysiology

TSC is an autosomal dominant condition with a high spontaneous mutation rate (66%). Mutations in two genes *TSC1* (hamartin) and *TSC2* (tuberin) cause the condition. TSC is a disorder of cell migration, proliferation, and differentiation. Hamartin and tuberin form a heterodimer that suppresses mTOR. Increased activation of mTOR kinase results in

Table 68.5 Surveillance screening in tuberous sclerosis complex (TSC)

			Child		Adult	
	"Asymptomatic" parent, child or first-degree relative at time of diagnosis of affected individual	Suspected case or initial diagnostic evaluation	Known case, no symptoms	Known case, symptoms or findings previously documented	Known case, no symptoms	Known case, symptoms or findings previously documented
Fundus examination	✘	✘	–	✘	✘	✘[d]
Brain MRI	✘[a]	✘	✘	✘	✘[c]	✘[e]
Brain EEG	–	–[d]	–	✘[e]	–	✘[e]
Cardiac ECG and ECHO	–[f]	✘	–	✘[g]	–	✘[e]
Renal MRI	✘[h]	✘	✘[i]	✘[g]	✘[b]	✘[g]
Dermatologic screen	✘	✘	–	✘[e]	–	✘[e]
Pulmonary CT	–	–	–	✘[e]	✘[j]	✘[e]

CT, Computed tomography; ECG, electrocardiography; ECHO, echocardiography; EEG, electroencephalography; MRI, magnetic resonance imaging.
[a]With negative physical examination MRI and/or CT is recommended.
[b]Every 1 to 3 years.
[c]Probably less frequently in children.
[d]Unless seizures are suspected, generally not useful for diagnosis.
[e]As clinically indicated.
[f]Unless needed for diagnosis.
[g]Every 6 months to 1 year until involution or size stabilizes.
[h]Recent studies recommend MRI as provides more detail than ultrasound and avoids radiation of CT.
[i]Every 3 years until adolescence.
[j]For women at age 18.
Modified from data from the Tuberous Sclerosis Alliance website (www.tsalliance.org).

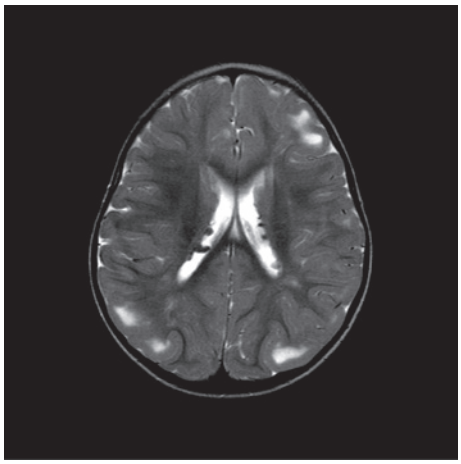


Fig. 68.12 T2 MRI, Tuberous sclerosis. Cortical tubers show as hyperintense signals and the calcified subependymal nodules as hypointense signals projecting into lateral ventricles (T2 axial magnetic resonance imaging scan).

disorganized cellular overgrowth, abnormal differentiation, and the formation of tumors.

Neurological features

CNS lesions include tubers in the cerebral cortex, and subependymal nodules (SENs) and subependymal giant cell astrocytomas (SEGAs) in the ventricular system (Fig. 68.12). Tubers are focal malformations of embryonal cortical development.[27] They are static lesions directly related to epilepsy, mental retardation, and autism.[28] Seizures are frequent with onset before 2 years of age. Infantile spasms are the predominant form (68%). Vigabatrin (γ-aminobutyric acid [GABA] agonist) is very effective with complete cessation in up to 95% of cases.

Moderate to severe learning disabilities occur in 38–80% of cases; their severity increases with increasing numbers of cortical tubers. However, a child with TSC whose development is normal up to 5 years of age is likely to continue along a normal trajectory.[29] Multiple behavioral problems including sleep disorders, hyperactivity, attention deficit, aggressiveness, and autism may also occur even with a normal IQ.

Clinical trials suggest that mTOR inhibitors (everolimus – a rapamycin analog) might improve both neoplastic features, such as slowing the growth of subependymal giant cell astrocytomas[30], as well as non-neoplastic features including epilepsy and cognitive function.[31]

Dermatological manifestations

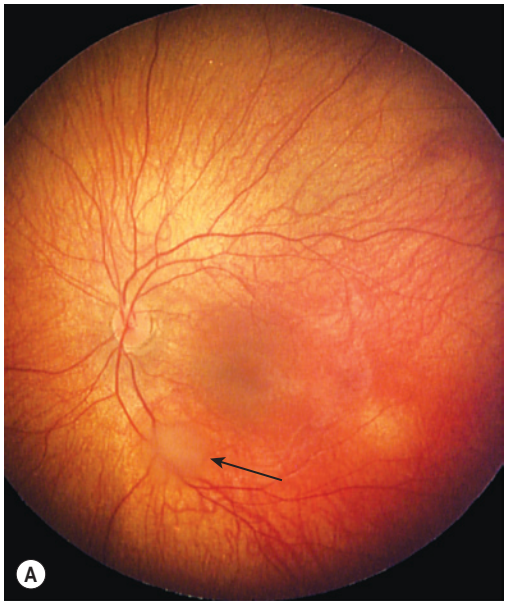
Facial angiofibromas (formerly known as adenoma sebaceum) are found in 75% of patients. Their onset is from 5–14 years of age and they are distributed on the face in a butterfly pattern (Fig. 68.13A). Topical rapamycin (0.1–1%) is a safe and effective treatment for facial angiofibroma.[32] Hypomelanotic macules (ash leaf spots) are present in 97% of children. They are present from birth in two-thirds of cases and 90% of cases by the age of 2 years. A Wood's ultraviolet light aids in their detection (Fig. 68.13B). Shagreen patches occur in 50% of cases. The lesions are flattened, yellowish-red or pink, with an orange-skin texture, located on dorsal surfaces, particularly the lumbar region (Fig. 68.13C). Forehead fibrous plaques occur in 25% of cases; these are slightly elevated yellowish-brown or flesh colored plaques. Periungual fibromas occur in up to 50% of cases.

Visceral features

Cardiac rhabdomyomas may be present from the neonatal period and occur in up to 45% of patients with TSC.[33] They are hemodynamically stable and regress in childhood. Renal



Fig. 68.13 Skin manifestations of tuberous sclerosis. (A) Facial angiofibromas (formerly adenoma sebaceum) are typically distributed in a butterfly pattern. (B) Hypomelanotic macules (ash leaf spots). (C) Shagreen patch on the lower back.





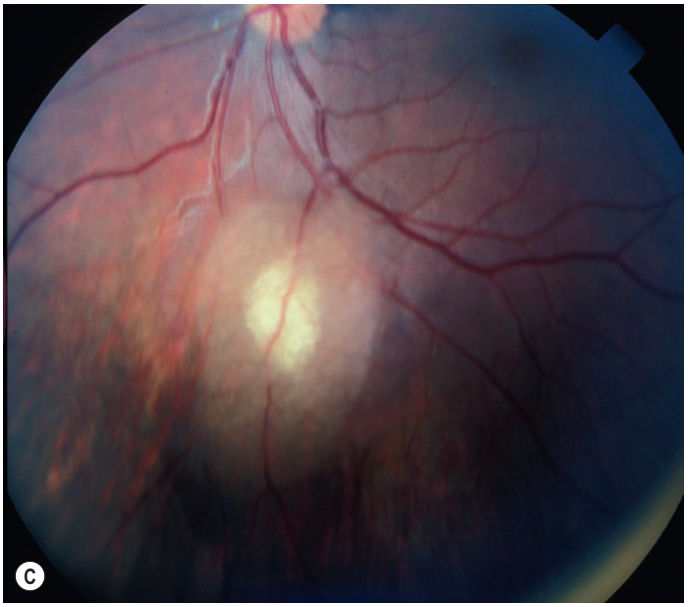


Fig. 68.14 (A) Left translucent retinal astrocytoma along inferior temporal vascular arcade. (B) Both translucent hamartomas and larger calcified hamartomas are shown in this case. The flat translucent lesions in this case are superior to the fovea within and above the superior vascular arcade. (C) A combined lesion with a flat hamartoma and a central nodular area.

lesions occur in nearly all (92%)[33] by age 18. Five renal lesions occur: (1) benign angiomyolipomas, (2) malignant angiomyolipomas, (3) cysts, (4) oncocytomas, and (5) renal cell carcinoma. Benign angiomyolipomas are the most common (70–80%). Other visceral involvement includes liver angiomyolipomas and lymphangiomyomatosis of the lung.[33]

Ocular features

Retinal hamartomas are one of the major diagnostic criteria. Three types are described: (1) a flat, smooth, non-calcified, gray translucent lesion (Fig. 68.14A); (2) an elevated, multinodular, calcified, opaque lesion resembling a mulberry (Fig. 68.14B);

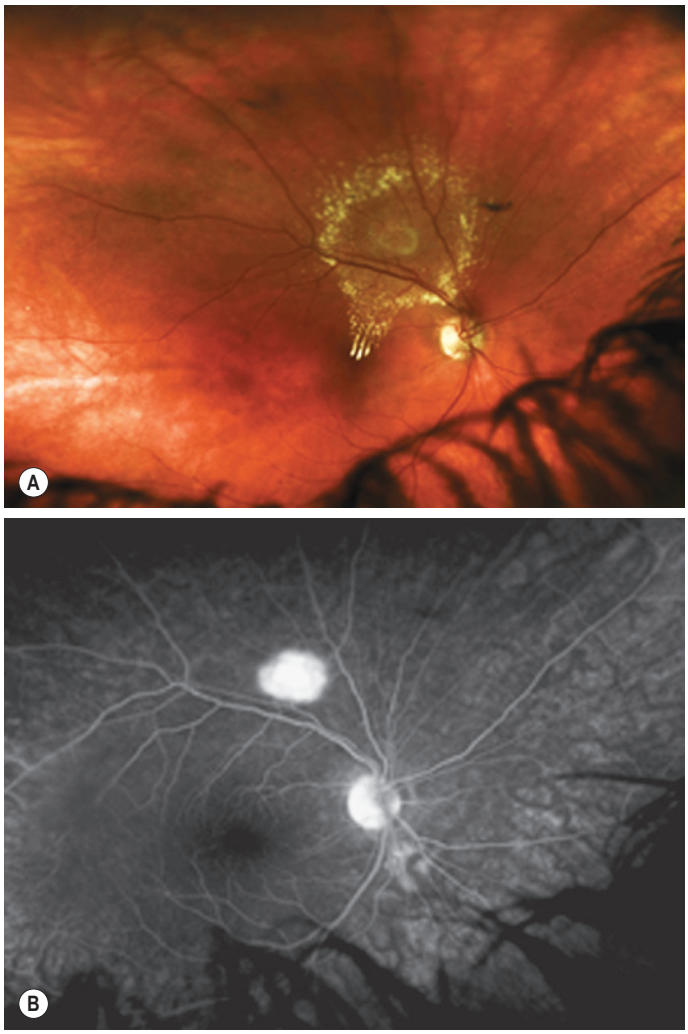


Fig. 68.15 (A) Exudate surrounding retinal astrocytoma with lipid encroaching on macula. (B) Fluorescein angiogram showing vascular leakage associated with retinal astrocytoma.

and (3) a transitional lesion, which has features of both (Fig. 68.14C). They occur in 50% of patients.[34]

The flat, smooth translucent type is the commonest, accounting for approximately 70% of hamartomas seen in TSC.[35] They may be difficult to detect, manifesting as an abnormal light reflex, approximately 0.25–2 disc diameters in size, located in the posterior pole frequently superficial to retinal vessels. The classic multinodular "mulberry" occurs in up to 50% of patients located on or within 2 disc diameters of the optic disc.[35] Ten percent of patients have a combined lesion with a flat hamartoma and a central area of nodular calcification, located at the posterior pole. Retinal hamartomas are not calcified in infancy but become so later in life. In general, the lesions remain static. Rarely vitreous hemorrhage may complicate the lesions, presumably due to abnormal vessels involved with the hamartomas (Fig. 68.15).

Chorioretinal hypopigmented punched-out lesions are also recognized as a retinal finding, occurring in up to 40% of patients.[35] They are less than one disc diameter in size and are distributed in the midperipheral fundus (Fig. 68.16).

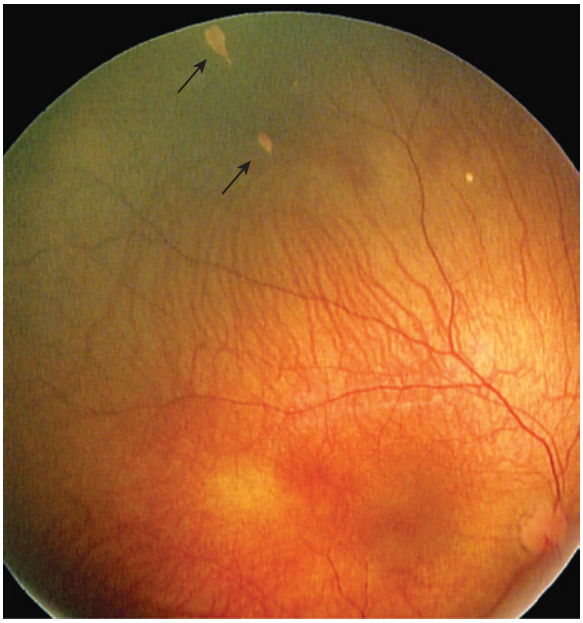


Fig. 68.16 Hypomelanotic punched-out lesions in midperiphery of right eye.

Ocular management

The management of TSC patients requires a multidisciplinary approach (see Table 68.5). The ophthalmologist plays an important role in screening, monitoring visual development, progress of lesions, and in the monitoring of ocular complications of systemic therapy.

Vigabatrin monitoring

Vigabatrin therapy maybe complicated (in 40–50%) by a specific visual field defect resulting in bilateral and concentric constriction within a 30° radius from fixation. This begins with nasal loss extending in an annulus over the horizontal midline, with a relative sparing of the temporal field.[36]

Monitoring is challenging in this group, particularly visual fields. For those unable to comply, a full-field electroretinogram (ERG) (altered cone function) or a multifocal ERG (electronegative b wave) are useful for monitoring therapy.[37] Retinal nerve fiber layer assessment with optical coherence tomography has been shown to provide an accurate estimate of the extent of vigabatrin retinal toxicity.[38]

von Hippel–Lindau disease

von Hippel–Lindau (VHL) disease is a rare familial cancer syndrome causing susceptibility to benign vascular tumors of the eye (retinal capillary hemangioblastomas; RCH) and CNS (angioma or hemangioblastoma), renal cell carcinoma (RCC), and pheochromocytoma. Diagnostic criteria have been developed (see Table 68.6). VHL affects approximately 1 in 36,000 individuals and is an autosomal dominant disorder. Symptoms typically develop from the second to the fourth decade.

Table 68.6 Diagnostic criteria for von Hippel–Lindau disease

Family history*	Required feature
Positive	Any one of the following: Retinal capillary hemangioma Central nervous system (CNS) hemangioma Visceral lesion**
Negative	Any one of the following: Two or more retinal capillary hemangiomas Two or more CNS hemangiomas Single retinal or CNS hemangioma with a visceral lesion**

*Family history of retinal or CNS hemangioma or visceral lesion.
**Visceral lesions include: renal cysts, renal carcinoma, pheochromocytoma, pancreatic cysts, islet cell tumors, epididymal cystadenoma, endolymphatic sac tumor, and adnexal papillary cystadenoma of probable mesonephric origin.
Adapted from Bausch B, Jilg C, Glasker S, et al. Renal cancer in von Hippel–Lindau disease and related syndromes. Nat Rev Nephrol 2013; 9: 529–38.

Table 68.7 Recommended intervals for screening for von Hippel–Lindau disease in at-risk individuals

Test	Start age	Frequency
Ophthalmic examination	0 years	Yearly
Neurological examination	0 years[a]	Yearly
Plasma or 24 h urinary catecholamines and metanephrines	2 years of age	Yearly and when blood pressure is raised
Imaging of CNS (MRI)	11 years of age	Yearly
CT and MRI of internal auditory canals	Onset of symptoms (hearing loss, tinnitus, vertigo, or unexplained difficulties of balance)	
Ultrasound of abdomen	8 years of age	Yearly MRI as clinically indicated
CT of abdomen	18 years of age or earlier if clinically indicated	Yearly
Audiological function tests	15 years	Baseline then when clinically indicated

[a]From 0 to 14 years: annual pediatric examinations are recommended.
Adapted from VHL Alliance. VHL screening protocol 2011. Available from: https://vhl.org/professionals/screening-diagnosis/importance-of-screening/. Accessed 16 June 2016.

Genetics and pathophysiology

VHL disease is caused by a germline mutation in the *VHL* tumor-suppressor gene. The VHL gene product, pVHL, interacts with the hypoxia-inducible factor (HIF). With loss of pVHL activity, HIF is not degraded, leading to overproduction of growth factors encoded by HIF target genes, such as VEGF and platelet-derived growth-factor B chain (PDGF β), contributing to tumor formation.[39] There is high penetrance of the disease, emphasizing the importance of screening, as early detection enables more conservative therapy (Tables 68.6 and 68.7).[40,41]

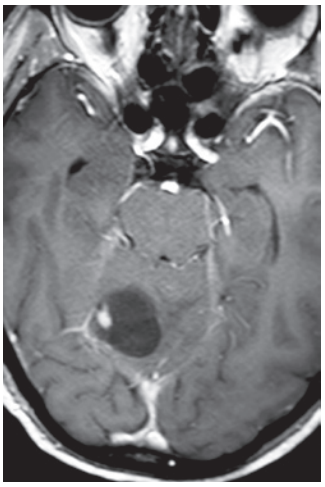


Fig. 68.17 An 11-year-old von Hippel–Lindau patient with cerebellar hemangioblastoma (T1 magnetic resonance imaging axial scan). *(Patient of Dr Mark Dexter, neurosurgeon, Sydney.)*

CNS and visceral features

CNS hemangioblastomas occur in 70% of patients, affecting predominantly the cerebellum (Fig. 68.17), spine, and medulla. Pheochromocytomas occur as a principal manifestation in some families. Renal cysts and tumors are present in 60% of patients.[41] Other systemic involvement includes endolymphatic sac tumors, pancreatic cystic disease, and pancreatic islet cell tumors. CNS hemangioblastomas and renal carcinoma are the main causes for death in VHL.

Ophthalmic features

Ocular involvement occurs in approximately 37% of VHL patients with 58% having bilateral involvement.[42] RCHs are classified on the basis of location (peripheral or juxtapapillary) (Figs 68.18 and 68.19), morphology (endophytic, exophytic, or sessile), and their effect on the retina (exudative or tractional). RCHs usually manifest by 30 years of age. Fluorescein angiography is important to visualize early vascular abnormalities, particularly for juxtapapillary RCHs, and to differentiate the feeder arteriole when laser therapy is considered.

Treatment is indicated if vision is deteriorating.[42] Current therapy for RCHs is based on the principle of tumor ablation and includes laser photocoagulation, cryotherapy, radiation, and photodynamic therapy. Treatment targeting specific growth factors is the goal for therapy.[43]

Sturge–Weber syndrome

Sturge–Weber syndrome (SWS) occurs sporadically in approximately 1 in 20,000–50,000 live births.[44] It is characterized by a port wine stain (cutaneous capillary vascular malformation [capillary malformation, CM]) of the face (Fig. 68.20) and is associated with venous–capillary abnormalities of the leptomeninges and the eye. It is classified into three types: Type I is most common, with the classic facial port wine stain (CM) and intracranial leptomeningeal vascular malformation, ± ocular abnormalities, e.g. glaucoma. Type II involves facial CM ± glaucoma, but no brain abnormalities. Type III is characterized by leptomeningeal angiomatosis without cutaneous lesions or ocular abnormalities.[45]

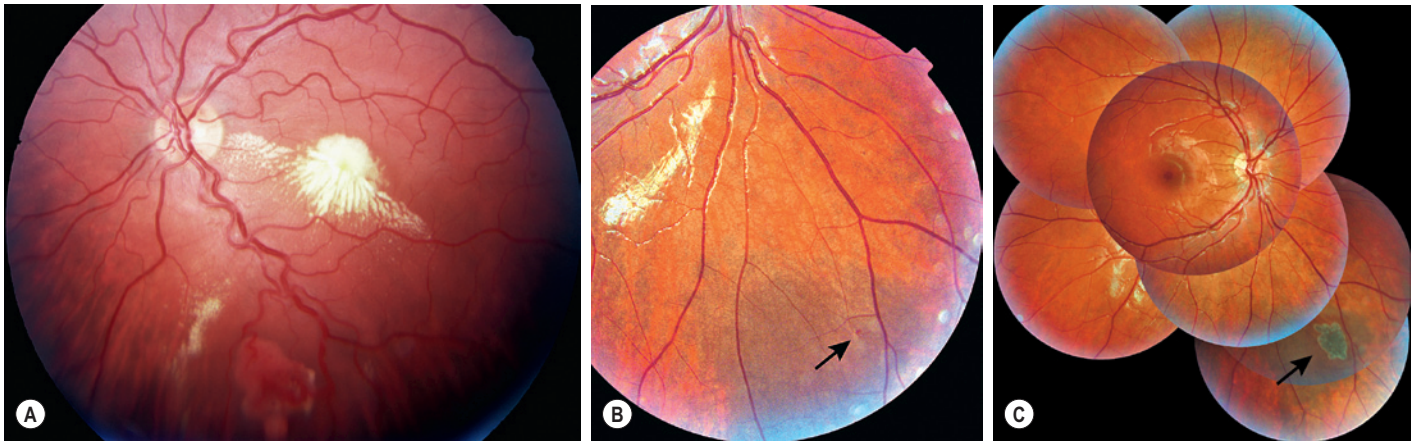


Fig. 68.18 Peripheral retinal capillary hemangioblastomas (RCH) (A) Inferior midperipheral hemangioma with dilated arteriole and venule and exudate (Patient of Professor FA Billson Save Sight Institute Sydney University). (B) Pre laser RCH (arrow) and (C) post laser photocoagulation of RCH (arrow). (Patient of Professor H.U. Møller Odense University Eye Clinic) (*Patient of Professor H.U. Møller Odense University Eye Clinic.)*



Fig. 68.19 (A) Juxtapapillary retinal capillary hemangioma with fluorescein angiogram. (B) Large juxtapapillary hemangioma with exudate. *([A] Patient of Associate Professor A.P. Hunyor, Sydney.)*



Fig. 68.20 (A) Sturge–Weber syndrome facial capillary malformation ("port wine stain") age 1 month; and (B) Age 8 years following multiple dye laser therapy sessions. (C) Repeat laser application to fill in untreated areas. Eyelid spared on this occasion due to recent trabeculectomy.

Pathogenesis

A somatic mosaic activating mutation in *GNAQ* has been found to be associated with both the Sturge–Weber syndrome and non-syndromic port wine stains.[46] *GNAQ* encodes Gαq, which activates downstream MAPK signaling, including endothelin, which has important roles in vasculogenesis.[46]

The International Society for the Study of Vascular Anomalies provides a classification for vascular birthmarks.[47] These skin lesions are termed "vascular malformations." In the ophthalmology literature, vascular malformations present in the choroid and conjunctiva have been termed "hemangiomas." However, the histology shows diffuse choroidal involvement similar to the skin lesions.[48]

Neurological features

Neurological complications are often progressive and include epilepsy, mental retardation, hemiparesis, headache, stroke-like episodes, behavioral problems, and visual field defects.[49] Ipsilateral leptomeningeal vascular malformations are the underlying structural lesions (Fig. 68.21). The extent and degree of the neurological symptoms is related to the area and severity of glucose hypometabolism. A stroke-preventative approach to SWS is important, including good hydration during illness, and low-dose aspirin which may reduce the frequency of stroke-like episodes.

Ophthalmic features and management issues (Table 68.8)[47,49]

Upper-lid skin involvement is commonly associated with intraocular involvement. Glaucoma is the principal ocular complication. It occurs in 58–71% of cases.[44] There is a bimodal presentation with an early-onset group featuring an angle anomaly with trabeculodysgenesis. The late-onset glaucoma group is related to raised episcleral venous pressure.[50] The early-onset group may later worsen due to increasing episcleral venous pressure.

Choroidal vascular malformations ("hemangiomas") are common. They may be localized to the posterior pole or extend to the whole fundus. There is loss of the normal choroidal vascular pattern with a diffuse uniformly red fundus (Fig. 68.22). Bilateral cases can be difficult to detect. Enhanced-depth OCT may assist in determining the extent.[51] These hemangiomas grow slowly and may lead to degenerative changes of the overlying retina with serous retinal detachment (Fig. 68.23).

Glaucoma management is a challenge in SWS. Angle surgery is the procedure of choice in the early-onset group. Anti-glaucoma medications have an adjunctive role in this group. Medications are the initial management for the late-onset group. Filtration surgery, when required, mandates alterations in technique to minimize hypotony and/or hemorrhage. For trabeculectomies, this entails preplaced scleral flap sutures, either viscoelastic or an anterior chamber maintainer, during the procedure. The

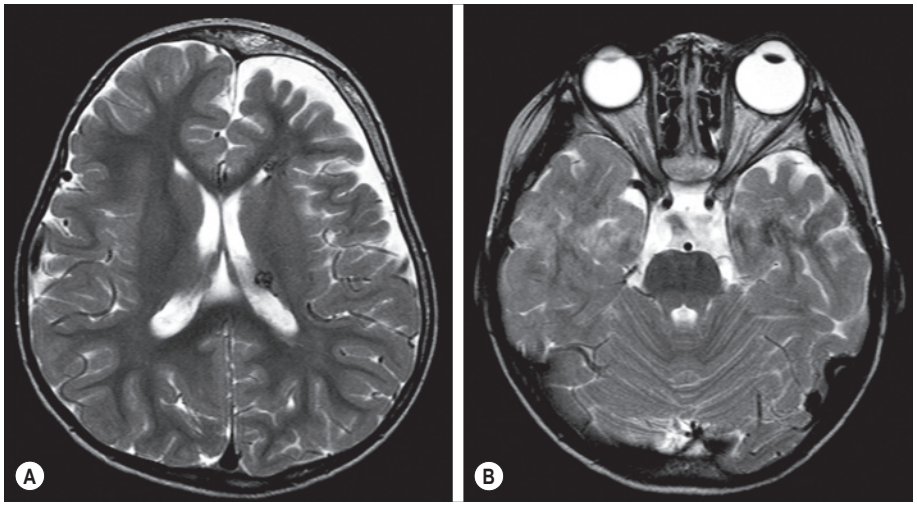


Fig. 68.21 (A) Leptomeningeal enhancement demonstrating the angiomatosis. Associated cerebral atrophy (post gadolinium T1 axial magnetic resonance imaging [MRI] scan). (B) Left temporal lobe leptomeningeal angiomatosis, cortical atrophy with calvarial skull bone thickening, and left buphthalmos (T2 axial MRI image).

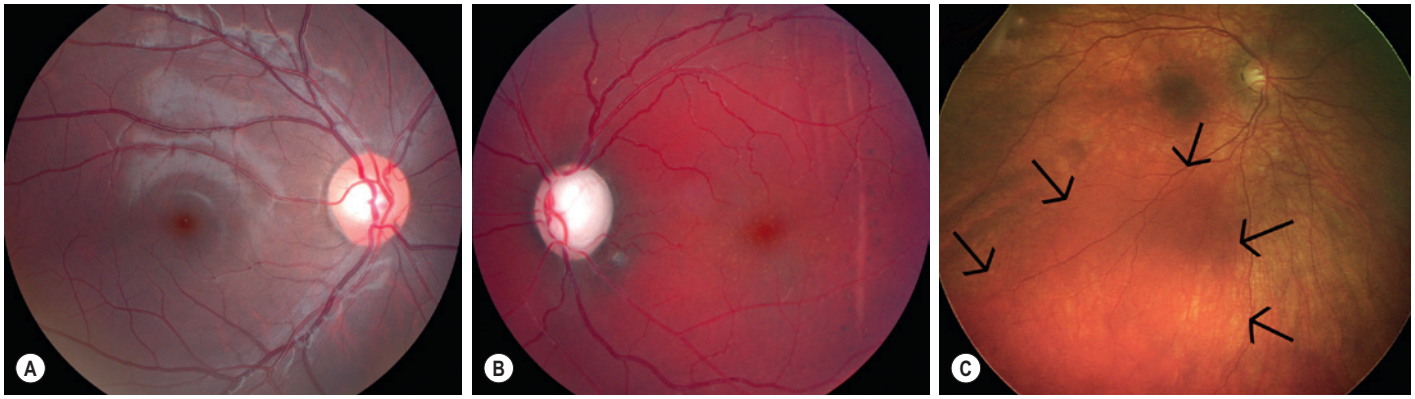


Fig. 68.22 Choroidal vascular malformation. (A) Normal right eye. (B) Diffuse posterior pole involvement – "tomato ketchup fundus"; same patient. (C) Circumscribed posterior pole choroidal vascular malformation.

Table 68.8 Recommendations for management of Sturge–Weber syndrome

Clinical issue	Recommendation
Facial port wine stain (PWS) • V1 distribution asymptomatic • V1 with eye and CNS abnormalities • V1 + V2/3 distribution	Dermatology review Ophthalmology evaluation + follow-up Ophthalmology evaluation + follow-up + MRI Ophthalmology evaluation + follow-up + MRI
Seizures	Parental education at diagnosis of PWS Early management with anti-epileptic medication Refractory cases: consider surgical options
Stroke-like episodes	Aspirin (3–5 mg/kg/day) Hydration during illness
Headaches	Standard abortive and preventive agents
Glaucoma	6-monthly ophthalmic review Medical/surgical intervention
Focal neurologic deficit • Hemiparesis • Visual field defect	Multidisciplinary team/rehab input Regular surveillance Adaptive training
Cognitive impairment	Neuropsychological assessment and intervention. Individualized educational programs
Psychosocial	Surveillance and early referral to support services
Endocrine	Monitor growth and thyroid function
ENT	Surveillance for ENT infections and obstructive sleep disorders
Other	Annual influenza vaccination Aggressive management of acute illness optimizing management of fever and hydration

ENT, Ear, nose, and throat; MRI, magnetic resonance imaging.
Adapted from Sudarsanam A, Ardern-Holmes SL. Sturge–Weber syndrome: from the past to the present. Eur J Paediatr Neurol 2014; 18: 257–66.

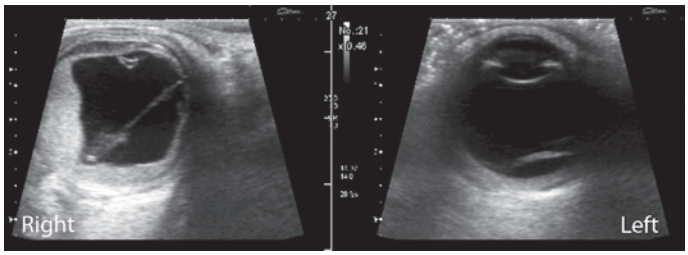


Fig. 68.23 Ultrasound of choroidal vascular malformations ("hemangioma") with associated exudative retinal detachment almost complete in right eye and localized in left eye.

risk of hemorrhage or effusion is proportional to the size of the choroidal vascular malformation. For tube implants, surgical techniques are required to minimize intraoperative and late hypotony including anterior chamber maintainer (25 G), and/or viscoelastic at time of tube insertion, ligation of tube, and the use of a tube stent. Use of a small-gauge needle (25 G) for tube entry into the anterior chamber is advised. If intraoperative choroidal effusions occur (may be dramatic and rapid) then wound closure assisted by elevation of anterior chamber infusion bottle height ± drainage via preplaced sclerostomies is required.[52]

Dermatologic features and management issues

Port wine stains are capillary vascular malformations located in the papillary as well as superficial and reticular dermis. They are present at birth, often darken to a violaceous color, and become raised by middle age. Pulsed dye laser (PDL) is the standard treatment; although complete resolution is rare, this treatment may help to reduce the cutaneous discoloration and associated hypertrophy (see Fig. 68.20). PDL in an animal model resulted in activation of the mTOR pathway, suggesting that angiogenesis pathways play an active role in the skin's blood vessel regeneration and revascularization, contributing to the incomplete effect of PDL. This provided the rationale for the clinical trial that demonstrated that the combination of topical rapamycin with PDL was more effective than laser alone in SWS.[53]

Other conditions sometimes grouped with phakomatoses

Klippel–Trénaunay–Weber syndrome

Klippel–Trénaunay syndrome (KTS) manifestations can be categorized into two groups: group A consists of capillary and venous malformations; and group B is defined by abnormal growth in terms of girth or length. Patients require manifestations in both groups for a diagnosis of KTS[54] (Fig. 68.24). The prevalence is approximately 1 : 100,000.[54] The vascular disorder in KTS is a combined capillary, venous, and lymphatic malformation.[55] Ophthalmic features include orbital varix, retinal varicosities, angioma of the choroid, heterochromia iridium, and ipsilateral optic nerve enlargement. The glaucoma of KTS has many features in common with Sturge–Weber syndrome.



Fig. 68.24 Klippel–Trénaunay–Weber syndrome clinical features. (A) Leg length inequality due to bone hypertrophy. (B) Venous and capillary malformations of lower limb.

Ataxia telangiectasia

See Chapter 31.

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Accidental trauma in children

William V Good and Susan M Carden

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Introduction

Accidental eye trauma in children is a leading public health concern throughout the world. A careful history in cases of eye trauma is important and yet potentially misleading; something unreported could have occurred. Children may try to please adults thereby providing incorrect answers, and may try to deflect blame for an injury with misleading statements. Any history provided by child or parent must fit the physical findings.

Epidemiology

The number of serious eye injuries in children has been estimated at 11.8 per 100,000 per year.[1] At least 35% of serious eye injuries occur in children; the majority occur in children under the age of 12.[2] Eye injuries account for 8–14% of total injuries in children[3] and are the most common cause of unilateral blindness in children. Aside from vision loss, significant disfigurement may accompany a serious eye injury. Several factors place a child at risk for serious accidental eye injury[4]: age between 0 and 5 years, male gender, and a lack of parental supervision. Non-compliance with optical correction and patching is an important factor after childhood perforating anterior eye injury.[5] Amblyopia may limit recovery of vision in children under 7 years of age, even in eye injuries that would carry a good prognosis in older individuals.

Self-inflicted injury

See Chapter 106.

Ophthalmic trauma caused by amniocentesis and birth injury

Eye injuries occur in association with amniocentesis (Fig. 69.1). Of five cases of presumed ophthalmic amniocentesis injury,[6] one had a hemianopia and gaze palsy, two had presumed needle perforation of the eye resulting in a peaked pupil in one case and chorioretinal scar in the other. In the remaining two, one showed a small leukoma and one a limbal scar. After amniocentesis, non-pigmented anterior iris cysts adherent to the posterior cornea with peripheral anterior synechiae are possibly a result of injury with the amniocentesis needle. Congenital aphakia with retinal scar has also been described following *in utero* perforation of the globe. The advent of ultrasonic guidance in the amniocentesis procedure has greatly reduced the incidence of needle injuries to the fetus.

Ocular adnexal injuries occur, albeit rarely, after episiotomy. The possibility of ruptured globe caused by childbirth is discussed below. Forceps should be suspected as the cause of a congenital corneal abnormality in which vertical ruptures in Descemet's membrane (Fig. 69.2) occur with a contralesional occipital depression caused by the other arm of the forceps (Chapter 34).

Eyelid and lacrimal system trauma

In eyelid margin laceration, careful re-approximation of the margins of the eyelid is essential. The etiology is sharp or blunt trauma to the lid margin. Injuries to the canalicular system will occur if the medial eyelid margin is injured, either of the upper or lower lid. These injuries are commonly caused by dog bites in children.[7] They require intubation with silastic tubing passed through both ends of the canaliculus and into the nose, or the use of a monocanalicular stent. With deeper injuries, the deep edges of the wound are closed with fine-grade absorbable suture and the more superficial edges of the wound are closed with fine suture. Additional problems in dog bite injuries may include an inferior oblique palsy or restrictive type of ocular motor problem. Generally, the laceration is closed first, as

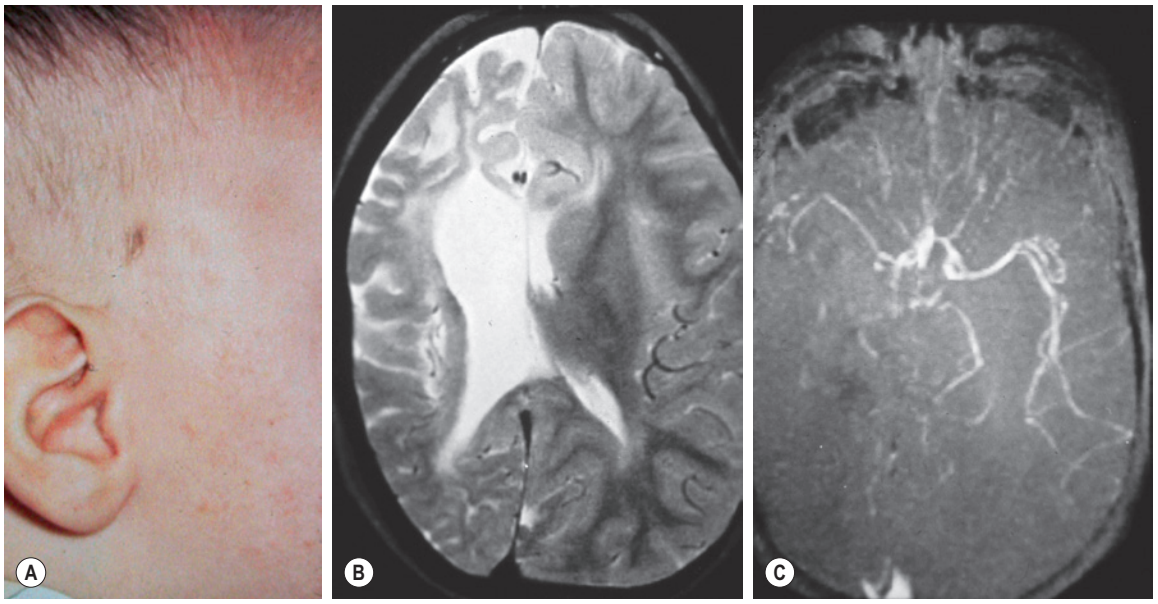


Fig. 69.1 Probable amniocentesis needle injury. (A) A small pigmented dimple on this baby's right temple coincides with radiologic evidence of a needle track. (B) Magnetic resonance (MR) scan showing right cerebral hemiatrophy. (C) MR angiography showing occlusion of the right middle cerebral artery.

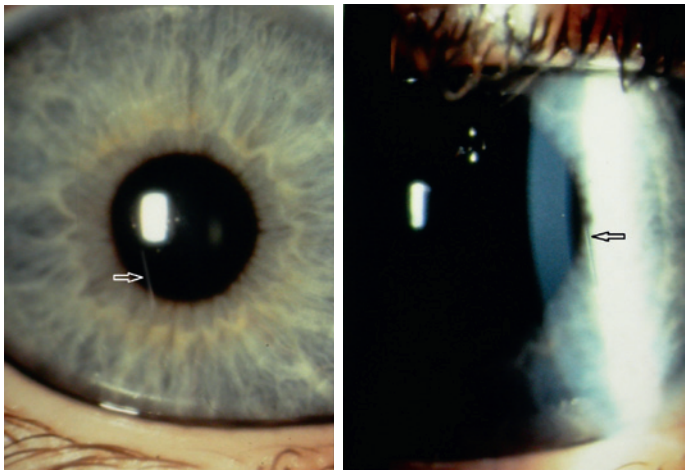


Fig. 69.2 Forceps injury to cornea. The vertically oriented rupture in Descemet's membrane can just be seen to one side of the pupil (arrows).



Fig 69.3 Subconjunctival hemorrhage. In this instance associated with shaking; there were severe intraocular injuries.

described above, followed later by strabismus management as required.

Anterior segment trauma

Subconjunctival hemorrhage (see Chapter 31)

Despite their dramatic appearance, subconjunctival hemorrhages are of virtually no significance except where enough swelling occurs near the limbus to interfere with corneal protection by the eyelids and tear film. In this case, a dellen may occur. A dellen is a non-inflammatory excavation of the cornea with or without epithelial defect, which occurs adjacent to a mass or bump near the corneal scleral limbus. It is probably caused by localized drying. Treatment consists of lubrication until the inciting mass resolves.

Subconjunctival hemorrhages associated with trauma indicate the need for a thorough search for a more serious eye injury (Fig. 69.3). The hemorrhage may mask a penetrating injury; look carefully for other signs of penetrating injury (e.g. uvea in a laceration, distorted pupil, lower intraocular pressure).

Corneal abrasion

Corneal abrasions occur when the corneal epithelium is traumatically removed from its underlying basement membrane. Abrasions can occur from blunt or sharp trauma: they are very painful. Fluorescein transiently stains the underlying basement membrane and fluoresces in a blue light.

The differential diagnosis for corneal abrasion includes viral (e.g. herpes simplex, adenovirus) keratitis and corneal basement membrane disease and dystrophies. Herpes infection is usually suggested by a dendritic appearance, while basement membrane disease occurs in older children and adults and is recurrent, with no history of trauma (see Chapter 16).

Corneal abrasions are managed with a broad-spectrum antibiotic ointment, cycloplegia to reduce pain from iridospasm,

with or without patching the eye for comfort. Most young children do not tolerate a patch, so more frequent dosing with a topical antibiotic ointment becomes the treatment of choice.

Corneal foreign body

Patients with a corneal foreign body complain of pain and a foreign body sensation. The foreign body is removed, usually with irrigation, a rotating "burr," or simply and carefully with a sharp needle brought toward the eye tangentially and used to flick the foreign body away from the surface of the eye. Another safer strategy is to anesthetize the cornea and gently rub off the foreign body on the corneal surface with a moistened cotton tip applicator. After careful examination excludes the possibility of a penetrating eye injury, the eye is managed as a corneal abrasion, once the foreign body is gone.

Eye wall injuries

Etiology

Eye wall lacerations can be categorized as either a simple laceration or a rupture, and either anterior laceration or posterior in location.

In simple lacerations, the eye is cut with a sharp object (Figs 69.4–69.7). Very young children usually suffer injury when they fall on a sharp object. Older children may suffer eye wall lacerations from glass (particularly when they wear spectacles) and projectiles.

Predisposition ("brittle corneas")

Certain eyes may be more likely to rupture with relatively minor trauma. In Ehlers–Danlos syndrome, defective collagen cross-linkage leads to scleral and corneal weakness (Fig. 69.8); in Ehlers–Danlos with blue sclera (due to scleral thinning), hyperextensible skin, and hypermobile joints, spontaneous corneal rupture can occur, and in the brittle cornea, blue sclera and joint hyperextensibility syndrome, spontaneous rupture of the globe may occur. Such patients may have red hair and develop keratoglobus, and, unlike Ehlers–Danlos syndrome, they have normal levels of lysyl hydroxylase. Osteogenesis imperfecta consists of blue sclera, deafness, and bone fractures.



Fig. 69.5 Limbal penetrating injury with iris prolapse.

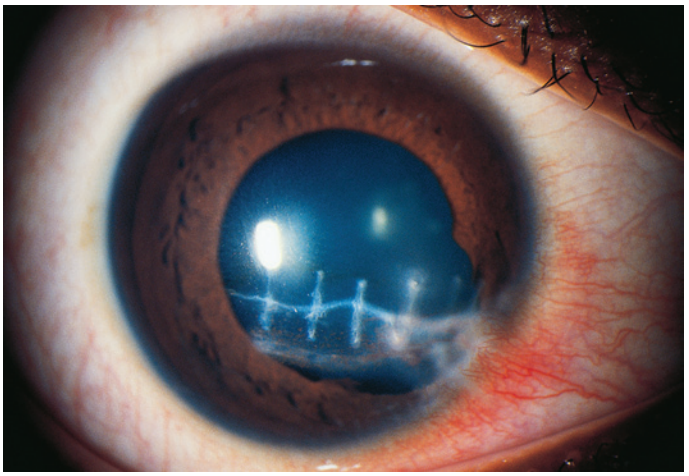


Fig. 69.6 After removal of the corneal sutures a scar persists. Failure to remove suture promptly may cause blood vessel migration and corneal opacification. Note the vessels at the corneoscleral limbus.

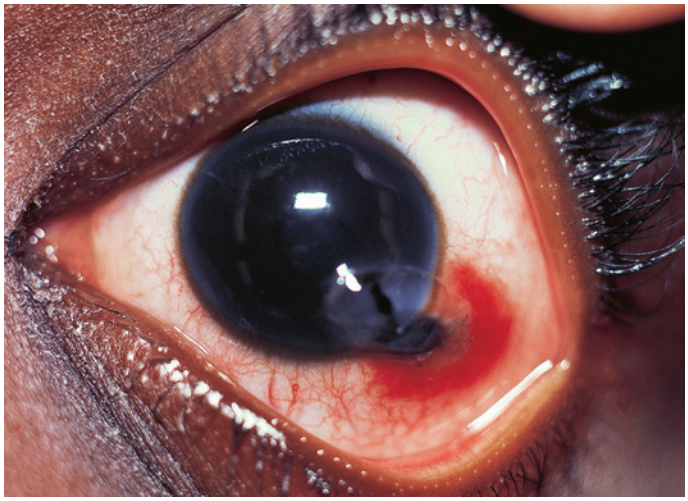


Fig. 69.4 Penetrating injury with iris prolapse and subconjunctival hemorrhage.

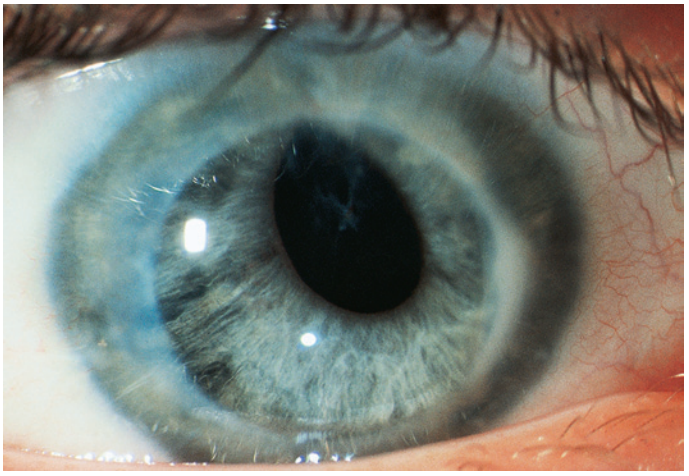


Fig. 69.7 This 5-year-old child had accidental corneal trauma as an infant. Prompt corneal grafting and amblyopia treatment resulted in an acuity of 6/12.

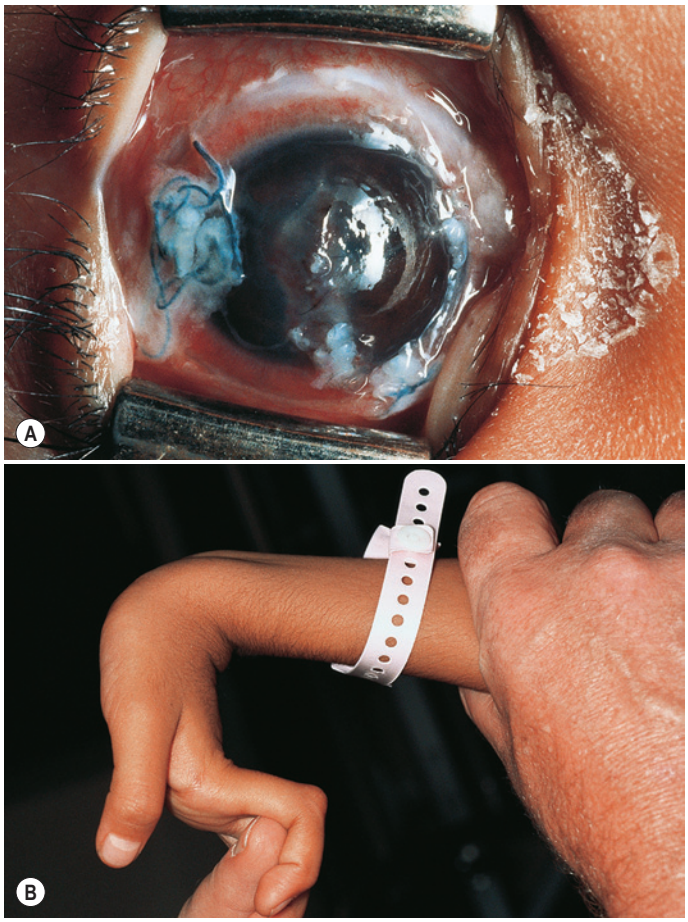


Fig 69.8 Ehlers–Danlos syndrome. (A) Spontaneous rupture of the cornea. This is an autosomal recessive disease. One of this child's siblings, also affected, had a bilateral corneal rupture at the same time during fisticuffs. (B) Hyperflexible joints.

Children with this syndrome may also be more prone to corneal rupture from minor trauma.

Globe rupture

When a globe is ruptured, it is pushed or squeezed so hard that the eye wall breaks under pressure. The results usually are devastating, with partial or complete expulsion of intraocular contents. Expulsion results from increase in intraocular pressure followed by sudden decompression through a hole in the wall of the eye. Events that can cause ruptured globes usually involve encounters with large, blunt objects. In many countries, sporting impacts and automobile crashes (airbag injuries) are major causes of globe rupture in older children.[8] Globe rupture is more common in boys than girls, reflecting the nature of the cause. Eyes are more likely to be ruptured or lacerated in areas where the sclera or cornea are thinnest, i.e. under the rectus and superior oblique muscle insertions and at the corneoscleral limbus.

Anterior versus posterior laceration

Anterior injuries carry a better prognosis, so long as the injury does not also cut the retina. Injuries anterior to the pars plana (5 mm posterior to the limbus) will not cut the retina, and therefore carry a better prognosis. If a cataract occurs with an anterior laceration, the prognosis for recovery of vision is not as good.[9] Posterior injuries cut the retina and often result in a complicated retinal detachment, with a far worse prognosis.

Penetrating eye injuries are those in which the causative agent enters the eye but does not pass all the way through. Perforating eye injuries are those that pass through two walls of the eye. The same definition holds true when referring to different parts of the eye. A penetrating corneal injury penetrates the cornea but does not pass all the way through it. A perforating injury passes all the way through the cornea into the anterior chamber or further.

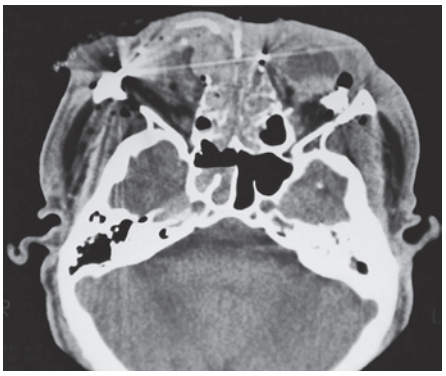


Fig. 69.9 Computed tomography scan showing disrupted right globe following a gunshot wound. The left eye was also injured from the concussive effect. Note the vitreous hemorrhage.

Diagnosis

The diagnosis of penetrating eye injury is obvious when a laceration is apparent. Clues to occult penetration include subconjunctival hemorrhage, distorted pupil, wrinkled lens capsule, and lowered intraocular pressure, particularly compared to pressure in the fellow, uninjured eye, reduced visual acuity, or an afferent pupillary defect.

Management

Prevention

The best form of management for eyeball lacerations is prevention. This includes wearing suitable safety glasses or goggles by players who participate in games involving a small ball, and supervision by parents and teachers when sharp objects (fencing, archery, etc.) are used.

The use of safety glasses in monocular children is valuable, especially at times of particular risk.

Treatment

Once the eye laceration or globe rupture is diagnosed, it is recommended that a protective shield be placed over the eye. Emergency surgery is indicated, but the patient's overall health should not be ignored. The eye laceration may accompany head trauma. An adolescent patient with multiple gunshot wounds needs to be fully assessed as experience has found that it is relatively easy to focus on the eye injury and almost miss a head injury. Systemic antibiotics and control of nausea and vomiting are recommended.

Imaging

In many cases, a computed tomography (CT) scan of the orbits (Figs 69.9 and 69.10) will help to identify the location of expected or unexpected intraocular foreign bodies. Ultrasound biomicroscopic evaluation also can be helpful to detect zonular deficiency, angle recession, iridodialysis, lens dislocation, and

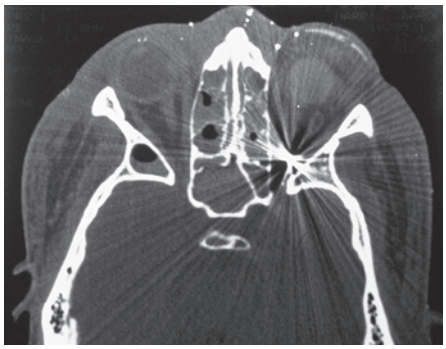


Fig. 69.10 Shotgun injury. Computed tomography scanning is particularly helpful in delineating the presence and location of ocular and orbital foreign bodies. This adolescent was shot in the face with a gun.

iridocorneal adhesions.[10] It is important to avoid contact ultrasound evaluation if a ruptured globe is suspected as any pressure might cause extrusion of intraocular contents.

Anesthesia

Some advocate avoiding a depolarizing agent for fear that the contraction of extraocular muscles (which initially occurs) could expel intraocular contents.

Surgery

Anterior full-thickness lacerations require prompt closure and re-evaluation of the patient's vision and ocular status in the ensuing days. The use of intraocular antibiotics is usually recommended. The prompt closure of an eye wall laceration would seem to be adequate to greatly reduce the incidence of traumatic endophthalmitis. In young children, delay in traumatic cataract extraction runs the risk of inducing amblyopia, but there is often a better chance of successfully implanting an intraocular lens if the eye is closed in two stages. In older children (>7 years of age), it is often an easier decision to plan a second operation with an intraocular lens implant. Although controversial, good results have been reported with combined lensectomy, vitrectomy, and primary intraocular lens implantation as the initial procedure.[11]

Posterior lacerations almost always cut through the retina. Even so, the initial goal of surgery is wound closure. Most authorities do not use cryosurgery or scleral buckling at initial surgery. The trauma alone is enough to cause a retinal scar around a break, and cryosurgery may increase the likelihood of proliferative vitreoretinopathy. A posterior vitreous detachment occurs 7–10 days after trauma; after this detachment has taken place, retinal surgery can be undertaken.

Management continues even after successful surgery. Children under the age of 7 years are at risk of amblyopia. Prompt refractive management with a contact lens over a corneal laceration (or spectacles if appropriate) and patching should be started as soon as possible. Corneal sutures in children attract vascularization and scarring much more quickly than in adults. Sutures may be removed in a few weeks in young children; failure to do this may result in a vascularized cornea, impeding vision.

Prognosis

Anterior lacerations carry a better prognosis than posterior lacerations. But in young children, with the risk of amblyopia, the prognosis may not be good, even with anterior lacerations. When anterior lacerations are combined with a traumatic cataract, the prognosis worsens. The prognosis is highly dependent upon success in the management of amblyopia.

Traumatic cataracts

Traumatic cataracts can occur as a result of a sharp penetrating injury to the lens capsule and/or lens, or a blunt concussive force. They may take days to years to develop. The diagnosis of traumatic cataracts is based on an abnormality in the red reflex. The cataract problem can be confirmed by examining the lens under magnification, either with loupes or a slit-lamp. In some cases, a Vossius ring may occur, i.e. a ring of pigment forms on the anterior lens capsule as a result of the posterior (pigmented) aspect of the iris striking the capsule. Examination should establish that there are no other ocular injuries.

In partial cataracts, an additional important aspect to the examination is an effort at measuring visual function in the involved eye. In older children this can be done with Snellen acuity. In younger children, an estimate must be made based upon experience with lens clarity and visual functioning. Attempts can be made to measure acuity with forced choice preferential looking techniques, but these may be misleading and probably should not be used as the sole determinant to undertaking surgery.

If there is doubt as to the value of removing a lens with a cataract, then it should be observed. So long as the child is beyond the age when amblyopia can develop, the initial repair of a corneal or scleral laceration can be followed at a later date with removal of the lens. This "wait-and-see" strategy has no deleterious effects on the child other than the necessity for a second general anesthetic.

Children with visually significant traumatic cataracts can have good outcomes if managed appropriately.[12] Surgical management consists of removal of the lens with or without preservation of the posterior capsule. If a lens is removed at the same time as the closure of an eye wall laceration, some authorities advocate simultaneous lens implant. One reason for caution is that the implant could foster survival of bacterial organisms that penetrated the eye as a result of the trauma. Another concerns the choice of the intraocular lens power required to correct the aphakia. In young children, eye growth leads to instability of the refractive power of the eye, making implant power selection problematic.[9] Decisions regarding subsequent implants depend on surgeon preference and the presence or absence of corneal refractive problems. If a child has a significant amount of astigmatism and will require contact lens rehabilitation anyway, then in some circumstances, the increased risk of a lens implant can be avoided, since the implant would not avert the need for contact lenses. Contact lenses can be successful in post-traumatic aphakia; rigid gas-permeable lenses seem to be most effective if there was a corneal perforation.[13] Combined keratoplasty and lens implantation may have a role in some cases.[14]

A special type of cataract can occur as the result of electrical injury.[15] A characteristic opacity in the posterior aspect of the lens forms as the result of the transmission of electricity to the eye (Fig. 69.11) itself.

Hyphema

A hyphema is a collection of blood in the anterior chamber of the eye. It occurs as a result of traumatic avulsion of blood vessels at the base of the iris. Bleeding occurs and then ceases

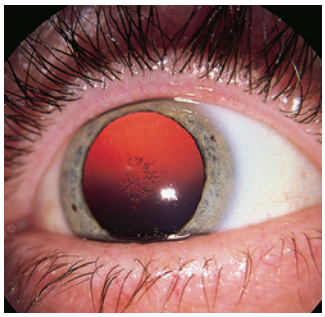


Fig. 69.11 Electric shock. After an electric shock, this young man slowly developed a monocular cataract.

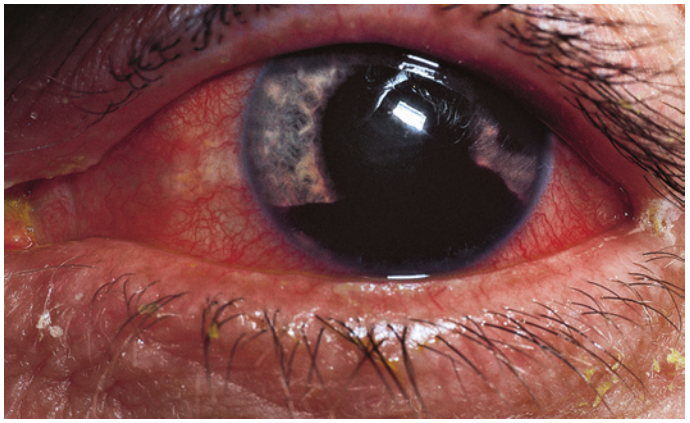


Fig. 69.12 A long-standing hyphema. This is shown by the dark color of the blood in this young man.

after clot formation or an increase in intraocular pressure. A hyphema may be small enough that it can be identified only with a slit-lamp examination, or it can be so extensive as to fill the entire anterior chamber with blood ("8-ball hyphema"). In most instances, a superiorly located meniscus develops due to the effects of gravity (Fig. 69.12).

The major cause of hyphema is trauma; it is much more common in boys than in girls,[16] but there are other etiologies. Herpes zoster iritis can occasionally cause a hyphema. Spontaneous hyphemas also occur with juvenile xanthogranulomatosis (JXG), usually in very young children, and may or may not be associated with cutaneous lesions. The risk of intraocular JXG increases with young age (<2 years), multiple skin lesions, and new diagnosis.[17] Hyphemas may occur rarely in association with tumors of the eye, particularly retinoblastoma, and with iris vascular abnormalities or rubeosis. In a hyphema the clot usually retracts between the third and fifth post-traumatic day, at which point the hyphema may recur. Very small "trickle" hyphemas are less likely to rebleed than larger ones. However, rebleeding cannot be predicted solely on the size of the hyphema if it is visible without magnification. For this reason, some sort of rest regimen for the child is generally advocated. Whether a child should be hospitalized in order to facilitate resting will certainly depend at least on the child's activity level, the family's ability to supervise the child, and perhaps also on the size of the hyphema.[16] A quick, substantial rise in intraocular pressure (a complication of hyphema) can cause nausea and vomiting, an indication for antiemetics. The author uses a long-acting cycloplegic agent in order to put the iris and pupil "at rest" and topical steroids if an inflammatory component (iritis) occurs. Systemic steroids or epsilon aminocaproic acid (which blocks fibrinolysis thereby reducing the risk of rebleeding) have been advocated by some. Topical epsilon aminocaproic acid may be effective in reducing rebleeding and is not associated with an increased risk of nausea and vomiting as is the case in its systemic use.[18]

Complications of hyphema include increased intraocular pressure and glaucoma. How much pressure and for how long it can be tolerated safely has not been determined for children. High pressure runs the risk of causing corneal blood staining and optic nerve damage. To prevent these complications, elevated pressure should be maintained below 30 mmHg. Persistent elevation of intraocular pressure is an indication for surgical evacuation of the hyphema. Elevated intraocular pressure can be managed with topical eye drops such as beta-blockers; it is safer to avoid cholinergic drugs such as pilocarpine because they cause constriction of the pupil and may affect fragile blood vessels. Systemic acetazolamide is often helpful.

When a child has sickle cell anemia or trait, the management of glaucoma caused by hyphema is more problematic. The only agent available is a topical beta-blocker, since other agents may either exacerbate the hyphema (e.g. pilocarpine) or lead to sickle cell crisis. Children with sickle cell with a hyphema are candidates for early surgical intervention. Evacuation of the clot through a limbal incision is generally preferred. Even in children who do not have sickle cell, but in whom glaucoma remains refractory, surgical evacuation is advisable.

Corneal blood staining is caused by erythrocytes crossing the corneal endothelium and Descemet's membrane and staining the cornea when the intraocular pressure is significantly elevated, and when the endothelium is damaged. Corneal blood staining is reversible, but takes several years and may lead to amblyopia. In order to avoid corneal blood staining in the context of a persistent large hyphema with elevated intraocular pressure that is unresponsive to medical management, some have advocated trabeculectomy surgery, closing the scleral flap quite loosely. Although conjunctival scarring will likely lead to bleb failure in the long run, the hyphema will have resolved without accompanying ocular hypertension, thus sparing the child from the profoundly amblyogenic complication of corneal blood staining.

Months and years later, if the angle of the eye has been traumatized and "recessed," "angle recession glaucoma" may develop. For that reason, any patient who has had a hyphema probably should have yearly ophthalmology examinations, with intraocular pressure measurements determined.

Posterior segment trauma

Commotio retinae

Commotio retinae, also known as Berlin edema, frequently occurs after blunt trauma to the front of the eye; in one study it occurred in 35% of cases of contusion or rupture of the globe.[19] The edema, which occurs in the outer retina, has a funduscopic appearance that is white or gray-white. The macula may be involved with or without macular hole formation, in which case central vision will be at least temporarily diminished.[20] Berlin edema can also involve extramacular areas. In most cases, the edema resolves; but in some cases, pigment migration in the

macula results in acuity loss. The differential diagnosis includes retinal infarction, cotton-wool spots, and shallow retinal detachment. No treatment is available for commotio retinae.

Purtscher retinopathy

Severe trauma to the torso or the head can cause Purtscher retinopathy. Airbag and seat belt injuries in automobile accidents account for a significant number of cases.[21] Purtscher disease can be associated with fat or air embolism or pancreatitis.[22] It has the appearance of massive whitening around the optic nerve head associated with hemorrhage. The whitening may represent ischemic areas or exudate. There is no specific treatment for this problem, which may resolve leaving anything from mild to profound vision loss.

Whiplash injury

A macular hole sometimes occurs as a consequence of a severe whiplash injury. Presumably, the head thrusting induces a vitreoretinal interface shearing force, which tugs at the fovea and creates a partial or full-thickness hole.

Choroidal rupture

Another complication of blunt injury to the eye is choroidal rupture, often associated with widespread damage and vitreous hemorrhage (Fig. 69.13). The choroid may be ruptured at the level of the inner choroid and retinal pigment epithelium, and often in the macula. The mechanism is mechanical disruption of tissue. Sometimes the rupture is associated with a serous or hemorrhagic retinal detachment, which obscures the nature of the injury. Once the detachment resolves, the patient may be left with diminished vision if there has been scarring or retinal pigment epithelial migration into the area of the macula. Later, choroidal rupture can predispose to choroidal neovascularization, leading to exudate and hemorrhage under the macula, also diminishing vision.

Retinal hemorrhages

Retinal hemorrhages can be caused by direct head or ocular trauma, or by indirect trauma, as in non-accidental trauma (see Chapter 70).

Hemorrhages occur commonly in normal infants in the perinatal period (Fig. 69.14). They usually resolve completely in less than 1 month, occasionally in up to 3 months. Retinal hemorrhages are uncommon in children born by cesarean section.[23] Hemorrhages may occur in any layer of the retina or in the vitreous. Subretinal pigment epithelial hemorrhages appear dark with an amorphous boundary. Intraretinal hemorrhages are red in appearance, usually small and round. Superficial retinal hemorrhages have a splinter or flame-shaped appearance because they often occur in the nerve fiber layer. Subhyaloid hemorrhages have a characteristic appearance where blood forms a meniscus in a large cystic filled cavity. Finally, vitreous hemorrhages may also occur in the setting of trauma, and may be localized or diffuse depending on their severity. Preretinal hemorrhages are particularly common in children with subdural or subarachnoid hemorrhages. Since central nervous system (CNS) hemorrhage is frequently caused by trauma in children, a traumatic etiology for preretinal hemorrhages should be suspected.

Prolonged obscuration of vision due to severe vitreous hemorrhage can cause deprivation amblyopia, and in some cases is a reason for early vitrectomy, particularly in the first 3–6 months of life.[24]

Traumatic retinal detachment

Blunt trauma to the eye can cause a retinal detachment even if the globe is not cut or ruptured. Typically, the detachment occurs as the result of avulsion of the vitreous base causing a retinal dialysis, which is often in the superonasal quadrant of the eye. Presumably this location is most vulnerable because a blunt blow to the eye arises from 180° away, in the inferotemporal segment; a blunt object strikes the eye and causes a retinal tear which, days to months later, leads to a retinal detachment.

Self-injury in severely mentally retarded children can also cause retinal detachments by similar mechanisms (see Chapter 106).

In atopy, constant rubbing to relieve itching may increase the risk of retinal detachment.

Orbit trauma

Orbital bone fractures

General

Fractures of the orbit frequently involve the eye and demand the involvement of an ophthalmologist.

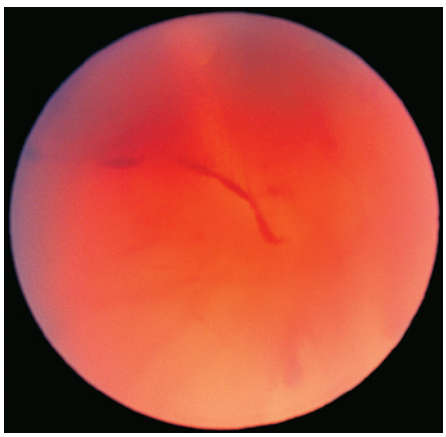


Fig. 69.13 Choroidal rupture. There is a marked vitreous hemorrhage largely obscuring a view of the fundus where a pale organizing clot can barely be made out.

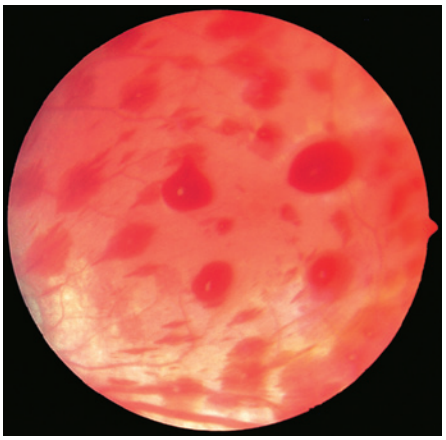


Fig. 69.14 Neonatal retinal hemorrhages in a normal child. *(Photograph courtesy of Dr Andrew Q. McCormick, Vancouver.)*

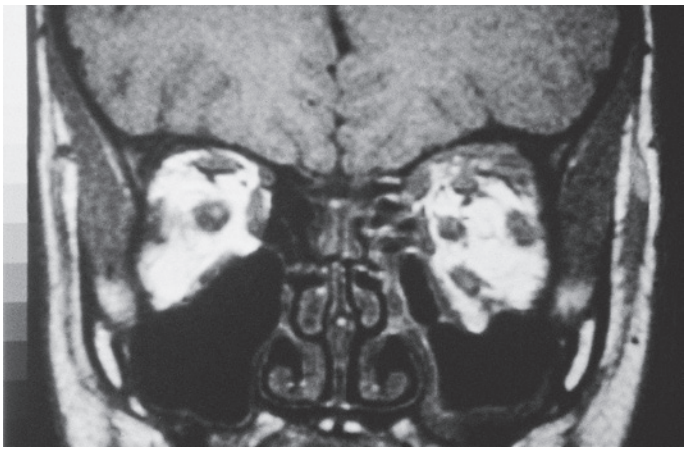


Fig. 69.15 Blow-out fracture. Entrapment of the tissues associated with the inferior rectus in the left orbit.

Blow-out fractures

Blow-out fracture refers to the caving out of one of the orbital bones that surround the eye. In most cases, the floor of the orbit is fractured (Fig. 69.15), but the medial wall of the orbit can also be damaged.[25] "Trapdoor" fractures, usually involving the orbital floor, are not uncommon in children. Blow-out fractures are unusual in young children, before the sinuses have formed.

Etiology

Blow-out fractures are caused either by compression of the orbit, increasing the pressure on the orbital contents, or by direct transmission of the force of a blow to the orbital rim, to the bones of the floor, or to the medial wall of the orbit. Experimental injuries to the orbital rim have demonstrated that a posterior orbital floor blow-out fracture can be induced in this fashion.

Complications

Two types of problems can result from a blow-out fracture. Enophthalmos can occur as a result of expulsion of intraorbital contents into fractures of the floor or medial wall of the orbit. Enophthalmos may not be apparent immediately after trauma due to edema and swelling but becomes apparent by 5–7 days after injury and should be evaluated then. If cosmetically significant, the fracture can be managed by replacing the orbital contents and repairing the fracture in order to return the orbit to its original volume.

A second problem is strabismus, including entrapped or paralyzed extraocular muscles, vertical displacement of the globe, Brown syndrome, and even cranial nerve injury if the force of the blow damage is sufficient. A trapped inferior rectus muscle is the most common cause of strabismus associated with a blow-out fracture (see Fig. 69.15). The muscle or inferior orbital tissues become incarcerated in the floor fracture, tethering the eye in a hypotropic position. Most patients experience vertical diplopia, worsening in upgaze. The incarcerated tissues should be freed as soon as possible to prevent irreversible damage to the inferior rectus, with fracture repair and accompanying strabismus being repaired.

Traumatic optic neuropathy (see Chapter 56)

Etiology

Traumatic optic neuropathy occurs when head or facial trauma causes direct or indirect injury to the optic nerve. In children, it is most commonly associated with motor vehicle accidents or sports injuries.[26] The result is unilateral or bilateral, partial or complete, loss of vision. Frontal bone trauma, occasionally even subtle and apparently insignificant, is most likely to result in optic nerve injury.

One special circumstance bears mentioning. Patients with severe psychiatric disturbances may attempt to enucleate their own eye and in the process sever the optic nerve at some point in its approach to the globe (see Chapter 106). If the severance is posterior near the chiasm, a unilateral blindness may be accompanied by a temporal hemianopia in the fellow eye due to chiasmal damage.[27] Patients who attempt to remove their own eye often experience temporary relief of their psychiatric symptoms if successful; a resurgence of symptoms may lead them to attempt to enucleate their other eye. Such patients should be guarded very closely and their psychotic symptoms should be managed aggressively.

Diagnosis and treatment

The examiner often must rely on signs of unilateral afferent visual dysfunction (afferent pupil defect, diminished color vision, decreased visual acuity). Unfortunately, many patients who experience such trauma may not be able to cooperate with a physical examination. We use high-dose steroids using methylprednisolone at a dose of 30 mg/kg as an intravenous bolus to treat traumatic optic neuropathy. A second option involves surgical intervention. Indications include optic sheath hemorrhage, orbital hemorrhage (focal, diffuse, or subperiosteal), and an optic canal fracture causing compression of the optic nerve. However, there is no convincing evidence that routine medical or surgical treatment alters the long-term visual outcome of patients with traumatic optic neuropathy.[26]

Traumatic retrobulbar hemorrhage

Trauma to the eye or orbit will occasionally cause orbital hemorrhage. Hemorrhage may be the result of blunt trauma, in which case shearing forces on retrobulbar veins or arteries are suspected. Sharp objects can also penetrate behind the eye without actually injuring the globe itself, and may lacerate blood vessels. The affected person will have pain with signs of a rapidly increasing retrobulbar mass: proptosis, an increase in intraocular pressure, chemosis, and diminished eye movements.

Trauma is not the only cause of these retro-orbital signs. Slowly progressive signs may indicate Graves disease, and conditions such as orbital cellulitis and traumatic carotid–cavernous fistula can also present similarly. Cellulitis may be diagnosed when other signs of infection are present (redness, heat in the area, considerable pain). Neuroimaging usually demonstrates sinusitis extending into the retro-orbital space, and the patient may have fever and leukocytosis. Carotid–cavernous fistula is suspected when there is pulsating exophthalmos and vessels that appear arterialized in the conjunctiva and retina.

Traumatic retrobulbar hemorrhage occasionally is an ophthalmic emergency.[27] When the intraocular pressure

is elevated and affecting optic nerve function the pressure must be lowered immediately. The author lowers intraocular pressure with carbonic anhydrase inhibitors (acetazolamide) and hyperosmotic agents. A lateral canthotomy and inferior cantholysis can relieve retrobulbar pressure almost immediately. He seldom uses aqueous paracentesis because it has only a short-term benefit and exposes the patient to the risk of cataract or intraocular infection.

Central nervous system trauma (see Chapter 60)

Prolonged cortical visual impairment following trauma

Many possible mechanisms can account for prolonged cortical visual impairment after head trauma.[28] A seizure could lead to cortical impaired vision. A cerebral contusion could result in generalized cerebral edema, causing either transient or prolonged cortical visual impairment. Increased cerebral edema can compress the posterior cerebral arteries leading to vascular insufficiency to the visual cortex. CNS hypoxic ischemia could be a sequel to either generalized trauma with blood loss or CNS vasospasm. The occipital region is quite susceptible to hypoxia and may be selectively involved (see Chapter 60).

Post-traumatic transient cortical visual impairment

Cortical visual impairment can be defined as complete or nearly complete, loss of vision with normal pupillary reflexes, and a normal fundus examination. Cortical visual impairment in children may differ in its manifestations from cortical blindness in adults. Children show fluctuating vision, a preference for observing color (versus black and white), light gazing, and, occasionally, photophobia. A relatively minor blow to the head can cause transient cortical blindness.

Traumatic cranial neuropathy (see Chapter 84)

Thirteen percent of non-fatal head injuries result in cranial neuropathy. The sixth cranial nerve is most commonly traumatized and the most common cause of multiple acquired cranial nerve palsies is trauma.[29] Most cases occur between the ages of 16 and 25 years, but even very young children can be affected.

Diagnosis

In sixth nerve palsy, difficulty or inability to abduct the involved eye is noted. The patient demonstrates a large-angle esotropia in primary gaze greater for distance than near; they can be bilateral.

Complete third nerve palsies cause a dilated pupil, complete ptosis, and an inability to adduct, depress, or elevate the eye. The resulting eye position is one of exotropia and hypotropia. Partial third nerve palsies may occur.

Traumatic fourth nerve palsies may be unilateral or bilateral. Unilateral cases typically show a hypertropia in primary gaze with inferior oblique overaction. Patients may demonstrate excyclotorsion of the eye, and cyclotorsional double vision up to 8°. Bilateral fourth nerve palsies occur in as many as 30% of cases. Bilaterality is suggested by the following physical findings:

- a "V" pattern esotropia greater than 25 prism diopters;
- alternating hyperdeviation (right hypertropia on right head tilt and left hypertropia on left head tilt);
- an excyclotorsion in primary gaze which exceeds 15°.

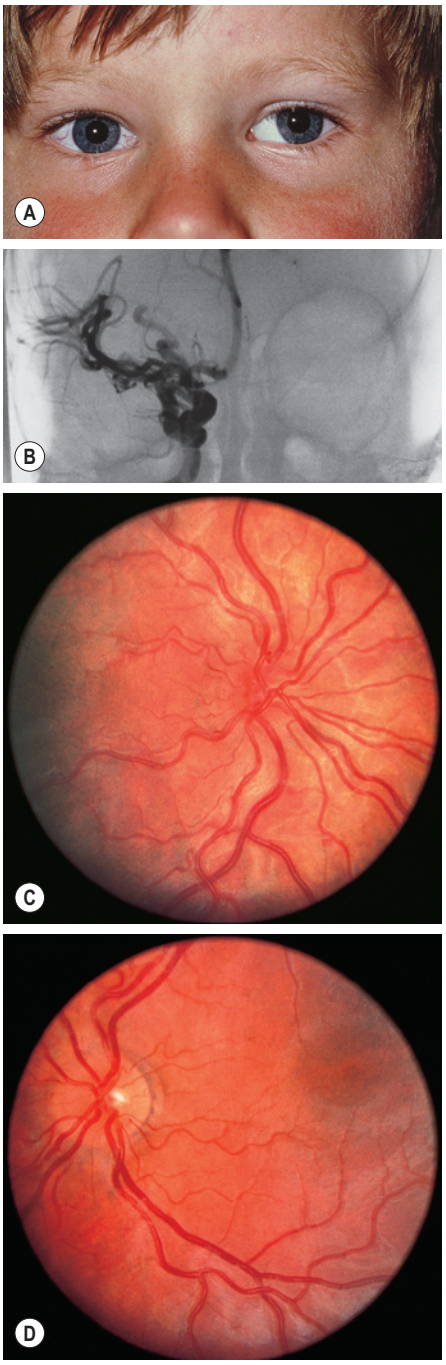


Fig. 69.16 Severe trauma. (A) This 5½-year-old boy developed right proptosis and a squeaky bruit a week after a severe road traffic accident. Dilated episcleral veins can be seen on the right. (B) Carotid angiogram showing the shunt that was later closed with a balloon catheter. (C) Retinal venous congestion and tortuosity with optic disc edema on the right. (D) Normal left fundus.

Management

In about 40% of cases, resolution may spontaneously occur. Neuroimaging is indicated when a cranial neuropathy is present, particularly when the trauma is slight and would not normally be expected to cause a nerve palsy: tumors present in this way. Magnetic resonance imaging is probably more sensitive

in detecting subtle intraparenchymal lesions or hemorrhages. After 6 months we consider surgical management.

Disorders following concussion

A surprising number of patients will complain of trouble focusing their eyes following head trauma.[30] Other concussive symptoms include photophobia and convergence insufficiency.

Carotid–cavernous fistulas are rare in children but may occur following severe trauma[31] (Fig. 69.16).

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Child maltreatment, abusive head trauma, and the eye

Patrick Watts

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Introduction

Ophthalmologists working with children should have the knowledge and skills to identify abuse and neglect. They should be aware of local safeguarding policies to protect children and promote their welfare.[1,2] Child maltreatment covers both child abuse and neglect.[3]

Child maltreatment is defined as any act or series of acts of commission or omission by a parent or caregiver that results in harm, potential harm, or threat of harm to a child (Box 70.1).

Epidemiology

In the year 2012, it was estimated that there were 686,000 victims of child maltreatment in the US.[4] However, it is well recognized that child maltreatment is often missed and this figure may represent only a small part of the problem. Neglect in various forms is the most common type of child maltreatment, followed by physical abuse, sexual abuse, and emotional abuse.

Currently 1 in 80 children in the UK, less than 11 years old (1.3%) have experienced physical violence at the hands of a parent or guardian.[5]

Ophthalmological features are commonly associated with abusive head trauma, which represent 1.8% of physical abuse.[6] The incidence of abusive head trauma ranges from 14.2/100,000 to 33.8/100,000 infants in the UK and is commonest in infants less than 6 months of age.[7,8] Abusive head trauma accounts for the majority of fatal life-threatening injuries due to abuse in infants.[9]

Risk and protective factors for child maltreatment

A combination of individual, relational, community, and societal factors may contribute to the risk of child maltreatment. Although children are not responsible for the harm inflicted on them, certain characteristics are associated with an increased risk of abuse. Parents either acting alone or with another person account for 71% of abuse of children in their care. Though there is no single profile that fits all perpetrators, a number of common characteristics are reported in many studies (Box 70.2).

There is scientific evidence that protective factors for child maltreatment include a supportive family and supportive social networks.

Presentation of child abuse victims to the ophthalmologist

Children are most commonly referred from child protection teams to an ophthalmologist when abusive head trauma is suspected. However, if the initial presentation is to an ophthalmologist, who suspects maltreatment, he/she should be familiar with local child protection proceedings and refer to the child protection team.[10]

The presenting features alerting the professional to child maltreatment include the following:

1. Physical signs of unusual bruising in non-mobile infants for which there is no explanation (Fig. 70.1A–C). Bruising in pre-independently mobile infants is

very rare (<1%)[11] and bruising that is periocular in infants should be investigated when there is no innocent explanation. Other signs include bites, burns, scalds; ligature or strangulation marks and abrasions may accompany a story that does not seem a plausible explanation.

2. Anogenital injuries and sexually transmitted diseases in children point to sexual abuse.
3. Clinical presentations include an apparent life-threatening event (where the child presents floppy and apneic), seizures, ingestion of poisonous substances, epistaxis, near drowning, unusual or poor attendance at medical services, and poor school attendance due to ill health.
4. Unkempt child with infestations and/or tooth decay may signify neglect.
5. Behavioral signs include sexualized behavior, the "frozen watchfulness" of a withdrawn child, overt hostility or friendliness of the caregivers, and an aggressively acting child.

Box 70.1

Classification of child maltreatment

Child abuse classified as acts of commission (words or overt actions) include:

- Physical abuse
- Sexual abuse
- Psychological abuse
- Fabricated or induced illness

Child neglect classified as acts of omission include:

- Failure to provide: physical, emotional, educational, medical/dental neglect
- Failure to supervise: inadequate supervision, exposure to violent environments

Management

Clinical records

Completion of a standardized ophthalmology clinical record[12] supplemented with wide-field retinal photography (Retcam 130) improves documentation that will help when giving evidence in family or criminal court[13,14] (Fig. 70.2).

Studies have described a number of ways of describing the distribution, location, and types of retinal hemorrhages.

Box 70.2

Risk factors for child maltreatment

Perpetrator individual risk factors[3]

- Poor parenting skills, lack of understanding of child's needs and development
- Family or parental history of abuse
- Mental health problems, depression, and history of substance abuse
- Young age, low income, single parents
- Mother's male partner
- Maltreatment not considered abusive and justified

Children at risk

- Children less than 4 years
- Special needs children

Family risk factors

- Social isolation
- Family disorganization, dissolution, and domestic violence
- Parenting stress, poor parent–child relationships, and negative interactions

Community risk factors

- Community violence and concentrated neighborhood disadvantages (poverty, unemployment, residential instability)

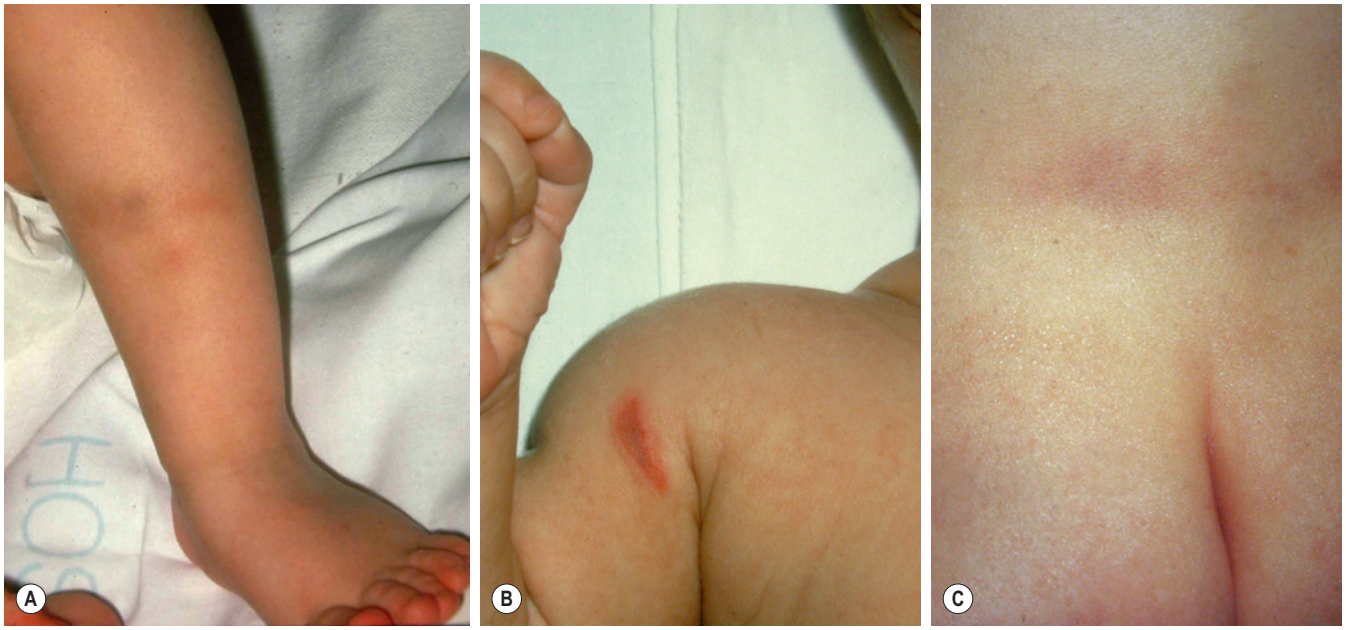
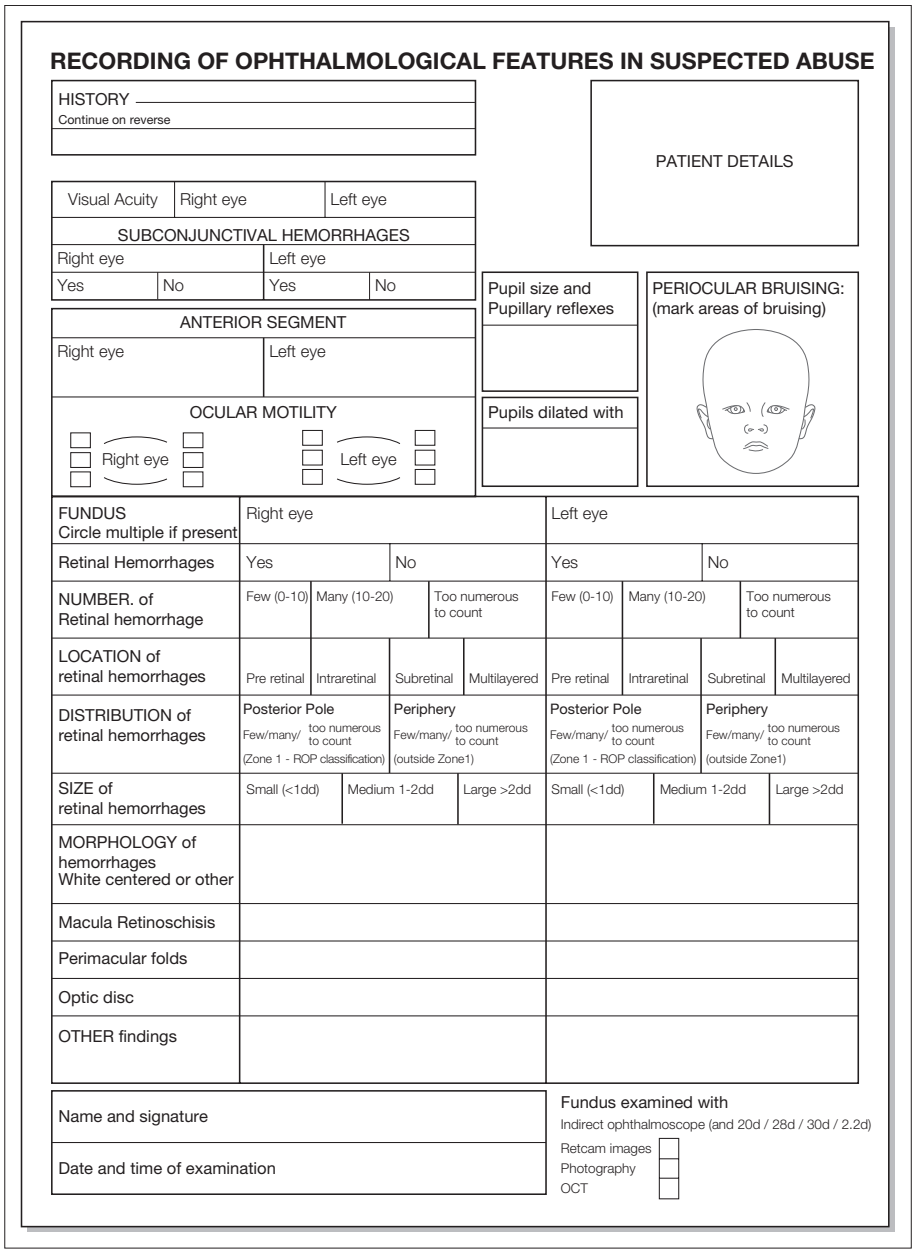


Fig. 70.1 Bruises on the left shin (A), right arm (B), and small of the back (C) in a non-independently mobile infant are suggestive of inflicted injury.



RECORDING OF OPHTHALMOLOGICAL FEATURES IN SUSPECTED ABUSE

HISTORY
Continue on reverse

PATIENT DETAILS

Visual Acuity	Right eye	Left eye

SUBCONJUNCTIVAL HEMORRHAGES

Right eye		Left eye	
Yes	No	Yes	No

Pupil size and Pupillary reflexes

PERIOCULAR BRUISING: (mark areas of bruising)

ANTERIOR SEGMENT

Right eye	Left eye

Pupils dilated with

OCULAR MOTILITY

Right eye Left eye

FUNDUS Circle multiple if present	Right eye				Left eye			
Retinal Hemorrhages	Yes		No		Yes		No	
NUMBER. of Retinal hemorrhage	Few (0-10)	Many (10-20)	Too numerous to count		Few (0-10)	Many (10-20)	Too numerous to count	
LOCATION of retinal hemorrhages	Pre retinal	Intraretinal	Subretinal	Multilayered	Pre retinal	Intraretinal	Subretinal	Multilayered
DISTRIBUTION of retinal hemorrhages	Posterior Pole Few/many/ too numerous to count (Zone 1 - ROP classification)		Periphery Few/many/ too numerous to count (outside Zone1)		Posterior Pole Few/many/ too numerous to count (Zone 1 - ROP classification)		Periphery Few/many/ too numerous to count (outside Zone1)	
SIZE of retinal hemorrhages	Small (<1dd)	Medium 1-2dd	Large >2dd		Small (<1dd)	Medium 1-2dd	Large >2dd	
MORPHOLOGY of hemorrhages White centered or other								
Macula Retinoschisis								
Perimacular folds								
Optic disc								
OTHER findings								

Name and signature
Date and time of examination

Fundus examined with
Indirect ophthalmoscope (and 20d / 28d / 30d / 2.2d)
Retcam images
Photography
OCT

Fig. 70.2 Ophthalmology clinical record in suspected abusive head injury.

Their use in routine clinical practice, however, has not been evaluated.[12,15–19] Recent systematic reviews of retinal hemorrhages in abusive injury identified the need for consistent and standardized description of retinal findings that would hold under scrutiny in medico-legal cases and help with future research in differentiating patterns of retinal hemorrhages from various causes.[20,21]

Fluorescein angiography to demonstrate retinal vascular non-perfusion[22] and optical coherence tomography elucidating vitreoretinal interface pathology[23–25] may help explain the mechanisms of retinal hemorrhages and help to elucidate whether the cystic lesions in the macula, are sub-hyaloid or intraretinal (retinoschisis).

Each entry in the clinical record should be labeled with the child's name, date of birth, clinician's name, designation, signature and date and time of examination. The clinical record should include a differential diagnosis list, which may suggest further investigations if considered appropriate by the lead child protection doctor. A standard list of investigations in suspected cases of abusive head injury has been suggested with a multidisciplinary assessment involving appropriate medical teams, social services, and the police[26] (Table 70.1).

A date for a follow-up examination should be clearly indicated on the clinical record.

History

When possible, a detailed history from the caregivers of the child is recorded. The ophthalmologist often relies on the history taken by other health care professionals, as the caregivers of the child may not be present when the child is examined. When they are present, the history of the presenting condition should be elicited and whether any prior eye disease (e.g. retinopathy of prematurity) or visual concern had been expressed about the child prior to presentation. A family history of eye disease or a bleeding disorder should be ruled out.

Table 70.1 Essential baseline investigations of an infant or young child with abusive head trauma[26]

1	Multi-agency assessment	Pediatrician with expertise in child protection Pediatric neurologist and neurosurgeon Neuroradiologist Ophthalmologist Social services and police
2	Clinical history	Complete pediatric history and documentation of all explanations of trauma
3	Social and police history	Any previous concerns, criminal records of caregivers
4	Examination	Thorough examination, documentation, photographs of injuries, monitor head circumference
5	Ophthalmology	Ophthalmologist to examine both eyes using an indirect ophthalmoscope through dilated pupils
6	Radiology	Initial magnetic resonance imaging of head repeated in 7–14 days Discuss with neuroradiologist Full skeletal survey – repeat between 10–14 days
7	Serology	Full blood count – repeated in 24–48 hours Coagulation screen, urea and electrolytes, liver function tests, and blood cultures

In abusive head trauma, the history may not be consistent in the timing and date of the events when taken by a number of health care professionals. The injury sustained may be incompatible with the explanation given.

Examination

It is good practice to examine the child within 24 hours of referral and as close as possible to the admission of the child to hospital.

- External eye examination should include descriptions, drawings, and photographs of any periocular injury or subconjunctival hemorrhages.
- If possible, the visual acuity and ocular motility should be recorded.
- The pupillary reactions, anterior chamber and lens position should be examined before the pupils are dilated. Poor pupillary responses are strongly associated with increased mortality and poor visual outcomes.[27]
- Examination of the retina should be with an indirect ophthalmoscope and a wide-field lens (28 or 30 diopter, or a 2.2 lens) following dilation of the pupils with short-acting mydriatics (phenylephrine 2.5% and tropicamide 1%). Pupillary dilation will affect neurological observations; this should occur after discussion with the admitting physicians. Descriptions of retinal hemorrhages should include their distribution, their location in terms of the retinal layers, their morphology, their number, and size.

Medico-legal issues[28]

The conduct of a case in court will depend on the operating legal framework but, universally, the underlying principal concern is the welfare of the child.

In the UK, a case may be considered subject to the following:

1. Care proceedings in a civil or family court: A verdict reached by the court is based on the "balance of probability."
2. Criminal court proceedings: A verdict is reached when it satisfies the statement of "beyond reasonable doubt."

Expert witness

When writing a report or giving evidence as a witness, the expert's duty is to the court and not to any side or to the lawyers who commissioned the report. Common threads of inquiry include the causes of positive findings, the differential diagnosis, the forces required to produce the injuries sustained, the mechanisms of injury, the timing of injury, and the contribution of confounding issues such as seizures, cardiopulmonary resuscitation, apparent life-threatening events, and coughing, which frequently co-exist in a child with traumatic brain injury. The report should take into account all material sent to the witness and should be well researched. A summary of publications addressing pertinent issues is often useful in providing a balanced view of the literature.[29–31]

The court will look for clarity in presentation and conclusions. The following issues are required by the court in any expert report[28]:

1. issues it has asked the expert to address;
2. the material the expert has considered;
3. the conclusions reached;
4. the reasons for reaching these conclusions.

Evaluation of child maltreatment literature

Ophthalmology literature frequently lacks strict definitions of abuse. This introduces circular reasoning where the certainty of the findings being truly due to abusive injury cannot be confirmed. Evaluation of the literature should be supported by the use of a ranking system of various levels of certainty of abuse based on criminal or family court proceedings, perpetrator confessions, multidisciplinary team assessments, and defined clinical criteria. The various levels of certainty of child abuse may be defined as definite, probable, or possible, or ranked 1 to 5, where rank 1 represent the highest level of certainty and 5 the least[32,33] (Table 70.2). This will not eliminate circularity, but makes it less likely if conclusions are based on studies that rely on cases that were "definite" or a high ranking (1 or 2) abuse.

Ophthalmic features of physical abuse

Direct injury

Reports from early literature suggest that direct injury to the eye and orbit may manifest with periocular swelling and bruising (Fig. 70.3), burns, lid lacerations, hyphema, cataracts, retinal dialysis, and retinal detachments.[34,35]

Indirect injury

Subconjunctival hemorrhages

Subconjunctival hemorrhages have been reported in abusive head trauma with or without intraocular injury and should

prompt a full child protection investigation and ophthalmology assessment in suspected cases of abuse[36] (Fig. 70.4).

Retinal hemorrhages

Retinal hemorrhages are highly suggestive of abusive head trauma (AHT), although they may be absent in confirmed cases of abusive injury. There is no pathognomic type (flame shaped, dome shaped, dot, blot, white centered), size, distribution, or location of retinal hemorrhages seen exclusively in abusive head injury[37] (Fig. 70.5A,B). Bilateral hemorrhages are reported in 74% of cases with a sensitivity of 75% and specificity of 94% for abusive head trauma.[38]

Retinal hemorrhages in the presence of head injury have a 71% positive predictive rate of abusive injury[39] (Fig. 70.6A–C).

Table 70.2 Ranking of abusive injury

Ranking	Criteria used to define abuse[33]
1	Abuse confirmed at case conference *or* civil *or* criminal court proceedings *or* admitted by perpetrator *or* independently witnessed
2	Abuse confirmed by stated criteria including multidisciplinary assessment (social services/law enforcement/medical)
3	Abuse defined by stated criteria
4	Abuse stated but no supporting detail given
5	Suspected abuse



Fig. 70.3 Periocular bruising in a child with direct abusive orbital injury.

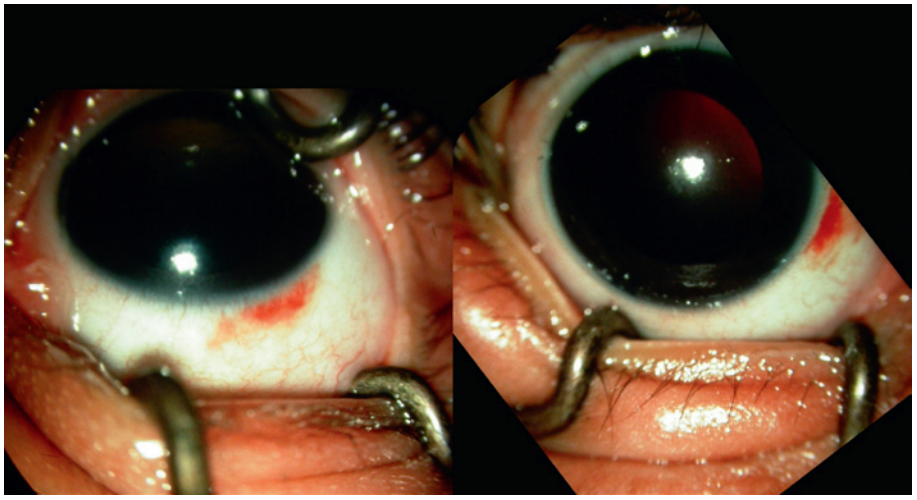


Fig. 70.4 Bilateral subconjunctival hemorrhage in an infant with abusive head injury.

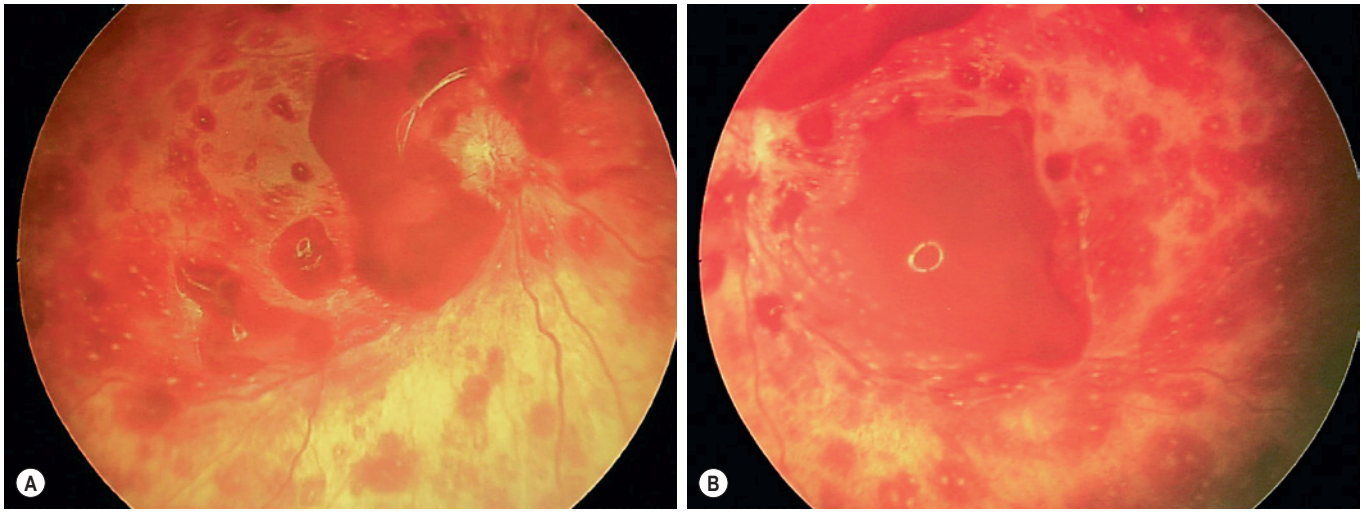


Fig. 70.5 Retinal hemorrhage. Bilateral ([A] right eye; [B] left eye) multilayered retinal hemorrhages in the posterior pole and periphery in a 3-month-old child with abusive head injury who presented with an apneic episode during feeding.

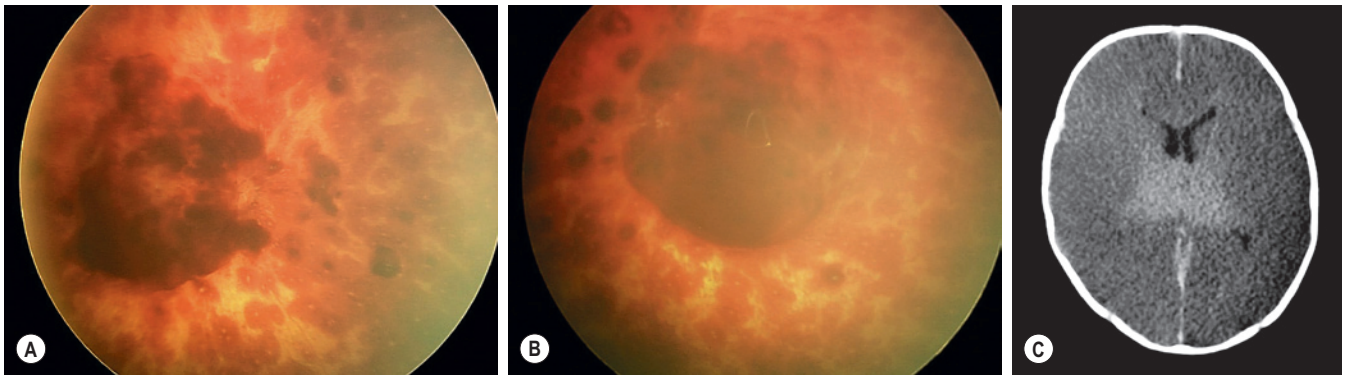


Fig. 70.6 Retinal hemorrhage. Extensive retinal hemorrhages in abusive head trauma in the right (A) and left (B) eye in a 2-month-old infant who was previously well presented with opisthotonus and seizures. The computed tomography scan (C) showed widespread edema, loss of gray–white matter differentiation, and interhemispheric blood. *(Courtesy of Dr A. Liu.)*

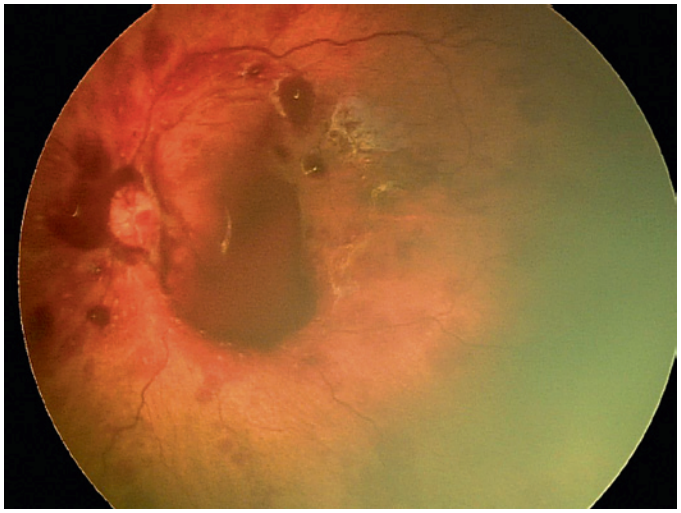


Fig. 70.7 Retinal hemorrhage. Unilateral dome-shaped retinal hemorrhages in the left eye of a 6-month-old infant who presented with an apparent life-threatening event.

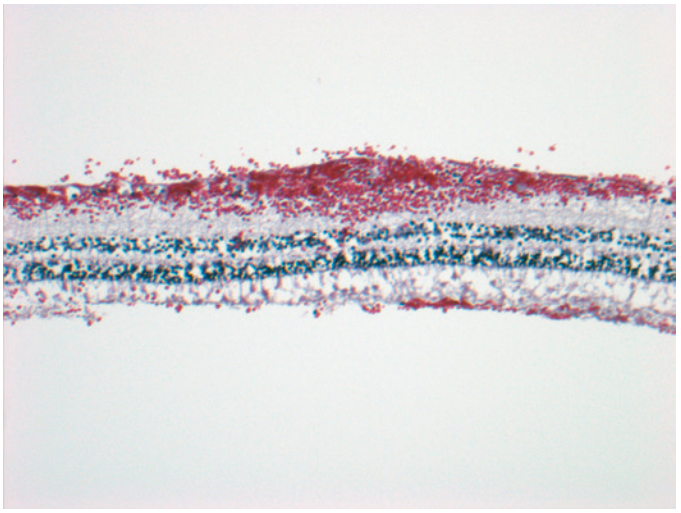


Fig. 70.8 Histology of the retina showing bleeding in multiple layers. *(Courtesy of Dr R. Bonsek.)*

The prevalence of retinal hemorrhages in abusive head injury varies between 77% and 83%.[27] Preretinal hemorrhages, dome-shaped hemorrhages situated in the posterior pole, are seen commonly in abusive head injury[37] (Fig. 70.7). Retinal hemorrhages in AHT may range from a few scattered hemorrhages to widespread hemorrhages extending from the posterior pole to the periphery and situated in multiple layers of the retina[40] (Fig. 70.8). Extensive retinal hemorrhages correlate with severe intracranial injury and poor visual outcome.[41] A recent systematic review reported that in the presence of head injury, retinal hemorrhages have a 91% probability of abusive etiology (odds ratio 14.7).[20]

Retinal folds

Perimacular folds are an important sign, seen in 6–8% of live cases (Fig. 70.9) and 23% of postmortem cases of inflicted injury[27,38,42] (Fig. 70.10). There have been isolated case reports of these in Terson syndrome in a child,[43] adult patients,[44] and accidental head injury in children.[45–48]

Retinoschisis

Cystic intraretinal cavities (Fig. 70.11A,B) in the macular area are recognized by vessels coursing over the surface or an electronegative ERG. Schisis cavities are seen in 14% to 23%

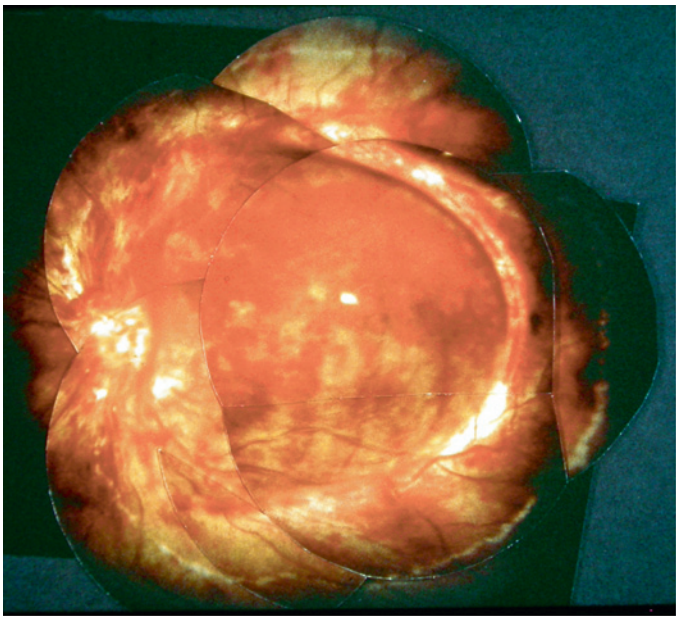


Fig. 70.9 Photomontage of a child with abusive head trauma showing a perimacular retinal fold with extensive retinal hemorrhages.

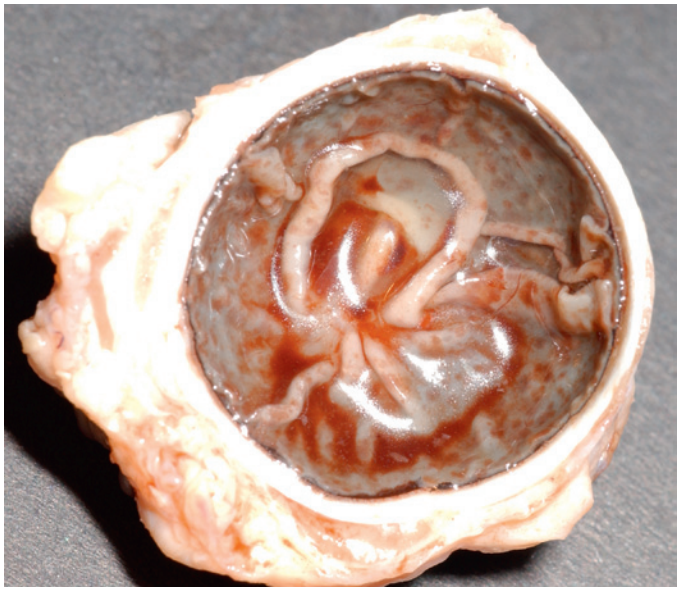


Fig. 70.10 Postmortem specimen showing numerous retinal hemorrhages and postmortem retinal folds.

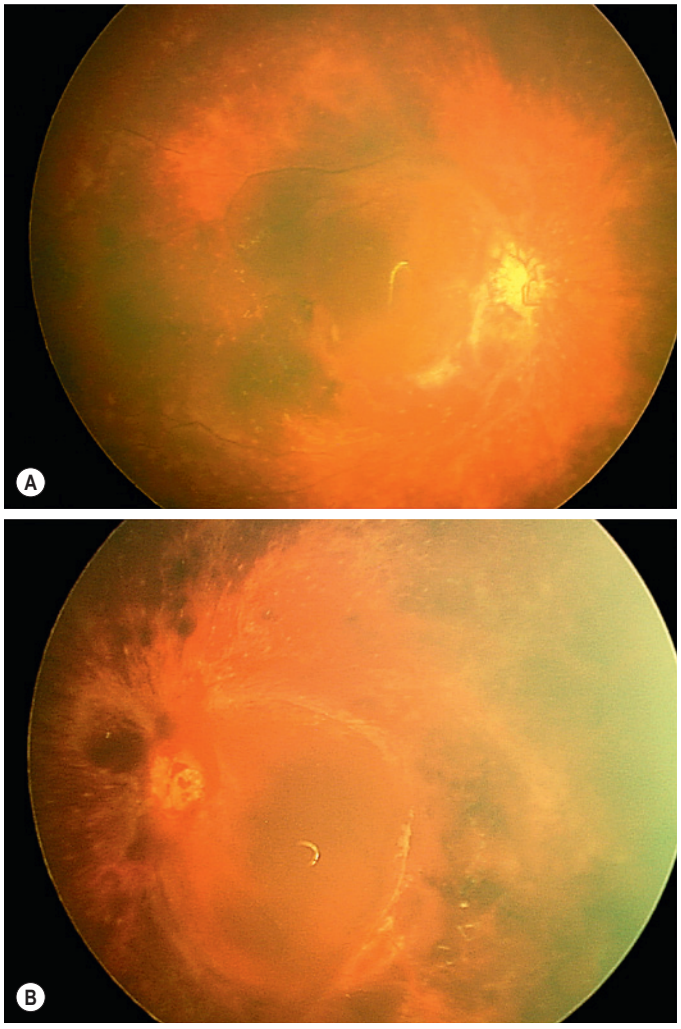


Fig. 70.11 Schisis cavities in the posterior pole in the right (A) and left (B) eye with extensive retinal hemorrhages.

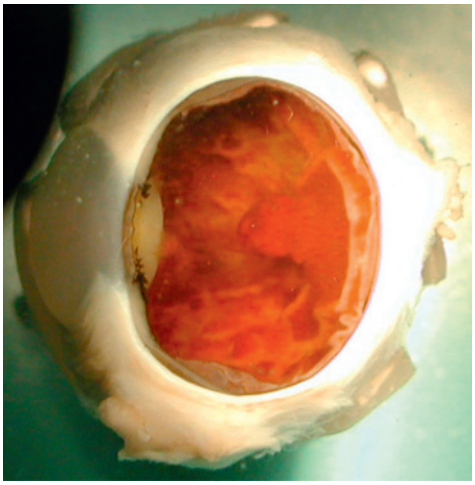


Fig. 70.12 Postmortem specimen of a child with abusive head injury demonstrating retinal blood extending into the vitreous and Cloquet's canal. *(Courtesy of Dr R. Bonsek.)*

of case studies involving live and postmortem findings. It has been previously stated that traumatic hemorrhagic macular schisis in not seen in any condition other than abusive head injury,[49] but recent case reports suggest similar cavities occur with severe trauma or crush injury.[47,48]

Vitreous hemorrhage

Hemorrhage in the vitreous cavity occurs in 14% of abusive head trauma cases and is seen more frequently in autopsy specimens.[27] It is believed to occur with breakthrough of the dome-shaped preretinal hemorrhages into the vitreous cavity (Fig. 70.12). Vitreous hemorrhages carry a poor prognosis for visual recovery, as they are frequently associated with cerebral visual impairment. Surgery to remove a non-clearing vitreous hemorrhage may be associated with minimal visual improvement.[50]

Optic disc edema

This is rare in clinical reports of children who have been abused, as the severity of the retinal hemorrhages frequently prevents a clear evaluation of the disc.[51] Optic disc swelling is seen histopathologically in many cases in postmortem studies.[52,53] Delayed papilledema in abusive head injury has been reported in a case that developed systemic hypertension and another case that developed communicating hydrocephalus weeks after the initial presentation.[54,55]

Orbital and optic nerve sheath hemorrhage

Hemorrhages have been demonstrated in the optic nerve sheath (Fig. 70.13), the orbital fat, the extraocular muscles, and motor nerve sheaths (Fig. 70.14). These findings have not been seen with non-abusive head trauma.[52,56]

Cranial nerve palsies

The development of acute third, fourth, and sixth cranial nerve palsies as a result of intracranial injury has been reported in abusive head injury.[27,57]

Ophthalmology outcome on follow-up of abusive head injury

1. Visual acuity: The prognosis for visual acuity at follow-up is poor for those with severe hemorrhagic retinopathy,



Fig. 70.13 Cross-section of optic nerve behind the globe showing intra-sheath hemorrhage.

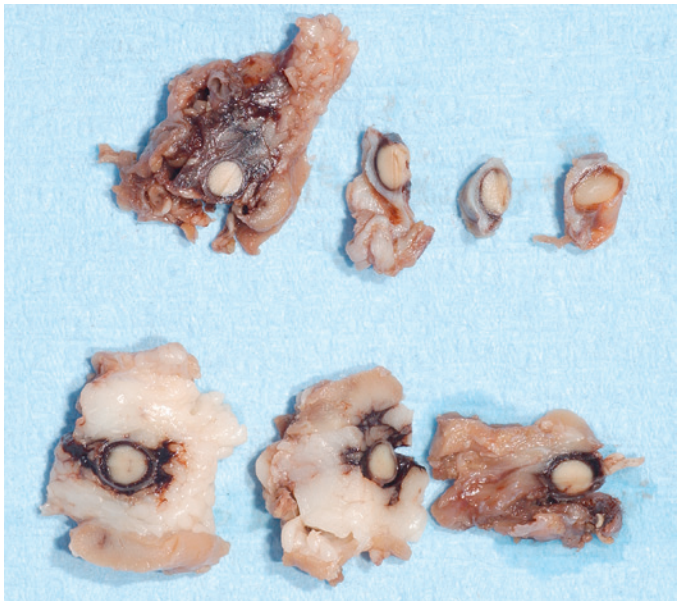


Fig. 70.14 Cross-section of the orbit from behind the globe showing optic nerve, orbital fat, and extraocular muscle hemorrhage.

vitreous hemorrhage, or poor pupillary responses. Fifty percent of children followed up have severe visual impairment due to retinal scarring, optic atrophy, or cerebral visual impairment.[27]

2. Ocular motility: This may be impaired due to: nystagmus, nerve palsies, or secondary strabismus due to visual loss.
3. Retina and optic nerve: Macular holes, epiretinal membranes, giant retinal tears, retinal detachment, optic atrophy, neovascularization of the disc, retinal scarring, and choroidal atrophy have been observed after the retinal hemorrhages have cleared[58–61] (Fig. 70.15).

Differential diagnosis of retinal hemorrhages

The ophthalmologist should be aware of the causes of retinal hemorrhages that may or may not have overlapping features

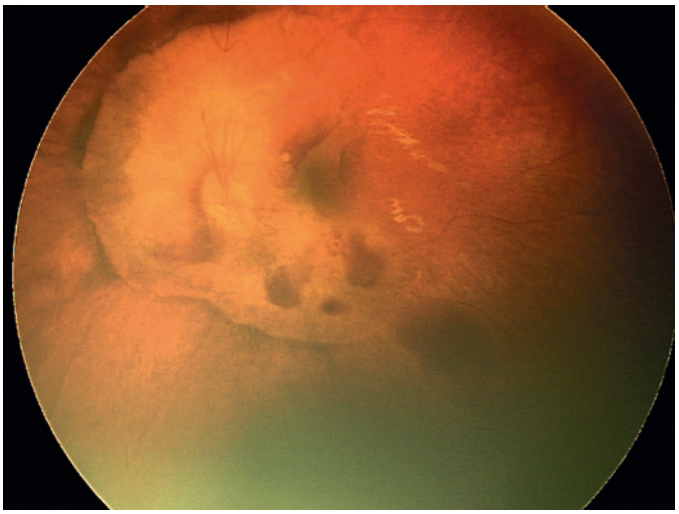


Fig. 70.15 Retinal folds and scarring with residual vitreous and retinal hemorrhage seen 3 months after absorption of extensive retinal and vitreous hemorrhage.



Fig. 70.16 Retinal hemorrhages. Seen with white centered hemorrhages in a full-term child born vaginally with the aid of vacuum extraction.

of abusive injury. In order to safeguard the child and prevent the wrongful conviction of innocent guardians of the child, it is vital to consider all relevant etiologies and eliminate them clinically or through the child protection team. This includes both clinical entities and disease states; confounding conditions seen at the time of evaluation of a sick child are frequently used by the defense team to explain the retinal findings.

Clinical entities or disease states

1. Birth-related hemorrhages:

A systematic review of retinal hemorrhages in the newborn reported retinal hemorrhages in 25% of spontaneous vaginal deliveries, 42% of vacuum-assisted deliveries, 52% of combined forceps and vacuum deliveries, and in 7.7% of cesarean sections.[62] The majority of retinal hemorrhages resolve within 10 days of birth leaving no sequelae[62–64] (Fig. 70.16). Macular retinal hemorrhages may persist for 4–5 weeks. Exceptionally, intraretinal hemorrhages can remain evident for 58 days.[64]

2. Accidental trauma:

This mechanism of injury includes motor vehicle accident, falls, and crush injuries. While no pattern of retinal hemorrhage consistently suggests accidental injury, the hemorrhages tend to be unilateral, few in number, and limited to the posterior pole.[65–71] Retinal hemorrhages are reported in 5% of accidental injuries which were mostly falls from heights less than 4 feet.[20] Associated findings of retinal folds and retinoschisis are rare in accidental injury. Retinal folds have only been reported in this context in single case reports of crush injury and a fall.[45–48]

3. Metabolic disorders[72–76]:
   - a. Galactosemia
   - b. Glutaric aciduria
   - c. Methylmalonic aciduria
4. Bony disorders[77,78]:
   - a. Osteogenesis imperfecta
   - b. Osteoporosis-pseudoglioma syndrome
5. Bleeding disorders:
   - a. Leukemia
   - b. Anemia
   - c. Thrombocytopenia
   - d. Protein C deficiency
   - e. Hemorrhagic disease of newborn
   - f. Platelet dysfunction in Hermansky–Pudlak syndrome
   - g. Low fibrinogen levels
6. Vascular disorders[43,55,79–81]:
   - a. Intracranial aneurysms with Terson syndrome
   - b. Fibromuscular dysplasia
   - c. Hypertension
   - d. Spinal cord arteriovenous malformations
7. Infections/infestations[82–84]:
   - a. Meningitis
   - b. Malaria
8. Carbon monoxide poisoning[85]
9. Asphyxia and strangulation[86,87].

Fifteen percent of critically ill children admitted to the intensive care unit have been reported to have retinal hemorrhages. However, the underlying causes were accidental injury, leukemia, and hemorrhagic disease of newborn, and not the fact that they were submitted to intensive care interventions.[88]

A recent systematic review reported a group of nine conditions that have overlapping features with abusive injury.[21] (Table 70.3).

Pre-existing eye disease

Retinal hemorrhages have been described in the vascularized retina of retinopathy of prematurity following cardiopulmonary resuscitation, and in a premature infant following a screening examination with a contact retina camera.[89,90] Hence, due consideration to pre-existing retinal disease should be given when evaluating infants with retinal hemorrhages.

Confounding conditions (Table 70.4)

Children who have sustained abusive head trauma frequently present either collapsed with apnea and requiring

Table 70.4 Retinal hemorrhages in confounding conditions of seizures and cardiopulmonary resuscitation (CPR)

	Retinal hemorrhage description			
Confounder	**Severity**	**Location**	**Layer**	**Laterality**
Seizures	Multiple	Posterior pole	Intraretinal Superficial flame shaped	Unilateral or bilateral
CPR	Multiple	–	Intraretinal small dot	Bilateral

Table 70.3 Retinal hemorrhages in conditions with clinical overlap for child abuse[21]

		Retinal hemorrhage description			
Condition	**Features of abuse**	**Severity**	**Location**	**Layer**	**Laterality**
Glutaric aciduria	ICH	Multiple	Posterior pole	Intraretinal (with unilateral vitreous right)	Bilateral and unilateral
Methylmalonic aciduria with homocysteinuria (cobalamin C deficiency)	ICH	Scattered	Posterior pole and post-equatorial	Intraretinal and vitreous hemorrhage	Bilateral
Osteogenesis imperfecta	ICH, bruise, fracture	Multiple	Posterior pole	Preretinal, intraretinal, vitreous hemorrhage	Bilateral and unilateral
Platelet function defect (Hermansky–Pudlak syndrome)	ICH	Few	Posterior pole	Subretinal, intraretinal and subhyaloid	Bilateral
Protein C deficiency	ICH, bruise	Florid and minor	N/A	Subretinal with vitreous hemorrhage	Bilateral and unilateral
Low fibrinogen levels	ICH, bruise	N/A	N/A	Intraretinal, subretinal	Bilateral
Hemorrhagic disease of the newborn	ICH, bruise	Multiple	N/A	Intraretinal, vitreous hemorrhage	Bilateral
Fibromuscular dysplasia	ICH	Extensive	Widespread	Intraretinal and subhyaloid	Bilateral
Spinal cord arteriovenous malformation	ICH	N/A	N/A	Intraretinal and preretinal	Bilateral

ICH, Intracranial hemorrhage; N/A, not available.

cardiopulmonary resuscitation, or with an encephalopathy or seizures. In addition, they may have acute coagulation abnormalities that resolve over a period of a few days. These following confounding events or conditions are often proposed in court as explanations for retinal hemorrhages, introducing uncertainty in the diagnosis of abusive head injury.[21]

Apparent life-threatening event (ALTE)

An ALTE is defined as a combination of apnea, color change, marked change in muscle tone, and choking or gagging, which is frightening to the observer. Children with abusive head trauma may present with ALTE; however, retinal hemorrhages have not been reported in ALTE in the absence of abusive injury.[91]

Prolonged coughing

Studies of prolonged coughing have not reported retinal hemorrhages.[92–94]

Seizures

Retinal hemorrhages are rarely reported with seizures. A number of studies revealed 2 of 218 cases with retinal hemorrhages, one case with tonic–clonic seizures for 5 minutes had unilateral hemorrhages around the disc, and the second case with hyponatremia had multiple bilateral hemorrhages at the posterior pole.[95–98]

Cardiopulmonary resuscitation (CPR)

A well-conducted prospective study of 43 pediatric cases (33 infants) who had received CPR found retinal hemorrhages were present in a 1-month-old infant who had received 60 minutes of open heart massage with co-existing coagulation defects. The hemorrhages were bilateral small multiple dot retinal hemorrhages.[99] Three other cases – a 6-week-old infant after 75 minutes of CPR had bilateral retinal hemorrhage; a 2-year-old after 40 minutes of CPR had a large unilateral hemorrhage next to the optic disc; and an 18-month-old infant with coagulation abnormalities and arterial hypertension – had a retinal hemorrhage. Hence, isolated prolonged CPR is rarely associated with retinal hemorrhages.

Use of extracorporeal membrane oxygenation (ECMO)

Retinal hemorrhages are rare in infants receiving ECMO. One study found a prevalence of 5%[100]; however, many of these children were premature and birth-related hemorrhages cannot be ruled out.[101,102]

Coagulopathy of abusive head trauma

Head injury is associated with acute coagulation abnormalities with prolonged prothrombin time, decreased platelets, and fibrinogen levels. These abnormalities are accentuated in children with parenchymal brain injury, where 54% have a prolonged prothrombin time. Of children who die with abusive head trauma with parenchymal brain injury, 94% display prolonged prothrombin time.[103] These abnormalities in coagulation seen in abusive head injury are not due to a preexisting hemorrhagic diathesis. The abnormalities are temporary, and do not explain retinal hemorrhages, which are also seen in children without coagulation abnormalities.[8]

Dating of retinal hemorrhages

Current evidence indicates that it is not possible to accurately date bruises in children.[104] Similarly, it is not possible from examination of the retina to estimate the duration of the retinal hemorrhages. There is some indirect evidence from birth-related retinal hemorrhages that most superficial retinal hemorrhages resolve in 10 days but that large macular hemorrhages may take up to 58 days to disappear.[62] In children with abusive head trauma, retinal hemorrhages took between 1 and 11 months to disappear.[105]

Systemic features of abusive head injury

Neurological

Brain injury may manifest acutely with symptoms and signs ranging from general malaise with drowsiness and lethargy to critically ill infants with impaired consciousness and death.[8] Head injury includes the presence of extra-axial blood (subdural, subarachnoid), intraparenchymal hemorrhage, diffuse axonal injury, hypoxic–ischemic injury, or any combination of the above (Fig. 70.17A–D). Although seizures and skull fractures are seen in abusive head injury, they are not discriminatory for abuse.[39] Neurological sequelae of parenchymal brain injury manifest later as cognitive and behavioral disturbances, cerebral palsy, seizures, and blindness, with a severe disability reported in 61% of children. Neuroradiological features suggestive of an abusive injury are: multiple complex wide fractures (diastatic), multiple-site subdural hematomas, inter-hemispheric blood, and loss of gray–white matter differentiation. The finding of blood around the spinal cord on magnetic resonance imaging (MRI) and postmortem (Fig. 70.18) in abusive trauma suggests that scanning of the spine should be included in the radiological investigations.

Fractures

Abusive injury should be suspected in children less than 3 years of age with multiple fractures. Abusive fractures involving the femur are more likely to be seen in non-ambulant children and fractures of the humerus involve the mid-shaft rather than the supracondylar region. Fractures that have the highest probability of abuse are posterior rib fractures.[106] Rib fractures are rare with cardiopulmonary resuscitation in children and are usually located anteriorly at the costochondral junction.[107]

Bites

A human bite is one of the only signs with which there is a possibility of identifying the perpetrator, both from the imprint of dental characteristics and the salivary DNA.[108] The hallmark of a human bite is the compression of tissue in two opposing concave arcs. The arcs are measured by the inter-canine distance, at about 3–4.5 cm in an adult and 2.5–3.0 cm in a child. An inter-canine distance of less than 2.5 cm suggests a child's deciduous teeth. Animal bites usually tear flesh, whereas human bites compress the flesh leaving an imprint.

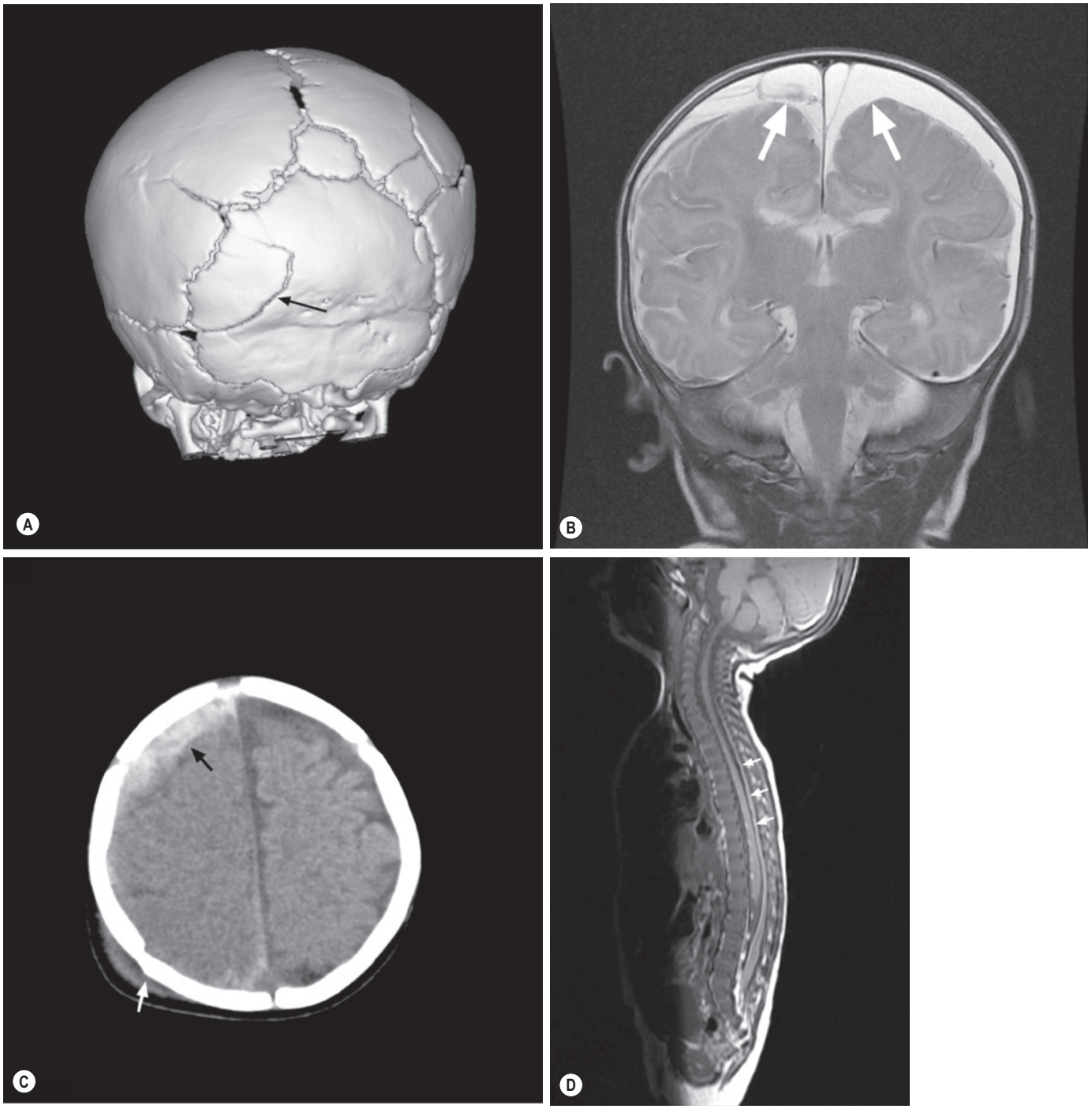


Fig. 70.17 Neuroradiological signs of abusive head trauma. (A) Left occipital fracture shown on 3D computed tomography scan reconstruction. (B) Bilateral subdural hemorrhage on magnetic resonance imaging (MRI) T2 scan (white arrows). (C) Subdural (black arrow) interhemispheric bleeding with scalp hematoma (white arrow). (D) MRI scan showing blood around the spinal cord. *(Courtesy of Dr A. Liu.)*

Burns and scalds

Burns and scalds are less common than other forms of physical abuse. Intentional scalds (immersion into hot water) are seen more frequently in abusive injuries. When intentional, they follow certain patterns of symmetry: on the extremities they have a clear upper margin and may have a glove- or stocking-like pattern; if involving the buttock, sparing of the perineal fold is seen.[33]

Unintentional cigarette burns are usually superficial, as contact with the lighted end, for example a child walking into a cigarette, initiates a prompt withdrawal response. Superficial burns should be observed over a period of 3 weeks, as they heal without a scar. Deep burns require a contact time of more than 2 seconds; they heal with a scar and are more likely to be intentional (Fig. 70.19).

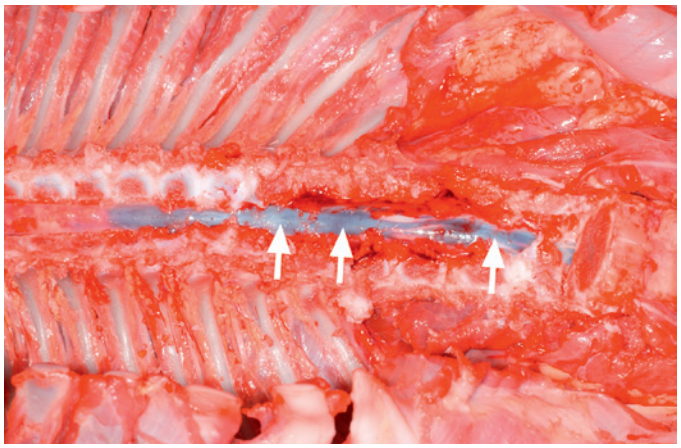


Fig. 70.18 Postmortem dissection of the spine of a child subjected to abusive head trauma. White arrows indicate subdural blood.



Fig. 70.19 Abusive cigarette burns on the left side of forehead.



Fig. 70.20 An abusive bruise on left cheek demonstrating the imprint of fingers.

Bruises

Bruising is the commonest presenting sign in abusive injury. Certain patterns of bruising help to distinguish abusive from accidental bruises: bruising in non-independently mobile infants; bruising away from bony prominences (e.g. face); large, multiple, occurring in clusters and bearing the imprint of an implement are highly suggestive of abusive injury[11] (Fig. 70.20).

Biomechanics of retinal hemorrhages

Theoretical considerations include:

1. vitreoretinal traction;
2. impaired retinal venous return from acute raised intracranial pressure;
3. hypoxic ischemia of retina.

Although controversies still exist as to whether a shaking injury alone or one with impact exceeds the threshold of force required to produce head injury, retinal hemorrhages are seen in both impact and non-impact head injuries.[109,110] Experiments with primates demonstrate that angular and rotational accelerations of the head rather than linear acceleration cause brain injury.[111,112] Until recently, the evidence for retinal injury was extrapolated from mechanisms underlying brain injury, which have been excellently reviewed in previous publications.[29,113] Current research does not provide conclusive evidence for the underlying mechanism of retinal hemorrhages in abusive injury.

Retinal hemorrhages are rare in neurologically normal children. Although they have been reported in children whose initial computerized tomography (CT) scans were normal, these children were not neurologically normal and were subsequently found to have abnormal MRI.[114,115] A single case report reported retinal hemorrhages with normal CT and MRI imaging; however, the patient had a gaze palsy and hemiparesis.[116]

Acute elevation of intracranial pressures from ruptured aneurysms has been shown to cause retinal hemorrhages in two infants.[43,117]

Experimental and naturally occurring animal models have failed to replicate the findings seen in abusive head trauma in infants.[118–120] Computer modeling using finite element analysis demonstrate that the majority of forces during simulated shaking cycles is exerted on the posterior retina or the vitreoretinal interface, suggesting that traction of the vitreous on the retina causes retinal hemorrhages.[121,122] In addition, clinical and postmortem studies and the use of optical coherence tomography have demonstrated vitreous attached to schitic cavities and folds in the retina, extrapolating this to vitreoretinal traction causing retinal hemorrhages.[123,124] Postmortem studies have suggested that retinal ischemia may explain the retinal findings in abusive head injury.[125] Although hypoxic–ischemic brain injury demonstrated on diffusion-weighted MRI (DW-MRI) in children with head trauma is associated with severe retinal hemorrhages, retinal

hemorrhages are also seen without hypoxic ischemia on DW-MRI in abusive head injury.[126]

Prevention

1. Primary prevention: Educational programs have been developed to address a broad segment of society, which should includes parents and other child carers. These programs include coping strategies to deal with inconsolable crying, known as the period of purple crying.[127]
2. Secondary prevention: This involves targeted programs for populations at higher risk of abusive injury, which include parents or carers from lower socioeconomic classes, young parents, or those with previous social services contact.
3. Tertiary prevention: this relates to programs directed at perpetrators to prevent recidivism.

The programs developed are educational and have been shown to reduce the prevalence of abuse in defined populations.[128]

Munchausen syndrome by proxy

This is an illness fabricated by the caregiver of the child for personal gain or attention. The perpetrator, who is frequently the mother, simulates or induces an illness in a child who is not capable or unwilling to identify the offender. The offender may fabricate the history; cause physical signs by exposing the child repeatedly to infectious agents, toxins, or physical trauma; or alter laboratory tests by tampering with the child's specimens. The following should alert the clinician to this possibility:

1. Over-attentive caregiver or caregiver does not seem to be as worried about the child as medical staff.
2. Investigations that do not tally with clinical signs.
3. Clinical signs that do not respond to treatment.
4. The child's condition improves when isolated from the caregiver and recurs in his/her presence.

Ophthalmic manifestations are rare, although case reports of recurrent conjunctivitis,[129] unilateral orbital cellulitis, and keratoconjunctivitis[129,130] induced by toxins have highlighted the difficulties in diagnosis (Fig. 70.21).

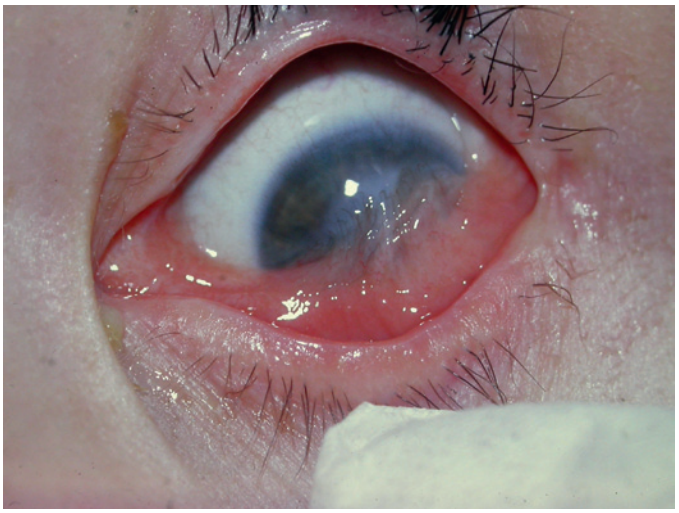


Fig. 70.21 Munchausen syndrome by proxy. Keratoconjunctivtis with vascularization and pseudopterygium of the inferior cornea seen in a child from repeated toxin instillation by her caregiver.

The ophthalmologist and child maltreatment

In summary:

- When confronted with suspected cases of child abuse or neglect, the ophthalmologist's overriding duty is to safeguard the child.
- An ophthalmologist should not intervene individually; all cases suspected of abuse should be discussed with a designated or named child protection physician/nurse.
- Knowledge of local child protection protocols and procedures is essential.
- The ophthalmic evaluation should never be considered in isolation but in conjunction with the findings of other specialties, fostering a close working relationship with multidisciplinary teams and child maltreatment experts.
- Meticulous documentation of evaluation, supplemented where possible with photography, in date and time order is paramount.
- Remember: there are no pathognomonic ocular signs of child abuse.
- As an expert witness, it is important to be well versed with all the documentation provided and with current literature. Do not be drawn by the counsel into giving opinions outside your area of expertise. Evidence is presented for the court and not to a particular side.

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Refractive surgery in children

Evelyn A Paysse

Chapter contents

INTRODUCTION
TYPES OF REFRACTIVE SURGERY USED IN CHILDREN
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Introduction

Excimer laser refractive surgery for high refractive error associated with amblyopia has been performed for almost two decades in children, with good visual acuity and refractive results and minimal complications.[1–26] Intraocular refractive procedures have been performed in smaller numbers in children for higher refractive errors for about a decade, also with good visual and refractive outcomes and few complications. Most recently, excimer laser refractive surgery has been performed for accommodative esotropia with reasonable results.

Conventional amblyopia therapy consists of the following:

1. clearing the ocular media of visual obstructions such as leukoma, cataract, or vitreous hemorrhage.
2. correcting significant refractive errors either with spectacles or contact lenses.
3. encouraging use of the amblyopic eye through occlusion or pharmacologic and/or optical penalization of the fellow eye (see Chapter 73).[27–29] This conventional therapy is successful in the majority of children with amblyopia.

There are, however, several subsets of children with amblyopia that often fail this standard therapy. These groups are:

1. children with severe isoametropia (bilateral high ametropia) who are spectacle non-compliant or intolerant;
2. children with severe anisometropia who are non-compliant or intolerant of spectacle and contact lens wear;
3. children with high ametropia, either anisometropia or isoametropia, who have other special circumstances such as craniofacial anomalies, ear deformities, or neck hypotonia that preclude the proper use of refractive correction.

There are many reasons for poor compliance with spectacles or contact lenses. Spectacles for the treatment of extreme myopia or hyperopia can cause prismatically induced optical aberrations, a narrow visual field, and social ostracism due to unattractive thick lenses. Group 1, above, consists primarily of children with neurobehavioral abnormalities and cognitive disability. They have severe tactile aversion and thus refuse to wear glasses or contact lenses in spite of being functionally blind without the refractive correction. Their visual impairment may impede their attention and social interaction, exacerbating significant behavioral and social problems, and further interfere with the development of normal communication skills. This group is mostly comprised of former premature infants with severe retinopathy of prematurity and high myopia, children with genetic mutations, or with autism spectrum disorder. In group 2, spectacle-induced aniseikonia and anisovergence impede stereopsis and binocular vision, and may cause asthenopia.[30]

Contact lenses, more than spectacles, improve the quality of vision, reduce the minification effect of high myopic spectacles, give better contrast sensitivity, and reduce social discomfort. Contact lenses, however, in children are often impractical due to difficulty with insertion, cost, intolerance, non-compliance, and frequent loss.

In the past, no other treatment options existed. The result was variable levels of visual impairment in the affected eye(s) depending on the severity of the refractive error. If the condition was bilateral, severe blur-induced amblyopia was the result. Refractive surgery, just as in adults, reduces refractive error in these children and thus reduces or eliminates these other related issues. Additionally, it greatly improves their quality of life.

A new mindset is needed when we think about the management of severe refractive error in children. Untreated high refractive error in young children can result in severe levels of blur-induced amblyopia akin to that found with a dense congenital cataract or leukoma. We should approach this form of amblyopia as aggressively as we would treatable

causes of form vision deprivation such as cataract. Surgery is effective in treating high refractive errors when standard therapy fails, with few complications.

Lastly, refractive surgery may prove to be a viable alternative in older children with accommodative esotropia if longer-term follow-up in children who have undergone refractive surgery for this indication demonstrates stability of ocular alignment. Some recent studies have shown refractive surgery to be effective though the sample sizes in the studies were small.[31–33]

Types of refractive surgery used in children

Corneal and intraocular procedures can reduce refractive error. Today corneal procedures are performed with the excimer laser and include photorefractive keratectomy (PRK), laser-assisted subepithelial keratectomy (LASEK) (these two procedures together will henceforth be referred to as advanced surface ablation [ASA]), and laser-assisted *in situ* keratomileusis (LASIK). ASA can be used to treat up to 10–12 diopters of myopia, 6 diopters of hyperopia, and 4 diopters of astigmatism. These numbers are typically reduced by about one-third for treatment using LASIK.

PRK and LASEK are surface ablations, with minor differences between them, that permanently change the shape of the cornea by ablating (via vaporization) tissue from the anterior corneal stroma, just under the corneal epithelium.

1. In PRK, the corneal epithelium is removed and Bowman's membrane and anterior corneal stroma are ablated with laser.
2. In LASEK, the epithelium is not removed, but an alcoholic solution is used to loosen the epithelial cells; the surgeon folds the epithelial layer out of the treatment field, performs the laser ablation on Bowman's membrane and anterior corneal stroma, and then replaces the epithelial layer.

In LASIK, a partial-thickness corneal flap, composed of epithelium, Bowman's membrane, and anterior stroma is created using either a mechanical microkeratome or a femtosecond laser microkeratome. A hinge is left at one end of this flap. The flap is folded back and the laser ablation is performed on the deeper corneal stroma. The LASIK flap is then positioned back in place over the treated corneal stroma. The flap is held in position after the procedure by natural adhesion. Current intraocular refractive procedures change the existing lens power and include phakic intraocular lenses (phIOLs), refractive lens exchange (RLE), and clear lens extraction (CLE). These procedures are used to treat higher refractive errors that fall outside the treatment parameters for the excimer laser, or in cases where the cornea is too thin for the excimer laser. Phakic IOL procedures can add or reduce lens power.[34] In these procedures, an intraocular lens (IOL) is placed into the anterior or posterior chamber, thus preserving the natural crystalline lens. Anterior or posterior chamber phIOLs can be used to treat extremely high myopia if the anterior chamber is deep enough to tolerate the lens (≥3.2 mm). It is rare that a highly hyperopic eye has a deep enough anterior chamber depth to be able to have a phakic IOL procedure. One significant advantage of phIOL over the other intraocular refractive procedures is the preservation of accommodation.

The other procedures that change lens power are refractive lens extraction (RLE) and clear lens extraction (CLE). They are technically identical to pediatric cataract surgery except the crystalline lens being removed is clear. In RLE, an appropriately powered IOL is placed in the eye after removing the crystalline lens; in CLE, the eye is left aphakic. Currently, both corneal and intraocular refractive procedures are utilized "off-label" in children and are not approved by the Federal Drug Administration (FDA) in the United States.

Safety of ASA versus LASIK

Box 71.1 outlines the risks of ASA and LASIK. While LASIK has been shown to be effective in children to correct refractive error, ASA has several advantages. First, no corneal flap is created, so there is no risk of flap loss, epithelial in-growth, or flap striae as with LASIK. In LASIK, the flap is held in position by natural suction; however, the flap never heals back to the posterior stroma completely and can be lifted years later. Second, since ASA is performed on the surface of the cornea, the remaining posterior stroma is thicker, with less risk of late keratectasia. Because most children who fail standard amblyopia therapy and are treated with excimer laser procedures require large excimer treatment doses, the depth of the corneal ablation is greater than in most adults. Keratectasia following ASA in adults in extremely rare and has never been reported in children. The main long-term risk of ASA is corneal haze, but, in the author's experience, it is uncommon and usually mild when it occurs. It is typically persistent when the topical steroid (fluorometholone or loteprednol) is discontinued too soon. Topical steroid must be used for 6 months following PRK to minimize the risk of this serious complication. Corneal haze can be further reduced by limiting ablation treatments to within the FDA-approved (in the USA) parameters and by the child ingesting vitamin C 250–500 mg daily for a year after the procedure Recently, the use of topical mitomycin has been reported to reduce the risk of corneal haze and regression in children.[35] The last issue with excimer laser procedures is refractive regression. Most of the regression following excimer refractive procedures occurs in the first year, but it can continue longer; it is more significant with higher excimer treatment doses.

Phakic intraocular lens safety

Phakic IOL implantation is not subject to refractive regression and may be the preferred surgical correction of pediatric

Box 71.1

Risks of ASA versus LASIK

ASA	*LASIK*
Dry eyes	Dry eyes
Mild to moderate discomfort for 3–4 days	Flap dislocation
Corneal haze	Flap loss
Long healing time	Epithelial ingrowth
	Keratectasia
	Posterior vitreous detachment
	Retinal detachment

ASA, Advanced surface ablation; LASIK, laser-assisted *in situ* keratomileusis.

myopia and hyperopia beyond the range of ASA.[36] Other major advantages are reversibility and the possibility for IOL exchange if needed with eye growth. The anterior chamber depth required for an "iris-enclaved" IOL precludes the use of this lens in some children. Children with high hyperopia, and those who have high lenticular myopia after retinopathy of prematurity may be unsuitable because of shallow chambers.[37] The major concern with a phIOL in a child is the long-term effect on the corneal endothelium. Experience indicates that thus far endothelial cell loss has been low[36,38,39] and no greater than after adult implantation; however, accurate endothelial cell counts are difficult to obtain in the children.[36] Any refractive surgical procedure, including ASA, LASIK, and RLE/CLE, will cause some reduction of endothelial cell density. We just need to know what the loss is in comparison to that in adults. Posterior chamber phIOLs have also been implanted in children[40–42]: Because they lie adjacent to the iris pigment and lens, the risks of pigment dispersion, secondary glaucoma, and cataract formation are the concern. These potential risks are important, but they must be weighed against the certainty of permanent blur-induced visual impairment if the child continues uncorrected. These potential complications, if they occur, will occur many years in the future, and there are effective treatments for them if they do.

Refractive lens exchange and clear lens extraction safety

RLE and CLE are useful in children who have severe refractive error that is beyond the range of effective ASA or who have anterior chambers that are too shallow for phIOLs.[43,44] An important disadvantage of removing the natural lens is that it abolishes accommodation. This can be rectified by implantation of a multifocal IOL, but multifocal IOLs have their own risks and complications. The major long-term risk of RLE/CLE are the same as for cataract extraction and include glaucoma, endophthalmitis, corneal decompensation, and retinal detachment (estimated prevalence of approximately 3%). If the axial length exceeds approximately 29 mm, prophylactic diode laser therapy may be considered, to reduce the risk of retinal detachment.[45,46] All of these risks must, again, be weighed against the certainty of severe blur-induced amblyopia in the affected eye(s) if the child is left uncorrected.

Strategy for pediatric refractive surgery

If standard therapy fails, children with hyperopic isoametropia or anisometropia of 3–6 diopters, or myopic isoametropia or anisometropia of 3–10 diopters, can be treated with ASA. Children with refractive errors beyond these ranges can be treated with a phIOL if the anterior chamber depth is ≥3.2 mm or with RLE/CLE if the anterior chamber depth is shallower than this. These procedures require general anesthesia in children.

Improvements in visual acuity and visual function

Is refractive surgery effective in children? Yes, with qualification. One must remember that the measure of effectiveness in children non-compliant with spectacles is uncorrected visual acuity (UCVA). Substantial gains in UCVA and best corrected visual acuity (BCVA) have been demonstrated using ASA, LASIK, phIOLs, or RLE/CLE in children. Impressive visual gains have been achieved in isoametropic children for both high hyperopia and high myopia[3–6,21,22,36,44,47] (Tables 71.1 and 71.2). More modest, but consistent, gains have been achieved in the amblyopic eyes of anisometropic children using ASA, LASIK, phIOLs, and RLE/CLE.[2,6,8,9,15,18,22,23,48–52] (Tables 71.1 and 71.3). Most reports on pediatric refractive surgery have used ASA to treat anisometropic amblyopia.[1–3,5–7,9,14,15,17,18,22,23,26,53–55] These series show an initial refractive correction of ±1.5 diopters from emmetropia in approximately 90% of treated eyes. The qualification for all pediatric refractive visual acuity results is that tolerances are wider than in adult refractive surgery. Seldom does one achieve the precision commonplace in adult refractive surgery where the treatment doses are much smaller as a rule. The goal in children is the prevention of high levels of refractive amblyopia. The gains in UCVA and BCVA range from mild to excellent (2–7 lines improvement), with only rare reported losses of acuity. Roughly, 50% of the children treated have improved binocular fusion and stereopsis after refractive surgery.[2,9,15,18,23]

Beyond the gains in acuity or binocularity, refractive surgery has positive effects on children's day-to-day visual function.[36,47] Enhanced visual awareness, attentiveness, and social interactions have been reported in approximately 80% of children treated for high isoametropia. When measured using Likert scale visual function questionnaires, before and after refractive surgery, scores for eye contact, tracking, observing and reacting, judging depth and distance, and reading improved by an average 73% in isoametropic children and 58% in anisometropic children.[36,56,57] Recently, improvements in development have been reported in two studies where children with cognitive disabilities and severe isoametropia underwent PRK. Using a battery of well-known standardized developmental tests, the developmental quotient, calculated as the mental age divided by the biological age ×100, was shown to significantly improve in many areas of development at 6 and 12 months after PRK.[47] These results were shown to persist 3 years after PRK.

Controversies in pediatric refractive surgery

Controversies exist regarding pediatric refractive surgery, even among its advocates. The main issues are the ideal age at which to perform refractive surgery and what procedure is optimal. Most experts recommend the procedure be performed early in the visual neuroplastic years when the possibility of reversal or even prevention of amblyopia is greatest. The disadvantages of doing the procedure at an early age, however, are similar to those with placing an IOL in a child. The eye is still growing and determination of the proper treatment dose can be difficult, as the refractive error will change with eye growth. In the majority of studies thus far, the refractive error treated was greater than 9 diopters of myopia or 4 diopters of hyperopia, so the risk of overtreatment is low. Another potential disadvantage is difficulty with centration of the excimer treatment as young children generally require the treatment to be performed using general anesthesia. Experience, however, has shown that centration is not problematic.[4–6,8,10,11,13,14,16,18–20,22–25,34]

Table 71.1 Refractive surgery for high bilateral hyperopia and hyperopic anisometropic amblyopia

Author(s)	Year	Procedure	No. of patients	Age range (years)	Disorder treated	Preoperative SE (D)[a]	Postoperative SE (D)[a]	Mean preoperative BCVA[a]	Mean UCVA[b]	Follow-up (Months)	Complications
Astle et al.[4]	2010	LASEK	47	0.8–17	Bilateral hyperopia and hyperopic anisometropia	3.42	0.59	NR	NR. States 41% improvement in BCVA	12	Two patients with mild ring-shaped haze and one with severe ring- shaped haze outside visual axis
Yin et al.[25]	2007	LASIK	42	6–14	Hyperopic anisometropia	6.41	0.60	20/100	NR (BCVA 20/40)	17	None
Utine et al.[51]	2008	LASIK	32	4–15	Hyperopic anisometropia	5.17	1.39	20/100	20/60	20	NR
Tychsen et al.[36]	2008	phIOL	2	NR	Bilateral hyperopia	10.5	1.0	NR for this patient, was part of larger group	NR for this patient, was part of larger group	9	None

[a]Mean unless range is given.
[b]These studies include patients treated for anisometropia in the same study.
BCVA, Best corrected visual acuity; D, diopters; LASEK, laser-assisted subepithelial keratectomy; LASIK, laser-assisted in situ; NR, not reported; PRK, photorefractive keratectomy; SE, spherical equivalent; UCVA, uncorrected visual acuity.

Table 71.2 Refractive surgery for high bilateral myopia

Author(s)	Year	Procedure	No. of patients	Age range (years)	Preoperative SE (D)[a]	Postoperative SE (D)[a]	Mean preoperative BCVA[a]	Mean postoperative UCVA[b]	Follow-up (months)	Behavior	Complications
Astle et al.[3,b]	2002	PRK	10	1–6	–10.7	–1.4	20/70	NR	12	Improved in 2/3 of patients	40% mild to moderate haze
Astle et al.[5,b]	2004	LASEK	11	1–17	–8	–1.2	20/80	NR	12	Improved in 50% to 83% of patients	22% mild haze
Astle et al.[6]	2006	LASEK	1	7	–7.5	–3.3	3/200	NR	12	Improved	None
Tychsen et al.[44]	2006	RLE/CLE	13	1–18	–19.1	0.8	20/76	20/38	54	Improved by questionnaire	One dislocated IOL and one posterior capsule opacity
Tychsen and Hoekel[22]	2006	LASEK	9	3–16	Range: –3.8 to –11.5	89% within 1 D of goal	20/133	20/60	17	Improved in 88% of patients	35% mild haze

[a]Mean unless range is given.
[b]These studies include patients treated for anisometropia in the same study.
BCVA, Best corrected visual acuity; D, diopters; IOL, intraocular lens; LASEK, laser-assisted subepithelial keratectomy; NR, not reported; PRK, photorefractive keratectomy; SE, spherical equivalent; UCVA, uncorrected visual acuity.

Table 71.3 Refractive surgery for high myopic anisometropia

Author(s)	Year	Procedure	Age range (years)	No. of patients	Preoperative SE (D)[a]	Postoperative SE (D)[a]	Preoperative BCVA[a]	Postoperative UCVA[b]	Mean follow-up (months)	Complications
Singh[54]	1995	PRK	10–15	6	−12.1	−2.9	20/82	20/44	1	Haze
Nano et al.[53]	1997	PRK	11–14	5	−8	−1.6	20/400	20/72	12	Mild haze
Alio et al.[1]	1998	PRK	5–7	6	−9.6	−2	20/114	20/35	24	Severe haze (1)
Rashad[20]	1999	LASIK	7–12	14	−7.9	−0.6	20/50	20/25	12	None
Agarwal et al.[55]	2000	LASIK	5–11	16	−14.9	−1.4	20/37	20/37	12	Free Flap
Nucci and Drack[26]	2001	PRK/LASIK	9–14	14	−8	−0.07	20/125	20/121	20	None
Nassaralla and Nassaralla[14]	2001	LASIK	8–15	9	−7.2	−0.2	NR	NR	12	None
Astle et al.[3,b]	2002	PRK	1–6	27	−10.7	−1.4	20/70	20/40	12	Mild haze
Autrata and Rehurek[9]	2004	PRK/LASEK	4–7	27	−8.3	−1.6	20/95	20/26	24	Mild haze (3)
Astle et al.[5,b]	2004	LASEK	1–17	13	−8	−1.2	20/80	20/50	12	Minimal haze
Phillips et al.[52]	2004	LASIK	8–19	17	−9.06	−3.74	20/25	20/20	18	None
Tychsen et al.[23]	2005	PRK/LASIK	4–16	35	−11.5	−3	20/87	20/47	29	Minimal haze (3)
Paysse et al.[17]	2006	PRK	2–11	11	−13.8	−3.6	20/316	20/126	31	Minimal haze
Yin et al.[25]	2007	LASIK	6–14	32	−10.1	−2.2	20/50	20/33	17	Minimal haze
Ali et al.[43]	2007	RLE/CLE	4–20	7	−16.7	NR	NR (UCVA 20/2550)	NR (UCVA 20/130	4	Posterior capsule fibrosis (1)
Pirouzian and Ip[39]	2010	phIOL	5–11	7	−14.28	−1.1	20/4000	NR (BCVA 20/40	35	None
Lesueur and Arne[41]	2002	phIOL	3–16	11	−12.7	NR (range −0.75 to +2.00)	NR (range CF to 20/63)	NR (BCVA 20/63)	21	None

[a]Mean unless range is given.
[b]These data include patients treated for bilateral high myopia and high myopia after penetrating keratoplasty in the same study.
BCVA, Best corrected visual acuity; CF, count fingers; D, diopters; LASEK, laser-assisted subepithelial keratectomy; LASIK, laser *in situ* keratomileusis; NR, not reported; PRK, photorefractive keratectomy; RLE/CLE, refractive lens exchange/clear lens extraction; SE, spherical equivalent; UCVA, uncorrected visual acuity.

Summary

Refractive surgery in children with high refractive error and amblyopia, unresponsive to standard therapy, appears to be safe and effective after nearly two decades of follow-up. Interventional case series and case-control studies of excimer laser refractive surgery, phIOLs, and RLE or CLE in children have reported few complications and demonstrated improved visual acuity, refractive error, and developmental quotient, with significant improvements in social functioning, coping skills, and verbal and nonverbal communication. While the majority of children with refractive error, either unilateral or bilateral, do well with contact lenses or spectacles, for the small subset that do not, refractive surgery is a useful treatment and a reasonable option to prevent a lifetime of severe visual impairment. Randomized clinical trials should be conducted to further validate efficacy.

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Binocular vision

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Introduction

Our two eyes view the world simultaneously from slightly different angles. The visual fields of the two eyes receive largely overlapping images on their two-dimensional retinal surfaces. The information contained in the separate and slightly dissimilar images arising in each eye is appreciated as a single image by the process of fusion, which blends sight from the two eyes to form a single percept. This process of normal binocular single vision depends on clear visual axes with reasonably good visual acuity in each eye, the ability of the visual cortical elements to appropriately combine the slightly dissimilar monocular inputs (*sensory fusion*), and the precise coordination of the two eyes for all directions of gazes, so that corresponding points on the two retinas are aligned (*motor fusion*). In addition to binocular single vision, our visual cortex has the ability to disambiguate the minute dissimilarities from the pair of two-dimensional retinal images and reconstruct the third dimension (*stereopsis*).

Normal development of binocular vision

Milestones in the normal maturation of binocular vision are achieved rapidly during infancy. By the time they are 2 months old, nearly all infants have orthotropic alignment, except for "very infrequent" misalignment.[1–3] While there is clear evidence that infants as young as 1 month are capable of motor fusion,[4,5] it is not until 2–4 months that consistent motor fusion responses are observed in nearly all infants.[5,6]

Sensory fusion has been assessed using a wide variety of test paradigms, from the clinical 4-prism diopter (PD) test to forced-choice preferential looking fusion-rivalry discrimination and visual evoked potentials to dynamic random dot correlograms. Overall, the results are consistent. Few normal infants demonstrate sensory fusion before they are 2 months old, whereas most 4-month-olds and older infants demonstrate sensory fusion (Fig. 72.1).[1,7–11]

Likewise, the onset of stereopsis has been investigated using a number of different paradigms, including forced-choice preferential looking with contour stereograms and random dot stereograms, and visual evoked potentials to dynamic random dot stereograms.[12] Again, despite the differences in stimuli and response measures used, there is general agreement across studies that the onset of stereopsis occurs at approximately 4 months (Fig. 72.2).[7,13,14] After the onset of stereopsis, the rate of stereoacuity maturation is rapid (Fig. 72.3)[13–15]; further slow improvement of stereoacuity continues for several years.[16–18]

Unlike visual acuity development, where preterm birth has been shown to have only a slight or no accelerating effect on the rate of maturation, binocular vision shows an intriguingly different pattern of results. For visual acuity, preterm infants typically achieve the same level of maturation as would be expected for their adjusted age, i.e. if the child was born 2 months preterm and is now 6 months old, we would expect to see visual acuity at the 4-month-old level. This finding suggests that, in an otherwise healthy infant, visual acuity is limited by a pre-programmed course of visual maturation that cannot be accelerated by precocious visual experience. On the other hand, recent research suggests that it is postnatal age that determines when binocular vision matures, with both preterm and term infants developing binocular vision around 4 months after birth (Fig. 72.4).[19] Thus, infants appear to acquire binocular vision as a result of visual experience, not solely due to pre-programmed visual maturation.

Testing binocular vision in infants and children

Measurement of fusion and stereoacuity in the clinic can provide important information about the status of the visual system that contributes to management decisions. Stereoacuity

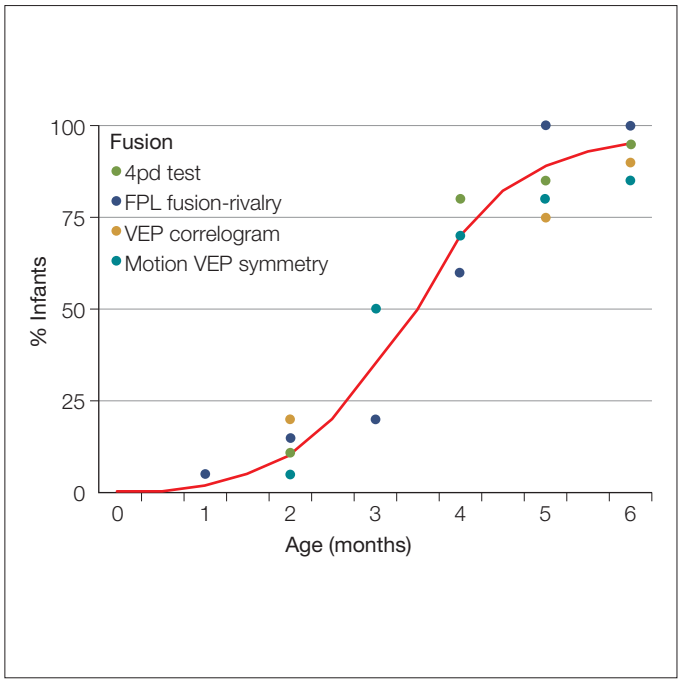


Fig. 72.1 Percentage of infants demonstrating fusion on clinical (4-PD base out) and laboratory-based tests, including forced-choice preferential looking (FPL) and visual evoked potentials (VEP).[1,7–11]

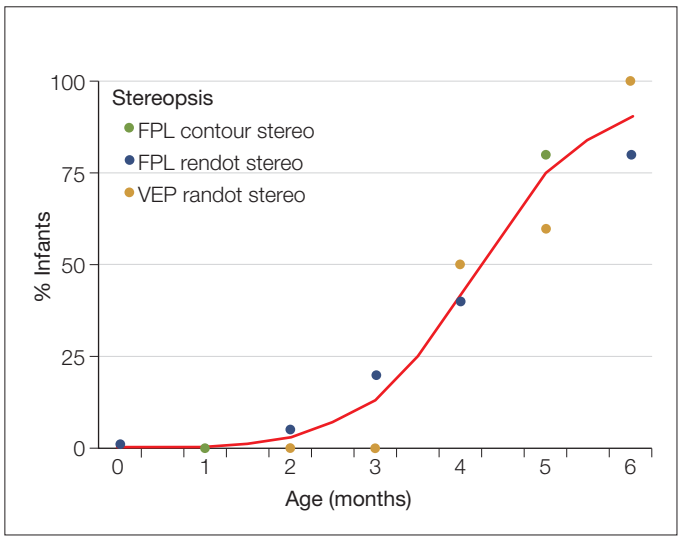


Fig. 72.2 Percentage of infants who demonstrate stereopsis when tested with forced-choice preferential looking (FPL) or visual evoked potentials (VEP) using contour or random dot stereograms with ≤3600 arcsecs disparity.[7,13,14]

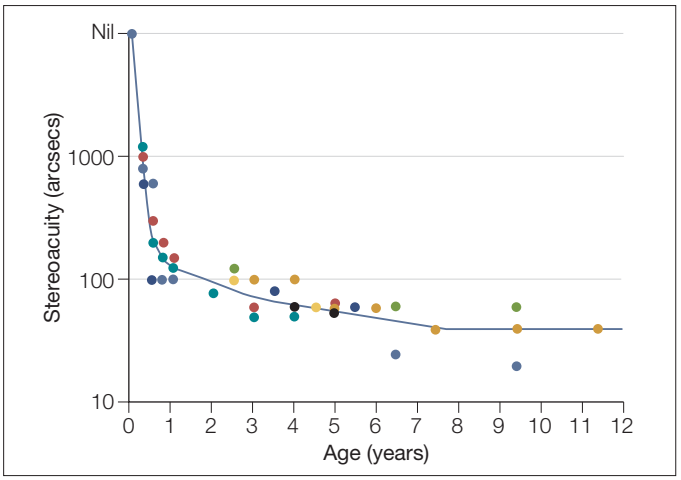


Fig. 72.3 Stereoacuity as a function of age for infants and children with normally developing vision.[13–15]

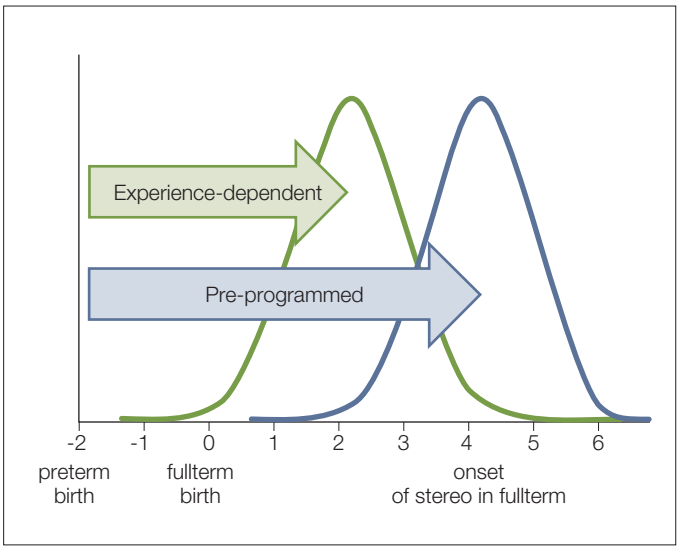


Fig. 72.4 Binocular vision is absent at birth and seems to switch on when a baby is about 4 months old. Jandó et al.[19] monitored the activity of the visual cortex region of the brains of babies who were born at term (9 months post-conception) and babies who were born 2 months prematurely to determine when they first displayed a binocularly evoked response. Binocular vision developed at 4 months after birth in both cohorts. This suggests that 4 months of postnatal visual experience is a key determinant of the onset of binocular vision (green curve). This is in contrast to the alternative scenario of a pre-programmed onset age that is guided by genetically encoded molecular and neuronal signals. In this case, additional visual experience should not alter the rate of maturation, and binocular onset would be expected to occur 6 months postnatally in the premature babies (blue curve).

depends on good vision in both eyes, accurate and stable alignment of the visual axes, and intact binocular cortical mechanisms. Abnormal binocular experience early in life associated with anisometropia or strabismus may result in maldevelopment of binocular vision, suppression, and reduced or no stereoacuity. Moreover, there is evidence to suggest that abnormal experience that is prolonged (>3 months duration) during the first years of life is likely to lead to permanent deficits in binocular visual function.[20–22]

The most widely used test of sensory fusion in the pediatric age range is the Worth 4-dot test. The child views four lights arranged in a diamond formation, with a red light at the top, two green lights at either side, and a white light at the bottom, while wearing anaglyphic glasses. If the child has normal binocular vision, they see all four lights, but if they suppress one eye, they will see only two or three lights. Diplopic children report five lights. There is also a version of this test that uses shapes rather than dots, called the Worth 4-shape test, designed for use with young children who have difficulty with color-naming and counting.[23] Before starting any assessment of sensory fusion, the angle of deviation should be neutralized with prisms. Note that, even with the use of prisms, absence

of sensory fusion may not reflect the potential outcome following surgical alignment. Use of a haploscopic device, such as the synoptophore, can correct for horizontal, vertical, and cyclorotational deviations simultaneously to direct stimuli onto each fovea and allow a truer assessment of the potential for sensory fusion.

Another limitation of the Worth 4-dot test is that the anaglyphic glasses could be dissociative. Because they are potentially an impediment to binocular vision, demonstrating fusion on the Worth 4-dot test can be interpreted as strong evidence that fusion is present but a test failure may be inconclusive. The Worth 4-dot test may also be used to estimate the size of a suppression scotoma by presenting the flashlight targets at different distances from the child. The size of the scotoma can be calculated in visual angle (degrees) using simple trigonometry (Table 72.1). The degree of fusion may also be classified as peripheral, macular, or foveal, based on the size of the scotoma (see Table 72.1). The 4-PD base out test is commonly used to detect small suppressions scotomas associated with monofixation syndrome or presence/absence of bifoveal fixation.

Motor fusion is the ability to maintain alignment of the eyes through a range of movements and consists of tonic (smooth movement when tracking an object) and phasic (quick changes in fixation from one object to another) components. The stimulus for motor fusion is peripheral retinal disparity outside Panum's area and the motor response is vergence. While the presence of motor and sensory fusion are linked, the amplitude of motor fusion is not related to the amount of sensory fusion.[24] Assessment in young children primarily consists of identifying the ability to maintain motor fusion in the presence of a 20- or 15-diopter base out prism (prism reflex test). While this does not quantify the fusional ability, it may identify a lack of motor fusion, or confirm the presence of binocular vision in a young child with suspected strabismus. In older children, quantification of motor fusion (prism fusion range) can be accomplished by measurement of a *break point*, at which vergence demand exceeds fusional reserve and a deviation becomes manifest, and a *recovery point*, where motor fusion can be recovered as vergence demand is lessened. In practice, the child is asked to observe a target at a fixed distance (typically ⅓ and 6 m) through a prism of increasing strength, while attempting to maintain a single image. The phasic range is assessed using a prism bar, with discrete intervals between prisms, and tonic is assessed using either a Risley rotary prism or the synoptophore, both of which allow a continuous increase in the prism strength. There is variation in the reported normative values, likely attributable to a precision of test distance, differences in target size, prism placement, and speed of prism change. Total fusion range (convergence and divergence combined) is normally about 25 diopters for phasic and 20 diopters for tonic measurements.[25]

Table 72.1 Estimating the extent of the suppression scotoma with the Worth-4 flashlight*

Viewing distance	Scotoma size (degrees)	Fusion quality
16 cm	12	Peripheral fusion
33 cm	6	
50 cm	4	
1 m	2	Macular fusion
1.5 m	1.3	
2 m	1.0	Foveal fusion
2.5 m	0.8	
3 m	0.7	

*On the face of the standard Worth 4-dot flashlight are spaced equidistant targets on a 35 mm diameter circle.

Two types of stereoacuity tests are widely available, contour tests and random-dot tests. Contour tests have the disadvantage of providing cues that enable some children with no stereoacuity to pass the initial 2–4 levels on the basis of monocular or nonstereoscopic binocular cues. Random-dot tests contain no monocular or non-stereoscopic binocular cues; depth can only be appreciated by global binocular evaluation of corresponding points and disparate points. Most stereoacuity tests are conducted at a near viewing distance, usually at 40 cm. Because stereoacuity is sensitive to blur, especially anisometropic blur, it is important to optically correct the child. It is always best to perform stereoacuity testing early in the examination, before the child's eyes are dissociated for other testing. For infants and preverbal children, preferential looking can be used with the Preschool Assessment of Stereopsis with a Smile (PASS) Stereotest. For children age 3 years and older, stereoacuity can be tested with the matching, pointing, or naming tasks available in the PASS, Randot Preschool, Toegepast Natuurwetenschappelijk Onderzoek (TNO), and Frisby Stereoacuity tests. Normative data for the infant and pediatric stereoacuity tests have been published (Table 72.2).[15–18] Despite the difficulties associated with interpretation of performance on the Titmus Fly, Titmus Animals, and the first 4 levels of the Titmus circles and Randot circles, results from these stereoacuity tests are commonly reported as outcome measures in pediatric ophthalmology. Passing the Titmus Fly test without stereopsis may be possible because the child knows it is a fly and expects the wings to be elevated, because the child has been repeatedly exposed to the same test with only two possible responses, or because the child alternates fixation and observes image jump in disparate portions of the test.

One limitation of currently available random dot stereoacuity tests for children is the maximum disparity available, e.g. 800 arcsecs for the Randot Preschool Stereoacuity Test and 440 arcsecs for the PASS. Thus, it is possible that some children who appear to have no stereoacuity are simply not within the measurable range of disparities available. A second factor that may limit performance on current random dot stereoacuity tests is dot size; most random dot tests require visual acuity of 0.4 LogMAR or better, in order to be able to appreciate the dot texture sufficiently to extract disparity information. In addition, the clinical tests consist of relatively small images that are static; there is some evidence to suggest that larger, dynamic stimuli provide additional information that may allow children who appear to have no stereoacuity on standardized tests to appreciate depth.[26,27]

There are also distance stereoacuity tests available, including the FD2, which has moveable real depth targets, and the Distance Randot; normative data are available for both of these tests (see Table 72.2).[28,29] Children and adults with normal

Table 72.2 Normative values for the most commonly used pediatric stereoacuity tests

Age (years)	Near stereoacuity								Distance stereoacuity			
	Pass[15,18]		Frisby[16]		RPST[17]		TNO[16]		Distance randot[28]		FD2[29]	
	Norm	Lower limit	Norm	Lower limit	Norm	Lower limit	Norm	Lower limit	Norm	Lower limit	Norm	Lower limit
0.5–0.9	300	480										
1	250	480										
2	80	240										
3	60	480			100	400			200	400	30	60
4	60	480			100	200						
5	60	480	25		60	200			100	200		
6			25	75	60	100	60	120			50	60
7					40	60						
8			20						60	100		
9			20	85	40	60	60	120				
10												
11					40	60			60	100		
12												

binocular vision generally have poorer stereoacuity at distance than at near. In addition, many electronic visual acuity test systems have implemented optional distance stereoacuity tests with liquid-crystal display (LCD) shutter glasses, polarized filter glasses, or anaglyphic filter glasses; few have been formally evaluated and most lack normative data. Distance stereoacuity may be especially useful for detecting deterioration of control of intermittent exotropia.[30–32]

Strabismus and stereopsis

Near the time of onset of esotropia, children with infantile esotropia show a capacity for stereopsis; deficits become apparent only after the onset of stereopsis, suggesting that they result from prolonged abnormal binocular experience.[33] This hypothesis is consistent with data from animal models in which there is an experience-independent initial phase of sensory development, followed by a period of susceptibility to abnormal experience that peaks just after the onset of stereopsis.[34] There is substantial evidence that early surgical correction improves binocular sensory outcomes for infantile esotropia, probably because the duration of constant esotropia is minimized.[20–22] Surgical alignment after the age of 24 months results in only 12% of children achieving any stereo vision[35,36]; whereas 75% of children aligned before 6 months of age achieve stereopsis (Table 72.3).[21,22,37–40] A few case series have reported excellent stereoacuity outcomes in a few infants who were surgically corrected by 6 months of age.[40–42] However, these case series may have inadvertently included some infants who had the potential for their esotropia to resolve spontaneously. When the Congenital Esotropia Observational Study (CEOS)-defined clinical profile[43] is used to identify a cohort of infants for whom spontaneous resolution was very unlikely (<2%), stereoacuity outcome data from six longitudinal studies of esotropia finds that more than 80% who were surgically aligned by 6 months achieved stereopsis but only 4% achieved normal stereoacuity (see Table 72.3).[21,22,37–40] Thus, the potential for preservation or rehabilitation of stereopsis via early surgery for infantile esotropia is good but the likelihood of achieving fine stereoacuity is almost nil.

Table 72.3 Summary of stereoacuity outcomes from six longitudinal studies using the CEOS definition of infantile esotropia[21,22,37–40] to evaluate outcomes only among children for whom spontaneous resolution was very unlikely (<2%)

Age at alignment	Stereoacuity outcome (months)		
	Nil	100–3000 arcsecs	≤60 arcsecs
≤6 months	24%	75%	<1%
7–12 months	64%	35%	<1%
13–18 months	61%	38%	<1%

CEOS, Congenital Esotropia Observational Study.

Children with late-onset accommodative esotropia might be expected to have good stereoacuity outcomes once their eyes are aligned, because the onset of esotropia occurs well after the infantile period of rapid stereoacuity maturation. However, even when children with accommodative esotropia are tested very early, while the esotropia is intermittent, more than 40% have reduced or no abnormal stereoacuity.[20] This finding suggests that stereodeficits may be primary in some children

with accommodative esotropia. In this subset of children, there may be a genetic factor or the stereodeficit may be due to other factors that were present prior to the onset of esotropia, such as hyperopic anisometropia (frequently associated with accommodative esotropia).[44] For some children, moderate hyperopic refractive error may need to occur in conjunction with abnormal stereoacuity to precipitate the onset of accommodative esotropia; most children with ≥+4.00 D never develop accommodative esotropia. The remaining 50–60% of children with accommodative esotropia initially present with normal stereoacuity, and prompt treatment to restore alignment is associated with excellent stereoacuity outcomes.[20]

Intermittent exotropia is usually associated with normal stereoacuity at near. However, distance stereoacuity, measured at ≥3 m viewing distance, may be normal or abnormal. The frequency with which intermittent exotropia deteriorates to constant exotropia is unclear, with some reports suggesting a high frequency and others describing long-term stability. Distance stereoacuity can be used to assess the severity of intermittent exotropia and to monitor for deterioration of control.[30,31] Moreover, deterioration in distance stereoacuity has been suggested as an indicator for surgery prior to the onset of constant exotropia and as an outcome measure to assess the success of surgery.[30–32,45] Improvements in distance stereoacuity have been reported using both the Distance Randot and FD2 stereoacuity tests in patients who had surgery for intermittent exotropia.[32,45]

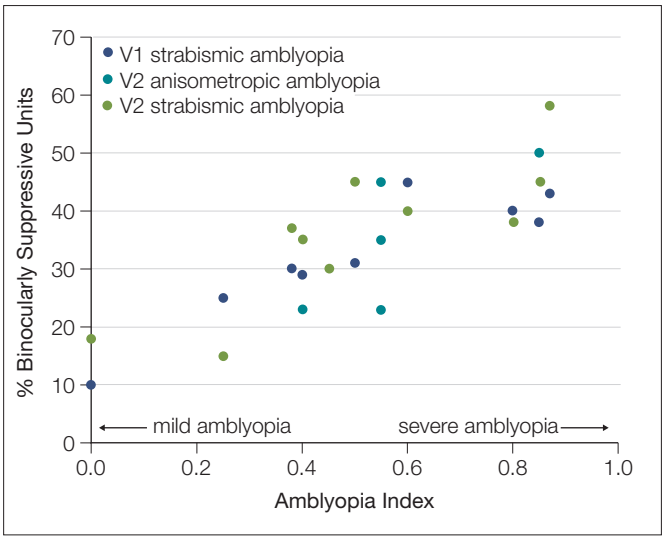


Fig. 72.5 Relationship between the proportion of binocularly suppressive neurons in two visual cortical areas and the depth of amblyopia in primate models of strabismic[46] and anisometropic[47] amblyopia. The amblyopia index is a similar but more comprehensive index of spatial vision deficits than the interocular acuity difference; it is calculated by integrating the area between the contrast sensitivity functions for the amblyopic and fellow eyes and dividing it by the area for the amblyopic eye. This index ranges from 0.0 (no measureable spatial vision deficit) to 1.0 (no measurable spatial vision in the amblyopic eye).

Binocular vision and amblyopia

When the input from the two eyes is significantly different in visual direction (strabismus) or focus (anisometropia), sensory fusion is impossible and the visual cortex relies on interocular suppression to block the discordant input from one eye. Amblyopia is a manifestation of this binocular barrier to normal development of the central visual pathways. Research on primate models of both strabismic and anisometropic amblyopia have shown a clear relationship between the severity of amblyopia and the percentage of binocularly suppressive neurons in the visual cortical areas V1 and V2 (Fig. 72.5).[46,47] Similarly, there is correlation between the severity of interocular suppression and amblyopic eye visual acuity deficit in amblyopic children and adults.[48–51]

Viewing amblyopia in the context of interocular suppression has important implications for treatment. Monocular treatment with patching cannot be expected to fully rehabilitate the child with amblyopia because the primary binocular dysfunction persists. In fact, most children treated for amblyopia have improvements in visual acuity with various monocular treatment modalities alone or in combination, but 15–50% fail to achieve normal visual acuity even after extended periods of treatment. Even among the children who do achieve normal visual acuity with amblyopia treatment, the risk for recurrence of amblyopia is high. In a series of prospective, longitudinal studies of infantile and accommodative esotropia conducted at one site,[20,22,38,39,44] 80% of esotropic children were treated for amblyopia at least once during the first 5 years of life and 60% had recurrent amblyopia that required re-treatment. The Pediatric Eye Disease Investigator Group (PEDIG) reported that 25% of successfully treated amblyopic children experience a recurrence within the first year of treatment.[52]

Patching treatment for amblyopia has only a modest benefit for stereoacuity. Two recent large clinical trial reports by the Monitored Occlusion Treatment of Amblyopia Study (MOTAS) and PEDIG groups[53,54] found that 37–66% of amblyopic children had no stereoacuity at baseline and after treatment 24–44% still had no stereoacuity. Only 28% had improved stereoacuity after amblyopia treatment in each study. We do not know exactly how patching works to improve visual acuity in amblyopia but, given how little effect it has on binocular vision outcomes, it likely affects only monocular mechanisms and has little or no effect on interocular suppression.

Current scientific consensus is that amblyopic individuals have a structurally intact binocular visual system that is rendered functionally monocular by interocular suppression, i.e. the two eyes are not working together. This has been demonstrated by using dichoptic presentation with reduced fellow eye contrast to allow the amblyopic eye to "break through" and participate in binocular vision.[55] The reduced fellow eye contrast approach has also provided a basis for crafting a new approach to amblyopia treatment. Repeated binocular visual experience with reduced fellow eye contrast (for example, in the context of an anaglyphic game on an iPod or iPad platform) allows the two eyes to work together. As amblyopic eye visual acuity and binocular vision improves, the interocular contrast difference can be gradually decreased day by day, with the goal that binocular vision will be functional even when contrast is equal in the two eyes. To date, results from short-term treatment (4 weeks) of 90 children have been reported in the literature; these were summarized in a recent review.[56] The children enrolled had all been treated with spectacles prior to enrollment, had moderate or severe amblyopia, and most had prior treatment with patching and had residual amblyopia following standard therapy. All of the children were aligned within 8 PD of orthotropia with surgery

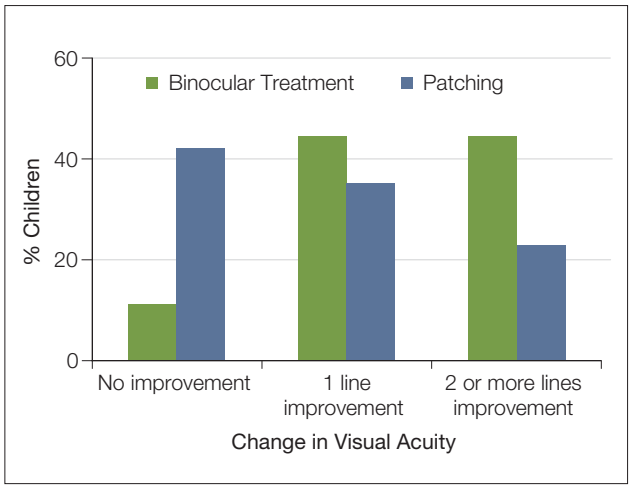


Fig. 72.6 Combined visual acuity outcome data from 90 amblyopic children across a number of binocular treatment studies (adapted from Hess and Thompson 2015[56]) and from children in the 2 hour/day patching arm of several Pediatric Eye Disease Investigator Group (PEDIG) randomized clinical trials.[57–61] All studies in the figure included children aged 3–17 years with moderate or severe amblyopia, who wore spectacles for approximately 12 weeks prior to treatment with binocular games or patching, and included a significant number of children who had residual amblyopia after prolonged treatment with standard therapies. Children were treated for 2–6 weeks in the various studies.

and/or spectacle prescription prior to beginning the binocular treatment. Overall, the mean improvement for children aged 3–17 years was 1.6 lines in 4 weeks; 44% improved ≥0.2 LogMAR (≥2 lines) and only 11% failed to improve (Fig. 72.6). Similar cohorts of children treated with 2 hours/day patching drawn from PEDIG randomized clinical trials[57–61] (aged 3 to 17 years, prior treatment with spectacles, moderate or severe amblyopia, and some with prior patching and/or residual amblyopia at entry; 4–10 weeks treatment) did not fare as well. Only 23% improved ≥0.2 LogMAR and 42% failed to improve with treatment (see Fig. 72.6). A recent study has reported a similar benefit obtained from watching dichoptic feature films with reduced fellow eye contrast.[62] Thus, active game play may not be a required component of the treatment; contrast-balanced visual experience may be sufficient. No adverse effects (e.g. diplopia) have been reported using a contrast-balanced binocular treatment approach in either the game or feature film format.

Why do we care about binocular vision?

Impaired binocular vision can result in debilitating symptoms, such as headaches, eye strain, and diplopia, impacting on quality of life, with lifelong consequences related to a child's future occupation choices. Symptoms can arise from reduced or absent motor fusion, resulting in asthenopia, diplopia, or absent stereoacuity.[63] In addition, sensory fusion and binocular summation are impaired in the presence of strabismus[64] and, if binocular inhibition develops, there is a significant impact on quality of life,[65] but improvements in binocular summation and quality of life are reported following surgical alignment of strabismus.[66]

It may seem only a minor inconvenience that a child with no stereoacuity cannot appreciate the vivid depth experience of a three-dimensional (3D) feature film, but this experience highlights how binocular deficits change the child's ability to perceive space. As the use of 3D technology is becoming more widely incorporated into homes and educational environments, a lack of binocular vision increases in significance. Visualization of structures can aid understanding, highlighted by the implementation of 3D technology in the classroom in subjects such as astronomy and biology; not being able to access these resources has the potential to impact on educational progress. From a social perspective, not being able to engage with the immersive, interactive 3D virtual worlds that children enter via games, children with abnormal binocular vision are not able to interact with their peers in this context.

Deficits resulting from a lack of binocular vision are not restricted to the accessibility of 3D technologies. Binocular vision disorders can impact on many aspects of motor functions, with studies demonstrating deficits in a range of fine motor skill tasks, resulting in decreased speed and/or reduced accuracy. People with stereoacuity are better at threading beads,[67] catching balls,[68] and completing a battery of timed manual dexterity tasks (sorting, drawing, placing pegs, etc.) than people with no measurable stereoacuity.[67,69] The reasons for the increased time or greater errors have been examined by assessing the kinematics of movement under binocular and monocular conditions. Figure 72.7 summarizes key elements of the movement that are affected in simple reaching and grasping tasks, with changes in the hand aperture, velocity of approach to the target, and errors in grasping.[70–74]

In addition to the errors in fine motor skill tasks, gross motor skills can be affected. Evidence shows an impact on gait, where reduced stereoacuity is associated with slower speed[75] and a more hesitant penultimate step and higher toe clearance when walking among obstacles, suggesting a more careful strategy for obstacle avoidance.[76] Additionally, there is evidence to suggest that monocular cues are potentially sufficient to localize ground level but stereoacuity is necessary to localize heights of steps and obstacles above ground level.[77] Later in life, there is evidence to demonstrate that reduced stereoacuity is risk factor for recurrent falls among the elderly.[78,79]

Overall, the best (quickest/most accurate) motor responses in all modalities are associated with high-grade stereoacuity, but those with reduced stereoacuity consistently perform better than those with no stereoacuity. While the precise relationship between binocular vision and functional ability is unclear, there are data to suggest it is not a linear pattern, where the presence of reduced stereoacuity has a slight impact but the absence of stereoacuity has a much larger impact.[80]

The consequences of abnormal binocular vision have also been reported by patients (and proxies) through quality of life questionnaires. The introduction of questionnaires designed specifically for strabismus, amblyopia, and diplopia address both functional and psychosocial impact, allowing analysis of these factors and the impact of treatment. There is now a significant body of evidence demonstrating improvements in patients following strabismus surgery. Most of the questionnaires are not designed specifically for children, and therefore address activities they will not or cannot do. However, there is consistent evidence in the literature for improvement in quality of life following treatment for disorders that disrupt binocular vision in adults.

Potential benefits of having binocular vision extend beyond those measured in motor task assessments and quality of life

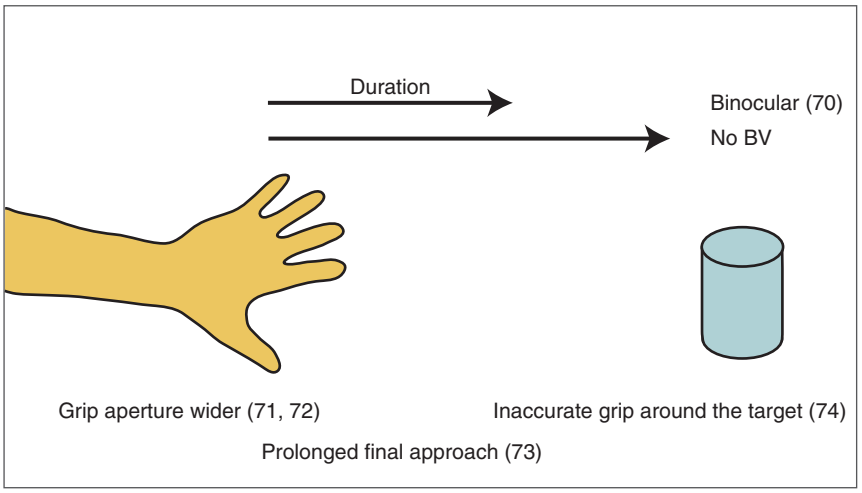


Fig. 72.7 Schematic of the deficits in reaching and grasping tasks in subjects without binocular vision (BV).[70–74]

questionnaires. Long-term management of strabismus often requires multiple surgeries, but the presence of stereoacuity is associated with more stable long-term eye alignment and fewer surgeries. Among children with infantile esotropia, those who had no stereoacuity after the initial surgical alignment procedure were 3.6 times more likely to require additional surgery later in childhood.[37] Similarly, children with accommodative esotropia whose alignment was corrected to within 4 diopters of orthotropia with the initial spectacle prescription but no stereoacuity, were 17 times more likely to decompensate and require surgery to restore alignment than those with stereovision.[37] Because there is a lower risk for recurrent and consecutive deviations, good eye alignment related to stereopsis is also associated with improved long-term quality of life, including self-image, employment opportunities, and success in school and sports.[81] Stereopsis is also associated with reduced risk for and severity of amblyopia, and amblyopic eye visual acuity is known to be an important determinant of quality of life.[82]

Conclusion

Given the wide-ranging impact that disorders of binocular vision can have, the restoration of high stereoacuity should be a primary goal of treatment. Early diagnosis and prompt surgery are imperative for maximizing stereoacuity outcomes. Even the attainment of reduced stereoacuity is associated with significant benefits, including long-term stability of alignment, better fine motor skills, and improved long-term quality of life. Management of other aspects of binocular vision in the treatment of pediatric eye disorders is less well understood. Most reports in the literature focus on optical management of associated refractive errors or surgical management of strabismus. Thus, one significant gap in our evidence base is the management of children with poor control of alignment (e.g. intermittent exotropia) or weak motor fusion (e.g. convergence insufficiency). These children are often treated with exercises designed to strengthen motor and sensory fusion to alleviate symptoms, but little evidence exists to evaluate their efficacy. Another key development to enhance management of pediatric binocular disorders will be the development of new tests that accurately identify and quantitatively evaluate each aspect of binocular vision.

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Amblyopia: basics, questions, and practical management

Michael X Repka

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Amblyopia is the most common cause of visual impairment in children; it often persists into adulthood. The prevalence in childhood is estimated to be 1–4%, depending on the population studied.[1,2] It is considered to be the leading cause of monocular vision loss of people between the ages of 20 and 70 years.[3] The prevalence of visual loss from amblyopia was 2.9% in one study of adults, indicating the need for improved detection and treatment.[4] Amblyopia is defined as a "decrease of visual acuity caused by pattern vision deprivation or abnormal binocular interaction for which no causes can be detected by the physical examination of the eye and which, in appropriate cases, is reversible by therapeutic measures."[5] Amblyopia may be unilateral or, less often, bilateral. Most cases are associated with eye misalignment, usually esotropia in infancy or early childhood, anisometropia, or a combination of strabismus and anisometropia (Table 73.1).

Visual loss in amblyopia varies from mild to severe. About 25% of cases have visual acuity worse than 6/30 and about 75% 6/30 or better.[6–9] The extent of the deficit may not be equivalent, but vary by cause. Strabismic amblyopia may represent a more severe physiologic deficit than isolated anisometropic amblyopia, and combined strabismic and anisometropic amblyopia is a more serious deficit still.[10]

Methods of detection

The gold standard for detection is measurement of visual acuity using a crowded or linear letter optotype test. Single optotype presentation and picture optotypes are less sensitive and should be used only when a child is unable to perform a test using surrounded or line optotypes. Tests based on the four letters "H," "O," "T," and "V" in a box or with contour surround bars are the basis of several popular test strategies.[11,12] A defined protocol for testing children with single-surround HOTV has been developed by the Pediatric Eye Disease Investigator Group (PEDIG).[12] The strategy includes a second chance at threshold determination and a portion designed to get the child back on track with some larger above-threshold stimuli. It has good testability, test–retest reliability, and has been automated.[13] The Amblyopia Treatment Study HOTV (ATS-HOTV) protocol slightly overestimated visual acuity relative to the electronic Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity protocol (0.68 lines for amblyopic eyes; 0.25 lines for fellow eyes).[14]

For children unable to perform with letter optotypes, clinicians have commonly used picture optotypes. However, standard picture optotypes overestimate the visual acuity of amblyopic eyes and are not recommended for screening or diagnosis of amblyopia. Dr Lea Hyvärinen designed four picture-like optotypes[15] to have similarities between optotypes and have contours like the Landolt C making them more difficult to successfully recognize. The objects (apple, circle, house, square) chosen are common in Western children's experience and eliminate cultural biases in that population. In one study, the single-surrounded Lea tests systematically overestimated acuity by 1.9 lines compared to the crowded Landolt C in normal eyes.[16] A comparison of the Lea symbols to line optotypes in amblyopic eyes has not been thoroughly studied.

Fixation preference testing may be used for children unable to perform any optotype-based testing. For strabismic children, the clinician compares the ability to hold fixation with each eye. The child may alternate, be unable to hold fixation after a blink, or be unable to hold fixation. For a patient with no misalignment, perform the test by placing a 10-diopter prism base down before one eye, having the child fixate a detailed target at distance or near, and assessing fixation preference. If there is a fixation preference for the eye without the prism, switch the prism to the fellow eye and again assess

Table 73.1 Association of amblyopia with strabismus, anisometropia, or both combined

	Woodruff et al.[6]	Shaw et al.[98]	PEDIG[99]
Number of cases	961	1531	2635
Strabismus as the cause	57%	45%	31%
Anisometropia as the cause	17%	17%	41%
Combined strabismus and anisometropia	27%	35%	28%

Precise percentages vary depending on how amblyopia is defined.

fixation preference. The prism might cause the other eye to be preferred. If the same eye is preferred under each testing condition, then the fellow eye is assumed to have amblyopia. A patient who fixates with the eye without the prism is alternating. Comparing fixation preference testing to optotype testing has shown fixation preference testing is unreliable as a means of diagnosing amblyopia, generally leading to an overdiagnosis of amblyopia. Optotype testing confirmed only 17 of 52 patients (33%) diagnosed with amblyopia by fixation preference testing.[17] In another study, 53 children had two or more lines of difference in visual acuity, yet 45 were graded as normal by fixation preference.[18] Amblyopia therapy is typically prescribed for a strong fixation preference, as discussed in the sections on treatment.

On occasion, visual acuity testing consists of noting whether the child can centrally hold fixation, has steady eye movements, and is able to maintain fixation on a target. This is noted as CSM (central, steady, maintained) when present. The clinician uses this scale to compare the two eyes.

Forced choice preferential looking using Teller acuity cards has been used as an alternative method for infants and non-verbal children.[19] This test is time consuming and requires an experienced tester to assure reliable results. Unfortunately, this test systematically underestimates amblyopia, reducing its clinical utility as a means of screening or detecting a successful treatment endpoint.

Methods of treatment

There are few data comparing the outcomes of amblyopia treatment to the natural history. Clinicians have noted improvement of acuity when children complied with therapy, but found little improvement when no therapy was actually completed. Simons and Preslan reported that among a case series of amblyopic patients who were not treated, there was no improvement in visual acuity.[20] However, demonstration of improvement in acuity of the amblyopic eye in a study without concurrent untreated or natural history controls is not sufficient to prove a benefit of therapy. This deficiency led to a recommendation in the United Kingdom to stop screening for amblyopia as well as treating it because of a lack of a proven benefit.[21]

Recent prospective studies have shown value in terms of visual acuity improvement. Two hours of daily patching modestly improves amblyopia in children 3–7 years of age compared to no patching, which is sustained.[22,23] Another study (Amblyopia Treatment Trial, UK) randomized a group of non-strabismic children with anisometropia to no treatment, treatment with glasses, or treatment with glasses and occlusion. This study found about one line of visual acuity improvement at outcome comparing glasses and occlusion treatment with no treatment.[24] Some limitations were present; not every child had amblyopia. In addition, the control group's visual acuity at baseline and at final measurement was without correction, whereas the treatment group was measured with best spectacle correction.

Refractive correction

The initial intervention for amblyopia of any type is to prescribe necessary refractive correction. The diagnosis is not made until refractive correction is prescribed, the glasses obtained, and the visual acuity deficit confirmed with the correction. The practice of prescribing spectacles for amblyopia varies with severity and age of the child, but most guidelines suggest correction of an anisometropia greater than 0.50 D and astigmatism of 1.50 D when amblyopia is suspected. Hypermetropia should be fully corrected in younger strabismic patients and corrected with the plus sphere reduced by up to 1.50 D in orthotropic patients. Myopic errors should be fully corrected during office testing with trial frames to confirm the diagnosis, although prescribed minus sphere may be cut in some cases, especially with younger children.

When should additional therapy such as occlusion be started? Some clinicians prescribe such therapy immediately, some wait a pre-specified time, others wait until improvement with spectacles alone ceases. Moseley et al. found that 8 of 12 patients prescribed spectacles for the first time improved three or more lines in the amblyopic eye.[25] PEDIG reported that amblyopia improved in previously untreated anisometropic patients (n=84) with optical correction by at least two lines in 77% of the patients and resolved in 27%.[26] Improvement took up to 30 weeks. A subsequent study (n=146) of the impact of refractive correction on strabismic or combined amblyopia found a nearly identical outcome: 75% improved at least two lines and 32% resolved.[27] This was in spite of not requiring alignment with the correction.

Based on these findings, the author prefers to prescribe any necessary spectacle correction and then wait for at least 6 weeks to re-evaluate visual acuity. The visual acuity is measured in trial frames when the glasses are prescribed at the initial (baseline) visit so it may be compared with the vision measured at the first follow-up visit. As long as the visual acuity is improving, the child may continue with just glasses before prescribing additional therapy. This staged approach may improve patient compliance with each portion of the therapy.

Occlusion therapy

Occlusion has been the mainstay of treatment for a century despite the lack of meaningful data demonstrating superiority over other modalities. Treatment commonly employs an adhesive patch placed over the fellow eye so that the amblyopic eye must be used. Opinions vary on the number of hours of patching per day that should be prescribed, ranging from a few hours to all waking hours in many textbooks.[5,28–31]

Flynn et al. found that the success rates were the same for part-time and full-time occlusion therapy based on reported outcomes in 23 studies.[32] Several authors have reported significant improvement in visual acuity using brief daily periods of occlusion (20 minutes to 1 hour).[33,34] Campbell et al. noted that 20 minutes per day was effective in improving the vision of 83% of children to 6/12.

The dosages prescribed by clinicians during the last few decades vary greatly and seem to be largely a matter of region or training.[35] For instance, more hours are prescribed in German-speaking countries than in the United Kingdom, yet the same outcome is expected.[36] These prospective multicenter randomized controlled clinical trials have included only patients with strabismic and anisometropic forms of amblyopia.[37–40] The first study compared occlusion to atropine treatment. The dosage of occlusion prescribed was a minimum of 6 hours up to full-time, but the investigator chose the actual occlusion dosage. Patients with acuity of 6/24 to 6/30 improved faster when more hours of patching were prescribed, but after 6 months the improvement was not significantly greater than that occurring with fewer hours of patching or with atropine (Fig. 73.1).[37]

Additional prospective randomized trials compared the efficacy of different occlusion dosages. There are two distinct studies, one for moderate amblyopia 6/12 to 6/24, and one for severe amblyopia 6/30 to 6/120, caused by strabismus, anisometropia, or both.[38,39,41] The studies found that 2 hours of daily patching produces an improvement in visual acuity of similar magnitude to the improvement produced by 6 hours of daily patching in treating moderate amblyopia in children 3 years to less than 7 years of age.[39] Each treatment group improved 2.4 lines over 4 months. More interesting was the lack of any benefit in terms of the rate of improvement from more hours (Fig. 73.2). When reviewing this study, it is important to consider that the visual acuity gain after 4 months likely does not represent the maximum improvement possible from either treatment.

The study for severe amblyopia compared 6 hours with full-time occlusion. The investigators found the improvement in the amblyopic eye acuity from baseline to 4 months averaged 4.8 lines in the 6-hour group and 4.7 lines in the full-time group (P=0.45).[38] In a recent study, children with severe amblyopia improved a mean of 3.6 lines with just 2 hours of daily patching for 17 weeks.[42]

Children's dislike of occlusion therapy is well known.[43] Reported compliance rates range widely. Parents have used coercion and clinicians have, on occasion, prescribed punitive measures such as elbow splints to enhance compliance. Lack of parental understanding seems to play a large role. In the United Kingdom, failure to comply with the prescribed regimen at least 80% of the time occurred in 54% of patients: the failure to comply related to the parents' lack of understanding that there is a "critical period" for effective therapy.[44]

Side effects from occlusion are uncommon, usually minor skin irritation or the social stigma of a patch.[40] Adhesive sensitivity to the patches does occur. The clinician should discontinue the patch and treat with an emollient facial cream. Rarely, topical hydrocortisone may be needed.

More serious is occlusion (or "reverse") amblyopia – a decrease in vision in the fellow (patched) eye of more than one line. It is more common with more intense therapy and longer treatment intervals, especially if the patient is lost to

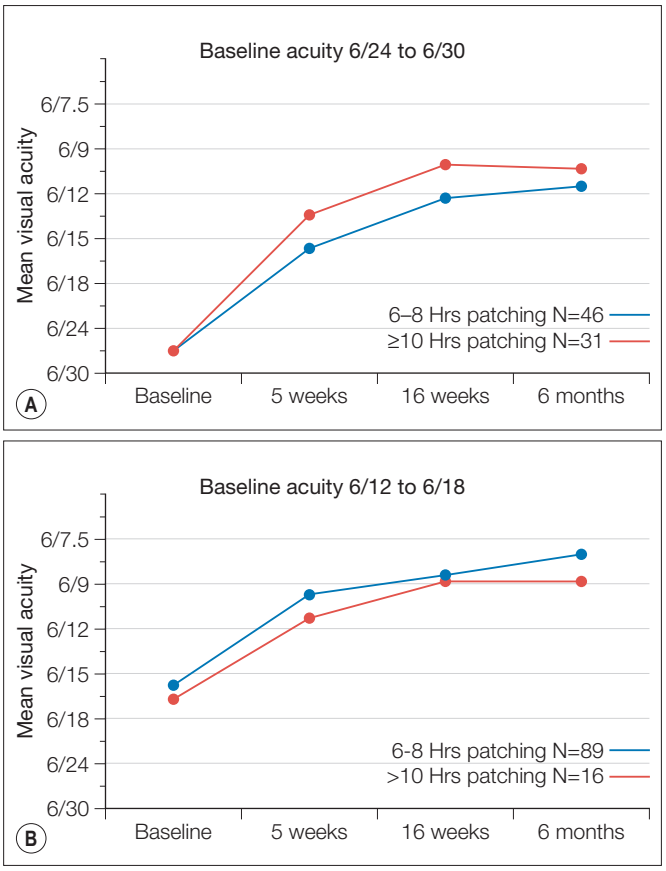


Fig. 73.1 Initial prescribed dosage of patching versus mean visual acuity from a randomized controlled trial.[40] Eighty percent of patients remained on their initial dosage throughout the study. Unsuccessful patients in each subgrouping had patching of 12 or more hours prescribed at the 17-week visit. (A) Patients with amblyopic eye acuity of 6/24 and 6/30: The patients initially treated with 10 or more hours compared to 6 or 8 hours per day had a faster rate of improvement, but by 6 months there was no significant difference in outcome. (B) Patients with amblyopic eye acuity of 6/12 to 6/18: There was no difference in the rate or magnitude of improvement between those initially treated with 10 or more hours compared to those with 6 or 8 hours.

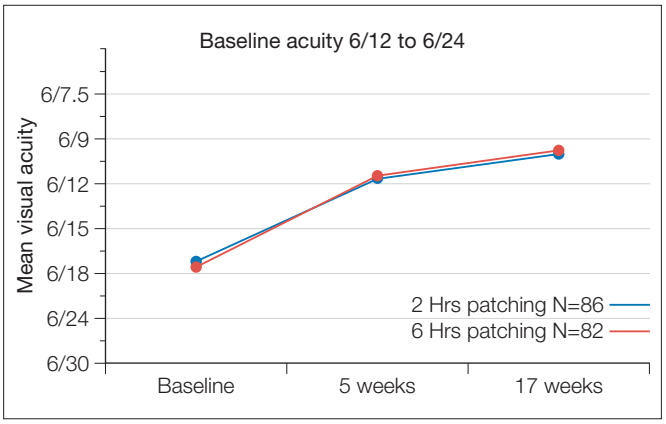


Fig. 73.2 Occlusion dosage of 2 versus 6 hours compared in a randomized controlled trial.[39] No increase in therapy was allowed by the protocol. There was no difference in the rate or magnitude of improvement during the 4 months of prescribed treatment.

follow-up. In one prospective study in which the majority of patients were treated with 6 or 8 hours of occlusion per day, only 1 of 204 patients was diagnosed with reverse amblyopia.[40] In most cases, occlusion amblyopia is reversible simply by stopping the treatment. Rarely, amblyopia therapy is needed for the original non-amblyopic eye.

The value of occlusion therapy is well established for anisometropic and strabismic amblyopia. The clinician and the parents should discuss the dosage of occlusion to be prescribed. The number of hours prescribed should be based on many factors including compliance and lifestyle.

An opaque adhesive patch is the best method currently available. Temperature-sensitive patches to monitor compliance may be available in the future.[45] Spectacle-mounted patches and non-adhesive patches may be less successful because they are easily removed. Once an occlusion dosage is prescribed, the patient must return for visual acuity monitoring. Traditionally, these intervals have been 1 week per year of age (i.e. a 3-year-old patient would return in 3 weeks). This approach is necessary when full-time occlusion is prescribed, but should be lengthened with part-time occlusion. An initial follow-up interval of 2 months for 2–6 hours per day patching is sufficient. If the amblyopic eye has improved and the fellow eye has not been impaired, the treatment interval can be increased. Therapy should be continued until no improvement occurs between two visits. Re-testing is warranted to be certain of the lack of improvement.

Most data on the treatment of amblyopia is derived from subjects who have strabismic, anisometropic, or both combined forms of amblyopia. An important group of patients experience form deprivation amblyopia, e.g. from a cataract or media opacity. For these patients, the amblyopia is often severe. Occlusion remains the best choice. The occlusion dosage should be individualized, as there is no clinical trial available to guide the clinician. For patients with unilateral deprivation amblyopia, occlusion dosages of half waking hours are reasonable to avoid damage to the binocular system or to the fellow eye. This dosage can be tapered as the child plateaus to maintain the improvement.

"Penalization" therapy

Penalization is an alternative to occlusion therapy for amblyopia. Both pharmacologic and optical means are used to blur the vision in the better eye for near and/or distance. Penalization was first advocated in 1903 by Worth.[46] It has mainly been employed as a second-tier treatment, for use with occlusion non-compliance, and for post-occlusion maintenance or titration.[47–51]

Pharmacologic penalization involves the instillation of a long-acting cycloplegic agent into the fellow eye. Most often, atropine 1% ophthalmic solution has been used, but sometimes shorter-acting cycloplegic agents. Cycloplegia prevents accommodation, thus blurring the eye at near fixation. The patient uses the amblyopic eye at near. Some clinicians have augmented the therapeutic effect by reducing or removing any plus sphere from the spectacle correction of the fellow eye, effectively blurring the fellow eye at all fixation distances.[40,52,53] Pharmacological penalization has been recommended for moderate amblyopia, but has also been found somewhat effective for amblyopia 6/30 to 6/60.[54] Compliance with pharmacologic therapy is easier for caregivers: 78% of patients had excellent compliance.[40] The treatment appears to take longer to reach a successful outcome compared with occlusion, but appears to be equally effective.

Optical penalization involves placement of "plus" fogging lenses over the fellow eye, blurring that eye at near, causing the patient to shift fixation at near to the amblyopic eye. Optical penalization has generally been advocated for only mild amblyopia (6/18 or better).[48,49] The power of the additional plus before the fellow eye may be arbitrarily chosen, usually +2.50 or +3.00 D. It is very convenient for a child wearing bifocals to simply extend the power of the bifocal throughout the entire lens creating an "over-plussed" single-vision lens. An alternative is to have the patient fixate a distance vectographic target and increase the plus sphere before the fellow eye until the fixation at distance switches to the amblyopic eye.[55] Compliance is a concern with optical penalization since it is dependent on the child wearing the glasses and not "peeking" around them. For that reason it is a method best reserved for older children and those with milder degrees of amblyopia. The clinician should be prepared to continue this treatment for 2 or more years.

Penalization with either optical or pharmacological blur appears effective because the blur produced selectively removes the high spatial frequency components of the image to the fellow eye, eliminating their suppression of the high spatial frequency components perceived by the cortex responsive to the amblyopic eye.[56] This appears to be critical because amblyopia is a deficit of neuronal responses to high spatial frequencies. With penalization, the high spatial frequencies become more dominant in the neurons to the cortex of the amblyopic eye.

Occlusion compared to penalization

Some studies have compared penalization with occlusion.[57–59] The first Amblyopia Treatment Study was a randomized controlled trial that enrolled 419 patients comparing occlusion to pharmacologic penalization.[40] Both daily patching (6 or more hours) and daily atropine were effective initial treatments for amblyopia throughout the range of 3 years to less than 7 years of age and the acuity range of 6/12 to 6/30. Each method produced nearly the same improvement of about 3 LogMAR lines over 6 months. Follow-up through age 15 years has found the improvement of the amblyopic eye to be maintained, although residual amblyopia is common.[23] The outcome was similar regardless of initial treatment.

Fogging

An alternative to occlusion or penalization is fogging. This may be done with Bangerter foils or even adhesive tape, which reduce the visual acuity in the fellow eye. The foils are available in graduated densities. The selected filter is typically one that is expected to reduce the fellow eye vision to less than the amblyopic eye. An alternative is to use a fairly dense filter for all patients. A randomized study compared Bangerter filter density of 0.3 (for 6/12–6/18 amblyopic visual acuity) or 0.2 (for 6/24 amblyopic acuity) with patching for 2 hours per day.[60] At 24 weeks, amblyopic eye improvement averaged 1.9

lines in the Bangerter group and 2.3 lines in the patching group. Similar percentages of subjects in each group improved three lines (Bangerter group 38% vs. patching group 35%; P=0.61) or had 6/7.5 amblyopic eye acuity (36% vs. 31%, respectively; P=0.86).

A readily available and inexpensive alternative is the use of an opaque adhesive tape placed on the glasses. Each of these is barely visible beyond 0.5 m. This method is ideal for mild visual deficits, long-term maintenance therapy, and in school-age children in which compliance with the glasses wear is possible.[61]

Active therapy

Active treatment has been suggested as an important supplement to occlusion therapy. Duke-Elder emphasized the importance of interesting play during occlusion.[62] Physicians have suggested that while patching, patients should be involved in some activity that promotes visual interaction. The simplest forms have been home-based activities, performed in conjunction with the occlusion, usually involving activities such as tracing, dot-to-dot tasks, coloring, stringing beads, reading, and playing computer/video games. These therapies may be helpful because they: (1) help overcome compliance problems with occlusion; and (2) may help to improve accommodation and fixation patterns. A study compared 100 patients who were occluded with another 100 who underwent occlusion with active home therapy twice weekly. They achieved the same visual acuities, but the actively stimulated group reached maximum improvement 2 months earlier.[63] Campbell and coworkers added intensive close work to 20 minutes per day of occlusion and found that 83% of children improved to 6/12.[34] Active therapy has been shown to be helpful when patching alone did not improve the visual acuity. Shippman added 1 hour of video game play to patients previously unsuccessfully treated with occlusion.[64] Fifteen of 19 (78%) had an additional two lines of improvement, and nearly 50% improved by three lines of acuity. Similar success in older children has been reported in uncontrolled studies.[65,66]

The Cambridge amblyopic vision stimulator employed intensive visual activities.[34] The initial report suggested excellent results. However, subsequent studies including sham stimulation found no significant difference in acuity outcomes.[67–69]

PEDIG studied adding 1 hour of near activities to 2 hours prescribed patching in children 3 years to less than 7 years of age.[70] After 8 weeks of treatment, improvement in amblyopic eye visual acuity averaged 2.6 lines in the patching-only group and 2.5 lines in the near activities group. At this time, the absence of a benefit means this approach may only be of use in some children as a compliance tool.

Binocular visual experience as treatment

Hess and his colleagues reported treating unilateral amblyopia in adults with a binocular approach using dichoptic stimuli.[71] This approach was translated to amblyopia treatment in children on an iPod (Apple, Inc.) using a Falling Blocks game.[72] Li and colleagues treated amblyopia with dichoptic stimuli, using red–green glasses with reduced contrast for the non-amblyopic eye, for 4 hours/week for 4 weeks.[73] The authors reported an average improvement from 0.47±0.03 LogMAR at baseline to 0.39±0.03 LogMAR (P<0.001) after 4 weeks in 50 children 4–12 years of age. In another study of preschool children 3 to < 7 years of age (n=35) treated 4 hours per week on an iPad (Apple, Inc.) platform at home, they improved about one line on average over 4 weeks of therapy, while there was no improvement for sham treatment.[74] Confounding analysis was the ongoing use of patching and a limited size control group (n=5). Greater treatment effect was seen in those children with better compliance.

PEDIG is conducting a prospective randomized study of this treatment in children and teens 5–16 years of age. The trial is using 1 hour per day of the game and no other treatment except glasses for 4 months of treatment. There is a 2 hours per day of patching control group.

Systemic therapy

Catecholamine neurotransmitters play a role in maintaining plasticity of the visual cortex during development. The administration of oral levodopa–carbidopa (L-dopa) combination therapy improves the acuity of amblyopic eyes.[75] Levodopa is converted to dopamine, which appears to play an important role in retinal function and in central visual processing.[76] Carbidopa is added to reduce the systemic effects of the levodopa by allowing a lower dose. When this pharmacologic therapy is combined with occlusion therapy the visual acuity improvement was greater than that with occlusion alone.[77] These studies noted regression after the treatment was stopped, but the outcome acuity was felt to be better when occlusion was combined with L-dopa.[75]

Three randomized placebo-controlled studies of levodopa with patching for residual amblyopia have been conducted.[78–80] Each of the studies found more improvement in the levodopa group compared with the placebo group. Two earlier studies were of 1 week or shorter duration. PEDIG has recently completed a larger randomized trial of levodopa (0.76 mg/kg/tid) plus occlusion compared with placebo plus patching for residual amblyopia in children 7–12 years of age.[80] Although both groups improved about one line, there was no meaningful benefit from adding oral levodopa to patching.

Side effects of nausea, dizziness, decreased respiration, and decreased body temperature have been reported with the use of levodopa, although they are reported by a minority of study participants.[80–82]

Citicoline (cytidine-5′-diphosphocholine) had some success in a study of 50 amblyopic patients.[83] Treatment involved daily intramuscular injections of the medication for 10 days. Both the fellow and amblyopic eyes improved and were stable with 4 months of follow-up. This drug has been less widely used because of the requirement for parenteral administration, but few side effects have been reported. An oral preparation is currently under study.

The lack of compelling evidence of success greater than that found with conventional treatments and the use of neuroactive drugs for a condition that does not threaten life or general health make it impossible to recommend systemic therapy at this time.

Combined therapies

Some clinicians simultaneously treat amblyopia with more than one approach. A common approach is to patch part-time and to prescribe topical atropine, thus allowing the child to be continuously treated. The child will use the patch when not in school or at other activities where the patch will not make them self-conscious. The effectiveness of this approach is uncertain. An alternative is to prescribe topical atropine and reduce the plus sphere in the fellow eye to plano (or some other reduction of plus power), thus blurring the fellow eye at all fixation distances.[52] In a randomized trial of 18 weeks of such treatment, amblyopia improvement averaged 2.8 lines in the group that received atropine plus a plano lens, and 2.4 lines in the group that received atropine alone.[84] More patients in the group that received atropine plus a plano lens had reduced fellow eye visual acuity at 18 weeks; however, there were no cases of persistent reverse amblyopia. Nonetheless, monitoring these patients for decreased vision in the fellow eye is prudent.

Discontinuation of treatment/ maintenance therapy

Most clinicians stop intensive therapy when the patient no longer shows improvement. However, the duration of treatment before cessation of therapy is unclear, but 3 months with no improvement before stopping or reducing therapy is a reasonable approach. Once therapy is thought to have reached its maximum benefit, the author begins to "wean" the patient over many months or even a year, reducing the treatment by 50% every 3 months. However, there are no data available to prove that weaning is superior to immediate cessation in retaining the treatment benefit. In any case, ongoing monitoring is needed until 7 or 8 years of age without any active treatment besides glasses to detect a recurrence, which is inconvenient but medically necessary.

The long-term stability of improved acuity in amblyopia therapy is an important public health goal if we are to reduce the high prevalence of amblyopia in adults. The chance of maintaining all, or a portion of, the improvement into adulthood is at least 75% in retrospective studies.[85–87] In a prospective study, most children treated for moderate amblyopia when younger than 7 years of age had good visual acuity, although mild residual amblyopia was common.[23] The results indicate that improvement occurring with amblyopia treatment is maintained until at least 15 years of age without evidence of regression.

Compliance

Compliance with amblyopia therapy is a key factor in the success of the therapy. However, compliance with occlusion therapy varies widely, from 30% to more than 90%.[88–91] Reasons for the inability to complete the prescribed occlusion regimen include visual impairment, skin irritation, and psychosocial reasons. Pilot studies of occlusion therapy with occlusion dose monitors have shown the expected correlation of treatment compliance with outcomes.[92,93] Compliance with topical pharmacologic therapy is simpler, having to put the drop in only once per prescribed day. Compliance was reported to be excellent or good in 96% of patients.[40]

Although children may reject amblyopia therapy, lack of understanding about the disease and the timing of therapy also seem to play a role.[44] Compliance may be improved with better education of the parents and some explanatory materials to take home.

Reverse amblyopia

Reverse amblyopia (occlusion amblyopia) is a form of deprivation amblyopia. It is a reduction of vision in the fellow eye of more than one line due to a treatment prescribed for amblyopia in the fellow eye. Reverse amblyopia has been associated with most forms of therapy of amblyopia. It seems to be most commonly associated with full-time occlusion. It occurs much less often with part-time occlusion and cycloplegic and optical methods of treatment.

Reverse amblyopia generally recovers quickly, although there are reports of permanent visual impairment or change in fixation.[94] Each patient thought to possibly have reverse amblyopia should be reassessed: Confirm the refractive correction being worn. Examine the patient for signs of optic neuropathy including the pupillary light reflex for evidence of an afferent pupil, color vision, and appearance of the optic nerve and nerve fiber layer. Check the refraction with cycloplegia. Re-test the vision. If the acuity reduction is confirmed, either stop the active amblyopia therapy and re-examine the patient in several weeks or continue the therapy with careful monitoring of the fellow eye. If the fellow eye is worse than the amblyopic eye, stop therapy and schedule a return visit. If the vision in the fellow eye is still reduced on the subsequent visit, consider treating the formerly fellow eye.

Treatment of older children and adults

Amblyopia therapy is widely thought to be more successful in younger patients, especially when less than 7 years of age. This is consistent with the demonstration of age-specific sensitive periods in neurologic development. Recent findings challenge this tenet.

PEDIG conducted a randomized trial comparing optical treatment to optical plus other active therapies.[95] Improvement with optical correction alone occurred in about a quarter of children 7–17 years of age; although most patients benefited from additional treatment for amblyopia, most patients were left with a residual visual acuity deficit. For patients 7–12 years of age, 2–6 hours per day of patching with near visual activities and atropine improved visual acuity even if the amblyopia had been previously treated. For patients 13–17 years of age, prescribing patching 2–6 hours per day improved visual acuity only when amblyopia had not been previously treated (Fig. 73.3). While there appears to be much less improvement in older children and teens, it is reasonable to conclude from this work that any amblyopic patient who has never been treated should be offered at least one cycle of therapy.

In several retrospective studies and two clinical trials for occlusion and pharmacologic therapy in patients less than 7 years of age, no age effect could be demonstrated.[6,39,40,96] Although somewhat surprising given long-standing consensus

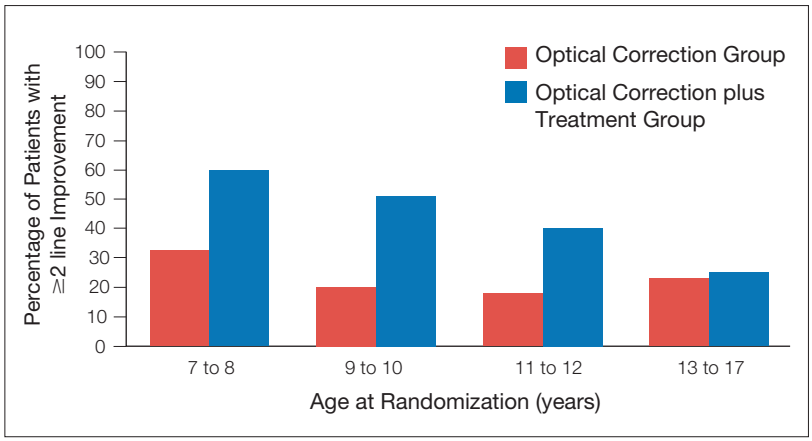


Fig. 73.3 Improvement in visual acuity of children 7–17 years of age with optical correction with or without additional treatment. Treatment for children 7–12 years of age was optical only or optical plus prescribing patching 2–6 hours per day with near visual activities and atropine ophthalmic solution 1% daily. For teens 13–17 years of age, treatment was optical only or optical plus prescribing patching 2–6 hours per day with near visual activities. *(Modified from Pediatric Eye Disease Investigator Group. Randomized trial of treatment of amblyopia in children aged 7 to 17 years. Arch Ophthalmol. 2005;123(4):437–47, with permission from the American Medical Association.)*

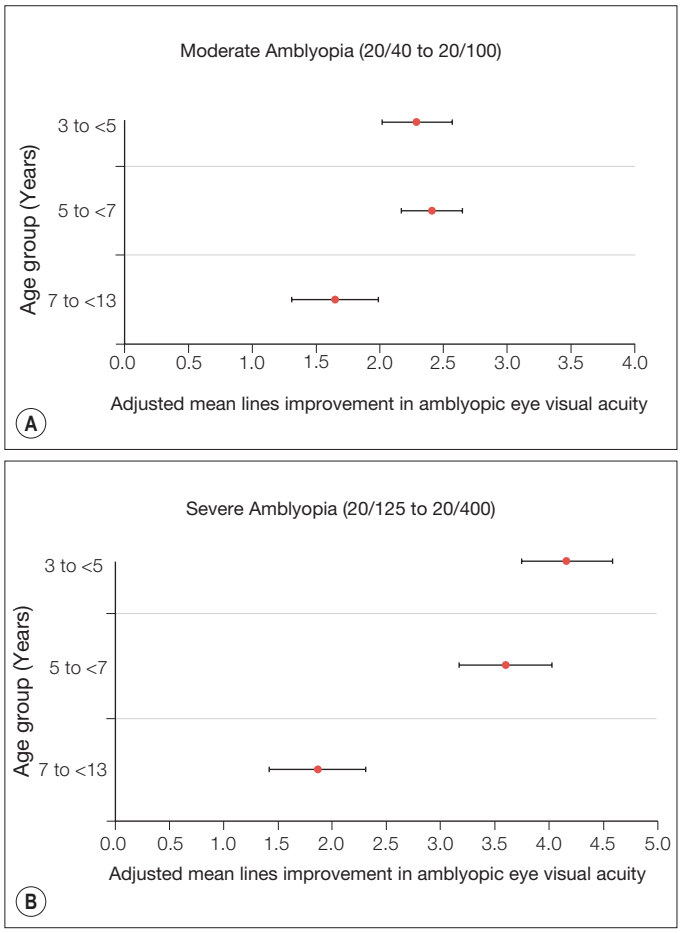


Fig. 73.4 Treatment effect by age for pooled Pediatric Eye Disease Investigator Group (PEDIG) studies data. Mean effects for each PEDIG trial weighted for sample size with 95% confidence intervals. (A) The treatment of moderate amblyopia shows no age effect below 7 years of age, but a striking reduction in the benefit after that age. (B) The treatment of severe amblyopia shows an age effect for each of the age cohorts with the youngest children able to achieve the greatest improvement.[97]

that there is an age effect in childhood, this finding may have been related to the relatively small ranges of age enrolled in each trial. A meta-analysis of PEDIG trials over a much wider age range found amblyopia more responsive to treatment in children younger than 7 years of age compared with children 7 years to less than 13 years of age[97] (Fig. 73.4). For moderate amblyopia, there was no difference in response seen among children less than 7 years of age, but for children with severe amblyopia, children 3 years to less than 5 years of age were likely more responsive than children 5 years to less than 7 years of age. These data would support the earlier identification and initiation of amblyopia treatment.

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Anatomy of strabismus

Joseph L Demer

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Introduction

Diagnosis and surgical correction of strabismus require anatomic knowledge of the extraocular muscles (EOMs) and their relationships with other orbital tissues. This chapter summarizes this anatomy and some surgical applications.

Overview of the extraocular muscles

The historically understood six EOMs are the effector arm of the ocular motor system.[1,2] The EOMs are loosely organized as "yoked pairs" of agonists and antagonists. These EOMs are highly specialized, and each EOM consists of two kinds of compartments.[3] The global layer (GL) controls oculorotary tension, while the orbital layer (OL) controls the pulling direction by regulating the position of the connective tissue pulleys. The GL and OL contain fiber types with different metabolic and structural properties. A second kind of compartmentalization divides the GL of each transversely according to specialized motor nerve arborizations that enables differential contraction. The pulleys, connective tissue EOM encirclements that are actively controlled by the OLs of the rectus EOMs, mechanically regulate most aspects of ocular kinematics, including Listing's Law (LL) of torsion. Exceptions to LL are implemented actively by the oblique EOM OLs. However, transverse compartmentalization allows for fine tuning EOM pulling direction, and is critical to ocular motor control during vergences, and to the interactions with vestibulo-ocular reflexes (VORs).

Details of the extraocular muscles

The six classical oculorotary EOMs pair as antagonists.[1] The medial rectus (MR) adducts and the lateral rectus (LR) abducts. The superior rectus (SR) and inferior rectus (IR) muscles form a vertical antagonist pair, with the SR supraducting and the IR infraducting. However, vertical rectus EOMs have additional actions. The superior oblique (SO) and inferior oblique (IO) muscles form a torsional antagonist pair: SO incycloducts, while IO excycloducts, but their additional actions are not strictly antagonistic.

Orbital and global layer compartmentalization of extraocular muscles

The oculorotary EOMs consist of two layers subserving distinct functions (Fig. 74.1).[1] The GL, containing approximately 10,000–15,000 fibers in the mid-length, is located adjacent to the globe in rectus EOMs and in the central core of the oblique EOMs.[4] In the rectus EOMs and the SO, the GL anteriorly becomes contiguous with the terminal tendon and inserts on the sclera.[5] In the IO, the GL inserts directly on the sclera. The OL of each rectus EOM contains 40–60% of its fibers. The OL does not insert on the eyeball at all, but instead inserts on connective tissue pulleys. The OL is located on the orbital

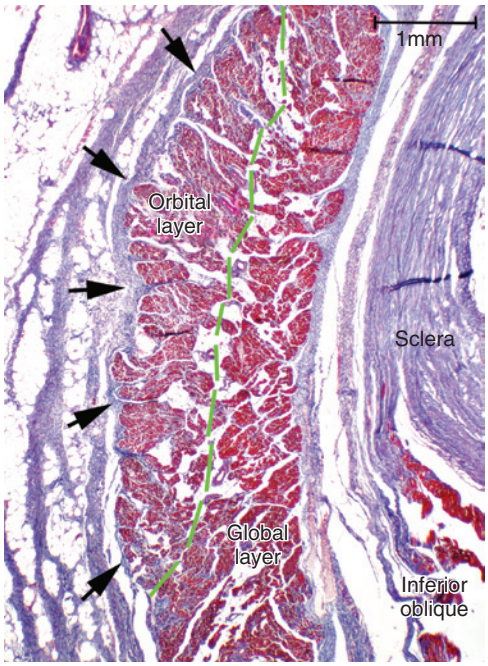


Fig. 74.1 Transverse histological section of 17-month-old human lateral rectus (LR) muscle stained with Masson's trichrome showing the smaller, darker-red staining fibers of the orbital layer (OL) to the left of the larger, brighter-red staining fibers of the global layer at right. Note insertion of OL fibers into the dense blue-staining collagen of the LR pulley (arrows). The inferior oblique muscle insertion into the blue-staining collagen of the sclera is seen at lower right.

surface of the rectus EOM, but constitutes the concentric outer layer of the SO.

The OL contains two muscle fiber types.[6] About 80% of fibers in the orbital layer of each EOM are fast, twitch-generating, singly innervated fibers (SIFs) resembling mammalian skeletal muscle fibers, while 20% are multiply innervated fibers (MIFs) that either do not conduct action potentials or do so only in their central portions.[6] Orbital SIFs have small diameter and numerous mitochondria. The metabolism and blood supply of orbital SIFs are tailored to their mechanical loading and nearly continuous activity, and thus specialized for intense oxidative metabolism and fatigue resistance.[6] The vascular supply in the OL is higher than in the GL.[7] Orbital SIFs express unique myosin isoforms.[6] The relatively sparse and primitive orbital MIFs may be proprioceptive.[8]

The GL contains one MIF type and three SIF fiber types.[6] The largest SIF is similar to the orbital SIF, while mitochondria are less abundant in the other two SIFs. Global MIFs resemble orbital MIFs. While spindles are absent in the GL, there are palisade endings along the width of each rectus tendon where the GL fibers terminate, perhaps subserving a proprioceptive function, although this is controversial.[8]

Several myosin isoforms occur in EOMs, with the predominant one in orbital SIFs, EOM-specific myosin, occurring uniquely in EOMs.[6] Neonatal and embryonic myosin isoforms persist throughout adult life at the anterior and posterior ends of SIFs. Differences in myosin expression may underlie the susceptibility of the EOMs to disorders such as thyroid ophthalmopathy, as well as their resistance to other disorders such as muscular dystrophy.[7]

Gross structure of the extraocular muscles[1]

Rectus EOMs originate in the orbital apex from the annulus of Zinn. The SO muscle originates from the periorbita of the superonasal orbital wall. The rectus EOMs course anteriorly through loose, areolar lobules of orbital fat until they enter their connective tissue pulleys that ensheath them as they penetrate posterior Tenon's fascia. Contrary to implications of many texts, there is no "muscle cone" of connective tissue among the adjacent rectus EOM bellies in the mid-to-deep orbit. The SO muscle remains tethered to the periorbita via connective tissues as it courses anteriorly, then thins to become continuous with its long, thin tendon. The concentric OL of the SO terminates posterior on a peripherally located sheath; the SO's GL terminates on parallel tendon fibers similar to rectus EOM tendons, but rolled up into a cylinder as it transits the trochlea, a cartilaginous rigid pulley attached to the superonasal orbital wall. After reflection in the trochlea, the SO tendon passes beneath the SR, thins, and flattens as it spreads out to its broad scleral insertion posterolaterally on the globe, while the sheath inserts on the SR pulley. The IO muscle originates from the inferonasal orbital rim, and runs laterally to enter its connective tissue pulley immediately inferior to the IR at the point the IO penetrates Tenon's fascia.

The axes of the bony orbits are angled about 23° laterally from the midsagittal plane. The array of the rectus EOMs and the SO is conical. As they continue anteriorly, the rectus EOMs thin to become strap-like bands about 10 mm in width, and ultimately their GLs become continuous with tendons that insert on the globe. The SO would do the same, except that its tendon rolls up within the trochlea and then unrolls anteriorly.

The rectus EOMs do not follow straight-line paths from their origins to their scleral insertions. In eccentric gazes, rectus paths are inflected sharply in the anterior orbit (Fig. 74.2). The inflections, due to the pulleys, cause the anterior paths of rectus EOMs, and thus their pulling directions, to change with eye position. Figure 74.2 is a set of axial magnetic resonance images (MRI) illustrating that the anterior IR path changes by half the change in duction angle. All four rectus EOMs behave in this manner.

Structure of pulleys

The rectus EOM inflections in the anterior orbit constitute the functional pulleys. Anterior to the pulleys, rectus EOM paths directly track to the scleral insertions. The pulleys thus act as mechanical origins of the rectus EOMs. The line segment between the scleral insertion and pulley thus defines the EOM's pulling direction. Pulleys consist of rings of dense collagen about 2 mm in length, co-axial with less substantial collagenous sleeves around the EOMs (Fig. 74.3). Anteriorly, these sleeves thin to form slings convex to the orbital wall and, more posteriorly, the sleeves thin to form slings convex toward the orbital center. The anterior pulley slings have also been called the "intermuscular septum," a time-honored but relatively vague term. Fibrils of pulley collagen in the pulleys have a crisscrossed configuration suited to high internal rigidity.[9] Elastic fibers in and around pulleys[10] provide reversible extensibility, particularly in bands that connect the pulleys

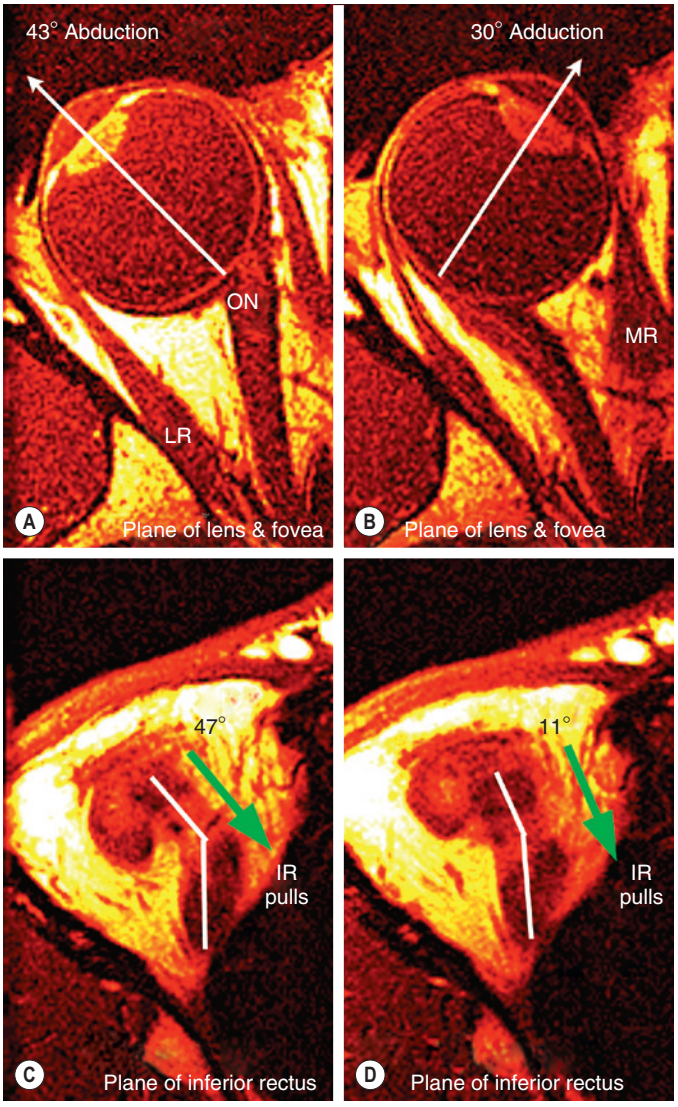


Fig. 74.2 Axial magnetic resonance imaging scans (2 mm thickness, T1 weighted) of a right orbit taken at the level of the lens, fovea, and optic nerve (A,B), and simultaneously along the path of the inferior rectus (IR) muscle (C,D), in abduction (A,C) and adduction (B,D). Note the bi-segmental IR path. For this 73° horizontal gaze shift, there was a corresponding 36° shift in IR muscle path anterior to the inflection at its pulley. This is a direct demonstration of half-angle shift of IR pulling direction with ocular duction.

to bony anchors on the orbital rim, suspending them under elastic tension that draws them anteriorly. Smooth muscle is present in pulley suspensions, particularly in a distribution called the inframedial peribulbar muscle between the MR and IR pulleys.[11]

The IR pulley is intimately coupled with the IO pulley in a bond that forms part of Lockwood's ligament where the IR and IO pulleys share a common collagenous sheath stiffened by a heavy elastin deposit at their point of crossing. The IR's OL inserts on its pulley. The IO's OL inserts partly on the conjoined IO-IR pulleys, partly on the IO's connective tissue sheath, and partly on the inferior aspect of the LR pulley. IO contraction displaces the conjoint IR/IO pulley nasally and the LR pulley inferiorly.[12] The overall arrangement of the entire pulley system is illustrated in Figure 74.4.

Although the rigid SO pulley – the trochlea – has been known since antiquity, the SO's OL inserts via the SO sheath on

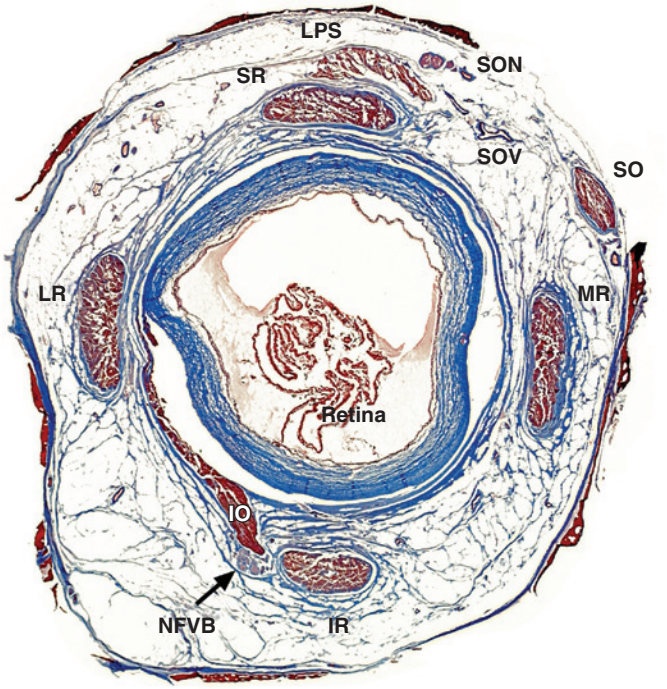


Fig 74.3 Quasi-coronal (perpendicular to orbital axis) histological section of 17-month-old whole human orbit stained with Masson's trichrome showing encirclement of the inferior rectus (IR), lateral rectus (LR), medial rectus (MR), and superior rectus (SR) muscles by the dense, blue-staining collagenous rings of their pulleys. The main part of the inferior oblique (IO) pulley is slightly anterior to this section, but can be seen in part as a dense collagenous mass adjacent to the muscle belly and its neurofibrovascular bundle (NFVB). The retina is detached as a postmortem artifact. LPS, Levator palpebrae superioris muscle; SO, superior oblique muscle; SON, supraorbital nerve; SOV, superior orbital vein.

the medial aspect of the SR pulley.[10] The SO pulling direction changes half as much as ocular duction despite an immobile pulley, because of the uniquely broad, thin insertion of the SO tendon as it wraps over the globe.

The foregoing anatomical relationships can be demonstrated in surgical exposures. Following engagement of a rectus EOM on a surgical hook, the white anterior pulley slings are visible. These tissues play little role in constraining EOM paths. The anterior pulley slings can usually be displaced posteriorly by blunt dissection, after which fine fibrous bands constituting the insertion of the OL of the EOM on the glistening white pulley suspension can be visualized (Fig. 74.5). This insertion is anterior to the pulley ring, which is obscured by the overlying white tissue of Tenon's capsule. After transposition of a rectus tendon for the treatment of, for example, LR palsy, the path of the transposed EOM continues to be toward the original pulley (Fig. 74.5). The clinical effect of rectus transposition can be improved by suture fixation from a posterior point on the transposed EOM belly to the sclera adjacent the palsied EOM.[13] This operation displaces the pulley further towards the transposed direction.[14]

Functional anatomy of pulleys

The insertion of each rectus EOM's OL on its corresponding pulley translates (linearly moves) that pulley posteriorly during

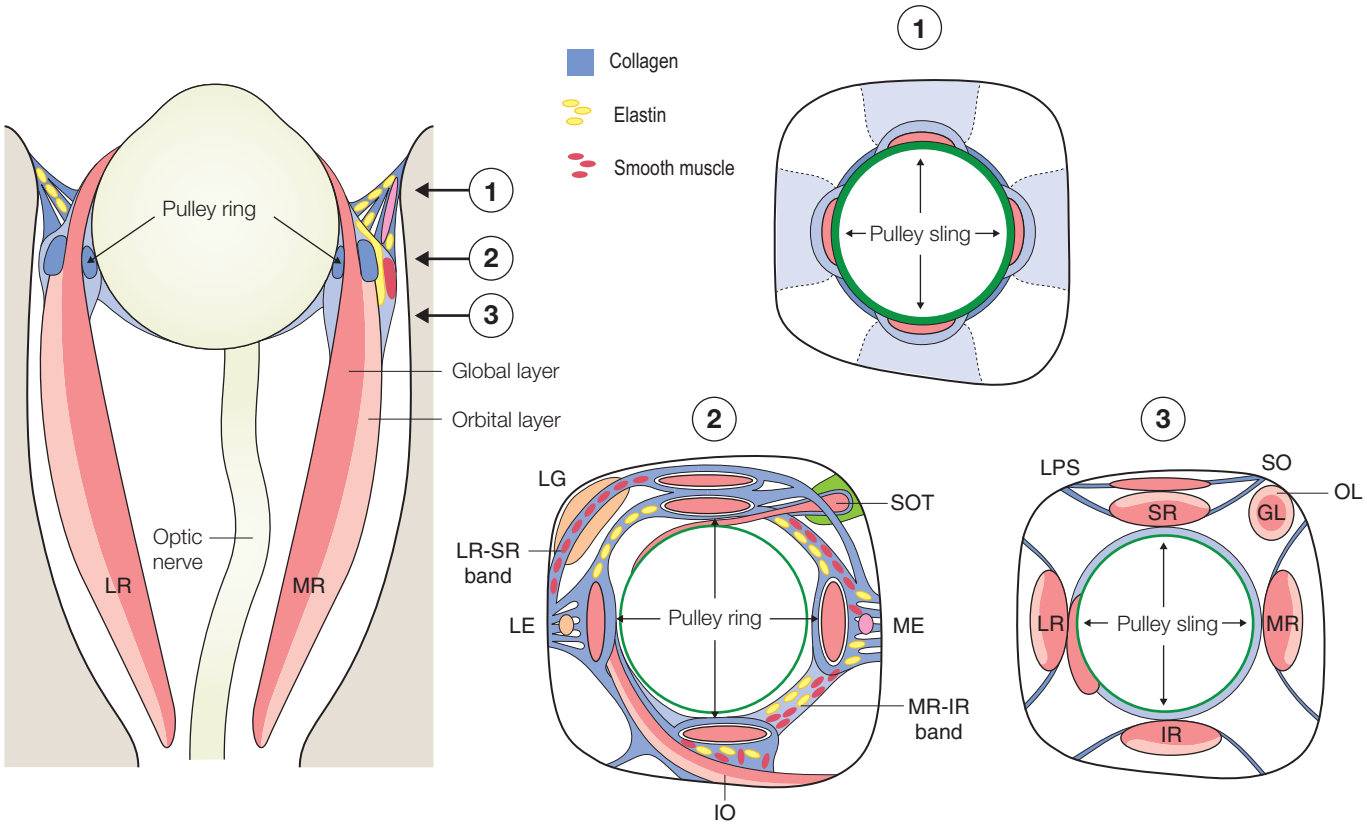


Fig. 74.4 Schematic of orbital connective tissues. Coronal views are depicted at three levels from the axial view. The functional pulleys are at the level depicted at lower right. Tissue composition is color coded as shown at right. GL, Global layer; IO, inferior oblique muscle; IR, inferior rectus muscle; LG, lacrimal gland; LE, lateral enthesis, the attachment of the pulley suspension to the orbital wall; LPS, levator palpebrae superioris muscle; LR, lateral rectus muscle; ME, medial enthesis, the attachment of the pulley suspension to the orbital wall; MR, medial rectus muscle; SO, superior oblique muscle; SOT, superior oblique tendon; SR, superior rectus muscle.

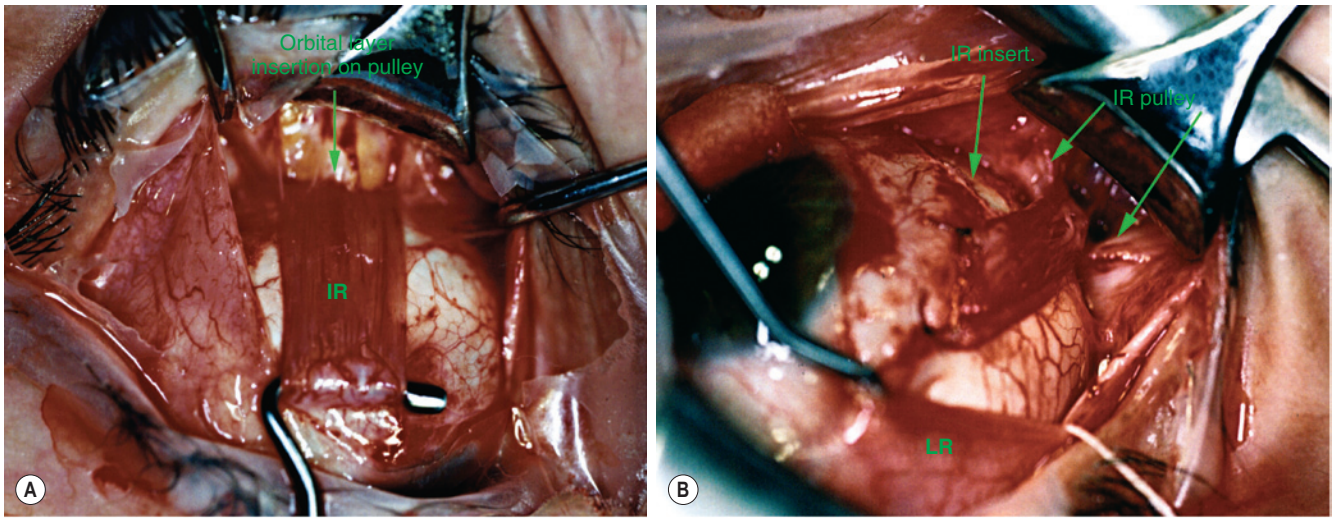


Fig. 74.5 Surgical exposure of right inferior rectus (IR) region, as seen from above the patient, using incision at the conjunctival limbus. The lateral rectus (LR) of this patient was palsied; magnetic resonance imaging showed that the deep LR belly was markedly atrophic. (A) Inferior rectus muscle, engaged on hook, courses posteriorly into the glistening white tissue of the IR pulley. Note fine connective tissue bands marking the anterior part of the orbital layer insertion into the pulley. (B) The IR tendon has been disinserted from the sclera, leaving a white line at the original insertion site. The IR tendon has been transposed temporally to adjoin the inferior pole of the insertion of the paralyzed LR muscle. Note the diagonal path of the transposed IR towards the original location of the IR pulley, now more visible as a discrete structure.

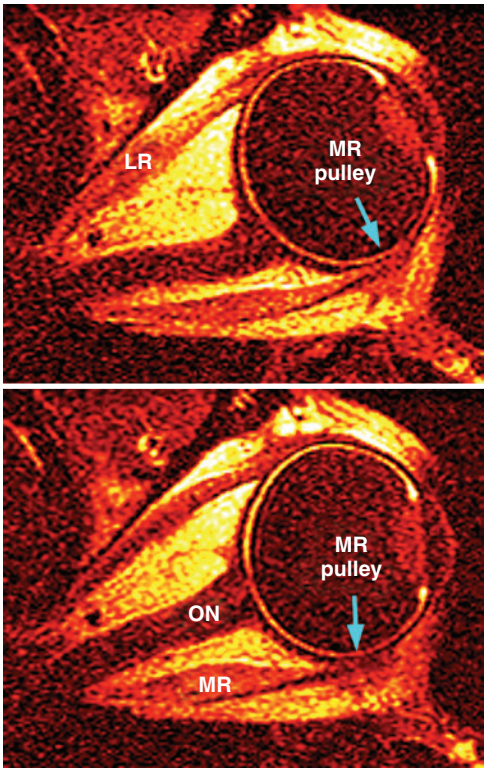


Fig. 74.6 Gadodiamide contrast-enhanced axial magnetic resonance image scans of a right orbit in central gaze and in abduction. Note that the medial rectus (MR) pulley moves anteriorly in abduction by the same amount as the MR insertion. LR, Lateral rectus muscle; ON, optic nerve.

EOM contraction. This may be seen in the axial, contrast-enhanced MRI scans in Fig. 74.6. Pulley tissues move in coordination with the insertion and sclera, although histological examinations show the absence of connections between these tissues. Coronal MRI scans shows changes in the anteroposterior position of the inflections in rectus EOM paths in tertiary gaze positions.[15] This behavior has been confirmed that all four rectus pulleys.

The IO pulley shifts anteriorly in supraduction, and posteriorly in infraduction. This shift is easily appreciated from the obvious change in the IO's path observed by MRI in the quasi-sagittal plane parallel to the long axis of the orbit (Fig. 74.7). As is also evident from Fig. 74.7 the IO pulley moves by half as much as the IR insertion,[12] as necessary to for optimal control of the IO's pulling direction.

The SR pulley also has discrete mechanical couplings to other pulleys.[10] The most prominent such coupling is a dense band extending from the lateral border of the conjoint SR/LPS pulley to the superior border of the LR pulley. This band contains dense collagen and elastin throughout, and divides the orbital lobe of the lacrimal gland.

Although the rectus and IO pulleys are mobile along the lengths of their EOMs, pulleys are located quite stably and stereotypically in the transverse directions. Since EOMs must transit their pulleys, and the pulleys encircle the EOMs, pulley locations may be inferred from EOM paths. Even the anteroposterior pulley locations can be determined by imaging EOM path inflections produced by the pulleys in eccentric gaze positions. In describing pulley location, it is essential that a coordinate reference be defined. Table 74.1 specifies the coordinates of the rectus pulleys of normal young adults in a coordinate system originating in the globe center. Remarkably, the 95% confidence intervals for normal rectus pulley coordinates range over less than ±0.6 mm.[16] Precise

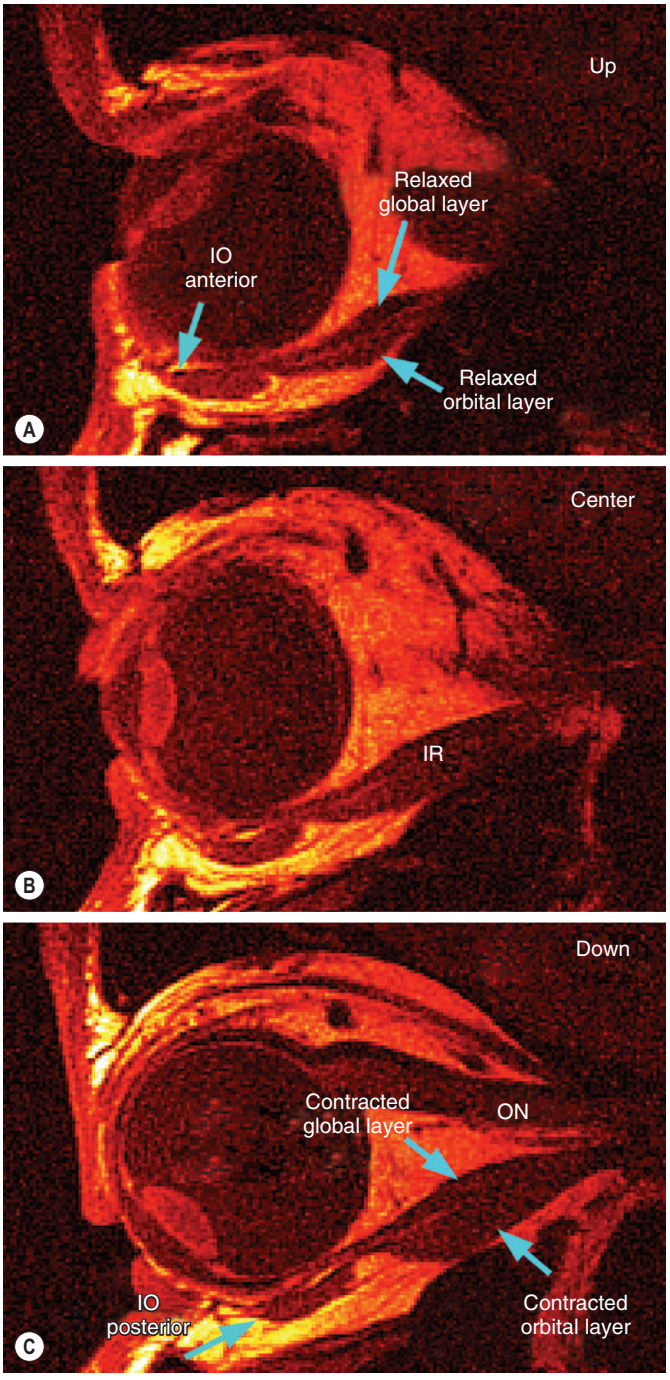


Fig. 74.7 Quasi-sagittal (parallel to the orbital axis) magnetic resonance images (2 mm thickness, T1 weighted) of orbit in three gaze positions. Note demarcation of the orbital and global layers of the inferior rectus (IR) muscle by a thin, bright, fatty septum. The global layer, in continuity with the scleral insertion, exhibits modest contractile thickening in infraduction. The orbital layer, terminating in the IR pulley (not directly seen), exhibits marked contractile thickening in infraduction. The inferior oblique (IO) muscle shifts posteriorly with infraduction, but only half as far as the lens and other ocular structures. ON, Optic nerve.

pulley placement is important since the pulleys serve as the functional mechanical origins of the EOMs, and since the pulleys are close to globe center. Normal aging causes cause inferior sagging of the horizontal rectus pulleys by 1–2 mm, and more in the sagging eye syndrome,[17] as described below. Vertical rectus pulley positions change little over the lifespan.[17]

The globe itself makes translations – linear shifts – during ocular ductions.[16] The globe translates 0.8 mm inferiorly from 22° infraduction to 22° supraduction, for example. The globe also translates slightly nasally in both abduction and adduction. These small translations affect EOM pulling directions since the globe center is only 8 mm anterior to the rectus pulleys.

Rectus pulleys make small transverse shifts under physiologic conditions.[16] The MR pulley translates 0.6 mm superiorly from 22° infraduction to 22° supraduction. Due to the insertion upon it of the IR's OL, the LR pulley translates 1.5 mm inferiorly from infraduction to supraduction. The IR pulley, due to the insertion upon it of the IO's OL, is drawn 1.1 mm medially by IO contraction in supraduction, but 1.3 mm temporally during IO relaxation in infraduction. The SR pulley is relatively stable in the mediolateral direction,[16] but moves inferiorly in supraduction as it is posteriorly displaced by the SR OL, and superiorly in infraduction as the SR OL relaxes. The small gaze-related shifts in rectus pulley positions are also highly uniform among people with normal eyes.

Table 74.1 Rectus pulley locations

	Millimeters from globe center		
Extraocular muscle	**Lateral**	**Superior**	**Anterior**
Medial rectus	−14.2 ± 0.2	−0.3 ± 0.3	−3 ± 2
Lateral rectus	10.1 ± 0.1	−0.3 ± 0.2	−9 ± 2
Superior rectus	−1.7 ± 0.3	11.8 ± 0.2	−7 ± 2
Inferior rectus	−4.3 ± 0.2	−12.9 ± 0.1	−6 ± 2

Rectus pulley positions averaged over 11 normal young adults. For lateral and superior positions, error limits represent 95% confidence intervals. For anteroposterior position, the error limits represent the magnetic resonance image plane thickness (2 mm).
Data from Clark RA, Miller JM, Demer JL. Location and stability of rectus muscle pulleys inferred from muscle paths. Invest Ophthalmol Vis Sci 1997; 38: 227–40.

Kinematics of pulleys[18]

Rectus pulleys are fundamental to ocular kinematics – the rotational properties of the eye. Successive rotations are not mathematically commutative, in that final eye orientation depends on the order of rotations.[19] Each combination of horizontal and vertical orientations of an arbitrary sphere could be associated with infinitely many torsional positions.[19] The eye, however, is constrained (when the head is upright and immobile) by a relationship known as Listing's Law (LL), a statement of classical observations that the torsion of the eye in any gaze direction is that which it would have if it had reached that gaze direction by a single rotation from primary eye position about an axis lying in a plane, Listing's plane.[19] LL is always satisfied if the ocular rotational axis shifts by exactly half of the shift in ocular duction.[20] For example, if the eye supraducts by 20°, then the vertical axis about which it rotates for subsequent horizontal movement should tip back by 10°. This is called the "half-angle rule." Conformity to the half-angle rule makes the sequence of ocular rotations appear commutative to motor control centers in the brain.[21]

Appropriate rectus pulley position implements the half-angle kinematics required by LL. Consider the horizontal rectus EOM schematized in Fig. 74.8A. It is seen from small angle trigonometry that the EOM's pulling direction tilts posteriorly by half the supraduction angle if the pulley is located as far posterior to globe center as the insertion is anterior to globe center. All four rectus EOMs behave identically in this regard.[19] Since the rotational axis of each EOM force rotating the globe observes half-angle kinematics, overall ocular rotation conforms to LL.

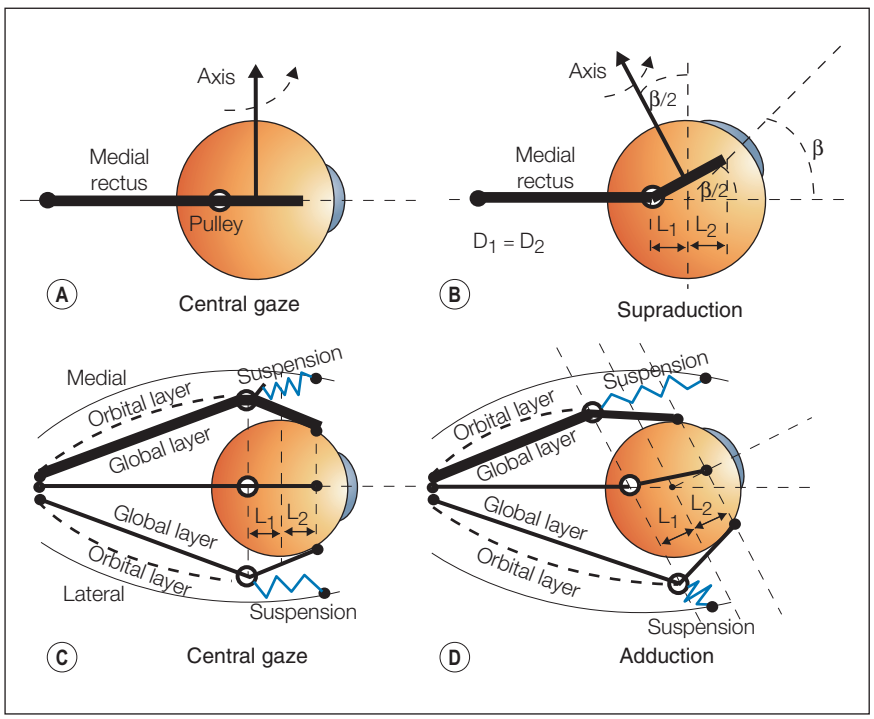


Fig. 74.8 Relationship of pulleys to the rotational axis of horizontal rectus muscles. (A) The medial rectus muscle's rotational axis is perpendicular to the segment between the pulley and the scleral insertion, and is thus vertical in central gaze. (B) In supraduction of angle β, the distance L1 from the pulley (ring) to globe center is equal to distance L2 from globe center to the insertion. This causes the muscle's rotational axis to tilt posteriorly by approximately angle β/2, the half-angle rule to implement Listing's Law. (C) Axial view showing pulleys (depicted as rings) of the horizontal rectus muscles in central gaze. (D) In adduction, the contracting medial rectus orbital layer shifts its pulley posteriorly, while the relaxing lateral rectus orbital layer allows its pulley to move anteriorly.

Were primary and secondary gazes the only ones required, rectus pulleys could be rigidly fixed. However, tertiary gazes such as adducted supraduction require the rectus pulleys actively to shift anteroposteriorly in the orbit along the EOM's length, so that the relationship is maintained in an oculocentric reference (Fig. 74.8B,C). This is the reason for coordinated anteroposterior motion of rectus pulleys described above. The *active pulley hypothesis* (APH) states that these shifts are generated by the contractile activity of the OLs of each EOM acting against the elasticity of the pulley suspensions.[1,19]

Under coordinated control, rectus pulleys shift anteroposteriorly in the orbit by the same distance as the scleral insertions. Nevertheless, the OL and GL require different neural commands. The GL's mechanical load is predominantly the viscosity of the relaxing antagonist EOM, a load proportional to the speed of eye rotation, and thus slight during sustained eccentric gaze.[1] The OL's mechanical load, however, is due to the elasticity of the pulley suspension. This elastic load is independent of speed, but proportional to gaze angle. Electromyography (EMG) in humans correspondingly shows high, phasic GL activity during rapid saccadic eye movements, with only a small, sustained activity change in eccentric gaze. In the OL, EMG shows sustained, high activity in eccentric gaze, but no phasic activity during saccades. Differing mechanical loads on OL and GL are associated with the corresponding biological specializations. The ratio of motor nerve to muscle fiber is exceedingly low in the GL, averaging about one for human rectus EOM,[1] and reflecting the high precision required of ocular rotation. The ratio is higher in the OL, averaging five fibers per axon in horizontal rectus and 2.5 in vertical rectus EOMs, reflecting less precision for pulley control.

While rectus EOMs alone can implement all the eye movements conforming to LL, some eye movements do not conform. Violations of LL occur during the vestibulo-ocular reflex (VOR)[22] and during convergence,[19] and involve the oblique EOMs.

Considered by itself, the IO muscle also observes half-angle kinematics. As noted above, the IO pulley shifts by half of vertical ocular duction because the IO OL inserts on the IR and LR pulleys.[12] In primary position, these two OL insertions constrain the distal IO to be co-planar with the IR and LR pulleys, so that IO rotational axis is perpendicular to the primary gaze line, and perpendicular to the rotational axes of the rectus EOMs. In the Listing's coordinate system, this gives the IO a purely torsional action, capable of nothing other than violating LL. (In other coordinate systems, particularly the coordinate system employed for clinical examination, the IO also exhibits the familiar supraducting and abducting actions.) With oblique gaze shift from supraducted adduction to infraducted abduction, the IO pulley moves anteroposteriorly by half the movements of the IR pulley.[12]

The SO, with its immobile pulley at the trochlea, is actually the exceptional case. The broad, thin SO insertion on the sclera resists sideslip by virtue of its fan-like shape as it courses from the narrow trochlea. The SO approximates half-angle kinematics because the distance from trochlea to globe center is approximately equal to distance from globe center to insertion, the SO rotational axis shifts by half the horizontal duction.[19]

In addition to convergence, stereopsis requires torsional eye rotations such as excyclotorsion in convergence that violates LL.[19] During asymmetrical convergence to a target aligned to one eye, this extorsion occurs in both eyes, independent of eye position.[23] MRI during 22° asymmetrical convergence in the orbit aligned to the target, analysis of IR, MR, and SR muscle paths demonstrated 0.3–0.4 mm extorsional shift of the their pulleys in the coronal plane.[23] Thus, during convergence, the rectus pulley array rotates in the coronal plane in coordination with ocular torsion, changing the pulling directions of all of the rectus EOMs without altering their fundamental half-angle kinematics. The torsional rotation of the pulley array is implemented by the oblique EOMs. Contraction of the IO, directly demonstrated by MRI during convergence, excycloducts the positions of the LR and IR pulleys.[23] Inferior LR pulley shift is coupled to lateral SR pulley shift via the dense connective tissue band between them.[10] The SO's OL inserts on the SO sheath posterior to the trochlea, with both the tendon and sheath reflected via that rigid pulley. Anterior to the trochlea, the SO sheath inserts on the SR pulley's nasal border. Relaxation of the SO OL during convergence is consistent with electrophysiologic recordings in the monkey trochlear nucleus. The inframedial peribulbar smooth muscle might also contribute to rectus pulley extorsion in convergence.

Physiologic ocular counter-rolling (OCR) is a torsional VOR responsive to changes in head orientation relative to gravity, as sensed by the inner ear. Since OCR can change torsion independent of horizontal or vertical eye position, it violates LL. MRI in right versus left lateral decubitus positions demonstrates shift in torsional position of the rectus pulley array directionally consistent with the OCR, and associated with SO contraction and IO relaxation.[22]

Thus, all six EOMs have pulleys that cause their force directions to vary by the half the angle of ocular duction. This "half-angle" behavior makes the sequence of ocular rotations effectively commutative. For visually guided eye movements with the head upright and stationary, half-angle behavior gives the incidental benefit of conformity of ocular torsion to LL. In special situations, non-LL torsion is advantageous: in convergence, torsion facilitates stereopsis, and for the VOR, torsion facilitates retinal image stability during head motion. Rectus pulley reconfiguration coordinated with ocular torsion maintains the half-angle behavior required by commutative ocular kinematics even during deviations from LL.

Transverse compartmentalization of extraocular muscles

It is paradoxical that the robust kinematic behavior of the pulleys appeared to prohibit one prominent violation of LL: the VOR velocity axis changes by one-fourth eye position, not half as for LL,[24] yet motoneurons controlling cyclovertical EOMs do not command the violation.[25] Since these violations of LL require torsion generation without cyclovertical EOM action, horizontal rectus EOMs must somehow generate ocular torsion. This insight motivated the discovery of transverse compartmentalization,[26,27] a general feature of most EOMs.

Anatomy of compartmentalization

The abundance of fibers in each rectus EOM[28] suggests that individual EOMs could perform several functions using

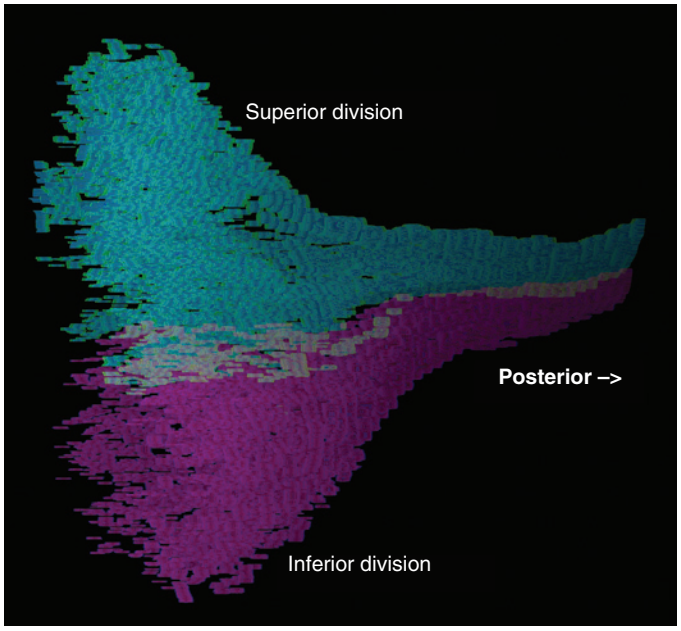


Fig. 74.9 Reconstruction of the intramuscular abducens nerve within the human lateral rectus muscle demonstrating non-overlapping superior and inferior divisions of the nerve innervating the corresponding compartments of extraocular muscles fibers.

specialized fiber groups. Motor nerves innervating horizontal rectus EOMs bifurcate into about equal regionally segregated intramuscular arborizations (Fig. 74.9).[27] Longitudinal LR splitting is evident in several congenital cranial dysinnervation disorders.[29–31]

The abducens nerve often divides into two or more trunks,[32,33] sometimes widely separated at the cavernous sinus.[32] The MR motor nerve also bifurcates into superior and inferior divisions.[27] The IO is also innervated in compartmental fashion by separate motor nerve trunks.[34] The IR has a selective lateral trunk overlapping arborization of another trunk throughout the entire EOM.[27] However, the SR lacks selective compartmental innervation.[27]

The SO is innervated in non-overlapping medial and lateral compartments by two divisions of the trochlear nerve, medial and lateral.[34,35] While its tendon insertion is broad, SO fibers roll into cylindrical configuration passing through the trochlea and unroll posterior to the trochlea where they become contiguous with muscle fibers.[34,35] The medial SO compartment is contiguous with tendon fibers inserting predominantly on the equatorial sclera that would have best mechanical advantage to produce incycloduction. The lateral SO compartment is contiguous with tendon fibers inserting predominantly on posterior sclera that would have best mechanical advantage to produce infraduction.

Compartmental biomechanics

EOMs and tendons are composed of parallel fiber bundles having sparse transverse interconnections. Tensile force transmission in arbitrary groupings of fibers is >90% independent of adjacent fibers,[36] as confirmed after marginal myotomy or tenotomy.[37] This supports empirically based EOM surgeries involving portions of rectus[38] or SO tendons,[39] and implies that EOM fiber groups can transmit tension independently, subject only to coordination of neural commands.

Strabismus surgeons have recognized that transverse shifting of rectus EOM insertions imparts cyclotorsion.[40,41] Computational simulation using the *Orbit 1.8* model suggests such shift could redirect 13–15% of LR force to vertical action, and 16–22% to cycloduction.[42] Compartmentalization could, therefore, create the torsion required to produce the LL violations that occur during the VOR.

Functional anatomy of compartmentalization

A similar ratio of inferior compartment to total LR transverse dimension prevails in cases where structural demarcations are evident,[43] consistent with postmortem nerve tracing from histology showing the ratio ranging from 0.4 to 0.6.[27]

During contraction, total EOM volume[44] and peak cross-section increase, and the peak shifts posteriorly,[43] usually by ~2 mm.[45] The best contractility index is change in posterior partial volume (PPV),[45] which robustly correlates with duction for horizontal rectus EOMs.[45] Correlations for maximum cross-section are almost as strong.[45] MRI studies have divided these EOMs into inferior and superior halves that are considered to represent the compartments. For both LR and MR, the inferior compartments are slightly larger than the superior compartments.[26] Contractility is similar for convergence and conjugate adduction in both inferior and superior LR compartments, and for the inferior MR compartment. However, the superior MR compartment exhibits much greater contractility in adduction than in convergence.

In normal subjects tilted on-side to produce ocular counter-rolling, MRI has demonstrated contractile PPV changes in the inferior but not superior LR compartments, and borderline contractile changes in superior MR but not inferior compartment.[26] These differential compartmental changes presumably contribute to cyclotorsion.[26] Differential compartmental changes in PPV were absent in vertical rectus EOMs.[26] During vertical duction, there are contractile changes in maximum cross-section and PPV of the superior MR compartment, without changes in the inferior MR compartment, or in either LR compartment.[46] Differential compartmental MR contractility might thus augment vertical duction.

Vertical fusional vergence

During vertical fusional vergence (VFV) in normal subjects induced by a monocular 2Δ base up prism, the LR exhibits differential compartmental contraction, along with a complex pattern of differential contractility in the SO compartments.[47] Differential contractile behavior of the LR during VFV suggest that the EOM mechanisms that normally compensate for vertical heterophoria are highly complex, presumably because of the necessity to regulate horizontal and torsional eye orientation.

Compartmental brainstem control

Differential compartmental behavior of EOMs requires control by selective motoneuron pools. The A and B groups of MR

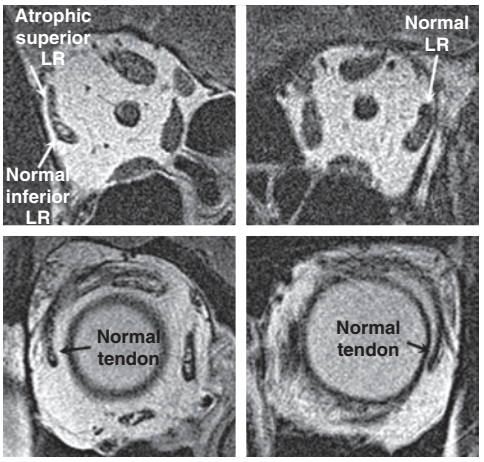


Fig. 74.10 Quasi-coronal magnetic resonance imaging (MRI) demonstrating right superior compartment lateral rectus (LR) palsy causing selective atrophy of the ipsilesional superior LR compartment.

motoneurons in the oculomotor nucleus are widely separated by the vertical rectus and IO motoneurons.[48] Both version and vergence signals are observed in MR and LR motoneurons.[49] The abducens nucleus has cyclovertical premotor inputs, including vestibular inputs from vertical eye movement pathways.[50] Neuroanatomic studies have suggested topographical segregation of motoneuron pools to the two LR compartments in monkey.[51]

Compartmental extraocular muscle pathology

Denervated human EOMs exhibit atrophy of cross-section and volume, and loss of contractile thickening.[52] About 30% of abducens palsy cases exhibit greater atrophy of the superior than inferior LR (Fig. 74.10), usually with ipsilesional hypotropia suggesting preserved inferior compartment function.[53] Many patients with paretic abduction deficiency have selective superior compartment LR weakness.[53] Many cases of isolated LR palsy exhibit hypertropia that increases in abduction, suggesting relationship to residual LR contraction.[54]

Pathologic anatomy of pulleys

Three forms of pulley pathology cause strabismus: heterotopy, instability, and hindrance. Heterotopy may be congenital or acquired.

Congenital pulley heterotopy

Many congenital cases of incomitant cyclovertical strabismus are associated with heterotopy of one or more rectus EOM pulleys >2 standard deviations from normal. Patterns of incomitance in individual patients consistently match those predicted by computer simulation based on pulley locations, suggesting that pulley heterotopy *caused* the strabismus.[55] In most of these cases, the strabismus exhibits "A" or "V" pattern. In a "V" pattern, for example, there is greater esotropia or less exotropia in downward gaze, with overelevation and overdepression in adduction (Fig. 74.11B). While this pattern of versions has been described as exhibiting "IO overaction" and "SO underaction," the pulley locations fully explain it, without necessity of abnormal contractile behavior by the oblique EOMs. Conversely, in "A" pattern strabismus, there is more esotropia or less exotropia in upward than downward gaze, and one or both LR pulleys are typically located superior to the MR pulleys (Fig. 74.11A). While this pattern of versions has been described as exhibiting "IO underaction" and "SO overaction," pulley locations fully explain the strabismus pattern, without necessity of abnormal contractile behavior by the oblique EOMs. The foregoing imaging findings suggest that clinical nosology be revised to avoid erroneous implications of oblique EOM contractile dysfunction, which can also be excluded directly by MRI observations of EOM function. For example, MRI demonstrated absence of correlation between IO size and contractility, and absence of correlations with variations in elevation in adduction in SO palsy. Evidence suggests that ocular torsion strabismus did not cause the pulley heterotopy: (1) typically only one or two pulleys were heterotopic; (2) ocular torsion was quantitatively insufficient to account for the pulley heterotopy; and (3) patients with similar ocular torsion due to SO palsy lack pulley heterotopy. Extreme pulley heterotopy is associated with esotropia and hypotropia in axial high myopia, the "heavy eye syndrome."[56]

Acquired pulley heterotopy

This may be the simple consequence of aging. The horizontal rectus pulleys of normal older people symmetrically sag inferiorly, probably causing the typical reduced supraduction range.[17] Histological examination shows that the dense connective tissue in the pulley tissues of children becomes attenuated in the elderly, with particularly striking age-related degeneration of attachments of the IO OL to connective tissues.[10]

Most cases of acquired pulley heterotopy are due to sagging eye syndrome (SES). Patients with SES typically exhibit adnexal laxity, including blepharoptosis, superior lid sulcus defect, and floppy lower lids.[17] Many have a history of blepharoplasty, brow lift, or facelift surgery. These changes are consistent with histologically demonstrable connective tissue degeneration.[10,57] MRI findings in SES are stereotypic. While orthotropic older controls exhibit 2 mm more LR pulley sag than young adults, LR pulley sag exceeds 6 mm in SES. LR sag is symmetrical in age-related distance esotropia (Fig. 74.11C), but in cyclovertical strabismus LR sag in the hypotropic eye exceeds its fellow by >1 mm (Fig. 74.11D). Degeneration of the LR-SR band in SES frequently causes temporal tilting of the superior aspect of the normally vertically oriented LR. Other rectus pulleys are also displaced in SES. EOMs are also elongated in SES. For example, the LR is elongated by ~50% from the normal value of 30–45 mm! This may be why surgery for age-related distance esotropia by MR recession requires dose augmentation in SES.[58]

Pulley instability

Pulleys may become unstable and shift markedly with gaze to alter EOM action, sometimes in one gaze position only. Inferior LR pulley shift in adduction may be acquired, and

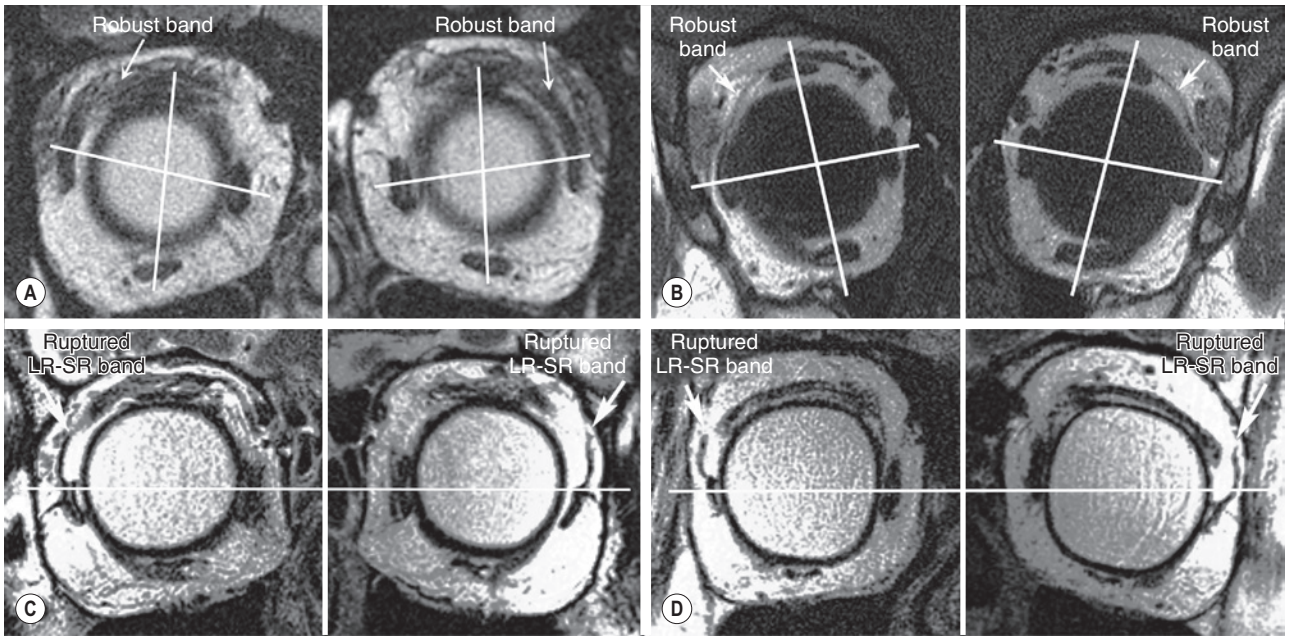


Fig. 74.11 Coronal plane MRI in strabismus due to pulley heterotopy.[63] (A) Typical pattern associated with congenital A pattern strabismus and over-depression in adduction, with LR pulley located superior to MR pulley. (B) Typical pattern associated with V pattern strabismus and over-elevation in adduction, with medial rectus (MR) pulley located superior to lateral rectus (LR) pulley. (C) Typical pattern of symmetrical LR pulley sag due to bilateral rupture of the LR-SR band ligament resulting in symmetrical inferior displacement of the LR, and presenting as age-related distance esotropia. (D) Typical pattern of asymmetrical LR pulley sag due to bilateral rupture of the LR-SR band ligament resulting in asymmetrical inferior displacement of the LR greater on the left than right, and presenting as left hypotropia and left excyclotropia. *(From Demer, JL. The Apt lecture: Connective tissues reflect different mechanisms of strabismus over the life span. J AAPOS 2014; 18: 309–315.)*

can mimic the restrictive hypotropia in adduction traditionally attributed to SO tendon sheath pathology (Brown syndrome), or "X" pattern exotropia.[59] An exaggeration of the physiologic excyclo-rotation of the rectus pulley array in convergence may produce a marked "Y" or "T" pattern exotropia, one present only in elevated gaze. Pulley instability can be diagnosed only by orbital imaging in multiple gaze positions. The most common instability is downward shift of the LR in supraduction or adduction,[60] the latter producing a restrictive hypotropia clinically identical to Brown syndrome of the SO tendon sheath.[60] Temporal shift of the SR is occasionally associated with inferior LR shift.

Pulley hindrance

Abnormally anterior pulley location, or failure of a pulley to move posteriorly during EOM contraction, can result in pulley collision with the scleral insertion and hinder duction. This is also the case after fadenoperation, where there is restriction to passive forced duction of the eye. Hindrance to posterior IR pulley shift due to scarring from inferior orbital[61] or lid surgery creates incomitant, restrictive hypertropia.[62]

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The orthoptic evaluation

Darren T Oystreck

Chapter contents

INTRODUCTION
DEFINING THE CONCEPT OF ORTHOPTIC EVALUATION AND ORTHOPTIC STATUS
INDICATIONS FOR AN ORTHOPTIC EVALUATION
THE BASIC ORTHOPTIC EVALUATION
DESIGNING A PATIENT-SPECIFIC ORTHOPTIC EVALUATION: FACTORS TO CONSIDER
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REFERENCES

Introduction

"I have double vision"… "I sometimes have double vision"… "Images overlap"… "Images tilt"… "Images shake"… "My eyes are crossed"… "My eyes are strained"… "My neck is sore"… "My eyes just don't work together!"

Disorders of binocular vision, disruption of ocular alignment and motility can induce numerous subjective symptoms; sorting through these falls within the domain of the orthoptic evaluation.

The aim of this chapter is to:

- describe the concept of orthoptic evaluation and orthoptic status;
- outline indications for conducting an orthoptic evaluation;
- outline an approach to the basic orthoptic evaluation;
- highlight important factors when designing a patient-specific evaluation.

Descriptions of strabismus are usually technically driven and communicate information to the clinician about the patient's binocular status. This chapter covers the principles underlying a basic orthoptic evaluation.

This is not a "how to" chapter. Excellent resources are available describing tests and how to perform them.[1–4] Nor does it deal with the neurophysiology of binocular vision and associated cortical pathways. The reader is again directed to other excellent sources.[3,5] This chapter also assumes that the reader is familiar with strabismus terminology (e.g. manifest, latent, comitant, incomitant, etc.) and a basic understanding of binocular vision and amblyopia.

Defining the concept of orthoptic evaluation and orthoptic status

The orthoptic paradigm for disorders of binocular vision involves generating clinical data through a standardized *orthoptic evaluation*, interpreting the results to define the *orthoptic status* of the patient, and to use this information to formulate the best management approach.

The orthoptic evaluation

The *orthoptic evaluation* consists of three essential components (Fig. 75.1):

- motor evaluation;
- sensory evaluation;
- vision evaluation.

The terms "motor evaluation" and "sensory evaluation" have been used before.[1] "vision evaluation" has been added as a separate component. Each component has main themes (Fig. 75.2).

The vision evaluation

Symptoms relating to the subjective clarity of vision are elicited from the history and the central visual acuity is determined under monocular and binocular conditions.

As well as the ocular and visual pathway integrity, it is also influenced by the sensory and motor systems. For instance, a patient may use accommodation-convergence to help control an exodeviation, thus blurring their binocular distance visual acuity. Conversely, vision can affect the motor and sensory evaluation. Reduced vision weakens the effectiveness of these systems and can lead to a degradation of the orthoptic status.

An accurately performed vision evaluation can:

- determine selection of appropriate motor and sensory tests and the reliability of the results; poor vision in one or both eyes reduces accuracy of quantifying strabismus and negatively impacts sensory testing;
- assess the significance of amblyogenic mechanisms when present;
- determine the outcome of management, e.g. correction of refractive error or amblyopia therapy
- distinguish between suppression and amblyopia when evaluating sensory adaptations.

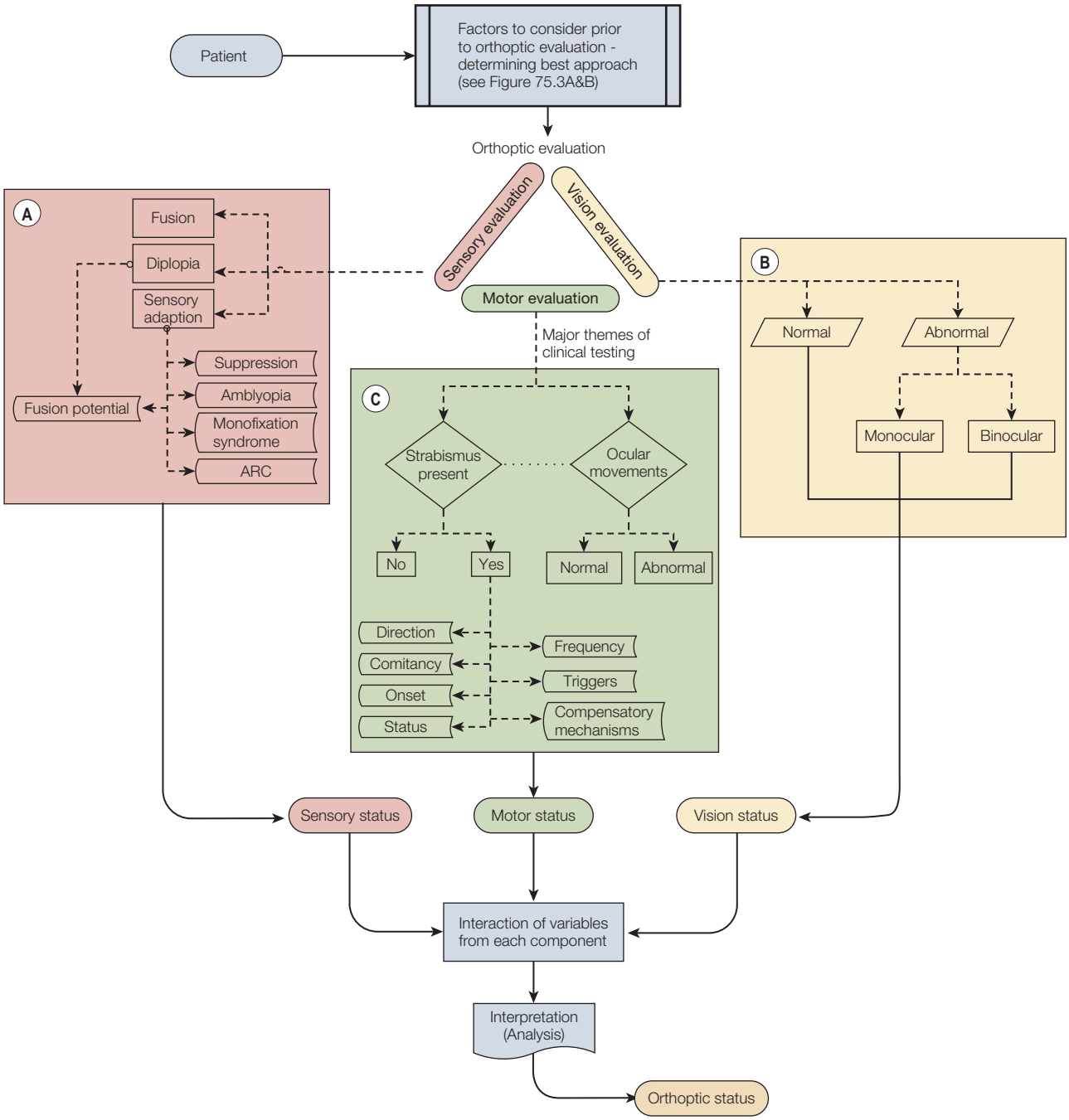


Fig. 75.2 The orthoptic paradigm pathway: main themes and determination of orthoptic status. Defining the orthoptic status involves a series of steps that ensures efficiency and accuracy. The first step identifies factors to help determine the best approach for a given patient or situation. Next involves specialized clinical testing to assess major themes within each of the core components (A, B, and C). The interaction between each component is analyzed and interpreted. The outcome constitutes the orthoptic status of a patient. This information is used to determine best management approach. (Additional details provided in Table 75.1.) ARC, Abnormal retinal correspondence.

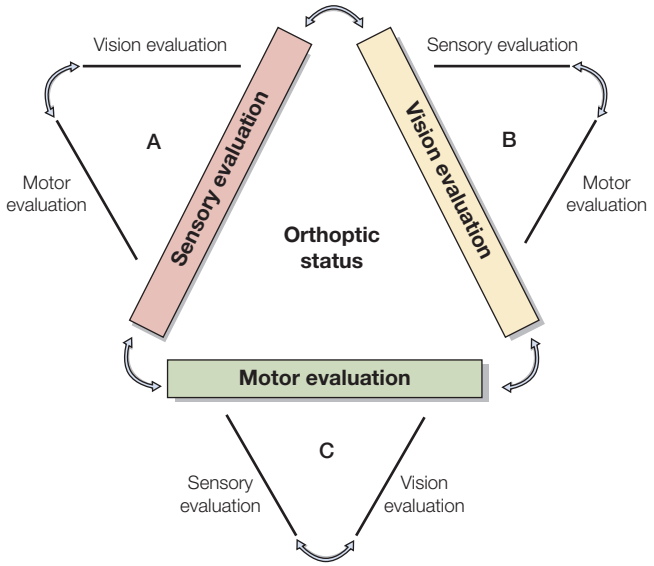


Fig. 75.1 Core components of the orthoptic evaluation. The orthoptic evaluation is represented as a triangle (or prism!). Each side represents one core component. Defining the orthoptic status of a patient requires information from each side of the intact triangle. A triangle with symmetrical sides (i.e. the inner triangle with colored sides) represents an evaluation requiring full assessment of all components. However, the dimensions may shift depending on clinical needs: (A) An orthoptic work-up weighted to a sensory evaluation. (B) An emphasis on a vision evaluation, e.g. amblyopia follow-up appointment. (C) An emphasis on a motor evaluation.

The sensory evaluation

The sensory evaluation represents the brain's processing of information coming from the two eyes. It is defined by the patient's subjective interpretation of this response. It is often the least understood component of the orthoptic evaluation and its important conclusions may be overlooked. The sensory evaluation has three main components: fusion, binocular diplopia, and sensory adaptions (Table 75.1).

Fusion

Fusion is the blending of an image from each eye into a single image. This necessitates the stimulation of corresponding retinal elements and occurs within the visual cortex.[5]

In order for fusion to occur, appropriate alignment of the visual axes and reasonable vision in each eye are necessary. However, several other clinical situations need to be recognized (Table 75.2). It is crucial to understand these to interpret how the eyes work together in order to avoid inappropriate management.

Diplopia

Binocular diplopia occurs when non-corresponding retinal elements of each eye are stimulated by the same object of regard in free space. As with fusion, it also represents a normal sensory system; however, one that is operating within an abnormal motor status, e.g. manifest deviation. Localization of diplopic images provides information about the direction and

Table 75.1 Sensory evaluation – assessment of the main themes

OBJECTIVES:

- To determine how the brain uses information from both eyes
- To determine what binocular information the brain permits the patient to perceive
- To determine if a normal sensory status (single vision with fusion) can be achieved (under the right setting)

SUBCOMPONENTS (MAIN THEMES):

- Fusion (including stereopsis)
- Diplopia
- Sensory adaptation (occurring secondary to disruption of motor system or vision during visually immaturity)

Specific items	Questions to be answered/comments
Fusion*	Present: yes or no? Actual versus potential? Actual fusion: • Occurs under normal binocular viewing conditions • Demonstrable with standard sensory tests e.g. Worth 4-dot test, Titmus stereotest, etc. Potential for fusion: • Fusion only achievable with use of prisms or major amblyoscope Quality? • Bifoveal fusion/central fusion: generally associated with high level stereopsis • Peripheral fusion: generally associated with reduced stereopsis and central suppression of one eye • Gross fusion: absence of stereopsis on clinical testing; binocular cooperation only demonstrable with minimally dissociated tests such as Bagolini striated lenses Strength? • Size of fusional amplitudes • Be aware of fragile or large amplitudes Quality and strength are regarded as stabilizing influences to maintain proper ocular alignment. Low-grade fusion (e.g. reduced or absent stereopsis on clinical testing) and fragile fusional amplitudes suggest a higher risk of losing control of an existing phoria or intermittent tropia or represent a suboptimal sensory outcome following previous strabismus management

Table 75.1 Sensory evaluation – assessment of the main themes—cont'd

Specific items	Questions to be answered/comments

Diplopia*	Is it true binocular diplopia?
	• Two images present both eyes open
	• Separation between images (exception can be torsional diplopia or with central fusion disruption)
	• One image eliminated with closure of either eye
	
	Image separation?
	• Horizontal, vertical, torsional, or combined
	
	Constant or intermittent?
	
	Is there appropriate localization of diplopic image?
	• Homonymous (uncrossed) diplopia with esotropia etc.
	• Confirms normal retinal correspondence
	
	Is diplopia eliminated by offsetting the deviation with prisms or major amblyoscope?
	• Does this permit fusion or utilize a pre-existing suppression area?
	• What components of the deviation and how much needs to be corrected?
	  • Horizontal, vertical, torsional component, or a combination
	  • Full correction vs. partial correction required

Sensory adaptation†	Does the patient have any binocular symptoms with both eyes open?
	If no, suggests presence of sensory adaptation in the setting of a manifest deviation
	
	Type of adaption?
	Suppression*
	• Only persists under binocular conditions
	• Area of suppression (in non-preferred eye) may include:
	  • visual field overlapping the preferred eye
	  • central suppression (macular area) with fusion involving peripheral retinal elements, e.g. monofixation syndrome
	• Depth of suppression
	  • diplopia appreciated under minimally dissociative conditions is considered fragile
	• Determine if there is fusion potential
	  • offset angle of deviation with major amblyoscope to simulate straight eye viewing condition
	Abnormal retinal correspondence*
	• Only persists under binocular conditions
	• Determine if fragile or well established – strabismus surgery may be contraindicated if well established
	Amblyopia*
	• Similar binocular sensory tests as suppression but with reduced monocular vision with closure of preferred eye
	• Responds to appropriate management if still within critical period

Sections correspond to Fig. 75.2A.
*Can exist with other sensory findings in the same patient.
†Specific to manifest or intermittent deviations.

Table 75.2 Defining the orthoptic status: examples of interactions between sensory and motor features (fusion and strabismus)

Situations when fusion occurs in the setting of a manifest deviation	
Small-angle heterotropia	Manifest deviation (less than 10 prism diopters) associated with peripheral fusion and mild amblyopia, e.g. monofixation syndrome
Well-established ARC	Fovea of fixating eye corresponds to a non-foveal point in the deviating eye Fusion, at best, is peripheral and usually fragile Clinical concern is for binocular relationship to persist after surgical correction resulting in postoperative diplopia
Fusion potential	Fusion under normal viewing conditions is not present; however, it can be demonstrated by "simulating" normal alignment with the use of prisms or major amblyoscope
Intermittent manifest deviation	A normal sensory status (presence of fusion) when the deviation is controlled (i.e. not manifest) Re-evaluation of alignment is warranted in presence of a presumed manifest deviation but a sensory status that indicates fusion
Situations when fusion occurs only in certain positions of gaze	
Incomitant strabismus with limited ocular movement	Visual axes become aligned in a certain gaze direction permitting fusion; diplopia/suppression may be evident in all other positions where the deviation is manifest, e.g. normal alignment in left gaze with a right abduction deficit Patients with this motor finding are not expected to have amblyopia or ARC
Incomitant strabismus without limited ocular movement	Includes strabismus patterns with: Distance/near disparities e.g. convergence excess type esotropia where esotropia may only be present at near "A" or "V" pattern with no manifest deviation in one vertical gaze position and a significant deviation in opposite direction

Continued

Table 75.2 Defining the orthoptic status: examples of interactions between sensory and motor features (fusion and strabismus)—cont'd

Situations when fusion may be influenced by refractive status	
Fully refractive accommodative esotropia	Esotropia eliminated by full correction of hyperopic refractive error
Intermittent exotropia	Improved control of an exodeviation after correction of myopia, i.e. improved vision and/or stimulation of accommodation helps control the deviation and promotes fusion

Above examples illustrate the ability to achieve fusion in the setting of an abnormal motor status.
ARC, Abnormal retinal correspondence.

comitancy of the ocular misalignment. Table 75.1 describes other important issues related to the evaluation of diplopia.

Sensory adaptions

A sensory adaption is a cortical defense mechanism. The goal is to prevent the appreciation of an unwanted image in the setting of abnormal binocular alignment. These develop during the visually immature period but, once established, can persist throughout life. In some cases, a crude level of binocular cooperation still exists. Strabismus during visual immaturity is a common stimulus for sensory adaptations. Thus, the absence of diplopia in the presence of a manifest deviation is an important clue to the age at onset. The commonest sensory adaption is cortical suppression where the visual field of the deviating eye that overlaps with the fixating eye is suppressed.[6] Other adaptions include: central suppression scotoma with peripheral fusion (e.g. monofixation syndrome), amblyopia, and abnormal retinal correspondence (see Fig. 75.2A). Identification of a sensory adaption is crucial to strabismus management and to predict the prognosis for restoring a normal sensory and motor status.

An accurately performed sensory evaluation can:

- define binocular symptoms (or lack of expected symptoms) in the presence of an abnormal motor or vision status;
- determine the actual and potential ability for the two eyes to work together;
- identify potential barriers for the eyes to work together, e.g. torsion, central fusion disruption;
- predict if surgical correction of strabismus will re-establish fusion and/or eliminate binocular symptoms, or identify risks of creating binocular symptoms.

The motor evaluation

The motor evaluation determines the presence and degree of a strabismus or ocular motility problem. These features are defined by their characteristics, e.g. comitant versus incomitant, and are discussed in detail in Table 75.3.

An accurately performed motor evaluation can:

- determine if a patient's symptoms are due to strabismus;
- determine function of the extraocular muscles, as well as the integrity of the neurological pathways and the other structures involved in movement of the eyes;
- identify strabismic patterns to help select best management strategies.

Defining the orthoptic status: putting it all together

The interplay between vision, sensory, and motor evaluations defines the *orthoptic status* of the patient. Correctly interpreting these interactions is crucial to understanding the test results. It is essential to correlate clinical findings with the patient's symptoms, or, in some cases, lack of symptoms. Figure 75.2 outlines this process, while Fig. 75.3A,B illustrates important pre-testing factors that also influence the final orthoptic status. Clinicians need to have an in-depth understanding of the synergy between these features and the various outcomes that can arise to ensure appropriate management. Table 75.2 gives some examples of these interactions.

Defining the orthoptic status can be a daunting task. This can be particularly confusing in patients who may have more than one motor and sensory finding (see Table 75.2: "intermittent manifest deviation" and "incomitant strabismus"). A useful approach to this process is to use an algorithm. One suggestion is to begin by determining the ocular alignment (motor status) with a simple cover test. The subsequent algorithm pathways are determined by the sensory responses that arise as the evaluation continues. Figure 75.4 illustrates this algorithm. Table 75.4 provides details for each section of the algorithm.

Indications for an orthoptic evaluation

Any patient with a known or suspected *abnormality of ocular motility* should undergo an orthoptic evaluation. The goal is to document the presence of the strabismus, to identify the presence and pattern of incomitance, and to note other features that may contribute to classification.

An orthoptic evaluation is also indicated in the presence of *visual symptoms*. These may be specific or vague and can represent a new sensory or motor problem. The goal is to determine the motor and sensory basis of the symptoms. Table 75.5 lists symptoms that warrant an orthoptic evaluation.

The presence of *specific signs* also warrants an orthoptic evaluation. Ophthalmologic, neurologic, or systemic disorders affecting binocular vision may not always be associated with visual symptoms. This is particularly true in patients with pre-existing childhood strabismus or very slow evolving strabismus (e.g. chronic progressive external ophthalmoplegia). Therefore, it is imperative for the clinician to be aware of certain signs suggestive of underlying pathology. Clinical signs that warrant an orthoptic evaluation are described in Table 75.5.

The basic orthoptic evaluation

Figure 75.5 outlines a simple flow chart for conducting a basic orthoptic evaluation. The steps within the flowchart are discussed here.

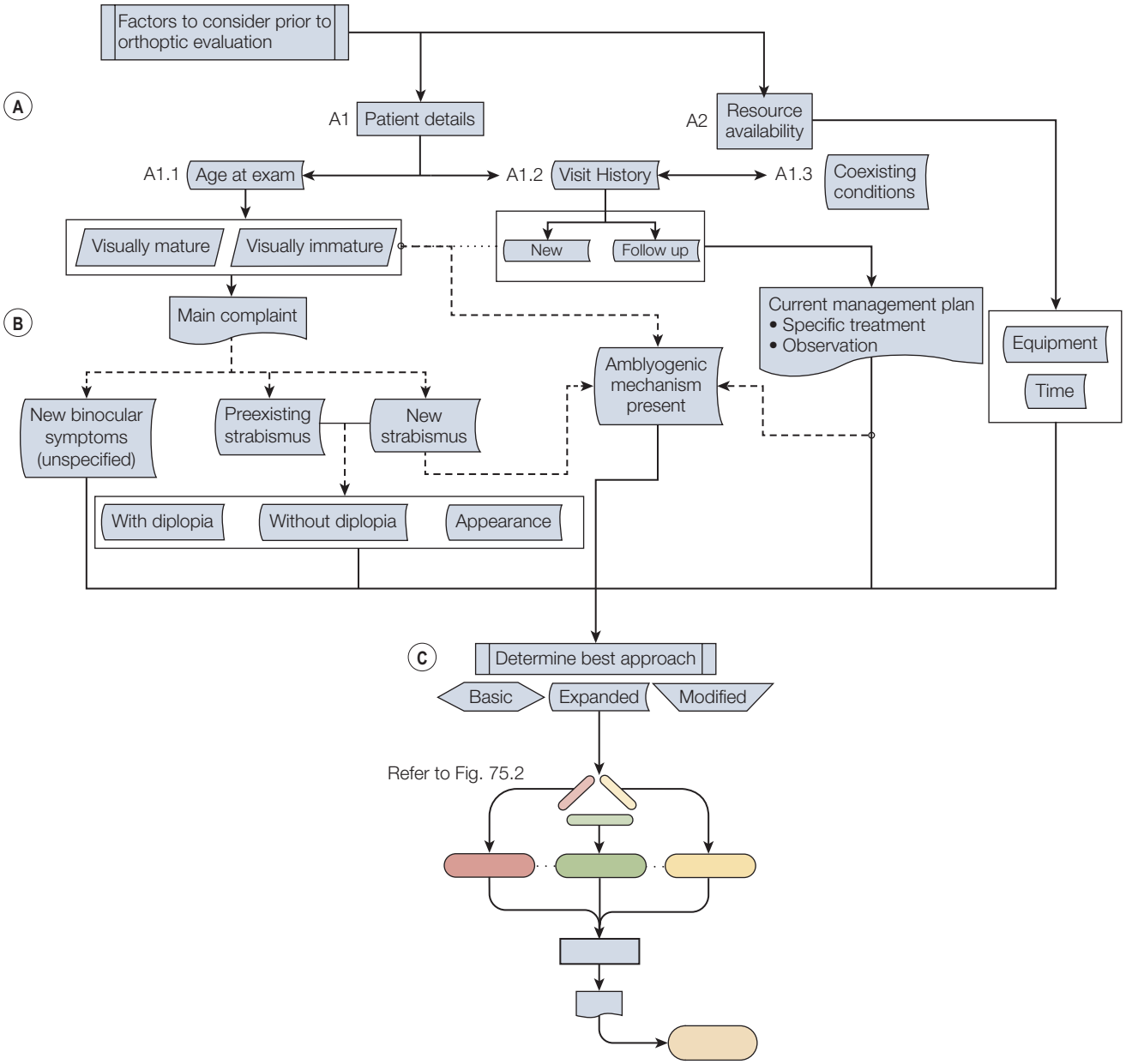


Fig. 75.3 Pre-testing factors to consider when determining best approach to the orthoptic evaluation. Section (A) and (B) expands step 1 in Figure 75.2. These are essential when designing the best approach to the orthoptic evaluation (C).

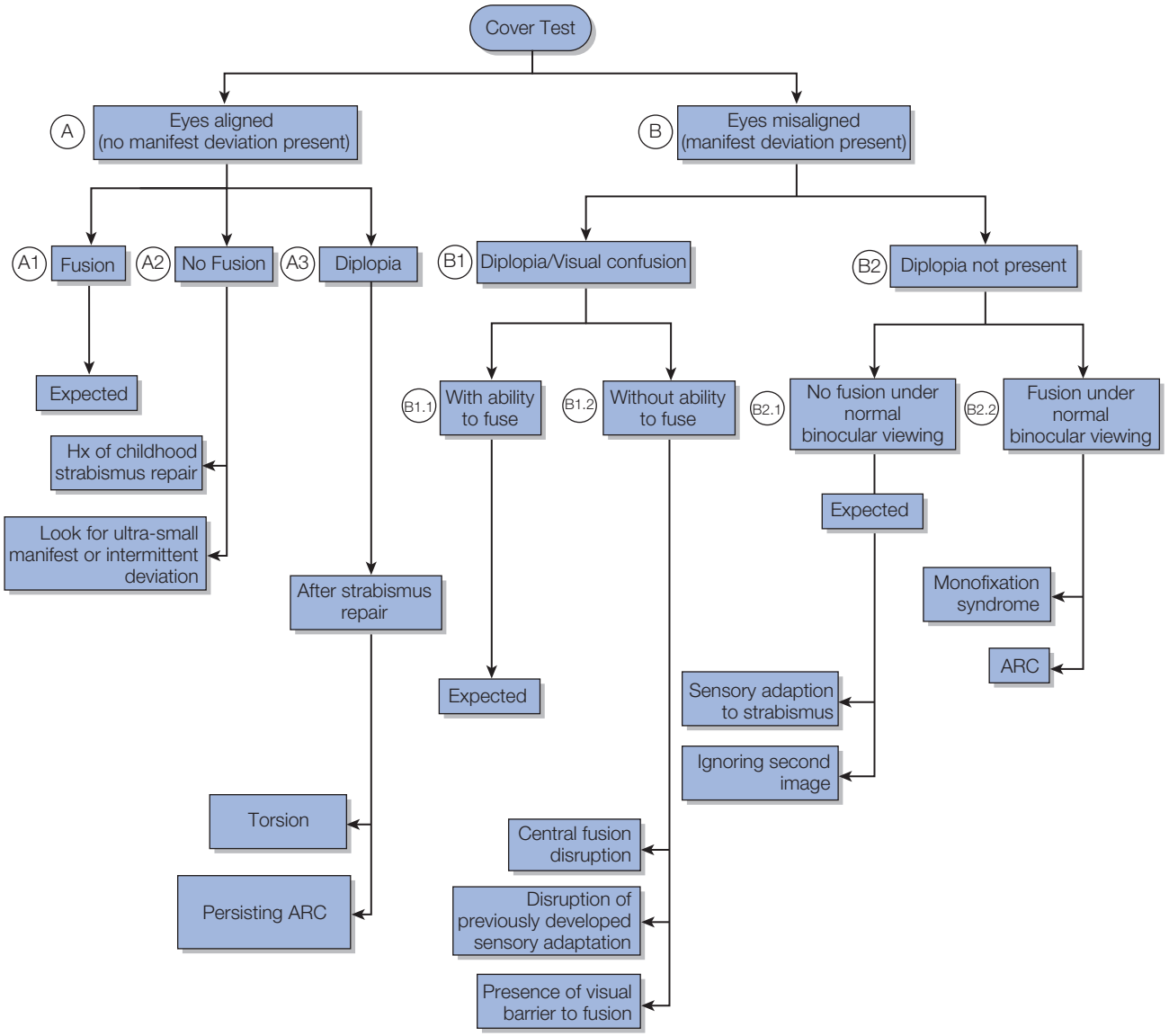


Fig. 75.4 Putting it all together – algorithm to determine the orthoptic status. A flowchart to facilitate determination of the orthoptic status. Pathways are determined by the sensory responses for a given ocular alignment as determined by the cover test. It already takes into account underlying influences of vision. Table 75.4 provides full details of each arm of the flowchart. ARC, Abnormal retinal correspondence; Hx, history.

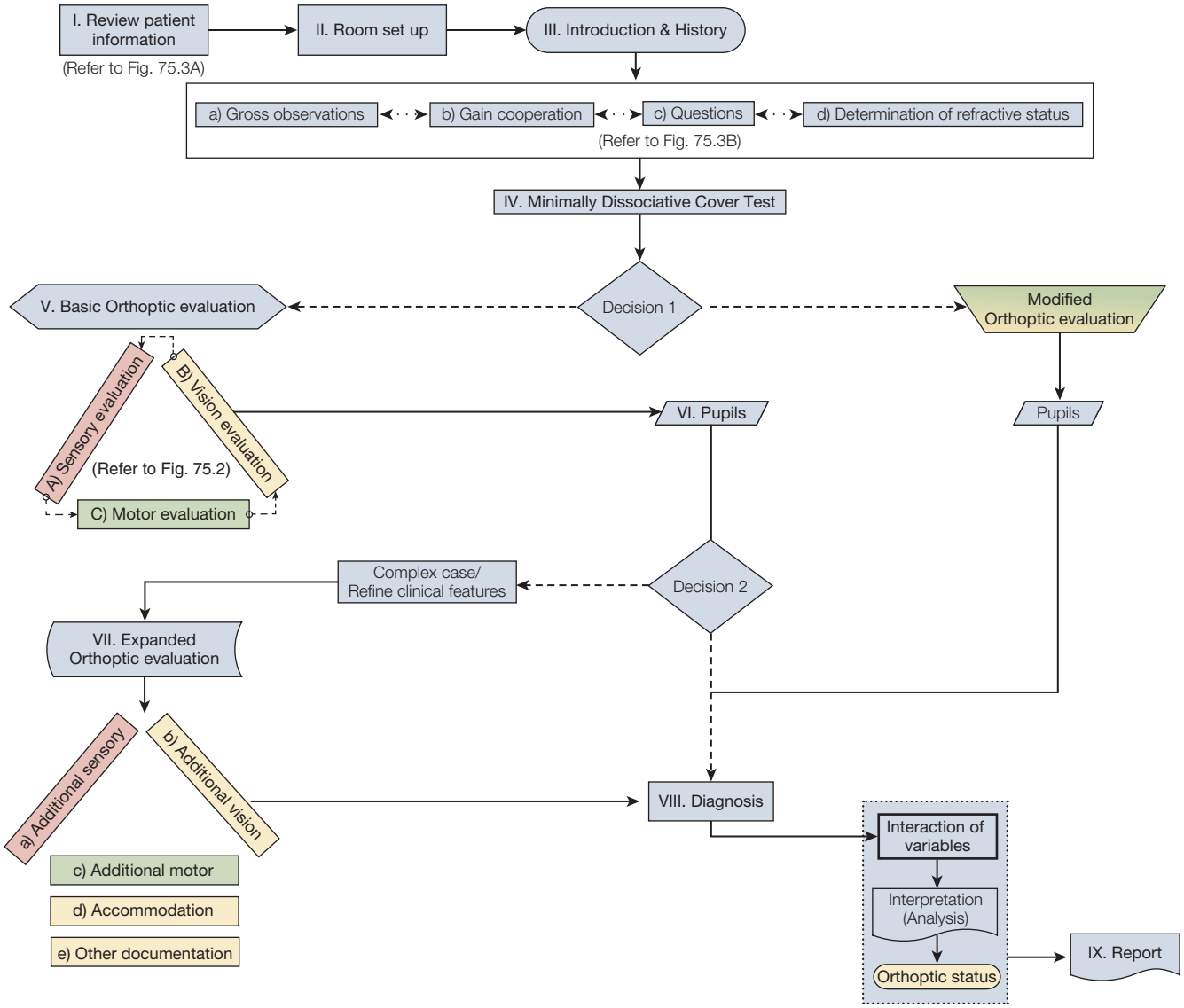


Fig. 75.5 The orthoptic evaluation: pathway for clinical testing. Refer to section "The basic orthoptic evaluation" for full details.

Table 75.3 Motor evaluation: assessment of the main themes

Determine if strabismus is present
Assess ocular alignment

If present
Assess the following characteristics

Direction:
Determine direction of the deviation, e.g. horizontal, vertical, torsional, or combination
- First step to generating differential diagnosis
- Combine with ocular movements to refine diagnosis, e.g. distinguishing exotropia with an adduction deficit from exotropia with full ocular movements

Frequency (control):
Refers to control of the strabismus, i.e. how often the eyes are aligned or misaligned
Determine if constant or intermittent
Dictates need and/or timing of treatment
Influences sensory status and vision status, particularly in visually immature patients

Comitancy:
Determine if angle is same (comitant deviation) or increases/decreases (incomitant deviation) in different gazes and distances. Used to classify the strabismus
- Assessment only in primary position can miss critical information leading to an erroneous diagnosis and poor management planning
- Incomitant strabismus can identify subtle limitations of ocular motility that might otherwise go unnoticed during gross evaluation of the eye movements

Triggers:
Determine if a strabismus can be induced or the size increased
- Examples: Looking up and in with Brown syndrome; or other factors such as fatigue
- These may be first identified in the history but must be documented in the motor evaluation

Compensatory mechanisms*:
Determine if a strabismus can be reduced or eliminated
- This is converse to identifying triggers that exacerbate strabismus
- This might be a conscious or unconscious effort by the patient to improve binocular functioning

Onset of the deviation:
Determine if newly acquired, longstanding, or congenital. Clues within the motor evaluation can help answer this.
- Examples: primary and secondary deviations; degree of incomitance; and fusional amplitudes

Status of the deviation:
Determine if deviation is worsening, improving, stabilizing, or variable over serial visits. This is influences management decisions
Examples:
- Observe and wait for resolution (getting better each visit)
- Proceed with medical investigation (worsening each visit)
- Proceed with strabismus surgery (unresolved stable angle)

Careful history taking can assist in this area but it is most accurately determined by serial orthoptic evaluations providing objective documentation

If *not* present

Confirms *pseudostrabismus*
Rules out disruption of motor system in patient with a vague unspecified binocular symptom
Attention to be directed to other areas such as accommodation, refractive status, media, or retina
Media or retinal anomalies may create monocular image distortion affecting binocular cooperation, e.g. *metamorphopsia* and *aniseikonia*. These are assessed within the sensory and vision components of the orthoptic evaluation

Determine if the eyes move normally
Evaluate the following features

Extent of ocular excursion in all directions of gaze:
Involves assessing versions and then ductions
- Greater ductional movement suggests innervational mechanism
- Equal limitations suggests restrictive mechanism

Quality of eye movements
Integrity of the eye movement subsystems must also be assessed, e.g. saccades, smooth pursuit, vestibular, OKN, and even presence of Bell's phenomenon

Other points:
Some forms of strabismus come with full ocular movements (e.g. comitant)
Absence of strabismus does not always rule out the absence of ocular motility deficits
- Supranuclear pathway anomalies that only affect the quality of eye movements (e.g. ocular motor apraxia)
- Nuclear or supranuclear anomalies resulting in bilateral symmetric limitation of eye movement (e.g. gaze palsy)

Sections correspond to Fig. 75.2C.
*Table 75.4 gives examples of commonly employed compensatory mechanisms, of which not all are related to strabismus.

Table 75.4 Putting it all together: working through an orthoptic algorithm to define the orthoptic status

Cover test finding*	Response by the sensory system	Explanation
A. Eyes aligned (no manifest deviation present)	A1. Fusion	The expected sensory finding The quality of fusion/stereopsis should then be assessed
	A2. No fusion	Alternative explanations must be sought This can include presence of poor vision or a history of having late surgery for a childhood strabismus These cases rarely come with completely straight eyes and the clinician should be vigilant for an ultra-small manifest deviation
	A3. Diplopia	May occur after strabismus repair Examples can include: Torsion • Residual torsion acting as a barrier to fusion following correction of vertical strabismus, e.g. superior oblique palsy • Torsional malposition of the globe cannot be visualized by cover test and eyes will appear aligned Persisting abnormal retinal correspondence (ARC): • Continued correspondence of fovea of one eye and a pseudofoveal point in fellow eye under binocular viewing conditions can result in appreciation of diplopia despite normalized ocular alignment
B. Eyes misaligned (manifest deviation present)	B1.1. Diplopia/visual confusion present – **with** ability to fuse	Diplopia is the expected sensory response in a visual adult with normal retinal correspondence. Some patients may alternatively appreciate visual confusion Fusion of the images is also expected if the deviation is offset by prisms or with the use of a major amblyoscope Important to identify an etiological mechanism such as incomitant strabismus or decompensation of pre-existing heterophoria or monofixation syndrome
	B1.2. Diplopia/visual confusion present – **without** ability to fuse	Fusion of images is not possible with use of prisms, major amblyoscope, or surgical re-alignment of the visual axes Potential explanations: **Central fusion disruption** following: • Severe closed head trauma • Restoration of vision after prolonged monocular visual disruption and development of a sensory strabismus, e.g. correction of longstanding aphakia with a contact lens or intraocular lens implant **Disruption of a previously developed sensory adaption:** Diplopia is appreciated if disruption occurs as a visual adult. Examples: • Surgical overcorrection of a childhood strabismus • Occlusion of dominant eye, e.g. aggressive amblyopia therapy in visual adults. Diplopia will be appreciated at all times • Reduction of vision in dominant eye, e.g. new cataract, corneal scar. Diplopia only present when fixing with previously non-dominant eye, i.e. fixation-switch diplopia **Presence of visual barriers to fusion:** Preceding or concurrent to onset of deviation visual barriers may prevent fusion of images. For example, dissimilar appearance of image from each eye such as aniseikonia or metamorphopsia
	B2.1. Diplopia not present – **no** fusion under normal binocular viewing	Awareness of this category is essential when evaluating an asymptomatic patient seeking correction of a longstanding childhood strabismus Absence of diplopia in the setting of a manifest deviation is not an expected sensory response. Potential explanations: **The patient has developed a sensory adaption:** • Expected if onset of strabismus was during visual immaturity • Once developed can persist into adulthood Examples: • Suppression • Amblyopia **Diplopia is present but not readily appreciated (i.e. ignoring second image):** • Marked image separation due to large angle strabismus • Significantly reduced vision (rare). Clinician should be cautioned that poor vision (excluding amblyopia) rarely inhibits the appreciation of diplopia. Patients with count fingers vision can still have binocular symptoms although they may not actually be able to identify the second image

Table 75.4 Putting it all together: working through an orthoptic algorithm to define the orthoptic status—cont'd

Cover test finding*	Response by the sensory system	Explanation
	B2.2. Diplopia not present – fusion **present** under normal binocular viewing	This category represents other sensory adaptions that may occur **Monofixation syndrome:** • Represents as subgroup of patients with a small manifest deviation (<10 prism diopters) who have developed peripheral fusion with a demonstrable central suppression scotoma under binocular conditions • Typically occurs following surgical correction of a larger deviation • Patients generally have good ocular cosmesis and do not seek further correction surgery **Abnormal retinal correspondence (ARC):** • Rare situation in which some degree of fusion develops in the presence of a modest sized manifest deviation (~12–20 PD) • A non-foveal point in the deviating eye now has a common visual direction with the fovea of the fixing eye. This relationship only occurs under binocular viewing • A patient with ARC generally presents without binocular symptoms and is usually seeking surgical correction to improve appearance of the ocular alignment • This sensory finding should raise a red flag for the clinician. Patient requires additional testing to evaluate the likelihood of inducing postoperative diplopia if surgical correction is done

Alphanumeric codes correlate to Fig. 75.4.
*Only considers primary position, therefore sensory status may differ in different positions of gaze.

Table 75.5 Indications for an orthoptic evaluation

Indication	Objective
Suspected motor system anomaly	Identify presence of true strabismus Classify type of strabismus (comitant vs. incomitant)
Known motor system anomaly	Provide evidence for etiological mechanism (e.g. innervational, mechanical, or sensory forms) Determine role of non-surgical management (e.g. prisms, monocular occlusion, utilizing head postures) Document stability of deviation over time Provide information to help selection of surgical plan Aim is to maximize outcome and minimize postoperative surprises (e.g. identifying incomitance that may need to be addressed – "A" or "V" patterns, lateral incomitance, distance/near disparities) Identify presence of a sensory adaption Determine effect of treatment e.g. postsurgical or medical intervention
Visual Symptom	
Double vision (diplopia)	Confirm true binocular diplopia arising from manifest or intermittent deviation
Two different images overlapping (visual confusion)	Alternate symptom to diplopia Objective same as above
Image moving or shaking (oscillopsia)	Confirm symptom is the subjective perception of moving or shaking images Identify presence of nystagmus as this symptom is typically due to acquired nystagmus as a visual adult Confirm if isolated symptom or in conjunction with diplopia
Eye strain or browache (asthenopia)	Determine if nonspecific symptom is due to increasing difficulty to control a pre-existing heterophoria This may occur in a patient who is increasing accommodative effort to improve control of an exodeviation This effort may also arise with new hypoaccommodation. An effort to increase accommodation can lead to this symptom as well as worsen control of an esodeviation as a result of increased accommodative-convergence
Changing clarity of binocular vision	Determine if this accommodation is being used to help control a deviation, either for an esodeviation (relaxes accomodation) or an exodeviation (increases accommodation) Determine if due to non-corrected, uncorrected, or inappropriately corrected refractive error
Vague visual symptom occurring with both eyes open	Useful in situations where a patient is unable to clearly articulate their binocular symptom Determines if symptom can be attributed to a motor, sensory, or vision anomaly for which appropriate investigation can be directed
New unexplained vision loss (suspected malingering or functional visual loss)	Generate information about the integrity of the afferent visual system by indirect means (e.g. document high-grade stereopsis)

Continued

Table 75.5 Indications for an orthoptic evaluation—cont'd

Indication	Objective
Specific Signs	
Eye appears deviated	Confirm presence of true strabismus and evaluate the resultant effect on the sensory system, i.e. does the patient have diplopia, ignores the second image, or developed a sensory adaption? Confirm pseudostrabismus and possible etiologies, e.g. quantify palpebral fissure asymmetries, lid malposition, and angle kappa
Eyes appear different sizes	Quantify exophthalmos and enophthalmos that may suggest orbital or systemic disease
Malposition of lid	Quantify ptosis or lid retraction Determine potential association with motor system anomalies. Examples: • constant ptosis arising from cranial nerve III palsy (innervational disturbance) • variable ptosis arising from myasthenia gravis (neuromuscular junction defect) • lid retraction from thyroid orbitopathy (myopathic disease)
Anisocoria	Confirm presence Determine which pupil is abnormal Document evidence of other signs of a cranial nerve III palsy in the setting of a non-reactive dilated pupil
Abnormal head posture	Confirm presence Determine reason for utilizing, i.e. is this attributable to an ophthalmological problem?
Monocular eye closure	Determine if frequent closure of one eye is to eliminate a diplopic image or if associated with intermittent exotropia
Detection of amblyogenic mechanism in visually immature patients	Determine the presence of a deviated eye (strabismus); defocused eye (refractive error or accommodative anomaly); or a deprived eye (blockage of visual axis by ptosis or media opacity)
Detection of amblyopia	Determine vision status in the presence of an amblyogenic mechanism
Change in vision status	Determine the effect on binocularity when there has been a change in refractive status, loss of vision, or even improvement in vision Elucidate symptoms arising from difference in image size (aniseikonia) and clarity or distortion of vision (metamorphopsia)
Vision assessment in difficult populations	Not specific to the orthoptic evaluation; however, assessment of vision in difficult patients frequently falls within the domain of the orthoptic evaluation

Review patient information (I.)

Reviewing all available patient information prior to bringing the patient into the exam room will save time and help to focus your questions, identify the main goals of the evaluation, and determine if additional testing may be indicated. Figure 75.3A illustrates factors to consider prior to initiating clinical testing.

Room set up (II.)

The next step is to prepare the exam room and make appropriate alterations. These may range from preparing the preverbal acuity chart for a young patient to distributing furniture for wheelchair access and ensuring equipment is clean and working properly.

Preparation helps ensure the exam is efficient and focused. This is important in young patients who may quickly lose concentration.

Introduction and history (III.)

The initial interaction with the patient and family sets the stage for the rest of the evaluation and provides an opportunity to determine the best approach.

The process includes:

Making gross observations (III.a)

These include:

Disposition:

- Is the patient cheerful, upset, or shy? Useful when determining best way to gain cooperation.

Body:

- Gait abnormality that may suggest cerebellar or neurological involvement.
- Obvious physical deformities suggesting previous trauma or congenital malformation.
- Neck or upper body anomaly that may prevent testing in some positions (e.g. prism cover test) or the need to avoid a test (e.g. vestibulo-ocular reflex [VOR]).

Head:

- Skull deformity or orbit anomaly (e.g. plagiocephaly).
- Abnormal head posture.
- Facial symmetry or weakness.
- Wearing glasses or hearing aids.

Periocular:

- Signs of injury suggesting orbital trauma (e.g. scars).

Palpebral fissure/lids:

- Upward or downward slant of the lid fissure (orbit position information).
- Ptosis or lid retraction.

Globe/ocular:

- Displacement of the globe (e.g. proptosis, enophthalmos, or hypoglobus).
- Chemosis, irregularities of conjunctiva, cornea, iris, or pupil.

Identification of any of these features can provide an early clue as to what to expect on clinical testing. For example, seeing a partial unilateral ptosis without a compensatory chin-up head posture in a young child raises the possibility of amblyopia.

Gain cooperation (III.b)

This part of the exam is an opportunity to build a rapport with the patient in order to gain cooperation for the rest of the visit. The degree of cooperation will determine the speed and complexity of testing that can be performed. This is generally considered when dealing with toddlers; however, it is just as important to gain rapport with the child's parents, and even extends to adult patients, to relieve any anxiety. Gaining trust can be achieved in young children by providing a brief explanation what to expect: "We're going to play lots of games looking at pictures!" Remind them that nothing in your room is going to hurt them, and give them your full attention (i.e. listen to what they are saying).

This is also an opportunity to get a sense of a patient's ability to participate with subjective testing. The first few minutes should help you decide the best way to interact with the patient, (e.g. how to explain tests, what is the best volume to speak, are there gestures or actions that seem to startle them, such as moving quickly, bringing things close to their face, etc.). Your ability to make any necessary adjustments will greatly increase the quality of information generated from the exam.

Questions (III.c)

Take the history while observing the patient and building rapport. The importance of a good history cannot be overemphasized. Detailed, relevant questions streamline the evaluation and help to predict the results of testing. The following are some key areas to address:

Age: Determine if the patient is visually immature (~birth to age 7). Age at time of testing combined with the reported age at onset of the problem predicts the sensory adaptations that may have ensued.

Main concern: Establish if the patient's concern is visual or appearance. This often helps in making decisions about the management of a problem. Be sure to ask the patient as well as any family members present. Patients may have difficulty distinguishing between image blur, image jump, image overlap, or even oscillopsia. However, the distinction is important since each symptom represents an anomaly of a different sensorimotor system. In this situation, clinical testing may, in fact, help the patient understand their visual symptoms.

Expectations: It is important to understand what expectations the patient may have. This includes their expectations of the orthoptic evaluation, as well as what they hope can be achieved by the treating ophthalmologist. Patient expectations need to be documented, and then addressed at the right time by the right person. This may be by the orthoptist at the completion of their evaluation or delayed until results of other investigations are available and discussed with their ophthalmologist.[7] It is important to avoid providing the patient and family with conflicting information.

Other pertinent details: Ask about: general medical history; family history of strabismus and any ophthalmic disorder; precipitating events if cause unknown; past ophthalmic treatment; and if there is any ongoing management, as well as compliance to treatment (e.g. use of prescribed optical correction, hours of occlusion for amblyopia, etc.).

At the end of taking a history, you should be able to generate a shortlist of differential diagnoses and determine the main emphasis of the evaluation. For example, the likely diagnosis in a 55-year-old diabetic with a 2-day history of horizontal double vision in right gaze is an acquired right sixth nerve palsy. Emphasis will be on the motor evaluation to document and quantify the right abduction deficit (see Fig. 75.1C). Conversely, emphasis should be shifted to a careful sensory evaluation in an adult complaining of a longstanding inturning eye without double vision (see Fig. 75.1A).

Determination of refractive status (III.d)

This is an ideal time to perform lensometry to determine the optical correction worn by the patient. This too can be accomplished while building rapport and taking a history. Knowing the power of the glasses, near correction, and prismatic correction is essential prior to orthoptic testing.

Formal clinical testing now begins.

Minimally dissociative cover test (IV.)

A useful starting point for clinical testing is to perform a cover test to determine ocular alignment. Brief occlusion of an eye avoids disrupting fusion in patients with fragile control while providing the clinician with valuable information to help interpret findings on upcoming tests (see Fig. 75.4 and Table 75.4). It should be performed at least in the straight-ahead position at near (⅓ m) and distance (6 m). The patient should be wearing their current optical correction (if any) while looking at an accommodative target. Additional positions and viewing situations (e.g. manipulating optical correction, using a light as a fixation target) can be reserved for later in the exam.

If strabismus is identified other characteristics should be noted:

- What is the direction of the deviation?
  - Is it horizontal (eso/exo), vertical (hyper, hypo, dissociated vertical deviation [DVD]) or a combination?
- What is the control?
  - Is it constant (manifest), intermittent, or always controlled under binocular viewing (latent)?
  - If intermittent, how easy can control be disrupted and then regained?

The cover test also provides other helpful information. Some examples include:

- Observing brisk recovery of ocular alignment after the occluder is removed, suggesting the presence of fusion and good vision.
- Occlusion of one eye with poor, inaccurate refixation of the fellow eye, suggesting reduced vision in that eye.
- No movement of an "apparently" deviated eye following occlusion of the fellow eye, suggesting a severe motor deficit or angle kappa.

Collecting this information early in the exam is helpful, particularly when cooperation may falter at any time (particularly in toddlers). It also predicts results on other tests and helps determine if modification of the exam may

be necessary. For example, if poor vision is suspected in one eye based on the inability for the non-covered eye to pick up fixation, poor results will be expected on all sensory tests; and measurement of the strabismus will need to be done with a Krimsky test rather than the prism cover test. Alternatively, if the initial cover test rules out a manifest strabismus and excellent visual acuity is present, it suggests that more coaxing is warranted if suboptimal results occur on subjective sensory tests.

Other benefits of an early cover test:

- Determines the patient's ability to follow instructions. Difficulty gaining cooperation with this test suggests subjective testing may be limited or at least warns the clinician extra effort may be required.
- Another opportunity to build a rapport with the patient. This will "warm them up" prior to conducting more detailed subjective tests.
- Confirms if symptoms identified in the history are binocular if they disappear with monocular occlusion.
- Provides the first formal opportunity to investigate an abnormal head posture or any other "compensatory" mechanism suspected during initial observation of the patient. Examples of are given in Table 75.6.

Nowhere else in the exam can so much information be obtained with only a few moments of testing!

Decision 1

If cooperation with the cover test is limited, a *modified* orthoptic evaluation may need to be considered. However, proceeding with the *basic* orthoptic evaluation can be as follows:

Sensory evaluation (V.A)

Sensory tests should be performed at a minimum of near and distance in the straight-ahead position. Additional positions should be considered if you suspect that the sensory status may be different there; for example, incomitant strabismus where normal alignment is present in one direction permitting fusion, or with nystagmus where the presence of a null zone improves vision to permit or improve stereopsis. It is important to explore and document multiple sensory findings in such patients. The sensory evaluation requires subjective responses that occasionally make accurate determination of the sensory status difficult. Reliability is improved by gaining cooperation, ensuring appropriate tests are selected, and that instructions are given at an appropriate level. Finally, be vigilant that the sensory results correlate with other findings. For example, high-grade stereopsis (normal sensory) with a manifest strabismus (abnormal motor) should raise a cautionary flag, and testing may need to be repeated. Table 75.7 provides a list of common sensory tests and the information they provide. Figure 75.6 illustrates some of these tests.

Vision evaluation (V.B)

The assessment of visual acuity as part of the orthoptic evaluation is generally restricted to quantifying high-contrast central acuity using optotypes. In some cases, it may need to be limited to observing visual behavior (e.g. young infants) (Fig. 75.7). The acuity with each eye should be tested at distance and near. Some impression of acuity level can be obtained in all patients, regardless of age and cooperation. To compare acuity at consecutive visits, the same test should be used. Optotype acuity tests should be introduced as early as possible. When "graduating" from one test to another, e.g. from "fix & follow" to Lea symbols, it is beneficial to test with both methods at the transition visit. Figure 75.8 illustrates several commonly employed vision tests and associated tools. Table 75.8 provides a description of these tests and tools.

Motor evaluation (V.C)

The motor evaluation is generally the most time-consuming portion of the work-up. Most tests are objective, but still require concentration by the patient and are influenced by the vision status of the patient. Table 75.9 provides an overview of the commonly employed clinical tests. The combination of tests used will depend on the approach taken for a particular patient (i.e. a *basic* evaluation versus an *expanded* or truncated [*modified*] one).

Pupils (VI.)

Examination of pupils is typically reserved for the end of the examination, or at least after vision tests have been completed. Standard assessment should be performed.[8] Attention should also be given to the presence of light-near dissociation, miosis associated with spasm of the near reflex, or aberrant regeneration following a third nerve palsy. In rare cases, patients with severe horizontal gaze anomalies may try to utilize convergence in an attempt to achieve some side gaze, resulting in pupillary miosis.[9,10]



Fig. 75.7 Clinical methods to assess vision in infants and young children. Examples of objective methods for assessing vision, i.e. observing visual behavior. Image (A) Teller acuity cards, (B) Cardiff card, (C) Heidi paddles, (D) optokinetic nystagmus (OKN) drum, (E) 10-diopter prism. Image (A) and (B) are examples of forced preferential looking techniques that require the child to detect the presence of a stimulus and direct his/her attention towards it. Other methods involve tracking a slow-moving fixation target (C); detecting a rotating stimulus (D); or determining the ability to hold fixation with an eye, which in this case requires inducing a manifest deviation with a small vertical prism. Here the patient is fixing with left eye. Note the central position of the corneal light reflex in the left eye and the vertically displaced reflex in the right eye (E).

Table 75.6 Examples of compensatory mechanisms

Strategy	Reason	Clinical examples
Abnormal head posture Any direction	Utilize null zone to improve visual acuity	Nystagmus
Abnormal head posture Head turn toward limited field of movement	Avoid gaze position to achieve binocular single vision (fusion) or eliminate diplopia	Unilateral sixth nerve paresis; unilateral Duane syndrome
Abnormal head posture Head tilt contralateral to higher eye	Avoid gaze position to achieve binocular single vision (fusion) or eliminate diplopia	Unilateral fourth nerve paresis
Abnormal head posture Chin up Increased frontalis effort	Avoid blockage of visual axis by a ptotic lid to maintain monocular vision and/or binocular single vision	Ptosis
Head thrusting; ± eye closure	Quickly move eyes to another fixation target to overcome lack of saccadic initiation	Ocular motor apraxia
Head movement	To substitute head movement for absent or severely restricted eye movement to view objects	Severe restriction of bilateral eye movement; bilateral horizontal gaze palsy
Under-accommodate	Avoid inducing an esotropia	Accommodative esotropia
Over-accommodate	Maintain control of deviation to eliminate diplopia or loss of fusion	Exophoria or intermittent exotropia
Close one eye; avoid near work	Avoid diplopia or asthenopic symptoms associated with near work	Convergence insufficiency
Squinting (narrow palpebral fissures)	Induce a pinhole effect to improve vision	Myopia
Adjusting glasses	Improve vision	
	• Achieved by titling glasses (or head)	Astigmatic correction off axis
	• Decreasing vertex distance with myopic correction or increasing vertex distance with hyperopic correction	Increases minus power Decreases plus power
	• Look over glasses with hyperopic correction	Accommodative esotropia (not tolerating new hyperopic correction)
	• Look over glasses with a myopic correction at near	Presbyopia (or any cause of inadequate accommodation)

To be considered a partial list of examples. Main objectives are to improve vision, maintain alignment of visual axis to avoid diplopia/gain fusion, or to achieve fixation with one or both eyes.

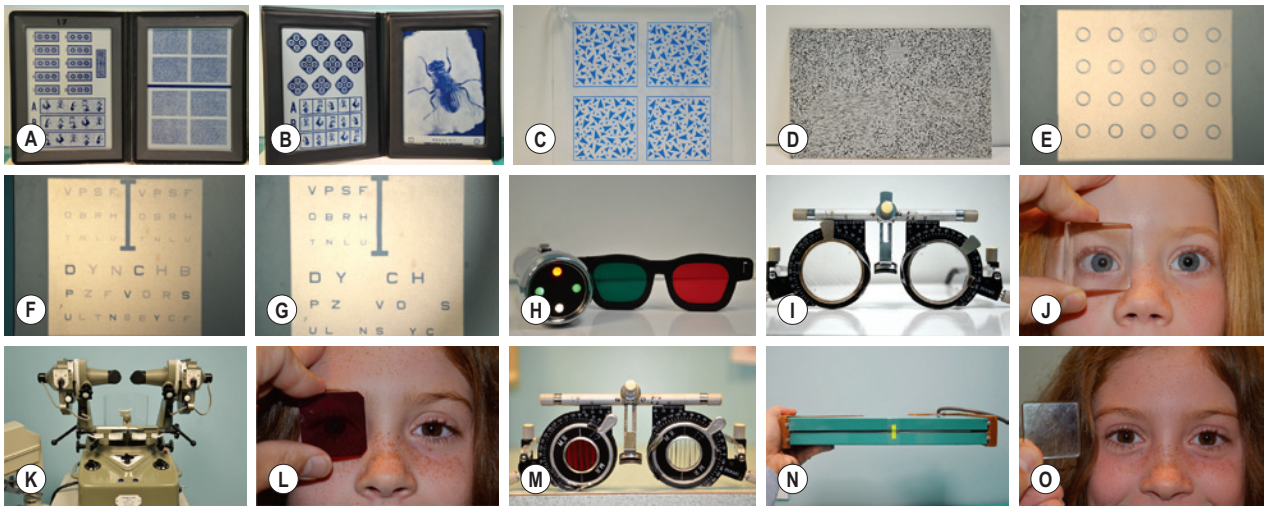


Fig. 75.6 Commonly employed sensory tests. (A) Randot stereotest. (B) Titmus stereotest. (C) Frisby stereotest. (D) Lang stereotest 2. (E) American Optical (AO) vectograph slide for distance stereopsis. (F) AO vectograph slide for suppression. (G) Same slide as in (F) illustrating unilateral suppression. (H) Worth 4-dot test, flashlight, and glasses. (I) Bagolini striated lenses in trial frame. (J) Introduction of a 20-diopter base-out prism eliciting bilateral convergence suggesting the presence of fusion. (K) Major amblyoscope (Synoptophore). (L) Red filter test. (M) Maddox rod lenses in trial frames, i.e. the double Maddox rod test. (N) After-image device. (O) Pre-introduction of a 4-prism diopter base-out prism. Absent movement noted in left eye suggests a central suppression scotoma of the right eye. (Table 75.7 provides information for these tests.)

Table 75.7 Sensory evaluation: common tests and key information

Test	Key information
Cover test	Alignment status: presence of manifest, intermittent, or latent deviation to predict expected sensory finding Recovery of alignment after dissociation suggests presence of fusion
Bagolini striated lenses	Retinal correspondence: fovea to extra-fovea Presence of central suppression scotoma Minimal dissociation making it useful in cases of fragile fusion/deviation control
After-image	Retinal correspondence: fovea to fovea
Worth 4-dot test (W4DT)	Retinal correspondence: fovea to extra-fovea Presence of central suppression scotoma Dissociative test – control of deviation through glasses suggests modest control or better
Titmus,* Randot,* Frisby,† Lang I and II†	Near stereopsis Indirect information about fusion and vision
AO Vectograph,* Mentor B-Vat system[β]	Distance stereopsis Indirect information about fusion and vision
Major amblyoscope (Synoptophore)	Retinal correspondence Fusion potential Fusional amplitudes Stereopsis Torsion
4-Diopter prism test	Presence of bifoveal fixation/central suppression scotoma
20-Prism diopter base-out test (aka: prism vergence test)	Objective test of motor fusion Useful in infants/patients with limited cooperation for subjective testing
Red filter test	Confirmation of true binocular diplopia Image localization
Double Maddox rod	Confirms subjective symptoms of torsional diplopia by detecting torsion (therefore also considered motor)
Prism adaption test	Fusion potential
Postoperative diplopia test	Confirmation of suppression region and presence of abnormal retinal correspondence
Important Concepts	
Testing done with optimal correction of refractive errors	Uncorrected refractive error that results in a reduction of vision will negatively impact sensory results
Appropriate selection of test for age and level of cooperation	To maximize reliability of results
Results to correlate to motor and vision status	Good vision and normal alignment should come with good sensory findings Reduced vision should inhibit good scores on sensory testing
Level of dissociation	More dissociative tests like W4DT may break control of a deviation in patients with fragile fusional ability
All tests do not assess same level of binocularity	Appreciation of random dot stereopsis requires a greater level of development of the cortical binocular system versus seeing an "X" with Bagolini lenses

*Requires the use of Polaroid glasses.
†No special testing glasses required.
[β]Requires liquid-crystal shutter glasses.

Decision 2

This is another opportunity to decide how to proceed with the rest of the evaluation. At this stage you must decide if sufficient data has been collected to make a clinical diagnosis and generate a report. Alternatively, if the case is complex or certain clinical features require further refinement, an expanded orthoptic evaluation can be pursued. However, it should be noted the orthoptic evaluation is a dynamic process and a decision to modify (limit testing) or expand (additional or specialized testing) the evaluation can be made at any time. This may be at the time of the chart review (see Fig. 75.3A) or after first interactions with the patient (see Fig. 75.3B).

Expanded orthoptic evaluation (VII.)

When a decision to expand the evaluation has been made, the following areas may be considered.

Additional sensory testing (VII.a): This may include further evaluation of:

- retinal correspondence with Bagolini striated lenses and after-image test;
- fusion potential with use of synoptophore testing;
- sensory fusion with prism adaption test;
- significance of torsion as a potential barrier to fusion;

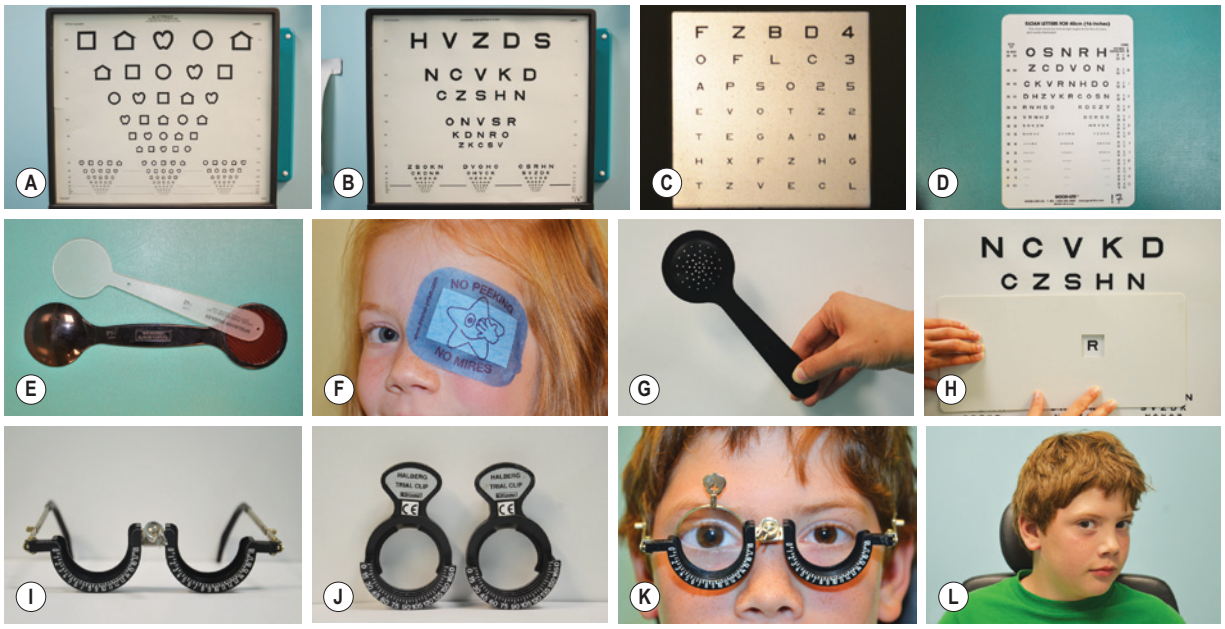


Fig. 75.8 Common vision tests and associated tools. (A) LH symbols, (B) EDTRS chart, (C) Snellen chart, (D) near Sloan chart, (E) eye occluder (opaque and translucent), (F) stick-on patch, (G) pinhole, (H) presentation of isolated optotype, (I) pediatric trial frame, (J) Halburg clips, (K) high plus lens (in a trial frame), (L) abnormal head posture. Images (A–D) are examples of standardized optotype charts with set testing distances. Images (E–L) are tools and techniques used to facilitate accurate assessment of vision.

Table 75.8 Vision evaluation: common tests and important concepts

Test/Concept	Comments
Pediatric	
Fix and follow	Assesses ability to pick up fixation and steadiness once fixation has been achieved
Heidi paddles	Fix and Follow method Permits crude quantification by using paddles of differing size Powerful stimulus for infants
Forced preferential looking	Fixation drawn toward a pattern stimulus rather than a plain background if detected Quantifiable but not comparable to other tests Examples: Teller acuity cards, Keeler cards, Cardiff cards, and Lea gratings
Binocular fixation pattern	Use in the presence of a manifest strabismus Assesses fixation preference between eyes under binocular conditions Crude quantification, not comparable to other methods
10-Diopter prism	Same principle as binocular fixation pattern but small vertical prism used to induce manifest deviation in a patient with straight eyes
OKN drum	Inducing optokinetic nystagmus indicates grating can be seen
Young children (optotype acuity)	
LH symbols (Lea symbols)	Various optotype presentations Naming or matching of optotypes by patient **Image A** shows distance LogMar method
Sheridan Gardiner letters	Various optotype presentations; naming or matching
HVOT	Various optotype presentations; naming or matching; standardized to Snellen principle
Allen pictures	Not standardized to Snellen principles
Tumbling E (Illiterate E)	Various optotype presentations Standardized to Snellen principles
Kay pictures	Various optotype presentations Naming or matching of optotypes by patient

Table 75.8 Vision evaluation: common tests and important concepts—cont'd

Test/Concept	Comments
Adult (optotype acuity)	
EDTRS	Standardized to LogMar principles **Image B**
Sloan near card	Standardized to LogMar principles **Image D**
Sloan low vision chart	Standardized to LogMar principles
Snellen chart	Standardized to Snellen principles
Important Concepts and Tools	
Standardized testing	Important to use standardized charts at the appropriate distances; patient should have the same test administered in the same way at each visit regardless of the room used; always use prescribed optical correction (can modify later if needed)
Age-appropriate methods	Selection of most appropriate test based on age and cognitive ability maximizes reliability of results
Maintain cooperation	Important to know when to coax a patient, when they are guessing, and even when to take a break
Be mindful of situations that can lead to loss of cooperation:	
Making patient wait	• A long wait in a noisy waiting room will fatigue a child. It also can frustrate the parent or care giver which will be sensed by the child further increasing his/her anxiety • Therefore be prepared for patients in advance (review notes in advance), book appointment times appropriately and try to stay on schedule as much as possible.
Testing good eye first	• Some children become distressed if good eye is tested first followed by the poorer seeing eye. Comprehension issues can be addressed by first practicing with both eyes. If clinician is confident optotypes are known then vision in the suspected poor eye can be tested next. Any lack of response at this time can be attributed to vision, not comprehension. This is further confirmed by the rapid identification of optotypes when the fellow eye is tested next (last).
Saying "no" or "that's wrong"	• Avoid negative responses to children. Most will stop "playing the game" if they feel they are doing poorly. Use alternative wording like "good try" or "I bet you can get this one"
Stick-on eye patch	Eliminates the need for patient to hold an occluder, thereby reducing chance of peeking; keeps hands free to hold matching card **Image F** shows complete occlusion of an eye with a sticky patch. This would still be placed on the eye behind the lens if patient was wearing glasses
Pinhole	To be used in any patient with reduced vision (~worse than 20/30; 6/7.5) that might be secondary to abnormal refractive status **Image G** shows a multi-holed pinhole
Optotype presentation	Full chart, line, or isolated optotype presentation to determine effect of crowding phenomenon **Image H** illustrates how to present an isolated optotype on a full chart
Testing vision with both eyes open	Important in setting of manifest-latent or latent nystagmus; or in patients over- or under-accommodating to control a deviation
Unilateral blur/fogging using high plus lens or translucent occluder	Use is indicated in any patient with latent or manifest-latent nystagmus **Image E** shows a translucent occluder that blocks form but still permits light to pass, **Image K** shows a high plus lens to reduce vision in the right eye without inducting or worsening nystagmus during left eye vision testing
Trial frames (pediatric or adult)	Used to hold specialized lenses (optical, prism, occluder, Bagolini, or Maddox rod) in front of an eye in a patient who does not wear glasses **Image I** is an example of a pediatric frame
Halberg clips	Same as above but used for patients wearing glasses These are clipped to the frame to hold a specialized lens in front of the spectacle lens **Image J**
AHP	May be adopted to utilize null zone in nystagmus, avoid ptosis, compensate for off-axis correction of astigmatism **Image L** represents a marked head turn left in a patient with a null zone in right gaze
Direct ophthalmoscope or muscle light	To evaluate pupillary responses to light

Images are seen in Figure 75.8.

Table 75.9 Motor evaluation: common tests and descriptions

Tests for basic evaluation	Remarks
Cover test	Repeated again during the formal motor evaluation Findings should be consistent with the initial cover test – changes could result if control decreases with testing fatigue Look for strabismus in all positions of gaze and document direction (eso, exo, hyper, hypo), control (phoria, tropia, or intermittent) and estimation of size (tiny, small, moderate, large) Used to predict strabismus classification (see below)
Document and Quantify Strabismus	
Prism cover test	Gold standard to quantify (measure) size of deviations • Positions to perform ◦ Distance (6 meters): • Straight ahead (primary position) • Right and Left gaze • Up and down gaze ◦ Near (1/3rd meter) • Additional positions ◦ Head tilt to either shoulder if vertical strabismus present ◦ Reading position (~25° down gaze at near) if near symptoms are present ◦ Fixing either eye if paretic strabismus suspected ◦ Supine position if skew deviation suspected • Information used to classification of strabismus ◦ Presence and amount of distance / near disparity, A/V patterns, other incomitance in lateral, vertical, or oblique positions of gaze. Methods • Alternate prism cover test (APCT) ◦ To measure full extend of deviation by maximizing the amount of dissociation between the eyes • Simultaneous prism cover test (SPCT) ◦ To measure minimum amount of manifest deviation (aka: the amount the patient typically walks around with under binocular viewing conditions) ◦ Important for sensory evaluation of monofixation syndrome
Synoptophore	Quantification of strabismus in any position of gaze Size of fusional amplitudes Detection and quantification of subjective torsion
Assessing and Quantifying Ocular Movement*	
Versions and ductions	Determine the extent of ocular excursion in all directions of gaze. Perform versions first then repeat with ductions if any anomaly of versions is suspected Underactions can be observed during both versions and ductions; however, ductions are usually quantified in this setting. Common grading systems include: • 0 to –4 scale: where 0 represents full movement and –4 represents no ductional movement into that particular field of action. In cases of severe restrictions or complete palsy with contraction of ipsilateral antagonist greater than –4 can be present • Percent of normal movement – clinician estimates what percent of normal movement is present • Percent of abnormal movement – generally avoided in lieu of estimating amount of movement possible. However, when documenting ocular movements it must be clear what the numbers represent Overaction can be graded only during versions
Tests for Expanded Evaluation	
Lees screen Hess screen Lancaster Red-Green test	Diagrammatical representation of eye movements in all positions of gaze • Sensitive to subtle limitations (and corresponding over actions) of ocular movement • Information on muscle sequelae
Field of binocular single vision	Quantifies area in which binocular single vision is present and where diplopia is appreciated
Specialized ocular motility assessment*	Suspected supranuclear involvement requires evaluation of other types of eye movements: • Saccades • Smooth pursuit • Vestibular ocular reflex • Optokinetic nystagmus • Bell's phenomenon Suspected paretic vs. restrictive etiology may include: • Saccadic velocities • Forced duction testing • Forced generation testing • Bell's phenomenon

Table 75.9 Motor evaluation: common tests and descriptions—cont'd

Tests for basic evaluation	Remarks
Double Maddox rod	Detection and quantification of subjective ocular torsion
Direct ophthalmoscopy	Detection and objective quantification of ocular torsion Can also be done with fundus photography
Tests for Modified Evaluation	
Hirschberg	Objective near test to detect and estimate size of a manifest strabismus Rarely indicated but useful in uncooperative patients
Krimsky test	Objective near test to estimate size of a manifest strabismus Useful in setting of poor vision in one eye where a standard prism cover test would not be reliable
Maddox rod	Detects direction of a heterophoria without the need for a cover test Does require subjective responses

*Assessment of eye movements includes both extent and quality of the movement.

Table 75.10 Additional testing in setting of reduced vision

Task	Remarks
Check vision at both near and distance	Equal reduction of vision at all distances is expected in the setting of amblyopia and organic disease. Differences between near (33 cm) and distance (6 m) may suggest refractive or accommodative anomalies and require further investigation
Check vision with and without identified anomalous head postures	Significant improvement in vision while using a head posture (outside primary position) is common in patients with nystagmus having a null zone
Repeat VA using a pinhole	Improvement suggests uncorrected or miscorrected refractive error
Use trial lenses	For VA assessment: • Add minus over a hyperopic correction to see if distance VA improves (overcorrected/not relaxed into correction) • Add plus lens (+1.00 to +3.00) to see if near VA improves (accommodative insufficiency) • Add 0.12 D lens to see if VA improves (element of functional visual loss) • Introduce high plus lens to fellow eye to test VA (in presence of latent or manifest-latent nystagmus) For ocular alignment assessment*: • Add minus (reduce plus) to determine if *control* improves in an exodeviation; or decreases control of an esodeviation • Add plus (reduce minus) to determine if control improves in an esodeviation; or decreases control of an exodeviation
Isolated optotypes	Assess influence of crowding phenomenon. More significant improvement in VA may be expected if due to amblyopia
Change optotypes or procedure	Careful selection of the vision test is important to ensure accurate quantification Be cognizant of patient not understanding what is required (e.g. always points to the same picture) or not absolutely sure about the names of letters or symbols Clinician should consider changing from letter chart to symbols or from asking for verbal responses to having patient "match" symbols
Other optic nerve function testing	Color vision and contrast sensitivity testing Look for RAPD

RAPD, Relative afferent pupillary defect; VA, visual acuity.
*Included here as the use of lenses to alter alignment in the clinic or as a management strategy may affect vision status.

- suppression scotomas and risk of inducing diplopia if strabismus surgery is performed (postoperative diplopia test);
- ability to eliminate diplopia by fitting a Fresnel prism (permitting fusion) or Bangerter occlusion foil (inducing blur to ignore).

Additional vision testing (VII.b): When vision is reduced (unilateral or bilateral), additional testing may be warranted. Table 75.10 outlines additional testing that should be performed when there is an unknown etiology. Other aspects of vision may also need to be evaluated such as visual evoked potential, contrast sensitivity, color vision, visual fields, dynamic visual acuity (vision during slight headshaking),[11] or tests for functional visual loss.

Additional motor testing (VII.c): This may include:

- further ocular motility testing by performing a tangent screen test (e.g. Hess screen, Less screen, or Lancaster red/green test), forced duction, and/or forced generation testing;
- additional prism cover test measurements:
  - fixing either eye;
  - other distances (e.g. past 20 feet);

  - other positions (e.g. oblique, head tilts, reading position, or even supine)[12];
  - with the use of additional lenses (e.g. more/less plus or minus power);
- investigation of torsion – detection and measurement (synoptophore, double Maddox rod, fundus photography).

Accommodation and other documentation (VII. d&e): Other testing may include formal investigations of accommodation (near vision, near point of accommodation, and dynamic retinoscopy), detection of nystagmus, red reflex assessment, measuring ptosis, or documenting improved visual functioning using an identified compensatory mechanism.

Diagnosis (VIII)

At completion of the evaluation there should be sufficient evidence to make a primary diagnosis and classify the strabismus type (e.g. incomitant intermittent exotropia). Multiple etiologies may be included e.g. partially accommodative esotropia with high accommodative convergence/accommodation (AC/A) ratio and amblyopia right eye.

Report (IX)

The final step in the process is to create a report. This succinct summary should provide the pertinent information that defines the orthoptic status of the patient. These details include:

- A summary of motor, sensory and vision findings used to support the diagnosis.
- A statement about the significance of these findings for the patient.

Examples:

New visit: "Patient's complaints of eye strain at near may be explained by his remote near point of convergence and reduced amplitude of accommodation."

Follow-up visit: "Vision in the right eye has improved 2 lines since last visit with full-time use of glasses and 6 hours/day patching of the left eye."

Follow-up visit: "Patient now has a manifest vertical strabismus in all positions of gaze. This fits with complaints of increasing awareness of double vision since last visit 1 week ago."

It should also include:

- A short list of differential diagnoses when a primary diagnosis is uncertain.
- Further description of any strabismus patterns that were found, particularly if strabismus surgery is being considered.
- Clearly highlight any red flags (e.g. worsening of symptoms, worsening of control of an intermittent deviation, increasing ptosis, or new fixation preferences, etc.).
- Identify specific items to be monitored (e.g. watch for amblyopia, changes in ductional deficits between visits, etc.). This is important when patients are shared between a team of clinicians.
- Re-state patient's/family's main concern. Frequently the formal orthoptic evaluation will be done by an orthoptist and later reviewed by a referring ophthalmologist. In these cases, it is useful to communicate the main concern or expectations of the patient, particularly when these are not in keeping with results of the exam or with planned management.

Including the following will be dependent on the institution from which the evaluation was performed:

- A suggested management plan (e.g. trial of a Fresnel prism, change in amblyopia management, etc.), a follow-up plan, and specific items to monitor between visits. Level of detail given will be institution-dependent.

Finish by signing your name and ensuring the report is directed to the appropriate members of the care team.

Designing a patient-specific orthoptic evaluation: factors to consider

The basic orthoptic evaluation involves three main components: sensory, motor, and vision. However, the procedure to conduct an evaluation is rarely static and should never be viewed as a check list of "tests" to complete. Rather, the approach frequently needs to be tailored for each patient to address their particular problem (see Fig. 75.1).

Figure 75.3A is an overview of factors to consider when designing the best approach for a particular patient. The following are brief descriptions for this flowchart.

Patient details (A1)

Important items to consider are: age of the patient, visit history, and co-existing morbidities.

Age at exam (A1.1)

This influences tests that can be performed, ability to get cooperation, and level of subjective feedback that may be possible. In general terms, the younger the child, the more limited the depth of the evaluation; however, age is not the only factor that dictates which tests should be performed:

Is the patient visually mature or immature?

Visually immature: Under the age of 7 years, patients are considered visually immature. Disruptions to normal binocular input below this age can permanently inhibit normal development. This group is liable to develop sensory adaptions.

Each visit for this age group must include:

- detection of amblyogenic mechanism(s);
- statement about presence of sensory adaption if amblyogenic mechanism is detected;
- statement about vision (and amblyopia), eye alignment, and eye movements;
- vigilance for any underlying mechanism to account for strabismus or poor vision when etiology is unclear (e.g. subtle duction deficit, and relative afferent pupillary defect).

Visually mature: Disruption of binocularity in this group should be accompanied by predictable visual symptoms. Be aware of the following:

- Motor system disruption – incomitant strabismus:
  - innervational, mechanical, neuromuscular, and myopathic.
- Sensory system disruption – comitant strabismus:
  - decompensating heterophoria in isolation or secondary to new monocular visual disruption (e.g. cataract or retinal anomaly);
  - disruption of pre-existing sensory adaption;
  - fusion disruption (e.g. correction of longstanding aphakia, etc.).

It is also important to identifying findings that do not fit the story (e.g. a patient who reports new strabismus but does not have double vision). You must think of possible explanations such as severe monocular visual loss, change in alignment of a childhood strabismus (e.g. previous suppression for childhood esotropia, with the eye now drifted into an exotropic position).

Visit history (A1.2)

Is this a new visit or follow-up visit?

New visit: Assessment at the first visit needs to create a baseline for future visits. Also pay careful attention to features that may be suggestive of neurologic or systemic disease. However, the time allotted must allow other testing at that visit such as the cycloplegic refraction and fundus exam.

Other key points:

- Visually immature: do not miss amblyogenic mechanisms or any sensory adaption that may already be present.
- Visually mature: detection and careful quantification of ocular misalignment and be able to correlate patient symptoms (or lack of) with results on the orthoptic evaluation.

Follow up visit: The follow-up visit depends on current management. Therefore, at each visit be sure the objective is clear in order to best tailor the evaluation. Questions would include:

What treatment is being considered?

- Is this a preoperative visit or does the patient need to be evaluated for the use of a prism? The evaluation of a surgical candidate will emphasize quantification of the strabismus while evaluation for use of a prism (Fresnel or incorporated) will be to identify an optimal amount of correction that permits comfortable binocular single vision in positions of gaze most appropriate to the patient's needs.

Is there ongoing treatment?

- Amblyopia therapy – is the visual acuity improving?
- Cessation of amblyopia therapy – has there been a reduction in the visual acuity?
- New glasses given for possible accommodative esotropia – what is the response to using hyperopic correction?
- Use of a prism – are the symptoms adequately reduced? Is there intolerance to prism suggesting a change in the size of the deviation?

Has management been observation only?

- Is there any change in symptoms?
- Is there any change in the orthoptic status?
  - Onset of amblyopia in an infant with previous alternating esotropia.
  - Difference in control of an intermittent deviation.
  - Resolution of a strabismus in a patient with a presumed microvascular cranial nerve palsy.
- Has anything changed from the first visit? Are things better, worse, or the same?

Has there been recent strabismus surgery?

- What change has occurred in the motor status?
- Has there been any change in the sensory status? Have symptoms been eliminated, has the procedure created new or unexpected symptoms?

Co-existing conditions (A1.3)

Co-existing neurologic or systemic conditions can influence testing and reliability. This may include cognitive and behavioral problems or motor issues such as cerebral palsy or even myasthenia gravis. Overall, the patient needs to be alert and physically able to participate in testing. This entails being able to move their head for measurements, to wear glasses for specific tests, and to be positioned appropriately (e.g. Hess screen, in front of a synoptophore).

Resource availability (A2)

To generate a basic orthoptic evaluation requires an in-depth understanding of several key components already discussed. However, it is also dictated by available resources. These resources include equipment and time.

Equipment

The level of the orthoptic evaluation will be determined by the equipment available in the clinic. An example of this is the major amblyoscope. Although it is an integral part of the orthoptic evaluation, not all centers have one. Reasons may involve cost of the equipment, lack of trained personnel, or a surgeon unfamiliar with the benefits of the data provided by the device. Other tests like Hess/Less/Lancaster may only exist in facilities dealing with complex strabismus that require detailed quantification of motility deficits. This information may not be required in centers that only conduct preliminary evaluations and refer management to other centers.

The following are minimum equipment requirements to conduct a basic evaluation:

- Basic sensory evaluation: near stereo test, red filter, and W4DT (or Bagolini lenses).
- Basic motor evaluation: occluder, prisms, accommodative targets.
- Basic vision evaluation: occluder/eye patch, fixation sticks, optotype chart.
- Bright light source, e.g. direct ophthalmoscope, muscle light.

Tables 75.7–75.9 list additional equipment (tests) involved in the basic and expanded orthoptic evaluation.

Time

The orthoptic evaluation will be dictated by time. A *modified* exam looking for strabismus, ocular motility anomalies, and gross deficits of vision can be performed in roughly

10 minutes by an experienced orthoptist. However, a *basic* evaluation is closer to 30–45 minutes (including a written report) and increases to 90 minutes or more for an *expanded* evaluation if the following additional testing is performed: field of binocular single vision, Hess screen, full synoptophore evaluation, formal testing of retinal correspondence, torsion, accommodation, quantifying complex forms of strabismus, and assessing (and fitting) a patient for a Fresnel prism. These times do not include patient factors that could further delay the work-up (e.g. developmental delay, autism, brain injury, etc.).

Summary

An orthoptic evaluation is dynamic. It must be flexible to address specific patient or care team needs while still generating useful and accurate information.

The evaluation is more than the sum of its parts. The paradigm discussed here separates the evaluation into three distinct components – a motor, a sensory, and a vision evaluation. The interaction between these components creates a synergy of information that ultimately defines the patient's orthoptic status.

The hope is that by understanding the concepts presented here, a better understanding of binocular vision will be elucidated. This will allow the clinician to better "visualize" the best approach for any patient in any situation, thereby maximizing the information gained from the orthoptic evaluation.

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Fig. 75.2 The orthoptic paradigm pathway: main themes and determination of orthoptic status.

Defining the orthoptic status involves a series of steps that ensures efficiency and accuracy. The first step identifies factors to help determine the best approach for a given patient or situation. Next involves specialized clinical testing to assess major themes within each of the core components (A, B, and C). The interaction between each component is analyzed and interpreted. The outcome constitutes the orthoptic status of a patient. This information is used to determine best management approach. (Additional details provided in Table 75.1.)

Fig. 75.3 Pre-testing factors to consider when determining best approach to the orthoptic evaluation.

Section (A) and (B) expands step 1 in Figure 75.2. These are essential when designing the best approach to the orthoptic evaluation (C).

Fig. 75.4 Putting it all together – algorithm to determine the orthoptic status.

A flowchart to facilitate determination of the orthoptic status. Pathways are determined by the sensory responses for a given ocular alignment as determined by the cover test. It already takes into account underlying influences of vision. Table 75.4 provides full details of each arm of the flowchart.

Fig. 75.5 The orthoptic evaluation: pathway for clinical testing.

Refer to section "The basic orthoptic evaluation" for full details.

Fig. 75.6 Commonly employed sensory tests.

(A) Randot stereotest. (B) Titmus stereotest. (C) Frisby stereotest. (D) Lang stereotest 2. (E) American Optical (AO) vectograph slide for distance stereopsis. (F) AO vectograph slide for suppression. (G) Same slide as in (F) illustrating unilateral suppression. (H) Worth 4-dot test, flashlight, and glasses. (I) Bagolini striated lenses in trial frame. (J) Introduction of a 20-diopter base-out prism eliciting bilateral convergence suggesting the presence of fusion. (K) Major amblyoscope (Synoptophore). (L) Red filter test. (M) Maddox rod lenses in trial frames, i.e. the double Maddox rod test. (N) After-image device. (O) Pre-introduction of a 4-prism diopter base-out prism. Absent movement noted in left eye suggests a central suppression scotoma of the right eye. (Table 75.7 provides information for these tests.)

Table 75.6 Examples of compensatory mechanisms.

Infantile esotropias

Glen A Gole and Jayne E Camuglia

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First, we must, I believe, firmly embed strabismus in the matrix where it belongs – an anomaly of neurodevelopment.
John T Flynn[1]

Infantile esotropia (IET) is a constant non-accommodative esotropia with onset before 6 months of age in a neurologically normal child (Fig. 76.1). The angle is generally greater than 30 prism diopters (PD), with mild or no amblyopia and low hypermetropia. "Congenital esotropia" is often used synonymously but the condition is rarely present from birth. There is accumulating evidence that these children have the potential for good binocularity if they are treated early, suggesting the underlying defect is not congenital. Animal studies support the idea that IET is caused by decorrelation of cortical inputs.[2]

IET is often accompanied by dissociated vertical deviation (DVD; 50–90%),[3,4] inferior oblique overaction (IOOA; 70%),[5] latent nystagmus (40%), and optokinetic asymmetry. IET and the secondary associations are often grouped under the term "infantile strabismus complex"; some components may exist in isolation even in the absence of strabismus.

History

The term "infantile esotropia" was initially introduced by Costenbader in 1961 to include age of onset <1 year.[6] He had previously defined "congenital" esotropia as having an onset <6 months.[7] The term "congenital esotropia" reflects Claud Worth's theory[8] that esotropia (ET) is caused by a congenital defect of fusion: "The essential cause of squint is a defect of the fusion faculty." Worth's theory implies that the "congenital defect" is irreparable and this has been taken to mean that surgery can be carried out at leisure, largely for cosmetic reasons. The opposing view, that the infant visual system is normal for a period of time until esotropia occurs as a result of extrinsic factors was taken by Chavasse.[9] Chavasse thought that "most infants with congenital squint are capable of developing fusion if the deviation is fully corrected before the age of two years." This view was accepted by Costenbader,[10] Parks and his fellows, and became widely accepted, particularly after the work of Ing.[11] It has not been widely accepted in Europe, where strabismus surgery is often carried out much later.[12] The evidence supporting Chavasse's view, that corrective surgery should be carried out quite early in infancy began to appear in the 1960s. During the 1980s there was an explosion of knowledge concerning development of vision in infancy[13–15], and a refinement of surgical techniques. Surgical case series have led to consolidation of clinical knowledge concerning IET.[16–18]

Epidemiology

There are few studies of the prevalence of IET as defined. The prevalence of any ET in a population of 38,000 children aged 1–2½ years was found to be 0.9% in 1980,[19] while the prevalence of IET over a 30-year period in one area of the US was found to be relatively constant at 0.25% of the population.[20] The overall rate of strabismus surgery in childhood has substantially declined in the UK in recent decades, possibly be due to the routine prescribing of the full cycloplegic refraction in strabismic children.[21] Despite the apparent overall decrease in strabismus surgery, Carney et al. stated that the rate of surgery in children under 1 year was unchanged.[22] Fewer ophthalmologists are now undertaking strabismus surgery, so the surgical work is being concentrated into fewer hands.[23]



Fig. 76.1 Large-angle infantile esotropia.

IET often runs in families and the hereditary component is reported in older literature. Primary monofixation syndrome occurs much more commonly in the parents and families of children with IET than in the general population.[24] Maumenee et al. concluded that the inheritance pattern was most likely Mendelian codominant.[25]

Natural history of the development of ocular alignment

In a study of normal neonates, Sondhi et al.[26] found that 55% had a constant deviation (66% of whom had an exodeviation) and only 30% were orthotropic. No neonatal esodeviations were seen after 2 months of age and 97.2% of their infants were orthotropic at age 6 months. In another study of neonates followed until 6 months of age[27] the same authors concluded that the time of onset of IET was between 2 and 4 months of age. Horwood described "neonatal misalignments" (NMs) as "fleeting, large angle, mainly convergent, ocular deviations"[28] occurring commonly in the first 2 months of life (73.2% of infants in the first month of life). The NMs declined to almost zero by 4 months of age except in those children who went on to develop IET, where the frequency of misalignment increased.[29] There was no relationship between frequent NMs in the first 2 months of life (which are probably due to early development of the vergence system) and the subsequent development of IET. Horwood's report of a high prevalence of convergent misalignments in (older) normal infants is apparently in direct contrast to the findings of Archer et al.,[27] of high prevalence of divergent deviations (especially in the immediate newborn period) in another healthy population. Sondhi and Archer[26,27] used a method that relied upon the infant fixating on the examiner's face. This may have had an artifact induced by the large positive angle kappa seen in early infancy and the particular fixation pattern of neonates when looking at a face.[30] Friedrich and de Decker[31] also found a high (50%) incidence of exotropia (XT) in neonates but only one of 1024 newborn infants developed an ET that was still present at 3 months of age. Children who develop IET begin to be different from normal infants at approximately 4 months of age. Transient misalignment of neonate eyes appears to be common, so parental reports of the age of onset of strabismus must be viewed with caution.

Birch et al. reported that none of 66 infants with misalignment ≥40 PD of ET and an onset between 2 and 4 months of age had spontaneous regression, suggesting that they were suitable candidates for early surgery.[32] The Congenital Esotropia Observation Study (CEOS)[33] reported that, before 12 weeks of age, the majority of esotropic infants had an intermittent or variable deviation, whereas after 12 weeks of age, the deviations were more likely to be constant. CEOS further concluded that normal infants over 10 weeks old with a constant ET of ≥40 PD (and ≤3.00 D of hypermetropia) had very little prospect of spontaneous regression (2%) and could be offered early surgery (Box 76.1).[34,35] However, if the deviation was <40 PD and intermittent or variable, it usually resolved.

Box 76.1

Clinical profile of infants who will benefit most from early surgery, i.e. unlikely to spontaneously resolve

1. Presence or persistence of ET between 10 weeks and 6 months of age
2. Constant ET 40 PD at near (⅓ m) on two examinations 2–4 weeks apart
3. Refractive error ≤+3.00 D
4. Absence of any of the following conditions:
   - Gestational age <34 weeks
   - Birth weight ≤1500 g
   - Ventilator treatment in the newborn period
   - History of meningitis or other major medical event
   - Developmental delay
   - Incomitant or paralytic strabismus
   - Manifest nystagmus or head bobbing
   - Prior eye muscle surgery
   - Presence of structural ocular anomalies

Adapted from Spontaneous resolution of early-onset esotropia: experience of the Congenital Esotropia Observational Study. Am J Ophthalmol 2002; 133: 109–18 by Wong AMF. Can J Ophthalmol 2008; 43: 643–51.

Clinical patterns

Dissociated vertical deviation

DVD (alternating sursumduction, occlusion hyperphoria) occurs in any ocular condition where there is disruption of early binocular development. DVD is not usually evident at presentation but is a later feature of IET (mean onset 2.8 years).[4] In DVD, the deviating eye elevates and extorts (Fig. 76.2) and is not associated with a corresponding downward movement of the other eye when fixation is resumed, i.e. DVD does not follow Hering's Law. In children with larger preoperative angles, surgery before 24 months resulted in a lower incidence of manifest DVD.[36] In any one patient, DVD can vary both in size and frequency of occurrence. It can occur spontaneously or only when the eye is occluded. Rarely, the patient adopts a head tilt to the same side. DVDs can

be quantified with base-down prism. The prism is placed in front of the eye with DVD until the upward and downward movements are identical on alternate cover testing.

Inferior oblique overaction

IOOA is visible in adduction only and is associated with fundus excyclotorsion (Fig. 76.3). DVD and IOOA are usually bilateral but can be asymmetric. If the eye elevates in adduction and there is a corresponding (equal in size) hypodeviation in the opposite eye on alternate cover testing, the deviation is due to IOOA. If there is no corresponding hypodeviation, then DVD is present. If the elevation of the adducted eye exceeds the hypodeviation in the fellow eye, then combined DVD and IOOA are present; the difference between the two vertical measurements is the extent of the DVD.

Dissociated horizontal deviation

Dissociated horizontal deviation (DHD) is defined as a change in horizontal ocular alignment, unrelated to accommodation, that is brought about solely by a change in the balance of visual input from the two eyes.[37] DHD occurs much less frequently than DVD. It is often asymmetric and can occur simultaneously with DVD. Indeed, DHD may merely be a DVD with a large horizontal component. It can be mistaken for consecutive (XT) and the two may co-exist. The two can be distinguished by a difference in horizontal measurements when measuring with the prism in front of each eye. The treatment is a supramaximal lateral rectus recession of the affected eye.[38]



Fig. 76.2 Right dissociated vertical deviation.

Fusion maldevelopment nystagmus syndrome

Fusion maldevelopment nystagmus syndrome (FMNS) was previously known as latent nystagmus.[39,40] FMN is a common accompaniment of IET and occurs on monocular occlusion. The fast phase is always toward the side of the uncovered eye. The nystagmus is lessened in adduction and worsened in abduction. Accurately measuring the visual acuity in the presence of latent nystagmus can be difficult because the nystagmus can dramatically lower the acuity in the uncovered eye. This can be obviated by fogging the eye not being tested with a +3.00 lens rather than occluding it. FMNS can become "manifest" (manifest latent nystagmus) when it is present in binocular viewing.

Optokinetic asymmetry

Infants under 2 months of age show greater sensitivity to objects moving from temporal to nasal than objects moving from nasal to temporal. This asymmetry disappears by 4–6 months of age in normal infants. This nasal-ward bias in infants persists when infants develop IET, and becomes permanent.

Differential diagnosis

The differential diagnosis and clinical forms of IET can be considered as either truly congenital or early in onset within first 6 months (Box 76.2). In most cases, a thorough history and ophthalmic examination helps to differentiate the subtypes (Fig. 76.4).

Pseudoesotropia is common. It can be confirmed by performing the Bruckner,[41] Hirschberg, and cover tests to determine that the eyes are orthotropic (Fig. 76.5). Note that the Bruckner test can have false positives in children younger than 8 months of age.[42] Flash photographs are useful to demonstrate pseudostrabismus to the parents. Infants initially diagnosed with pseudostrabismus showed a 12% rate of strabismus or amblyopia at 3 years of age,[43] but these findings were not replicated in another study.[44]

In type 1 Duane syndrome, the diagnosis is confirmed by limitation of abduction and globe retraction in adduction. Bilateral type 1 Duane syndrome can be difficult to distinguish from IET, particularly if the child is cross-fixating, as the globe retraction in adduction can be quite subtle in infants.

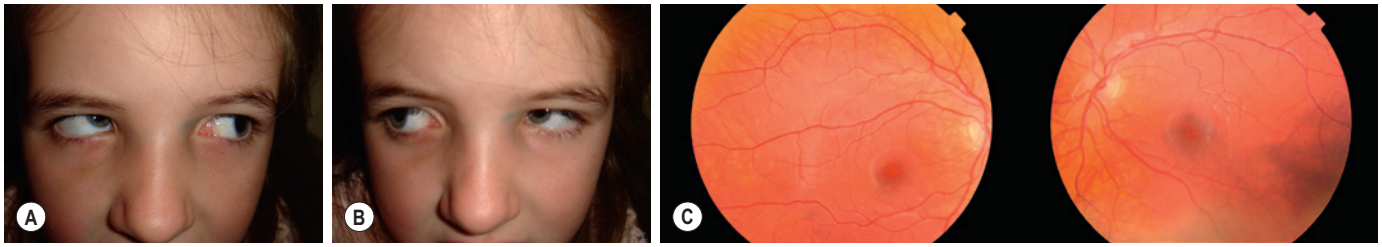


Fig. 76.3 Right inferior oblique overaction (IOOA) (A), left IOOA (B), and fundus excyclotorsion (C) in the same patient. Note the fovea now lies below a line passing through the inferior edge of the optic discs.

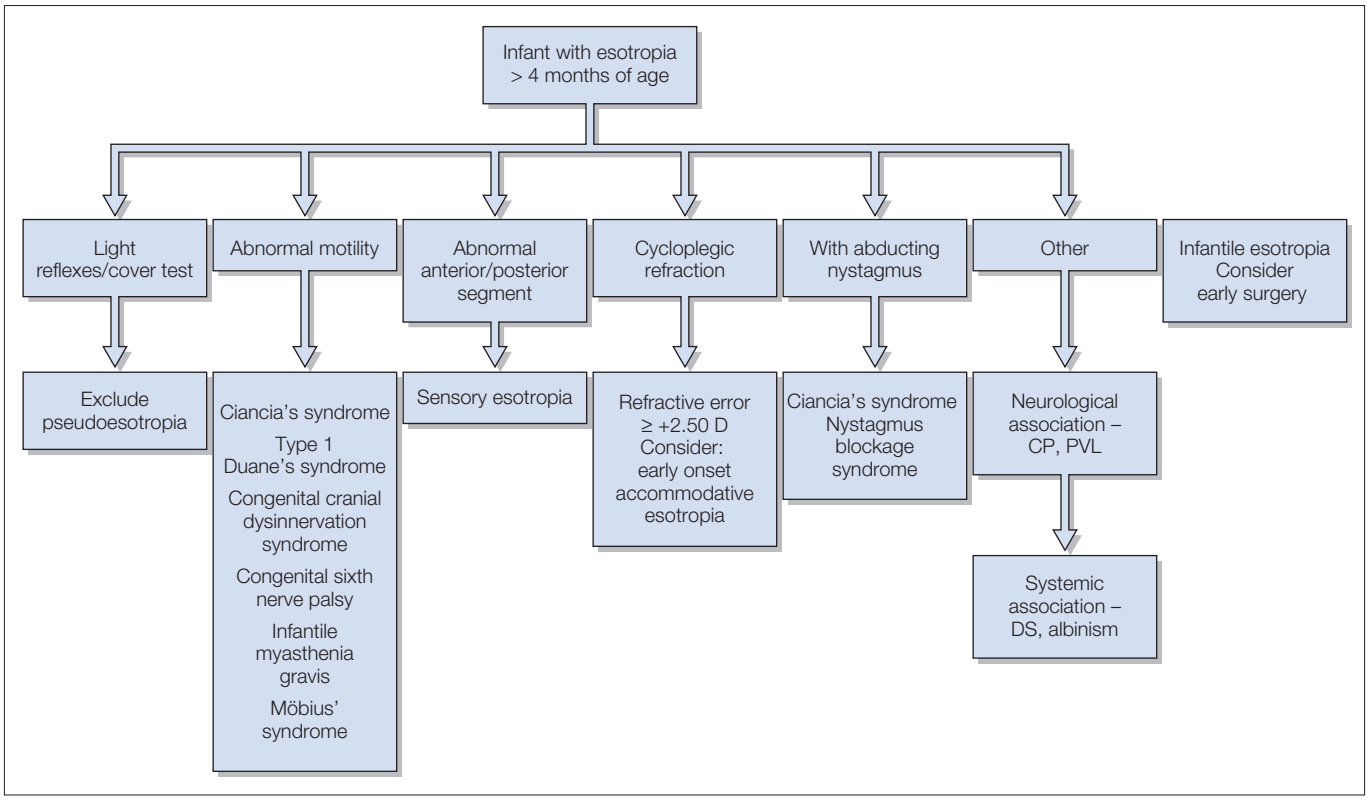


Fig. 76.4 Work-up of infant ≥4 months of age with esotropia. CP, Cerebral palsy; PVL, periventricular leukomalacia; DS, Down syndrome.

Box 76.2

Differential diagnosis of infantile esotropia (IET)

True congenital-onset ET	*Infantile-onset ET*
(True) congenital ET	Infantile ET
Pseudoesotropia	Early-onset accommodative sensory ET
Type 1 Duane syndrome	Ciancia syndrome
Congenital sixth nerve palsy	Associated neurologic – CP, PVL
Nystagmus blockage syndrome	Associated systemic – DS, albinism
Congenital fibrosis syndrome	
Infantile myasthenia gravis	
Möbius syndrome	

CP, Cerebral palsy; PVL, periventricular leukomalacia; DS, Down syndrome.

If the angle of misalignment is such that the child requires surgery, then bilateral medial rectus recessions (BMRc) are the treatment of choice for mild cases of IET or Duane syndrome. Performing a doll's eye maneuver demonstrating full abduction will exclude a Duane syndrome or congenital sixth nerve palsy (a generally benign condition that usually resolves by 6 weeks of age).[45] Other techniques to elucidate abduction include rotating the child or using monocular occlusion to force abduction in the non-occluded eye. A sixth and seventh nerve palsy occurring together may be due to Möbius syndrome, which is usually associated with a number of other orofacial and limb abnormalities (Fig. 76.6).

A full ophthalmic examination (including cycloplegic refraction) will exclude any anterior or posterior segment cause of a sensory ET.



Fig. 76.5 Pseudoesotropia. The child appears to have an esodeviation due to a prominent left epicanthic fold limiting the amount of visible nasal sclera; however, the light reflexes are symmetric and cover test was normal.

Ciancia described a subset of ET[46] that others describe as "cross-fixation congenital ET."[18,47] Ciancia syndrome has the following features:

1. esotropia of early onset;
2. a generally large angle of deviation;
3. bilateral limitation of abduction;
4. jerk nystagmus with the quick phase toward the side of the fixating eye, increasing with abduction and decreasing with adduction;
5. torticollis with face turn toward the side of the fixating eye;
6. head tilt toward the side of the fixating eye.[48,49]



Fig. 76.6 Möbius syndrome.

Nystagmus blockage syndrome (NBS) was first described in 1966 by Adelstein and Cuppers[50], with a reported prevalence of 4.8–10.3% of congenital esotropes.[51] The syndrome is characterized by:

1. nystagmus with early-onset large/variable-angle ET;
2. pseudoabducens paralysis;
3. head turn in direction of fixing eye;
4. absent nystagmus with the fixing eye in adduction;
5. increasing amplitude of manifest nystagmus with abduction.

NBS and Ciancia syndrome should be considered in any esotropic child with abducting nystagmus. However, the underlying pathophysiology is different. In Ciancia syndrome, the ET and nystagmus are coincidental,[16] whereas, in NBS the patient has congenital idiopathic nystagmus with the null point in adduction (causing ET). Accommodation/convergence innervation may play a role and pupillary constriction in adduction may assist in making the diagnosis of NBS.[52]

With alternating ET and cross-fixation, there is no nystagmus in the primary position or abduction. The fixating eye usually is in the primary position with the non-fixating eye adducted (unlike in NBS, where both eyes are in adduction) and there is often no amblyopia (unlike in NBS).[51] These features may assist in differentiating NBS from IET. Treatment in all these syndromes is often the same, with large BMRs producing good motor outcomes[53] in most cases.

The prevalence of strabismus in children with developmental delay is variably reported between 27% and 100%.[54,55] The population-based longitudinal study by Haugen et al. found that strabismus was present in 42% of patients with Down syndrome and was predominantly early-onset ET (84%) and associated with hypermetropia.[56] The prevalence of strabismus in patients with cerebral palsy is 44% on average (15–62%).[57]

Surgery for ET in developmentally delayed children has variable postoperative alignment outcomes. Some groups report high rates of overcorrection and unpredictable outcomes when using standard surgical tables.[58] Muen et al. reported suboptimal surgical results in seven patients who were subsequently diagnosed with periventricular leukomalacia after presenting with strabismus.[59] While some authors decrease the surgical dosage, Yahalom suggested that reduction of standard surgical dosages for ET in Down syndrome is unnecessary.[58] The authors follow this practice.

Does stability of preoperative alignment affect outcomes?

Ing showed that the majority of patients observed prior to surgery for IET showed an increase of at least 10 PD, with 50% showing an increase of at least 20 PD.[60] When surgery was based on the measurements taken 1 day before surgery, there was no difference in alignment between the group with an increase in angle and those with stable measurements. In a study of infants with IET grouped into "stable" (<10 PD difference in measurements between visits) or "unstable" (≥10 PD difference in measurements between groups), Birch et al. demonstrated that there was no difference in postoperative alignment, re-operation rates, rates of prescription of hyperopic or bifocal spectacle prescription, or stereoacuity.[61] In a further study, the motor outcomes (alignment) were the same regardless of the stability of measurements before surgery.[62] Of note, there does appear to be an improvement in measurement stability after 6 months of age.[63]

Measurement uncertainty

Schutte et al. identified the sources of human error in strabismus surgery.[64] They estimated that half of re-operations were due to inaccuracy in measurement of the angle of strabismus, variability in surgical strategy, or imprecise surgery.

In the Early vs. Late Infantile Strabismus Surgery Study (ELISS) pilot study, the three masked examiners found high inter-observer agreement with the Hirschberg test, but in 10% of cases it exceeded 10° (20 PD).[65] In another study, experienced strabismologists reviewed a series of photographs of patients with a variety of common strabismus entities (25Δ L ET, 25Δ R XT, 80 Δ ET, 75 Δ IET) and estimated the angle of squint using the Krimsky and Hirschberg tests with an expert examiner prism cover test (PCT) as the "gold standard."[66] The majority of examiners overestimated at least one patient by 10Δ with the Krimsky test and differences of 5Δ were difficult to distinguish. With the Hirschberg test, each patient was underestimated by 10Δ by at least one examiner, with more inaccuracy for larger angles. The authors concluded that the Krimsky test is more accurate than Hirschberg, especially for larger angles of strabismus, but both tests are substantially less accurate than PCT. Thompson and Guyton reported that it is impossible to accurately measure extremely large angles of strabismus with prisms.[67] A Pediatric Eye Disease Investigator Group (PEDIG) study[68] looked at inter-observer reliability of the prism and alternate cover tests. They concluded that in childhood ET of greater than 20Δ, differences of 12Δ or more are likely to indicate real change but smaller differences could be due to measurement error. We should, therefore, be skeptical about the accuracy of our measurements.

The PCT is the "gold standard" for strabismus measurement but can be limited by the child's cooperation. The Krimsky test is easy to perform in infants with the prism split between the two eyes for angles of squint ≥40 PD. When the child is

uncooperative, the authors have found it useful to combine the Krimsky and Bruckner tests[69] to confirm accuracy of the PCT. Loose plastic prisms are used for the PCT. Plastic right-angled prisms should be held in the frontal plane position and plastic isosceles prisms should be held close to the position of minimum deviation.[70] In practical terms, this means that for both types of prism, each prism is held with the base in the sagittal plane. The authors acknowledge that the prismatic effect of two split prisms is not the arithmetic sum of the two individual prisms, but for most angles of ET encountered in clinical practice, the difference is still within the observer's measurement error. What is absolutely crucial for any strabismologist is to use the same measurement technique consistently and adjust surgical doses according to results over time. The measurement of distance deviation is often problematic in small infants, but it is always possible to measure the near angle, so the authors usually base their surgical plan on the near angle, as is now common practice in acquired ET.[71,72]

Nonsurgical management

Refraction is crucial to the management of IET, especially, but not limited to, the follow-up period after surgery. Hypermetropia occurs in 15% of children with IET.[73,74] At presentation, we treat infants with ≥2.5 D hypermetropia with full spectacle prescription[73,75] to determine whether the ET is partially or fully accommodative. This resolves the ET completely in almost 50% of cases, so prevents unnecessary surgery.[73,74] However, 20% of infants initially controlled with glasses will decompensate and ultimately require surgery.[76] Spectacle correction can reduce a large-angle strabismus so that only two muscles need to be operated (for the corrected angle) rather than three. Correction of hypermetropia is essential for maintaining postoperative stability.

Amblyopia can be inferred by the child's fixation pattern. Fixation should be maintained through a blink in both eyes if the vision is equal.[77,78] Cross-fixation occurs when an infant fixes across their nose at the object of interest (Fig. 76.7). As an object of interest (e.g. a toy) is moved from one side to the other, fixation switches at the midline if the vision is equal. If fixation switches past the midline, amblyopia is present in the eye toward which the toy is being moved.[79] It would seem logical to treat amblyopia before surgery. However, in one series of surgery in (older) children with untreated amblyopia, there was no difference in postoperative outcomes compared to those children who were patched preoperatively. One-sixth of the amblyopic patients had spontaneous resolution of the amblyopia as a result of surgery alone.[80] In a larger series, operating for IET in the presence of mild amblyopia made no difference to outcome but the results were worse in infants with moderate amblyopia.[81] Preoperative alternate daily patching of each eye has been recommended to prevent the development of suppression,[82] but was argued against by Parks,[83] in particular because he felt that suppression rarely occurs until after the eyes are aligned and some binocularity develops. Ing reported no difference in alignment outcome[84] between alternate-day preoperative patching with unpatched controls, but the study was underpowered to detect less than a 25% difference in outcome.

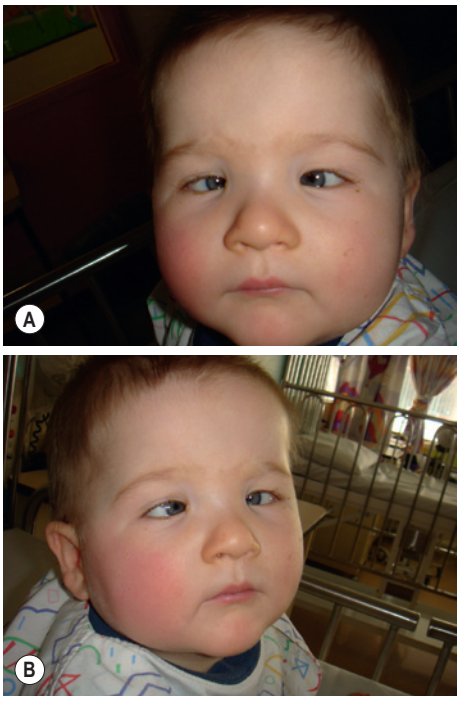


Fig. 76.7 Cross-fixation. Left gaze with right eye fixating (A), right gaze with left eye fixating (B).

Timing of surgery: why early surgery

Fusion and stereopsis are absent before 2 months of age but develop rapidly between 3 and 5 months of age.[14] Forced-choice preferential looking and visual evoked potential stereoacuity both reach adult levels by 6–7 months of age.[85] Infants with a recent onset of strabismus (within weeks) that had been corrected with prisms had similar stereoacuity to normal infants of the same age[86,87] (Fig. 76.8). The critical period for disruption of stereopsis in IET peaks at 4.3 months of age, so the time window for correction of IET with the aim of obtaining high-grade stereopsis may be very narrow.[88] Wong reviewed the evidence in favor of early surgery.[35] She showed there was a clear trend of declining stereopsis outcomes with increasing age at surgery (Fig. 76.9). Cerman et al. identified 16 months of age as a critical time point after which even an excellent motor outcome will not produce stereopsis.[89]

Chavasse argued that most infants with IET could develop fusion if the squint was fully corrected before the age of 2 years. This was confirmed by Ing,[11] who reported a significant difference in sensory outcome between infants surgically aligned before and after age 2 years. Zak and Morin demonstrated that the development of Worth 4-dot fusion was related to the age at time of surgery.[90] Surgery after age 12 months was related to the development of latent nystagmus, inferior oblique overaction, amblyopia, and reduced degrees of fusion.

Better sensory outcomes with surgery before age 2 years has been confirmed by a controlled prospective multicenter study (ELISS), but the study had a high dropout rate.[12]

Birch and Stager compared two groups of infants who had surgery before age 1 year.[91] The first group had surgery at or before 6 months of age and the second between 7 and 12 months of age, with a follow up of 4–17 years. Both cohorts were

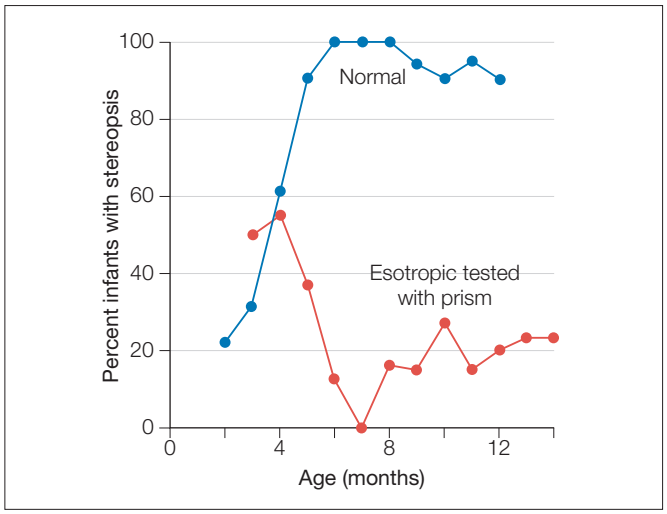


Fig. 76.8 Prevalence of stereopsis as a function of postnatal age in a population of normal versus esotropic infants. Esotropic infants were aligned using prisms and tested before surgery. *(Adapted from Stager DR, Birch EE. Preferential-looking acuity and stereopsis in infantile esotropia. J Pediatr Ophthalmol Strabismus 1986; 23: 160–5 by Tychsen L. J AAPOS 2005; 9: 510–21. Reprinted by permission of Slack.)*

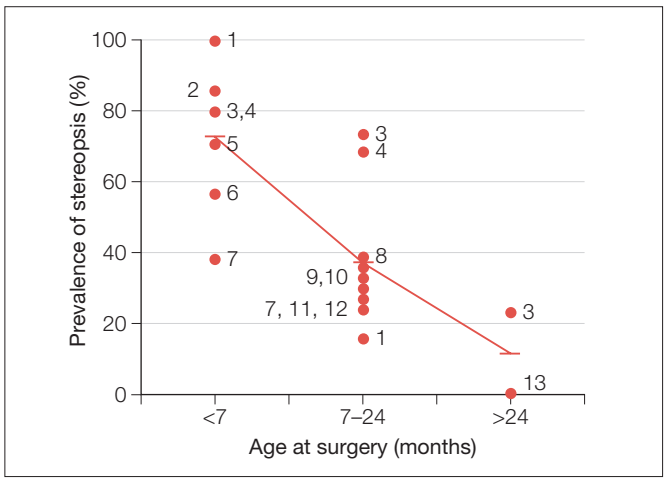


Fig. 76.9 Summary of prevalence of stereopsis by age at the time of surgery. Each circle indicates the prevalence of stereopsis from published studies. Short horizontal dashes represent mean prevalence of stereopsis for different age groups. *(From Wong AMF. Timing of surgery for infantile esotropia: sensory and motor outcomes. Can J Ophthalmol 2008; 43: 643–51. Reprinted by permission of Elsevier.)*

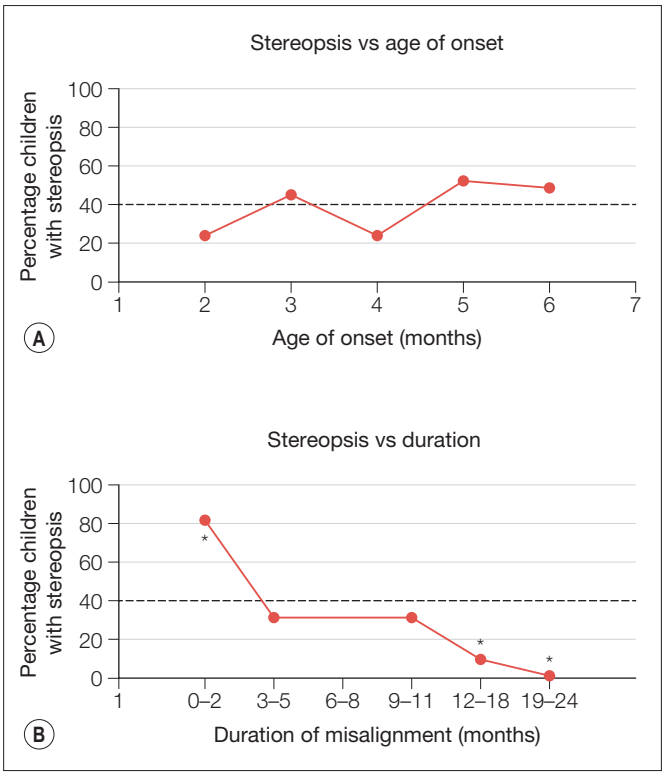


Fig. 76.10 (A) Stereopsis versus age of onset. (B) Stereopsis versus duration of misalignment. There is an inverse relationship between duration of misalignment and development of stereopsis. *(From Birch EE, Fawcett S, Stager DR. Why does early surgical alignment improve stereoacuity outcomes in infantile esotropia. J AAPOS 2000; 4: 10–14. Reprinted by permission of Elsevier.)*

similar at entry and had similar motor outcomes (83–94% had alignment within 6 PD) but the early group had significantly better peripheral and central fusion, Randot stereopsis, and Randot stereoacuity of ≥200 seconds of arc. Even with early surgery, only 38% of infants developed Randot stereopsis and only 20% developed Randot stereoacuity of ≥200 seconds of arc, indicating that even short periods of misalignment may be enough to disrupt binocular development.[91]

Birch et al.[92] concluded that the duration of misalignment (not age of onset or age at alignment) was the significant factor in determining stereopsis outcomes (Fig. 76.10). If the misalignment was longer than 2 months, then excellent stereopsis was not achieved, and after 12 months duration of misalignment, only 4% of patients had Randot stereopsis. Patients with Randot stereopsis had fewer re-operations, and a lower prevalence of DVD, but no difference in the prevalence of amblyopia or the need for vertical muscle surgery. Subsequently, they reported that patients with absent Randot stereopsis recorded immediately after surgery had 3.6 times more risk of surgery for recurrent ET or consecutive XT after surgery than those with measurable stereoacuity.[93] Ing and Okino[94] confirmed loss of stereopsis was related to the duration of misalignment. In a further paper, Ing and Rezentes[95] reported that there was no significant difference in fusion in subgroups of infantile esotropes who had up to 21 months of misalignment or who were surgically aligned by 6, 12 or 24 months of age. They concluded that the time window for the development of fusion was wider than that for the development of stereopsis.[21]

The importance of Birch and colleagues finding that duration of strabismus is the major determinant of sensory outcomes (less than 3 months of duration is the cut-off for good sensory outcomes) corresponds to the duration of misalignment in esotropic monkeys known to produce irreversible deficits in binocularity.[2,96] The authors believe, along with Tychsen,[87] that it has major implications for the rapidity with which referrals must be made and surgery carried out for children with IET if high grades of binocularity are a desired outcome.

The best functional outcome for most infants with IET after surgery is the monofixation syndrome[97]; a small residual tropic misalignment of 8 PD or less, peripheral fusion, and gross stereopsis. The vast majority of patients with the monofixation syndrome show good long-term stability, even over decades.[98]

However, Wright reported excellent motor alignment and high-grade stereopsis in two of seven patients operated on between 13 and 19 weeks of age.[99] Ing reported on a series of 16 patients aligned before 6 months of age[100]; only one achieved high-grade stereopsis. However, Helveston et al. cautioned that children operated on before 6 months of age had an average of one additional procedure later on, in order to retain a satisfactory alignment.[101]

There are several studies reporting delayed development in children with IET prior to surgery with improvement within months after surgery.[102–104] Drover et al. tested fine and gross motor development in infants with IET.[102] The pre-surgery group showed both delayed sensorimotor and gross motor milestones (Fig. 76.11). After surgery, the delays disappeared, suggesting that early surgery is beneficial to infant development (Fig. 76.12).

Using a decision analysis approach, Trikalinos et al. concluded that it is probably warranted to attempt surgery for IET "as early as possible."[105] In one series, parental satisfaction with their child's surgical outcome was reported as 85% and this correlated with a postoperative alignment in the microsquint range (≤8 PD.[97,106] Parents noted improved eye contact and appearance of their children. Patients with IET were reported to have a 2.6 times increased rate of mental illness when compared with controls; this did not occur with children with other types of strabismus and was not related to premature birth.[107] So, the psychosocial benefits of early surgery should not be underestimated.

Why delay primary surgery?

The usual reasons advanced for delaying surgery include:

1. difficulties with measuring the angle of misalignment;
2. the lack of stability of deviation in young infants;
3. the possibility of spontaneous resolution;
4. anesthetic risk;
5. technical difficulties of surgery on infants' eyes;
6. the difficulty of diagnosing amblyopia in infants with microtropia after successful surgery.

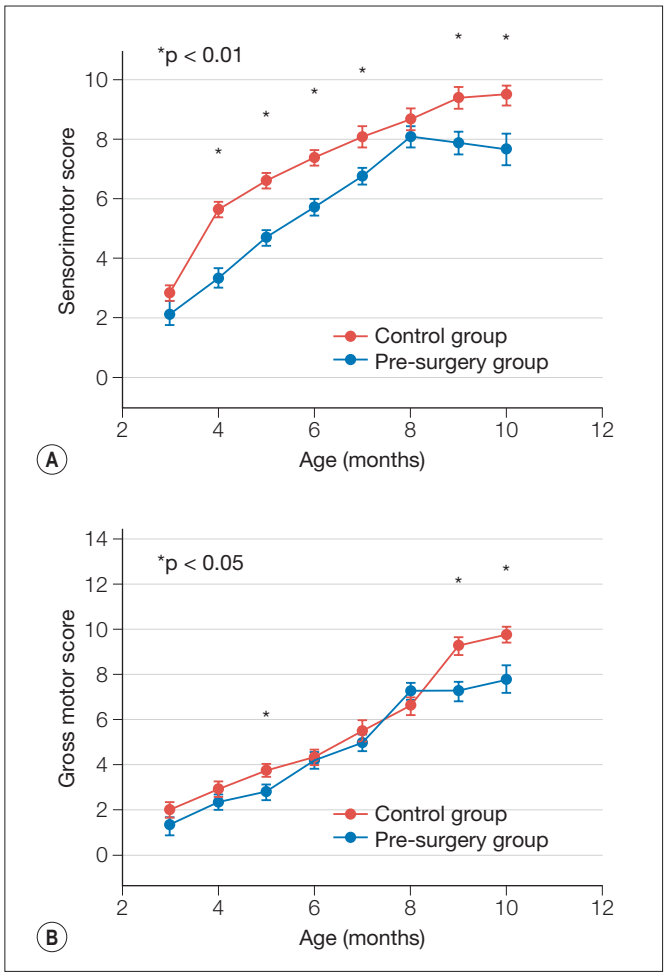


Fig. 76.11 Comparison of fine motor (A) and gross motor (B) score of presurgery and control groups. Bars represent 1 standard error. Asterisks represent significant differences. Planned comparisons indicated that the delay of sensorimotor milestones was significant at 4, 5, 6, 7, 9, and 10 months of age ($p < 0.01$). Delay of gross motor milestones was significant at 5, 9, and 10 months of age ($p < 0.05$). *(From Drover JR, Stager DR, Morale SE, et al. Improvement in motor development following surgery for infantile esotropia. J AAPOS 2008; 12: 136–40. Reprinted by permission of Elsevier.)*

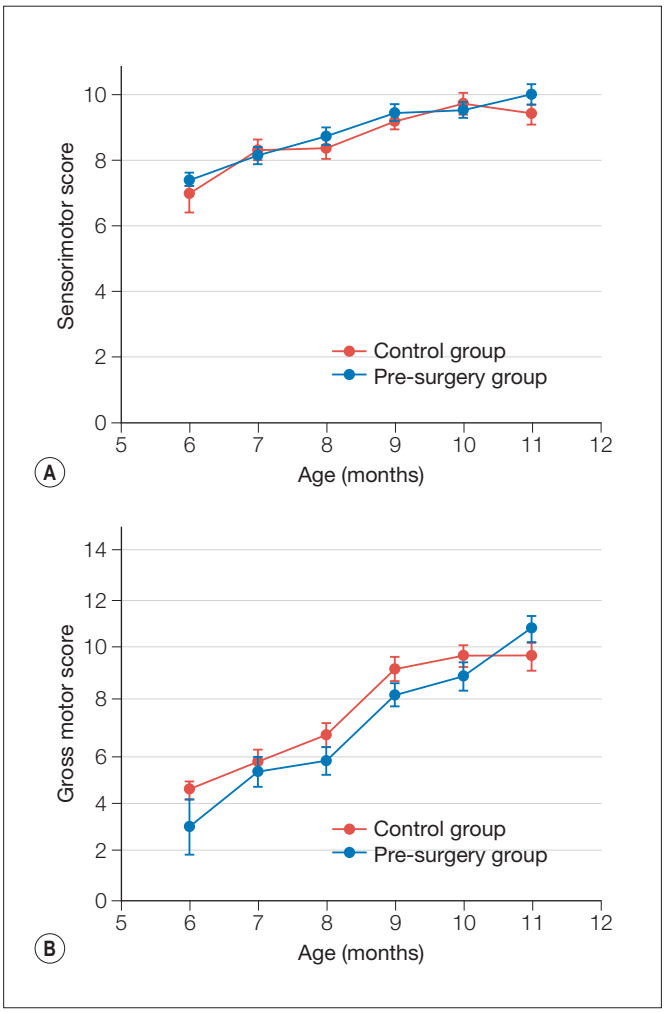


Fig. 76.12 Comparison of fine motor (A) and gross motor (B) score for postsurgery and control groups. Bars represent 1 standard error. *(From Drover JR, Stager DR, Morale SE, et al. Improvement in motor development following surgery for infantile esotropia. J AAPOS 2008; 12: 136–40. Reprinted by permission of Elsevier.)*

Spontaneous resolution has been reported in a small percentage of patients.[34] CEOS reported that spontaneous resolution usually occurs when the deviation is <40 PD in size and is intermittent or variable in infants <20 weeks of age.[34] In infants with a constant deviation >40 PD, only 2.4% of cases spontaneously resolved.

In infants <1 year of age with intermittent, small-angle ET, Fu et al.[108] reported a 46% likelihood of spontaneous resolution or control with spectacle correction alone. However, patients with a constant small- or variable-angle ET progressed to a constant large-angle ET requiring surgery.

Calcutt and Murray reported on a series of adult patients with unoperated IET. The prevalence of amblyopia was 14%, in whom two-thirds were anisometropic.[109] Later they reported an improvement in sensory status in 88% of IETs who were operated on aged >8 years, with a widening of the visual field in 76% patients.[110]

Posterior segment eye growth is rapid in the first few months of life[111] producing major alterations in the insertion sites of the muscles relative to the equator, so the determination of surgical dosage under the age of 6 months may be difficult. However, Helveston reported that this was not an issue when surgery was carried out at 4 months of age or later.[112]

Surgical management

The majority of patients with IET require surgical correction. Orthotropia or microesotropia gives better long-term results than microexotropia.[113] Surgery for IET can be technically demanding in children under 2 years of age. Surgical approaches include BMRc (measured from the insertion or the limbus), unilateral recess/resection, and, for larger angles, BMRc with added unilateral or bilateral lateral rectus resection.[114–118] The authors no longer perform four horizontal muscle surgery due to an unacceptable rate of overcorrections. For moderate angles of strabismus, amounts of surgery based on those reported by Helveston are used (Table 76.1). For larger angles of strabismus ≥60 PD, the authors have developed and validated a surgical table for three-muscle squint repair (Table 76.2).[119]

The authors perform BMRc rather than a unilateral recess/resect procedure because it is technically easier, quicker, and does not involve a loss of muscle tissue. A controlled randomized comparison of BMRc and unilateral recession/resection procedures reported no difference in outcome in children with IET.[120] The position of the muscle insertion varies from 3–6 mm from the limbus and can also vary according to the degree of traction exerted during surgery.[122] Kushner and Morton proposed that unreliable results may be minimized by measuring surgical recession from the limbus rather than the insertion.[123] They reported success in 84% of cases of mean preoperative deviation 53 PD after performing 10.5 mm BMRc from the limbus. This was significantly better than graded recession from the insertion. The authors prefer measuring from the limbus because this is a constant ocular landmark (Fig. 76.13). A table of numbers for recession amounts measured from the muscle insertion is listed elsewhere in this book.

Successful alignment with BMRc (measured from the insertion or the limbus) in children with IET (30–100 PD)

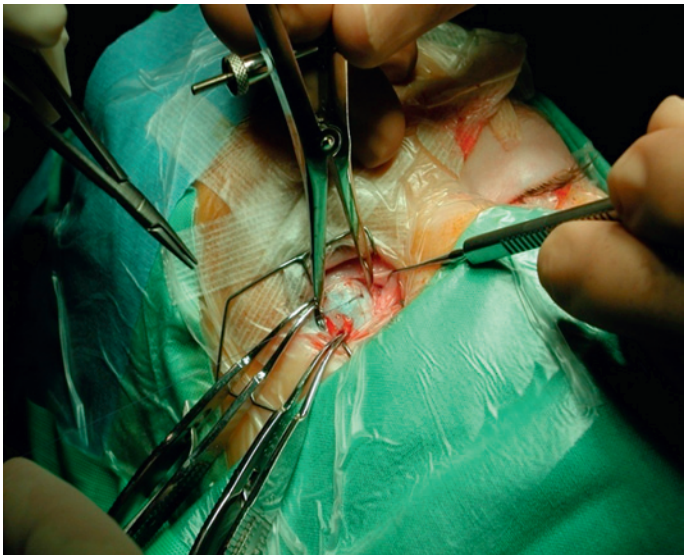


Fig. 76.13 Measurement of right medial rectus recession 11 mm from the limbus. Left arm of caliper at 3 o'clock position on limbus. Note infantile type insertion approximately 3 mm from limbus. *(Measurement technique is described in Camuglia JE, Walsh MJ, Gole GA. Three horizontal muscle surgery for large-angle infantile esotropia. Eye 2011; 25: 1435–41.)*

Table 76.1 Two horizontal muscle surgery dosage for infantile esotropia <60 PD*

Preoperative deviation (PD)	Bilateral medial rectus recessions (mm)	
	Age <1 year	Age >1 year
25	8.5	9.0
35	9.5	10.0
40	10.0	10.5
45–50	10.5	11.0
55	10.5	11.5

*Amount of recession is measured from the limbus.
Adapted from Helveston EM. Surgical Management of Strabismus: Atlas of Strabismus Surgery, 4th ed. St Louis, MO: Mosby; 1993: 110.

Table 76.2 Three horizontal muscle surgery dosage for large-angle infantile esotropia ≥60 PD*

Preoperative deviation (PD)	Bilateral medial rectus recessions (mm)		LLRs (mm)
	Age <1 year	Age >1 year	
60–65	10	10.5	4
70	10	10.5	5
75	10	10.5	6
80	10.5	11	6
85	10.5	11	8

LRR, Lateral rectus resection.
*Amount of recession is measured from the limbus and recession amounts for 3 muscle squint repair (3MSR) are reduced to lower the risk of consecutive exotropia.

has been variably reported to be between 30–90%[100,101,114,124–127] with a wide range of duration of follow-up. Many series report success rates of approximately 80% with one operation. The prevalence of larger angles >60 PD among children with IET is 18% and few studies have reported the results of surgery for this group in isolation. Undercorrection rates are still significant and have been proposed to be due to inadequate surgery amounts and/or the variability of the medial rectus insertion.[114,121] Scott retrospectively compared BMRc 5–6.5 mm from insertion with three horizontal muscle surgery (BMRc measured from the limbus with lateral rectus resection) in angles >50 PD.[114] Success to orthophoria was 37.3% for two horizontal muscle repair group with residual ET in 58%. Success in the three-muscle group was 64.5%.

We conducted a validation study of a table guiding surgical dosage for three horizontal muscle surgery for 51 patients with larger-angle IET and reported successful alignment to within 10 PD of orthotropia in 91.3% at 1 year, 77.8% at 4 years, and 73.6% at 8 years.[119] Chatzistefanou et al. reported similar results in patients with large-angle IET >50 PD from a single surgeon performing three horizontal muscle surgery.[118]

Inferior oblique surgery can be included at the time of initial surgery if the IOOA is significant, especially with a "V" pattern ≥20 PD. The options for inferior oblique weakening include recession, anterior transposition, and myectomy. Mims et al. reported that bilateral anterior transpositions also reduced the need for DVD surgery.[128] The authors do not perform inferior oblique myectomy in patients with IET because this prevents its use to treat DVD in the future. If IOOA exists in isolation, a graded IO recession is performed. If IOOA and DVD co-exist, the preferred operation is graded IO anterior transposition. For isolated DVD, the authors perform a large ipsilateral superior rectus recession.[128]

Review of botulinum and its theoretical rationale

The role of botulinum toxin A injections in children as the sole primary treatment, adjunct at the time of primary surgery or secondary treatment for failed surgery, is still under debate. Botulinum toxin as a primary treatment in IET has been studied in a number of prospective and retrospective studies,[129,130] and is discussed in Chapter 85 in more detail. Follow-up of children after botulinum toxin treatment is the same as that following surgery.[131] Despite the reasonable motor and sensory outcomes with multiple botulinum toxin injections, its use as the primary therapy in IET has not become widespread, so surgery remains the standard in most centers.

Postsurgical management

In the immediate postoperative period, the most important considerations are to exclude a lost muscle, conjunctival dehiscence, and to detect postoperative infection. The authors review patients on day 1, week 1, week 3 and week 6 postoperatively. The 6-week postoperative alignment correlates with the likelihood of long-term success.[132] Postoperatively, the authors prescribe antibiotic drops qid and steroid drops (bd only to reduce steroid-induced ocular hypertension)[133] for 2 weeks. At week 1, if the strabismus is undercorrected, cycloplegic refraction should be repeated and the full plus correction given. Miotic drops (e.g. phospholine iodide 0.06% bd) can also be used for undercorrections as a temporizing measure but phospholine iodide drops are no longer widely available. Pilocarpine 0.5% is an alternative.

If the alignment is ≥15 PD ET at the 6-week postoperative visit, further surgery needs to be considered. For residual ET the authors perform lateral rectus resections rather than medial rectus re-recessions due to a lower rate of consecutive XT.[134,135] A small-angle XT with normal ductions in the immediate postoperative period usually resolves spontaneously; however, an underacting medial rectus muscle in the immediate postoperative period is a predictor for consecutive XT. If there are no active issues, patients are reviewed 3-monthly for 2 years after surgery, then 6-monthly until age 6, then yearly until age 8. If the uncorrected alignment is satisfactory, the authors discharge after age 8. All parents should be warned of the long-term risk of their child developing consecutive XT even decades later.

Long-term follow up of IET is essential for the early detection of amblyopia, refractive errors, accommodative ET and secondary associations of DVD, and IOOA. Postoperative amblyopia rates vary due to the differences in definition but the reported prevalence is between 17% and 39%.[11,91,136–138] Risk factors for its development include preoperative amblyopia and uncorrected refractive errors (particularly anisometropia). Approximately 60% of patients with IET will develop accommodative ET within 2–3 years of their initial surgery.[139,140] Birch et al.[75] identified three risk factors for the development of accommodative ET after IET surgery:

1. delay from diagnosis to surgery >3 months;
2. a sustained increase in hypermetropia of as little as +0.5 D;
3. absent or poor stereopsis.

The usual decrease in hypermetropia seen in normal infants in the first 9 months of life does not occur in IETs, making it necessary to carry out long-term refraction follow-up until after 8 years of age.[141]

Follow-up studies have shown that despite early postoperative motor success, alignment to orthotropia can fail over time. Prieto Diaz et al. estimated that 75% patients still have successful alignment at 10 years in a long-term follow up of IETs[142] and 55% of patients maintain a satisfactory alignment after 18 years (Fig. 76.14). Helveston reported failed alignment in 70% after initial BMRc 8–10 mm from the limbus in children <6 months old (with true congenital ET) with mean preoperative angle of 50 PD (range 35–60 PD).[101] Over an 8–12-year follow-up period, there was a 52% reoperation rate. In the follow-up of 130 children, Louwagie et al. determined that repeat surgery was required in 51% by 10 years and 66% by 20 years.[143] Preoperative moderate amblyopia is a risk factor for loss of alignment.[144]

Conclusion

It is now well established that we should operate early to promote the development of binocular vision and some stereopsis. We recommend anytime from 6 months of age for children with a constant ET ≥40 PD. The onset of IET is often around 4 months of age. This produces profound deficits in

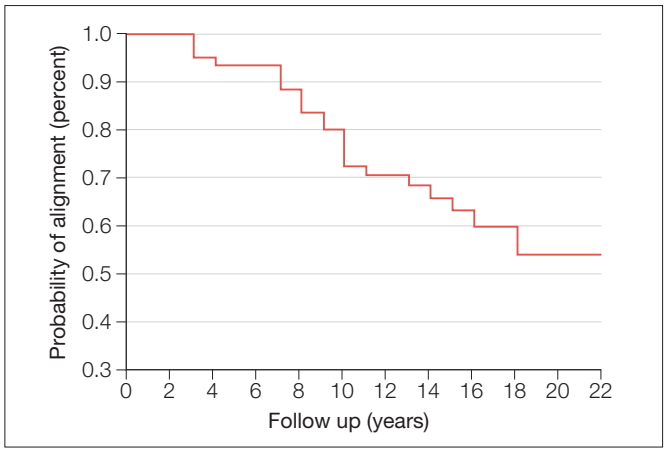


Fig. 76.14 Kaplan–Meier survival curve showing the percentage of patients with long-term success after two-muscle surgery for infantile esotropia. *(From Prieto-Diaz J, Prieto-Diaz I. Long term outcome of treated congenital/infantile esotropia: does early surgical binocular alignment restoring (subnormal) binocular vision guarantee stability? Binoc Vision Strab Q 1998; 13: 249–54. Reprinted by permission of Binoculus Publishing.)*

binocular vision if not corrected promptly. Early alignment appears to produce better functional results, particularly if good follow-up is maintained. Some measurement uncertainty and instability of alignment occurs but does not appear to affect results. Much of our clinical knowledge is still based on retrospective case series. The only new treatment for IET in recent decades has been botulinum toxin. A Cochrane review did not find any randomized controlled trials of surgical intervention for IET and concluded that while early surgery should be the standard we are not yet finally able to resolve the controversies regarding type of surgery, nonsurgical options, and specific age of intervention.[145]

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Accommodative esotropias

David R Weakley and Erika Mota Pereira

Chapter contents

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Characteristics

Accommodative esotropia describes an esotropia caused in whole, or in part, by the use of accommodation to clear vision in the presence of uncorrected hypermetropia. This association is widely attributed to Donders.[1] Accommodative esotropia is one of the most common forms of childhood strabismus accounting for about a third of all strabismus patients in most studies in Europe and North America.[2]

The typical age of onset ranges from 2 to 5 years old, but may present earlier ("infantile accommodative esotropia") or, less commonly, at a later age. Caregivers typically report crossing that is intermittent initially and most apparent when the child is fixing on a near object or when fatigued. With time, the crossing occurs more frequently and, without treatment, often becomes constant. Accommodative esotropia may manifest suddenly following a minor illness, trauma, or without any obvious precipitating event.

Classification

The most widely accepted classification of accommodative esotropia includes four distinct types:

1. Fully accommodative esotropia (refractive esotropia): those patients in whom the distance and near deviation are equal and the esotropia is caused entirely by uncorrected hypermetropic refractive error. In one study, these patients had a mean age of onset of 3½ years and a mean refractive error of +4.75 D.[3] They have a normal accommodative convergence to accommodation (AC/A) ratio and respond to correction of the full cycloplegic refractive error (Figs 77.1 and 77.2).
2. High AC/A ratio accommodative esotropia: those patients who have a significant near–distance disparity in the magnitude of the esotropia, with the deviation being at least 10 prism diopters (PD) more at near than at distance. They have a younger age at presentation (mean 2.7 years old),[4] and a lower degree of hypermetropia than patients with typical fully accommodative or refractive esotropia. They have a normal hyperopic refractive error for age and little or no esotropia in the distance.
3. Refractive esotropia with high AC/A: this, arguably the most common type, has elements of both of the preceding types. These patients have a significant hypermetropic refractive error and some level of high AC/A ratio that leads to a deviation that is greater at near than distance by at least 10 PD.
4. "Early-onset esotropia" or "infantile accommodative esotropia": these terms refer to patients with fully accommodative esotropia presenting at a very early age. They may present with esotropia as early as 6 months of age and typically have very high hypermetropia and are more likely to have inferior oblique overaction.

The accommodative convergence/accommodation ratio (AC/A)

The AC/A plays an important role in the development, treatment, and prognosis in accommodative esotropia. Patients with a high AC/A ratio present earlier, are more likely to require surgery, and have a poorer prognosis for long-term binocular vision.[5] There are different ways to calculate the AC/A ratio although in clinical practice this is not necessary. A clinical comparison of distance to near deviation is most commonly used to determine whether or not the AC/A ratio is high. Patients can be further classified based on the degree of near–distance disparity:

grade I: 10–19 PD more deviation at near;
grade II: 20–29 PD more deviation at near;
grade III: 30 PD or more deviation at near than distance.

To calculate the AC/A ratio, either the gradient or heterophoric method can be used. For the gradient method, measure the



Fig. 77.1
A 3-year-old girl presented with a new onset of left esotropia (with strong fixation preference for the right eye). The deviation was 35 PD at near and distance fixation. The cycloplegic refraction was +4.25 in the right eye and +4.50 in the left eye.



Fig. 77.2 The same girl as in Fig. 77.1, 4 weeks later, wearing her full hyperopic correction. She had a small left esotropia with fixation preference for her right eye. Part-time occlusion therapy of the right eye was begun.

deviation at a fixed distance while relaxing accommodation by introducing plus lenses as follows:

$$\mathbf{AC/A = (D1 - D0)/p}$$

where p is the power of the lens used; D0, the deviation without lenses; and D1, the deviation with lenses.

In the heterophoric method, near and distance deviations are compared while taking into account the interpupillary distance (IPD) as follows:

$$\mathbf{AC/A = IPD\,(cm) + (Dn - Dd)/D}$$

where D is the fixation distance at near, Dn is the deviation at near, and Dd is the deviation in the distance. The gradient method is more easily performed and more accurate. By this method, a normal AC/A ratio is between 3 : 1 and 5 : 1.

Risk factors for accommodative esotropia

The most commonly recognized risk factor for the development of accommodative esotropia is excess hypermetropia. Its prevalence increases with increasing levels of hypermetropia. Other factors including family history, subnormal binocularity, and the presence of anisometropia all increase the risk of developing accommodative esotropia.

The prevalence of affected first-degree relatives in patients with accommodative esotropia is 18–23%, with as many as 75% of patients having an affected sibling, parent, grandparent, aunt, or uncle. Subnormal stereopsis or fusion preceding the onset of accommodative esotropia is a contributing factor in its development. These patients may develop accommodative esotropia with lower levels of hypermetropia.[6] Anisometropia of >1 D and amblyopia, in patients with hypermetropia, increase the likelihood of developing accommodative esotropia, particularly in patients with lower levels of hypermetropia.[7]

Clinical evaluation

Evaluation of patients with presumed or suspected accommodative esotropia requires a systematic approach. First, determine if a family history is present and if the child has any developmental issues or recent illness. The caregivers should be questioned about duration, frequency, and constancy of the crossing. Triggering factors such as near viewing or fatigue should be ascertained. Though accommodative esotropia is typically intermittent in the early stages, delay in treatment will often result in deterioration of fusion and development of a constant deviation and amblyopia.

The examination should include age-appropriate acuity testing, extraocular motility evaluation with attention to other causes of acquired esotropia (decreased abduction in sixth nerve palsy, etc.), as well as measurement of the deviation at near and distance. Evaluation for oblique muscle dysfunction and the presence of "A" or "V" patterns should be assessed. Inferior oblique muscle overaction, though less common than in infantile esotropia, may occur, particularly in cases of infantile accommodative esotropia or in the presence of significant amblyopia.[8,9] As noted, the AC/A ratio need not be calculated but can be graded based on the near–distance disparity.

A cycloplegic refraction is essential. Though some believe atropine refractions are necessary, the additional hypermetropia detected with atropine compared to cyclopentolate is unlikely to be of clinical significance, especially if blue-eyed, because they dilate and cycloplege more readily. The authors feel adequate cycloplegia can be obtained using 0.5% cyclopentolate (Mydrilate, Cyclogyl, Pentolair) under 6 months of age, 1% cyclopentolate from 6 months up to age 2 years, and 2% cyclopentolate may be used in patients over 2 years of age. Typically, the authors use 2.5% neosynephrine (phenylephrine) to facilitate dilation. The drops may be repeated in 5 minutes if needed and 30–40 minutes should be allowed to pass before refracting the patient. Children who do not dilate or become cyclopleged with cyclopentolate should be atropinized.

A fundus examination is critical; attention should be directed to any structural lesions that could result in a sensory deviation,

as well as assessment of the optic disc to detect swelling that that could indicate increased intracranial pressure.

Nonsurgical treatment

Initial treatment of presumed accommodative esotropia is proper spectacle correction. In most cases, the full cycloplegic refraction should be prescribed (see Fig. 77.2). In a patient in whom the angle of deviation is small and the hypermetropia significant, an undercorrection of 1–2 D can be prescribed to facilitate initial compliance with spectacles. However, one should increase to the full cycloplegic refraction if the child is not well aligned at the first follow-up visit. The authors do not initially prescribe bifocals even if the AC/A is high. It is important to correct any anisometropia as well as astigmatic error even if the full spherical correction is not prescribed.

If significant amblyopia is present, treatment should be instituted initially, although in mild to moderate cases it may be preferable to wait until the child has been in the glasses for a few weeks before beginning amblyopia therapy. Spectacle correction alone improves acuity in amblyopic eyes even in the presence of strabismus.[10] Once the child has adapted to the spectacles, a more accurate baseline acuity can be determined to assess the response to amblyopia therapy. Atropine penalization or patching is effective (see Chapter 73), though decreasing the spectacle power of the sound eye when using atropine does not significantly improve its effectiveness.[11]

Alignment in spectacles should be assessed after about 6–8 weeks. If the eyes are well aligned at near and distance, the child can be seen in 6 to 12 months unless amblyopia therapy necessitates more frequent follow-up. If alignment is unsatisfactory, longer observation in spectacles is generally acceptable, particularly if compliance with glasses is in question. Administration of atropine 1% to both eyes each morning for 1 to 2 weeks often improves compliance. Repeat cycloplegic refraction can be performed if its accuracy is in question.

If distance alignment is good, but significant esotropia persists at near after 3 months of spectacle wear, +3.00 bifocals can be considered. The bifocals should be executive or flat topped and set at the level of lower edge of the pupil. Miotics, such as phospholine iodide, may be considered, though their potential side effects and difficulty of administration limit their usefulness.

Surgical treatment

Surgery is indicated when the eyes are not aligned adequately with glasses; the definition of what constitutes "adequate" differs among clinicians. The decision to proceed with surgery involves a number of factors in addition to alignment with glasses. These include the patient's age, family or patient desires, presence or absence of amblyopia, and previous experience and compliance with spectacle or contact lens correction.

In the visually formative years, alignment that allows for fusion and prevention of amblyopia is paramount. Surgery should not be delayed if alignment is unsatisfactory. Fusion disruption for as little as 4 months can risk permanent loss of binocularity.[5] Common situations in which surgery is indicated are:

1. Partially accommodative esotropia: patients who never achieve good alignment in glasses alone.
2. Deteriorated accommodative esotropia: patients with initially good response to spectacles who later lose it. Deterioration of previously controlled accommodative esotropia has been associated with early-onset, high AC/A ratio, and amblyopia.[7,12]
3. Surgery may be indicated in patients with marginal control, those with good distance alignment but residual esotropia at near who do not tolerate or desire bifocals.[13]
4. Older patients whose hypermetropia may have normalized but who cross without minimal correction.

Surgery need not be deferred until amblyopia therapy is complete. Amblyopia therapy may benefit from improved alignment.[14]

In general, bilateral medial rectus recessions are the preferred surgical approach. Undercorrection is common in patients with accommodative esotropia if standard surgical dosages are followed. This is particularly true in the presence of a clinically high AC/A ratio. Various approaches can improve results, including adding additional recession to standard surgical dosages,[15] operating for the near deviation,[16] or combining medial rectus recessions with traditional or "muscle pulley" posterior fixation sutures.[17]

Long-term prognosis

One of the most commonly asked questions by parents of children with accommodative esotropia is "Will my child always have to wear glasses?" While it is important to keep patients in their full hyperopic correction through the visually formative years, many clinicians "wean" patients out of their full correction (and bifocals, if worn) to decrease spectacle dependence over time.

Mohney et al. reported 20% of accommodative esotropes will be free of spectacles by 10 years after diagnosis (Fig. 77.3).[18] Patients with high hypermetropia,[19] high AC/A ratio (bifocal dependence), and anisometropia are more likely to need glasses long term. Those with low hypermetropia, normal AC/A ratio, and those that undergo surgery are more likely to be successfully weaned from spectacles.

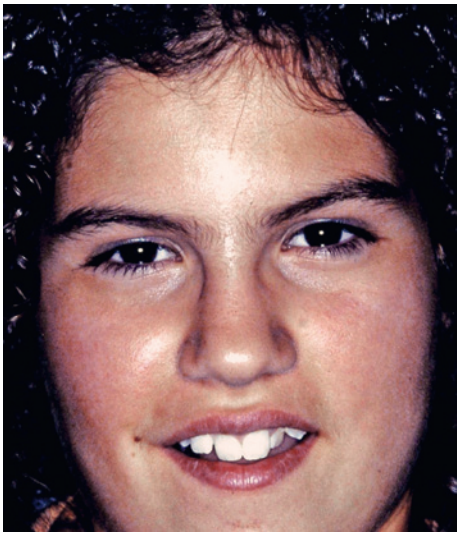


Fig. 77.3 The same girl as in Figs 77.1 and 77.2 at 15 years of age. She has been weaned from glasses. Her cycloplegic refraction is +1.50 in the right eye, +1.50 in the left eye. Visual acuity is 20/20 in each eye and she is orthotropic at near and distance fixation with high-grade stereoacuity.

For those patients that need correction beyond 10 years of age, contact lenses are a viable option and may improve compliance; additionally, refractive surgery has been used successfully in small series of older children and young adults.[20,21]

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Special esotropias (acute comitant, sensory deprivation, myopia-associated and microtropia)

John J Sloper

Chapter contents

ACUTE COMITANT ESOTROPIA
SENSORY DEPRIVATION ESOTROPIA
MYOPIA-ASSOCIATED ESOTROPIA
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SYNTHESIS
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These esotropias mostly occur later in childhood when binocular fusion is stable. There is considerable overlap between some groups and all patients do not fit neatly into a category. They are best approached by trying to understand the pathophysiology of each individual case and attempting to identify the cause of the breakdown of fusion.

Acute comitant esotropia

In a child presenting with sudden-onset comitant esotropia, a reason needs to be sought for loss of fusion at an age when binocular function is usually stable. This is commonly a benign condition, but children with intracranial pathology, particularly posterior fossa tumors, can present in this way.[1,2]

Children with acute-onset comitant esotropia can be divided into three groups[3]:

1. Acute onset esotropia following artificial interruption of fusion (Swan-type esotropia): This can occur with patching for anisometropic amblyopia, but has also been described following patching for a corneal abrasion. Loss of fusion may be associated with uncorrected hypermetropia. It can also occur following visual loss in one eye (see below, sensory esotropia).
2. Comitant esotropia of the "Franceschetti" type: This is an acute-onset comitant esotropia with diplopia and good potential binocular cooperation. It may be intermittent at first. The accommodative element is usually minimal. In most patients no immediate cause can be found; in some, an illness or shock may precede the onset.[3]
3. Comitant esotropia of the "Bielschowsky" type: These patients have up to 5 diopters (D) of myopia. There is uncrossed diplopia for distance, with fusion for near. The mechanism of a causal relationship between the myopia and esotropia is debated.

In groups 1 and 3 there is generally a clear cause for loss of fusion and investigation is not indicated in the absence of any other abnormalities. In group 2, there is no clear cause for the breakdown of fusion and there is concern about underlying neurological disease.

The decision on neuroimaging depends on the features of each case.[4] The risk of underlying pathology must be balanced against the risks associated with the X-ray dose for a computed tomography (CT) scan and a general anesthetic for CT or magnetic resonance imaging if required.

History and examination should determine whether there is evidence of a pre-existing cause for the esotropia and whether there is evidence of any associated neurological disease. If there is a cause for the esotropia (significant uncorrected hypermetropia or myopia, a high accommodative convergence/accommodation [AC/A] ratio, or anisometropic amblyopia), without other suspicious features, imaging is not required. Untreated anisometropic amblyopia may result in decompensation. Patching can precipitate a manifest squint in a child with a pre-existing microtropia or esophoria.

Features suggesting neurological disease include age of onset after the age of 5 years and distance diplopia prior to the onset of the esotropia. Diplopia at presentation indicates esotropia of recent onset without pre-existing suppression and so higher risk. Suspicious features of the examination include a distance angle larger than the near angle, an increase in esotropia in lateral gaze, lateral rectus underaction, and nystagmus. Lack of fusion on testing with prisms or the synoptophore is more common when there is a brain lesion. An "A" pattern esotropia may be associated with hydrocephalus secondary to an Arnold–Chiari malformation, a tumor, or aqueduct obstruction. Papilledema or optic nerve dysfunction causing reduced acuity or color vision or abnormalities of pupil responses mandate imaging.[4] Visual fields and clinical electrophysiological testing may provide valuable information.

Headache, clumsiness, evidence of developmental regression, or abnormalities of other cranial nerves may indicate neurological disease.

Initial treatment consists of full correction of any refractive error and treatment of amblyopia. If re-alignment is not achieved with refractive correction alone, then early surgery is indicated to realign the eyes before the potential for fusion is lost. As an alternative treatment, botulinum toxin may result in the long-term re-establishment of high-grade stereoscopic function.[5]

Early re-alignment carries a good prognosis for re-establishing fusion. The failure to re-establish fusion may indicate an underlying neurological problem.[1] However, fusion following strabismus surgery has been reported in patients after a tumor has been treated.[2] Patients with treated intracranial tumors and *incomitant* strabismus have a better chance of re-establishing fusion.[6] In the absence of involvement of brainstem fusion centers, the duration of misalignment is generally considered a major prognostic factor for the re-establishment of binocular function. However, the timeframe for loss of fusion potential varies from child to child and some older children have regained fusion after several years[7] and more than one surgical procedure.[8] In younger children, fusion potential may be lost in a few months. Early surgery or botulinum toxin to re-establish alignment is likely to be beneficial even in children with (treated) intracranial tumors.

The children with Franceschetti-type acute-onset esotropia probably represent the end of a spectrum of children with acquired non-accomodative esotropia (ANAET) in whom the onset may not be acute (or recognized as acute by parents) but who are otherwise similar and have a good chance of re-establishing binocular function after strabismus surgery,[9–11] even after early onset between 6 months and 3 years of age.[10] Of well over 200 children in these studies, none developed any neurological problems, even with long-term follow-up.

Sensory deprivation esotropia

The visual cortex fuses the images from the two eyes into a single image. If the image from one eye is severely degraded or lost, fusion cannot occur. In adults, divergence is common, but in children an eye with poor vision and absent binocular function will commonly become convergent, perhaps because they are hyperopic. Sensory esotropia may occur with early-onset conditions (monocular congenital cataract or optic nerve anomalies; Fig. 78.1), or with later acquired visual loss (trauma; Fig. 78.2). Hypermetropia of the fixing eye should be corrected before surgery is considered, since doing so is likely to reduce the deviation.

Management must address whether vision can be restored in the affected eye and, if so, whether fusion can be re-established. A common cause of reversible monocular visual loss in an older child is a traumatic cataract. In the absence of other ocular damage, the visual prognosis is good. Amblyopia does not develop in older children, but fusion may be lost rapidly and restoration of vision following cataract surgery may result in intractable diplopia, even with straight eyes. For this reason, cataract surgery should be undertaken as promptly as possible.

In a child with no prospect of visual improvement, strabismus surgery can be undertaken if the appearance of the deviation is unacceptable. All hypermetropia of the fixing eye should be corrected. The author prefers medial rectus recession and lateral rectus resection of the deviating eye, with the goal of leaving a small convergent deviation with no adduction deficit to minimize consecutive exotropia.



Fig. 78.1 Left sensory esotropia in a 6-year-old boy with left optic nerve hypoplasia. The left acuity was LogMAR 1.1 (6/76, 20/250, 0.07). The esotropia is controlled to an acceptable appearance by his hypermetropic spectacle correction.

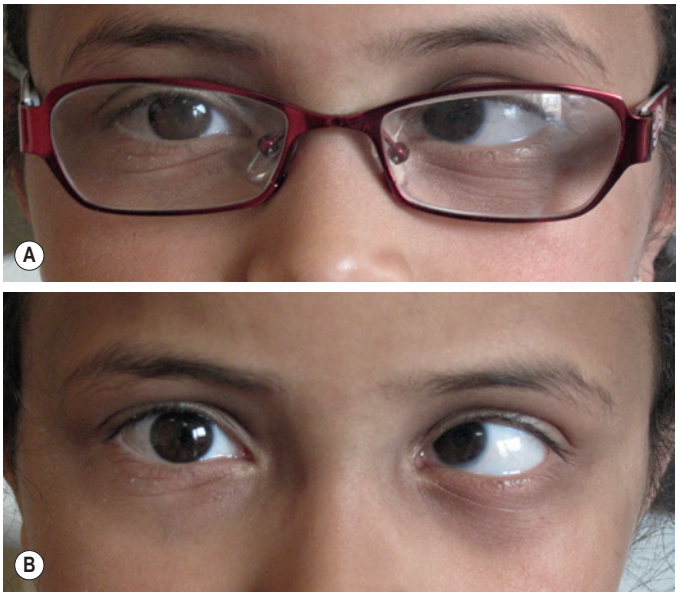


Fig. 78.2 Left sensory esotropia with left inferior oblique overaction in a 9-year-old girl following blunt trauma to her left eye as a baby. The left acuity is LogMAR 1.30 (6/120, 20/400, 0.05). The fundus was normal, but electrodiagnostic testing showed left optic neuropathy and maculopathy. Although the deviation is smaller with glasses (A) than without (B), surgery will be needed to improve the appearance.

Some children adopt a face turn toward the fixing eye because of manifest latent nystagmus in this eye that can substantially reduce their acuity. Acuity is maximized by adducting the fixing eye and turning the head. The abnormal head posture can be improved by recession of both medial recti or medial rectus recession and lateral rectus resection of the fixing eye, provided that parents and patient are comfortable with surgery to the only good eye. Inferior oblique overaction may also develop in both eyes. In the fixing eye this results in downdrift of the non-fixing eye on abduction ("the fallen eye syndrome"). This can be improved by weakening the inferior oblique in the fixing eye.

Myopia-associated esotropia

Esotropias have been described in association with different degrees of myopia. Bielschowsky[12] described distance esotropia

occurring in patients with myopia of up to −5.00 D. This can be of acute onset, but the time of onset can be difficult to determine because the diplopia is intermittent. This occurs mainly in adults, but also in older children.[3] Inadvertent optical overcorrection of the myopic error stimulates accommodation and convergence and must be avoided. There is typically a small distance esotropia with diplopia, and binocular fusion for near, although this may eventually break down.[13] Slight lateral rectus underactions may occur, potentially simulating sixth nerve palsy, a diagnosis that should be excluded in any patient with distance esotropia. Prisms give good symptomatic control. Most patients eventually undergo strabismus surgery, with good results.

Patients with high myopia develop esotropia by two overlapping mechanisms. With esotropia of high myopia, there is good corrected acuity in each eye and a purely convergent deviation with good motility and mild restriction of abduction. These patients do well with medial rectus recession and lateral rectus resection of the deviating eye. Histological examination of the resected lateral rectus may show fibrotic change. This may be an important etiological factor.[14]

Other patients have the eso-hypotropia of high myopia.[15] This is due to stretching and dehiscence of the connective tissue band running between the pulleys[16] of the superior and lateral recti in the super temporal quadrant. This results in downward slippage of the lateral rectus and nasal slippage of the superior rectus muscles.[17,18] There is superolateral dislocation of the posterior pole of the globe out of the muscle cone, with inferonasal displacement of the cornea resulting in an eso-hypotropia. This has been confirmed by high-resolution magnetic resonance imaging studies.[17,18] Significant secondary contracture of the medial rectus may occur. Motility may be very restricted and vision in one or both eyes is often poor from myopic macular change or amblyopia. Binocular function is commonly absent.

Horizontal recess–resect procedures are of limited value, but several forms of "muscle-path" surgery have been reported as successful. The lateral border of the superior rectus is sutured to the superior border of the lateral rectus at 15 mm behind the muscle insertions using a non-absorbable suture to appose the muscle borders and reposition the posterior pole of the globe into the muscle cone.[19,20] If the medial rectus is contractured, it is recessed. This improves both the deviation and ocular motility[19,20] and is valuable in patients with a wide range of myopia and eso-hypotropia, even those with good vision in both eyes and binocular function who present with intermittent diplopia.[21]

Microtropia

A microesotropia is a small angle convergent squint with anomalous binocular function. Microtropia is best considered as a description of the binocular status of the patient who may have any of a number of different types of squint. It represents the first stage in the breakdown of binocular function caused by abnormal visual experience during visual development. It is often seen with anisometropic amblyopia, but may be a primary abnormality.[22] It may be the result of reduced binocularity from intermittent misalignment of the eyes during visual development, e.g. Duane syndrome. In patients with accommodative esotropia, it may be the end result of treatment rather than bifoveal binocular fusion. A microtropia is often the outcome of early strabismus surgery,[23] particularly in younger children.

Patients with a microtropia demonstrate the monofixation syndrome, with peripheral fusion but a central area of suppression in the deviating eye.[24] However, not all patients with monofixation have a clinically demonstrable microtropia.[24] Anomalous binocular function can be maintained up to an angle of about 8 prism diopters.[24] Stereopsis is present, but reduced; smaller deviations are associated with better stereopsis.[25] Receptive fields of visual cortical neurons in the foveal part of the visual field representation are small and become progressively larger with increasing eccentricity. For a small angle of ocular misalignment, the fields no longer overlap centrally, but binocular correspondence can be maintained with the larger, more peripheral fields. Thus, there is central suppression of the deviating eye while peripheral binocular function is maintained.

Patients with a microtropia may demonstrate central monocular fixation with their deviating eye, in which case there is a small flick on cover–uncover testing. However, some children have eccentric monocular fixation with their deviating eye and fixate monocularly using the same eccentric retinal point that corresponds to the fovea of the non-deviating eye under binocular conditions. In this case, there is no movement on cover test.[26] Eccentric fixation can be demonstrated with the visuoscope. A few patients fix monocularly with an eccentric point that differs from that corresponding to the normal fovea and they show a flick on cover test.

The central suppression scotoma can be demonstrated by the 4-D base-out prism test. When a 4-D base-out prism is placed in front of one eye, a patient with bifoveal fixation makes a small conjugate movement of both eyes to re-establish fixation, followed by a small vergence movement to re-establish bifoveal alignment. In monofixation, this latter vergence movement will not occur if the prism is placed in front of the fixing eye, and no movement at all occurs if the prism is placed in front of the eye with the suppression scotoma. Testing with Bagolini glasses shows lateral displacement of the arm of the cross seen by the deviating eye, together with a break in the center of the line corresponding to the central suppression area.

A stable microtropia is not amenable to surgical or prismatic treatment. The microtropia, acuity, and stereopsis may improve with patching for anisometropic amblyopia.[27]

A microtropia occasionally decompensates to a large esotropia in childhood, particularly following patching or in hypermetropic children who do not wear their glasses. If this happens, full hypermetropic correction is required. If this is unsuccessful, then early re-alignment by surgery or botulinum toxin will likely lead to recovery of binocularity. Patients with a microtropia have good motor fusion and stable ocular alignment. Ing et al.[28] found 92% of patients with a microtropia had remained stable for a mean of 13.9 years and the few who decompensated recovered stereopsis following surgery. Arthur et al.[29] studied 80 early-onset esotropes surgically aligned to within 8 PD. Those achieving monofixation were aligned at a significantly earlier age than those without monofixation. Seventy-five percent of those with monofixation remained stable, whereas only 45% of non-monofixators maintained stability. Patients who have monofixation and subsequently lose alignment have a good prognosis for recovering monofixation with surgery.[28,30]

Synthesis

Different esotropias have been described. The distinction between them is not always clear-cut and there is considerable overlap. Patients are best approached by attempting to understand the underlying pathophysiology of each case. The common thread in many cases is the breakdown of binocular fusion relatively late in childhood. The reasons for this can be divided into three main categories:

1. sensory impairment;
2. motor imbalance;
3. impairment of central fusion centers.

Some cases may be multifactorial. Some patients show weak fusion easily disrupted by one of the other factors. In a child where there is no sensory or motor reason for the loss of fusion, symptoms or signs of neurological disease must be sought and neuroimaging considered.

In a child with previously normal binocular function, diplopia occurs until suppression develops and binocular potential will be retained for an unpredictable period of misalignment. Binocular function can often be recovered by early re-alignment. In an older child, fusion potential is likely to be retained for longer, but if it is lost and suppression does not develop, intractable diplopia results.

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Intermittent exotropia

Michael P Clarke

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Definition

Intermittent exotropia (XT) is a strabismus condition with outward drifting of either eye interspersed with periods of good alignment or orthotropia (Fig. 79.1). Monocular eye closure may occur during exodeviation. Near stereoacuity is often normal during periods of alignment, though it may deteriorate if the condition progresses.

Cause

The causes of intermittent exotropia are not fully understood. The following have been suggested:

1. An imbalance between active convergence and divergence,[1] although it is not clear that divergence is active.[2]
2. Abnormal orbital anatomy.[3]
3. Abnormalities of extraocular muscle proprioception,[4] although the existence of active proprioceptors in extraocular muscles is disputed.[5]

It is tempting to speculate that X(T) relates to the ability to switch between a state of suppression and relatively normal binocular function seen in children with the condition. In macaque monkeys there is reduced metabolic activity in the ocular dominance columns that serve the ipsilateral eye's peripheral temporal retina. This is consistent with the topographic organization of suppression scotomas in humans with exotropia.[6]

Accommodative convergence may help to maintain alignment during near viewing.[7]

Epidemiology

X(T) is the most common form of divergent strabismus.[8,9] As divergent strabismus is much more common than convergent strabismus in Asia, it is now the most common form of strabismus worldwide.[10,11] The prevalence of exotropia in children less than 11 years of age was estimated as 1%.[12] X(T) accounted for approximately half of all cases of exotropia.[9] In Singaporean children aged between 6 and 72 months, the prevalence of strabismus was 0.8%, with an exotropia : esotropia ratio of 7 : 1. Sixty-three percent of cases of exotropia were intermittent.[11] In Japanese elementary school children, the incidence of X(T) was estimated as 0.12%.[13] By contrast, intermittent exotropia appears rare in South African black and mixed race children.[14] A female predominance has been found in some studies.[15]

Clinical features

The onset is typically in the second to third year of life,[16,17] when an intermittent outward drift of one eye or monocular eye closure in bright sunlight is noted (Fig. 79.2). Monocular eye closure in X(T) has been attributed to photophobia,[18] although it is difficult to explain why more light should enter exotropic than orthotropic eyes. Monocular eye closure may be due to diplopia or an abnormal visual percept, or reduction in threshold for bright lights, induced by divergence of the eyes.[19,20] It may resolve following surgery.[21,22]

It is usually not possible to measure stereoacuity accurately at presentation because the children are too young, but older children with X(T) have normal, or near normal (for age), near stereoacuity.[16] One study found reduced visual acuity in one or both eyes of 26% of children at presentation, although this reduction was generally just below age-related normal thresholds and due to anisometropia.[14]

X(T) is traditionally classified into three types:

1. *True divergence excess*: the deviation is more than 10 prism diopters (PD) larger when measured at distance fixation than at near.



Fig. 79.1 A 7-month-old child with intermittent exotropia that progressed to constant exotropia. (Top center) At age 7 months, note orthotropia in primary gaze; (top left) large angle exotropia with right eye fixing; (top right) large angle exotropia with left eye fixing. Patient was initially managed conservatively with patching and convergence exercises with good control of the deviation after only 3 months. Patient failed to follow-up regularly. (Bottom) At the time of last evaluation at age 2 years, she had a large angle constant exotropia with a left eye preference. Photos also show deviation with either eye fixing.



Fig. 79.2 Two brothers standing in Southern California sunshine. Boy on the left has no strabismus. Boy on the right has intermittent exotropia with monocular eye closure, a common sign of intermittent exotropia.

2. *Simulated divergence excess*: initially greater at distance fixation, but the misalignment at near fixation increases to within 10 diopters of the angle at distance following disruption of near binocular vision by monocular occlusion and/or +3 lenses.
3. *Basic*: the size of the misalignment is equal, to within 10 PD, whether the misalignment is measured at distance or near fixation.[23,24]

The measurements required may be difficult in young children but the distinction between the types helps to plan appropriate surgical treatment,[25] although this has been disputed.[26]

One of the most striking neurophysiologic features of X(T) is that children with the condition alternate between a state of apparently normal (or near normal) binocular vision, with normal stereoacuity when the eyes are aligned, and a state of suppression, and anomalous retinal correspondence, when the eyes are divergent.[27–29] However, when the eyes are straight, binocular function is not entirely normal in X(T). Children with X(T) have reduced positive fusional vergences (reduced convergence in response to a base-out prism).[30] Also, suppression can be demonstrated even during periods of normal ocular alignment, indicating that it can be triggered by purely retinal information.[31]

A subset of children with X(T) have subnormal binocular function even when the eyes are "straight" because when "straight" a small constant divergent deviation is present.[32] This may underlie the reduced stereoacuity seen following treatment of X(T) in some cases.[33]

While X(T) is not associated with neurodevelopmental abnormalities, it has been associated with later development of psychiatric disorders.[34,35] The reason for this is unknown, but it is unlikely to be due to the consequences of an abnormal appearance in childhood, as it is not seen in children with esotropia,[34] nor is it altered by eye muscle surgery.[36] X(T) has also been associated with attention-deficit hyperactivity disorder.[37]

Quality of life

The Pediatric Quality of Life Inventory was used for patients with X(T); no significant effect was observed.[38,39] Hatt et al.[40,41] developed a specific quality of life measure based on interviews with children with X(T). They identified concerns about the presence of exotropia relating to observers' awareness of the strabismus, but also the child's awareness of strategies they used to control exotropia, such as blinking. They identified parental anxiety about exotropia as the most significant concern.[42] Childhood concerns related both to anxiety about the social consequences of X(T) and monocular eye closure.[43] Reduced parental and proxy health-related quality of life are also associated with the decision to undertake surgery for X(T).[44]

Clinical evaluation

Possible measures of progression or outcome in X(T) are:

- angle (size) of misalignment;
- stereoacuity (for near and/or distance fixation);
- deterioration of convergence;

- control of misalignment;
- deterioration to constant exotropia (± development of strabismic amblyopia).

Measurements of stereoacuity and convergence are not consistent in children under the age of 4 years, and control, constancy, and angle (particularly at distance) are also challenging to measure in this group. Any therapy for children under the age of 4 years with X(T) is necessarily based on imperfect clinical measurements, making assessment of the effect of therapy difficult. Thus, many clinicians defer treatment until later, despite the theoretical benefits of early therapy.[16]

The traditional outcome measure for the effect of therapy on X(T) is the size of the angle of the misalignment, with successful outcomes following therapy often taken as angles of between ±10 PD of orthophoria.[45–47]

Ocular alignment (usually with a range of ±10 PD), is, however, an inadequate outcome measure for treatment of X(T). The measurement given usually includes latent and manifest (tropia and phoria) components of the misalignment. Thus, small constant misalignments, both esotropic and exotropic, with worse functional correlates than X(T)s, are included as treatment "successes."[48]

Assessing the control of intermittent exotropia

A more relevant measure of treatment of X(T) is the degree of control of the misalignment, as measured by the frequency with which a strabismus is manifest, and the ease with which an induced misalignment can be re-aligned. Diplopia is not a feature of X(T), and the mechanisms underlying control are obscure, but some children report awareness of their misalignment.[40]

Two scoring systems for the measurement of control of X(T) are in common usage: the Mayo office-based scale,[39] and the Newcastle Control Score.[49,50]

The Mayo scoring system is outlined in Box 79.1. The Mayo scale is based solely on timed observations. An average of three scores are recommended to provide a reliable measure.[51]

The second scoring system is the Newcastle Control Score for Intermittent Exotropia (NCS).[52] The criteria for assigning an NCS are given in Table 79.1. The NCS is based on the criteria for surgical intervention popularized by Rosenbaum.[53] These criteria consist of a parental report of the frequency with which a divergent misalignment of the eyes is observed (home control) and an objective assessment of the ease with which the eyes can be re-aligned following the induction of strabismus with a cover test (office control). Rosenbaum suggested that surgery should be considered if the strabismus was present more than 50% of the time and was poorly controlled on examination. The relationship between these two criteria requires further study, but correlations have been shown between home and office control.[54]

The home control element is potentially subject to observer bias but does have the merit of being a parent-reported outcome measure.

Measuring the deviation

For measurements to be reproducible, any significant refractive error must be corrected. This is usually the maximum tolerated plus or the least minus prescription. An accommodative fixation target slightly above threshold must be used; for example, a patient with 20/20 vision in both eyes needs to be presented with a 20/50 line. In preverbal children, videos or toys presented as targets should have sufficient detail to control accommodation.

Distance measurements should be made at more than 20 feet to eliminate accommodation. In some cases, distance deviation may have to be measured outside or beyond the confines of the standard visual lane. Breaking fusion by prolonged monocular occlusion for 30–60 minutes may be required to eliminate all fusional vergence.[55,56] The patch is removed by the examiner, and fusion, no matter how momentary, is not allowed.

Stereoacuity in intermittent exotropia

In X(T), the eyes usually remain aligned for near fixation, or are capable of re-alignment in response to a stereoscopic image.

Box 79.1

The Mayo scale for scoring control in intermittent exotropia[39]

5 = Constant exotropia
4 = Exotropia >50% of the exam before dissociation
3 = Exotropia <50% of the exam before dissociation
2 = No exotropia unless dissociated, recovers in >5 seconds
1 = No exotropia unless dissociated, recovers in 1–5 seconds
0 = No exotropia unless dissociated, recovers in <1 second (phoria)

Notes:
The score is measured at distance and near fixation, and so yields an overall control score ranging from 0 to 10.
Levels 5 to 3 are assessed during an initial 30-second period of observation at distance fixation and repeated at near fixation for another 30-second period.
Levels 2 to 0 are then graded as the worst of three rapidly successive trials; an occluder is placed over the right eye for 10 seconds and then removed, measuring the length of time it takes for fusion to be re-established. The left eye is then occluded for 10 seconds and the time to re-establish fusion is similarly measured.
A third trial of 10-second occlusion is performed, covering the eye that required the longest time to re-fuse.
The worst level of control observed following the three 10-second periods of occlusion should be recorded.
If the patient has a microesotropia by simultaneous prism and cover test, but exodeviation by alternate cover test, the scale applies to the exodeviation.

Table 79.1 The revised Newcastle Control Score for Intermittent Exotropia (NCS)[41]

NCS criteria	Score
HOME CONTROL (XT OR MONOCULAR EYE CLOSURE SEEN)	
Never	0
<50% of time fixing in distance	1
>50% of time fixing in distance	2
>50% of time fixing in distance + seen at near	3
CLINIC CONTROL (SCORED FOR NEAR AND DISTANCE FIXATION)	
Immediate re-alignment after dissociation	0
Re-alignment with aid of blink or re-fixation	1
Remains manifest after dissociation/prolonged fixation	2
Manifest spontaneously	3
Total score: n/9	

XT, Exotropia.

Values of near stereoacuity in X(T) are normal,[27] making near stereoacuity a poor measure of severity. Near stereoacuity may be lost completely if X(T) deteriorates to a constant exotropia, but it may be restored surgically in some cases.[57]

The initial abnormality in X(T) is misalignment at distance fixation. Measurement of stereoacuity at distance fixation is, therefore, a potential measure of X(T) severity. The tendency to diverge at larger viewing distances may introduce a "pedestal disparity" between the reference surface and the fixation point, thus lowering stereoacuity.[29]

Measurement of stereoacuity at distance fixation is technically challenging. Previous studies used a liquid crystal system (Binocular Visual Acuity Test)[58] requiring goggles during measurement, limiting its use in young children. This is no longer available. Subsequent studies have utilized the Frisby Davis Distance Stereotest[59,60] and the Distance Randot Test.

The effect of X(T) on distance stereoacuity is variable, depending on the characteristics of the test used. It has been reported as being either normal or absent.[61] Conversely, others have found distance stereoacuity to be degraded in X(T),[62] and to be improved by surgery.[63,64] This may be due to the way in which absent distance stereoacuity was recorded, as in some studies a nominal value was ascribed to absent stereoacuity. It is not clear if improvements in distance stereoacuity following surgery represent regression to the mean of a series of measurements, as surgery is more likely to be performed when a poor distance stereoacuity measurement is found.

Differential diagnosis

X(T) is not associated with neurologic pathology.[9,65] However, a constant exotropia with variable angle can mimic X(T), and constant exotropia is associated with neurological and ocular pathology[65] (see Chapters 43 and 57) as in optic nerve glioma or retinoblastoma reducing vision in one eye which may masquerade as cases of X(T).[66–68]

Children with craniofacial anomalies are frequently exotropic (see Chapter 28). Alphabet pattern deviations are common. "V" patterns mimic inferior oblique overaction; "A" patterns mimic superior oblique overaction. Dynamic magnetic resonance imaging (MRI) of the rectus muscles may suggest heterotopic rectus muscles (Fig. 79.3). These patients benefit from transposition surgeries correcting the muscle displacements to improve the pattern deviations. Inferior oblique surgery is usually unnecessary.

Management

The evidence underpinning the management of X(T) is poor, but this situation is improving.[69,70] Most outcome studies of treatment of X(T) consist of highly selected retrospective case series, which use multiple, often conflicting, outcome measures.[71] There is evidence that the long-term success of treatment in curing X(T) is poor.[72] Assessing the true effects of treatment must await the results of robust, prospective, long-term randomized studies.

One recent trial compared part-time patching with observation in children aged 3–10 years with intermittent exotropia.[73] This trial showed only a marginal benefit from patching over a 6-month period. A recent pilot trial comparing surgery to active monitoring for X(T) was hampered by low recruitment, and was not powered to meaningfully assess clinical outcomes; however, it showed no meaningful change in the condition of those children undergoing active monitoring, and improved alignment in those undergoing surgery, at the expense of a 10–20% overcorrection rate with deterioration of stereoacuity.[74]

The long-term outcome in a cohort of patients with X(T) is unknown; studies of untreated patients are biased by the drop-out of patients with more severe X(T) who go on to have treatment. However, a significant proportion of children with X(T) do not progress to constant exotropia. One study of 73 patients, with an average 10-year follow-up, showed a reduction in the angle of exotropia over time; however, 82% of the patients received some form of non-surgical treatment,[75] which the authors suggested might represent regression towards the mean of varying measurements. Many children with X(T) do not need active management[16,76]; prior to any intervention, parents should be counseled regarding the uncertainties of the evidence for treatment.

Overminus lenses

Minus lenses may have a beneficial effect on angle and control of X(T)[54,77] and be useful as a temporizing measure, allowing surgery to be deferred until an age when amblyopia is unlikely to develop in the event of a surgical overcorrection. The amount of overminus used should be assessed with trial frames. It commonly is around 2 diopters. Overminus lenses may have a particular application for children with X(T) and a high accommodative convergence/accommodation (AC/A) ratio. It is possible that the beneficial effect observed is due to spontaneous improvement since there has been no randomized controlled trial of this treatment in X(T).

Correction of hypermetropic refractive errors

Correction of significant hypermetropic refractive errors may improve control of X(T).[78]

Orthoptic/occlusion treatment

Occlusion for early-onset unilateral exotropia[79] for 4–6 hours per day for 3–6 weeks has been advocated to modify suppression. Orthoptic/occlusion treatment prior to surgery may improve surgical success rates.[80] The results of the recent randomized controlled trial, however, suggest that this treatment is of limited efficacy.[73] Its use is probably limited to those parents who wish to avoid surgery for a child too young to tolerate minus lenses.

Chemodenervation

There are few reports of the use of botulinum toxin in X(T)[81,82] and it is rarely used in X(T) except for surgical overcorrection of X(T).[83]

Surgical management

X(T) is commonly treated surgically. Some, with support from visual physiology data,[84] recommend surgery shortly after diagnosis because early restoration of normal ocular

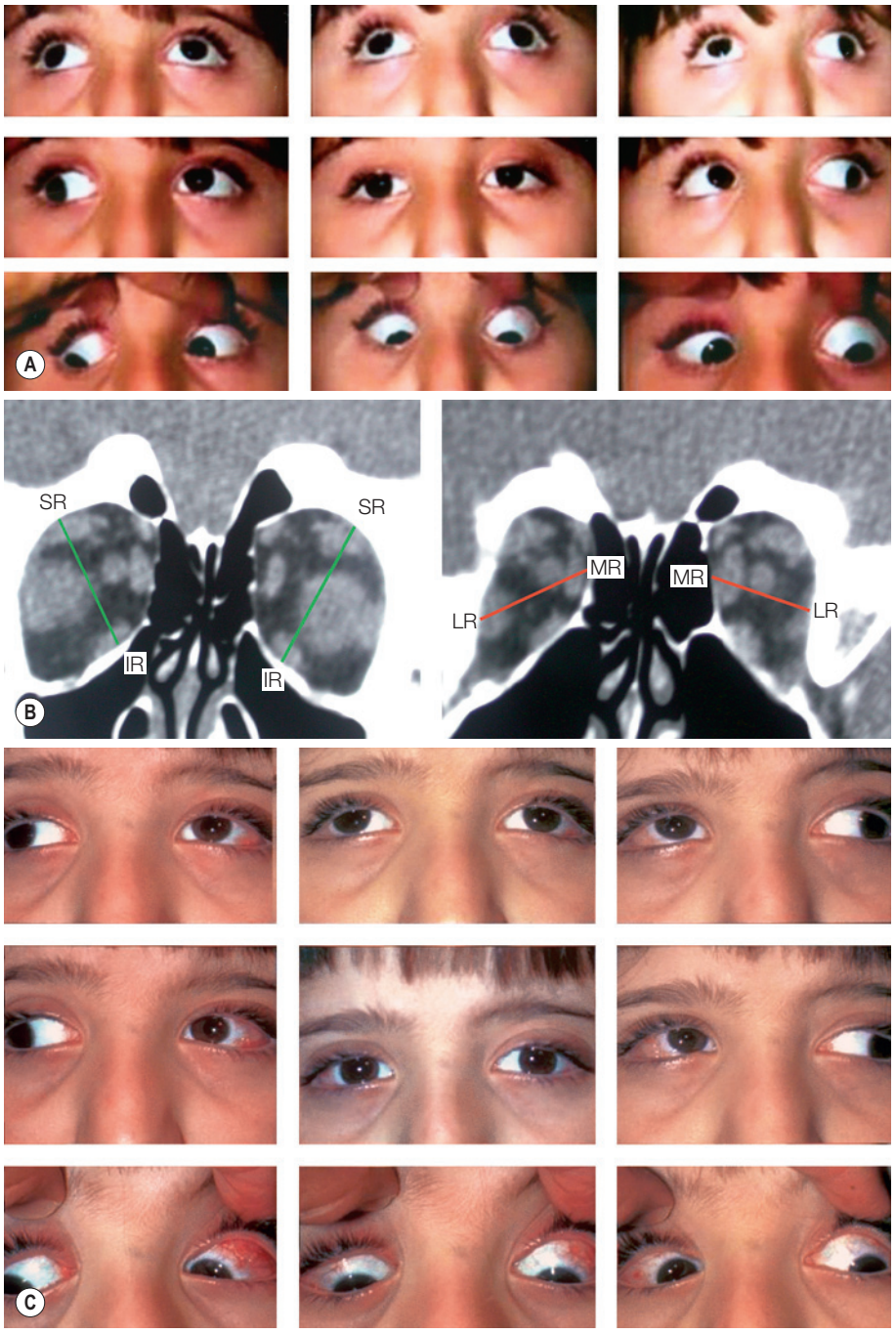


Fig. 79.3 (A) Patient with craniosynostosis showing a "V" pattern deviation with apparent pseudo-overaction of the inferior oblique. (B) Dynamic magnetic resonance imaging shows lateral displacement of the superior rectus muscles (SR), downward displacement of the lateral rectus muscles (LR), and medial displacement of the inferior rectus muscles (IR). (C) After repositioning of the lateral rectus muscle bellies superiorly, the "V" pattern deviation is improved.

alignment is desirable to promote normal visual development. Surgery in young children with X(T) may present practical challenges: Inaccurate and incomplete assessments mean that measurements are uncertain and the diagnosis can only be provisional. Also, surgical overcorrection may result in constant suppression and amblyopia in young children, a worsening of sensory status in a group of patients whose preoperative visual acuities and stereoacuity are usually normal.

Thus, many surgeons defer surgery until the age of 4 years or older, provided that there is no deterioration in the condition to a constant exotropia. These views are supported by retrospective case series, which suggest that age at surgery does not influence outcome.

Ekdawi et al.[85] reported 33% of X(T) patients had surgical treatment, with 19.7% undergoing a second procedure. Buck et al. reported a rate of surgery of only 7.6% in the first 12 months following diagnosis in a UK cohort,[16] rising to 17% after 2 years.[86] The continued observation of these children represents a significant use of health care resources. While recovery of stereopsis has been reported in cases of X(T) that have progressed to constant exotropia,[47] Wu et al. reported significantly better stereoacuity results in X(T) compared to constant exotropia and a history of previous X(T),[57] despite similar rates of motor alignment. Initial overcorrection of the deviation has been associated with improved long-term alignment[48,87]; however, others have challenged this view.[88]

Exotropias tend to recur following initially successful surgery; in one large study, orthotropia or mini-microtropia was achieved in 60.2% of patients 1 month after surgery, but half of these patients developed recurrent X(T) by 4 years after surgery.[26] Ekdawi et al. found the rate of developing greater than 10 diopters of misalignment at distance after the first surgery for X(T) was 54% by 5 years, 76% by 10 years, and 86% by 15 years.[85]

Surgical procedures

A weakening procedure on the lateral rectus muscle and/or a strengthening procedure on the medial rectus muscle may be used. Lateral rectus recession is believed to affect the distance deviation more than near; the reverse is thought to be true for the medial rectus muscle. The choice of surgery is suggested by the clinical pattern of the deviation.

If a patient has true or simulated divergence excess exotropia, bilateral lateral rectus recession is appropriate; patients with basic exotropia with equal near and distance deviation are treated with a recess–resect procedure.[89] A prospective, randomized clinical trial revealed only a 52% success rate in patients with basic exotropia if only lateral rectus recessions are performed. This increased to 82% if a recess–resect procedure was chosen.[25]

Desired early postoperative alignment

Within the first 2 weeks, the aim is to achieve a small angle (5–10 PD) esotropia. The eyes are brought beyond the temporal hemiretinal suppression scotoma to increase diplopia awareness. This may stimulate fusional vergences and stabilize postoperative alignment. Intentional overcorrection has risks in children with an immature visual system. In the immediate postoperative period, base-out prisms to neutralize residual deviation to maintain bifoveal fixation may be useful to prevent development of monofixation esotropia with foveal suppression.

In older children and adults who develop X(T) after the visual system has matured, diplopia and visual confusion occur with little or no suppression. The surgical goal in these cases should be orthotropia, even on the first postoperative day using adjustable sutures. Base-out prisms are used temporarily if overcorrection occurs. Non-surgical management of postoperative overcorrection should be tried for at least a month before reoperation is contemplated because of the high likelihood of spontaneous resolution. Botulinum toxin to the medial rectus is often used before considering repeat surgery.[83]

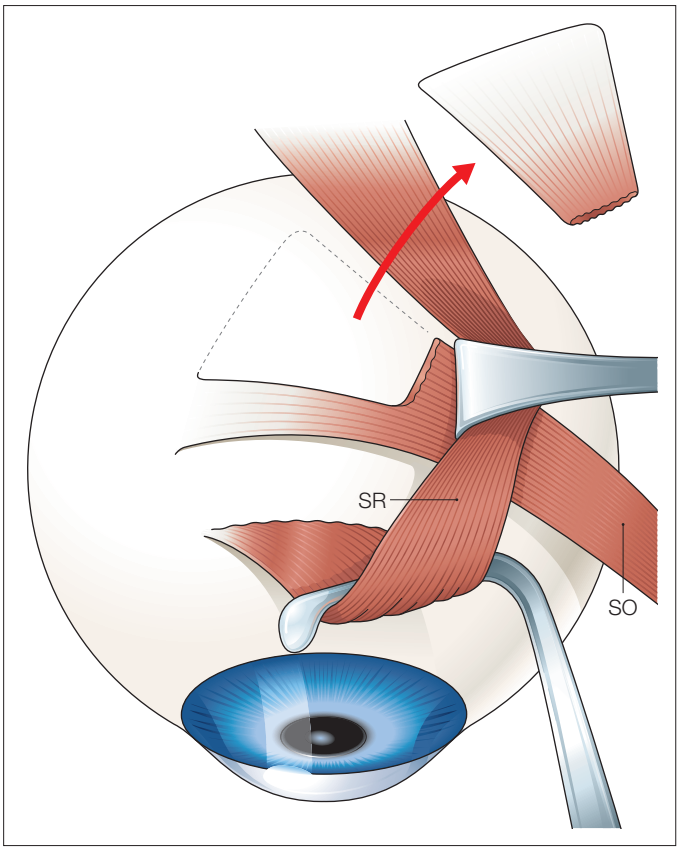


Fig. 79.4 Posterior three-quarters superior oblique tenectomy. A quadrilateral posterior tenectomy is performed on the superior oblique tendon (SO) where it fans out, leaving the anterior 1–2 mm of the tendon intact to preserve intorsion. *(From Shin GS, Elliott RL, Rosenbaum AL. Posterior superior oblique tenectomy at the scleral insertion for collapse of A-pattern strabismus. J Pediatr Ophthalmol Strabismus 1996; 33: 211–8. Reprinted with permission from Slack, Inc.)*



Fig. 79.5 Four-year-old patient with intermittent exotropia with "V" pattern and inferior oblique overaction. Photograph shows right exotropia that increased in upgaze and reduced in downgaze.

Other associations

Pattern deviations (see Chapter 82)

In patients without significant oblique muscle dysfunction, we perform vertical transposition of the horizontal recti. In "A" pattern exotropia with superior oblique overaction we prefer a posterior three-quarters tenectomy of the superior oblique tendon (Fig. 79.4). In "V" pattern deviations with inferior oblique overaction (Fig. 79.5), we weaken the inferior oblique muscle.

In patients with craniofacial syndromes, dynamic MRI may show that rectus muscles are excyclorotated and that the X(T) in upgaze is due to the lateral displacement of the superior rectus with downward displacement of the lateral rectus. Repositioning the muscle to its normal anatomic position may improve the pattern deviation (see Fig. 79.3).

In patients with longstanding exodeviations, a tight lateral rectus muscle may cause an "X" pattern deviation (Fig. 79.6). Both the inferior oblique and superior oblique muscles appear

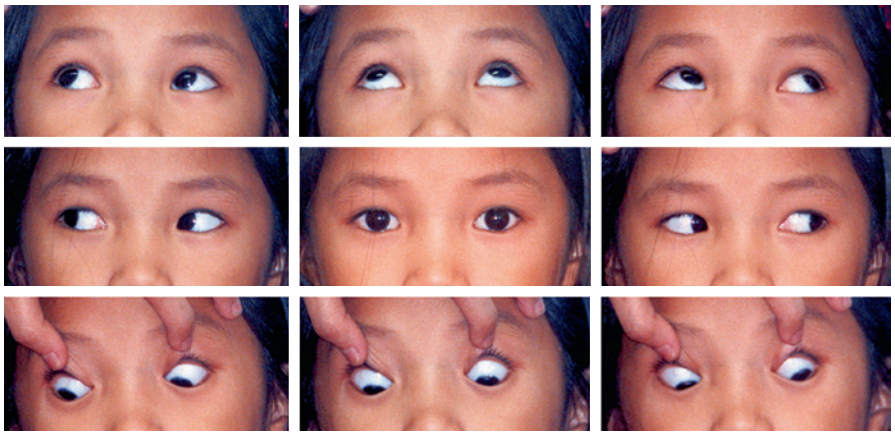


Fig. 79.6 Patient with "X" pattern deviation because of longstanding exotropia. Tight lateral rectus muscles act as a leash. Forced duction testing will show resistance to full adduction. Only weakening procedures on the lateral rectus are necessary to relieve the "X" pattern. No surgery is required on the oblique muscles. *(From Santiago AP, et al. Intermittent exotropia. In: Rosenbaum AL, Santiago AP, editors. Clinical Strabismus Management: Principles and Surgical Techniques. 1st ed. Philadelphia: Saunders; 1999. With permission from Elsevier.)*

to overact. The tight lateral rectus muscles cause a leash effect, creating pseudo-overaction of the oblique muscles. The apparent oblique muscle dysfunction disappears after lateral rectus weakening. The tight lateral rectus syndrome is uncommon and probably found only in a very large poorly controlled decompensated X(T). It is more common with longstanding constant exotropia.

Lateral or horizontal incomitance

Patients whose primary deviation exceeds right and left lateral gazes by 20% or at least 10 PD have significant horizontal incomitance, which is associated with postoperative overcorrection and reoperation.[90] They may benefit from reducing the intended surgical weakening procedure on the lateral rectus muscle. This modification prevents overcorrection on lateral gazes but risks undercorrection in primary position. When lateral incomitance is due to a tight medial rectus muscle, resection procedures on this muscle worsens the incomitance. We recommend preoperative forced duction testing and recession of the tight medial rectus with enhanced lateral rectus recession to compensate for the effect of the medial rectus recession. Adjustable sutures improve results, but are challenging to perform in young children.

High AC/A ratio

Patients with X(T) and a high AC/A ratio are at risk of postoperative overcorrection,[91] and may be better managed with overminus lenses. There is significant test/test variability in the measurement of AC/A ratio, particularly in the young.

Concomitant vertical deviations

Small vertical deviations may occur with X(T), and may resolve after surgical treatment.[92] Vertical deviations of less than 10 PD can be corrected by vertical transposition of the horizontal rectus muscles. For example, the recessed lateral rectus and the resected medial rectus muscle may be displaced superiorly one-half to a whole tendon width in the hypotropic eye (directions are reversed for a hyperdeviation). This adds an additional upward vector assisting in the control of the vertical deviation. Large vertical deviations should be addressed by appropriate surgery on the vertical muscle at the time of exotropia surgery.

Postoperative undercorrection

Severe early postoperative undercorrection may arise because of a slipped resected medial rectus muscle. Adduction is usually limited; there is widening of the palpebral fissure on attempted adduction. Early surgical exploration and repair is indicated. More commonly, X(T) persists or recurs following surgery. Further treatment including surgery should be considered and discussed with the parents.

Postoperative overcorrection

Overcorrection that persists beyond the immediate postoperative period is less common than undercorrection, even when surgery for the largest recorded angle of exodeviation is the target; however, rates of postoperative overcorrection are probably around 15%.[93] Transient esotropia for near targets is common in the first few postoperative weeks. A small angle esotropia that persists at distance, with only exophoria or orthotropia at near, is usually stable and best left untreated, provided diplopia is not problematic. Rarely, a large overcorrection following an over-recessed, slipped, or lost lateral rectus muscle may occur. It is most bothersome in the field of gaze of the weakened lateral rectus (Fig. 79.7).

In the early postoperative period, a rather large esotropia may not necessarily mean a poor response to surgery. Long-term stability of alignment after bilateral lateral rectus recession was achieved in patients who demonstrated up to 20 PD of esotropia in the first 10 days after surgery.[46,48]

Esotropia at near that persists beyond 3 weeks is worrisome, especially in children susceptible to suppression and deterioration of fusional status. Children can develop monofixational esotropia even if aligned to within 8 PD of orthotropia. Older children and adults, on the other hand, tolerate overcorrection poorly because of diplopia.

Further treatment with occlusion, prisms, and botulinum toxin injection to the medial rectus and further surgery (usually medial rectus recession) should be considered if the overcorrection does not settle within an acceptable time period.

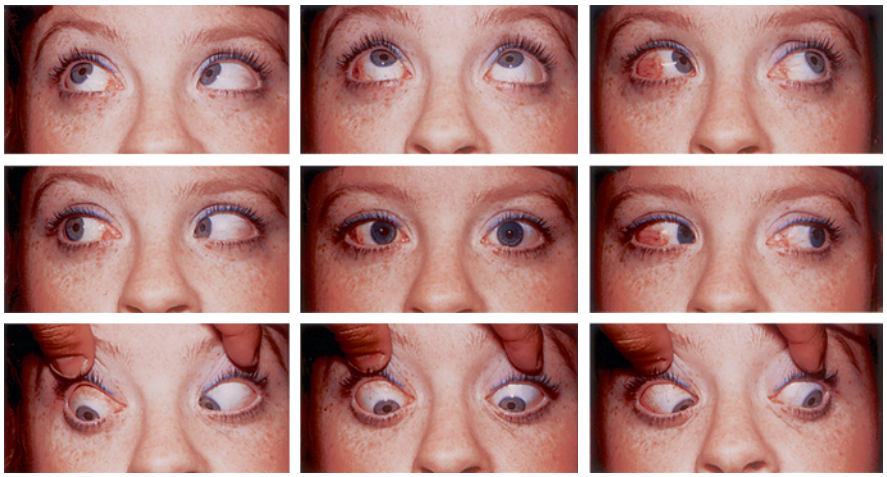


Fig. 79.7 Overcorrection after bilateral rectus recession for intermittent exotropia. Patient developed 25 PD of right esotropia with abduction deficit in right gaze. Differential diagnosis should include slipped or lost lateral rectus muscle. A lost muscle, however, seems less likely because of relatively good right lateral rectus rotation despite the observed deficit. *(From Santiago AP, et al. Intermittent exotropia. In: Rosenbaum AL, Santiago AP, editors. Clinical Strabismus Management: Principles and Surgical Techniques, 1st ed. Philadelphia: Saunders; 1999. With permission from Elsevier.)*

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Special forms of comitant exotropia

Stephen P Kraft

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Introduction

Exodeviations in children can be comitant or non-comitant. Non-comitant exodeviations result from either innervational causes, i.e. third nerve paresis and Duane syndrome, or mechanical causes, such as tumors or trauma (see Chapters 83 and 84).

The most common comitant type in children is intermittent exotropia, and there are other comitant exodeviations whose management can be challenging. This chapter deals with infantile exotropia, monofixational exotropia, exotropia associated with hemianopic visual field defects, and sensory exotropia. Although they are considered as comitant deviations, they may develop incomitance from secondary changes in the lateral rectus muscles in longstanding cases, especially in sensory exotropia or infantile exotropia with a large deviation.

Infantile exotropia

Introduction

Infantile exotropia is an exodeviation that develops within the first few months of life and persists. While infantile esotropia is generally defined as having its onset by age 6 months, the term infantile exotropia is used for exodeviations that first manifest up to 1 year of age.[1–4] It can be a primary disorder or secondary to an ocular or systemic problem.

Primary infantile exotropia, unrelated to a systemic or ocular disorder, is rare, occurring in approximately 1 per 30,000 births.[1] In primary strabismus in infancy, for every case with exotropia, there are between 150 and 300 cases with esotropia.[1] Intermittent exotropia can manifest by age 12 months, and it may represent a large proportion of cases of exotropia seen before age 1 year (see Chapter 79).[2–4] Infantile exotropia is often associated with ocular or systemic disorders. It is seen with ptosis, albinism, ocular motor apraxia (saccadic initiation failure), optic nerve anomalies, and with diseases that lead to vision loss, including retinoblastoma, retinoschisis, iridolenticular abnormalities, and cataracts.[1,5] Exotropia can be a feature of several congenital strabismus syndromes, including third nerve palsies, Duane syndrome, congenital fibrosis of the extraocular muscles, and strabismus fixus[1,5] (see Chapter 83). It is described in association with many systemic disorders including prematurity, cerebral palsy, seizure disorders, hydrocephalus, craniofacial syndromes, and various chromosomal anomalies.[1]

Ocular or systemic disorders are more common in infantile exotropias than in esotropias, and infants with constant exotropia have a much stronger chance than those with intermittent exotropia of having a co-existing problem.[5] The incidence of systemic anomalies may also be positively correlated with the size of the angle of deviation[1]: it is prudent to consider a neurodevelopmental assessment of a child with infantile exotropia.[5]

Etiology

Vergence abnormalities

Exodeviations appear in over one-third of healthy neonates, while esodeviations are rare.[1] Mostly, they are transient and resolve by 6 months of age as the vergence system matures.[1] Therefore, primary infantile exotropia may be an arrested development of the convergence system.

Abnormal convergence may be a primary or secondary phenomenon. There may be a primary deficit in the convergence system, or it may arise from defective cortical binocular development.[2] Disruption of binocular connections in the immature visual cortex can hinder the normal development of vergence, leading to strabismus and to functional deficits, loss of fusion, asymmetric monocular smooth pursuit, and asymmetric monocular motion perception.[2] The asymmetries are characterized by better tracking and detection of targets when they are followed from the temporal to the nasal visual field than when they are tracked in the reverse direction. This directional asymmetry should lead to infantile esotropia, rather than exotropia. Therefore, the severity of a primary or secondary convergence system deficit must override the other abnormal processes so that divergence is predominant. The

identical pursuit asymmetry seen in infantile esotropia also occurs in infantile exotropia.[6]

Anatomic factors

The structure of the lateral and medial rectus muscles is asymmetric; length–tension curve studies show the lateral rectus muscle to be stiffer than the medial rectus. The diameter of the lateral rectus may be congenitally larger than normal, allowing it to "overpower" the medial rectus.[1] Finally, orbital dysmorphism, as in craniofacial syndromes, can produce a divergent positioning of the eyes.

Genetic factors

Infantile exotropia occurred in three consecutive generations of one family, suggesting autosomal dominant inheritance. It may be more common in Asians and Africans than in Caucasians.[1]

Clinical features

Infantile exotropia occurs by 12 months of age.[2–4] The deviation may vary from 20 to 90 prism diopters (PD), and is greater than 35 PD[2,5] in most cases (Fig. 80.1). The angle is usually stable initially but increases slowly. Amblyopia occurs in up to 25%, usually caused by strabismus rather than anisometropia.[1] It responds to the usual treatments (see Chapter 73). There is a normal distribution of refractive errors.[2] If the deviation is large, an "X" pattern strabismus is common, as also seen in adults with large angle exotropia who have a tight lateral rectus syndrome. The deviation is larger in upgaze and downgaze than in the primary position with mild limitation of adduction in one or both eyes and upshoots and downshoots in adduction (see Fig. 80.1) that has been ascribed to overaction of the oblique muscles, to sideslip of the lateral rectus around the globe (a "leash effect"), or to the globe having more room to elevate and depress when it is not fully adducted.[1] Alternatively, there may be "A" or, more commonly, "V" patterns.[2] Latent nystagmus, dissociated vertical deviations (DVD), and inferior oblique overaction are frequent associations, similar to infantile esotropia.[2] The reported frequencies of DVD and inferior oblique overactions in primary infantile exotropia are as high as 60% for both features.[3] In fact, these vertical anomalies are rarely seen in early-onset intermittent exotropia, and their presence would confirm that the exotropia is, in fact, an infantile form rather than an acquired intermittent form.[3]

Examination

Some pertinent points must be noted in the evaluation of infantile exotropia.

1. The general behavior and physical features of the child may suggest a systemic or orbital association.
2. Anterior and posterior segment disorders can be associated with infantile exotropia. Cycloplegic refraction and fundus examination are vital.
3. The examiner must observe the corneal light reflexes to rule out a positive angle kappa that gives a false appearance of exotropia[2]: the cover test will confirm a true exodeviation rather than a pseudo-exotropia (see Chapters 7 and 75).
4. When the angle is large, the examiner needs to use two prisms oriented base-in and split between the two eyes to get an approximation of the total angle, whether the angle is measured by the Krimsky or prism and alternating cover methods (see Chapter 75).
5. The examiner should search for features of the infantile strabismus complex including dissociated vertical deviations and oblique muscle overactions. Optokinetic testing may detect monocular nasal–temporal motion asymmetries.



Fig. 80.1 Photos of nine diagnostic gaze positions of a child with infantile exotropia. Note the large angle of exotropia in the primary position (central photo). There is limited adduction of each eye and an "X" pattern. Each eye shows an upshoot and downshoot in the adducted position. *(From Kraft SP. Selected exotropia entities and principles of management. In: Rosenbaum AL, Santiago AP, editors. Clinical Strabismus Management. Philadelphia, PA: Saunders; 1999: 176–201. Copyright Elsevier 1999.)*

Management

Non-surgical therapy

Infantile exotropia usually requires surgery after any refractive errors and amblyopia have been treated. Although the angle of the deviation is generally stable, it may reduce with occlusion.

Botulinum toxin has been used for infantile esotropia, but there is no reported series of this for the rarer infantile exotropia. Success rates for treating childhood exotropia with botulinum toxin range from 50% to 70%, with bilateral, not unilateral, lateral rectus injections.[1] Most had intermittent exotropia: the success rates for exotropia over 35–40 PD was much lower, and, since most infantile exotropias are larger than this, surgery is the preferred treatment.

Surgery

Timing

Patients with primary infantile exotropia should be approached in the same manner as those with infantile esotropia where the general consensus among pediatric ophthalmologists for many years was to align the eyes before the age of 24 months to achieve optimal motor and sensory outcomes.[1] In recent years, earlier surgery for infantile strabismus has been favored in the belief that it is more effective in reversing the binocular vision and vergence deficits. Evidence suggests that the optimal "window" for treating infantile esotropia may be the first 8–10 months of life,[2] but whether it is applicable to infantile exotropia is not known. The consensus still favors re-aligning the eyes before 24 months of age, although one study showed that the likelihood of surgical success may be greater if the eyes are re-aligned within 24 months of onset of the exotropia rather than by a specific age.[7] Once the diagnosis of infantile exotropia is confirmed and any refractive error or amblyopia corrected, the child should be followed for a few weeks to document that the angle of the strabismus is stable.

Surgical planning

Strabismus surgery techniques for exotropia are described in Chapter 86, but there are some specific recommendations for surgical treatment of infantile exotropia:

1. The aim in primary infantile exotropia is to create an esotropia in the immediate postoperative period, as in most exotropias in older children and adults.[1,2] This principle also applies to children with infantile exotropia and developmental delay or cerebral palsy, as the postoperative drift is usually in the divergent direction whether they originally had esotropia or exotropia immediately after surgery.[1,2] For either category, the best result from a single operation is with an immediate postoperative angle in the range of 10–14 PD, slightly larger than the desired postoperative angle in later-onset intermittent exotropia. In a recent study, the average exotropia drift rate was 10.4 PD over 3 years after surgery, and the success rate was best when surgery achieved a mean esotropia of 10 PD immediately after surgery.[8]
2. The strategy generally involves weakening (usually recession) of one or both lateral rectus muscles, as they are often tight.[8] If the deviation is larger at near than that at distance, then a strengthening procedure of a medial rectus muscle should be included.[1,2]
3. Strabismus angles under 40 PD can usually be successfully treated with surgery on two horizontal muscles, either bilateral lateral rectus recessions or a unilateral lateral rectus recession with a medial rectus resection.[2] Treatment of angles over 40 PD may require "supramaximal" amounts of recessions or resections if surgery is limited to two muscles. Alternatively, surgery of more "regular" dosages can be planned on three or four horizontal muscles.[1,2] Another strategy involves large recessions of both lateral rectus muscles combined with simultaneous injections of botulinum toxin into the two muscles.
4. Surgery for any co-existing dissociated vertical deviations or oblique overactions can be planned for the same sitting or at a later date, as in infantile esotropia.

Results

The overall success rates for infantile exotropia surgery, defined as a microtropia angle under 10 PD, are not high, with one study reporting 40% at 3 years after the first surgery.[8] Reoperation rates are as high as 50% of patients: Undercorrections are much more common than overcorrections.[1] The size of the preoperative angle is an important factor in the eventual success rate, as the results for exotropia under 40 PD are better than those for larger deviations.[3,9] A recent study on early-onset exotropia with deviations 40 PD or less reported a success rate of 67% up to 3 years after surgery.[4]

Up to 50% of children whose exotropia is corrected before age 24 months develop peripheral fusion. Some may show gross stereopsis.[2,4] The best binocular outcomes reported are monofixation syndromes.[1,2] Re-aligning patients with infantile exotropia after the age of 2 years can still lead to stable long-term results, and sensory fusion may be achieved in some patients after this age.[1,4]

Monofixational exotropia

Introduction

The monofixation syndrome is characterized by fixation with the fovea of only one eye under binocular conditions.[1] Sensory features include intact peripheral fusion, preserved gross stereopsis, and, frequently, amblyopia of the non-foveating eye. The motor features include manifest heterotropia, <8 PD, a larger heterophoria, and preserved convergence and divergence fusional amplitudes (see Chapter 75).[1,2] When there is no heterotropia on cover test but with sensory findings of monofixation, these are termed monofixational phorias. Some show a heterotropia without a superimposed heterophoria: these are sometimes termed microtropias (see Chapter 78).[1,2]

In most patients with monofixation syndrome who have a manifest deviation, this is an esotropia and any associated heterophoria is an esophoria. However, between 5% and 20% have an exotropic orientation for the tropia and the phoria.[1,10] Most cases of monofixational exotropia are secondary, either associated with anisometropia or following surgery for exotropia. However, a monofixation syndrome may underlie some cases of intermittent exotropia and its true nature may only become evident after surgery for the total exodeviation.[11,12]

Most cases of monofixational exotropia retain a stable long-term small exotropia under binocular conditions by virtue

of intact vergence amplitudes. In a minority, fusion control is disrupted and the exophoria becomes predominant: this is termed a decompensated monofixational exotropia.[1,10,13,14] It has been suggested that sensory changes along with decreasing horizontal and/or vertical fusion amplitudes may be important factors in leading to decompensation.[13] The risk of decompensation does not seem to be related to the depth of amblyopia.[13]

The reported rates of decompensation in monofixation exotropia vary, ranging from zero to 25% with up to 20 years or more follow-up.[10,13,14] The risk of decompensation is less the better the binocular function (motor amplitudes and depth of stereopsis) and the smaller the initial angle of the heterotropia when the monofixation adaptation is established, whether it is a primary disorder or it develops after eye muscle surgery.[13,15]

Etiology

The monofixation syndrome can be primary or secondary to anisometropia, a macular lesion, or previous surgery for infantile or acquired strabismus.

Primary monofixation exotropia

Patients with the primary form have a deficit in fovea-to-fovea correspondence: they cannot attain bifoveal fusion.[1,2] This may be a hereditary error in foveal correspondence that may exceed the capability of Panum's fusional space to compensate for it, leading to suppression of the less dominant fovea.[1,2] Alternatively, there may be a reversal of the normal dominance of the nasal over the temporal hemifield. As a result, any degree of foveal disparity can lead to a facultative scotoma on the temporal side of the fovea rather than in its usual location on the nasal side.[1]

A primary monofixational exotropia can decompensate because of an acute illness or chronic fatigue as the "all-or-none" suppression in exodeviations is less flexible than that of esodeviations.[1] If the latent heterophoria begins to manifest, then the strong hemiretinal suppression mechanism may increase the propensity for the exodeviation to decompensate.[1]

Secondary monofixational exotropia

The majority of secondary forms in children result from surgery for constant or intermittent exotropia.[11,12] Monofixation after surgery suggests a pre-existing defect in bifoveal fusion, and this may underlie a minority of cases of seemingly typical intermittent exotropia.[2,11] Anisometropia is a less common cause but, as an obstacle to bifoveal fusion, it may lead to suppression of the less dominant fovea. Finally, a unilateral macular lesion can lead to a progressive manifest exotropia; small lesions can result in a small scotoma with the attributes of a monofixation syndrome.[1]

Secondary monofixation exotropia has the same propensity for deterioration as the primary form. There is an abnormal binocular state, and any loss of the "peripheral fusion lock" allows the heterophoria to manifest. If the control deteriorates then the hemiretinal suppression adaptation may take over and increase the likelihood that the exotropia becomes constant.[1]

Clinical features

Motor features

Most patients with a monofixation syndrome show a heterotropia of 2–8 PD under binocular conditions (see Chapter 75). Up to one-third of cases will show no shift on cover test – most commonly in the form secondary to anisometropia.[1,2]

The exophoria uncovered on alternating prism and cover test tends to be larger than that seen in bifoveal patients who have exophoria, although it rarely exceeds 25 PD[1] and the fusional amplitudes are nearly normal.[1] When exotropia and exophoria co-exist, the simultaneous prism and cover test should be performed initially to measure the static heterotropia. Then the prism and alternating cover test measures the superimposed heterophoria[1] (see Chapter 75).

Cases of decompensated monofixational exotropia can appear as intermittent exotropia while chronic cases may show a constant exotropia.[11,12] Children whose monofixation exotropias decompensate may complain of asthenopia as their deviations stress their fusional amplitudes, or give them diplopia if the separation of the perceived images exceeds the size of their suppression scotoma. These symptoms are more common with decompensating monofixation exotropia than for esotropia, but asthenopia in monofixation exotropia is less frequent than in bifoveal patients with exophoria.[1]

Sensory features

Binocular sensory testing in monofixation confirms a foveal scotoma in the non-dominant eye with preservation of peripheral fusion. In monofixation exotropia, there may be a suppression scotoma extending temporally from the fovea. Depending on the test, the size of targets, the patient's age, and the size of the deviation, they can indicate either normal retinal correspondence or anomalous correspondence, even in the same patient.[1,2] Eccentric fixation may also be demonstrated in the non-dominant eye, especially if amblyopia is severe. In fact, scanning laser ophthalmoscopy microperimetry has shown that the preferred eccentric fixation points in monofixation syndrome are more than 2° from the fovea in 40% of eyes.[16]

Stereopsis is often present but subnormal in monofixational exotropia.[1,2] Stereoacuity is higher in the primary than in the secondary form, in both monofixational esotropia and exotropia.[1]

Where the exodeviation has decompensated and is almost constantly manifest, sensory testing with the angle corrected with prisms may show subnormal binocular vision, suggesting an underlying monofixation syndrome.[1,11,15]

Amblyopia (see Chapter 73)

The incidence of amblyopia in monofixation exotropia ranges from 30% to 65%, slightly less than in monofixational esotropia.[1] It occurs most commonly with anisometropia and least often with the postsurgical form.[2] Up to 50% of patients with monofixation and moderate-to-severe amblyopia may also show eccentric fixation on monocular testing.[16]

Treatment

Once a primary or secondary monofixation syndrome develops, it is difficult to restore bifoveal fixation.[1] Aggressive attempts to break down the facultative macular scotoma to achieve this may risk diplopia.[2] There are anecdotal cases of conversion of monofixation to bifoveal fixation with aggressive therapy in children.[2]

In children there are two clear indications for treatment in monofixation exotropia: the reversal of amblyopia and the restoration of alignment in a decompensated exotropia.

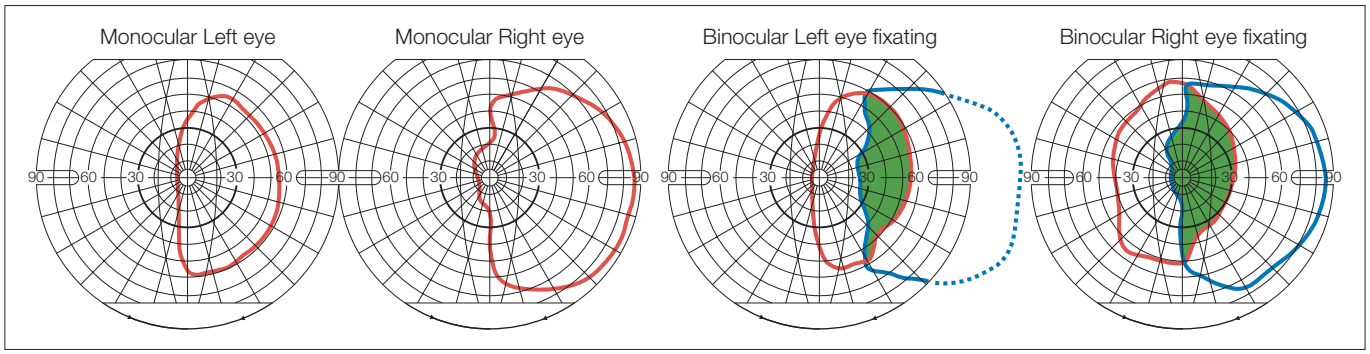


Fig. 80.2 Monocular and binocular visual fields in a patient with congenital complete left homonymous hemianopia and exotropia. The first two plots show the monocular visual fields of the left and right eyes. The third plot shows the binocular field with the left eye fixating, and the fourth plot shows the binocular field with the right eye fixating. The shaded area is the overlap of the monocular fields. Note that the panorama of the binocular field is greater when the right eye is used for fixation than when the left eye takes up fixation. *(From Kraft SP. Selected exotropia entities and principles of management. In: Rosenbaum AL, Santiago AP, editors. Clinical Strabismus Management. Philadelphia, PA: Saunders; 1999: 176–201. Copyright Elsevier 1999; after Gote H, Gregersen E, Rindziunski E. Exotropia and panoramic vision compensating for an occult congenital homonymous hemianopia: a case report. Binocul Vis Eye Muscle Surg Q 1993; 8: 129–32, with permission of Binoculus Publishing.)*

Amblyopia

6/9	20/30	0.63	0.18

Amblyopia of worse than LogMAR 0.40 (6/15, 20/50, 0.40) should be treated, even in a monofixation syndrome, by correcting the refractive errors and anisometropia with glasses, and patching or penalization.[2] In decompensated monofixational exotropia, treatment of the amblyopia can improve control of the exotropia and reduce symptoms such as asthenopia. The aim is to improve the visual acuity to LogMAR 0.18 (6/9, 20/30, 0.63) or better and achieve a stable monofixation – a small angle exotropia with peripheral fusion.[1,2]

Alignment

No treatment is indicated for asymptomatic patients with small, infrequently manifest exodeviations, but those with frequent exotropia who complain of asthenopia or diplopia warrant intervention. The goal is comfortable single vision, usually by achieving monofixation exotropia rather than bifoveal fixation.[1,11]

Non-surgical options include part-time occlusion, prisms, and minus lens overcorrection (see Chapter 85). Orthoptic exercises are not usually indicated for decompensated monofixation exotropia as the fusional amplitudes are good. Anti-suppression therapy is contraindicated, as in decompensated monofixational esotropia, to avoid breaking down suppression.[1,2] Botulinum toxin and surgery are used to treat children whose exodeviation has decompensated or is not corrected by amblyopia treatment or non-surgical interventions discussed above (see Chapters 86 and 87). Botulinum toxin has a good success rate for children with deviations of less than 20–25 PD.[1] Surgery has about the same rate of success as for the common forms of intermittent exotropia. However, the result is a monofixation syndrome rather than bifoveal fixation.[1,2,11]

Exotropia with hemianopic visual field defects

Introduction

Exotropia occurs with both homonymous and bitemporal hemianopias. The field loss is usually extensive when an exotropia develops in association with one of these disorders. Binasal hemianopias are very rare and will not be discussed in this chapter.

Homonymous hemianopias

Etiology

Exotropia can occur with homonymous hemianopias caused by congenital or acquired intracranial disorders. It is mostly acquired before the age of 2 years, but it can be an adaptation with hemianopia onset as late as 7 years.[1,17,18] The divergent strabismus is likely an adaptive compensation to enlarge the binocular field[1,18–20] (Fig. 80.2), although some argue that the exodeviation is an epiphenomenon and not adaptive.[1]

Clinical features

In contrast to patients who develop homonymous hemianopias later, children with congenital or early-acquired brain lesions adapt well. They are often unaware of their field loss[1] and develop eye movement strategies that include large saccadic movements into the blind field followed by smooth pursuit into the intact field to fixate a target.[19] They may develop a face turn to the side of the hemianopia in order to better center their remaining hemifield.[2,18,19]

Children who later develop a homonymous hemianopia do not adapt as well: they often bump into objects on the side of the hemianopia, and reading is difficult (see Chapter 102).[19]

Motor features

Exotropia mostly occurs as an adaptation if visual field is lost congenitally or early in life, although this has also been described in a teenager.[17] The compensatory exotropia can be seen either in childhood or later.[17,19] In early-acquired cases, the onset of exotropia can be as soon as 8 weeks after the cause of the hemianopia. One study reported that among 45 children with early-onset total homonymous hemianopia due to hemispherectomy, 40% developed a compensatory exotropia contralateral to the side of the surgery.[17] The deviation is usually constant but intermittent deviations can be seen.[17] This contrasts with the intermittent exodeviations that are more frequently reported with later-acquired hemianopias. The angle in early-onset cases ranges from 20 to 70 PD and it is often larger for distance fixation than for near.[1,19] It may be associated with a vertical heterotropia or a pattern strabismus.[1]

Children with later-acquired hemianopia and exotropia usually have deviations less than 20 PD.[1] They can be an exophoria or an intermittent or constant exotropia. Exotropias in such cases may not be adaptive.[1,21]

Sensory features

Young children adapt better to homonymous hemianopia than do older children; those who develop exotropia have complete defects.[1] With the exotropia, the expansion of the visual field to the side of the missing field ranges from 20° to 45°. This strategy is only relevant if the exotropia develops in the eye ipsilateral to the field loss (that is, contralateral to the cerebral damage), while the child fixates with the eye on the side of the intact field (see Fig. 80.2). The amount of expansion is proportional to the size of the exotropia.[1]

Children with exotropia with congenital or early-onset hemianopia rarely complain of diplopia or asthenopia because they may develop anomalous retinal correspondence (ARC).[1,21] They suppress within the overlapping portions of the monocular fields, and elsewhere they show ARC. This can be tested by the synoptophore or with sensory tests performed while the angle of exotropia is corrected with base-in prisms.[1,21]

Patients with later-acquired hemianopias generally complain of diplopia since they retain normal correspondence, cannot develop ARC, and cannot develop suppression.[1,21]

Treatment

Surgery for exotropia with congenital or early-onset homonymous hemianopia should be undertaken with caution. First, the re-alignment of the eyes reduces the total binocular visual field.[1,19] Second, patients who develop ARC in response to the exodeviation may experience paradoxical diplopia if the eye is re-aligned once the adaptation is complete.[2,20] Patients should be tested before surgery with a monocular patch to see whether they can adapt to the smaller binocular field and then with a prism to see whether they develop diplopia.[21] Some patients with large angle exodeviations may elect to undergo surgery for cosmetic reasons.[20] These patients require detailed discussion and education prior to surgery.[20]

Patients with later-onset hemianopia who develop diplopia or asthenopia because of an exodeviation may be treated initially with a prism or a patch, or they may require surgery or botulinum toxin injections.[21]

Bitemporal visual field defects

Clinical features

The disruption of the vergence reflex may lead to exodeviation, which can cause several sensory phenomena, especially if the field loss in each eye is extensive enough to involve the two maculae.

Motor features

The exodeviation measures a few PDs, often variable because of poor fusional vergences. The endpoints can be difficult to measure.[1] Patients may have an exophoria or exotropia. With complete hemianopia, an exophoria can decompensate due to the loss of vergence reserves and the loss of correspondence between the intact nasal fields of the two eyes.[22] The extraocular movements are usually normal.

Sensory features

Patients with bitemporal hemianopia may have two unusual and often missed symptoms. First, the loss of overlapping visual fields can lead to "hemiretinal slide" as the intact nasal visual fields of the two eyes cannot be juxtaposed.[22–24] In the presence of an exodeviation (either an exotropia or exophoria), there is a reduction of the binocular field and overlap of the partial images seen by the intact, but non-corresponding, nasal fields.[1,22] Any target can appear elongated, and there is duplication of features within the target leading to diplopia[1,21,23] (Fig. 80.3). This leads to reading difficulties.

Second, complete bitemporal hemianopia produces "postfixation blindness" from stimulation of non-seeing nasal retina by objects that lie behind the fixation target[1] (Fig. 80.4). An exotropia places the area of postfixation blindness further from the eyes and any proximal object, including the fixation target, may be double, as most patients have normal retinal correspondence (NRC)[1,21,22] (see Fig. 80.4). This leads to difficulty with daily tasks such as reaching accurately, pouring, or picking things up off a flat surface.

Very young children with bitemporal hemianopia and exotropia may not have symptoms. They may be able to develop suppression as an adaptation to diplopia.[23] Others may adapt to their abnormal binocular vision in the same way that children can learn strategies to overcome symptoms of bilateral homonymous hemianopia.[1]

Treatment

Exotropia with total or almost complete bitemporal hemianopia can be difficult to treat, whether it appears in young or older children. Prisms can be tried to alleviate diplopia, but they are not always helpful due to the variability of the exodeviation.[23] Prisms can be helpful if the hemianopia is not complete.[22] One study showed some benefit of midline stereopsis training in two patients with total bitemporal hemianopia.[22] Patching one eye reduces the visual field. Surgery to eliminate diplopia and exotropia can help if the misalignment is eliminated. However, the result is rarely stable with complete hemianopia due to lack of adequate fusional vergences.[23,24] In cases of almost complete hemianopia, strabismus surgery can be successful, especially if adjustable sutures are used for optimal alignment.[24] Pre-operative testing with prisms is helpful to assess the potential stability of the result and to give the patient a sense of the reduced binocular field that will be generated by the surgery.[21,24]

Sensory exotropia

Sensory exotropia – a unilateral exodeviation – develops as a result of loss of vision or chronic poor vision in one eye.[1] Children under age 5 or 6 years who develop strabismus due to vision loss in one eye tend to develop esotropia more often than exotropia, especially if the child's sound eye has a hyperopic refractive error.[2,25–27] After 6 years of age, exotropia develops much more often.[25–27]

Etiology

Sensory exotropia occurs in children as a result of congenital and acquired ocular disorders. Congenital disorders compromise vision development; normal binocular vergence reflexes cannot develop and strabismus is a frequent result. Acquired causes include traumatic and non-traumatic diseases, such as cataracts, that disrupt the fusion reflex[1] (Fig. 80.5). One specific

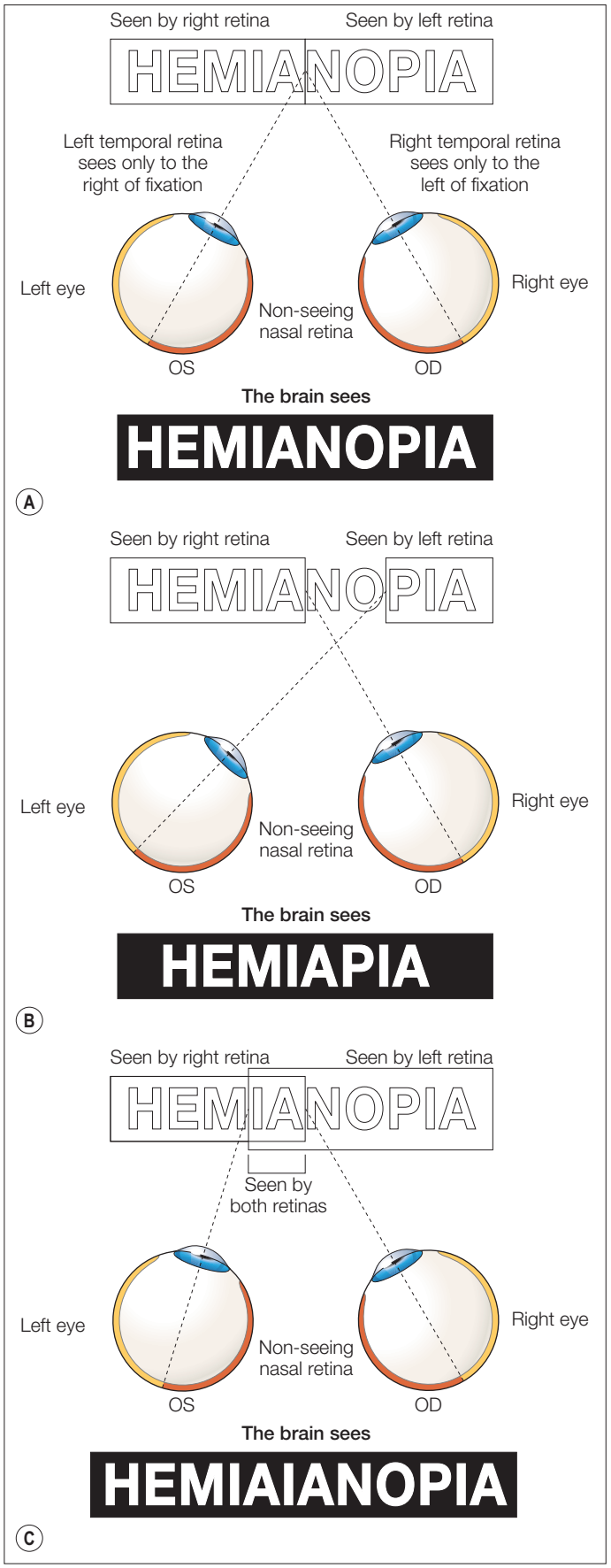


Fig. 80.3 Hemifield sliding and abnormal binocular phenomena in a patient with complete bitemporal hemianopia. (A) Straight eyes: the two separate monocular visual fields juxtapose to form a complete image of the target. (B) Left esotropia: central portions of the target are missing. (C) Left exotropia: central portions of the target are duplicated as a result of redundant reception by the functioning temporal retinas of both eyes. *(From Kraft SP. Selected exotropia entities and principles of management. In: Rosenbaum AL, Santiago AP, editors. Clinical Strabismus Management. Philadelphia, PA: Saunders; 1999: 176–201. Copyright Elsevier 1999; after Fritz KJ, Brodsky MC. Elusive neuro-ophthalmic reading impairment. Am Orthoptic J 1992; 42: 159–64, with permission of University of Wisconsin Press.)*

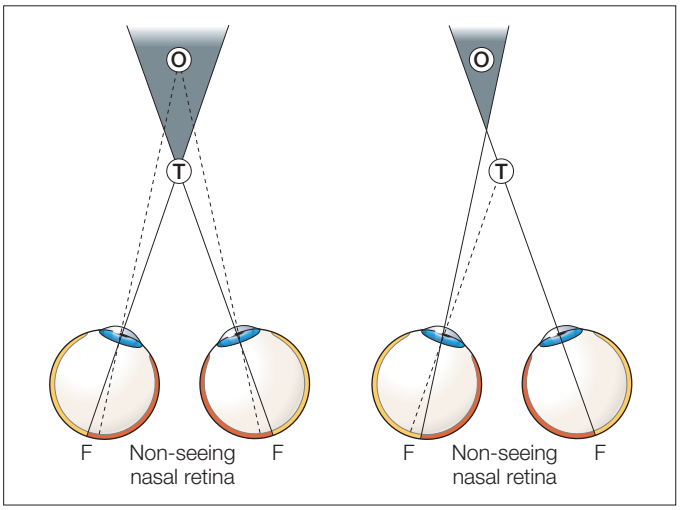


Fig. 80.4 Postfixation blind area in a patient with complete bitemporal hemianopia. (Left) The diagram shows the situation when the eyes are straight. When both foveae (F) fixate on a target (T), the retinal image of any second object (O) located within the shaded area would fall on the non-functioning nasal retinas of both eyes and not be seen. (Right) The diagram shows the situation in the presence of a left exotropia with the right eye fixating. The target (T) may be seen as diplopic because the image falls on the fovea of the right eye and on the functioning temporal retina in the left eye. A second object (O) is not visualized as it is located in the postfixation blind area, which is more remote from the patient compared to the orthotropic state. *(From Kraft SP. Selected exotropia entities and principles of management. In: Rosenbaum AL, Santiago AP, editors. Clinical Strabismus Management. Philadelphia, PA: Saunders; 1999: 176–201. Copyright Elsevier 1999; after Roper-Hall G. Effect of visual field defects on binocular single vision. Am Orthoptic J 1976; 26: 74–82, with permission of University of Wisconsin Press.)*

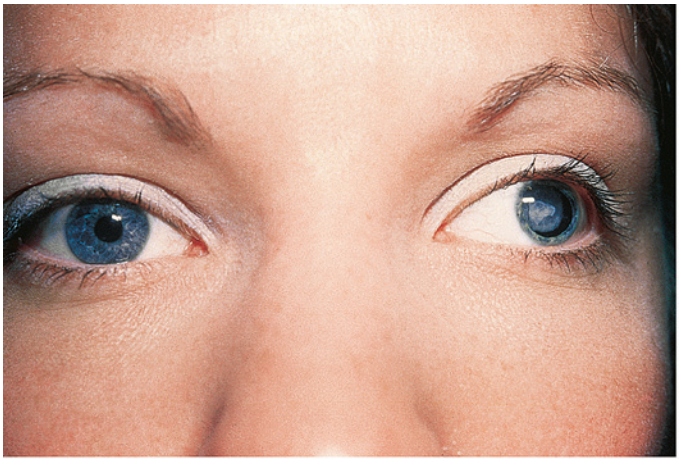


Fig. 80.5 Child with sensory left exotropia due to traumatic cataract. Note the large angle of the deviation. *(From Kraft SP. Selected exotropia entities and principles of management. In: Rosenbaum AL, Santiago AP, editors. Clinical Strabismus Management. Philadelphia, PA: Saunders; 1999: 176–201. Copyright Elsevier 1999.)*

cause is anisometropic amblyopia, especially anisohyperopia. Older children whose vision remains reduced are at particular risk of developing exotropia, although esotropia is common among children with vision loss in one eye and hyperopic refractive errors in the sound eye.[2,26]

The mechanisms for the development of exotropia when vision is lost in one eye are the following:

1. *Binocular rivalry*: When the retinal image of one eye is degraded, it sets up a rivalry between that and the fellow eye. Normal visual signals become inhibitory to the disadvantaged eye; this is even more powerful with partial than with total loss.[1] Also, there is a superiority of the nasal retina over the temporal retina in response to bright and formed stimuli, and this becomes exaggerated when an eye loses vision. These factors lead to disruption of the vergence system, and an active retinomotor divergence takes hold with a progressive exodeviation, especially in older children.[1]
2. *Decompensation of exophoria*: A well-controlled exophoria can decompensate from loss of fusion if one eye loses vision. This appears to be a settling of the poorer eye into its "elastic" rest position, not an active divergence reflex. The divergent position results from an imbalance of muscle tone between the lateral and medial rectus muscles.[1]
3. *Mechanical factors*: Orbital dysmorphism or muscle anomalies predispose to an exotropia if one eye suffers a loss of vision. Strabismus in which there is congenital tightness or restriction of the lateral rectus, such as in Duane syndrome, can show progressive exotropia if vision deteriorates in the affected eye.

Clinical features

Motor features

Sensory exotropia is usually over 30 PD, and the angles can be very large in some patients,[1] although one paper reported a large series of patients with sensory exotropia whose angles were less than 30 PD.[28] If the cause of the vision deficit persists, then the angle can increase progressively,[28] although this is not always the case.[27] There is a positive correlation between age of the patient and size of the exotropia.[26] A longstanding large exotropia leads to secondary muscle changes. The lateral rectus contracts and the overlying soft tissues shorten, creating a tight lateral rectus syndrome (see the "Clinical features" subsection of Infantile Exotropia, above): an updrift and downdrift in the adducted position, and possibly an "X" (see Fig. 80.1), "A," or, less commonly, a "V" pattern.[1] The exotropic eye may exhibit a small hypertropia.

Measuring the angle of the exotropia can be tricky when the vision is poor in one eye. The prism and alternating cover test may not be accurate since the poor fixation in the eye does not allow the examiner to see a stable endpoint during the measurement; thus, the angle is better measured with the modified prism and light reflex (Krimsky) test: After the angle kappa is noted for the fixating eye, progressive base-in prism power is placed over that eye until the exotropic eye is drawn over sufficiently in the nasal direction to create a matching angle kappa in that eye.[2]

Sensory features

Several adaptations can occur in sensory exotropias. If the vision is very poor, there may be deep suppression and no binocular responses. Children whose vision is not severely reduced and who have exotropia not exceeding 40 PD may develop ARC.[1] Children with anisometropic amblyopia and exotropia may retain NRC.[1] Young children can avoid diplopia by suppressing the displaced image. Older children with sensory exotropia may experience diplopia because they cannot develop ARC.

Sensory tests in a patient can vary, ARC or NRC, depending on the depth of suppression and the dissociating ability of the tests, the brightness of ambient lighting, the distance of the testing apparatus from the patient, and the size of the exotropia.[1]

Management

Treating the underlying cause of the vision loss is paramount: cataracts, corneal opacities, anisometropic amblyopia, ptosis, eyelid hemangioma, retinoblastoma, and retinal detachments are potentially reversible examples. If the problem is present early, then the exotropia can be prevented if vision can be restored by treatment, especially of amblyopia. If exotropia has already developed, it may still reduce if vision can be recovered.[1] If exotropia persists despite correction of the underlying disorder, or if the vision loss is chronic and irreversible, it can be treated with either non-surgical or surgical options.

Non-surgical therapy and safety precautions

Prescription of safety lenses for patients with unilateral vision loss is important: those who already wear glasses should be sure that their lens and frame designs meet safety specifications.

Patients with diplopia or asthenopia can be helped with prisms if the angle of the exotropia is not over 30 PD.[29] In some patients, the prism can be weaned with the restoration of stable single binocular vision.[29] Children who are aware of the second image but are not helped by base-in prisms may be helped by base-out prisms to further separate the two images. Patients with intractable diplopia may be helped by Bangerter or MIN occlusion foils to reduce the clarity, and therefore awareness, of the displaced image in the exotropic eye.

Botulinum toxin injections are successful in re-aligning angles of exotropia under 35 PD.[1] However, the angles in sensory exotropia tend to be larger, with a lower long-term success rate. Patients with a large exotropia angle who choose botulinum injections rather than surgery must understand that periodic re-injections may be needed.[1]

Surgery

Surgical planning

Children with sensory exotropia should undergo preoperative prism testing to see whether they can be re-aligned without inducing intractable diplopia.[29] If a prism, placed base-in and matching the strabismus angle, is introduced before the misaligned eye and the child does not complain of diplopia, then the surgeon can plan to align the eyes close to orthotropia. If the child complains of diplopia when the prism used corrects the whole deviation, a reduced amount of prism for partial correction can be tried. However, a diplopia response to correction of the whole angle does not necessarily predict postoperative diplopia. In such a case, a trial with a Fresnel prism correction of the whole angle for several days should be used to determine if the child can adapt to perfect alignment.[1]

A complete eye examination is mandatory prior to surgery. The surgeon must be sure that the eye is healthy enough to

undergo strabismus surgery. Problems such as phthisis, corneal compromise, and orbital factors may make it risky to perform muscle surgery. Older children may allow a forced duction test on their eye to detect a contracture of the lateral rectus or any other restrictive phenomena that will help in the planning of surgery.

Most cases of sensory exotropia require surgery on two muscles due to the large angles typically seen in these patients.[30] Sensory exotropia of 25 PD or less can be successfully treated with unilateral lateral rectus recession alone.[28] Weakening of the lateral rectus is almost always a component of the surgery plan, and, if the overlying conjunctiva is also tight, it should be recessed as well.[1] The medial rectus can be lax and may be strengthened. The surgeon should perform several forced ductions at surgery as each layer is dealt with, to be sure that restrictions are released. For large angles, from 55 to 90 PD, supramaximal lateral rectus recession (10 mm or more) along with medial rectus resection or plication (9 mm or more) have been reported to lead to successful long-term alignment.[30] Alternatively, the addition of ipsilateral inferior oblique and superior oblique weakening to more traditional dosages of horizontal rectus surgery can increase the success of surgery for these large angles.[1]

If the surgical goal is orthotropia, then the immediate postoperative alignment should be a small angle esotropia, as there is typically a drift toward exotropia of several degrees in the first few weeks.[1,31] Adjustable sutures may be help to achieve the desired target angle, although one study showed no difference in success rates for long-term alignment with or without the use of adjustable sutures.[31] In general, the postoperative target angle should be slightly larger than that recommended for routine cases of intermittent exotropia, of the order of 10–14 PD, similar to that recommended above for infantile exotropia. To achieve this and to improve the long-term stability, the forced duction at the conclusion of surgery should be mild-to-moderately limited to abduction and the spring-back balance test should be biased in the esotropic direction. Some authors caution against aligning to orthotropia any older patient with sensory exotropia caused by anisometropia, and they recommend leaving such patients undercorrected.[1]

Results

Patients with preoperative exotropia angles under 40 PD have at least 75% chance of a stable small angle heterotropia. Over 45 PD, the results decrease dramatically to 40–50% long-term success.[26] Once the eye is re-aligned, the secondary muscle phenomena such as upshoots and downshoots and "X" patterns often resolve within weeks.[1]

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Further reading: fourth edition references

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Vertical strabismus

Burton J Kushner

Chapter contents

OVERVIEW AND DEFINITIONS
PHYSIOLOGY
PATIENT EVALUATION
GENERAL TREATMENT PRINCIPLES
SPECIFIC CLINICAL ENTITIES
SPECIAL FORMS OF VERTICAL STRABISMUS
REFERENCES

See online for supporting video for this chapter.

Overview and definitions

For a patient with vertical strabismus, one should first determine whether the deviation is comitant or incomitant. If the latter, one next determines if the problem is paretic, restrictive, or a manifestation of primary oblique muscle dysfunction. Finally, one determines if the deviation is dissociated (e.g. does not appear to follow Hering's Law with respect to the vertical component).

It is best to describe the deviation as it is actually manifested. Thus, if a patient fixes with the left eye and has a restrictive right hypotropia, you should call it a right hypotropia rather than using the old convention of describing it in terms of a hypertopia – in this example a left hypertropia. If the patient freely alternates fixation, you should then use the old convention. There has also been confusion about the terminology for describing dissociated vertical divergence (DVD). Terminology should be descriptive by addressing three issues; indicate if the deviation is:

1. constant or intermittent;
2. latent of manifest (e.g. a phoria or tropia);
3. dissociated or not dissociated.

The most common presentation for DVD is for one eye to have a hypertropia that is intermittently manifest and for the other to have a hypertropia that is latent (only present in the dissociated state, e.g. under cover). Appropriate terminology for describing such a patient would be "intermittent manifest DVD in one eye and latent DVD in the other." An alternative would be "an intermittent dissociated hypertropia in one eye and a dissociated hyperphoria in the other."

Physiology

The cyclovertical muscles have a triple function that includes a vertical, torsional, and, to a lesser degree, horizontal action. With head tilt right or left, there is a small partial compensatory torsional rotation of each eye, which corrects for about 5–10% of the head tilt.[1] This comes from stimulation of the intorters (superior oblique and superior rectus) in the eye on the side to which the head is tilted, and the extorters (inferior oblique and inferior rectus) in the fellow eye, and forms the basis for the Bielschowksy head tilt test and the Parks' three-step test.[2] Although the vertical rectus muscles have their main vertical action in adduction, they are still the primary elevators and depressors across the horizontal gaze fields. Oblique muscles have a relatively weak vertical action. If the superior rectus is detached from the globe, the inferior oblique alone cannot elevate the eye above the midline.[1] The superior oblique, however, has a stronger vertical action than the inferior oblique.

Patient evaluation

History

Before measuring the deviation, observe whether the patient has a spontaneous compensatory head posture (CHP) with visual effort. Although there are many causes for CHPs, this author finds they mostly serve to place the eyes in a gaze field in which the deviation is less, or to damp nystagmus (see Chapters 82, 84, and 89). The presence of facial asymmetry typically identifies the CHP as dating back to early childhood. There is a shortening of the midface between the horizontal canthus laterally and the corner of the child's mouth on the side to which the head is habitually tilted[3] (Fig. 81.1). Measure the deviation with the head posture using the prism and alternative cover test, and then in the head-erect position. Although a diagnosis can often be made by just measuring a patient in seven fields of gaze (primary, up, down, right, and left) and on head tilt right and left, an optimum treatment plan often requires additional measurements in the four oblique fields. Ductions and versions should be assessed with particular attention to the presence of overelevation or overdepression in the oblique fields. If there is overelevation of the adducting eye on side gaze, do a cover test in that gaze field to ascertain if the vertical deviation is

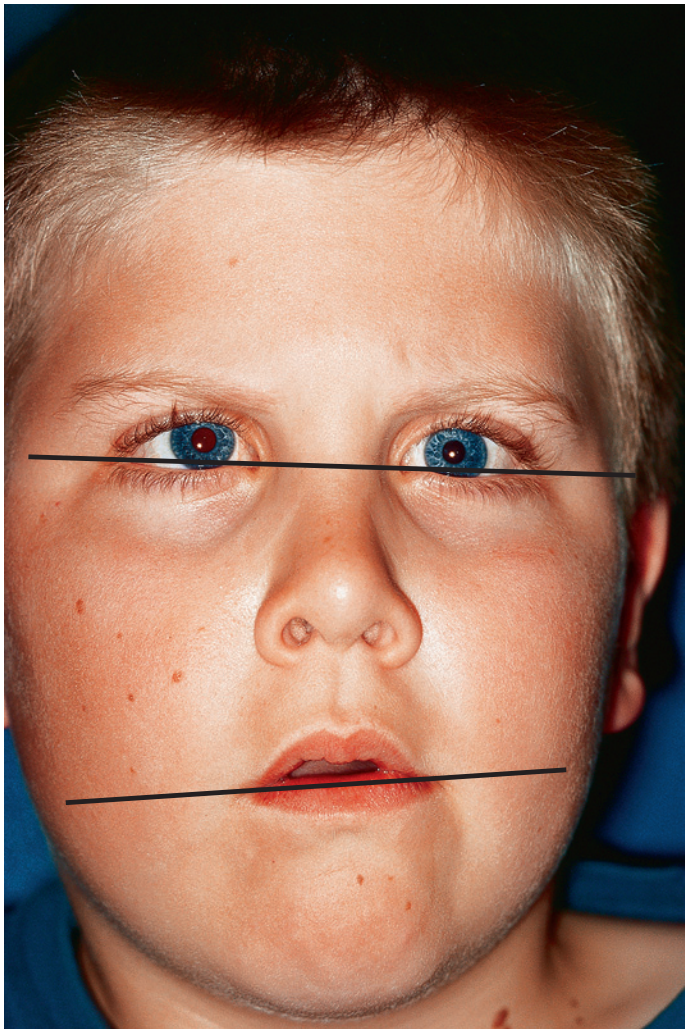


Fig. 81.1 Facial asymmetry. There is shortening of the left side of the face in this boy with a longstanding head tilt to the left for control of a right superior oblique palsy.

a manifestation of DVD or true inferior oblique overaction. In Video 81.1, both boys show overelevation of either eye in adduction. The first boy does not have a hypotropia of the abducting eye when cover testing is done in side gaze. His overelevation in adduction is solely due to DVD. The second boy does have a significant hypotropia of the abducting eye when cover testing is done in side gaze. He has DVD coexisting with true inferior oblique overaction.

Determine if the deviation is dissociated or not. With a non-dissociated deviation, a hypotropia is present in the contralateral eye when fixation is with the higher eye. Unless a secondary deviation is present due to paresis or restriction, the hypotropia in one eye will be of equal size to the hypertropia of the other eye. With DVD, the hypotropia of the fellow eye is either smaller or absent when fixation is with the eye with the DVD (see section "Dissociated vertical divergence").

The Parks' three-step test will tell, in theory, which of the eight cyclovertical muscles is paretic; however, in practice it works best for confirming the diagnosis of unilateral superior oblique palsy.[2,4] Even in cases of isolated superior or inferior rectus palsy, it may be misleading. Most importantly, it does not tell whether a vertical strabismus is due to a palsy of one of the cyclovertical muscles, but is based on the assumption that it

Box 81.1

Situations in which the Parks' three-step test may be misleading[4]

Dissociated vertical divergence
Multiple muscle involvement
  Bilateral fourth nerve palsy
  Multiple other muscle weakness
Pulley heterotopia
Superior rectus overaction/contracture
Inferior rectus restriction
Superior rectus palsy
Inferior rectus palsy
Skew deviation
Prior extraocular muscle surgery

is. Box 81.1 lists some of the common situations in which the three-step test leads to an incorrect diagnosis. The man in Video 81.2 developed vertical diplopia immediately after closed head trauma from a motor vehicle accident. He had a left hypertropia that increased in right gaze and on left head tilt, thus meeting the three-step test criteria for a left superior oblique palsy. In fact, he had an orbital floor fracture in his right eye. He consistently fixed with his right eye due to mild amblyopia in his left eye. His diplopia resolved when the fracture was repaired.

You should test for the presence of torsion, both objectively and subjectively. The latter is accomplished with the double Maddox rod test using two red lenses, because the use of one red and one white lens frequently leads to a localization artifact; if the eye behind the white lens is the one that is torted, the patient will frequently perceive the torsion as being in the eye behind the red lens.[5] However, even when this author uses two red lenses, he sometimes finds that the double Maddox rod test just reveals the total amount of torsion between the two eyes, and may be misleading with respect to localizing to the specific eye affected. Objective torsion is determined with the indirect ophthalmoscope and may be more useful in determining which eye actually is torted.[6] Normally the position of the fovea should be level with the lower one-third of the optic disc (Fig. 81.2). The absence of subjective torsion in the presence of objective fundus torsion usually means the deviation is longstanding and sensory adaptations have occurred. If a patient describes torsion, determine if the patient can fuse when the vertical and horizontal deviations are offset with prisms. If the patient can fuse comfortably despite the presence of torsion, it may be possible to ignore the torsion when designing a surgical strategy. If they cannot fuse, there may be a central disruption of fusion. Testing on the synoptophore, which can offset the torsion, may determine whether one can expect fusion if the strabismus is successfully treated.

General diagnostic pointers

1. Are history and symptoms helpful in determining etiology? Is there diplopia, childhood strabismus (if the patient is an adult), and is there DVD?
2. Is incomitance greater vertically or horizontally? If it is greater vertically, consider a restriction or palsy of a vertical rectus. If the largest difference is horizontal, consider an oblique problem.

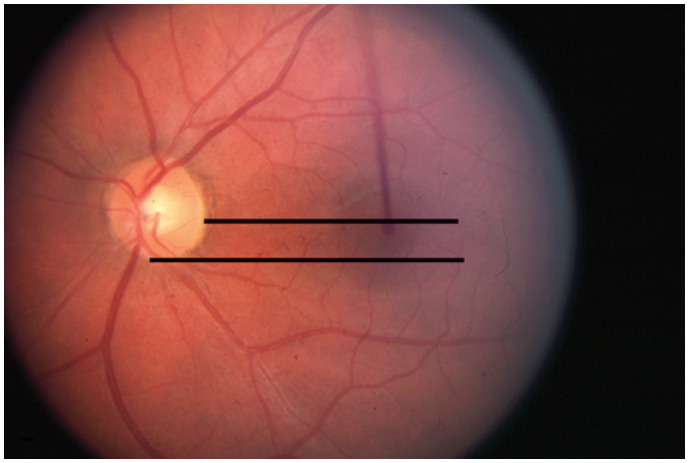


Fig. 81.2 Normal relationship of fovea to disc with respect to torsion. The fovea is normally positioned level with the lower third of the optic disc. The borders of normal lie between the two black lines in the figure. This photograph indicates an absence of objective torsion but is near the border for intorsion.

3. Is there a limitation of rotation? Differentiate restriction from paresis with forced duction and active force generation testing.
4. Is there substantial torsion? If so, consider oblique problems or a vertical restriction.
5. Might the patient be fixing with the involved eye? Always consider this if there is asymmetric best-corrected visual acuity. Check for a secondary deviation.

General treatment principles

You should choose a treatment plan that will give the maximum correction in the field of gaze in which the deviation is greatest. Thus, you need to pay attention to the pattern of incomitance and the presence of torsion. Keep in mind that the primary position and downgaze (for reading) are the two most important fields of gaze and should not be sacrificed for the benefit of eccentric gazes. Oblique muscle surgery will give much more correction in adduction than abduction, but with vertical rectus surgery the difference in correction between abduction and adduction is less dramatic. Also, oblique muscle surgery causes more torsional change than rectus muscle surgery. An exception is with vertical rectus restrictions in which releasing the restriction may correct substantial torsion.

In general, surgery on the superior oblique is least "forgiving," with surgery on the inferior rectus running a close second. Inferior rectus recessions of 5 mm or more may cause a lag of that eye in downgaze unless there was a hypotropia that increased in downgaze prior to surgery. Also, large recessions of the inferior rectus may cause lower eyelid retraction postoperatively, which can be minimized by advancement of the capsulopalpebral head at surgery.[7] Large resections of the inferior rectus muscle may cause narrowing of the palpebral fissure, and large recessions of the inferior rectus using a suspension technique (hangback adjustable suture) have a higher incidence of muscle slippage or non-adherance. This is probably caused by the shorter arc of contact of that muscle, which can cause the muscle to lose apposition with the globe in downgaze after surgery if the muscle is not fixed to the sclera.[8] Slippage can be prevented by using the semi-adjustable suture technique,[9] or a non-absorbable suture.

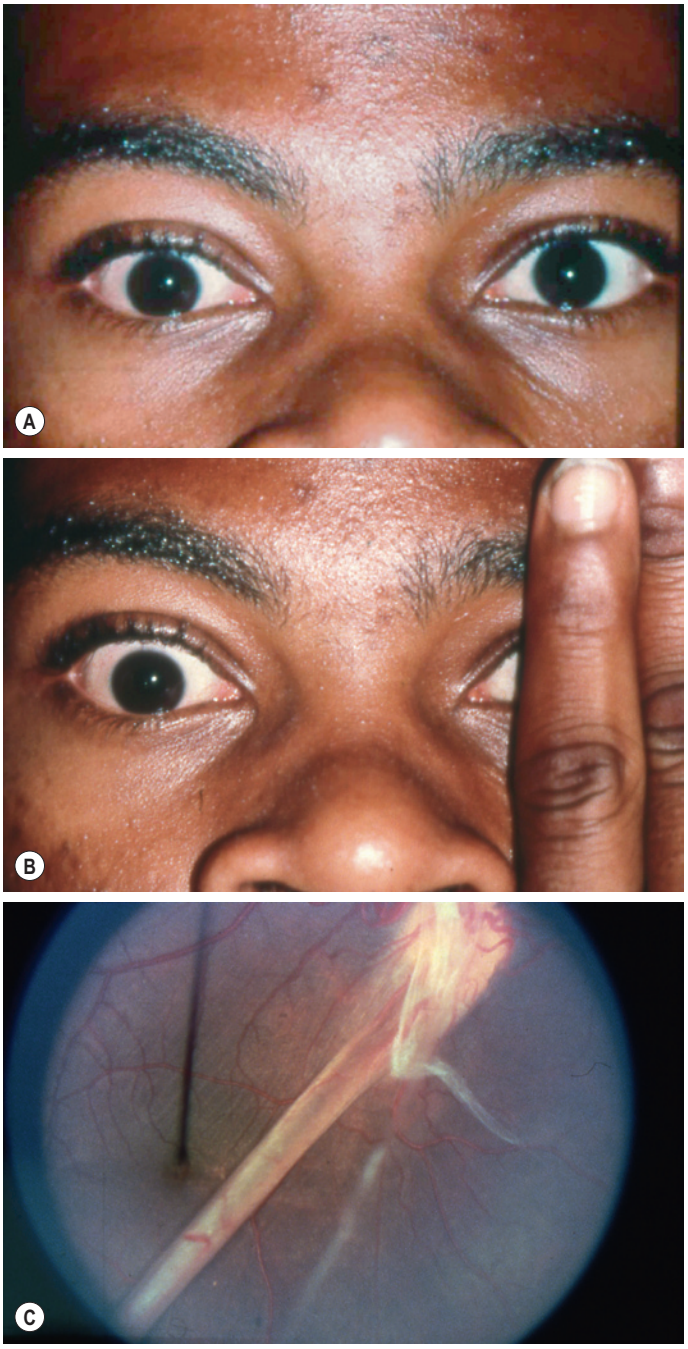


Fig. 81.3 Pseudohypotropia. (A) Patient with what appears to be a right hypotropia. (B) Cover test shows he is actually fixating with the eye when it appears to be infraducted. (C) His right fovea is dragged inferiorly due to traction secondary to retinopathy of prematurity, resulting in a large vertical angle kappa.

Specific clinical entities

Pseudohypertropia

Some patients may appear to have a hypertropia when in fact they do not. These include cases of orbital dystopia, anterior segment anomalies, or vertical angle kappa (Fig. 81.3). This latter

may be due to a displaced fovea secondary to retinopathy of prematurity (see Chapter 44) or other causes of retinal dragging.

Comitant deviations

Small comitant hypertropias, unrelated to prior strabismus surgery, are common. If they are more than several prism diopters (PD), they may cause symptoms of asthenopia or diplopia, which are often managed successfully with prisms. Large comitant vertical deviations not associated with horizontal strabismus are relatively uncommon. When present, they most likely represent a spread of comitance in a patient that initially had paralytic strabismus. If the deviation is large but comitant, vertical rectus muscle surgery is usually appropriate.

Incomitant deviations: non-restrictive non-paretic

Primary oblique dysfunction

Primary overaction of the inferior oblique muscles, and to a lesser degree the superior oblique muscles, is a common accompaniment of primary horizontal strabismus. Oblique muscle overaction is not usually present at birth but after 1 year of age. Inferior oblique overaction is characterized by an overelevation in adduction and is associated with a "V" pattern. Superior oblique overaction is associated with overdepression in adduction and is associated with an "A" pattern (see Chapter 82). Typically objective extorsion is present with inferior oblique overaction and intorsion with superior oblique overaction. Subjective torsion may not be present as the patient develops sensory adaptations. The main differential diagnosis between primary oblique overaction and palsy of the antagonist oblique muscle is settled with the head tilt test. With bilateral superior oblique palsy, the Bielschowsky head tilt test should reveal alternating hypertropias (right hypertropia on right head tilt and left hypertropia on left head tilt) for the reasons above. With primary oblique dysfunction, the difference in the vertical deviation with head tilting is minimal.[10] The boy in Video 81.3 has marked inferior oblique overaction, superior oblique underaction, and a large "V" pattern. On head tilt right and left, there is a negligible hypertopia, thus distinguishing primary inferior oblique overaction from bilateral superior oblique palsy. He had a history of previously undergoing medial rectus recessions for infantile esotropia (IED). Subsequently, a computed tomography scan for unrelated reasons showed the superior obliques were of normal size. I believe primary inferior oblique overaction is primarily due to inferior oblique muscle contracture,[10] possibly due to a chronic excyclorotation of the eye. It can be treated with inferior oblique muscle weakening.

It is rare for bilateral superior oblique overaction to be secondary to inferior oblique palsy. If superior oblique overaction is bilateral and symmetric, there will be no hypertropia in the primary position, but an "A" pattern is typically present. If the superior oblique overaction is unilateral, there may be a small hypertropia in the primary position. For mild superior oblique overaction, this author prefers a posterior 7/8 tenectomy performed at the insertion of the superior oblique. For greater amounts of superior oblique overaction, the split tendon lengthening procedure[11] allows titration of the effect, is potentially reversible, and unlike the silicone expander, does not place a foreign body in the orbit.

Paralytic strabismus (see Chapter 84)

Fourth cranial nerve palsy

Fourth nerve palsy is the most common form of paralytic vertical strabismus. The diagnostic criteria include a hypertropia of the affected eye that increases on adduction and ipsilateral head tilt (Fig. 81.4). A useful test for differentiating fourth cranial nerve palsy from skew deviation is to measure the deviation in the head erect and supine position. A decrease in the hypertropia by 50% or more is strongly suggestive of skew deviation.[12]

When treating fourth nerve palsy, slightly undercorrect the deviation or the patient may have bothersome diplopia. The primary position measurement determines how many muscles need surgery, and the pattern determines which muscles. Although Knapp's classification of superior oblique palsy is sound, it does not take into account the use of adjustable sutures and some newer observations about superior oblique anatomy and function.[13] The author follows this approach:

1. If the deviation is 15 PD or less, do one muscle. That threshold may be lowered to 10 PD if adjustable sutures are used.
2. If the deviation is greater in the inferior oblique field, recess the ipsilateral inferior oblique. If it is greater in the superior oblique field, tuck the superior oblique. An alternative to tucking the superior oblique in this setting is to recess the contralateral inferior rectus muscle for the vertical deviation, and transpose the ipsilateral inferior rectus nasally for the torsion.[14] This is useful for surgeons who are not comfortable tucking the superior oblique; however, it should not be done if there is anything more than a few prism diopters of esodeviation in downgaze, as it may exacerbate a downgaze esodeviation.[15]
3. If the deviation in primary mandates more than a one-muscle procedure, recess the ipsilateral inferior oblique and the contralateral inferior rectus. The author finds the semi-adjustable suture technique useful in this setting.[9]
4. If there is 10 PD or more of hypertropia in the horizontal abducted field, there is most likely some degree of superior rectus overaction/contracture. Often this is more a manifestation of overaction than contracture, and may not be detectable by forced ductions.[10] Then recess the ipsilateral superior rectus a small amount along with the ipsilateral inferior oblique. Small superior rectus recessions are indicated to avoid crippling upgaze.

Many patients with congenital superior oblique palsy have lax superior oblique tendons.[16] The dogma is that, if a lax tendon is found, it should be tucked and, if it is not lax, a tuck is to be avoided. This is based on the belief that the primary problem is a tendon anomaly. The author feels this philosophy has never been validated clinically and may not be sound. Lax tendons are associated with atrophy of the superior oblique muscle,[17] so trying to strengthen a paralyzed superior oblique would be comparable to resecting a paralyzed and flaccid lateral rectus muscle, for which a transposition of the vertical rectus muscles would be a better choice. Tucking a non-lax superior oblique would be akin to resecting a mildly paretic lateral rectus, which is often successful. Perhaps the wisest approach is to tuck tendons that are not lax if the incomitance pattern justifies it, but do a small tuck.



Fig. 81.4 Three-step test for left superior oblique palsy. This girl has a left hypertropia that increases on right gaze and left head tilt, meeting the three-step test criteria for a left superior oblique palsy. There is overaction of the left inferior oblique muscle and mild underaction of the left superior oblique muscle.

Fourth nerve palsy, particularly if acquired, is often bilateral. If the degree of paresis is very asymmetric, the palsy in the lesser-affected eye may not be evident on routine testing, and only becomes apparent after surgery is performed on the more paretic eye. This is called a bilateral masked superior oblique palsy. Diagnostic signs of a bilateral problem include a large "V" pattern, more than 10 degrees of excyclotropia, bilateral objective fundus torsion, a relatively small Bielschowsky head tilt difference, and reversal of the hypertropia in any field of gaze (particularly the contralateral superior or inferior oblique field) or on forced head tilt.[18] This is one of the reasons that proper surgical planning necessitates measuring in all nine diagnostic fields of gaze plus on head tilt right and left. If there are findings that suggest a bilateral masked palsy, the author does bilateral surgery even without reversal of the hypertropia in the routinely measured gaze fields. Surgery depends on the specific pattern of incomitance, but usually involves bilateral oblique muscle surgery. This may be bilateral but asymmetric inferior oblique recessions, a Harada-Ito procedure in one eye, and a superior oblique tuck in the other, or symmetric oblique surgery to treat torsion and a vertical rectus recession to treat primary position hypertropia.

Inferior oblique palsy

Inferior oblique palsy is relatively rare and can be treated with ipsilateral superior oblique weakening. It must be differentiated from Brown syndrome, which has a similar appearance on versions in the inferior oblique field. A diagnostic criterion is an "A" pattern, which is typically present with inferior oblique palsy, whereas a "V" pattern is typical of Brown syndrome (Fig. 81.5).

Vertical rectus palsy

Vertical rectus palsy is usually treated with recession of the antagonist vertical rectus if mild, the same combined with a resection of the paretic muscle if moderate, or a transposition procedure of the horizontal rectus muscles if severe. In mild

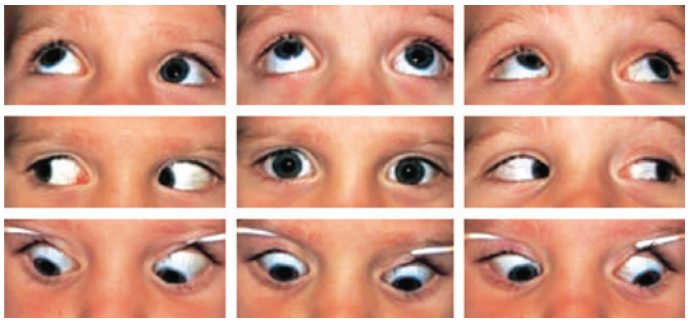


Fig. 81.5 Brown syndrome. This boy has marked limitation of elevation of the left eye in adduction. Although the appearance in that gaze field alone suggests a left inferior oblique palsy, there is a "V" pattern as opposed to an "A" pattern suggesting Brown syndrome.

cases, recession of the same vertical rectus muscle in the other eye to match the deficit can give good results. The head tilt test is inconsistent with vertical rectus palsy.[4]

Dissociated vertical divergence

DVD is a marker for early-onset strabismus, but it is unusual at birth. Most commonly it appears after 1 year of age, and may not be evident until after surgery for IET. It may present as a subtle deviation, which may be small and only present on cover testing. Or it may be associated with a large and frequently manifest vertical deviation that can be as cosmetically disfiguring as the initial horizontal strabismus. Although DVD is a bilateral disease, it may appear to be unilateral because the preferred eye only has a latent deviation. This is particularly the case with amblyopia: fixation always occurs with the non-amblyopic eye. However, this can also occur in patients with equal vision.

DVD is characterized by a slow upward drifting of the eye; the eye extorts when it elevates, simultaneously, intorsion occurs in the fixing eye. It is typically associated with latent or manifest latent nystagmus. The hallmark is that, when the fixing eye is covered and the patient regains fixation with the deviating eye, the previously fixing eye does not have a commensurate hypotropia. If the DVD is significant in both eyes, the formerly fixing eye will elevate under cover. Thus, it appears that DVD is characterized by an uncoupling of Hering's Law. Often DVD appears worse in adduction, simulating inferior oblique overaction. Differentiating the two conditions includes performing a cover test on side gaze to see whether there is hypotropia of the abducting eye when it is occluded. With DVD the abducting eye will not show a hypotropia and may be hypertropic if the DVD is bilateral (Fig. 81.6; Video 81.1). Because of the nature of DVD, and that there is not an equal hypotropia of the contralateral eye, one cannot neutralize this deviation with the alternate prism and cover test. To accurately measure DVD, one must use the prism under cover test. This test is carried out by first estimating the size of the DVD. Then a prism equal to the estimated size of the deviation is placed base down in front of the affected eye, while the eye is dissociated behind a cover. The cover should then be rapidly switched to the other eye. If the estimated amount of prism was correct, no movement of the eye being tested should occur. If there is still a downward movement, the test should be repeated with a larger prism; if an upward movement occurs, it should be repeated with a smaller prism. However, many patients with DVD have a marked redress movement and an accurate endpoint cannot be obtained, even with the prism under cover test. In that case, the deviation must be estimated by determining whether the upward and downward components of the redress movement were of equal magnitude, or by using a light reflex test.[19]

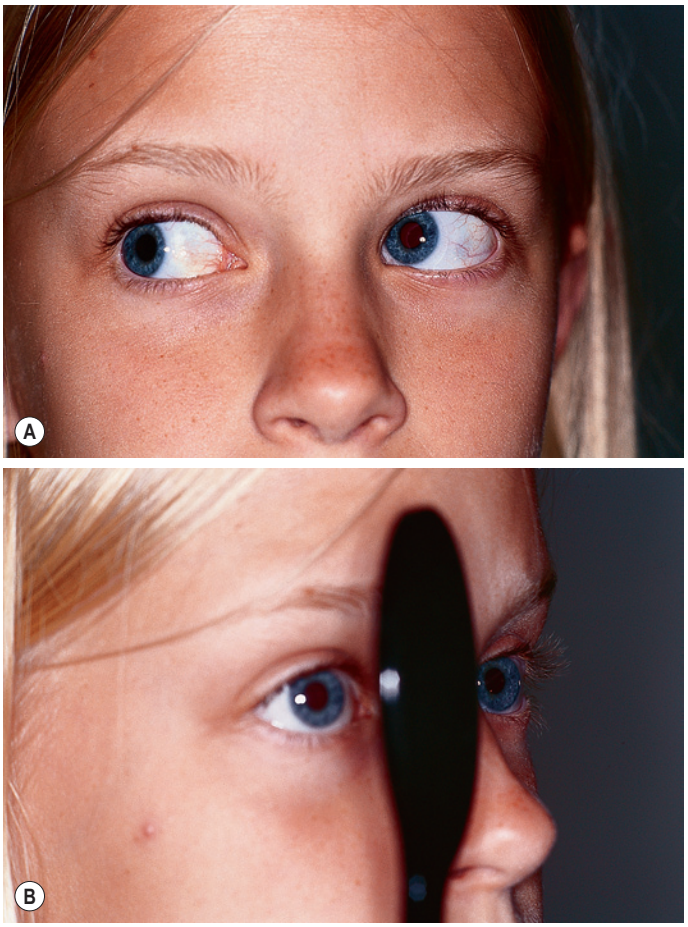


Fig. 81.6 Dissociated vertical divergence (DVD) mimicking inferior oblique overaction. (A) This girl shows overelevation of the left eye in adduction, which is consistent with left inferior oblique overaction. (B) Under cover, however, a hypertropia is seen in the right eye, confirming that this child, in fact, has DVD.

Approximately one-third of patients with DVD have a spontaneous abnormal head posture.[19] Most patients with DVD show an increase in the size of the DVD on contralateral head tilt (e.g. right DVD increases with left head tilt); however, some show the converse (Fig. 81.7).

Similar, but somewhat different, theories by Guyton and Brodsky have shed light on the etiology and pathophysiology of DVD. They suggest that DVD is a result of damping of nystagmus by complex interactions of the cyclovertical muscles,[20] possibly via a vestigial remnant of the dorsal light reflex of lower animals.[21]

Surgical management of DVD depends on whether inferior oblique overaction is present, the size of the deviation, and if it is bilateral or unilateral. If it is unilaterally manifest, the possibility that the patient may shift fixation after surgery should be taken into account. If amblyopia is present, a shift in fixation is unlikely. If inferior oblique overaction is present

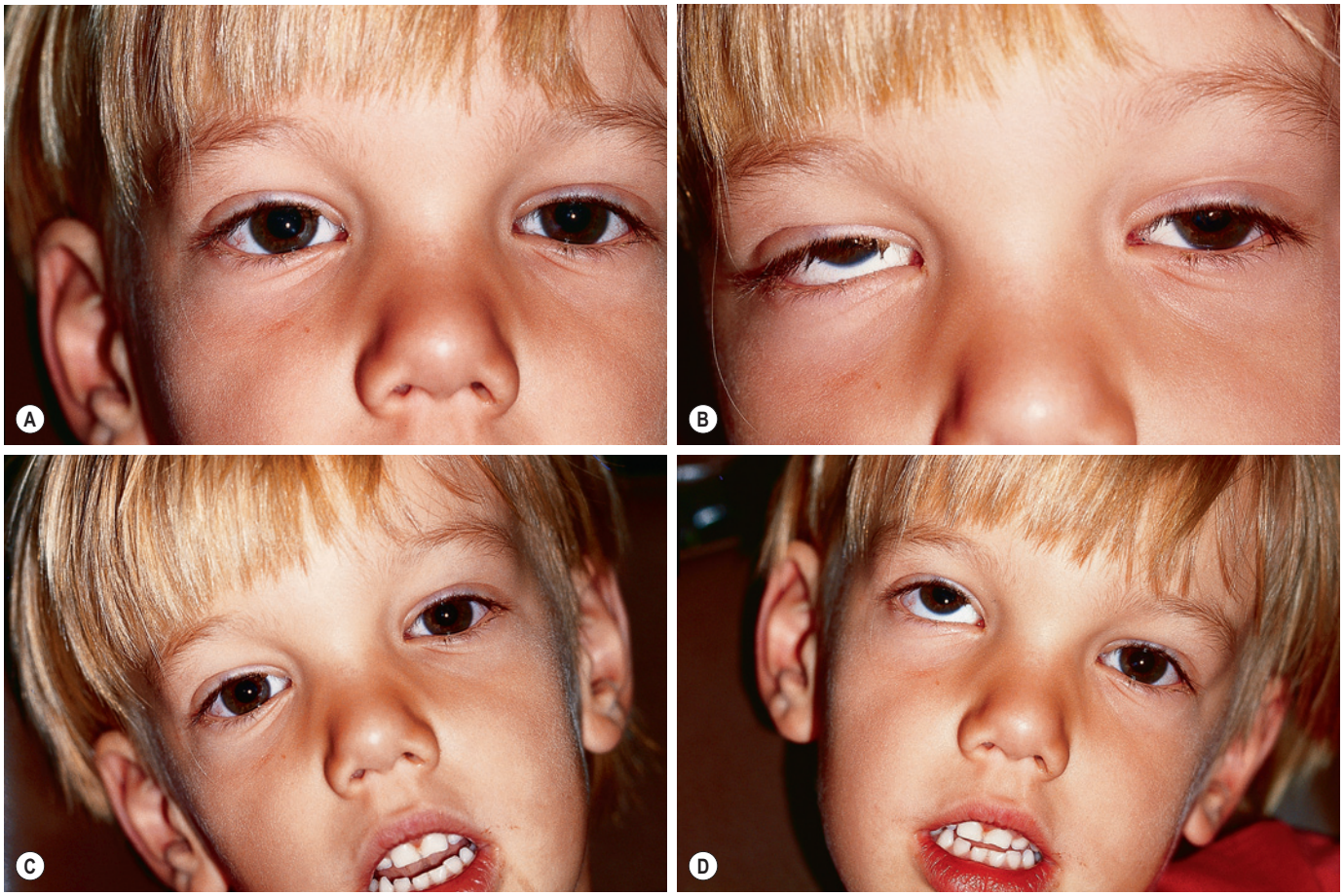


Fig. 81.7 Head tilt test with dissociated vertical divergence (DVD).This boy has the typical head tilt response for DVD. (A) His DVD is latent and his eyes are often well aligned. (B) A right DVD is intermittently manifest. (C) The deviation is absent on head tilt to the right. (D) The deviation increases on head tilt to the left, which is common for a right DVD.

concurrently with DVD, this author prefers to anteriorly transpose the inferior oblique muscle to a point level with the inferior rectus insertion.[22] Weakening the inferior oblique without anterior transposition may not adequately treat DVD. If anterior transposition of the inferior oblique is planned, it should be done bilaterally or there will be a resultant hypotropia of the operated eye in upgaze. It should not be performed if the inferior obliques are not overacting, or if there is substantial superior oblique overaction.

If DVD is significant and there is no overaction of the inferior obliques, recession of the superior rectus muscles is the treatment of choice. Even if DVD is unilaterally manifest, bilateral surgery is advisable if the dominant eye shows latent DVD under cover and if equal vision is present. Then, if unilateral surgery is performed, it is likely that the patient will shift fixation postoperatively and manifest a DVD in the previously preferred eye. For guidelines for the magnitude of superior rectus recession for DVD see Table 81.1. As is depicted in the table, with unilateral surgery (which is desirable if amblyopia is present), the amount of superior rectus recession for a given amount of DVD should be less.

Symmetric inferior rectus resections in the range of 4–7 mm can be used to treat DVD. This procedure is generally reserved for use as a secondary procedure after other treatments have failed. This magnitude of inferior rectus resection will often cause narrowing of the palpebral fissure by raising the height of the lower eyelid.

Table 81.1 Amount of superior rectus recession for DVD

Deviation (PD)	Bilateral superior rectus recession (mm)	Unilateral superior rectus recession (mm)
<10	7	5
10	8	6
15	9	7
20	10	8
25 and up	10	9

Special forms of vertical strabismus

Brown syndrome

Brown syndrome is caused by a mechanical restriction of the superior oblique tendon moving through the trochlea, which results in a restriction of elevation in adduction. On version

testing, it mimics an inferior oblique palsy, except that a "V" pattern is present; an "A" pattern is expected with inferior oblique palsy. Most cases of Brown syndrome are congenital, but can be acquired due to either trauma or inflammation. If an inflammatory etiology is suspected, a systemic work-up for autoimmune disease is appropriate. Inflammatory Brown syndrome may resolve spontaneously. If not, it can be treated with steroid injection in the region of the trochlea. Systemic anti-inflammatory medications may play a role, but this author has found the results disappointing.

Some cases of congenital Brown syndrome resolve spontaneously. Treatment may be indicated if a child needs to assume an unacceptable head posture for fusion. At surgery, forced ductions with attention to elevation in adduction should be performed. They will be positive if Brown syndrome is present and negative if there is an inferior oblique palsy. The surgical treatment of Brown syndrome consists of one of many procedures to weaken or lengthen the superior oblique tendon.

Duane syndrome (see Chapter 83)

Patients with Duane syndrome frequently have an upshoot or downshoot of the affected eye on adduction (Fig. 81.8). Although this appears to be caused by overaction of an oblique muscle, it is in fact caused by co-contraction of the lateral rectus muscle. This causes the lateral rectus to slip above or below the midline on adduction, creating the vertical deviation. Treatment in the form of oblique muscle weakening is usually not helpful. Successful treatment involves releasing the lateral rectus muscle in the form of either recession or Y splitting with recession. In severe cases, it should be disabled by suturing it to the lateral orbital periosteum.

Restrictive strabismus

Common forms of restrictions that cause vertical strabismus include orbital floor fracture, primary ocular muscle fibrosis, Graves orbitopathy, myotoxicity from local anesthetic, and scarring after prior strabismus surgery. In these cases, there will be a limitation of rotation of the eye in the field opposite the affected muscle. Treatment involves recession of the affected muscle and freeing of any scar tissue (Fig. 81.9).

Oblique muscle incarceration

Surgery on one of the vertical rectus muscles and/or the adjacent oblique muscle may result in the oblique muscle becoming incarcerated in the insertion of the rectus muscle. When this occurs with the superior oblique tendon, a restrictive hypertropia and incyclotropia results[23] (Fig. 81.10).

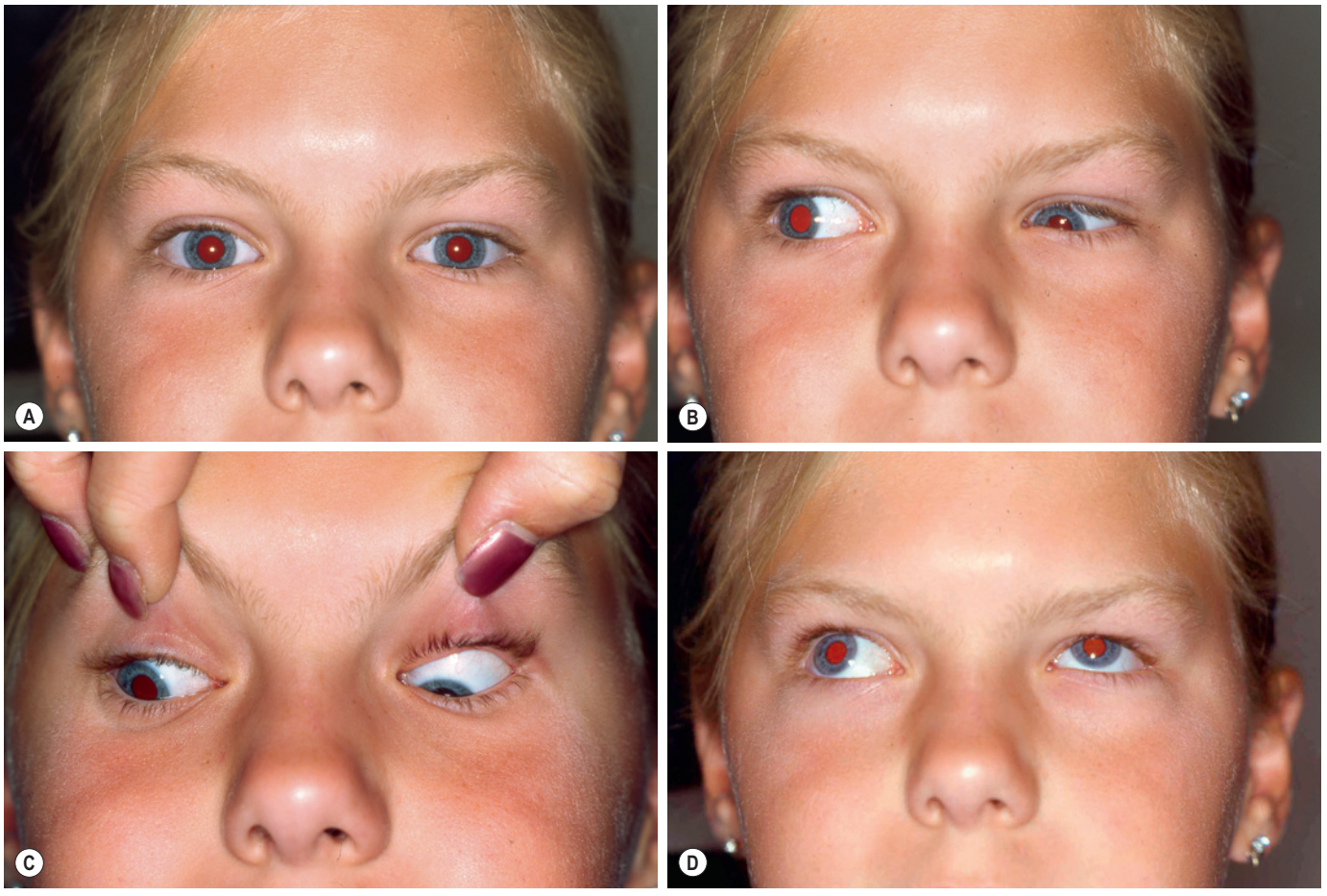


Fig. 81.8 Exotropic Duane syndrome with upshoot. (A) This girl has a small left exotropia (B) associated with limited adduction in her left eye secondary to Duane syndrome. (C) There is a marked downshoot of the left eye with adduction and (D) a large upshoot of the left eye with adduction above the midline. Narrowing of the left palpebral fissure and globe retraction are seen in the left eye on adduction. Although this resembles oblique muscle overaction, weakening of the apparent overacting oblique muscle is ineffective but weakening the lateral rectus may be effective.

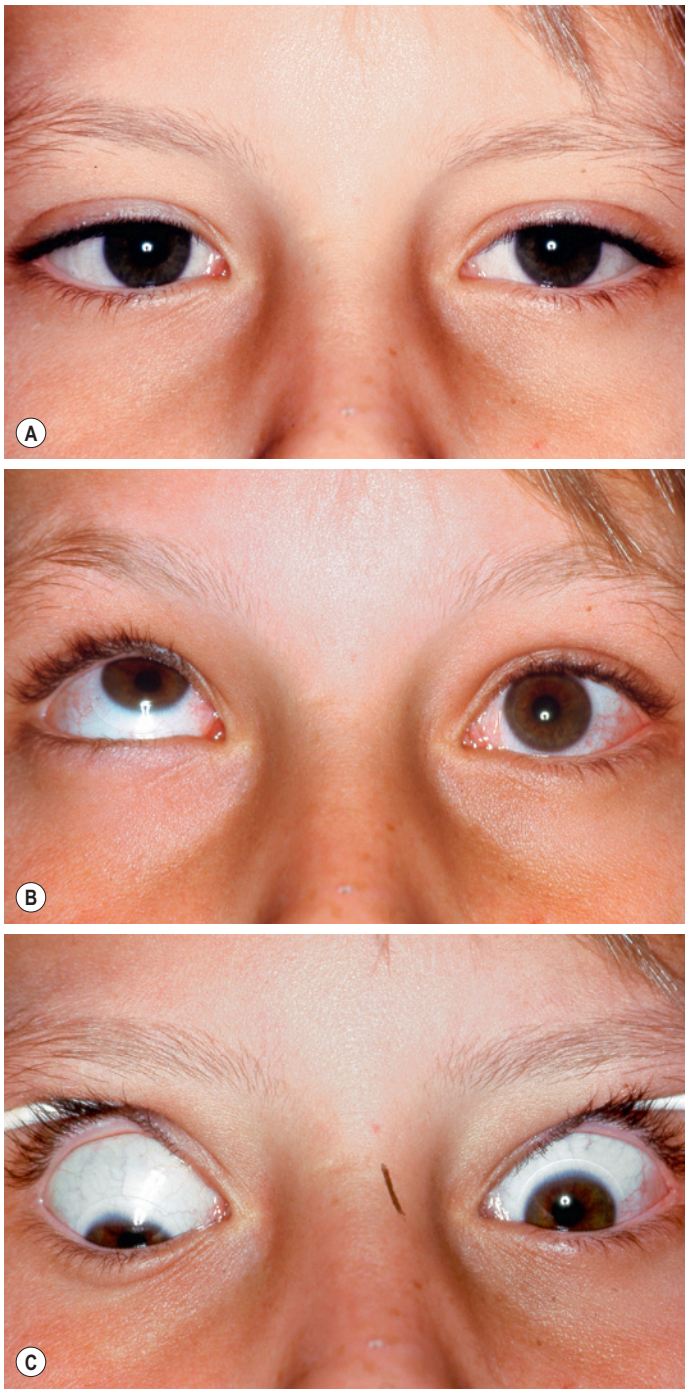


Fig. 81.9 Orbital floor fracture. This boy was struck in his left eye with a baseball, resulting in a large posterior orbital floor fracture. (A) He is straight in the primary position. (B) There is limitation of elevation of the left eye with positive forced ductions, and (C) a pseudo-paresis of the left inferior rectus resulting in a limitation of depression.

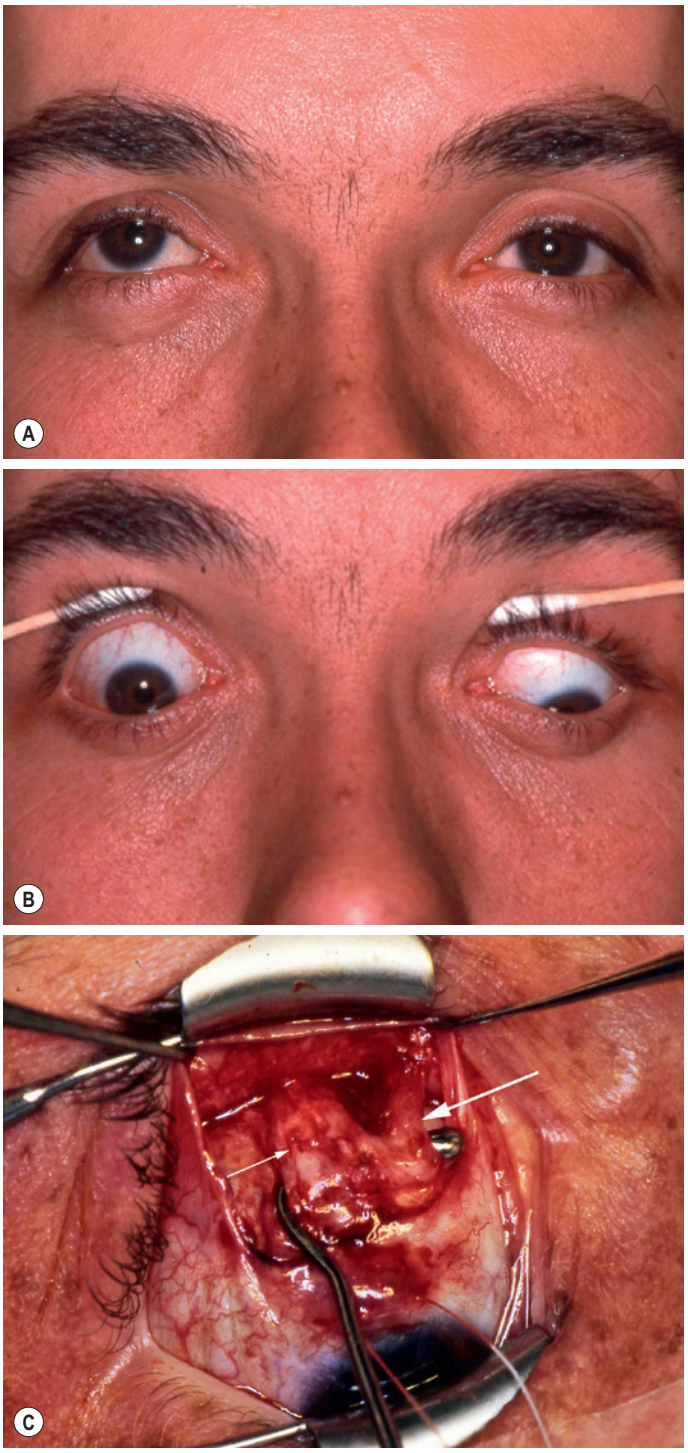
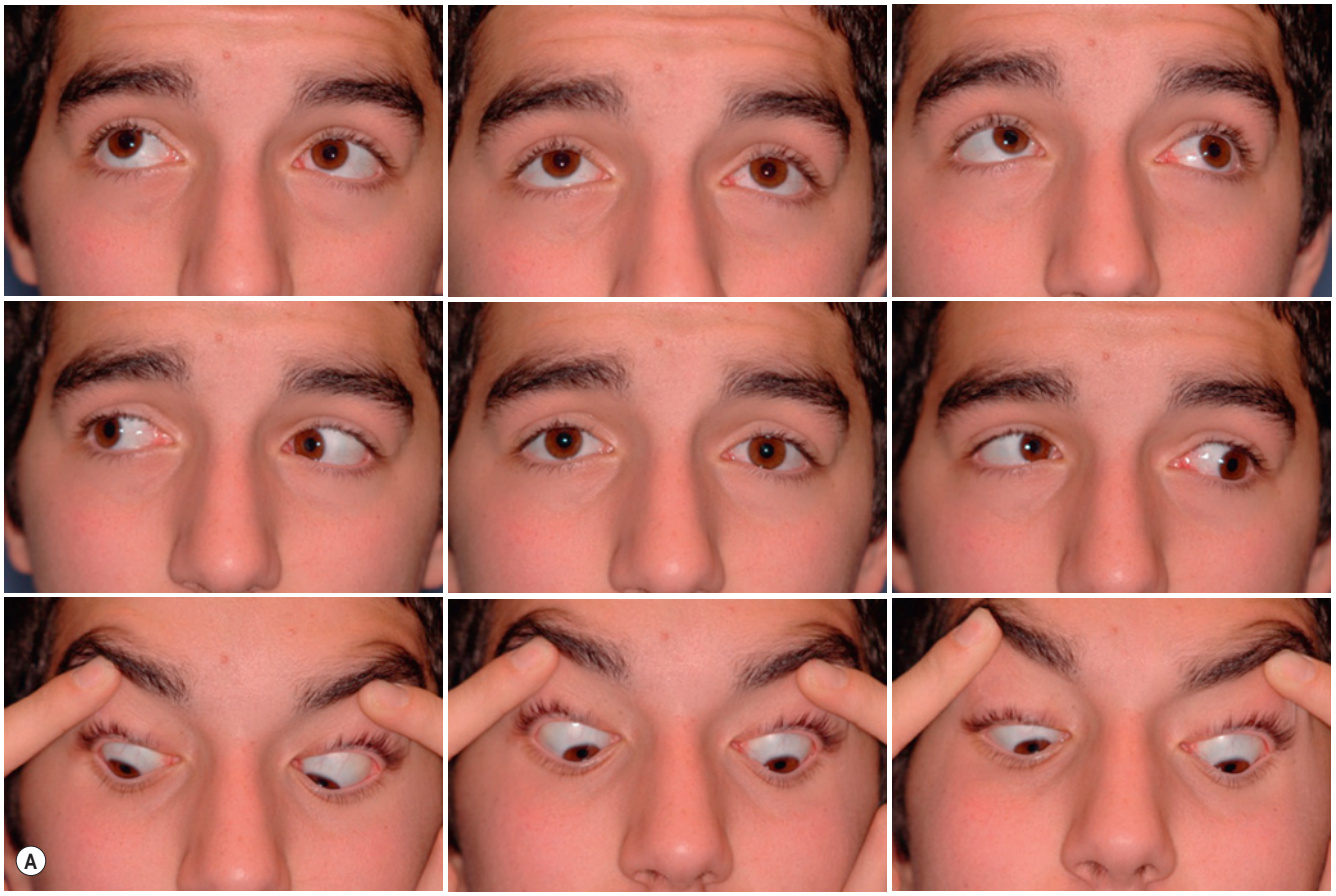


Fig. 81.10 Superior oblique incarceration. (A) This man developed a restrictive right hypertropia and large right incyclotropia after undergoing a small right superior rectus muscle resection. (B) There is limitation of depression of the right eye. (C) At subsequent surgery, the right superior oblique tendon (large arrow) was found scarred into the right superior rectus insertion (small arrow) causing the restriction.

With the inferior oblique muscle, a restrictive hypotropia is found.[24] Treatment can be difficult and consists of freeing the incarcerated oblique muscle or tendon, and often recessing the adjacent vertical rectus muscle.

Altered rectus muscle path

Alteration of the normal path of the rectus muscles due to pulley heterotopia or pulley laxity may result in a vertical strabismus that may mimic other more common forms of vertical strabismus.[25] Inferior slippage of the lateral rectus muscle can mimic Brown syndrome, and high-quality imaging is needed to make the diagnosis. It can be treated by using posterior fixation sutures to reposition the muscle in the proper position (Fig. 81.11). The 14-year-old boy in Video 81.4



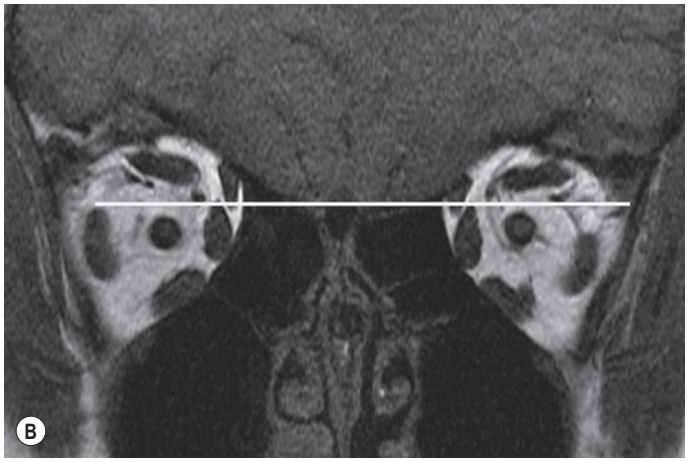


Fig. 81.11 Pulley heterotopia. (A) This 14-year-old boy has a left hypotropia with diplopia to the right and left of the primary position. There is a downshoot of the left eye on adduction and a mild limitation of elevation in adduction. (B) Orbital imaging shows inferior displacement of the left lateral rectus muscle.

has diplopia to the left and right of the primary position. His left eye has a downshoot on abduction and is mildly limited in adduction. Orbital imaging shows the left lateral rectus is to be slipped inferiorly.

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Part 4
Vertical, "Pattern" Strabismus and Abnormal Head Postures

"A," "V," and other pattern strabismus

Burton J Kushner

Chapter contents

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OCCURRENCE
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See online for supporting video for this chapter.

Overview and definitions

The terms "A" and "V" pattern describe horizontal strabismus that is vertically incomitant. It is characterized by a substantial difference in the horizontal deviation between the midline upgaze and downgaze positions. A patient with a "V" pattern is more esotropic or less exotropic in downgaze than upgaze (Fig. 82.1); an "A" pattern is characterized by the converse (Fig. 82.2). By convention, the difference between upgaze and downgaze must be 15 prism diopters (PD) or greater to diagnose a clinically significant "V" pattern, and 10 PD to diagnose an "A" pattern. Less commonly, there are variations of pattern strabismus in which there is minimal change from downgaze to the primary position, but the eyes diverge in upgaze resulting in a "Y" pattern. The girl shown in Figure 82.3 and Video 82.1 was first diagnosed with this motility pattern at 3 years of age. This author has continued to care for her for 37 years and her motility is unchanged. She is symptom free without treatment.

Converse to a "Y" pattern, the main exo shift may be between the primary position and downgaze to form a "λ" (lambda) pattern.

History

Duane first described a "V" pattern in 1897 in a patient with bilateral superior oblique palsy.[1] Subsequently, little attention was given to the importance of measuring the angle of strabismus in upgaze and downgaze until Urrets-Zavalia described vertically incomitant horizontal strabismus in 1948.[2,3] Urist brought the "A" and "V" patterns into the English literature in 1951.[4]

Occurrence

Estimates of patients with strabismus having an "A" or "V" pattern range from 12% to 50%.[5–8] The wide range is because ethnic and systemic factors influence the incidence of pattern strabismus and the make-up of each series. In one series of 421 patients with "A" or "V" patterns, 58% had an onset of strabismus prior to 12 months of age.[6] "A" or "V" pattern strabismus occurs much more frequently in congenital or paralytic strabismus than in non-paralytic acquired strabismus. Brown syndrome (see Chapter 81, Fig. 81.5) characteristically has a "V" pattern, differentiating it from inferior oblique palsy, in which an "A" pattern is found. Duane syndrome often presents with a "V" or "Y" pattern, and less commonly an "A" or "λ" pattern (see Chapter 81, Fig. 81.8). "A" patterns with overdepression in adduction are frequently seen in patients with spina bifida and/or hydrocephalus with a 31% incidence having been reported.[9,10] Frontal bossing in children with hydrocephalus (see Chapter 59) may result in anterior displacement of the trochlea, mechanically enhancing the vertical vector of the superior oblique tendon with strengthening of the depressing action of the superior oblique, and this may be the cause of. However, the exact mechanism that causes "A" patterns to occur with hydrocephalus is unclear.

Etiology

There are differing theories as to the etiology of "A" and "V" patterns, in part because different mechanisms may be responsible in different patients.

Oblique muscle dysfunction

The most popular theory, suggested by Knapp in 1959,[11] attributes most cases of "A" and "V" pattern to oblique muscle dysfunction. Abduction is a tertiary action of the oblique muscles. Thus, if the inferior obliques are overacting and



Fig. 82.1 "V" pattern esotropia. This girl has a "V" pattern esotropia with associated inferior oblique muscle overaction and superior oblique muscle underaction.

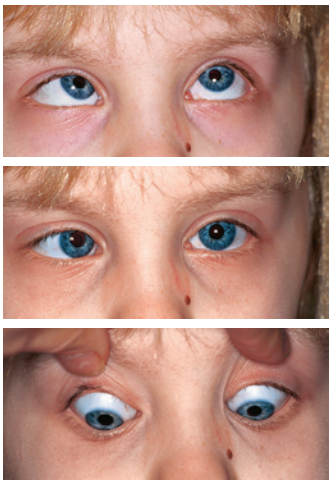


Fig. 82.2 "A" pattern esotropia. This girl has an "A" pattern esotropia showing an increase in the deviation in upgaze and orthophoria in downgaze.

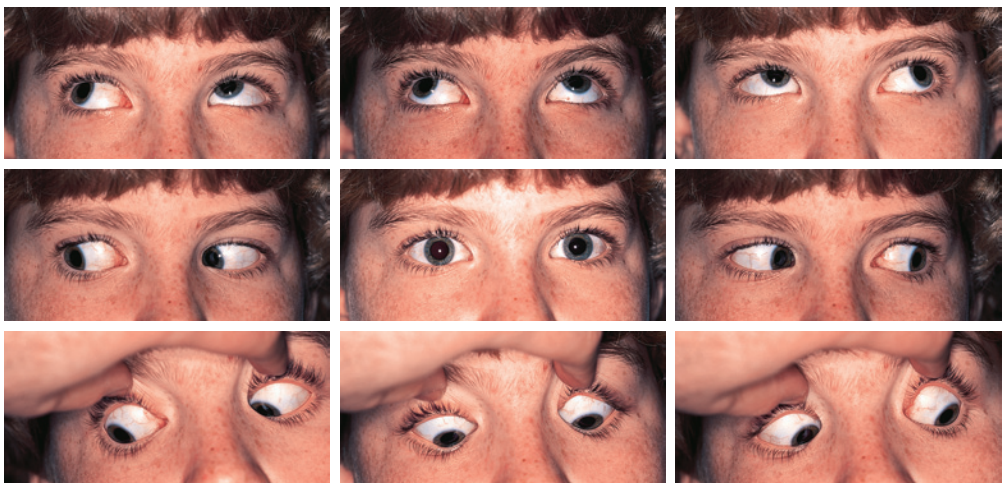


Fig. 82.3 "Y" pattern exotropia. This girl has a "Y" pattern exotropia with pseudo inferior oblique overaction. She is orthophoric in the primary position, horizontal sidegaze, and all downgaze fields. In all upgaze fields she has a large exotropia.

the antagonist superior obliques are underacting, one would expect a relative convergence in downgaze and divergence in upgaze, resulting in a "V" pattern. The converse occurs if the superior obliques are overacting and the inferior obliques are underacting, resulting in an "A" pattern. One typically finds the oblique muscles to be dysfunctional in this manner in most patients with pattern strabismus. This clinical observation, combined with the theoretical construct, has led to the justified implication of oblique muscle dysfunction as a cause of many "A" and "V" patterns.

Torsion as a cause of "A" and "V" patterns

The torsion that accompanies oblique muscle dysfunction should theoretically cause or contribute to "A" and "V" patterns.[12] Patients with a "V" pattern typically have excyclotropia, which is most likely secondary to the accompanying inferior oblique overaction. This excyclotropia results in rotation of the rectus muscles (Fig. 82.4). The superior rectus muscles would become partial abductors and the inferior rectus muscles partial adductors, which will contribute to a "V" pattern. The medial

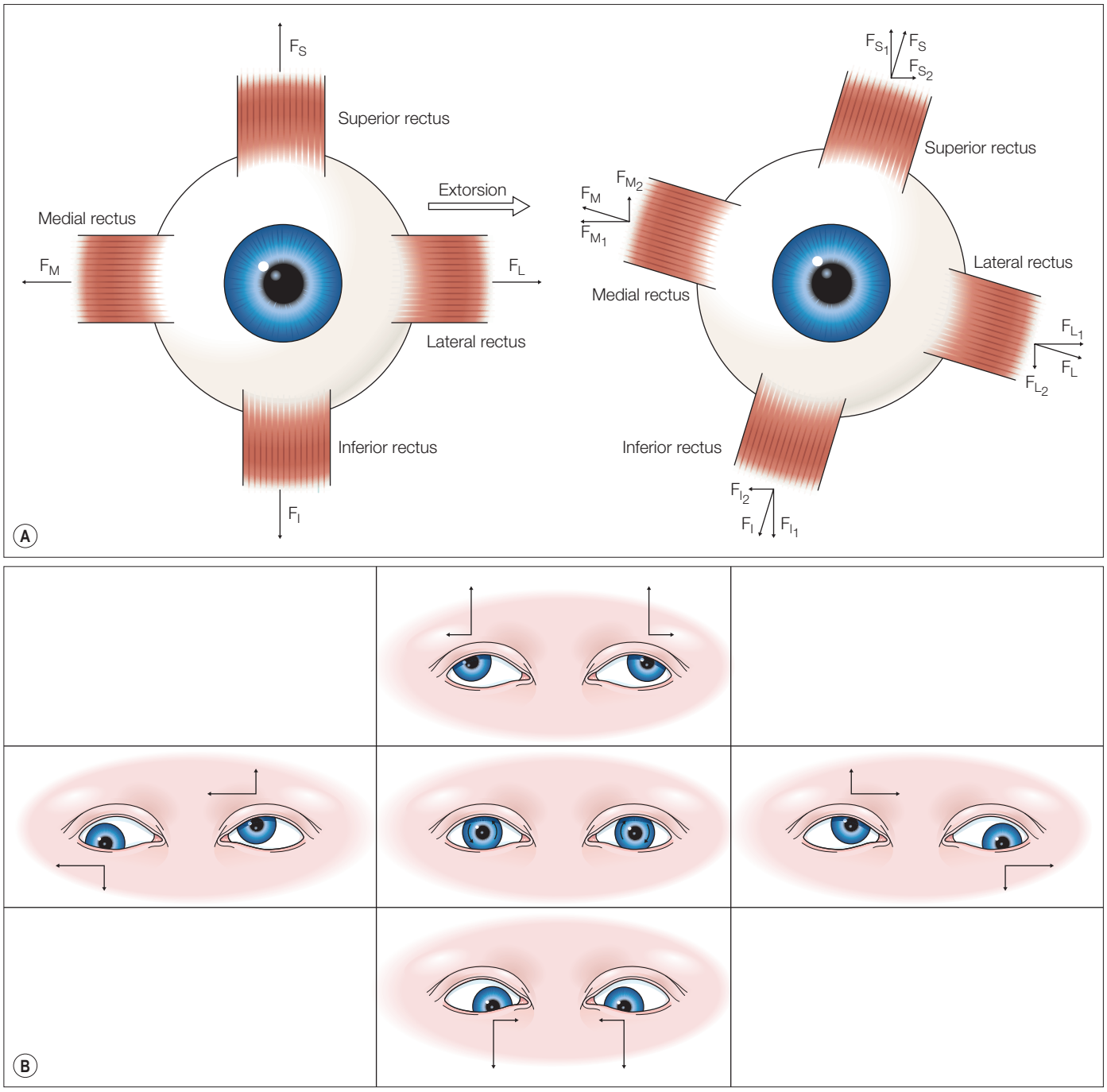


Fig. 82.4 (A) Effect of torsion on individual muscle function. An excyclorotation of the left eye will result in a clockwise rotation of the insertion of the muscles. This will create a vector for elevation for the medial rectus muscle, abduction for the superior rectus, depression for the lateral rectus, and adduction for the inferior rectus. (B) Effect of torsion on motility pattern. If the torsional changes that are depicted in (A) occurred in both eyes, the new force vectors would cause divergence in upgaze and convergence in downgaze. In addition, there would be an elevation of the adducting eye and depression of the abducting eye. Thus, these torsional changes that occurred as a result of extorsion contribute to both the "V" pattern and the elevation seen in adduction.

rectus muscles also have elevating force vectors and the lateral rectus muscles depressing force vectors, contributing to the elevation seen in adduction with overacting inferior obliques. I believe, however, that torsion is only a minor contributing cause of pattern strabismus rather than the main cause. Several observations support this belief.[13] First, the rise or fall of an eye with oblique muscle overaction, as it moves into adduction, is curvilinear. The boy seen in Video 82.2 has primary inferior oblique overaction. The rise of each eye on adduction appears to increase exponentially, rather than linearly. If the rise or fall were primarily caused by the change in force vectors of the rectus muscles as seen in Figure 82.4, one would expect a linear trajectory. Secondly, surgery like the Harada–Ito procedure that mainly corrects torsion has a negligible effect on the overelevation in adduction in patients with fourth cranial nerve palsy, even when it eliminates the excyclotropia. In addition, it has been shown that objective extorsion may precede the development of overelevation in adduction and a "V" pattern

in patients with infantile esotropia (see Chapter 76), by as much as several years. If the torsion caused the overelevation in adduction and the pattern, they should occur concurrently. Finally, surgery in the form of vertical transposition of the horizontal rectus muscles that successfully eliminates an "A" or "V" pattern will predictably worsen the underlying torsion (see section "Horizontal transposition of vertical rectus muscles" below).

Orbital structural anomalies

Orbital anomalies are often associated with "A" and "V" patterns. There is a frequent occurrence of "A" pattern esotropia accompanied by inferior oblique underaction in patients with upslanting palpebral fissures and an association of "V" pattern exotropia with inferior oblique muscle overaction.[14] In patients with downslanting palpebral fissures the opposite occurs. There is also a very high incidence of "A" and "V" patterns in patients with craniofacial syndromes[15,16] (Fig. 82.5). Clark et al. and Demer have attributed some cases of "A" and "V" patterns to orbital pulley heterotopia or laxity.[17,18] This is an evolving concept with no good data as to the frequency that pulley issues are causative of pattern strabismus.

Iatrogenic

An "A" or "V" pattern may develop as a result of prior strabismus surgery. This can result from an overcorrection from prior treatment of "A" or "V pattern strabismus. On occasion, a marked "Y" pattern can occur in the form of the anti-elevation syndrome after anterior transposition of the inferior oblique muscles[19] (Fig. 82.6). The girl in Video 82.3 had undergone

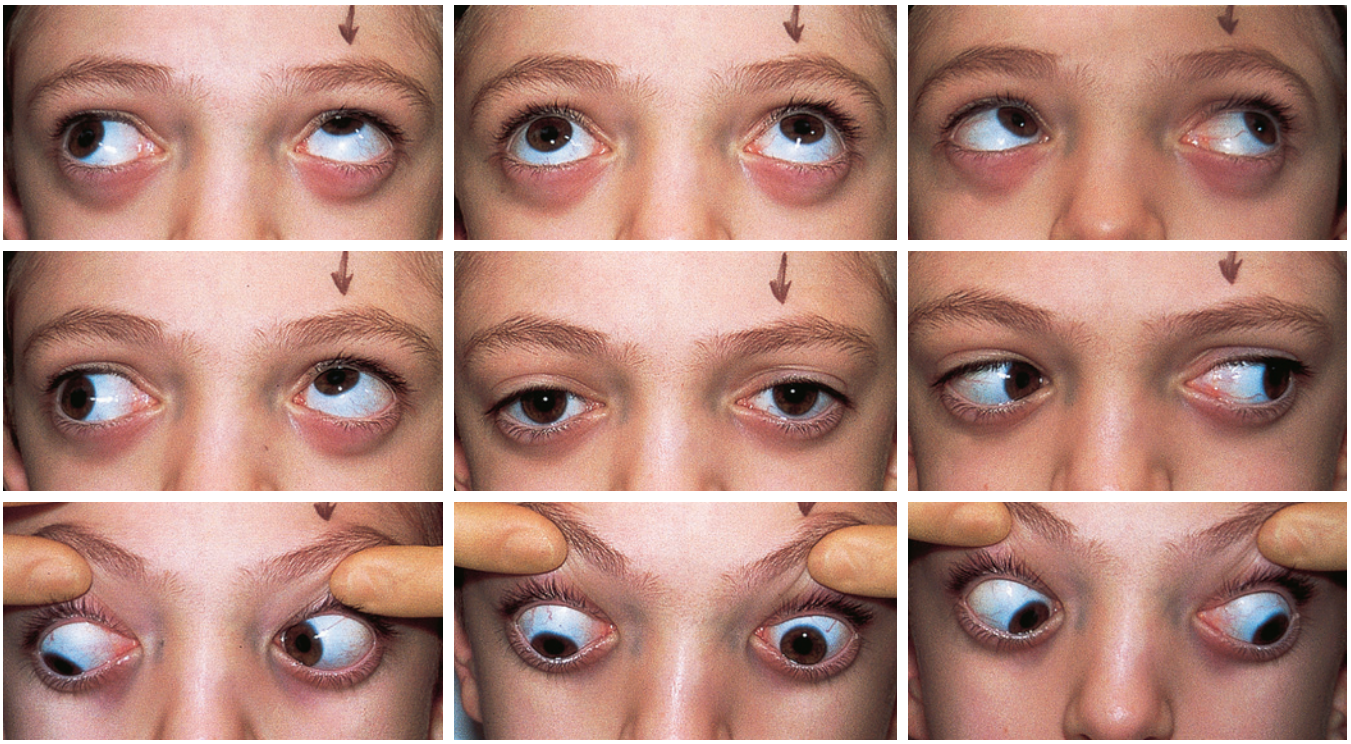


Fig. 82.5 Craniofacial anomaly with associated pattern: Crouzon syndrome. This boy shows the classic "V" pattern seen in Crouzon syndrome (see Chapter 28). There is overelevation and underdepression of each eye in adduction. *(Photo courtesy of Ken K. Nischal, FRCOphth.)*



Fig. 82.6 The anti-elevation syndrome. This boy has a large "V" pattern after previously undergoing inferior oblique anterior transposition bilaterally to treat dissociated vertical divergence. What looks like residual inferior oblique overaction is actually a result of fixation duress to the abducting eye on attempted elevation, due to the anti-elevating property of the transposed inferior oblique muscle. This drives the adducting eye superiorly and mimics contralateral inferior oblique overaction.

bilateral anterior transpositions of the inferior oblique muscles with both muscles placed 2 mm anterior to the inferior rectus muscle insertions. The overelevation she now shows on attempted elevation in adduction is due to fixation duress secondary to a limitation of elevation of the abducted eye. Also, an "A" pattern frequently occurs following large bilateral recessions of the inferior rectus muscles, commonly in thyroid eye disease. This occurs from a loss of the adducting effect of the inferior rectus muscles in downgaze secondary to surgical weakening, and by an increase in innervation to the yoke superior oblique muscles.[20]

Horizontal rectus muscles

Urist felt overaction or underaction of the horizontal rectus muscles were responsible for "A" and "V" patterns[4,5] and that the medial rectus muscles were more active in downgaze and the lateral rectus muscles were more active in upgaze. His surgical recommendations involved weakening the offending muscles. Although this theory is less compelling than others, it may explain the occurrence of some cases of "A" or "V" pattern where there is no other apparent cause. It can also explain the small decrease in "V" pattern observed after bilateral medial rectus recessions. Recent work by Demer and coworkers has described distinct and separate innervation to the superior and inferior compartments of the horizontal rectus muscles.[21,22,23] In theory, this could give rise to "A" or "V" patterns if the superior and inferior compartments are recruited separately on upgaze or downgaze. At this point, the role of this compartmental innervation on "A" or "V" patterns is not clear and is still evolving.

Other less popular theories

Brown felt that "A" and "V" patterns were caused by a weakness of the inferior and superior oblique muscles respectively, resulting in apparent overaction of the yoke oblique muscles due to fixation "duress."[24] This theory is not widely accepted.

Gobin suggested that the primary event that causes a "V" pattern is an abnormal sagittalization of the inferior oblique muscles, which decreases its vector for torsion, resulting in an incyclotropia. Subsequently, to correct this abnormal incyclotropia, there is increased innervation to the excyclorotary muscles, resulting in inferior oblique overaction.[25] In the author's opinion, this theory is inconsistent with the clinical findings of torsion in patients with pattern strabismus. According to the sagittalization theory, a patient with a "V" pattern should have no fundus torsion as the inferior oblique overaction served the purpose of eliminating an abnormal intorsion. In fact, these patients typically have objective extorsion.

Presentation

The manner of presentation of a patient with an "A" or "V" pattern depends on the underlying strabismus and the size of the deviation. If there is a sufficiently large deviation in the primary position such that, despite the presence of an "A" or "V" pattern, there is no head position in which fusion is possible, the pattern may not affect the presentation. If the deviation is small enough that fusion is possible in upgaze or downgaze, the patient may assume a chin-down or chin-up head posture in order to fuse. Some adults with an "A" or "V" pattern may not become symptomatic until they become presbyopic. Their symptoms may not become manifest until they need to get their eyes into downgaze to read through a bifocal segment. Prior to becoming presbyopic, they may have unconsciously held reading material closer to the primary position. Similarly, some presbyopic patients with strabismus that is only significant in downgaze may become symptomatic if they switch from a flat-top to a progressive bifocal, which has a wide transition zone that requires the eyes to move further into downgaze in order to permit vision through the prescribed add.

Examination

Motor exam

The diagnosis of an "A" or "V" pattern must be made by measuring with the prism and alternate cover test 25–30° above and below the midline. Testing should be done at 6 m to eliminate the near reflex. You can be misled by assessing the size of the deviation on version testing using a light reflex, as this will not bring out the latent deviation. Particularly in patients with intermittent exotropia, the deviation may be controlled in the primary position; however, fusion may break down when the eyes are rotated into extreme fields of gaze giving the false appearance of a "Y," "λ," or "X" pattern. Testing should be done with full optical correction in place *and* while fixation is maintained on an accommodative target: if not, a pseudo "A" or "V" pattern may be observed.

Special care should be taken to assess any relative overelevation or overdepression in adduction, and the presence or absence of fundus torsion should be assessed with indirect ophthalmoscopy.

Sensory findings

Sensory findings depend on whether the patient is orthotropic in any field of gaze. Patients who are well aligned in the primary position may have surprisingly good fusion. If the patient is tropic in all fields of gaze, suppression and varying depths of anomalous retinal correspondence (ARC) may be found. In many patients with ARC and pattern strabismus, the angle of anomaly varies with the angle of deviation, thus resulting in ARC that is harmonious in all fields of gaze. This speaks to the fluidity of ARC.

Surgical treatment of "A" and "V" patterns

If a pattern needs to be eliminated, the treatment is surgery. However, first you need to determine whether the pattern itself needs to be addressed. If the patient has a significant chin-up or chin-down head posture in order to fuse, surgery is appropriate. A continuous change in the size of the deviation that varies with change in gaze direction is destabilizing for binocular fusion. Thus if an "A" or "V" pattern is clinically significant, it should be addressed in any child undergoing horizontal strabismus surgery, in whom there is any likelihood of some degree of binocularity being gained. This is probably the case in all children unless there is dense amblyopia. You

should also pay attention to the location of the pattern. The primary position and downgaze are the two most important fields of gaze. You might ignore the pattern completely in an asymptomatic patient with a "Y" pattern who only manifests a deviation in upgaze. This is particularly true if treating a pattern might be at the expense of the good alignment in the primary position and downgaze. If the strabismus is cosmetically unacceptable because of an "A" or "V" pattern, surgery for the pattern is appropriate. For most adults undergoing surgery for other reasons, a pattern should be treated if also present. Exceptions include patients in whom treating the pattern might adversely affect the outcome in the primary position or downgaze, and if dense amblyopia is present, one may decide to ignore the pattern.

Oblique muscle surgery

If you decide to treat a pattern in a patient in whom there is substantial oblique muscle overaction, the overacting oblique muscles should be weakened because doing so:

1. decreases the excessive abducting force in the gaze direction in which the eyes diverge (upgaze for a "V" pattern, downgaze for an "A" pattern);
2. decreases the torsion that contributes to the pattern and may be an obstacle to fusion;
3. corrects any cosmetically unacceptable upshoot or downshoot occurring in adduction.

Oblique muscle surgery should be combined with any necessary horizontal surgery, the latter based on the angle of misalignment in the primary position. No allowance is necessary for the loss of abducting force of the oblique muscles, because it is negligible in the primary position. Weakening both inferior oblique muscles will result in 15–25 PD of esotropic shift in upgaze, depending on the degree of overaction of the inferior oblique muscles; the greater the degree of overaction, the more effect is obtained. There will be little or no effect on the horizontal deviation in the primary position. Initially, there will also be no horizontal effect in downgaze from weakening the inferior oblique muscles. Later, however, there may be some increased divergence in downgaze because the previously underacting superior obliques may recover function after the antagonist inferior obliques have been weakened.

The effect of weakening the superior obliques depends on the technique. Weakening the superior obliques nasally, by any technique, has a large effect and can correct up to 40 PD of exotropia in downgaze. Weakening the superior obliques temporally is a less powerful operation, but is also less likely to cause complications. A posterior 7/8 tenectomy will cause a reduction of approximately 15–20 PD of exotropia in downgaze.[26,27] A somewhat more powerful operation than a posterior tenectomy is a complete disinsertion of the superior oblique tendon. A still greater effect can be obtained with a tenectomy of the superior oblique tendon at the insertion or a graded recession. Weakening the superior oblique has no effect on the horizontal deviation in upgaze. In the primary position, it will only correct between 0 and 3 PD of exotropia.[28,29] You need little or no adjustment in your horizontal surgery if you do bilateral superior oblique weakening.

When treating a pattern by weakening oblique muscles, it is important to perform the surgery symmetrically unless you are also trying to correct a vertical deviation in the primary position. Otherwise you will create an unwanted vertical strabismus. Complete weakening procedures of the superior obliques, such as nasal tenectomy or tendon expansion, have a powerful effect on torsion. They may lead to a disruption of fusion in a patient with bifoveal fusion and can create postoperative torsional diplopia in a fusing patient. Exercise extreme caution when weakening the superior obliques in such patients! A posterior tenectomy procedure may be adequate for addressing the pattern and is safer than doing a complete superior oblique tenectomy or tendon expansion. Alternatively, it might be prudent to address the pattern with vertical transpositions of the horizontal rectus muscles, and just decrease, rather than eliminate, the pattern, if it is large.

If oblique muscles are not overacting, they should not be weakened when treating an "A" or "V" pattern. Finally, "V" patterns with superior oblique underaction can be treated with superior oblique tucks.

Vertical transpositions of the horizontal rectus muscles

Many patients with "A" or "V" patterns can be treated effectively with transpositions of the horizontal rectus muscles, combined with the usual recession or resection you would perform based on the primary position deviation. You should not make any adjustment in your standard surgical formula because of the transposition.

Horizontal rectus transpositions are based on the principal that, when a rectus muscle is transposed, its primary action is decreased when the eye rotates into the field of gaze toward which the muscle was moved, and its action increases when the eye moves in the opposite direction (Fig. 82.7). For example, if a medial rectus muscle is transposed inferiorly, it becomes a weaker adductor when the eye is in downgaze and a greater adductor when the eye is in upgaze. This occurs because the insertion of the transposed muscle has a new relationship to the center of rotation of the globe, as seen in Figure 82.7. Thus, for treating a "V" pattern esotropia, you can recess and infraplace the medial rectus muscles, because downgaze is the field in which you want them to have less adducting action. However, when transposing rectus muscles, it is important to consider that two additional changes in their function occur simultaneously (Fig. 82.8). One effect is the creation of a force

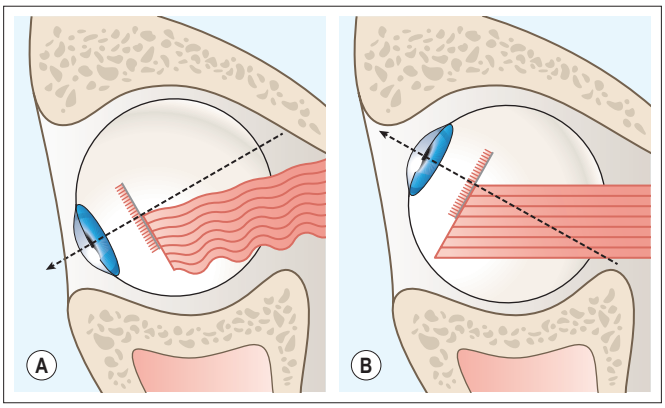


Fig. 82.7 Effect of vertical transposition of rectus muscle on its primary action. If a muscle is infraplaced, there will be more slack in the muscle when the eye is in downgaze (A) than in upgaze (B). This weakens the primary action of the muscle more in downgaze than in upgaze.

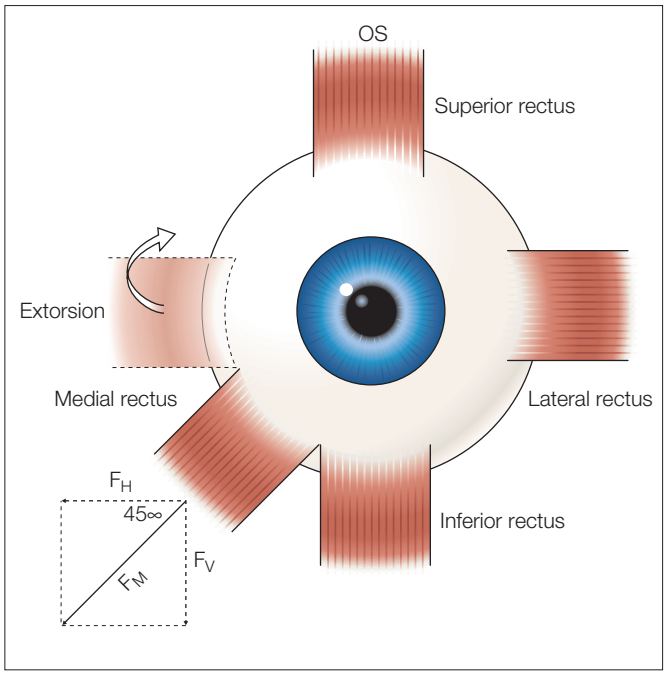


Fig. 82.8 Multiple effects of transposition of rectus muscle. If a medial rectus muscle is infraplaced, a new force vector for depression will be created. In addition, a torsional force vector will be created in the direction toward the original insertion. With infraplacement of the medial rectus, a vector for extorsion is created.

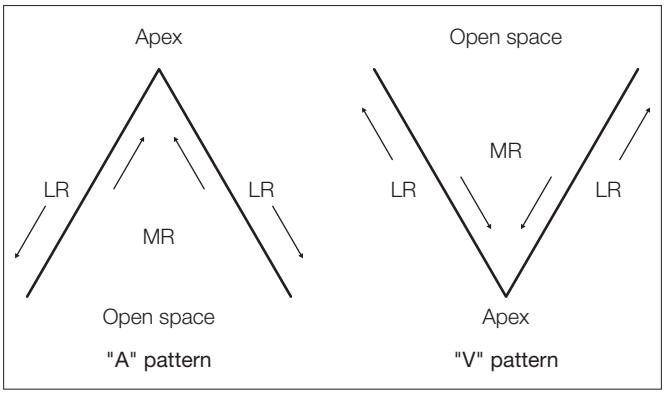


Fig. 82.9 Mnemonic for transposing horizontal rectus muscles. This diagram depicts the directions to move the horizontal rectus muscles for the treatment of an "A" pattern (left) and a "V" pattern (right). The lateral rectus muscles (LR) are always moved toward the open space and the medial rectus muscles (MR) always move toward the apex of the pattern.

vector in the direction in which the muscle is moved. Thus, if a medial rectus muscle is infraplaced, an additional force vector for depression is established. For this reason, it is important to always use this treatment symmetrically; otherwise an unwanted vertical deviation in the primary position will be induced. The exception might be those circumstances in which you want to treat a pre-existing primary position vertical deviation, in which case you might perform a unilateral transposition or a bilateral transposition that is asymmetric.

The other effect of transposition of rectus muscles relates to torsion. When a muscle is transposed, a torsional vector is created in the direction from which the muscle is moved. For example, moving a medial rectus inferiorly creates a force vector that results in extorsion as shown in Figure 82.8. Importantly, this torsional rotation is in the opposite direction to the torsional correction one desires when treating most "A" or "V" patterns. A "V" pattern esotropia is typically associated with inferior oblique overaction and excyclotropia. Transposing the medial rectus muscles inferiorly successfully treats a "V" pattern but makes excyclotropia worse.[13,30] This rarely results in adverse symptoms, probably because most patients with "A" and "V" patterns do not have bifoveal fusion, and also because the amount of torsional change is small.

A simple mnemonic for remembering the direction in which to transpose the horizontal muscles for treating pattern strabismus is presented in Figure 82.9. The medial rectus muscles are always transposed toward the apex of the pattern (down for a "V" pattern and up for an "A" pattern) and the lateral rectus muscles are always transposed toward the open space of the pattern (up for a V" pattern and down for an "A" pattern). This holds true whether the muscles are recessed or resected, and if the patient is esotropic or exotropic. Vertical transposition of the horizontal rectus muscles is generally effective for treating pattern strabismus if there is no significant oblique dysfunction, but is less effective if the obliques are significantly overacting. This is understandable in light of the fact that transpositions worsen the torsion that is already present if there is oblique dysfunction and because torsion contributes to the pattern.

The author finds that, in most cases of "A" or "V" pattern without oblique muscle dysfunction, a symmetric vertical transposition of the appropriate horizontal rectus muscles by one-half tendon width (5 mm) is effective in reducing an average of 15–20 PD of pattern. In most cases in which the pattern is more than 20 PD, there is usually significant oblique muscle dysfunction, and the author usually addresses the pattern with oblique muscle surgery. If oblique muscle surgery is not indicated in a patient with a large pattern (perhaps it has already been performed but a pattern persists), transposition of the appropriate horizontal rectus muscles three-quarters or a full tendon width can be effective for patterns that are greater than 20 PD. Also, transpositions of the horizontal rectus muscles can be combined with oblique muscle surgery. For example, a patient with a very large "V" pattern (perhaps 40 PD or more), and inferior oblique overaction plus superior oblique underaction, might benefit from bilateral medial rectus recessions with infraplacement and bilateral inferior oblique weakening.

One can also apply the principles of transposition when doing unilateral surgery in the form of a recess–resect procedure. One muscle can be raised and the other lowered. Keep in mind, however, that doing so does not create an equal balance of forces. If you raise a weakened (recessed) muscle the same amount as you lower a tightened (resected) muscle, you are creating an increased force vector in the direction the resected muscle was moved. Unwanted vertical deviations can be created from this surgical approach. Although unilateral transposition is often successful, the author prefers symmetric surgery when performing transpositions.

Horizontal transposition of vertical rectus muscles

Horizontal transposition of the vertical rectus muscles can treat "A" and "V" patterns.[31,32] The theoretical efficacy of this

Table 82.1 Summary of directions in which to transpose vertical rectus muscles

Strabismus	Transposition
"V" esotropia	IR OU temporally
"V" exotropia	SR OU nasally
"A" esotropia	SR OU temporally
"A" exotropia	IR OU nasally

IR, inferior rectus; OU, both eyes; SR, superior rectus.

approach is based on a different principle than that of vertical transposition of the horizontal rectus muscles. It is predicated on one of the effects depicted in Figure 82.8 – specifically that a force vector is created in the direction a muscle is moved. This same principle is the basis for transposition procedures to treat paralytic strabismus. Thus a "V" pattern esotropia can be treated by temporal transposition of the inferior rectus muscles along with appropriate recessions of the medial rectus muscles; typically the vertical rectus transpositions are 7 mm. A summary of the directions to transpose the vertical rectus muscles for treating "A" and "V" patterns is presented in Table 82.1.

Notably, horizontal transposition of the vertical rectus muscles may create a torsional shift that exacerbates a pre-existing cyclotropia for the reasons depicted in Figure 82.8. This is particularly relevant in treating patients with Graves orbitopathy with large bilateral inferior rectus recessions, which often results in a postoperative "A" pattern with intorsion. The author has seen such patients in whom the inferior rectus muscles were transposed nasally at the time of recession in hopes of preventing the occurrence of an "A" pattern, and an unexpectedly large and symptomatic incyclotropia was created.[30] The author prefers to combine large inferior rectus recessions with posterior tenectomy of the superior oblique tendon to prevent an "A" pattern in this setting.

Horizontal transposition of the vertical rectus muscles never gained popularity for treating routine cases of "A" or "V" pattern strabismus. In the author's opinion, this is largely because it involves operating on an additional rectus muscle in each eye, which is not necessary when oblique muscle surgery or vertical transposition of the horizontal rectus muscles can be performed.

Surgery to correct pulley abnormalities

If pulley heterotopia or laxity is the cause of an "A" pattern, surgery could be performed to stabilize or reposition the orbital pulleys. Diagnosis of pulley abnormalities requires orbital imaging.[17,18]

Insertion slanting surgical procedures

Mathematical modeling of extraocular muscle mechanics indicates that one can theoretically consider an extraocular muscle as inserting at a point in the middle of its insertion[33] (Fig. 82.10A). If there is unequal tension along the edges of the muscle, one can still consider the muscle as inserting at a point that is then shifted toward the edge with greater tension (Fig. 82.10B). In theory, this principle can be used to treat

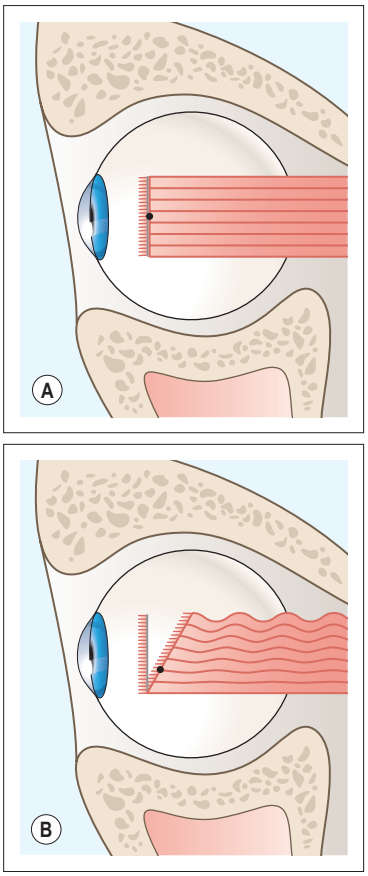


Fig. 82.10 (A) Mathematically one can consider a rectus muscle to insert at a point (black dot) at the middle of its insertion. (B) If there is unequal tension along the edges of a muscle as occurs with a slanting procedure, the muscle still can be thought of as inserting at a point (black dot). However, the point shifts toward the edge under greater tension. If the superior pole of a horizontal rectus muscle is slanted back, the point shifts toward the inferior edge, which is akin to infraplacing the muscle.

pattern strabismus by selectively slanting the superior or inferior pole of the recessed muscles to simulate transposition. For example, for a "V" pattern esotropia, the superior poles of the medial rectus muscles are recessed more than the inferior poles, which simulates the effect of an infraplacement. This approach has been used successfully to treat pattern strabismus.[34] Paradoxically, good results have been reported with slanting the muscles in an opposite manner by numerous authors.[33,35] For a "V" pattern esotropia, these authors would recess the inferior pole of the medial rectus muscles more than the superior poles. The rationale for this approach is based on the thought that the inferior edge of a horizontal rectus muscle is more taut in downgaze and the superior edge more taut in upgaze. The authors arrived at this conclusion through a misinterpretation of known facts about extraocular muscle mechanics. In fact, the opposite is true. This leads to a conundrum: How can opposite methods of slanting both produce good results (Fig. 82.11)? For the same "V" pattern esotropia, some investigators would slant in the manner depicted in Figure 82.11A and others would use the configuration shown in Figure 82.11B. I believe that, despite their popularity, insertion-slanting procedures in either manner should have a negligible effect on pattern strabismus. Sarcomere remodeling should rapidly occur and even out the edge tension after an insertion-slanting procedure (Fig. 82.12). This should occur even if the aforementioned investigations on the compartmental innervation of the horizontal rectus muscles proves that there is selectively different innervation to the superior and inferior compartments on upgaze and downgaze.[21,22,23] Probably the good outcomes reported with

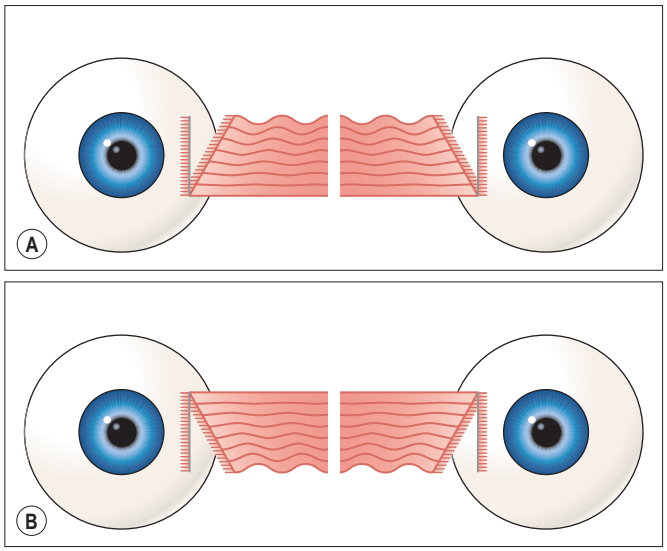


Fig. 82.11 (A) The treatment of a "V" pattern esotropia with insertion slanting according to the principles shown in Fig. 82.10. The superior poles of the medial rectus insertions are slanted back, which simulates infraplacement. (B) The treatment of a "V" pattern esotropia according to the concept that the inferior fibers are more taut in downgaze.

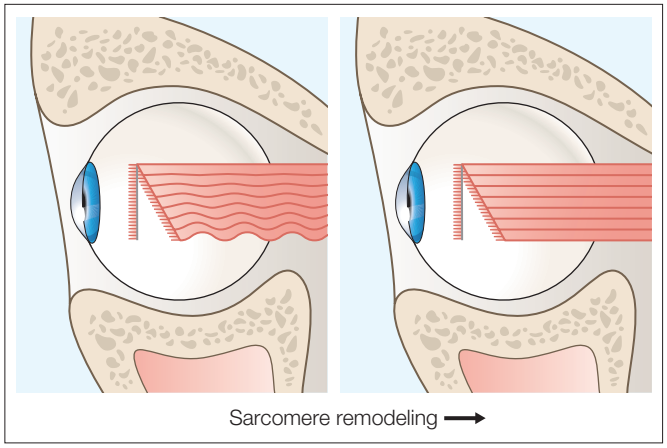


Fig. 82.12 Initially after slanting back the inferior pole of a rectus muscle, there is substantial slack induced in the inferior muscle fibers (A). After a period of several weeks, sarcomere remodeling should even out the differential edge tension and largely negate the effect of the slanting procedure (B).

these procedures were the result of the recession or resection performed.

Summary of surgical planning

In all cases, the author does the standard horizontal surgery based on the primary position measurement except perhaps allowing for up to 3 PD of eso shift in the primary position with superior oblique weakening. Table 82.2 summarizes recommendations for the surgical management of "A" and "V" patterns.

Optical management

Some patients with "A" or "V" patterns may have good alignment in the primary position but have an esotropia or exotropia in downgaze. As stated earlier, such patients may first become symptomatic as they become presbyopic. Some patients of this type can be managed by either using single vision reading glasses, or having a separate bifocal for prolonged reading with a segment that is higher than is typically prescribed.[36]

Table 82.2 Summary of surgical recommendations

If oblique dysfunction is present[a]	
"V" eso with IO OA	Recess MR or resect LR and weaken IO OU
"V" exo with IO OA	Recess LR or resect MR and weaken IO OU
"A" eso with SO OA	Recess MR or resect LR and weaken SO OU[b]
"A" exo with SO OA	Recess LR or resect MR and weaken SO OU[b]
Without oblique dysfunction[a]	
"V" eso	Recess MR and infraplace or resect LR and supraplace OU
"V" exo	Recess LR and supraplace or resect MR and infraplace OU
"A" eso	Recess MR and supraplace or resect LR and infraplace OU
"A" exo	Recess LR and infraplace or resect MR and supraplace OU

[a]Perform the usual amount of recession or resection of the horizontal rectus muscles based on the deviation in the primary position.
[b]Avoid a powerful superior oblique weakening procedure in patients with bifoveal fusion.
IO, Inferior oblique; LR, lateral rectus; MR, medial rectus; OA, overaction; OU, both eyes; SO, superior oblique.

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Congenital cranial dysinnervation disorders

Ramesh Kekunnaya and Virender Sachdeva

Chapter contents

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DUANE RETRACTION SYNDROME
HUMAN HOMEOBOX A1 SPECTRUM
HORIZONTAL GAZE PALSY AND PROGRESSIVE SCOLIOSIS
MÖBIUS SYNDROME AND ITS VARIANTS
SUMMARY
REFERENCES

See online for supporting video for this chapter.

The term "congenital cranial dysinnervation disorders" (CCDDs) denotes a group of congenital, non-progressive disorders resulting from developmental abnormalities of one or more cranial nerves or their nuclei and primary/secondary dysinnervation.

They may be sporadic or familial, but most are either proven or suspected to have a genetic basis[1,2] (Box 83.1). Ophthalmologists are frequently consulted about these conditions because of the involvement of the extraocular muscles. Although many of these conditions are characterized only by abnormal extraocular muscle innervation, facial innervation, or both, some have associated systemic and/or neurologic abnormalities, such as cerebrovascular, cardiovascular, and skeletal malformations that also are attributable to the underlying genetic defect.[2] At present, a total of seven disease genes and ten phenotypes have been identified.[2]

This chapter focuses on CCDDs characterized wholly or in part by abnormalities of eye movements. These include the three main types of congenital fibrosis of the extraocular muscles (CFEOM), Duane retraction syndrome (DRS), homeobox A1 (*HOXA1*) spectrum, horizontal gaze palsy with progressive scoliosis (HGPPS), and Möbius syndrome. For the ease of understanding, these can be subclassified into those that affect the vertical movements (CFEOMS [oculomotor and trochlear nerve]) or the horizontal movements (DRS, Möbius syndrome, HGPPS, and HOAX1 spectrum [abducens nerve and supranuclear pathways]).

Congenital fibrosis of extraocular muscles

This group of disorders is characterized by congenital ocular motility abnormalities, congenital ptosis, and fibrotic extraocular muscles. Most of these patients present first to ophthalmologists because of ptosis or deviation of the eyes. Although previously thought to be secondary to muscle fibrosis (myopathy), clinical and pathological evidence suggest absence of the oculomotor/trochlear/abducens nerve or nuclei (neuropathy). To date, three primary CFEOM phenotypes have been described – CFEOM1, CFEOM2, and CFEOM3. CFEOM3 has three phenotypic variants: CFEOM3A, CFEOM3B, and CFEOM3C.[2,3]

Congenital fibrosis of the extraocular muscles type 1 (MIM #135700)

CFEOM1 is the most common of the CFEOM phenotypes. It is autosomal dominantly inherited with full penetrance.[4] It is characterized by congenital bilateral ptosis, bilateral infraducted globes, restricted upgaze, variably restricted horizontal gaze, and a compensatory chin-up head posture (Fig. 83.1). These patients have positive forced duction testing and misdirected eye movements such as a marked synergistic convergence on attempted upgaze. Neuropathologic studies reveal significant atrophy and fibrosis of the superior rectus and levator palpebrae muscles, with variable reduction in the size of the other extraocular muscles. Histopathologic studies have shown that the oculomotor nerves may be absent or hypoplastic. The diameter of the optic nerves is reduced by 30–40%.[5] CFEOM1 is caused by a heterozygous missense mutation in *KIF21A*, chromosome 12 (12q12)[3] that encodes a kinesin microtubule-associated protein associated with anterograde organelle transport in neurons.[6]

Congenital fibrosis of the extraocular muscles type 2 (MIM #602078)

CFEOM2 is an autosomal recessive disorder characterized by bilateral ptosis, bilaterally absent adduction, upgaze, and downgaze (Fig. 83.2A,B).[7] Although abduction is present, it is limited and the pupils are often irregularly shaped, unequal in size, and non-reactive to both light and near stimulation. The appearance is that of bilateral oculomotor (third) nerve palsies and neuroimaging shows a bilateral absence of the third nerves.[8] This condition is caused by homozygous mutations in the *PHOX2A* gene located on chromosome 11 (11q13.3–q13.4)[7] that codes for a homeodomain transcription factor expressed predominantly in developing oculomotor and trochlear neurons that is essential for their survival. Mutations alter the factor sufficiently that the oculomotor (and probably trochlear) nerves never develop.



Fig. 83.2 Congenital fibrosis syndrome type 2 (CFEOM2). (A) This patient with the typical congenital exotropia and bilateral ptosis (note furrowed brow to elevate the lids) associated with CFEOM2.

Box 83.1

Common features of congenital cranial dysinnervation disorders

- Onset from birth
- Non-progressive
- Sporadic or familial
- Developmental abnormalities of one or more cranial nerves/nuclei
- Dysinnervation:
  - Primary – due to absence of the nuclei/neurons, or
  - Secondary – from branches of another nerve during development



Fig. 83.1 Congenital fibrosis syndrome type I (CFEOM1) in a father and son. Because of their bilateral ptosis and deficient upgaze, both have adopted a head posture with the chin elevated.

Congenital fibrosis of the extraocular muscles type 3

CFEOM3 is an autosomal dominantly inherited disorder that has clinical features similar to those of CFEOM1 except that they are more variable and sometimes associated with the ability to elevate the eyes above the midline[9] (Fig. 83.3A,B). The phenotypic variability results at least partly from heterozygous mutations in at least two genes: *TUBB3* (CFEOM3A; MIM #600638) and, rarely, *KIF21A* (CFEOM3B).[10,11]

In addition, several different missense mutations may occur in the *TUBB3* gene, which codes for a component of microtubules. Thus, some patients with CFEOM3A have isolated ocular motor deficits (some even have isolated absence of upgaze), whereas others have bilateral facial weakness, peripheral sensory or sensorimotor neuropathies, wrist and finger contractures, cognitive dysfunction, or a combination of these features. Magnetic resonance imaging (MRI) may show dysgenesis of the corpus callosum and anterior commissure in some cases.[11] Patients have been described who have a phenotype similar to CFEOM1, except for the presence of some upgaze, and who have a mutation in *KIF21A*. They are said to have CFEOM3B.[2] A single family has been described in which three generations have what appears to be CFEOM3 but who carry a reciprocal translocation involving chromosomes 2q and 13q,[12] termed CFEOM3C (MIM #609384).

Management of CFEOM patients

CFEOM patients pose a significant challenge, as there is a problem of dysinnervation of multiple muscles, often associated with large angle deviation, ptosis, and abnormal head posture. They may have complex and unremitting ocular motor deficits and ptosis, but also systemic and/or neurologic deficits. Even though the outlook is guarded, there are some options and the following steps may help these patients:

a. Appropriate refractive correction/amblyopia therapy: A study of 40 patients with CFEOM by Chen et al.[13] reported an incidence of amblyopia of about 95%. In addition, they found that 85% of the patients had astigmatism, and 11.7% had simple hyperopia. Thus, all patients with CFEOM should undergo a cycloplegic refraction, part-time occlusion therapy or atropinization as appropriate (see Chapter 73), and regular follow-up throughout their period of visual development.

b. Management of strabismus:
   - Often these patients have a large hypotropia and chin elevation or moderate to large angle exotropia or esotropia due to tight inferior and lateral/medial rectus muscles. In some patients with trochlear nerve dysfunction, there may also be fibrosis and tightness of superior oblique muscles.
   - These patients usually benefit from large recessions/tenotomy of the inferior and lateral rectus muscles, thereby reducing the hypotropia.
   - Intraoperatively, the duction tests can be repeated for both inferior rectus and superior oblique muscles. Following inferior rectus weakening, patients with residual superior oblique tightness might benefit additionally from weakening of these muscles.
   - *Small recessions are often ineffective and may necessitate a repeat procedure.*
   - In addition, resections tend to be ineffective against tight antagonists.
   - Strabismus management requires an individualized approach based on the clinical presentation.

c. Management of ptosis:
   - Significant ptosis is frequently observed and may alone contribute to chin elevation.

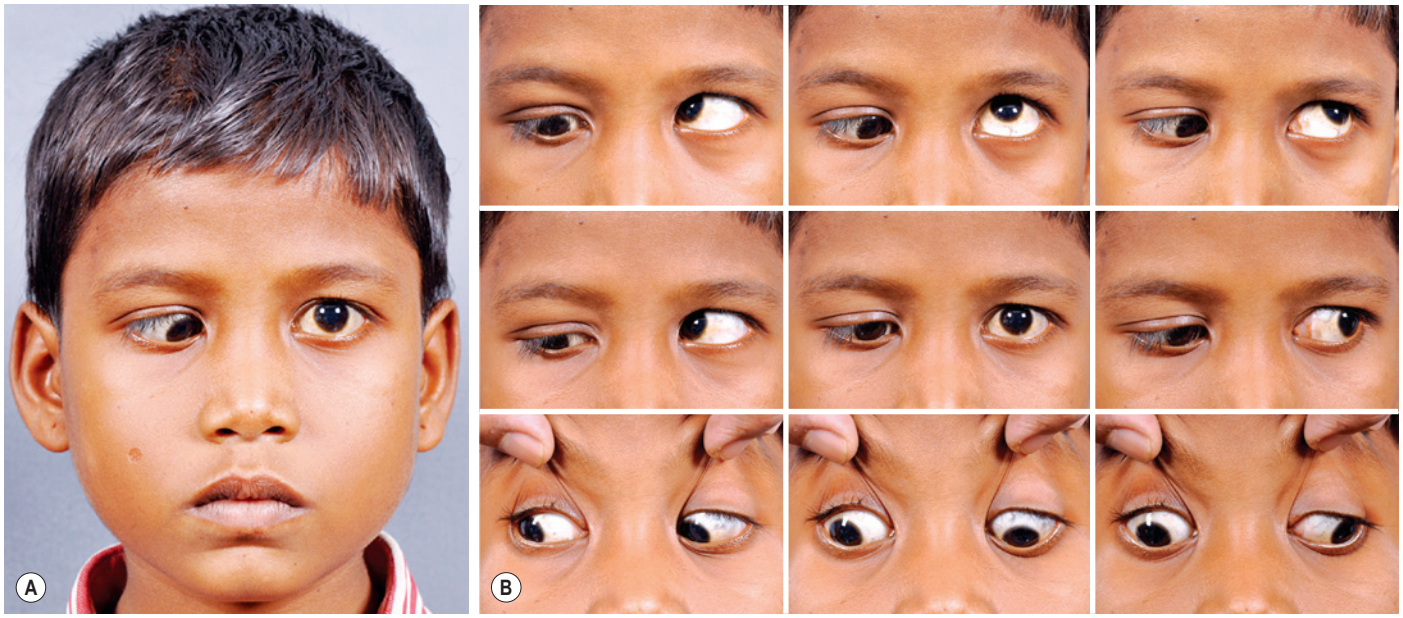


Fig. 83.3 This patient has: (A) unilateral ptosis with esotropia; (B) significant elevation deficit and normal horizontal movements.

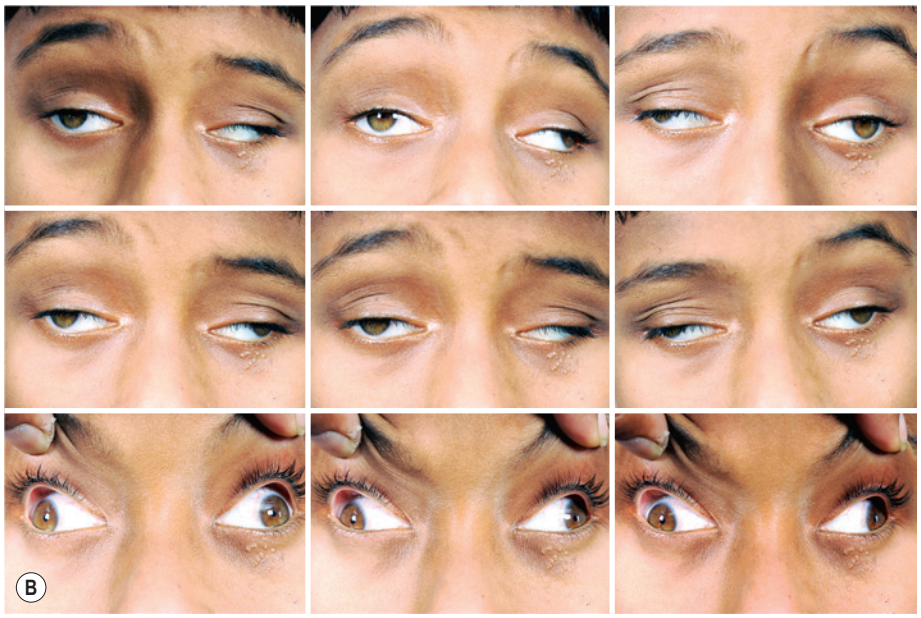


Fig. 83.2 Congenital fibrosis syndrome type 2 (CFEOM2). (A) Available online. (B) He had no upgaze or downgaze of either eye and no adduction of either eye.

- Ptosis should be reassessed and surgical correction considered after strabismus surgery.
- *Surgical overcorrection is hazardous*: this may result in exposure keratopathy because of the restricted eye movements and lack of a Bell's phenomenon.
- Frontalis sling procedure is usually more effective than levator resection. It can be managed relatively easily in case of overcorrection. If a levator resection is performed, the eyelids should be raised to a level just above the visual axis in the primary position.
- In patients with a poor Bell's phenomenon, surgery may not be possible. Conservative management with ptosis crutch glasses may be helpful.

The strabismus associated with CFEOM is not particularly amenable to surgery. Limited improvement can be attained in the ocular motility and alignment in the primary position by performing very large recessions and occasionally resections.[14] Recent work by Sener et al.[15] has suggested following an individualized approach. Satisfactory alignment may be achieved in a fair number of patients with CFEOMS; however, multiple procedures may be needed. Thus, the patient's parents should be counseled accordingly so that they have realistic expectations from the surgery.

Duane retraction syndrome

Duane retraction syndrome (DRS) is the most common CCDD resulting from abnormalities of the abducens nerve and its nucleus.[2] It is associated with the absence of normal innervation of the lateral rectus muscle by the abducens nerve, with paradoxical innervation of this muscle by the division of the oculomotor nerve innervating the medial rectus muscle. Hence, the characteristic feature is a co-contraction of the globe when the patient attempts adduction with globe retraction. There are several variants[16]: type I (limited abduction with normal to near normal adduction), type II (limited adduction with normal to near normal abduction), type III (limited abduction and adduction), and type IV (synergistic divergence). The most common presentation is type I characterized by marked limitation or absence of abduction, variable limitation of adduction, and palpebral fissure narrowing with globe retraction on attempted adduction (Fig. 83.4).

Most cases are unilateral (see Fig. 83.4), but bilateral DRS occurs in 15–20% of affected patients (see Fig. 83.7A).[17,18] In unilateral cases, females are more commonly affected than males, and the left eye is more frequently affected than the right. A face turn towards the affected side is observed in 40–60% of patients to avoid diplopia and maintain binocular vision. Upshoots or downshoots may be seen in about 40–45% of patients, especially those with unilateral disease and type III DRS.[18]

Most commonly patients are esotropic, followed by orthotropia, and least commonly exotropia. Up to 66% of the patients with DRS may have refractive error – most commonly hypermetropia or hypermetropic astigmatism (31.5%) followed by myopia or myopic astigmatism (22%).[18] An associated strabismic, ammetropic, or combined mechanism amblyopia may exist. Thus, all patients with DRS should undergo cycloplegic refraction and amblyopia therapy.

In addition, patients with DRS may have significant ocular associations such as cataract, nasolacrimal duct block, retinal degenerations, epibulbar dermoid, crocodile tears, and systemic associations such as hearing impairment, cleft lip, club foot, and Goldenhaar syndrome (Fig. 83.5).[18]

A myogenic vs. neurogenic phenomenon?

Although initially believed to occur secondary to pathology in the extraocular muscles (fibrosis) or orbital bands, recent electromyographical studies, MRI, and histological studies have established the neural basis of the disorder that is often associated with absence of the abducens nerve/nucleus.[16,19,20,21,22]



Fig. 83.5 Unilateral (right) Duane retraction syndrome type I in a 6-year-old girl. Note the presence of preauricular tag and limbal dermoid.

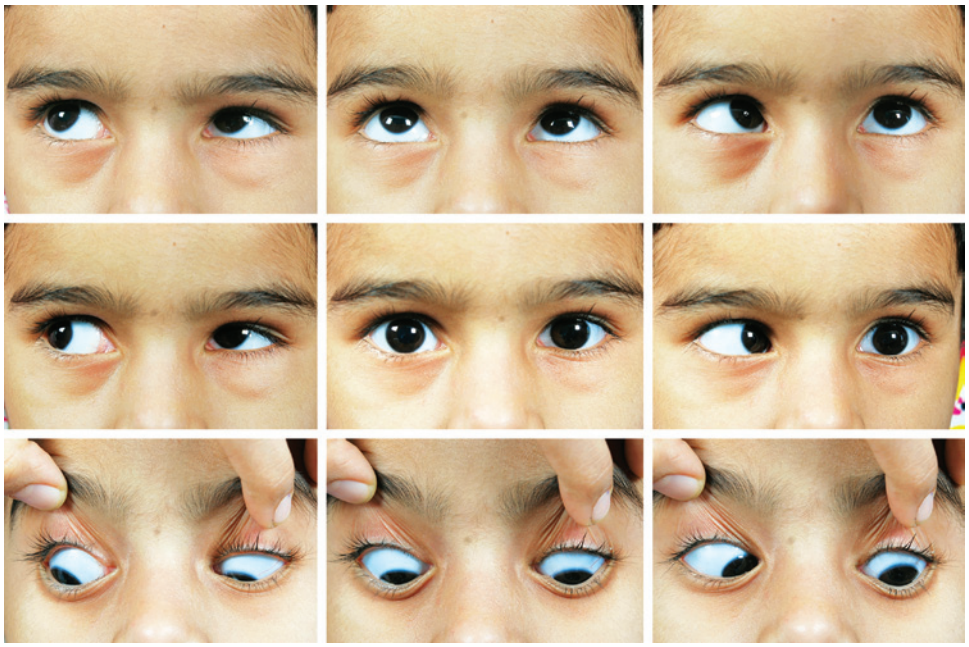


Fig. 83.4 Unilateral (left) Duane retraction syndrome type I in a 4-year-old girl. Note limitation of abduction of left eye and widening of left palpebral fissure on attempted left gaze.

Inheritance

Most cases of DRS are sporadic, but familial unilateral and bilateral cases occur.[23] Familial DRS usually is transmitted in an autosomal dominant pattern. Affected individuals in such families show substantial clinical variability.

Duane retraction syndrome 1 (MIM #126800)

In the Duane retraction syndrome 1 (DURS1) phenotype, the syndrome may be unilateral (see Fig. 83.4) or bilateral (see Fig. 83.7A) and, depending on the size of the deletion, it may be associated with other features including mental retardation, branchio-oto-renal syndrome, genital tract anomalies, and other somatic mutations. The gene disrupted by overlapping cytogenic abnormalities at the DURS1 locus located on chromosome 8 (8q13) may be CPAH, a carboxypeptidase gene with eight exons.[24,25]

Duane retraction syndrome 2 (MIM #604356)

The DURS2 phenotype is almost always bilateral. Associated findings include a variety of vertical deviations such as apparent superior oblique underaction and dissociated vertical deviation. Patients may have decreased abduction with or without decreased adduction. Amblyopia is common. It is autosomal dominantly inherited. The responsible gene, *CHN1*, is located on chromosome 2 (2q31).[26–28] It is involved with neuronal path finding during the development of the abducens nerve and, to a lesser extent, the oculomotor nerve.[29,30]

Duane radial ray syndrome (Okihiro syndrome, MIM #607323)

In this condition, unilateral or bilateral Duane syndrome is associated with unilateral or bilateral radial dysplasia. Thumb hypoplasia is most common, but the defect may range from hypoplasia of the thenar eminence to phocomelic limbs. Patients often have deafness and somatic malformations. Inheritance is autosomal dominant and is caused by truncating *SALL4* mutations on chromosome 20 (20q13),[31,32] which encode putative zinc finger transcription factors.

Box 83.2

Indications for surgery in Duane retraction syndrome

- Significant deviation in the primary position
- Abnormal head posture
- Significant overshoots (uphsoot or downshoot)
- Significant globe retraction
- To increase the field of binocular vision

Wildervanck cervico-oculo-acoustic syndrome (MIM #314600)

This syndrome of congenital deafness, Klippel–Feil anomaly (fusion of cervical vertebrae giving a short neck), and bilateral abduction palsy with retraction on adduction (Duane phenomenon) is almost completely limited to females, suggesting X-linked dominance with lethality in the hemizygous male.

Management of Duane retraction syndrome

Indications for surgical treatment of Duane syndrome are summarized in Box 83.2. A significant deviation in primary gaze is the most common indication.

Although many clinicians rely upon Huber's classification of DRS into types 1, 2, and 3,[16] classifying patients as esotropic, exotropic, or orthotropic[33,34] may be more useful for surgical

planning and treatment. Treatment depends on the amount of deviation in primary position, severity of the head turn, the degree of limitation of add- and abduction, the amount of retraction, up- and downshoots, and the results of forced duction testing (FDT). Although recessions of the medial and lateral rectus muscles have been the mainstay of management in DRS, in the last decade there have been significant advances in the efficacy of transposition procedures (i.e. vertical rectus transposition [VRT] and superior rectus transposition [SRT]).

General guidelines for the management of strabismus in DRS

Unilateral esotropic DRS

Unilateral esotropic DRS is the most common subtype of DRS (especially DRS type I). Depending on the amount of esotropia, these patients may be managed by unilateral or bilateral medial rectus recessions. While many strabismologists prefer unilateral or bilateral medial rectus recessions for esotropic DRS,[35] some recommend transposition procedures[36,37] to improve ocular alignment and abduction. While both medial rectus recessions and transposition procedures may lead to similar success in achieving alignment in primary position, vertical rectus transpositions may result in greater expansion of the binocular visual field.[36–39] In addition to VRT to the lateral rectus, Mehendale et al.[37] and Yang et al.[38] reported good success with SRT and medial rectus muscle recession (Fig. 83.6A,B). The authors have also reported greater improvement in abduction with SRT (1.5 units) compared to none in the medial rectus recession alone.[38] However, patients should be carefully selected: Transposition procedures should not be performed on patients with severe retraction/

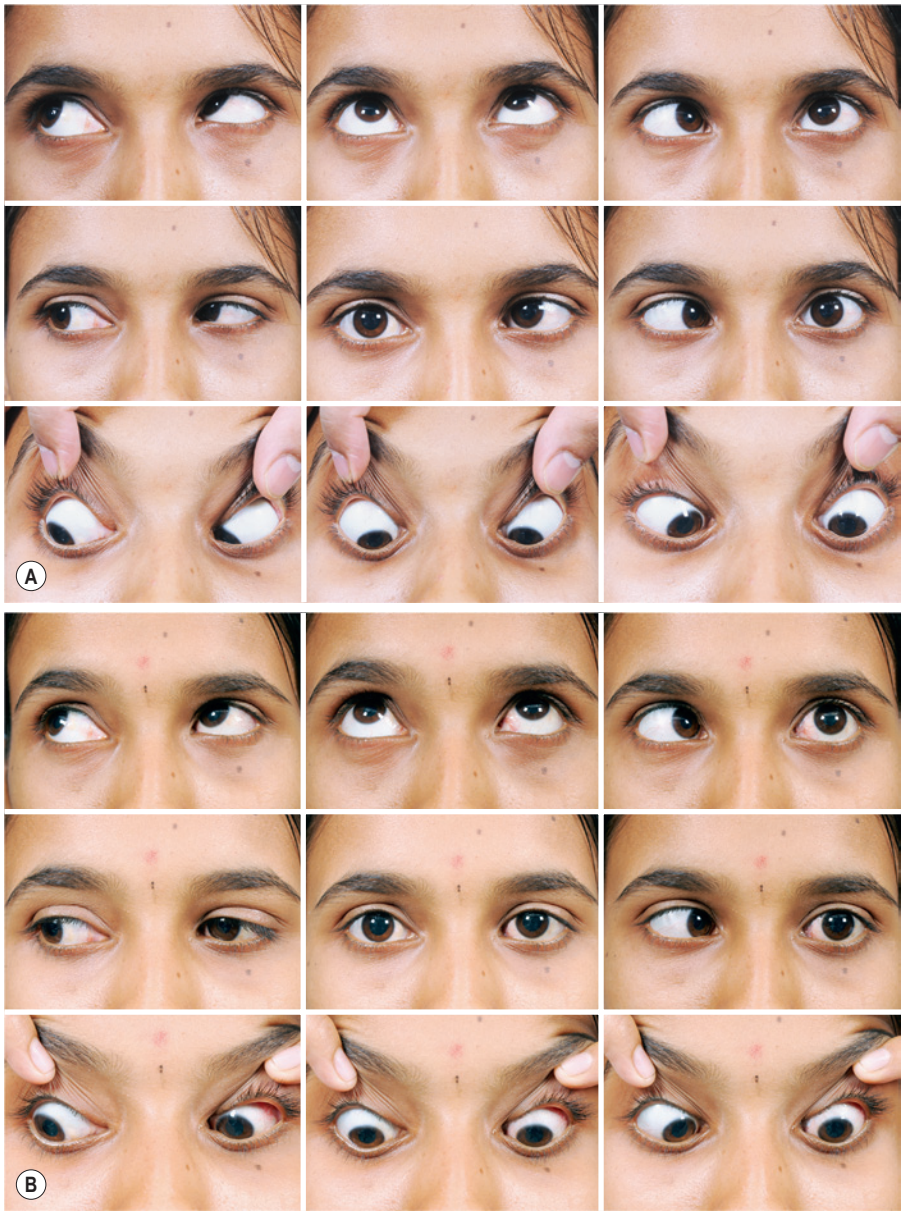


Fig. 83.6 Unilateral esotropic (right) Duane retraction syndrome type I. Preoperative (A) and postoperative (B) nine gaze picture. Please note the improvement in abduction.

co-contraction/exotropia in adduction. Table 83.1 summarizes the management of patients with esotropic DRS.

Bilateral esotropic DRS

This pattern is present in up to 15% of the patients with DRS. It is more common in males. They need to be distinguished from patients with infantile esotropia, Ciancia syndrome, and Möbius syndrome. The amount of esotropia may vary from small to large (reported up to 70 PD).[40] In general, similar principles may be applied to their management as in unilateral DRS. Bilateral medial rectus recession is the surgical procedure of choice. The amount of the surgery is dependent on the angle of the deviation and good success may be achieved in up to 86% of patients. Other options include bilateral medial rectus recessions with SRT/VRT (Fig. 83.7A,B); however, transposition procedures have been reported to have a similar success as bilateral medial recti recessions.[41]

Table 83.1 Surgical procedures and possible indications for patients with unilateral Duane retraction syndrome

No.	Clinical feature	Indicated procedure
1	Esotropia <20 PD	Unilateral medial rectus recession alone (MRc) If deviation <14 PD without significant retraction: superior rectus transposition (SRT) alone
2	Esotropia: 20–45 PD	Bilateral medial rectus transpositions: preferable if tight medial rectus and severe globe retraction Unilateral MRc + SRT* Unilateral MRc + vertical rectus transpositions*

*Preferable if not much globe retraction/overshoots.

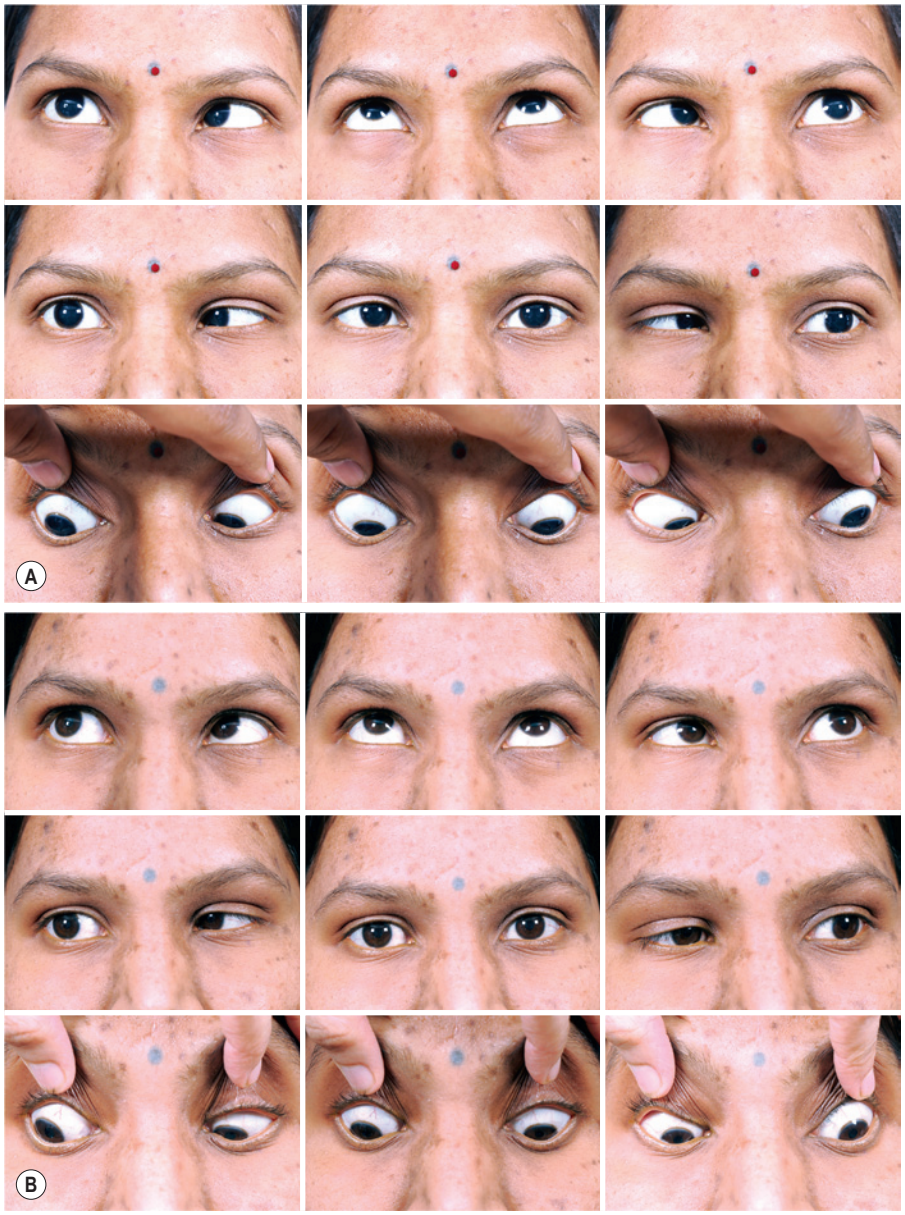


Fig. 83.7 Bilateral esotropic Duane retraction syndrome type I. Preoperative (A) and postoperative (B) pictures. Notice the improvement in the primary position deviation and globe retraction. However, the limitation of abduction still persists.

Exotropic DRS

Exotropic DRS accounts for 10–15% of all DRS cases and is most commonly associated with type II DRS. In these patients, the lateral rectus muscle is usually tight and there may also be globe retraction and overshoots. They may be managed by lateral rectus recession alone (unilateral if deviation <20 PD; bilateral if >20 PD; and lateral rectus recession with Y-split if associated with overshoot [Fig. 83.8A,B]). In patients with severe retraction and overshoots, fixation of the lateral rectus to the periosteum, with partial tendon vertical rectus transpositions to the lateral rectus insertion, may improve the retraction as well as the ductions.

DRS with overshoots (upshoot or downshoot)

Overshoots, defined as overelevation or overdepression, are usually caused by co-contraction of the horizontal rectus muscles, most commonly with type II and III DRS (see Fig. 83.8A). They are believed to be secondary to mechanical factors (leash effect of the tight lateral rectus muscle causing a slippage of the globe). Alternatively they may be due to dysinnervation of the vertical rectus or oblique muscles. While patients with "mechanical overshoots" tend to have an abrupt overshoot on attempted adduction, patients with "innervational overshoots" tend to have a more gradual overshoot with a primary position hyperdeviation. These patients may also have an associated inferior oblique overaction. Various surgical approaches have been proposed; however, a detailed discussion of each is beyond the scope of this chapter. In patients with mechanical overshoots, good results may be obtained with Y-splitting of the lateral rectus muscles (see Fig. 83.8A,B). This procedure may be combined with lateral rectus recession if there is a concurrent exotropia. In a study of 10 patients with a significant upshoot, with or without exotropia, Rao et al.[42] reported elimination of overshoots with improvements

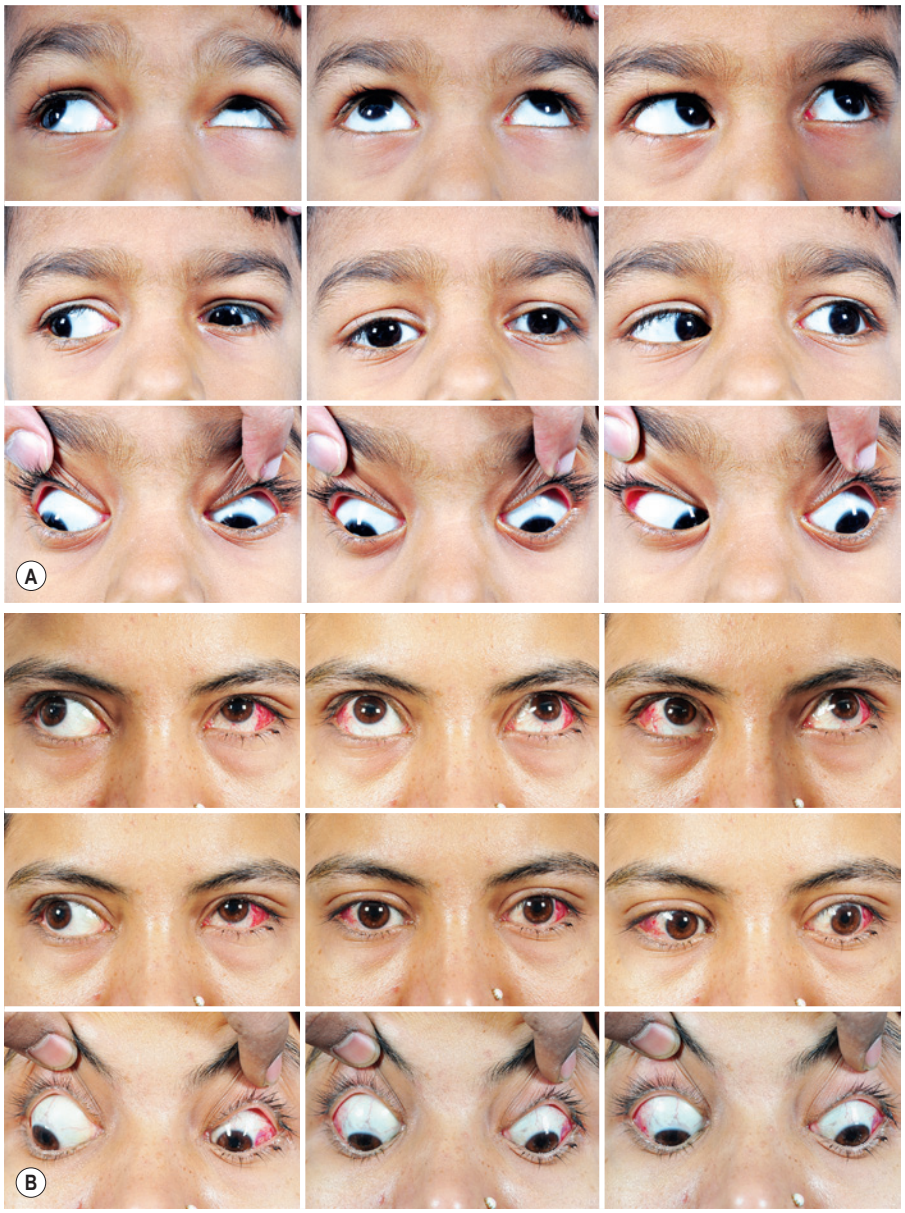


Fig. 83.8 Exotropic Duane retraction syndrome. Preoperative (A) and postoperative (B) pictures. Note the improvement in deviation in primary gaze and downshoot in the left eye.

in head turn, primary gaze deviation, and globe retraction (when present). Conversely, in patients with innvervational overshoots, recessions of the superior rectus or inferior oblique muscles may give good alignment.

Orthotropic DRS

Patient with orthotropic DRS may rarely need surgical procedures for associated severe retraction or overshoots. The management of the overshoots is discussed above. In patients with significant globe retraction as the primary indication, asymmetrical recessions of both medial and lateral rectus muscles may be beneficial. In general, the lateral rectus muscle should be recessed about 1 mm more than the medial rectus muscle. (and an adjustable suture used where possible to avoid inducing any new deviation in the primary position).

Human homeobox A1 spectrum (MIM #601536)

The *HOXA1* spectrum is autosomal recessive and characterized by bilateral DRS with absent abduction and reduced adduction (Fig. 83.9) associated with deafness, cerebrovascular and cardiovascular malformations, and, in some cases, autism that may be profound.[43–45] Some affected persons, particularly those with the Native American variant, have associated facial weakness, cognitive dysfunction, central hypoventilation, or a combination of these features.[46] MRI has demonstrated absence of both abducens nerves and almost completely absent development of the acoustic and vestibular structures in the petrous bone of many patients.[43–45]

The *HOXA1* spectrum is caused by homozygous mutations in the *HOXA1* gene on chromosome 7 (7p15.3), a gene that has been shown in animal models to be critical for hindbrain development.[3]

Practical management of the *HOXA1* spectrum

Patients with this condition may be quite impaired by their systemic disease. Ophthalmologists should focus on prescribing appropriate refractive correction, amblyopia therapy and, based on primary position ocular deviation, appropriate and timely strabismus surgery. However, more importantly, ophthalmologists should be aware of this entity while examining patients with bilateral DRS and be ready to involve their colleagues for multidisciplinary care of the child.

Horizontal gaze palsy and progressive scoliosis (MIM #607313)

HGPPS is an autosomal recessive syndrome characterized by complete or near complete bilateral horizontal gaze limitation (Figs 83.10 and 83.11), normal vertical gaze, variable convergence, variable congenital nystagmus, and asynchronous blinking.[47] Scoliosis begins in early childhood and may be both rapidly progressive and severe. MRI shows intact abducens nerves but deep anterior and posterior clefts in the medulla and lower pons, a large fourth ventricle, and no decussation of the axons of the corticospinal tract, medial lemniscus, or superior cerebellar peduncle.[48,49]

The mutations responsible for this disorder are in the gene *ROBO3* located on chromosome 11 (11q23–q25), a gene responsible for producing a transmembrane cell adhesion molecule that is a receptor for axon guidance during development of the hindbrain.[3,50]

The explanation for absence of horizontal gaze in patients with HGPPS is unclear; however, it may be due to aberrant supranuclear input onto the abducens motor neurons by axons from the paramedianpontine reticular formation that cannot



Fig. 83.9 Human homeobox A1 (HOXA1) spectrum. This patient with homozygous mutations in *HOXA1* has the classic triad of congenital bilateral type III Duane retraction syndrome, deafness due to almost complete absence of inner ear development bilaterally, and cerebrovascular malformations. She has a moderate esotropia in primary gaze, no abduction of either eye, and limited adduction of both eyes associated with obvious globe retraction and narrowing of the palpebral fissure; however, she has full upgaze and downgaze bilaterally.



Fig. 83.10 Horizontal gaze palsy with progressive scoliosis. This young man with homozygous mutations in *ROBO3* has a horizontal gaze palsy and a severe progressive scoliosis. His eyes are orthophoric in primary gaze, and he has excellent visual acuity in both eyes, binocular fusion, and no diplopia. He has essentially no conjugate gaze to the right, and can only move both eyes minimally to the left; however, he has full upgaze and downgaze. He also has small-amplitude horizontal pendular nystagmus. The disturbance of ocular motility was present at birth.

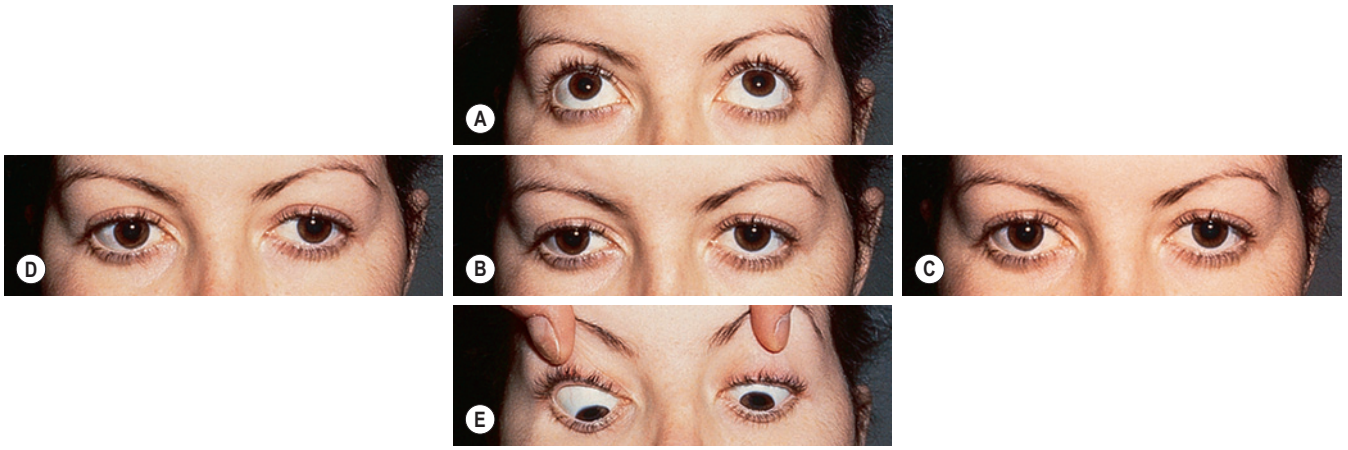


Fig. 83.11 Horizontal gaze palsy with progressive scoliosis. Note intact vertical movements. (A) Patient looking up. (B) Patient in primary gaze. (C) Patient attempting to look right. (D) Patient attempting to look left. (E) Patient looking down.

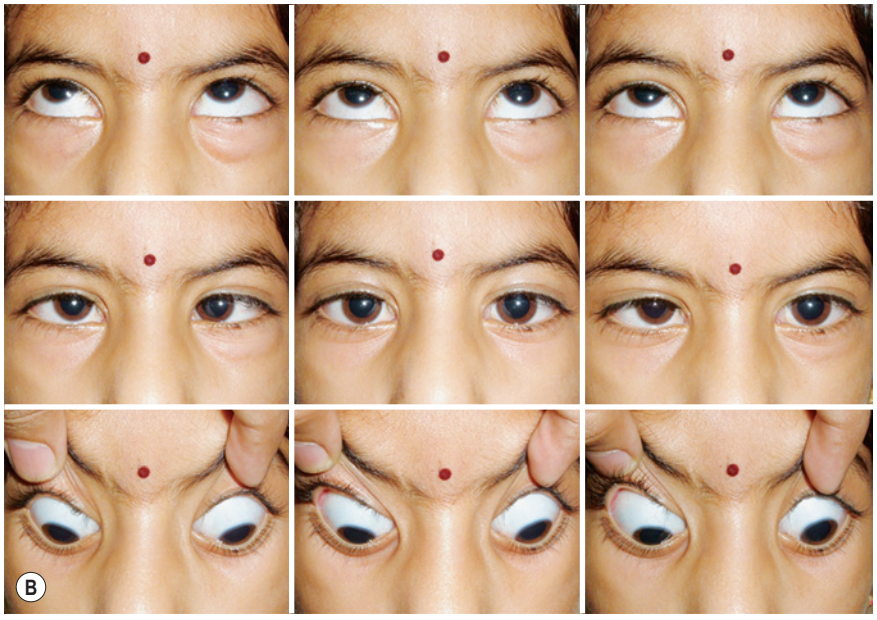


Fig. 83.12 Möbius syndrome in a 9-year-old girl. (A) Available online. (B) Nine gaze picture. Note the presence of a bilateral limitation of abduction in both eyes with intact vertical movements in both eyes.

cross the midline and/or to inability of developing axons in the medial longitudinal fasciculus to cross the midline.[51]

Practical management of horizontal gaze palsy and progressive scoliosis

Because the horizontal gaze deficit in patients with HGPPS is always bilateral and symmetric, such patients almost never have diplopia and, thus, do not require treatment for their ocular motility disturbance; however, they often benefit from surgery to correct their scoliosis.

Möbius syndrome (MIM #157900) and its variants

The eponym "Möbius syndrome" is reserved for the congenital combination of non-progressive facial weakness and at least an abduction deficit in one or both eyes. Möbius syndrome is usually a sporadic disorder, frequently accompanied by lingual or pharyngeal dysfunction, craniofacial dysmorphisms, and limb malformations. Several associated cytogenetic abnormalities have been reported.

Characteristically, affected children have mask-like faces. The mouth may be constantly held open preventing adequate nursing. The appearance may interfere with normal bonding and attachment. The eyelids often cannot be closed completely. There may be excess lacrimation with epiphora. Usually there is an associated esotropia (Fig. 83.12) with or without unilateral or bilateral limitation of abduction. However, the eyes may be orthotropic in many patients, despite limitation of horizontal movements. Henderson reviewed 61 cases of Möbius syndrome in the literature.[52] He found that bilateral abducens palsy was present in 43 cases, unilateral abducens nerve palsy in two cases, and horizontal gaze palsy in the rest. In rare cases, vertical eye movements are also abnormal.



Fig. 83.12 (A) Note esotropia and bilateral facial weakness.

Patients with Möbius syndrome may have deafness, webbed fingers or toes, congenital "amputations," supernumerary digits, defects of the muscles of the chest, neck, and tongue, and even absence of the hands, feet, fingers, or toes. Abnormalities of lower cranial nerves, with speech and swallowing difficulties, are extremely common. Less commonly, it may be associated with low-set ears, a small mouth opening, micrognathia, epicanthal folds, congenital heart defects, or a combination of these abnormalities. Some patients may have respiratory difficulty and tachypnea. Others have a combination of anosmia and hypogonadotrophic hypogonadism (Kallmann syndrome). Many patients with Möbius syndrome have some degree of mental retardation and autism. Patients with Möbius syndrome who undergo neuroimaging show heterogeneity of findings ranging from normal imaging to intracranial calcifications, brainstem hypoplasia, or changes consistent with ischemia.

The inheritance is usually sporadic, although some patients with Möbius-like phenotypes have mutations in *TUBB3* or *HOXA1*.[2] Baraitser concluded that the risk of another affected sibling is no greater than 2% in pedigrees in which the syndrome includes limb abnormalities.[53]

Towfighi et al. divided neuropathologic findings in Möbius syndrome into four groups as follows.[54] Group I: hypoplasia or atrophy of cranial nerve nuclei (4 cases). Group II: neuronal loss with evidence of active neuronal degeneration in the affected facial nerve nuclei (2 cases). It was postulated that these neuronal changes were caused by physical injury to the facial nerve, arising from a malformed temporal bone or from application of forceps during delivery. Group III: reduction in the number of neurons and reactive changes in the affected cranial nerve nuclei *along with* frank necrosis of the tegmentum of the lower pons (6 cases). These lesions are probably acquired later during fetal life rather than during early embryonic development, and both hypoxia and viral infections are implicated in their etiology. The final group, Group IV, consisted of three cases in which no lesions were found in the brainstem or cranial nerves. A primary myopathy may have been responsible for these cases.

The diversity of pathologic findings in patients with Möbius syndrome suggests that the syndrome is a heterogeneous group of congenital disorders caused by genetic and/or developmental defects related to a variety of insults, such as ischemia or toxic effects of prenatal prescribed drugs including misoprostol, a synthetic prostaglandin, or one of the benzodiazepines.

Practical management of Möbius syndrome

Most patients with Möbius syndrome do not require strabismus surgery because they have bilateral and symmetric horizontal gaze paresis; however, children with severe esotropia in primary gaze may benefit from surgical treatment. Surgical options include bilateral medial rectus recessions, medial rectus recession combined with lateral rectus resection, and, in severe cases, muscle transposition. A reasonable cosmetic appearance can be achieved in most cases, although more than one operation may be required.

Patients with Möbius syndrome and associated corneal anesthesia are at risk of developing exposure keratopathy in the setting of incomplete lid closure. This complication is of particular concern in young children, who may require tarsorrhaphy when simple corneal lubrication is not sufficient to provide adequate corneal lubrication.

Summary

Based on both neuropathologic and genetic evidence, it is clear that there exists a group of disorders for which absent or anomalous innervation of the extraocular and/or facial muscles is the most likely pathophysiology. These disorders are appropriately referred to as "congenital cranial dysinnervation disorders" and include CFEOM types 1, 2, and 3, Duane retraction syndromes 1 and 2, the Duane radial ray syndrome, the *HOXA1* spectrum, congenital horizontal gaze palsy with progressive scoliosis, and Möbius syndrome. The above list of clinical phenotypes and genetic loci is almost certainly incomplete and will undoubtedly increase with time. Since many of these affect extraocular muscles, patients may present first to ophthalmologists. The management of these conditions involves refractive correction, treatment of amblyopia, and strabismus surgery if indicated. The child should be assessed for systemic associations where appropriate, and referral to a specialist, since a multidisciplinary approach may improve the condition of these patients significantly.

Bonus e-book content online

Fig. 83.2 (A) This patient with the typical congenital exotropia and bilateral ptosis (note furrowed brow to elevate the lids) associated with CFEOM2.

Fig. 83.3 This patient has: (A) unilateral ptosis with esotropia; (B) significant elevation deficit and normal horizontal movements.

Fig. 83.5 Unilateral (right) Duane retraction syndrome type I in a 6-year-old girl. Note the presence of preauricular tag and limbal dermoid.

Fig. 83.12 (A) Note esotropia and bilateral facial weakness.

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Ocular motor nerve palsies

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Introduction

Cranial nerve palsies in childhood represent one of the more difficult evaluation and management challenges in pediatric ophthalmology. Severity and acuity of pediatric cranial nerve palsies can range from those that simply can be observed, to those that could represent life-threatening emergencies. Determining onset of ocular motor nerve palsies and dividing them into congenital and acquired forms aids in determining etiologies for these disorders, and therefore directs the approach to evaluation, treatment modalities employed, and subsequent outcomes – not only for the ocular alignment, but for morbidity and mortality. A multidisciplinary approach may be necessary in the evaluation and management of these children, dependent upon the acuity of the underlying causative disorder and its treatment. All children with ocular motor nerve palsies in the amblyogenic age range should be monitored for the development of amblyopia, with treatment initiated when necessary (see Chapter 73).

Examination techniques

When examining a child with ocular misalignment, determination of the presence of a cranial nerve palsy may be difficult with a non-cooperative child. Observing the ductions and versions of a young child in the office may reveal a gross limitation of ocular motility in a certain direction in complete cranial nerve palsies. However, partial nerve palsies leading to strabismus may be discovered by closely observing saccadic velocities, with a slowed, or "floating" saccade, suggestive of paresis of the muscle. Restrictive etiologies are possible causes for incomitant strabismus, and this should be accounted for when taking a history and examining the child. Forced duction and force generation tests may be performed in the office on adults, but are impossible on most children. Restriction to forced duction testing may only be uncovered in a child in the operating room. The surgeon should be ready to alter their plan based upon forced duction testing should paralytic strabismus be in question, keeping in mind the possibility of antagonist contracture following longstanding paresis.

Epidemiology

The combined annual population-based incidence of all ocular motor nerve palsies is 7.6 per 100,000, with fourth nerve palsies being the most common, followed by sixth nerve palsies, and third nerve palsies.[1] In this population-based incidence study, the most common etiology for fourth and third nerve palsies was congenital, while indeterminate origins were most common for sixth nerve palsies.[1] In an analysis of acquired cases seen at a tertiary referral center, the most common etiology was trauma.[2] Among cases presenting to tertiary referral centers, third nerve palsies are most frequently congenital or traumatic, fourth nerve palsies are most frequently congenital, and sixth nerve palsies are often associated with underlying neoplasms (Table 84.1).

Congenital third nerve palsy

Isolated oculomotor nerve palsies noted at birth are presumed to be the result of a prenatal or perinatal insult (Figs 84.1 and 84.2). High-resolution magnetic resonance imaging (MRI) may reveal a hypoplastic third nerve.[3] Many patients with a congenital third nerve palsy will exhibit aberrant regeneration, leading to complex motility dysfunction. Patients who have other neurologic deficits in association with an oculomotor palsy should undergo neuroimaging, as these children are likely to have more abnormalities of neuroanatomy. Bilateral

Table 84.1 Etiology of cranial nerve palsies presenting to tertiary care centers[5,14,26]

	Congenital	Trauma	Neoplastic	Inflammatory or Infectious	Craniofacial anomalies	Vascular	Idiopathic	Elevated intracranial pressure	Other
Third nerve palsy	34%	31%	13%	8%	X	11%	2%	X	X
Fourth nerve palsy	61%	5%	3%	1%	13%	X	15%	X	X
Sixth nerve palsy	11%	12%	45%	7%	X	X	5%	15%	5%

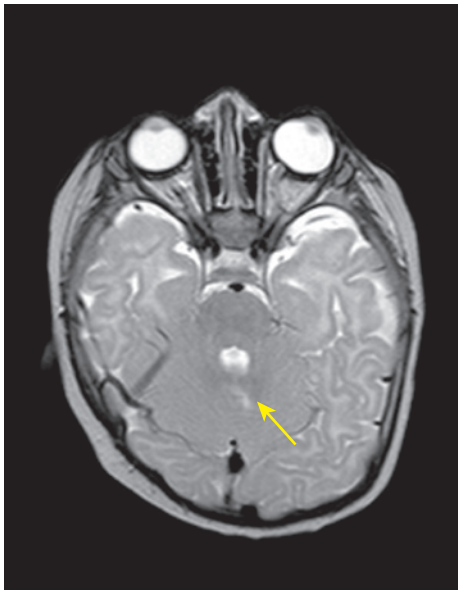


Fig. 84.1 Congenital left third nerve palsy. Axial T2-weighted scan shows superior vermis lesion (yellow arrow). (Other presumed perinatal hypoxic ischemic lesions seen elsewhere.)



Fig. 84.2 Congenital right third nerve palsy. Clinical photograph of a baby with a right congenital third nerve palsy. Note the miosis of the involved pupil, which can be seen in congenital third nerve palsies.

third nerve palsies should also undergo neuroimaging, which may reveal abnormal development of the third nerve nuclei, fourth nerve nuclei, and fibrosis of the extraocular muscles as part of the congenital cranial dysinnervation disorders[4] (see Chapter 83). Congenital third nerve palsies have been reported in association with PHACE syndrome, neurofibromatosis type II, neuroenteric cyst, agenesis of the internal carotid artery, and septo-optic dysplasia.

Patients with congenital third nerve palsies are likely to have visual impairment as a result of amblyogenic risk factors, including strabismus and ptosis. Treatment of the ptosis and strabismus may improve cosmesis, but restoration of binocular function is uncommon even after surgical and medical treatment.[5,6] Amblyopia treatment may be necessary, not only to attempt to improve vision in the amblyopic eye, but also to maintain visual acuity.

Acquired third nerve palsy

Approaching the child with a third nerve palsy starts with a good history and examination. A history of trauma or infection makes the diagnosis obvious, and many of these patients will come to see the ophthalmologist after undergoing neuroimaging. A history of remission and recurrence or headache also helps to direct the evaluation. However, any case of new-onset oculomotor nerve palsy should undergo neuroimaging.

The most common cause of an acquired third nerve palsy in childhood is trauma.[2,6] In closed head injuries, the entire length of the nerve, from nucleus to orbit, may be susceptible to injury. Shearing forces, skull fractures, brainstem herniation, and orbital fractures can all cause damage to the oculomotor nerve. Recovery of function altered by aberrant regeneration may be seen following the initial injury, particularly in complete third nerve palsies. Neoplasms of any type may cause third nerve palsies by compression at any point in the course of the third nerve. The presence of a slow-growing tumor such as a schwannoma or meningioma should be suspected if primary progressive signs of third nerve palsy are noted with evidence of aberrant regeneration. Tumors are the second most common cause of an acquired oculomotor nerve palsy.[2,6] Third nerve palsies may be seen in patients with meningitis from any organism. Direct inflammation and infection of the oculomotor nerve may lead to its dysfunction, or it can be affected by cavernous sinus thrombosis. Post-infectious or post-viral third nerve palsies usually resolve completely without recurrence, and are associated with normal neuroimaging. Aneurysms, in contrast to adults, are a rare cause of third nerve palsy in children. However, they do remain a possible etiology, with case reports in the literature.[7] For a patient with a painful third nerve palsy, angiography should be performed to rule out the possibility of an aneurysm. Vascular malformations can also lead to a third nerve palsy (Fig. 84.3). An interesting cause of third nerve palsy is the ophthalmoplegic migraine, now called "recurrent painful ophthalmoplegic neuropathy." Diagnosis is based upon fulfilling the criteria from the International Headache Committee of at least two attacks of unilateral headache accompanied by ipsilateral paresis of at least one ocular motor nerve, with absence of a causative lesion, and not consistent with another headache syndrome.[8] Enhancement of the third nerve may be present on MRI (Fig. 84.4). Resolution of the palsy may help to distinguish this entity from a schwannoma involving the oculomotor nerve, although schwannomas have been reported to mimic recurrent painful ophthalmoplegic neuropathy.[9] Treatment with steroids may be of some benefit. However, with recurrent attacks, a permanent deficit may develop.

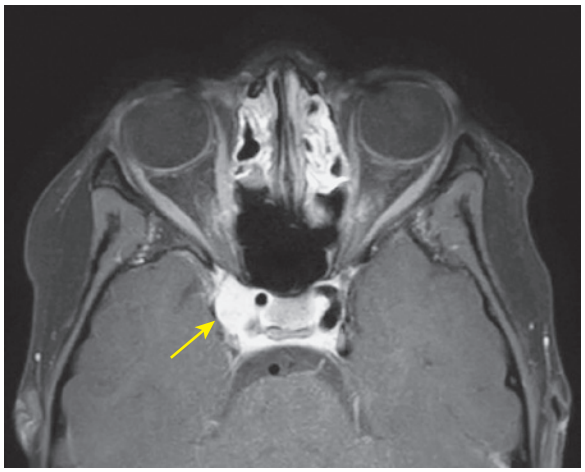


Fig. 84.3 Acquired partial right third nerve palsy. Axial T1-weighted fat-suppressed magnetic resonance imaging scan revealing a right cavernous sinus hemangioma (yellow arrow) in a patient with a partial right third nerve palsy.

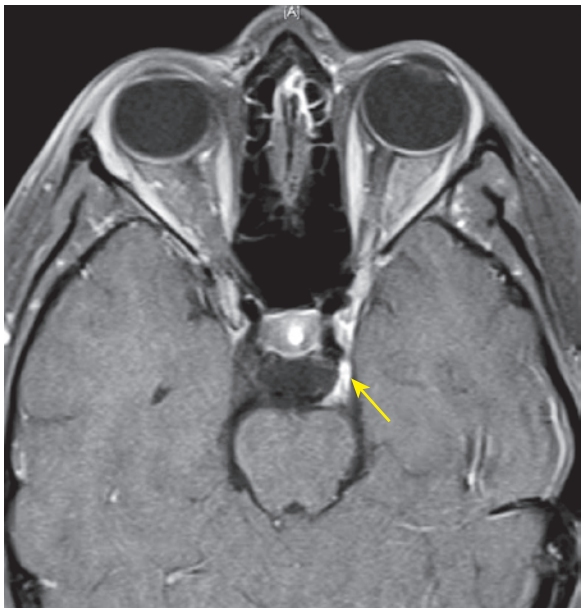


Fig. 84.4 Recurrent left third nerve palsy. Axial T1-weighted fat-suppressed magnetic resonance imaging scan revealing enhancement of the left third nerve (yellow arrow) in a patient with recurrent painful left third nerve palsy.

Treatment

Patients in the amblyogenic period should be pre-emptively treated to prevent the development of amblyopia while awaiting surgery or recovery of function. Recovery may take up to 6–12 months. Resolution of the third nerve palsy is associated with better visual outcomes in terms of visual acuity and binocularity. Strabismus from oculomotor nerve palsies is among the most complex and difficult disorders to treat. A complete third nerve palsy leaves only two functioning muscles: the superior oblique muscle and lateral rectus muscle. The eye is in a "down and out" position. Although the goal of surgery is to restore binocular single vision in primary position, this is difficult to achieve, and in children, binocularity is rarely restored.[5,6] Adoption of a head position may maintain binocularity in some children.[10] Strabismus surgery may be complicated by bizarre motility patterns caused by aberrant regeneration and misinnervation of the extraocular muscles. Many surgical procedures have been developed to treat complete oculomotor nerve palsies. These include large recess/resect procedures, transposition of the superior oblique tendon nasally,[11] disinsertion of the lateral rectus muscle with attachment to the periosteum of the orbit,[12] suture fixation of the globe to the periosteum, extirpation of the lateral rectus muscle, and nasally transposing the split halves of the lateral rectus muscle. Partial oculomotor nerve palsies are easier to treat as there are either fewer muscles involved, or the muscles involved are not completely paralyzed. This allows for more conventional surgery involving recession and resections of the appropriate muscles to expand the field of binocular single vision. Visual outcomes in patients with amblyopia are best in congenital cases, and traumatic and neoplastic etiologies for third nerve palsies have worse outcomes.[6] If the eyelid is malpositioned, strabismus surgery should precede ptosis repair. The eyelid position may change with strabismus surgery, and a ptotic eyelid will prevent diplopia, should strabismus surgery be unsuccessful.

Congenital fourth nerve palsy

Trochlear nerve palsies are the most common ocular motor nerve palsy in children, and the most common cause of hypertropia in childhood.[13] The majority of fourth nerve palsies were congenital in origin among patients under 8 years old presenting to a tertiary referral center, and none had previously unidentified underlying intracranial pathology.[14] Congenital fourth nerve palsies are the most common cause of pediatric fourth nerve palsies overall. Routine examination in asymptomatic patients may reveal an incidentally found head tilt or hyperphoria without diplopia that is consistent with a fourth nerve palsy.[1] The underlying cause of most congenital trochlear palsies is unknown, but some cases of nerve aplasia exist, which could possibly be on the spectrum of congenital cranial dysinnervation disorders[15] (see Chapter 83). The motility findings suggestive of a fourth nerve palsy include an ipsilateral hypertropia greater on contralateral gaze and ipsilateral head tilt. The Parks–Bielschowsky three-step test is classically used to identify a paretic muscle; however, its use in fourth nerve palsies associated with superior oblique atrophy demonstrated that the three-step test failed to identify 30% of cases.[16]

The finding of a head tilt is common in children who have a fourth nerve palsy. The head tilt is usually directed to the contralateral side of the palsy as a compensatory mechanism. In cases of longstanding and congenital fourth nerve palsies, the head tilt can be identified on previous photographs.[17] The patient may additionally have midface hypoplasia on the side of the head tilt. On MRI, the superior oblique tendon may be hypoplastic or absent in congenital cases. The belly of the superior oblique muscle atrophies in superior oblique palsy, and differential degrees of atrophy affect the clinical features observed.[18] The trochlear nerve itself may be congenitally absent, as has been revealed in MRI investigations.[19] Upon performing alternate cover testing, the examiner may find that the existing hypertropia increases in amplitude with prolonged

testing. Patients with congenital fourth nerve palsies tend to have larger than normal vertical fusional amplitudes, normal being about 2–3 primsm diopters (PD). Over time, young patients who were able to fuse large vertical amplitudes may experience a reduction in their fusional abilities and begin to experience diplopia despite being able to compensate earlier in their lives.

In patients who have congenital trochlear palsy, some demonstrate extreme laxity of the tendon on the exaggerated forced duction test.[20] Subjective and objective torsion should be measured, when possible, with double Maddox rod testing, synoptophore and fundus photography. The presence of excyclotorsion increases the likelihood of a superior oblique palsy, even if patients do not complain of torsion. Care should be taken to consider bilateral fourth nerve palsies, especially in cases in which excyclotorsion measures >10° in the primary position, a "V" pattern is present, and there is a hypertropia that reverses between right and left gazes.[21]

Many children with congenital fourth nerve palsies do not develop amblyopia or decreased binocular vision, likely because of the compensatory mechanisms of increased fusional amplitudes and head tilt. However, some children have very large manifest hypertropias. These children should be treated aggressively for amblyopia, and require strabismus surgery to improve alignment and promote binocularity. Patients with synostotic plagiocephaly may have abnormal eye movements due to abnormal anatomy that simulates superior oblique palsy due to excyclorotation of the entire orbital contents, altering the forces upon the globe during muscle contraction. This finding may also be present in patients without craniofacial disorders.[22]

Treatment

Initial management of small comitant deviations can be successfully achieved with prisms.[23] However, many children with a congenital fourth nerve palsy have torticollis, which can be corrected with strabismus surgery. In general, the surgical procedure of choice for isolated unilateral congenital fourth nerve palsy with a small hypertropia (<15 PD) and inferior oblique overaction is inferior oblique weakening, such as recession. If there appears to be restriction of the ipsilateral superior rectus, then this muscle should be recessed. If there is a larger deviation, an inferior oblique recession can be combined with an ipsilateral superior rectus recession in cases of superior rectus restriction, or the contralateral inferior rectus muscle can be recessed. In patients with a larger hypertopia in downgaze and no ipsilateral inferior oblique overaction, a contralateral inferior rectus recession may be the surgical procedure of choice. Laxity of the superior oblique tendon makes superior oblique tendon tucking an alternative procedure. Motor outcomes tend to be good in children, but sensory outcomes are poorer in younger patients.[14]

Acquired fourth nerve palsy

Unlike patients with congenital fourth nerve palsies, patients with acquired etiologies are much more commonly diplopic, unless they are very young and are easily able to suppress one eye. These patients do not have the large fusional amplitudes that patients with congenital fourth nerve palsies have. The trochlear nerve has the longest course of all the cranial nerves, and is particularly sensitive to trauma. The nerve can be damaged as it exits the brainstem dorsally. It can also be damaged by contrecoup injuries as it enters the tentorium, where it is particularly sensitive to shear forces. Bilateral fourth nerve palsies should be suspected in traumatic cases. Patients who present with new-onset non-traumatic fourth nerve palsy should undergo neuroimaging studies. Although rare, these patients may have more serious causes of their fourth nerve palsy. Hydrocephalus may be a cause of acquired unilateral or bilateral fourth nerve palsies. Idiopathic intracranial hypertension can also lead to fourth nerve palsies.[24] Neuroimaging is higher resolution and easier to obtain than in the past, and so abnormalities such as trochlear schwannomas are more frequently recognized as a cause of fourth nerve palsy. These lesions are benign, and can be serially monitored for the development of brainstem compression, and the underlying strabismus can be treated if stable.[25] However, rarely, an isolated new-onset fourth nerve palsy can be the harbinger of another compressive lesion such as a brain tumor. When evaluating children who are suspected of having a fourth nerve palsy, care should be taken to exclude other etiologies of a hypertropia such as skew deviations and dissociated vertical deviations.

Treatment

Similar to congenital superior oblique palsies, acquired superior oblique palsies can be treated with prisms alone if the deviation is small and comitant. The treatment algorithm is similar, with inferior oblique-weakening procedures the operation of choice for small incomitant hypertropias, with or without an inferior rectus recession if the deviation is greatest in downgaze, or combined with a superior rectus recession if there is superior rectus restriction and a large deviation. Torsion tends to play a larger role in diplopia complaints for patients with an acquired fourth nerve palsy. In cases where torsion is the main complaint and there is a very small or absent vertical diplopia component, a surgery should be performed to address torsion alone. The Harada–Ito procedure (as described in Chapter 86) allows for selective transposition of the anterior superior oblique tendon fibers involved in incylorotation of the globe. Various modifications of the Harada–Ito procedure have also been described, such as the Fells modification that involves disinserting the anterior fibers of the superior oblique tendon and transposing them 8 mm posterior to the superior insertion of the lateral rectus muscle. Bilateral Harada–Ito procedures are indicated in some cases of bilateral fourth nerve palsy (Fig. 84.5). Intraoperative adjustment of a Harada–Ito procedure is possible by visualizing objective torsion of the fundus using indirect ophthalmoscopy. Postoperative adjustment of a Harada–Ito procedure has also been described using adjustable sutures.

Congenital sixth nerve palsy

Sixth nerve palsies are most often acquired, in contrast to fourth nerve palsies. At a tertiary referral center, only 11% of pediatric sixth nerve palsies were determined to be congenital in origin.[26] There are cases of true congenital sixth nerve palsy

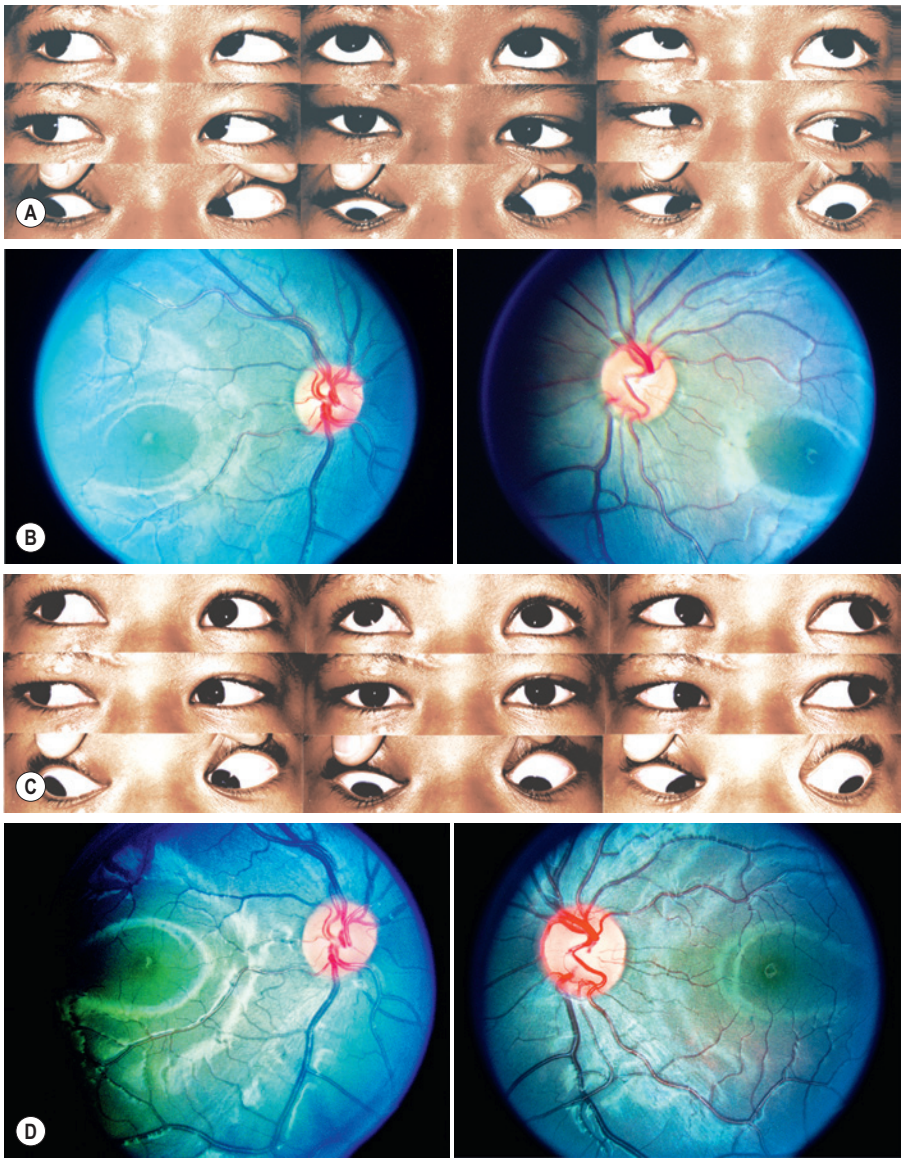


Fig. 84.5 Traumatic bilateral fourth nerve palsies. (A) Preoperative motility photographs in a patient with bilateral traumatic fourth nerve palsies. Note the "V" pattern esotropia and alternating hypertropia. (B) Preoperative fundus photographs demonstrating bilateral excyclotorsion. (C) Postoperative motility photographs demonstrating resolution of esotropia and alternating hypertropia following bilateral Harada–Ito procedures. (D) Postoperative fundus photographs demonstrating improvement in bilateral excyclotorsion following bilateral Harada–Ito procedures.

without misinnervation that present at or shortly after birth. These usually spontaneously resolve and are presumably secondary to birth trauma. Duane syndrome, a member of the congenital cranial dysinnervation disorders, is associated with absence of the sixth nerve nucleus and aplasia of the nerve[27] (Fig. 84.6 and see Chapter 83). Congenital bilateral sixth nerve palsies and seventh nerve palsies are the hallmarks of Möbius sequence (Fig. 84.7). Horizontal gaze palsy may be present as well due to involvement of the horizontal gaze centers. In the absence of classical findings of Duane syndrome, neuroimaging is required to eliminate the possibility of a more sinister cause of sixth nerve palsy in a neonate. Examination of the neonate or infant suspected of having a sixth nerve palsy can be difficult, and differentiating Duane syndrome from a sixth nerve palsy and infantile esotropia with cross-fixation may be challenging. Limited abduction or adduction, and narrowing of the palpebral fissure an attempted adduction and globe retraction are the hallmarks of Duane syndrome. Attempts can be made to have the child perform saccadic maneuvers with toys, to evaluate for a "floating" saccade suggestive of lateral

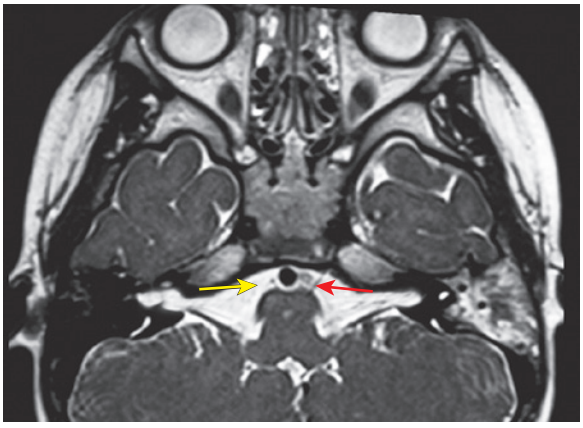


Fig. 84.6 Duane retraction syndrome. Axial oblique high-resolution reformatted volumetric T2-weighted magnetic resonance imaging scan demonstrating congenital absence of the right sixth nerve (yellow arrow) in comparison to a normal left sixth nerve (red arrow).

rectus palsy. Another technique is to hold an infant in one's arms and spin in the direction of the presumed paresis. The re-fixation movement will be in the direction of the suspect muscle, and a slowed re-fixation saccade indicates lateral rectus muscle weakness. As many patients with true congenital sixth nerve palsies experience spontaneous resolution within a few weeks to months, they may be observed without further treatment. Should surgery be necessary, it can be performed as described below for acquired sixth nerve palsies.

Acquired sixth nerve palsy

The majority of sixth nerve palsies in childhood are acquired. At a tertiary referral center, 45% of the patients seen with sixth nerve palsies had neoplasms or their treatment as the underlying etiology, while a population-based study found 17% were due to brain tumors.[1,26] Etiologies in descending order of frequency following tumor were: elevated intracranial pressure (such as from idiopathic intracranial hypertension or hydrocephalus), trauma, inflammatory, and idiopathic.[26] Due to the association of sixth nerve palsies with conditions of high morbidity, early neuroimaging is warranted. Younger patients may be capable of suppressing one eye, and do not complain of diplopia. A recent history of significant head trauma makes the diagnosis clearer, and these children often will already have had neuroimaging performed (Figs 84.8 and 84.9). The sixth nerve is particularly sensitive to traumatic injury where it passes under the petroclinoid ligament into Dorello's canal. Increased intracranial pressure is an important cause of unilateral and bilateral sixth nerve palsies and is usually accompanied by papilledema. Elevated intracranial pressure causes descent of the brainstem, leading to stretching of the sixth nerves at the skull base, leading to sixth nerve palsies. Any cause of elevated intracranial pressure can cause sixth nerve palsies, such as idiopathic intracranial hypertension, meningitis, venous sinus thrombosis, dural fistula, obstructive hydrocephalus, or tumor. The sixth nerve palsies, after treatment of the underlying cause of elevated intracranial pressure, usually spontaneously resolve. Brainstem and posterior fossa tumors are the most feared cause of a sixth nerve palsy in a child. It should be noted that a recent review of patients diagnosed in the emergency department with a brain tumor found that patients presented with symptoms and signs of sixth nerve palsies 6.9% of the time.[28] Brainstem and posterior fossa tumors, such as pontine gliomas, ependymomas, clival chordomas, and medulloblastomas, may lead to compression of the sixth nerve nuclei, nerves, or elevated intracranial pressure (Figs 84.10 and 84.11). Treatment of the underlying tumor and elevated intracranial pressure may lead to improvement of the sixth nerve palsy, or may worsen it through iatrogenic trauma. Cavernous malformations of the pons may spontaneously hemorrhage, leading to a sixth nerve palsy (Fig. 84.12). Cavernous sinus lesions may cause sixth nerve palsies, although it is unusual to be clinically isolated (Fig. 84.13). The finding of a sixth nerve palsy with an ipsilateral Horner syndrome should prompt neuroimaging to evaluate for a lesion in the cavernous sinus. Pituitary tumors may invade the cavernous sinus and cause a sixth nerve palsy. Sixth nerve palsies with retro-orbital pain (from involvement of the ophthalmic branch of the trigeminal nerve) following middle ear infections should prompt an evaluation for Gradenigo syndrome (infection involves the petrous apex) (Fig. 84.14). Multiple sclerosis may cause sixth nerve palsies, which usually recover. Following a viral infection or vaccination, patients may develop a post-viral sixth nerve



Fig. 84.7 Möbius sequence. Clinical photograph of a patient with Möbius sequence (congenital bilateral sixth and seventh nerve palsies) and a resulting left corneal ulcer.



Fig. 84.8 Acquired right sixth nerve palsy. Clinical photograph of an infant with a traumatic right sixth nerve palsy.



Fig. 84.9 Acquired right sixth nerve palsy. Motility photographs of a child with a traumatic right sixth nerve palsy.

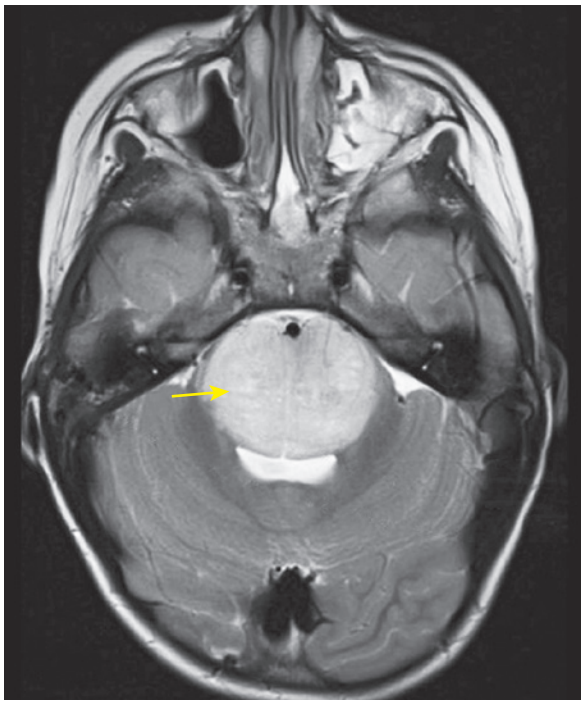


Fig. 84.10 Acquired left sixth nerve palsy. Axial T2-weighted magnetic resonance imaging scan revealing a pontine glioma (yellow arrow) causing a left sixth nerve palsy.

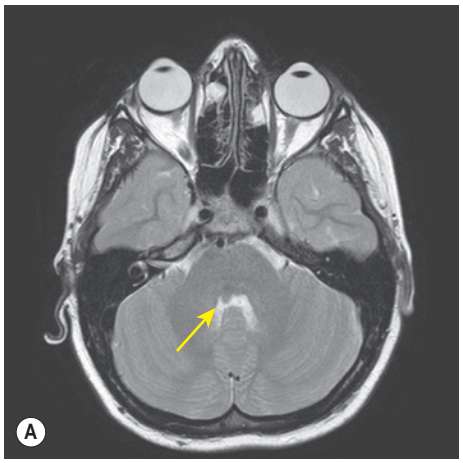




Fig. 84.11 Acquired bilateral sixth nerve palsies. (A) Axial T2-weighted magnetic resonance imaging scan revealing enlargement of the right facial colliculus; the child has bilateral sixth and right partial seventh nerve palsies. (B) Clinical photograph of the child demonstrating large-angle esotropia due to bilateral sixth nerve palsies.

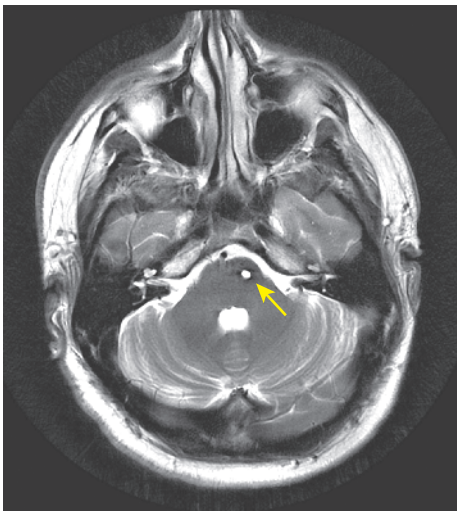


Fig. 84.12 Acquired left sixth nerve palsy. A 16-year-old presented with sudden onset left sixth nerve palsy. Axial T2-weighted magnetic resonance imaging scan shows a pontine cavernoma with signal rim from hemosiderin.

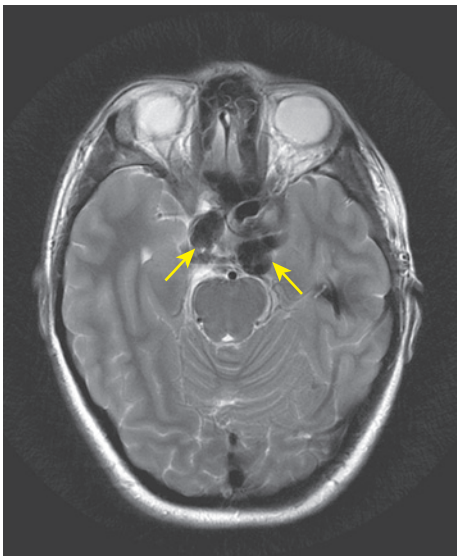


Fig. 84.13 Loeys–Dietz syndrome. Axial T2-weighted magnetic resonance imaging scan showing large flow voids in bilateral internal carotid artery aneurysms due to autosomal dominant connective tissue disorder. Patient has bilateral sixth nerve palsies.

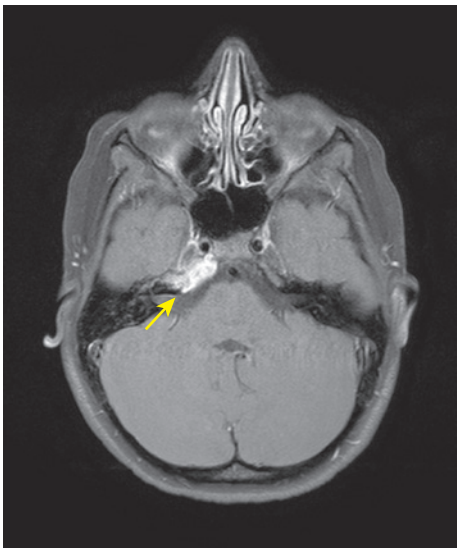


Fig. 84.14 Petrous apicitis. Axial T1-weighted post-gadolinium fat suppressed magnetic resonance imaging scan showing enhancement of the right petrous apex in a 6-year-old patient presenting with a painful right sixth nerve palsy.

palsy, which usually resolves spontaneously. Sixth nerve palsies may also occur on an idiopathic basis and are referred to as benign recurrent sixth nerve palsy. These children experience the sudden onset of an isolated complete sixth nerve palsy, which recovers, with no known etiology.[29] Older patients with benign or idiopathic sixth nerve palsies tend to experience recurrence less frequently.[30]

Treatment

Patients in the amblyogenic age range should be examined for the development of amblyopia when a sixth nerve palsy is discovered. Close follow-up for amblyopia is recommended, and preventative patching can be performed if one eye is noted to be dominant. Spontaneous recovery may occur, although recovery rates in children with traumatic sixth nerve palsies may be lower than that for adults. Small deviations may be treated with prism spectacles. However, patients who have incomitant strabismus may be best served by surgical intervention. Careful examination should be performed to evaluate the saccadic velocity of a child who had a sixth nerve palsy and a residual esotropia, to look for contracture of the medial rectus muscle following recovery of function of the lateral rectus muscle. Intraoperative forced duction testing will help with this diagnosis as well. Patients who have a partial sixth nerve palsy are best served by horizontal rectus recess/resect procedures to strengthen the abducting effect while treating any contracture of the ipsilateral medial rectus muscle. Patients who have a complete abduction deficit require a transposition operation to restore an abducting force. Surgical procedures that have been described to treat a sixth nerve palsy with a complete abduction deficit include: full vertical rectus muscle transposition, a Hummelsheim procedure (transposition of the lateral half of the superior and inferior rectus muscles), a Jensen procedure (suture fixation of the superior and inferior rectus muscles to the lateral rectus muscle), vertical rectus muscle transposition without tenotomy, and a superior rectus muscle transposition coupled with medial rectus muscle recession.[31]

These operations can be combined with an ipsilateral medial rectus muscle recession for medial rectus muscle contracture, either concurrently or at a later date, depending upon the vascular supply to the anterior segment. Pre- or intraoperative botulinum toxin injection to the medial rectus is a helpful non-surgical alternative. A contralateral medial rectus muscle recession with or without Faden operation can also be performed to match any residual lateral rectus abduction deficit and/or residual esotropia.

Multiple cranial nerve palsies

Clinical examination aids the neuroanatomic localization of a lesion in cases of multiple cranial nerve palsies. For instance a sixth nerve palsy associated with ipsilateal decreased corneal sensation (fifth nerve palsy) points to a cavernous sinus lesion, whereas sixth nerve palsy with ipsilateral facial nerve palsy suggests pontine pathology. Multiple ocular motor nerve palsies associated with pain on the same side can be localized to the cavernous sinus. Multiple ocular motor nerve palsies and an optic neuropathy can be localized to the orbital apex. Localization of the lesion is of utmost importance to assist the neuroradiologist in interpreting the study. Without the appropriate clinical information, the neuroradiologist may identify a small lesion if they knew where to focus their attention. Review of the actual images from neuroimaging studies by the ordering physician should be routine practice. Causative lesions of multiple cranial nerve palsy include cavernous sinus thrombosis, orbital apex tumors, Tolosa–Hunt syndrome, trauma, leukemia, and any brainstem neoplasm. Following viral illnesses, a patient may develop multiple cranial nerve palsies due to Miller–Fisher syndrome, a form of Guillain–Barré syndrome. Surgical correction of strabismus from multiple cranial nerve palsies surgically can be very difficult, especially when the palsies are complete.

Role of botulinum toxin

Botulinum toxin can be used as a temporizing method of improving binocular vision while awaiting possible spontaneous recovery in sixth nerve palsies. The botulinum toxin is injected into the antagonist medial rectus muscle. However, botulinum toxin for acute sixth nerve palsies has been reported to have no long-term effect on the outcome.[32]

Mimickers of paralytic strabismus

Restrictive etiologies of strabismus may be obvious by history, such as post-traumatic orbital fracture with muscle entrapment and fibrosis, or may be shown on neuroimaging of the orbits. Myasthenia gravis is the great mimicker of cranial nerve palsies. Fluctuating ptosis, variable measurements, a Cogan's lid twitch, fatiguability, are all suggestive of myasthenia gravis. Children with ocular myasthenia gravis may be treated with pyrodistigmine alone and the ocular findings may resolve or stabilize over time.[33] The development of generalized myasthenia gravis in patients who present with ocular findings alone occur in 23% of patients.[34] Amblyopia may develop from ptosis or strabismus and should be treated aggressively. Finally, forced duction testing should be performed on every patient intraoperatively to determine if there is a restrictive component to their strabismus. The results may influence the surgical plan.

Acknowledgments

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Strabismus: nonsurgical treatment

Alejandra de Alba Campomanes

Chapter contents

OPTICAL CORRECTION
OCCLUSION THERAPY
PRISMS
ORTHOPTIC EXERCISES/VISION THERAPY
DRUGS
REFERENCES

See online for supporting video for this chapter.

Many treatments used to manage children and adults with strabismus are nonsurgical. Even in patients who require surgery to restore normal alignment and/or binocular function, our surgical approaches are usually complemented by nonsurgical treatments ranging from altering the refractive correction to using pharmacological chemodenervation with botulinum toxin. The treatment of some forms of strabismus is entirely nonsurgical. For example, the treatment of convergence insufficiency includes vergence-accommodative exercises, or passive treatment with base-in prisms, but surgery is rarely required. This chapter reviews some of the most common nonsurgical treatments used in the management of strabismus, concentrating, when possible, on the best available evidence that supports their use.

Optical correction

Refractive errors, whether corrected or uncorrected, have a major impact on strabismus and its management. Correcting a refractive error may result in better control of a misalignment solely by gaining optimal visual acuity. Conversely, previously uncorrected non-alternating strabismus patients can be made symptomatic if correcting their refractive error results in spontaneous alternation or switch of fixation to their non-dominant eye.[1]

All children and young adults with strabismus or suspected strabismus require a cycloplegic refraction to determine the basic refractive state without the influence of accommodation. This can be done with 0.5% to 2% cyclopentolate (plus 1% tropicamide in dark irides), or 1% atropine. Cyclopentolate is commonly preferred over atropine due to its shorter onset and duration of action. The mean residual accommodation of these agents is less than 0.1 D for a 3-day administration of 1% atropine, and between 0.4 and 0.6 D for 1% cyclopentolate with 1% tropicamide.[2] The difference between atropine and cyclopentolate cycloplegia has consistently been measured to be between 0.4 and 0.7 D,[2–5] but it is important to recognize that 15–20% of children who have a cycloplegic refraction with 1% cyclopentolate alone will have a hyperopic undercorrection of 1 D or more.[2,3] Therefore, in accommodative esotropia with a residual deviation, an atropine refraction is still essential to uncover the maximal amount of hyperopia that needs to be corrected. The pupillary dilation achieved with any of these agents allows for an adequate funduscopic exam, which is mandatory during the initial evaluation of a strabismus patient to exclude visual axis opacification or abnormalities of the posterior segment.

Considering the optimal optical correction for each patient is essential in the management of their strabismus. In acquired esotropia, particularly accommodative esotropia, all degrees of hypermetropia may be significant, and should be fully corrected with spectacles. The full hyperopic correction should be prescribed in order to remove all accommodative convergence. In most forms of esotropia (including essential infantile esotropia), following surgical alignment, spectacle correction may be of considerable value in improving a small residual deviation. However, in patients with surgical overcorrections of partially accommodative esotropia, reduction of the hypermetropic correction of more than +2.50 D may be associated with long-term instability of the alignment: such overcorrections should be avoided.[6,7]

Bifocals may be indicated in children with a high accommodative convergence to accommodation ratio (AC/A) accommodative esotropia (convergence excess esotropia), if the full hypermetropic spectacle correction aligns the eyes for distance fixation, but a residual esotropia is seen at near.[8,9] Bifocals can be prescribed either as +3.00 D add or with the minimum near addition, which controls the near esotropia.[8] The recommended strategy is then to gradually and incrementally reduce the bifocal correction once the patient has demonstrated stable alignment and fusional amplitudes. It is important to make sure that when the child looks down, as when reading, the line of sight will be through the bifocal segment (executive style or large flat-top segment bisecting the pupil) and that the glasses are properly fitted to prevent slippage on the nose. It is surprising how often these details are neglected.

In patients with intermittent exotropia (IXT), it may seem logical not to correct moderate to high hypermetropia since accommodative convergence has a beneficial effect on the

control of the exodeviation. However, patients with high hyperopia and IXT may not be accommodating fully and may be experiencing blur, resulting in poor control of the deviation. In fact, a small study of children with moderate to high hyperopia (3–7 D) and IXT showed that full hyperopic prescription corrected the manifest deviation and improved the binocular status in all the patients.[10] In contrast, a different study showed that partial spectacle correction of hyperopia increased the exodeviation by an average of 10 prism diopters (PD) in one-third of patients with moderate hyperopia and IXT. This was not observed in patients with fully corrected hyperopia, emmetropia, or myopia.[11] High hyperopia, anisometropia, significant astigmatism, and myopia should always be corrected in patients with IXT. It is unclear if moderate hyperopia needs to be corrected unless the patient has decreased vision, or if surgical planning should be done wearing moderate hyperopic corrections to improve long-term surgical outcomes.[11]

For the treatment of IXT, much controversy still exists regarding what is the optimal nonsurgical treatment and its timing. Ideally, nonsurgical interventions improve the ability to control the deviation, preserve stereoacuity, and eliminate, or at least delay, surgical treatment. Most of these interventions have not been rigorously studied and their efficacy remains unclear.[12,13] Over-minus lens therapy (1.5–4 D additional minus) has been proposed to stimulate accommodative convergence and improve control of the exodeviation. In three prospective studies of children treated with over-minus glasses, some form of improvement (depending on the outcome measure used) was seen in 45–70% of patients.[14–16] This improvement was seen irrespective of the initial angle of deviation and, in some patients, was maintained after discontinuation of therapy. Over-minus therapy does not appear to increase myopia.[16,17]

In children with IXT, part-time occlusion of either the preferred eye or alternate patching has been reported to aid in eliminating suppression, improving the frequency or decreasing the magnitude of the deviation. Published studies have varied in terms of patching dosage, duration, and outcome measures, and have reported varying success rates.

The Pediatric Eye Disease Investigator Group (PEDIG) conducted a multicenter randomized controlled trial to determine the effectiveness of part-time patching (3 hours per day) compared with observation alone for reducing the risk of IXT deterioration over 6 months among 324 previously untreated children 3 to <11 years of age. This study is the first phase of a 3-year natural history study of IXT. The primary outcome measure of deterioration was the loss of motor control (IXT changing to a constant exotropia) or worsening of sensory fusion (decrease in stereoacuity). The effects were evaluated after 1 month of discontinuing patching.

The study found a small treatment effect of patching over observation but the proportion of patients who deteriorated in both groups was very small. At 6 months, deterioration occurred in only 6% of the patients in the observation group and 0.6% in the patching group (95% confidence interval [CI], 1.6–10.3%). Additionally, there were no statistically significant differences in rates of improvement in deviation magnitude, motor control, or stereoacuity in either group. The authors calculated the number of children who would need to be patched to prevent a single deterioration (number needed to treat) to be between 19–33 (depending on what definition of deterioration was used).[18] Similar findings were reported for the 12–35 months of age cohort,[19] where the rate of deterioration at 6 months was 2.2% for the patching group and between 2.3% and 4.6% for the observation group, making it unlikely that part-time patching provides a meaningful short-term benefit for young children with IXT. However, it also seems evident that immediate surgical intervention is not necessary to prevent IXT from deteriorating. Parental concern appears to be one of the more important drivers for immediate treatment of IXT[18,19] and patching did not have a deleterious effect on subjects with IXT. When deciding whether or not to initiate occlusion treatment in patients with IXT, one must consider several factors: age, compliance, psychosocial impact of patching on patient and caregiver, potential to delay surgery, presence of amblyopia, parental concern, and unknown effect over longer treatment periods.

Occlusion therapy

Some practitioners recommend treating amblyopia fully before strabismus surgery, even though in some cases this means delaying strabismus surgery. Two prospective studies evaluated the need for completion of amblyopia therapy versus early operation with continuation of occlusion postoperatively. Neither study detected a significant difference in motor or sensory outcome whether amblyopia was fully or only partially treated before surgery, provided that amblyopia treatment continued after surgery.[20,21] A recent study reported that, in patients with partially accommodative esotropia, the mean angle of deviation decreased significantly after occlusion treatment for amblyopia and noted that occlusion may resolve the non-accommodative component of the deviation, obviating the need for surgery. In that study, surgery would have been performed in 81% of patients if performed before the termination of amblyopia treatment, compared to 38% of patients that ultimately required surgery.[22] Another study showed that 61% of 46 small-angle strabismic children 1½–9 years of age, undergoing part-time treatment with Bangerter foils for amblyopia, developed motor fusion with no additional interventions.[23]

Prisms

Prisms have limited value in the management of early childhood strabismus. If a child has a temporary deviation that is expected to improve, as in consecutive esotropia after surgery for exotropia or in a post-viral sixth nerve palsy, temporary Fresnel prisms may be used to maintain binocularity while the deviation resolves. Prisms can be used for preoperative evaluation and calculation of surgical dosages (prism adaptation test) in patients with strabismus.

A recent case report documented the use of Fresnel prism to treat cyclic esotropia in a 6-year-old female with anisometropic amblyopia and esophoria who then developed cyclic esotropia. The authors report long-term resolution of the strabismus after 1 month of treatment with prisms, breaking the cyclic rhythm, perhaps, by restoring binocular function immediately.[24] Base-in prisms for reading can be used in patients with symptomatic convergence insufficiency.

Orthoptic exercises/vision therapy

Orthoptic exercises are sometimes used to teach patients how to use their fusion ability more efficiently. Orthoptic exercises may help in establishing control of strabismus in a small group of patients with good fusion potential. The effectiveness of orthoptic exercises (and the broader practice of "vision therapy" supported by some branches of optometry) in treating most forms of strabismus is debated. A comprehensive review of the evidence supporting orthoptic exercises/vision therapy from the UK concluded that there was little evidence-based research to support these practices.[25] A notable exception is the management of convergence insufficiency.[26,27] The Convergence Insufficiency Treatment Trial, a placebo-controlled randomized clinical trial, demonstrated that a 12-week office-based program of vergence and accommodative exercises (the patient is asked to converge on targets placed on a string or on a handheld card) with home reinforcement was more effective in reducing convergence insufficiency *symptoms* than home-based "pencil push-ups," home-based computer therapy plus "pencil push-ups," or office-based placebo therapy in children.[28] A similar conclusion was reached by the same researchers investigating convergence insufficiency treatment in young adults.[29] Symptomatic relief versus objective changes in accommodation and convergence, and the question of the true intrinsic treatment effects of office-based therapy versus the effects of motivation, effort, practice, and placebo due to therapist encouragement, continue to be debated.[30]

Drugs

Irreversible cholinesterase inhibitors, such as echothiopate (Phospholine Iodide® 0.125%, 0.0625% and 0.0325%) drops, can be used to control accommodation and, thereby, accommodative convergence. Pilocarpine, a muscarinic receptor agonist, can be used to decrease the synkinetic convergence response. Contraction of the ciliary body produces increased convexity and forward shifting of the lens, resulting in a myopic shift and reduction in the active accommodation effort made. The most common indications for these medications include persistent consecutive esotropia after surgical overcorrection of exotropia, small residual postoperative esotropia, and as a supplement to glasses in patients with high AC/A accommodative esotropia with residual esodeviation at near.

Phospholine iodide is rarely used now due to its limited commercial availability and side effects (supraorbital pain, poor vision [especially at night], and iris cysts and lens opacities with long-term use). Systemic absorption of the drops causes a depletion of plasma cholinesterase, making the patient susceptible to depolarizing muscle relaxants. If a child treated with cholinesterase inhibitors requires general anesthesia, a depolarizing relaxing agent such as succinylcholine should be avoided, as prolonged respiratory paralysis may result. The depletion may last up to 6 weeks and parents should be advised appropriately. To reduce the risk of iris cyst formation, phenylephrine eye drops can be prescribed concurrently.

In hypermetropic esotropic children who do not tolerate their newly prescribed spectacles, atropine 1% once daily for 5 days can be used to blur the vision and give the child an incentive to wear glasses (pharmacological encouragement).

In contrast to strabismus surgery, the treatment of strabismus with pharmacologic agents has the advantage of changing the functional qualities of the extraocular muscles (contractile strength, elastic stiffness, muscle length) without resecting tissue or compromising orbital mechanics.[31] Pharmacologic agents that have been used with success in the treatment of strabismus include botulinum toxin and the amino amide anesthetic, bupivacaine.

Botulinum toxin

The pharmacologic treatment of strabismus was pioneered by Scott, who experimented with the direct injection of various substances into the extraocular muscles. In 1990, botulinum toxin type A was granted Food and Drug Administration (FDA) approval. Botulinum toxin type A (BTX-A) is a large protein molecule of 150,000 daltons. After intramuscular injection, the toxin enters and remains at the nerve terminal for several days to weeks, inhibiting the release of acetylcholine by cleaving SNAP-25, a protein integral to the successful docking and release of the neurotransmitter in vesicles within the nerve endings, resulting in muscle weakness or paralysis maximal within 3–5 days after the injection. Although an irreversible binding occurs, extrajunctional acetylcholine receptors may develop. The nerve reinnervates the muscle with a reversal of the paralysis and eventual recovery. Extraocular muscle paralysis usually lasts from 2 to 8 weeks.

The mechanism by which permanent alignment can occur after the paralyzing effect of botulinum toxin is gone is not completely understood. One theory is that if the antagonist muscle remains contracted for a certain time because of reduced force in treated muscle, it will develop structural alterations that shorten it[32,33] and decrease its elasticity (contracture). Conversely, the chemodenervated muscle will undergo lengthening as its antagonist contracts. This length adaptation is believed to occur through the addition and deletion of sarcomeres.[32] The alterations induced in extraocular muscles by botulinum treatment have been shown to be specific to the orbital singly innervated muscle fibers.[33,34] This fiber-type specificity is thought to explain the permanent effect on static alignment but sparing the saccade kinematics after BTX-A injection.[34,35] Sensory mechanisms must also play a role in the permanent re-alignment after treatment with BTX-A in selected types of strabismus.[36] The structural theory (selective fiber-type atrophy) is clearly an insufficient explanation, as permanent double vision is rarely seen in patients who have diplopia immediately after periorbital BTX-A injections.[34]

The lyophilized drug is supplied in 100-IU vials and is reconstituted with non-preserved saline solution (0.9% sodium chloride injection), resulting in doses from 1 IU/0.1 mL to 12 IU/0.1 mL. One unit is equivalent to one-fiftieth of a lethal dose in a rat, or 4 ng. The estimated systemic toxic dose is 40 IU/kg body weight. Botulinum toxin is now commercially available as BOTOX™ (OnabotulinumtoxinA), Dysport™ (AbobotulinumtoxinA), Xiomin™ (IncobotulinumtoxinA), and Myobloc™ (RimabotulinumtoxinB).

Injection technique

Transconjunctival injection of botulinum toxin can be done with or without electromyography (EMG) guidance (Fig. 85.1). Adult patients can have the procedure with topical anesthesia; in younger patients, injections should be administered under

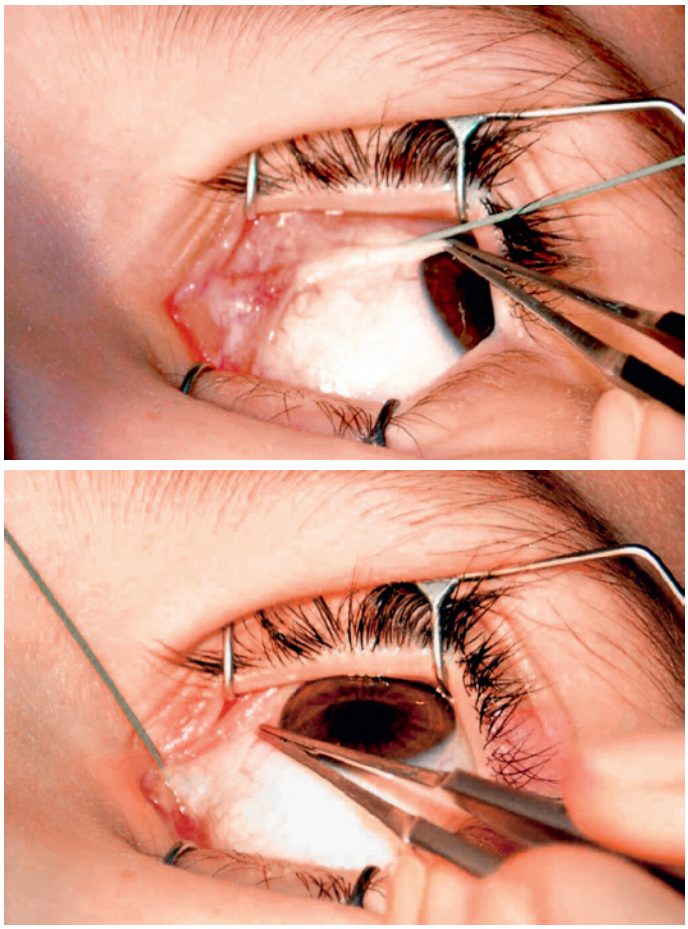


Fig. 85.1 Botulinum toxin A injection with electromyography. *(Courtesy of Pilar Gómez de Liaño, Madrid, Spain.)*

sedation using very low doses of ketamine if EMG is used. Ketamine produces unpleasant dreams or hallucinations when emerging from the dissociative state in about 5% of patients. To curb this reaction, some surgeons add a benzodiazepine, such as midazolam, at the end of the procedure, but the effectiveness is controversial.[37] The incidence of this unpleasant emergence reaction increases with age and with psychiatric comorbidities. It is contraindicated in patients with psychosis or those younger than 3 months of age.[37] When the injection is done without EMG assistance, sevofluorane, propofol, ketamine, or nitrous oxide can be used.[38] The efficacy and complication rates with and without EMG control appear comparable.[39–41]

This author performs most of the injections using a closed conjunctival technique without EMG (Fig. 85.2). Others prefer to inject under direct visualization using an "open sky" technique,[36] but this negates some of the advantages of BTX-A treatment over surgery (shorter anesthesia time, reduced scarring, etc.) We reserve the open sky technique for patients with previous large muscle recessions (Fig. 85.3). After placing a lid speculum, the eye is rotated into the opposite direction of the muscle being injected using conjunctival forceps. The insertion is identified and firmly grasped using toothed forceps such as Elschnig or Mendonça forceps[41] (Fig. 85.4) and a 25- to 27-gauge needle, with the bevel toward the sclera, on an insulin syringe is passed through the grasped tendon. The eye is then rotated to the straight position and the needle is introduced into the muscle belly. The desired dose of

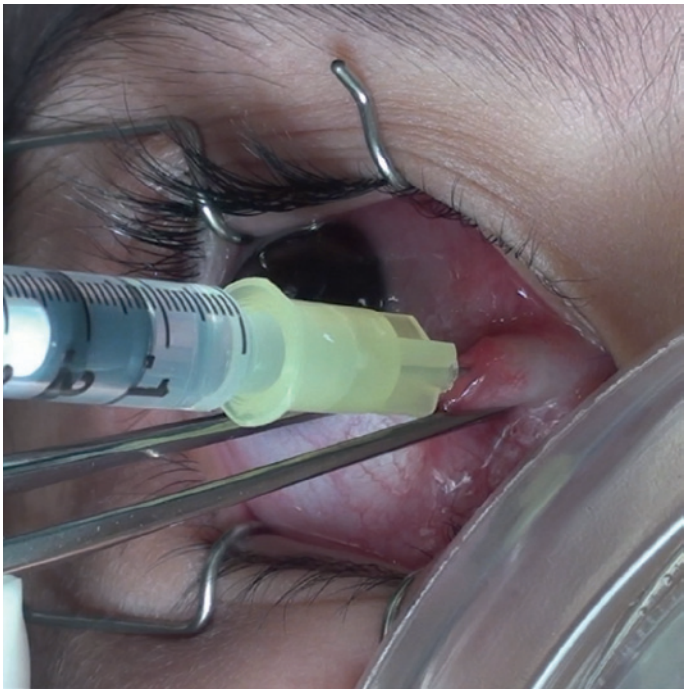


Fig. 85.2 Botulinum toxin A injection with closed conjunctiva technique.

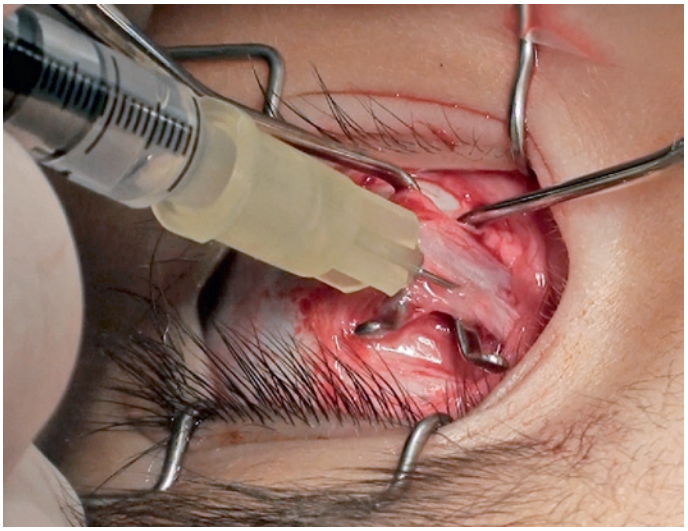


Fig. 85.3 Botulinum toxin A injection with open sky technique.

the drug is injected and the needle is retrieved; care is taken not to retract the needle too fast to avoid having the drug track back with the needle and diffuse out of the muscle.

Under EMG guidance, a special needle acts also as an EMG electrode connected to an amplifier that converts the electrical signal from the muscle to sound. The needle is introduced through the conjunctiva and conducted to the muscle until a characteristic cracking sound is heard, confirming that the tip is in the muscle body. The needle must penetrate the muscle posteriorly, close to the nerve insertion.

The doses used vary, most authors recommending 1.25–7.5 IU per muscle[42–44] in a volume of 0.05–0.15 mL per muscle (Table 85.1).

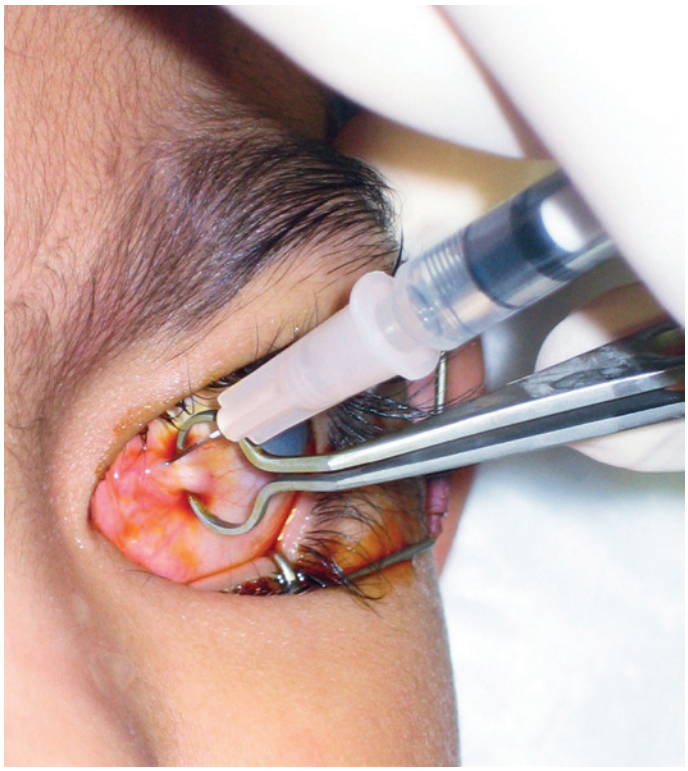


Fig. 85.4 Botulinum toxin A injection using Mendonça forceps.

Table 85.1 Examples of botulinum toxin type A doses

Indication	Dose
STRABISMUS	
Horizontal/vertical strabismus <20 PD	1.25–2.5 IU
Horizontal/vertical strabismus 20–50 PD	2.5–5.0 IU
Re-injection	1.5–2× original dose
CHILDHOOD ESOTROPIA	
Initial	2.5–5 IU
Re-injection	5–7.5 IU
SIXTH NERVE PALSY	
Initial LR weakness	1.5–2.5 IU
Recovered LR function, persistent small ET	2.5 IU
Large ET, paretic LR	5 IU
With transposition	2.5–5 IU

ET, Esotropia; LR, lateral rectus muscle.

Indications

The conditions that are most amenable to treatment with BTX-A are summarized in Box 85.1. The most common indications include small-to-moderate angle infantile and acquired childhood esotropia, postsurgical residual esotropia, and sixth nerve palsy in the acute phase. Unfortunately, most studies supporting or rejecting the efficacy of BTX-A as an alternative to surgery have lacked the methodological rigor of evidence-based medicine.[45]

Box 85.1

Common current indications of botulinum toxin type A

- Infantile esotropia without vertical deviations, little or no contraction, and moderate to small angle in patients less than 2–3 years old
- Acquired esotropia of less than 30 PD
- Residual esotropia of <30 PD (after surgery)
- Esotropia in patients with developmental delay (especially with angle variability)
- Consecutive exotropia if no duction deficit
- Acute sixth nerve palsy
- Diagnostically for the investigation of sensory or motor status in complex strabismus cases
- Treatment of oscillopsia in acquired nystagmus (retrobulbar or 4 muscle injection)

In two randomized controlled trials, BTX-A injection was as effective as re-operation in the treatment of residual esotropia after surgery for acquired[46] or infantile[47] esotropia, in terms of both motor and sensory outcomes. For acquired esotropia in children, the same authors reported that 1–3 injections of BTX-A as primary treatment was effective in 88% of patients.[44]

The success rate of BTX-A for the treatment of infantile esotropia (alignment within 10 PD of orthotropia) varies between 33% and 89%.[36,42,43,48–51] McNeer reported a high success rate of alignment (89%) in selected patients with infantile esotropia and a small to moderate angle of deviation.[49] Campos reported similar findings with a single injection in patients younger than 8 months old and small-to-moderate deviations.[36] Other studies have found an unacceptable rate of treatment failure, concluding that the prolonged period of misalignment and the need for multiple injections could interfere with early alignment and establishment of binocular vision.[52,53] The validity of these studies is limited due to no randomization and masking, small sample sizes, short follow-up, or ill-defined patient populations.

The author's group conducted a prospective, single center, non-randomized comparison between BTX-A and surgery as primary treatment in infantile esotropia before the age of 36 months. The primary outcome was alignment within 10 PD of orthotropia after one surgery or 1–3 bilateral botulinum injections.[42] BTX-A was injected in 322 patients and 120 patients underwent surgery. The odds of achieving a successful outcome at the average angle of deviation pretreatment (38.6 PD) was 2.3 times higher in the surgical group than in the patients receiving BTX-A. However, there was a significant interaction between treatment group and pretreatment angle of deviation. A *post hoc* subgroup analysis was conducted using stratification by angle of deviation. This revealed that in subjects with deviations ≤30 PD, there was no statistical difference between groups, with 60% success rate in the surgery group and 59% in the botulinum toxin group (relative risk [RR], 1.03; 95% CI, 0.78–1.35). At deviation >30 PD, surgery achieved 69% success versus 36% with botulinum toxin (RR, 1.95; 95% CI, 1.53–2.49) (Fig. 85.5).

The relationship between the size of the strabismus angle and BTX-A effectiveness is well documented.[42,44,51] Studies that do not include appropriate stratification and effect modification analysis by different predictors, especially

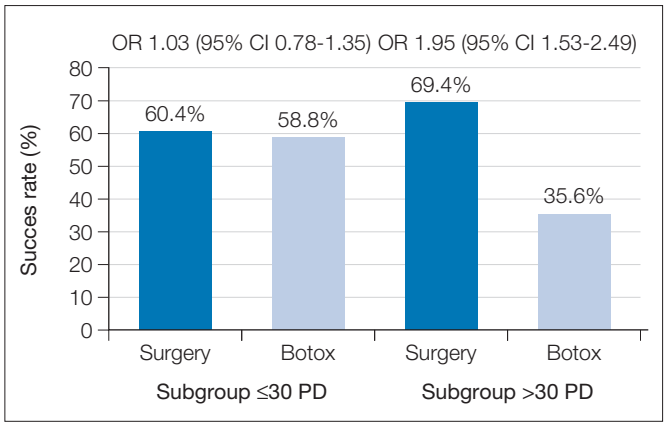


Fig. 85.5 Effectiveness of surgery versus botulinum toxin A (BTX-A) by angle of deviation. The pretreatment angle of deviation was statistically associated with a successful outcome in the BTX-A group only (the mean angle in the success group was 35.2 PD compared to 41.6 PD in the group with an unsuccessful outcome, $p<0.0001$). The magnitude of deviation did not predict a successful outcome in the surgical group ($p=0.17$). A *post hoc* subgroup analysis of those deviations classified as "small-angle esotropias" (≤30 PD) was performed. Stratification by this angle of deviation revealed that among subjects with deviations ≤30 PD, there was no statistical difference between groups (surgery 60%, botulinum toxin 59%; odds ratio [OR], 1.03; 95% confidence interval [CI], 0.78–1.35). At deviation >30 PD, surgery achieved 69% success versus 36% with botulinum toxin (OR, 1.95; 95% CI, 1.53–2.49).

magnitude of the deviation, will fail to demonstrate BTX-A true efficacy compared to surgery. Other possible interactions and confounders such as sensory status,[54] age,[36,49] and duration of misalignment may also play an important role in predicting which patients will have a favorable response to this treatment. The paucity of randomized clinical trials and well-conducted prospective studies have limited our understanding of which patients will obtain the greatest benefit from BTX-A.

BTX-A is less frequently used for exotropia and vertical deviations. Some use it in residual XT <15 PD or in young children (less than 3 years of age) with poorly controlled IXT, with the objective of delaying surgery until the age of 5–6 years. It has also been used successfully in patients with overcorrected exotropia and fusion potential.[55]

For cranial nerve palsies, the most common application of BTX-A is in the acute phase of a sixth nerve palsy to prevent contracture of the unopposed ipsilateral medial rectus muscle. Such contracture may lead to persistent esotropia even when there is recovery of the lateral rectus function. Reports of cases successfully treated with BTX-A injection, even after years of the onset of the esotropia, supports this concept, but whether this secondary contracture can be prevented is controversial. If truly effective, botulinum toxin injection into the medial rectus soon after the onset of the esotropia would improve the spontaneous recovery rate of sixth nerve palsies and decrease the rates of surgery.

Lee et al. reported their experience with non-traumatic acute sixth nerve palsy randomized to observation versus BTX-A injection to the ipsilateral medial rectus muscle.[56] At 6 months, no statistically significant difference was observed. Control of the deviation (within 10 PD of ortho) and single vision was achieved in 86% of the patients treated with BTX-A, and in 80% of the control patients. Despite randomizations, the two groups were different with respect to their initial angle of deviation (10 PD larger on average in the BTX-A group) and duration. Multivariate analysis adjusting for these differences (re-analyzed from published data) suggests that there may be an advantage to using BTX-A (odds ratio, 5.9; 95% CI, 0.6–57.8), although the power was insufficient to reach statistical significance. A non-randomized study conducted by the PEDIG reported that in 84 patients, age 2–79 years, with acute traumatic sixth nerve palsy, the adjusted relative risk of recovery in patients that received BTX-A within 3 months of injury was only 14% higher than in patients managed with observation alone (RR, 1.14; 95% CI, 0.70–1.35).[57]

The same investigators prospectively studied 56 patients with sixth nerve palsies of more than 6 months duration non-randomly allocated to observation, BTX-A alone, surgery alone, or a combination of surgery plus BTX-A. The success rates (absence of diplopia and ET <10 PD in primary gaze) were 10% (95% CI, 0–45%) in the BTX-A and 39% (95% CI, 17–64%) in the surgical groups. However, the authors warned that the different success rates might be due to selection bias and confounding by indication. For example, patients that received BTX-A were on average 27 years older than those who received surgery; 40% of patients that received BTX-A had complete paresis of the sixth nerve compared to 27% in the surgical group and most of the cases with a neoplastic etiology were treated with BTX-A alone. This study is also limited by its small sample size; the 95% confidence interval for the success rates in these two groups overlap significantly. Additional care should be taken when interpreting these results since these patients had a chronic longstanding deviation (median 270 days from onset to injection) and prevention of secondary contracture would not be expected.[58]

Medial rectus muscle injection of BTX-A prior to or during vertical muscle transposition can be used as an alternative to medial rectus recession, especially when anterior segment ischemia is of concern.

Complications

The complications of BTX-A treatment include subconjunctival hemorrhage, transient ptosis (Fig. 85.6) and hyperdeviations that usually resolve within 6 months (most resolving within several weeks of the injection). Transient vertical deviations occur in 5–30% of patients and ptosis in 15–35%. It is usually unilateral, and the risk increases with higher doses.[59] The amblyogenic potential of ptosis must be considered in young children, but most authors report only partial reversible ptosis with no amblyogenic effects observed. Pupillary abnormalities have also been reported after BTX injection; this has been described as a tonic pupil in the first week after the injection with delayed denervation hypersensitivity to pilocarpine.[60–63] It is unclear if this is due to direct trauma to the ciliary ganglion, anticholinergic toxicity from intraconal diffusion of BTX-A affecting the ciliary ganglion, and/or intraocular diffusion affecting the pupillary sphincter.[61,64] Rare, but severe, complications include globe perforation and retrobulbar hemorrhage. No systemic paralytic effect has been observed or suspected in any patient treated with the small doses of BTX-A used for strabismus. Antibodies to the toxin have not been detected in patients given small doses for ocular use. Therefore, repeat injections can be given when necessary.

In infantile esotropia, a temporary exotropia is not considered a complication of treatment; it is not only expected, but considered a sign of good prognosis.[36] It usually resolves by 6 weeks (4–10 weeks). Re-injection is recommended

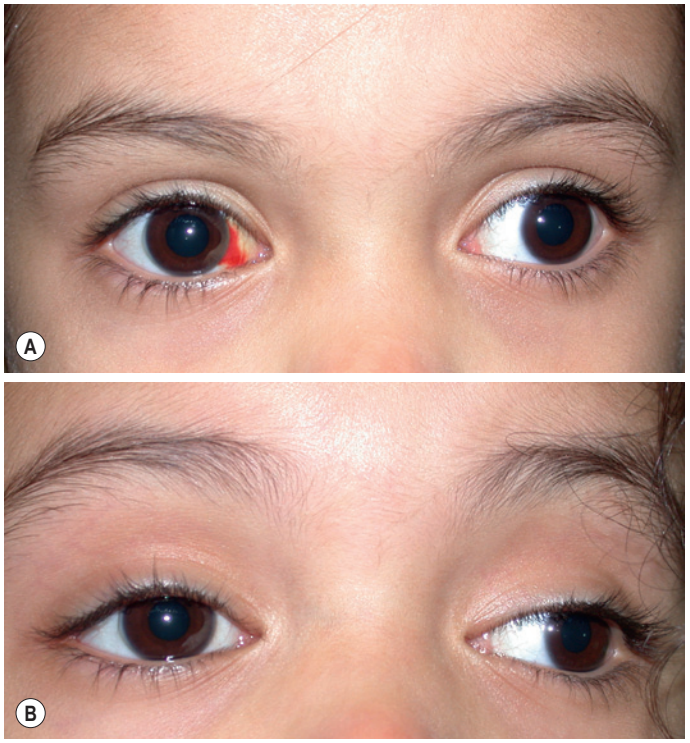


Fig. 85.6 Exotropia, ptosis (A) and subconjunctival hemorrhage (B) are commonly seen after botulinum toxin A injection.

after 4 months if the angle of esodeviation is more than 10 PD although, in many cases, we would consider earlier re-injection, especially in those cases in which an initial exodeviation was not obtained. Permanent exotropias are rare but patients with developmental delay or central nervous system abnormalities appear to be at higher risk of developing persistent overcorrections.[36,42,44,65]

Bupivacaine

The intramuscular injection of bupivacaine was first proposed as an alternative to muscle resection by Scott et al.[66] The recovery from the myotoxic effect of the anesthetic on the myofibrillar system of the extraocular muscles results in shorter, hypertrophic muscles with increased contractile strength and elastic force (stiffness).

The injection is done under topical anesthesia and EMG guidance using a volume of 1.5–3.0 mL (0.75–3%). Bupivacaine does not diffuse freely throughout the extraocular muscle so it is important to inject most of volume in the posterior third of the muscle, withdrawing the needle slowly while injecting the rest into the middle of the muscle to allow anterior spread. Low dose BTX-A (1–3 IU) can be injected simultaneously into the antagonist muscle to prevent the initial stretching of the bupivacaine-injected muscle, as the length at which the muscle is rebuilt is influenced by the position of the muscle during this process. At larger doses, significant orbital inflammation and edema can be observed and it is recommended to pretreat with oral prednisone for a few days. The paralysis caused by the anesthetic initially increases the strabismic deviation; 6–10 days later the improvement in alignment starts to occur.

In patients with small comitant non-paralytic horizontal strabismus (esotropia <25 PD and exotropia <35 PD) improvement (10–20 PD) and stability of alignment has been demonstrated for up to 5 years with 1–2 injections of bupivacaine (alone or together with BTX-A).[31]

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Strabismus surgery

David K Coats and Scott E Olitsky

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See online for supporting video for this chapter.

Introduction

The management of patients with strabismus begins like any other patient. A careful history and examination is undertaken to understand current patient concerns, past treatments, and optimal treatments for the patient's current concerns. Treatment of strabismus may involve one or more of the following: correction of refractive error, orthoptics, patching, botulinum toxin injection, and surgery. This chapter will provide an overview of the surgical treatment of strabismus.

The indications, goals and risks of surgery should be clearly explained to the parents and the child, or, in the case of adults with strabismus, the patient. Parents and patients should understand the importance of ongoing follow-up, particularly during the period of visual development that extends through roughly the first decade of life.

Traditionally, the goal of strabismus treatment has been to re-align the visual axes in order to eliminate diplopia, or to maintain, or restore, binocular vision. Other functional indications for surgery might include the need to improve an abnormal head posture, eliminate abnormal eye movements, increase the area of single binocular vision in a patient with an incomitant deviation, or increase the functional visual field of a patient with esotropia. Restoring the normal anatomical position of the eyes without any other potential benefit is also a well-accepted indication for surgery. The psychosocial benefit of surgery for patients with strabismus has now been well documented, even in patients who may not achieve any other functional visual benefit.[1]

Surgically important anatomy

An understanding of the relevant anatomy and anatomical variations is an important prerequisite to performing strabismus surgery. The strabismus surgeon must not only be familiar with the anatomy of the extraocular muscles, but must also be cognizant of adjacent structures in the orbit and the ocular adnexa.

The conjunctiva

The conjunctiva is often inappropriately considered to be little more than a structure that must be incised to gain surgical access to the extraocular muscles. An understanding and recognition of key features of the conjunctival anatomy, especially medially, is necessary to perform appropriate conjunctival incisions to optimize access to the extraocular muscles. It also helps to ensure proper conjunctival closure and good cosmesis following surgery, and to avoid scarring and contracture of the conjunctiva, which can produce restrictive strabismus postoperatively.

The conjunctiva is a mucous membrane that covers the posterior surface of the eyelids and the anterior surface of the globe with the exception of the cornea (Fig. 86.1). The bulbar conjunctiva merges with the stroma and epithelium of the cornea. The palpebral conjunctiva begins on the lid margin at the mucocutaneous junction. The conjunctiva is tightly adherent to the underlying tarsus. The conjunctiva in the fornices is loose and is reflected into several folds, allowing movements of the globe not to be limited by connections between the palpebral and bulbar conjunctiva.

There is some redundancy of the conjunctiva so that excision of small portions of the conjunctiva is well tolerated without significantly altering its appearance or function. Only the bulbar conjunctiva is routinely incised during strabismus surgery. A fold of conjunctiva, known as the plica semilunaris conjunctivae (referred to simply as *plica* here), is present in the medial angle of the conjunctiva and represents a fold in the bulbar conjunctiva. When malpositioned or accidentally incised during strabismus surgery, it can result in serious cosmetic and/or functional problems.

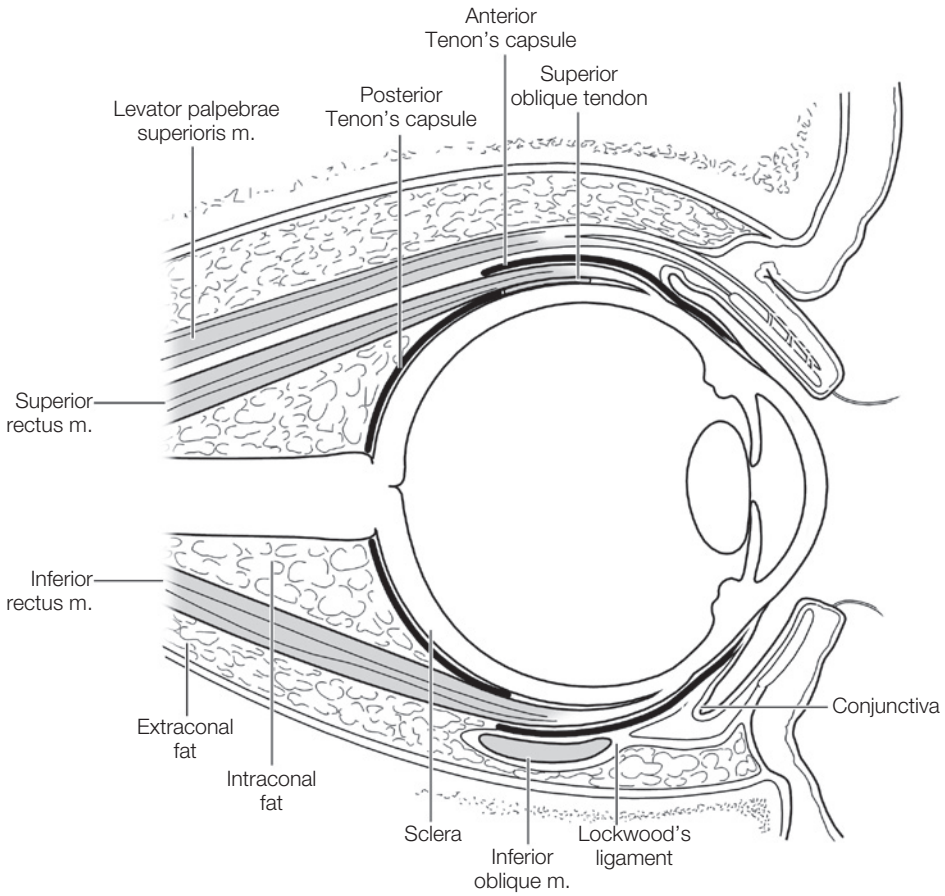


Fig. 86.1 Relationship of orbit fat to Tenon's capsule and other structures. Violation of the posterior portions of Tenon's capsule can result in protrusion of orbital fat into the surgical space. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/ Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

The sclera

The sclera is composed of densely packed collagen lamella. It is continuous with the dura mater of the optic nerve. It is continuous across the optic nerve head, forming the lamina cribrosa. The sclera is penetrated by a variety of vascular and neural structures anteriorly and posteriorly. The thickness of the sclera varies with age. It is typically thinnest in a newborn. The thickness of the sclera varies depending on its location on the globe. The sclera is thinnest behind the insertions of the rectus muscles, where its thickness is approximately 0.45 mm, a fact that is important to the strabismus surgeon since sutures may need to be passed into this thin area of the sclera to recess a rectus muscle. The sclera is approximately 0.6–0.7 mm thick at the corneal limbus and 1.1–1.3 mm thick at the posterior pole.

Tenon's fascia

The globe is suspended within the bony orbit by a fascial system, the bulk of which is known as Tenon's capsule. Tenon's capsule is a condensation of fibrous tissue that covers the globe from the entrance of the optic nerve at the posterior aspect of the globe extending to within 1 mm of the corneal limbus, where it fuses with the overlying conjunctiva. Tenon's capsule is thick and readily manipulated surgically in young patients, but becomes thin and fragile in older patients. A potential space exists both deep and external to Tenon's capsule known as the episcleral space (also known as sub-Tenon's space) and the subconjunctival space, respectively. These spaces are important during strabismus surgery, as they must be entered in order to gain access to the extraocular muscles. Several large and small structures penetrate Tenon's capsule including the optic nerve, the extraocular muscles, the vortex veins, and numerous other neurovascular structures.

The extraocular muscles penetrate Tenon's capsule to enter the episcleral space, coursing toward their insertions into the sclera (Fig. 86.2). Thus it is in the episcleral space, containing a length of about 7–10 mm of the rectus muscles, that the majority of extraocular muscle surgery is performed. After entering the episcleral space, the muscles have no sheath, but instead are covered by episcleral connective tissues that are loosely fused with the muscle. This tissue expands laterally along the edges of the muscles to form the intermuscular membrane and is present all the way to the muscle insertion. These tissues fuse with Tenon's capsule posteriorly where the muscles penetrate Tenon's capsule.

Tenon's capsule, as with all orbital tissues, should be handled with care. Tenon's capsule acts a barrier to orbital fat, and violation of the posterior aspects of the capsule can result in unwanted protrusion of orbital fat into the surgical space. This surgical complication can cause significant difficulties in completing planned surgery and can also lead to fat adherence and restrictive strabismus postoperatively.

The orbital aspect of the sheath of the superior rectus muscle is adherent to the internal surface of the sheath of the

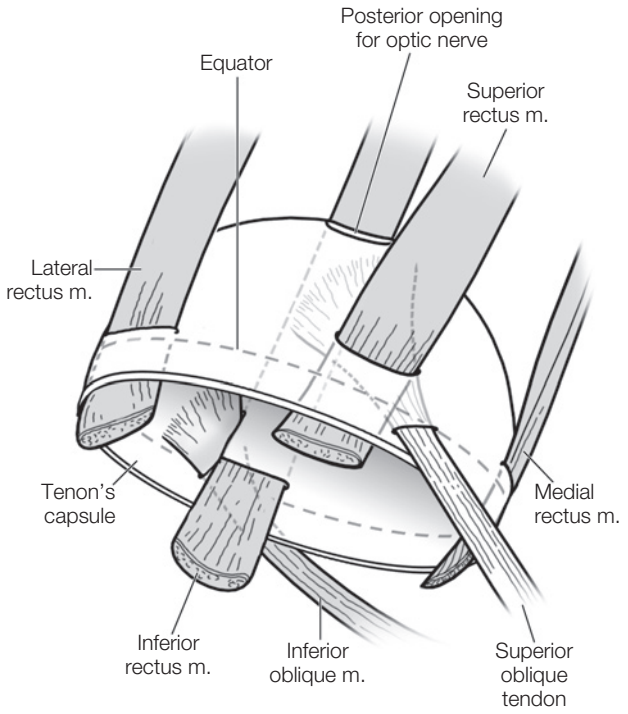


Fig. 86.2 Diagrammatic representation of Tenon's capsule and relationship to the extraocular muscles. Note that the rectus muscles are located external to Tenon's capsule posteriorly. They penetrate Tenon's capsule to enter the episcleral space, then course anteriorly to insert on the sclera. The inferior oblique muscle and superior oblique tendon enter the episcleral space anteriorly and course posteriorly to insert on the sclera. The rectus muscle pulleys, muscle capsule, and intermuscular capsule are not represented in this diagram. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

levator palpebral superioris muscle of the upper eyelid. The close association of these two muscles through their fascial sheaths accounts, in part, for the cooperative action seen during contraction of these two muscles, such as depression of the upper eyelid with downgaze. The surgeon must be aware of these connections because they can have important implications for the patient following strabismus surgery on the vertical rectus muscles, with resulting asymmetry of the eyelids postoperatively. The global portion of the sheath is tenuously associated with the sheath of the superior oblique tendon.

The fascial sheath surrounding the inferior rectus muscle is complex. It tends to be thicker than the fascial sheath surrounding the other rectus muscle, and this is readily apparent during surgery. The global portion of this sheath fuses with and becomes continuous with Tenon's capsule, while the orbital portion contributes to the formation of Lockwood's ligament of the lower eyelid, helping to explain why surgery on the inferior rectus muscle can alter the position of the lower eyelid.

The fascial sheath surrounding the portion of the superior oblique tendon distal to the trochlea is both strong and thick. The potential space inside of the superior oblique tendon sheath is continuous with the episcleral space. Numerous attachments extend from the sheath to adjacent structures including attachments to the global aspect of the sheath of the superior rectus muscle and attachments to the sheath of the levator palpebral superioris muscle of the upper eyelid. Abnormalities involving this sheath may play a role in the etiology of Brown syndrome.

The fascial sheath of the inferior oblique muscle surrounds the muscle from origin to insertion. It becomes thicker as the muscle approaches its insertion and it is usually tightly adherent to the orbital aspect of the sheath of the inferior rectus muscle. Small extensions of the sheath near the inferior oblique muscle insertion are directed to the sheath of the lateral rectus muscle and to the sheath surrounding the optic nerve posteriorly.

The rectus muscle pulley system

A reflection extending from Tenon's capsule envelops the posterior portion of the extraocular muscles that are extrinsic to the capsule at this position in the orbit. Fibroelastic sleeves consisting of dense bands of collagen, elastin, and smooth muscle surround the rectus muscles. These sleeves are suspended from the orbit and adjacent extraocular muscle sleeves by bands of tissue having similar composition. Often referred to as check ligaments, the function of these sleeves and their connections to the orbital walls is significantly more complex than simply to "check" movement of the globe. The term "check ligaments" should be discarded. Condensations and extensions from these muscle sheaths ultimately are also associated with anterior connections. Collectively, these structures form the rectus muscle pulley system and perform a specialized function within the orbit.

High-resolution computed tomography and magnetic resonance imaging have demonstrated that the paths of the rectus muscles remain stable relative to their adjacent orbital walls throughout most of their course in the orbit, even during eye movements and following large transposition procedures. Only the anterior aspect of the muscles actually move during normal eye movements into secondary gaze positions, while the posterior aspects of the rectus muscles are relatively fixed in position by rectus muscle pulleys, which are, in part, located near the equator of the globe. These rectus muscle pulleys essentially function as the effective origins of the rectus muscles. The pulleys are important for altering both the paths of the rectus muscles through the orbit and altering their function.[2]

Innervation of the extraocular muscles

The third cranial nerve (oculomotor nerve) is the most complex of the cranial nerves supplying innervation to the extraocular muscles. It provides innervation to four of the six extraocular muscles and to the levator palpebral superioris muscle. The inferior division of the third nerve innervates the medial and inferior rectus muscles as well as the inferior oblique muscle. The superior division innervates the superior rectus muscle and levator palpebral superioris muscle. The neurovascular bundle supplying the inferior oblique muscle enters the muscle from its posterior surface near the lateral border of the inferior rectus muscle.

The superior oblique muscle is innervated by the fourth cranial nerve (trochlear nerve). It is the only extraocular muscle that receives its innervation from the external or orbital surface of the muscle. The nerve passes superiorly from the medial side of the superior oblique muscle to the orbital side of the muscle prior to entering the muscle as several small branches.

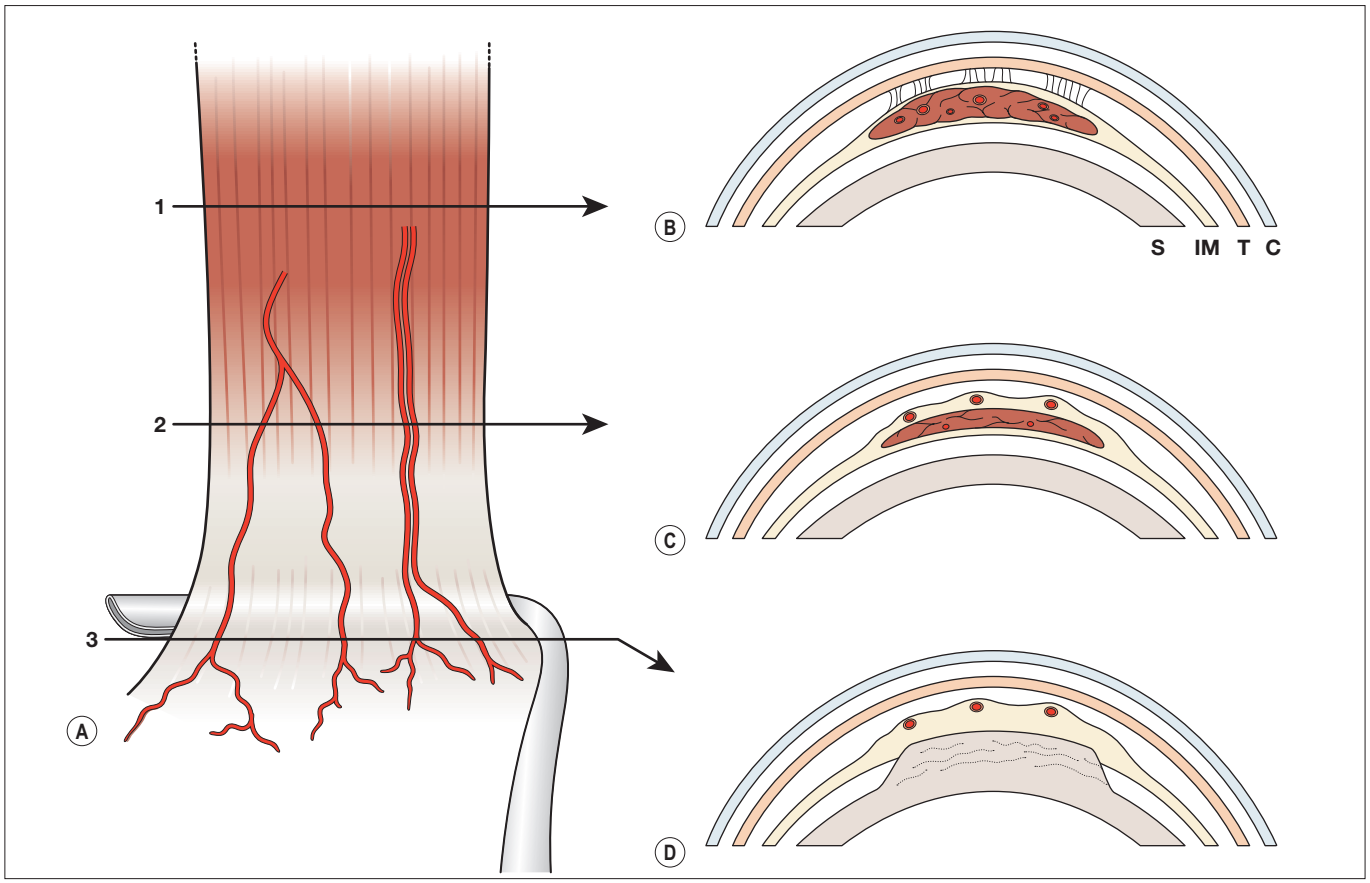


Fig. 86.3 Diagram of typical rectus muscle showing position of anterior ciliary vessels (ACVs). (A) Surgeon's view of inferior rectus. The ACVs emerge from the substance of the muscle, posterior to the transition from muscle to tendon. Anterior to this point, the ACVs travel on the surface of the muscle and tendon, following a somewhat serpentine course in a plane that is continuous with the muscle capsule, continuing onto the surface of the sclera. (B) Transverse section of rectus muscle at position A-1, posterior to the point of emergence of the ACVs. The vessels are deep in the muscle, not visible to the surgeon. (C, conjunctiva; IM, intermuscular septum (continuous with the muscle capsule); S, sclera; T, Tenon's capsule.) (C) Transverse section at position A-2 showing three ACV "groups" on the surface of the tendon, in a plane that is continuous with the capsule of the muscle and tendon. Each anterior ciliary vessel group can contain more than one anterior ciliary vessel. (D) Transverse section at position A-3: the tendon insertion site. The ACVs remain on the surface and continue onto the sclera, anterior to the tendon insertion.

The lateral rectus muscle is innervated by the sixth cranial nerve (abducens nerve). The muscle is innervated from the internal or bulbar surface of the muscle near the junction of the anterior two-thirds and posterior one-third of the muscle.

Blood supply to extraocular muscles

Each of the extraocular muscles receives its blood supply from the medial and lateral muscular branches of the ophthalmic artery. The medial branch supplies the inferior and medial rectus muscles as well as the inferior oblique muscle, while the lateral branch supplies the lateral and superior rectus muscles, the superior oblique muscle, and the levator muscle. The inferior rectus and inferior oblique muscles also receive a small contribution of blood supply from other sources.

The muscular arteries of the four rectus muscles enter the muscles on their global surfaces at approximately the junction between the anterior two-thirds and posterior third of the muscle. They course anteriorly, emerging onto the orbital surface of the muscle/tendon approximately 10–12 mm from the insertions of the tendons into the sclera, where they are known as the anterior ciliary arteries (Fig. 86.3). Each rectus muscle characteristically has two anterior ciliary arteries, except for the lateral rectus muscle, which characteristically has only one, though there is much variation. The course of the anterior ciliary arteries along the muscles and their tendons is highly variable. It is important to recognize this variation when planning surgery on patients who are at risk for anterior segment ischemia. The anterior ciliary vessels course forward to the episclera, where they supply branches to the sclera, limbus, and the conjunctiva. They enter the sclera near the limbus where they ultimately anastomose with the long ciliary arteries to form the major arterial circle of the iris. Veins corresponding to the muscular arteries drain into the superior and inferior orbital veins.

Gross anatomy of the extraocular muscles

Rectus muscles

There are four striated rectus muscles arising from the annulus of Zinn in the apex of the orbit. Each is 40 mm in length and inserts on the sclera anterior to the equator of the globe. Following the "spiral of Tillaux," the medial rectus inserts

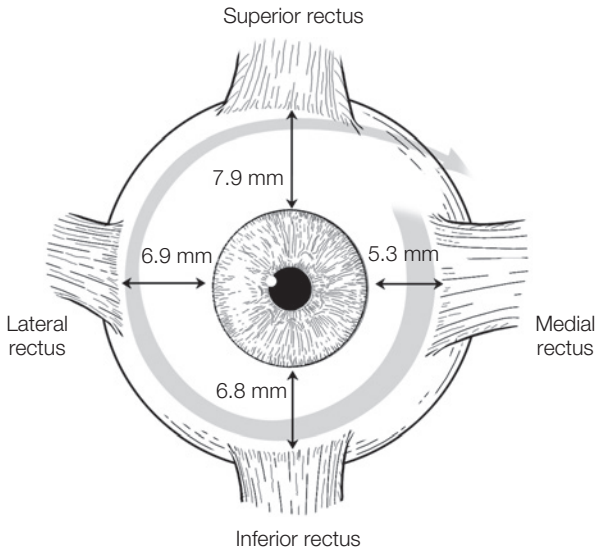


Fig. 86.4 The spiral of Tillaux. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

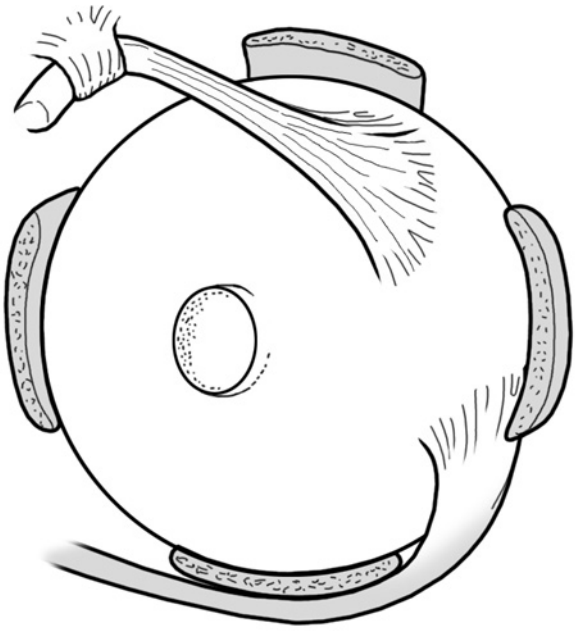


Fig. 86.5 Insertion of the inferior oblique muscle under the lateral rectus muscle. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

5.5 mm from the limbus, the inferior rectus 6.5 mm, the lateral rectus 6.9 mm, and the superior rectus inserts 7.7 mm from the limbus (Fig. 86.4). However, in actuality, the location of their insertions is somewhat variable. The insertions of the rectus muscles are curvilinear, particularly the vertical rectus muscles, whose temporal border insert further from the limbus than their nasal border.

The medial rectus muscle courses anteriorly along the medial wall of the orbit, inserting on the sclera without fascial attachments to an oblique muscle. Given its innate tension and relatively short arc of contact, the medial rectus muscle is at the greatest risk of inadvertent loss during surgery.

The lateral rectus muscle courses anteriorly along the lateral orbit, inserting on the sclera with a 10 mm arc of contact with the globe. The insertion of the inferior oblique muscle is in close proximity to the lower border of the lateral rectus muscle, 8–10 mm posterior to the lower pole of the lateral rectus muscle insertion (Fig. 86.5). Because of the close proximity of its insertion to the lateral rectus muscle, the inferior oblique muscle is often inadvertently hooked along with the lateral rectus muscle when isolation of the lateral rectus muscle is attempted during surgery. This complication is more likely to occur when the lateral rectus muscle has been previously recessed. Failure to recognize that the inferior oblique muscle has been inadvertently hooked can result in a significant postoperative motility disturbance that is restrictive in nature. The fascial attachments between the lateral rectus and the inferior oblique muscle help to locate the lateral rectus muscle if it becomes detached during surgery or trauma.

The inferior rectus muscle courses anteriorly, laterally, and inferiorly to insert on the sclera. It inserts an average of 6.8 mm posterior to the limbus. The temporal border of the tendon inserts approximately 2 mm more posteriorly than the nasal border of the insertion, a fact that should be considered when recessing or resecting the muscle. When hooking the inferior rectus muscle, the surgeon should avoid passing the hook too deeply into the orbit. A vortex vein can typically be seen posteriorly near both the medial and lateral borders of the

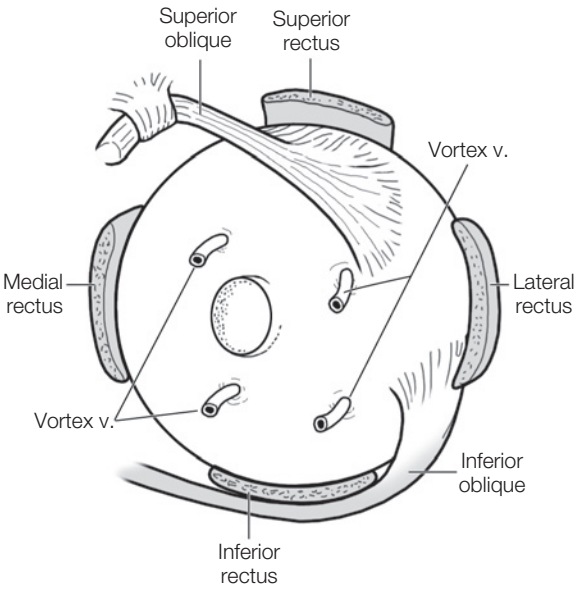


Fig. 86.6 Vortex veins as seen from the posterior aspect of the globe. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

inferior rectus muscle (Fig. 86.6). Disturbance of a vortex vein can result in considerable bleeding; continuation of surgery in this situation may be hazardous. The inferior rectus muscle forms a 23° angle with the visual axis when the globe in the primary gaze position. It has fascial attachments to the inferior oblique muscle and the lower eyelid retractors. If these attachments are not severed during significant recession or resection of the inferior rectus muscle, eyelid fissure changes may occur. Connective tissue attachments between the superior

rectus and the superior oblique muscles may assist the surgeon in locating a "lost" superior rectus muscle.

The superior rectus muscle courses anteriorly, laterally, and superiorly to insert on the sclera. The temporal border of the tendon inserts almost 3 mm more posteriorly then the nasal border. It is the only rectus muscle that inserts posterior to the ora serrata. As such, perforation of the eye wall near the insertion of the superior rectus muscle may involve the retina. A vortex vein can usually be found posteriorly near the border of the superior rectus muscle nasally and temporally (see Fig. 86.6). Vortex veins are infrequently damaged during surgery on the superior rectus muscle. Compared to the inferiorly located vortex veins, it is more difficult to inadvertently hook or otherwise manipulate when attempting to isolate the superior rectus muscle because it is somewhat protected by the superior oblique tendon. The superior rectus muscle forms a 23° angle with the visual axis when the globe is in the primary gaze position. The global aspect of the superior rectus muscle sheath is attached to the superior oblique tendon through relatively tenuous connections (Fig. 86.7). If the close relationship between these two structures is not recognized, the superior oblique tendon can sometimes be inadvertently hooked, along with superior rectus muscle tendon. If unrecognized, the superior oblique tendon may be recessed or resected along with the superior rectus muscle, producing unexpected torsional and vertical misalignment. The superior rectus muscle also has fascial attachments to the levator palpebrae muscle. If the attachments to the levator palpebrae muscle are not divided during recession or resection of the superior rectus muscle, eyelid fissure changes may occur.

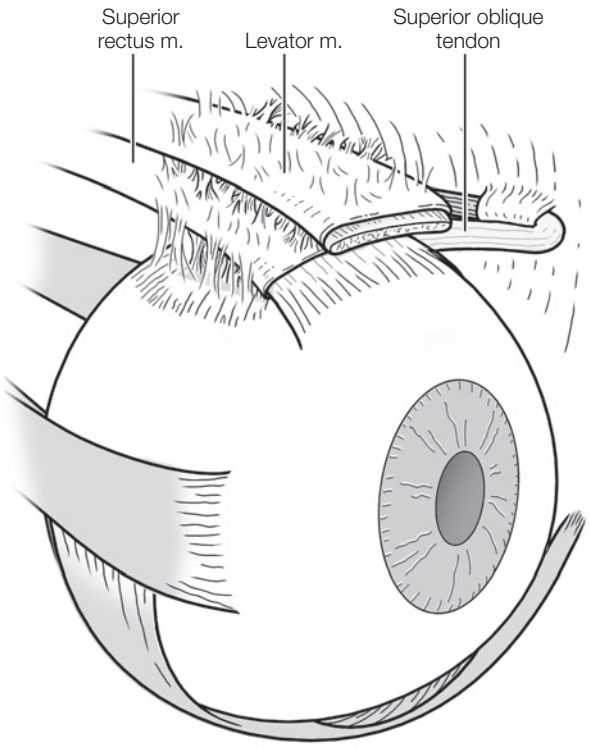


Fig. 86.7 Complex sheath of the superior oblique tendon. Note tenuous attachments to the sheath of the superior rectus muscle and to the levator muscle. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

Superior oblique muscle

The actions of the superior oblique muscle are incyclotorsion, depression, and abduction. The superior oblique muscle arises from the periosteum in the orbital apex above the annulus of Zinn and travels anteriorly along the superomedial orbital wall. It becomes a cord-like tendon, passing through the trochlea to run in a posterolateral direction at an angle of approximately 51° to 54° with the sagittal plane. The tendon passes under the superior rectus and fans out, inserting on the sclera in the superotemporal quadrant. The anterior pole of its insertion is located close to the lateral border of the superior rectus muscle, beginning 4–6 mm posterior to the superior rectus insertion. Its tendon is thin and broad, extending posteriorly for about 11 mm, but with considerable variability. The posterior end of the insertion lies 6–7 mm from the optic nerve. The superior temporal vortex vein can exit the sclera temporal to the superior oblique insertion, under the insertion or sometimes split the fibers of the insertion and pass through them (see Fig. 86.6).

Inferior oblique muscle

The actions of the inferior oblique muscle are excyclotorsion, elevation, and abduction. The inferior oblique muscle forms an antagonist pair with the superior oblique muscle with respect to torsion. The additional actions of the inferior oblique are not strictly antagonistic with the superior oblique.

The inferior oblique muscle originates from the maxillary bone adjacent to the lacrimal fossa. It passes posteriorly and laterally, forming approximately a 51° angle with the sagittal plane. After passing beneath the inferior rectus muscle, the inferior oblique muscle travels upward, inserting on the sclera, close to the macula. The tendon of the inferior oblique muscle is 1–2 mm long, the shortest of the extraocular muscle tendons. The anterior aspect of the inferior oblique muscle insertion is 8–12 mm posterior to the lateral rectus insertion, adjacent to its lower border. There is considerable variability in the location and configuration of the inferior oblique muscle insertion.

The inferior temporal vortex vein lies close to the posterior border of the inferior oblique muscle (see Fig. 86.6). It can be damaged when the surgeon isolates the inferior oblique muscle, or when repositioning an inferior oblique muscle near the sclera exit of the vortex vein exits during the process of recession.

The neurovascular bundle enters the inferior oblique muscle as it passes beneath the inferior rectus muscle. The neurovascular bundle may serve as the effective origin of the inferior oblique muscle, particularly after anterior transposition of the muscle.

General surgical considerations

Anesthesia

Most strabismus surgery is performed in an outpatient setting. The type of anesthesia depends upon one or more of the following factors: patient preference, surgeon preferences, nature of the operation planned, health of the patient,

and the recommendations of the anesthesiologist. No single anesthesia modality universally applies to all patients in all situations. Options include general, local, and even topical anesthesia. Children, and even most young adults, require general anesthesia because they usually are unable to tolerate surgical manipulation under local anesthesia.

Preoperative patient preparation

Safe and effective strabismus surgery begins even before the patient enters the operating room. The patient, and/or parents, should understand the risks, benefits, and alternatives of the proposed operation as well as have realistic expectations for the surgery. Ideally, this conversation will have occurred before the day of surgery and will be documented in the medical record. A surgical consent that properly documents these issues should also be signed and placed into the record. The laterality of the procedure should be recorded and the patient marked when indicated. Once the patient is brought into the operating suite, all parties in the room should perform a "time-out" and agree upon the procedure and other important details. The patient is then prepared for the operation.

The patient is properly positioned, and many strabismus surgeons instill one drop of 2.5% phenylephrine in the operated eye(s) prior to the surgical preparation to provide vasoconstriction and dilate the pupil should postoperative fundoscopy be needed. Alternatively, brimonidine 0.1% may be used. This causes effective conjunctival vasoconstriction without pupillary dilatation. The patient's skin, lid margins, and conjunctiva are the most common source of bacterial contamination, potentially causing serious postoperative infection following eye surgery. Thus cleansing these structures with an antimicrobial solution prior to surgery is among the most important ways the risk of postoperative infection can be reduced. Skin preparation can be accomplished with 5–10% povidone-iodine solution. Irrigation of the conjunctiva with half strength (5%) povidone-iodine solution prior to surgery has been shown to be effective in reducing conjuctival bacterial flora. Draping should sufficiently overlap the cleansed area of the skin, while allowing easy access to the operative site. The eyelashes can be covered with an adhesive drape if desired. Markings made on the skin preoperatively to identify the surgical site should be visible after the drapes have been placed (Fig. 86.8).

Surgical instruments and equipment

While there is a wide variety of instruments of various shapes and sizes available for strabismus surgery, the reality is that strabismus surgery can usually be performed very well with a set of basic instruments as shown in Figure 86.9. Many surgeons find 0.5 locking forceps and grooved muscle hooks to be particularly valuable in facilitating strabismus surgery.

Sutures used for strabismus surgery should generally be bioabsorbable, though not all surgeons agree. Polyglactin 910 (Vicryl®, Ethicon, Somerville, NJ) is one commonly used bioabsorbable synthetic suture. Two polyglycolic-based sutures that have been used for strabismus surgery are Biosorb™ C (Alcon, Fort Worth, TX) and Dexon™ S (Covidien/Medtronic, Dublin, Ireland). Non-absorbable suture, such as polyester fiber suture (Mersilene®; Ethicon, Somerville, NJ) is often used for procedures where a permanent suture is desired.

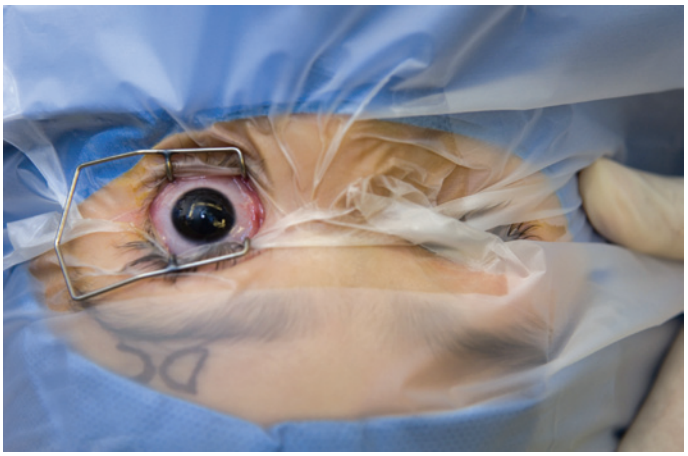


Fig. 86.8 Isolation of the lashes preoperatively with an adhesive drape. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

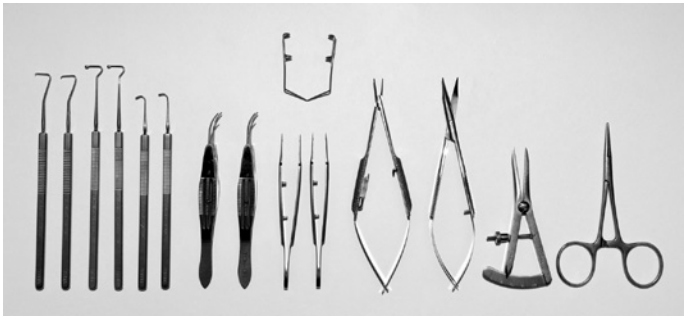


Fig. 86.9 A-List instruments that should be available for every case on the instrument stand. This list will vary depending on the personal preferences of the surgeon. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

Table 86.1 Characteristics of several available and commonly used spatula needles for strabismus surgery

Type of needle	S14	S24	S28	TG 100
Cross section				
Point of needle	Top	Top	Bottom	Top
Curvature (degrees)	112	90	164	97
Chord length (mm)	7.23	7.31	5.28	5.94
Radius (mm)	4.37	5.16	2.67	3.96
Thickness (mm)	0.33	0.33	0.2	0.2

Spatulated needles are preferred for making scleral passes during strabismus surgery because they facilitate keeping the needle in the surgical plane, thereby reducing the risk of scleral perforation. The features of four commonly used spatulated needles are highlighted in Table 86.1. A collagen suture, such as 6.0 plain gut suture is a good choice for closing the conjunctiva. These come on a variety of needles, the choice of which is based on surgeon preference.

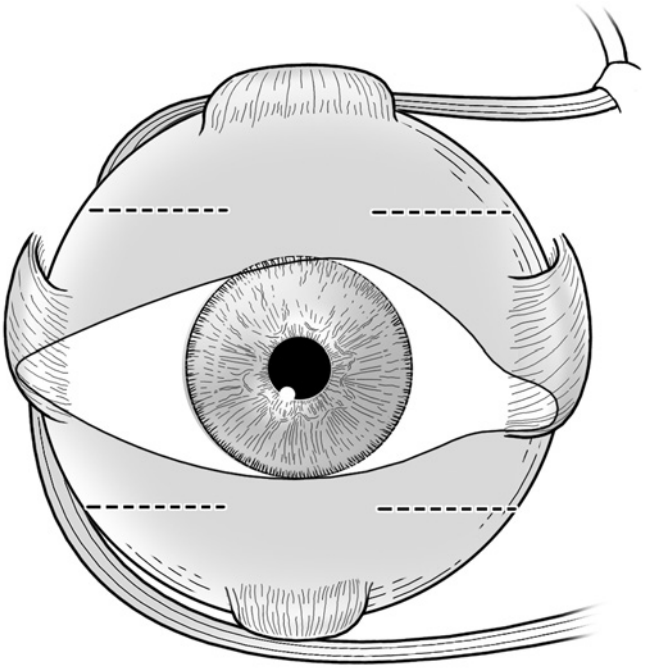


Fig. 86.10 Potential locations for placement of a fornix incision for rectus muscle surgery. Incisions placed in the lower quadrants are preferred, when possible. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

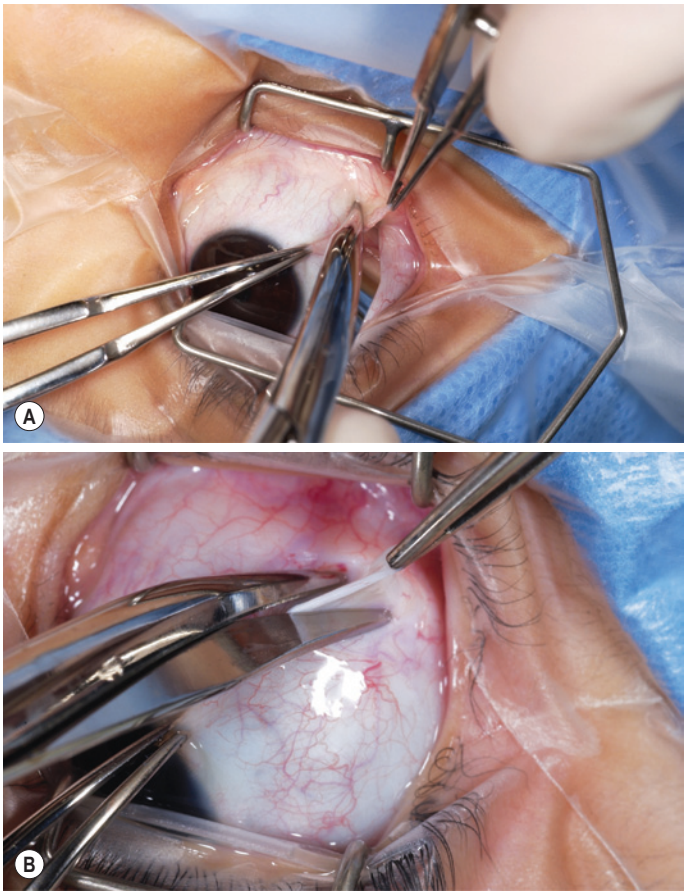


Fig. 86.11 Initiation of a fornix incision using one of two approaches. (A) Placing the adjacent conjunctiva under traction followed by incision; (B) Tenon's fascia is then incised to gain access to the episcleral space. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

The type of magnification, and even the choice of using or not using magnification during strabismus surgery, is based upon the personal preference of the surgeon. When magnification is desired, it can be accomplished through the use of a surgical microscope or through the use of surgical loupes.

Conjunctival incisions for rectus muscle surgery

All strabismus surgery requires an incision through the conjunctiva and through Tenon's fascia to gain access to the episcleral space, and all standard surgical manipulation of the extraocular muscles and associated structures occur in this space. The fornix and the limbal approaches represent the two most commonly utilized surgical approaches for strabismus surgery. Each has a set of advantages and disadvantages.

Fornix (cul-de-sac) approach

The fornix conjunctival incision approach to strabismus surgery was popularized by Parks and has undergone modifications by several surgeons.[3] A fornix conjunctival incision can be made in any of the oblique quadrants between adjacent rectus muscles (Fig. 86.10). Incisions in the inferior quadrants are preferable, when possible. The incision is made approximately parallel to the lid margins, 8–10 mm posterior to the limbus. The precise location and orientation of a fornix incision depends on a number of factors, including which muscle(s) is to be operated on, surgeon preference, the type of surgery (recession vs. resection), size of the recession, presence of other ocular pathology, and previous surgery.

The globe is rotated to expose the incision site. The conjunctiva is grasped with a fine-tipped forcep, placed under mild anterior traction, and a 6–8 mm incision is made (Fig. 86.11A). Tenon's fascia is then incised to gain access to the episcleral space (Fig. 86.11B). A hook is passed through the incision into the episcleral space and is advanced to isolate the rectus muscle insertion (Fig. 86.12). Many surgeons pass a second hook to assure that the entire width of the muscle has been isolated. A small muscle hook is used to retract the conjunctiva over the muscle insertion (Fig. 86.13A). The intermuscular septum, now visible, is placed under tension and incised to expose the toe of the muscle hook and underlying bare sclera (Fig. 86.13B). The toe of small hook is placed on bare sclera located behind the muscle insertion. While maintaining contact on the globe, the hook is slowly moved around the muscle insertion to assure that the full width of the muscle insertion has been isolated. The muscle insertion is then exposed by dissection of the muscle capsule and intramuscular septum. The amount of dissection required is dependent upon the procedure planned and the personal preference of the surgeon (Fig. 86.14). After completion of surgery, the incision can be closed with bioabsorbable suture, or the edges of the incision can be re-approximated without suture closure. This is largely a matter of surgeon preference.

Limbal approach

The limbal approach to strabismus surgery was popularized by von Noorden.[4] Many surgeons prefer limbal incisions because they are universally applicable to any and all rectus muscle operations. The limbal approach to strabismus surgery involves creation of a conjunctival flap that is initiated at the limbus and has its base in the fornix. The incision typically involves 2–3 clock hours of conjunctiva adjacent to the corneal limbus, with radial incisions that are 8–10 mm in length into adjacent oblique conjunctival quadrants between adjacent rectus muscles. Placement of limbal incisions for surgery on each of the rectus muscles is shown in Figure 86.15.

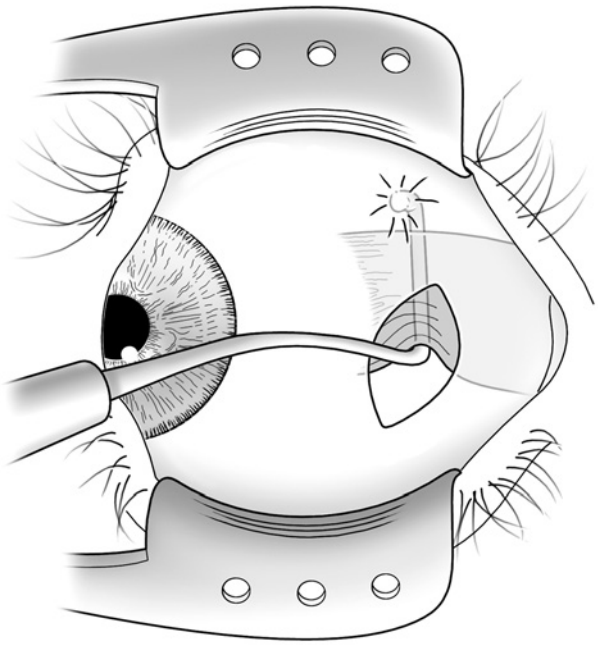


Fig. 86.12 Isolation of a rectus muscle insertion. The small hook is replaced by a larger hook to engage the entire muscle insertion. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

The conjunctiva incision is created using sharp dissection (Fig. 86.16A,B). The intermuscular septum is opened with blunt dissection on one or both sides of the muscle, adjacent to the muscle border (Fig. 86.17A). The muscle insertion is then isolated on a muscle hook, under direct visualization (Fig. 86.17B). The muscle capsule and intermuscular septum are then dissected to expose the rectus muscle (Fig. 86.17C). The amount of dissection of these structures depends on the preference of the surgeon and the procedure being performed. The incision is closed at the conclusion of surgery by placing a bioabsorbable suture at each edge of the conjunctival flap and suturing it to the adjacent intact conjunctiva. Additional sutures to close the radial relaxing incisions are permissible, but not required.

Conjunctival incisions for oblique muscle surgery

Surgery on the oblique muscles is generally performed through a fornix incision. The incision is created in a manner similar or identical to that described above. Oblique muscles can also be



Fig. 86.14 Dissection of the rectus muscle fascia. A sharp dissection of the intermuscular septum is done to expose the muscle border. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

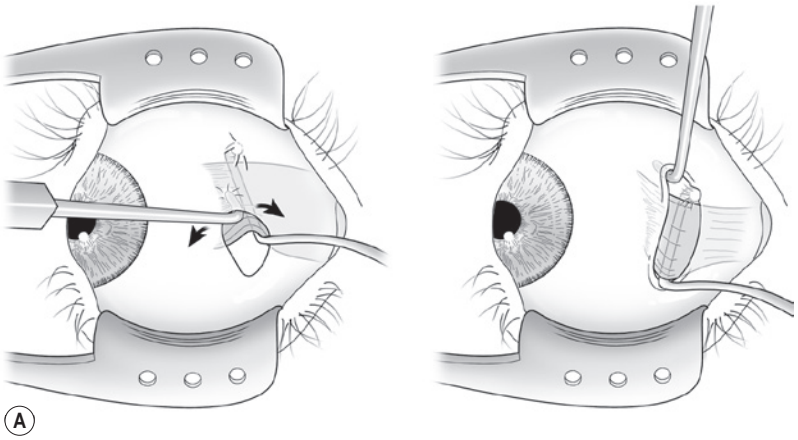


Fig. 86.13 Exposure of a rectus muscle insertion. (A) A small hook is used to slowly retract the conjunctiva over the muscle insertion while simultaneously rotating the muscle insertion into the incision. (B) The intermuscular septum is grasped with a pair of toothed forceps and incised, exposing underlying bare sclera. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

approached through a limbal incision. Techniques to isolate the oblique muscles will be described in later sections.

Recession of the rectus muscles

General principles for recession of the rectus muscles

By moving a rectus muscle posterior to its original insertion site and re-attaching it to the sclera, the length/tension curve of the muscle is altered. This has the effect of "weakening" the muscle's effect on the globe. For most recessions, this effect is seen clinically only as a change in the alignment of the eye. Ocular ductions are not clinically limited unless a very large recession is performed, typically involving placement of the muscle posterior to the equator. This weakening effect probably occurs both because of a reduction in the distance between the origin and new insertion of the muscle, and because of changes in the relationship between Tenon's capsule, the intermuscular septum, and the rectus muscle pulley system. The relationship between the amount of recession required and the size of the deviation treated is not linear. As can be seen in Table 86.2, the effect obtained from recessing the medial rectus muscle is initially linear, but as the size of the recession increases, the relative effect of the procedure increases. Once the muscle is placed behind the equator, the incremental effect of further recession will then be reduced.

The "safe" limit for a recession depends on the condition being treated. In the mid-20th century, it was believed that the medial rectus muscle could not be recessed more than 5.0 mm without significantly interfering with movement of the eye. This belief resulted in many cases of congenital esotropia being undertreated. In an effort to improve the success rate of surgery, three or four muscles often were operated on at one time. It was later recognized that medial rectus recession of at least 7 mm could be performed without producing an adduction deficit. This led to a higher surgical success rate, particularly for larger deviations, while avoiding the need to operate on additional muscles. Some studies have shown that even larger recessions can be performed on the medial rectus muscle without creating a duction deficit. It may be necessary to accept a postoperative duction limitation for treatment of some conditions. For example, a patient with a large exotropia in a poorly seeing eye will usually gladly tolerate the requisite abduction deficit that will occur after a large recess-and-resect operation in order to avoid the need to operate on the "sound eye." The notion that there is a "maximum" amount of rectus muscle recession, should be avoided.

Recessions can be performed by attaching the muscle to the sclera at the desired position or by employing "hang-back," "hemi hang-back" recession, or various modifications of these techniques. Direct fixation of the recessed muscle to

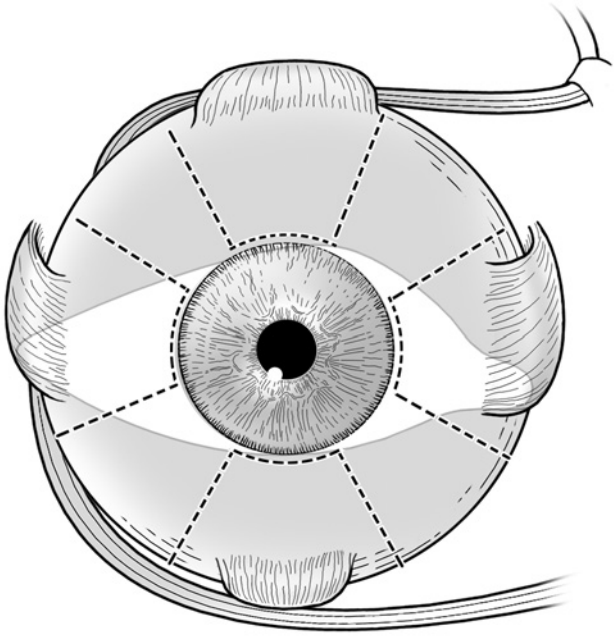


Fig. 86.15 Position of limbal incisions for surgery on the rectus muscles. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

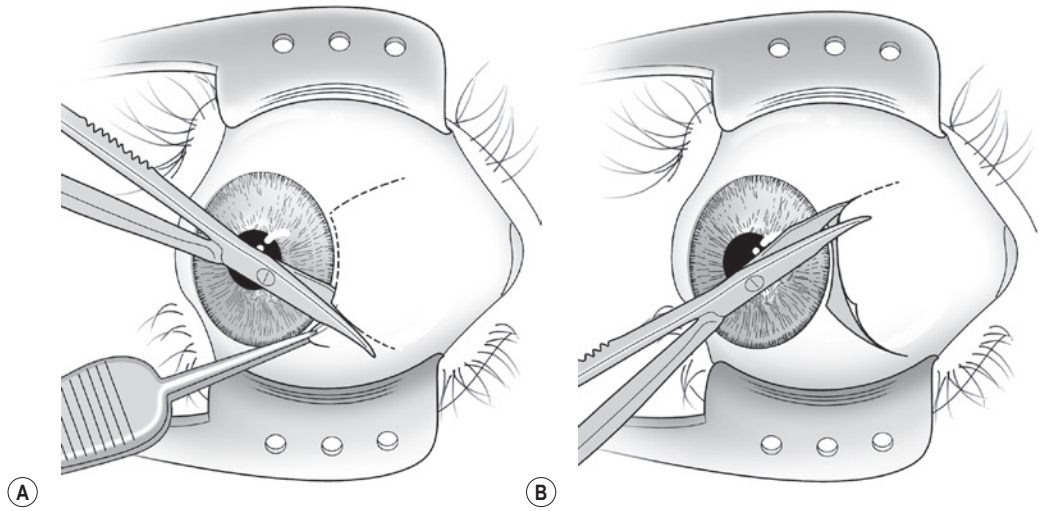


Fig. 86.16 Creating a limbal incision. (A) The conjunctiva is incised for 2–3 mm posterior to the limbus, and (B) bunt-tipped scissors used to create a radial incision. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

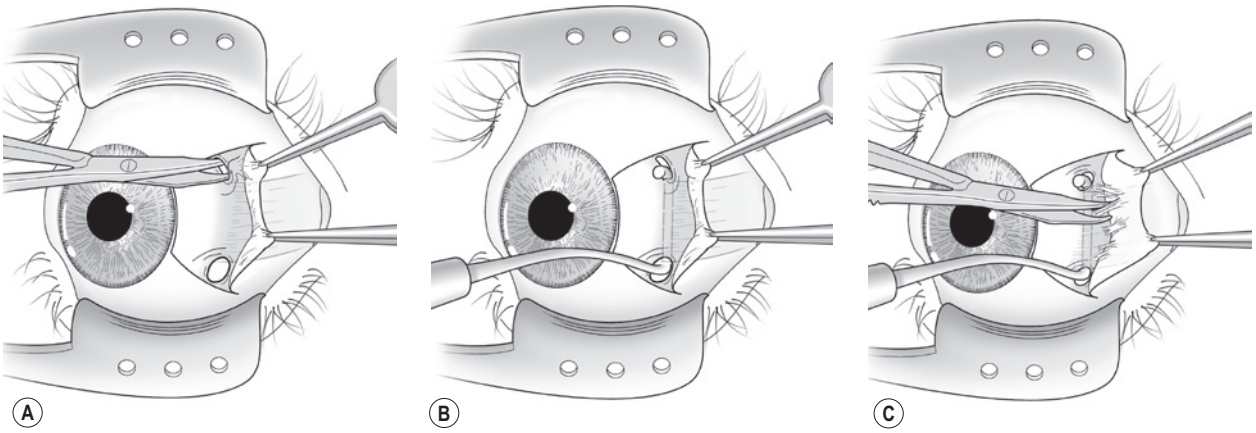


Fig. 86.17 Isolation of the muscle and dissection of the muscle fascia. (A) The intermuscular septum is opened with blunt dissection on one or both sides of the muscle. (B) The muscle insertion is then isolated on a muscle hook, under direct visualization. (C) The corners of the conjunctival flap are then elevated and sharp dissection of the muscle capsule and intermuscular septum done. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

Table 86.2 Bilateral medial rectus recession for esotropia

Deviation (PD)	Recession from the original insertion
15	3 mm
25	4 mm
35	5 mm
50	6 mm
70	7 mm

the sclera is widely used. The muscle is sutured at the desired new location of the muscle and, unless intentionally offsetting the muscle, the muscle should be placed directly posterior to the original insertion site. The muscle is typically spaced to maintain the width of the recessed muscle in order to avoid "central sag." If sagging occurs, the center of the muscle can be sutured to the sclera. Because the muscle is sutured directly to the sclera, it allows accurate supra- and infraplacement and "slanting" of the recession, if desired, in "A" and "V" patterns.

Both experienced and occasional strabismus surgeons may use the hang-back and hemi hang-back techniques. The hang-back procedure can be used with recession of any of the rectus muscles. The muscle can be approached using either a limbal or fornix incision. The techniques have several potential advantages. The procedure is conducted at the original insertion site (hang-back) or more anterior then a conventional recession (hemi hang-back). Because of this, surgical exposure is typically excellent regardless of the amount of recession being performed. This makes the surgeon much less dependent on the skills of a surgical assistant, especially for large recessions. Improved exposure, and the more anterior location of the area to be manipulated during surgery, may result in less risk for deep needle passes, thus reducing the risk of scleral perforations. This may be especially true for less experienced strabismus surgeons. In the event that a perforation does occur when using a hang-back approach, it unlikely to result in damage to the retina because the rectus muscle insertions, with the exception of the superior rectus muscle insertion, are located anterior to the ora serrata.

In some animal experiments, very large rectus muscle recessions performed with the hang-back technique have been demonstrated to migrate anteriorly following the procedure.[5] If this occurred following hang-back surgery in patients, a surgical undercorrection would be predicted. To mitigate this potential problem, some surgeons prefer to use the hemi hang-back recession technique for recessions larger than 8 mm. In this method, the suture needles are passed through the sclera approximately half the distance between the original insertion site and the desired new recession position.

Measurement of recession

The distance a muscle is moved during a recession procedure can be measured from either its original insertion site or its distance from the limbus. There are a number of articles in the literature demonstrating variability of rectus muscle insertion sites as referenced to the limbus. The relationship between the muscle insertion site and the limbus has been shown to be particularly variable in young patients before the anterior segment is fully developed.

The distance the muscle is moved along the globe can be measured using a cord length or arc measurement. Most strabismus surgeons use a caliper. For larger recessions where the use of a caliper can be cumbersome, the measurements can be made in two steps. The amount of recession to be performed is divided in half. The caliper is then used to mark the sclera for one half the distance of the recession. This mark is then used to perform a second measurement of equal magnitude to mark the final position for suture placement. Alternatively, a curved Scott ruler may be applied to the globe. Graduated in millimeters, it avoids the error introduced by calipers, which becomes significant for larger recessions.

General recession technique

The general technique for rectus muscle recession is similar for each of the four rectus muscles. Specific concerns regarding each individual rectus muscle are discussed later. Each of the rectus muscles may be exposed using either a limbal or a fornix incision. In most situations, the choice of surgical approach depends entirely on the preference of the surgeon. There are

a few isolated situations in which one surgical approach may be preferred over the other. Re-operations and patients with thin or friable conjunctiva are sometimes operated through a limbal incision since it requires minimal stretching of the conjunctiva, reducing the risk of tearing the conjunctiva, a complication that may make conjunctival closure more difficult. However, even most re-operations and surgery on elderly patients with thin sclera can be conducted through a fornix incision.

Placing suture near the muscle insertion

After the rectus muscle is isolated on a muscle hook, a suture is placed in the muscle near its insertion into the sclera. The suture should generally be placed no closer than 1 mm from the muscle's insertion into the sclera. Most surgeons prefer the use of a single double-armed suture. A suture pass is started in the center of the muscle and passed half thickness through each edge of the muscle (Fig. 86.18). This is referred to as the transverse pass.

Following completion of the transverse pass, locking suture passes are made at the borders of the muscle near the insertion. The needle is passed full thickness through the muscle from the posterior to the anterior aspect of the muscle and behind the transverse suture pass (Fig. 86.19A). The needle should not be passed through the anterior ciliary vessels, as this may result in significant bleeding. It is sometimes helpful to pass the needle around these vessels in order to ligate them and prevent bleeding when the muscle is detached from the globe. Care should be taken to pass the needle directly through the muscle. After the suture is passed full thickness through the muscle, the needle holder is passed through the suture loop, grasping the needle and pulling it through the suture loop to create a locking bite (Fig. 86.19B). It is preferable to grasp the suture rather than the needle during this step to prevent damage to the needle.

Detachment of the muscle from the globe

The muscle sutures are placed between the index finger and thumb of the hand holding the muscle hook. Independent control of the sutures is helpful. If the surgeon grasps the muscle hook in his hand and is able to pull the sutures with his fingers independently of the hook, more space can be created between the insertion site of the muscle and the sutures, facilitating detachment of the muscle and reducing the risk of cutting the suture in the muscle (Fig. 86.20).

Securing the muscle to the sclera at its new location

Locking forceps are placed on the edges of the muscle stump after the muscle has been detached from the sclera, or at the edges of the muscle insertion prior to disinserting the muscle from the sclera. The sclera is marked to identify the entrance site for the upcoming needle pass where the new insertion site of the muscle will be placed. The mark on the sclera is made

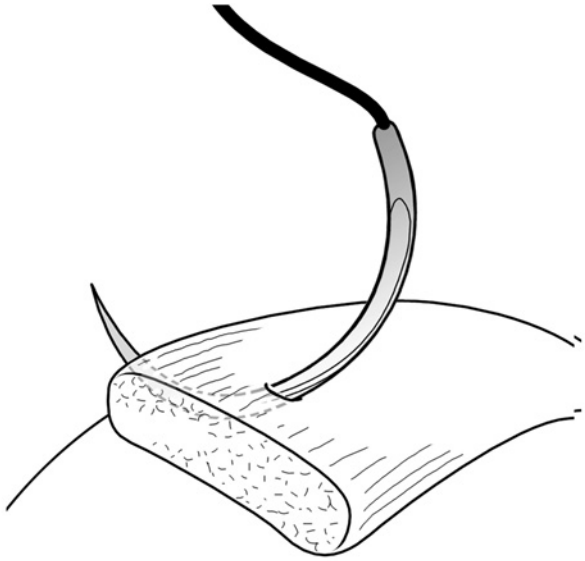


Fig. 86.18 Transverse needle pass near the muscle insertion. The needle is placed into the muscle near the midpoint of the muscle width near the insertion site. It is passed half thickness through the muscle until the needle tip exits the edge of the muscle. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

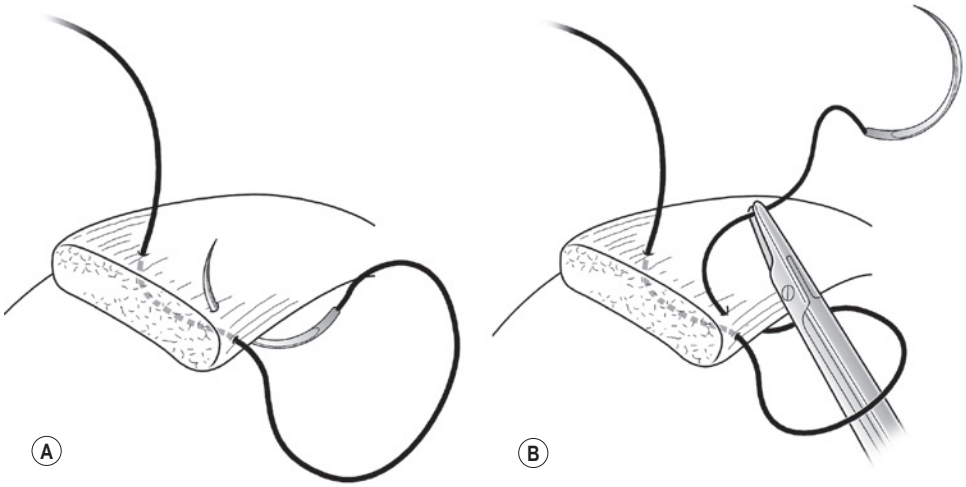


Fig. 86.19 Locking suture pass. (A) The suture is passed full thickness through the muscle posterior to the transverse pass and around nearby anterior ciliary vessels. The locking bite should be at least 1 mm in width. (B) Completion of the locking bite. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

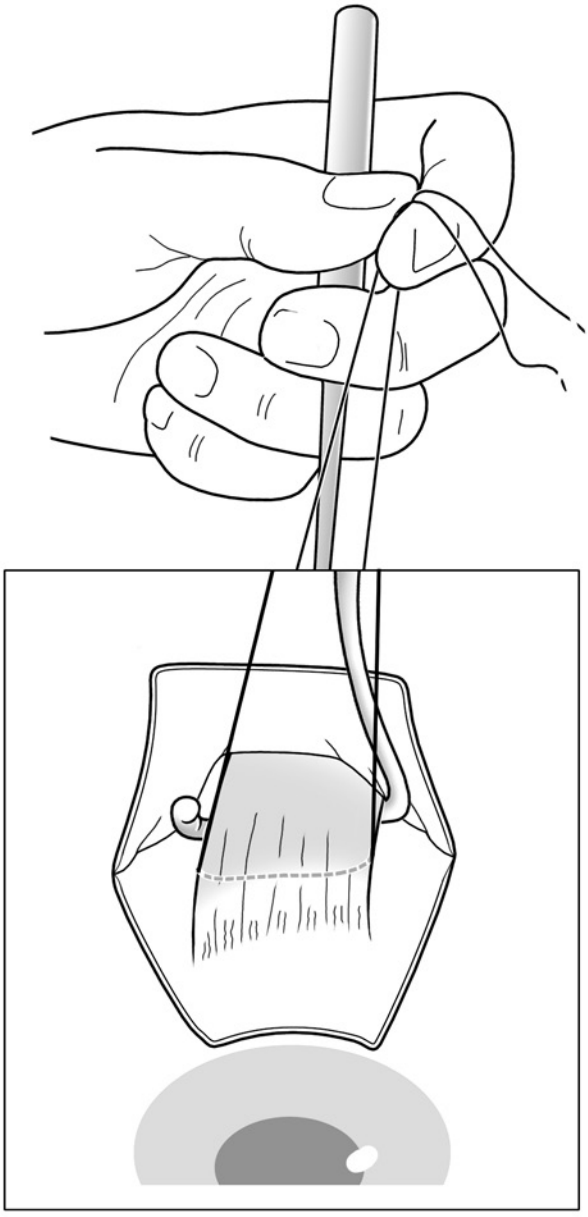


Fig. 86.20 Independent control of the muscle hook and the sutures while detaching the muscle from the sclera. Note that the surgeon is able to independently lift the sutures and provide more space to safely cut the muscle from its insertion site. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

by indenting the sclera at the desired recession site using a caliper (Fig. 86.21). This displaces fluid from the sclera and allows visualization of the underlying choroid which appears as a blue spot on the sclera.

The needle is then placed into the sclera at the previously marked positions. The sutures are then pulled through the sclera, tied and cut, making certain that the muscle remains in place in its new insertion site by maintaining anterior traction on the sutures when they are being tied (Fig. 86.22). If the needle passes are made too close to each other, the central portion of the muscle may sag posteriorly. This can be corrected by passing the needle back through the mid-portion of the muscle and behind the original suture, prior to cutting the muscle sutures. The suture is then tied to bring the central portion of the muscle up to its intended attachment site (Fig. 86.23).

Hang-back recession techniques

Securing the muscle to the sclera

The muscle is isolated and disinserted as previously described, and locking forceps are placed on the borders of the original insertion site. The suture needles are passed through the original insertion site. The needles are passed at an angle that allows both to emerge anterior to the insertion and as close together as possible (Fig. 86.24).

Measuring the recession

The sutures are advanced anteriorly through the sclera until the muscle rests firmly against the posterior aspect of the insertion. Unexpected, additional recession will occur if the muscle is not brought fully anteriorly in this step. This is especially likely to occur when the muscle is tight, where there is an increased tendency to retract away from the insertion site during this step of the procedure.

Calipers are placed perpendicular to the globe at the insertion site and a locking needle holder placed across the sutures as directed by the caliper measurements (Fig. 86.25). During this step, the caliper should rest gently on the insertion site. A smaller than intended recession will result if the caliper is pressed too firmly into the sclera during this step.

The suture is then tied and trimmed with the needle holder in place. The needle holder is removed and the globe is rotated away from the muscle, which causes the muscle to retract posteriorly. Alternatively, the muscle can also be placed into its new position by gently pulling the suture through the suture tract with a needle holder until the suture knots restrict further movement. If desired, the final position of the muscle can be confirmed by caliper measurement (Fig. 86.26).

Specific considerations for surgery on individual rectus muscles

There are unique considerations for performing surgery on each of the rectus muscles.

Medial rectus muscle

The medial rectus muscle does not have any direct attachments to adjacent oblique muscles, unlike the other rectus muscles. Because of this, the medial rectus muscle is more difficult to retrieve should it be lost at the time of surgery. Excessive dissection of the intermuscular membrane and muscle capsule is discouraged, in part for this reason. In addition to being unnecessary, it may alter the muscle pulleys and cause inadvertent muscle damage.

Inferior rectus muscle

The inferior rectus muscle has fascial attachments to Lockwood's ligament, the inferior orbital septum, and the tarsus of the lower eyelid. Because of these attachments, recession of the inferior rectus may produce retraction of the lower eyelid. Lid retraction may be seen with even moderate inferior rectus muscle recessions. Therefore, techniques designed to minimize the risk of lid retraction when performing a recession on an inferior rectus muscle are recommended, especially when large

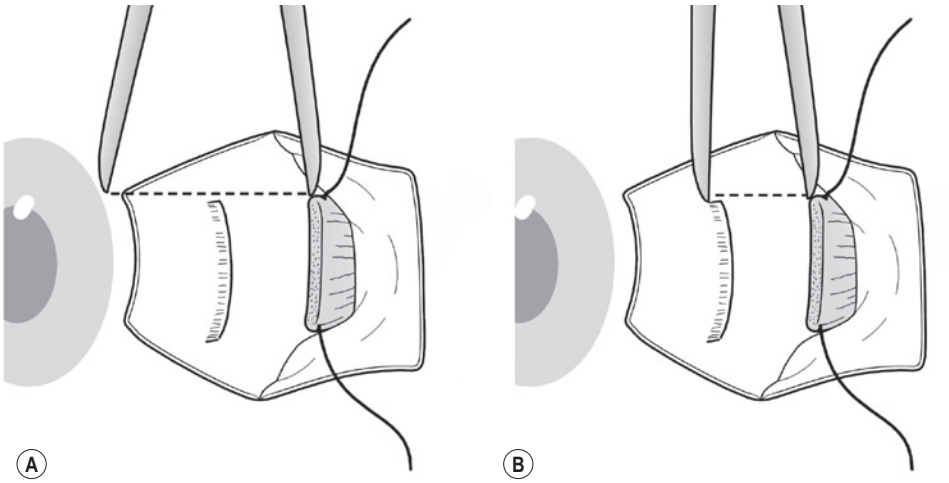


Fig. 86.21 Marking the sclera for a recession. (A) Measurement from the limbus. (B) Measurement from the original insertion site. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

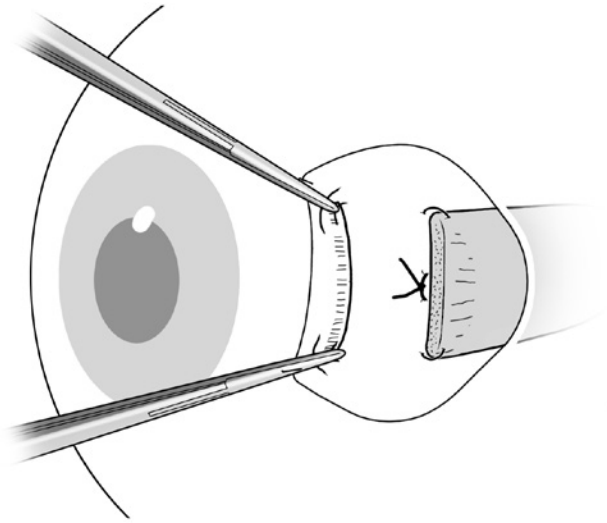


Fig. 86.22 The muscle has been pulled up to its new insertion and the sutures have been tied and cut. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

recessions are performed.[6,7] These may include advancement of the capsulopalpebral head after the recession is performed, or generous dissection of the attachments between the inferior rectus muscle and the lower eyelid prior to the recession.

Lateral rectus muscle

The insertion site of the inferior oblique muscle lies posterior to the insertion of the lateral rectus muscle. Therefore, the strabismus surgeon should exercise caution when attempting to isolate the lateral rectus muscle insertion on a muscle hook, to avoid inadvertently incorporating the inferior oblique on the muscle hook. This risk can be minimized by either passing the muscle from the superior side of the lateral rectus muscle insertion or by avoiding the tendency to pass the hook too deeply into the orbit during attempts to hook the lateral rectus muscle.

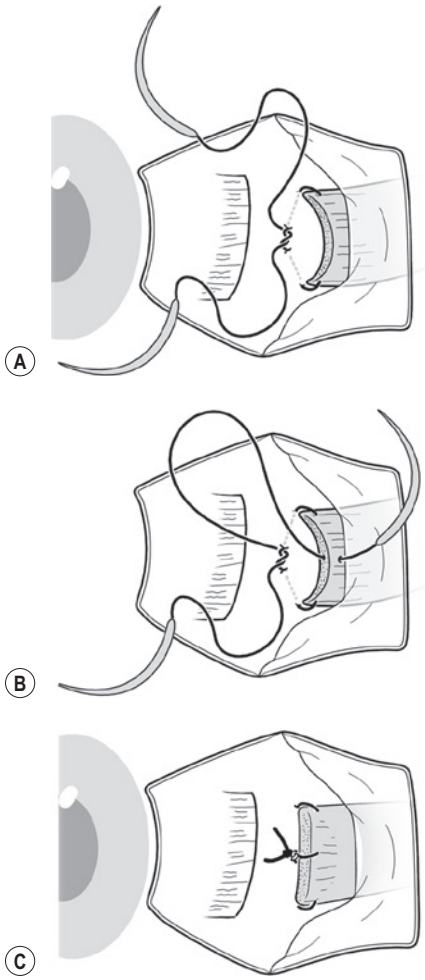


Fig. 86.23 Correcting malposition of the new muscle insertion. (A) The scleral sutures have been placed too close together causing the central aspect of the muscle to sag posteriorly. This can be corrected by (B) passing the needle through the central portion of the muscle, behind the original suture line, and (C) tying the suture to bringing the center of the muscle forward. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

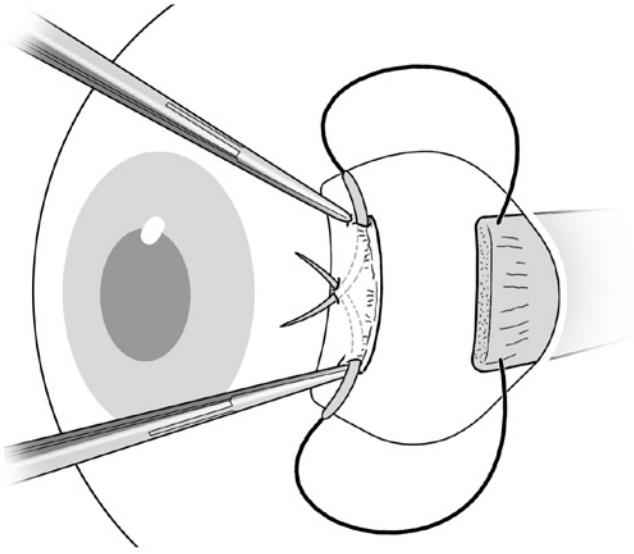


Fig. 86.24 Scleral needle passes during the hang-back recession technique. The needles are passed through the original insertion site to emerge side-by-side in a crossed swords pattern. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

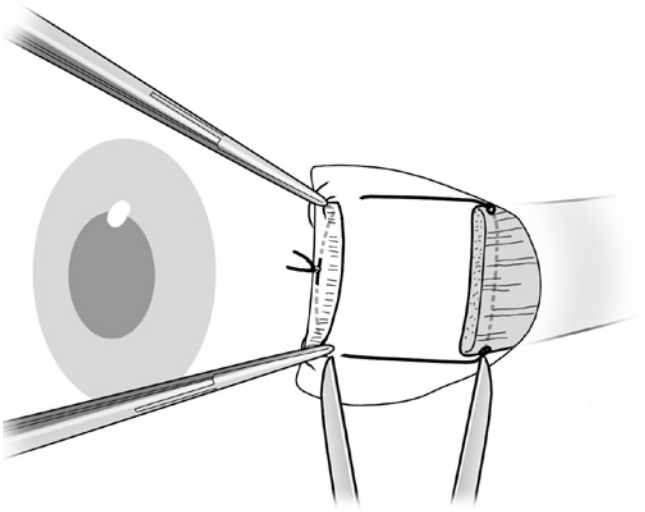


Fig. 86.26 Completing the hang-back recession. The sutures are cut and tied against the needle holder. The muscle moved to its new posterior position by gently pulling on the sutures. The accuracy of the recession can verified with a caliper, if desired. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

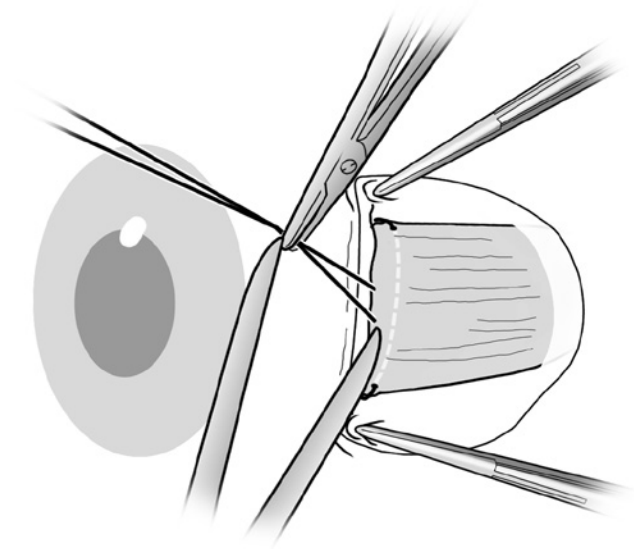


Fig. 86.25 Marking the suture for hang-back recession. The muscle is pulled firmly forward against the original insertion site and the caliper is placed along the suture arms. A locking needle holder is placed across the sutures inside the proximal caliper tip. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

Superior rectus muscle

The superior oblique tendon passes inferior to the superior rectus muscle starting approximately 5 mm posterior to the nasal border of the superior rectus muscle insertion. As with the lateral rectus muscle, it is important to avoid inadvertently hooking the superior oblique tendon when the superior rectus muscle is initially hooked. If the superior oblique tendon is unknowingly hooked along with the superior rectus muscle insertion, it is possible to perform an unintentional tenotomy on the superior oblique tendon when the superior rectus muscle is detached from the globe, potentially producing a significant iatrogenic motility disturbance. Once the insertion of the superior rectus muscle is isolated on a muscle hook, it should be inspected to ensure that the superior oblique tendon has not been inadvertently hooked. If this has occurred, the superior oblique tendon can be gently lifted off the surface of the globe while a new muscle hook is placed under the superior rectus muscle insertion, excluding the superior oblique tendon (Fig. 86.27).

Similar to the relationship between the inferior rectus muscle and the lower eyelid retractors, the superior rectus muscle has significant attachments to the levator muscle of the upper eyelid through the fascial sheaths of these two muscles. Moderate to large recessions of the superior rectus muscle may also cause eyelid retraction. Dissecting these attachments at least 12 mm posterior to the insertion site of the muscle at the time of superior rectus muscle recession will help to minimize this postoperative complication.

Strengthening procedures of the rectus muscles

Though rectus muscle resection and plication are commonly referred to as strengthening procedures, this characterization is technically inaccurate. In reality, these surgeries alter the relationship of the rectus muscle to the globe, changing its length–tension curve. Like the clinical effect of recession, the "strengthening" of a muscle is generally seen only in the change that occurs in the alignment of the eye(s) upon which the resection is performed. A change in the movement of the eye is not clinically obvious following surgery.

Resection

General resection principles

Compared to rectus muscle recession, a resection procedure generally produces more postoperative discomfort and redness

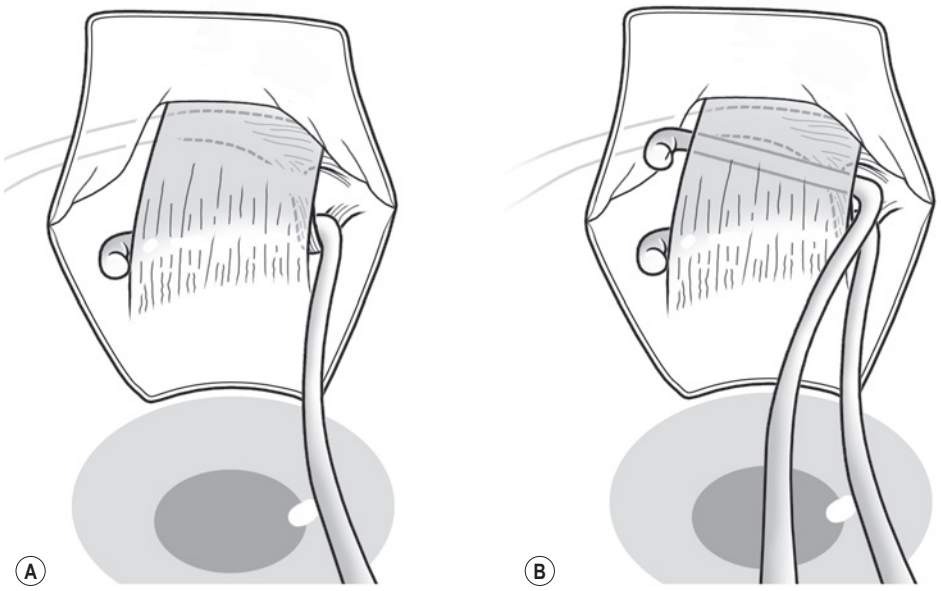


Fig. 86.27 Isolation of the superior rectus. (A) The tendon of the superior oblique has been unintentionally isolated in the hook along with the superior rectus muscle. (B) The superior rectus muscle and superior oblique tendon are lifted off the surface of the globe to allow passage of a second muscle hook to isolate the insertion of the superior rectus muscle only. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

of the conjunctiva. Additionally, the muscle that is sutured to the original insertion site after the resection has taken place is thicker than the tendon, and may become visible beneath the conjunctiva postoperatively. This is especially true for the medial rectus muscle, a finding that can be cosmetically distressing to some patients. Dellen formation is more likely to occur due to greater edema of the conjunctiva adjacent to the limbus following resection surgery. Large resections of the medial rectus may result in mild to moderate anterior displacement of the plica semilunaris, which can be a cosmetic concern. For these reasons and others, many surgeons prefer to perform recession procedures when possible. Despite these drawbacks, rectus muscle resection procedures are effective and they do play an important role in the treatment of strabismus. Common indications in which a resection may be preferred include the desire to limit surgery to only one eye, and treatment of a consecutive deviation in a patient who has previously undergone recession surgery.

General resection technique

Preparation of the muscle for resection

Once the rectus muscle has been isolated, the intermuscular membrane, muscle capsule, and other fascial tissues are dissected to allow for suture placement posterior to the insertion site of the muscle. During dissection, the surgeon should be careful to avoid penetrating Tenon's capsule, which can promote intrusion of extraconal fat into the operative site; this can produce restrictive strabismus that is difficult to repair.

Resection of the muscle

A second hook is placed between the muscle and the sclera, posterior to the hook that has been used to isolate the muscle insertion. A caliper is used to mark the position of the posterior limit of the resection. Coating the tip of the caliper with a sterile gentian violet skin-marking pen prior to this step may be helpful (Fig. 86.28A). When the caliper makes contact with the muscle, the ink will be transferred to the muscle surface, facilitating later steps of the procedure. Some surgeons place a central safety knot in the muscle at the caliper mark while others do not (Fig. 86.28B). Transverse passes are made, followed by locking bites at the borders of the muscle. A small straight hemostat is placed anterior to the suture and the posterior muscle hook removed (Fig. 86.28C).

The muscle is then detached from its insertion on the globe (Fig. 86.29) and the distal portion of the muscle is excised. During this step, the surgical assistant should assure that the sutures are retracted from the surgical site, to avoid inadvertently cutting them. Some surgeons prefer to cauterize the distal edge of the muscle prior to removal of the hemostat, though this step is not universally necessary. The hemostat can be left in place and used to help hold the muscle in position at the insertion while suturing, if desired.

Re-attaching the muscle to the sclera

The sutures are then passed through the original insertion site of the muscle and the now-shortened muscle pulled up to the original insertion site. The surgical assistant may facilitate this process by retracting the globe toward the muscle using locking forceps attached to the insertion site, to reduce the amount of tension placed on the muscle during this step of the procedure, or the hemostat may be used to hold the muscle in position if it has not yet been removed. The sutures are then tied and trimmed. Occasionally, the muscle is noted to have retracted posteriorly during the process of tying the sutures. In the event that the muscle does move posteriorly and this is noted after the sutures have been tied, a suture may be passed through each pole of the muscle and brought through the insertion site. The sutures are then tied and cut to bring the muscle back to its proper position (Fig. 86.30).

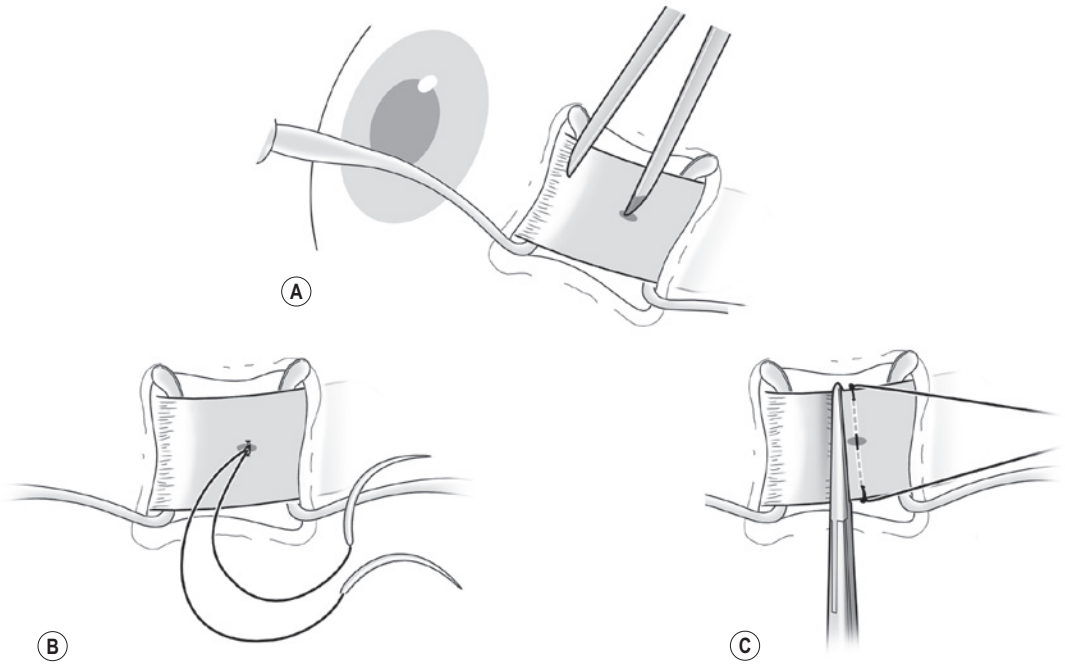


Fig. 86.28 Measuring and marking the resection. (A) After coating the tip of the caliper with ink from a sterile gentian violet skin-marking pen, the caliper is used to mark the resection position on the muscle. (B) A central knot is placed at this site, and (C) transverse passes and locking bites placed in the muscle and a hemostat is placed anterior to the sutures. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

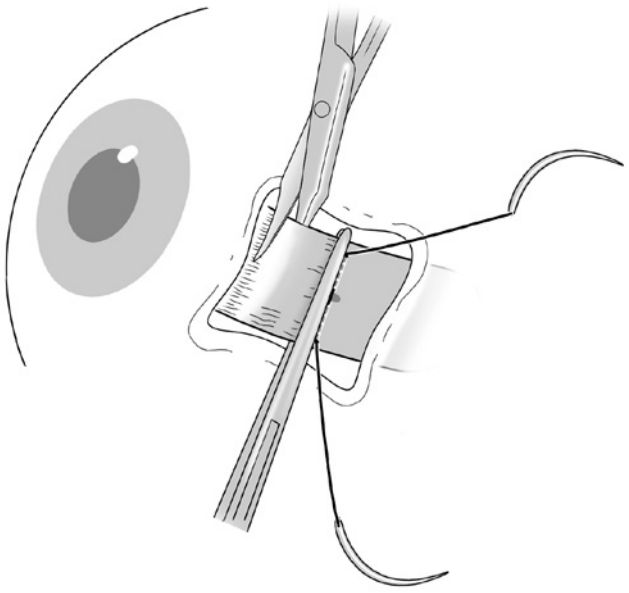


Fig. 86.29 Detachment and resection of the muscle. The muscle is detached from the globe at its insertion. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

Rectus muscle plication

A rectus muscle plication can be used in lieu of a resection. Plication has the potential advantage of preserving the anterior ciliary circulation, thereby reducing the risk of anterior segment ischemia in susceptible patients. It also eliminates the potential loss of a muscle. In addition, the surgery tends to be less traumatic than a standard resection. In one version of this technique, two single-armed sutures are placed at each edge of the muscle. The needles are then passed just anterior to the insertion of the muscle and the sutures are used to pull the posterior portion of the muscle forward and fold it on itself.[8]

Surgery on the inferior oblique muscle

The most common indications for surgery on inferior oblique muscles include superior oblique palsy, primary inferior oblique overaction, "V" pattern horizontal strabismus with inferior oblique overaction, and dissociated vertical deviation associated with inferior oblique overaction. Most surgical procedures done on the inferior oblique muscle are designed to weaken its function, and will be the focus of this section.

Identification and isolation of the inferior oblique muscle

Most surgical procedures performed on the inferior oblique muscle are performed on its distal end. A discussion of the full scope of procedures that can be performed on the inferior oblique muscle is beyond the scope of this chapter, which will highlight the most important procedures performed on this muscle. Surgical access is generally gained through a standard fornix conjunctival incision, followed by incision of Tenon's capsule to gain access to the episcleral space. Excellent visualization of the inferior oblique muscle can usually be obtained by retracting the globe superiorly and nasally. The posterior border of the muscle can usually be identified

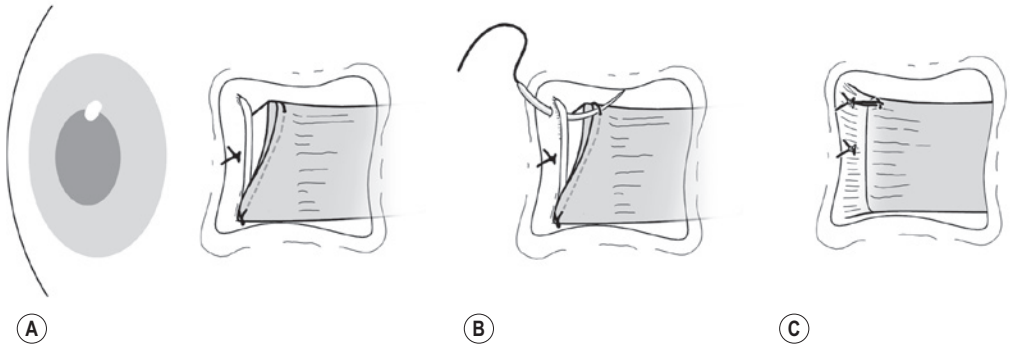


Fig. 86.30 Correcting posterior movement of the muscle during resection. (A) The suture has been tied and the muscle is not in direct contact with the original insertion site. (B) To correct this, a suture is passed through the insertion site and behind the muscle suture at each pole of the muscle, and (C) the newly placed sutures are tied and cut, bringing the muscle to the desired location. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

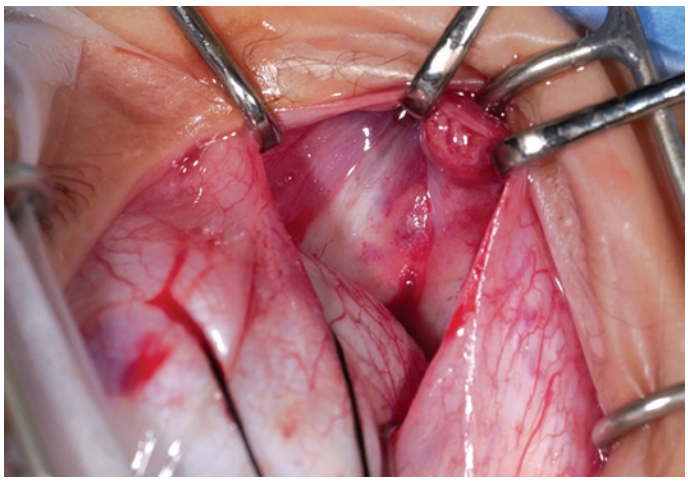


Fig. 86.31 Surgical exposure of the surgical site for inferior oblique surgery using a lateral rectus muscle bridle suture. One or two hooks are placed into the incision and retracted inferiorly. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

approximately 10–12 mm from the limbus in Tenon's fascia as it is retracted from the globe (Fig. 86.31).

The posterior border of the inferior oblique muscle can be easily identified if good exposure has been obtained. Important landmarks that can aid the surgeon in confirming that the posterior border of the inferior oblique muscle has been identified include visualization of the posterior border of the inferior oblique muscle, the sclera, and the adjacent vortex vein simultaneously (see Figs 86.31 and 11.2C). A muscle hook is passed under the posterior border of the inferior oblique muscle, directed first toward the floor of the orbit and then drawn anteriorly (Fig. 86.32). The surgeon then sharply dissects the capsule to expose the inferior oblique muscle insertion on the sclera temporally (Fig. 86.33).

Inferior oblique muscle recession

The inferior oblique muscle is detached from the sclera at its insertion. This process can be facilitated by placement of a hemostat across the inferior oblique muscle several millimeters proximal to its insertion into the sclera, if desired (Fig. 86.34A). Cautery may be applied to the proximal muscle edge to prevent bleeding when the hemostat is removed. An absorbable suture such as 6-0 polyglactin is then placed in the muscle near its distal end (Fig. 86.34B). The muscle is then sutured to the sclera along the normal course of the inferior oblique muscle. The authors most commonly place the anterior muscle suture 2–4 mm posterior to the temporal border of the inferior rectus muscle insertion, and near the temporal border of the inferior rectus muscle (Fig. 86.34C). Some surgeons prefer graded recession of the inferior oblique muscle based on the degree of inferior oblique overaction.

Inferior oblique myectomy

After isolation and dissection of the inferior oblique muscle, two hemostats are placed across the inferior oblique muscle (Fig. 86.35A). This is followed by myectomy of the tissue between the hemostats. Cautery is applied to the cut edges of the muscle (Fig. 86.35B) prior to releasing them from the hemostats.

Denervation and extirpation

Denervation and extirpation of the inferior oblique muscle is an infrequently used procedure. It is reserved for pronounced overaction of the inferior oblique muscle and many surgeons reserve the procedure for recurrent inferior oblique overaction, despite previous weakening procedures on the inferior oblique muscle. The procedure involves identification and transection of the neurovascular bundle combined with removal of a large distal segment of inferior oblique muscle.

Inferior oblique anterior transposition

The most common indications for the inferior oblique anterior transposition procedure is dissociated vertical deviation coupled with inferior oblique overaction in the same eye. The procedure is usually performed bilaterally because asymmetry of the eyelids can occur after unilateral inferior oblique anterior transposition.[9] Anterior transposition of the inferior oblique muscle is virtually identical to inferior oblique recession except that the new muscle insertion is placed at or near the insertion

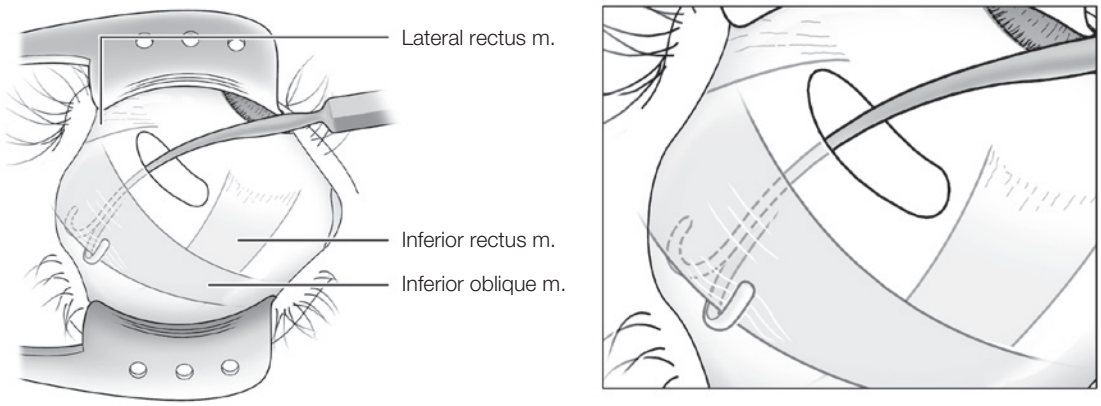


Fig. 86.32 Isolating the inferior oblique muscle on a muscle hook. A Scobee muscle hook is placed at the posterior border of the inferior oblique muscle. The hook is gently advanced inferiorly and then anteriorly, to bring only the inferior oblique muscle anteriorly on the hook. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

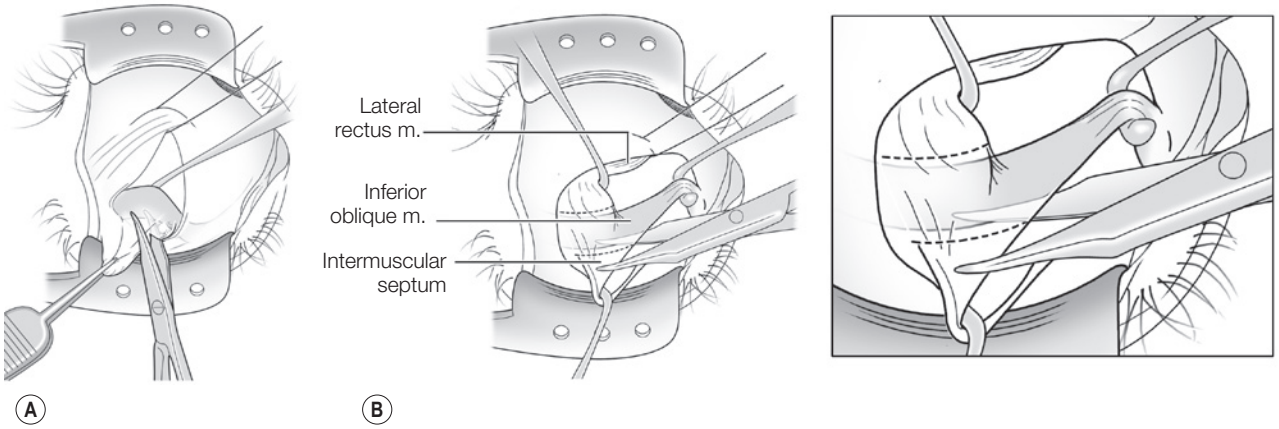


Fig. 86.33 Dissection of the muscle capsule of the inferior oblique. The surgeon sharply dissects the muscle capsule while the assistant surgeon places the capsule under mild traction. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

of the inferior rectus muscle. It is generally placed no more than 1 mm anterior or posterior to the insertion, and is most commonly placed at the level of the insertion, at its lateral edge (Fig. 86.36).

Surgery on the superior oblique tendon

Surgical procedures involving the superior oblique tendon are among the most intricate surgical procedures performed by a strabismus surgeon. Both the complex functions of the superior oblique muscle and its complex anatomical configuration make surgery on the superior oblique tendon unforgiving when proper indications and techniques are not followed. Postoperative problems are often difficult to remedy satisfactorily.

The function of the superior oblique muscle/tendon can be enhanced or reduced. The broad insertion of the superior oblique tendon into the sclera, as well as the anatomy of the insertion relative to the equator of the globe and the functional origin of the muscle in the superonasal aspect of the orbit, allow the surgeon to alter specific functions of the superior oblique muscle/tendon by manipulation of different portions of the superior oblique tendon and its insertion. The anterior fibers of the superior oblique tendon, insert anterior to the equator of the globe. They are thought to be primarily responsible for incyclotorsion of the globe. The posterior fibers course behind the equator and are primarily responsible for abduction and depression.

Forced traction testing of the superior oblique tendon

Both forced traction testing and exaggerated forced traction testing are useful adjuncts during surgery on the superior oblique tendon (Figs 86.37 and 86.38). They can be very useful in identifying a lax superior oblique tendon that is commonly found in patients with a congenital superior oblique palsy. They are also useful to confirm that the entire tendon has been transected when performing a tenotomy or tenectomy.[10]

Superior oblique strengthening procedures

Superior oblique strengthening procedures can be performed on the anterior portion of the tendon or on the full thickness

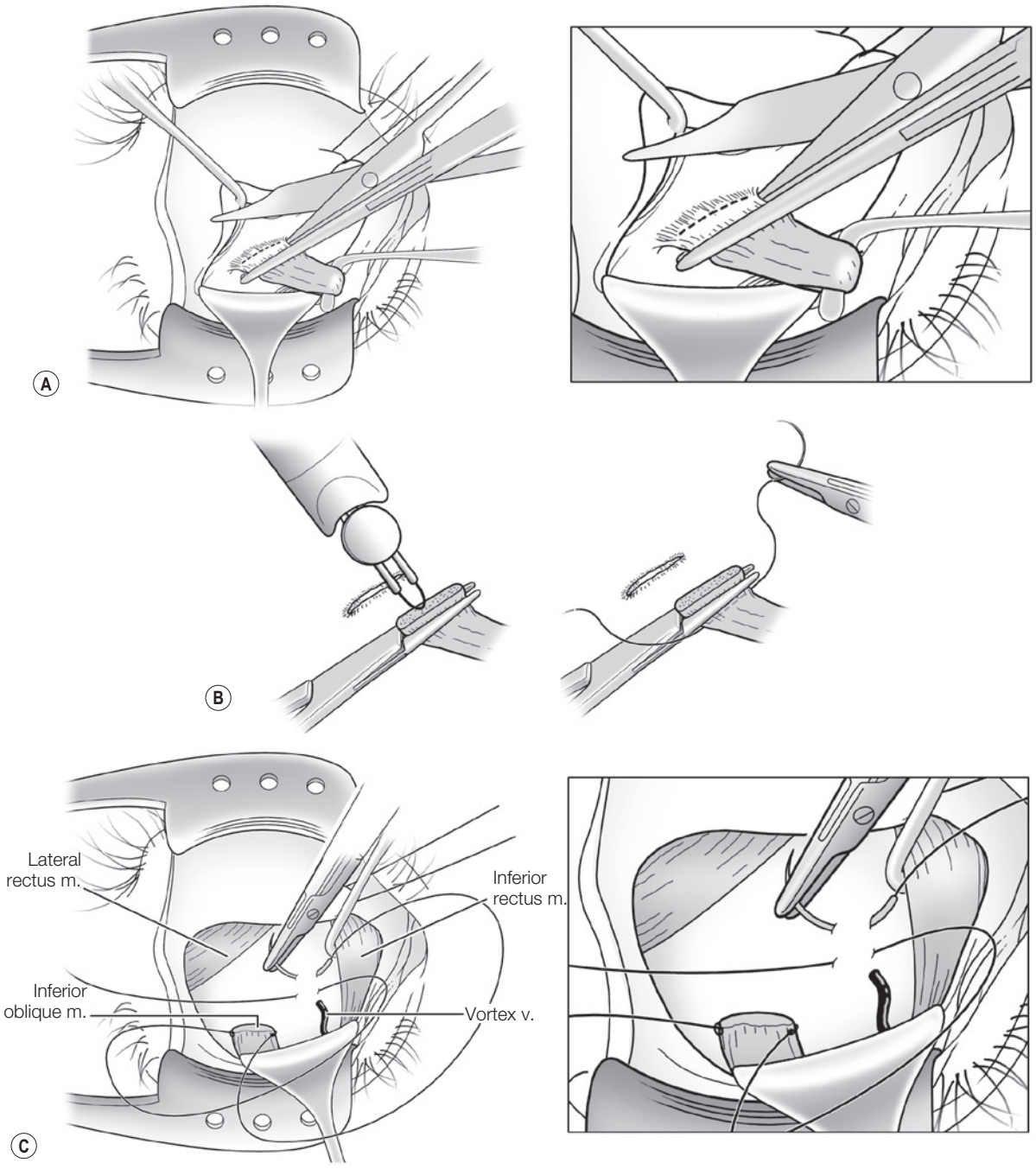


Fig. 86.34 Inferior oblique recession. (A) The muscle is transected distal to a hemostat placed across the muscle near the insertion. (B) Cautery is applied to the proximal muscle edge and absorbable sutures placed in the muscle posterior to the hemostat. (C) The muscle is sutured to the sclera; the anterior suture is most commonly placed 2–4 mm posterior to the temporal border of the inferior rectus muscle. Note the vortex vein just behind this location. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

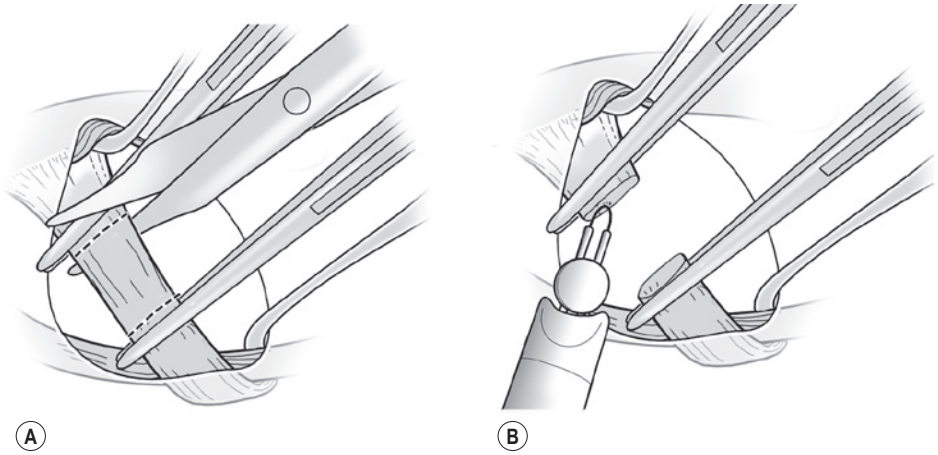


Fig. 86.35 Inferior oblique myectomy. (A) Two hemostats are placed across the muscle, separated by 5–10 mm. (B) The myectomy is performed, the muscle edges cauterized. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

of the tendon through tucking procedures. Tucking the full width of the tendon tightens both the anterior and posterior tendon fibers and therefore increases all three functions of the superior oblique muscle including incyclotorsion, depression, and abduction. Tucking of only the anterior fibers of the tendon selectively increases the incyclotorsion function of the superior oblique muscle and is used when excyclotorsion is the primary problem.

Superior oblique tucking procedure

A tuck of the superior oblique tendon may be performed for the treatment of superior oblique palsy as an isolated procedure, or combined with a weakening procedure of another cyclovertical muscle such as the ipsilateral inferior oblique muscle, ipsilateral superior rectus muscle, or contralateral inferior rectus muscle. Following a tuck of the superior oblique tendon, some degree of iatrogenic limitation of elevation in adduction can be anticipated. This is most likely to occur when a superior oblique tendon tuck is performed in conjunction with a weakening procedure of the ipsilateral inferior oblique muscle.

Identifying the superior oblique tendon

The superior rectus muscle is isolated and a small muscle hook is used to retract conjunctiva and Tenon's fascia posteriorly along the lateral border of the superior rectus muscle. A small dissection of the check ligaments above the superior rectus muscle may facilitate its exposure. A Desmarres or other retractor can be placed in the posterior aspect of the incision, to improve exposure of the temporal border of the superior rectus muscle as well as the superior oblique tendon. The insertional fibers of the superior oblique tendon can usually be easily identified traveling underneath the superior rectus

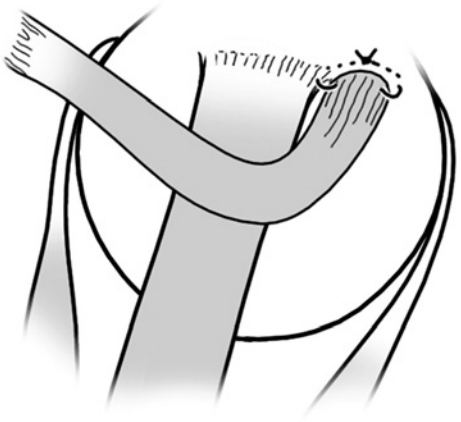


Fig. 86.36 Inferior oblique muscle anterior transposition. The new insertion of the muscle is placed 1 mm anterior or posterior and adjacent to the temporal border of the inferior rectus muscle insertion. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

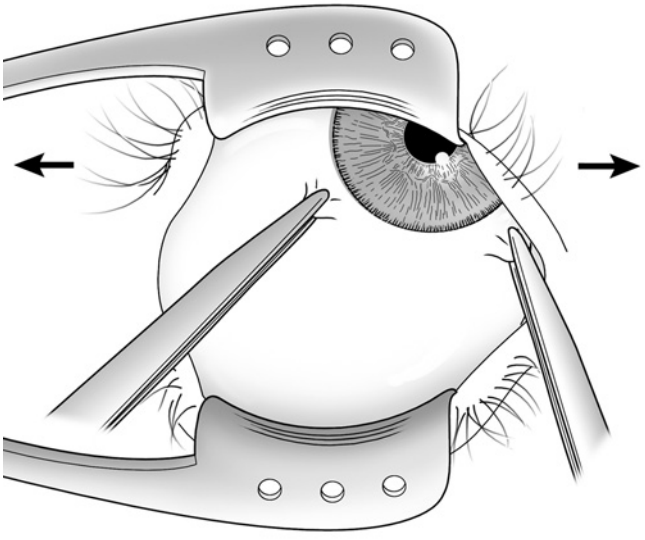


Fig. 86.38 Eye with a superior oblique tendon having normal tauntness. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

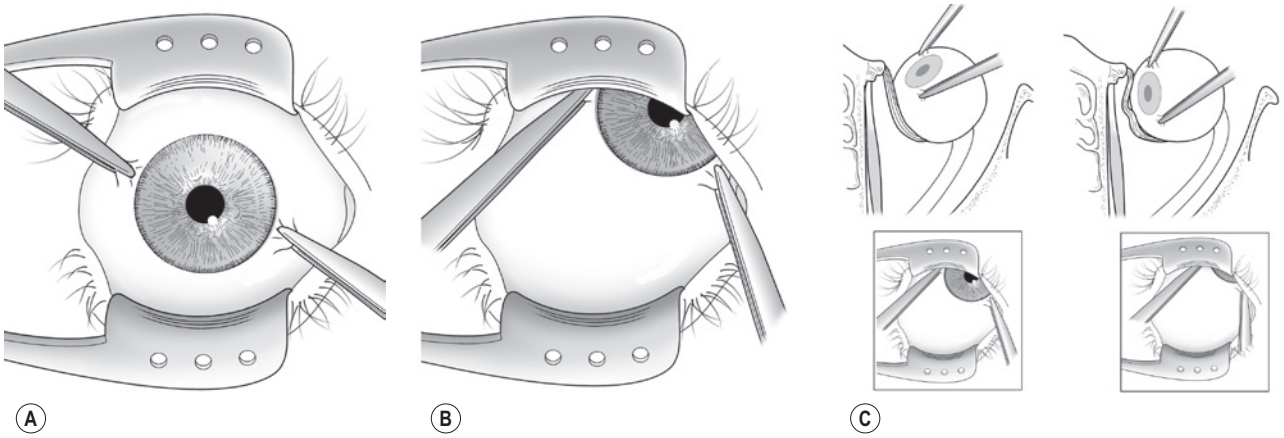


Fig. 86.37 Superior oblique traction testing. (A) The globe is firmly grasped at the 4 o'clock and 10 o'clock positions for the right eye (2 o'clock and 8 o'clock positions for the left eye). (B) While gently pressing the globe into the orbit, the surgeon simultaneously elevates and adducts the eye. (C) The superior oblique tendon is put on stretch. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

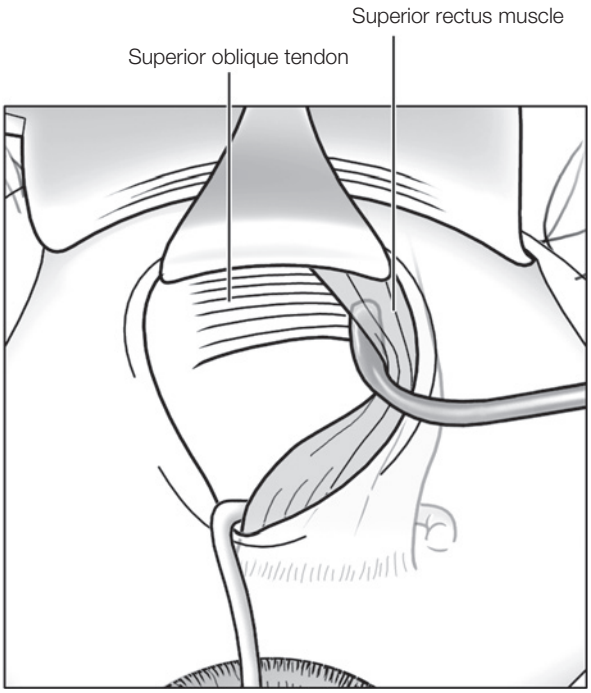


Fig. 86.39 Identification of the superior oblique tendon allowing visualization of the superior oblique tendon on the temporal side of the superior rectus muscle. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

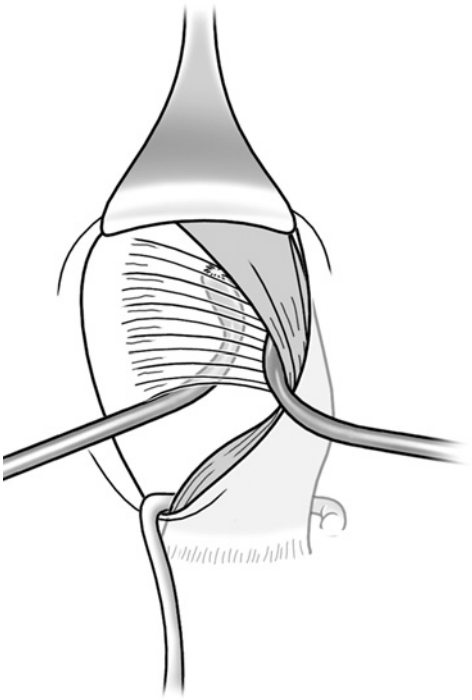


Fig. 86.40 Isolating the superior oblique tendon. A small hook is drawn anteriorly as it is held against the sclera posterior to the superior oblique tendon, resulting in isolation of the superior oblique tendon. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

muscle and fanning out to insert into the sclera posteriorly on the temporal side of the superior rectus muscle (Fig. 86.39).

Isolation of the superior oblique tendon

A small hook is placed on the sclera adjacent to the temporal border of the superior rectus muscle and anterior to the superior oblique tendon. The small hook is moved posteriorly as it is held against the sclera. It is then turned superiorly and withdrawn anteriorly, resulting in isolation of the superior oblique tendon (Fig. 86.40). The small hook can be exchanged for a larger hook that will more securely maintain control of the tendon. Attachments between the superior oblique tendon and superior rectus muscle can bluntly be dissected if needed.

Tucking of the superior oblique tendon

The tendon is engaged on a tendon tucker or hook and the desired size of the tuck is measured (Fig. 86.41A). A non-absorbable suture is passed through the mid-portion of the tendon at the desired level and tied around the tendon (Fig. 86.41B). The tucked portion of the tendon is then allowed to retract back into the episcleral space.

Fells modification of the Harada–Ito procedure

The Fells modification of the Harada–Ito procedure is used to correct excyclotorsion, typically in the setting of a bilateral superior oblique palsy with minimal vertical deviation in primary position.[11] The procedure involves advancement of the anterior portion of the superior oblique tendon. After isolation of the superior oblique tendon on the temporal side of the superior rectus muscle, two small muscle hooks are used to divide the superior oblique tendon longitudinally extending from its insertion into the sclera for approximately 8–10 mm. The anterior 3 mm portion of the tendon fibers is separated from the remainder of the tendon. An absorbable suture is secured in the anterior tendon fibers (Fig. 86.42A). The fibers are then detached from the sclera at the insertion and advanced temporally. This portion of the tendon is sutured to the sclera approximately 8 mm posterior and 2 mm superior to the superior edge of the lateral rectus muscle insertion (Fig. 86.42B).

Superior oblique weakening procedures

Techniques to weaken the superior oblique include both graded and non-graded procedures. Graded procedures include silicone expander insertion and recession of the superior oblique tendon. Non-graded techniques include tenotomy and tenectomy. Posterior tenectomy combines some degree of both graded and non-graded weakening procedures. The advantages of a graded weakening procedure include the ability to titrate the surgical effect, perform asymmetric bilateral surgery, reversibility, and improved access to the operated tendon should further surgery be needed in the future.

Superior oblique tenotomy and tenectomy

A superior oblique tenotomy or tenectomy may be performed on the tendon, either nasal or temporal to the superior rectus muscle. During isolation of the tendon, the surgeon should minimize disturbance of the fascial tissues surrounding the tendon, which will minimize the risk of scarring between the cut ends of the tendon and the sclera.

The superior rectus muscle is isolated on a large muscle hook. A small muscle hook is used to retract the conjunctiva and Tenon's fascia nasally. The toe of the large muscle hook

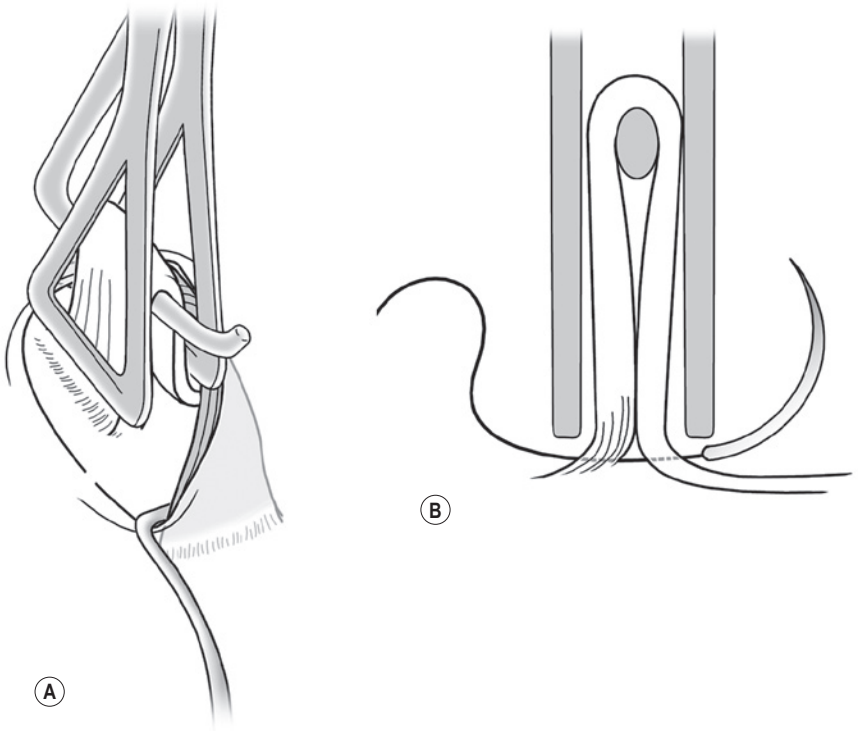


Fig. 86.41 Tucking the superior oblique tendon with a tucking device. (A) The tendon is engaged on a tendon tucker and the desired size of the tuck dialed into the tucker. (B) A non-absorbable suture is passed through the tendon to plicate the base of the tuck. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

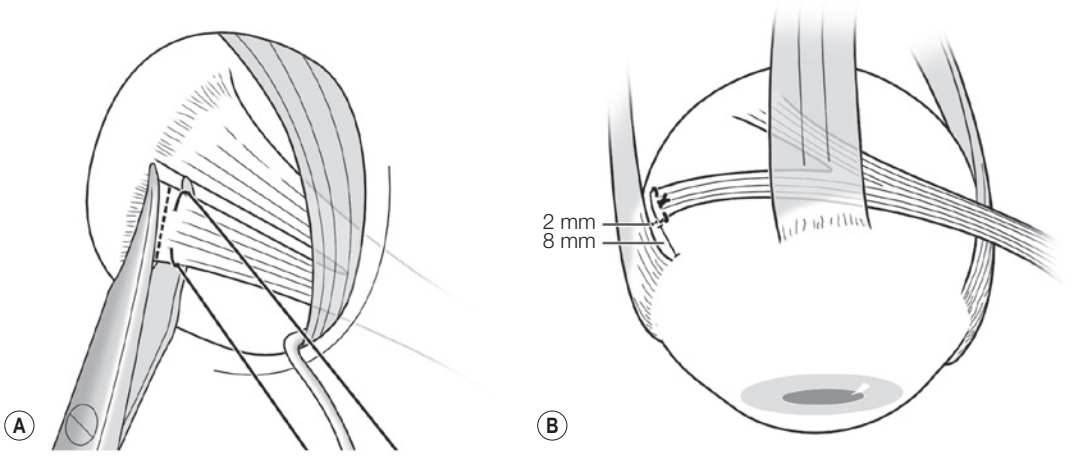


Fig. 86.42 Fells modification of the Harada–Ito procedure. (A) The superior oblique tendon is split longitudinally, separating the anterior 25% of the tendon from the remainder of the tendon. (B) An absorbable suture is secured in the anterior tendon fibers, which is then detached from the sclera. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

securing the superior rectus muscle will be covered by the intermuscular septum, which should not be disturbed. A retractor is placed along the nasal border of the superior rectus muscle and retracted posteriorly. The superior oblique tendon can be visualized through its surrounding fascia as white fibers running perpendicular to the superior rectus muscle against the sclera. Once the superior oblique tendon is visualized, a small incision is made through Tenon's fascia directly over the tendon. The tendon is then hooked with a small muscle hook and brought through the incision and the exposed tendon is then transected (tenotomy) or a portion of the tendon excised (tenectomy).

A superior oblique tenotomy/tenectomy can also be performed from the nasal side of the superior rectus muscle (Fig. 86.43A). Once the superior oblique tendon has been isolated on a muscle hook, temporal traction is placed on the tendon to expose as much of the nasal portion of the tendon as possible. Once the nasal portion of the tendon is adequately exposed, a tenotomy or tenectomy is performed (Fig. 86.43B). The weakening effect of surgery is greater when surgery is performed on the nasal aspect of the tendon.

Superior oblique tendon expander

The placement of an expander to lengthen the superior oblique tendon offers several potential advantages. A graded weakening procedure can be performed, the risk of creating an iatrogenic superior oblique palsy can be minimized, and the technique facilitates re-operation, if needed.[12]

The superior oblique tendon is isolated nasal to the superior rectus muscle as previously described for a nasal

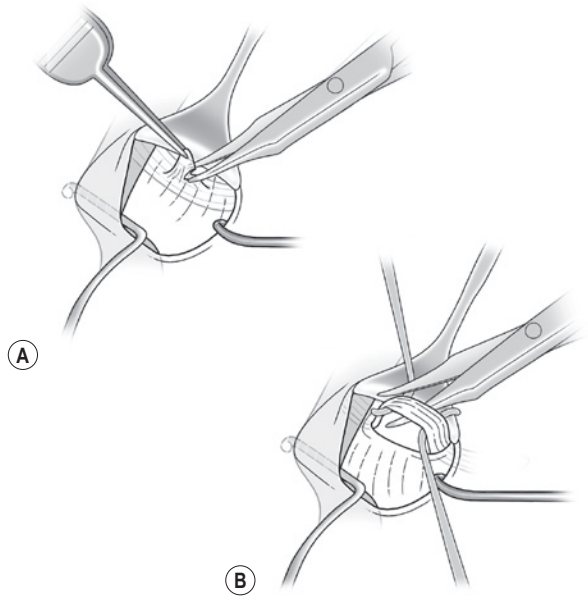


Fig. 86.43 Superior oblique nasal tenotomy and tenectomy. (A) A small incision is made through Tenon's fascia directly over the tendon, (B) transected (tenotomy) or a portion of the tendon is excised (tenectomy). *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

tenotomy/tenectomy procedure. Two double-armed 5-0 or 6-0 Mersilene® sutures are placed in the tendon (Fig. 86.44A). The first suture is placed approximately 3 mm nasal to the border of the superior rectus muscle and the second suture is placed approximately 2 mm nasal to the initial suture. The tendon is then transected between these two sutures and a silicone retinal band that has been cut to the desired length is sutured between the cut ends of the superior oblique tendon (Fig. 86.44B). Tenon's capsule overlying the tendon and expander is then closed with absorbable suture.

Superior oblique posterior tenotomy/tenectomy

Posterior tenotomy/tenectomy of the superior oblique is performed at its insertion site into the sclera. The procedure provides a predictable weakening of the function of the superior oblique muscle for the treatment of "A" pattern strabismus, primarily weakening its depression and abduction functions.[13] The insertion of the superior oblique tendon is isolated temporal to the superior rectus muscle. The posterior 7/8 of the insertion is detached and a small wedge of the posterior tendon is excised (Fig. 86.45).

Transposition procedures

Rectus muscle transposition procedures

Transposition procedures are used almost exclusively in cases of muscle paralysis or near paralysis. Common indications for rectus muscle transposition surgery include treatment of isolated rectus muscle paralysis, such as a sixth nerve palsy. Rectus muscle transposition procedures are most effective when the function of only one rectus muscle is severely compromised.

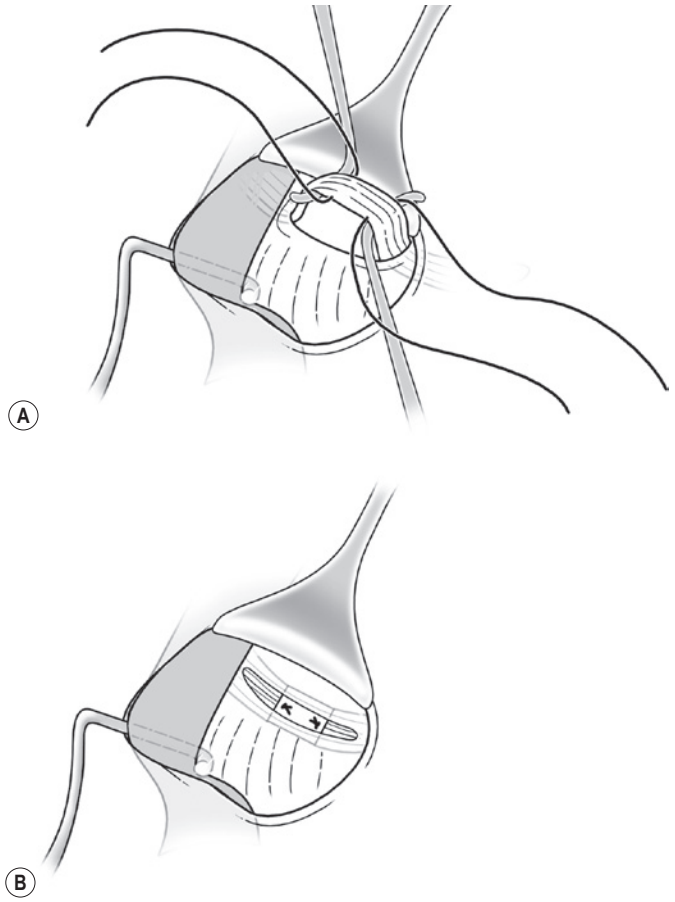


Fig. 86.44 Superior oblique tendon silicone expander. (A) Two double-armed 5-0 or 6-0 Mersilene® sutures are placed in the tendon, and (B) a silicone retinal band is sutured between the cut ends of the tendon using a horizontal mattress technique. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

The goal of transposition surgery is primarily to re-align the deviating eye as close to the primary position as possible, usually also attempting to achieve single vision for patients with diplopia. The results of transposition surgery are often good, but never perfect. Ocular alignment outcome from a transposition procedure can be enhanced by weakening the antagonist of the paralyzed muscle, either through recession or through injection of botulinum toxin, in selected cases. Weakening of the yoke muscle in the sound eye may be of value in some cases. This section will concentrate on the most important transposition procedures among a large number of potential options.

Transposition procedure can be performed through a large limbal incision or through two fornix incisions in adjacent quadrants. The incisions are placed as shown in Figure 86.46. The approach chosen is largely dependent on surgeon preference.

Full tendon rectus muscle transposition

A full tendon rectus transposition procedure is indicated when there is complete or near complete paralysis of a rectus muscle, such as a lateral rectus muscle paralysis. The two adjacent rectus muscles are transposed to a position adjacent to the insertion of the paralyzed muscle. The intermuscular

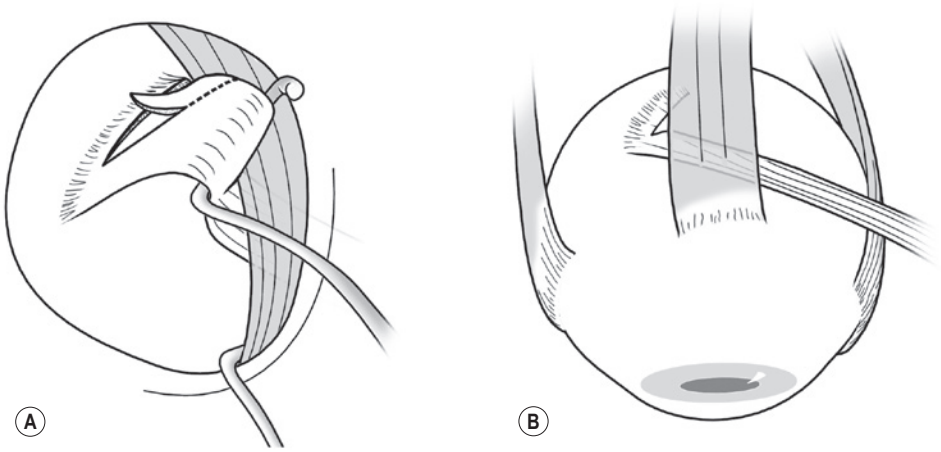


Fig. 86.45 Posterior 7/8 tenotomy of the superior oblique tendon. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

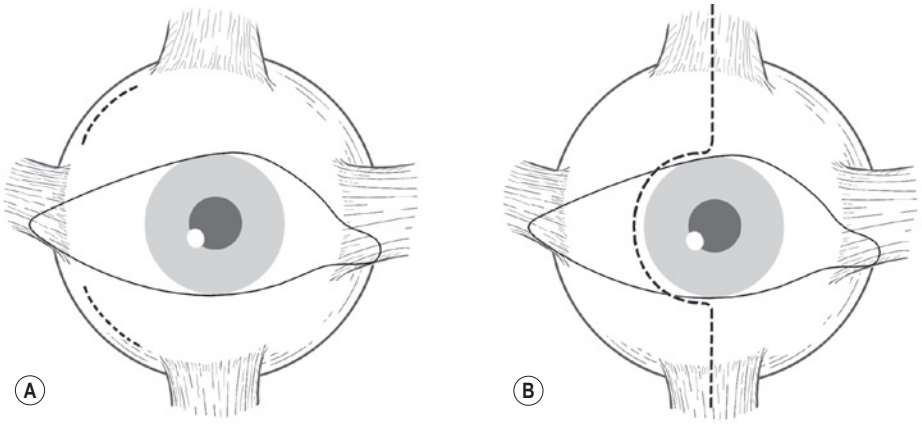


Fig. 86.46 Conjunctival incision for full tendon transposition. (A) Fornix incisions, and (B) limbal incision. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

septum of the adjacent rectus muscle is generously dissected for approximately 10–12 mm posterior to the insertion. The muscles are then detached from their insertions and sutured back to the sclera adjacent to the insertion of the paralyzed muscle (Fig. 86.47).

Transposition of both the superior and inferior rectus muscles was traditionally believed to be necessary for successful correction of esotropia due to complete sixth nerve palsy. Recently, superior rectus muscle transposition combined with medial rectus recession has been reported to be a successful alternative for the treatment of both isolated sixth nerve palsy and esotropia associated with Duane syndrome.[14]

Full tendon transposition with posterior fixation suture augmentation

A modification of the standard full tendon transposition involves placement of non-absorbable sutures to redirect the transposed muscle borders to the sclera adjacent to the borders of the paralyzed muscle 12–14 mm posterior to limbus[15] (Fig. 86.48). Concurrent recession of the antagonist muscle may result in overcorrection. Recession of the yoke muscle in the sound eye may be done if additional effect is needed. The procedure has been reported to improve ductions in the field of action of the paralyzed muscle. Augmentation of the standard full tendon transposition procedure, by suturing the border of the transposed muscles directly to the paralyzed muscle, has also been described.

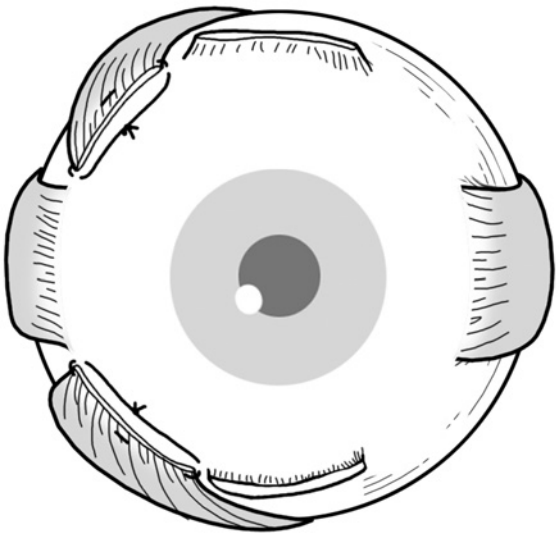


Fig. 86.47 Full tendon transposition of the superior and inferior rectus muscle insertions for treatment of a lateral rectus muscle paralysis. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

Vessel-sparing full tendon or near full tendon transposition

When concerned about the risk of anterior segment ischemia, transposition procedures may be modified to reduce compromise of the anterior segment circulation. Dissection with isolation and sparing of one or both anterior ciliary vessels associated with the vertical rectus muscle prior to transposition of the muscles is one such approach[16] (Fig. 86.49). Partial tendon transposition involving repositioning of ⅘ of the transposed rectus muscles leaving the remaining muscle and its intact anterior ciliary vessels intact has also been reported to be of value and avoids the need for tedious dissection of the anterior ciliary vessels in the former approach.[17]

Partial tendon transposition

Hummelsheim described a procedure involving transposition of the temporal half of the superior and inferior rectus muscles and suturing them to the lateral rectus muscle insertion. Today, half tendon transposition of adjacent rectus muscles generally involves suturing the transposed muscle segments directly to the sclera adjacent to the paralyzed muscle's insertion. This procedure can be used to treat any isolated rectus muscle paralysis in an eye. The effect can be augmented by simultaneously resecting a 5–7 mm section of the transposed muscle segments[18] (Fig. 86.50).

Nasal transposition of the lateral rectus muscle for third nerve palsy

Longitudinal splitting and redirection of the lateral rectus muscle posteriorly to the nasal side of the globe was reported to be a useful procedure in the management of third nerve palsy in a small series of patients. The procedure may be

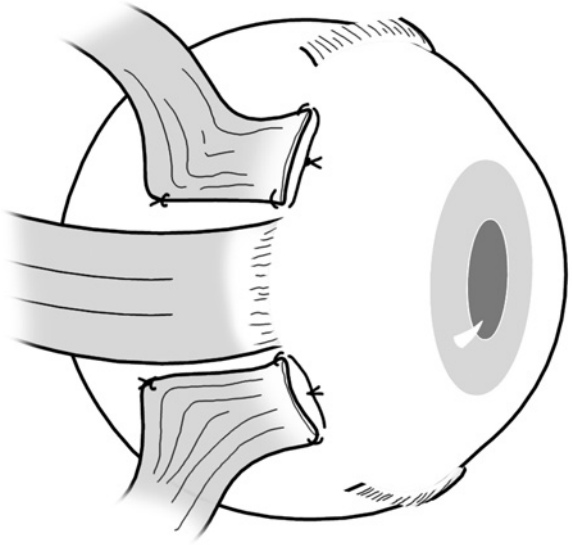


Fig. 86.48 Augmented full tendon transposition procedure described by Foster. The belly of each transposed muscle is sutured to the sclera adjacent to the borders of the paralyzed rectus muscle. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

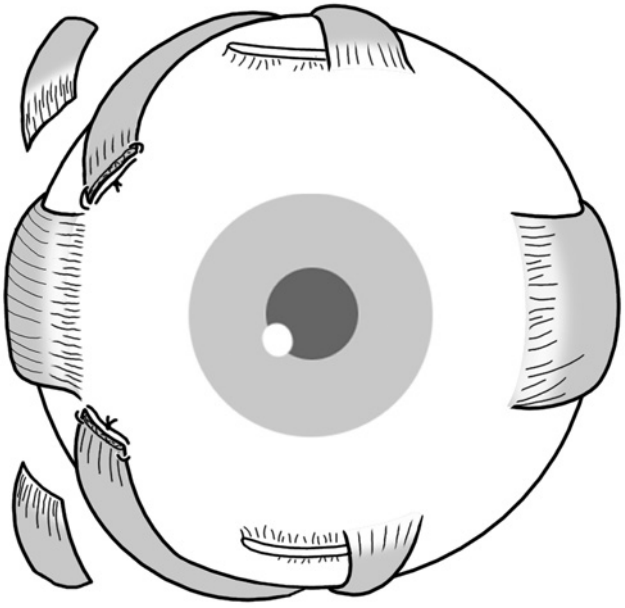


Fig. 86.50 Augmented Hummelsheim-type procedure. A 5 mm resection of each transposed muscle segment is done prior suturing them to the sclera adjacent to the borders of the paralyzed rectus muscle insertion. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

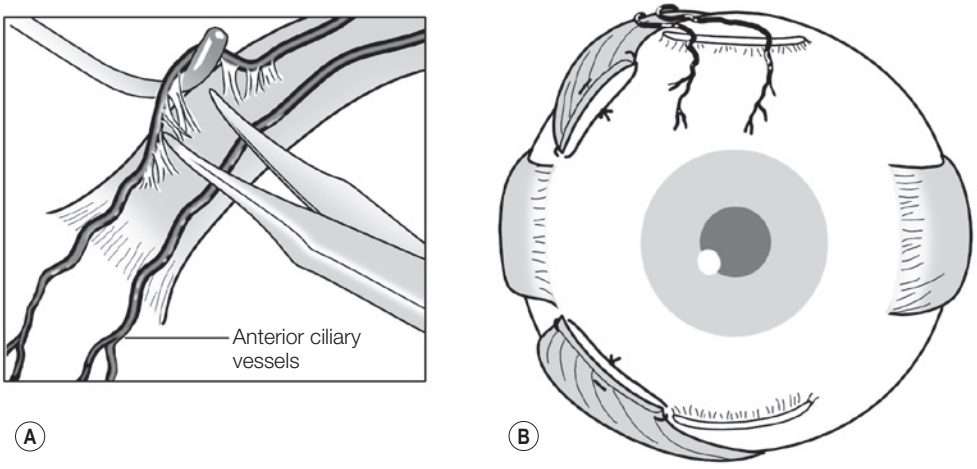


Fig. 86.49 Full tendon transposition after dissection and sparing of the anterior ciliary vessel. (A) Dissection of the vessels and (B) appearance after transposition. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

difficult to perform on patients who have previously undergone lateral rectus muscle surgery due to tightness of the previously operated muscle, making it impossible to effectively transpose the muscle.[19]

Superior oblique tendon transposition

Superior oblique tendon transposition can be used to improve ocular alignment in patients with complete or near complete third cranial nerve palsy, and is most useful as an adjunct to other, more effective procedures. The superior oblique tendon is transected near the nasal border of the superior rectus muscle. It is then sutured to the sclera above the medial rectus muscle insertion under tension with non-absorbable suture, discarding the distal aspect of the tendon (Fig. 86.51). The procedure can be done with or without fracturing the trochlea.

Adjustable suture techniques

Some surgeons strongly believe that adjustable sutures offer a distinct advantage, improving outcomes, while other surgeons do not see a significant enough benefit to justify their use.[20] While this section highlights commonly used adjustable suture techniques, the reader should recognize that many variations have been reported. Adjustable suture techniques can be performed through a limbal or a fornix incision. The adjustment process can be done at the time of the primary surgery in the operating room, or even days after surgery in the office.

Technique for bow-type adjustable sutures

The bow-type technique can be applied to a recessed or resected rectus muscle. The suture ends are then tied into a half bow (Fig. 86.52A). To adjust the muscle position, the bow is untied, the muscle position adjusted, and the bow retied (Fig. 86.52B). The bow is then converted into a permanent knot after ocular alignment is satisfactory (Fig. 86.52C).

Technique for cinch knot adjustable sutures

After placement of the muscle sutures into the sclera, a second absorbable suture is tied around the two muscle sutures after they exit the sclera. Adjustment is later accomplished by sliding the cinch suture in an anterior or posterior direction, as needed (Fig. 86.53A). When the desired position of the muscle has been achieved, the muscle sutures are then tied securely over the cinch knot (Fig. 86.53B).

Special procedures

Mechanical fixation of the globe

When standard strabismus surgery techniques are not, or will not, effectively result in re-alignment of eyes with paralytic or restrictive strabismus, mechanical fixation of the globe near the primary position can be useful.

Autogenous periosteal flaps can be utilized to tether the globe in a fixed position.[21] The technique is effective and the

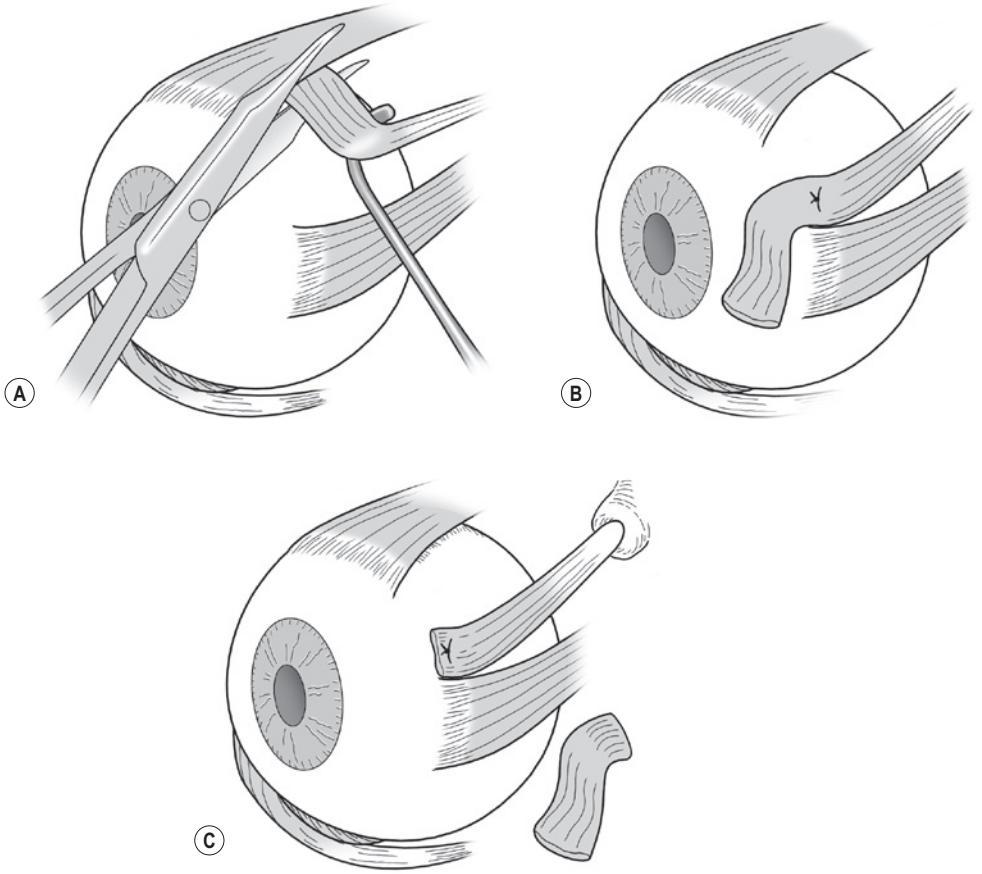


Fig. 86.51 Superior oblique tendon transposition. (A) The superior oblique tendon is isolated nasally and cut near the superior rectus muscle. (B) The tendon is sutured to the sclera above the medial rectus muscle insertion under tension with non-absorbable suture. (C) The protruding anterior portion of the tendon is excised. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

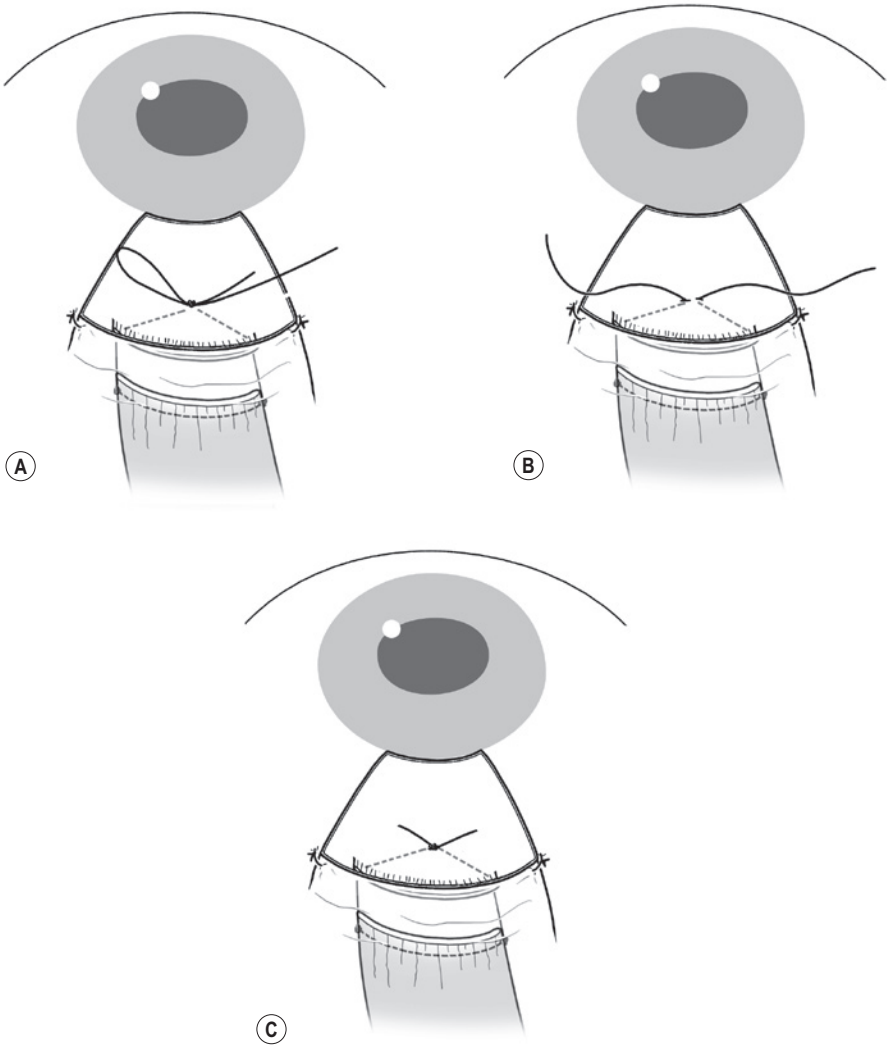


Fig. 86.52 Bow-type adjustable suture technique. (A) After determining desired placement of the muscle, a half bow knot is tied. (B) The knot is untied for adjustment, and (C) converted to a permanent knot when alignment is satisfactory. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

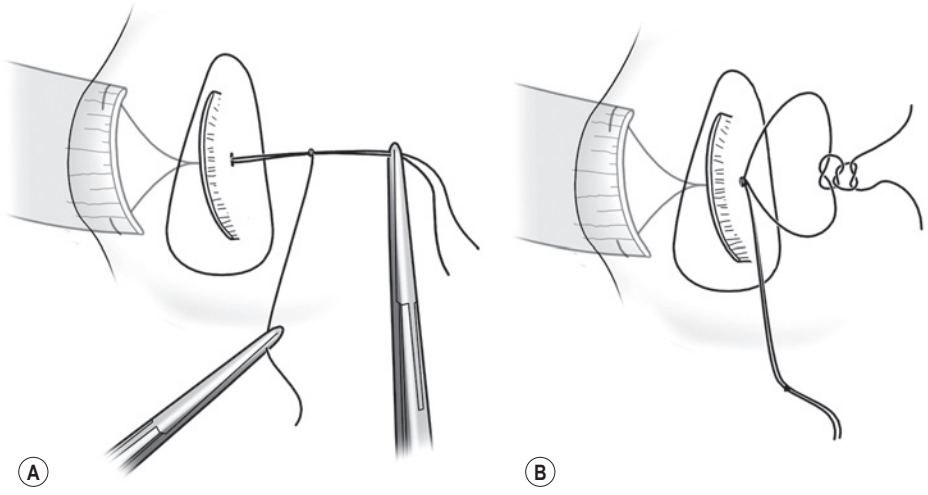


Fig. 86.53 Cinch knot adjustable suture technique. (A) Adjustment is accomplished by sliding the cinch suture along the muscle sutures, as needed. (B) When the desired alignment has been achieved, the muscle sutures are tied securely over the cinch knot. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

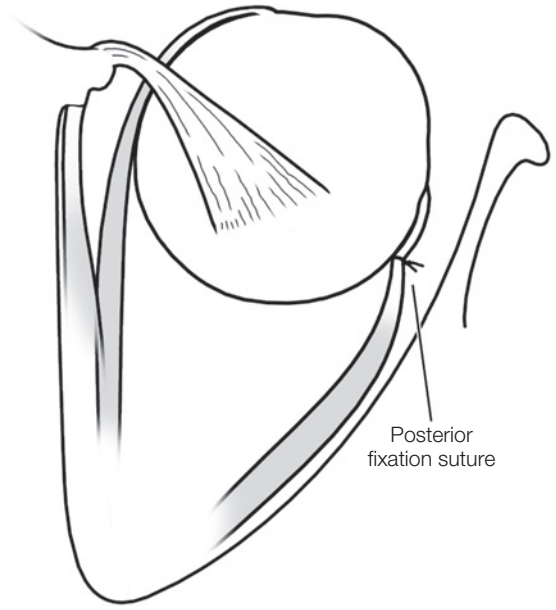


Fig. 86.54 Posterior fixation suture technique. (A) Sutures are placed in the sclera at, or posterior to, the equator. (B) The sutures are passed through the muscles and tied. (C) View from the side of the globe showing the eye in primary position. (D) View of the eye as it is rotated toward the muscle showing the new effective insertion site. *(Copyright 2006 Springer-Verlag; Coats DK, Olitsky SE. Strabismus Surgery and Its Complications. Berlin/Heidelberg: Springer-Verlag, 2006. Susan Gilbert, Illustrator.)*

involvement of an oculo-plastic surgeon skilled in surgery on the orbit is helpful. An apically based periosteal flap can be created from any one of the four orbital walls. A periosteal elevator is used to separate the flap from the underlying bone and a 5-0 Mersilene® suture secured to the anterior edge of the flap. The flap is then sutured to the sclera anterior to the paralyzed rectus muscle insertion. The globe is then rotated toward the periosteal flap and tied into place. The surgeon may not be able to actually visualize the surgical site as the flap is secured into place on the sclera. Initial overcorrection is desirable.

Plate and suture fixation procedure

A titanium plate is affixed to the orbital wall adjacent to the paralyzed rectus muscle. A suture, affixed to the posterior aspect of the plate is brought anteriorly and sutured to the sclera anterior to the paralyzed rectus muscle insertion. This suture is then tied to fixate the eye near the primary position. An initial overcorrection is desirable.

Posterior fixation suture

Cuppers first described the posterior fixation suture technique for the treatment of incomitant strabismus.[22] The mechanism of action of the posterior fixation suture that has historically been taught is that the procedure shifts the effective insertion site of the rectus muscle posteriorly. Recently this has been challenged and studies have demonstrated that posterior fixation sutures posteriorly displace the pulley sleeve during contraction of the muscle and that mechanical restriction after surgery might actually be the mechanism by which this technique works. Non-absorbable sutures are used to secure the muscle belly to the sclera 12–16 mm posterior to the limbus. The suture can be placed with or without prior recession of the muscle (Fig. 86.54). A similar effect can be achieved using pulley fixation rather than fixation in the sclera.[23]

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Minimally invasive strabismus surgery

Saurabh Jain and Daniel Mojon

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Introduction

There is a trend in most surgical specialties to move towards minimally invasive surgery with reduced incision sizes. They help achieve the same effects as conventional surgery, with the added advantages of reduced tissue trauma, improved wound healing, shortened recovery times, and improved cosmesis.[1]

The most striking example of reduction in wound size in ophthalmology has been in cataract surgery,[2] but minimally invasive surgery has been also been used to correct ptosis,[3] in penetrating and non-penetrating surgery for glaucoma,[4,5] smaller gauge instruments for vitreoretinal procedures,[6,7] and endonasal dacryocystorhinosotomy for lacrimal surgery.[8]

Minimally invasive strabismus surgery (MISS) is a term introduced to encompass strabismus surgery techniques that minimize tissue disruption and improve postoperative comfort and cosmesis. This is achieved by creating several small keyhole openings through the conjunctiva through which the procedure is performed instead of the usual large opening. Due to the nature of the incisions, the view of the extraocular muscles is limited; if necessary, tunnels can be created between these incisions to facilitate ease of maneuver and carry out further surgical steps. Most types of strabismus surgeries can be carried out in this manner including rectus muscle recession, resection, plication, advancement, transposition and retroequatorial myopexy, and oblique muscle recession, myectomy, or plication. It is also possible to carry out strabismus procedures on adjustable sutures and vessel-sparing rectus muscle displacements.

As this form of surgery minimizes conjunctival trauma and restricts dissection of the muscle and perimuscular tissue, it results in reduced postoperative inflammation, congestion, chemosis, and improved cosmesis. It also reduces hospital stay and allows patients to resume normal activities sooner.

Conjunctival incisions in strabismus surgery

Strabismus surgery was first described in 1739. Various conjunctival incisions have been used through the ages.

Swan[9] described a transconjunctival incision over the rectus muscle insertion, followed by a radial incision of Tenon's capsule over the bulk of the muscle. This incision is seldom used now because it can be associated with intraoperative hemorrhage from the muscular vessels and postoperative scarring over the muscle.

The most widely used incision in strabismus surgery is limbal, which was initially described by Harms in 1949 and later popularized by Von Noorden.[10] This involves a peritomy along the limbus, as well as radial conjunctival relaxing incisions. It offers excellent exposure of the muscle, prevents the need to carry out the procedure over the muscle belly, and facilitates the use of adjustable sutures. However, as the conjunctival incision involves the limbus, it can lead to significant postoperative discomfort, dellen formation in the perioperative period, and long-term perilimbal scarring. Perilimbal conjunctival scarring often results in conjunctival tearing and buttonholing during re-operations.

Parks[11] described a fornix cul-de-sac incision that is usually placed in the lower fornix and is thus completely covered by the lids. The incision can also be placed in the superior fornix for the superior rectus muscle or if muscles are to be superiorly transposed. While this incision affords excellent cosmesis, it is hampered by reduced access to the extraocular muscles, the need to stretch the conjunctiva over the muscle insertion, which is not always possible in older patients or during re-operations, and difficulty in placing the scleral sutures.

There has been an effort to achieve the same goals through smaller incisions, and alternative techniques have been described by Velez,[12] who suggested a radial incision covered by the upper lid, and Santiago,[13] who advocated a paralimbal approach between the limbus and muscle insertion.

Gobin[14] described accessing the rectus muscles through two small radial openings along the superior and inferior muscle margin to perform loop recession or resection. Mojon[15] has adapted this technique and has described using it to carry out most forms of strabismus surgery including primary or repeat plication, recessions, transpositions, and retroequatorial myopexies. It can also be utilized for oblique muscle recession, plication, and transposition.

Principal and methods of minimally invasive strabismus surgery

MISS is carried out by accessing the muscle through two small keyhole openings and dissecting the muscle from its surrounding tissue followed by resection, plication, or transposition. The majority of the surgical procedures include perimuscular dissection and suturing of the muscle to the sclera. To facilitate some surgical maneuvers, it may be necessary to create tunnels between these incisions. These openings are kept as far away from the limbus as possible, in such a way that if needed they can be joined together to form a larger opening, which may be helpful in the early stages of surgical transition to these technique. The incisions are covered completely by the lids except in upgaze or extreme lateral gazes.

Use of the microscope is advocated for this technique as it aids better visualization of the tissues, smoother dissection and recognition of the sclera while passing sutures, making the procedure safer by avoiding scleral perforation.

Surgical procedure

The surgical procedure is carried out using the operating microscope and can often be completed without the need for an assistant. The globe is stabilized through a limbal traction suture (Ethicon Prolene 6-0 C-1). This is secured using an artery forceps to direct the eye away from the field of action of the muscle to be operated upon. It is essential to ensure this suture does not abrade the cornea during the procedure and this can be accomplished by tying them over the speculum.

The edges of the muscle are then visualized and two small radial incisions placed along either border of the insertion, starting at the insertion and traveling backwards along the length of the muscle. On rotation of the eye, the linear muscle vessels do not move in relation to the insertion, while conjunctival vessels do, and this can be used to aid localization of the muscle before making these incisions (Fig. 87.1A).

The size of the incisions depends upon the amount of muscle displacement to be achieved and in most cases an incision of 1 mm less than the displacements of up to 5 mm, and 2 mm less than those more than 5 mm, is adequate. The conjunctiva needs to be stretched backwards in order to pass the scleral sutures. In older people or those undergoing re-operations, the conjunctiva is relatively inelastic, making this difficult, and larger openings maybe required. The same is true for children below 2 years of age, due to the abundance of Tenon's tissue, which impairs visualization.

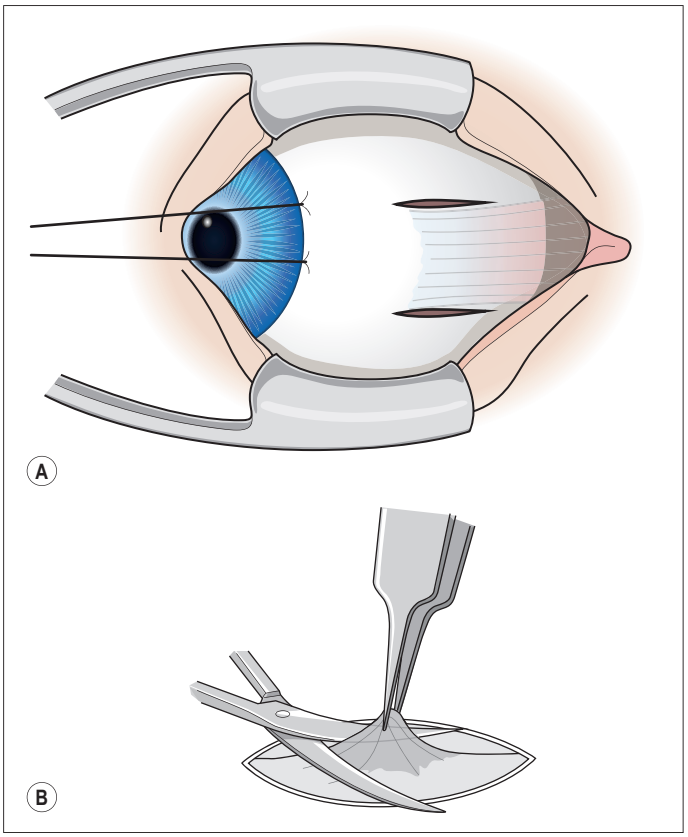


Fig. 87.1 (A) The eye is held in adduction by a stay suture placed at the limbus. The edges of the muscle (the medial rectus in this case) are then identified and two small radial incisions placed along either border of the insertion, starting at the insertion and traveling backwards along the length of the muscle. (B) Using Westcott scissors, the episcleral tissue is separated from the upper and lower edges to better delineate the borders of the muscle. The dissection can then be continued over the insertion of the muscle to join the two incisions, thereby creating a tunnel, and backwards to include the check ligaments and intramuscular septum.

Once the incisions are made, a small squint hook can be inserted to ensure the edges of the muscle have been clearly identified. Using Westcott scissors, the episcleral tissue is separated from the edges to better delineate the borders of the muscle. The dissection can then be continued over the insertion of the muscle to join the two incisions, thereby creating a tunnel (Fig. 87.1B).

Once this is complete, the muscle can be hooked and a dissection of check ligaments and intramuscular septum carried out to about 6–7 mm behind the insertion (Fig. 87.2A).

Recessions

To perform a recession, hemostasis is first achieved at the muscle insertion using a 20 g bipolar monoaxial cautery. Then, the cut ends of two sutures (Vicryl 6-0 ¼ circle-shape S-14 needle, Ethicon) are applied to the superior and inferior borders of the muscle tendon for the horizontal recti (nasal and temporal for the vertical), as close as possible to the insertion (Fig. 87.2B). The amount of recession is measured, marked on the sclera (Fig. 87.3A), and both sutures attached (or preplaced) at these points (Figs 87.3B and 87.4A). The tendon is then disinserted from the globe using Westcott

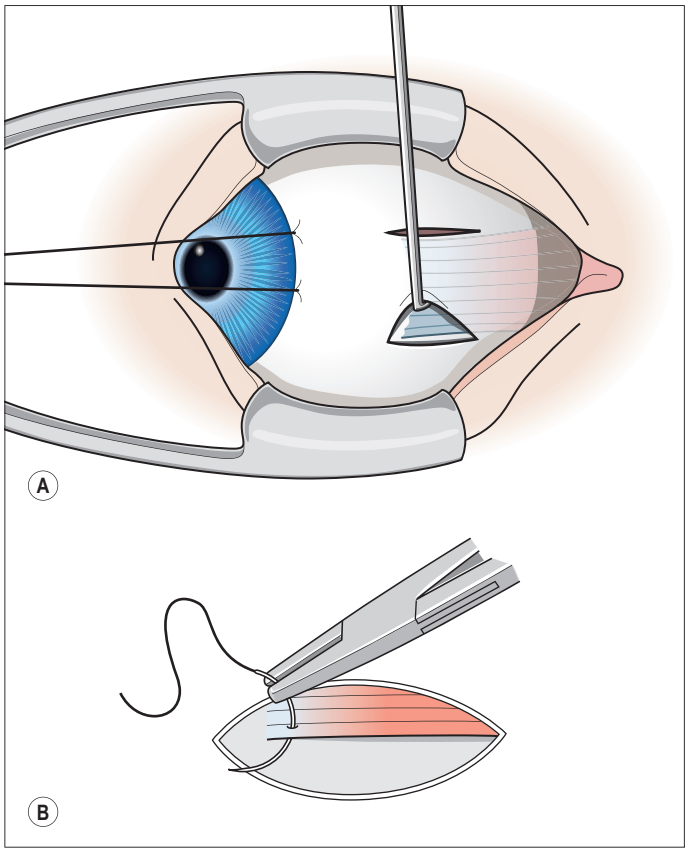


Fig. 87.2 (A) The conjunctiva is then retracted over the muscle to expose the tendon, and (B) a full-thickness pass made through the muscle tendon using 6-0 Vicryl suture that has been cut in half. This is then knotted to ensure the tendon edge is secured to the suture. An alternative method to perform this step is using the TRASU technique that is illustrated in Fig. 87.9.

scissors, taking care to not damage the sutures (Fig. 87.4B). The sutures can then be tied off safely (Fig. 87.5A,B) and the conjunctiva re-sutured (Fig. 87.6A,B) (Vicryl Rapid 8-0, with a spear-shaped GS-9 spatulated needle, Ethicon). The advantage of preplacing the sutures is that once the muscle is disinserted they can be tied off, obviating the need to pass scleral sutures under suboptimal viewing conditions if the muscle bleeds. This technique also results in precise displacement of the muscle along its original path. The disadvantage is the risk of inadvertently cutting the sutures. The alternative is placing the sutures once the muscle has been successfully taken off the globe, which requires meticulous hemostasis.

In fibrotic muscles, as in Duane retraction syndrome or thyroid eye disease, it may not be possible to place scleral sutures before the eye is adequately turned away from the field of surgery. Therefore, in such cases, scleral anchoring at the new site can only be performed after muscle disinsertion. Some surgeons prefer adjustable sutures for these cases.

Plications

The cut ends of two sutures (¼ circle Vicryl 6-0 S-14 needle, Ethicon) are applied to the edges of the muscle tendon at a distance corresponding to the plication amount (Figs 87.7 and 87.8). The sutures are then passed through the sclera at the tendon insertion site. Using an iris spatula, the muscle is drawn forward and plicated by tying the ends of the sutures. The conjunctiva is sutured as above (Figs 87.9–87.11)

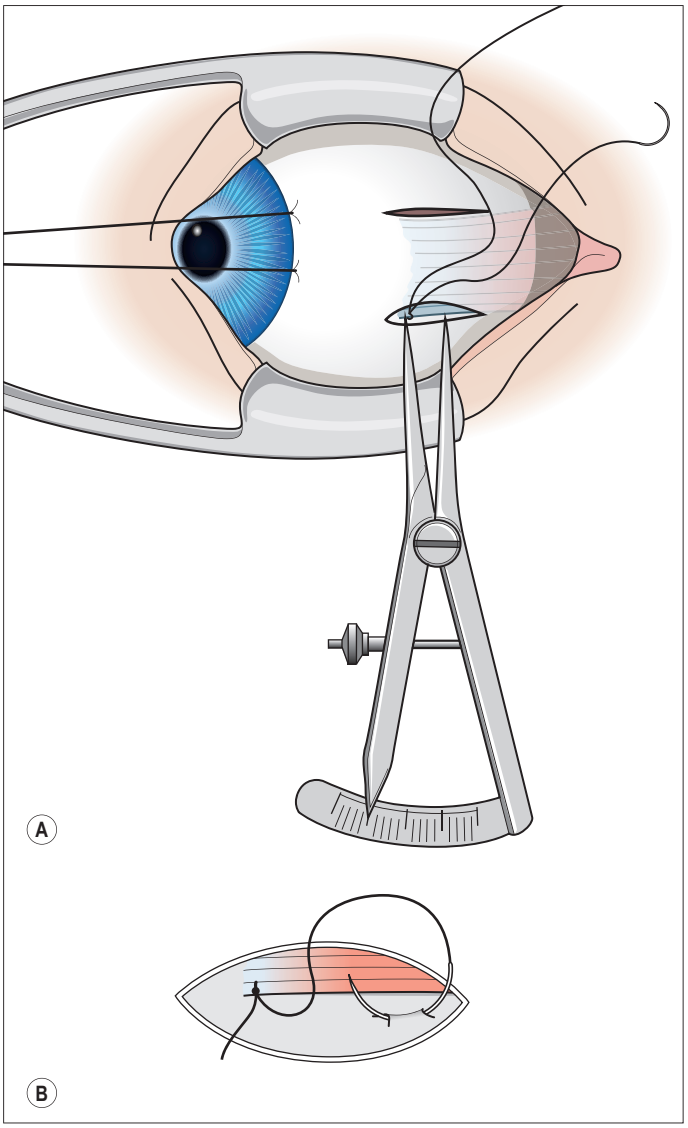


Fig. 87.3 (A) The amount of recession is measured, marked on the sclera, and (B) the suture preplaced at this point through a partial-thickness pass.

Resections

The muscle is grasped at a distance equal to the amount to be resected. If there are any prominent vessels present at this site, they are cauterized. The cut ends of two sutures (Vicryl 6-0 with ¼ circle-shape S-14 needle, Ethicon) are applied to the superior and inferior borders of the muscle tendon at a distance corresponding to the resection amount and then to the sclera at the insertion. The muscle is divided under the conjunctiva and drawn up to the insertion site as the sutures are tied off. The conjunctiva is sutured with 8-0 Vicryl suture as previously described.

Retroequatorial myopexy

This is carried out by placing two L-shaped cuts slightly anterior to the location where the musculo-scleral sutures

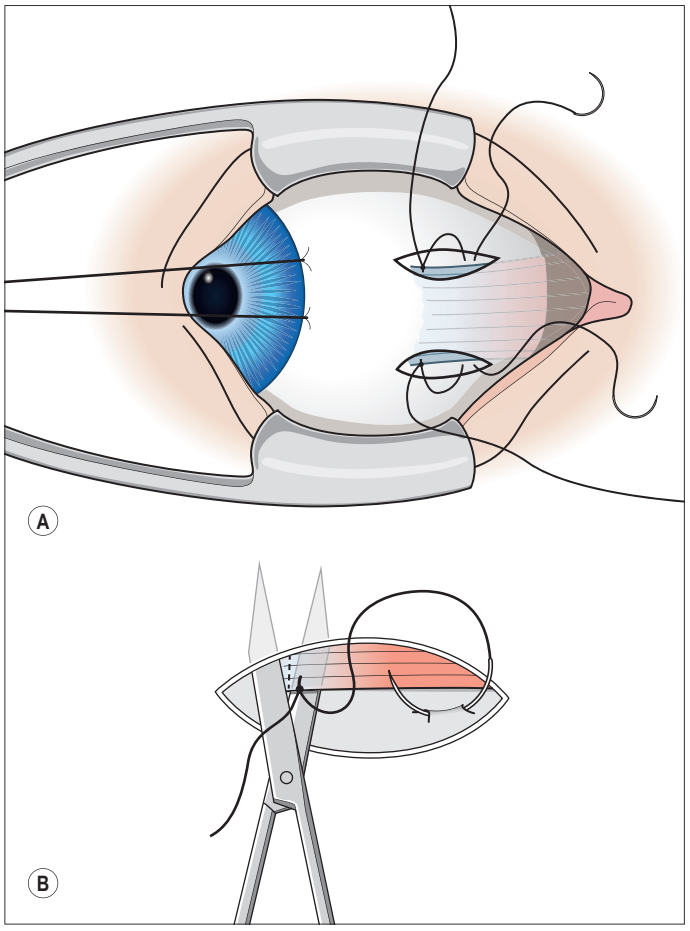


Fig. 87.4 (A) A similar procedure is repeated at the superior edge. Once both sutures have been preplaced, (B) the muscle is disinserted off the globe using a Westcott scissors, under the conjunctiva, taking care not to damage the sutures.

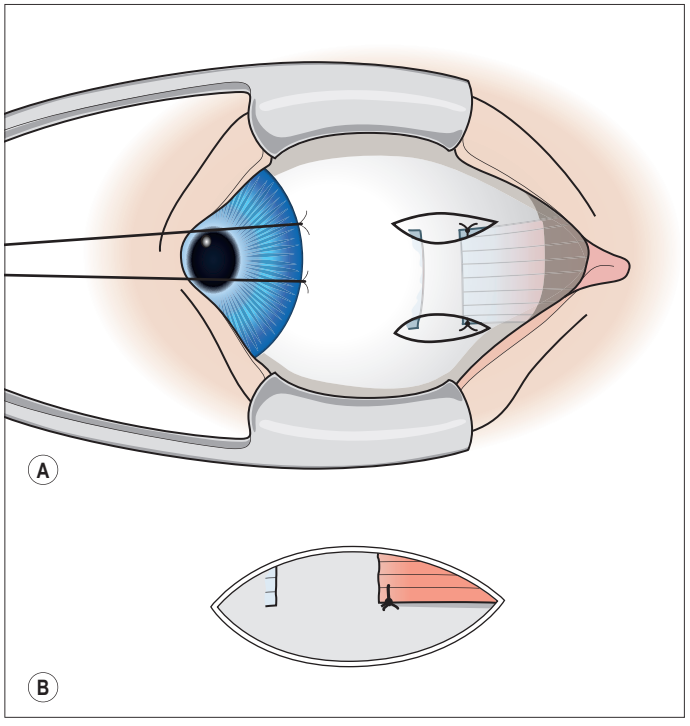


Fig. 87.5 (A) The muscle is secured to the sclera at the intended distance from the limbus by tightening the sutures, (B) which are then tied off.

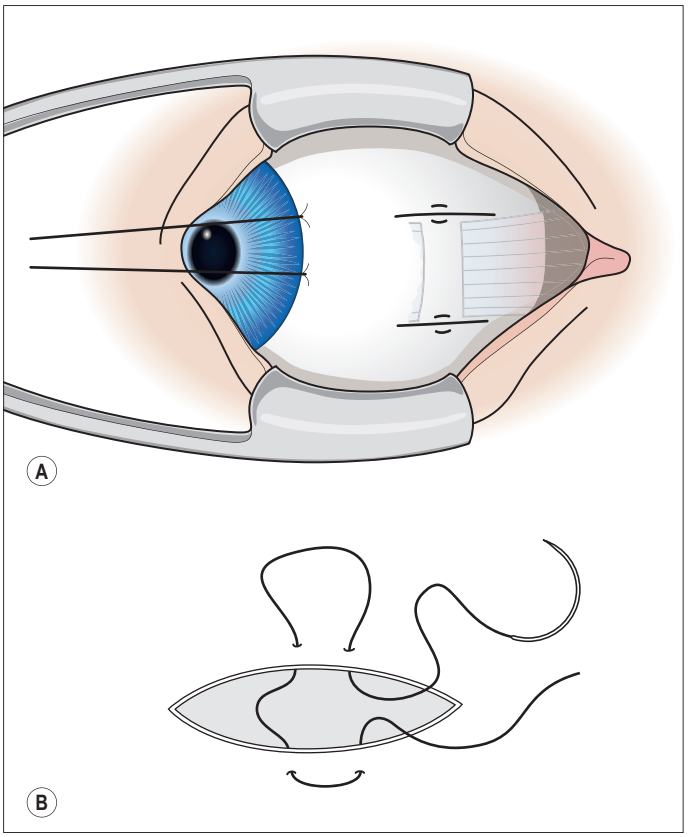


Fig. 87.6 (A) The conjunctival openings are closed with 8-0 Vicryl sutures. (B) The sutures are applied in a manner that ensures the knot is buried within the wound to aid cosmesis and comfort postoperatively.

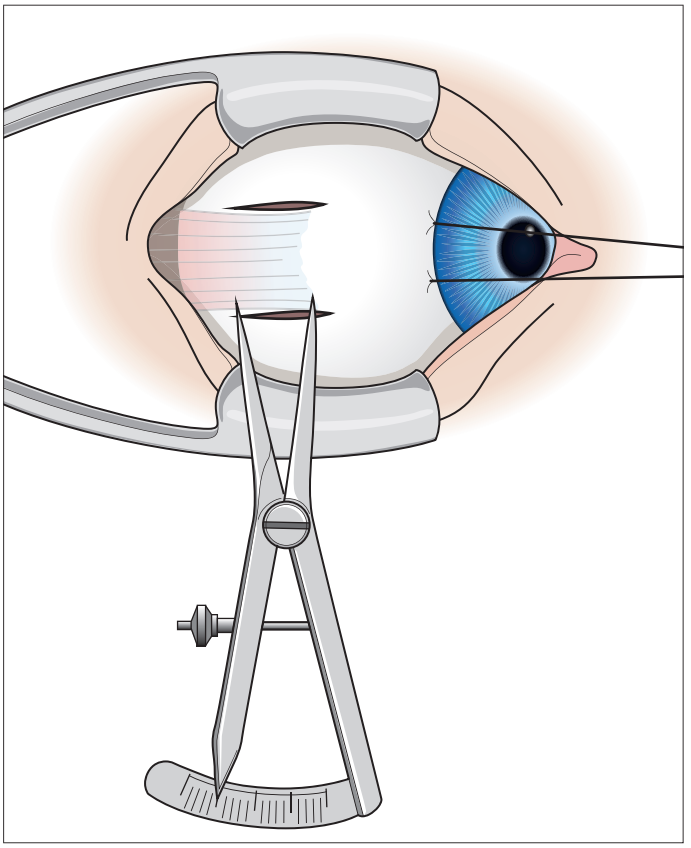


Fig. 87.7 To carry out a plication, the conjunctival openings are fashioned as above along the superior and inferior aspects of the lateral rectus. The amount of plication to be carried out is measured via calipers.

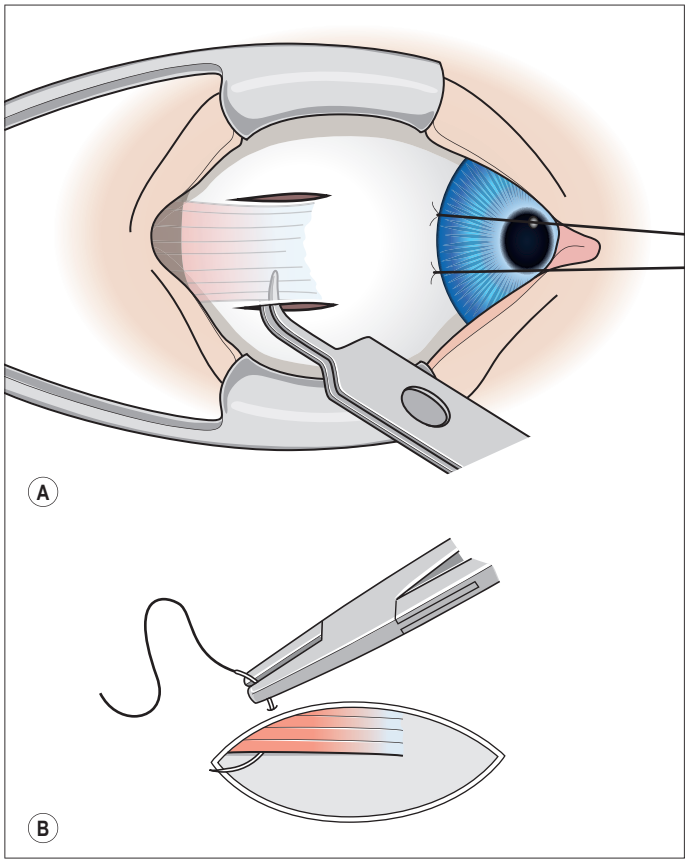


Fig. 87.8 (A) The muscle tendon is grasped at the desired amount of plication with a jeweler's forceps or similar, and (B) a 6/0 Vicryl suture passed through the conjunctiva, Tenon's capsule, and full-thickness of the muscle belly, emerging through the conjunctival opening.

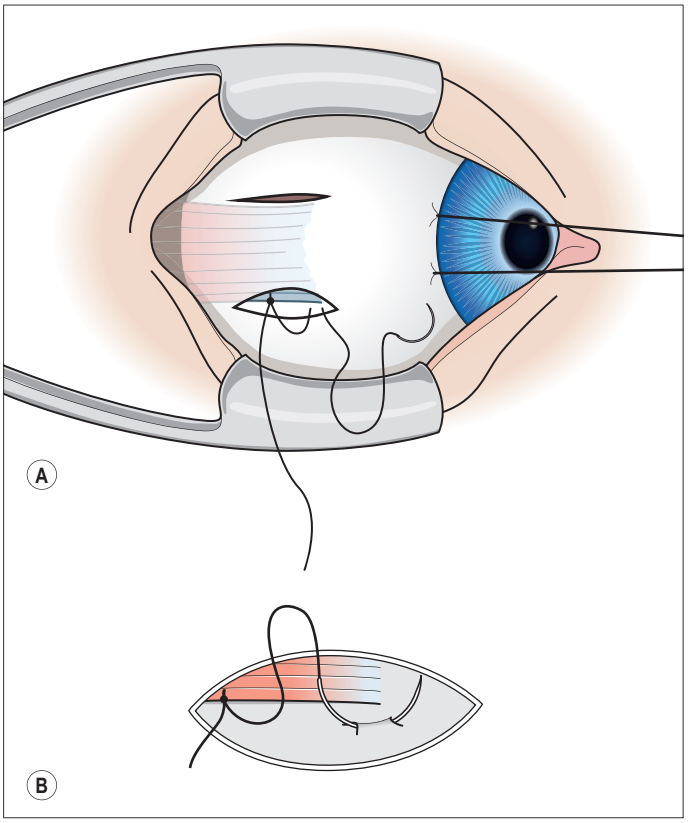


Fig. 87.10 (A) The needle is then passed partial thickness through the sclera, (B) adjacent to the insertion of the muscle tendon. This procedure is then repeated at the superior edge of the muscle.

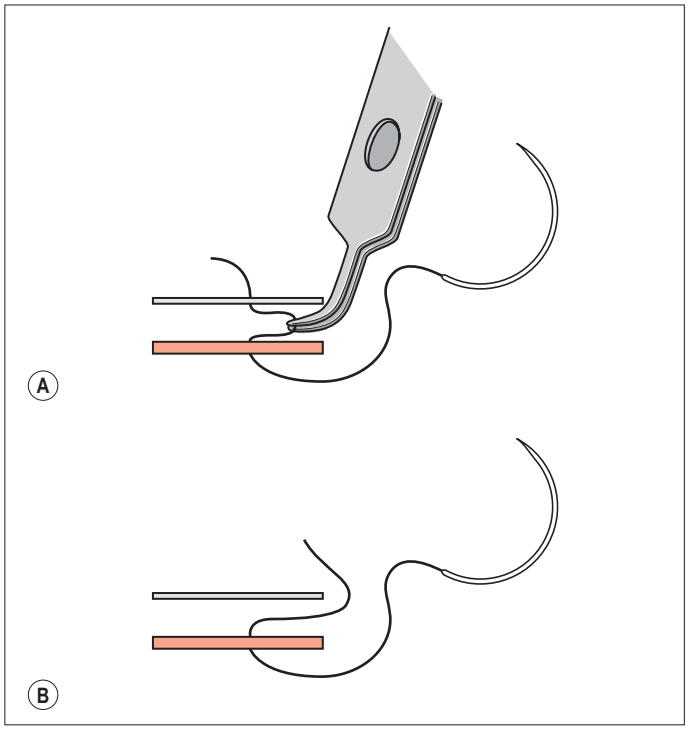


Fig. 87.9 (A) The suture is grasped between the muscle and conjunctiva and drawn out the incision site, (B) freeing up the conjunctiva and Tenon's tissue, and leaving the suture running just through the muscle. This is then tied off to secure the tendon.

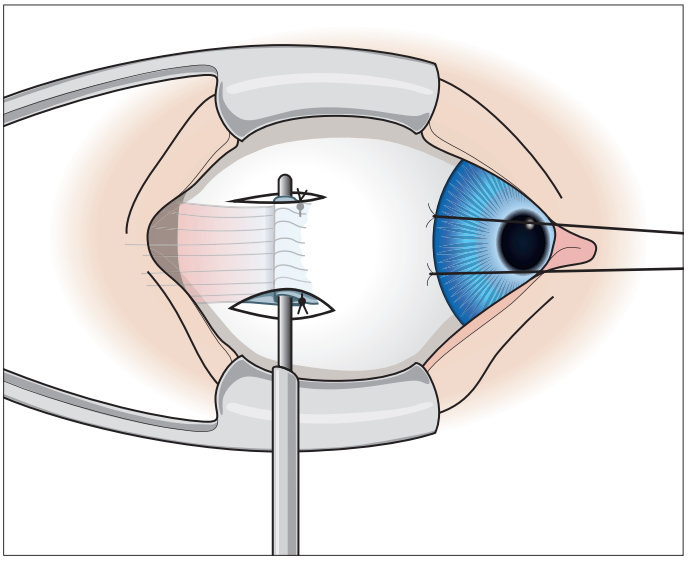


Fig. 87.11 The muscle tendon is drawn forward using an iris spatula or similar instrument and the sutures tied off to achieve plication of the muscle. The conjunctiva is then closed off using 8/0 Vicryl as above.

will be passed. This is usually 14 mm, or so, posterior to the limbus to ensure the suture is posterior to the equator. With Westcott scissors, the episcleral tissue is dissected from the muscle sheath and sclera. The posterior fixation is then carried out by passing a non-resorbable suture through the sclera, followed by the muscle, to include approximately one-third of the tendon on both sides. Anterior elongation of the cuts will allow retroequatorial suturing to be combined with a MISS recession or plication of the same rectus muscle.[16]

Transpositions

Either partial- or full-tendon transpositions can be carried out using this technique. Partial transposition of two adjacent rectus muscles can be performed using four incisions, while six openings are necessary for complete transposition. Partial transposition is more effective at sparing vessels, which might become important should there be a need to recess the ipsilateral antagonist of the paralyzed rectus muscle in the future. However, this technique is more at risk of inducing postoperative cyclodeviations and vertical deviations.

The half-muscle to be transposed is exposed by a small, radial cut. Perimuscular dissection is carried out as above to 7 mm posterior to the insertion. A curved ruler is used to measure the muscle insertion width and to determine its midpoint. Starting at the midpoint, the muscle is gently split using a small muscle hook from a point 15 mm away, all the way to the scleral insertion. Two single sutures (¼ circle, Vicryl 6-0 S-14 needle, Ethicon) are applied to the muscle tendon, which will be transposed, and the split half-muscle is disinserted. The same technique is used to split the other rectus muscle. Precise splitting usually avoids unwanted postoperative deviations. The minimally invasive transposition is now performed by exposing the weak rectus muscle through two small parainsertional keyhole cuts. In order to safely displace the needles, a blunt 20G sub-Tenon's anesthesia cannula is inserted through one of these openings and advanced in order to emerge through the incision next to the half-muscle to be displaced. After scleral anchoring, the half-muscles are transposed by gently pulling the sutures. If additional force has to be generated, the weak muscle can be crossed under by the two half-muscles. In the authors' experience, the effect of this undercrossing is similar to a full transposition to the adjacent rectus muscle insertion border.

For full-tendon transpositions, two additional keyhole openings must be performed at the rectus muscle insertions lying opposite to the paralyzed muscle.[17]

MISS transposition surgery is no more demanding than open transposition surgery. However, there is an increased risk, at least in the beginning, of inducing involuntary cyclodeviations and deviations perpendicular to the new force vector if asymmetric portions of the muscles are transposed, as precise splitting is more difficult to perform through smaller openings.

Re-operations

Prior to operating on an eye that has undergone previous muscle surgery, it is helpful to delineate the position of the extraocular muscles. This can be done preoperatively, using the slit lamp, or intraoperatively, by observation of the movement of the vessels. The advantage of using MISS in these eyes is that the surgeon will not have to open scarred and fragile perilimbal conjunctiva. Once the position of the muscles has been established, incisions can be placed adjacent to them. Most of the scar tissue involving the muscle can be released by blunt dissection under direct visualization. However, the surgeon should be prepared to extend the incision if visualization is inadequate. Since the incisions can often be placed far from the limbus, postoperatively, the incisions are often barely visible and there is minimal discomfort.[18]

Oblique muscle surgery

Minimally invasive surgery for superior and inferior oblique recessions of up to 6 mm can be performed using one incision; but for larger recessions, two keyhole openings are required. The first is used to disinsert the muscle insertion and the second for scleral anchoring. In order to safely pass the needle between the two cuts, a blunt 20G sub-Tenon's anesthesia cannula is used to transpose rectus muscles. MISS inferior and superior oblique muscle plications are carried out through one L-shaped opening over the insertion.[19]

MISS transconjunctival suturing technique

MISS transconjunctival suturing technique (TRASU) allows large recessions to be performed without the need to open the conjunctiva where the muscle is re-attached to the sclera. The suture is performed as usual and the needle exits completely through the sclera but also through the overlying Tenon's capsule and conjunctiva. The needle is then retrieved by pulling backwards on the suture allowing the surgeon to place a standard knot.[20] This allows larger recessions than previously possible without increasing the length of the conjunctival incision.

Marginal dissection of rectus muscles

To further refine the surgical technique for plications, the marginal dissection of rectus muscles (MADI) technique[21] can be utilized. The amount of dissection of perimuscular tissue is reduced using this technique. Instead of creating a tunnel between the two conjunctival openings (total dissection [TODI]), dissection is performed only along the margins of the muscle to be plicated. This eliminates the need of an iris spatula. The authors have found that this technique is associated with the same dose–response relationship, but with better postoperative recovery and less tissue trauma.

Specific complications of minimally invasive strabismus surgery

The keyhole conjunctival incisions may tear while moving instruments. If the tear does not involve Tenon's capsule, it is usually of no consequence. If Tenon's capsule tears, a visible scar may result. If the tear occurs over the muscle, increased scarring may make re-operations more difficult. If the muscle is removed too close to the sclera, a visible bluish line may be visible; if too far away, the remaining tendon may visibly elevate the conjunctiva. If excessive bleeding occurs, it maybe necessary to enlarge the incisions or even convert to a limbal opening. Sometimes, a relatively large subconjunctival hemorrhage may develop. In one case, the authors observed the extrusion of non-resorbable sutures through the keyhole openings 2 years

after Faden surgery. They cannot yet determine if such events occur more frequently when compared with Faden procedures performed through Harms' opening.

Advantages and disadvantages of minimally invasive strabismus surgery

Postoperatively, the MISS openings will all be covered by the eyelids, thus minimizing their visibility and patient discomfort. Since they are far from the limbus, the risk of corneal complications (e.g. dellen formation) is reduced. The long-term benefits include decreased scarring of the perimuscular tissue, which facilitates re-operations and preserves the limbal conjunctival and stem cells. This technique is especially valuable for re-operations, since it avoids re-opening the scarred perilimbal conjunctiva. MISS preserves the perilimbal episcleral vessels and, therefore, reduces the risk of anterior segment ischemia. Since MISS also reduces the anatomical disruption between the muscle and the surrounding tissue, re-operations will be easier.

Disadvantages of minimally invasive strabismus surgery (MISS) include a higher risk of sclera perforation and a long learning curve.

Strategies to aid beginners

Surgeons switching from magnifying loupes to the operating microscope should first perform several procedures under the microscope with their customary technique before using keyhole openings. They should start with primary horizontal rectus muscle displacements of 4 mm or less. In the authors' experience, plications and resections yield the same dose–response relationship. Therefore, they suggest switching to plications, since the less traumatic MADI rectus muscle reinforcement technique can be used. The resultant muscle knuckle is visible under the conjunctiva for the first few days but soon ceases to be visible. Patients between ages 14 and 40 years are ideal for MISS. Abundant Tenon's tissue in very young patients makes the surgery more difficult. Reduced conjunctival elasticity in older patients increases the risk for a conjunctival tear when introducing or manipulating instruments through the keyhole openings. Ideally, a surgeon interested in using this technique should observe a surgeon experienced using MISS. The authors of this chapter would be happy to have surgeons wanting to learn this technique to observe them performing MISS

When switching to MISS, surgeons usually find their surgical times are increased. However, once surgeons become experienced, they can perform rectus muscle resections or plications faster using MISS. The MADI plication technique, in particular, is very quick. Oblique muscle procedures will not be significantly faster. Conversely, rectus muscle transposition can be performed much faster using MISS.

One of the initial stumbling steps is incorrect placement of incisions by situating them too far from the muscle or on top of the muscle. In the former case, this causes difficulties in the isolation and dissection of muscles and hemorrhage and scarring in the latter. This can be avoided by identifying the muscle insertion using the differential movement of the muscular and conjunctival vessels on movement of the globe. A small incision by the insertion can then be made and enlarged as necessary.

Hemorrhage from scleral or anterior ciliary vessels can also be a challenge and is best avoided by using bipolar coaxial diathermy that allows gentle cauterization of vessels while preventing damage to overlying conjunctiva.

Adequate exposure to perform posterior scleral bites during recessions can be difficult to achieve and inadequate visualization increases the risk of scleral perforation. This can be prevented by using longer incisions, at least initially, rotating the eye in the opposite direction of the muscle being operated upon, and stretching the conjunctiva to obtain adequate exposure

Instrumentation for minimally invasive strabismus surgery

When performing routine strabismus surgery via a limbal opening, the size of the instruments is not critical. However, if large instruments are used with small MISS openings, conjunctival tearing will occur. The following instruments are helpful for MISS:

- Clamping a small artery forcep to the traction sutures, using a forceps over the eyelid speculum, will prevent the sutures from rubbing on the cornea.
- Colibri forceps with interdigitating teeth are used to fix the conjunctiva when creating keyhole openings and to stabilize the eye for traction and scleral anchoring sutures.
- Small, curved needle holders are ideal to suture through small openings, especially if the TRASU method is used.
- Small conjunctival scissors with a curved, blunt tip are used to cut the conjunctiva, the sutures, and muscle or tendon insertions.
- Curved forceps with serrated tips should be used to hold the conjunctiva after performing the keyhole openings, since this will prevent unnecessary conjunctival trauma.
- Spatulas of different sizes are helpful to visualize tissue through the cuts. Diathermy is best performed using a system with a bipolar, coaxial tip. This allows gentle cauterization of vessels at the muscle insertion through the tunnel, without damaging the overlying conjunctiva.
- A small strabismus hook can easily be introduced through the small openings and will allow, if necessary, another instrument to be introduced through the same cut.
- Angled forceps are necessary to stabilize the muscle insertion during disinsertion. If they are not used, the traction suture should be slightly released before disinserting the muscle; otherwise there is a considerable risk that the insertion will tear. By pressing the blunt tips of a Castroviejo caliper for approximately 10 seconds against the sclera, a bluish indentation mark is formed, which will be visible for up to 1 minute. This indentation technique also works transconjunctivally to perform TRASU since no dye is necessary.

- A blunt cannula is helpful to safely displace needles through the tunnel between two key openings when rectus muscles are transposed, or for larger, graded oblique muscle recessions.

Adjustable sutures

Adjustable suture can be used with MISS surgery. The adjustable sutures have to be placed in a manner that they become visible after removal of the conjunctival sutures, in the event an adjustment becomes necessary. An adjustment will not increase the postoperative discomfort and visibility of the incision sites. After an adjustment, the conjunctiva only needs to be closed if the adjustable sutures protrude through the openings. Frequently, an adjustment can be performed at the slit lamp.

Conclusion

MISS is a safe and effective alternative to traditional strabismus surgery that that is associated with reduced postoperative discomfort, improved cosmesis, and a reduced incidence of postoperative corneal dellen and perimuscular scarring.

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Strabismus surgery complications and how to avoid them

John A Bradbury and Rachel F Pilling

Chapter contents

INCIDENCE
MILD COMPLICATIONS
SEVERE COMPLICATIONS
CONSENT IN STRABISMUS SURGERY
REFERENCES

See online for supporting video for this chapter.

Severe complications of strabismus surgery are rare but they can be devastating. This chapter will explore the frequency and management of problems related to this surgery; it will also discuss the consent process to ensure patients are well informed.

Incidence

The incidence and outcomes data quoted here were obtained from a 2-year prospective survey of severe complications of strabismus surgery coordinated through the British Ophthalmic Surveillance Unit (BOSU)[1] and data from the available literature. The incidence of severe complications of strabismus surgery was 1 per 400 operations, with equal frequency in adults and children. Globe perforation is the most common complication with an incidence of almost 1:1000. Retinal detachment and endophthalmitis were the least commonly reported (Fig. 88.1 and Table 88.1). Anterior segment ischemia (ASI) was not part of the BOSU study, but may occur in 1:13,000 operations.[2]

The group devised a five-point scale depending on the severity of outcome of the complication. This is outlined in Box 88.1. The number of complications in the five categories split into adults and children is shown in Table 88.1 with the *p*-values. Although there were more infections and globe perforations in children and more surgically induced necrotizing scleritis (SINS) and lost muscle in adults, only SINS reached statistical significance.

Looking at the outcome, 16% of patients with a complication had a poor or very poor outcome. This means that about 0.04% or 1:2400 of patients operated on had a poor or very poor outcome.

Mild complications (Box 88.2)

Dellen

Dellen tend to occur in the peripheral cornea, specifically nasal and temporal quadrants in the first 1–2 weeks following strabismus surgery. Dellen are thinning of the cornea due to the drying out of the collagen in the stroma related to poor corneal wetting. They are related to tear film disruption and altered anterior segment contour due to swollen conjunctiva, which prevents the smooth travel of the eyelids. They are more common in adults, but may occur in children (who are rarely examined on the slit-lamp). The reported incidence is between 0.3% and 22%.[3] It is usually self-limiting or responds to topical lubricants; rarely, a bandage contact lens is required.

Chronic red eye

Redness is common, especially after repeated strabismus surgery, but some patients have a persistent red eye for many weeks or months. These patients are unhappy, feeling their appearance is harmed. Some of this may be related to a corneal wetting issue and responds to topical lubricants. Prolonged postoperative inflammation or violation of the orbital fat may contribute to a chronic red eye, most often of the medial rectus and surrounding tissue. This complication is reduced by meticulous surgical procedure with avoidance of orbital fat, careful hemostasis, and thinning and reduction of thickened and redundant medial conjunctiva, especially in adults with longstanding or consecutive exotropias. The authors give such patients intensive topical steroid drops for a month following strabismus surgery. Occasionally, long-term lubricants and topical steroids are required. If the eye is still red after 3 months, one can give subconjunctival depot steroids to settle the inflammation and reduce the conjunctival bulk.

Pyogenic granuloma

This fleshy mass appears a few weeks after surgery and is composed of inflammatory cells and capillary proliferation. It may be confused with a suture granuloma. It responds to topical steroids but occasionally requires surgery.

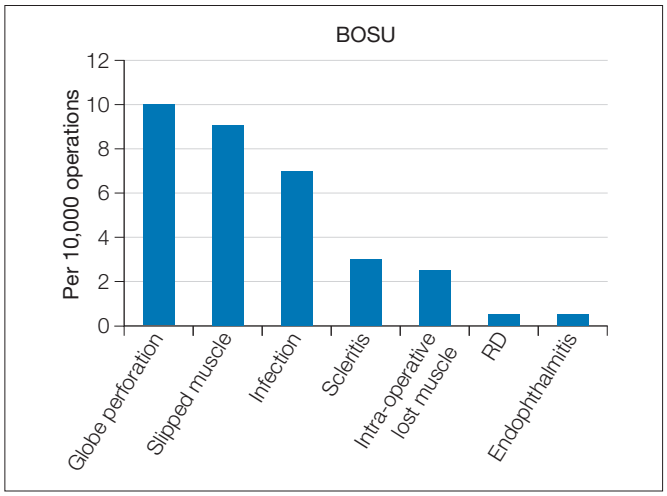


Fig. 88.1 Incidence of severe complications of surgery, per 10,000 operations. BOSU, British Ophthalmic Surveillance Unit; RD, Retinal detachment.

Prolapsed Tenon's capsule

This occurs in children and young adults with a prominent Tenon's layer. It is caused by poor conjunctival closure. If the prolapse is large, it may need to be trimmed, but it usually resolves spontaneously.

Epithelial inclusion cyst (Fig. 88.2)

This rare complication is caused by deposition of conjunctival epithelial cells into deeper tissues. Most are small, but some can be large, especially those at muscle insertions. They enlarge and need surgical removal.

Chemosis

Chemosis occurs after most strabismus surgery. It is rarely severe, but it can be so severe that the conjunctiva is exposed and the chemosis is exacerbated by drying: intensive topical lubricants and steroids usually resolve it. Rarely, it may be necessary to tape the lid shut or perform a temporary

Box 88.1

Classification of outcome

Grade 1: Good outcome
Grade 2: Surgical or medical intervention but good outcome
Grade 3: Surgical or medical intervention asymptomatic but compromised outcome
Grade 4: Surgical or medical intervention but poor outcome, e.g. double vision or up to two lines of vision loss on a Snellen chart
Grade 5: Very poor outcome, greater than two lines of visual loss on a Snellen chart

Box 88.2

Mild complications of strabismus surgery

Dellen
Chronic red eye
Pyogenic granuloma
Tenon's fascia prolapse
Epithelial inclusion cyst
Chemosis
Suture granuloma

Table 88.1 Number of complications reported in the BOSU study[1]

	Infection	SINS	Perforation	Lost muscle	Slipped muscle	Retinal detachment	Endophthalmitis	Total
ADULTS								
1			1					
2	2	4	2	1	7			
3			4	3		1		
4	1	1		1				
5		1						
								29
CHILDREN								
1			1					
2	8		10		4			
3	1				4			
4	2				3			
5			1				1	
								35
p-values*	0.0573	0.0312	0.3591	0.0625	0.4805	1.00		1.00

*The *p*-value compares adult and child rates for each complication.
SINS, Surgically induced necrotizing scleritis.

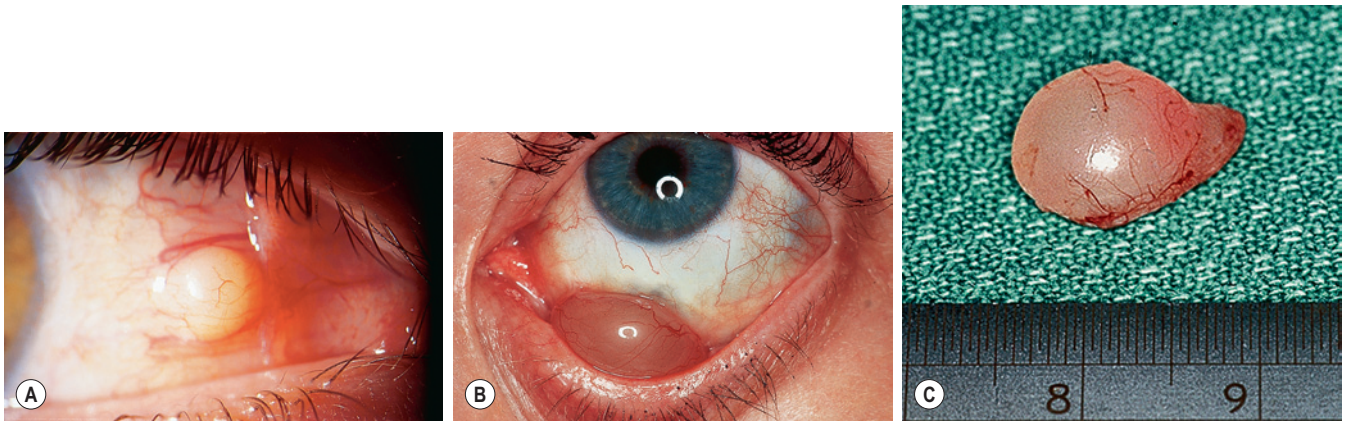


Fig. 88.2 Conjunctival epithelial inclusion cysts. (A) Cyst over medial rectus. (B) Cyst over inferior rectus. (C) Cyst over inferior rectus following excision. *(Courtesy of Mr. Robert Morris.)*

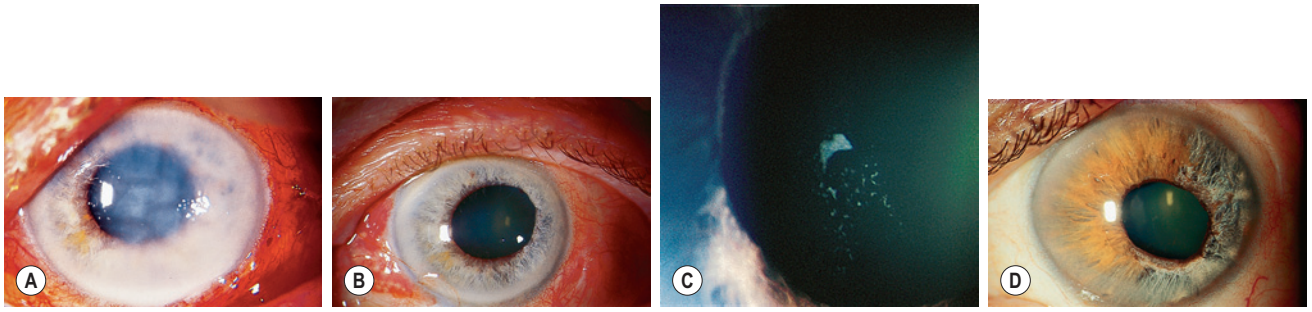


Fig. 88.3 Anterior segment ischemia. (A) Severe ischemia causing corneal edema. (B) Same eye 6 months later; note mid-dilated pupil. (C) Anterior lens opacities following anterior segment ischemia. (D) Iris atrophy following anterior segment ischemia. *(Courtesy of Mr. Robert Morris.)*

"superglue" tarsorrhaphy (with caution in children because of distress and amblyopia risk). An option is to suture the conjunctiva into the fornices.

Suture granuloma

A granuloma is a reaction to a foreign body characterized by the organized presence of macrophages, which can be infective or, in this case, a reaction to a foreign material. All absorbable sutures cause some form of inflammatory reaction; this is how they dissolve. In most cases this is mild, but less commonly a more severe reaction occurs causing pain, discharge, and redness around the suture. Often this can be managed by topical steroids and analgesia until the suture dissolves. This takes 56–70 days in the case of coated Vicryl® (Ethicon), probably the most common suture used. Even more rarely is the reaction so severe that the suture needs to be removed. It is best not to re-suture the tissue in order to prevent another reaction; this is not usually a problem with conjunctiva over a week postoperatively, but if the reaction is around a muscle suture, this may mean replacement with a non-absorbable suture. It is difficult, clinically, to tell if a reaction around a muscle suture is a sterile one and it is prudent, therefore, to assume it is infective until proved otherwise.

Severe complications (Box 88.3)

Anterior segment ischemia (Fig. 88.3)

Two anterior ciliary arteries (branches of the ophthalmic artery) run on each rectus muscle to supply the anterior segment, except for the lateral rectus, which has only one. The obliques have no anterior ciliary arteries.

The incidence of significant ASI is approximately 1 : 13,000 cases.[2] It was not surveyed in the BOSU study because the incidence of ASI is difficult to determine; it is probably under-reported, especially in children where postoperative slit-lamp examination is not normally performed. Severe outcomes are rare, although phthisis bulbi has been reported.[2] Risk factors for ASI include increasing age, previous rectus surgery, operations on multiple muscles (especially recti) in the same eye, circulatory problems (hypertension or diabetes), similar surgery on adjacent rectus muscles, surgery on vertical rectus muscles, and limbal incision.

In children, it may be safe to operate on more than two rectus muscles per eye at once; most surgeons avoid operating on all four rectus muscles simultaneously. If it is necessary

Box 88.3

Severe complications of strabismus surgery

Globe perforation
Orbital infection
Endophthalmitis
Surgically induced necrotizing scleritis
Slipped muscle
Lost muscle
Retinal detachment
Adherence syndrome
Anterior segment ischemia

to operate on more than two rectus muscles on one eye in an adult, or if the patient has a very high risk of developing ASI, anterior ciliary artery-sparing surgery can be performed by dissecting out the anterior ciliary arteries from the muscle or performing a partial tendon transposition, sparing at least one of the anterior ciliary arteries.

Symptoms and signs of ASI can vary from mild uveitis and reduced iris perfusion to keratopathy[2,4] (Table 88.2).

- Grade 1 ASI can only be detected by iris angiography.
- Grade 2 ASI is caused by areas of iris hypoperfusion, sometimes an abnormally shaped pupil. It rarely requires treatment.
- Grades 3 and 4 ASI usually require treatment with topical or systemic corticosteroids. Unusual treatments include hyperbaric oxygen. The vast majority recover with only minor sequelae including iris atrophy, corectopia, or a poorly reacting pupil.

Globe perforation (Fig. 88.4)

Globe perforation is the commonest severe complication of strabismus surgery, reported in 0.13% to 1% of cases.[5,6] In the BOSU study, the incidence was 1 : 1000. Although, as noted previously, this complication was more common in children, possibly due to surgical access issues, it did not reach statistical significance. One patient developed endophthalmitis and had to have an evisceration. Although globe perforation is relatively common, a poor or very poor outcome is extremely rare. Complex surgery, such as faden procedures may have a higher incidence of globe perforation.

In the BOSU study, globe perforation sometimes occurred when placing a traction suture. This resulted in some cases of penetration into the anterior chamber and a soft eye, making strabismus surgery difficult. Most cases of posterior segment perforation had immediate treatment, usually cryotherapy or laser. There was one case of retinal detachment in a high myope who had bilateral globe perforation from bilateral Harada–Ito procedures.

The management of globe perforation is not evidence-based. Ninety percent of cases are treated with cryotherapy and/or laser.[7] In children, where globe perforation is more likely, retinal detachment is unlikely as they have formed vitreous. The authors perform a fundus examination to confirm the diagnosis with the pupil dilated peroperatively by injection of 1 or 2 mL of local anesthetic sub-Tenon's. The authors do not perform peroperative treatment themselves, but seek a vitreoretinal opinion, if available. In adults, they do a fundus examination and, in patients with a high risk of retinal detachment (i.e. high myopes), they perform peroperative treatment of the hole and then seek vitreoretinal opinion. They do not treat those at low risk, but seek a later vitreoretinal opinion. All patients have systemic antibiotics to reduce the risk of endophthalmitis. The BOSU study reported one case of endophthalmitis leading to evisceration in a 3-year-old.

Rathod[7] reported two cases of endophthalmitis, two retinal detachments, one suprachoroidal hemorrhage, and one choroidal scar.

Strategies to prevent globe perforation include:

1. avoiding suturing in areas with scleral thinning;
2. techniques (i.e. hang-back procedures) that do not involve direct scleral suturing in thinner areas or where access is difficult.

Orbital infection (Fig. 88.5)

Orbital infection following strabismus surgery tends to be equally either diffuse orbital cellulitis or an abscess at the muscle insertion. In the BOSU study there were 13 cases, only

Table 88.2 Grading of anterior segment ischemia

Grade	Clinical feature
Grade 1	Reduced iris perfusion
Grade 2	Pupillary abnormalities
Grade 3	Postoperative uveitis
Grade 4	Keratopathy

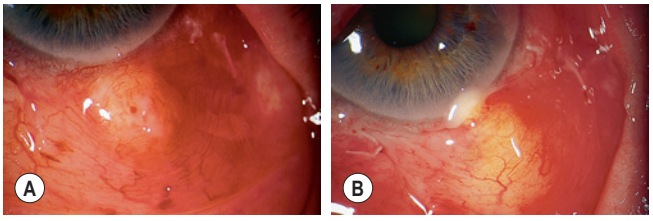


Fig. 88.5 Localized abscess. (A) Localized subconjunctival abscess. (B) Pus released by pressure on abscess. *(Courtesy of Mr. Robert Morris.)*

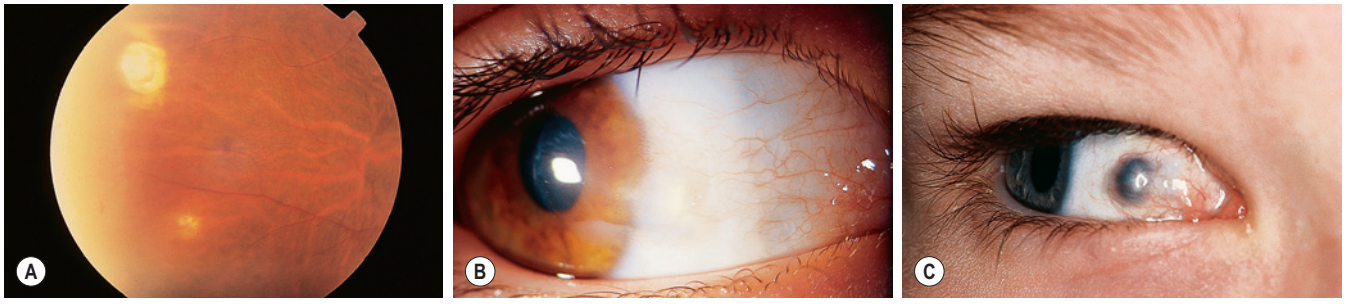


Fig. 88.4 Globe perforation complications. (A) Localized chorioretinal scar following scleral perforation at strabismus surgery. (B) Bleb formation following unrecognized scleral perforation from limbal traction suture 3 years previously. (C) Scleromalacia 4 years after strabismus surgery at site of original muscle insertion. *(Courtesy of Mr. Robert Morris.)*

two in adults. Three muscle insertion abscesses developed a slipped muscle requiring surgical exploration. Kothari[8] reported a similar bilateral case. Management depends on whether it is a diffuse orbital infection; systemic antibiotics are usually curative. A muscle insertion abscess, if associated with a slipped muscle, requires surgical exploration and drainage, and systemic antibiotics.

Histolopathological examination of a number of eyes with endophthalmitis after strabismus surgery (Professor Simonsz, personal communication) showed that infection gained access to the eye from a postoperative muscle insertion infection, suggesting that a more aggressive approach to postoperative muscle insertion infections is indicated. No such cases occurred in the BOSU study.

Surgically induced necrotizing scleritis

SINS is a rare but serious complication of strabismus surgery. There is only one pediatric case in the literature,[9] but the BOSU study identified six adult cases (i.e. an incidence of 1 in 4000), which presented 1–6 weeks postoperatively, usually with ocular pain. They were treated usually with topical and systemic non-steroidal anti-inflammatory drugs (NSAIDs) or steroids. One severe case required treatment with cyclophosphamide and developed posterior synechiae and a cataract reducing the vision to logMAR 0.60 (6/24, 20/80, 0.25). Another patient, who presented 14 days following surgery, had a corneal melt and required a conjunctival autograft nearly 2 years later with a good visual acuity. Fifty percent of cases had a poor or very poor outcome. Most patients were elderly but two were in their 20s. Figure 88.6 shows a case of SINS. This responded to oral and topical non-steroidal agents with no significant sequelae. Presentation of postoperative scleritis can be delayed (up to 40 years).[10] The BOSU study follow-up was for 6 months only, and so the reported incidence may represent an underestimation. In this study, information was not collected on pre-existing conditions that might predispose to scleritis such as systemic autoimmune conditions and ischemia. O'Donoghue et al.[11] reported a high prevalence of collagen vascular disease in postoperative scleritis. Bearing this in mind, together with the poor prognosis that the BOSU study highlighted for this condition, patients with SINS may best be seen by an inflammatory diseases specialist.

Mild scleritis may be common following strabismus surgery, presenting with pain – more severe and deep-seated than normal – with diffuse scleral inflammation requiring oral NSAIDs. Risk factors include advancing age, poor circulation, scleral diathermy, and ischemia.

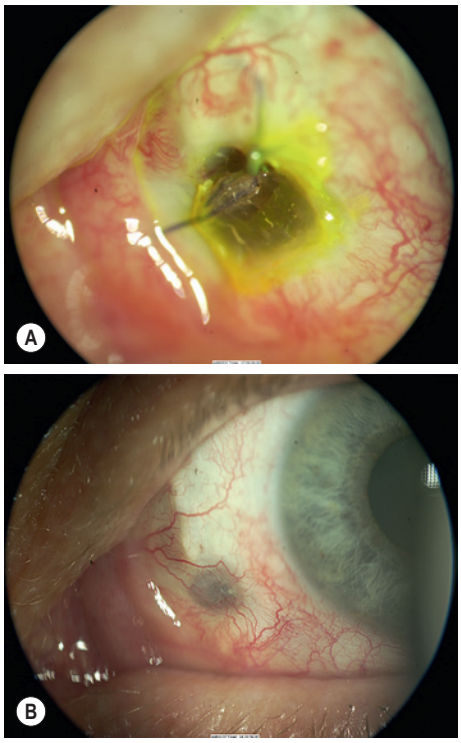


Fig. 88.6 (A) This 56-year-old male developed surgically induced necrotizing scleritis having had medial rectus recession on adjustable sutures after a blow-out fracture. There is a suture holding the conjunctiva covering the area of scleritis. (B) The appearance after treatment with topical steroids and oral non-steroidal agents.

Lost muscle

In the BOSU study, lost muscle was defined as a muscle lost peroperatively. There were six lost muscles, five in adults (i.e. an incidence of 1 in 4000). Most were in elderly patients, four of whom had undergone previous strabismus surgery. The lost muscles were medial recti (four) and lateral recti (two). Medial recti are the most common muscles lost at surgery.[10,11] This may relate to how frequently the muscle is operated on, or to its anatomy. The other recti have attachments to the oblique muscles, which prevents the muscle retracting into the orbit. All patients with lost muscles in the BOSU study had the muscle found preoperatively; only one had a poor or very poor outcome (only one had diplopia in the primary position). They must have been managed well and all had the lost muscle found.

If a muscle is lost, it is best to find it immediately. A common mistake is to look for the muscle around the globe when in fact the rectus muscles lie slightly away from the globe. Get help from an experienced surgeon, use suitable retractors for exposure, and control hemostasis. Careful exploration usually finds the muscle sheath and the muscle within. Some authors have suggested using the oculo-cardiac reflex to help identify the muscle, since traction on muscle fibers result in cardiac slowing. This technique is not always helpful. If the muscle cannot be found, suture the check ligaments and Tenon's surrounding the muscle to the original muscle insertion[9]; some muscle action may be transferred though these tissues to the eye. A muscle transposition could be performed; however, beware of ASI in adults. A more experienced strabismus surgeon may be able to find the muscle at a subsequent exploration. Postoperative investigations may include magnetic resonance imaging and computed tomography scans, especially with lost muscles due to trauma or where the orbits are congenitally abnormal or traumatized. An orbital approach may be necessary to retrieve a posteriorly situated lost muscle.[10]

Slipped muscle (Fig. 88.7)

In the BOSU study, slipped muscle was defined as a patient with a postoperative overcorrection and 50% or more reduction in movement in the action of a previously operated muscle. There were 18 cases (i.e. incidence of 7.5 per 10,000 operations), slightly more common in children. In three of these, the slipped muscle resulted from a muscle insertion infection. Three other patients had a poor or very poor outcome; all were children.

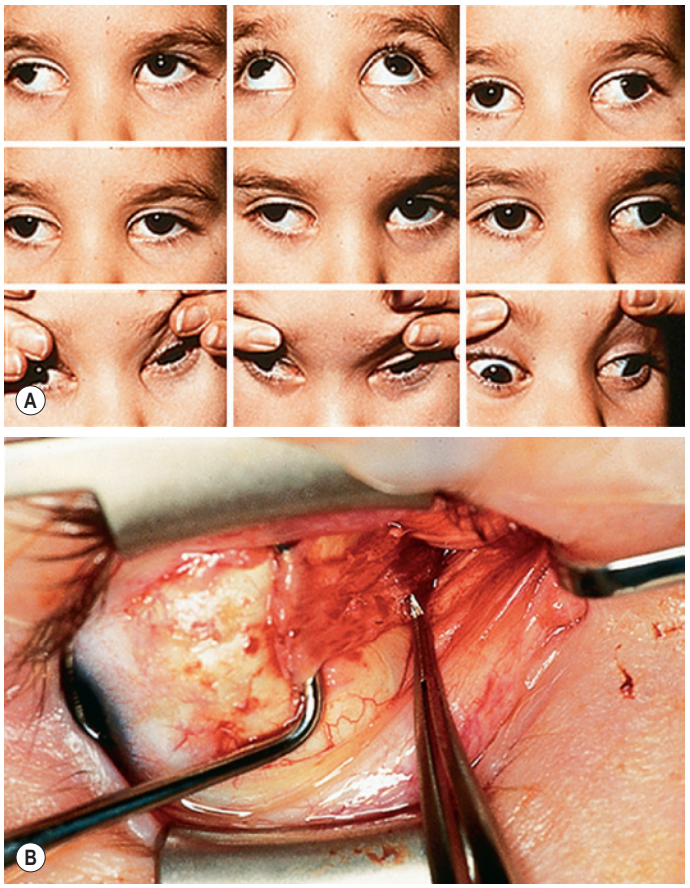


Fig. 88.7 Patient with slipped right medial rectus muscle. (A) Note large exodeviation and underaction of right medial rectus. (B) Findings at surgery: strabismus hook under pseudotendon of medial rectus 11 mm from limbus. Forceps indicating proximal end of medial rectus muscle. Note the change in color between muscle tissue and pseudotendon. *(Courtesy of Mr Robert Morris.)*

Slipped muscles take two main forms. A true slipped muscle is similar to a lost muscle: a problem with the sutures or insertion soon after the operation. The suture fails and the muscle slips. One deals with this as with a lost muscle. The more common presentation occurs many weeks to even years later, with a gross limitation of action of the muscle that has slipped. Exploration often finds the muscle on a large pseudotendon, not attached directly to the sclera but indirectly via stretchy scar tissue. This may occur due to stretching of a poorly inserted muscle over time. The pseudotendon is removed and the muscle re-attached to the globe. Because a contracture of the ipsilateral antagonist may have occurred, this muscle may need to be recessed along with its overlying conjunctiva.

Adherence syndrome

This is a restrictive condition, often progressive, caused by orbital fat prolapsing through a surgically disrupted posterior Tenon's. Surgery to the inferior oblique is often implicated. Occasionally it is caused by trauma or by lid surgery. To prevent this, care must be made to visualize the posterior edge of the inferior oblique so only the muscle is hooked at the time of surgery, avoiding damage to Tenon's and fat. Excessive bleeding may interfere with visualization and contributes to the scarring process. If orbital fat prolapses during surgery it can be repositioned or excised and the posterior Tenon's repaired. Often the problem is found postoperatively as the patient develops progressive hypotropia and limitation of elevation (Fig. 88.8). Surgical options are to explore the inferior fornix, excise any orbital fat, repair the posterior Tenon's capsule defect, and then recess the inferior rectus, Tenon's, and conjunctiva, followed by an amniotic membrane graft.

Endophthalmitis

There was one case of endophthalmitis in the 2 years of the BOSU study, giving an incidence of 1:24,000 cases. For diagnosis and treatment of endophthalmitis, see Chapter 15.

Consent in strabismus surgery

Placing a signature on a consent form should be the last event in a patient's journey from first appointment to the operating theater.[11] The principle of taking consent prior to treatment is directed towards protecting a patient's autonomy. To be valid, it must be given voluntarily by an informed patient with capacity to consent.[12,13] According to the Mental Capacity Act 2005[13] (UK Law), capacity is defined by a person's ability to fulfill the following four conditions below. The patient is able to:

1. retain information;
2. understand the information;
3. use the information to weigh up risk and benefit;
4. communicate the decision.

Consent is a process, not an event

During consent, the patient should develop a clear understanding of options, rationale, and outcomes, then weigh risks and benefits to make an informed decision and develop reasonable expectations for surgical results.

It is considered best practice to document the discussions you have with your patient at each stage of the consent journey and record what written information is given. Adequate time for discussion in clinic and gaining consent before the day of surgery allows the patient to reflect upon their decision. Any additional queries can be answered during confirmation of consent on the day of surgery.[14] Some authorities recommend that consent should be performed by the physician providing treatment,[15] whilst others allow delegation of consent to another team member so long as they have sufficient knowledge to describe risks and benefits, and to answer questions.[16]

Surprisingly, there is no specific "risk threshold" that mandates which complications need to be mentioned preoperatively. The legal standard describing what risks should be disclosed to the patient varies within and between countries. The standard of ethical care expected of health care professionals by their regulatory bodies may exceed the legal requirements. It is advisable to inform your patient (Box 88.4)[16,17] of all significant possible adverse outcomes or unavoidable risks of surgery, and make a record of the information given.[12]

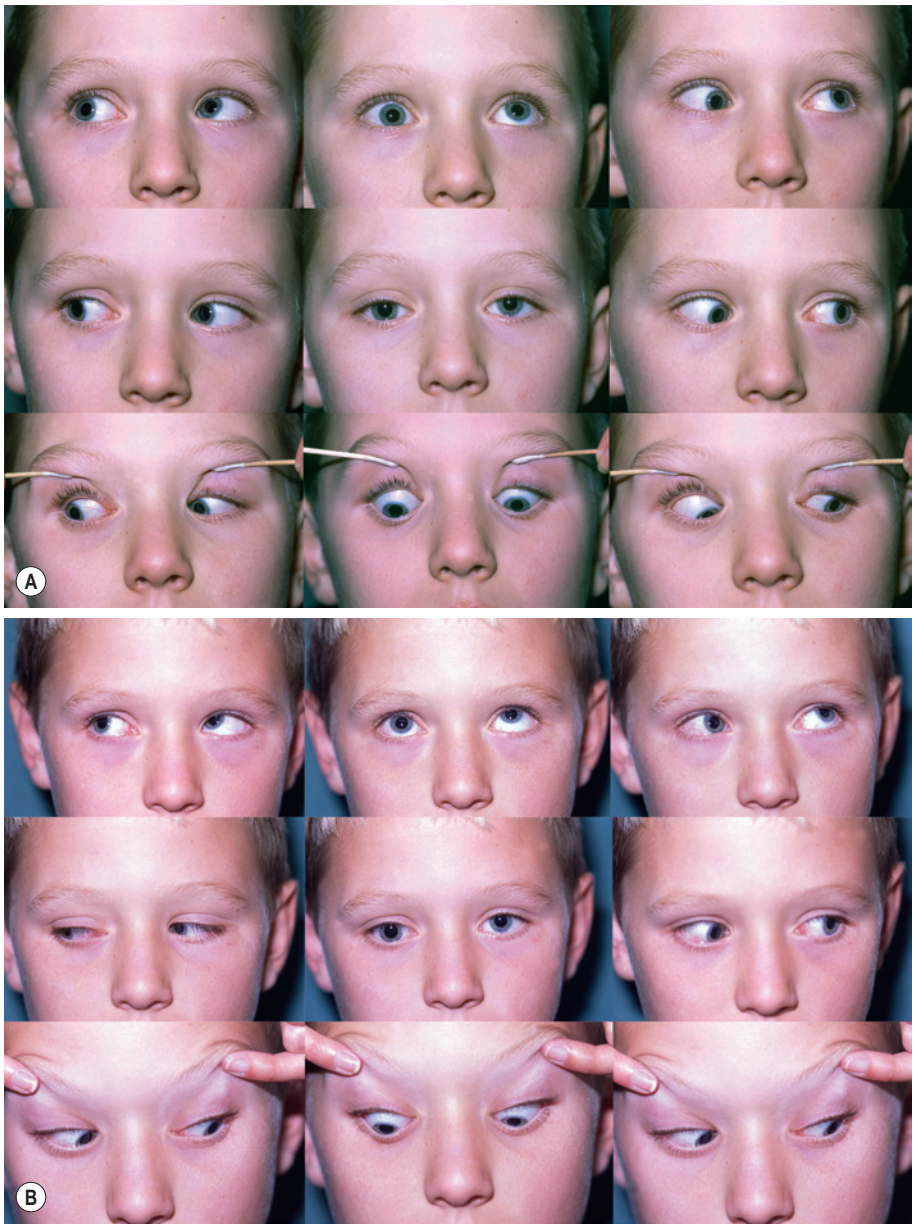


Fig. 88.8 A 14-year-old boy underwent routine right inferior oblique myectomy for a right fourth nerve palsy. (A) Two weeks postoperatively he developed restriction in elevation in the right eye as a result of right inferior fornix adherence syndrome. (B) His postoperative ocular motility showed improvement in elevation of his right eye.

Box 88.4

Informed consent should cover these areas[16,17]

Diagnosis
Treatment options, including no treatment
Other possible procedures that may be necessary during surgery
Common side effects/complications
Rare, significant complications
Anesthetic options and risks

Encourage a dialogue between you and your patient

A careful balance needs to be struck between listening to what your patient wants and ensuring they have sufficient information (Box 88.5) to make an informed decision.[18,19]

It is the duty of the surgeon to ascertain the patient's needs and wishes and discuss everything relevant to them,[16] to present information in a balanced way, and check that the patient has understood the information. In many countries, the surgeon also explains the risks of anesthesia, including morbidity and death; in others this is done by the anesthetic team.

Decision making in children should be centered around shared responsibility between surgeon and parents

For minors, informed consent is required from a parent or legal guardian prior to medical treatment. In most cases, a decision will be made that represents the best interests of the child. Although only one parent signature is required, it may be appropriate to involve both parents in decision making.

Box 88.5

Ophthalmic Mutual Insurance Company informed consent for strabismus surgery

Major risks of strabismus surgery:

1. Need for additional surgeries
2. Persistent misalignment, altered eyelid position, limitation of eye movements, persistent visual problems
3. Double vision
4. Scar tissue formation
5. Infection
6. Hemorrhage or bleeding
7. Severe infection or bleeding leading to damage to the eye or rarely visual loss
8. Allergic reaction
9. Temporary side effects, such as corneal abrasion, conjunctivitis, eye ache

Ophthalmic Mutual Insurance Company (OMIC). Strabismus Surgery Consent Form. Version 4/16/09. Available at: http://www.omic.com/strabismus-surgery-consent-form/ [accessed June 2016].

Consider an adolescent's developing capability for involvement in decision making[20,21]

A young person's ability to consent depends more on their understanding of the nature of the proposed treatment and its possible consequences than on their age.[18,22] There is no simple criterion or measure of competence; your skill lies in assessing the young patient's competence in a particular context for a specific decision.[23] The legal age at which a minor may give consent varies widely from country to country and should be considered on a case-by-case basis.[24,25] The law on consent is constantly evolving and varies internationally. Legal advice should always be sought if there is doubt regarding the legal validity of a proposed intervention.

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Nystagmus in childhood

Frank Antony Proudlock and Irene Gottlob

Chapter contents

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QUALITY OF LIFE AND INFANTILE NYSTAGMUS
CLASSIFICATION OF INFANTILE NYSTAGMUS
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See online for supporting video for this chapter.

Introduction

Nystagmus consists of rhythmic ocular oscillations. Pathological nystagmus is involuntary, although it may be modulated when performing certain tasks such as reading. Infantile nystagmus is defined as nystagmus developing in the first 3–6 months of life. Nystagmus can be acquired later in life, usually due to neurological diseases. Patients with acquired nystagmus have oscillopsia, the illusion that the environment is moving. Patients with infantile nystagmus, however, usually have a stable view of the environment, probably due to neuronal plasticity and adaptation during visual development.

Nystagmus in childhood can be idiopathic or associated with retinal diseases, low vision in infancy, and a variety of syndromes and neurological diseases. Nystagmus associated with neurological disorders in childhood may be similar in appearance and pathophysiology to acquired nystagmus. Onset may also be after 6 months of age. The estimated prevalence of nystagmus (including both infantile and acquired nystagmus) is 24 in 10,000. The prevalence of infantile nystagmus is 14 per 10,000.[1] Among the infantile forms of nystagmus, idiopathic nystagmus is the most common, followed by nystagmus associated with ocular disease. The clinical diagnoses associated with infantile nystagmus are shown in Figure 89.1.

Causes of infantile nystagmus

The causes of most forms of infantile nystagmus are as yet unknown, although this is currently an active field of research.[2] In general, infantile nystagmus is considered to be a disorder of gaze-holding and slow eye movement systems,[3] leading to sinusoidal oscillations and/or drifts of the eye away from the intended point of fixation. These involuntary slow eye movements constitute nystagmus slow phases. The slow phases are interrupted and shaped by the interposition of nystagmus quick phases, which serve to re-align the eyes.

Many types of infantile nystagmus are associated with the presence of sensory abnormalities during early visual development.[4–9] With afferent diseases such as achromatopsia and congenital cataract, the nystagmus is clearly the result of changes in the otherwise healthy ocular motor systems in response to afferent deficits present during visual development. For other conditions such as albinism and various syndromes, it is uncertain whether the nystagmus is also due to afferent deficits or directly caused by abnormalities in ocular motor neural circuitry.

Quality of life and infantile nystagmus

Investigations into the quality of life of adults and children with infantile nystagmus show that the effects on visual function are considerable and are comparable to the effects of diseases such as age-related macular degeneration.[10] Infantile nystagmus has a much wider impact than simply reducing vision. It affects social interaction, due to lack of confidence caused by the cosmetic appearance of nystagmus, and restriction in mobility of many patients, as they are not able to drive. Consequently, treatment of nystagmus should not only aim at improving visual acuity but also at improving cosmesis. This might include, for example, the correction of abnormal head postures and the reduction of nystagmus intensity in patients with poor visual potential. Patients may also benefit from counseling services and support groups such as Nystagmus Network, UK (http://www.nystagmusnet.org) or the American Nystagmus Network (http://www.nystagmus.org).

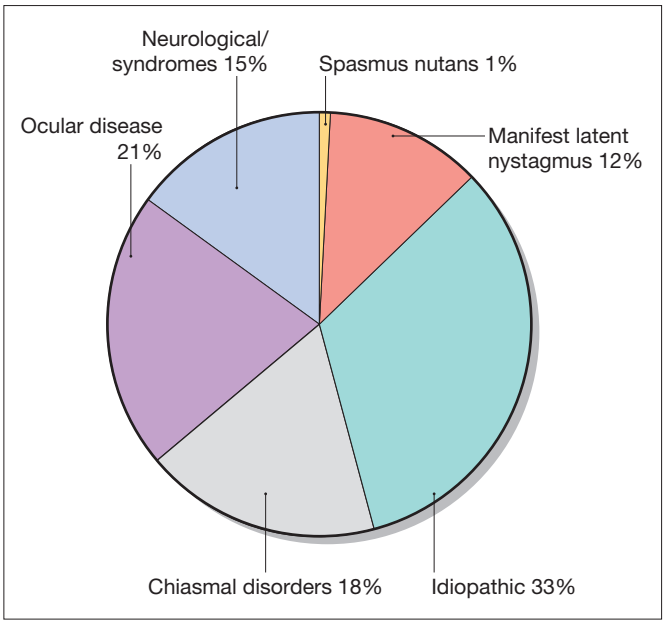


Fig. 89.1 Prevalence of the main types of nystagmus in childhood. A breakdown of the various disorders in individuals 18 years and under with infantile nystagmus from the Leicestershire Nystagmus Survey.[1] The majority of patients with chiasmal disorders had albinism.

Classification of infantile nystagmus

There has been significant controversy over the classification and terminology used in nystagmus. This is because some researchers have been mainly interested in the morphology of nystagmus waveforms and others in clinical etiology.

The advantages of using a clinical classification of infantile nystagmus based on the associated diseases are that the clinical implications such as prognosis, possible genetic counseling, or treatment options are immediately highlighted.[11] Figure 89.2 lists examples of disorders using this type of classification. Idiopathic nystagmus has historically been a diagnosis of exclusion where all other eye examinations are negative. The visual acuity is 0.3 LogMAR or better in most patients, suggesting relatively good retinal function.[12,13] However, retinal abnormalities have been recently identified in idiopathic nystagmus using optical coherence tomography (OCT).[6] Mutations in the *FRMD7* gene have been identified as a major cause of X-linked idiopathic nystagmus.[14,15] Several genetic mutations are known for other disorders such as albinism[16,17] and achromatopsia.[18] It is likely that the nystagmus genotype will be the principal method of classification in the future.

The Committee for the Classification of Eye Movement Abnormalities and Strabismus Workshop (CEMAS; http://nei

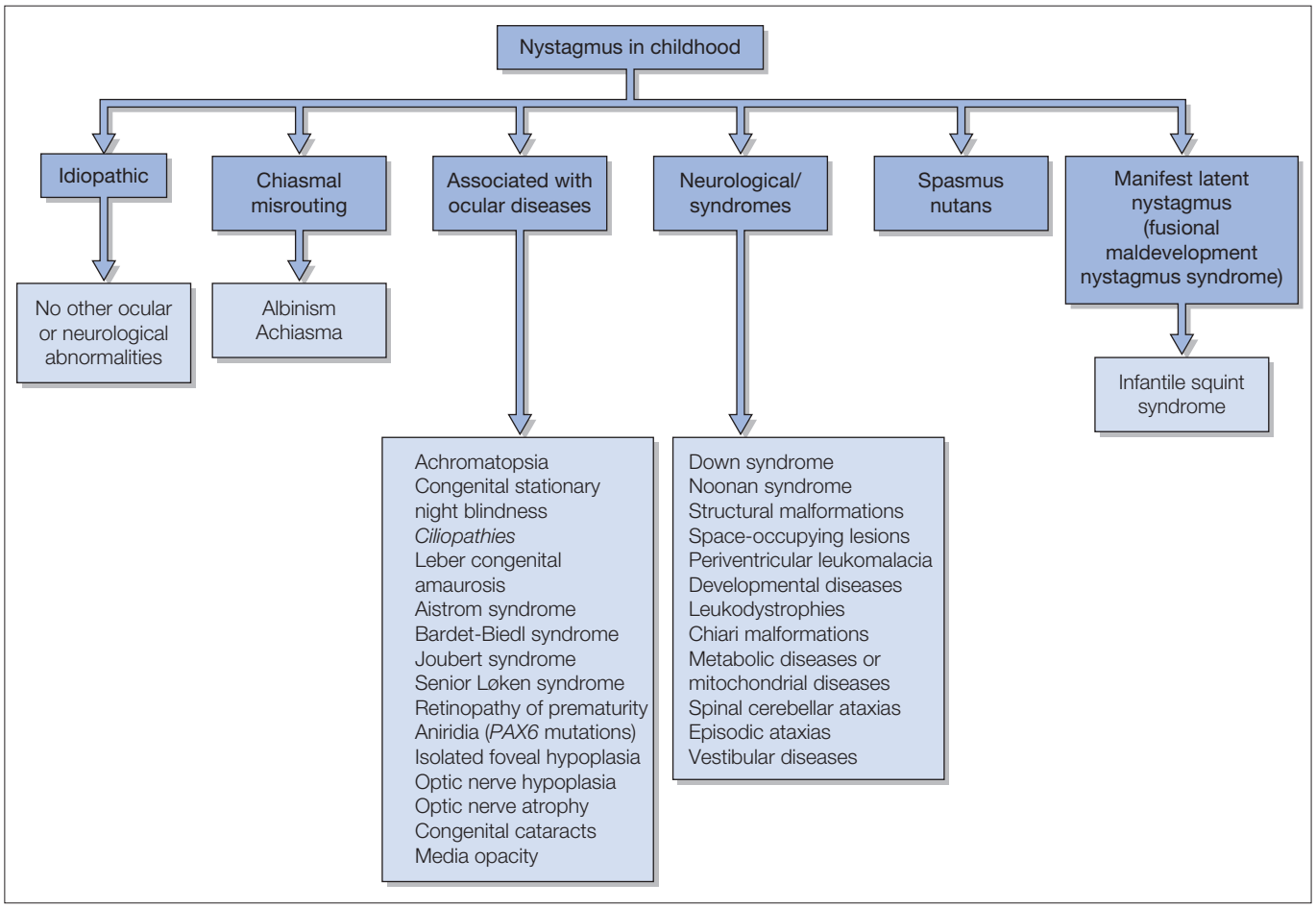


Fig. 89.2 Classification of nystagmus based on associated diseases.

.nih.gov/sites/default/files/nei-pdfs/cemas.pdf) have grouped together idiopathic nystagmus, nystagmus associated with ocular diseases, and nystagmus associated with chiasmal misrouting into one category called "infantile nystagmus syndrome." In a clinical setting, this classification is less helpful and makes unconfirmed assumptions about a common mechanism leading to nystagmus in all of the underlying pathologies.

Clinical assessment

History

It is important to establish the time of onset for the nystagmus since infantile nystagmus occurs usually in the first 3, or sometimes 6, months of life.

As several forms of infantile nystagmus are hereditary, establishing whether other family members have nystagmus or associated ocular diseases can help with the diagnosis. If there is a positive family history, determining the mode of inheritance is very important. Idiopathic nystagmus often occurs in an X-linked pattern in which heterozygous females are fully affected in approximately 50% of cases (i.e. 50% penetrance).[14,15] In contrast, only males are fully affected in X-linked congenital stationary night blindness (CSNB),[19] blue cone monochromatism,[18] or ocular albinism.[17] Oculocutaneous albinism[16] and achromatopsia[18] are usually autosomal recessive. The most common form of autosomal dominant nystagmus is caused by mutation in *PAX6* genes.[20]

Where neurological deficits such as cerebral palsy, metabolic diseases, or other causes of developmental delay are present, they are likely to play a key role in the etiology of the nystagmus.

It is important to establish whether parents think their child has poor vision. Although nystagmus can be of very large amplitude at onset and parents can have the impression that the child is visually unresponsive, usually the nystagmus amplitude is considerably smaller by 6–9 months of age.[21] Explaining to parents that nystagmus generally changes and becomes less evident as their child becomes older is important, and therefore caution should be taken about predicting poor vision later in life.

Often children with nystagmus have head nodding or bobbing. This seems to be an independent abnormal head movement, which can decrease or disappear with age. Only in spasmus nutans has head nodding been shown to reduce or abolish nystagmus (Fig. 89.3D).

A history of photophobia should be specifically asked for. This would be indicative of a retinal disease, particularly achromatopsia or blue cone monochromatism. Similarly, a history of night blindness should be specifically asked for. This suggests a rod–cone dystrophy and is common in congenital stationary night blindness.

Symptoms of oscillopsia are a feature of acquired nystagmus and seldom occur in children. Some patients with infantile nystagmus, however, perceive oscillopsia if they look away from the null region[22] or if the nystagmus changes, for example in manifest latent nystagmus (MLN), which can change with the degree of strabismus. The oscillopsia in acquired nystagmus is usually sudden in onset and severe. In contrast, the time of onset of oscillopsia in infantile nystagmus is generally not as well defined and the symptoms are milder.

Clinical examination

Visual acuity

Visual acuity (VA) needs to be examined with the best optical correction and tested with both eyes open and either eye covered with a free head position. This is important, as manifest latent nystagmus, alone or superimposed on other infantile nystagmus waveforms, can increase the nystagmus and decrease VA when one eye is covered. VA should also be measured at distance and near. In infants, VA tests can be performed using preferential looking cards. In patients with horizontal nystagmus, measurement of VA can be assisted by vertically aligning the cards,[23] making it easier to identify changes in fixation when the child looks up or down at the visual targets on the card. This can be masked by the horizontal nystagmus if the card is aligned horizontally. The presence of vertical optokinetic nystagmus can also be used to predict the likelihood of better VA in horizontal nystagmus.

Abnormal head posture

Abnormal head posture (AHP) (or torticollis) occurs commonly in nystagmus because many patients can reduce their nystagmus by looking in a certain direction of gaze, for example by directing gaze towards the null region. In most patients, the full extent of torticollis is only observed during visual effort. So to identify the full amount of AHP, ask the patient to read or look at pictures (Fig. 89.5A). Glasses can prevent the patient adopting the full head turn due to the spectacle frame and optical decentration. VA measurements should be repeated, therefore, without spectacles. Figure 89.5B shows a child with idiopathic infantile nystagmus (IIN) and a right head turn increasing as he reads smaller letters. With a greater visual demand, a large head turn is adopted and he looks over his glasses or prefers to read without glasses since the full head turn is prevented by the glasses.

Manifest latent nystagmus dampens on adduction. As a result, the patient adopts a head turn to keep the fixing eye adducted (Fig. 89.5C). In manifest latent nystagmus, the head position also needs to be examined with each eye covered, as the head position can change depending on the fixing eye (Fig. 89.5D). Patients with "A" or "V" pattern strabismus may adopt a chin-up or -down head position in order to maintain binocular function and thus reduce the amplitude of the nystagmus (Fig. 89.5E). Eye movement recordings are helpful in understanding abnormal head postures, for example in establishing whether the head posture is due to idiopathic nystagmus (see Fig. 89.4A) or manifest latent waveforms (see Fig. 89.4C). They can also be used to determine whether the adopted head posture leads to a reduction or change in the nystagmus.

Orthoptic examination

Orthoptic examination should include an assessment of strabismus at distance and near, the range of motility of each eye, binocularity, stereopsis, and fusion ranges if binocular vision is present.

Color vision testing

This is important to detect achromatopsia and other retinal or optic nerve diseases.

Terminology used in nystagmus

Nystagmus can be characterized by clinical examination of the patient. Eye movement recordings can help by providing greater precision in detecting and describing nystagmus waveforms, which can assist in the diagnosis (Figs 89.3 and 89.4). The following parameters can be used to describe nystagmus:

Plane: The plane of oscillation can be horizontal, vertical, torsional, or a combination of more than one plane (e.g. Fig. 89.3C2).

Intensity: The intensity of the nystagmus is a measure of the speed of the eye movements and is obtained by multiplying the nystagmus amplitude (in degrees) and frequency (oscillations per second in Hertz).

Waveform: Nystagmus can be broadly classified into jerk and pendular waveforms. Jerk nystagmus consists of alternating slow and quick phase eye movements. The nystagmus direction is defined using the quick phase. Slow phases can have an increasing velocity profiles where the eyes start slowly and accumulate speed (e.g. Fig. 89.4A in right gaze). Alternatively, slow phases may have decreasing velocity (e.g. Fig. 89.4C) or linear velocity profiles. In contrast, pendular nystagmus consists of approximately sinusoidal oscillations without quick phases (e.g. Fig. 89.4A at null region). Dual jerk nystagmus is a combination of large jerk nystagmus waveforms with small pendular nystagmus waveforms superimposed along the same plane.

Conjugacy: If both eyes move together, i.e. with the same amplitude, frequency and plane, the nystagmus is conjugate. Dysconjugacy or dissociated nystagmus occurs if the eyes move with different amplitude (e.g. torsional eye movements in Fig. 89.3A3), frequency, phase (e.g. vertical eye movements in Fig. 89.3C2) or along different planes.

Foveation: Most types of infantile nystagmus show periods in the nystagmus cycle when the eyes move at a slower velocity. These slow periods are often used to align the fovea with visual targets to improve visual acuity, and hence are called foveation periods.

Null region: Many patients with infantile nystagmus prefer a particular gaze direction where the nystagmus is reduced in intensity and visual acuity is optimal. This is called the null region. If the null region is not in the primary position, patients may adopt an abnormal head posture (AHP) using the null region to improve vision when looking straight ahead. An example is shown in Figure 89.4A2 where the null region is in right gaze.

Infantile nystagmus is not always uniform but can change depending on several factors:

Change with gaze: Patients with nystagmus associated with albinism and idiopathic nystagmus usually have a null region. The nystagmus becomes more jerk-like (see Fig. 89.4A1) and intense (see Fig. 89.4A2) away from the null region.

Change with time: Most patients have a consistent oscillation when attempting to maintain a fixed gaze position. However, certain types of nystagmus vary with time. In periodic alternating nystagmus (PAN) the fast phase beats periodically to the right and to the left with quiet periods at the changeover periods (see Fig. 89.4B).

Change upon covering one eye: In manifest latent nystagmus (MLN), the fast phase of nystagmus changes direction beating towards the open or fixing eye (see Fig. 89.4C).

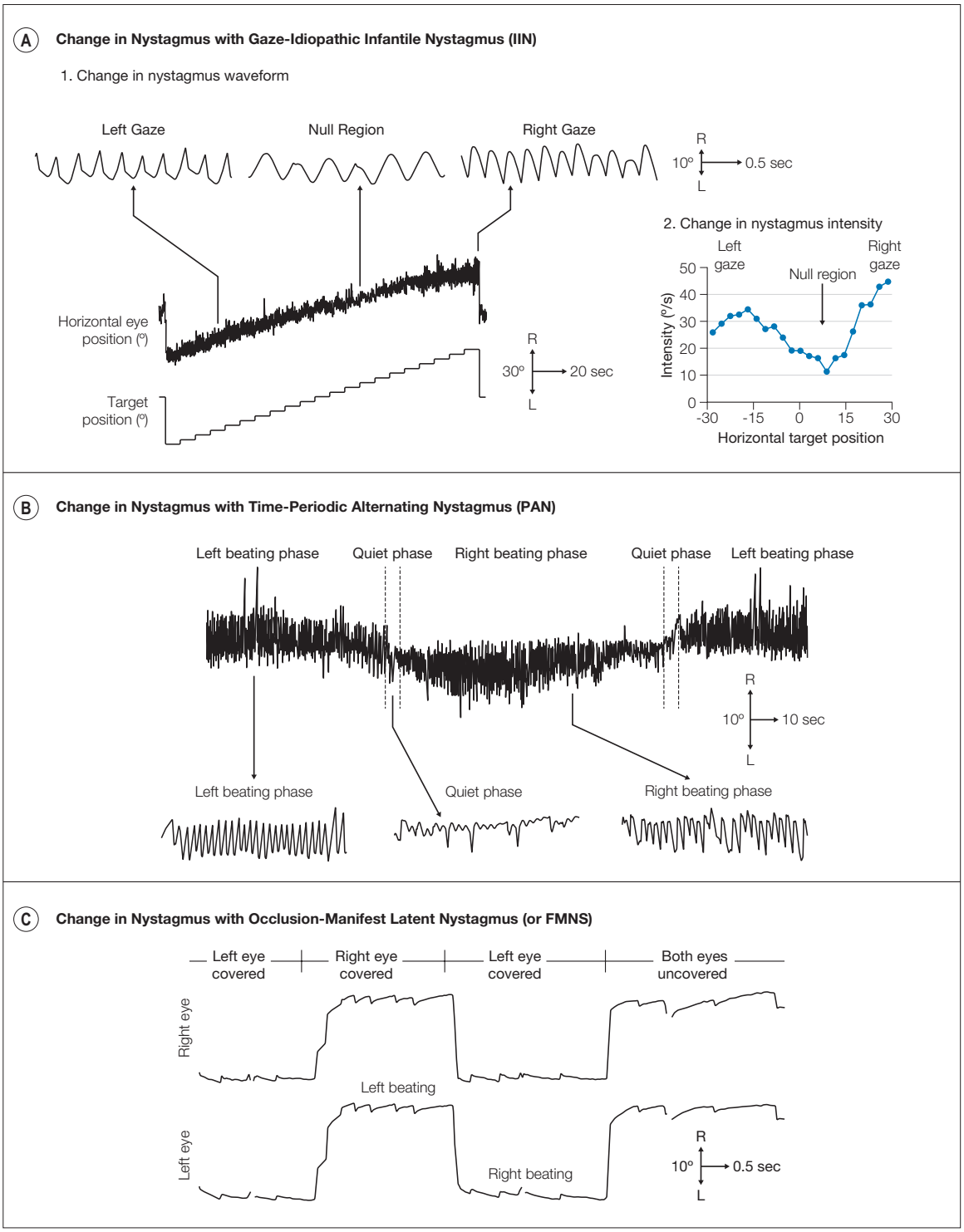


Fig. 89.4 Change in nystagmus with (A) gaze, (B) time and (C) occlusion. (A) Shows an example of the null region in a patient with idiopathic infantile nystagmus using original eye movements from a patient. The patient follows a target moving from the left to right in steps of 3° every 8 seconds (lower traces). The horizontal nystagmus changes both in waveform (A1) and intensity (A2) as the direction of gaze changes. The changing waveforms can be seen from the expanded views in the upper traces. At the null region, which is 9° to the right of central fixation, the nystagmus waveform is predominantly pendular, with occasional foveating saccades. Jerk waveforms are present to the left and right of the null region, with the nystagmus beating to the left in left gaze and right in right gaze. A plot of the nystagmus intensity in relation to the horizontal gaze angle is shown in A2. (B) Shows a patient with idiopathic infantile nystagmus and periodic alternating nystagmus as an example of a nystagmus waveform changing with time. The nystagmus completes a full cycle of left beating and right beating nystagmus every 200 seconds, with short quiet phases of several seconds between each change in beating direction. Expanded views are shown in the lower traces. (C) Shows a patient with manifest latent nystagmus illustrating the change in beating direction on covering either eye. The eyes always beat towards the open or fixing eye. The waveforms all show decreasing velocity slow phases. Note the step change in eye position on covering either eye, which is due to a large esotropia. The left eye is the dominant eye. The nystagmus is less intense when both eyes are open.

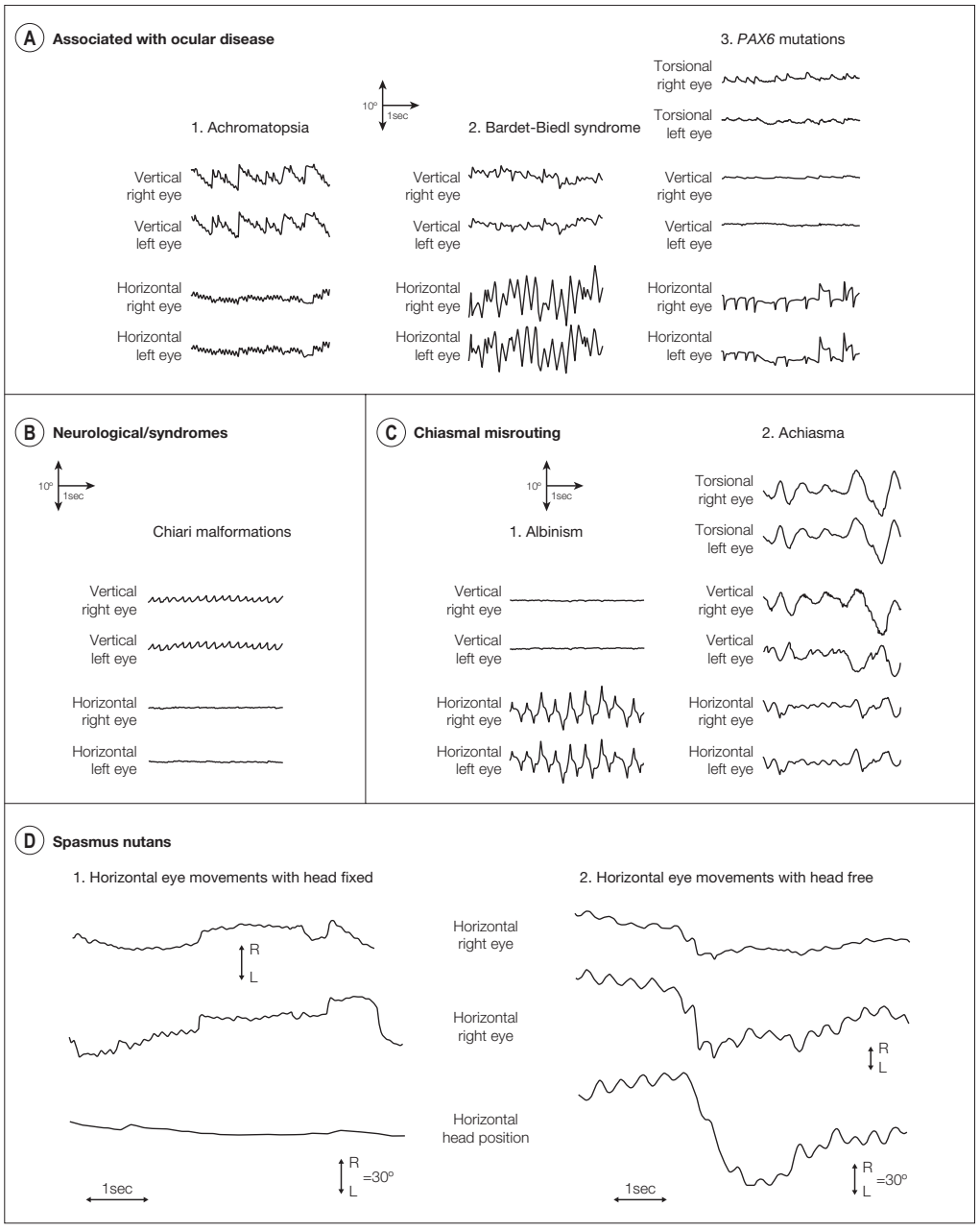


Fig. 89.3 The use of eye movement recordings in the diagnosis of nystagmus. Examples of eye movement recordings from patients with infantile nystagmus associated with (A) ocular diseases, (B) neurological disorders and syndromes, (C) chiasmal misrouting disorders, and (D) spasmus nutans. (A) Ocular diseases: In achromatopsia, a fine pendular nystagmus with a vertical component is often present. In the achromat shown (A1), a fine mainly horizontal pendular nystagmus of 1–2° amplitude and 8 Hz frequency co-exists with a vertical upbeat jerk nystagmus of approximately 5° and 1.5 Hz. A patient with Bardet–Biedl syndrome (A2) has horizontal pendular oscillations that are much larger than in the achromat (8–10° amplitude and 3 Hz frequency in the example shown), but the vertical component to the nystagmus is smaller. *PAX6* mutations (A3) lead to a variety of waveforms, with the two eyes sometimes showing dysconjugate eye movements. The example here shows unusual horizontal waveforms with both increasing and decreasing velocity components. A significant torsional component is apparent, which is larger in the right eye. (B) Neurological disorders and syndromes: These can be associated with vertical eye movements. The example shown is from a patient with a Chiari malformation leading to a downbeat jerk nystagmus of 2–3° amplitude and 3–4 Hz frequency, with little horizontal nystagmus. (C) Chiasmal routing disorders: Similar to idiopathic infantile nystagmus (see Fig. 89.4A), nystagmus associated with albinism (C1) can have pendular or jerk waveforms but always along the horizontal plane and usually with a null region. Jerk waveforms can be left beating, right beating, or bidirectional as shown in example here. Achiasmatic disorders (C2) lead to seesaw nystagmus, so called because the eyes give the appearance of rotating around an invisible pivot positioned somewhere between the two eyes. Consequently, as one eye moves up, the other eye moves down, leading to a dysconjugate vertical waveform. The eye moving up intorts and the eye moving down extorts, leading to a large-amplitude torsional nystagmus. There is also a horizontal component to seesaw nystagmus. (D) Spasmus nutans: Nystagmus in spasmus nutans is altered by head movements. When the head is fixed, a rapid pendular oscillation develops, which is dysconjugate between the two eyes. When the head is free, head bobbing occurs with the eyes moving in the opposite direction due to the vestibulo-ocular reflex. This leads to suppression of the rapid oscillation. *([D] Reproduced from Gottlob I, Zubcov AA, Wizov SS, et al. Head nodding is compensatory in spasmus nutans. Ophthalmology 1992; 99: 1024–1031.)*



Fig. 89.5 Abnormal head postures. (A) Patient with IIN and a mild head tilt to the left when reading large letters on VA chart (A1), which significantly increases (A2) when reading smaller letters. (B) Moderate head turn to the right due to IIN when reading large letters (B1). As the patient reads smaller letters, the head increasingly turns to the right and the patient looks over his glasses as the frames do not allow a larger head turn to the right (B2). He prefers to read without glasses in order to adopt a large head turn (B3). (C) Child with a blind right eye due to optic nerve hypoplasia adopting an extreme head turn and tilt to the left to dampen manifest latent nystagmus (C1). When the left eye is covered and there is no vision, the head turn is absent (C2), which shows that there is no muscular torticollis. (D) Manifest latent nystagmus and alternating exotropia. The patient turns the head alternately to the right to fix in adduction with the right eye (D1), or the left to fix in adduction with the left eye (D2) to dampen the manifest latent nystagmus. When one eye is patched, he turns the head continuously to the right when the right eye is open (D3), and to the left when the left eye is open (D4). (E) Girl with manifest latent nystagmus adopting chin elevation while reading (E1). She has "V" pattern exotropia with bilateral inferior oblique overaction (E2–E5). On downgaze she has some amount of binocularity (Bagolini positive), which causes the nystagmus to dampen. Hence she adopts a chin-up position when reading the visual chart. (F) Head turn to the left due to IIN (nystagmus null region to the right), which does not allow the patient to wear glasses as the frame is obstructing her vision (F1). After Kestenbaum surgery (F2), her head is straight and she is able to wear her 4 diopters of astigmatic correction, significantly improving her vision. (G) A patient with albinism and pronounced head tilt to the left before surgery when reading the visual acuity chart (G1). After surgery, he reads the same line on the acuity chart without a head tilt (G2).

Examination of light sensitivity and nyctalopia

Photophobia is easily noted on slit-lamp or fundus examination and points to achromatopsia or other retinal dystrophies. Nyctalopia can be objectively measured using dark adaptometry and indicates congenital stationary night blindness or other retinal dystrophies.

Structural examination

The most common abnormal sign of the anterior segment is iris transillumination, which is strongly associated with albinism. The amount of iris transillumination varies and can be easily missed on examination if it is mild, especially in patients with dark irides or in small children. Slit-lamp examination should be performed in a completely dark room with retroillumination. It is helpful to examine the parents also, as carriers commonly have mild iris transillumination. It is important to examine for corneal changes, aniridia, or abnormal iris structure and the presence of cataracts. The retina can appear normal in the early stages of retinal dystrophy. Foveal hypoplasia often manifests as a missing foveal reflex and abnormal vessels in the foveal area. This can be difficult to establish in a child with nystagmus. In retinal diseases such as achromatopsia and congenital stationary night blindness, the retina can appear normal. Optic nerve hypoplasia or atrophy can cause nystagmus, particularly if it is bilateral. Large refractive errors are also commonly a sign of retinal dystrophies, albinism, *PAX6* mutations, or other diseases associated with low vision. Paradoxical pupillary response (initial pupillary constriction when the room light is turned off) can be a sign of retinal diseases.

Electrophysiology

Every patient with infantile nystagmus should have an electrophysiological examination. Hemispheric visual evoked potentials (VEPs) represent the gold standard examination for determining increased crossing of the optic nerves in albinism and reduced crossing in achiasma (see Chapters 41 and 57).

Electroretinography (ERG) is essential to investigate possible retinal dystrophies (Fig. 89.6).

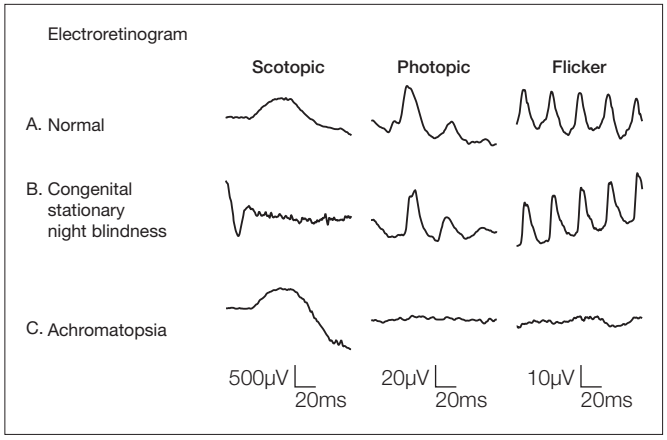


Fig. 89.6 Electroretinography in infantile nystagmus. Examples of scotopic, photopic, and flicker electroretinograms (ERGs) of (A) a normal subject, (B) a patient with congenital stationary night blindness (CSNB) with a negative scotopic ERG, and (C) a patient with achromatopsia with extinguished photopic ERG and flicker ERG.

Eye movement recordings

Eye movement recordings are very useful in clarifying the pathophysiology of the nystagmus, in differential diagnosis, and in planning surgery. Figures 89.3 and 89.4 show examples of eye movement recordings in each of the main classes of infantile nystagmus.

Nystagmus associated with albinism (see Fig. 89.3C1) or idiopathic nystagmus (see Fig. 89.4A) is conjugate, almost always horizontal, with a combination of pendular and jerk waveforms that vary with gaze.[12] Away from the null region, the slow phases typically increase in velocity and drift towards the null region (see Fig. 89.4A). In contrast, nystagmus associated with manifest latent nystagmus usually has decreasing velocity slow phases (see Fig. 89.4C). Nystagmus waveforms associated with retinal diseases are variable and can be dissociated, vertical, and can have increasing or decreasing slow phase velocities (see Fig. 89.3A). Vertical nystagmus is also often associated with neurological disorders (see Fig. 89.3B).

Optical coherence tomography

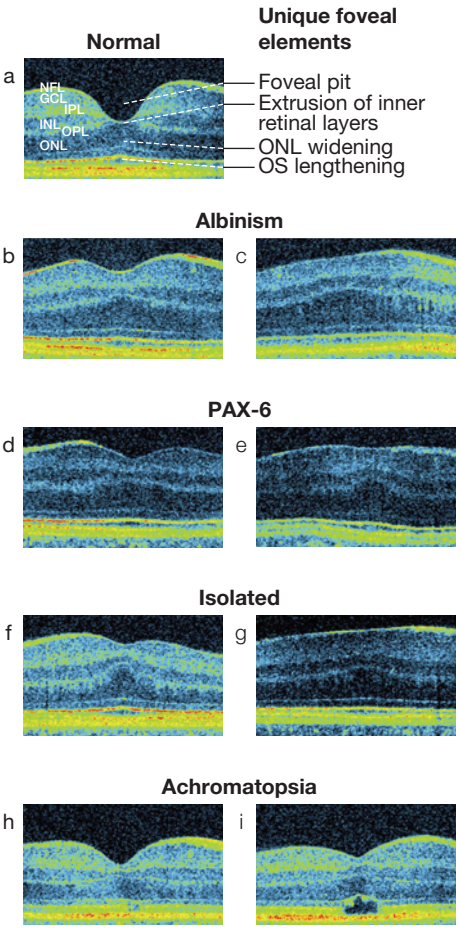
OCT has recently been added as a useful investigative tool for the differential diagnosis of nystagmus and can be performed easily and quickly.[5–9] It is particularly helpful in identifying foveal hypoplasia and results can be obtained at the time of appointment. Figure 89.7 shows OCT images of a control subject and patients with albinism, idiopathic foveal hypoplasia, *PAX6* mutation, and achromatopsia. If foveal hypoplasia is detected on OCT, the most likely diagnosis is albinism[5]; however, mutations in the *PAX6* gene or idiopathic foveal hypoplasia cannot be ruled out.[8] These diseases have similar morphological changes in the fovea. In contrast, foveal hypoplasia in achromatopsia is atypical.[4,7,24] In many patients with achromatopsia, there is a pathological continuation of inner and outer plexiform layers. Typically, there is disruption of the inner segment/outer segment junction and cone outer segment tip, and thinning of the outer nuclear layer. The most striking sign is a "punched out" hyporeflexive zone, which often only appears in older patients. Morphological changes in achromatopsia appear to increase with age on OCT.[4,7,24] Structural grading of foveal hypoplasia based on retinal imaging using OCT can be used to estimate VA (Fig. 89.7[2]).[5,8]

Hand-held OCT is also now available for use in infants and children, and can assist in diagnosing patients that are too young to comply with other diagnostic tests.[25] Figure 89.8 shows a diagnostic algorithm for infantile nystagmus that has been developed for use in infants and children using hand-held OCT.

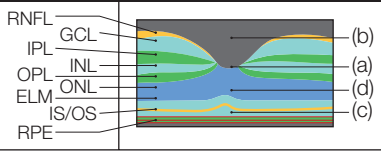
Magnetic resonance imaging of the brain

Magnetic resonance imaging (MRI) is necessary if the nystagmus is not typical of idiopathic nystagmus (i.e. dysconjugate, vertical, or oblique) and cannot be explained by ocular or systemic disease. MRI is generally not indicated when the associated disease (e.g. albinism, achromatopsia, or manifest latent nystagmus/infantile squint syndrome) has been determined and when no other neurological/developmental problem is present. Any suspicion of neurological disease, optic atrophy, optic nerve hypoplasia, or developmental delay should prompt neuroimaging. In the presence of optic nerve hypoplasia,

(A) Examples of OCT images from normal retina and individuals with foveal hypoplasia



(B) Grading scheme devised to grade foveal hypoplasia based upon stage at which retinal development was arrested

Normal foveal structural features detectable using optical coherence tomography	Illustration
(a) Extrusion of plexiform layers (b) Foveal pit (c) OS lengthening (d) ONL widening	

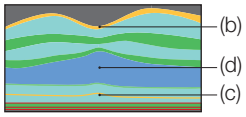
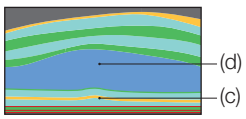
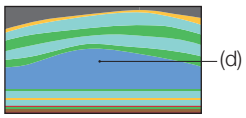
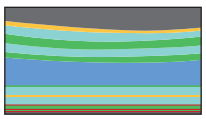
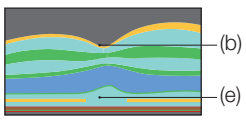
Grade of foveal hypoplasia	Structural features detected on optical coherence tomography	Present or absent	Illustration	Median LogMAR visual acuity (interquartile range)
1	(a) Extrusion of plexiform layers (b) Foveal pit - shallow (c) OS lengthening (d) ONL widening	(a) Absent (b) Present (c) Present (d) Present		0.20 (0.12)
2	(a) Extrusion of plexiform layers (b) Foveal pit (c) OS lengthening (d) ONL widening	(a) Absent (b) Absent (c) Present (d) Present		0.44 (0.18)
3	(a) Extrusion of plexiform layers (b) Foveal pit (c) OS lengthening (d) ONL widening	(a) Absent (b) Absent (c) Absent (d) Present		0.60 (0.0)
4	(a) Extrusion of plexiform layers (b) Foveal pit - shallow (c) OS lengthening (d) ONL widening	(a) Absent (b) Absent (c) Absent (d) Absent		0.78 (0.11)
Atypical	(a) Extrusion of plexiform layers (b) Foveal pit - shallow (e) IS/OS disruption	(a) Absent (b) Present (e) Present		1.0 (0.08)

Fig. 89.7 Optical coherence tomography (OCT) in infantile nystagmus. (A) Optical coherence tomograms are shown for (a) a normal fovea, (b,c) albinism, (d,e) associated with *PAX6* mutations, (f,g) isolated cases, and (h,i) an atypical form of foveal hypoplasia seen in achromatopsia. In (i), hyporeflective zone (cavitation) is also seen, indicating cone photoreceptor degeneration. Foveal hypoplasia of varying degrees is seen in all disorders. In achromatopsia, there is an atypical form of foveal hypoplasia with a shallower pit, incursion of the plexiform layers, and disruption of the inner segment/outer segment junction. INL, Inner nuclear layer; IS, inner segment; NFL, nerve fiber layer; ONL, outer nuclear layer; OS, outer segment. (B) Illustrates the principles used for structural grading of foveal hypoplasia. A schematic of the unique features of a normal fovea detectable on optical coherence tomography is shown with the typical and atypical grades of foveal hypoplasia through a series of schematics. All grades of foveal hypoplasia had incursion of inner retinal layers. Atypical foveal hypoplasia also had incursion of the inner retinal layers. Grade 1 foveal hypoplasia is associated with a shallow foveal pit, outer nuclear layer (ONL) widening, and outer segment (OS) lengthening relative to the parafoveal ONL and OS length, respectively. In grade 2 foveal hypoplasia, all features of grade 1 are present except the presence of a foveal pit. Grade 3 foveal hypoplasia consists of all features of grade 2 foveal hypoplasia except the widening of the cone outer segment. Grade 4 foveal hypoplasia represents all the features seen in grade 3, except there is no widening of the ONL at the fovea. The final image shows an atypical form of foveal hypoplasia in which there is a shallower pit with disruption of the inner segment/outer segment (IS/OS) junction, possibly a sign of photoreceptor degeneration. The atypical form of foveal hypoplasia is seen with achromatopsia, whereas grades 1–4 are seen with albinism, *PAX6* mutations, and isolated cases. ELM, External limiting membrane; GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; OPL, outer plexiform layer; RNFL, retinal nerve fiber layer; RPE, retinal pigment epithelium. *(Reproduced from Thomas MG, Kumar A, Mohammad S, et al. Structural grading of foveal hypoplasia using spectral-domain optical coherence tomography a predictor of visual acuity? Ophthalmology 2011; 118: 1653–60.)*

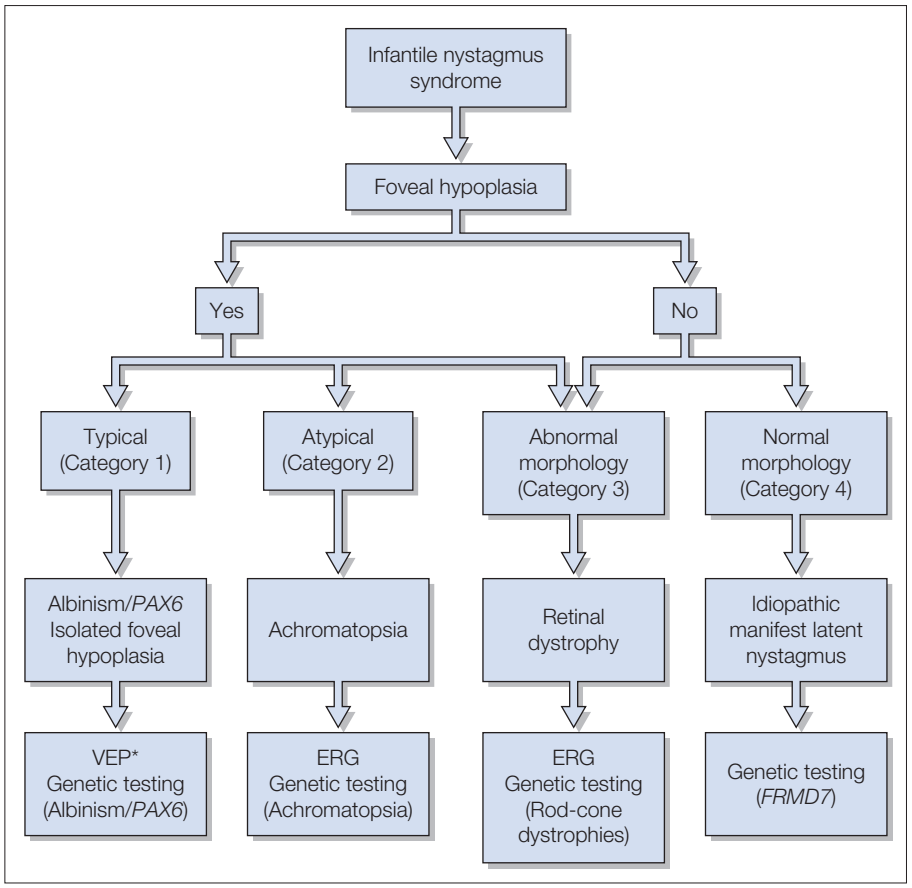


Fig. 89.8 A diagnostic algorithm for using hand-held optical coherence tomography (OCT) to diagnose the type of infantile nystagmus in infants and children. Four diagnostic categories can be ascertained on the basis of OCT findings. Depending on the presence or absence of foveal hypoplasia or the presence or absence of other abnormal macular morphology, the cause of nystagmus can be predicted and diagnostic tests can be selected to confirm the diagnosis. *In the presence of grade 1 foveal hypoplasia (see Fig. 89.7) with no evidence of crossed asymmetry, visual evoked potential (VEP) testing for mutations on the *FRMD7* gene should be considered. ERG, Electroretinogram; *FRMD7*, FERM domain containing 7 gene; *PAX6*, paired box 6 gene. *(Reproduced from Lee H, Sheth V, Bibi M, et al. Potential of handheld optical coherence tomography to determine cause of infantile nystagmus in children by using foveal morphology. Ophthalmology 2013; 120: 2714–24.)*

investigation for septo-optic dysplasia (de Morsier syndrome) and hormone deficiency is important.

Clinical characteristics of infantile nystagmus types

Idiopathic infantile nystagmus

IIN has historically been diagnosed by exclusion of other ocular or neurological pathology. Anterior segment, fundus examination, VEPs and ERGs are normal. However, retinal abnormalities may be apparent on OCT imaging such as shallow foveal pits and smaller optic discs, cups, and retinal nerve fiber layer thickness.[6] If the IIN is familiar, the most frequent inheritance mode is X-linked, where approximately 50% of female carriers are clinically affected.[14,15] Autosomal dominant inheritance has also been described. Recently the first gene (*FRMD7*) in which mutations cause X-linked IIN has been found.[14,15] Knockdown of *FRMD7* during neuronal differentiation results in altered neurite function.[26]

Patients with IIN have a median VA of 6/9.5, strabismus is uncommon (less than 10%), and good stereoacuity is often present.[13] Interestingly, patients with mutations in the *FRMD7* gene often have less abnormal head postures compared to patients with IIN without mutations in this gene.[13] Nystagmus is conjugate and usually horizontal, especially when associated with *FRMD7* mutations (see Fig. 89.4A).[13] Nystagmus waveforms in IIN have been described as having increasing velocity slow phases. However, the nystagmus is usually more complex, consisting of underlying pendular oscillations regularly interrupted by quick phases (see Fig. 89.4A). Increasing velocity slow phases are more apparent away from the null region.

Nystagmus waveforms are often of very large amplitude in the first few months of life but become smaller as children become older. Changes in waveform characteristics also occur, with more jerk waveforms becoming apparent with age.[21] Possibly these are adaptive mechanisms to allow better vision through the development of foveation periods – periods where the eyes move at a relatively slower velocity. Typically, the nystagmus has a null region where nystagmus intensity is reduced, causing an abnormal head posture if the null region is not in the primary position of gaze (see Fig. 89.4A). Over 20% of patients with idiopathic nystagmus due to mutations in *FRMD7* have PAN, but this is usually not detected clinically, only on eye movement recordings (see Fig. 89.4B).[27] Albeit rare, IIN can be vertical.

Chiasmal misrouting

Albinism has very similar nystagmus characteristics to IIN (see Fig. 89.3A,C). The diagnosis of albinism can be easily missed

and signs such as iris transillumination, hypopigmentation of the retina, optic nerve hypoplasia, and abnormal crossing on VEP need to be assessed carefully. OCT is very helpful in detecting foveal hypoplasia (see Fig. 89.7B,C). Albinism is discussed in detail in Chapter 41.

Patients with achiasmia have congenital seesaw nystagmus. The diagnosis is confirmed on MRI and VEP. Achiasma is discussed in detail in Chapter 57.

Nystagmus associated with ocular disease

Nystagmus can occur in most types of retinal dystrophy. The diagnosis of achromatopsia (Fig. 89.6) or blue cone monochromatism is likely in a patient with marked light sensitivity, poor vision, poor color discrimination in combination with a small-amplitude and high-frequency nystagmus. Inheritance is autosomal recessive in achromatopsia, and mutations in four genes have been described for which molecular genetic testing is available.[18] Patients with mutations in the same gene can have widely varying phenotypes.[18] This can range from profound visual impairment with no color vision, to incomplete achromatopsia with some color perception, and, less commonly, to oligocone trichromacy with almost normal color vision and visual acuity as good as 0.1 LogMAR.[28] Patients with achromatopsia often have fast pendular nystagmus superimposed on jerk nystagmus, and also vertical nystagmus (see Fig. 89.3A1).[29] Recently, atypical findings on OCT examination have been described in achromatopsia (see Fig. 89.7H,I).[4,7,26] The diagnosis can be confirmed by extinguished or severely reduced photopic electroretinography (see Fig. 89.6C). In blue cone monochromatism, the VA is usually better and the inheritance is X-linked.[18]

Congenital stationary night blindness (CSNB) is often associated with nystagmus that can have waveforms corresponding to infantile or manifest latent nystagmus. Patients have variable VA, reduced night vision, often high myopia, and the ERG is negative (see Fig. 89.6B). Pendular, oblique, and mostly dysconjugate nystagmus of high frequency and low amplitude and dual jerk nystagmus has been described. Inheritance is most commonly X-linked and mutations of two genes have been found to be causative.[19] Nystagmus in retinal dystrophies can occur in ciliopathies, which consists of dysfunction of the primary cilium, an organelle involved in intracellular and intercellular sensing and signaling (e.g. Alström syndrome, Bardet–Biedl syndrome, Joubert syndrome, Senior–Løken syndrome, and Leber congenital amaurosis). In retinal dystrophies, nystagmus can occasionally appear later in life as the VA deteriorates.

Nystagmus can be associated with low vision in early infancy due to numerous causes such as retinopathy of prematurity, congenital cataracts, corneal opacity, and optic nerve hypoplasia. In these patients, nystagmus can have the same characteristics as in achromatopsia or CSNB, or have characteristics of manifest latent nystagmus. Early treatment of cataract or other media opacities can prevent the development of nystagmus. Mutations in the *PAX6* gene, inherited in an autosomal dominant pattern, are associated with nystagmus that can be horizontal, vertical, or torsional (see Fig. 89.3A3).[9,20] OCT typically shows foveal hypoplasia (see Fig. 89.7D,E) but the VEP does not show misrouting of the optic nerve that is characteristic of albinism. Aniridia is common but not always present.

Nystagmus in neurological diseases or syndromes

Childhood nystagmus is a common feature of a range of syndromes, developmental and neurological disorders, for example Down syndrome, Noonan syndrome, structural malformations, space-occupying lesions, periventricular leukomalacia, cerebral palsy, leukodystrophy, Chiari malformation, metabolic disease, or mitochondrial disease.[30] Vertical, torsional, seesaw, or dysconjugate nystagmus waveforms are common in neurological disorders (see Fig. 89.3B, showing vertical nystagmus in Chiari malformation). MRI is essential if there are other neurological symptoms, developmental delay, optic atrophy, or any suspicion of atypical nystagmus.

Spasmus nutans

Spasmus nutans consists of a triad of nystagmus, head nodding, and abnormal head posture. The onset is later than in infantile nystagmus, usually developing after 6 months of age. The nystagmus is of high frequency and pendular. The nystagmus may be intermittent and dysconjugate between both eyes or sometimes clinically apparent in only one eye (see Fig. 89.3D).[31] Clinically the nystagmus usually disappears spontaneously 1–2 years after onset, although subclinical nystagmus persists on eye movement recordings. In spasmus nutans, head nodding suppresses the nystagmus since the vestibulo-ocular reflex stabilizes the eyes, which can permit development of binocular vision (see Fig. 89.3D).[31] The etiology of spasmus nutans remains unclear; however, it has been associated with a lower socioeconomic status.[32] The same nystagmus characteristics combined with head nodding and torticollis can also occur in suprasellar tumors such as chiasmal glioma.[33] If there is afferent pupillary defect or optic nerve pallor, a tumor should be suspected. Some retinal diseases such as achromatopsia and CSNB can mimic spasmus nutans.[34] The authors recommend, therefore, that ERG and/or MRI be performed in children presenting with spasmus nutans.

Manifest latent nystagmus

MLN or fusional maldevelopment nystagmus syndrome (FMNS) is part of the congenital squint syndrome. The nystagmus is typically larger upon covering one eye, the fast phase beats to the fixing or open eye, and the slow phase has decreasing velocity (see Fig. 89.4C). FMNS is discussed in Chapter 76.

Treatment

Spectacles and contact lenses

The incidence of refractive error in nystagmus is high.[35] Children with nystagmus under 6 years of age, therefore, need repeated refraction every 3–12 months to prevent amblyopia. Contact lenses can be helpful because they may give better optical correction. Contact lenses allow patients to adopt large AHPs with better optical correction, as contact lenses do not have

the problems of decentration and obstruction of the visual axis by spectacle frames (see Fig. 89.5B). Some studies have also suggested that contact lenses reduce nystagmus by providing sensory feedback through the eyelids, although recent studies suggest that improvements are not clinically significant.[36]

Surgical treatment and treatment with prisms

Patients often use compensatory strategies to reduce nystagmus. These strategies are different in individual patients. Fully understanding the compensatory mechanisms used by a patient allows formulation of a therapeutic plan. Compensatory mechanisms can often be assisted using surgery or prisms. Surgery for abnormal head postures usually yields excellent and sustained improvement.

Kestenbaum-type procedures

Patients with infantile nystagmus, especially idiopathic nystagmus and nystagmus associated with albinism, commonly have a null region, i.e. a direction of gaze in which nystagmus intensity is reduced and foveation is increased. If the null region is not in the primary position, patients often adopt an abnormal head posture using the eccentrically positioned null region for better vision (see Figs. 89.4A [null region on eye movement recordings] and 89.5A,B,F,G; Case study 1). Usually the null region is either in the primary position of gaze or along the horizontal plane. Some patients, however, despite having horizontal nystagmus, have vertical head postures or head tilts, or a combination of abnormal head postures in different planes. Patients with infantile vertical nystagmus can also show horizontal head postures. These mechanisms are not well understood.

If patients have vertical head postures, recess or resect procedures can be performed on vertical and/or oblique rectus muscles. For head tilt, rotatory Kestenbaum procedures can be performed, either by recession and resection of oblique muscles or by inducing torsion by moving the insertion of the rectus muscles.[37] If the two horizontal or vertical rectus muscles are operated on in either eye, they can be shifted up and down or left and right from the insertion to induce a rotator effect on the eye. If the patient has manifest strabismus, surgery for the abnormal head posture needs to be performed on the fixing eye. The amount of strabismus resulting from preoperative strabismus and possibly surgery for the abnormal head posture can be corrected in the non-fixing eye (Case study 2). Significant amounts of horizontal muscle recession and resection are necessary for large head turns.[38]

Surgery for abnormal head postures is usually very successful. Surgery can be performed at any age; however, it is important to wait until the cause of the head turn can be well established. If amblyogenic factors are caused by the child not being able to wear glasses due to a large abnormal head posture, surgery should be performed as early as possible. Otherwise a convenient age for surgery is around 6–8 years of age, when the child is cooperative and can be easily examined. However, the time of surgery needs to be assessed with the parents and child according to the child's symptoms. It should also be borne in mind that head turns do not often fully develop until school age, when the head posture may become more frequent and pronounced with increasing school work. Kestenbaum-type procedures are effective even in adults. It is preferable to record eye movements before and after surgery to better understand mechanisms.

Artificial divergence

Convergence reduces the intensity of infantile nystagmus in many individuals. In these patients, artificial divergence can be induced to increase convergence and to trigger a convergence impulse, even at distance. Good binocular vision is essential for the effectiveness of artificial divergence. Without binocular vision, surgery or prisms would simply change the angle of squint without inducing convergence. Fusion range and the optimal strength of base-out prisms to reduce the nystagmus should be tested. It is often best to wear Fresnel prisms for at least 1 or 2 weeks during normal activities and to adjust the amount of prisms, if needed, before making a surgical decision. If prisms are small, then they can also be incorporated into glasses.

Nystagmus blockage syndrome

Some patients with manifest latent or infantile nystagmus can dampen nystagmus by over-convergence (Fig. 89.9). Bilateral medial rectus recession can help to permanently dampen the nystagmus (Case study 3).[39] This forces the patient to maintain convergence in order to keep the eyes straight and in doing so improves the visual acuity.

Adduction

Adduction dampens manifest latent nystagmus. If, for example, the left eye is dominant, the patient will fix in adduction with the left eye and turn the head to the left (see Fig. 89.5C). If strabismus surgery is performed, the dominant fixing eye should be operated on to correct the abnormal head turn simultaneously. If a patient with manifest latent nystagmus has an alternating strabismus, the head turn can change in the

Case study 1

A 4-year-old girl with idiopathic infantile nystagmus needed spectacle correction of 4 diopters astigmatism in each eye. Since she had a large head turn to the left she could not wear her glasses because the frame obstructed the view. She had 12-mm recession of the right lateral rectus muscles and left medial rectus muscle and 12-mm resection of the right medial rectus muscle and left lateral rectus muscle. After surgery, her head was straight. Because she could now wear her glasses, her binocular visual acuity increased from 0.6 to 0.2 LogMAR (see Fig. 89.5F). The head position remained straight at follow-up 8 years later.

Case study 2

A 9-year-old boy came to clinic because of nystagmus and a pronounced head tilt increasing on visual effort. He also had "V" pattern esotropia and bilateral inferior oblique overaction. Surgery consisted of moving the right lateral rectus and left medial rectus muscle one tendon-width down and the right medial rectus and left lateral rectus muscle one tendon-width up. In addition, recession of the left medial rectus for esotropia and bilateral inferior oblique recession to correct overaction and "V" pattern was performed. After surgery the head tilt was significantly reduced (see Fig. 89.5G).

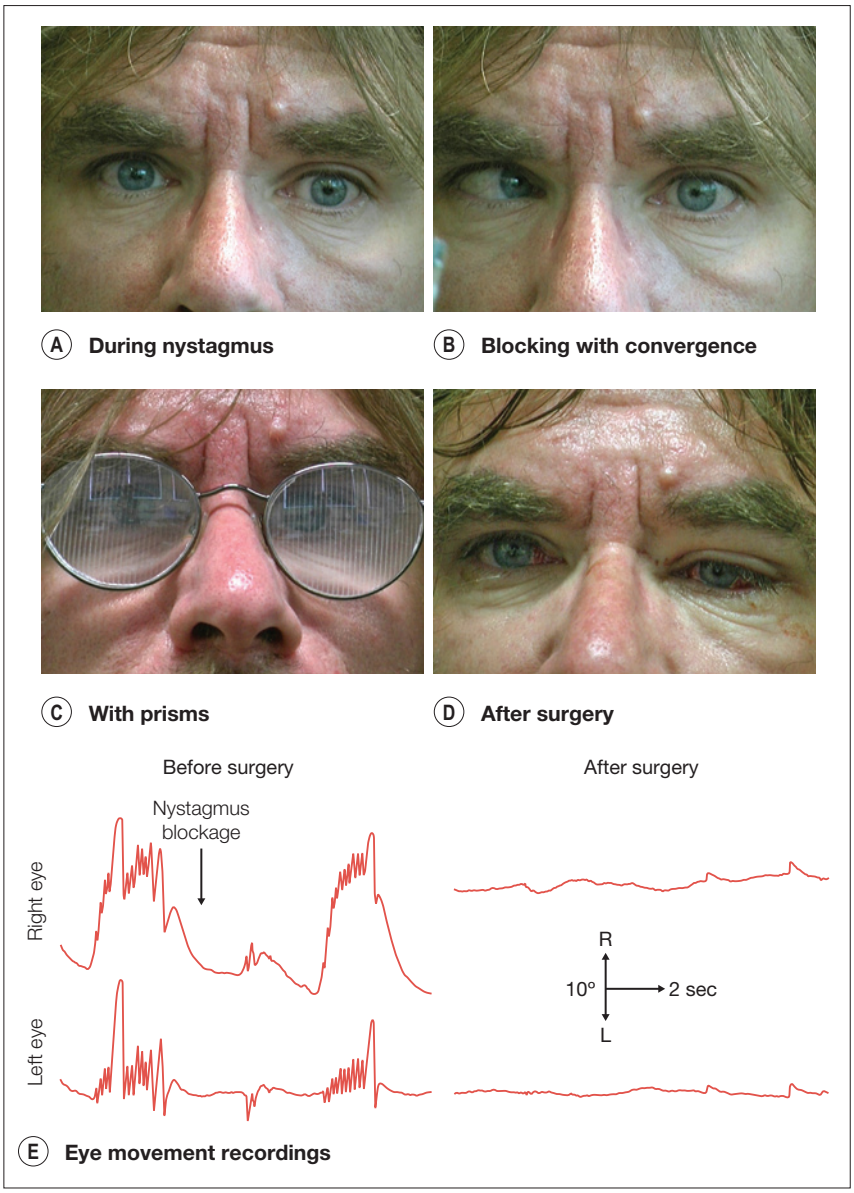


Fig. 89.9 Nystagmus blockage syndrome (see Case study 3).

direction of the fixing eye and this can give the false appearance of PAN (Case study 4) where more than one head posture can be adopted (see Fig. 89.5D). If a patient with manifest latent nystagmus fixes with one eye at near and the other at distance, the head turn may change accordingly.

Reduction of strabismus

Reduction of strabismus and improvement of binocular vision in manifest latent nystagmus can reduce nystagmus intensity.[40] Thus, patients with "A" and "V" pattern strabismus may adopt a chin-up or chin-down head position in order to reduce the angle of strabismus and improve the nystagmus (see Fig. 89.5E). In patients with manifest latent nystagmus, strabismus surgery, ideally with the objective of achieving a degree of binocular vision with microstrabismus, can substantially improve nystagmus (Case study 5).

Periodic alternating nystagmus

If the quiet phase of PAN is not static, then the head posture can slowly oscillate from left to right. It is very important to recognize if a patient has PAN before surgery is performed, as Kestenbaum procedures may increase the head turn to one side in PAN. About 23% of patients with IIN associated with mutations in *FRMD7* and 29% of patients with albinism have PAN.[12,27] Ideally patients should have eye movement recordings over a period of at least 8 minutes as the cycle of PAN in infantile nystagmus has been found to be between 90 and 280 seconds (see Fig. 89.4B).[27] However, many patients with PAN do not have alternating head position, probably because their null region is not moving. In PAN, one can recess all four horizontal muscles to improve head position.

Tenotomy of four rectus muscles

This procedure consists of detaching and re-attaching the rectus muscles at their insertion. It has been reported that tenotomy reduces nystagmus and broadens the null region due to changes in proprioceptive feedback from the eye muscles.[41] The procedure can be performed on horizontal or vertical muscles and be combined with correction of strabismus. More results and corroboration between several research groups need to be obtained before drawing firm conclusions over the value of tenotomies.

Pharmacological treatment

Baclofen, gabapentin, cannabis, memantine, aminopyridines, and several other drugs were primarily used in acquired nystagmus.[42] Baclofen was also found to be effective in infantile PAN.[43] Recently, gabapentin and memantine have been found to be effective in a double-masked randomized controlled study including patients with infantile nystagmus.[44] Gabapentin (up to 2400 mg) and memantine (up to 40 mg) were used in slowly increasing dosages. Although the medications are effective in IIN, it is not clear which patients respond best to which type of treatment. Larger trials are now underway.

Other treatments

Botulinum toxin has been reported to reduce infantile nystagmus.[45] However, injections need to be repeated and can induce strabismus and ptosis. Other methods such as auditory feedback have been shown to be ineffective or impractical in infantile nystagmus.

Acknowledgement

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Case study 3

A patient with nystagmus from birth complained about constant "unquiet eyes" and needing to make an effort to turn in one eye in order to have better vision. On examination, he had nystagmus and intermittent large-angle esotropia. Eye movement recordings showed jerk nystagmus with waveforms showing IIN and manifest latent nystagmus reducing on convergence. Bilateral medial rectus recessions of 5 mm reduced the nystagmus and esotropia. Visual acuity with both eyes open improved from 6/12 to 6/9 (Fig. 89.9).

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Case study 4

A 5-year-old boy attended clinic complaining of an alternating head turn and exotropia. He had manifest latent nystagmus confirmed on eye movement recordings, bilateral inferior oblique overaction and a large exotropia. To correct the head turn large bilateral medial rectus recessions of 10 mm were performed to limit adduction. However, since medial rectus recession would increase the exotropia, simultaneously bilateral lateral rectus recessions of 16 mm were performed. Postoperatively the head turn disappeared but a remaining moderate exotropia was present. Seven years after surgery, however, the exotropia and the nystagmus were reduced (see Fig. 89.5D).

Case study 5

A patient reported having nystagmus since birth but his vision had deteriorated over the last year. On examination, he had manifest latent nystagmus and exotropia without any binocular function. Pictures from several years ago showed that the patient previously had a small esotropia. Base in prisms were fitted to restore the esotropic microstrabismus. The patient had subnormal binocular vision (Titmus fly positive) and reduced nystagmus. Binocular visual acuity increased by 2 LogMAR lines.

Bonus e-book content online

Fig. 89.4 Change in nystagmus with (A) gaze, (B) time, and (C) occlusion. (A) Shows an example of the null region in a patient with idiopathic infantile nystagmus using original eye movements from a patient. The patient follows a target moving from the left to right in steps of 3° every 8 seconds (lower traces). The horizontal nystagmus changes both in waveform (A1) and intensity (A2) as the direction of gaze changes. The changing waveforms can be seen from the expanded views in the upper traces. At the null region, which is 9° to the right of central fixation, the nystagmus waveform is predominantly pendular, with occasional foveating saccades. Jerk waveforms are present to the left and right of the null region, with the nystagmus beating to the left in left gaze and right in right gaze. A plot of the nystagmus intensity in relation to the horizontal

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gaze angle is shown in A2. (B) Shows a patient with idiopathic infantile nystagmus and periodic alternating nystagmus as an example of a nystagmus waveform changing with time. The nystagmus completes a full cycle of left beating and right beating nystagmus every 200 seconds, with short quiet phases of several seconds between each change in beating direction. Expanded views are shown in the lower traces. (C) Shows a patient with manifest latent nystagmus illustrating the change in beating direction on covering either eye. The eyes always beat towards the open or fixing eye. The waveforms all show decreasing velocity slow phases. Note the step change in eye position on covering either eye, which is due to a large esotropia. The left eye is the dominant eye. The nystagmus is less intense when both eyes are open.

Fig. 89.9 Nystagmus blockage syndrome (see Case study 3).

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Supranuclear eye movement disorders, acquired and neurologic nystagmus

Richard W Hertle and Nancy N Hanna

Chapter contents

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See online for supporting video for this chapter.

Introduction

Abnormal eye movements in the infant or young child can be congenital or acquired, associated with abnormal early visual development, or a sign of underlying neurologic or neuromuscular disease or orbital disease. Abnormal eye movements in an apparently well child should never be labeled as congenital or benign without careful investigation, including medical history, clinical examination, neuroimaging, laboratory testing, and electrophysiologic investigation of the visual sensory system. Ocular motility analysis can indicate the type of eye movement disturbance and whether this is associated with an underlying ocular or neurologic condition.

Anatomy and physiology (Table 90.1)

Neural integrator

The neural integrator is an engineering term applied to an ocular motor "function" carried out by groups of cells in the cerebellum (flocculus and paraflocculus) and the prepositus hypoglossus and medial vestibular nucleus (MVN).[1] The neural integrator is needed for all conjugate eye movements. To move the eyes at a constant speed or hold them in an eccentric gaze position, two neural signals must overcome the elastic tendency of the eyes to go back to their "resting" position. These signals are the desired speed (phasic component) and a tonic component that counterbalances the elastic restoring forces. A changing tonic component can be precisely generated by a premotor neural signal that mathematically computes the "integration" of the velocity signal, thus the term "neural integrator." The role of the neural integrator in generation of saccades and maintenance of eccentric gaze positions occurs after inhibitory burst neurons (IBNs) are inhibited and excitatory burst neurons (EBNs) fire rapidly, yielding an intense phasic signal that is transmitted to the appropriate yoked pair of extraocular muscles via the appropriate cranial nerves. The "burst" signal is also transmitted to the neural integrator, which "integrates" that burst signal (counts the number of discharge spikes) and generates a neural signal (again transmitted via the cranial nerves) appropriate to hold the eye steady at the new position (tonic discharge).

The neural integrator is not perfect and the "tonic" signal slowly decays or "leaks" over time. This decay is normally not seen in lighted conditions because visual feedback, with the use of the smooth-pursuit (SP)/fixation system, aids in holding the eye steady.[2] At birth, the neural integrator is leaky, but by about 1 month of age it functions well.[3]

Saccadic system

A saccade is a rapid eye movement, which may occur volitionally (voluntary saccade), reflexively, or as part of the fast phases of nystagmus, which serves to purposefully redirect the fovea to a specific target. Voluntary saccades may be predictive command generated (i.e. look right), memory guided, and antisaccades. Involuntary saccades include the fast phase of nystagmus, spontaneous saccades, and reflexive saccades. The pathway of saccades proceeds through the anterior limb of the internal capsule and then through the diencephalon. It then divides into dorsal and ventral pathways, the dorsal limb going to the superior colliculi and the ventral limb (which contains the ocular motor pathways for horizontal and vertical eye movements) to the pons and midbrain. The superior colliculus acts as an important relay for some of these projections.[4] In the brainstem, the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) and pontine paramedian reticular formation (PPRF) provide the saccadic velocity commands, by generating the "pulse of innervation" immediately before the eye movement, to cranial nerves III, IV, and VI. Horizontal saccades are generated by EBNs in the PPRF, which are found just ventral and lateral to the MLF in the pons, and by IBNs in the nucleus paragigantocellularis dorsalis, caudal to the abducens nucleus in the dorsomedial portion of the rostral medulla (Fig. 90.1). Vertical and torsional components of saccades are generated by EBNs and IBNs in the riMLF, located in the midbrain[4] (Fig. 90.2).

Table 90.1 Types of eye movements

Type of eye movement	Function	Stimulus	Clinical tests
Vestibular	Maintain steady fixation during head rotation	Head rotation	Fixate on object while moving head; calorics
Saccades	Rapid re-fixation to eccentric stimuli	Eccentric retinal image	Voluntary movement between two objects; fast phases of OKN or of vestibular nystagmus
Smooth pursuit	Keep moving object on fovea	Retinal image slip	Voluntarily follow a moving target; OKN slow phases
Vergence	Disconjugate, slow movement to maintain binocular vision	Binasal or bitemporal disparity; retinal blur motion	Fusional amplitudes; near point of convergence

OKN, Optokinetic nystagmus.

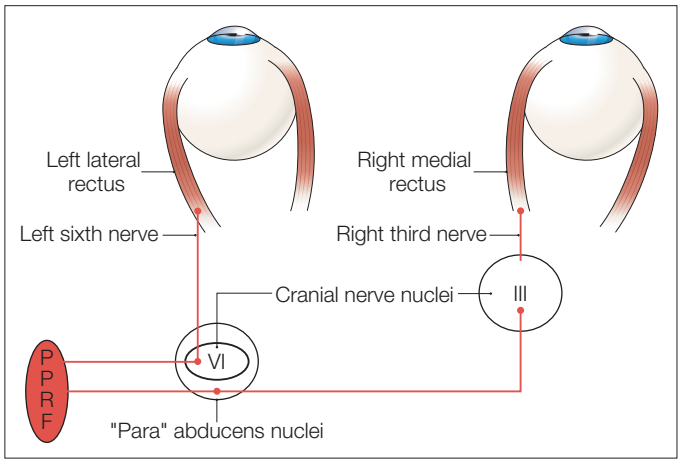


Fig. 90.1 Schematic of brainstem pathways coordinating horizontal saccades. The pontine paramedian reticular formation (PPRF), after receiving input from the ipsilateral cortical centers and superior colliculus, stimulates two sets of neurons in the abducens nucleus: (1) those that send axons to innervate the ipsilateral lateral rectus, and (2) those whose axons join the medial longitudinal fasciculus (MLF) and subsequently activate the medial rectus subnuclei of the contralateral third nerve. III, Third cranial nerve nuclei; VI, sixth cranial nerve nuclei.

Following a saccade, a "step of innervation" occurs, during which a higher level of tonic innervation to ocular motor neurons keeps the eye in its new position against orbital elastic forces that would restore the eye to an anatomically "neutral" position in the orbit. For horizontal saccades, the step of innervation comes from the neural integrator (NI), most importantly from the nucleus prepositus–MVN complex. The eye is held steady at the end of vertical and torsional saccades by the step of innervation provided from the interstitial nucleus of Cajal in the midbrain.[4,5] Other burst neurons termed long-lead

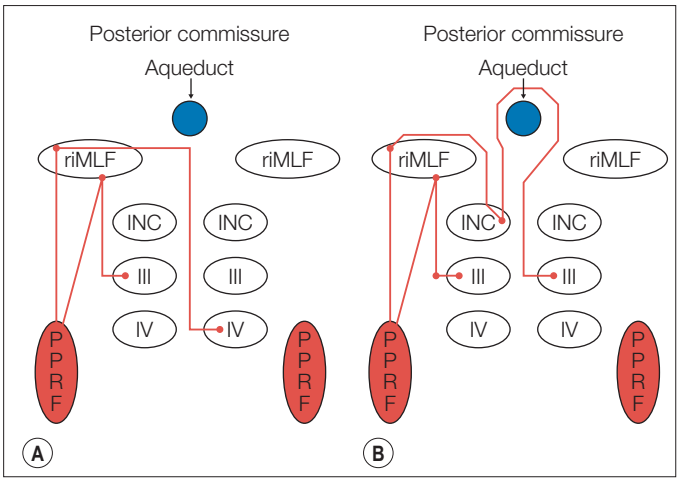


Fig. 90.2 Schematics of brainstem pathways coordinating downward (A) and upward (B) saccades. (A) The pontine paramedian reticular formation (PPRF) activates neurons in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) that send fibers caudally to synapse upon the inferior rectus subnucleus of the ipsilateral third nerve and the contralateral superior oblique nucleus. Not shown in this diagram, fibers from the contralateral PPRF carry corresponding signals simultaneously. (B) The PPRF activates neurons in the riMLF that send fibers through the posterior commissure to the superior rectus subnucleus of the contralateral third nerve and fibers to the inferior oblique subnucleus of the ipsilateral third nerve. Not shown in this diagram, fibers from the contralateral PPRF carry corresponding signals simultaneously. III, Third cranial nerve nucleus; IV, fourth cranial nerve nucleus; INC, interstitial nucleus of Cajal.

burst neurons (LLBNs) discharge 40 ms prior to saccades, whereas excitatory burst neurons (EBNs) discharge 12 ms prior to saccades. Some LLBNs lie in the midbrain, receiving projections from the superior colliculus and projecting to the pontine EBNs, medullary intermediate burst neurons (IBNs), and OPNs. Other LLBNs lie in the nucleus reticularis tegmenti pontis (NRTP), projecting mainly to the cerebellum but also to the paramedian pontine reticular formation (PPRF). It appears that LLBNs receiving input from the superior colliculus may play a crucial role in transforming spatially coded to temporally coded commands, whereas other LLBNs may synchronize the onset and end of saccades.[4,5]

The saccadic system is not fully developed until about 1 year of age; infants make multiple hypometric saccades to reach the target.[6] If the head is held still, this hypometria can be seen clinically in infants less than 3 months of age, especially for large saccades. There is a progression toward "normometria" during the first 7 months of life.[7] In healthy adults and children older than 1 year, saccades are typically hypometric, reaching about 90% to 100% of the target distance, followed by secondary saccades – normometria. In optokinetic nystagmus (OKN) and vertical nystagmus, quick phases occur less frequently in children than in adults.

Smooth pursuit system

The function of SP is to hold fixation on a moving target, and both eye and head movements are required. This requires a prediction to overcome the time delays of the visuomotor system and the ability to suppress the vestibulo-ocular reflex (VOR).[8] VOR suppression is required because, when the head moves, there is a reflexive VOR that moves the eyes equally in the opposite direction. SP and VOR suppression are probably

the same ocular motor functions. The frontal and extrastriate visual cortexes transmit information about the motion of both the target and the eyes to the dorsolateral pontine nuclei, thence to the paraflocculus, flocculus, and dorsal vermis, and then via the vestibular and fastigial nuclei to the ocular motor nerve nuclei III, IV, and VI. Unilateral lesions in the cortex and cerebellum affect ipsilateral SP. Brainstem lesions are less well defined clinically.[1]

SP is present in the first week of life but is immature in the young infant. Horizontal gaze probably develops before vertical gaze.[9] SP gain increases with age, and at 5 months the SP is more apparent. It is not known at what point in time pursuit matures to the adult form. It does not appear to happen before 6 months of age, and may not be until late adolescence.[10]

Vestibulo-ocular response system

The vestibular apparatus drives reflex eye movements to keep images steady on the retinas as we move our heads. The eyes move in the opposite direction to the head so that they remain in a steady position in space. The three-neuron arc – vestibular ganglion, vestibular nuclei, and ocular motor nuclei – are the principal connections. The direct neuronal pathways include both excitatory and inhibitory contributions. Each semicircular canal influences a pair of extraocular muscles that move the eyes in the plane of that canal (Table 90.2). The anatomy of the vestibular nuclei has been well characterized[11]; they receive projections from the 14,000 to 18,000 axons of the vestibular nerve.[11]

There are four major vestibular nuclei and accessory subgroups, including the interstitial nucleus, with its cells distributed among the vestibular rootlets as they enter the brainstem, and the y-group, near the superior cerebellar peduncle. The MVN has the greatest volume and is the longest vestibular nucleus. The lateral vestibular nucleus (LVN) also has projections to the spinal cord, mainly via the ipsilateral lateral vestibulospinal tract but also through the contralateral medial vestibulospinal tract. In its most rostral aspect, the dorsal vestibular nucleus (DVN) also projects to the ocular motor nuclei.

The primary vestibular afferents enter the medulla at the level of the LVN. Almost all bifurcate, giving a descending branch to terminate in the MVN and DVN and an ascending branch to the superior vestibular nucleus (SVN), with a final destination in the cerebellum, especially the anterior vermis and the nodulus and uvula. All canals and otoliths project to the borders of ventromedial LVN, medial MVN, and dorsomedial DVN. All canals also converge on a small patch in the ventromedial SVN. Utricular afferents project to the rostral MVN and saccular afferents project to the y-group. For both the horizontal and vertical VOR, many neurons in the vestibular nuclei that receive inputs from primary vestibular afferents encode head velocity, eye position, and varying amounts of SP and saccadic signals. Vestibular nuclei neurons do not project just to motor neurons; they also send collaterals to the nucleus prepositus hypoglossi, the nucleus of Roller, and the cell groups of the paramedian tracts.[11]

When testing the VOR in the infant, it is not unusual to find a slightly high VOR gain, which gradually decreases during preschool years, and a short VOR time constant.[12] In the premature infant and in some healthy full-term infants, rotation induces a tonic deviation or "locking up." The eyes deviate in the direction opposite to rotation when the doll's head maneuver or the Barany chair rotation test is used. They deviate in the same direction as the rotation when the infant is rotated at arm's length. A "corrective" fast phase develops at approximately 45 weeks postconceptual age.[6] This lock up may be prolonged in the infant with delayed visual maturation. Usually there are no more than a couple of beats of postrotational nystagmus when the child stops spinning; if there are more than a few beats of nystagmus, a severe visual deficit or abnormality of the SP pathway should be suspected.[13] This test can be influenced by behavioral state and wakefulness.

Vergence system

Vergences are eye movements that turn the eyes in opposite directions so that images of objects will fall on corresponding retinal points. In other words, it is the ability to change the angle between the two visual axes to permit near (convergence), far (divergence), and torsional (cyclovergence) foveation, for binocular vision. Three major stimuli are known to elicit vergences: (1) retinal disparity that leads to fusional vergences; (2) retinal blur that evokes accommodative

Table 90.2 Effect of stimulating a single semicircular canal

Canal	Head movement	Eye movement in		Agonist		Antagonist	
		R gaze	L gaze	R	L	R	L
R Post	R and up	L Tors	Down	SO	IR	IO	SR
R Ant	R and down	Up	L Tors	SR	IO	IR	SO
R Lat	R	L	L	MR	LR	LR	MR
L Post	L and up	Down	R Tors	IR	SO	SR	IO
L Ant	L and down	L Tors	Up	IO	SR	SO	IR
L Lat	L	R	R	LR	MR	MR	LR

Ant, Anterior; IO, inferior oblique; IR, inferior rectus; L, left; Lat, lateral (horizontal canal); LR, lateral rectus; MR, medial rectus; Post, posterior; R, right; SO, superior oblique; SR, superior rectus; Tors, torsional (cyclotorsion with upper poles of eyes moving to subject's right/left).
Data from Leigh RJ, Zee DS. The Neurology of Eye Movements, 4th ed. New York, NY: Oxford University Press, 2006.

vergences; and (3) motion induces both disparity and accommodative vergence. The neural substrate for vergence lies in the mesencephalic reticular formation, dorsolateral to the oculomotor nucleus where neurons discharge in relation to vergence angle (vergence tonic cells), velocity (vergence burst cells), or both angle and velocity (vergence burst–tonic cells). Although most of these neurons also discharge with accommodation, some remain predominantly related to vergence.[2,14] Like versional movements, a velocity-to-position integration of vergence signals is necessary: the NRTP is important in this integration. The cells in the NRTP that mediate the near response are separate from cells that mediate the far response. Lesions of the NRTP cause inability to hold a steady vergence angle. The NRTP has reciprocal connection with the cerebellum (nucleus interpositus) and receives descending projections from several cortical and subcortical structures.[2,14]

The eyes of neonates, particularly if premature, often appear divergent, and there is little voluntary convergence until 2–3 months. By 3 to 6 months of age, 75% of premature and 97% of full-term infants have no deviation.[9] Fusion is not completely established until 6 months. Accommodation-driven vergence can be detected at 2 months of age and disparity-driven vergence at about 4 months, which is when stereopsis and fusion develop.

Optokinetic system

The optokinetic system is responsible for conjugate slow following of the eyes to movement of large areas of the visual field. Optokinetic nystagmus (OKN) is a reflex conjugate physiologic nystagmus in which a slow-phase pursuit response to movement of the visual surround (optokinesis) is followed by a corrective saccade or quick phase. OKN is elicited naturally during head and eye movements, or unnaturally by looking out of the window of a moving vehicle. Together with the vestibular system, the optokinetic system holds images steadily on the retina during sustained motion of the head or world or both. The neural substrate for optokinesis includes the nucleus of the optic tract and accessory optic pathways. Optokinesis can be elicited by either full-field (natural head or eye movements) or small-field (foveal) motion (a moving drum or tape). Both SP and optokinetic systems contribute to the stabilization of images of stationary objects during head rotations. In primates, OKN has two components, each of which has a separate but parallel neural pathway.[11] Delayed (indirect, slow) OKN (OKNd) has a slow buildup (tens of seconds) and gives rise to optokinetic after-nystagmus (OKAN), which is a gradual decay of the nystagmus after the lights have been extinguished. OKNd is closely related to VOR and is driven by visual motion signals in the visual cortex via the nucleus of the optic tract in the pretectum and the vestibular nuclei.[15] Early (direct, fast) OKN (OKNe) has a rapid buildup (<1 s) and does not give rise to OKAN; it ceases promptly in the dark. The OKNe pathway is similar to the SP pathway, which is mediated by a corticopontocerebellar route, and it is doubtful that the pretectum has a direct role in OKNe/SP, although it may be involved in its adaptive control.[15]

Finally, the cerebellum plays an important role in eye movements. Together with several brainstem structures, including the nucleus prepositus and the medial vestibular MVN, it appears to convert velocity signals to position signals for all conjugate eye movements through mathematical integration. Figure 90.3 shows the anatomical areas of the brain responsible for the " localizing " forms of acquired nystagmus.

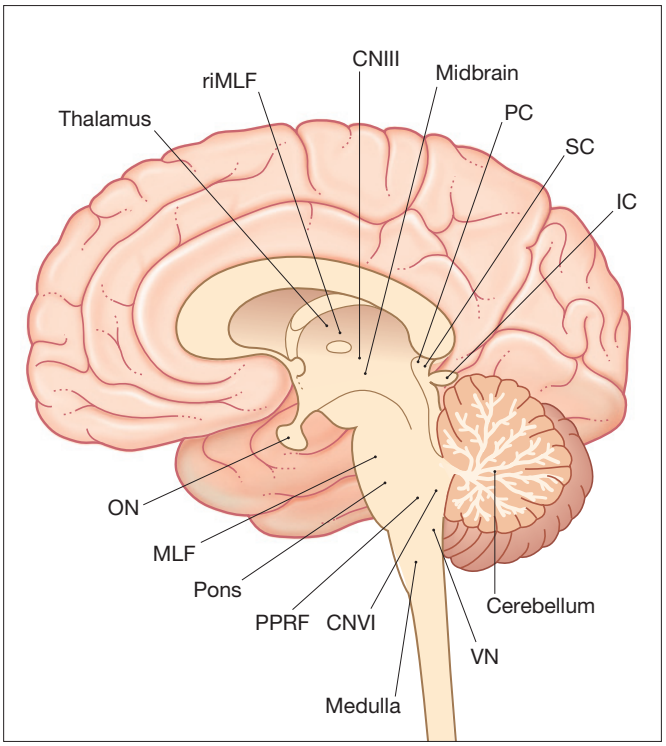


Fig. 90.3 Midline sagittal section of a human brain. Sites within the brain responsible for the "localizing" forms of acquired nystagmus. CNIII, Third cranial nerve nuclei; CNVI, sixth cranial nerve nuclei; IC, inferior colliculus; MLF, medial longitudinal fasciculus; ON, optic nerve; PC, posterior commissure; PPRF, pontine paramedian reticular formation; riMLF, rostral interstitial nucleus of the medial longitudinal fasciculus; SC, superior colliculus; VN, vestibular nucleus.

Clinical assessment

General patient investigations

The workup of supranuclear eye movement disorders and nystagmus is directed toward identifying associated ophthalmic and neurologic features with which, if found, the etiology is usually apparent by history, examination, or neuroimaging.

General examination

The history and physical examination determines whether the nystagmus has been present from early or acquired later. A family history of neonatal eye disease, the pregnancy, labor, delivery, and growth and development since birth should be sought. Neonatal forms are generally benign, while acquired forms require further investigation. Since anxiety can affect nystagmus, the eye movements should be observed at a comfortable distance, in a non-threatening manner, while talking to the child or the parent. The most important features of nystagmus can usually be ascertained while "playing" with the child. Head turns or tilts while the child is viewing distant or near objects should be noted. An adequate fundus examination is a necessary part of the evaluation of eye movement

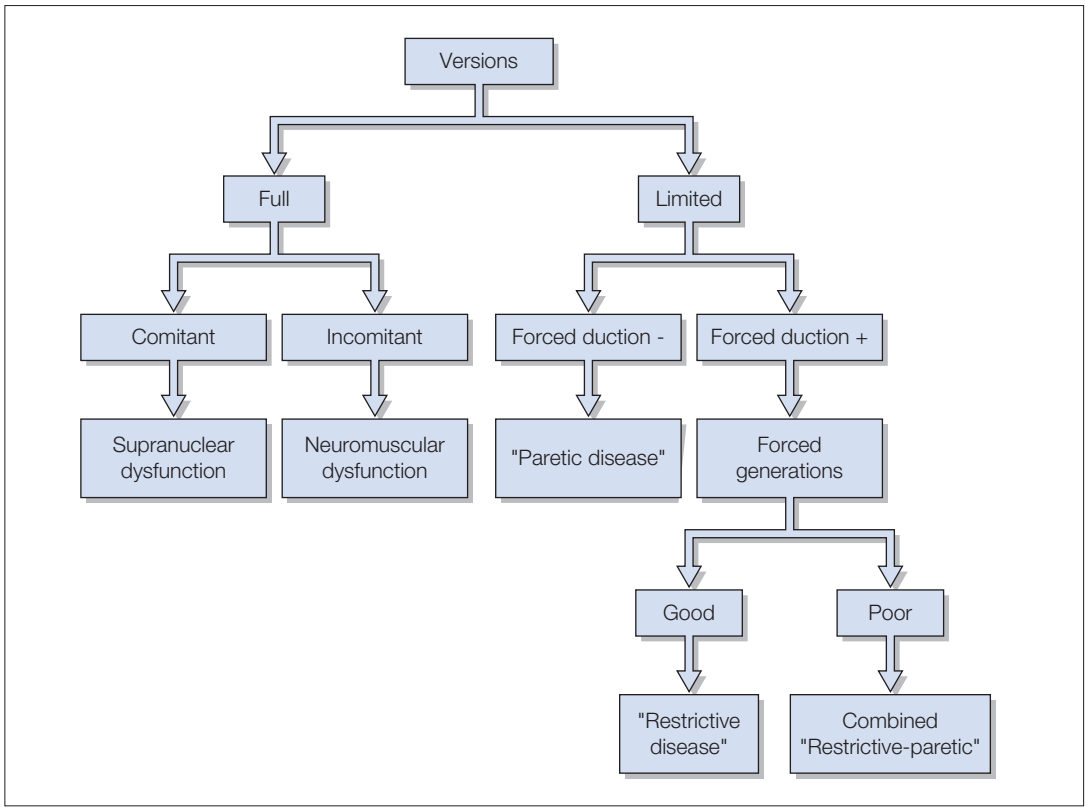


Fig. 90.4 Clinical evaluation of range of eye movements. Versions and cover test measurements allow the examiner to decide whether the eye movements are normal (no limitation) or limited. Forced duction testing is used to differentiate a restriction (positive resistance to movement of the globe) from a "paresis" (no resistance to movement of the globe).

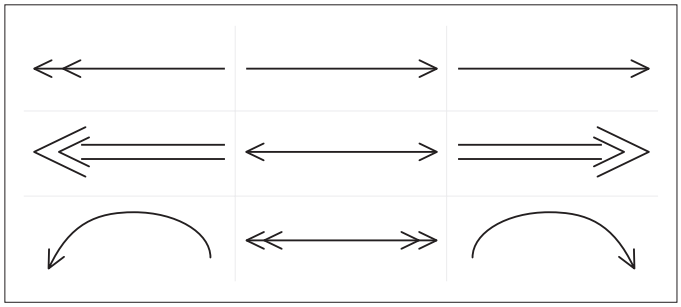


Fig. 90.5 Diagram of nystagmus in nine positions of gaze. Arrowheads indicate direction of jerk fast phase if on one end, pendular nystagmus if on both ends, and increasing frequency with more arrowheads. Additional lines indicate increased nystagmus amplitude. The curved lines indicate torsional nystagmus.

disorders and involuntary ocular oscillations in infants and children (Figs 90.4 and 90.5).

Vision testing

Subjective accuracy of vision testing depends on the patient's age and their neurologic status. The "binocular acuity" should be tested first. The patient must be allowed to assume any anomalous head posture (AHP). During the examination of visual acuity in nystagmus patients with an AHP, the direction of the posture must be observed over a 5- to 7-minute period. Up to 17% of patients with infantile nystagmus and some forms of acquired nystagmus have a periodicity to the direction of their fast phase with a changing head posture.

Binocular acuity is the "person's" acuity and monocular acuity is the "eye's" acuity; they are often very different in patients with nystagmus. In a non-verbal child or adult, various tests can be used to help determine both binocular and monocular acuity. These include fixation behavior, the 10-prism diopter base-down test, Teller acuity cards, and matching of single, surrounded, HOTV optotypes or Lea symbols. Simple testing of binocular function is always attempted as the results are important if convergence is to be stimulated or fusion is to be aided by refractive therapy, e.g. Worth four-dot and near stereopsis.

Refraction

In older children, a subjective refraction is the foundation for any type of refractive therapy. All refractionists develop their own idiosyncrasies that assist them with rapid and accurate refraction. Try to ignore the oscillation and start with distance retinoscopy in a phoropter for patients without an AHP or trial frame (for those with a significant AHP). The next step is to do binocular refraction: this is the most important step in these patients because some patients have significant changes in their nystagmus under monocular conditions. The best way to do this is to fog the eye not being refracted with enough plus to decrease the vision by 1–3 lines.

It is important in infants and young children to perform an objective refraction procedure; a cycloplegic refraction provides additional and important data for treatment decisions. In those patients in whom there is a different refraction under cycloplegia, record both subjective and objective refraction for decision-making regarding spectacle prescription.

Ocular motility evaluation

Clinical evaluation of the ocular oscillation includes fast phase direction, movement intensity, conjugacy, gaze effects, convergence effects, and effect of monocular cover. The amplitude, frequency, and direction of the nystagmus in all directions of gaze can be documented with a simple diagram (see Fig. 90.5). The clinician can also observe the nystagmus while moving the patient's head. Associated motility systems (e.g. strabismus, pursuit, saccades, and VOR) can be clinically evaluated and recorded. Changes in the nystagmus with convergence or monocular viewing should be noted. If the nystagmus increases beneath closed eyelids, vestibular or brainstem pathology should be suspected since visual fixation may suppress nystagmus from lesions in these regions. Conjugacy of eye movements should be observed.

Ocular motility recordings

Eye movement recordings provide a basis for eye movement abnormality classification, etiology, and treatment, and have impacted on eye movement systems research (Figs 90.6 and 90.7). There are four commonly used methods:

- electro-oculography;
- infrared reflectance oculography;
- scleral contact lens/magnetic search coils: this is the most sensitive technique and is minimally invasive, but its use in children between 6 months and about 10 years is difficult (see Figs 90.6 and 90.7);
- video oculography.

Practical applications of eye movement recording technology in clinical medicine include diagnosis/differentiation of eye movement disorders and utility as an "outcome measure" in clinical research.[16,17] Eye movement recordings display the data during continuous periods of time. Position and velocity traces are clearly marked, with up being rightward or upward eye movements and down being leftward or downward eye movements. The basic types of nystagmus patterns observed after eye movement recordings are shown in Figure 90.8.

Specific system evaluation

Neural integrator

To test the neural integrator clinically, observe primary position fixation, fixation in eccentric gaze, saccades, pursuit, and OKN, and also test for rebound nystagmus and VOR cancellation. To examine for rebound nystagmus, first ask the patient to fixate on a target from the primary position, then to re-fixate on an eccentric target for 30 seconds, and then return to the primary position target. A patient with rebound nystagmus shows transient nystagmus with the slow phases toward the previous gaze position. To evaluate a child's VOR cancellation, it is easiest to place your hand on top of the patient's head to control both the head and a fixation target that will extend in front of the child's visual axis. If the child is unable to cancel the VOR, you will observe nystagmus instead of the steady fixation expected in normal subjects.

"Gaze-evoked" nystagmus is a sign of a leaky neural integrator and occurs with attempts to maintain eccentric gaze.

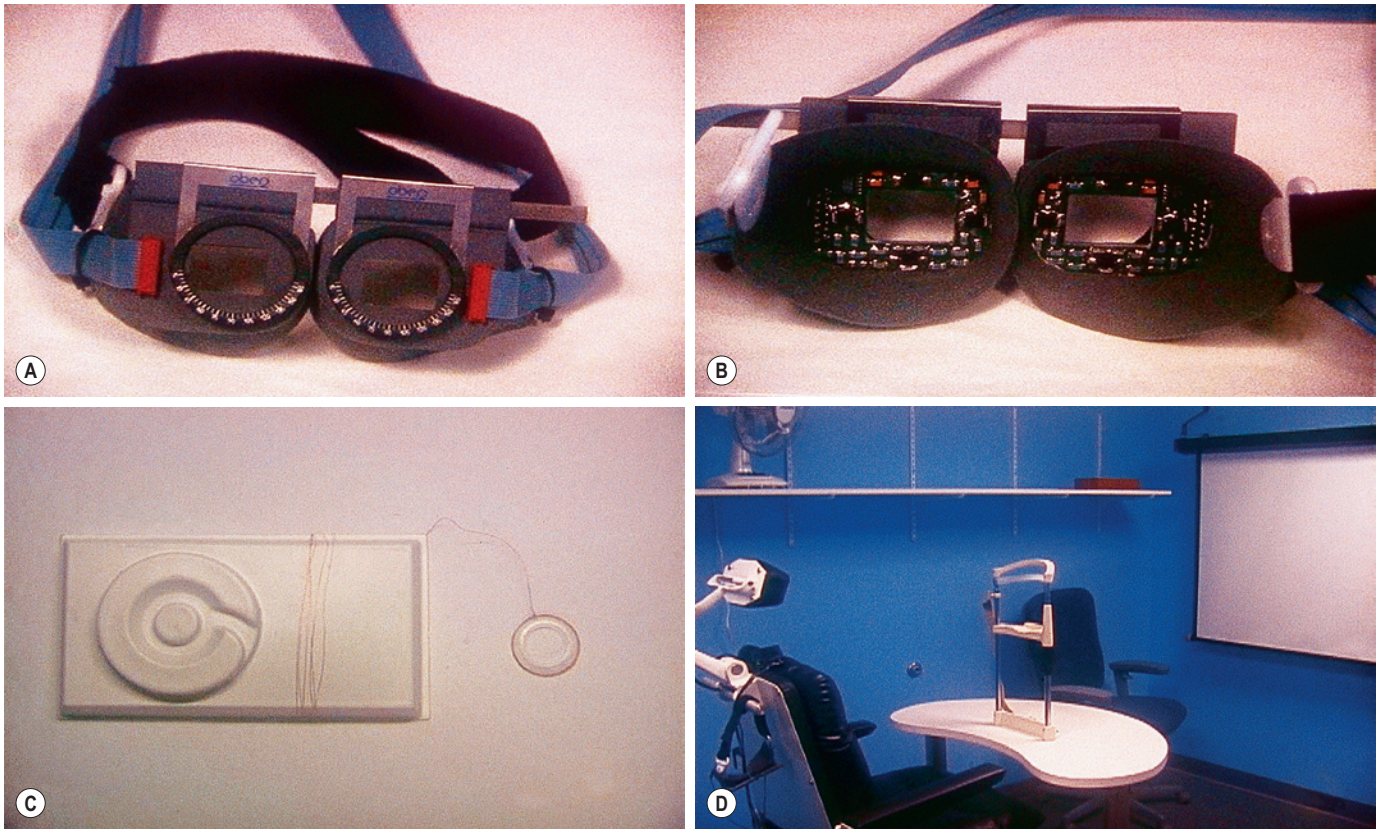


Fig. 90.6 Ocular motility recording equipment. Ocular motor laboratory showing infrared reflectance goggles – front (A), back (B); silicone contact lens (C); flexible exam chair, chin rest, and stimulus screen (D).

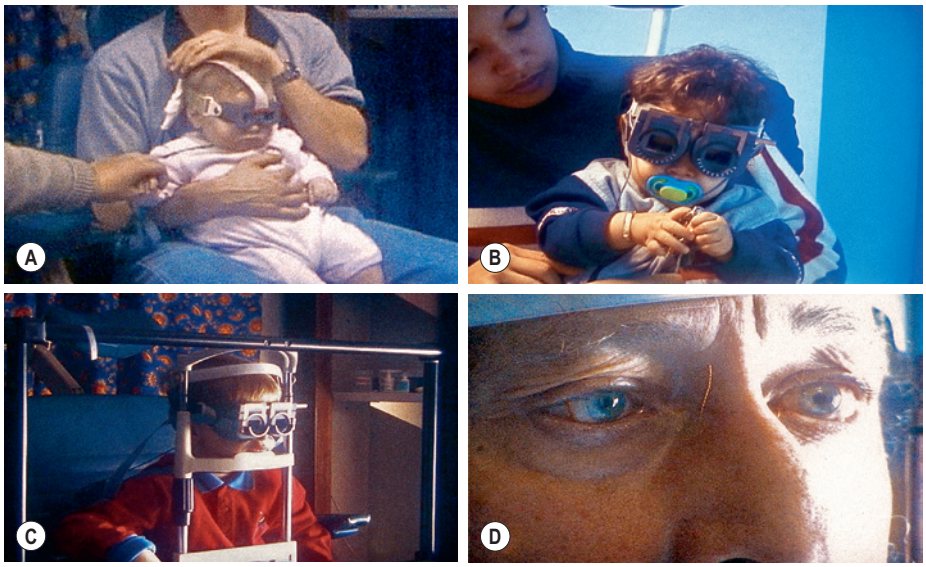


Fig. 90.7 Ocular motility recording techniques. Infrared reflectance performed on an infant (A), toddler (B), and a young child (C), and scleral search coil recordings performed on an adult (D).

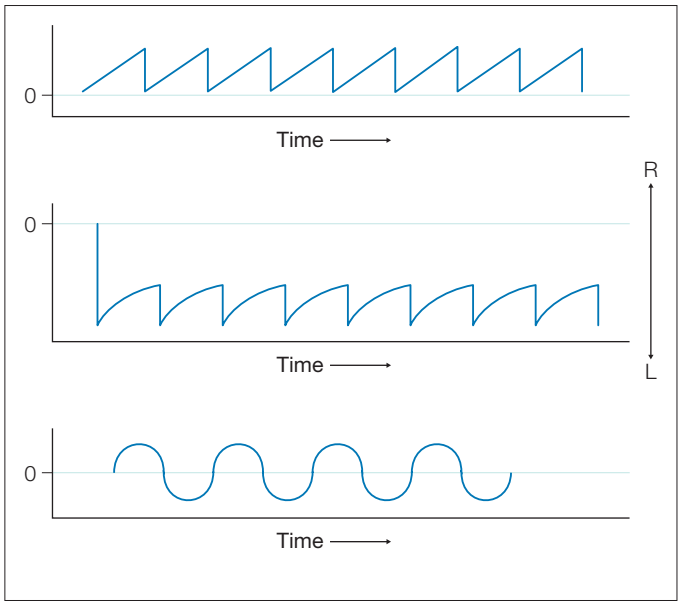


Fig. 90.8 Ocular oscillations. Artist's representation of major types of nystagmus waveforms. Continuous periods of time are depicted in each tracing. Rightward eye movements are up and leftward eye movements are down. The top trace shows pure jerk left nystagmus with linear slow phases to the left interrupting fixation in primary position. The middle trace shows jerk left nystagmus in left gaze with decreasing velocity slow phases. The bottom trace shows pure pendular nystagmus interrupting primary position fixation.

These "beats" of nystagmus toward the eccentric position persist as long as the child attempts to view a peripherally placed target. This is different to physiologic endpoint nystagmus, where only a few beats of nystagmus, gradually decreasing in amplitude, are present while viewing eccentrically placed targets.

Saccades

If an abnormality of saccadic eye movements is suspected, the quick phases of vestibular and OKN can be easily evaluated in infants and young children. To produce and observe vestibular nystagmus, hold the infant at arm's length, maintain eye contact, and spin first in one direction and then in the other (Fig. 90.9A,B). An OKN response can be elicited in the usual manner by passing a repetitive stimulus, such as stripes or an OKN drum, in front of the baby, first in one direction and then in another (Fig. 90.9C). In addition, reflex saccades will be induced in many young patients when toys or other interesting stimuli are introduced into the visual field. Older children are asked to fixate alternately upon two targets so that the examiner can closely observe the saccades for promptness of initiation, speed, and accuracy (Fig. 90.10). However, do not confuse a saccade toward sound as a visually guided saccade in a child with poor vision; it should first be established that the child can see. In children with strabismus, it is necessary to test saccades monocularly. The OKN drum/tape or the VOR response can also be used to assess saccadic function. It is sometimes easier to observe the eyelashes moving vertically while testing vertical saccades using a vertically rotating OKN drum (see Fig. 90.9C).

Smooth pursuit and vestibulo-ocular response systems

SP is tested by having the child follow a slow-moving, easily seen target (e.g. a brightly colored toy or mirror), both horizontally and vertically. The child's head should initially be kept still. If the child is uncooperative or is thought to have hysterical blindness, a mirror should be slowly rotated before his/her eyes, or an OKN drum or tape can be used. When examining the pursuit system, one should always include an assessment of VOR suppression, which is an essential component of the SP task during motion. In the older child, VOR suppression can be examined by asking the child to hold his/her finger about 6–8 cm in front of their face. The child is then asked to slowly rotate his/her head with their finger from left to right while maintaining fixation on their finger. If the VOR response is suppressed, there is no movement of the eyes relative to the head. Failure of VOR suppression results in a jerk nystagmus beating in the direction of the rotation. In an infant or young child, you can test VOR suppression by holding the child in outstretched arms and spinning in both clockwise and counterclockwise directions, while encouraging the child to fix on your face.

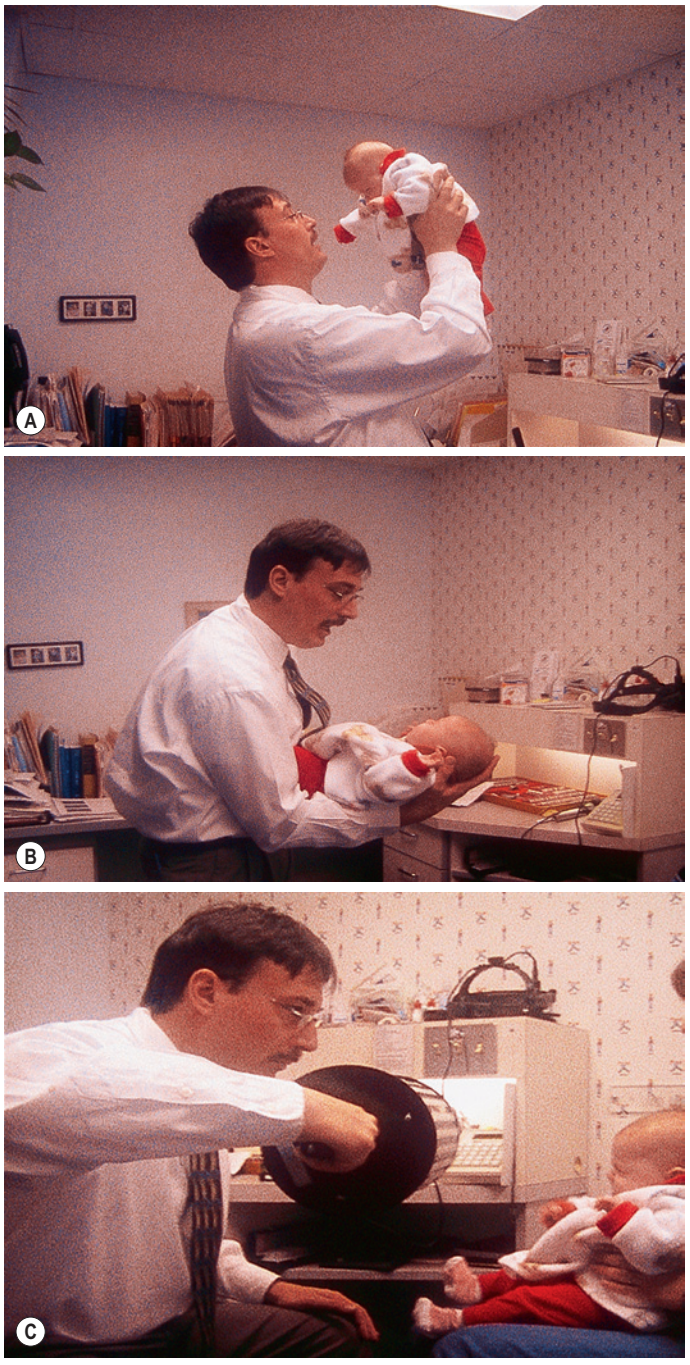


Fig. 90.9 Clinical evaluation of infant eye movements. The child is rotated in the examiner's arms in the vertical (A) and horizontal (B) planes to test the vestibulo-ocular, optokinetic, and saccadic systems. (C) An optokinetic drum is rotated close to the child in the vertical direction to assess visual fixation and saccadic and optokinetic functions.

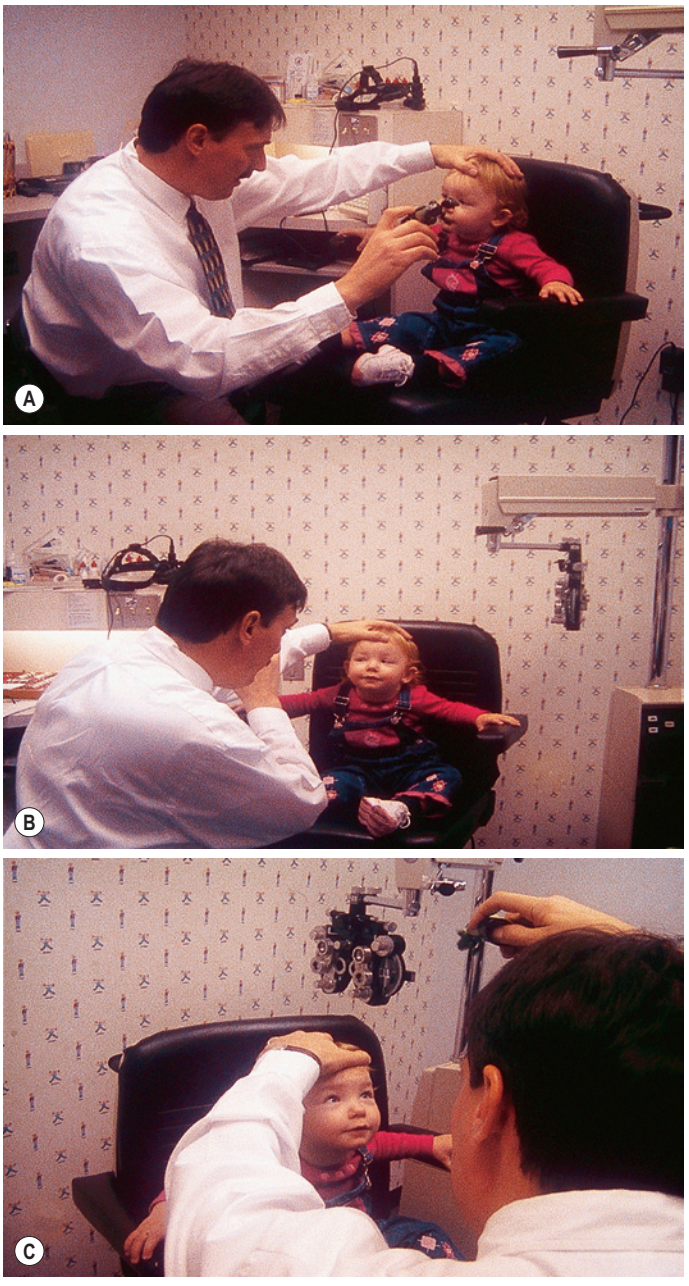


Fig. 90.10 Clinical evaluation of child voluntary saccadic eye movements. The child is seated while the head is held steady and targets are placed in the peripheral visual field horizontally (A,B) and vertically (C).

Vergence system

Vergence is usually tested by objective tests such as cover/uncover testing, alternate cover testing, prisms in front of the eye, and manual tests of near point of accommodation and vergence. Subjective aspects of vergence are tested by measuring the child's ability to perceive stereopsis. Many of these tests are dependent on the child's ability to cooperate, but alternate cover testing can be performed as soon as the child is able to fix on a near object.

Optokinetic system

Both slow and fast phases of OKN can be elicited by using OKN drum, tape, or full-field OKN stimuli (see Fig. 90.9C). OKN responses are observed with both eyes open in the full-term infant on the first day of life.[18] In healthy neonates, a monocular OKN response can be obtained when the stimulus is moved in the temporal-to-nasal direction, but not in the nasal-to-temporal direction (physiologic/developmental, monocular OKN asymmetry). After 3 months, this monocular OKN asymmetry declines for moderate stimulus speeds, but persists beyond 6 months of age at high stimulus speeds.

Disorders of supranuclear eye movements

Neural integrator

Neural integrator dysfunction

Neural integrator dysfunction manifests clinically as gaze-evoked nystagmus and is often associated with low pursuit gain (gaze-holding deficiency nystagmus, eccentric gaze nystagmus) and rebound nystagmus. Quick phases are away from the central position (see Fig. 90.8). Neurologic signs and symptoms include vertigo, nausea, dizziness, and oscillopsia. Gaze-evoked nystagmus is induced by moving the eye into lateral or vertical gaze, with sustained attempts to look eccentrically (Fig. 90.11). After the eyes are then returned to the central position, a short-lived nystagmus with quick phases opposite to the direction of the prior eccentric gaze occurs (rebound nystagmus). Abnormal suppression of the VOR and low-gain OKN responses are also associated with clinical findings and, again, probably reflect cerebellar disease[19,20] (see Fig. 90.11).

Most types of pathologic nystagmus increase their intensity as the eyes move in the direction of the fast phase (Alexander's law); this is believed to be due to a physiologically adapted "leaky" neural integrator responding to the pathologic vestibular imbalance that is part of the nystagmus.[19,20]

Most frequently, gaze-holding deficiency nystagmus is seen in conjunction with use of anticonvulsants and sedatives, cerebellar and brainstem disease, or other drug intoxication. Magnetic resonance imaging (MRI)/computed tomography (CT) scan of the brain reflects underlying disease and ocular motility recordings show slow phases that have decelerating velocity characteristics.[19,20] Acquired eye movement abnormalities suggesting defective neural integration, whether isolated or associated with other neurologic deficits, alert the examiner to investigate for a serious central nervous system (CNS) abnormality. Structural anomalies affecting the brainstem and cerebellum, e.g. Arnold–Chiari malformation, as well as metabolic, vascular, and neurodegenerative disorders, may also produce abnormalities of the neural integrator.

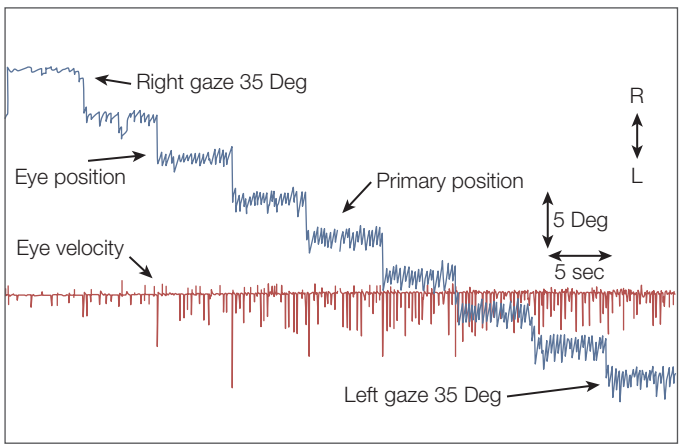


Fig. 90.11 Ocular motility recording of gaze-evoked nystagmus. This is a typical 45 s position and velocity trace of ocular motor recordings from the right eye of a patient with left gaze-evoked nystagmus. Right gaze 35° shows minimal intensity jerk left nystagmus with linear/decreasing velocity slow phases, while increasing left gaze, shows increasing intensity jerk left with linear and decreasing velocity slow phases. The horizontal arrows point to 35° right gaze and primary position. Deg, Degrees; L, leftward eye movements and left gaze; R, rightward eye movements and right gaze; sec, seconds.

Disorders of saccades

Saccadic accuracy

Normal and abnormal saccades are often dysmetric (inaccurate). Saccadic inaccuracy can be a result of gain dysmetria or pulse-step dysmetria. In saccadic dysmetria, the saccade misses the target and corrective saccades are needed for foveation (Fig. 90.12). If the saccades fall short of the target, they are known as hypometric; if they overshoot the target, they are hypermetric. In both cases, one or more secondary saccades are needed to eventually fixate the target. Hypometria is often seen in cerebellar disease, including autosomal dominant spinocerebellar ataxia type 3, and ocular motor apraxia (OMA). It is far more common than hypermetria. Consistent marked hypometria below 90% that persists beyond 7 months of age suggests neurologic disease. Hypometric saccades can be secondary to changes in visual magnification; for example, the removal of aphakic spectacles may lead to a temporary hypometria until adaptation takes place.[21]

Hypermetria is much less common and appears flutter-like (but should not be mistaken for ocular flutter). With the exclusion of centripetal saccades, hypermetria is abnormal at any age, and, when conjugate, it is almost always associated with cerebellar disease, including spinocerebellar ataxia type 1. If hypermetria is severe, the corrective saccade may be as large as the primary saccade, thus causing the eyes to oscillate back and forth with saccades. This phenomenon has been termed "macrosaccadic oscillations." After recovery of opsoclonus, there may be persistent hypermetric saccades (see Fig. 90.12).[22,23]

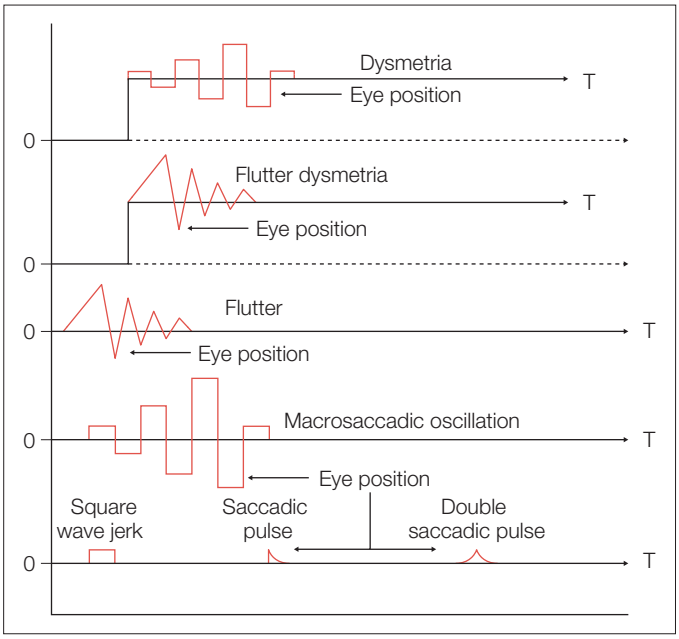


Fig. 90.12 Saccadic intrusions. Artist's representation of major types of saccadic instabilities and their ocular motor characteristics. Continuous periods of time are depicted in each tracing. Rightward eye movements are up and leftward eye movements are down. 0, Primary position fixation; T, target.

Saccadic velocity

Slow saccades may not be obvious clinically, especially in children. They may result from an abnormality involving the paramedian pontine reticular formation and have been thought to be pathognomonic of burst cell dysfunction. Slow saccades may be seen in mitochondrial disorders, progressive external ophthalmoplegia, myasthenia gravis, basal ganglia disease, Duane syndrome, and families with spinocerebellar ataxia type 2. Slow horizontal, and sometimes vertical, saccades may occur in patients with Gaucher type 3 disease.[24]

Saccadic latency

The time between the onset of a stimulus and the beginning of a saccade in healthy infants is up to about 1 s (about 200 ms in adults). In childhood, prolonged saccade latencies usually occur in association with saccade initiation failure.

Saccade initiation failure/ocular motor apraxia

The term saccade initiation failure (SIF) or OMA is used to specify impaired voluntary saccades and variable deficit of fast-phase saccades during vestibular or OKN.[24] Congenital OMA is characterized by defective horizontal saccades, but it does not represent a true apraxia since reflex saccades may also be impaired.[25]

Patients with congenital SIF show abnormal initiation and decreased amplitude of voluntary saccades; saccadic velocities in these patients are normal and fast phases of nystagmus of large amplitude can occasionally be generated. This suggests that the brainstem burst neurons that generate saccades are intact.[24,26] Acquired SIF may be due to conditions as listed in Table 90.3. Some of these patients with the acquired type, such as those with Gaucher disease (type 1 and some type 3 patients), have abnormal saccadic velocities.[27] Although the exact cause or localization of the defect in congenital SIF has not been determined, there is strong evidence that most can be localized subtentorially, particularly to the cerebellar vermis.[24,26]

Affected infants and children with poor head control are commonly thought to be blind since the expected re-fixations are not observed. In such an infant, demonstration of vertical saccades, vertical pursuit, OKN response in any direction, and normal acuity on visual-evoked response testing suggests the diagnosis of SIF. Another clinical sign in young infants is an intermittent tonic deviation of the eyes in the direction of slow-phase vestibular or OKN; in these infants, fast-phase saccades may be impaired.

By 4–8 months of age, the child develops a striking "head thrusting" behavior in order to re-fixate. First, the eyelids blink ("synkinetic blink") and the head begins to rotate toward the object of interest (Figs 90.13 and 90.14). Next, the head continues to rotate past the intended target allowing the tonically deviated eyes, which are now in an extreme

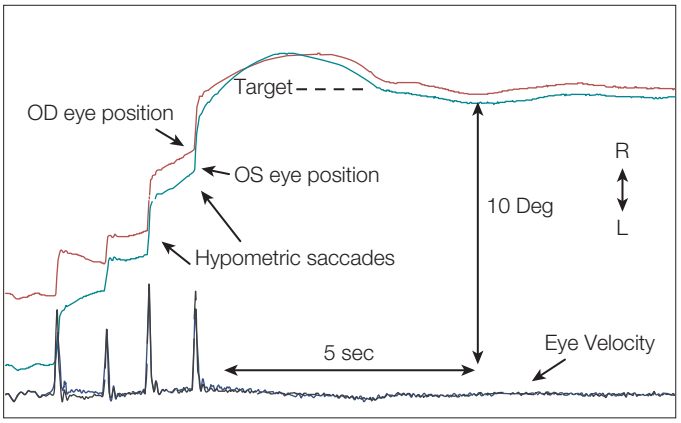


Fig. 90.13 Ocular motility recording of saccadic initiation failure. This is a 12 s position and velocity trace of ocular motor recordings from a patient with saccadic initiation failure. Attempts at fixation of rightward 10° target are followed by hypometric saccades, followed by a dysmetric fixation on the target. Deg, Degrees; L, leftward eye movements; OD, right eye; OS, left eye; R, rightward eye movements.

Table 90.3 Congenital and acquired saccade initiation failure (SIF)

Classification by cause	Specific etiologies
Idiopathic	
Perinatal problems	Cerebral palsy; hypoxia; hydrocephalus; seizures
Congenital malformations	Agenesis of corpus callosum; fourth ventricle dilation, and vermis hypoplasia; Joubert syndrome; macrocerebellum; dysgenesis of cerebellar vermis and midbrain; Dandy–Walker malformation; immature development of putamen; heterotropia of gray matter; porencephalic cyst; hamartoma near foramen of Munro; macrocephaly; microcephaly; posterior fossa cysts; chondrodystrophic dwarfism and hydrocephalus; encephalocele; occipital meningocele; COACH syndrome (cerebellar vermis hypoplasia, oligophrenia, congenital ataxia, coloboma, hepatic fibrocirrhosis)
Neurodegenerative conditions with infantile onset of SIF	Infantile Gaucher disease (types 2 and 3); Gaucher disease type 2; Pelizaeus–Merbacher disease; Krabbe leukodystrophy; propionic acidemia; GM1 gangliosidosis; infantile Refsum disease; 4-hydroxybutyric aciduria
Neurodegenerative conditions with later onset of SIF	Ataxia telangiectasia; spinocerebellar degenerations; juvenile Gaucher disease (type 3); Huntington disease; Hallervorden–Spatz disease; Wilson disease
Acquired disease	Post-immunization encephalopathy; herpes encephalitis; posterior fossa tumors
Other associations	Alagille syndrome; Bardet–Biedl syndrome; carotid fibromuscular hypoplasia; Cockayne syndrome; Cornelia de Lange syndrome; juvenile nephronophthisis; Lowe syndrome; neurofibromatosis type I; orofacial-digital syndrome; X-linked muscle atrophy with congenital contractures

Adapted from Cassidy L, Taylor D, Harris C. Abnormal supranuclear eye movements in the child: a practical guide to examination and interpretation. Surv Ophthalmol 2000; 44: 479–506.

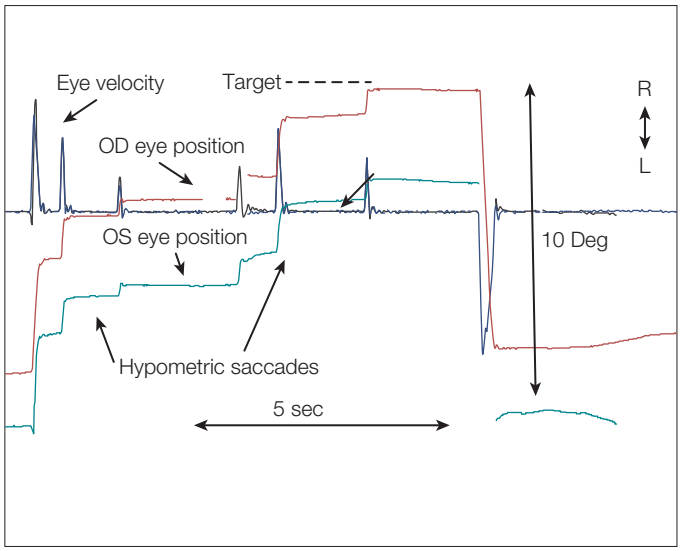


Fig. 90.14 Ocular motility recording of saccadic initiation failure. This is a 15 s position and velocity trace of ocular motor recordings from a patient with saccadic initiation failure during the resolution phase. Multiple hypometric ("staircase") saccades to the right with eventual excellent fixation are illustrated. Deg, Degrees; L, leftward eye movements and left gaze; OD, right eye; OS, left eye; R, rightward eye movements and right gaze; sec, seconds.

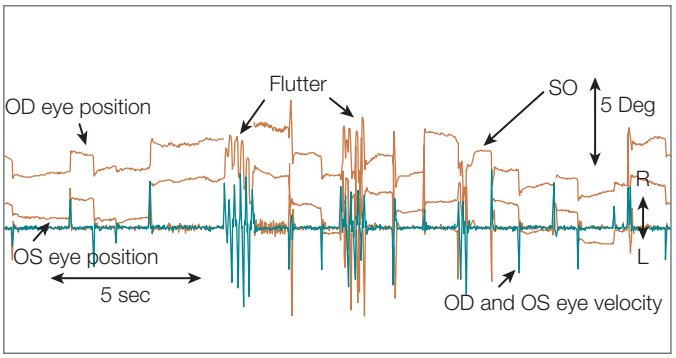


Fig. 90.15 Ocular motility recording of flutter and saccadic oscillations. This is a typical 20 s position trace of ocular motor recordings from a patient with ocular flutter. Back-to-back saccades with macro-sacccadic oscillations (SO) and without (flutter) an intersaccadic interval, both interrupting fixation and occurring on re-fixation are demonstrated. Deg, Degrees; L, leftward eye movements and left gaze; OD, right eye; OS, Left eye; R, rightward eye movements and right gaze; sec, seconds.

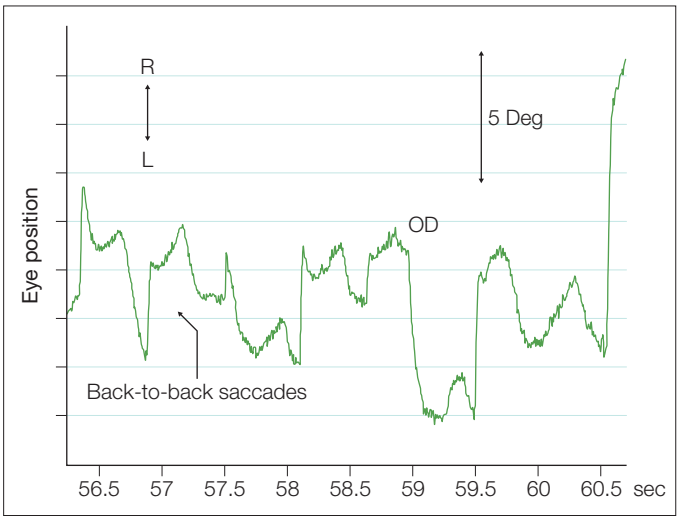


Fig. 90.16 Ocular motility recording of opsoclonus. This is a typical 4 s position trace of ocular motor recordings from a patient with opsoclonus. High-frequency back-to-back saccades without (flutter) an intersaccadic interval are demonstrated (arrows). Deg, Degrees; L, leftward eye movements and left gaze; OD, right eye; R, rightward eye movements and right gaze; sec, seconds.

contraversive position, to come into alignment with the target. Finally, as the eyes maintain fixation, the head rotates slowly back so that the eyes are in primary position. This apparent use of the VOR to re-fixate continues for several years, but with increasing age, patients demonstrate less prominent head thrusting and may even be able to generate some saccades, although they are abnormal. The blink–saccade synkinesis adaptation may persist. In some infants, generalized hypotonia may be associated.[28]

A brain MRI is necessary for suspected neurologic disorders to look for midline malformations, particularly around the fourth ventricle and cerebellar vermis.

Gaucher disease, ataxia telangiectasia and its variants, and Niemann–Pick variants may also present with the inability to generate saccades, as well as blinking and head thrusting prior to re-fixation. Unlike SIF, these disorders generally involve vertical as well as horizontal saccades and eventually manifest systemic signs.

The prognosis of the congenital type is good. Many adapt to allow gaze shifts with less head thrusting and can generate some saccades, albeit abnormal. There is no treatment for SIF, but children who have this condition should be investigated appropriately and recognized as having learning and living difficulties, and they should receive extra help and other educational benefits at school. Whether the condition improves with age is not known; any apparent improvement may be a result of the improvement of the adaptive strategies these children use to enable rapid shifts of gaze.

Opsoclonus/ocular flutter

Opsoclonus, also referred to as "saccadomania" or dancing eyes, is a rare, but striking, saccade disorder characterized by intermittent involuntary bursts of wild conjugate multidirectional back-to-back saccades.[23] If the eye movement is purely horizontal, it is known as ocular flutter (Fig. 90.15). During resolution, opsoclonus may revert to ocular flutter, and finally saccadic dysmetria, before eventually reverting to normal eye movements. Opsoclonus is often triggered by attempted fixation, SP, convergence, upgaze, eyelid closure, or OKN or vestibular nystagmus. The frequency is high, usually ranging between 5 and 13 Hz, and the amplitude can be tens of degrees, although it may be so small that the oscillations cannot be seen without a slit-lamp, ophthalmoscope or eye movement recordings (Figs 90.16 and 90.17). Opsoclonus usually persists during sleep, although it may be diminished or even absent.[23] Acquired opsoclonus is often associated with limb myoclonus. In such cases, it is described as opsoclonus–myoclonus, dancing eye–dancing feet syndrome, myoclonic encephalopathy of infants, or infantile polymyoclonia.[23] Opsoclonus–myoclonus syndrome is more common in children.[23]

Onset may be acute or subacute and is often accompanied by ataxia, vomiting, and irritability. It may be a manifestation of occult malignancies, in particular, neural crest tumors

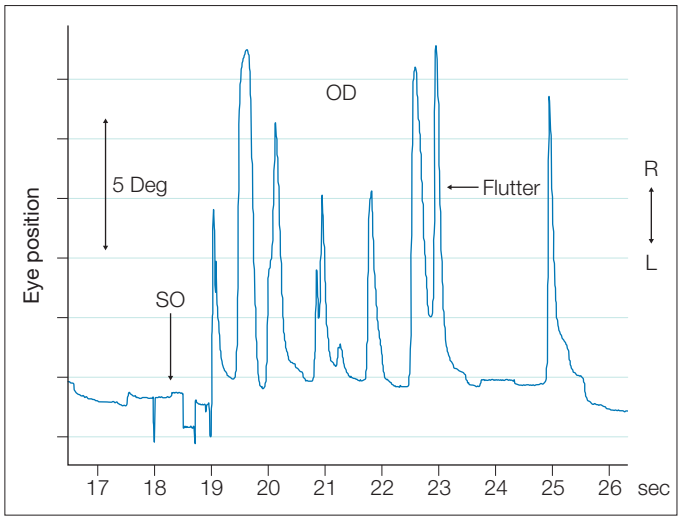


Fig. 90.17 Ocular motility recording of opsoclonus. This is a 20 s position trace of ocular motor recordings from a patient with opsoclonus. Asymmetric, conjugate, multiplanar, small amplitude, high-frequency back-to-back saccades without an intersaccadic interval (flutter) are present. Deg, Degrees; L, leftward eye movements and left gaze; OD, right eye; R, rightward eye movements and right gaze; sec, seconds; SO, saccadic oscillation.

(neuroblastoma, ganglioneuroblastoma, ganglioneuroma), hepatoblastoma, infection (Coxsackie B, human immunodeficiency virus [HIV], mumps, parainfluenza virus, psittacosis, *Salmonella*, syphilis, St. Louis encephalitis, rickettsia, enterovirus, Epstein–Barr virus), or toxic (amitriptyline, cocaine, diazepam, lithium, phenytoin) or metabolic disorders (biotin-responsive multiple carboxylase deficiency, hyperosmolar non-ketotic coma).[6]

In children with neural crest tumors or brainstem encephalitis, opsoclonus is commonly accompanied by diffuse or focal myoclonus. Although opsoclonus–myoclonus is rarely a presenting feature of neuroblastoma, it is seen in about 50% of children with an occult neuroblastoma, and the presence of opsoclonus confers a favorable survival rate.[29] Paraneoplastic opsoclonus is associated with a single copy of the N-*myc* oncogene, and those children with amplification of this oncogene who do not develop opsoclonus carry a worse prognosis.[30] It is hypothesized that in paraneoplastic opsoclonus, the tumor and some CNS structures share an epitope, and that this common epitope triggers an immune response against the tumor and the CNS, resulting in the neurologic symptoms.[30]

Opsoclonus may be mistaken for nystagmus and vice versa. Formal eye movement recordings will differentiate the two, demonstrating that opsoclonus is a burst of back-to-back saccades with no intersaccadic interval, without the slow phases of nystagmus (see Figs 90.15–90.17). However, on rare occasions, there may be a constant high-frequency acquired pendular nystagmus. Once opsoclonus has been confirmed, children should be screened for urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA), and have an oncologic workup. This may include chest and abdominal CT and/or MRI. Elevated levels of urinary VMA and HVA are diagnostic; however, normal levels occur in 26% of children with paraneoplastic opsoclonus.[30] Blood and cerebrospinal fluid (CSF) samples should also be taken and sent for virology and bacteriology. CSF pleocytosis has been reported in children with paraneoplastic opsoclonus and there are occasional oligoclonal bands. There have been occasional reports of autoantibodies, including anti-Hu and antibodies against neurofilaments, in the sera of children with paraneoplastic opsoclonus.

Acquired opsoclonus is probably immune mediated. Its neural substrate remains a mystery, and there may be no single site involved in the causation of opsoclonus.

Opsoclonus–myoclonus, especially when it occurs with brainstem encephalitis, may be a benign self-limiting condition. Although children with paraneoplastic opsoclonus tend to have a better oncologic prognosis, the neurologic outcome is unpredictable. Children who have become cancer free may have significant neurologic sequelae. Adrenocorticotropic hormone or systemic steroid treatment has a dramatic short-term effect on symptoms in 50% to 90% of children with opsoclonus.[31] However, not all children have such a good response, and the opsoclonus and ataxia may become steroid dependent, re-emerging when treatment is tapered or during intercurrent illnesses. Other drugs used to treat opsoclonus–myoclonus include intravenous immunoglobulin G, azathioprine, propranolol, and divalproex sodium. A combination of systemic steroids and high-dose immunoglobulin can be used for the treatment of opsoclonus–myoclonus in patients who do not respond to first-line therapy with steroids.

Regardless of the short-term response, these children often have long-term developmental problems, including speech, motor, and cognitive disabilities.[32] Abnormal eye movements may persist. Parents, teachers, and caregivers should be informed of such problems. Occupational therapists, psychologists, and social services should be involved at an early stage.

Antisaccades

An antisaccade requires the subject to suppress a reflexive saccade to an abruptly appearing peripheral target, and generate a voluntary saccade in the equidistant but opposite direction. The ability to suppress reflexive responses in favor of voluntary motor actions is necessary in everyday life, and both of these abilities can be assessed with use of the antisaccade task. The correct execution of an antisaccade requires at least two functioning subprocesses: an intact fixation system and the ability to generate a voluntary saccade in the opposite direction. Infants as young as 4 months have a fixation system adequate to allow inhibition of reflex saccades, but the ability to generate a voluntary antisaccade develops much later, usually over 10 years of age, with a steep decrease in the mean error rate from 10 to 15 years, then a more gradual decrease toward 20 years.[33] Difficulty in making antisaccades has also been described in people with schizophrenia, children with attention-deficit hyperactivity disorder, autosomal dominant cerebellar ataxia type 2, male dyslexics, and Tourette syndrome.[34]

Saccadic intrusions and oscillations

There are saccadic eye movements that may intrude on steady primary position fixation or interrupt re-fixation and, hence, mimic nystagmus (see Figs 90.12, 90.17, and 90.18). Saccadic intrusions (SIs) must be differentiated from nystagmus, in which a drift of the eyes from the desired position of gaze is the primary abnormality, and from saccadic dysmetria, in which the eye over- or undershoots a target, sometimes several times, before achieving stable fixation. Only eye movement recordings can definitively distinguish SIs and saccadic oscillations (SOs) from nystagmus.

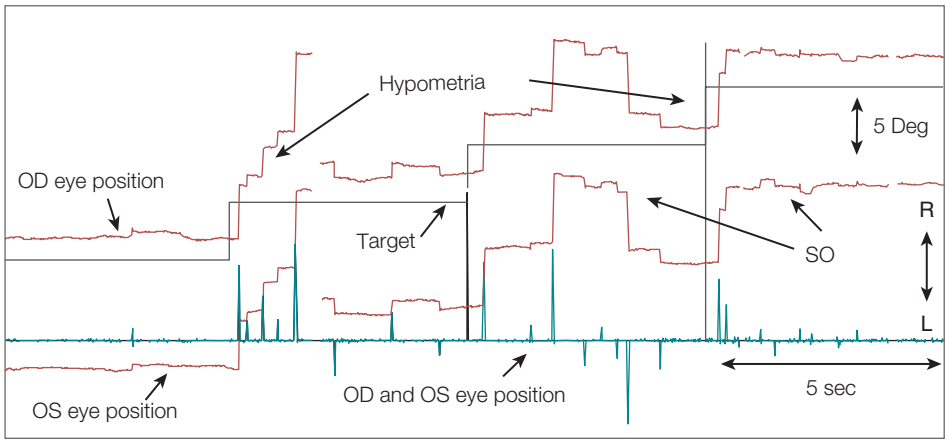


Fig. 90.18 Ocular motility recording of saccadic intrusions. This is a 20 s position trace of ocular motor recordings from a patient with saccadic intrusions. Small to moderated amplitude back-to-back saccades with an intersaccadic interval occur on re-fixation and interrupt fixation and are present throughout the recording. There are associated hypometric saccades to peripheral targets. Deg, Degrees; L, leftward eye movements and left gaze; OD, right eye; OS, left eye; R, rightward eye movements and right gaze; sec, seconds; SO, saccadic oscillation.

Square wave jerks consist of a conjugate displacement of the eyes up to 5° from fixation, followed by a re-fixational saccade after a normal intersaccadic interval of 200 ms. They occur in normal healthy subjects of any age. However, if they are more frequent (more than 9 square wave jerks per minute in a young person should be considered abnormal), they are referred to as square wave oscillations, and are seen in cerebellar disease, progressive supranuclear palsy, and multiple sclerosis.[35] Square wave jerks and oscillations are rarely seen in childhood (see Fig. 90.18).

Macro-square wave jerks are also rare in childhood. They consist of conjugate displacement of the eyes away from fixation by more than 5°, and, after a shorter than normal latency of 80 ms, there is a re-fixation saccade. They occur in bursts and may be mistaken for flutter. The amplitude is variable, and they are present in the dark. They occur in diseases that disrupt cerebellar outflow, i.e. multiple sclerosis or olivopontocerebellar degenerations, including Huntington disease.[35]

Macrosaccadic oscillations represent a severe form of saccadic hypermetria. They are characterized by conjugate oscillations of the eyes around fixation, with a normal intersaccadic interval of 200 ms. Oscillations increase and then decrease in amplitude during each episode. They are a result of lesions affecting the midline cerebellum and underlying nuclei. They are not present in darkness.

Disorders of smooth pursuit

Smooth-pursuit asymmetry–initiation failure

Monocular SP asymmetries may persist in patients with early-onset, but not with late-onset, strabismus. Impaired SP to the side of the lesion has been most frequently reported in patients with lesions restricted to the posterior cortical areas and underlying white matter, but it also occurs with frontal lobe lesions and in hemidecortication. Ipsilateral pursuit deficit may also be seen in unilateral lesions of the lower portions of the pursuit pathway, including the thalamus, midbrain tegmentum, dorsolateral pontine nucleus, and cerebellum. Nuclear vestibular lesions may affect either ipsilateral or contralateral SP.[36]

Abnormal smooth-pursuit gain

Low pursuit gain, which may be seen clinically as saccadic or jerky pursuits, occurs in the elderly and in patients with basal ganglia disease, cerebellar disease, large cerebral lesions, or posterior cortical lesions. Low pursuit gain has been described in spinocerebellar ataxia types 1 and 3. If gaze-holding deficiency nystagmus is associated with saccadic pursuit, the lesion is most likely to be cerebellar, whereas saccadic pursuit in the absence of gaze-holding deficiency nystagmus is more likely to indicate a cerebral lesion.

Abnormal visual fixation

Steady fixation may be disrupted by slow drifts, nystagmus, or involuntary saccades. The frequency of square wave jerks increases in certain neurologic conditions, i.e. progressive supranuclear palsy, Friedreich ataxia, and focal cerebral lesions. Detection of nystagmus during attempted steady fixation is abnormal. If the slow-phase velocity or intensity of nystagmus is similar both during fixation and when fixation is prevented (e.g. by Frenzel goggles or in darkness), then a disorder of the fixation system is inferred.

Disorders of the visual system lead to instability of gaze, the extreme example being blindness. Monocular loss of vision may lead to unstable gaze in the affected eye, which is predominantly due to slow, low-frequency vertical drifts. Binocular loss of vision causes loss of gaze stability and a continuous horizontal and vertical nystagmus.[37] This nystagmus characteristically changes direction over the course of seconds and minutes, a feature also encountered following experimental cerebellectomy. Thus, the nystagmus that follows bilateral visual loss reflects a gaze-holding mechanism that has never been calibrated by visual inputs. Acquired lesions of the cerebellum without specific involvement of the visual pathways may disrupt fixation with SIs and with slow drifts, especially in the vertical plane, that lead to nystagmus. The pathogenesis of pendular oscillations occurring in association with visual loss is unknown.[38]

Disorders of vergence

Strabismus

See Chapters on Strabismus.

Spasm of the near reflex (convergence spasm)

Spasm of the near reflex, also referred to as convergence spasm, is characterized by intermittent spasm of convergence, of miosis, and of accommodation. Symptoms include headache, photophobia, eye strain, blurred vision, and diplopia. Patients

may appear to have bilateral sixth nerve palsies, but careful observation will reveal miosis and high myopia (8–10 D) on dry retinoscopy, accompanying the failure of abduction. This key clinical clue will prevent misdiagnosis and misdirected testing. Most commonly, spasm of the near reflex is psychogenic, and treatment may include simple reassurance, psychiatric counseling, or cycloplegia with bifocals.

Spasm of the near reflex associated with organic disease has been reported with encephalitis, tabes, labyrinthine fistulas, pituitary adenoma, Arnold–Chiari malformation, posterior fossa lesions, trauma, myasthenia gravis, anticonvulsant toxicities, midbrain lesions, metabolic problems, and cyclic oculomotor palsy. Disturbances that are clearly functional do not exclude co-existing organic disease!

Divergence insufficiency/paralysis

Divergence insufficiency is characterized by an esotropia for distance and orthophoria for near and normal convergence; the esotropia may be constant or intermittent. The fusional divergence may be reduced or completely absent. Divergence paralysis is characterized by complete loss of divergence amplitude. It appears as a constant esotropia for distance, with normal convergence, and it usually indicates an underlying neurologic problem, such as a tumor or head trauma resulting in elevated intracranial pressure, or the onset of Miller Fisher syndrome. Bilateral sixth nerve paresis should be excluded in these cases.

Convergence insufficiency/paralysis

Convergence insufficiency is characterized by reduced fusional convergence at near and a variable exophoria (occasionally intermittent exotropia) at near. It usually appears in adolescence and gives rise to vague symptoms of eye strain, headache, diplopia, and blurring associated with close work. Eye movements and reading acuity are normal, and there should be no neurologic abnormalities.

Convergence insufficiency usually has no underlying cause, but it can be associated with stress, fatigue, and anxiety, and it may follow infection or trauma.[39] Underlying intracranial lesions are rare. The child and parents should be reassured that there is no disease, and orthoptic near-point exercises can be tried. If orthoptic exercises fail, prisms may be required.

Complete convergence paralysis is highly suggestive of an intracranial lesion, such as encephalitis, demyelination, neurosyphilis, or a condition resulting from trauma or toxins. The patient is usually completely unable to converge.

Disorders of the vestibulo-ocular response system

Abnormal VOR gain

VOR gain is the peak slow-phase velocity divided by rotation speed and is higher in infants than in adults. Abnormalities of VOR gain in the small child are not easily detected clinically but require eye movement recordings. If VOR gain is abnormal, a child's visual acuity will deteriorate by several lines while moving the head compared to the acuity taken with the head stationary. Abnormally high gain has been described in lesions of the cerebellar flocculus and the inferior olive. Mildly high gains have also been reported in familial vestibulocerebellar disorders.[40]

Abnormal VOR time constant

The time constant is measured as the time taken for the eye velocity of per-rotational or postrotational nystagmus measured in the dark to fall to 37% of its initial value. As a rule of thumb, the nystagmus will persist for a total time of about three times the time constant. Measurements in animals have shown that the time constant of the decay of per-rotatory or postrotatory nystagmus as measured at the vestibular ganglion is about 5 or 6 s. However, the nystagmus takes much longer to decay, with a time constant of approximately 12 s in humans. This augmentation of the cupula time constant is known as the velocity storage mechanism (VSM). It is also under adaptive control by the nodulus and uvula in the cerebellar vermis, and experimental lesions result in a prolonged VSM time constant. Abnormally short time VSM constants can be caused by disease of the end organ, the vestibular nerve, or central disease. Very short time constants have been reported in Chiari type I malformation, olivopontocerebellar degeneration, demyelinating disease, congenital and acquired blindness, and bilateral vestibulopathy secondary to ototoxic drugs. Abnormally long time VSM constant is rarely seen.

Absent VOR quick phases

Absent quick phases are seen in children with SIF. Most of these children will show a similar failure during OKN, but occasionally only vestibular nystagmus demonstrates the failure. This may indicate a very subtle form of saccade failure, and as an isolated phenomenon it is probably of little clinical significance. Absent quick phases may also be seen in neonates up to 2 to 3 weeks, or in older infants with delayed visual maturation.[13]

Absent VOR

The VOR appears clinically absent or very erratic in children with infantile nystagmus, whether elicited by calorics, constant rotation, or sinusoidal oscillation.[41] The VOR may be absent in children with the CHARGE association and in children with Usher syndrome type 1.

Disorders of the optokinetic system

Absence of OKN

No OKN can be elicited in a completely blind child, as it is a visually induced reflex. However, the absence of OKN alone must not be used as an indicator of visual acuity, as the sighted infant who may appear visually unresponsive may have absence of OKN for another reason. The response to a full-field OKN stimulus is difficult to suppress, so the very presence of OKN demonstrates some vision. Bilateral lesions of the optokinetic pathway in the cortex, cerebellum, or brainstem may completely obliterate all OKN and SP. Infants with cortical dysplasia may have absent OKN, they may be cortically blind, or they can have a normal visual evoked potential and no OKN. If the optokinetic response is assessed with a hand-held device in the clinic, quick-phase failure in children with SIF can be mistaken for absent OKN if the eyes are not driven to the limit of gaze. If there is any doubt, the child should have full-field OKN assessment, which will readily demonstrate the typical "locking up" of SIF.

Binocular asymmetry of OKN

Any unilateral lesion in the optokinetic pathway, as it passes through the brainstem, cerebellum, or parietal lobe, can result in asymmetric abnormalities of binocular OKN and SP. With brainstem and cerebellar lesions, there may be accompanying localizing neurologic signs, whereas isolated binocular OKN asymmetry is suggestive of a parietal lesion and has been reported in children as young as 4–5 months.

Monocular asymmetry of OKN

With early disturbances of binocular vision caused by strabismus, anisometropia, or unilateral congenital cataract, the normal early monocular OKN asymmetry persists in both eyes[42]; after 1–2 years, the monocular asymmetry persists.[42] The persistence of monocular OKN asymmetry and poor binocular vision, together with the fact that OKN becomes symmetric in normal infants around the time that binocular function is detectable, has led to the hypothesis linking binocularity and OKN asymmetry, but they may be separate processes.[19]

Miscellaneous disorders

Induced convergence retraction (dorsal midbrain syndrome)

Lesions of the posterior commissure in the dorsal rostral midbrain may result from many disease processes and can affect a variety of supranuclear mechanisms, including those that control vertical gaze, eyelids, vergence, fixation, and pupils. Other terms such as pretectal syndrome, Koerber–Salus–Elschnig syndrome, Sylvian aqueduct syndrome, posterior commissural syndrome, and collicular plate syndrome all refer to this condition.

Among the many underlying causes of this condition are hydrocephalus, stroke, and pinealomas. Table 90.4 lists other reported etiologies and systemic associations.

Limitation of upward saccades is the most reliable sign of the convergence retraction. Upward pursuit, Bell phenomenon, and the fast phases of vestibular and OKN may also be affected, either at presentation or with progression of the underlying process. It is rare for upgaze to be unaffected. Pathologic lid retraction and lid lag are also common (Collier's sign).

Unlike the pathways from upward saccades, the pathways for downward saccades do not appear to pass through the posterior commissure (see Fig. 90.2). Perhaps because of this, disturbances of downgaze are not as predictable or uniform. Usually down-going saccades and pursuit are present, but they may be slow. Sometimes, especially in infants and children, there is a tonic downward deviation of the eyes that has been designated the "setting sun" sign, and downbeating nystagmus may also be observed. The setting sun sign may also be seen in children with hydrocephalus.

Convergence spasm may occur during horizontal saccades and result in a "pseudoabducens palsy", since the abducting eye moves more slowly than the adducting eye. All children with convergence retraction deserve thorough, prompt neurologic and neuroradiologic evaluation, since timely intervention may be decisive. The natural history of this disorder is dependent on the underlying etiology.

Table 90.4 Causes of childhood dorsal midbrain syndrome

Classification by cause	Specific etiologies
Tumor	Pineal germinoma, teratoma and glioma; pineoblastoma; others
Hydrocephalus	Aqueductal stenosis with secondary dilation of third ventricle and aqueduct, or with secondary suprapineal recess compressing posterior commissure, commonly caused by cysticercosis in endemic areas
Metabolic disease	Gaucher; Tay–Sach; Niemann–Pick; kernicterus; Wilson disease; others
Midbrain/thalamic damage	Hemorrhage; infarction
Drugs	Barbiturates; carbamazepine; neuroleptics
Miscellaneous	Benign transient vertical eye disturbance in infancy; trauma; neurosurgery; hypoxia; encephalitis; tuberculoma; aneurysm; multiple sclerosis

Transient vertical gaze disturbances in infancy

Vertical gaze abnormalities may be benign and transient in infants. Infants with episodic conjugate upgaze that became less frequent over time have been described. During these episodes, normal horizontal and vertical vestibulo-ocular responses could be observed.[27]

Tonic downgaze has been observed in 5 of 242 consecutively examined healthy newborn infants as well as in other infants. Again, the eyes can easily be driven above the primary position with the VOR. Premature infants with intraventricular hemorrhage may also develop tonic downgaze, usually in association with a large-angle esotropia. These infants do not elevate the eyes with vestibular stimulation. Upgaze often returns during the first 2 years of life, but the esotropia does not resolve when upgaze returns.

Internuclear ophthalmoplegia

In the absence of peripheral lesions such as myasthenia gravis, failure of adduction combined with nystagmus of the contralateral abducting eye is termed internuclear ophthalmoplegia (INO) and localizes the lesion to the medial longitudinal fasciculus (MLF) unequivocally.

The abducens nucleus consists of two populations of neurons that coordinate horizontal eye movements (see Fig. 90.1). Fibers from one group form the sixth nerve itself and innervate the ipsilateral lateral rectus muscle; fibers from the second group join the contralateral MLF and project to the subnucleus of the third nerve, which supplies the contralateral medial rectus muscle. In this way, the neurons of the sixth nerve nucleus yoke the lateral rectus with the contralateral medial rectus.

Clearly, lesions of the abducens nucleus will cause ipsilateral conjugate gaze palsy. Lesions of the MLF between the midpons and oculomotor nucleus will, in turn, disconnect the ipsilateral medial rectus subnucleus from the contralateral sixth nerve nucleus and cause diminished adduction of the ipsilateral eye on attempted versions. The signs of INO may be accompanied by an ipsilateral hypertropia or skew deviation.

A host of structural, metabolic, immunologic, inflammatory, degenerative, and other processes can interfere with the

function of the MLF and nearby structures. In young adults, multiple sclerosis is by far the most common cause of INO.[43] Additional causes of INO include Arnold–Chiari malformation, hydrocephalus, meningoencephalitis, brainstem or fourth ventricular tumors, head trauma, metabolic disorders, drug intoxications, paraneoplastic effect, carcinomatous meningitis, and others. Peripheral processes, particularly myasthenia gravis and Miller Fisher syndrome, may closely mimic INO and should be considered in any patient with INO-like eye movements.[44]

Variable diplopia and/or ptosis most often prompt an ophthalmologic evaluation. Since there is no stereotypical myasthenic eye movement, this diagnosis should be considered in any child with an unexplained, acquired ocular motility disturbance and clinically normal pupils – particularly when the deviation is variable – whether or not ptosis is present. Any pattern of abnormal motility is suspect, including an apparent gaze palsy, INO, isolated cranial nerve palsy, one and one-half syndrome, incomitant strabismus, accommodative and vergence insufficiency, and gaze-evoked nystagmus. Prolonged OKN may demonstrate slowing of the quick phases; large saccades may be hypometric; small saccades may be hypermetric; and characteristic "quiver movements," which consist of an initial small saccadic movement followed by a rapid drift backward, may be seen.[44]

Acquired and neurologic nystagmus

Eye care practitioners may be among the first to evaluate infants and children with involuntary ocular movements, producing anxiety in the medical care provider as well as the family. The eye care professional choosing to specialize in infants and children may, in fact, see more patients with nystagmus than any other specialist. This is due to the frequent association of nystagmus with strabismus.[17] It may be that nystagmus gets "less press" (e.g. literature, teaching, research, education) because there is less we understand or can do about it than strabismus or other childhood eye diseases.

Historical perspective

Nystagmus comes from the Greek word "nystagmos," to nod, drowsiness and from "nystazein" to doze, probably akin to Lithuanian "snusti," also to doze. It is a rhythmic, involuntary oscillation of one or both eyes. Using the information obtained from complete histories, physical examinations, and radiographic and oculographic evaluations, over 40 types of nystagmus can be distinguished. Some forms of nystagmus are physiologic, whereas others are pathologic. Although nystagmus is typically described by its more easily observable fast (jerk) phase, the salient clinical and pathologic feature is the presence of a slow phase in one or both directions. Thus, clinical descriptions of nystagmus are usually based on the direction of the fast phase and are termed horizontal, vertical, or rotary, or any combination of these. The nystagmus may be conjugate or disconjugate. The nystagmus may be predominantly pendular or jerky, the former referring to equal velocity to-and-fro movement of the eyes, and the latter referring to the eyes moving faster in one direction and slower in the other. Involuntary ocular oscillations containing only fast phases are "saccadic oscillations and intrusions" and not nystagmus. It is well documented that these differences may be difficult, if not impossible, to differentiate clinically. Recent advances in eye movement recording technology have increased its application in infants and children who have clinical disturbances of the ocular motor system (see Figs 90.8 and 90.12).

Incidence

In 1991, Stang retrospectively reviewed the records of Group Health Inc. (White Bear Lake, MN) and in their pediatric population of 70,000 found a prevalence of clinical "nystagmus" of 1 in 2850.[32] Other estimates of its incidence range from 1 in 350 to 1 in 6550.[45,46] It is difficult, if not impossible, to give accurate prevalence/incidence on all types of nystagmus combined, but it is known that up to 50% of the infantile strabismic population will have some associated nystagmus. This could increase the prevalence of nystagmus to up to 0.5% of the population.

Etiology

All the theoretical neuronal mechanisms of nystagmus are constantly evolving and are beyond the scope of this chapter. Particularly controversial is the role of cortical motion processing in the development of some forms of infantile nystagmus. However, major supranuclear inputs to the oculomotor system are reasonably well accepted for their role in stabilization of eye movements. These include the pursuit system, vestibular system, and the neural integrator. The vestibular system maintains a constant resting firing rate that tends to drive the eyes contralaterally. This tendency is counterbalanced by the vestibular system on the opposite side unless the balance is changed by head rotation. The counterbalance is lost with unilateral vestibular damage, and the eyes tend to drift toward the affected side. A corrective saccade is then made toward the unaffected side. The slow phase of the nystagmus toward the affected side is of constant velocity as recorded by ocular motility recordings. This is a distinguishing feature of vestibular nystagmus. Most forms of acquired nystagmus are due to disease of the vestibular system (centrally or peripherally). Ocular motility recordings show various combinations of uniplanar or multiplanar, simple pendular, linear, or decelerating velocity slow phases[47] (Fig. 90.19).

Neurologic and acquired nystagmus types

Spasmus nutans

Spasmus nutans is an ocular oscillation beginning in infancy and consisting of the association of high-frequency, small-amplitude, disconjugate oscillations, a head nodding oscillation, and a head tilt (Fig. 90.20). The head nodding associated with spasmus nutans syndrome (SNS) is a combination of vertical head nodding together with a lateral shaking of the head in an unpredictable pattern. The head nodding is of lower frequency than the nystagmus and becomes prominent when the child attempts to inspect something of interest. It disappears during sleep but may persist when the child is lying down. The head tilt in SNS is a variable finding that is present in less than half of cases. Although the reason for the associated head tilt is unclear, Gottlob et al. have suggested that it may serve to directionalize the head nodding to its optimal trajectory.

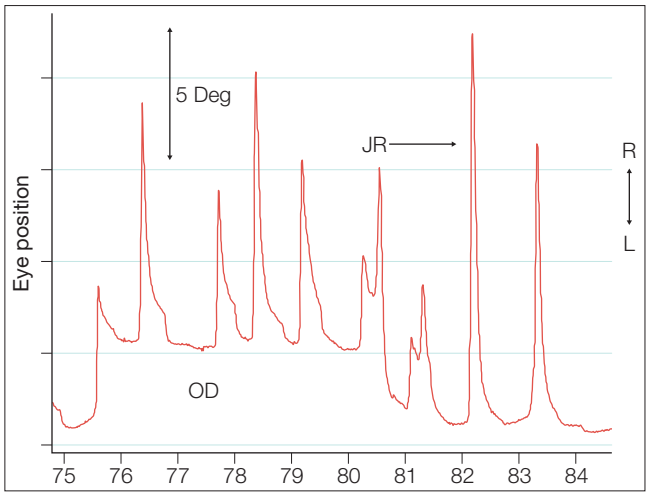


Fig. 90.19 Ocular motility recording of acquired jerk nystagmus. This is a typical 10 s position trace of ocular motor recordings from a patient with acquired jerk nystagmus. The jerk right nystagmus has decreasing velocity slow phases. Deg, Degrees; JR, jerk right; L, leftward eye movements and left gaze; OD, right eye; R, rightward eye movements and right gaze.

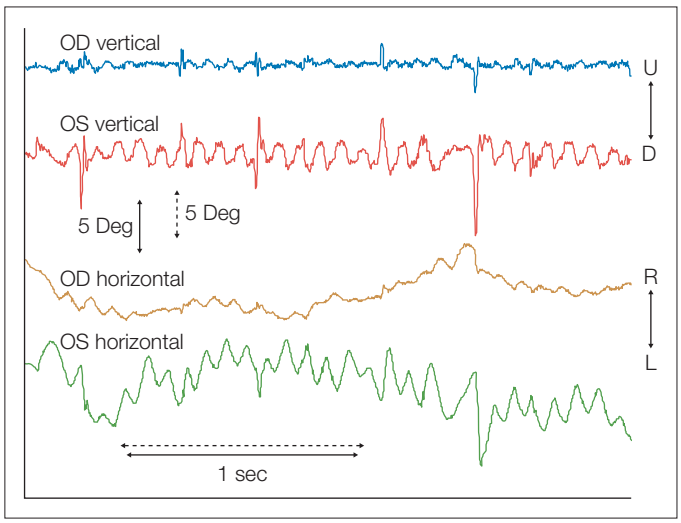


Fig. 90.20 Ocular motility recordings of spasmus nutans. OU open high-frequency (12–14 Hz), asymmetric, disconjugate, multiplanar (torsional), pendular nystagmus typical of spasmus nutans. Continuous periods of time are depicted in each tracing. Rightward eye movements (R) are up and leftward eye movements (L) are down. Deg, Degrees; OD, right eye; OS, left eye; OU, both eyes; sec, second; U, up; D, down.

The characteristic feature of spasmus nutans is the very fine, rapid, pendular nature of the nystagmus. The eyes appear to have a shimmering movement. It may be horizontal, vertical, or torsional. It is usually asymmetric to the point that it may appear unilateral. Pure unilateral forms are not uncommon. It may appear to switch eyes with changes in direction of gaze, and frequently appears worse in the abducting eye. Tremendous asymmetry is associated with amblyopia of the more involved eye.[17,48] A key clinical eye movement recording observation is the variable phase difference between the two eyes, which is reflected clinically as an asymmetry in the oscillations between the two eyes.

Spasmus nutans may be a completely benign condition with onset in infancy and resolution within 2 years. However, tumors of the diencephalon can cause a condition indistinguishable from spasmus nutans. Consequently, neuroimaging or careful monitoring for visual, neurologic, or endocrinologic decline is essential. An intracranial tumor should be strongly suspected in any child who develops spasmus nutans after 3 years of age. Neurodegenerative disorders such as Pelizaeus–Merzbacher disease and Leigh disease may produce nystagmus and head nodding that are indistinguishable from spasmus nutans. These disorders should be suspected in children with clinical signs of ataxia or developmental delay, or with MRI evidence of white matter signal abnormalities. Achromatopsia, congenital stationary night blindness, and Bardet–Biedl syndrome can also masquerade as spasmus nutans.

Drugs/toxins

Many drugs (some in therapeutic dosages) or toxins can cause nystagmus. The most common of these include anticonvulsants (i.e. phenobarbital, phenytoin, and carbamazepine), sedatives, hypnotics, and alcohol. Aspirin and quinine drugs causing nystagmus include chloroquine, quinidine, and quinine. Loop diuretics causing nystagmus include bumetanide, ethacrynic acid, furosemide, and torsemide. Aminoglycoside antibiotics causing nystagmus include amikacin, dihydrostreptomycin, gentamicin, neomycin, netilmicin, ribostamycin, streptomycin, and tobramycin. Antineoplastic drugs causing nystagmus include carboplatin and cisplatin. Environmental chemicals/toxins causing nystagmus include butyl nitrite, carbon disulfide, carbon monoxide, hexane, lead, manganese, mercury, styrene, tin, toluene, trichloroethylene, and xylene.[49,50]

Intracranial disease

Developmental, traumatic, and inflammatory brain diseases commonly cause acquired nystagmus. Consequently, nystagmus associated with other systemic, historical, and physical findings nearly always requires further neurologic and radiologic evaluation (see "localizing" forms of nystagmus below for further discussion.)

Voluntary flutter

Voluntary flutter ("nystagmus") (present in 7% to 15% of the population) is a misnomer, referring to a series of volitional, rapid alternating saccades with little to no intersaccadic interval[25] (see Figs 90.12 and 90.15). They are usually horizontal, but may be vertical or torsional, and can only be sustained for a few seconds. Voluntary nystagmus is a popular "party trick," and is often seen in patients with functional visual complaints. It is frequently associated with convergence of the eyes or facial grimacing. Voluntary nystagmus warrants no laboratory or radiographic investigation.

"Localizing" forms of nystagmus due to neurologic disease (Box 90.1)

(A)periodic alternating nystagmus

Periodic alternating nystagmus may resemble infantile nystagmus or be "acquired." Patients with acquired form usually have vertigo, nausea, dizziness, and oscillopsia. The key clinical component is that the null point shifts position in a cyclic pattern. This results in changes in the amplitude and direction of the nystagmus every few minutes. Adequate observation of the patient for several minutes should exclude this diagnosis. However, it should be considered any time a

Box 90.1

Neurological nystagmus types

See-saw nystagmus

Rostral midbrain lesions
Parasellar lesions (e.g. pituitary tumors)
Visual loss secondary to retinitis pigmentosa

Downbeat nystagmus

Lesions of the vestibulocerebellum and underlying medulla (e.g. Arnold–Chiari malformation, microvascular disease with vertebrobasilar insufficiency, multiple sclerosis, Wernicke encephalopathy, encephalitis, lithium intoxication)
Heat stroke
Approximately 50% have no identifiable cause

Upbeat nystagmus

Medullary lesions, including perihypoglossal nuclei, the adjacent medial vestibular nucleus, and the nucleus intercalatus (structures important in gaze holding)
Lesions of the anterior vermis of the cerebellum
Benign paroxysmal positional vertigo

Periodic alternating nystagmus

Arnold–Chiari malformation
Demyelinating disease
Spinocerebellar degeneration
Lesions of the vestibular nuclei
Head trauma
Encephalitis
Syphilis
Posterior fossa tumors
Binocular visual deprivation (e.g. ocular media opacities)

Pendular nystagmus

Demyelinating disease
Monocular or binocular visual deprivation
Oculopalatal myoclonus
Internuclear ophthalmoplegia
Brainstem or cerebellar dysfunction

Spasmus nutans

Usually occurs in otherwise healthy children
May be caused by chiasmal, suprachiasmal, or third ventricle gliomas

Torsional

Lateral medullary syndrome (Wallenberg syndrome)

Abducting nystagmus of internuclear ophthalmoplegia

Demyelinating disease
Brain stem stroke

Gaze-evoked

Drugs: anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) at therapeutic dosages

patient's head turn is different from one examination to the next. This is more common in patients with oculocutaneous albinism.[51,52]

Periodic alternating nystagmus is usually congenital and benign. However, it may be associated with vestibulocerebellar lesions, neurodegenerative conditions such as Friedreich ataxia, or even visual loss. Neuroimaging is warranted in all cases unless the nystagmus has been stable for a prolonged period of time. Periodic alternating nystagmus may respond to treatment with low doses of baclofen in acquired forms of periodic alternating nystagmus.[53]

Gaze-evoked nystagmus

Gaze-evoked nystagmus is a jerk nystagmus that occurs in the direction of eccentric gaze. In contradistinction to infantile nystagmus, most forms of gaze-evoked nystagmus can be stabilized by visual fixation and are accentuated by darkness or image blur (see Fig. 90.11). Gaze-evoked nystagmus is called gaze-paretic nystagmus if it occurs in the direction of limited eye movement, as it may be associated with a cranial nerve palsy or myasthenia gravis. Gaze-paretic nystagmus may appear dissociated if the limitation of eye movement is asymmetric between the two eyes. One form of gaze-evoked nystagmus that is completely benign is endpoint nystagmus. This occurs in extreme positions of lateral or upward gaze. It can be distinguished from pathologic forms of gaze-evoked nystagmus by its low amplitude, symmetry on right and left gaze, poor sustainability, and absence of associated neurologic abnormalities. With endpoint nystagmus, the eyes attempt a saccade out to an extreme gaze position and have an initial difficulty finding this position. After a short amount of jerk nystagmus, the position is found, and the eyes maintain the eccentric gaze. Endpoint nystagmus is a normal finding and differs from gaze-evoked nystagmus by the fact that gaze-evoked nystagmus is a constant nystagmus with larger amplitude (defined as 4° or more) and is often asymmetric. Gaze-evoked nystagmus is caused by a deficiency, usually a structural lesion, in the neural integrator network. Gaze cannot be held at an extreme position, and the eyes drift back toward the null point of the integrator, which often is straight-ahead gaze. A corrective saccade is attempted to move the gaze back to the eccentric position, and the process repeats.

Disease in the posterior fossa or drugs, particularly anticonvulsants and sedatives, are the most common causes of pathologic gaze-evoked nystagmus. Disease of the cerebellum or vestibular system usually results in asymmetry of gaze-evoked nystagmus between directions of gaze. For example, tumors of the cerebellopontine angle may result in high-amplitude, low-frequency nystagmus (caused by cerebellar damage) when looking to the side of the lesion, and low-amplitude, high-frequency nystagmus (caused by vestibular imbalance) when looking to the contralateral side, a condition known as Brun nystagmus. Associated neurologic abnormalities such as ataxia, hearing loss, tremor, or hemiparesis should always be sought.

Vestibular nystagmus

Certain characteristics of vestibular nystagmus can localize the etiology to the peripheral or central neuronal pathways of the vestibular systems. Central vestibular nystagmus is frequently uniplanar in contrast to peripheral vestibular nystagmus, which is usually torsional or multiplanar. Visual fixation easily inhibits peripheral vestibular nystagmus, but not central vestibular nystagmus. Vertigo and tinnitus are common in peripheral vestibular nystagmus, and uncommon in central vestibular nystagmus.

Acquired pendular nystagmus

Acquired pendular nystagmus may be due to tumors, infarction, inflammation, or degeneration of the brainstem or cerebellum. The nystagmus may be horizontal, vertical, or

both. A single lesion in the brain will result in horizontal and vertical components that oscillate at the same frequency of 2–7 cycles per second. If the horizontal and vertical components are in phase, the nystagmus will appear oblique. If they are out of phase, it will appear circular or elliptical. Circular or elliptical nystagmus that is constantly changing character is due to horizontal and vertical components oscillating on different frequencies.

See-saw nystagmus

See-saw nystagmus is a pendular, upward incyclotorsion of one eye with a simultaneous downward excyclotoresion of the other eye. The pendular waveform see-saw nystagmus is commonly due to a midline mesodiencephalic, bilaterally compressing mass[54] (see Fig. 90.21). See-saw nystagmus can also be associated with traumatic or congenital chiasmal abnormalities,[54] and is mostly due to a unilateral lesion in the mesodiencephalic junction. Congenital see-saw nystagmus is a rare form of neonatal nystagmus with upward excyclotorsion of one eye and concomitant downward incyclotorsion of the other eye.

Downbeat nystagmus

Downbeat nystagmus is usually produced by lesions in the cerebellum that also damage pathways that control horizontal tracking and visual–vestibulo-ocular interactions.[53,55] The most frequent causes are infarction, cerebellar and spinocerebellar degeneration syndromes, and multiple sclerosis and developmental anomalies affecting the pons and cerebellum.[53,55] It is also commonly due to drugs (particularly lithium or sedatives) or lesions at the cervicomedullary junction.[53,55] In children, it is usually due to Arnold–Chiari malformation or syringomyelia. Without a drug history, downbeat nystagmus should be evaluated in all patients with a sagittal MRI scan of the brainstem and cervical spinal cord. All patients have jerk-down nystagmus in some positions of gaze and a few patients have jerk-down nystagmus only with convergence, in the dark, or with positioning of the head and body. Horizontal gaze increases the nystagmus. The nystagmus slow components usually have constant velocity or increasing-velocity waveforms. Associated patterns of abnormal horizontal eye movements are characteristic of damage to the midline structures of the cerebellum (impaired pursuit, impaired OKN, and inability to suppress VOR).

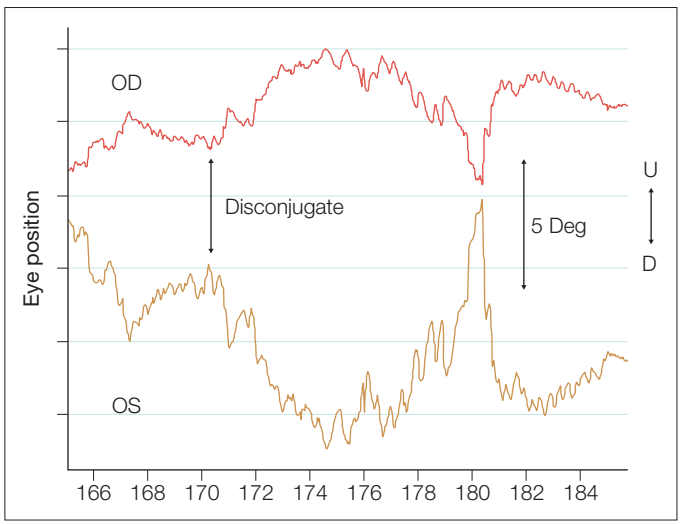


Fig. 90.21 Ocular motility recording of see-saw and pendular nystagmus. This is a 20 s vertical position trace of ocular motor recordings from a patient with see-saw and pendular nystagmus. On a background of a continuous, 2–4 Hz, pendular, small-amplitude, conjugate, ocular oscillation there is a slower, vertically out of phase, disconjugate oscillation representing the see-saw component. D, downward eye movements and downgaze; Deg, degrees; JL, jerk left nystagmus; OD, right eye; OS, left eye; U, upward eye movements and upgaze.

Upbeat nystagmus

Upbeat nystagmus with its fast upward movement usually increases on extreme upgaze and generally follows Alexander's Law. The oscillations may be enhanced by a head tilt, and with convergence the nystagmus can increase or change to downbeat nystagmus. Upbeat nystagmus is probably caused by midbrain dysfunction or cerebellar disease. It is very similar to downbeat nystagmus but is generally less common.

Treatment and prognosis

There are a number of signs and symptoms due to nystagmus that are amenable to treatment. The first and most obvious is decreased vision ("central visual acuity," "gaze-angle acuity", near acuity). Correction of significant refractive errors in children with nystagmus is the single most powerful therapeutic intervention for improving vision and visual function in these patients. Refractive etiologies of decreased "vision" include either one or a combination of conditions, e.g. myopia, hyperopia, astigmatism, and anisometropia. These refractive conditions can contribute significantly to already impaired vision in patients with other "organic" etiologies of decreased vision, e.g. amblyopia, optic nerve and/or retinal disease, oscillopsia, and the oscillation itself. The use of telescopes, magnification, and other low-vision aids are valuable refractive adjuncts that can be used situationally in nystagmus patients with and without associated sensory system deficits. The second is AHP. The etiology of the AHP includes a "gaze null" due to INS or acquired nystagmus (e.g. chin-down in downbeat nystagmus), an "adduction null" due to infantile nystagmus or latent/manifest latent nystagmus (manifest strabismus with the preferred eye fixing in adduction), convergence damping ("nystagmus blockage"), and a periodically changing head posture due to (a)periodic alternating nystagmus. The third is oscillopsia, which is usually due to either acquired nystagmus or a change in the sensory/motor status of the patient with infantile nystagmus (e.g. "decompensated" strabismus, a change in the gaze null angle, or decreasing acuity).[56] Other less common associated signs and symptoms include hypoaccommodation and photophobia (i.e. congenital cone dystrophy and albinism).

The prognosis of all these ocular oscillations depends on the type of underlying ocular and systemic disease. In general, infantile forms improve with time unless they are associated with a degenerative ocular or systemic disease. Acquired forms are more visually disturbing and follow the course of the underlying neurologic disease.

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"I think my baby can't see!"

Ingele Casteels

Normally, a full-term baby shows visual fixation at birth or shortly afterward. Absent, poor, or delayed visual contact is a common reason parents bring their baby to their ophthalmologist. They are anxious to understand why the baby seems not to see, and want to know the cause and prognosis. Although this is not usually a medical emergency, parents need to have their baby diagnosed soon. In some babies, the underlying cause is evident on clinical examination; in others, additional investigation will be necessary. The diagnosis depends on a thorough birth, family, and clinical history and a systematic clinical examination (Fig. 91.1). The clinician should verify the cause and degree of visual impairment, give a prognosis, and make a plan of management and counseling for the family.

History

It is important to take a detailed history from the parents and caretakers. While talking to the parents, you can observe the infant's visual behavior. The history of the pregnancy, delivery, and postnatal development is important. Was the baby premature? Visual development depends on the postmenstrual age at birth. Premature infants with intraventricular hemorrhage are at risk of optic atrophy (see Chapter 56), hydrocephalus, and cerebral visual impairment (CVI) (see Chapters 59 and 60). Visual development in premature babies can also be delayed due to associated retinal or neurological problems. The presence of seizures, developmental delay, and dysmorphic features may suggest a brain problem. Maternal infections, trauma, hypoxia, and medication during pregnancy can have significant visual consequences. Babies exposed to opiates and benzodiazepines *in utero* may present with nystagmus and reduced visual acuity, due to insults to the central nervous system.[1]

It is important to find out whether there is a significant problem or whether the baby is just different from others. Some normal babies can just be less responsive. Has there been a change in visual behavior since birth? Vision can deteriorate after the onset of seizures or progressive neurological or ocular diseases.

A positive family history, or a history of consanguinity, makes certain diseases more likely. For instance, a baby whose parents are first cousins and who has searching eye movements and hypermetropia is liable to have a congenital retinal dystrophy (see Chapter 46). The pediatric ophthalmologist should inquire about other family members, examine them and the first-degree relatives. Specific questions to parents or caregivers regarding the visual behavior in dark or bright light can give an additional clue to the diagnosis: some congenital retinal disorders, especially achromatopsia, cone–rod dystrophy, and Leber congenital amaurosis, may present with photophobia or day blindness (see Chapter 46). Babies with CVI can show reluctance to look at a light, or, in contrast, will develop light-gazing (see Chapter 60).[2] Lens (see Chapter 37) and corneal opacities (see Chapters 34 and 35), i.e. congenital glaucoma (see Chapter 38), albinism (see Chapter 41), and aniridia (see Chapter 39), can cause photophobia.

Have the parents noticed wobbling eyes? Nystagmus and searching eye movements can be the presenting symptoms in many babies with poor vision from birth, but usually appear at 2–3 months of age. Roving or drifting eye movements are often seen in babies with very poor vision.

Are there any specific hand movements? Blind babies tend to press or poke their eyes (Fig. 91.2). Some visually impaired children rapidly flicker their fingers in front of their eyes while staring at lights[3] (Fig. 91.3).

Examination

It is often difficult to quantify visual acuity in babies, especially in those with poor visual contact. Parental estimations of vision and changes in vision can be helpful, but it is relevant to obtain a measure of overall visual function. Despite advances in research, behavioral observations remain of primary importance in assessing visual function in infancy. In a term baby, a visual following response should be present by 2 months, and the baby should smile responsively to a parent. At 4 months, a child should reach for an object. Complex stimuli with contrast should interest a happy and wakeful baby. The presence of optokinetic nystagmus (OKN) in a baby excludes a very severe visual problem. In congenital ocular motor apraxia (saccadic initiation failure), the eyes will deviate on being spun around without developing the fast "return" phase of nystagmus ("locking up" in sidegaze). In most cases, the vertical OKN is normal. A measure of vision can also be achieved with the dynamic vestibulo-ocular reflex (VOR) by evaluating the "after" nystagmus, which is much longer in a blind baby. In addition to the normal immaturity of pursuit and saccadic movements in the newborn, congenital ocular motor

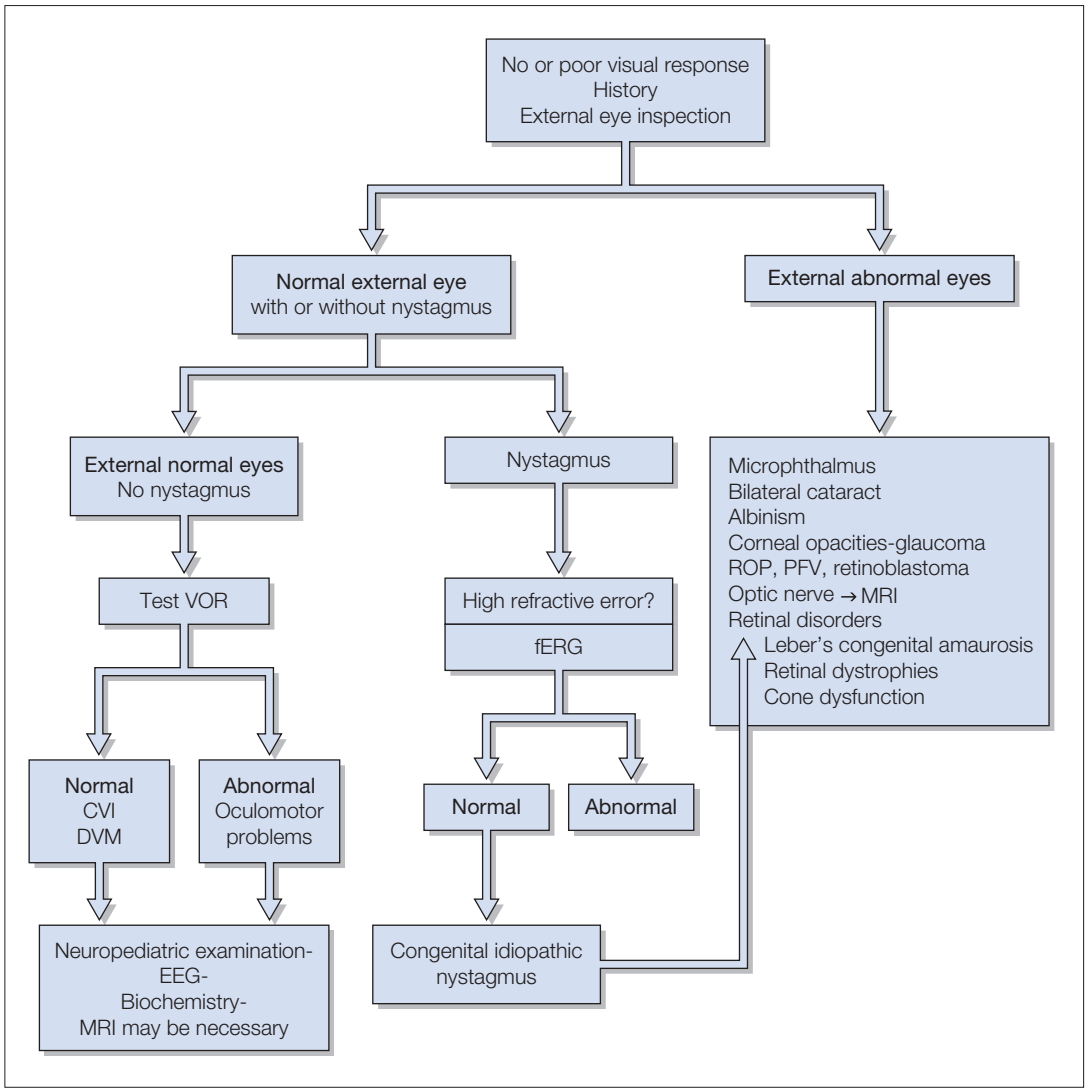


Fig. 91.1 Evaluation of an apparently blind infant. CVI, Cerebral visual impairment; DVM, delayed visual maturation; EEG, electroencephalogram; fERG, flash electroretinogram; MRI, magnetic resonance imaging; PFV, persistent fetal vasculature; ROP, retinopathy of prematurity; VOR, vestibulo-ocular reflex.



Fig. 91.2 Eye poking in a blind baby with Leber amaurosis.



Fig. 91.3 Babies with limited vision tend to wave their hands between their eyes and a light source.

Table 91.1 Common causes of poor vision in infants with apparently normal eyes on clinical examination

Diagnosis	Clinical signs apart from poor vision	Pupils	Slit-lamp	Ophthalmoscopy	Refraction	Flash ERG	Flash VEP	Pattern VEP	MRI	Neuropediatric examination/ EEG	Visual outcome
DVM	Poor visual contact	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Cerebral visual impairment	Eccentric viewing/ light gazing	Normal	Normal	Usually normal	Normal	Normal	Usually abnormal	Usually abnormal	Usually abnormal	Usually abnormal	Usually poor perceptual defects
Idiopathic nystagmus syndrome	Nystagmus Head tilt	Normal	Normal	Normal	Normal/ abnormal	Normal	Normal	Abnormal	Normal	Normal	Good
Leber congenital amaurosis	Roving eyes Photophobia Eye poking	Paradoxical Sluggish or normal	Normal	Usually normal	High hypermetropia	Absent	Abnormal	Absent	Usually normal	Normal	Poor
Retinal dystrophy	Nystagmus Night blindness	Usually normal	Normal	Usually abnormal	Usually normal	Abnormal	Usually normal	Abnormal	Normal or abnormal	Normal or abnormal	Poor
Achromatopsia/ cone dystrophy	Photophobia Day blindness Color blindness Nystagmus	Paradoxical or normal	Normal	Normal	Normal or high hypermetropia Blue cone dystrophy, myopic	Absent cone response	Normal	Abnormal	Not indicated	Normal	Poor, photophobia Stationary
Bilateral optic nerve hypoplasia or atrophy	Poor vision Roving eye movements	Afferent defect	Normal	Abnormal, direct ophthalmoscopy necessary	Normal	Normal	Abnormal	Abnormal	Normal or abnormal	Normal or abnormal + endocrine exam	Variable
Albinism	Nystagmus Photophobia	Normal	Abnormal	Abnormal	Myopia or astigmatism	Normal or enhanced	Crossed asymmetry	Crossed asymmetry	Usually not indicated	Normal	Variable

DVM, Delayed visual maturation; EEG, electroencephalogram; ERG, electroretinogram; MRI, magnetic resonance imaging; VEP, visually evoked potential.

apraxia, Möbius syndrome, and bilateral Duane syndrome may be the cause of apparently poor visual contact because the baby cannot move the eyes. Rotation to induce VOR should exclude an eye movement defect.[4]

Examination of the eyes and eye movements may reveal nystagmus and strabismus. It is difficult to distinguish between nystagmus waveforms clinically. Eye movement recordings have shown some useful clinical information. A high-frequency, low-amplitude pendular nystagmus in otherwise normal eyes is often seen in cone dystrophies[5] (see Chapter 46). Searching eye movements with very poor vision are seen in Leber congenital amaurosis (see Chapter 46). Early-onset nystagmus can be divided into three groups: sensory defect nystagmus, in which there is a proven sensory defect; congenital idiopathic nystagmus (sometimes called motor nystagmus), in which no visual or neurological impairment can be found; and neurological nystagmus, which is associated with neurological disease.[6]

Pupil reactions can be useful and should be examined carefully (see Chapter 66). In most babies, the cause of poor vision from birth is obvious to a pediatric ophthalmologist after clinical examination. A structural abnormality (e.g. microphthalmos) may be obvious at first glance. The presence of the red reflex excludes media opacities. Slit-lamp examination may reveal anterior segment problems: cataracts (see Chapter 37), colobomas, aniridia (see Chapter 39), or albinism (see Chapter 41), and is particularly important in infants with nystagmus. In cases of albinism, iris transillumination is evident. Especially in ocular albinism, the diagnosis is less straightforward without a good look at the anterior segment. Slit-lamp examination should be repeated after dilatation of the pupils in order to better visualize lens opacities or lens subluxation.

Bilateral pupillary dilatation is necessary in order to perform indirect and direct funduscopy and retinoscopy. On funduscopy, attention is paid to both the vitreous and the retina. Vitreous haze and hemorrhages, seen in bleeding disorders, uveitis (see Chapter 40), retinal vasculitis, non-accidental injury (see Chapter 70), retinopathy of prematurity (see Chapter 44), retinal dysplasia (see Chapter 46), hyaloid abnormalities, and retinoblastoma (see Chapter 43), may be found. Indirect ophthalmoscopy will reveal retinal problems such as chorioretinal colobomas, macular toxoplasmosis (see Chapter 40), retinal detachment (see Chapter 52), retinal folds, chorioretinal dysplasia, and sometimes, retinal dystrophy. However, many cases of congenital retinal dystrophies will present with a normal-appearing retina on ophthalmoscopy.

Direct ophthalmoscopy and fundus photographs are best for subtle optic disc anomalies such as colobomas and optic disc hypoplasia or dysplasia (see Chapter 53). An examination under sedation or anesthesia may occasionally be necessary to see the optic nerve in detail.

Refraction is essential. High refractive errors – hypermetropia in particular – can give rise to poor visual contact from birth. Correction of moderate and high myopia in babies with apparent delayed visual maturation may improve poor visual behavior.[7] Refractive errors can provide a clue to the underlying diagnosis.

When the eyes of a baby with poor visual contact appear to be normal, with or without nystagmus, further investigation is necessary (Table 91.1). The flash electroretinogram (fERG) may diagnose retinal diseases. The fERG and flash visually evoked potential (VEP) have conspicuous immature features during the early months and may not aid in establishing the diagnosis. The fERG may be more useful at a later age.[8,9]

A pediatric neurological consultation and further investigations, such as biochemistry and brain magnetic resonance imaging (MRI), are carried out where indicated. Babies affected with CVI usually have a normal eye examination, no nystagmus or strabismus; some have associated optic nerve atrophy (see Chapter 60).

An electroencephalogram (EEG) should also be included in the initial investigation of every infant with apparent delayed visual maturation (DVM) in order to detect a treatable underlying seizure activity.[10] "Delayed visual maturation" is a term used to describe a normal baby with a transient visual deficit (see Chapter 4). There are no data to establish that any primary visual system is delayed in its development (see Chapter 3). DVM is a retrospective diagnosis, which can only be made after a long enough follow-up to exclude neurological problems. DVM is not a single diagnostic condition but rather a sign common to neurological abnormalities affecting several areas of the brain (see Chapter 3). The visual prognosis of infants with isolated delayed visual maturation is good, but there is an increased risk of neurodevelopmental and educational problems in the future.[4]

An incorrect or unclear diagnosis of visual impairment in an infant can be devastating to the family. In most infants presenting with poor visual contact, clinical signs are diagnostic, but additional studies may be necessary to establish the correct diagnosis. A long enough follow-up by the ophthalmologist in collaboration with the pediatrician should be planned and it is essential to be encouraging whenever you can, but not to be dogmatic about either the diagnosis or the prognosis, as both can change!

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"My baby's got a red eye, Doctor!"

Giovanni Castano

Introduction

The classical clinical description of conjunctival injection differentiates clearly deep and superficial congestion. Dilation of the superficial posterior conjunctival vessels is more intense at the fornix; the vessels branch irregularly, appearing bright red. This type of congestion indicates a purely conjunctival problem. Pericorneal or deep injection is more intense at the limbus, where the ciliary vessels radiate in a regular pattern and are violet or rose colored. Deep congestion is present when a pathological process involves the eyeball itself, particularly when anterior segment structures are affected. Both may co-exist but the ophthalmologist must determine which is more prominent to make the correct diagnosis.[1]

Babies with a red eye must have a complete ocular examination. Although ideally slit-lamp biomicroscopy should be a part of this evaluation, assessment with simple magnification may be all that is possible and is often sufficient to make a diagnosis. Red-free illumination is very useful to differentiate the type of conjunctival congestion; fluorescein staining helps to reveal conjunctival and corneal epithelial defects or foreign bodies.[2]

In some instances, a red eye might be considered "normal" in an infant. Transient subconjunctival hemorrhages are not rare in newborns, especially after vaginal delivery.[3] During the first hours of life, the conjunctival vessels have also been described as prominent.[4] Crying (a frequent feature when visiting the ophthalmology clinic) is a Valsalva maneuver and thus may induce ocular congestion.[5] This phenomenon is extremely variable during the exam, an important difference from the constant abnormal injection.[6] As a rule, however, a red eye in an infant must be considered a pathological sign. Certain clinical "red eye" situations in infancy may prompt a search for distinct diagnoses.

Superficial conjunctival congestion with discharge

Conjunctivitis is the most common cause of red eye in infancy.[7] The presence of superficial congestion and purulent discharge suggests a diagnosis of bacterial conjunctivitis. Conjunctivitis of the newborn, once a typical gonococcal infection, is now more frequently caused by *Staphylococcus aureus* than by *Chlamydia trachomatis*. Nevertheless, in endemic areas, chlamydial and gonococcal etiologies are of concern.[8]

Fornix conjunctival injection with a watery discharge is a sign of viral conjunctivitis. Neonates with this clinical picture could have Herpes simplex-2 conjunctivitis acquired through the birth canal. In an older infant with bilateral conjunctival congestion and watery discharge, follicular adenoviral conjunctivitis is a probable diagnosis, especially if there is clear history of close contact with another infected person.[9]

Superficial conjunctival congestion with itching

Although allergic conjunctivitis is rare in infancy, babies living in highly polluted areas may develop this.[10,11] When there is no corneal involvement, bilateral superficial congestion and itching become diagnostic features.[12]

Pericorneal or deep injection

Pericorneal injection must be recognized because it is associated with serious ocular diseases. Limbal congestion may be present in a 360° distribution pattern. This finding means a diffuse or serious involvement of any structure of the anterior segment, and its cause must be identified in all patients.[13]

Limbal congestion with photophobia and tearing

Keratitis of any etiology can cause these symptoms. Children with infectious keratitis are at risk of developing visual loss from structural damage or amblyopia. Although keratitis may be present at birth as a result of intrauterine infection, it is usually acquired. Trauma, contact lens wear, previous corneal surgery, exposure, immunodeficiency, and prolonged steroid treatment are the most frequent predisposing factors.[14,15] Although frequent in childhood, herpetic keratitis is rare in infants.[16,17]

Corneal abrasions or ulcers may occur in aphakic contact lenses wearers, and may resolve with conservative treatment.[18] Diffuse punctate keratitis is the hallmark of congenital corneal anesthesia and hypoesthesia. A similar picture is seen in patients with congenital alacrimia. Intense lubrication and every other barrier or surgical method are necessary to avoid corneal perforation and blindness.[19–21]

Localized punctate epithelial defects or ulcers are common in exposure keratitis. The most important clinical clue is a localized pericorneal injection. Preterm babies in the neonatal intensive care unit or sedated infants in intensive care unit are at risk of developing lagophthalmos with inferior corneal exposure.[22] Exposure keratitis also occurs in patients with eyelid defects such as congenital ectropion and coloboma.[23,24] Congenital entropion, distichiasis and isolated trichiasis can also induce keratitis.[25,26] Facial nerve paralysis in patients with Möbius syndrome does not usually cause exposure keratitis because Bell's phenomenon usually protects the corneas, except in some cases with limited elevation or defective corneal sensation where corneal integrity is severely threatened.[27,28] Isolated facial nerve palsy in the newborn has been related to birth trauma. Although complete recovery is common, attention must be paid to the ocular surface to prevent exposure and complications.[29] Forceps-induced injuries may include Descemet's membrane rupture.[30] Retrobulbar masses and infections, or shallow orbits in patients with craniosynostosis, can induce exposure keratitis or even globe luxation.[31,32]

Corneal dystrophies and deposits affecting the epithelium can cause a red eye, photophobia, and tearing in infancy. This can be seen in tyrosinemia II and Reis–Bücklers dystrophy.[33,34]

Primary congenital glaucoma presents in infancy with corneal opacification, buphthalmos, tearing, photophobia, and perilimbal injection.[35] Babies with secondary glaucoma can have a similar clinical picture. Pathophysiological mechanisms include uveitic or lens-induced pupil block, and anterior displacement of the iris–lens diaphragm, as seen in stage 5 retinopathy of prematurity and growing intraocular tumors. Anterior chamber deposits with cellular accumulations (pseudo-hypopyon) may be seen in babies with retinoblastoma and leukemia.[36–38] Any orbital tumor can induce vascular engorgement or exposure of the globe, causing a red eye. Conjunctival congestion may persist after treatment and, in these cases, therapy-associated keratitis could be a common cause.[39–41]

Accidental and non-accidental injuries are not rare in infants. A common cause of corneal ulcer or abrasion is accidental self or "sibling-inflicted" trauma. Pericorneal congestion is usually localized and its location indicates the exact place where the cornea is affected. Subconjunctival hemorrhages are also frequent is these cases. A unilateral, watery red eye in an irritable baby is the classical clinical picture. Corneal foreign bodies may have a similar presentation.[42] As in every non-accidental trauma, inconsistent history of mechanism of injury and particular social and demographic risk factors require investigation for possible child abuse.[43] Chemical and toxic keratitis have been described as part of non-accidental injuries.[44,45] Iatrogenic instillation of formaldehyde instead of prophylactic antibiotic just after delivery has been described to cause cloudy cornea and deep congestion, which cleared up after a few months.[46]

The painless red eye

Conjunctival nevi and limbal dermoids can be vascularized, causing a red eye.[47] Conjunctival hemangiomas may occur, characteristically enlarging some weeks after birth.[48] Dilated episcleral vessels may be a feature of Sturge–Weber syndrome. These patients may also develop glaucoma with additional ciliary injection.[49] Conjunctival angiomas and telangiectases are found in many patients with other vascular phacomatoses.

Hyphema could be present in ocular trauma of any origin, but spontaneous bleeding is seen in patients with juvenile xanthogranuloma. Identifying the typical skin lesions that are sometimes present in this disorder could avoid an erroneous diagnosis of child abuse.[50]

Unexpected causes of a red eye in infants

Neonatal chemical conjunctivitis associated with prophylactic silver nitrate eye drops is now rare, but current prophylactic drugs, including povidone-iodine, could also induce a transient red eye.[51,52] Topical latanoprost causes conjunctival hyperemia in infants with glaucoma and, sometimes, atropine causes a red eye.[53,54]

Scleritis and episcleritis are rare in infants. When present, a localized area of vascular congestion is the key for the right diagnosis. B-scan ultrasound is a helpful confirmatory test.[55–57]

Bacterial endophthalmitis is also uncommon in infancy. Open-globe trauma and glaucoma surgery are the most frequent causes in children. Endogenous origin is the least common cause. The severity of the clinical picture, including the ocular congestion, correlates with the virulence of the infecting microorganism.[58]

Uveitis causes circumcorneal injection. Although intraocular inflammation is seldom seen in infants, its presence often indicates a serious underlying problem. It is a challenge to detect anterior chamber cells and flare in a baby, but biomicroscopic examination is essential in infants with unexplained perilimbal congestion. Deep injection could be minimal, and its intensity is usually proportional to the severity of uveitis.[59] Besides traumatic etiology (accidental, non-accidental, or surgical), uveitis in an infant could be part of Kawasaki disease (acute systemic vasculitis plus coronary findings), ocular intrauterine infection, atypical intraocular tumor, and other unusual etiologies.[60–69] Although Blau syndrome (dominantly inherited, granulomatous dermatitis, symmetric arthritis, and recurrent uveitis) can start in the neonatal period, uveitis is usually seen later in childhood.[70] Outbreaks of acute enterovirus uveitis have been reported in infants.[71] Although reported only in adults, uveitis after intravitreal injection of bevacizumab will become an important issue in preterm babies, as more patients with retinopathy of prematurity are treated with anti-vascular endothelial growth factor (anti-VEGF) molecules.[72,73]

In severe vitamin A deficiency, conjunctival congestion is present due to dry eye, corneal vascularization, and Bitot's spots. Early administration of high doses of vitamin A may restore the ocular surface, and retinal function, preserving the patient's vision.[74]

Acute Horner syndrome usually causes transient conjunctival congestion in the ipsilateral eye.[75] Similarly, carotid artery aneurysm also causes transient ipsilateral conjunctival injection by impeding cavernous sinus venous return.

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"My child keeps blinking and closing his eye"

Kimberley Tan

Introduction

This common problem in pediatric ophthalmology practice has several possible causes. The diagnosis is usually apparent after a careful history and examination. Parents are often anxious that these overt, potentially stigmatizing movements could be a sign of more sinister neurological or complex behavioral disorders. The vast majority of children have ocular surface irritation, usually allergic eye disease, or a simple, isolated tic.

Etiology

The causes of a child presenting with blinking/closing an eye include:

1. tic;
   a. transient tic disorder (provisional tic disorder);
   b. chronic tic disorder;
   c. Tourette syndrome;
   d. functional blinking;
2. excessive blinking in response to ocular irritation;
3. closing one eye in intermittent exotropia;
4. "squinting" to see (pinhole effect);
5. rarer causes (Table 93.1).

The pediatric ophthalmologist will usually see either of the first two conditions, often a combination of the two. Eyelid tics may be isolated, or part of more generalized tic disorder. It should be emphasized that they are a common finding in normal children.

In a prospective, consecutive case series of 99 children presenting with excess blinking, Coats et al.[1] found an underlying etiology that would be discovered by a standard comprehensive ophthalmological examination in 62%. Anterior segment and/or lid abnormalities were the underlying cause in 37% of children, uncorrected refractive errors in 14%, and intermittent exotropia accounted for 11%. Tic disorder was divided into "habit tic" and "psychogenic blepharospasm" by the presence of an identified stressful event, and accounted for 23% and 10% respectively. Vrabec et al.[2] found a temporally related stressful event, which coincided with the onset of the blinking, in 41% of children they classified as "functional blinking." Other authors have shown a much higher proportion of tic disorder in children presenting with frequent eye blinking. Jung and coworkers[3] prospectively examined a series of 50 children with frequent eye blinking, excluding children with refractive error, intermittent exotropia, or lid disorders. Eighty-six percent were diagnosed with a tic disorder, with 78% being transient tic disorder. Seven out of the 50 children had ocular surface disease, mostly allergic conjunctivitis. In contrast to Coats et al.,[1] Jung[3] found that treatment of the surface disorder did not resolve the frequent eye blinking.

As a first step in making a diagnosis, exclude any serious ocular cause of irritation that could be the primary cause of the blinking behavior. Ocular irritation may also be the trigger to precipitate a bout of blinking from an alternative etiology, such as a tic. The comprehensive ophthalmological examination will exclude any significant ocular allergy, glaucoma, or keratitis, as well as eliminating intermittent exotropia as a reasonably common cause of monocular closure. Coats et al.[1] found vision-threatening ocular disorders in six of 99 children with excessive blinking. These included trichiasis, foreign bodies, and keratitis. These conditions should be obvious if a comprehensive ocular examination is performed. Here, blinking is simply a reaction to the ocular irritation. The overlap between ocular allergy and tic disorders, frequently seen in the same age group, is more subtle. The ocular allergy may be a primary cause of blinking, or a part contributor to episodic exacerbations of the blinking tic. A trial of a preservative-free mast cell stabilizer, such as topical ketotifen or olopatadine may be helpful.

Investigations for serious neurological disease

Coats and colleagues[1] found that four of their 99 children had life-threatening neurological disease. However, the existence of the life-threatening condition was known before the presentation of excess blinking, thus the blinking disorder did not prompt re-investigation.

The similarities between excess blinking and the predominantly adult disorders of blepharospasm, and other focal dystonias seen in basal ganglia disease,[4,5] suggest that neurological disease needs to be considered and excluded. A careful history is important to ensure there are no symptoms of more significant neurological disease, as these conditions will almost always have associated symptoms and signs (see Table 93.1). Ask about altered consciousness, other

Table 93.1 Less common differential diagnoses of simple eyelid blinking tic, with differentiating features and pathological concern

Differential diagnosis of simple tic	Historical clue	Differentiating examination sign(s) and concern
Seizures	Altered consciousness	Abnormal eye movement, lids, gaze and facial signs, field deficits, visual hallucinations[16]
PANDAS	Explosive onset	Concurrent streptococcal infection, choreiform movements[13]
Lid nystagmus		Rapid, jerky upper lid movements. Other ocular motility signs. Needs imaging: dorsal midbrain, cerebellar disease[17]
Myokymia		Fine, undulating, rippling superficial muscle contractions. If persistent, brainstem glioma needs exclusion[2]
Myoclonus		Prolonged orbicularis contraction. Cannot be suppressed. Occurs on eye closure. Investigate for epilepsy. Jeavon syndrome: eyelid myoclonia with absence spells[18]
Blepharospasm	Usually adult	Forceful, sustained contracture of orbicularis oculi. Neurometabolic work-up and imaging necessary. Exclude Wilson, Huntington[4]
Hemifacial spasm	Usually adult	Contracture entire half of facial nerve musculature. Neuroimaging of posterior fossa required for vascular anomaly or tumor[19]
Huntington disease, basal ganglia disease	Usually adult	Systemic basal ganglia signs: rigidity, myoclonus, bradykinesia[5,6]
Oculogyric crisis/ocular flutter/opsoclonus		Usually repetitive eye movements, not just lid disorder. Seizures, toxicity, cerebellitis, neuroblastoma[8]
Ocular motor apraxia		Blink is used to break fixation in saccadic initiation failure. Due to a wide variety of intracranial pathology and neurodegenerative etiologies[20]
Schwartz–Jampel syndrome		Short stature, blepharophimosis, spinal anomalies, general myotonia[21]
Phenothiazines, antiseizure drugs, stimulants, cocaine, heroin, carbon monoxide, mercury	History of drug use or toxin exposure[6]	

PANDAS, Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection.

abnormal movements, or more generalized tics. Inquire about development, milestones, and other events that may represent muscle weakness or seizures. If a careful history and comprehensive ophthalmological examination reveal no other concerns, then further investigation, including neuroimaging, is unnecessary.[1,6,7]

Table 93.1 lists the less common differential diagnoses of simple eyelid blinking tic, along with differentiating features in the history and clinical examination. The clinical findings guide the need to investigate for any possible sinister etiology.

Tic disorders

Given the prevalence of tic disorders, a basic understanding of their nature is helpful. Tics are involuntary, sudden, repetitive, purposeless, stereotyped intermittent movements or sounds.[6,8] They are fragments of normal movements or sounds that are inappropriate for the situation or context. The patient can voluntarily inhibit them, but the tic itself is not truly voluntary. The tics are suppressible but irresistible, and therefore still fundamentally involuntary. Tics have a key relationship to voluntary movements in the same body area: for example, eye-blinking tics will abate during visual tracking.[7] In contrast, dystonia, myoclonus, and simple partial seizures override voluntary movement, and psychogenic tics are often worse with voluntary movement in that same body area.[7]

Tics are common in children. A meta-analysis published in 2012 found a prevalence of 2.99% for transient tic disorder (TTD), 1.61% for chronic tic disorder (CTD), and 0.77% for Tourette syndrome (TS).[9] All are more common in boys. The primary differences between the three disorders are defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).[6] In TTD, the tics wax and wane but are not present for longer than 12 consecutive months. In CTD, the tics are present for longer than 1 year, with no tic-free period of more than 3 consecutive months. TS is similar to CTD but with multiple motor and one or more vocal tics.[6]

The onset of tics is usually between the ages of 3 and 8 years,[9] and for chronic disorders, the tics are usually at their greatest intensity between the ages of 10 and 12 years. For most children, the tic severity and related impairment improve through late adolescence and early adulthood.[10,11] The tics usually occur in bouts or clusters, aggravated by stress, tiredness, or boredom. They are often more prominent watching television[6] and thus bother the parent or carer seemingly more than the child.

Tic severity is rated by tic intensity (forceful or loud), tic complexity (longer bouts or orchestrated patterns), as well as tic interference (impeding intended actions). The combination of the three is used to grade the likely overall impact of the tic disorder on the patient.[10] However, the majority of children (between 50% and 90%) with chronic tic disorders have a co-occurring condition, and the comorbidity is often the primary source of functional impairment and disability.[6] The commonest co-occurring condition seen with CTD is attention-deficit hyperactivity disorder (ADHD), followed by social phobia, generalized anxiety disorder, and obsessive compulsive disorder.[10] These disorders contribute to poorer global psychosocial functioning. The pediatric

ophthalmologist needs to be aware of their likely existence to facilitate appropriate referral.

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)

A group of children present with tics and obsessive–compulsive symptoms after streptococcal infection. There is still some debate about the existence of this subgroup as a recognized separate classification.[12] However, in children where the tic onset is abrupt, even "explosive, overnight," PANDAS should be considered. Further, these children usually present within 7–14 days of the streptococcal infection, and the subsequent course is episodic, relapsing–remitting rather than the usual waxing and waning of common CTD.[13] Throat cultures and anti-streptococcal titers should be obtained where appropriate, and consideration given for treatment if acute streptococcal infection is demonstrated.

Management of eyelid blinking tics

The clinician should keep in mind that tics may be suggestible, so discussion of the problem may result in re-emergence of a specific tic.[6] Standard neurologic exam is important but is "inevitably normal." With no other symptoms or signs, neuroimaging is unnecessary.[6]

Transient tics or mild CTD need child and parental reassurance and information. An explanation of the involuntary, but suppressible, nature of tics is important. The clinician should try to establish if there are any comorbidities, and refer appropriately. If isolated, the diagnosis of "transient" tic disorder is nicely optimistic for the clinician and the parents. However, recognition of the possibility of chronicity should be mentioned. In a series of 43 children from a pediatric neuro-ophthalmic practice,[8] 44% of the children who presented with eye "rolling/blinking and widening" tics had become chronic, but the vast majority of these had noted an improvement in the severity of their tics. Only one patient (3%) had been formally diagnosed with Tourette syndrome.[8] Parents can be reassured that most children with CTD or TS still show improvement in their tic severity through adolescence and into early adulthood.[10,11]

If the tics do not settle, successful treatments exist. *Habit-reversal training* is a proven behavioral treatment used by pediatric psychologists to decrease tic severity, and should be considered as first-line therapy.[14] This behavioral treatment has been shown to reduce tic severity and improve global functioning.[15] If it is unsuccessful or adjunctive therapy is required, various medications have been used to treat the comorbid disorder, such as ADHD, as well the tics themselves. These include alpha-2-adrenergic agonists like clonidine.[6] Dopamine antagonists such as haloperidol are very effective for tics but may have significant side effects.[7]

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"My child seems to hate the bright light"

Luis H Ospina

See online for supporting video for this chapter.

Introduction

Light intolerance in a child may be isolated or, more frequently, may present in combination with other symptoms prompting consultation. In most cases, the child is likely to have a benign condition, or simply have lower tolerance to light, as "thresholds" vary among normal individuals.[1] The causes of photophobia are, nonetheless, heterogenous and include ocular or neurologic conditions, some potentially serious (Table 94.1).

An organized approach should facilitate the diagnosis of the etiology of photophobia.

Clinical approach

Clinical history

Given that ocular causes of photophobia outnumber neurological causes in a pediatric ophthalmology practice, a good strategy is to start with a targeted history by focusing on the symptoms and signs that accompany the ocular pathologies. A neurological history can then be taken subsequently, if appropriate. The patient's age, the laterality, duration, and nature of the symptoms should be noted (Table 94.2).

Physical exam

Given the nature of the problem, the examination can be challenging. The targeted history should guide your targeted exam. While talking to the parents, observe the child carefully: eyelid and conjunctival redness or swelling, blinking, watering and rubbing may suggest ocular surface disease. Nystagmus may indicate retinal pathology, or a small pupil in a red eye may indicate uveitis. Assessing visual acuity and pupillary responses is essential: a paradoxical pupillary response can indicate retinal dystrophies, especially in the presence of poor vision and nystagmus. Slit-lamp examination will confirm anterior segment causes of photophobia. Topical anesthetic drops and fluorescein help to diagnose a surface problem. Significant ametropia on cycloplegic refraction can accompany retinal disease, such as hypermetropia seen in achromatopsia or myopia in blue cone monochromatism. A hand-held refractometer may facilitate the exam of a photophobic child. A dilated fundus evaluation is important.

Ancillary testing

Testing color vision and visual fields is appropriate when compressive optic pathway lesions are suspected. Decreased color vision can also indicate retinal dystrophy.

Electroretinography and neuroimaging can be necessary to evaluate retinal and neurological disease respectively, and should be ordered on a case-by-case basis. Optical coherence tomography may be useful, e.g. determining foveal hypoplasia in achromatopsia.

Ocular causes

Corneal and ocular surface disorders

Given that the surface of the eye is richly innervated, the sensation of light intolerance is closely linked to that of pain.[2] Consequently, the pathologies that irritate the eye surface constitute the commonest ocular cause of photophobia: traumatic abrasions, foreign bodies, herpetic and other infectious keratitis, blepharokeratoconjunctivitis, allergic keratoconjunctivitis, etc. Establishing the diagnosis is relatively easy, based on the clinical presentation and slit-lamp findings. Dry eye, a common cause of adult photophobia,[2] is less prevalent but certainly under-recognized in children. It occurs in multiple syndromic and systemic diseases, after bone marrow transplantation, and even in common disorders like allergic conjunctivitis.[3]

The crystalline infiltration of the cornea in cystinosis causes significant photophobia that starts early (3–4 years) and will be present in varying degrees in most patients by the age of 10 years, especially if surface breakdown occurs.[4,5] Similarly, the accumulation of glycosaminoglycans in mucopolysaccharidosis can also lead to light sensitivity.

The corneal dystrophies can cause light aversion. Congenital hereditary endothelial dystrophy (CHED), sometimes seen soon after birth, presents with epiphora, corneal clouding, and photophobia. Later in childhood, Meesmann and Reis–Buckler corneal dystrophies (MECD and RBCD) can present with pain, hyperemia, and photophobia, notably with corneal epithelial erosions on waking that are common to these pathologies.[6]

Table 94.1 Important causes of photophobia in each age group

Infants	Infantile glaucoma Inherited corneal dystrophies, especially congenital hereditary endothelial dystrophy (CHED) Keratitis Descemet's break due to forceps delivery Cerebral visual impairment (CVI) Stationary cone dysfunction syndromes, e.g. achromatopsia and blue cone monochromatism
Young children	Glaucoma Corneal abrasions and foreign bodies Blepharokeratoconjunctivitis Vernal keratoconjunctivitis Herpes simplex or bacterial keratitis Meesmann and Reis–Buckler corneal dystrophies (MECD and RBCD) Cataract Albinism Aniridia Stationary cone dysfunction syndromes, e.g. oligochrome trichromacy and bradyopsia CVI Acquired central nervous system (CNS) pathology
School-age children	Progressive cone dystrophies Partial aniridia Cataract or ectopia lentis Intermittent exotropia Migraine Acquired CNS pathology

Modified from Funnell CL. My child seems to hate the bright light. In: Hoyt C, Taylor D, editors. Pediatric Ophthalmology and Strabismus, 4th ed. Edinburgh: Elsevier/Saunders, 2012: 968–70.

Table 94.2 Considerations in photophobia

Severity?	If severe photophobia, consider infantile glaucoma, corneal surface disease, achromatopsia, oculocutaneous albinism, or aniridia Migraine, and less often other central nervous system (CNS) pathologies can cause significant photophobia
Recent onset or present since very young?	Acquired corneal pathology is common in children Longstanding problem more likely to be due to an inherited corneal or retinal disease New-onset photophobia with a normal ocular examination may be due to migraine, or less often, to other acquired CNS pathologies
Reduced vision?	Most corneal and retinal pathologies causing photophobia also reduce visual acuity Cerebral visual impairment (CVI)
Nystagmus?	Common in retinal dystrophies, albinism, aniridia Absent or rare in CVI
One or both eyes?	Acquired corneal and ocular surface disease is often asymmetric Unilateral photophobia can occur in unilateral anterior uveitis, unilateral iris or lens defects, and trigeminal autonomic cephalalgias
Constant or intermittent?	Consider migraine or fluctuating corneal pathology (e.g. recurrent erosion in MECD and RBCD)
Associated redness of eyes?	Suggests corneal and eye surface pathology Anterior uveitis Unilateral redness can occur in trigeminal autonomic cephalalgias
Squint?	Intermittent exotropia
Family history or history of consanguinity?	MECD and RBCD, aniridia, and many congenital cataracts are dominantly inherited Cystinosis, and achromatopsia are recessive Albinism has multiple modes of inheritance CHED can be autosomal dominant or recessive
Medical history in CVI?	History of hypoxic–ischemic brain injury with or without prematurity, CNS infections, hydrocephalus, trauma (e.g. shaken baby), infantile spasms, brain malformation, metabolic disease. Seek other neurobehavioral signs: light-gazing, variable visual performance, head shaking, etc.

CHED, Congenital hereditary endothelial dystrophy; MECD, Meesmann epithelial corneal dystrophy; Reis–Buckler corneal dystrophy.
Modified from Funnell CL. My child seems to hate the bright light. In: Hoyt C, Taylor D, editors. Pediatric Ophthalmology and Strabismus, 4th ed. Edinburgh: Elsevier/Saunders, 2012: 968–70.

Descemet's breaks due to use of forceps or glaucoma can induce photophobia.

Infantile glaucoma

The triad of excessive tearing, blepharospasm, and photophobia in an infant or young child must prompt consideration of glaucoma, especially in the context of an enlarged cornea.

Lens abnormalitites

Light scattering through a partially opacified lens, or ectopia lentis, can induce photophobia.

Uveal abnormalities

Iris defects (colobomas, aniridia, dilated pupil, iris transillumination in albinism) can cause overstimulation of photoreceptors. Concomitant cataracts or corneal epithelial defects contribute to photophobia in aniridic patients. In albinism, the lack of retinal pigmentation further contributes to the photophobia.

Photophobia is a well known symptom of anterior uveitis.

Retinal dystrophies

Photophobia is common in the stationary cone dysfunction syndromes and progressive cone and cone–rod dystrophies. It starts in early infancy in achromatopsia and blue cone monochromatism, and early childhood in oligochrome trichromacy and bradyopsia[7,8] (see Chapter 46). The progressive cone dystrophies tend to become symptomatic in later childhood or early adulthood, and light aversion is often a prominent early symptom that can precede visual deterioration.[8] Features that should raise suspicion of retinal disease include decreased vision, hemeralopia (the inability to see clearly in bright light), nystagmus, significant ametropia, and paradoxical pupillary responses. When any of these diseases are suspected, electroretinography is necessary.

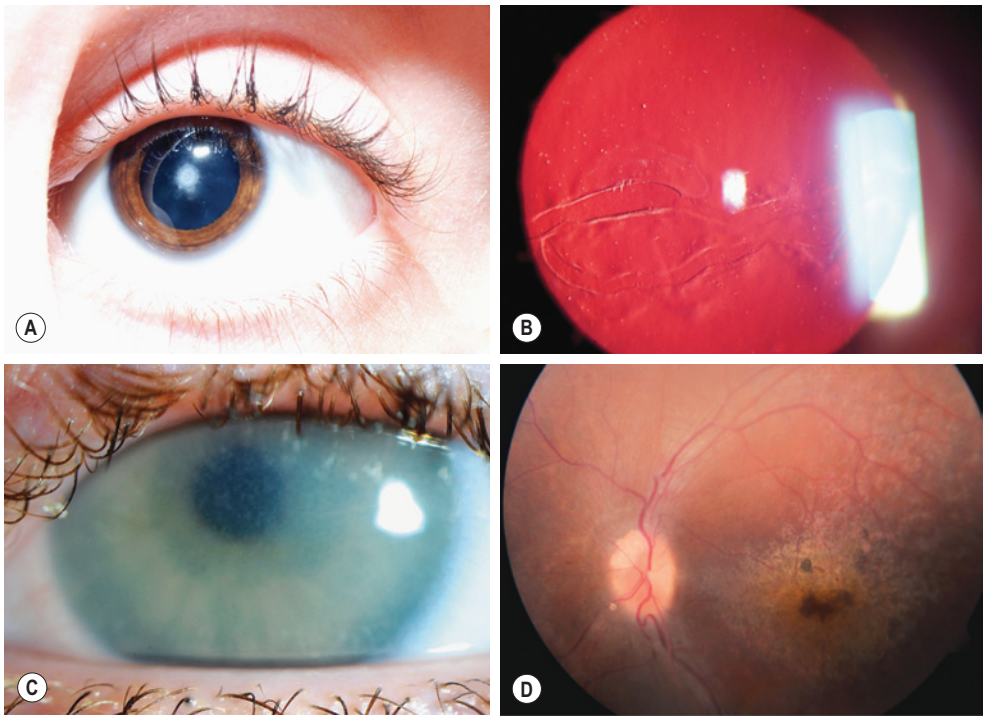


Fig. 94.1 Photophobia of ocular origin. (A) Anterior polar cataract causing glare to a 9-year-old boy who sees 20/50. (B) Five-year-old boy with Haab striae. His glaucoma is well controlled but he is photophobic from light scattering through Descemet tears. (C) Corneal clouding in a photophobic 12-year-old girl with muchopolysaccharidosis type 6. (D) Sixteen-year-old boy with progressive cone–rod dystrophy linked to Alström syndrome, known to cause photophobia starting early in life. *([A] and [B] courtesy of Dr Patrick Hamel.)*

Strabismus

Patients with intermittent exotropia often close one eye when outdoors in bright light (Fig. 94.1).

Neurologic causes

The most common neurological cause of light aversion is migraine, a frequent disorder in children and adolescents (prevalence estimated at 9.2%).[9] Photophobia is one of the major criteria used to diagnose migraine without aura,[10] the most frequent variant affecting children. Younger children may not verbalize photophobia, but it can be inferred from their preference to seek comfort in a dark room. Light exposure can trigger or exacerbate migraine attacks. The presence of symptoms such as irritability, nausea, or phonophobia can substantiate this diagnosis. Cluster headache, hemicrania continua, and other *trigeminal autonomic cephalagias* are especially rare in children. Unilateral photophobia associated with ipsilateral autonomic symptoms (i.e. eyelid edema, nasal congestion, conjunctival hyperemia, etc.) and ipsilateral retro-ocular pain are commonly associated with these diagnoses.[11]

One-third of children with *cerebral visual impairment* (CVI) are photophobic, irrespective of the cause. This is counterintuitive in view of their well-known habit of light-gazing.[12] Their photophobia decreases over time. A history of poor vision along with neurological insults such as hypoxic-ischemic brain injury, prematurity, encephalitis, brain malformation, or hydrocephalus is often present.[13]

Children with *meningitis* and *subarachnoid hemorrhage* will rarely present first to the ophthalmologist. Photophobia accompanies the traditional symptoms and signs in both pathologies. Headache and light sensitivity are common complaints following *traumatic brain injuries*.[2]

Compressive lesions seldom present with photophobia. The triad of ipsilateral photophobia, tearing, and torticollis has been described in children with *posterior fossa astrocytomas*.[14,15] *Chiasmal lesions* have been described in adults with isolated photophobia,[16] and should be considered in children.

Blepharospasm may be associated with photophobia, but this is exceptional in childhood.

Role and mechanisms of photophobia

Photophobia is thought to have a protective role by reducing the intensity of migraine headaches and pain from eye diseases.[17] It may also protect the central retina, since subjects exposed to central photic stimulation are more photophobic than those exposed to eccentric stimulation.[18] Furthermore, shorter wavelength light, which is potentially more damaging, induces more photophobia.[18]

The elucidation of neural pathways whereby light stimulation triggers trigeminal pain in both ocular surface diseases and migraine has provided a partial explanation of the mechanism of photophobia.

In ocular diseases, a pathway allowing photic stimulation to stimulate the abundant nociceptors of the cornea, uvea, etc., has been demonstrated. Retinal ganglion cells project signals to the olivary pretectal nucleus that in turn projects to the superior salivatory nucleus. The latter, via the sphenopalatine ganglion, causes release of parasympathetic neuropeptides,

inducing ocular vasodilatation and activation of nociceptors on blood vessels.[19,20]

Migraine worsening with light could be explained by photic signals arising from retinal ganglion cells that converge onto trigemino-vascular neurons of the posterior aspect of the thalamus. From there, axons project to cortical vision- and pain-processing areas. Interestingly, migraine patients with little residual vision can also experience photophobia, due to the involvement of image-forming and non image-forming retinal ganglion cells. The light sensitivity occurring during migraine attacks would result from nociceptive stimuli passing through the posterior thalamus and then arriving at the visual cortex.[21,22]

Proposed mechanisms to explain photophobia in CVI include damage of luminance-sensitive cells in the cerebral cortex and thalamic involvement. Unlike controls, children with CVI have improved grating acuity in low-luminance conditions.[23]

Postulated explanations for photophobia related to chiasmal lesions include chemical meningeal irritation, stretching of meningeal or vascular pain-sensitive structures of the cranial base,[16] as well as thalamic injury.[24]

Management

The treatment of photophobia depends on the underlying pathology. Wearing a sunhat, promoting home and school activities in areas with comfortable illumination conditions, and facilitating access to low vision services when deemed appropriate are examples of general supportive measures that help improve the child's quality of life.

Darkly tinted lenses can also be helpful, but their use should not be generalized because decreasing the dark-adapted state is important.[2] Tinted lenses can be considered in albinism. FL-41 tinted lenses (rose-colored) appear to decrease the frequency of migraine attacks in children.[25] Deep red- or brown-tinted contact lenses can provide comfort and improve vision in cone dystrophies.[26,27] Responsible handling must be assured. Filter lenses sometimes decrease dazzle in children with CVI, and their value is best assessed in low vision centers.

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"My child's eyes keep watering!"

Anthony G Quinn

Up to 20% of infants have a watery eye in the first month of life.[1] The vast majority have congenital nasolacrimal duct obstruction; the rest may have potentially serious problems. Acquired watering eyes present another range of diagnoses.

Congenital nasolacrimal duct obstruction and its management are discussed in Chapter 21.

Signs and symptoms

History

A child with excessive tearing can be a source of concern. Mucus in the tear film causes "stickiness" and constant spillage of tears causes redness and irritation of the lower lid skin. The lids may be stuck together on waking and require frequent cleaning. Parents may complain that the appearance "ruins" childhood photographs and they may feel the child's appearance reflects poorly on them as a parent. The primary care physician may feel compelled to prescribe repeated courses of topical antibiotics, to no lasting effect.

Try to establish whether the watering had its onset soon after birth, or if it is recent. Photophobia must specifically be asked about, as it is common in congenital glaucoma. The typical presentation is a child who avoids opening their eyes in normal daylight, often burying the eyes behind an arm or hand. Photophobia is also a symptom of corneal disease (such as cystinosis; see Chapter 34), uveitis, and a foreign body in the conjunctival sac or cornea. The possibility of trauma needs to be kept in mind, as children cannot always give a detailed history. Herpes simplex conjunctivitis can sometimes be associated with canalicular stenosis and scarring, causing a watery eye. A child with excessive lacrimation may have a watery nostril on the same side as the watery eye. Ask if the child rubs the eyes, or has a history of eczema, suggesting allergic eye disease. A history of eye rubbing or poking and concerns about whether the child can see suggests a retinal dystrophy, such as Leber congenital amaurosis (see Chapter 46).

Examination

External inspection

Tearing, red macerated skin, and stickiness may be seen. Look for misdirected lashes or lid malposition such as entropion, particularly if trachoma is possible. Check there is no facial nerve weakness, which would compromise the tear "pump." In nasolacrimal duct obstruction, the tear lake is thickened, brimming the lower lid margin. Normally, the tear film is virtually invisible, and, with fluorescein staining, measures less than 1 mm. With obstruction, it typically measures 2 mm or more. Look for perilimbal injection suggesting keratitis or uveitis, and look for evidence of blepharoconjunctivitis. Generalized corneal haze with secondary corneal epithelial edema may be a sign of glaucoma. An estimate should be made of horizontal corneal diameters using a ruler held close to the lid. A congenital swelling over the nasolacrimal sac is probably a dacryocystocele.

Slit-lamp examination

This is often best done with a portable model in young children. Look for presence or absence of puncta, punctal ectopia or fistula, or epiblepharon with inturned eyelashes. Inspect the inferior conjunctival fornix looking for diffuse redness and swelling of the conjunctiva, suggesting chlamydia conjunctivitis. Everting the upper lid is unlikely to be possible in a young, awake child, but it is possible to retract the upper lid digitally and inspect the tarsal conjunctiva and fornix with the portable slit-lamp, looking from below. Corneal crystals, abrasions, scars, ulcers, and foreign bodies can be excluded, as can signs of uveitis, e.g. keratitic precipitates, hypopyon, posterior synechiae, or cataract (also check red reflex). Haab striae and corneal edema should be excluded.

Fluorescein testing

This is a very sensitive test for detecting any defect in the corneal epithelium, and fluorescein will diffusely stain the cornea with epithelial edema. The fluorescein dye disappearance test is excellent for confirming nasolacrimal duct obstruction (see Chapter 21). Place a drop of fluorescein 1–2% in the conjunctival sac; in a normal child, the fluorescein will disappear from the tear meniscus after 5 minutes; the presence of fluorescein after 5 minutes indicates obstruction of both canaliculi or nasolacrimal duct. Fluorescein may also appear in the nose, confirming drainage.

Intraocular pressure

It is possible to check this in the majority of awake infants or young children with an Icare tonometer (see Chapter 38). If congenital glaucoma is likely, an examination under anesthesia

may be necessary. Tactile measurement is inaccurate and may mislead.

Cycloplegic refraction, fundus examination

Refraction and fundus examination will highlight unilateral myopia in a child with unilateral glaucoma, posterior synechiae, disc cupping, and any posterior segment pathology such as retinoblastoma, which can present as a red, watery eye with a "pseudohypopyon." Unilateral congenital nasolacrimal duct obstruction can be associated with anisometropia and amblyopia.

Causes and treatment

Non-patent nasolacrimal drainage system (see Chapter 21)

Spontaneous resolution occurs, with about 70% of affected children free of symptoms by 3 months of age and over 90% resolving by their first birthday. Spontaneous resolution may also occur later than 12 months of age, and those children whose epiphora does not resolve spontaneously after age 2 years are likely to have more complex lacrimal drainage problems. Children with white eyes (no evidence of secondary conjunctivitis) should not be treated with antibiotic drops. Many physicians advocate massage of the lacrimal sac, but its efficacy is not known. Lid cleaning may help prevent secondary infection and skin excoriation. Sometimes epiphora due to nasolacrimal duct obstruction will spontaneously resolve, only to recur with an upper respiratory tract infection, due to mucosal edema in the nasolacrimal system.

Treatment

There are a number of treatments (see Chapter 21); the commonest, probing, is safe,[2] but even in the best circumstances can have complications; it is sometimes traumatic and may, rarely, cause canalicular stenosis.

Occasionally an older child may acquire watery eyes due to punctal stenosis. This can be treated with punctal enlargement, but first may require an examination under anesthetic to determine the cause.

Foreign body/corneal abrasion

A history of sudden onset of pain, epiphora, conjunctival redness, and a foreign body sensation suggest either a corneal/conjunctival abrasion or foreign body. A careful history from the child and/or caregivers is essential in understanding the likely injury and predicting its severity. Fluorescein stains a corneal or conjunctival abrasion, and staining vertical scratches suggest a superior subtarsal foreign body caused by the foreign body being dragged over the corneal surface with each blink. If there is a full-thickness corneal laceration, the Seidel (fluorescein leak) test will sometimes be positive. A corneal foreign body is often visible with a check of the red reflex using the direct ophthalmoscope, but the portable or table-mounted slit-lamp is the ideal way to examine the cornea.

Corneal abrasions usually resolve quickly with antibiotic ointment and no patching is required. Removal of an embedded corneal foreign body in a child may require general anesthesia.



Fig. 95.1 Thygeson superficial punctate keratitis (TSPK). This 8-year-old child had a variably watering eye for 9 months that did not respond to a variety of treatments. TSPK follows a relapsing and remitting course over several months.

Loosely adherent foreign bodies in the conjunctival sac or on the cornea may be removable with a sterile cotton bud.

Keratitis and conjunctivitis (see Chapter 16)

A watery eye is a common symptom in keratitis (Fig. 95.1). There is frequently associated photophobia, conjunctival injection, increased mucus production, and a foreign body sensation. Visual acuity is often reduced in keratitis. Conjunctivitis is not associated with photophobia, unless there is an accompanying keratitis. Conjunctivitis is commonly infective (viral, bacterial), or allergic or traumatic. Allergic conjunctivitis typically presents as itchy, watery eyes, and is often a bilateral, although sometimes asymmetrical, problem. There may be a family history of allergic disease, and a clinical history of exacerbations in spring/summer, or of other allergic diseases such as eczema, hay fever, or asthma. "Shield" ulcers associated with giant subtarsal conjunctival papillae produce a characteristic loss of corneal epithelium and are easily seen with fluorescein and slit-lamp microscope.

Contact lens-related epiphora

In the older child, or the aphakic infant with contact lenses, epiphora may result from numerous causes. Poorly fitting lenses, change in corneal curvature, build-up of deposits on the contact lens, and chips or tears at the edge of the contact lens can all cause watery eyes from epithelial trauma or drying. The superior tarsal conjunctiva must be assessed for giant papillary conjunctivitis (GPC) in the long-term contact lens wearer. Treatment may include revising contact lens hygiene, replacing lenses, refitting lenses, replacing lenses with a different material or edge design, and treatment of GPC with appropriate pharmacologic agents (see Chapter 16). Infectious keratitis or corneal abrasion should be actively excluded and parents warned to be sure to remove the lens and seek ophthalmological advice within a few hours if the child's eye becomes red, sticky, watery, or photophobic.

Congenital glaucoma

Epiphora with photophobia may indicate a diagnosis of congenital glaucoma. Buphthalmos, corneal clouding, Haab

striae, increased intraocular pressure, and enlarged optic disc cup are also usually present. Anisometropia and strabismus may occur (see Chapter 38). Prompt treatment, usually surgical, is needed to prevent optic nerve damage.

Crocodile tears

One peculiar form of tearing occurs only when the patient salivates, typically when eating, but is also possible when the patient is thinking of a good meal. This is usually a congenital problem, and is an example of a range of disorders known as "congenital cranial dysinnervation disorders." Crocodile tears can also occur after trauma or surgery on the ear, or as a sequel to Bell palsy, representing aberrant nerve regeneration.

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CHAPTER 96

Proptosis at different ages

Alan A McNab

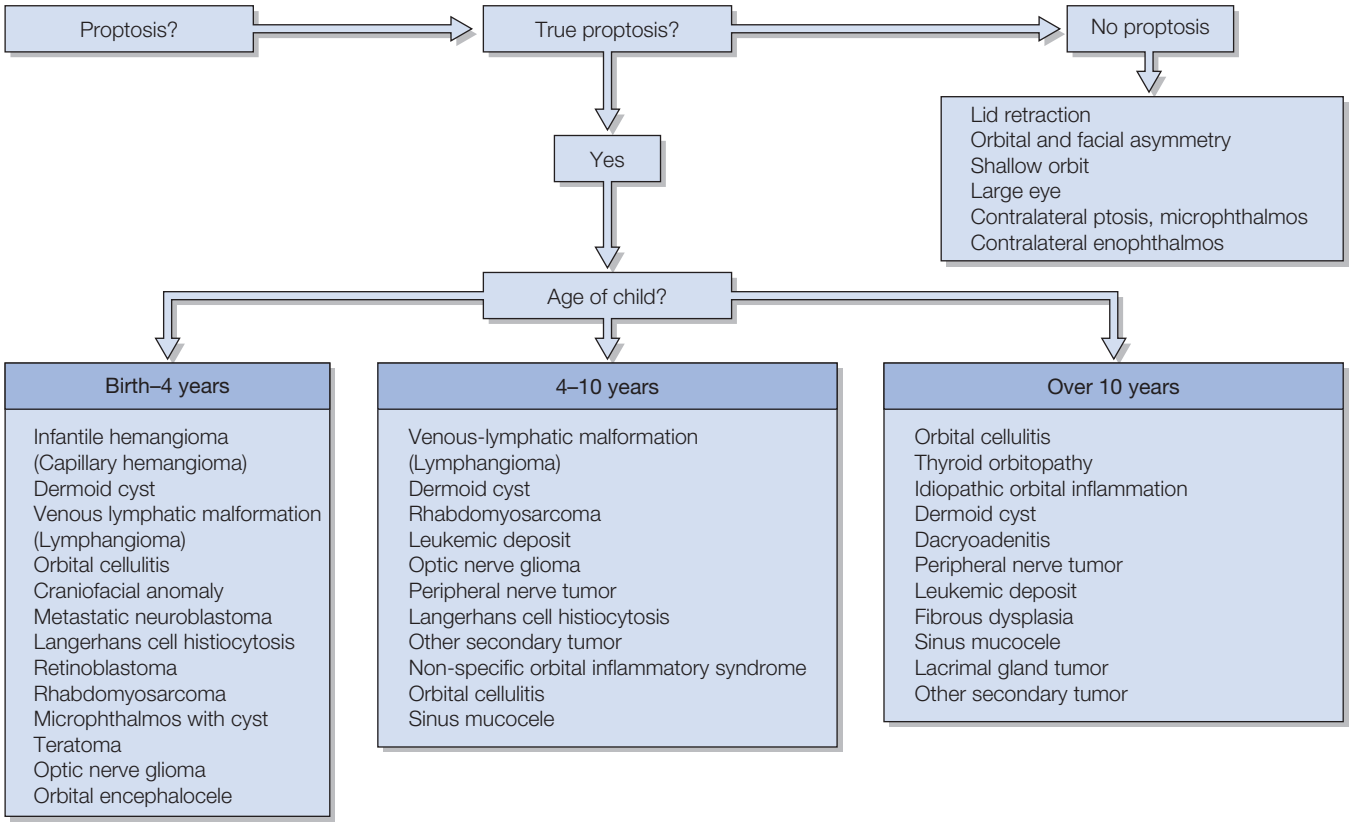


Fig. 96.1 The causes of proptosis vary with the age of the child and there is considerable overlap between age groups. This figure lists causes in approximate order of frequency. Details of each condition should be sought in the text. In making a clinical diagnosis, the history and progression of the condition, as well as the clinical findings, are of vital importance. See Chapter 22 for a more detailed approach.

"My child's teacher says she can't see properly!"

Hanne Jensen

Mode of presentation

When a child is brought to the ophthalmologist because his/her teacher suspects reduced vision it suggests that the parents have not been aware of any such problems. This may be because the parents do not expect the child to see any better or that the child's visual disability has been constant and non-progressive. The child who never had normal vision will not complain, but problems may become apparent as education makes increasing visual demands.

The teacher may notice problems with reading (near work), looking at the blackboard (distance vision), problems with color pictures in textbooks, reports of strange color combinations, or peculiar behavior in class. The child may miss what is going on, appear uninvolved, or may need extra time to keep up with the class. There may be problems in the playground: the child doesn't want to play, gets tired, often falls, is light-shy, or has an abnormal head posture. Other symptoms might be squeezing the eyes or complaining of headache.

Table 97.1 describes the signs and symptoms that might arise from various ocular abnormalities.

Diagnosis

History

Specific questions are necessary because parents may not associate the visual problems with a change in behavior. Is there a history of trauma? Has the child's situation been longstanding or has a change occurred with higher demands? Does the child like to play where it is dark? Is he/she comfortable walking alone or do they always want to hold someone's hand? Has his/her behavior suddenly changed? Aggression or passivity can be symptoms of progressive visual loss. Any other systemic symptom must be noted. It is sometimes necessary to talk with the child without the parents present. Children may only distinguish blurred vision (de-focus) from reduced vision when they are older.

Blurred vision implies an optical problem. A complaint of decreased vision after strenuous exercise or after warm baths suggests Uhthoff's sign of demyelinating disease. You must ask for the family history: an affected uncle in the mother's family may indicate a X-linked disease; likewise, consanguinity may suggest a recessive disease. Finally, it is important to ask for any drug history and make certain that no medicines have been given that might influence the vision or the visual field, e.g. vigabatrin.

Examination

Observe the child entering the clinic: are there difficulties; is the child afraid or curious; and can the child hear? Children who have been attending several clinics throughout childhood are often afraid and shy with professionals: it is important to make the child feel safe and cooperative.

Ocular examination

Measure the visual acuity; an accurate refraction is a vital part of the examination of a child with reduced vision. The media should be examined before and after the pupils are dilated, either with a slit-lamp, ophthalmoscope, or retinoscope. Direct ophthalmoscopy should be used for fundus details, including subtle changes in the retinal nerve fiber layer and fovea. Indirect ophthalmoscopy is useful to obtain an overall view of the retina and its periphery; problems such as bull's eye maculopathy, less obvious at high magnification, may become apparent with the indirect ophthalmoscope.

The optic nerve is assessed by its appearance but also by testing pupillary responses, contrast sensitivity, color vision, and visual fields. Color vision and pupillary responses are often normal in retinal diseases with markedly reduced visual acuity, whereas they can be abnormal even in mild optic nerve disease.

Neurological examination

Neurological examination is necessary in children with reduced vision since many systemic diseases cause eye symptoms. It is important to inquire about other symptoms, including hearing problems, in every child with visual loss. Children with concentration deficits must be examined by a neurologist to exclude a seizure disorder, autism, or attention disorders.

Special investigations

Electrophysiology such as electroretinography, visual evoked potential, and electro-oculography, as well as ultrasound and optical coherence tomography, can be very useful supplements. A magnetic resonance imaging (MRI) scan may be necessary if there are any indications of intracranial pathology.

Table 97.1 Symptoms and signs giving clues to the diagnosis

The teacher describes problems with:	Refractive error	Accom. spasms	Convergence insufficiency	Media opacities	Corneal dystrophies	Keratoconus	Macular disorders	Retinal dystrophies	Optic nerve disorder	Neurological disease	Metabolic disease
Reading	X	X	X	X	X	X	X	X	X	X	X
Blackboard	X	X		X	X	X	X	X	X		
Squeezing eyes	X			X	X						
Eye strain	X	X	X								
Keeping up/gets tired	X		X				X	X		X	X
Behavior							X	X	X		
Bright light				X	X			X		(X)	
Dim light								X	X		
Orientation								X	(X)	X	X
Falls								X		X	X
Head tilt	X									X	X
Color vision							X		X	X	X
Eye movements								X		X	X
Concentration	X	X	X							X	X

X, Present; (X), rarely present.

Causes and treatment

Refractive errors

Uncorrected refractive error is the most common reason for a child to not see properly at school. Cycloplegic refraction is helpful in children to detect hypermetropia and in order not to overestimate the degree of myopia.

Accommodative anomalies

Older school children often have problems when looking at the blackboard, but not when reading a book. This is most commonly due to progressive myopia. However, this complaint may also be caused by a high accommodative tone, which induces a myopic refractive error. It is important to do a cycloplegic refraction to avoid missing this diagnosis and prescribing myopic glasses in error. Occasionally, treatment with cycloplegic drops and reading glasses is the only way to help the child relax accommodation. Children may accommodate to compensate for a low hypermetropic refractive error, but some children do not (e.g. Down syndrome, cerebral palsy) and they become asthenopic; reading glasses may help in this situation. Children with convergence insufficiency may have blurred vision while reading; they seldom complain of double vision. Orthoptic treatment may help, but surgery is sometimes necessary.

Orbital disease (see Chapter 22)

Orbital inflammation or tumor may present with proptosis, but the presenting symptom may be reduced vision accompanied by restriction of eye movement and eventually pain and redness. Distortion of the globe results in astigmatism and hyperopia, which, left untreated, may reduce visual acuity.

Media opacities

Corneal diseases (see Chapter 34)

Corneal clouding due to keratitis from any cause may reduce acuity with irritation and watery discharge. Symptoms due to keratoconus usually present during the second decade as slowly progressive visual loss, often leading to multiple attempts at correction with glasses or contact lenses. Dystrophies presenting at a young age (Fig. 97.1) can result in recurrent epithelial defects and reduced vision (see Chapter 35).

Anterior chamber anomalies

Blurred vision due to anterior segment inflammation is usually associated with pain, redness, and photophobia. In chronic uveitis, particularly related to juvenile idiopathic arthritis, vision may be reduced without symptoms (see Chapter 40).

Lens anomalies (see Chapter 36)

Dislocation of the lens is a rare but important cause of reduced vision, causing astigmatism and/or myopia. Glaucoma and retinal detachment can occur. In older children cataract can be detected by the parents or by professionals, due to blurred vision or photophobia, particularly if the child has a predisposing condition such as diabetes mellitus, long-term steroid treatment or there is a family history of juvenile-onset cataract (see Chapter 36).

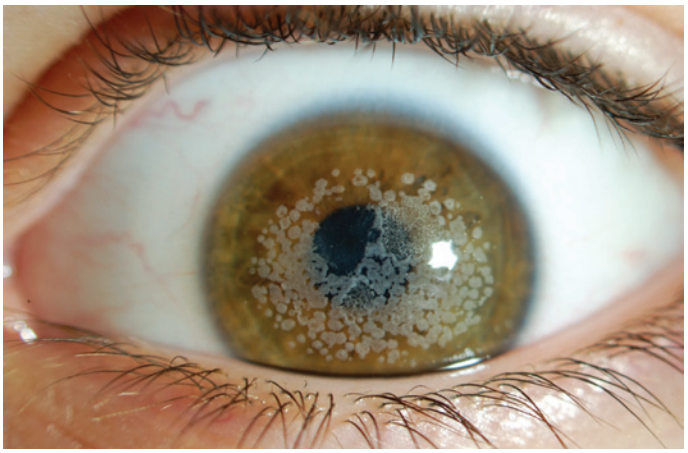


Fig. 97.1 This 8-year-old girl was referred when her dentist noticed a greyish corneal discoloration in both eyes. On examination, her visual acuity was 6/18. A diagnosis of Groenouw type 1 corneal dystrophy was made; the consanguineous parents were asymptomatic; both had subtle corneal abnormalities suggestive of this diagnosis.

Vitreous disorders

Vitreoretinal degenerations such as Stickler syndrome or juvenile X-linked retinoschisis may be diagnosed at or before school age because of reduced visual acuity from myopia or retinal detachment (see Chapter 52).

Vitreous opacities including hemorrhage, vitritis, and retinoblastoma seedlings are uncommon causes of blurred vision. When the vitreous is too opaque to allow retinal visualization, other diagnostic tests may be indicated, e.g. ultrasound, computed tomography (CT), or MRI.

Retinal disorders

Retinal dystrophies (see Chapter 46)

Visual disturbances with retinal dystrophies are variable. A family history of bilateral visual loss may be present, and there may be systemic findings. Blurred vision is rarely an early complaint in retinitis pigmentosa; night blindness and loss of peripheral visual field are more usual. These children often have high refractive errors (hypermetropia or myopia). Macular dystrophies make reading difficult, but there may be few fundoscopic signs at the first visit, so some children are suspected of visual conversion disorder (hysterical blindness) (Fig. 97.2).

Systemic disease

It is important to remember that systemic disease may cause characteristic retinal and other ocular findings; thus, ocular findings may lead directly to a systemic diagnosis. Diabetes mellitus may present early, but retinopathy is uncommon in the first decade of the disease. Blurred vision may result from myopia caused by rapid shifts in blood glucose levels, cataract, or from optic atrophy associated with DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness – Wolfram syndrome).

Many neurometabolic disorders, including Batten disease, mucopolysaccharidoses, and mucolipidoses, can present with reduced visual acuity from retinal dysfunction. However, they will often present before the vision is reduced, with

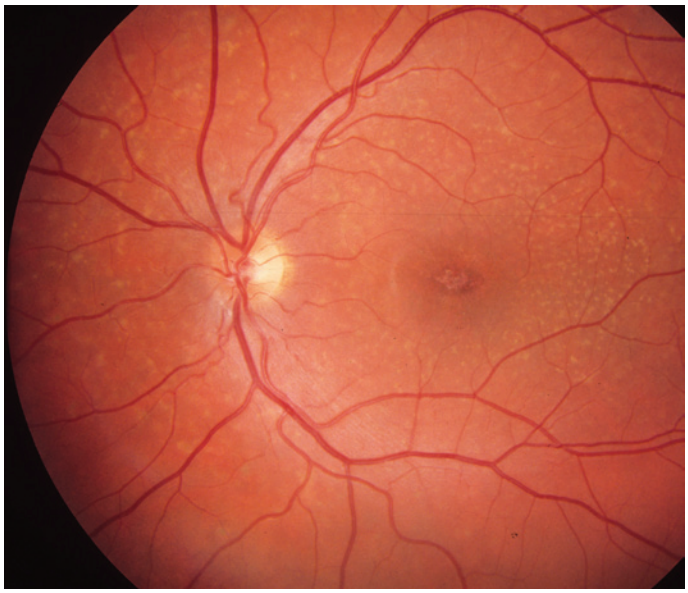


Fig. 97.2 This 14-year-old child with visual acuity of 6/12 had reading difficulty. Visual conversion disorder (hysterical blindness) was suspected, as the eye examination was normal. Four years later typical retinal changes of Stargardt disease were apparent. The visual acuity had decreased to 6/60 in each eye.

seizures, abnormal behavior, or even reduced visual fields. Electroretinography is often necessary to secure the diagnosis.

In leukemia (Chapter 67), vision may be affected by retinal, choroidal, or iris infiltration or hemorrhage.

Optic nerve diseases

Reduced visual acuity and color vision, central scotoma or constricted field, poor pupillary responses (an afferent defect), and variably swollen or atrophic optic discs in a child all point to optic neuropathy (see Chapters 54 and 56). Optic atrophy without ocular, post-inflammatory, or hereditary causes suggests a central nervous system abnormality. It is usually bilateral, but may present unilaterally. Congenital optic nerve anomalies (coloboma, hypoplasia) can be associated with poor vision and can be discovered late at school testing (see Chapter 53).

Central nervous system diseases

Visual pathway disease may result in decreased vision; a lesion proximal to the chiasm results in optic atrophy. Increased intracranial pressure may cause papilledema, usually without visual symptoms, but, if severe, there may be episodic or permanent loss of vision. A severely atrophic optic nerve cannot appear swollen despite increased intracranial pressure because there is no retinal fiber layer to swell. A child with a central nervous system tumor (especially in the posterior fossa) is often ill, vomiting, and complaining of headache, and will not be overlooked. These children may also have varying double vision from a cranial nerve palsy.

The parachiasmal syndrome of visual defect, growth, and other hypothalamic disturbances in children is often caused by optic gliomas or craniopharyngiomas. Various combinations of optic atrophy and papilledema occur, depending on the duration of the process and how rapidly the intracranial disease has developed (see Chapter 59).

Cerebral visual impairment is associated with very few ophthalmologic findings. The reduced visual acuity may vary according to the state of the child. Vision is often better when the child is relaxed, has no seizures or pain, and the surroundings are well known. It is sometimes very difficult to establish the visual function in the clinic (see Chapter 60).

Non-organic visual disorders

These are often seen in teenage girls who may have problems either in the family, with their friends, or related to schoolwork. They can be very difficult to diagnose, and some children may undergo several tests in order to be sure that no organic disability is present (see Chapter 63).

Varying degrees of acuity and visual field loss are found, often becoming worse with time, but rarely to an extent that the child becomes blind. The child's success in managing day-to-day visual tasks is out of keeping with the alleged severity of visual loss.

"My child could see perfectly but now the vision is weak!"

Luis Carlos Ferreira de Sá

Introduction

Visual loss in an otherwise healthy child is an alarming finding for both the family and clinician. Children often do not complain of decreased vision, and it is common for them to only present once the visual loss is severe. Visual loss may result from congenital problems, only noticed later in life when visual requirements increase at school, or when the child had normal vision followed by chronic or acute visual loss (Fig. 98.1).

When investigating acquired visual loss, a comprehensive medical history is essential. Ask about the pregnancy, delivery, gestational age, birth weight, perinatal problems, developmental milestones, ocular and medical anomalies, medications, and family history of systemic and/or visual problems (Fig. 98.2). Seek details regarding trauma, timing, duration, and severity of visual loss.

Irrespective of whether the onset of visual loss is acute or chronic, ophthalmic examination will, in most cases, reveal abnormalities in the anterior and/or posterior segment, although the site of visual loss may be intracranial (see Chapters 57 and 60). Details about photophobia and eye movement disorders, including strabismus and nystagmus, may be especially helpful in reaching a diagnosis.

Examination

First, observe the child's visual behavior. There may be different degrees of visual loss, including visual inattention. The child may not respond to visual stimuli such as lights, faces, or toys. The examiner should not use animated and noisy objects; the child may be attracted to the sound rather than the visual stimulus. Whenever possible, visual acuity should be measured with age-appropriate methods.

Pupillary responses (grade of reactions, presence of an afferent pupillary defect, or paradoxical reaction) and assessment of alignment and eye movement disorders provide the clinician with important diagnostic clues.

Anterior segment

Cornea

Developmental glaucoma may present with increased corneal diameter because of the elasticity of the collagen fibers in young children. Corneal transparency may be reduced by several conditions, including developmental glaucoma (see Chapter 38), infectious keratitis (see Chapter 34), and metabolic diseases (mucolipidoses, mucopolysaccharidoses, and cystinosis; see Chapters 34 and 65). Corneal shape is altered in keratoconus (see Chapter 34), which may be present in childhood and progress at puberty.

Iris

Iris abnormalities are usually not associated with acquired visual loss, although colobomas (see Chapter 39) and iris transillumination (albinism; see Chapter 41) may be related to fundus problems causing congenital visual loss.

Lens

The lens should be carefully evaluated. Developmental cataracts can be secondary to trauma, radiation, metabolic/storage diseases, medications, or associated with genetic syndromes that may develop later in childhood (see Chapter 37). Ectopia/subluxated lens may also be observed and can be related to trauma, genetic syndromes, and metabolic diseases (see Chapter 36).

Posterior segment

Vitreous

Signs of inflammation or hemorrhage related to uveitis, trauma, or tumors may be seen in the vitreous. Vitreous changes are part of a vitreoretinopathy (see Chapter 42). Past medical history of prematurity, high refractive errors, familial history of retinal detachment, joint pains, or cataracts may suggest retinopathy of prematurity, Stickler syndrome, familial exudative vitreoretinopathy, or congenital stationary night blindness. Electroretinography (ERG) may be useful. Ultrasound, magnetic resonance imaging (MRI), or computed tomography (CT) scans may be indicated when vitreous opacities impede observation of the retina, or when calcification is suspected (retinoblastoma).

Retina/choroid

The retina/choroid should be evaluated. Subtle, but important, anomalies are not always readily observed. Retinal dystrophy and metabolic/storage diseases (see Chapters 46 and 65) commonly start without pigmentary changes. They develop later as the disease progresses. When the condition is bilateral and present from birth, nystagmus develops as in cases of Leber congenital amaurosis, toxoplasmosis, and albinism.

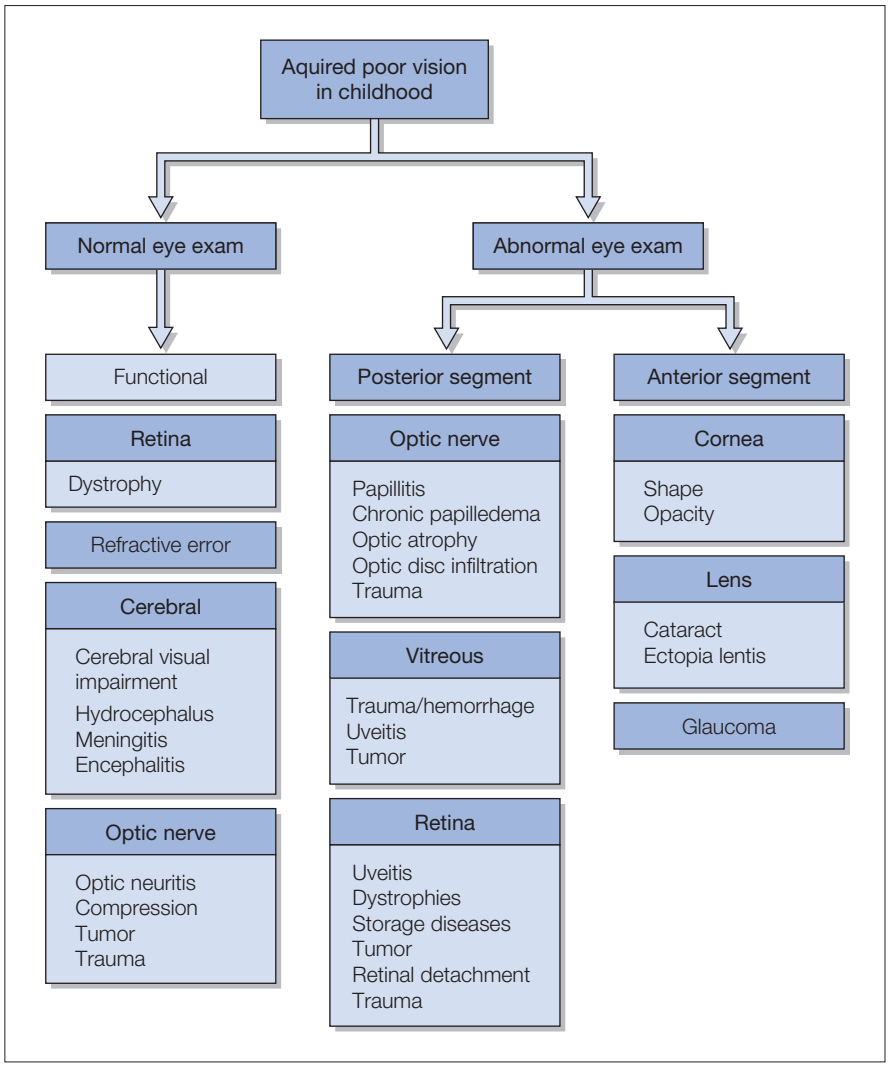


Fig. 98.1 Guidelines for diagnosis of acquired poor vision in childhood.

Color vision abnormalities and presence of paradoxical pupil reaction may suggest cone dysfunction. Retinal dystrophies will require ERG for specific diagnosis. Severely reduced electro-oculogram (EOG) is an important diagnostic feature of vitelliform dystrophy (Best disease; see Chapter 48). Recently, optical coherence tomography (OCT) has revolutionized the investigation, diagnosis, and management of many eye conditions. The development of handheld OCT has helped in the evaluation of visual loss in children associated with inherited retinal dystrophies and even chorioretinal vascular diseases when the appearance of the fundus is still normal using ophthalmoscopy (see Chapter 10). Fluorescein angiography, although difficult in children, is particularly useful in Stargardt disease ("dark choroid" sign), when visual loss and macular changes may be minimal (see Chapter 50). A work-up for uveitis (see Chapter 40) and retinal detachment (see Chapter 52) may be necessary. Both conditions develop at any age and are important causes of acquired visual loss.

Optic nerve, chiasm, and optic tract

The size, color, and contour of the optic disc merit attention since optic disc abnormalities may be related to congenital and acquired visual loss. In evaluating optic atrophy, the color of the optic disc is an important assessment. However, the optic discs may appear pale in infants compared to older children and adults. Moreover, inherited optic atrophy including Leber hereditary and autosomal dominant forms rarely manifests in the first year of life. Optic atrophy may be due to panretinal degeneration and ERG may occasionally be necessary. Optic atrophy may occur secondary to longstanding papilledema or compressive lesions of the anterior visual pathway; neuroimaging studies may be indicated. The chiasm and optic tract may be involved in a variety of conditions, including tumors (glioma, craniopharyngioma, neuroblastoma, and retinoblastoma "trilateral"), trauma, infection, inflammation (post-viral, post-immunization, and demyelinating diseases such as multiple sclerosis), vascular anomalies, and radiation. OCT can be useful to evaluate optic nerve head and retinal nerve fiber layer (RNFL). The RNFL is thicker in children with pseudotumor cerebri and may be thinner in patients with optic pathway gliomas, multiple sclerosis, optic neuritis, and disseminated encephalomyelitis.

Central nervous system and cortical visual impairment

Visual loss is frequently associated with disturbances of the visual cortex as the result of trauma, infection, hydrocephaly,

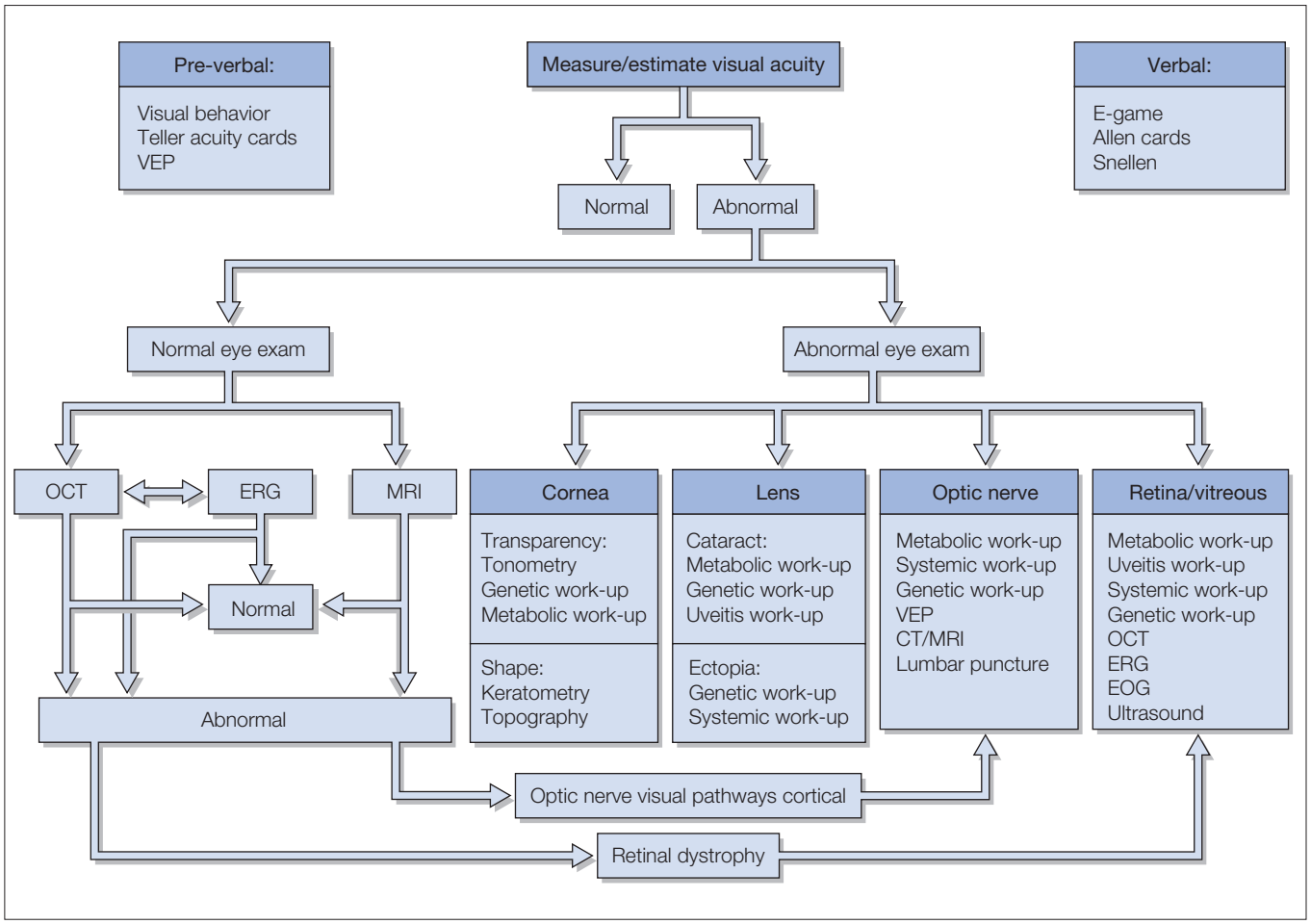


Fig. 98.2 Guidelines for investigation of acquired vision loss in childhood. CT, Computed tomography; EOG, electro-oculogram; ERG, electroretinogram; MRI, magnetic resonance imaging; OCT, optical coherence tomography; VEP, visual evoked potential.

hypoxemia, and vascular or metabolic insults (see Chapters 59 and 60).

What if the eye exam is normal?

In a child with acquired visual loss and no ocular explanation for it, it is important to rule out functional visual loss (see Chapter 63) and refractive errors. Electrophysiological tests, neuroimaging studies, and OCT may be necessary to rule out organic disease. In some patients, acquired visual loss is part of a multisystem disorder.

Electrophysiological tests (see Chapter 9)

ERG is invaluable in diagnosing the etiology of poor vision in children. It may be performed in a child with poor vision and normal ocular examination because many retinal disorders are not associated with any visible pigmentary changes early in the course of disease. EOG is rarely indicated for small children; conditions in which EOG is indicated (Best and Stargardt disease) rarely manifest in the first decade. Visual evoked potential (VEP) can be helpful for estimating visual acuity and in providing information about the neural visual pathway, as in optic neuritis where there may be a prolonged latency.

Neuroimaging studies

MRI and/or CT scan are indicated when the clinical examination and electrophysiological tests fail to explain the poor vision. Resolution of MRI is superior to that of a CT scan, providing better images of the central nervous system (CNS), and it does not expose the child to radiation. However, MRI acquisition time is longer, it does not visualize the bone as well as a CT scan, and may require anesthesia in small children. Neuroimaging studies are important in cases of compressive lesions of the visual pathways, cortical abnormalities, and demyelinating process.

The decision to perform electrophysiological tests before neuroimaging studies should be based on the individual child, availability of an electrophysiological test laboratory, and the possibility of associated CNS pathology.

Optical coherence tomography (OCT)

Advances in OCT technology, with enhanced image-acquisition speeds, wider fields, and handheld/portable units will allow OCT to be used as a routine investigative exam in children. OCT is a noninvasive investigative technique that can help to evaluate vision loss in a variety of conditions including amblyopia, glaucoma, chorioretinal vascular diseases, inherited retinal diseases, and optic nerve anomalies.

The child with a dual sensory loss (deafblind)

Nicoline Schalij-Delfos

Introduction

Deafblindness or dual sensory loss (DSL) is a combined vision and hearing disability; affected children have complete and incomplete loss of hearing and/or vision. It can be congenital or acquired. Congenital deafblindness is defined as blind and deaf from birth or very early in life, before the development of speech (pre-lingual deafblindness). Acquired deafblindness arises after the development of language (post-lingual deafblindness).[1–3] A Danish study found an overall prevalence of 1:15,000 among children <18 years and 1:29,000 for congenital deafblindness.[3,4] In the United States, a National Deaf-Blind Child Count is performed annually and remains relatively stable in the total population, with a slight shift towards the younger children. The 2014 count identified 7260 youngsters (3–18 years) and 561 infants (0–2 years); +/− 5.5% were totally blind and +/− 19% had a profound hearing loss.[5]

Etiology

Changes in health care have influenced the etiology for congenital deafblindness. Rubella has diminished significantly due to immunization programs, and perinatal causes such as prematurity and perinatal asphyxia have increased as a result of improved survival of extremely premature and sick babies.[1,3] Currently, the most common causes for congenital deafblindness are CHARGE syndrome, prenatal infection with cytomegalovirus (CMV), prematurity, and meningitis. The most important cause for acquired deafblindness is Usher syndrome. Infections can cause early as well as late vision and/or hearing loss dependent on type and time of occurrence. Apart from that, many other syndromes and genetic disorders are involved in vision and hearing loss[6,7] (Table 99.1).

Concomitant disorders

Vision and hearing are important tools for interaction. Loss of these functions has implications for communicative, cognitive, emotional, and social development and function. In addition, not being able to identify the origin of a source of sound or identify movement of objects may impact one's sense of safety. The earlier and more profound the defect, the more serious the consequences.[1]

Mental and behavioral disorders are much more frequent and autism spectrum disorder (ASD) has been found in 6% of children with DSL.[8,9] Intellectual disabilities (ID) and ASD are more difficult to detect in patients with DSL. Conversely, a high prevalence of undetected deafblindness has been reported in patients with ID, as common as 70% in patients with profound ID. Detection of ASD is significantly delayed due to an overlap in behaviors between children with DSL and ASD and the absence of adequate tests.[10–12] Lack of awareness delays detection and interferes with adequate interventions.

Ophthalmological assessment

Many countries have programs to detect hearing defects at a very early age. Despite the high prevalence (approximately 40–60%) of ophthalmic disorders in children with hearing loss, standard ophthalmological screening has not been widely implemented. Refractive errors (18–39%), strabismus (5.3–18%) with subsequent loss of stereopsis and amblyopia (4.4–14.4%) are the main disorders. Hyperopia is the most commonly reported refractive error, followed by myopia, astigmatism, and anisometropia.[13] Depending on the cause, cataract (Down syndrome), glaucoma (Stickler syndrome, Sturge–Weber syndrome), retinal changes, or a deficit in contrast sensitivity (Usher syndrome) may be found. Cerebral visual impairment (CVI) has seldom been studied in this specific population, but a study performed in 1995 identified CVI in 26% of deafblind subjects.[14] An increase can be anticipated as more extremely premature infants, an important risk factor for CVI, survive.[15]

Orthoptic and ophthalmologic examinations should include visual acuity measurements not only for distance but also for near, as children with vision and hearing loss often perform their tasks close up. Furthermore, assessment of binocularity, cycloplegic refraction, slit-lamp examination, and fundoscopy should be performed. Visual symptoms of acquired deafblindness are not always easy to detect at an early age. Subtle retinal changes in the eyes of children with Usher syndrome can be seen in the first decade, but often the characteristic retinal pigmentation develops later. Electroretinography (ERG) or visual fields can be performed for

Table 99.1 Causes for deafblindness categorized as: early (congenital or infantile) vision and hearing loss, early vision loss with subsequent hearing loss, early hearing loss with subsequent vision loss, and late vision and hearing loss

Early vision and hearing loss	Early vision – subsequent hearing loss
Congenital infections Cytomegalovirus (CMV) Toxoplasmosis Syphilis Herpes simplex Rubella Meningitis CHARGE association Down syndrome Premature birth Asphyxia Trisomy 13, 4p Chromosome 5p- (Cri du Chat) Ring chromosome 18 Other syndromes: Aicardi, Dandy–Walker, fetal alcohol, Smith–Lemni–Opitz, Waardenburg	Leber congenital amaurosis Norrie disease Alstrom syndrome Infections
Early hearing – subsequent vision loss	**Late vision and hearing loss**
CHARGE Trisomy 21 Usher type I, II syndromes Prematurity Infections Möbius syndrome Stickler syndrome Treacher Collins	Intracranial pathology Usher type II and III Trisomy 4p Chemical induced Infections Other syndromes: Alport, Apert, Bardet Biedl, Batten, Cockayne, Cogan, Cornelia de Lange, Crigler–Najjar, Crouzon, Hunter, Hurler, Kearns, Sayre, Klippel–Feill, Kneist, Leigh, Marfan, Maroteaux–Lamy, Marshall, neurofibromatosis type 1 and 2, Pierre Robin, Pfeiffer, Prader–Willi, Refsum, Sturge–Weber, Turner, Zellweger

early diagnosis. Institutes specialized in counseling of children with vision and hearing impairment should be involved in assessments for CVI and contrast sensitivity or illumination measurements.

Early identification is extremely important as disorders might be correctable, treatable, or require environmental adaptations and appropriate support from specialized services.[6] Optical correction or clear visual axes facilitates development of spoken or sign language, communication, and social interaction. Treatment of amblyopia or glaucoma can prevent children from additional deficits. Repeated ophthalmological assessment is necessary as disorders might deteriorate or appear later; however, no uniform screening guidelines are available.

Cochlear implantation

Cochlear implants (CI) are used in children with severe DSL with sensorineural hearing loss. In congenital cases this should preferably occur before the age of 2 years. Neonatal screening programs allow earlier detection of infants with sensorineural hearing loss. CIs are important for development of speech, language, and cognitive skills. The majority of infants with CI can use spoken language as the primary mode of communication. Again, the earlier the implantation, the greater the impact on rehabilitation, which is especially important in infants with a concomitant visual disability.[16,17]

Approach to the deafblind child

It is important to realize that children with dual sensory loss need a specialized approach. Children with hearing loss have difficulties perceiving speech, especially in a noisy environment, often have language and speech delay, concentrate on faces for speechreading, have difficulties in registration of the origin of sounds, and can be frightened by sudden noise. Infants often need longer pauses to process information or may exhibit unusual or stereotypic behavior.[18] A combined disability aggravates these symptoms, impedes eye contact, and can result in a sense of insecurity. Verify if the child is completely deafblind or if there is any residual function. Approaching a child with hearing loss and restricted visual fields from the side can cause adverse reactions. Always address the child with DSL by name. Appreciate the cognitive age. Look directly at the child in an appropriately lit room so he can see your face and articulate carefully. Do not speak too fast. Playing music for comfort or singing and making noises to attract attention is not helpful if the child is deaf, and makes understanding more difficult for the impaired. Facial expression can be hard to interpret. In consultation with the caregiver, tactile communication can be used in completely deafblind children.

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"My little girl tells me she sees strange things"

Göran Darius Hildebrand

Introduction

Unusual visual experiences are not rare in children, but are often difficult to interpret due to the difficulty for the child to express the peculiar sensation. Most complaints will be of a benign and usually transient nature requiring only reassurance. However, a visual complaint may have a more significant meaning, indicating a serious underlying disorder. It is important to take the child's and parents' complaint seriously and to approach its evaluation systematically.

A short mnemonic may help when dealing with such cases. "OSCE" stands for:

O-ptical (refractive, optic media);

S-ensory (visual pathway);

C-erebral (neurologic, psychologic/functional, psychiatric);

E-fferent (motor, e.g. nystagmus, superior oblique neuromyokymia, or accommodative spasm) causes.

This should ensure that the evaluation of the problem is complete (Table 100.1). An appropriate history should be taken, followed by a clinical examination. Ancillary investigations and referral to other specialists may be required (Box 100.1). A definitive diagnosis is not always reached (Fig. 100.1). Remember that even apparently bizarre symptoms can arise from organic disease (Fig. 100.2).

Below the complaints are divided into individual visual symptoms and ranked from common to rare. There are excellent reviews of this subject.[1–8]

Entoptic phenomena

Entoptic phenomena are visual perceptions arising from sources within the eye rather than the outside world. Most are harmless phenomena that are usually either not perceived or ignored but that may be noticed by a bright young child. They are noticed under special viewing or light conditions. Most people will have experienced some of them at some point in their life. Clinicians use them to assess the presence of gross retinal and optic nerve visual function when no direct fundal view is possible due to dense media opacities. Children with very poor sight due to retinal causes will often rub and poke their eyes to stimulate entoptic phenomena (oculodigital sign; see Chapter 62).

Scheerer (*or blue field entoptic*) *phenomenon* consists of seeing tiny bright spots that rapidly move in squiggly lines, especially when looking into the bright clear blue sky or an open field of snow. They are thought to be due to the movements of white cells in the capillaries near the macula. Blue field entoptoscopy has been used to measure retinal capillary flow.

Most children with normal vision will notice *Purkinje trees*, which are images of their own retinal circulation. They are best seen when a bright light is shone through the closed eyelids, when the retinal vessels cast a shadow on the unadapted, underlying photoreceptors.

Other harmless entoptic phenomena include Purkinje blue arcs, Haidinger brushes, light diffraction through eye lashes, as well as floaters, photopsia, and phosphenes.

Photopsia and phosphenes

Phosphenes and photopsia are brief entoptic phenomena. Phosphenes can be induced by mechanical (eye rubbing, sneezing), electrical, and magnetic stimulation of the retina and visual cortex as well as by the spontaneous firing of retinal cells. *Pressure phosphenes* consist of seeing colors and lights with eye rubbing. *Flick phosphenes* are flashes of light that are seen during eye movements, especially when the retina is dark-adapted and the lids are closed. *Accommodative phosphenes of Czermak* occur with sustained accommodative effort and may be due to ciliary muscle traction on the peripheral retina.

Photopsia and phosphenes may also be pathologic and associated with several important pathologies of the retina (retinal traction, tear, detachments, retinal inflammation, outer retinal disease), the optic nerve (optic neuritis, papilledema), or the brain (typically migraine). In the anterior segment, irritating reflections, glare, and dysphopsia may be caused by corneal pathology, cataracts, the edge effect of a dislocated or scratched intraocular lens, or posterior capsular opacification. Thorough examination, especially of the peripheral retina, is indicated to exclude potentially sight-threatening pathology.

Floaters (myodesopsia, mouches volantes)

At birth, the tertiary vitreous is perfectly transparent. *Myodesopsia* is the perception of a floater caused by imperfections or deposits within the vitreous body that cast a moving shadow on the retina. Floaters have been likened to "flying flies" (synonyms: *mouches volantes* in French or *muscae volitantes* in

Table 100.1 Systematic approach to children who complain of seeing peculiar things

Mnemonic "OSCE"	
O-ptical	Refractive Optic media (red reflex)
S-ensory (visual pathway)	Anterior segment Posterior segment Optic nerve, chiasma, optic tract, visual cortex
C-erebral	Neurologic Psychologic/functional Psychiatric
E-fferent (motor)	Extraocular movement exam (nystagmus, superior oblique myokymia) Lid movements (myokymia) Accommodation (loss/spasm)

Box 100.1

Overview of diagnostic management

History
Sensory assessment
- Visual acuity
- Color vision
- RAPD
- Amsler grid
- Visual field test (confrontation if young)

Optical media and refraction
- Red reflex/Brückner test
- Refraction

Ocular exam
- Examination of anterior segment
- Examination of posterior segment

Motor
- Hirschberg corneal reflex
- Cover and alternating cover test
- Extraocular movements (pursuit, saccades, convergence)
- Accommodation

Investigations
- Corneal topography (in keratoconus)
- Ocular imaging (OCT, AF, FFA, ultrasound)
- Neuroimaging (MRI, CT)
- Electrodiagnostic testing (ERG, VEP, EEG)
- Referral (pediatrician, neurologist, psychologist)

AF, Autofluorescence; CT, computed tomography; EEG, electroencephalography; ERG, electroretinography; FFA, fluorescein angiography; MRI, magnetic resonance imaging; OCT, optical coherence tomography; RAPD, relative afferent pupillary defect; VEP, visual evoked potential.
See also Chapters 7, 9 and 10.

Latin). The floater is most noticeable against a uniform, bright background and when it comes closest to the retina. Unlike a scotoma, which is fixed in space, a floater comes and goes and moves from second to second.

Most floaters are entirely harmless, albeit annoying, and require reassurance only. These are due to normal degenerative changes in the vitreous (vitreous syneresis, uncomplicated posterior vitreous detachment, Weiss ring) and become ubiquitous with increasing age, affecting myopes earlier than emmetropes. Occasionally, they are caused by asteroid hyalosis, synchysis scintillans, or a persistent primary vitreous remnant in Cloquet's canal, which are of no further consequence.

However, new floaters may be of concern, especially if associated with photopsia, a shadow, or reduced vision. This always warrants an ophthalmologic examination to exclude a retinal tear, retinal detachment, vitreous hemorrhage, or uveitis.

A visual sensation similar to a vitreous floater may be seen with precorneal tear film abnormalities (dry eye, meibomian gland dysfunction, foreign body), but can easily be differentiated from these by the clearing effect of blinking, the associated external symptoms of ocular irritation, and by ocular examination.



Fig. 100.1 This 9-year-old boy complained of constantly seeing a color grid in front of both eyes. Five months later, the color grid in one eye persisted, but changed to constant black and white vision in the other eye. He has no history of seizures or systemic illness or trauma. He is a well-adjusted boy who likes school. His ocular and neurologic examination and all his investigations, including brain magnetic resonance imaging and electrodiagnostic testing (electroretinography, visual evoked potential, and electroencephalography), have remained normal.

Benign blurred ("fuzzy") vision

Children will frequently complain of their vision being "fuzzy" or "blurry." The most common cause will be an unrecognized refractive error. Other frequent causes include intermittent or constant strabismus, amblyopia, afterimages after looking at bright light, entoptic phenomena, tear film, and conjunctival or corneal abnormalities (e.g. dry eye, unstable tear film with meibomian gland dysfunction).

Transient loss of vision

Important *non-ischemic* causes of transient visual loss include *migraine* (associated with nausea and headaches and photopsia/teichopsia), *ictal/postictal visual loss* in epilepsy (may be associated with motor, sensory, autonomic signs, or automatisms), *visual obscurations* in papilledema (associated with symptoms of raised intracranial pressure that are worse with postural change and Valsalva maneuvers), *optic neuritis*

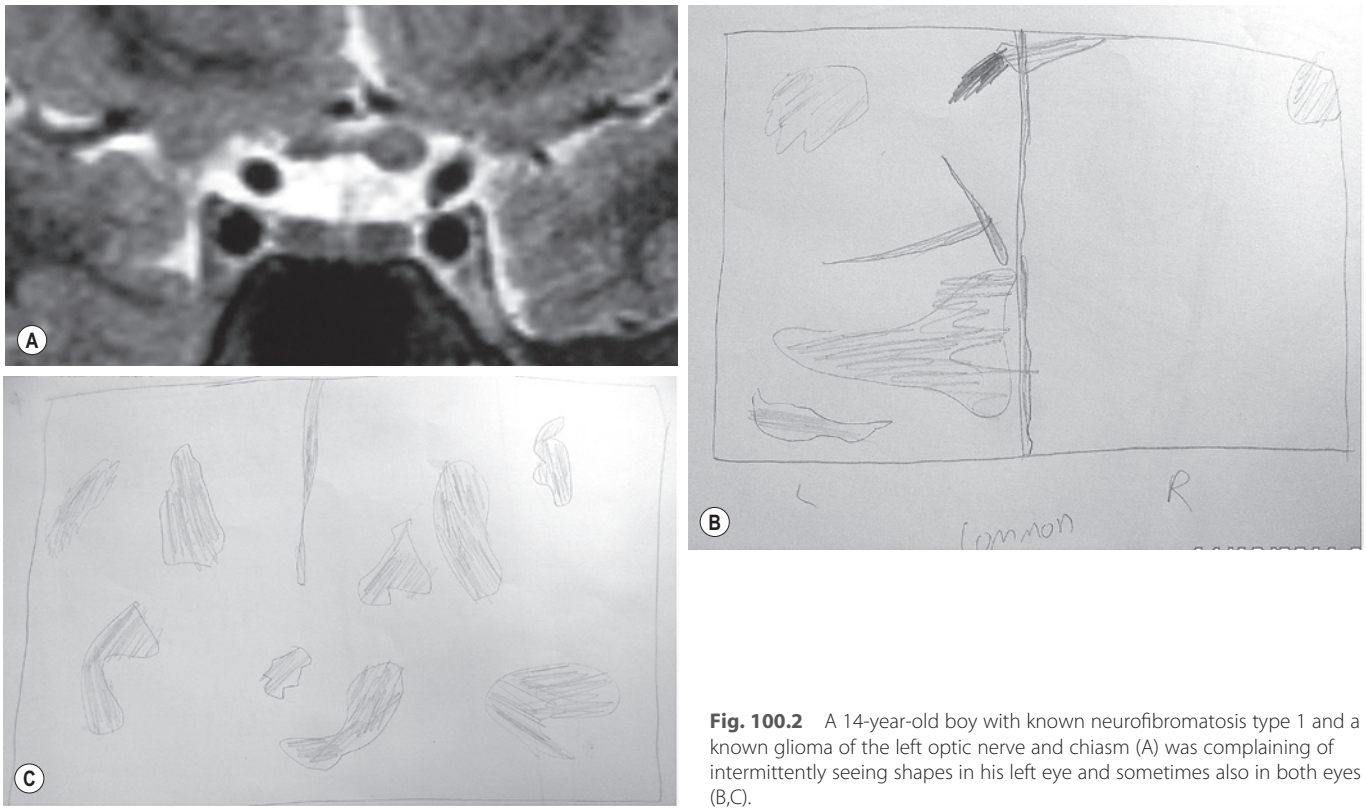


Fig. 100.2 A 14-year-old boy with known neurofibromatosis type 1 and a known glioma of the left optic nerve and chiasm (A) was complaining of intermittently seeing shapes in his left eye and sometimes also in both eyes (B,C).

(associated with discomfort with eye movements and recent infections/immunizations in children), *Uhthoff phenomenon* in optic neuropathy (loss of vision associated with rising body temperature, e.g. in a hot shower), *post-traumatic transient cerebral blindness* (associated with occipital lobe injury), *gaze-evoked amaurosis* due to transient compression of the intraorbital optic nerve or ophthalmic artery (associated with eye movements), transient *intraocular pressure* rise, poor diabetic control, *intraocular inflammation*, and *hemorrhages*.

Ischemic causes include hypertension/hypotension, cardiac (arrhythmia, septal defects), arterial (dissection, aneurysmal, vasculitis, moyamoya disease, vasospasm), and prothrombotic and rheologic/hematologic (polycythemia, leukemia) disorders, all of which require urgent pediatric referral.

Movement illusions (oscillopsia and Pulfrich phenomenon)

Visual perception of movements may be motor, sensory, or cerebral in origin. Motor causes are *oscillopsia* due to either *nystagmus*, in which case it tends to be acquired, or *superior oblique myokymia*. In superior oblique myokymia, the oscillopsia is monocular and vertical and/or torsional. The diagnosis is made by making the patient look into the field of action of the superior oblique and looking for brief saccadic movements on ophthalmoscopy. *Eyelid myokymia* are involuntary and usually harmless lid contractions that are differentiated from true oscillopsia by history and examination.

A sensory cause is the *Pulfrich phenomenon*, caused by delayed conduction in optic neuropathy. The stereoscopic effect is a result of the retinal disparity cue caused by the latency disparity between the two optic nerves. This can be tested by swinging a ball in a line perpendicular to the subject from side to side. Instead of seeing the object swing from side to side, the patient perceives an elliptical movement in a horizontal plane.

Epileptic kinetopsia is an ictal illusory perception of motion seen in temporal lobe epilepsy.

Color (dyschromatopsia)

Loss of color vision is physiologic under scotopic light conditions due to the relative insensitivity of cones compared to rods ("all cats are gray in the dark").[9] Children may describe colorful afterimages after looking at a bright object, which persist for a while, even when closing both eyes. A clear history and a simple explanation will reassure the child and parents.

True *dyschromatopsia* is a disturbance in color vision. Congenital color blindness is the most common cause for dyschromatopsia. Deuteranomaly affects approximately 5–8% of boys, but only 0.4% of girls. Commonly, this is noticed by others rather than the child, for example when observing the child naming or drawing objects' colors incorrectly or during vision screening at school. Acquired dyschromatopsia is common with media changes (e.g. cataract, vitreous hemorrhage), optic nerve disease (e.g. optic neuritis), and, less often, with retinal and macular disease (e.g. retinal and macular dystrophies). *Köllner's rule* pertains to the causes of acquired color vision loss and states that diseases of the outer retina (e.g. in macular disease) typically result in blue–yellow color defects, while disorders of the inner retina, the optic nerve, and beyond tend to cause red–green color loss; however,

important exceptions to this general rule include blue–yellow deficits in glaucoma and dominant hereditary optic atrophy, red–green deficits in Stargardt disease, and mixed red–green and blue–yellow deficits in optic neuritis. Relative bitemporal red desaturation on confrontation is an early clinical indicator of compression of the optic chiasm. Cerebral causes of color loss are rare (cerebral achromatopsia).

Seeing multiples (monocular diplopia, triplopia, and polyopia)

A child may use "seeing double" to simply express visual blur or shadowing around an object rather than true diplopia. A bright child noticing physiologic diplopia in front of or behind a fixation point is not an uncommon cause of referral. Most pathologic diplopia is binocular due to ocular misalignment. In patients with chiasmal disease and strabismus, complete bitemporal field loss can result in the slide phenomenon, diplopia, or central visual field loss. The hallmark of binocular diplopia is that the double vision disappears under monocular cover. True monocular diplopia and polyopia, however, persist under monocular conditions. Most monocular diplopia is due to an abnormality of refraction, the precorneal tear film, corneal pathology, cataract formation, lens dislocation, polycoria, or rarely a retinal cause. Cerebral causes of diplopia and polyopia are very rare and often associated with other defects (e.g. visual field) and are discussed in the section on visual perseveration, below.

Size (micropsia, macropsia, teleopsia, lilliputianism)

Objects may appear abnormally large (*macropsia*), far away (*teleopsia*), or small (*micropsia*) (Fig. 100.3). In *lilliputianism*, people appear to be very small. Simple benign global micropsia is an isolated complaint, affecting children mostly at school age. It may be associated with prior reading at night and resolve spontaneously after some months. Micropsia of macular origin is associated with reduced or distorted vision. Cerebral causes include migraine and, less frequently, epilepsy and infections.

If the micropsia is isolated and present in an otherwise healthy child with no distortion of reality or hallucinations, full visual fields, and normal orthoptic and ocular findings, clinical observation is reasonable. In all other cases or where symptoms do not resolve, investigations (pediatric assessment, infective screen, neuroimaging) are indicated.

Distortion (dysmetropsia, metamorphopsia, and "Alice in Wonderland" syndrome)

Dysmetropsia and metamorphopsia are related visual illusions where object shapes appear distorted and straight lines bent. Metamorphopsia is best assessed with an Amsler grid. Even relatively young children will be able to say whether the lines are straight or not and report "funny lines." Visual distortions are either optical (common), macular (occasional), or cerebral (rare) in origin. Optical causes include high corneal, lenticular, or retinal (staphylomatous) astigmatism, high ametropia, anisometropia, and new glasses. Macular causes include macular edema and choroidal neovascularization (e.g. associated with myopic Fuchs maculopathy, inflammatory ocular disease, and macular dystrophies). Rarely visual distortion is of cerebral origin, as in the "Alice in Wonderland" syndrome. A cerebral cause is likely to be accompanied by other neurologic symptoms and signs.

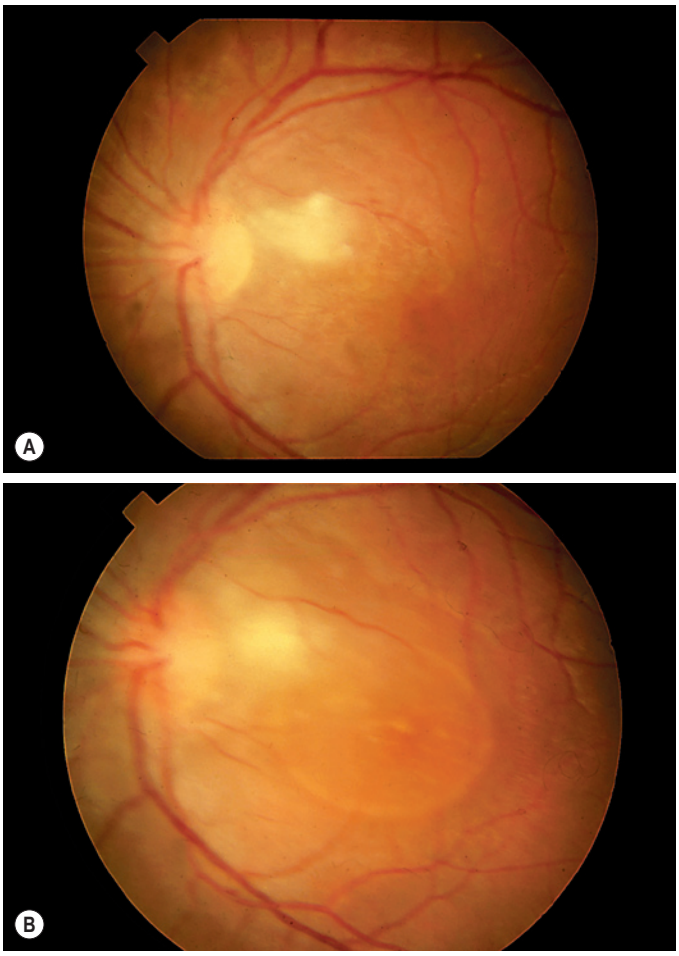


Fig. 100.3 Neuroretinitis with micropsia. This 9-year-old girl complained of dullness of vision in both eyes and smallness of objects with distortion on the left. (A) The white area temporal to the optic disc represents retinal nerve fiber swelling and vascular leakage, extending to the fovea. (B) As the retinal edema increased and extended across the macula, the acuity dropped to 6/36 and the micropsia disappeared.

If the Amsler grid confirms the presence of distortions, the management includes refraction and detailed slit-lamp examination of the anterior and posterior segments. Investigations may include optical coherence tomography or fundus fluorescein angiography with macular disease, corneal topography (if keratoconus is suspected) and neuroimaging (magnetic resonance imaging [MRI]) if a cerebral cause is suspected.

Metamorphopsia, micropsia, macropsia, and the Alice in Wonderland syndrome more commonly accompany childhood than adult migraine. Alice in Wonderland syndrome is frequently associated with migraine, but may also be due to epilepsy, drugs/medication (topiramate), varicella infection, or infectious mononucleosis.



Fig. 100.4 Picture drawn by a right-handed young person with an ultimately fatal metastatic carcinoma in the right parietal lobe. The presenting symptom was the recurrence of an image of the kitchen window that impinged itself involuntarily on the visual environment in different circumstances for several hours after the original stimulus.

Bradyopsia

Rarely, children may take excessive time to adapt to changing levels of brightness and darkness and find it difficult to track moving objects due to a defect in the photoreceptor deactivation mechanism in the phototransduction cascade. In addition to markedly delayed dark and light adaptation, the visual acuity is moderately reduced. There is mild photophobia with normal color vision and normal fundi (see Chapter 46).

Visual perseveration and other rare cerebral visual disturbances

Palinopsia is the visual perseveration of an image in time (Fig. 100.4). In the immediate type, the image persists for minutes after the true object has disappeared. In the delayed type, the image of a previously seen object reappears, sometimes for days or weeks. The picture is formed and different from afterimages created by retinal overstimulation from prolonged looking at a light, for example. In *cerebral diplopia* or *polyopia*, the visual image persists in space and two or more copies of the same image are seen simultaneously. Unlike binocular diplopia, cerebral diplopia and polyopia is monocular and is differentiated from ocular causes of monocular diplopia and polyopia by refraction followed by examination of the eye to exclude corneal pathology, lens displacement, iris defects (polycoria), or cataract. In cerebral diplopia/polyopia, each perceived image is equally clear, pinhole viewing has no beneficial effect, and no difference is seen with binocular versus monocular viewing. In *illusory visual spread*, the image expands beyond the real object size. Palinopsia, polyopia, and illusory visual spread will often be seen in the context of other cerebral disturbances, such as homonymous visual field defects. In *cerebral akinetopsia*, any perception of motion is completely lost due to bilateral cerebral lesions. *Visual disorientation* and *simultanagnosia* is the ability to interpret individual parts of a picture, but not the totality of the image seen and is part of *Balint syndrome*.

Visual disturbances associated with migraine

Children with migraine can have a large spectrum of visual disturbances, classically visual hallucinations with enlarging scintillating scotomas and fortification patterns (*teichopsia*) or simple unformed light flashes (*cerebral photopsia*). Visual field loss (e.g. hemianopia) is a wellrecognized complication. Visual illusions of micropsia, macropsia, metamorphopsia, and Alice in Wonderland syndrome are associated with migraine. Other reported visual disturbances in migraine include palinopsia and polyopsia. Rarely, complex visual hallucinations containing people or animals (*zoopsia*) and out-of-body experiences may be experienced in which the migraineur views his own body (*autoscopy*). Other rare disturbances are complete achromatopsia (cerebral color loss), prosopagnosia (no recognition of faces), and visual agnosia (no recognition of objects).

Hallucinations

Hallucinations are sensory perceptions generated by the mind *sui generis* in the absence of true external stimulation (Fig. 100.5). Illusions are misinterpretations or distortions of existing external stimuli.

Hallucinations in darkness and with social deprivation

Non-formed random noise of tiny lights and dark points are seen with eye closure or in complete darkness (*closed-eye hallucinations and visualizations*). *Eigengrau* (German for "intrinsic gray") or *Eigenlicht* (German for "intrinsic light") is the gray or light seen in perfect darkness as a result of baseline intrinsic retinal electrical activity. The *Ganzfeld effect* describes visual hallucinations caused by prolonged staring into a featureless field of vision or field of color. Prolonged *sensory deprivation* in darkness (e.g. at night or in a dark room) may give rise to hallucinations of formed light of different colors or even human figures.

Charles Bonnet syndrome (visual release phenomenon)

Visual hallucinations may be release phenomena.[10] Visual hallucinations associated with visual loss in a lucid person who realizes that the hallucinations are not real are called Charles Bonnet syndrome. They can occur after simultaneous or sequential, not necessarily complete, bilateral visual loss (Fig. 100.6) due to any cause in the visual pathway (e.g. dense cataracts, macular, optic nerve, or cortical disease, after enucleation). The hallucinations are typically vivid, formed, and complex (often people or scenes), filling in the blind scotoma. The hallucinations are strictly visual (e.g. people do not speak in the hallucinations). They represent release visual phenomena caused by the loss of cortical stimulation after

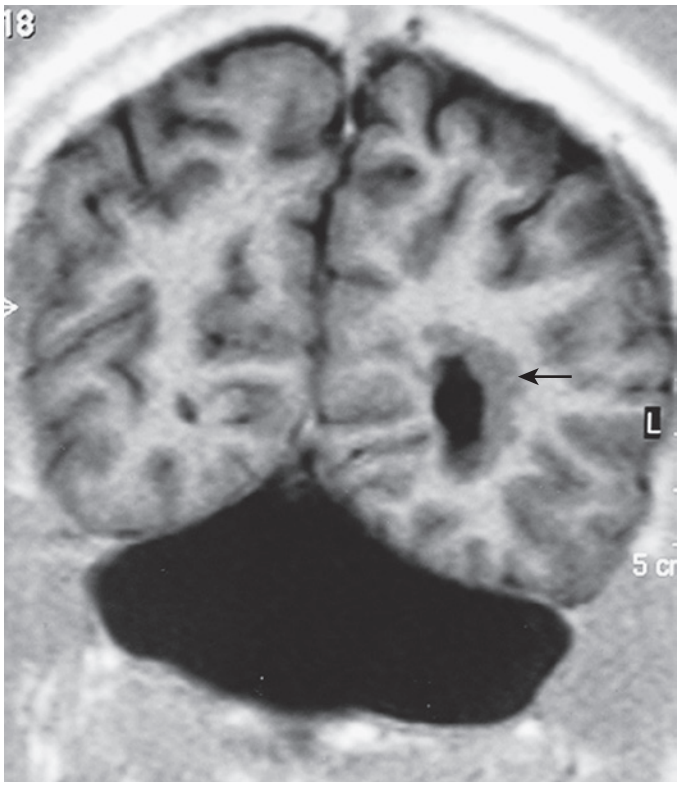


Fig. 100.5 This boy with a Möbius-like syndrome started, at the age of 18, to get unformed hallucinations in the right half of his visual field accompanied by nausea followed by sleepiness, without seizures. The magnetic resonance imaging shows an area of dysplastic ectopic gray matter in the left posterior parieto-occipital region (arrow).

visual loss and are potentially reversible (e.g. after successful cataract surgery). Many patients may be understandably very reluctant to admit to these hallucinations. The individual is typically relieved, once reassured of their true nature.

Hypnagogic and hypnopompic hallucinations

Visual hallucinations at sleep onset (hypnagogic) and on awakening (hypnopompic) are normal, but a child with daytime somnolence should be investigated for narcolepsy if hypnagogic hallucinations are associated with sleep attacks, cataplexy, or sleep paralysis.

Occipital and temporal lobe epilepsy

Another important cause of hallucinations is occipital and temporal lobe epilepsy (rarely parietal lobe). Visual hallucinations tend to be simple (photopsia, white phosphenes, steady colored lights) with occipital lobe epilepsy, and more often complex (e.g. faces, people) with temporal lobe epilepsy. Visual seizures will often be accompanied by other ictal signs, such as focal motor seizures, automatisms (e.g. lip pursing, chewing), and sensory (e.g. olfactory hallucinations) and autonomic changes (e.g. pupillary changes, salivation, urinary incontinence). Occipital lobe epilepsy with visual hallucinations only may be difficult to differentiate from acephalic migraine with visual aura.

Benign childhood epilepsy with occipital epilepsy is an idiopathic epilepsy syndrome in children of school age that ceases spontaneously when they become teenagers. The seizures are associated with simple or complex visual hallucinations (or transient visual loss), may progress to motor or partial complex seizures, and be followed by postictal headaches similar to migraine. Electroencephalography (EEG) is diagnostic and pharmacologic treatment is available.

Peduncular hallucinosis

In this rare syndrome, vivid, colorful, kaleidoscopic images, geometric patterns or elaborate pictures of landscapes, flowers, animals or even human beings are seen. The pathology typically involves the midbrain and may be associated with other signs of midbrain disease as well as sleep and cognitive disturbances.

Drug-induced hallucinations

Visual hallucinations and illusions may be caused by medication (e.g. steroids, lamotrigine, cyclosporin, digoxin, sildenafil [for pulmonary arterial hypertension], gancyclovir, vincristine, lidocaine, itraconazole, lithium, levodopa), its withdrawal (e.g. barbiturates in epileptic children, baclofen), anesthetics (ketamine), eye drops (idiosyncratic response to atropine and cyclopentolate), alcohol, as well as hallucinogens (e.g. LSD, phencyclidine [PCP], cocaine, marijuana).

Psychogenic ("functional") visual loss

Psychogenic, or "functional," visual loss is not uncommon in children. The estimated incidence is 1.4/1000 per year. It is more common in girls, clustered in immediate prepuberty and puberty teenage years. It should be suspected when an unexplained discrepancy exists between purported subjective visual loss and objective findings, or when reported visual findings are optically or physiologically contradictory (see Chapter 63). It is a diagnosis of exclusion. Some children with an element of psychogenic visual loss will also be found to have an underlying organic disease with time. The manifestations can be diverse and range from purported total loss of vision to relatively unusual visual experiences. Some children clearly are pretending, but most affected teenagers appear genuinely affected. Brodsky has classified these into four groups:

group 1: the visually preoccupied child;
group 2: conversion disorder;
group 3: possible factitious disorder;
group 4: psychogenic visual loss superimposed on true organic disease.

Medical conditions

Visual hallucinations and illusions may be seen in a number of medical conditions, including febrile delirium, encephalitis, and encephalopathy from metabolic disease. Urgent medical referral is required in the management of these cases.

Psychiatric disease

Hallucinations, in which all insight into the false nature of the perception is lost, are part of psychosis, a profound thought disorder in which the individual loses the control over his

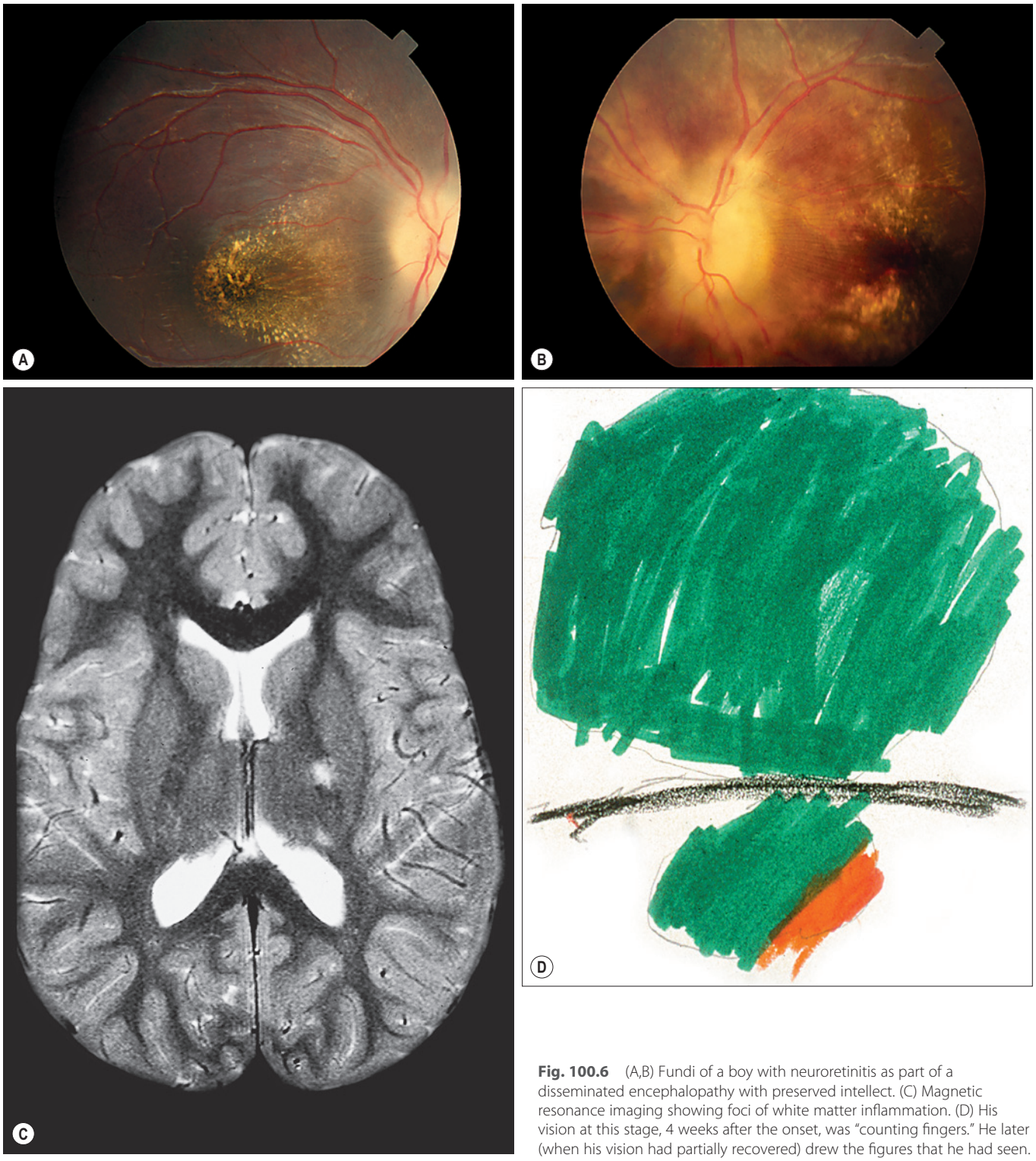


Fig. 100.6 (A,B) Fundi of a boy with neuroretinitis as part of a disseminated encephalopathy with preserved intellect. (C) Magnetic resonance imaging showing foci of white matter inflammation. (D) His vision at this stage, 4 weeks after the onset, was "counting fingers." He later (when his vision had partially recovered) drew the figures that he had seen.

sense of reality. Unreal voices and visions become real. Often frightening visual and acoustic (hearing voices) hallucinations are associated with delusional beliefs, bizarre behavior, and a general decline in self-care as part of this grave thought disorder. Recognizing a teenager with frank psychosis (not infrequently following the consumption of illicit drugs) is usually not challenging. Urgent referral to a psychiatric team is indicated due to the substantial risks of harm to the affected individual and others.

Psychiatric patients can have genuine visual problems as well. One should therefore take the psychiatric patient with visual complaints seriously if his/her complaint is persistent and consistent after the mental state has stabilized. The author recalls being asked to see a young psychiatric inpatient that

said that he could neither read well at near nor see people in the distance. His psychiatrist was doubtful of any organic basis to this, but referred him: he had marked keratoconus!

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Wobbly eyes in infancy

Narman Puvanachandra

Below is a guide on how to differentiate the main types of nystagmus seen in children. But first, a brief summary of each group

Infantile nystagmus syndrome (INS)

This group includes:

- sensory nystagmus: with identifiable cause;
- idiopathic nystagmus (previously motor nystagmus), where vision is often good and no sensory cause can be found. Nystagmus in this group tends to be early onset before 3 months of age, uniplanar horizontal (but may have rotational and rarely vertical components), dampens on convergence, but worsens on attempted fixation and stress. Null points are often present.

Fusional maldevelopment nystagmus syndrome (FMNS)

Disorders in this group, which includes manifest latent nystagmus with strabismus, typically have infantile esotropia or exotropia. They are associated with dissociated vertical deviation (DVD) and a large latent component to the nystagmus. Some may have nystagmus blockage syndrome.

Spasmus nutans (SN)

A much rarer form of nystagmus, with high frequency, small amplitude dysconjugate nystagmus along with head nodding and head tilt. Most cases are early onset, but after 6 months of age, and have a benign recovery over years. A similar triad may be rarely seen with intracranial tumors, especially of the visual pathway. Imaging is warranted in children with onset after infancy and with other neurological signs.

Neurological nystagmus (NN)

This group includes all the other acquired nystagmus and is associated with later onset after 3 months and nystagmus atypical of INS. Neurological signs may be present, and further urgent investigation, in collaboration with pediatric neurologists, is required. It may be associated with a previous central nervous system insult, drugs, neurological or metabolic disease.

Nystagmus-like saccadic disorders, e.g. opsoclonus, ocular flutter

This comprises a range of erratic non-sustained non-repetitive movements that warrant further investigation as a general rule. Opsoclonus – "dancing eyes," for example, may be associated with neuroblastoma.

Here are some clues on how to assess and differentiate these types of nystagmus:

The history

Many important elements in the history can point to the etiology of the nystagmus, helping the clinician to advise the parents and guide investigations:

Prenatal insults Was there maternal diabetes, drug or alcohol ingestion in pregnancy?

Perinatal insults Was there any hypoxic insult, traumatic birth, or prematurity?

Development Does the child have global developmental delay, cerebral palsy, or other medical disorders, e.g. epilepsy, neurological or metabolic conditions?

Drug history Is the child taking drugs such as anti-convulsants?

Onset of nystagmus Was onset before 3 months of life? (If so, this is typical of INS rather than acquired NN, where onset is typically after 3 months of age.)

Visual response Do the parents feel the child looks at them? Poor visual response points to sensory INS, although can also be seen in acquired NN if visual pathways are significantly affected.

Pattern of nystagmus waveform over time Many parents state that the nystagmus was wide and roving to start with, becoming pendular and of smaller amplitude before ending up as rapid jerk nystagmus. This pattern is typical of INS.

Oscillopsia Does the older child complain of the world shaking? This is more typical of acquired NN, although can be intermittent in INS.

Family history Is there a family history of ocular disease such as retinal dystrophy, albinism, aniridia, congenital cataracts, idiopathic INS, neurological or metabolic diseases?

Observation by parents and clinician

The observations that parents make about their children over time and the clinician's observations prior to examining the child can prove useful.

Strabismus Is there a large-angle esotropia or exotropia present that appeared by 3 months of age? This suggests FMNS.

Head nodding Did the parents notice a tendency for head nodding, especially early after onset of the nystagmus? Does the child appear to see better when they nod (part of the triad of spasmus nutans).

Corrected head posture Does the child adopt a specific head posture? This is seen mainly in idiopathic INS, although it can be seen in SN.

Photophobia Exaggerated dislike of bright light may point to several pathologies such as achromatopsia, aniridia, cataract, Leber congenital amaurosis, and albinism, all causing sensory INS.

Observation of the nystagmus

The type of nystagmus may be distinguished from observation of the nature of the nystagmus and its variation:

Bilateral/unilateral True monocular nystagmus onset after 3 months of age is associated with unilateral reduced visual acuity in the context of optic nerve or chiasmal glioma. However, more commonly it is seen in strabismic amblyopia.

Direction INS tends to be horizontal but can have additional vertical and horizontal components. It is rarely purely vertical or rotational. This directional pattern rarely changes significantly over time in INS.

Amplitude Large amplitude nystagmus is associated with poorer vision, although this can vary from visit to visit and even during a single consultation.

Foveation period The longer this period is of relative stillness before the slow phase restarts, the better the vision generally is.

Latent component Increase in amplitude on covering one eye is seen in FMNS and INS. In FMNS, the nystagmus reverses in each eye with the fast phase away from the occluded side.

Assessment of vision

- Binocular vision is key; it is the most reliable due to the latent component of nystagmus that accompanies both FMNS and INS.
- If uniocular vision is attempted, then fogging one eye with a high plus lens is more accurate.
- Value the parents' opinion about vision, as they often see the child in a less stressful environment where they may perform better.
- Visual acuity measurements can vary significantly from visit to visit due to variation in the child's emotional stress, age, test, and tiredness.
- Near vision is often better than distance vision due to the dampening effect of convergence.
- Typically, vision of 6/6 to 6/24 is seen in idiopathic INS, while vision of 6/24 or worse is more usual in sensory INS.
- Color vision problems in the older child can point towards abnormal cone function.
- Lack of stereopsis in the older child can indicate FMNS, even in the absence of large-angle strabismus.
- Use of an optokinetic (OKN) drum can help establish if vision is present despite nystagmus. Reversal of the OKN response with the fast phase in the direction of the drum movement is seen in INS.

Examination of the eye

Careful assessment of the eye can identify causes for sensory INS.

Microphthalmia or, indeed, buphthalmos Developmental abnormalities of the eye or congenital glaucoma can lead to sensory nystagmus.

Media Bilateral opacity occluding the visual axis, such as corneal clouding, congenital cataracts or persistent fetal vasculature can cause sensory nystagmus.

Pupils Sluggish pupillary light reflexes indicate either aniridia (partial or complete) or profoundly decreased vision, e.g. Leber congenital amaurosis or optic nerve hypoplasia.

Iris Transillumination of the iris can be florid or subtle in albinism. Placing the baby at the slit-lamp in the "superman" position can often reveal even subtle transillumination defects.

Retina Severe bilateral macular pathology, e.g. toxoplasmosis scars, chorioretinal colobomas, foveal hypoplasia (typical of albinism), may be evident. Optical coherence tomography in the older child can help confirm the presence of foveal hypoplasia.

Optic nerve Optic nerve hypoplasia or pallor are sensory causes that are easily missed. Optic nerve swelling, e.g. accompanying optic nerve tumors, can also be the cause.

Table 101.1 When and when not to consider early investigation of nystagmus in children: a rough guide

	When early investigations are not indicated	When electrophysiology may be indicated	When early neurological imaging is indicated
Type	Idiopathic INS or sensory INS with identifiable cause, FMNS	Sensory INS without identifiable cause	NN/SN/opsoclonus (include abdomen and chest)
Onset	<3 months	<3 months	>3 months
Family history	Positive family history	–	–
Visual function	Good visual function	Poor visual function	Oscillopsia noted (if verbal child)
Eye exam	Identifiable cause found	Normal exam	RAPD, optic nerve swelling or pallor
Strabismus	Large infantile esotropia/exotropia	+/–	Incomitant strabismus, e.g. sixth nerve paresis
Nystagmus Waveform	Typical INS waveform	Roving, irregular	Opsoclonus; localizing nystagmus, e.g. convergence retraction, periodic alternating, Bruns, see-saw, up- or downbeat; pure vertical/rotational nystagmus
Dampening features	Null point with corrected head posture	–	Worse on eye closure, e.g. vestibular or brainstem related
Dissociated	If monocular with clear amblyogenic cause identified	–	Monocular or very asymmetric nystagmus without amblyopia
Conjugacy	Conjugate	–	Dysconjugate, e.g. internuclear ophthalmoplegia or convergence retraction
Neurological features	None	–	Seizures, ataxia, developmental delay, myoclonus, localizing neurological signs
Eye movement recording	Increasing velocity slow phase	–	–

FMNS, Fusional maldevelopment nystagmus syndrome; INS, infantile nystagmus syndrome; NN, neurological nystagmus; RAPD, relative afferent pupillary defect; SN, spasmus nutans.

Examine the parents

Although examination of the child can sometimes be limited due to cooperation, examining both parents can be very helpful to secure the diagnosis. This is particularly the case with transillumination defects of the iris (often seen in the mother of boys with ocular albinism), partial aniridia, anterior segment abnormalities, retinal dystrophies, and dominant optic nerve atrophy.

When to investigate

Some argue that electrophysiology, neurological consultation, neuroimaging, and eye movement recordings should be performed in all cases of nystagmus. However, most clinicians lack access to some of these and sedation is often needed to achieve neuroimaging. The table above gives rough guidelines on what features should point you toward early investigations, but it is clearly important to take the whole clinical picture into consideration. Electrophysiology can be delayed in some cases and avoided altogether in identifiable sensory INS and FMNS (see Table 101.1).

Further reading

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Abnormal head postures in children

Stephen P Kraft

Introduction

The medical term for an abnormal head posture (AHP) is "torticollis," from the Latin "tortus" (twisted) and "collum" (neck).[1,2] Torticollis from eye-related problems is termed "ocular torticollis".[1–4] Ocular torticollis that persists long term can lead secondarily to a musculoskeletal torticollis and even scoliosis.[1,4] The assessment of AHP in a child is often multidisciplinary, involving input from pediatricians, orthopedic surgeons, neurologists, psychologists, and occupational and physical therapists.[5] It is common for an ophthalmologist to be consulted to rule out ocular causes for an AHP.

Torticollis can involve rotation of the head around any of the three main axes (Fig. 102.1).[1,2] These include:

- vertical axis: head rotated to one side away from the primary (straight-ahead) gaze direction ("yaw");
- horizontal axis: chin elevated or depressed relative to the primary position ("pitch");
- anteroposterior axis: head tilted to one shoulder ("roll");
- combination of two or three orientations.

Congenital torticollis is most often due to muscular or skeletal anomalies.[1,6] Ocular torticollis almost never presents within the first few weeks of life.[1,4] Trauma must be ruled out as a cause of any acquired abnormal head posture, whether as a result of damage to the neck or due to disruption of eye muscle balance.[1,6]

Non-ocular causes of head postures (see Fig. 102.1; Box 102.1)[1]

Congenital disorders

Congenital muscular torticollis (CMT) is the most common type of birth-onset torticollis, caused by a painless, discrete "fibroma" on one side of the neck adjacent to the sternocleidomastoid muscle.[2,3,5,6] Other congenital causes include postural torticollis from an abnormal fetal position, and skeletal or osseous abnormalities in the cranial junction or cervical spine, such as Klippel–Feil syndrome.[6]

Acquired disorders

Acquired disorders include traumatic and non-traumatic causes. A traumatic cause, involving damage to bones, ligaments, muscle, or soft tissue, must be considered in any case of pediatric torticollis.[1,6]

Non-traumatic causes include skeletal or osseous pathology, postural torticollis produced by prolonged maintenance of the head in an awkward position, neurologic problems localized to the posterior fossa and spine, or associated with dystonia or medications, otolaryngologic diseases of the nasopharynx or inner ear, deafness, gastroenterologic illnesses, and psychologic disturbances.[1,6]

Specific note should be paid to a triad of photophobia, epiphora, and torticollis, which can be associated with posterior fossa lesions.[7] In addition, the "ocular tilt reaction," a triad of vertical divergence of the eyes, bilateral ocular torsion, and head tilt, is a postural reflex originating in the otolithic apparatus. It can be caused by lesions of the vestibular nucleus or its central connections.[8]

Ocular causes of head postures

The ophthalmologist's goal is to determine whether there is an ocular cause for the posture. If so, treatment can be planned to eliminate or reduce the problem, and restore a normal head posture.[9]

Ocular torticollis arises from disturbances in the input from the afferent visual pathway, ocular motor nerves, or the vestibular apparatus, leading to alterations in the normal balance of inputs to the neck muscles.[1,8] The posture may achieve one of several goals[1]:

1. optimize visual acuity (e.g. infantile nystagmus with an eccentric null zone);
2. maintain single binocular vision (e.g. incomitant strabismus);
3. center a narrowed visual field with respect to the body (with hemianopic field loss);
4. enable fixation with one or the other eye, when the patient is unable to center the eye due to extreme mechanical problems in the orbit or as a result of innervational problems to the eye muscles;
5. gain miscellaneous benefits (e.g. paradoxical tilt to maximize separation of diplopic images).

Diagnostic considerations

The child must be observed for an extended period of time to determine whether the torticollis is constant in orientation

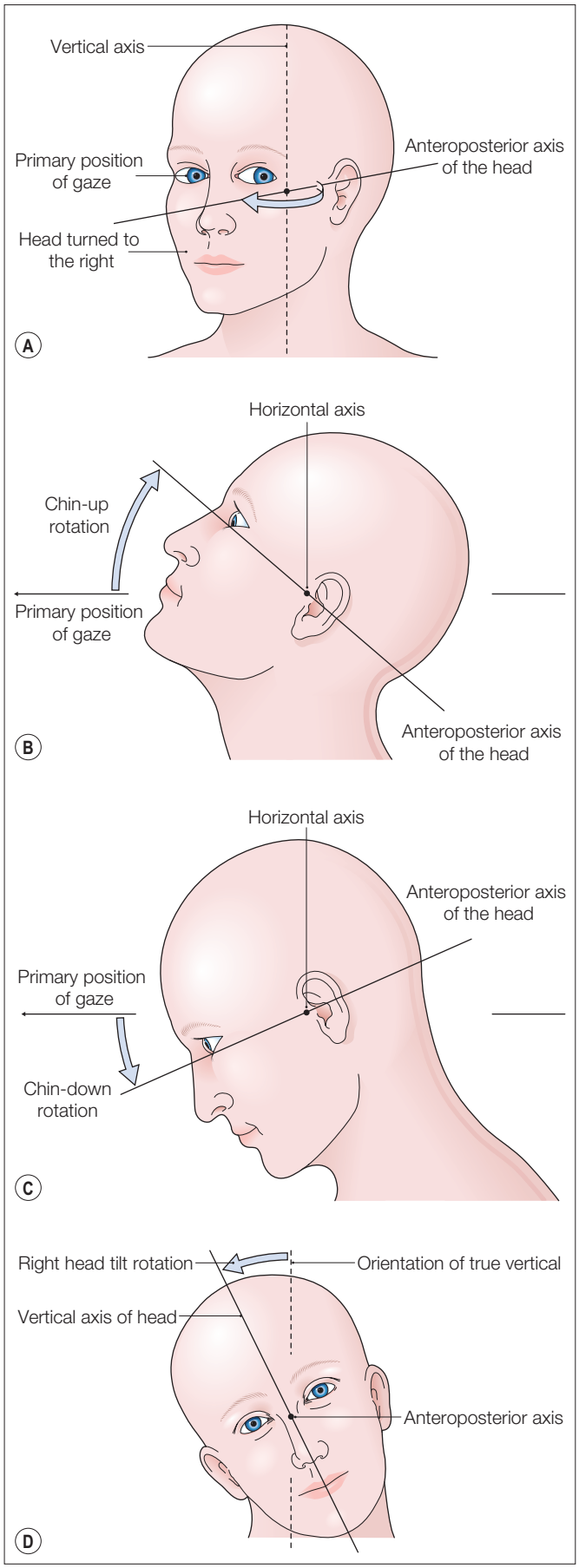


Fig. 102.1 Orientations of abnormal head postures. (A) Head turn to the right. The anteroposterior axis of the head is rotated from primary gaze direction to the right about the vertical axis. (B) Chin-up posture. The anteroposterior axis of the head is rotated upward from the primary gaze direction about the horizontal axis. (C) Chin-down posture. The anteroposterior axis of the head is rotated downward from the primary gaze direction about the horizontal axis. (D) Head tilt to the right shoulder. The vertical axis of the head is rotated away from the vertical axis about the anteroposterior axis.

Box 102.1

Non-ocular causes of torticollis

I. Congenital
   A. Muscular
      1. Congenital muscular torticollis
      2. Postural torticollis
      3. Absent cervical muscles
   B. Skeletal/osseous
      1. Atlant-oaxial bony deformity
      2. Klippel–Feil syndrome
      3. Sprengel deformity
      4. Miscellaneous anomalies
II. Acquired
   A. Traumatic
      1. Skeletal/osseous
         a. Atlanto-axial displacement
         b. Subluxation of C2–C3 joint
         c. Fractures
      2. Ligament
      3. Muscle or soft tissue
   B. Non-traumatic
      1. Skeletal/osseous
         a. Inflammation
         b. Tumors
         c. Ligamentous laxity
      2. Postural
      3. Neurologic
         a. Spinal and posterior fossa pathology
         b. Dystonia
         c. Infections
      4. Otolaryngologic
         a. Nasopharyngeal infections
         b. Benign paroxysmal torticollis of infancy
         c. Deafness
         d. Ocular tilt reaction
      5. Miscellaneous
         a. Gastroenterologic
         b. Metabolic
         c. Pharmacologic
         d. Psychogenic/functional

or if it changes, and whether it is unchanging or is dependent on the visual task.[1,2] Abnormal physical features such as dysmorphism or manifest nystagmus may yield clues to the etiology. Photographic records or videos from the early years of life should be sought whenever possible.[1,2] To quantitate the different components, one can use an orthopedic goniometer or torticollometer.[2]

If the AHP helps maintain binocularity, then occluding one eye abolishes or reduces the magnitude of the posture.[2] Conjugate eye movements (versions) elicited early in the examination

can detect an incomitant strabismus or a nystagmus null zone. Another maneuver is to move the head into a position opposite to that adopted to expose a zone of increased nystagmus intensity or a larger heterotropia.[2] Eye movement recordings may confirm the presence of a nystagmus and the pattern of the nystagmus waveform.[10]

A common cause for vision-driven head postures is an uncorrected or partially corrected refractive error, or an incorrect prescription of glasses or contact lenses. A careful refraction is an essential: correcting a significant error may eliminate the head posture.[1,2]

Fundus evaluation can confirm cyclotropia with oblique muscle disorders or detect a sub-clinical low-amplitude nystagmus. In cases where strabismus or nystagmus do not seem to be causative factors, it is helpful to perform visual field testing to identify a field defect.[2] Finally, palpation of the neck muscles and passive straightening of the head can help detect congenital muscular torticollis.[1,2,5]

Causes of ocular torticollis (Fig. 102.2)

Uncorrected refractive errors, or incorrectly prescribed lenses, as well as nystagmus with an eccentric null zone can be causes of any orientation of head posture.[1,2] The additional etiologies specific for the various head positions are[1]:

Head turn

1. Incomitant strabismus: Innervational and/or orbital mechanical disorders in one both eyes leading to a worsening horizontal or vertical heterotropia in the field of gaze ipsilateral to the turn.
2. Comitant strabismus: An extreme exotropia or esotropia whereby neither eye can fixate in primary position.
3. Conjugate eye movement deficit (bilateral gaze palsy).
4. Contralateral complete homonymous hemianopia.
5. Miscellaneous causes – including spasmus nutans, periodic alternating nystagmus, eccentric fixation, oculomotor apraxia, and "heavy eye" syndrome with high myopia.

Chin-up

1. Incomitant strabismus: Innervational and/or orbital mechanical disorders in one or both eyes leading to a worsening vertical heterotropia in the upgaze field.
2. "A" pattern esotropia or "V" pattern exotropia.
3. Ptosis of one or both upper eyelids.
4. Bilateral superior homonymous visual field deficits.
5. Miscellaneous causes – including supranuclear gaze disorders and "heavy eye" syndrome.

Chin-down

1. Incomitant strabismus: Innervational and/or orbital mechanical disorders in one or both eyes leading to a worsening vertical heterotropia in the downgaze field.
2. "A" pattern exotropia or "V" pattern esotropia.
3. Bilateral inferior homonymous visual field deficits.
4. Miscellaneous causes – including supranuclear downgaze disorders.

Head tilt

1. Incomitant strabismus: Innervational and/or orbital mechanical disorders in one or both eyes leading to a worsening vertical or horizontal heterotropia in primary position and on tilt to contralateral side.
2. Dissociated vertical deviation (DVD).
3. Cyclotropia.
4. Ocular tilt reaction.
5. Miscellaneous causes – including spasmus nutans and paradoxical head tilt.

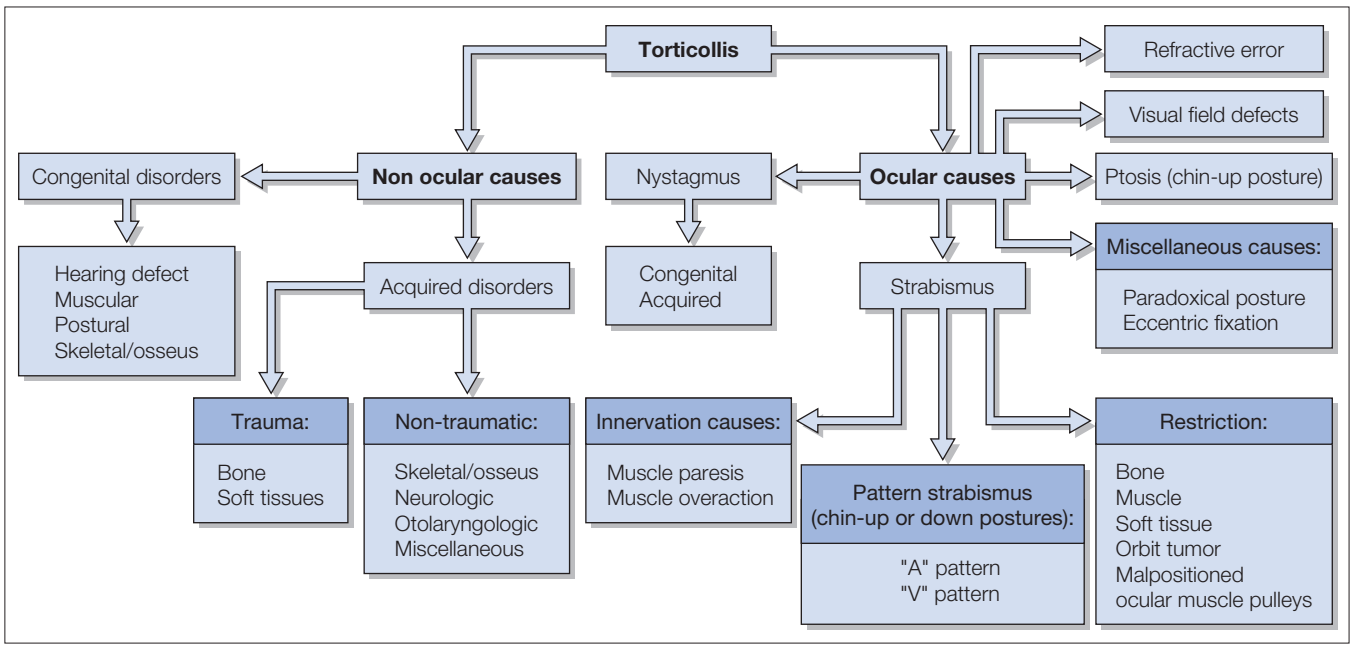


Fig. 102.2 Differential diagnosis of torticollis in children. The causes are divided into non-ocular and ocular causes (ocular torticollis). The non-ocular disorders include congenital and acquired conditions. Nystagmus, strabismus, and refractive errors must be ruled out as possible etiologies for any head posture orientation, whereas other etiologies apply to selected orientations.

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Hand defects and the eye

Luis Carlos Ferreira de Sá and Chong Ae Kim

The combination of hand and eye defects is frequent and may be observed in several genetic disorders that includes chromosomal abnormalities (trisomies 21, 18, and 13) and monogenic disorders (Marfan and Cornelia de Lange syndromes, mucopolysaccharidosis, Desbuquois dysplasia, and hemifacial microsomia).[1,2]

Moreover, there are some cases in which an association of a genetic defect with environmental factors determines phenotypic abnormalities (Möbius sequence, fetal alcohol syndrome, and fetal warfarin syndrome) as well as developmental abnormalities (e.g. amniotic bands, oligohydramnios, and local vascular disruption are also associated with limb abnormalities).[1–3]

With recent advances in molecular and cytogenomic techniques, it is now possible to determine more genetic defects that lead to these anomalies, although it is not always possible to identify the underlying mechanism.

Embryology

It is important to consider the embryology of eye and hand development to understand why such defects may occur simultaneously. During the third week of gestation, at about 22 days, the optic primordium becomes identifiable in the human embryo. It is the first morphological evidence of the eyes. At 25 days, as the optic cup and embryonic fissure emerge, upper limb buds appear. By 36 days, closure of retinal fissure is almost complete and the retina is incompletely pigmented. At the same time, the hand plate has formed with condensation of mesenchyme. In the hand plate, a central carpal region is surrounded by a crescentic flange, the digital plate, from which originates the five-finger rays. At 45 days, the fingers are partially separated.

Etiology

The etiology of most limb defects (Table 103.1) is variable and, as mentioned, may include a genetic defect or an environmental factor.[1,2,4,5] It is essential to take a family history including pre- and postnatal history and to inquire about other *major* malformations (e.g. congenital cardiac defects, nervous system malformations) that may help establish the diagnosis. Furthermore, it is important to emphasize two basic concepts in monogenic disorders: phenotypic and genotypic heterogeneity. The first one refers to the clinical variability and the second happens when mutations in different genes lead to a same disorder.

Eye defects and hand/finger anomalies originate usually between the third and fifth week of gestation. The various hand and eye defects may be grouped according to their similarity in overall features, or according to one major feature among the patterns of malformation, in the same manner as Smith's Recognizable Patterns of Human Malformation.[2] Many conditions present with occasional hand and eye defects, but only the most important and consistent associations are described in Table 103.2.

Table 103.1 Common terms used for malformations of limbs and fingers

Anomaly	Definition
Arachnodactyly	Long and thin bones of the fingers
Brachydactyly	Abnormal shortness of the fingers
Camptodactyly	Permanent and irreducible flexion of fingers
Clinodactyly	Deviation or deflection of one or more fingers
Ectrodactyly	Absence of any number of fingers (split-hand or split-foot)
Macrodactyly	Abnormal largeness of the fingers
Meromelia	Absence of part of a limb
Micromelia	Shortening of all segments of a limb
Phocomelia	Absence of segment of a limb or limbs
Polydactyly	Extra digits or parts of digits
Syndactyly	Fusion of digits

Table 103.2 Disease and related eye/ocular region and hand/finger anomalies

Group/disease	Eye/ocular region anomalies	Hand/finger anomalies
CHROMOSOMAL SYNDROMES		
Down syndrome (trisomy 21)	Upslanting palpebral fissures, epicanthal folds, iris Brushfield's spots, keratoconus, strabismus, nystagmus, myopia, cataracts	Short metacarpals and phalanges, fifth finger mid-phalanx hypoplasia with clinodactyly, simian crease
Edwards syndrome (trisomy 18)	Short/slanted palpebral fissure, ptosis, hypertelorism, iris coloboma, cataract, microphthalmos	Clenched hand, overlapping of fingers, absence of distal crease, hypoplasia of nails, hypoplastic or absent thumb, syndactyly, polydactyly, ectrodactyly, short fifth metacarpals
Patau syndrome (trisomy 13)	Microphthalmia, iris coloboma, retinal dysplasia, hypotelorism, hypertelorism, anophthalmos, cyclopia, slanting palpebral fissures, shallow orbital ridges, absent eyebrow	Flexion of fingers, overlapping, camptodactyly, polydactyly, syndactyly, retroflexible thumb
Triploidy syndrome and diploid/triploid mixoploidy syndrome	Hypertelorism, coloboma, microphthalmia, iris heterochromia	Syndactyly, simian crease, clinodactyly, proximally placed thumb
Aniridia–Wilms tumor association (Deletion 11p13)	Aniridia, cataracts, nystagmus, ptosis, glaucoma	Clinodactyly of fifth finger
VERY SMALL STATURE, NOT SKELETAL DYSPLASIA		
Cornelia de Lange syndrome	Bushy eyebrow, synophrys, long, curly eyelashes	Micromelia, phocomelia, oligodactyly, simian crease, proximal implantation of thumbs
Rubinstein–Taybi syndrome	Heavy/highly arched eyebrows, long eye lashes, epicanthal folds, strabismus, nasolacrimal duct stenosis, ptosis	Broad thumbs with radial angulation, fingers broad, clinodactyly, persistent fetal fingertip pads
MODERATE STATURE, FACIAL, GENITAL		
Smith–Lemli–Opitz syndrome	Ptosis, epicanthal folds, strabismus	Simian crease, occasional flexed fingers, short fingers, polydactyly
Williams syndrome	Epicanthal folds, stellate iris pattern, occasional strabismus, hypotelorism	Hypoplastic nails, occasional clinodactyly
Noonan syndrome	Hypertelorism, downslanting palpebral fissures, prominent corneal nerves, myopia, keratoconus, strabismus, nystagmus	Clinodactyly, brachydactyly, blunt fingertips
UNUSUAL BRAIN AND/OR NEUROMUSCULAR FINDINGS WITH ASSOCIATED DEFECTS		
Cohen syndrome	Decreased visual acuity, strabismus, constricted visual fields, chorioretinal dystrophy, optic atrophy	Narrow hands, mild shortening of metacarpals, simian crease
Zellweger syndrome	Cataracts, optic nerve hypoplasia, retinal pigmentary changes, glaucoma, nystagmus	Variable contractures, camptodactyly
FACIAL DEFECTS AS MAJOR FEATURE		
Möbius sequence	Sixth and seventh nerve palsy, strabismus	Syndactyly, limb reduction defects
Fraser syndrome	Cryptophthalmos, associated with eye defects	Partial cutaneous syndactyly, occasional absent phalanges/thumb
FACIAL–LIMB DEFECTS AS MAJOR FEATURE		
Miller syndrome	Eyelid coloboma, ectropion	Absence of fifth digits, syndactyly
Oculodentodigital syndrome	Microphthalmos, microcornea, short palpebral fissures, epicanthal folds, fine porous iris	Syndactyly, camptodactyly, phalangeal hypoplasia
Stickler syndrome (hereditary arthro-ophthalmopathy)	Myopia, chorioretinal degeneration, retinal detachment, cataract	Severe arthropathy, occcasional arachnodactyly
Ectrodactyly–ectodermal dysplasia–clefting (EEC) syndrome	Blue iris, photophobia, blepharophimosis, lacrimal system anomalies, blepharitis	Syndactyly, ectrodactyly, nail dysplasia

Continued

Table 103.2 Disease and related eye/ocular region and hand/finger anomalies—cont'd

Group/disease	Eye/ocular region anomalies	Hand/finger anomalies
CRANIOSYNOSTOSIS SYNDROMES		
Apert syndrome (acrocephalosyndactyly)	Hypertelorism, strabismus, shallow orbits, downslanting of palpebral fissures	Osseous and/or cutaneous syndactyly, broad distal phalanges of thumb, fingers may be short
Pfeiffer syndrome	Ocular hypertelorism, shallow orbit, proptosis	Broad distal phalanges, syndactyly
Carpenter syndrome	Cornea opacity, microcornea, optic atrophy	Brachydactyly, syndactyly, polydactyly, clinodactyly, camptodactyly
OTHER SKELETAL DYSPLASIA		
Weill–Marchesani syndrome	Spherophakia, ectopia lentis, myopia, glaucoma	Brachydactyly, broad metacarpals and phalanges, stiff joints (hands)
CONNECTIVE DISORDERS		
Marfan syndrome	Lens luxation/subluxation, myopia, retinal detachment, glaucoma	Arachnodactyly
Homocystinuria	Lens subluxation (inferiorly), myopia, cataract, glaucoma, optic atrophy	Arachnodactyly
Ehlers–Danlos syndrome	Blue sclera, myopia, microcornea, glaucoma, ectopia lentis, keratoconus	Hyperextensibility of joints
Osteogenesis imperfecta	Blue sclera (thin and translucent), keratoconus, embryotoxon posterior	Hyperextensibility of joints, fractures, occasional syndactyly
HAMARTOSES/PHAKOMATOSIS		
Linear sebaceous nevus sequence	Esotropia, lipodermoid, cloudy cornea, coloboma, optic atrophy, microphthalmia	Polydactyly, syndactyly
Klippel–Trénaunay–Weber syndrome	Glaucoma, cataracts, heterochromia	Asymmetric limb hypertrophy, occasional macrodactyly, syndactyly, polydactyly or oligodactyly
ENVIRONMENTAL AGENTS		
Fetal alcohol syndrome	Optic nerve hypoplasia, coloboma, nystagmus, cataract, ptosis, microphthalmos	Small distal phalanges, small fifth finger nail
Thalidomide	Duane/ocular motility disorders, lacrimation	Phocomelias or longitudinal deficiencies of the extremities, sometimes in combination with absent hand function
Anticonvulsants	Myopia, prominent long eye lashes	Hypoplasia of the distal phalanges of the fingers; shortening of the distal phalanges and hypoplasia or aplasia of the nails. Possible simian creases
MISCELLANEOUS SYNDROMES/ASSOCIATIONS		
Bardet–Biedl syndrome (Laurence–Moon–Biedl)	Retinal dystrophy (retinitis pigmentosa), astigmatism, nystagmus, cataracts	Polydactyly, syndactyly, brachydactyly
Goltz syndrome	Coloboma, microphthalmia, strabismus	Syndactyly



Fig. 103.1 (A) Apert syndrome. (B) Same patient after surgery for syndactyly. (C) Syndactyly of toes.



Fig. 103.2 Möbius syndrome: Right hand ectrodactyly and left meromelia.

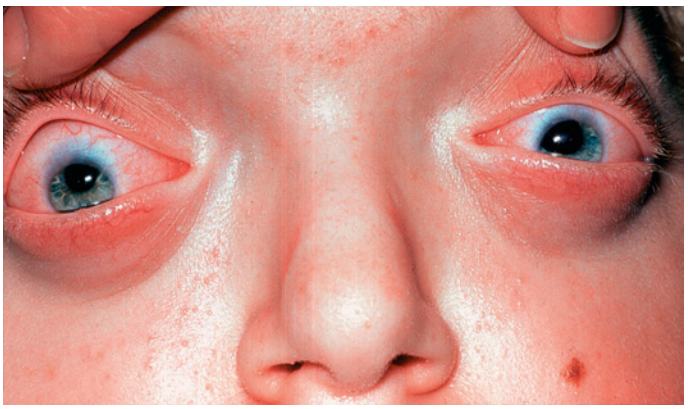


Fig. 103.3 Atypical iris coloboma in a patient with Pfeiffer syndrome.



Fig. 103.4 Arachnodactyly, frequently found in patients with Marfan syndrome.

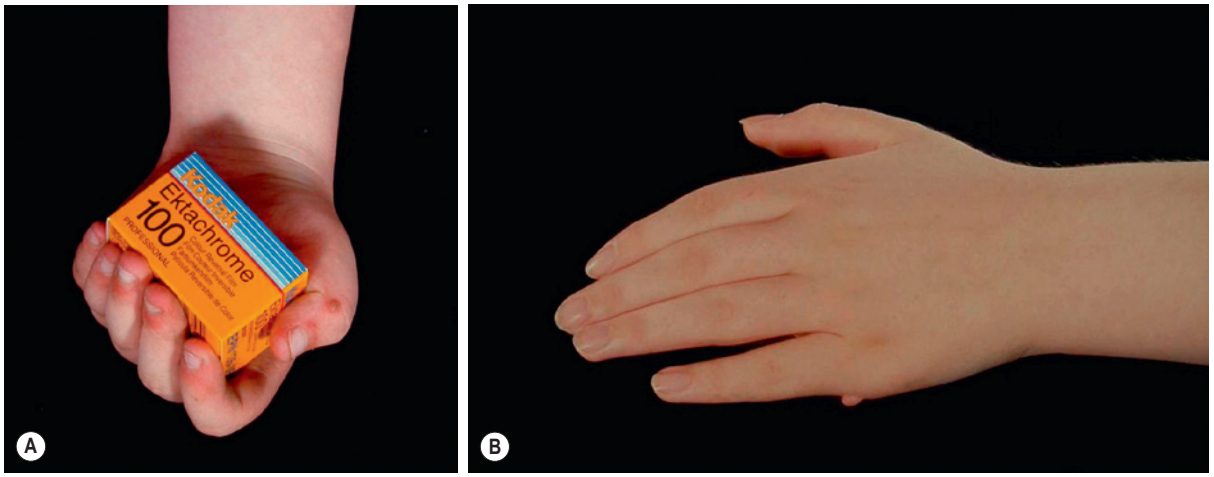


Fig. 103.5 (A) Post-axial polydactyly in a patient with Bardet–Biedl syndrome. (B) Small post-axial polydactyly. By the time of presentation to the ophthalmologist with visual failure, the extra finger has often been removed.

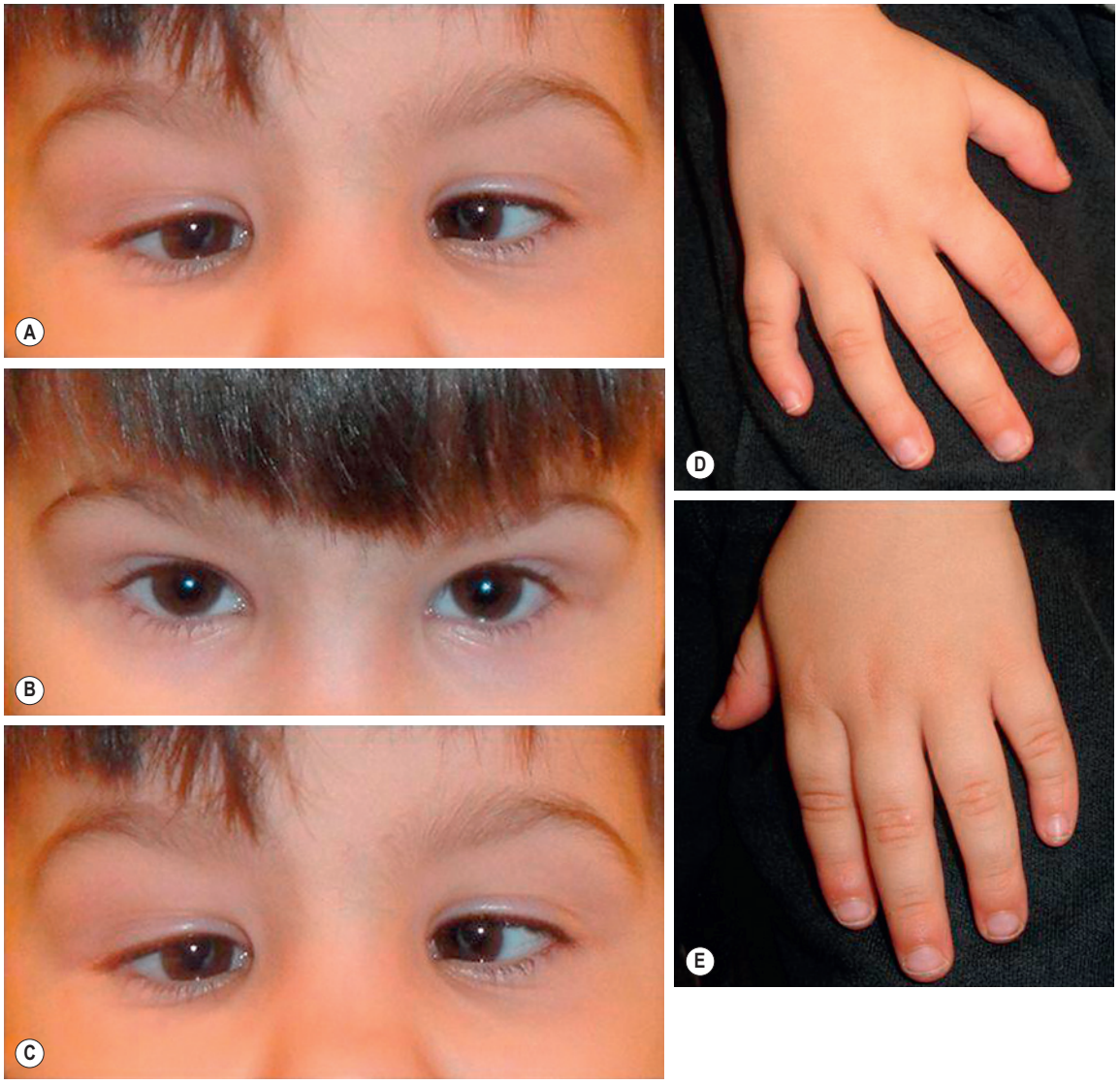


Fig. 103.6 Duane syndrome type III. (A) Looking right: absent right abduction and slight narrowing of the left palpebral fissure. (B) No strabismus in the straight-ahead position but there is bilateral horizontal gaze palsy, abnormal blinking, and tearing. (C) Looking left: absent left abduction and reduced right adduction with narrowing of the right palpebral fissure. (D,E) Bilateral clinodactyly.



Fig 103.7 Mucopolysaccharidosis type VI. (A) Corneal opacity. (B) Typical facial dysmorphisms. (C) Macrodactyly and clinodactyly.

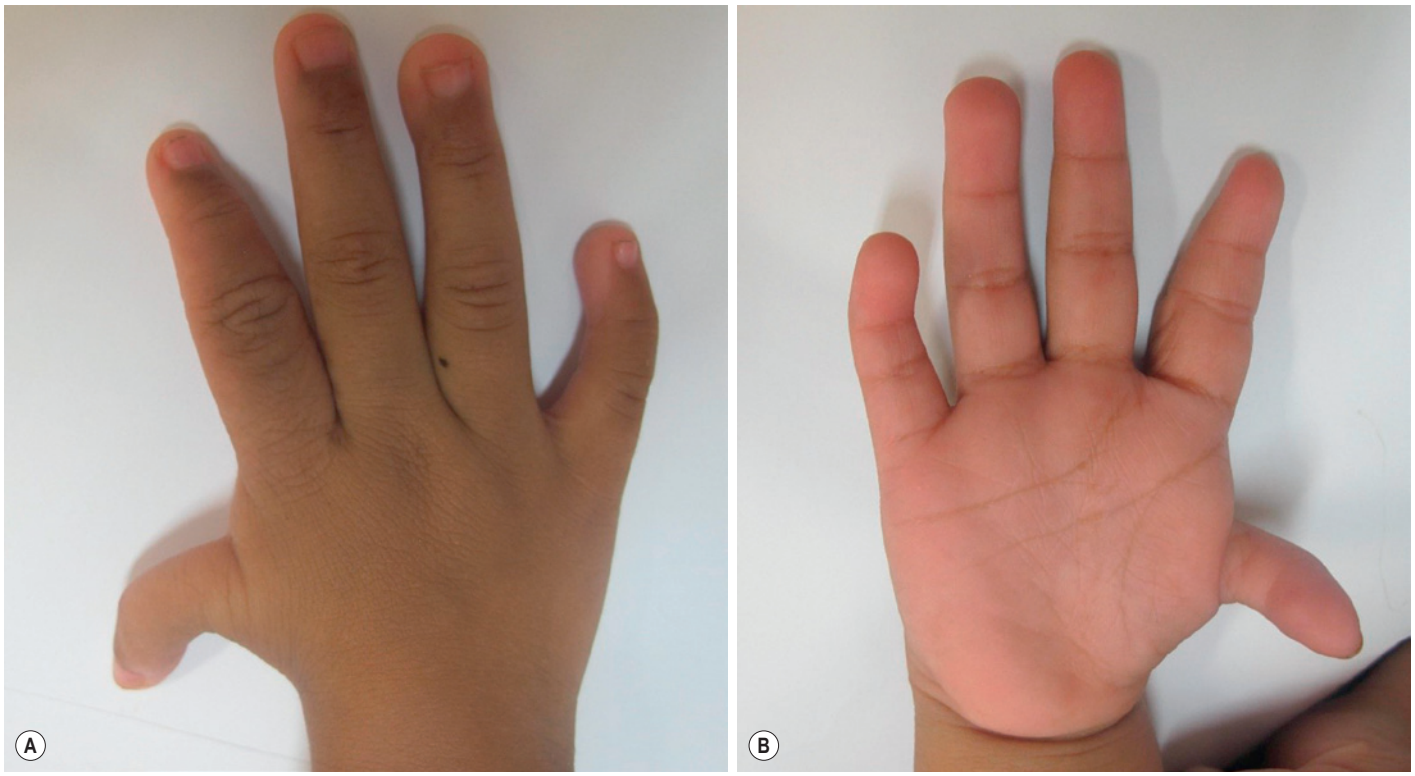


Fig 103.8 Fanconi pancytopenia syndrome: hypoplasia of thumb and clinodactyly of fifth finger.

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Optimizing compliance in patching therapy

Christy Giligson and Vaishali Mehta

Occlusion therapy remains the first line of treatment for amblyopia for many ophthalmologists and orthoptists. One of the main predictors of success with this treatment is the ability of parents and children to do this.[1] Many factors influence a family's compliance with the treatment as prescribed. Identifying these factors allows the clinician to offer advice and tailor management to optimize compliance and results. These strategies could be applied to all types of amblyopia therapy including optical and pharmacologic treatments.

The family does not understand the treatment

- Insufficient patient and family education: If the family does not understand the problem and the rationale and goals of treatment, they are far more likely to deviate from the treatment plan between visits.[2]
- Cultural beliefs: When caring for a socially, ethnically, or religiously diverse patient population it is important to recognize that a treatment may not be equally acceptable or even possible across all groups. These considerations may include family structure and roles of the caregiver, and social concerns about appearance associated with wearing a patch or glasses.
- Language barriers: Patient and family understanding will be affected if the patient/parent and the clinician do not speak the same language.
- Multiple caregivers: When advising a family that their child should wear a patch and/or glasses, try to identify the individuals who will be supervising the child. This may include multiple family members, daycare workers or teachers, among others.[3]

To address these issues:

- Take adequate time for patient and parent education; discussion as well as written information are helpful when the treatment is first prescribed.[2] This will often prevent false starts and will save time at future appointments. Written information may also be provided for caregivers who may supervise treatment but are unable to attend clinic appointments.
- During the patient education process, concerns related to cultural beliefs may be discussed and a management plan developed that will best fit with the family's values.

When language barriers exist have a translator

This is particularly important at the first visit. When available, translated copies of written information should be given. Remember that even professional translators may have difficulty with medical terms, so explanations are best given in simple language. Family members, particularly older siblings, may act as translators.

Inconsistencies in occlusion regimens between team members

The treatment is sometimes started by one clinician but follow-up may be performed by a different team member. Changes in management plans or differences in information provided can lead to confusion and questions about the validity of treatment.[3]

To address these issues:

- Ideally the clinician who will be following the patient during their treatment should educate the patient and family and set the treatment plan from the beginning.
- In clinics where it is difficult to schedule all follow-up appointments with the same team member, record and communicate clearly to the team the information that has been provided to each patient along with treatment plan.
- A documented clinic protocol for amblyopia management including occlusion times, intervals between visits, and indications for adjusting treatment based on outcomes can be a valuable tool to ensure consistency.[4]

Motivation

- Understanding the reasons for treatment and treatment goals: As discussed above, patients and families will find it difficult to follow treatment regimens if they do not understand why it is being done and the expected outcomes.

- Lengthy intervals between visits: While it may seem that prescribing shorter daily intervals of occlusion with long intervals between visits is an advantage to both the family and the clinic, it can be difficult for patients to keep up with a treatment regime without reinforcement over several months.[1] This is particularly the case when the child does not cooperate with treatment well.
- Lack of improvement at subsequent visits: When the amount of occlusion time prescribed is at the minimum shown to give results there is a great risk that it will be reduced, falling below an effective therapeutic dose.[5] A child who is not cooperative will often stubbornly fight occlusion during these short daily intervals, leading to an exhausted parent and lapses in treatment. Families are likely to become disillusioned when they return after months of struggle to see no improvement in visual acuity.
- Positive reinforcement for the child: Maintaining a positive attitude and explaining to a child that the treatment is not a punishment can be a challenge.

To address these issues:

- The authors recommend starting with a longer daily patching schedule and a short interval between visits. This is based on the belief that enforcing longer patching time (up to full-time) for the first few days or weeks will often overcome any initial resistance from the child. It has been the authors' experience that a longer daily patching schedule establishes a routine for the child, ensures that an effective therapeutic amount is done, even if the full amount prescribed is not done. This is likely to result in a tangible improvement at each visit.
- The child may become motivated to wear the patch in several ways: The authors recommend positive rewards for good patching behavior, with daily or weekly small prizes such as stickers or small toys. A child's favorite activities may be reserved for patch time. Child-friendly computer games are an engaging distraction from the patch; those with large and brightly colored images may be possible even with a reduced visual acuity. Younger children may need more interaction with other children or a caregiver during treatment periods. Clinicians can also offer rewards if the child's vision has improved at follow-up.
- iTunes (itunes.apple.com) and Android (play.google.com) applications are available at little to no cost to manage and track goals: such as iRewardChart, EasyKidToken and Behavior World Reward Chart. Patch Pirate is an app specifically to track and encourage amblyopia treatment.

Level of vision

- Poor visual acuity levels, particularly at the beginning of treatment, can make patching more challenging.[5]
- In school-aged children, families and teachers are often concerned that patching may affect their educational experience.[6]

To address these issues:

- Families should be told about the child's visual level and educated regarding safe and unsafe activities while patching. Often, the child's function is not as limited as expected.
- Offer suggestions on how activities may be adapted for school. In the preschool and early elementary grades, print materials are often in a very large font that the child may still see when patched. If the amblyopia is severe, many preschool and early years activities are still possible while patched.
- In very severe amblyopia, such as that associated with ocular anatomic abnormalities, the child's function may be severely limited while patching; each case must be considered individually to plan the best course of action.

Adverse reactions to the treatment method

- Children may have skin reactions related to wearing or removing an adhesive patch.
- Adverse reaction to pharmacologic penalization.

To address these issues:

- For skin irritation, a different brand of patch may be better tolerated. Patches may be removed after bath time when they become wet and loose; the adhesive may be softened by applying oil or lotion to the patch several minutes before removal. A compliant child who wears glasses could wear a sticky or cloth patch over one spectacle lens.
- Alternative treatment methods such as atropine penalization may be offered.

Cost

- Expense of patches, eye drops, or glasses.
- Time off work or school to attend appointments.

To address these issues:

- Adhesive patches or cloth patches can be homemade to reduce costs.

Glasses may be a major expense. In some areas, social programs or charitable organizations may offer assistance.

- Appointments can be scheduled to minimize impact on work or school.

Psychosocial concerns

Parents may worry about the potential for teasing, stigma, or the perception of disability when their child is wearing a patch.[6] The authors recommend a positive attitude in all discussions of the treatment. Less conspicuous treatment methods such as pharmacologic penalization are an option if these issues do arise.

Concurrent health concerns

Additional systemic health concerns and treatments in children with multisystem disorders can make it challenging to maintain consistency with amblyopia treatment. Families may need help identifying a routine that will have the best potential for success.[7]

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Vision screening

Sean P Donahue

What is screening?

"Screening is the systematic application of a test or inquiry identifying individuals at sufficient risk of a specific disorder to benefit from further investigation or direct preventative action, amongst other individuals who have not sought medical attention and accounts of symptoms of that disorder."[1] In ophthalmology, healthy children are impacted primarily by amblyopia, strabismus, cataract, and uncorrected refractive error. Screening can detect each of these disorders. The need for screening has been recognized by the fact that over 50% of pediatric eye conditions that affect children's' sight are detected by pediatricians or family doctors.[2]

Screening of the visual system is performed by primary care providers and subspecialists at various times during childhood. The disease being screened for depends on the age of the patient. For example, screening for retinopathy of prematurity is performed primarily by pediatric ophthalmologists and retina specialists and is limited to children who meet certain criteria – in the United States, typically those children having birth weights less than 1250 g or gestational age less than 32 weeks.[3] Red reflex testing is performed by the primary care provider beginning in the neonatal nursery, and should be performed throughout childhood.[4] However, the primary purpose of this chapter is to discuss the role of screening for amblyopia and its risk factors (strabismus and high refractive error) in preschool children, and for other causes of decreased vision (primarily refractive error) in school-aged children.

When is screening appropriate in pediatric ophthalmology?

Some conditions are appropriate to screen for, whereas others are not. Conditions that should be detected by screening generally are of moderate prevalence, have a latent period, have a known treatment, and have a treatment that has a significant benefit. The World Health Organization (WHO) has defined criteria that are important for screening (Box 105.1).[5] Screening for retinopathy of prematurity in at-risk neonates, screening for amblyopia and its risk factors in preschool children, and screening for decreased acuity from refractive error at school entry all meet the criteria established by the WHO. On the other hand, screening for retinoblastoma in patients without a family history would not meet the WHO criteria because of the low prevalence of the disease in the population, and the relatively long period of time over which the disease could present. Similarly, screening for optic nerve hypoplasia, another rare condition, is also not recommended, because there is a low prevalence of the condition, no latent period, and no treatment.

Amblyopia

Amblyopia is a significant public health problem, with a prevalence of approximately 2%.[6,7] It is the most common cause of monocular visual impairment in children and young adults,[8] and is associated with increased risk of vision loss in the fellow eye.[9] A series of multicenter randomized clinical trials has demonstrated that amblyopia can be treated with a high likelihood of success provided it is detected early and treated appropriately.[10] The natural history of amblyopia has also been determined to not improve without treatment.[11] Screening for amblyopia meets the criteria established by the WHO.

Screening for amblyopia

Screening for amblyopia should occur during regular well child check-ups with the primary care physician. Initially, children should be screened for strabismus or asymmetries in the red reflex.[4] Once a child reaches approximately 1 year of age, he or she can cooperate for photoscreening. Photoscreening detects risk factors for amblyopia rather than amblyopia itself. Once a child can read the eye chart, direct detection of amblyopia by visual acuity testing is preferred.

Several studies have shown that screening for amblyopia is highly effective in decreasing the risk of reduced visual acuity in childhood.[12–15] Eibschitz et al. found the prevalence of amblyopia to be 1.0% in a population screened for amblyopia compared to 2.6% in the unscreened population.[12] Moreover, the prevalence of moderate amblyopia was only 0.1% in the screened population.[12] Kvarnstrom et al. found the prevalence of amblyopia in three Swedish municipalities dropped from 2% to 0.2% following the implementation of a screening program.[13] Finally, the ALSPAC study (Avon Longitudinal Study of Parents and Children) in the UK found that an intensive screening program brought the prevalence of amblyopia at the age of 7.5 years to 0.6% from a baseline of 1.8%.[14]

Box 105.1

World Health Organization criteria for an effective screening program

1. The condition should be an important heath problem
2. There should be a treatment for the condition
3. Facilities for diagnosis and treatment should be available
4. There should be a latent stage of the disease
5. There should be a test or examination for the condition
6. The test should be acceptable to the population
7. The natural history of the disease should be adequately understood
8. There should be an agreed policy on whom to treat
9. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole
10. Case finding should be a continuous process, not just a "once and for all" project

From Wilson JMG, Jungner G. Principles and practice of screening for disease. Public Health Paper No. 34. Geneva: WHO, 1968.

Previously, screening for amblyopia began when a child could read an eye chart. Various pictures and symbols were used for the pre-literate child. Currently, Lea or HOTV symbols are the preferred testing optotypes[16]; Allen figures, Lighthouse characters, Sailboat chart, tumbling Es, and Landolt "C" letters are no longer recommended, as these have been poorly validated. Optotype-based screening is technically feasible by age 3 years, but is very challenging in this age group, as it takes significant time, it is technically difficult, and there is minimal reimbursement. As a result, only a minority of 3-year-old children are screened using optotype techniques.

Mandatory eye examination bills have been proposed or passed in several state legislatures in the United States. In addition to having insufficient numbers of adequately trained specialists to screen the vast number of children, there are several problems with this approach. These bills have also been marred by the lack of mandate for cycloplegia, something which is mandatory for a pediatric refraction and ocular examination.[17] The unintended consequences of such legislation has been the prescription of unnecessary spectacles for children with healthy eyes,[18] anecdotal reports including "accommodative" esotropia in children produced by inappropriate spectacles dispensed without cycloplegia, and multiple referrals for "glaucoma" in children with healthy eyes.

Automated vision screening has become more widespread during the last decade. In contrast to traditional screening, which detects amblyopia and decreased visual acuity directly, automated vision screening detects risk factors for the development of amblyopia. Two advantages of the detection of risk factors rather than amblyopia *per se* are detection during a latent period before amblyopia begins and the ability to detect in younger children. However, these are offset by the fact that many children with risk factors for amblyopia never develop amblyopia; therefore, many children may be treated unnecessarily. Since the risk of amblyopia increases with increasing magnitude of refractive error, levels of refractive error that are felt to put a child at significant risk of developing amblyopia needed to be defined.

In 2003, a working group from the Vision Screening Committee of the American Association of Pediatric Ophthalmology and Strabismus (AAPOS) published guidelines delineating what levels of refractive error constituted risk factors for amblyopia.[19] These were very similar to the "targeted conditions" that had been similarly defined by the optometry-led Vision in Preschoolers Study.[20] An evidence-based update of the 2003 Amblyopia Risk Factors was recently published.[21] This refinement in amblyopia risk factors was based upon published prevalence studies, and the recognition that screening needs a high specificity in younger children, but a high sensitivity in older children.

Types of automated vision screening

There are generally two types of commercially available automated vision-screening instruments. Photoscreening makes use of an analysis of the red reflex to detect amblyopia risk factors. The original instruments used analog film, but now a digital capture of the image has allowed automated interpretation of the red reflex. In addition, the images obtained from some photoscreening devices can now be analyzed to detect strabismus and media opacities. However, it is difficult to create an algorithm to detect strabismus and media opacities with automated photoscreening.

Photoscreening

The MTI photoscreener was the original analog photoscreening instrument. Two linear flashes oriented orthogonally detected refractive error in each of two principal meridians. Manual interpretation of the images was necessary. The MTI instrument is no longer commercially available. However, multiple studies have demonstrated the usefulness of the MTI photoscreener.[22–24] Following successful validation studies using the MTI instrument, other instruments became commercially available. Business models include selling the photoscreening instruments to volunteer screening organizations and primary care providers, or contracting directly with school systems or physician groups for screenings.[25] Generally the other automated instruments have less published validation than the original MTI Photoscreener. However, the technology underlying automated photoscreening is evolving rapidly, and detailed discussion of each of these instruments is beyond the scope of this paper. Nevertheless, the American Academy of Pediatrics policy statement supports photoscreening as an appropriate technique for vision screening beginning as early as 1 year of age and continuing at yearly intervals until a child can reliably perform optotype-based screening.[4,16] In addition, the United States Preventative Services Task Force has also endorsed photoscreening as a technique to screen children in the 3–5 years age range.[26] (Table 105.1). This same organization provides an "insufficient evidence" rating for photoscreening in children aged 1–2 years; however, this should be obviated by a recent large study from Iowa demonstrating the effectiveness of community photoscreening in children in this age group.[27]

Autorefractors

The technology that underlies use of autorefractors for adult ophthalmology clinics has been retooled to make them appropriate for vision screening in children. Autorefractors provide an estimate of the refractive error for each eye (sphere, cylinder, and axis), and then an estimate of the difference

in refractive error between the eyes (anisometropia). These estimates can be compared to predetermined referral criteria to determine if it is appropriate to refer a child for care. Some autorefractors make their measurements binocularly and sequentially, whereas others provide binocular data acquisition and analysis. Some of the newer autorefractors also now make a preliminary assessment of ocular alignment to allow the detection of strabismus.

It is important to recognize that the referral criteria for an autorefractor are not the same as the actual amount of refractive error that should be detected (the AAPOS criteria; Table 105.2). Instead, the referral criteria are those estimates of refractive error that, when placed into the instrument hardware, provide the best likelihood of detecting children having a targeted condition. This is often misunderstood with automated preschool vision screening.

The first autorefractor that was designed and marketed for preschool vision screening was the Welch Allyn SureSight. It was extensively validated through the Vision in Preschoolers Study,[20] and has since had additional validation in the field.[28] The referral criteria initially specified by the manufacturer produced a low positive predictive value, and resulted in low specificity; new referral criteria were proposed by the Vision in Preschoolers Study[7] and validated in the field.[28] However, a limited ability to achieve high sensitivity without jeopardizing specificity has hampered the widespread implementation of this instrument in clinical practice,[29] and this device is being phased out by the manufacturer.

Table 105.1 Vision screening in children ages 1 to 5 years: clinical summary of United States Preventative Services Task Force recommendation

Population	Children younger than 3 years of age	Children ages 3–5 years
Recommendation	No recommendations	Provide vision screening
	Grade: I (insufficient evidence)	Grade: B
Screening Tests	Vision screening test are used in primary care to identify visual impairment in children, including: • Visual acuity test • Stereoacuity test • Cover–uncover test • Hirschberg light reflex test • Autorefraction • Photoscreening	

Two autorefractors have captured most of the market for automated vision screening in the United States. The plusoptiX instrument has undergone several modifications, with high levels of published validation.[30,31] Advantages of the most recent model include the ability to modify the referral criteria based upon age, and to choose several different possibilities for referral criteria based on desired sensitivity and specificity along a published ROC (receiver operator characteristic) curve.[30,31]

The SPOT vision screener was recently acquired by Welch Allyn, as another option to replace the Welch Allyn SureSight screening instrument. Validation of the SPOT instrument continues to evolve, but good outcomes have been reported from several field validation studies.[32,33] The SPOT instrument also allows the imputation of various referral criteria in an age-adjusted manner to maximize sensitivity and specificity for a particular screening environment. As these technologies are evolving rapidly, further discussion of the various instruments is beyond the scope of this chapter. Nevertheless, photoscreeners and autorefractors can both be used in the field with high degrees of effectiveness, and have been demonstrated to decrease the risk of amblyopia when used in these settings.[34–35]

Recently, a new technology that has the potential to detect amblyopia directly even in the pre-literate child has been described. This technology makes use of retinal birefringence to detect foveation.[36] The advantage of this technology is that it allows direct detection of amblyopia and that it appears to be highly sensitive to detect strabismic and anisotropic amblyopia. However, a disadvantage, in addition to it not being commercially available or well validated, is that it does not allow detection of amblyopia risk factors during a latent period prior to the development of amblyopia.[36] Further research is warranted and currently underway.

Traditional acuity screening

Traditional acuity visual screening using lines of optotypes is the gold standard for visual acuity testing in the screening environment. Because it detects decreased visual acuity directly, rather than risk factors for amblyopia, there is no intrinsic over-referral as is seen with automated screening instruments. In addition, by the age at which acuity can be tested directly, children are unlikely to develop amblyopia if they have a risk factor, so the detection of risk factors during a latent period is not relevant for this age group.

Table 105.2 American Association for Pediatric Ophthalmology and Strabismus Vision Screening Committee amblyopia risk factors

Age (months)	Refractive risk factors			
	Astigmatism	Hyperopia	Anisometropia	Myopia
12–30	>2.0 diopters	>4.5 diopters	>2.5 diopters	>–3.5 diopters
31–48	>2.0 diopters	>4.5 diopters	>2.0 diopters	>–3.0 diopters
>48	>1.5 diopters	>3.0 diopters	>1.5 diopters	>–1.5 diopters
	Non-refractive risk factors			
All ages	Media opacity >1 mm			
	Manifest strabismus >8 prism diopters in primary position			

For many healthy children, optotype-based acuity testing can occur at age 3 years, but for the normal child, high degrees of success are not typical until age 4 years or older. Screening using optotypes must be done monocularly, ensuring the child does not peek with the fellow eye. The choice of test method is crucial for obtaining the most accurate screening results.[16] Eye charts should use lines of optotypes (rather than isolated optotypes), or matching cards with crowding bars around each optotype. Use of single optotypes without crowding bars can overestimate visual acuity. The currently preferred optotypes are the Lea symbols or HOTV letters. Allen figures, Lighthouse characters, Sailboat charts, tumbling Es, and Landolt "C" charts are no longer recommended because they have relatively poor validation. Once children can read individual letters, the traditional Snellen chart or Sloan letter charts are preferred to picture-based acuity testing.

Testing can be performed either by *threshold line evaluation* or a *critical line evaluation*. For threshold line evaluation, the child starts to read at the top of the eye chart and continues down each line until he or she can no longer identify the optotypes. Threshold acuity testing is time honored and helps to identify the best levels of acuity in each eye. However, threshold line evaluation is quite time-consuming and can result in the loss of a child's attention, especially in young children.

Critical line evaluation is an effective alternative to threshold testing to identify children with decreased acuity, and is quicker than theshold testing. The "critical line" is the age-dependent line which a child is expected to see normally and pass.[16] For children age 36–47 months, the critical line is 20/50; for 48–59 months, it is 20/40; and for children 5 years and older it is 20/30 (or 20/32 on Sloan eye charts).

Traditional visual acuity testing requires a quiet examination room, free from distraction, as well as an appropriate test distance of 10 or 20 feet. However, computer-based applications are now becoming more common for screening purposes. The Jaeb visual acuity screener incorporates all current screening guidelines and is available free of charge for download and unlimited use at the following website (http://pedig.jaeb.org/JVAS.aspx).

Although traditional acuity testing remains time honored, it is unclear whether it is superior to photoscreening technology. For young children who are barely able to read optotypes, photoscreening may be better. In fact, a randomized controlled crossover trial of photoscreening and traditional acuity screening demonstrated that photoscreening (with the MTI photoscreener) substantially outperformed traditional acuity screening in children aged 3–4 years.[37] Nevertheless, there remains some age at which acuity screening of a healthy literate child will outperform photoscreening because of the lack of over-referrals and the ability to detect mild myopia. This age range remains a subject of further research.

Support for vision screening

The United States Preventative Services Task Force recently issued a policy statement that gives vision screening a "B" level evidence rating for children aged 3–5 years. Traditional visual acuity screening techniques as well as photoscreening are both recommended as appropriate methodologies for screening this age group (see Table 105.1). The United States Preventative Services Task Force gives an "insufficient evidence" rating for vision screening for children under the 3 years. It should be noted that this report was released prior to the publication of photoscreening data for this age group by the Iowa Group,[27] which demonstrated similar effectiveness of children who were photoscreened between 1–2 years of age as those who were aged 3–4 years. This should provide adequate evidence of effectiveness and raise the rating in the next statement cycle.

The American Academy of Pediatrics recently released a policy statement and accompanying clinical report entitled "Visual System Assessment in Infants, Children, and Young Adults by Pediatricians." This policy statement supplants the previous statements "Instrument Based Pediatric Vision Screening", "Eye Examinations in Infants, Children, and Young Adults by Pediatricians", and " Red Reflex Examination in Neonates, Infants, and Children." This policy statement outlines various types of visual system assessment for children from newborn through young adulthood. Highlights include the use of instrument-based screening when available, beginning as young as 1 year, and being offered at regular well-child visits.[16] Traditional screening can supplant photoscreening for the older individual.

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Self-inflicted ocular injuries

David S Taylor

Dermatitis and keratoconjunctivitis artefacta

Self-inflicted injury to the skin around the eye (dermatitis artefacta, DA) and to the surface of the eye (keratoconjunctivitis artefacta, KA) are rare in childhood. Although not usually sight threatening, it may be a warning of physical or sexual abuse and there are often associated complex psychological and emotional problems, sometimes with underlying psychopathology. When DA or KA occur with a long history of psychiatric illness, recovery mostly occurs with a change in the patient's underlying disease. Affected children usually deny the cause of their injury and are deceptive. Their motivation, often not clear, may be a "cry for help." They are often difficult to treat, requiring skilled psychiatric intervention[1]; but when both patient and parents admit to the self-destructive nature of their problem, the outcome may be better. Malingerers, classically trying to escape military service,[2] were described by Dr Stanley Thompson as "villains who, with malicious intent, deliberately feign visual loss." Malingering is very rare in young children.

The diagnosis of KA is suggested by the combination of delineated lesions in the inferior and nasal quadrants of the cornea, bulbar and lid conjunctiva. DA is commonly associated with keratoconjunctivitis (Fig. 106.1). It is variable in character and it may contain some of the irritant such as chalk grains.[3] There is often an unconcerned attitude ("belle indifférence") and other psychological features.

Management

1. Consider the differential diagnosis and ensure that there is no possible, even rare, natural disease that could cause the symptoms and signs. It is not unusual for an initial diagnosis to be artefacta but the final one a significant disease. A positive diagnosis is not made because of an inability to identify a pathological disease but on the finding of *positive* evidence of a *clearly* artefactual cause.
2. A pediatric ophthalmologist might collaborate with a colleague who has appropriate expertise, such as an external eye diseases consultant, a dermatologist, or eye trauma expert.
3. Collaborate with a suitably qualified psychiatrist when the diagnosis is suspected.
4. In young children, rule out congenital anesthesia as a cause of keratoconjunctivitis (Fig. 106.2).
5. Stop the application of the noxious substance or substances. This is easy if the child and the parents can be helped to understand the cause and seriousness of the condition, but may need admission to an observation unit.
6. Treat the injury in a manner appropriate for the cause. If it is a non-specific irritant or inflammatory agent, then topical steroids may be appropriate.
7. The treating ophthalmologist needs to be open and honest with the parents and child, kind to both, and aware that the disease is very serious to the patient and family.

Trichotillomania

Trichotillomania, in which the affected person pulls out hair, sometimes the eyelashes and eyebrows, has a prevalence of between 1% and 5%.

Boys, although affected about half as frequently as girls, have an earlier age at onset (8 years)[4] and are less likely to pull their eyebrows and eyelashes. Trichotillomanics frequently conceal their habit; the hair pulling can become ritualized, with close inspection of the pulled hair, and the hair may be swallowed.

Affected lids and brows have healthy skin with multiple broken hair shafts (Fig. 106.3). Some patients are depressed. Stress at school or at home is implicated as a precipitating factor in many cases.

It is not usually a serious condition and the hair loss is reversible when the pulling stops, but it may become chronic and older ex-trichotillomanics may develop other, related disorders.

Management

1. Consider the differential diagnosis. Loss of eyelashes occurs with skin diseases such as alopecia, ichthyosis, and ectodermal dysplasia, following radiation or chemotherapy, after lid infections, or endocrine disease (see Chapter 19).
2. Most cases respond to reassurance and explanations after a detailed history by the ophthalmologist, which must include details that many ophthalmologists are not comfortable with probing. A psychosocial and



Fig. 106.1 This teenage girl had recurrent attacks of keratoconjunctivitis artefacta, which was associated with desquamation of the skin around the affected eye. The agent may have been alum.

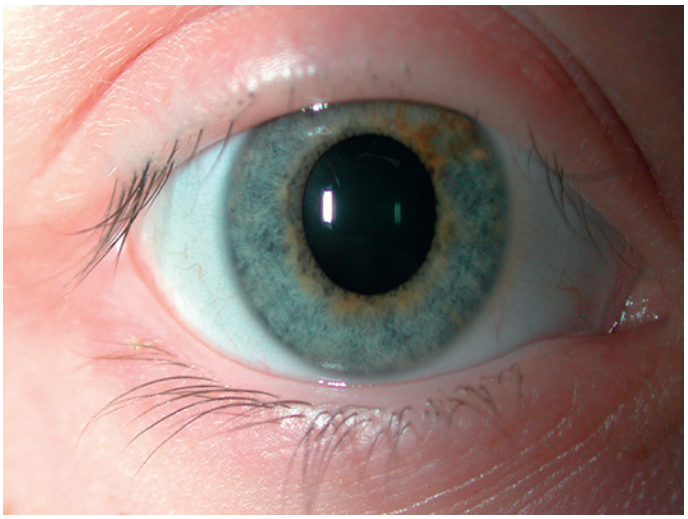


Fig. 106.3 Trichotillomania. The eyelids of both eyes of this 12-year-old girl have broken and missing lashes.



Fig. 106.2 Left corneal anesthesia. This child developed a recurrently red and irritable left eye from about 8 months of age from repeated corneal scratching (see Chapter 34). The diagnosis of Goldenhar syndrome, in which corneal anesthesia is not uncommon, was suggested by the right corneal dermoid and the preauricular tag seen in front of the left earlobe.

psychosexual history is often the key to the underlying cause and it is often best if a pediatrician collaborates.

3. Behavior therapy, drugs, and other treatment may sometimes help, as the condition has similarities to an obsessive–compulsive disorder.[5]

Ocular self-mutilation: direct eye trauma

Ocular self-mutilation typically occurs in young men with a history of severe psychiatric illness, especially schizophrenia, serious criminality, or drug abuse.[1]

From early childhood, self-inflicted injuries may occur in severely developmentally delayed children. The injury may be by laceration,[6] but is more frequently a result of severe direct blows[7] or headbanging.[8] Self-inflicted injuries occur more frequently in certain syndromes, mostly associated with severe mental retardation. At least 15 syndromes are associated with self-mutilation, of which the Lesch–Nyhan, Gilles de la Tourette, and Smith–Magenis syndromes are the most important to ophthalmologists. Self-inflicted injuries also occur commonly in children with autism spectrum disorder.[9]

A case where an apparently normal child injured herself in both eyes with needles[10] serves to remind us to be wary of cases that outlie the normal patterns of diseases and causes. Such cases also need inquiry into the possibility of an inflicted injury.

Autoenucleation

This occurs mostly in hallucinating young adult schizophrenics of either gender and is rare in children.[2,11]

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Apps and all that … (How my smartphone changed my life)

Patrick Hamel

According to the website techcrunch.com,[1] as of June 2016, there were 2.6 billion smartphone subscriptions globally and the predicted total mobile subscriptions by 2020 is 9.2 billion. Indeed, in the United States, smartphone adoption rates, also called maturity, have been higher than for most, if not all, major technologies since the telephone was patented by Alexander Graham Bell in 1876.[2] The number of available applications for smartphones has also risen dramatically. A few years ago, typing the word "ophthalmology," into the search box of the Apple App Store revealed only a handful of relevant apps. Now they are so numerous that it is hard to decide which are useful.

As a pediatric ophthalmologist, I am always exploring new and useful resources in information technology that relate to my work. I will share the applications that have helped me the most in my practice. The list is far from being exhaustive and the applications have not been peer reviewed so the reader is warned to use them with caution, especially when referring to medical knowledge and expertise. Also, as some of them allow for data storage and/or transfer, one has to take care with regard to the handling of confidential patient-related information and the related legal implications.

All cited applications in this chapter can be used either on an iOS or an Android device, or both. Many of them can also be downloaded on a Windows-based or Mac OS computer. Some are free, while others are not.

Around the office

First, let's look at general applications. Without being purely medical, some apps can be extremely useful in our day-to-day life as healthcare workers. Dropbox (www.dropbox.com) and Google Drive (www.google.com/drive/) are cloud storage applications that allow easy sharing of documents between one's smartphone, tablet, and computer. Then, on iOS and Mac OS, iBooks (www.apple.com/ibooks) is an excellent way to store books and PDF documents, easily accessing and reading them as needed.

As many, if not most, documents are now circulated in a PDF format, the following apps allow for storage, viewing, editing, annotations, signature, questionnaire filling, and sharing: I find PDF Expert (www.readdle.com/products/pdfexpert5), iAnnotate (www.iannotate.com), PDFPen (smilesoftware.com/PDFpen) and Adobe Acrobat DC (acrobat.adobe.com) to be useful.

Microsoft Office (products.office.com) is now available for almost all recent OS platforms and also has its own cloud storage system. Therefore, Excel, Word, and PowerPoint documents can easily be created, shared, and edited on a smartphone, a tablet, a desktop or laptop computer. Apple (www.apple.com/iwork-for-icloud), through Pages, Numbers, and Keynotes offer the same functionalities, but only for its devices, unless used as web applications on Windows-based PCs.

If you want to write quick notes and have them available wherever you are, Evernote (evernote.com) is a world-renowned note taking and sharing software that is available for most operating systems and devices. Notes can be shared through ones own devices or between users.

Dragon (www.nuance.com) is a world leader in voice recognition and transcription. It comes in different styles and at different prices. The simplest version is very handy when dictating instead of typing an email on your smartphone's small keyboard. Alternatively, the very powerful desktop version comes with a whole medical lexicon.

With the rapidly growing number of usernames and passwords we need to remember, why not use software that will store them, and even type them for you? 1Password (agilebits.com) is one of the many available applications on the market for this purpose.

Applying one's handwritten signature directly in an electronic document, and then sending it though email, saves the trouble of printing and scanning. iOS 9 from Apple recently made it quite easy, but with Autograph (tenonedesign.com/autograph.php) it is possible to sign a Word or PDF document on a Mac computer, directly from the touch pad or on an iPhone hooked up through its USB port or through Wi-Fi.

With DocScanner (docscannerapp.com) or Scanner Pro (readdle.com/products/scannerpro), the smartphone or tablet's camera becomes a document scanner, saving the file in a digital form. It can then be saved or shared through devices or emailed to another user as a PDF document.

Medical references

Not so long ago, having medical references at hand meant carrying several heavy books. Most of them now have an

electronic version and many sources of information only exist on the Internet. ClinicalKey (www.clinicalkey.com) is a medical search engine and database that offers access to medical books, including this title, journals, clinical trials, drug monographs, guidelines, patient education material, and other sources of information owned by Elsevier.

Medscape (www.medscape.com) is both an application and a website with up-to-date medical news, information on diseases, drugs, and treatment procedures, and continuing medical education activities, just to name a few features. Lexicomp (www.wolterskluwercdi.com/lexicomp-online) and Pepid (www.pepid.com) are huge paid medical databases, differing somewhat in their content, but with drugs, toxicology, allergy, and infectious disease information, and can help in medical decision making. Epocrates (www.epocrates.com), now familiar to most physicians, has both free and paid versions, and carries a very up-to-date drug database. It is a must-have app on any smartphone or tablet, or as a website on a laptop or desktop computer. Eponyms (www.eponyms.net) provides short descriptions of common and rare diseases, symptoms and signs on your portable device. The Sanford Guide to Antimicrobial Therapy (www.sanfordguide.com) is a leading reference of its kind and provides information on antibiotic coverage, as well as bacterial sensitivity and resistance.

References in ophthalmology

There are many electronic references available that are specific to ophthalmology. Through Omnio (omnio.com), *The Wills Eye Manual: Office and Emergency Room Diagnosis and Treatment of Eye Diseases* can be bought and downloaded.

Expert Consult (expertconsult.inkling.com) is Elsevier's eBook platform. Among numerous titles, it hosts the online and enhanced digital version of this edition of *Pediatric Ophthalmology and Strabismus*, along with the video and extra images/content elements.

The American Academy of Ophthalmology has its own eBook reader (http://store.aao.org/shop-by.html?media_type=eBook) that makes it possible to carry the whole *Basic and Clinical Science Course* series, as well as other electronic references, in a tablet. *Eye Handbook* (www.eyehandbook.com) is an amazing source of information for ophthalmologists, with the following topics included: a disease database, symptom illustrations for showing patients, an eye atlas, a coding database, various calculators and patient tests. Optics Clinical Calculator (http://www.regularrateandrhythm.com/apps/optics.html) is one of the few apps that come handy for solving ocular optical problems. Eyetube (eyetube.net) is, according to their website, the largest online surgical video archive dedicated to ophthalmology.

Eye tests and vision screening

There are several applications available either for smartphones or tablets that reproduce different eye tests, which can be used either by the ophthalmologist or the patient. Many reading charts, for far or near vision testing, can be found, including Eye Chart Pro (www.eyechartproapp.com) and Optos' Chart Remote (blog.optos.com/index.php/optos-chart-remote-ipad-app). Some applications offer a certain number of tests, e.g. Ishihara color vision plates, Amsler grid, red desaturation, and more, such as eyeTests Easy (georgekongsoftwares.weebly.com) and Pocket Eye Exam (pocket-eye-exam.appstor.io).

With SightBook (www.digisight.net/patients/vision_testing), and Vision Test (https://itunes.apple.com/ca/app/vision-test/id380288414?mt=8 or https://play.google.com/store/apps/details?id=com.threesidedcube.visiondroid). Patients and anyone in the community can test themselves, friends, or family members. The AAPOS Vision Screening App (www.aapos.org/ahp/aapos_vision_screening_app) has optotypes for both adults and children, and can be used by anyone including healthcare workers. Optodrum (www.linsay.com/Linsay_Associates_Medical/OptoDrum.html) replaces the expensive and bulky optokinetic drum for adults and children. It even has a version for the iPad that uses its camera to record a video of the patient's eye movement while looking at moving patterns.

Videos and animations

My most frequent use of my smartphone in clinic is to play a video to capture a child's attention. I have found buying one of the Pixar Short Films Collections (itunes.com or play.google.com) to be very worthwhile.

Patient and family education

To help the ophthalmologist explain diseases and surgeries to patients and parents, Sight Selector (www.patienteducationconcepts.com/sight-selector-products), DrawMD (visiblehealth.com/drawmd), EyeDraw (www.optimed.co.uk/eyedraw), and Eye Sketch (www.edmondoborasio.com/Doctor_Edmondo_Borasio/The_Apps.html) use anatomy pictures, videos, and live annotation to help in patient education.

"Video game" for the ophthalmologist

Instead of a video game, why not combine business with pleasure by practicing your surgical dexterity "playing" the cataract surgery simulators CataractSurgery and CataractMobile (georgekongsoftwares.weebly.com)?

As a final word, there are so many different types of software and applications available to us that it is impossible to list them all. Changes are happening so fast in the world of technology that, as for CME (continuing medical education), we ought to have some kind of CTE (continuing technology education) to keep us up-to-date with all the new tools that are convenient, if not crucial, to our everyday life as ophthalmologists!

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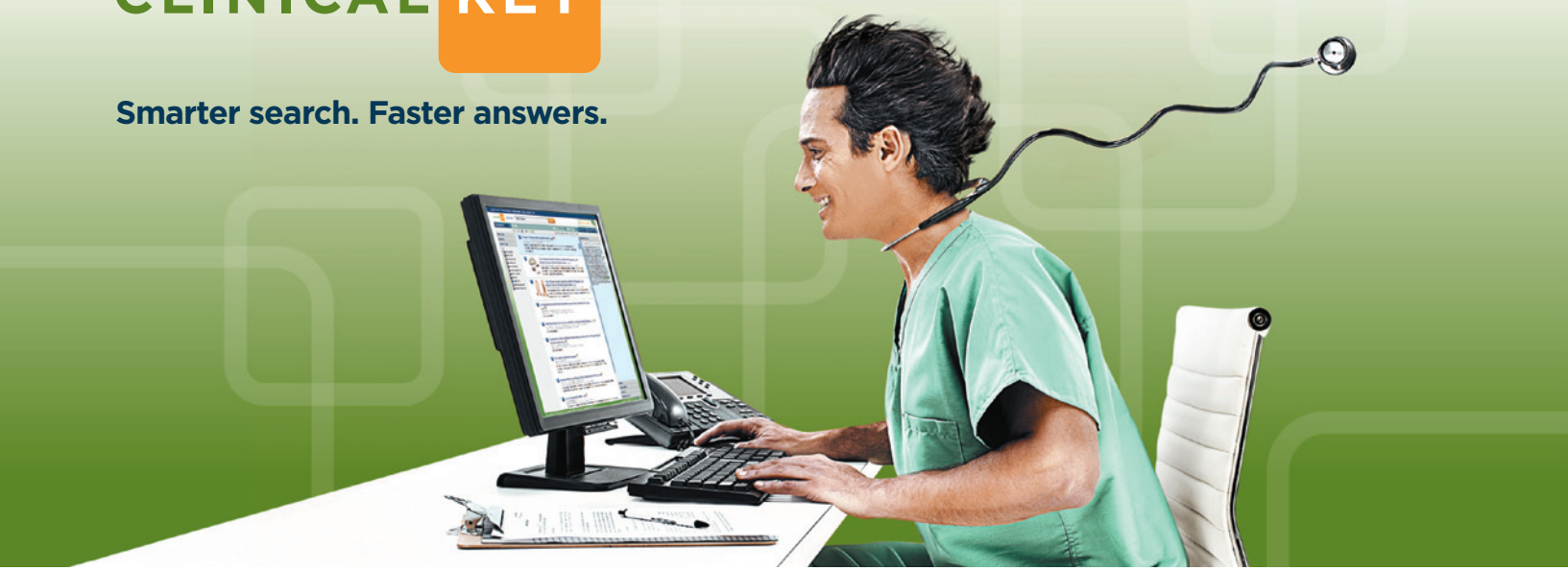
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