Elias I. Traboulsi
Virginia Miraldi Utz
Editors

Practical Management of Pediatric Ocular Disorders and Strabismus

A Case-Based Approach

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To Mayya, Alex, and Nadeem, loves of my life. To Marshall Parks, mentor and friend.

Elias I. Traboulsi

To my parents, David and Leslee Miraldi, and my husband, Christopher, and son, Brendan David, for their unending love and encouragement.

To my mentor and friend, Elias Traboulsi, for his inspiration and continuing support throughout my career.

Virginia Miraldi Utz

Foreword

With the advent of the internet and effective search engines, there are few questions pertaining to pediatric ocular disorders, or most things for that matter, that cannot be answered by conducting a careful search online. This phenomenon is relatively new and expanding. The most widely used search engine, Google, started on September 4, 1998. As a generation, this makes Google a "millennial" and not so old—just entering adulthood.

A person wishing to learn more about a subject or condition as it relates to pediatric ophthalmology can find it online. Asking the right question while using the best search engine allows you to access information about diagnosis and treatment of fourth nerve palsy, management of cataract in a child, persistent fetal vasculature, and just about anything else you might want to find related to the subject in question. For example, more than 230 papers, parts of book chapters, and isolated comments pertaining to hyphema in a child can be accessed now. When you read this, there are likely to be few more or less, but there will be many. Some will offer gems and some will not. But all will have in common the need to validate the information you find and the time necessary to find the information you need to validate. Stated another way, "Am I asking the right question and is the information I am finding credible?" The need to even ask questions like these is eliminated by a book like *Practical Management of Pediatric Ocular Disorders and Strabismus.*

Pertinent material about disorders of the child's eye is covered in 15 sections containing 73 chapters and is followed by 13 appendices. In the case of this book, the editors asked the right questions for you. Then they chose qualified authors to sort through the material available, call on their own experience, and in many cases work with colleagues and mentors to put the best material available in a reader-friendly format. The authority commanded by this book relies on the careful editing of the senior editors, the conscientious efforts of more than two scores of junior authors and more than a dozen senior authors, and the unsung efforts of mentors known and unknown who have supported the work that went into comprehensive work.

In more than 50 years as a pediatric ophthalmologist, I have seen many changes. Knowledge has expanded greatly, diagnoses have become more accurate, and treatments have improved making better results possible. During this time, dozens of new books have been written dealing with pediatric ophthalmology, and that number includes a few that I bear responsibility for. I commend all who have worked diligently to make the latest information available to as many as they can reach. *Practical Management of Pediatric Ocular Disorders and Strabismus*, a comprehensive, authoritative, and updated book worthy of your attention, deserves a prominent place in the pantheon of literature on the subject of children's eye disease.

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Preface

This project stemmed from a desire to provide an educational resource for residents, fellows, and ophthalmologists that is practical and focused on management of the child with an eye problem or the adult with strabismus.

The book was not designed to be a comprehensive textbook on pediatric ophthalmology, but rather one that is replete with cases, diagrams, and tables that recapitulate the way we teach trainees or handle particular clinical situations. We tried to focus specifically on clinical pearls, an algorithmic approach to differential diagnoses, current evidence for therapy, or preferred practice patterns for diagnosis and treatment followed by case examples to reinforce the material. We gave the authors some discretion in terms of formatting, but we encouraged them to provide diagnostic/treatment algorithms and tables to supplement text content and to enhance its practical value. Every chapter was subjected to at least two and often several rounds of reviews and modifications before it reached its final and current state.

We believe that the reader will find the contents of help in their daily training and clinical practice. We are grateful to our families for their patience during the gestation of this book, to our patients for inspiring us to improve on our skills to take care of them, and to our residents and fellows for teaching us how to become better teachers.

Cleveland, OH

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Part I

The Pediatric Clinical Examination

Approach to Visual Acuity Assessment and Strabismus Evaluation of the Pediatric Patient

1

Cindy Pritchard and George S. Ellis Jr.

Abstract

Children present unique ophthalmologic considerations and require an examination approach that corresponds to his or her level of visual and psychosocial development. Employment of age-related, patient-specific strategies may be utilized to maximize the information obtained from the clinical examination as well as make the examination both enjoyable and rewarding for the patient, family, and practitioner. This chapter will discuss the approach to the ophthalmologic examination in pediatric patients including visual assessment, motility, strabismus, and motor fusion.

Keywords

Motility • Cover-uncover test • Cover test • Visual acuity • Strabismus • Fusion

Introduction

Examination of the pediatric patient can be very challenging for even the most experienced clinicians. This is especially true for strabismus evaluations. Many other pediatric eye conditions such as glaucoma and retinal, corneal, and optic nerve diseases can be assessed under anesthesia, if necessary. Strabismus, however, is a dynamic condition that requires a cooperative and alert subject if an accurate, detailed examination and useful data are to be obtained. Although there are obvious limitations to how much control the examiner has over the level of cooperation or state of alertness of the child, there are strategies that can enhance cooperation or state of alertness of the child, hence the quality of the exam and the ease with which information is obtained.

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Approach to Examining the Pediatric Patient

Optimizing Cooperation

The most significant barrier to obtaining the child's cooperation is fear. The fearful child often closes his eyes tightly or continuously turns his face away from the examiner, not allowing instruments or the examiner's hands near his face. Conversely, the comfortable child who feels safe will often interact with the examiner, optimizing the opportunity for adequate ocular assessment. Therefore, establishing a good initial rapport is an essential element to the examination process, especially when the child is very young. This is best accomplished by maintaining a calm, pleasant demeanor. The examiner should interact/play with/entertain the child while obtaining needed information from the parents. For example, one can show the very young child a small toy that will be used later as a fixation target, talking to them about the toy and allowing them to touch it if he shows interest. With young children who are verbal, engaging them in casual

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conversation can be disarming. One might ask them about the superhero or Disney princess on an item of clothing that they are wearing or tell them about some of the toys that the examiner will show them during the exam. If they are sitting in a parent's lap, another strategy for creating a feeling of safety is to involve the parent in the exam by having them hold the fixation target or by holding a prism or trial lens to the parent's eye to show the child that, although the examiner's hands and tools are very close to their face, they will not hurt them. When these strategies are successfully employed, the child can actually enjoy having his eyes examined and look forward to return visits.

Optimizing Alertness

Since visual attention is necessary for accurate ocular motility evaluation, the sleeping, unarousable child can be difficult or impossible to examine. This occurs more commonly with infants. When the infant cannot be suitably awakened by removing him from a comfortable lying position, the examiner can try talking to him somewhat loudly but calmly while gently moving his/her arms and legs in a playful manner. If the baby remains asleep or too drowsy to be attentive to your targets, one can use the visit as an opportunity to gather information that is available in the sedate state such as pupil reaction, retinoscopy, tonometry when appropriate, and funduscopy. The doll's head maneuver can be used to determine if ocular rotations are full. With the lids manually lifted, the examiner can rotate the infant's head side to side and up and down. The vestibular system will drive the eyes into peripheral gazes allowing the examiner to rule out any limitation of movement. For example, if an infant has a left type I Duane's syndrome, one will see that the left eye fails to fully abduct as the head is rotated to the infant's right. With an unarousable infant, the remainder of the motility exam can be obtained at a subsequent visit. The parents should be instructed to avoid an appointment at nap time and to avoid feeding the child shortly before the visit. A hungry child is more alert, but also could be more irritable. The infant can be given a bottle during the exam to keep him calm while motility testing is performed.

Additional Strategies

The examination is initiated at first sight of the child. As one talks to the parents, one watches the child for nystagmus, ptosis, head thrusting, or obvious strabismus. If the child appears to be maintaining an abnormal head posture, the examiner can casually encourage fixation away from his preferred gaze looking for nystagmus or strabismus. If the child has an obvious strabismus, the preferred fixating eye is noted. By observing the child gaze around the room, it is sometimes possible to gain useful information regarding ocular versions. For example, as the child looks to the side, one might notice a hyperdeviation suggesting oblique dysfunction. It is important to recognize that attention and cooperation might be limited to the first few minutes after meeting the child. Sometimes the period of time *before* the actual examination begins is the *only* time that the child is calm enough to make these important observations. Often the young patient remains calm until the examination begins, and attention is drawn to him. The child may become fearful, and cooperation is subsequently lost. One should begin the examination with the least threatening tests. The farther away one is from the child, the less threatened the child will feel. Remote, nonthreatening testing can begin while one is talking to the parents. For example, dry retinoscopy screening (without lenses) performed 2–3 ft away from the child will enable the practitioner to determine if the media is clear centrally, if there is any significant refractive error or anisometropia, if corneal light reflexes suggest the presence of manifest strabismus, or if there is anisocoria. The Bruckner simultaneous red reflex test can be performed by comparing the red reflexes between the two eyes as the pupils are viewed simultaneously with the direct ophthalmoscope. Any asymmetry in the color, brightness, or size of the two red reflexes indicates a potential amblyogenic condition such as media opacity, strabismus, or asymmetric refractive error. One can test versions by moving a small toy into various gazes without getting too close to the child. These strategies allow the examiner to obtain important information before the actual hands-on examination even begins. The examiner should be aware and relay to the parents that infants, very young children, and children with significant developmental delays may require more than one visit to obtain a full ocular assessment.

Vision Assessment

The method used to assess visual acuity will be dictated by the child's level of development and degree of cooperation. Prior to the child reaching the stage at which Snellen acuity can be obtained, there are several approaches to obtain an estimate or measure of visual acuity; some are quantitative, others qualitative.

Preverbal Child

Quantitative Methods

Most quantitative preliterate vision tests employ the forced-choice preferential looking method in which the child is presented a target that has gratings, forms, or contours on one

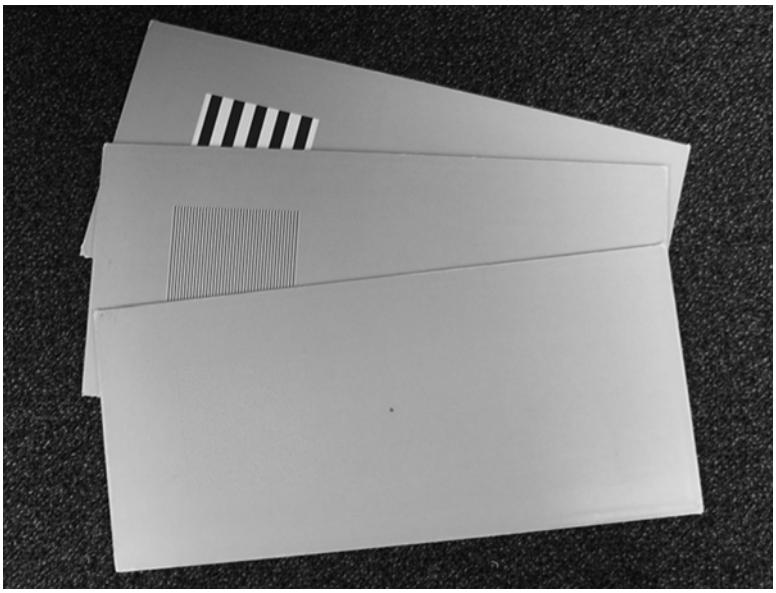

Fig. 1.1 Teller acuity cards. Sample of three Teller acuity cards with spatial frequency gratings. Sets of Teller acuity cards contain 12 cards with a gratings ranging in spatial frequency from 0.23 to 38 cycles per centimeter

half and is blank on the other half. The Teller acuity cards were the first of these tests to be fairly commonly used in clinical practice (Fig. 1.1). If the child looks toward the side with the gratings when presented the Teller acuity card, it is presumed that the child can see them. Cards with progressively higher spatial frequency gratings are presented until the child randomly looks to either side of the card, implying that the child cannot see the gratings. The grating acuity can then be translated to estimated logarithm of minimal angle of resolution (logMAR) Snellen acuity by referring to a chart provided with the test [1–3]. Testing distance varies by age: infant births to 6 months (38 cm), 7 months and 3 years (55 cm), and >3 years (84 cm). Patients with poor visual acuity may require an unusually close distance (19 and 9.5 cm). Other forced-choice preferential looking tests have subsequently been developed for quantifying infant acuity [4–6]. Visual evoked potentials have also been used to quantify infant acuity [7, 8]. With this technique, electrodes are placed over the occipital lobe, and the patient is presented with a series of bar or grid patterns. If the pattern is observed, the impulse will be recorded by the electrodes. The smallest grating pattern that stimulates an impulse is an estimate of visual acuity.

Qualitative Methods

Central, Steady, Maintained

A commonly used qualitative method of preverbal estimation of vision involves describing fixation for each eye monocularly, then comparing the subjective data between eyes. A small toy is often used as the test target. It is best to use one's hand as an occluder for monocular testing. A standard occluder is more threatening to the child and can be a distraction. The target should be slowly moved during testing, watching for appropriate pursuit eye movements and quality of fixation. Monocular fixation is described as central (C) if the child appears to be fixating with his/her fovea. If fixation is grossly eccentric in which case the child does not appear to look directly at the target with his fovea, the vision would be noted as not central (nC).

This method also assesses fixation in terms of steadiness (S) or not being steady (nS). Fixation in which the eye does not remain steadily on the target (nS), rather displays unsteady searching movements, implies poor vision. Nystagmus also prevents steady fixation on the target and may be recorded as CnS in each eye.

The third part of this qualitative test is performed under binocular conditions. The acuity in one eye is indirectly compared to that of the fellow eye. If manifest strabismus is present, this part of the test can be performed by evaluating for a fixation preference for one eye. As an example, a child with a 30^{Δ} esotropia will view the target with either the left eye or the right eye, with the fellow eye in an obvious deviated position. The examiner covers the fixing eye, forcing the child to take up fixation with the deviated fellow eye. While performing this test, the examiner can assess fixation in the previously deviated eye in terms of C or nC and S or nS. When the cover is removed, the examiner notes whether the child immediately reverts to fixation with the eye that was under cover or if the child maintains fixation with the eye that was originally the deviated eye. If the child maintains fixation with the previously deviated eye under binocular conditions, vision is recorded as maintained (M) for each eye. Therefore, a child with central and steady fixation without a preference for one eye would have acuity documented as CSM for each eye. If, however, during the binocular part of the assessment the child reverts to fixation with the eye

Table 1.1 Gradations of visual acuity using the CSM method as compared to the fellow eye

Notation	Interpretation
nCnSnM	Unsteady and eccentric or wandering fixation, very poor visual acuity; if eccentric fixation, can estimate degree of eccentricity for subsequent comparison
CnSnM	Central but unsteady fixation will not hold fixation under binocular conditions, implies poor visual acuity
CSnM	Central and steady fixation but will not continue to fixate with that eye under binocular conditions, implies visual acuity is poorer than fellow eye
CSM briefly[a]	Briefly holds fixation under binocular conditions, implies fairly good visual acuity but not as good as fellow eye, rarely vision equal to fellow eye
CSM to a blink[a]	Holds fixation under binocular conditions but reverts to preferred fellow eye following a blink, implies good visual acuity but still not equal to fellow eye
CSM through a blink[a]	Will continue to hold fixation with non-preferred eye beyond a blink, implies good visual acuity, better than CSM to a blink but still not equal to fellow eye
CSM prefers right or left eye[a]	Implies almost equal visual acuity
CSM alternates	Implies equal visual acuity

[a]Although visual acuity might be equal, implying the absence of amblyopia, in these states, the preference for fixation with one eye can lead to amblyopia in the fellow eye. Treatment might be indicated to prevent the development of amblyopia depending upon the strength of the preference and the age of the patient

under cover when the cover is removed, acuity for the non-preferred eye would be noted as not maintained (nM). A child with mild or moderate amblyopia, for example, might have central and steady fixation with the amblyopic eye but will not maintain fixation with that eye under binocular conditions because the child sees more clearly with the sound eye. Their vision would be recorded as CSM for the sound eye and as CSnM for the amblyopic eye.

When a fixation preference for one eye exists, it is useful to describe the strength of the preference. For example, when the cover is removed, the child might continue to maintain fixation briefly before returning fixation to the dominant eye. A comment such as "holds briefly" should be added to CSM for that eye. A blink can be used to further describe fixation preference. The child might maintain fixation with the non-preferred eye under binocular conditions until he/she blinks, at which point he shifts back to fixation with the dominant eye. In this case, a comment such as "holds to a blink" would be added to CSM for the nondominant eye. Another possibility is that he maintains fixation beyond a blink but eventually returns to fixating preferentially with the dominant eye. A comment would then be added "holds through a blink." By adding these comments, vision can be compared from visit to visit (Table 1.1). A child that is being treated for amblyopia might begin as CSnM, then progress with treatment to holding to a blink, later through a blink, then ideally begin to alternate fixation without a preference suggesting equal vision.

If the eyes are well aligned, a large prism can be used to simulate manifest strabismus for the "maintained" (M or nM) portion of vision assessment. For example, the 20^{Δ} base-down prism test involves placing a 20^{Δ} prism base down in front of one eye, optically inducing vertical strabismus. This will force the child to fixate with one or the other eye. If the child's eyes appear to be viewing above the target with the prism in place, he is fixating with the eye in front of which the prim is being held. If, however, the eyes appear to be looking straight at the target, the child is viewing with the eye that does not have the prism in front of it (Fig. 1.2). One might see vertical saccades equal in amplitude to the size of prism used. When this occurs, the child is freely alternating between eyes suggesting equal vision. In this case, each eye would be recorded as CSM. If a preference for fixation for one eye is detected with the prism in place, the examiner can proceed to determination of the strength of the preference with the prism-induced simulated strabismus in the same manner as described above for the child with true manifest strabismus.

A significant limitation to the CSM method of vision assessment is that central and steady fixation does not necessarily equate with normal vision. For example, even an uncorrected high myope has central and steady fixation. The strength of this test, however, is that it is somewhat reliable in detecting amblyopia [9–11]. Most conditions that limit acuity can be detected without subjective responses (refractive errors, media opacities, retinal, and optic nerve diseases). On the other hand, although *amblyogenic* conditions can be detected objectively, amblyopia itself is diagnosed by either subjective response or, in preverbal children, by comparing vision between the two eyes during the "M" portion of CSM testing. If one eye is preferred over the fellow eye, it implies unequal vision. If the disparity in vision cannot be explained by findings on the physical exam, amblyopia should be suspected and treated.

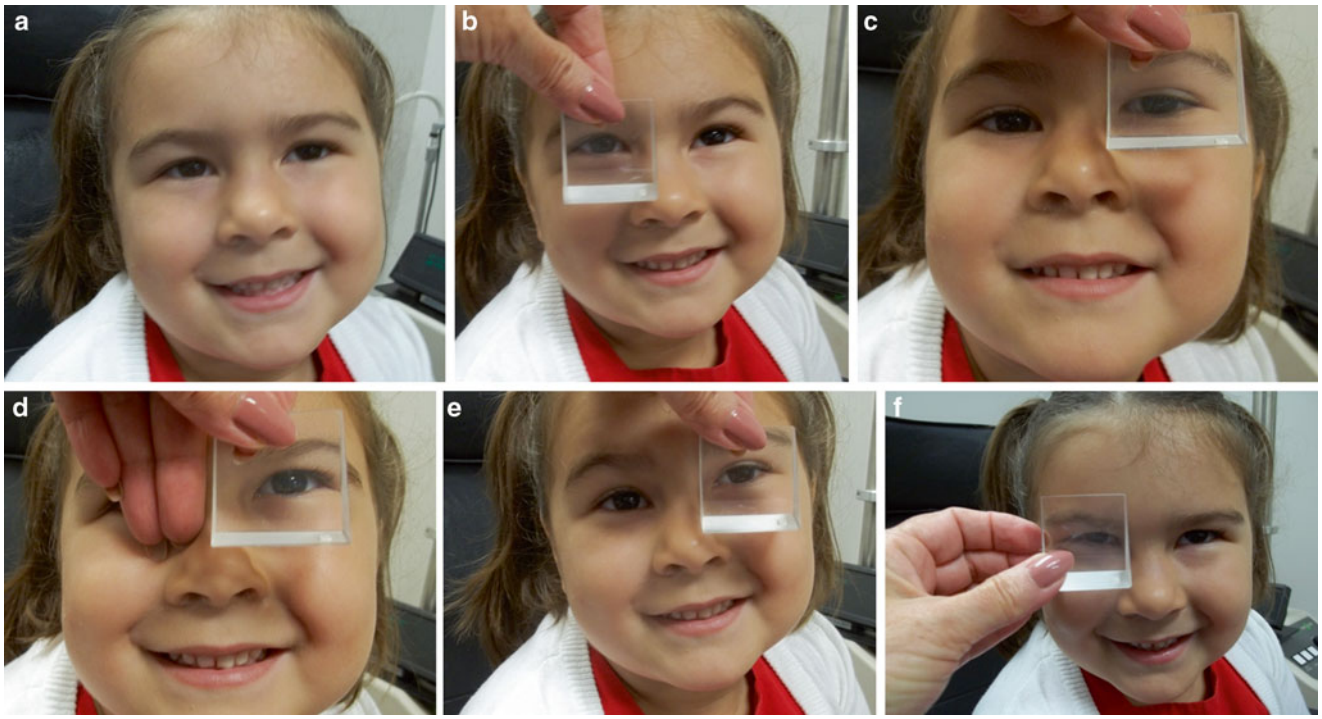

Fig. 1.2 20Δ base-down prism assessment of vision. (**a**) Child without strabismus has central and steady fixation in both eyes. (**b**) 20Δ base-down prism test is employed to compare visual function between eyes. With prism over right eye, visual axes shift up indicating child is fixating through prism with right eye. (**c**) With prism over left eye, no shift in visual axes indicates child continues to fixate with right eye. (**d**) With right eye covered, child fixates through prism with left eye. (**e**) With right eye uncovered, child returns to right eye fixation. (**f**) Prism placed again over right eye. Upward shift of visual axes confirms right eye preference. Outcome of test reveals vision as central, steady, and maintained (CSM) right eye and central, steady, non-maintained (CSnM) left eye

Poor Vision/Visual Attention

A child with poor vision or poor visual attention might not fixate on any target. In this case, it can be useful to test for optokinetic nystagmus (OKN) using an OKN drum. The OKN response consists of a series of reflexive eye movements induced by a repetitive pattern of lines or objects moving across the frontal field of vision (slow phase or pursuit movements and reflex saccadic movements in the opposite direction). If an OKN response is observed, this indicates that the vision is probably better than 20/400. Importantly, pursuit movements do not develop until approximately 3–6 months of age. If there is no response to the OKN drum, infants can be held up by the examiner and rotated, looking for an OKN response with the exam room serving as a full-field OKN stimulus. If vision is present, a few beats of OKN will likely be observed. If, however, the child has extremely poor vision, there will be an absence of optokinetic nystagmus. The vestibular system will cause the eyes to move in the opposite direction that the child is being rotated. For example, if a child with extremely poor vision is being rotated clockwise, the eyes will drift to the child's right and remain in right gaze until rotation is stopped or direction of rotation changes. One can also test for suppression of the vestibular input by attempting to get the child to look at the examiner's face while being rotated. Suppression of the vestibular ocular reflex suggests that the child does have some vision. A child can also be tested for light perception by looking for any reaction to changes in room lights or reaction to a bright light source such as that used for indirect ophthalmoscopy.

Preliterate Verbal Child

The most commonly used preliterate vision charts are the E game, LEA symbols, HOTV chart, Allen figures, and Landolt rings. These charts either require the child to verbalize or to indicate a response and to understand verbal instructions.

The distance HOTV chart has the letters H, O, T, and V as the optotypes and requires the child to understand the concept of matching. A card with large print letters H, O, T, and V is held by the child. As the examiner points to letters on the distance chart, the child is instructed to point to the same letter on the card they hold.

Landolt ring and E game charts involve having the child indicate which direction the E or the gap in the Landolt ring is pointing. Developmentally, children are often able to name or match figures before they are able to reliably indicate the direction of E's and Landolt rings.

Allen and LEA symbols require the child to name the figures. Some children are able to identify the figures but

refuse to speak during the exam. In such cases, the test can be adapted to be performed in a similar matching manner as the HOTV chart.

Special Considerations

Linear optotype monocular visual acuity cannot always be obtained, even when the child is developmentally ready for such testing. Some children are distracted by occlusion to the point that they will not cooperate for monocular vision testing. In such cases, obtaining a binocular acuity can suffice for that visit. As the child becomes more comfortable with the testing process, monocular testing can be performed at subsequent visits. The parents can take home photocopies of the test figures to practice the testing process with the child. Familiarity with the figures will enhance cooperation at the subsequent examination. In addition, when a child is first being tested with preliterate symbols, presenting isolated symbols can be less confusing to the child than rows of symbols. One must keep in mind, however, that the diagnosis of amblyopia can be missed or depth of amblyopia misjudged under isolated symbol testing conditions. One of the characteristics of amblyopia is the "crowding phenomenon" or contour interaction, where optotypes become more difficult to recognize when they are surrounded by similar forms secondary to abnormalities in spatial summation in the amblyopic eye [12, 13]. The visual acuity for amblyopic eyes can be several lines poorer when the symbols are presented in a row (crowded) as compared to isolated symbols. The examiner should use crowding bars that surround isolated targets when they are available and progress to linear testing with rows of symbols as soon as the child is able to adequately cooperate and to understand such testing.

When assessing a child's vision, one should observe for and document any abnormal head postures. The child should be tested in his preferred head position. This is especially important for children with nystagmus as they will position their gaze to utilize a null zone if one exists. The null position or zone is the position of gaze in which the nystagmus dampens, and visual acuity is maximized. Children with infantile strabismus often have an associated latent nystagmus. Manifest nystagmus can have a latent component, as well. When one eye is covered, the latent component causes an increase in nystagmus intensity, hence a decrease in monocular acuity. Latent nystagmus dampens in adduction. The best acuity will be obtained with the eye in an adducted position. Latent nystagmus can also be dampened by using the blur of a high plus lens instead of an opaque occluder to "cover" the non-tested eye. In addition to testing visual acuity monocularly, children with latent nystagmus and children with manifest nystagmus should have visual acuity tested under binocular conditions. Binocular testing will eliminate or minimize latent nystagmus and can result in a significant improvement in visual acuity when compared to that obtained monocularly. The binocular acuity is, in fact, more representative of the child's functional vision since under ordinary viewing conditions, the child has both eyes open simultaneously.

Detecting and Measuring Strabismus

Fusion State

Strabismus can be manifest or latent. When strabismus is manifest, normal fusion is not present, and the visual axes are not aligned under binocular conditions. Strabismus is designated as latent if fusion allows the visual axes to become aligned under binocular viewing conditions. A latent deviation is referred to as a phoria, while a manifest deviation is referred to as a tropia. It is important to determine whether a deviation is latent or is manifest as this can impact management decisions and assessment of treatment response. In some cases, deviations are sometimes latent, at other times manifest, presenting as a combination of both. This is most commonly seen with exodeviations and is discussed further in Chap. 51.

Herring's and Sherrington's Laws

Whether a deviation is latent or manifest, it is important to understand that the deviation involves both eyes. This fact should be communicated and explained to families. The bilaterality of strabismus is due to Herring's law of equal innervation. There are special forms of strabismus that appear to violate Herring's law. Dissociated strabismus, discussed in Chap. 56, is an example of a deviation that initially appears to violate Herring's law. Herring's law states that when the muscles of one eye contract or relax, the yoke muscles in the fellow eye will receive an equal change in innervation (Fig. 1.3). Sherrington's law of reciprocal innervation states that as a muscle is stimulated to contract, its antagonist receives an equal reduction in innervation allowing it to relax. For example, if a subject with a blind left eye performs a leftward saccade with his sighted right eye, the right medial rectus muscle (RMR) will receive the amount of innervation needed to move the eye to the intended target, while according to Sherrington's law of reciprocal innervation, the antagonist, the right lateral rectus muscle (RLR), will receive an equal reduction in innervation to allow the RLR to relax the appropriate amount. The yoke of the contracting RMR is the left lateral rectus muscle (LLR). According to Herring's law, the LLR will receive the same amount of innervation as its yoke, the RMR. The antagonist of the LLR, the left medial rectus muscle, receives an equal reduction in innervation according to Sherrington's law. The result is that the blind eye moves in harmony with the sighted eye just as the eyes of

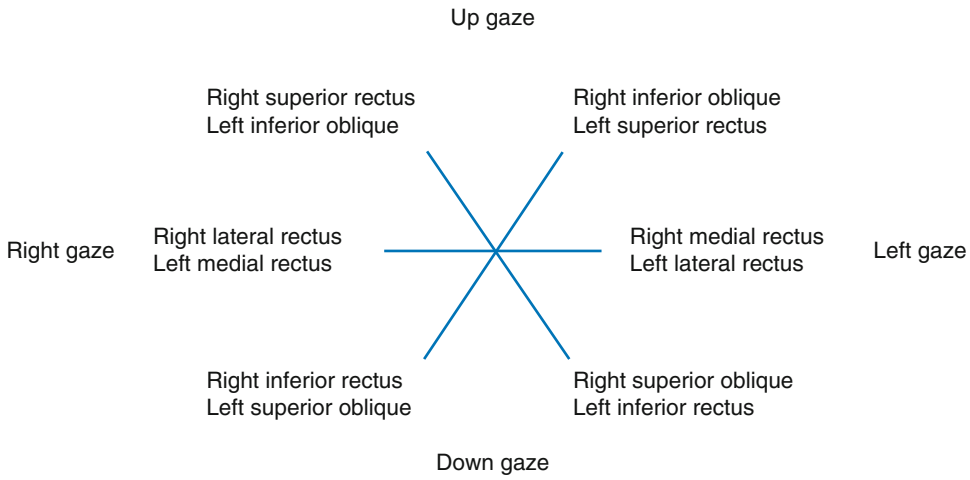

Fig. 1.3 Yoked muscle pairs in gazes for comparing muscle function. Cardinal positions of gaze are essential for isolating field of action for each muscle. If versions are abnormal, then duction testing should be performed

normally sighted subjects move together whether they are aligned or misaligned, following Herring's and Sherington's laws, respectively.

Cover Testing

Strabismus and motor fusion state can be evaluated by cover testing. Cover testing requires that the child be able to fixate centrally on a discrete target. Ideally, the fixation target should have detail that requires appropriate accommodation for clarity. Controlling accommodation is important, especially for horizontal strabismus. When accommodation fluctuates, changes in accommodative convergence can cause variability in horizontal alignment. When accommodation is not appropriate for the testing distance, measurement of the deviation can be inaccurate. The relationship between accommodation and ocular alignment will be discussed in Chaps. 47 and 51 and will be discussed in more detail later in this chapter.

Cover testing is typically performed with an occluder. Young children, however, are often distracted or feel threatened by the occluder. In such cases, using one's hand in place of the occluder is advisable and will enhance cooperation and attention to the fixation target. Accurate cover testing requires that fixation on the target be well-maintained. The younger and more active the child, the more encouragement they will need to maintain visual attention. The examiner should utilize near targets that the child will find interesting when possible. Ideally, the targets should have details that require appropriate accommodation to be visible. It is necessary to draw the child's attention to the target. This can be accomplished by asking the child questions about the target. For example, if the near target is a cartoon character sticker on a tongue depressor or a small toy, one asks the child questions about the toy or character (e.g., What color is Mickey's shirt?). For distance testing, one can have the parent take a toy to the end of the room. The parent can encourage the child to fixate on the toy. Changing to a new target when the child becomes disinterested is critical—"one toy, one look." Having a variety of interesting targets on hand will provide more opportunities to obtain the needed information. For toddlers and older preliterate children, movies or cartoons playing on a monitor or screen at the end of the room are useful targets to control fixation and allow qualitative evaluation and quantitative measurements of strabismus. Some of the computerized visual acuity systems are programmed to include movies or other animations for distance fixation targets. Most children are excited to be given the opportunity to "watch TV" while at the doctor's office, enabling them to relax while motility tests are performed. Accommodation must be controlled for clear viewing of the movie allowing for accuracy when measurements are obtained. Having the child describe what he is seeing on the monitor ensures attention and controlled accommodation. In addition, the sound from the movie helps maintain attention to the target. For older children, some projectors or computerized systems allow a single 20/60 optotype (or smaller) to be placed on cycle mode, and distance fixation can be assured by encouraging the child to verbalize the letter as it changes. When cycling mode is not available, presenting three full lines of letters will assist in maintaining visual attention at distance. The examiner can change the letters as needed. When vision or attention is extremely poor, accurate cover testing will not be possible, and other methods for strabismus evaluation involving corneal light reflexes will be necessary.

Detecting a Manifest Deviation

The cover test used to detect the presence of a manifest deviation (tropia) is referred to as the single cover test or the cover-uncover test. As with all cover testing, the child must be encouraged to maintain fixation on the target throughout

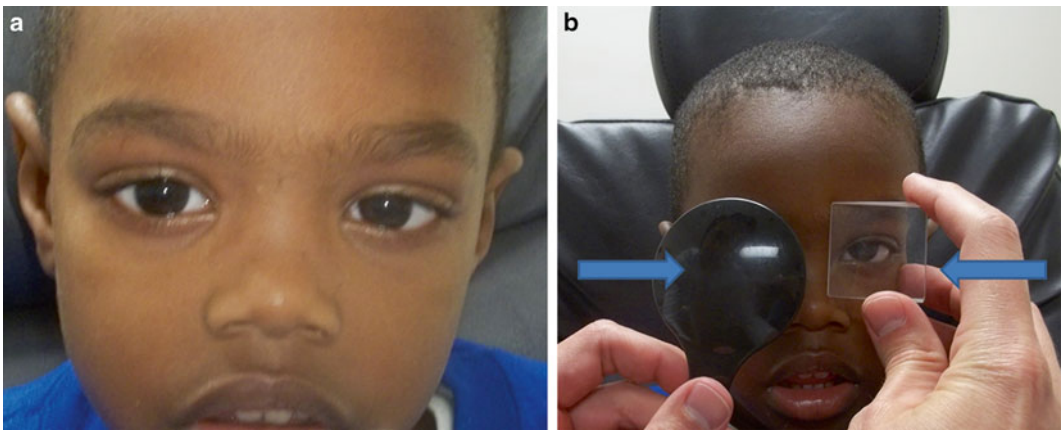

Fig. 1.4 Simultaneous prism and cover test. (**a**) Small angle left esotropia can be seen by corneal reflections. (**b**) Occluder is placed over fixing right eye as base-out prism in an amount equal to the estimated size of esotropia and is placed over the deviated left eye. Occluder and prism are simultaneously placed in front of each eye. Test is repeated with adjustments in prism power until left eye does not shift as prism, and occluder is simultaneously introduced. *Blue arrows* denote the simultaneous placement of cover and prism when testing

testing. To perform the single cover test, one eye is covered while watching for a shift in position of the fellow eye. The occluder is then removed, allowing the child to regain binocular vision. The test is repeated, now covering the other eye, looking for a shift in the fellow eye as the cover is introduced. If there is no shift when either eye is covered, no tropia is present. If, however, there is a shift when one eye is covered, it indicates that the fellow eye is deviated and that a tropia is present. This shift reflects the movement required for a deviated eye to achieve fixation on the target. If an inward deviation is present, the examiner will see an outward shift in position as the fellow eye is covered. This indicates that the child has an esotropia. If the shift in position is in a nasal direction, it indicates that the uncovered eye was deviated temporally. The child therefore has an exotropia. A vertical shift indicates that there is a hypertropia.

Often the single cover test is repeated several times to ensure accurate interpretation or to see if one eye is consistently the deviated eye when a tropia is detected. Some patients will alternate their fixation allowing either eye to be the deviated eye. In such cases, the child maintains fixation with the formerly deviated eye, with the fellow eye now deviated. When repeat testing is conducted, it is very important to allow binocular viewing between each test.

Measuring a Manifest Deviation

The size of the manifest deviation can be measured by performing the simultaneous prism and cover test (SPCT). The examiner first estimates the size of the shift detected on the single cover test. The SPCT will be performed using a prism equal in power to the estimated size of the deviation. The prism will be "simultaneously" placed over the deviated eye as the occluder is placed over the fixing eye. The test is repeated, adjusting the prism power until no shift is seen as the prism and cover are simultaneously placed in front of the child's eyes. No shift indicates that the deviation has been successfully neutralized by the prism. If, for example, a 12^{Δ} base-out prism is placed over the left eye as the right eye is covered, the child would have 12 prism diopters of left esotropia by SPCT (Fig. 1.4). Conventional nomenclature for this deviation would be 12^{Δ} LET. The ET refers to esotropia; the L indicated that it was the left eye that was deviated. This can also be documented as ET with strong right fixation preference. When measuring deviations, whether it be by SPCT or by alternate cover testing discussed in the next section, prisms should be held with the apex pointing in the direction of deviation. For example, for an outward deviation (exotropia), the apex of the prism should be temporal with the base placed nasally ("base in"). If the right eye is hypertropic, deviating in an upward direction, the prism should be held with the apex up, base down over the right eye. When performing the SPCT, the prism must be held over the deviated eye.

It is not necessary to measure manifest deviations in all cases. The SPCT is most often performed when the manifest deviation appears to be significantly smaller than the combined manifest and latent deviation.

Detecting Latent Deviations

The cover test used to detect a latent deviation (phoria) is known as the alternate cover test or the cross cover test. This test is performed by alternating the cover from one eye to the other *without* allowing binocularity as the cover is transferred from one eye to the other. Latent deviations remain latent by

means of fusion. Allowing binocular viewing would allow the eyes to possibly realign if fusion ability exists. The alternate cover test is intended to disrupt fusion. When a latent deviation is present, the eyes will deviate while covered. In performing the alternate cover test, the examiner watches the eye that is being uncovered as the cover is transferred to the fellow eye. If the eye was deviated under the cover, there will be a shift in the position of the covered eye as the cover is moved to the fellow eye. Because of Herring's law, the fellow eye will now be deviated under the cover. As described in the section on single cover testing, the direction of movement will indicate the type of deviation present. For example, if a subject has a right hyperphoria, fusion is enabling both eyes to fixate on the target under binocular conditions. In this phoric state, single cover testing will reveal no shift. As the examination proceeds to alternate cover testing, however, fusion will be suspended, allowing detection of the latent deviation (right hyperphoria). When the right eye is covered, it will drift up under the cover. As the cover is moved to the left eye, the right eye will be required to make a downward saccade to take up fixation on the target. This downward movement will be observed by the examiner, indicating the presence of a right hyperphoria. According to Herring's law, as the right eye shifts down to take up fixation, the left eye, now under cover, will also shift in a downward direction. The covered left eye will now be in a hypophoric position beneath the cover. As alternate cover testing continues, the cover is now moved back to the right eye. The examiner will see the hypophoric left eye make an upward saccade to regain fixation on the target. This upward shift of the left eye and downward shift of the right eye will continue as the cover is transferred from one eye to the other. Vertical deviations are defined by the higher eye by convention.

Measuring Latent Deviations

Latent deviations are measured with alternate cover and prism testing. This technique is used whether or not a tropia was present on single cover testing. Prisms are placed in front of one or both eyes with the amount of prism adjusted until it neutralizes all movement as the cover is moved from one eye to the other. Because of Herring's law, when measuring deviations with the prism and alternate cover test, the prism can be placed over either eye. When measuring combined horizontal and vertical deviations, the horizontal prism can be placed on the vertical prism to simultaneously neutralize both the horizontal and vertical deviations. For example, if the subject has an esophoria and right hyperphoria, a base-out prism and a base-down prism can be placed over the right eye while on alternate cover testing to neutralize the deviation. The deviation can also be neutralized by placing a base-out prism and a base-up prism over the left eye. Two prisms with the base in the same direction, however, cannot be placed in front of the same eye. For example, if a subject with a 65^{Δ} exodeviation requires two base-out prisms to neutralize the large deviation, one prism must be placed over one eye, with the other prism placed over the fellow eye. Both prisms cannot be placed in front of the same eye. The effective power of two stacked prisms with the base in the same direction is different than the sum of the power of the two prisms [14].

Latent Versus Manifest Deviations

Deviations can initially present as a tropia or can require alternate cover testing for detection of the deviation in its latent form (phoria). Fusion enables a deviation to present as a phoria. Alternate cover testing, however, disrupts fusion and can cause a latent deviation to become manifest if fusional amplitudes are not sufficient to allow the patient to regain fusion when the cover is removed. When a deviation is at times latent, and at other times manifest, it is designated as an intermittent tropia. Distinguishing between a constant tropia, a phoria, and an intermittent tropia is important as the fusional state can impact management decisions. Nomenclature for documenting direction of the deviation and the fusional state is presented in Table 1.2. It is also helpful to document comments regarding the level of control of intermittent deviations. For example, a patient can be primarily phoric but briefly became tropic during the examination, while another patient might be primarily tropic but fuse (became phoric) briefly during the examination. Both

Table 1.2 Nomenclature for strabismus documentation[a]

Deviation	Phoria	Tropia	Intermittent tropia
Exodeviation (outward)	X	XT	X(T)
Esodeviation (inward)	E	ET	E(T)
Right hyperdeviation[b]	RH	RHT	RH(T)
Left hyperdeviation[b]	LH	LHT	LH(T)

[a]Prime added for near deviation (e.g., RHT′)

[b]Documentation of vertical deviations is based on higher eye by convention

patients would be described as having an intermittent tropia, however, because of the difference in control of the deviation, each might be managed differently.

Incomitance by Gaze

Alternate prism and cover test measurements should be obtained at distance fixation and at near fixation in primary position. Discrepancies between distance and near measurements can impact diagnosis and management. It is also important to measure deviations in peripheral gazes, as this, too, can impact diagnosis and management. When the measurements change with with respect to direction of gaze, the deviation is referred to as incomitant. Ideally, peripheral gaze measurements are obtained with the subject fixing at distance. Measurement in up, down, left, and right gazes is usually sufficient for horizontal deviations. When a vertical deviation is present, measurement in nine fields of gaze and with the head tilted to the left and to the right may be necessary for diagnosis and surgical planning. Gaze measurements are documented as shown in Fig. 1.5.

Incomitance by Fixation

For most forms of strabismus, the deviation measures the same amount whether the left or right eye is fixating. This is because of Herring's law and is the reason that one can hold the prism over either eye when measuring strabismus. The fixating eye is the eye without the prism. For example, if one is measuring a 50^{Δ} esotropia in primary position, and the prism is held over the right eye, the right eye will be viewing in an adducted position as it looks through the base-out prism. It is the left eye that is in primary position as the measurement is taken. Therefore, with the prism held over the right eye, the primary position measurement is by left fixation in this example. If, however, there is a mechanical restriction or a cranial nerve palsy that limits the range of motion of an eye, the deviation can be incomitant by fixation and will measure more with affected eye fixating than with the sound eye fixating. For example, if a subject has a left lateral rectus palsy, the primary position measurement with the sound right eye fixing (prism over the left eye) might measure 30^{Δ} LET, with the left eye in a 15° adducted position under the prism. The deviation with the sound eye fixing is referred to as *the primary deviation*. If the subject is then measured while the left eye fixates and the prism now placed over the right eye, the left eye will be in primary position during the measurement. Because of the left lateral rectus weakness, an excessive amount of innervation to the weak left lateral rectus will be required to move the eye to primary position. Because of Herring's law, the yoke, the right medial rectus muscle, will also receive excessive innervation, driving the right eye further into adduction, increasing the size of the esotropia. The deviation with the affected eye fixating is a larger deviation and is referred to as the *secondary deviation*. A similar phenomenon can be seen when a mechanical restriction causes excessive innervation to the affected eye as the gaze approaches the restricted field. In such cases, the examiner must be alert to which eye is fixing when obtaining measurements.

Attention to incomitance by fixation is particularly important when following paretic strabismus for signs of recovery or stability. If on one visit, the deviation is measured with the paretic eye fixing, then measured with the non-paretic eye fixing at the next visit, one could incorrectly interpret the smaller deviation at follow-up as a sign of recovery. In addition, if a patient with incomitance by fixation is going to be managed with a press-on prism, it is important to measure the deviation with the prism held over the eye that will be viewing through the prescribed prism.

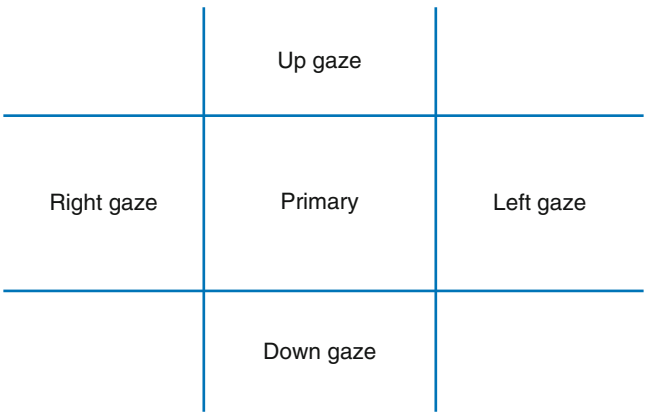

Fig. 1.5 Documentation of gaze measurements

Maddox Rod Test

Cover testing is an objective method of detecting and measuring strabismus. Strabismus can also be assessed subjectively with the Maddox rod test. When viewing a point light source through a Maddox rod, the point of light appears as a streak of light. If the rods are held in a vertical orientation in front of the eye, the streak will appear horizontal; with the rods in a horizontal orientation, the streak will be vertical. If a Maddox rod is placed in front of one eye as the subject views a light, one eye will see the light, and the other sees the streak. If the eyes are aligned, the streak will pass through the light. Horizontal alignment is tested with the rods in a horizontal position and vertical alignment with the rods placed in a vertical position.

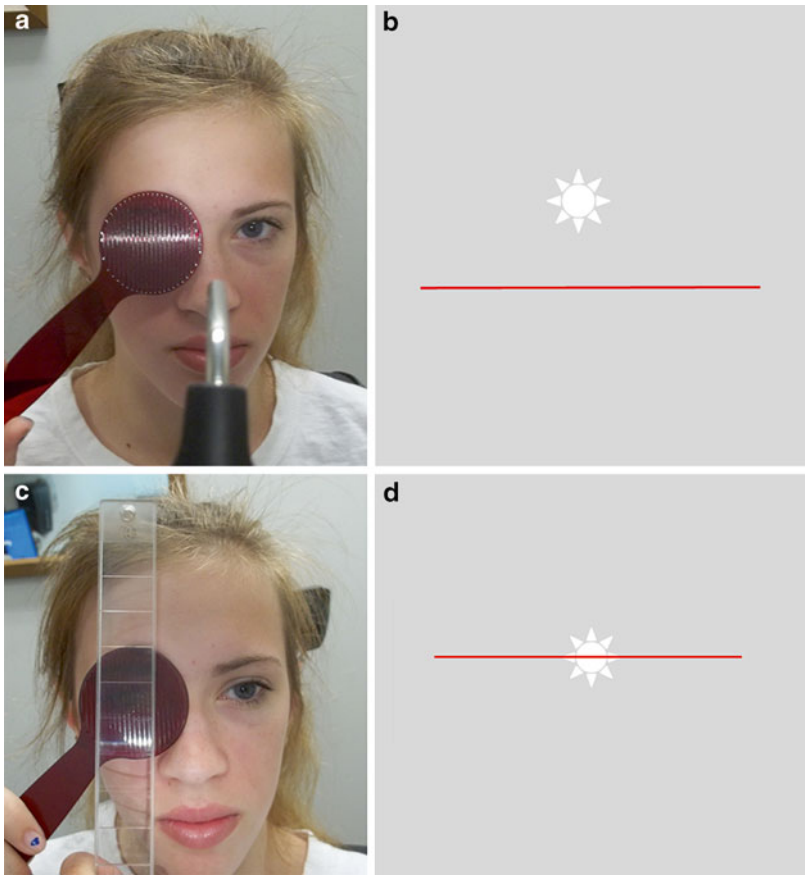

Fig. 1.6 Measuring strabismus with Maddox rod. (**a**) Subject with right hypertropia with Maddox rod over right eye. (**b**) Subject's view. *Red line* induced by Maddox rod (right eye) will be localized below the fixation light (left eye). (**c**) Subject is instructed to describe location of line with respect to the light as base-down prism is introduced to neutralize deviation. (**d**) Subject's view when the correct amount of base-down prism is over the right eye

With the Maddox rod oriented horizontally over the left eye, an esodeviated subject will see a light with a streak to the left (uncrossed localization). An exodeviated subject will see a light with a streak to the right (crossed localization). With the rods oriented vertically over the left eye, a subject with a right hyperdeviation will see a light with a streak above the light. With a left hyperdeviation, the streak will be seen as below the light.

The size of the deviation can be measured with loose prisms or by using a prim bar or rotary prism. When the appropriate amount of prism is in place, the subject will see the streak passing through the light (Fig. 1.6).

One advantage of Maddox rod testing is that it often takes less time than alternate prism and cover testing. It also is useful for detecting very small deviations that are difficult to detect with the cover test. A disadvantage of Maddox rod testing is that for horizontal deviations, accommodation is not controlled. In addition, one must use caution when measuring vertical deviations in head tilt positions in the presence of a horizontal deviation as the results can be inaccurate. Young children often are not good candidates for Maddox rod measurements.

Corneal Light Reflex Assessment

Assessing ocular alignment by evaluating the position of the corneal light reflex is useful when cover testing is not possible due to poor vision in the deviated eye or when cooperation does not allow cover testing or Maddox rod testing. This method cannot be used to detect or measure latent deviations. It only detects manifest deviations. Like the Maddox rod test, corneal light reflex tests do not control accommodation. Although corneal light reflex testing is not as accurate as other methods, it provides an opportunity to quickly obtain measurements in difficult situations.

Angle Kappa

An angle kappa exists if under monocular viewing conditions, the corneal light reflex is nasal (positive angle kappa) or temporal (negative angle kappa) to the center of the pupil. A positive or negative angle kappa can make the results of strabismus assessment by corneal light reflex less accurate. Positive angle kappa simulates exotropia, and negative angle

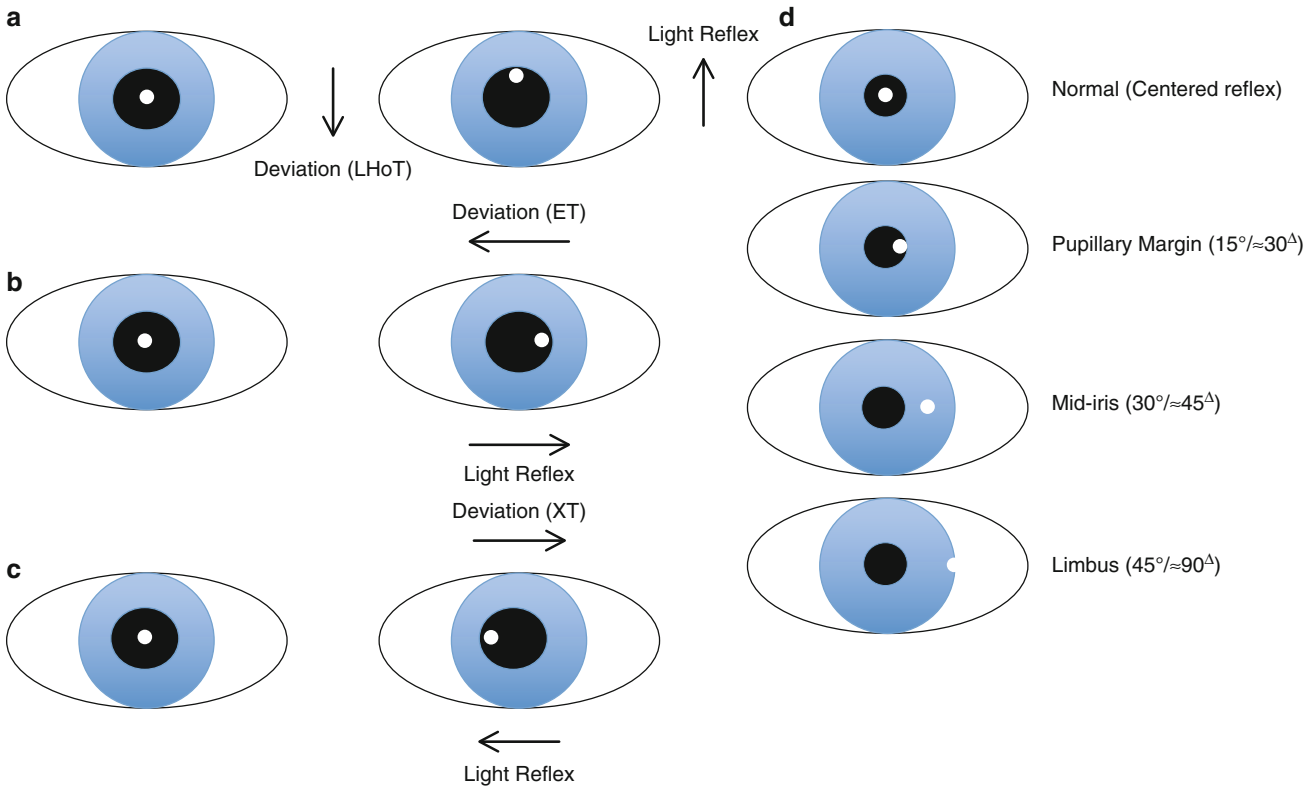

Fig. 1.7 Hirschberg method of detecting manifests strabismus. (**a**) Upward displacement of left corneal light reflex indicates left hypotropia (LHoT). (**b**) Temporal displacement of left corneal light reflex indicates left esotropia (ET). (**c**) Nasal displacement of left corneal light reflex indicates left exotropia (XT). (**d**) The extent to which the corneal light reflex is displaced from the center of the pupil in degrees provides an approximation of the angular size of the deviation in prism diopters (PD) (approximately 22 PD/mm, although significant variability is present among individuals)

kappa simulates esotropia. Before estimating the amount of strabismus using either the Hirschberg or Krimsky method (see below), the examiner must ascertain the location on the cornea of the light reflex in each eye individually under monocular viewing conditions. The following procedure is performed with each eye. One eye is covered, while the child's attention is directed toward the light source. The location of the corneal light reflex in relationship to the pupil is noted and becomes the de facto "center" or location of the visual axis. Assessment of strabismus utilizing the corneal light reflex then relies upon this actual reflex location rather than the center of the pupil as a reference point.

Hirschberg Method

The Hirschberg method involves estimating the amount of decentration of the corneal light reflex in the deviated eye with the subject viewing a light source. Each millimeter of decentration corresponds to ~7° of deviation or 15Δ. With exotropia, the corneal light reflex will be decentered nasally, with esotropia temporally. A downward displacement of the corneal light reflex indicates hypertropia; an upward displacement indicates hypotropia (Fig. 1.7).

Krimsky Method

The Krimsky method of corneal light reflex assessment is more accurate than the Hirschberg method but still less precise than the prism and cover test method. Prisms are placed over the deviated eye. The amount of prism needed to center the corneal light reflex indicates the size of the deviation. This test can also be conducted with prisms over the fixing eye. Herring's law will cause the deviated eye to move centrally as prism is added to the fixing eye. Again, the amount of prism needed to center the light reflex in the deviated eye corresponds to the size of the deviation. This method, with prisms over the fixating eye, is known as the modified Krimsky test (Fig. 1.8).

Other Methods for Measuring Strabismus

Haploscopic devices that present different images to each eye can be used to measure strabismus. Three of the most common of these are the Lancaster red-green test, the Hess chart, and the major amblyoscope. The Lancaster red-green test and the Hess chart offer the advantage of measuring in nine fields of gaze relatively efficiently [15]. The Lancaster

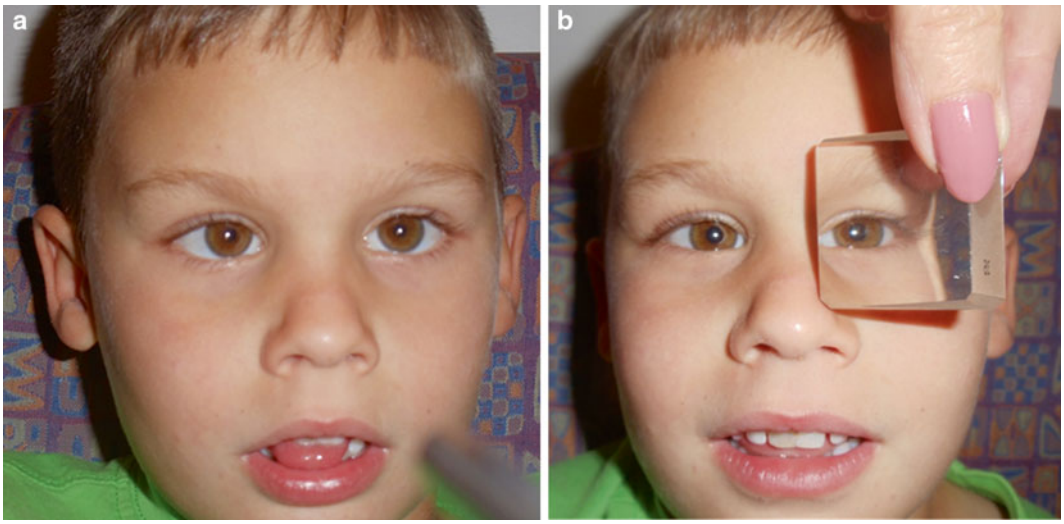

Fig. 1.8 Modified Krimsky test. (**a**) Temporal displacement of corneal light reflex indicates right esotropia. (**b**) Left eye shifts to the right when viewing light through base-out prism. Herring's law causes right eye to also shift to the right with the corneal light reflex becoming more central

Table 1.3 Primary, secondary, and tertiary muscle actions

Muscle	Primary action	Secondary action	Tertiary action
Lateral rectus	Abduction	–	–
Medial rectus	Adduction	–	–
Inferior rectus	Depression	Excycloduction	Adduction
Superior rectus	Elevation	Incycloduction	Adduction
Inferior oblique	Excycloduction	Elevation	Abduction
Superior oblique	Incycloduction	Depression	Abduction

red-green test has the added advantage of measuring cyclodeviations, as well. These tests require equipment that is often not available in most practices in North America and are often performed by orthoptists. The major amblyoscope can measure strabismus; however, it is more often used for sensory testing than for obtaining measurements (see Chap. 2 on Sensorial Adaptation to Strabismus).

Ocular Rotations

Ocular rotations can be tested monocularly (ductions) or binocularly (versions). When versions show a full range of motion for both eyes in all fields of gaze, testing ductions is not necessary. Therefore, ocular rotation testing begins with evaluating versions.

Versions

Muscle function is evaluated with version testing. In order to correctly interpret version testing, the examiner must understand the relationship between field of action and muscle action. Vertical recti and oblique muscles have three actions (Table 1.3). The *primary action* of the superior recti is elevation and the inferior recti, depression. For anatomical reasons relating to the location of their insertion and to their arc of contact, the superior recti elevate most efficiently, and the inferior recti depress most efficiently when the eye is in an abducted position. Therefore, the right superior rectus is tested in gaze up and right and the right inferior rectus in gaze down and right. The left superior rectus is tested in gaze up and left and the left inferior rectus in gaze down and left. Although the primary action of the inferior oblique and superior oblique muscles is torsion, their function is evaluated by examining their *secondary action*, elevation and depression, respectively. For anatomical reasons, the oblique muscles elevate and depress most efficiently in adduction. Therefore, the right superior oblique is tested for its ability to depress in gaze down and left; the right inferior oblique is tested for its ability to elevate in gaze up and left. Similarly, the left superior oblique is tested for its ability to depress in gaze down and right and the left inferior oblique for its ability to elevate in gaze up and right.

Version testing involves testing muscles for their ability to fully move the eye into their field of action (location

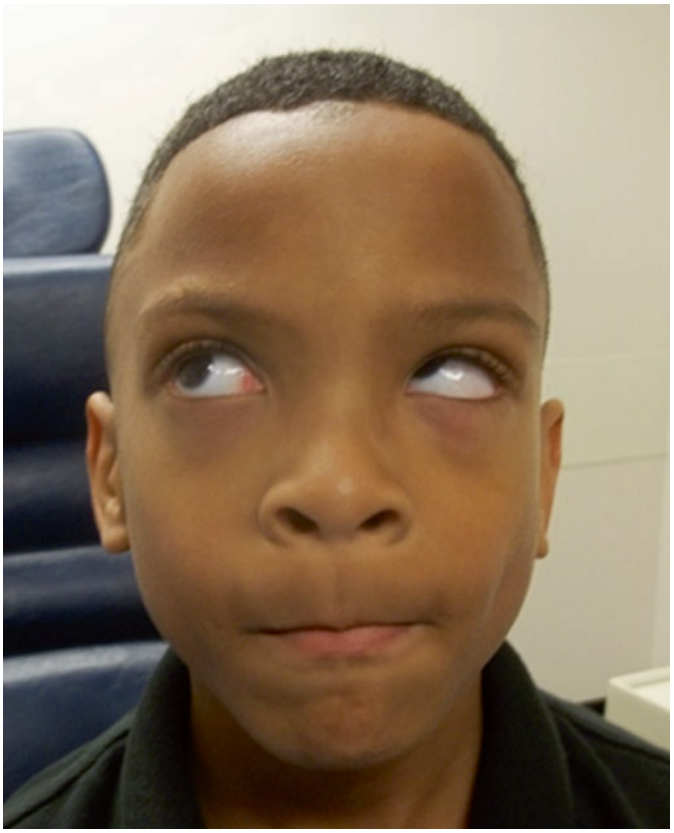

Fig. 1.9 Left inferior oblique (LIO) overaction. Left eye higher than right eye in gaze up and right indicating LIO overaction

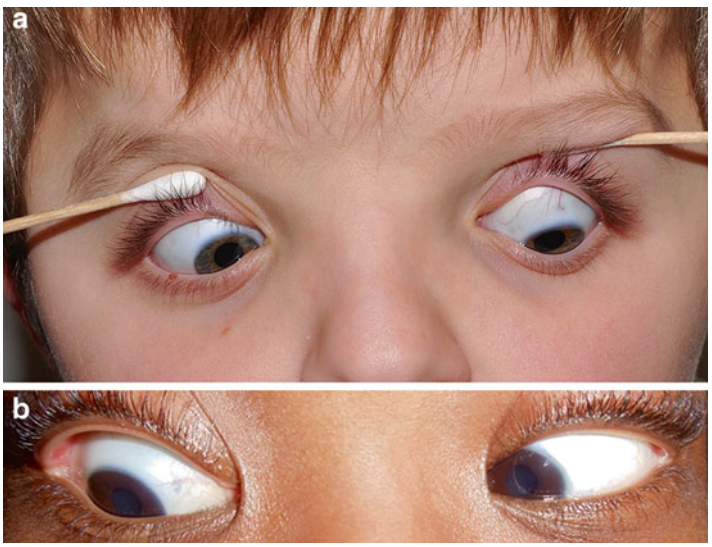

Fig. 1.10 (**a**) Patient with right superior oblique (RSO) underaction in a patient with craniosynostosis. Right eye is higher than left eye in adduction indicating RSO underaction. (**b**) Patient with left superior oblique (LSO) underaction. The left eye higher in adduction induction indicating LSO underaction

where one muscle action is effectively isolated). To increase the examiner's sensitivity to muscle weakness, the function of each muscle is compared to that of its yoke (Fig. 1.3). To accomplish this, the patient is instructed to follow a target as the examiner moves the target into left, right, up and left, down and left, up and right, and down and right gazes. For example, the elevating ability of the right superior rectus would be compared to the elevating ability of the left inferior oblique in gaze up and right. If the right superior rectus is able to fully elevate the right eye in that field, but the left eye is in a position that is higher than the right, the finding would be described as left inferior oblique overaction (Fig. 1.9). Another example of dysfunction would be if, when testing yoke muscles, the right inferior rectus and left superior oblique in gaze down and right, the left eye is higher than the right eye, the left superior oblique would be described as underactive (Fig. 1.10). If full depression of the left superior oblique could not be demonstrated on ver-

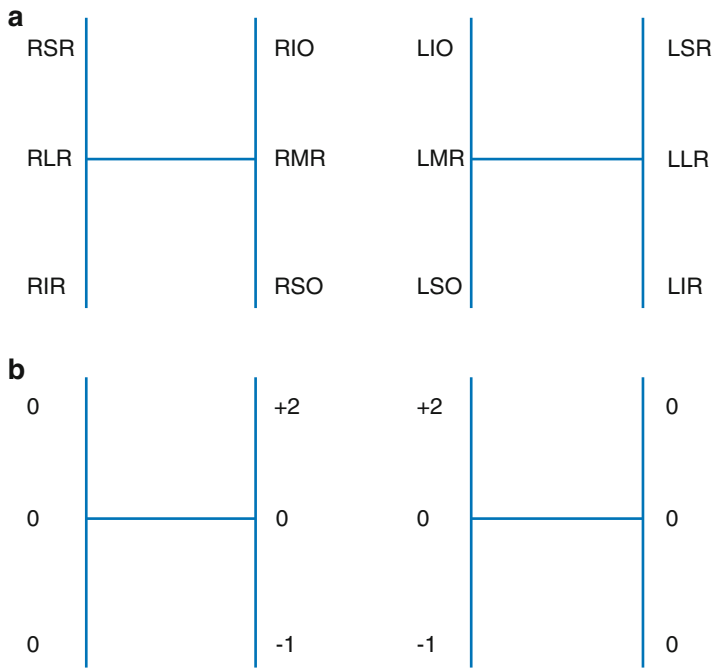

Fig. 1.11 (**a**) Versions in cardinal positions of gaze. (**b**) Extraocular muscle overaction/underaction ratings are placed in respective positions on the diagram. In this example, bilateral inferior oblique overaction and superior oblique underaction are present. This patient likely has bilateral superior oblique palsies with secondary inferior oblique overaction. Cover and alternate cover testing in all fields of gaze and on head tilt as well as observation of fundus torsion would help to further determine pathophysiology

sion testing, duction testing would be necessary to ensure full rotation.

Extraocular muscle overaction and underaction revealed on version testing is graded on a scale from +4 to −4, respectively. An example of version documentation is presented in Fig. 1.11.

Version testing is also useful for detection of "A" and "V" patterns associated with horizontal strabismus, particularly when it is not possible to obtain measurements. When testing for pattern strabismus, the child follows a target directly up and down from primary position as the examiner looks for obvious increases or decreases in the size of the horizontal deviation. Version testing is also used for comparing the relative excursions of both eyes, for example, evaluating the patient with thyroid eye disease and unequal restriction of the inferior rectus muscles.

Ductions

When version testing reveals that a muscle does not move the eye fully into the field of action of that muscle, duction testing is performed. Ductions are tested monocularly. If, for example, version testing reveals that the right eye does not elevate as well as the left eye in gaze up and left, the two most likely conclusions are that either the right inferior oblique is weak relative to the left superior rectus or there is a right Brown syndrome. Brown syndrome involves a tight or restricted superior oblique tendon (see Chap. 58) in which case the restriction prevents the right eye from elevating fully in adduction. To differentiate inferior oblique weakness from a Brown syndrome, duction testing of the right eye should be performed with the left eye covered. If, on duction testing, the right eye now elevates fully in the inferior oblique field (up and left), this would suggest a relative weakness of the right inferior oblique compared to its yoke, left superior rectus. However, if the right eye cannot elevate fully on duction testing, this would be suggestive of Brown syndrome.

When ductions reveal a limitation of movement, additional information can be gathered to aid in diagnosis. Limitations of movement can be due to mechanical restriction or can be of infranuclear, nuclear, or supranuclear origins. The examiner should evaluate for retraction of the globe as the eye moves into the limited field. Globe retraction is suggestive of Duane syndrome (see Chap. 52) or of a mechanical restriction. For example, when there is significant scarring after muscle surgery, globe retraction is sometimes seen in the field of gaze opposite the scarring. One might also examine the quality of saccades in the direction of the limited gaze. For example, if there is limitation of abduction of the right eye, a target is held in primary gaze and another target to the right of primary gaze. As the subject looks from one target to the other, the rightward saccade in the right eye is compared to that in the left eye. If the abduction deficit is due to a right sixth nerve palsy or to a slipped muscle following surgery to the right lateral rectus muscle, the rightward saccades of the right eye might appear less brisk than those generated by the sound left eye. The OKN drum can be useful when comparing quality of saccades as well. With mechanical causes for limitations of movement, saccades are usually brisk until reaching the point of restriction. When considering a supranuclear cause

for limitation of movement, diagnosis can be aided by assessing response to vestibular input by means of the doll's head maneuver and, in cases of limitation of elevation, testing for a Bell's phenomenon.

Sensory Testing

Sensory adaptations to strabismus and testing sensory status are discussed in detail in Chap. 2. Since most sensory tests require a subjective response, when testing children, there can be some question with regard to the reliability of the response. Testing is limited when the child is young; however, some tests can be adapted to allow for testing very young children, including infants.

Stereo Testing

Most verbal children can perform stereo testing. Children, however, have a tendency to want to get close to near tasks. Care must be taken to not allow the child to lean into the test page as this increases the image disparity and can lead to an exaggerated stereo acuity. Most stereo tests are designed for testing at 15 in. The examiner should instruct the patient to maintain the appropriate test distance for accurate results. If a child is too young to follow instructions for stereo testing, sometimes just showing them the Titmus fly will result in the child attempting to touch it or trying to grab it. If they appreciate the three-dimensional image, one can sometimes see the inaccuracy of their reach indicating a positive response.

Worth 4-Dot Testing

For preverbal children, children who cannot count, or children who do not know colors, the Worth 4-dot test can be performed by asking the child to touch the lights. The examiner can encourage the child to touch the lights by taking the child's finger and placing it on the white light, asking them to now touch another light. If they only touch the red light, they are suppressing their left eye. If they only touch the green lights, they are suppressing their right eye. If they touch red and green lights, it is not known if they are alternating suppression, fusing, or diplopic; one knows only that they are not completely suppressing one eye.

Prism Neutralization

It is uncommon for children to report diplopia as a symptom. When they do, however, it is important to establish whether or not they have any fusion ability and, if not, whether they have an area of suppression that can be utilized to eliminate the diplopia. One method of obtaining this information is prism neutralization of their angle of deviation. When prisms are in place and are neutralizing the deviation, the image should be on or near the fovea of the deviated eye. If the child reports seeing one image, adding a red filter can determine if the child is fusing or is suppressing one eye. If the child reports seeing two images, the amount of prism can be adjusted in an attempt to achieve fusion. When fusion ability or the area of suppression cannot be determined with this technique, the major amblyoscope, described in Chap. 2, is an excellent tool for further examination of the child's sensory status.

Motor Fusion Testing

Preverbal Child

When no subjective responses can be obtained on sensory testing, even with the methods described earlier in this section, motor fusion can be detected using a 4^{Δ} or 6^{Δ} base-out prism. This test is performed just as the 4^{Δ} base-out prism test described in Chap. 2. As the base-out prism is placed in front of one eye, a small convergent eye movement should be seen if the child is fusing. This test can be used in infants or older uncooperative children. Just as with sensory fusion testing, ideally, motor fusion testing should be conducted with optical correction of any significant refractive error.

Fusional Vergence Amplitude Testing

A more thorough assessment of motor fusion is possible with older, cooperative children. Fusional vergence amplitude testing provides information that relates to strength and stability of single binocular vision. For comfortable single vision, motor fusion must be intact with an adequate reserve of fusional amplitudes. The amblyoscope can be used to measure horizontal, vertical, and torsional fusional amplitudes. Prism bars or a rotary prism can be used to measure horizontal and vertical fusional amplitudes. Measuring fusional amplitudes with prisms involves introducing prism with the base in the appropriate direction for the vergence being tested as follows:

1. Fusional convergence tested with base-out prism
2. Fusional divergence tested with base-in prism
3. Vertical vergence with base up, then base down over the same eye

The amount of prism is gradually increased until the patient reports diplopia and cannot regain fusion or when, in

Table 1.4 Normal values for fusional vergences

Vergence	Normal break point at distance	Normal break point at near
Convergence[a]	25	35
Divergence[a]	7	10
Vertical vergence	4–6	4–6

[a]Values taken from Fray [16]

the presence of suppression, the examiner sees the eyes no longer verging in the appropriate direction. This is recorded as the **break point**. The prism amount is then gradually reduced until the patient regains fusion. This is recorded as the **recovery point**.

When interpreting the results of testing, one must consider the size and direction of any existing phoria. For example, if a subject has 10^{Δ} esophoria, he is already diverging 10^{Δ} to fuse. If, with a base-in prism bar, his break point is 2^{Δ}, he has actually diverged a total of 12^{Δ}. His total divergence amplitudes are actually greater than normal. However, his reserve fusional divergence, that is, the amount he has in excess of what he needs to fuse (10^{Δ}), is only 2^{Δ} and is likely not adequate for comfortable single binocular vision. Normal ranges for vergence amplitudes are presented in Table 1.4.

An additional step can be added when measuring fusional convergence. Subjects will sometimes over-accommodate during fusional convergence testing, using the associated accommodative convergence to help maintain fusion. The over-accommodation will induce pseudomyopia, causing the image to blur. Therefore, for more thorough testing of fusional convergence, the patient should be asked to state when the image becomes double *or* blurred. The blur point is recorded as relative fusional convergence. The examiner continues to increase the prism amount until fusion breaks. This is recorded as absolute convergence. This step can also be added when testing fusional divergence at near. In the normal state, at 1/3 m, patients are accommodating 3 diopters to maintain a clear image. When testing fusional divergence, as the limit of divergence is reached, some subjects will relax accommodation to reduce accommodative convergence, allowing them to maintain fusion. The reduction in accommodation will result in a blurred image. Here, too, the blur point is referred to as relative fusional divergence, the break point as absolute fusional divergence.

Fusional amplitude testing need not be performed on every patient. Examples of settings in which fusional amplitude testing would be useful are as follows:

Asthenopia, Headaches, or Diplopia in the Presence of a Phoria Weak fusional amplitudes in the direction needed to maintain fusion can lead to these symptoms. For example, an esophoria requires adequate fusional divergence; an exophoria requires fusional convergence. The most common condition in this category is convergence insufficiency. Convergence insufficiency is diagnosed when an exodeviation is significantly greater at near than at distance fixation and is associated with poor fusional convergence amplitudes and a remote near point of convergence (NPC) [17].

Differentiating Newly Acquired from Long-Standing Deviations Larger than normal fusional vergences suggest a deviation has been present for a long time, enabling the subject to, over time, gradually develop larger fusional amplitudes in the direction needed to control the deviation. For example, a subject with 16^{Δ} of RH(T) in primary position due to a CN IV palsy has a break point of 6^{Δ} base-up right eye. He is already vertically verging 16^{Δ} to control the deviation giving a total base-up right eye vertical vergence of 22^{Δ}. This is far in excess of normal, suggesting that the palsy is not acute. This can impact the physician's decisions with regard to whether or not a neurological workup is necessary.

Following Subjects with Intermittent Exotropia for Improvement/Decompensation in Control As fusional convergence amplitudes diminish, it is a sign that control is worsening and can be an indication to move forward with muscle surgery. Conversely, improvement in fusional convergence amplitudes can indicate a positive response to treatment with convergence exercises or to alternate patch anti-suppression therapy and suggest that surgery can be delayed.

Near Point of Convergence

Fusional convergence can also be assessed by evaluating the near point of convergence. With the subject fusing on a near target, the target is slowly moved toward the bridge of the nose. The point at which fusion is lost and the eyes begin to diverge is measured and recorded as the near point of convergence (NPC). The break point is usually associated with diplopia. Subjects with temporal suppression associated with X(T), however, are less likely to experience diplopia with this test.

Unlike fusional convergence amplitude testing, this test can be performed on very young children and infants. NPC

testing is used in diagnosing convergence insufficiency and convergence paresis. It can also be used in the assessment of control of intermittent exotropia. NPC testing may be used as a tool in determining deterioration of control of the deviation during the course of follow-up of intermittent exotropia and is used in monitoring response to treatment of convergence insufficiency.

Special Tests

Double Maddox Rods

When the possibility of a cyclodeviation is a concern, double Maddox rod testing should be performed. Subjects with suspected inferior oblique or superior oblique palsy and subjects with a torsional component to their diplopia are candidates for this test.

To perform the test, two Maddox rod trial lenses are placed into the astigmatism sleeves of an adult trial frame at an oblique axis. Room lights should be lowered as much as possible to avoid any view of room structures that could provide the subject clues regarding the true horizontal plane. It is often less confusing for subjects if they are first tested monocularly. A bright light source viewed through the trial lens will give rise to a streak of light. The subject is instructed to make the streak perfectly horizontal by turning the knob that rotates the astigmatism lens sleeve. The orientation of the rod is then recorded. The same procedure is then conducted with the fellow eye viewing, with the final orientation recorded. The subject is then allowed to view with both eyes open. In the presence of a vertical deviation, he will see two streaks of light. If he sees only one, he likely is fusing. In such cases, a vertical prism can be placed in front of one eye to separate the images from the left and right eyes. Now, with the subject aware of two horizontal streaks, he is asked if they are perfectly parallel. If so, testing is complete. If not, he is instructed to adjust the streaks so that they are both perfectly horizontal and parallel. Settings at 90° indicate that there is no cyclodeviation. For the right eye, a setting higher than 90° indicates an excyclodeviation; a setting lower than 90° indicates an incyclodeviation. For the left eye, settings above 90° indicate an incyclodeviation, and settings below 90° indicate an excyclodeviation. Some clinicians advocate testing in various fields of gaze; however, conventional testing is in primary gaze [18].

Accommodative Convergence/ Accommodation Ratio

The near reflex consists of accommodation, pupillary miosis, and convergence. The accommodative convergence/accommodation (AC/A) ratio defines the amount of accommodative convergence that occurs for each diopter of change in accommodation. This ratio is used in classifying esodeviations and exodeviations and can influence management decisions. When measuring the AC/A ratio, it is important that the target used for measurements has a detail that requires the subject to accommodate appropriately to maintain clarity. If accommodation is not controlled in this way, the resulting values may not be accurate. There are two methods for determining the AC/A ratio: the heterophoria method and the gradient method.

Heterophoria Method

This method requires that the subject be wearing his full refractive correction. The formula for this method is as follows:

For this formula, PD is the interpupillary distance in centimeters; Δn and Δd represent alternate prism and cover test measurements at near and distance, respectively. The value D is the reciprocal of the near testing distance in meters. For example, if the near measurement was taken at 1/3 M, the D would be 3. For Δn and Δd, esodeviations are a positive number and exodeviations a negative number. The following is an example of how to measure AC/A using the heterophoria method:

A child with a PD of 8 cm measures $10^{\Delta}X'$ at 1/3 M and $25^{\Delta}X$ at distance.

A normal AC/A ratio is 3 or 4, so the above child has a very high AC/A ratio. A high AC/A ratio is consistent with his near exodeviation being significantly smaller than his distance exodeviation.

Gradient Method

The gradient method of measuring AC/A ratio involves changing accommodation by increasing or decreasing accommodative demand. The test can be performed at distance or near fixation. After measuring the deviation at distance or near, measurements are repeated with minus lenses added to both eyes for distance testing and minus or plus lenses added for near testing. The change in deviation divided by the power of lenses used is the AC/A ratio. Here are two examples:

1. A subject measures 25^{Δ} X(T) at distance. With −2D lenses in front of both eyes, he measures $18^{\Delta}X(T)$. The change in deviation is 7^{Δ}. Seven divided by the lens power 2 equals 3.5. The AC/A ratio for this subject is 3.5. This is a normal AC/A ratio.
2. A subject measures $25^{\Delta}ET'$ at near. With +3D lenses in front of both eyes, the subject measures $4^{\Delta}ET'$ at near.

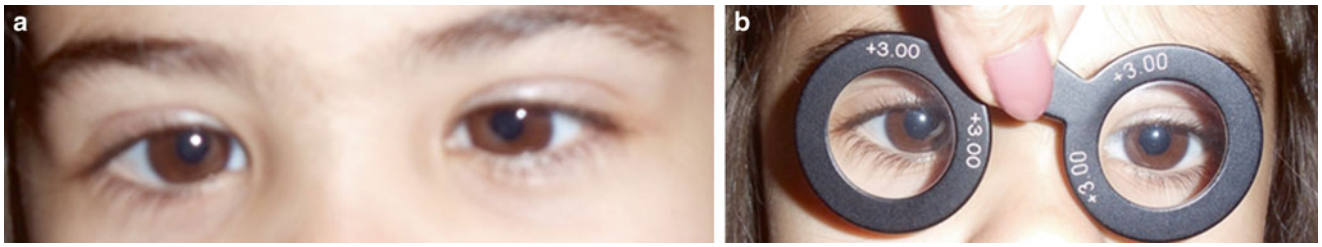

Fig. 1.12 Gross assessment of AC/A ratio. (**a**) Child with esotropia fixating at 1/3 M. (**b**) Marked reduction in esotropia at 1/3 M viewing through +3.00 lenses suggesting high AC/A ratio

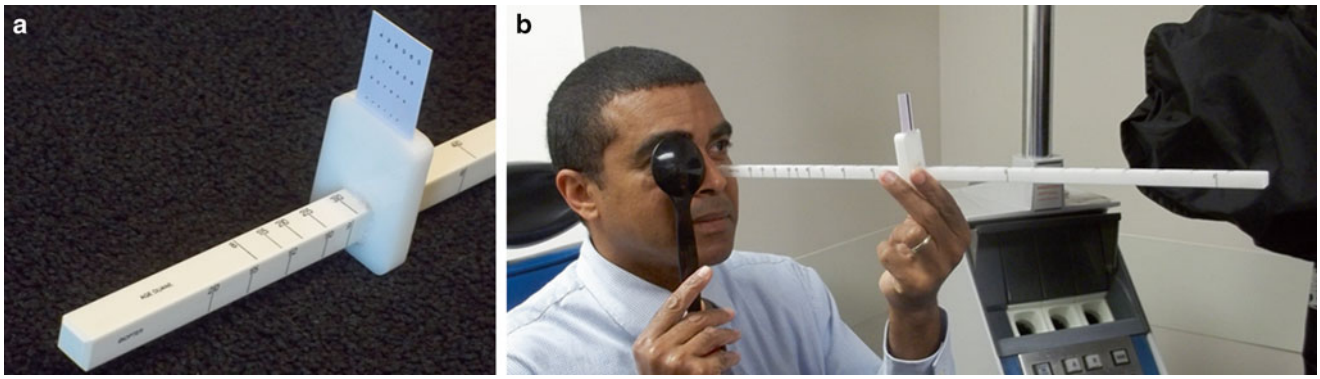

Fig. 1.13 Measuring accommodation (accommodative amplitude and near point of accommodation). (**a**) Prince Rule used to measure accommodation. Small print on sliding fixation card enables determination of blur/clear points. (**b**) Monocular testing with Prince Rule

The change in deviation was 21$^{\Delta}$. Twenty-one divided by lens power 3 equals 7. The AC/A ratio for this subject is 7. This is a high AC/A ratio.

Gross Assessments of AC/A Ratio

It is often clinically important to know the AC/A ratio in children too young for accurate testing with the above formulas. In such cases, the examiner can simply hold up lenses to cause changes in accommodation while looking for gross changes in angle of deviation. For example, +3D lenses can be placed in front of the eyes of a young child with an esotropia at near. If, after the lenses are in place, a significant reduction in the deviation is noted, it is likely that the child has a high AC/A ratio (Fig. 1.12). If, however, little or no change is noted in the deviation, it is likely that the child has a normal AC/A ratio. Similarly, minus lenses (−2D or −3D) can be placed in front of the eyes of a child with intermittent exotropia. If the lenses cause the eyes to converge to a fusion position, the child likely has an AC/A ratio that is high enough to consider minus lens treatment of their deviation (see Chap. 56 on Exodeviations).

Accommodation

Accommodative amplitude can be measured in older children and estimated in young or uncooperative children. Cases in which accommodative amplitude testing might be indicated in older children include those in whom asthenopia at near is a concern and cases of third nerve paresis. Estimating accommodative ability can be important if the child is neurologically impaired or developmentally delayed. Studies have shown that some of these children do not adequately accommodate. Awareness of accommodative insufficiency in these children can impact decisions regarding bifocals and spectacle correction of hyperopia.

Measuring Accommodation

The instrument used for testing accommodative amplitude is the Prince Rule (Fig. 1.13). Full refractive correction should be worn for testing. If performed with no correction or partial correction, the residual uncorrected refractive error will need to be calculated into the outcome measure for accurate interpretation with regard to normal values. The square rod is posi-

tioned at the bridge of the subject's nose when testing binocularly or on the lower orbital rim when testing monocularly [19]. A card with small print slides along the rod. The test can be performed in two ways. Testing can begin with the card at the proximal end of the rod, in which case, the examiner slowly slides the card farther away from the subject. The subject is instructed to indicate when the print becomes clear. This point is recorded as the near point of accommodation (NPA). The other method of testing involves starting with the card at the distal end of the rod. The card is slowly moved toward the subject, with the subject instructed to indicate when the print becomes blurred. This point is then recorded as the NPA. The four sides of the square rod display different measures; one side is marked in inches, another in centimeters, another in diopters, and another is marked with age in years. The NPA can be recorded in inches or centimeters. The year markings are at distances determined to be the normal NPA for the indicated age at various points along the rod. The diopter markings indicate the amount of accommodation required at that point for an emmetropic subject or a subject wearing their full refractive correction. One can determine accommodative amplitude by viewing the diopter markings and can determine if the subjects NPA and accommodative amplitude are normal for their age by viewing the age markings.

Estimating Accommodation

Dynamic retinoscopy can provide a gross estimate of accommodative ability and is fairly easy to perform with uncooperative or developmentally delayed children. Myopic subjects should be tested with spectacle correction; hyperopes can be tested with or without correction if the amount of hyperopia is not excessive. The test begins with the subject viewing a distance target. Dry retinoscopy should reveal a slightly "with" motion consistent with a plano refractive error for the corrected myope and for a hyperope with normal accommodative ability. The child is then encouraged to view a near target, while the examiner continues to retinoscope the child. If normal or near normal accommodation occurs when changing fixation from distance to near, the retinoscopic reflex should change from a "with" motion to an "against" motion. Abnormal responses would include seeing a stronger "with" motion than would be expected for a plano refractive error in an uncorrected or under-corrected hyperope at distance fixation. This indicates that the child, when fixing at distance, is not accommodating enough to compensate for their uncorrected hyperopia. Another abnormal response would be little or no change in the retinoscopic reflex when fixation changes from distance to near, suggesting insufficient accommodation. This is discussed in more detail in Chapter 72 on Dynamic Retinoscopy; a simulation of this technique can be viewed online at *** = Electronic supplementary material for Chapter 72: The online version of this chapter (doi:10.1007/978-1-4939-2745-6_72) contains supplementary material, which is available to authorized users.

Ptosis

Evaluation of the child with ptosis should begin with observation while walking into the examination room, making note of any compensatory chin-up head posture. When the posture is severe, it can lead to skeletal and muscular changes, therefore impacting timing of surgical repair of the ptosis. Gross inspection should also include evaluating the presence, absence, and symmetry of lid creases as well as lid curvature and direction of lashes. If surgery is planned, these features can impact the choice of procedures. Look for lid lag in extreme downgaze as this suggests long-standing ptosis (congenital) with fibrosis.

Closer inspection should include measuring the marginal reflex distances and levator function. Marginal reflex distances should be measured monocularly if the child has strabismus. This is especially important in the presence of vertical deviations as they can be associated with significant pseudoptosis if the deviation is large and the hypertropic eye is preferred for fixation. The patient is evaluated for anisocoria, heterochromia, and anhydrosis, all of which are indicative of Horner's syndrome. Acquired Horner's syndrome requires prompt neuroimaging to evaluate for neuroblastoma of the sympathetic chain. Associated third nerve palsy or monocular elevation deficiency (secondary to superior rectus palsy or to inferior rectus restriction or a combination of both mechanisms) should be evaluated by testing ocular rotations and by alternate cover testing in all fields of gaze when possible. Variability of the ptosis should be noted as this could suggest myasthenia gravis. Variability can also suggest Marcus Gunn jaw-winking syndrome. If jaw winking is suspected, the diagnosis can be aided by having infants suck on a bottle or older children chew a piece of gum.

Ptosis can lead to or be associated with astigmatic changes. Therefore, with cases of childhood ptosis, it is important to perform cycloplegic refractions on a regular basis. Anisometropia is common; therefore, amblyopia or risk factors for amblyopia must be evaluated. In cases of severe unilateral or asymmetric ptosis, deprivation amblyopia can be a concern. If preverbal visual function is routinely tested using the 20^{Δ} base-down prism test, use instead a 20^{Δ} base-up prism. A base-down prism moves the image up. This higher image might be obscured by the ptotic lid, confounding interpretation of the test.

Nystagmus

Detailed assessment of nystagmus characteristics requires eye movement recordings. Clinically significant information can be gained, however, from simple observation of the nystagmus

characteristics (see Chap. 70 on Nystagmus). Compensatory head postures should be documented as evidence of a null zone. Additionally, one should look for dampening of the nystagmus on convergence and for head nodding.

When presented with manifest nystagmus combined with esotropia, nystagmus blockage syndrome should be considered. With this syndrome, the esotropia is typically variable in size. To assist in diagnosis, a large base-out prism should be placed in front of the fixating eye. The prism will drive the fixing eye into an adducted position. Herring's law will cause the esotropic non-fixing eye to shift toward primary position. With nystagmus blockage syndrome, the non-fixing eye will then converge, returning to an adducted position to dampen the nystagmus.

Nystagmus can be associated with many other ocular and neurologic conditions. Some of the ocular conditions, such as aniridia and ocular albinism, can be detected on clinical exam. Evidence of ocular albinism can be apparent by looking for iris transillumination defects and for foveal hypoplasia. Iris transillumination defects are best assessed at the slit lamp; however, this is often difficult for infants and uncooperative children. When slit lamp examination is not possible, iris transillumination can be easily detected by placing the tip of the transilluminator on the lower lid with the light directed at the globe. Transillumination defects will become apparent in a darkened room.

Some ocular diseases associated with infantile nystagmus are not apparent on clinical exam. Examples are congenital achromatopsia and congenital stationary night blindness. These conditions are frequently associated with a paradoxical pupillary response to darkness [20, 21]. When the room is darkened, the pupils will briefly constrict before dilating. This test should be conducted on all infants for whom the etiology of the nystagmus is unknown. Infants that are found to have paradoxical pupils should have an electroretinogram to evaluate for a retinal dystrophy. Early detection is important for genetic counseling as well as for visual prognosis.

One must be familiar with the many forms and causes of nystagmus and other eye movement disorders. It is sometimes necessary to observe nystagmus for a period of time to fully appreciate its characteristics. Periodic and aperiodic alternating nystagmus, for example, can only be diagnosed by observation. Cycles can occur at 90 s intervals or longer. Oculomotor apraxia is another condition that can easily be missed unless the examiner is alert to unusual maneuvers occurring while the child is casually viewing his surroundings. Head thrusting and frequent blinking are often associated with oculomotor apraxia. As with many ocular motility disorders in children, simple observation can provide an abundance of valuable information useful for diagnosis and management.

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Sensorial Adaptations to Strabismus

2

Allison E. Babiuch

Abstract

This chapter discusses binocular vision, its disorders, as well as sensorial adaptations. A single object produces two separate retinal images, one in each eye, and binocular vision allows fusion of these two images together into a single image. Binocular vision allows for separate and dissimilar images arising in each eye to fuse together into a single image. Disorders of binocular vision result in sensorial adaptations that differ between visually mature and immature systems. In the visually immature system, adaptations of suppression and anomalous retinal correspondence prevent diplopia. Adults with mature visual systems are unable to develop these sensorial adaptations causing diplopia or visual confusion. A number of tests can be utilized to determine retinal correspondence, diplopia, suppression, and stereovision.

Keywords

Sensory • Retinal correspondence • Fusion • Stereopsis • Confusion • Diplopia • Suppression • Monofixation

Sensorial Adaptations

Substantial research on primates has demonstrated that binocular pathways and binocular cortical cells are present at birth. An abnormal visual experience due to visual deprivation, anisometropia, or strabismus during the critical visual development period has been shown to result in changes in neuroarchitecture and loss of binocular cells [1]. These neurodevelopmental changes result in what is clinically known as sensorial adaptations. The specific type of sensorial adaptation depends on the timing of the abnormal visual stimulation occurred, the severity of the abnormal stimulation, and the type of binocular disruption.

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Normal Binocular Vision

The visual axis refers to the line connecting the fixation point and the fovea, and normally, with central fixation, it is subjectively localized straight ahead. *Binocular vision* means using the two eyes together to see a single image. Sensory binocular cooperation is based on a system of correspondence and disparity.

Retinal Correspondence

Retinal areas of two eyes that share a common subjective visual direction are said to be corresponding. When retinal areas in both eyes are simultaneously stimulated and perceived as two separate images (diplopia), these retinal areas are said to be disparate or noncorresponding. *Normal retinal correspondence* (NRC) occurs when corresponding retinal areas in the two eyes have identical relationships to the fovea in each eye. *Anomalous retinal correspondence* (ARC) is

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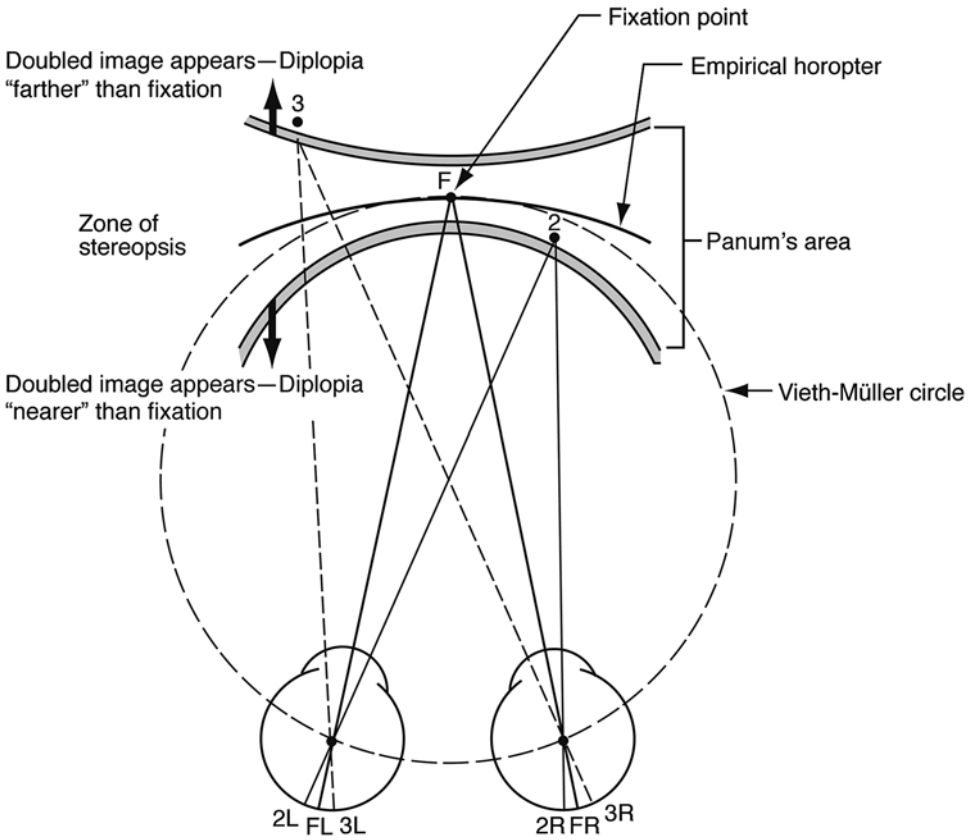

Fig. 2.1 Empirical horopter. *F* Fixation point, *FL* and *FR*, *left* and *right* foveas, respectively. Point 2, falling within Panum's area, is seen singly and stereoscopically. Point 3 falls outside Panum's area and is therefore seen double. (Reproduced with permission from Chap. 4, Sect. 6: Pediatric Ophthalmology and Strabismus, American Academy of Ophthalmology, Basic Science Clinical Series)

present when there is a dissimilar relationship in two eyes between corresponding retinal areas and their respective foveas. Single vision is the hallmark of retinal correspondence, normal or anomalous. If the two eyes have NRC and each fovea fixates on the same point, then this point is seen as a single image. Points to both sides of this fixation point fall on corresponding retinal areas and are also seen singly, creating a curved surface called the empirical horopter (Fig. 2.1). Points lying within a limited area surrounding the horopter curve, called Panum's area of single binocular vision, are fused by the visual system, resulting in single binocular vision with stereopsis (Fig. 2.1). Therefore, stereopsis is a response to horizontally disparate retinal stimulation. The slightly different images caused by the three dimensional object stimulate stereoscopic perception. Outside of Panum's area, objects fall on widely disparate retinal areas and cause physiologic diplopia (Fig. 2.1). *Physiologic diplopia* can be readily demonstrated by holding a pencil up at reading distance in front of the midplane of your eyes and fixate on a small distant object on the wall. When fixating on the distant object, the pencil will appear double and vice versa; when fixating on the pencil, the distant object will appear double. The brain typically ignores physiologic diplopia since it is a normal part of binocular vision, but occasionally a person will suddenly become aware of physiologic diplopia. This patient can be reassured that this is a normal visual phenomenon and that it is actually an indicator of binocular vision [2].

Fusion

Fusion is the cortical unification of images by simultaneous stimulation of corresponding retinal areas. *Central fusion* occurs in the areas near the fovea and, because of their small receptive fields, allows very little disparity before diplopia is elicited. Only when the foveal images from each eye are aligned can stereopsis be achieved. *Peripheral fusion* occurs in the area outside of the fovea and because of the larger receptive fields, more overlap is tolerated without eliciting diplopia. Thus, peripheral fusion provides a less precise form of single images when small-angle strabismus or amblyopia is present. Central fusion develops early in life and, if lost, is not recovered, whereas peripheral fusion is more easily regained.

Monofixation syndrome constitutes a specific group of patients who have a macular scotoma precluding bifixation and active extramacular binocular fusion. Patients are either orthophoric or have a small-angle strabismus (less than 8 Δ), a macular scotoma, and peripheral fusion resulting in limited stereovision (60–3000 s of arc). Patients with monofixation syndrome have associated strabismus,

anisometropia, a unilateral macular lesion, or an inherent inability to fuse similar images on each macula. Patients with monofixation typically demonstrate a microtropia on cover-uncover test with a larger phoria on alternate cover test. This likely indicates that these patients reduce the angle of deviation using fusional vergence to permit peripheral normal retinal correspondence (NRC). There is a significantly greater frequency of monofixation syndrome after correction of esotropia rather than exotropia likely due to the difference in constancy and intermittency of the deviation prior to treatment. Peripheral fusion with absence of central fusion is demonstrated with Worth 4-dot test and 4 Δ base-out prism test (described in detail later in this chapter). There is no treatment for monofixation syndrome as all attempts to disrupt monofixation and begin foveal bifixating have failed. Monofixation syndrome is actually considered to be a good outcome after strabismus surgery and is a good prognostic indicator of stable alignment [3].

Sensory fusion is the ability to take the images from corresponding retinal areas and superimpose them in binocular cells at the level of the occipital cortex. In order for sensory fusion to occur, the images must be located on corresponding retinal areas and must also be similar in size, brightness, and sharpness. *Motor fusion* is the ability to physically align the eyes so that sensory fusion can be maintained. The stimulus for this fusional movement is retinal disparity outside of Panum's area and is a function of the extrafoveal retinal periphery (Fig. 2.1). For example, if base-out prisms of progressively increasing power are introduced before both eyes while a target is viewed, the retinal images move temporally over both retinas if the eyes remain in fixed position. Fusional convergence movements cause the eyes to converge in order to maintain similar retinal images on corresponding retinal areas. The "fusion range" refers to the range over which the motor fusion mechanism is able to "pull" the two eyes together. Fusional vergence amplitudes can be measured with rotary prisms, haploscopes, and other devices. Average convergence, divergence, and vertical fusional amplitudes in prism diopters (PD) at distance (6 m) and near (0.33 m), respectively, are as follows:

- Convergence fusional amplitudes: 14 PD, 38 PD
- Divergence fusional amplitudes: 6 PD, 16 PD
- Vertical fusional amplitudes: 2.5 PD, 2.6 PD

Larger than normal fusional vergence amplitudes may develop in the setting of early onset strabismus (e.g., congenital fourth nerve palsy). The distance fusional amplitudes are less than the near amplitude, as near amplitudes are generated by a combination of fusional and accommodative convergence.

Stereopsis

Stereopsis is the highest form of binocular vision—it is the perception of depth and the impression of three dimensions. Stereopsis occurs when horizontally disparate retinal elements are stimulated simultaneously and fused to create a single visual impression with depth. It occurs when retinal disparity is too great to fuse but not enough to cause diplopia. Stereopsis and depth perception are not entirely synonymous. Depth perception includes monocular clues, including relative object size and overlap, highlights and shadows, motion parallax, and perspective, whereas stereopsis is a binocular sensation of relative depth caused by horizontal retinal image disparity. Nasal disparity between two retinal images is perceived as farther away, and temporal retinal disparity is perceived as nearer. At distances greater than 20 ft, mainly monocular clues provide depth perception.

Abnormalities of Binocular Vision

Visual development occurs until approximately 7–8 years of age, after which the visual system is considered to be mature. Although minimal changes take place after that, there are some exceptions and prolonged visual plasticity that persists even into adulthood [4]. Certain sensorial adaptations may develop due to acquired strabismus in the visually mature system. When a manifest deviation of the eyes occurs, the image of the object is no longer directed to the same corresponding retinal elements, and the patient is at risk for developing visual confusion and diplopia.

Confusion

Under rare circumstances, *visual confusion* occurs, whereby two different objects are projected onto corresponding retinal areas and are perceived simultaneously. The patient will see two different images superimposed on each other, one image from each eye. *Retinal rivalry* occurs when different images are presented to corresponding retinal points of each eye and instead of perceiving two images superimposed on each other, the subject perceives patchy dropout of each image where the images overlap or the images will appear to rapidly alternate.

Diplopia

Diplopia results from an acquired misalignment of the visual axes that causes an image to fall simultaneously on disparate retinal areas (the fovea of one eye and more

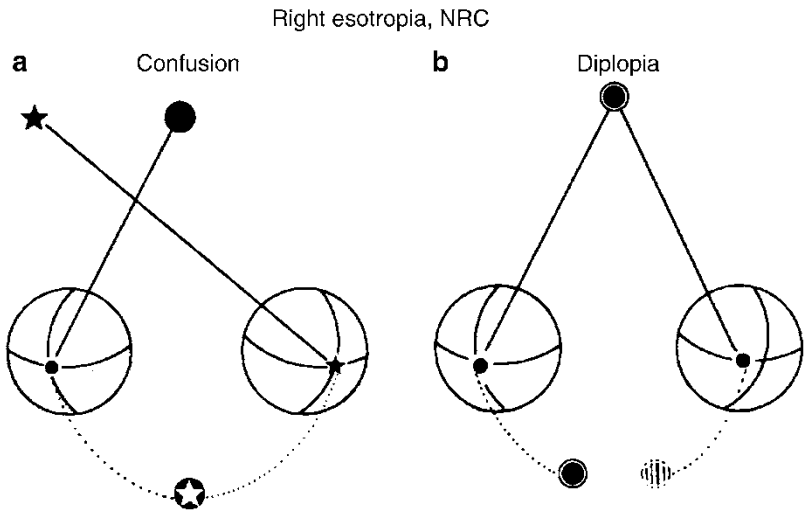

Fig. 2.2 (**a**) Confusion. Different objects are imaged on corresponding areas (the two foveas) and therefore are seen in the same visual direction and overlap. (**b**) Diplopia. Identical objects are imaged on disparate retinal areas (the fovea of one eye and the peripheral retina of the other eye) and therefore are seen in different visual directions; they are seen as double. [Reproduced with permission from Burian HM: Adaptive mechanisms. Trans Acad Ophthalmol 57: 131, 1953 (copyright: American Academy of Ophthalmology)]

peripheral retina of the other eye). The object that falls on the nonfoveal area must be outside of Panum's area in order to cause diplopia. The foveal image of the fixating eye is always perceived as clearer than the nonfoveal image of the nonfixating eye. The symptom of diplopia depends on the age of onset of the deviation, duration, and subjective awareness. The younger the patient, the greater the ability to suppress the nonfoveal image. Esotropia causes the image to fall on the nasal retina of the deviating eye, which projects temporally and causes *uncrossed diplopia* because the diplopic image is on the same side as the deviated eye, whereas in exotropia, the image falls on the retina temporal to the fovea, which projects to the nasal field and produces *crossed diplopia* [5] (Fig. 2.2).

Horror fusionis is a rare entity characterized by an inability to fuse or suppress images presented to both foveas resulting in intractable diplopia. Horror fusionis can occur in a number of clinical situations: after disruption of fusion for a prolonged period, after head trauma, and in long-standing strabismus. Unfortunately, management can be quite challenging. Total field occlusion with an occlusive contact lens or partial field occlusion with tape or clear nail polish applied to glasses can provide some relief [6].

Sensorial Adaptations in Strabismus

In order to avoid diplopia and confusion, the visual system has developed two mechanisms: suppression and anomalous correspondence. Suppression, amblyopia, and changes in retinal correspondence only occur in the visually immature system. Once childhood sensorial adaptations are acquired, they usually persist through adulthood.

Suppression

Suppression is the active inhibition of disparate and confusing images from the deviating eye during binocular visual activity. Strabismus, or a monocular blurred retinal image, causes dissimilar retinal images to fall on corresponding retinal areas. If the images cannot be fused, the visually immature system adapts by inhibiting cortical activity from the blurred or deviated eye. This cortical inhibition is termed suppression. Images that fall within the field of cortical suppression are not perceived, forming an area called a suppression scotoma. Suppression only occurs during binocular conditions when the dominant eye is fixating and disappears when the dominant eye is occluded [2]. Suppression that results from strabismic misalignment of the visual axes is a pathologic process, whereas, *physiologic suppression* is a normal adaptation that prevents physiologic diplopia (diplopia elicited by objects outside of Panum's area) from reaching consciousness. In order to avoid confusion and diplopia, suppression must occur in two locations in the deviated eye, both the fovea and the region of the periphery of the deviated eye on which the object of attention is imaged. *Central suppression* is the term used to describe the mechanism that keeps the foveal image of the deviating eye from reaching consciousness, thereby preventing confusion. *Peripheral suppression* is the mechanism that eliminates diplopia by preventing awareness of the image that falls on the peripheral retina in the deviating eye, the image that resembles the image falling on the fovea of the fixating eye. Patients who equally alternate fixation have alternating suppression with scotomas in both eyes. Intermittent exotropes often have *facultative suppression*—suppression when their eyes are in the exodeviated

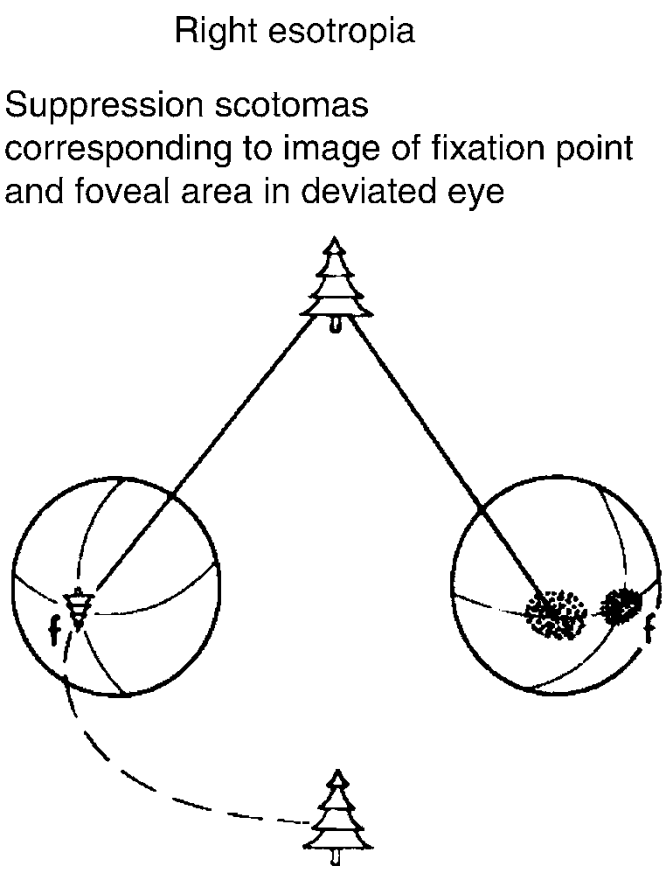

Fig. 2.3 Peripheral fixation point and central suppression scotomas in deviated eye. [Reproduced with permission from Burian HM: Adaptive mechanisms. Trans Am Acad Ophthalmol 57: 131, 1953 (copyright: American Academy of Ophthalmology)]

and high-grade stereopsis when the eyes are orthophoric. The suppression scotoma in esotropia usually is D-shaped and extends from the optic disc across the nasal retina, stopping in a vertical line at the fovea of the deviating eye. The suppression seen in exotropia typically encompasses the entire temporal half of the retina of the deviating eye [7]. Management of suppression often involves treatment of the strabismus itself (Fig. 2.3).

Anomalous Retinal Correspondence

Anomalous retinal correspondence (ARC) is a neural adaptation to eye misalignment that allows the brain to accept parafoveal retinal images from the deviated eye and superimpose them on the foveal images from the fixating eye. The fovea of the fixating eye acquires an anomalous common visual direction with a peripheral retinal element in the deviated eye termed the pseudo-fovea [8]. Cortical reorganization allows the two images to be superimposed leading to subnormal binocular fusion. ARC may be harmonious or nonharmonious, depending on whether the angle of anomaly is equal to (harmonious) or less than (nonharmonious) the angle of strabismus. The more long standing the deviation, the more deeply rooted the ARC may become. ARC is more commonly found with smaller angle strabismus (15–30 Δ) but an angle that is too large to allow peripheral fusion or monofixation [9].

A phenomenon termed *paradoxical diplopia* can occur when ARC persists after strabismus surgery and the eyes are aligned. Since postoperatively the image is displaced from the pseudo-fovea, the patient will have diplopia if the image falls on the true anatomic fovea. Fortunately, this is often a temporary, postoperative phenomenon, seldom lasting longer than a couple of weeks. Very rarely does this condition last longer and become so bothersome that it requires reoperation to recreate the initial strabismus to eliminate paradoxical diplopia. To predict preoperatively if a patient will have postoperative paradoxical diplopia, neutralize the angle of deviation with prisms and see if the patient has diplopia while viewing distant and near targets. If the patient has diplopia with prism neutralization, they should be warned that there is a small risk that they will have persistent diplopia if the eyes are aligned with strabismus surgery [10].

Testing for Diplopia, Suppression, and ARC

ARC is a binocular phenomenon and therefore tested under binocular conditions. This is in contrast to *eccentric fixation*, which is a monocular phenomenon detected on testing under monocular conditions. In eccentric fixation, patients do not fixate with the fovea when the fellow eye is covered, and on cover testing, the eye remains deviated. Eccentric fixation can affect the test results when testing for ARC by stimulating the fovea of each eye. Many tests disrupt fusion by obscuring, or eliminating, peripheral fusion clues. Tests that disrupt fusion are referred to as dissociative. If ARC represents an adaptation to natural conditions in which a patient uses his or her eyes, tests that duplicate these conditions should demonstrate this adaptation. Tests that are "foreign" or unnatural to the visual experience of the patient should be least likely to do so. Some of the tests and methods for determining of the status of the sensory relationship of the two retinas, in order of more dissociating to least dissociating, are afterimage test, Worth 4-dot test, red glass test, amblyoscope, and Bagolini striated glasses. Tests that are more dissociative are more likely to produce a NRC response unless ARC is deeply rooted. In the development of ARC, the innate normal sensory relationship is only gradually replaced and then not always completely. Patients with long-standing deviations have more deeply rooted ARC. In those whom a deviation is not long standing, ARC can be elicited only if the tests closely duplicate ordinary environmental conditions (least dissociative). The depth of the sensory rearrangement can vary widely, thus an individual can test positive for both NRC and ARC. The tests should always be performed in conjunction with a cover test to decide whether a fusion response is due to orthophoria or ARC. A patient with a fusion response on sensory testing and a tropia on cover test has ARC with a suppression scotoma rather than NRC.

A summary of sensory tests and key findings is presented in Table 2.1.

Table 2.1 Summary of sensory tests and key findings

Test	Main use	Dissociative?	Convention	Responses
Worth 4-dot	• Suppression detection • Monofixation syndrome diagnosis	Dissociative	Red glass over OD	• 2 = suppresses OS • 3 = suppresses OD • 4 = normal or ARC if strabismus • 5 = diplopia
Red glass test	• Suppression test • ARC test	Dissociative	Red glass over fixating eye	• ET = uncrossed diplopia • XT = crossed diplopia
Bagolini striated glasses test	• Most sensitive for ARC • Also tests suppression	Least dissociative	• OD streak at 135° • OS streak at 45°	• Suppression = one line • Scotoma = gap in one streak • ET = uncrossed diplopia (A-shaped) • XT = crossed diplopia (V-shaped) • ARC = no diplopia
4Δ base-out test	• Test for microstrabismus or monofixation syndrome • Detects small suppression scotomas		Observe refixation behavior of both eyes	• Prism OD, no movement = suppression OD • Prism OD, OS moves but does not refixate = suppression OS or ARC • Prism OD, OS moves then refixates = normal
Afterimage test	ARC text	Most dissociative test	• Perform monocularly • Labels each eye separately • Vertical flash on suppressed eye (if unknown, horizontal flash OD)	• ET + ARC = crossed • XT + ARC = uncrossed • NRC/ortho/ET/XT = normal test • Eccentric fixation confounds test results (diagnose eccentric fixation with visuscope)
Major amblyoscope	Ultimate ARC text	Dissociative (separate test object to each fovea)	• Each eye targets through a tube that can be adjusted horizontally, vertically, and cyclorotationally • Comparison of subjective to objective angle strabismus	Subjective same as objective = NRC Objective not the same as subjective = ARC – Subjective is 0 = harmonious – Subjective not 0 but less than objective = unharmonious

Red Glass Test

When testing for diplopia, the clinician can determine the subjective localization of a single object point imaged on the fovea of the fixating eye and an extrafoveal retinal area in the other eye. With diplopia it can be difficult for the patient to determine whether the images are crossed or uncrossed, so in the red glass test, the two visual fields are differentiated with a red glass placed in front of one eye. The patient fixates on a small light source and states whether the red light is to the right, left, above, or below the white light. By convention, the red glass filter should always be placed before the fixating eye, but the test should be repeated with the red filter in front of the other eye to check for changes in deviation. In esotropia, the fixation point image of the deviating eye falls on the retina nasal to the fovea, producing *uncrossed diplopia*. In exotropia, the image of the fixation point in the deviated eye falls on the retinal area temporal to the fovea, producing *crossed diplopia*. In NRC, double images should be properly oriented and also have a distance equal to the angle of strabismus.

Worth 4-Dot Test

In the Worth 4-dot (W4D) test, a red lens is worn over one eye (usually the right eye by convention) and a green lens is worn over the other eye. Looking through the red-green glasses, the patient views a box with four lights (one red, two green, one white) at 6 m and 33 cm. If four lights are seen, the patient has fusion capability. Central fusion is tested at distance and peripheral fusion is tested at near. If five lights are seen, the patient has diplopia and no fusion. If only two or three lights are seen, the patient is suppressing one eye. When testing the patient for monofixation syndrome, the W4D test can be used to demonstrate both the presence of peripheral fusion and the absence of foveal bifixation. The standard W4D flashlight projects onto a central retinal area of 1° or less when viewed at 6 m, well within the 1–4° scotoma characteristic of monofixation syndrome. Patients with monofixation syndrome will report two or three lights when viewing at 6 m, depending on their ocular fixation preference. As the W4D flashlight is brought closer, the dots begin to project on the peripheral retina outside of the central scotoma until a fusion response (four lights) is obtained by 33 cm [3] (Fig. 2.4).

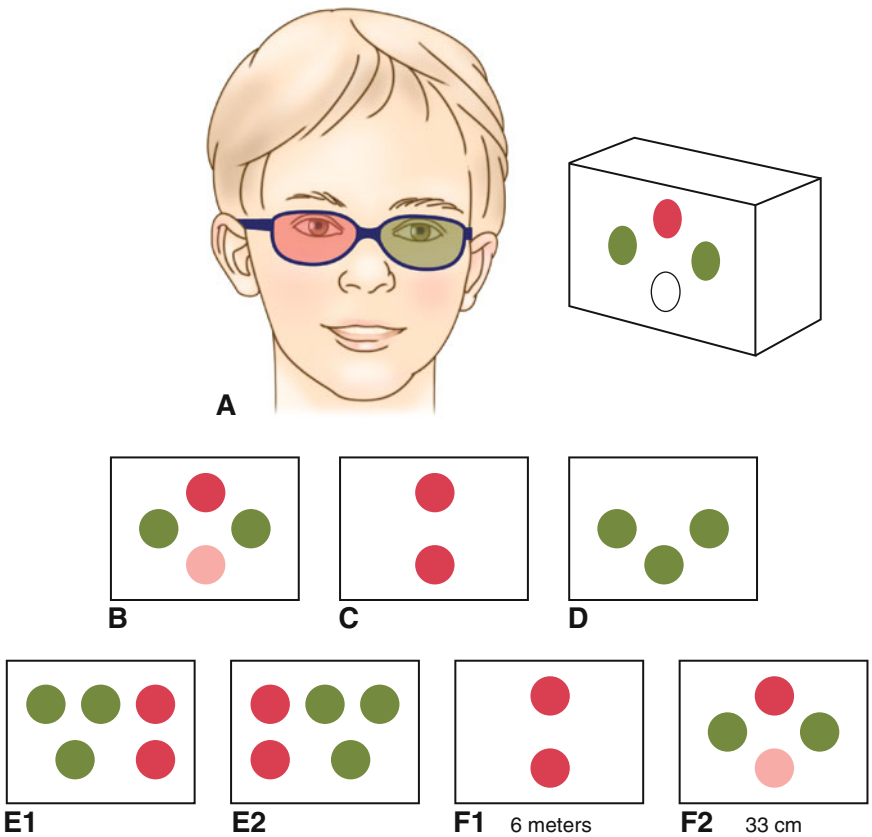

Fig. 2.4 Worth 4-dot testing. By convention, the *red lens* is placed over the right eye. (**A**) The patient views a *box* with four lights (one *red*, two *green*, and one *white*) at 6 m and 33 cm. Depending on the ocular dominance, the light at 6 o'clock is viewed as *light green* (*left dominant*) or *pink* (*right dominant*). The possible responses are as follows: (**B**) patient sees all lights, peripheral fusion with orthophoria or strabismus with anomalous retinal correspondence (ARC). (**C**) The patient sees two *red lights* indicating suppression of the left eye. (**D**) The patient sees three *green lights* indicating suppression of the right eye. (**E**) The patient sees five lights (diplopia). (**E1**) Uncrossed diplopia in esotropia or (**E2**) crossed diplopia in exotropia. (**F**) Monofixation syndrome (central suppression with peripheral fusion). (**F1**) Testing at 6 m reveals suppression of the left eye. (**F2**) Testing at 33 cm reveals normal testing because testing subtends an angle outside of suppression scotoma

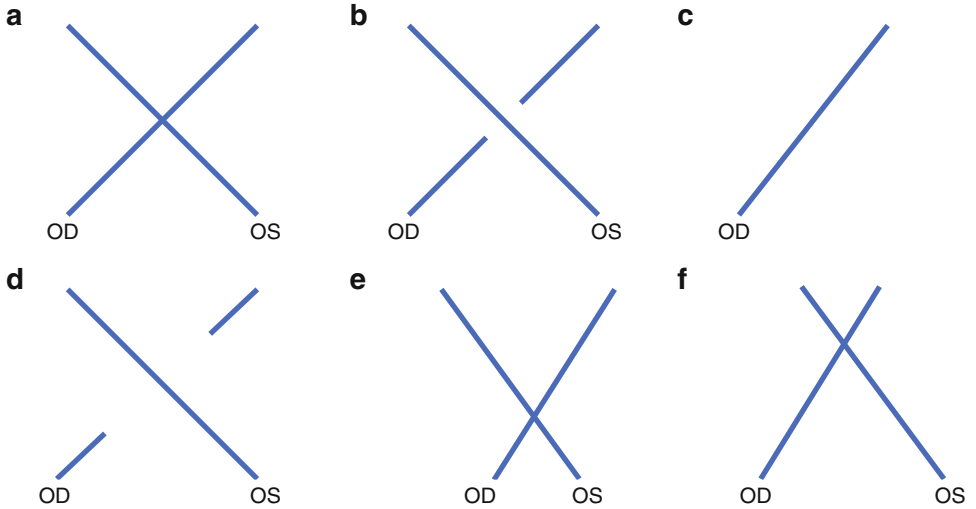

Fig. 2.5 Results of testing for suppression and retinal correspondence with Bagolini lenses. (**a**) Orthophoria with normal retinal correspondence. Cover testing results in no shift. (**b**) Monofixation syndrome with left eye fixating. There is a small central scotoma under binocular conditions in the right eye. Cover testing is likely to reveal either no shift or a small microtropia (<8 PD). Alternate cover testing would likely reveal a larger phoria in the setting of strabismus. If the etiology is anisometropia without strabismus, no shift would be observed on either test. (**c**) Total suppression of the left eye, right eye dominant. Cover testing would likely reveal a shift. (**d**) Anomalous retinal correspondence (ARC) with suppression (large scotoma in right eye under binocular conditions). Cover testing would likely reveal a large shift (>10 PD). The deviation could be esotropia or exotropia. (**e**) Exotropia with diplopia (no suppression) and NRC. A shift is likely observed on cover testing. (**f**) Esotropia with diplopia (no suppression) and NRC. A shift is likely observed on cover testing

Bagolini Striated Lenses

Bagolini lenses are the least dissociating method to detect ARC, but they require a high level of cooperation and understanding. Bagolini striated lenses have no dioptric power and have narrow striations running parallel in one median. The lenses cause the fixation light to appear as an elongated streak or line. The lenses are arranged at 90° to each other (usually 135° OD and 45° OS), so with both eyes open, a point source of light is perceived as a cross. Bagolini lenses are useful in detecting ARC in a patient with strabismus on Hirschberg testing but no refixation movement on cover testing. If the Bagolini glasses result is normal with an obvious strabismic deviation, then ARC must be present [8] (Fig. 2.5).

4 Δ Base-Out Prism Test

The 4 Δ base-out prism test helps determine whether a patient has bifoveal fusion or a small suppression scotoma under binocular conditions. A 4 Δ base-out prism is held before one eye and then the other during binocular viewing, and motor responses are observed. Patients with bifixation usually show a version (bilateral) movement away from the eye covered by the prism followed by a unilateral fusional convergence movement of the eye not behind the prism. A similar response occurs regardless of which eye the prism is placed over. Often, no movement is seen in patients with monofixation syndrome when the prism is placed before the nonfixating eye. A refixation version movement is seen when the prism is placed before the fixating eye, but the expected fusional convergence does not occur. The 4 Δ base-out prism test is the least reliable method to test for the presence of a macular scotoma. Patients with monofixation syndrome may switch fixation each time the prism is inserted and show no movement, regardless of which eye is tested.

Afterimage Test

Afterimage test is performed by covering a camera flash with black paper and then exposing a narrow slit, the center of which is covered with black tape to serve as a fixation point and to protect the fovea from exposure. Each macula is stimulated or marked with a different afterimage of the flash, horizontal in one eye and vertical in the other. The patient is then asked to draw the relative positions of the perceived afterimages. With NRC, the patient will see a cross with a single hole in the center. If the vertical afterimage appears to the left or right of the hole of the horizontal afterimage, this displacement implies that the two foveas have different visual directions, or ARC. Because suppression scotomata extend along the horizontal retinal meridian and may obscure most of the horizontal afterimage, the vertical afterimage is placed on the deviating eye and the horizontal afterimage on the fixating eye (Fig. 2.6).

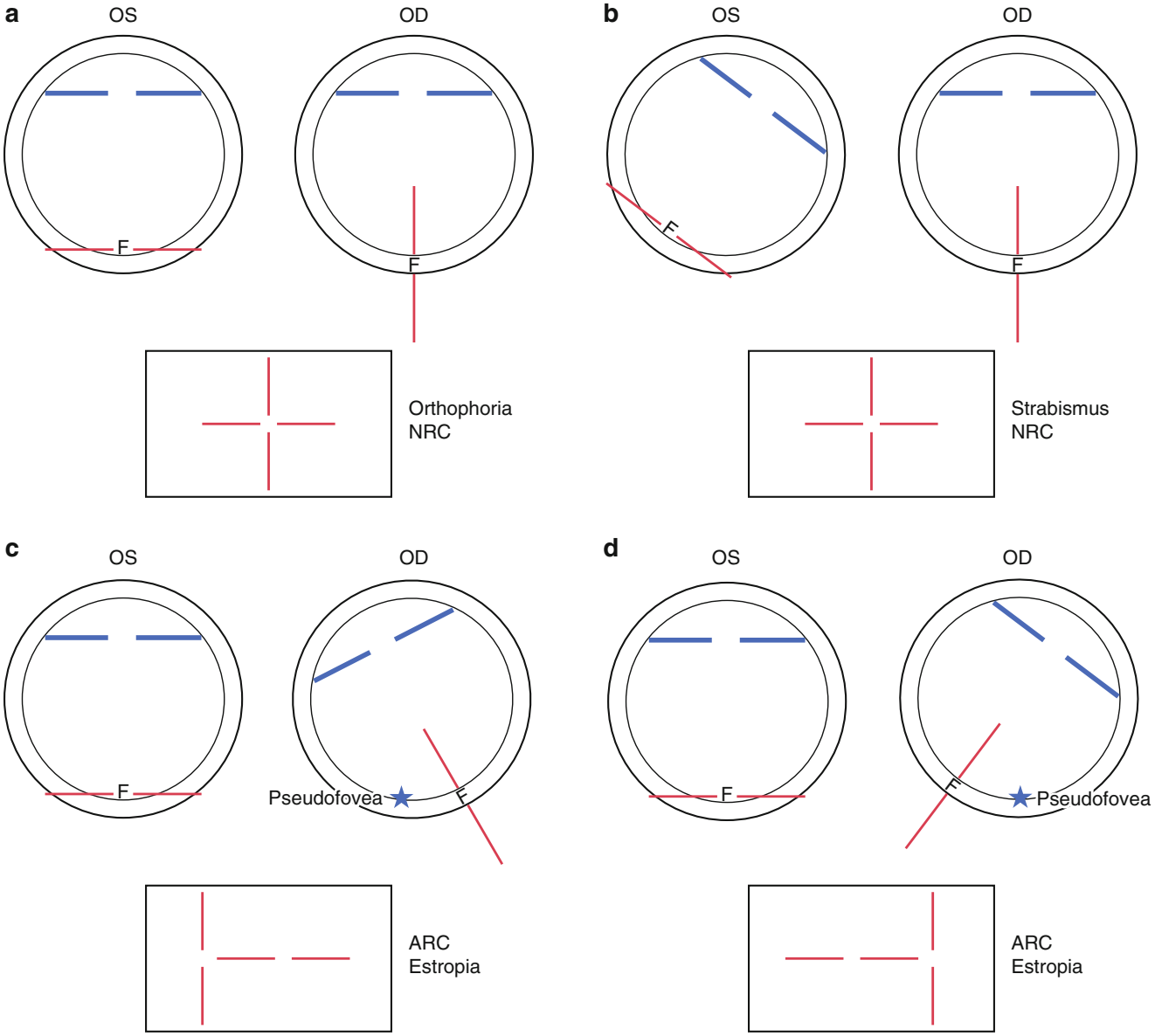

Fig. 2.6 Afterimage testing for anomalous retinal correspondence. (**a**) Normal localization and normal retinal correspondence (NRC) in orthophoric patient. (**b**) Strabismus (can be any type—hypertropia, esotropia, exotropia) and NRC. (**c**) Esotropia with ARC (anomalous crossed). (**d**) Exotropia with ARC (anomalous uncrossed)

Haploscopic Tests

Haploscopic tests have two fixation targets, one for each eye, and the targets can be moved separately to align with each fovea. An amblyoscope, or synoptophore, is a type of haploscope that utilizes mirrors to measure horizontal, vertical, and torsional deviations; diagnose suppression and retinal correspondence; and determine fusional amplitudes and the degree of stereopsis. While previously considered to be one of the mainstays of strabismus management, its use has declined over the years.

Tests of Stereopsis

Patients with measurable stereopsis must have sensory fusion; hence if the stereopsis test is normal, then sensory fusion tests are unnecessary. Patients with manifest strabismus are unlikely to have measureable stereopsis. The results of tests of stereopsis are quite helpful in determining when to intervene in patients with intermittent deviations or distance/near deviations. Reduction or loss of stereo acuity indicates decreased control of strabismus, which results in diminished fusional control and a potential

loss of binocularity. Stereopsis measurement should be performed before the eyes are dissociated by other tests such as cover tests or W4D.

Titmus Stereo Test

With the Titmus stereo test, the patient wears polarized glasses and views a vectograph made of Polaroid material on which two targets are imprinted so that each target is polarized at 90° with respect to the other. If the patient sees the targets stereoscopically, they appear to be elevated off of the page. Titmus test measures 3000 s of arc with the fly, 100–400 s of arc with the animals, and 800–40 s of arc with the circles.

Random Dot Stereoacuity Test

Random dot stereograms consist of two fields of randomly scattered dots or specks, with one field of dots projected to each eye separately through polarized glasses. Each field of random dots is identical except for a group of the dots that have been displaced nasally, which stimulates bitemporal retinal points and produces the perception that this area of dots is coming up off the page. Random dot tests have almost no monocular clues resulting in few false-positive responses [2].

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Part II

Refractive Errors

3 Management of Asymptomatic Hypermetropia in Infancy and Early Childhood

Virginia Miraldi Utz and Elias I. Traboulsi

Abstract

Controversy exists as to the benefit of early refractive correction of hypermetropia in asymptomatic patients in relation to the development of strabismus and amblyopia. A combination of historical, examination findings and cycloplegic refraction can aid in the decision to prescribe glasses in this group of patients. The physician should initially determine if risk factors for amblyopia or strabismus (i.e., history of prematurity, developmental delay, or family history of amblyopia or strabismus in a first-degree relative) are present. A complete ophthalmologic examination including dynamic and cycloplegic retinoscopy should be performed. Subsequently, the decision to treat an asymptomatic patient should be based on clinical findings and risk factors present. The results of ongoing clinical trials will help to clarify this controversy and to provide evidence-based management for the treatment of asymptomatic hypermetropia.

Keywords

Hypermetropia • Refractive error • Strabismus • Accommodative esotropia • Amblyopia

Introduction

Most young children are mildly to moderately hypermetropic secondary to a combination of axial length, corneal curvature, and lenticular power. The magnitude of hypermetropia gradually decreases toward emmetropia with age. Because healthy infants and children have the ability to accommodate up to 12 diopters (D) or more [1], refractive correction is not prescribed for low to moderate hypermetropia in those who do not have asthenopic symptoms or accommodative esotropia [2]. In contrast, if the child has an esodeviation, the recommendation has been to correct the full hypermetropic cycloplegic refractive error [3]. Likewise, in patients with hypermetropic anisometropia with a difference in refraction of ≥+1.50 between eyes, at least partial refractive correction of the spherical correction in each eye should be prescribed to prevent the development of amblyopia [4].

High hypermetropia has been associated with the development of strabismus and amblyopia; however, the threshold for initiation of refractive correction is less well defined. Early studies by Ingram and colleagues compared the incidence of accommodative esotropia in infants screened at 6 months with a refractive error greater than +4.00 D who either received glasses or not [5]. The incidence of strabismus was not statistically different between the treated and untreated group; however, consistent glasses wear was associated with a decreased incidence of refractive amblyopia [5]. In contrast, the Cambridge Infant Screening Program [6] demonstrated decreased incidence of amblyopia and

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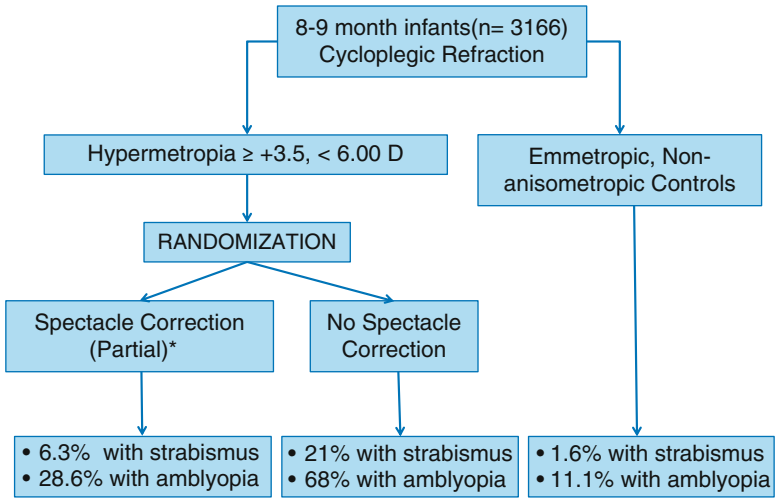

Fig. 3.1 Results of the Cambridge Infant Screening Program [6]. Infants were screened for refractive error by cycloplegic refraction at 8–9 months and followed for 7 years. The percentage of patients who developed strabismus and amblyopia are compared among those with hypermetropia >+3.50 and <+6.00 treated with refractive correction versus those who were observed as compared to emmetropic controls

strabismus in moderate hypermetropic treated with refractive correction (Fig. 3.1). In this last study, a total of 3166 infants were screened for refractive errors at ages 8–9 months and followed until the age of 7 years [6]. Approximately 5 % had hypermetropia greater than 3.5 D, with average refractive error of +1.50 D at age 8–9 months [6]. The patients with cycloplegic refractive errors ≥+3.50 and ≤+6.00 were randomly assigned to observation or treatment, which consisted of partial spectacle correction of sphere minus 1.00 D, to minimize risk of child being overcorrected in between visits. The incidence of both amblyopia and strabismus was reduced in the treatment group as compared to the untreated moderate hypermetropes (Fig. 3.1) [6]. However, the treatment group still had an increased incidence of amblyopia and strabismus as compared to emmetropic controls (Fig. 3.1).

Current Practice

The decision to prescribe refractive correction in asymptomatic hypermetropia is largely based on the magnitude of hypermetropia relative to patient age and is guided by preferred practice patterns and surveys of prescribing practices [2, 3, 7]. Lyons and colleagues conducted a survey of prescribing practices for optometrists and ophthalmologists. While prescribing practices for moderate levels of hypermetropia (+3.00 to +4.00) varied among specialists, young children with higher degrees of hypermetropia (>+5.00 D) and without strabismus or amblyopia were prescribed at least a partial correction by most practitioners [7]. Miller and Harvey published a survey of members of the American Association for Pediatric Ophthalmology and Strabismus and found that 75 % would prescribe glasses for hypermetropia of +5.50 (<2 years), +5.00 (between 2 and 4 years), and +4.50 (between 4 and 7 years) [8]. The American Academy of Ophthalmology preferred practice pattern has similar guidelines to the practices in the AAPOS survey; however, there is no numerical threshold for patients older than 3 years and glasses are recommended if the patient is symptomatic (e.g., visual acuity reduced) [2]. Note in a cohort of 6-year-olds, hypermetropic refractive error did not reduce visual acuity until the refractive error exceeded +4.00 [9].

In addition to preferred practice patterns, screening programs have been developed to detect significant refractive errors. The American Association for Pediatric Ophthalmology and Strabismus (AAPOS) vision screening committee has proposed age-based criteria for automated screening (Table 3.1) [11].

Thus, the preferred practice patterns provide a framework for consideration of refractive correction in patients with

Table 3.1 Prescribing practices and screening guidelines for patients with hypermetropia

	Age < 1	1–2 years	2–4 years	4–7 years
Miller and Harvey [8]	+5.00 (50 %)		+4.00 (50 %)	+4.00 (50 %)
	+5.50 (75 %)		+5.00 (75 %)	+4.50 (75 %)
AAO PPP [2]	≥+6.00	≥+5.00	≥+4.50	No numerical threshold, consider if improves VA
AAPOS policy statement [10]	Consider for any child >+3.50 hypermetropia in any meridian			
AAPOS vision screening committee[a] [11]	≥+4.50		≥+4.00	≥+3.50

Percentages refer to percentages of professionals who would prescribe refractive correction at specific hypermetropic refractive errors
[a]These are automated screening guidelines, not prescribing recommendations
AAO American Academy of Ophthalmology, *PPP* preferred practice patterns, *AAPOS* American Association for Pediatric Ophthalmology and Strabismus

asymptomatic hypermetropia. Currently, the Pediatric Eye Disease Investigator Group [PEDIG] is exploring the natural history of this patient group and randomizing asymptomatic children to glasses versus observation in the Hypermetropia Treatment Study 1 (HTS1) (Available: http://clinicaltrials.gov/ct2/show/NCT01515475). The results of this trial will hopefully provide evidence-based guidelines for treating hypermetropia.

Considerations in Prescribing

In the evaluation of the asymptomatic hypermetrope, certain historical and clinical factors may aid in the practitioner's decision to prescribe or not to prescribe glasses. When obtaining the history, risk factors for amblyopia and strabismus should be assessed including a history of prematurity, maternal substance abuse during pregnancy, developmental delay, or Down syndrome. Patients with Down syndrome may have hypoaccommodation placing them at higher risk for an esodeviation at near and may benefit from correction of lower degrees of hypermetropia. (Please see Chap. 69.) The clinician should also inquire as to whether there is a family history of strabismus, especially accommodative esotropia, anisometropia, or amblyopia in a first-degree relative, as this places the patient at high risk for the development of strabismus and amblyopia.

The examination should be comprehensive and should include best-corrected visual acuity, assessment of extraocular movements, motor alignment, stereopsis, and pupillary reaction. Dynamic retinoscopy should be performed to assess for hypoaccommodation or accommodative lag. (See Chap. 73 on Performing Dynamic Retinoscopy.) Anterior segment and posterior segment of the eye should be assessed for any abnormalities. Lastly, cycloplegic refraction should be performed. If at all possible, the cycloplegic refraction should be subjectively confirmed by testing the child's monocular vision with the cycloplegic refraction in place. A manifest cycloplegic refraction may be performed to obtain the best-corrected visual acuity (Fig. 3.2).

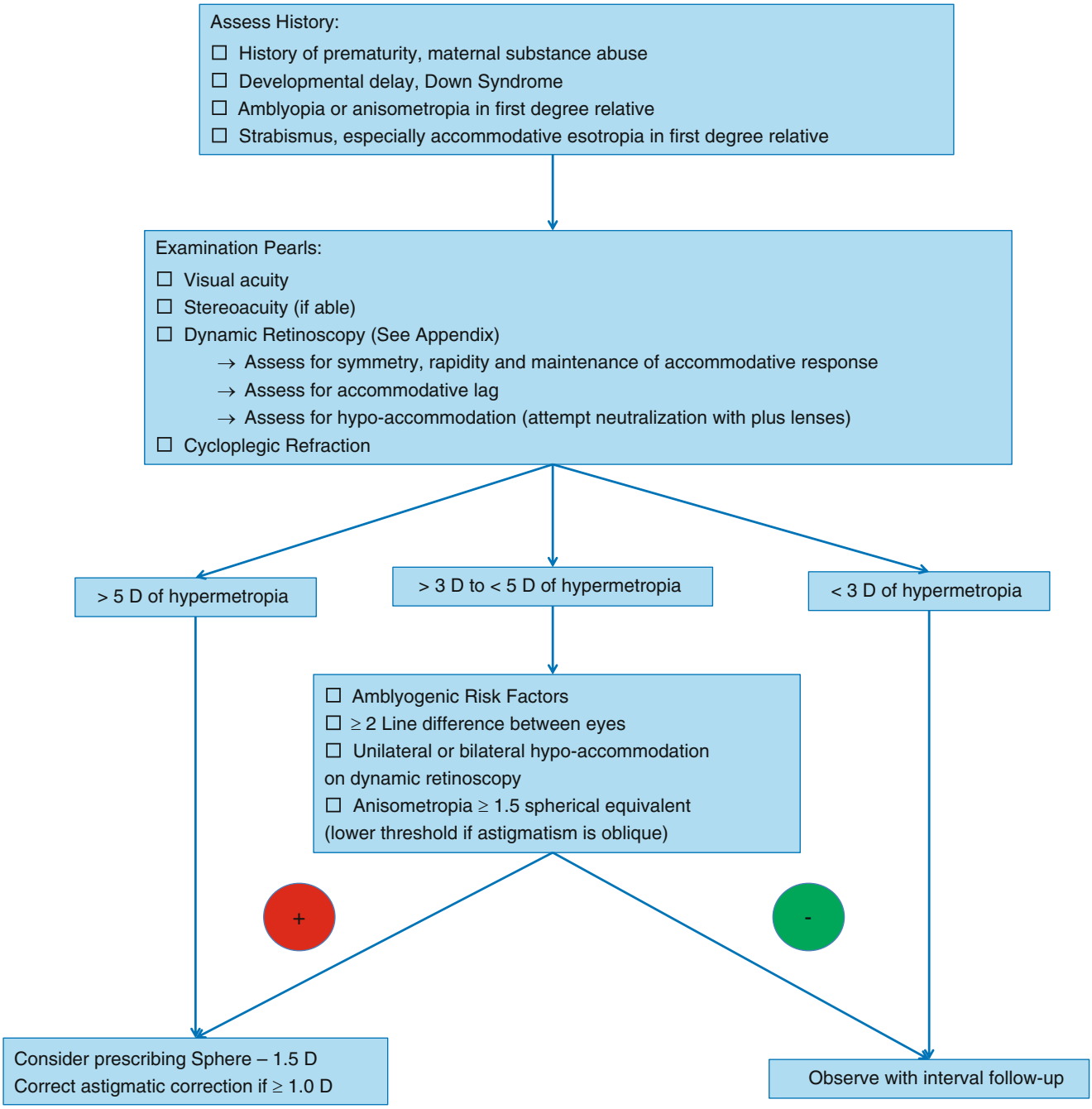

Fig. 3.2 Algorithm to evaluation and management of hypermetropia

Case Studies

Case 1

An 8-month-old healthy girl presents with history of "intermittent crossing" since birth. Birth, past medical and family history is noncontributory.

Key Examination Findings

Visual acuity: Central, steady, and maintained (CSM) in each eye
Anterior segment examination: Wide nasal bridge and prominent epicanthal folds
Sensorimotor examination:
Versions and ductions: Full OU
Alignment: Orthophoric (Nsc, alternate cover testing)
Stereoacuity: Unable to test
Dynamic retinoscopy: Inconclusive
Cycloplegic refraction: +6.00 OD and +7.00 OS
Dilated fundus examination: Unremarkable

Assessment: This patient has pseudoesotropia; however, given the high hypermetropia, well-controlled intermittent esotropia cannot be completely excluded. The patient is also mildly anisometropic.

Management Options at This Time Include

- Observation
- Prescription of full cycloplegic refraction
- Prescription of partial cycloplegic refraction

Plan: Because of the high hypermetropia and absence of esodeviation on examination, partial correction of the cycloplegic refraction was prescribed (+4.50 OD, +5.50 OS). The hypermetropic correction was symmetrically reduced by +1.50 D as per the Pediatric Eye Disease Investigator Group [12]. Follow-up was scheduled in 4 months.

Interval history (patient age, 12 months): The patient wore glasses for 2 months only and then refused to wear them. No esodeviation has been observed by parents.

Key Examination Findings

Visual acuity: CSM in each eye
Sensorimotor examination:
Versions and ductions: Full OU
Alignment: Near (sc) orthophoria by alternate cover testing
Dynamic retinoscopy: Inconclusive

CRx confirmed

Assessment: Asymptomatic hypermetropia

Plan: Continue wearing glasses that partially correct the cycloplegic refraction. Monitor for amblyopia and esodeviation. Follow up in 6 months.

Interval history: Patient was lost to follow-up and returns 1 year later (now age 2). She is not wearing glasses.
Visual acuity: (Allen, single optotype)
OD: 20/40 (tested first). OS: Not cooperative, objected to covering OD
Alignment: Orthophoric
Dynamic retinoscopy (SC): Normal OD, hypoaccommodation OS
Cycloplegic refraction: +5.00 OD and +6.00 +0.50 × 100 OS

Assessment: History of high hypermetropia, hypoaccommodation OS. Possible amblyopia OS

Management Options

- Observation with short interval follow-up (test OS first in the next visit)
- Full cycloplegic refraction
- Partial cycloplegic refraction

Plan: Partial cycloplegic refraction prescribed (+3.50 OD, +4.50 + 0.50 × 100 OS). Follow up in 3 months.

Interval history: Patient wearing glasses full-time since last visit.

Key Examination Findings

Visual acuity with correction:
OD: 20/30 (Allen). OS: 20/70 (Allen), tested first
Dynamic retinoscopy (with correction): Brisk and sustained OU

Assessment: High hypermetropia and amblyopia OS

Management Options

- Continue refractive correction, and if visual acuity improvement in the left eye plateaus, consider penalization therapy.
- Continue refractive correction and begin patching the right eye 2 h/day.

Plan: Discussion between the ophthalmologist and family resulted in the initiation of occlusive therapy at this visit.

Interval history (30 months): Patient wearing refractive correction full-time and patching 2 h/day.

(continued)

Key Examination Findings

Visual acuity with correction: (single bracketed HOTV)
OD: 20/20. OS: 20/20
Stereoacuity (Randot): 40″ arc

Assessment: High hypermetropia and amblyopia OS resolved

Plan: Continue wearing eyeglasses.

Clinical Synopsis

This is a case of high hypermetropia with pseudoesotropia, with anisometropia of +1.00 D (≥1.5 D generally considered amblyogenic). Partial refractive correction was prescribed for both the high hypermetropia and anisometropia. However, adherence to glasses was poor until the development of amblyopia in the left eye. The amblyopic eye exhibited hypoaccommodation in the absence of refractive correction, which subsequently resolved with refractive correction. The amblyopia was treated initially with full-time refractive correction alone followed by occlusive therapy. The eventual visual outcome was satisfactory.

Case 2

A 3-year-old healthy boy presented for initial examination because of a family history of strabismus and amblyopia in first-degree relatives. He has a younger brother with accommodative esotropia and his father had anisometropic amblyopia. His parents do not have any concerns about his vision and have not noted any strabismus.

Key Examination Findings

Visual acuity: (isolated bracketed HOTV)
OD: 20/25. OS: 20/25

Sensorimotor examination:
Versions and ductions: Full OU
Alignment: (Cover test, alternate cover test)
Distance and near (sc): Orthophoria
Stereoacuity: Unable to test
Cycloplegic refraction: +4.25 + 0.50 × 090 OU
Dilated fundus examination: Normal

Assessment: 3-year-old with family history of strabismus and amblyopia in first-degree relatives and moderate asymptomatic hypermetropia

Management Options

- Observe with periodic follow-up.
- Prescribe partial cycloplegic refraction.
- Prescribe full cycloplegic refraction.

Plan: Observe with interval follow-up of 6 months.

Note: Because of the sibling with accommodative esotropia, dynamic retinoscopy would have been helpful in the assessment of this patient. (See Chapter 73 on Dynamic Retinoscopy.) **However, it was not completed on the initial examination.**

6-month interval history (current age, 3.5 years): Parents report no problems.
Visual acuity: (isolated bracketed HOTV)
OD: 20/40 (tested first). OS: 20/25

Sensorimotor examination:
Versions and ductions: Full OU
Alignment: (Cover test, alternate cover test)
Distance and near (sc): Orthophoria
Stereoacuity: Unable to test
Dynamic retinoscopy: Distance target, "with motion"
Near target: Accommodative lag ("with" motion initially observed with slow transition to appropriate "against" motion)
Plus lenses added until no accommodative lag observed (≈+3.00)
Cycloplegic refraction: +4.25 + 0.50 × 090 OU

Assessment: Accommodative lag, but no esodeviation observed in the setting of moderate hypermetropia and family history of strabismus and amblyopia. Visual acuity difference of two Snellen lines

Management Options

- Observe with interval follow-up.
- Prescribe partial cycloplegic refraction.
- Prescribe full cycloplegic refraction.

Plan: Prescribed partial cycloplegic refraction (+2.75+0.50 × 090 OU). Follow up in 3 months to retest vision.

Interval follow-up (current age, 3 years and 9 months): Wearing glasses well, no complaints

Visual acuity with correction: (isolated bracketed HOTV)
OD: 20/20. OS: 20/20
Sensorimotor examination:

(continued)

Versions and ductions: Full OU
Alignment: (Cover test, alternate cover test)
Distance and near (sc): Orthophoria
Stereoacuity: 3/3 animals, did not understand Randot
Dynamic retinoscopy in correction: Brisk and sustained OU

Assessment: 3-year-old doing well in partial refractive correction, normal accommodation in glasses, and equal visual acuity

Plan: Interval follow-up

Clinical Synopsis

This is a patient with moderate hypermetropia and a strong family history of amblyopia and strabismus in first-degree relatives. He was initially observed, and there was concern for amblyopia in the right eye at the subsequent visit. Dynamic retinoscopy revealed hypoaccommodation and was a key examination component. He was successfully treated with partial refractive correction.

Conclusions

Controversy exists as to the benefit of early correction of hypermetropia to prevent the development of strabismus and amblyopia. Currently, published preferred prescribing practices are utilized to guide the clinician. Risk factors for strabismus and amblyopia should be assessed, and a comprehensive ophthalmologic examination with cycloplegic refraction and dynamic retinoscopy should be performed (Fig. 3.2). In some cases, the patient may appear to be asymptomatic; however, examination findings such as hypoaccommodation may dictate a lower threshold for prescribing corrective glasses. The results of the HTS1 trial will likely help to clarify this controversy and provide evidence-based management for the asymptomatic patient with hypermetropia.

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Myopia

4

Timothy E. Hug

Abstract

At birth, the eye is short and hyperopic, and while hyperopia regresses in the first 3–5 years of life, some eyes progress toward further myopia. Myopia can be associated with increased axial length, steep corneal curvature, or lenticular changes. Contributing factors to myopia and its progression include hereditary factors, environmental factors, as well as concurrent ocular and systemic disorders. Depending on patient age and degree of myopia, various modalities of refractive correction can be considered to aid in visual development and to meet the visual requirements of the patient. Current research is focused on understanding the underlying genetics of myopia and on developing interventions to reduce myopic progression in children.

Keywords

Myopia • Refractive error • Prematurity • Amblyopia

The Problem

In the myopic eye, the image from distant objects is focused in front of the retina (Fig. 4.1). Two forms of myopia exist:

1. Refractive myopia: myopia secondary to an abnormal curvature of cornea and/or lens or refractive index of the lens. The refractive media of the eye have "too much focusing power" relative to axial length.
2. Axial myopia: the axial length is too long for the optics (refractive power) of the eye, again leading to the image being focused in front of the retina.

Both forms of myopia are correctable with glasses or other forms of myopic correction that diverge light and effectively reduce vergence to allow the image of distant objects to be focused on the retina. Light from distance (infinity) has no vergence power, and when imaged through an uncorrected myopic eye, the eye's optical power will focus the image in front of the retina. The addition of diverging lenses will change the focal point of this distance light to achieve a focal point that coincides with the retina. Light from objects at near is already diverging and in an uncorrected myopic eye will focus closer to the retina. If the uncorrected myopic eye's focal point is placed conjugate with a near object, that near object will be focused on the retina. Thus an uncorrected myopic eye may see near objects in focus. Once compensatory lenses are placed in front of a myopic eye, the patient can accommodate to refocus the diverging light from near objects.

In the United States, the prevalence of myopia in the pediatric population based on age is as follows: 5–7 years, 3 %; 8–10 years, 8 %; 11–12 years, 14 %; and 12–17 years, 25 % [1].

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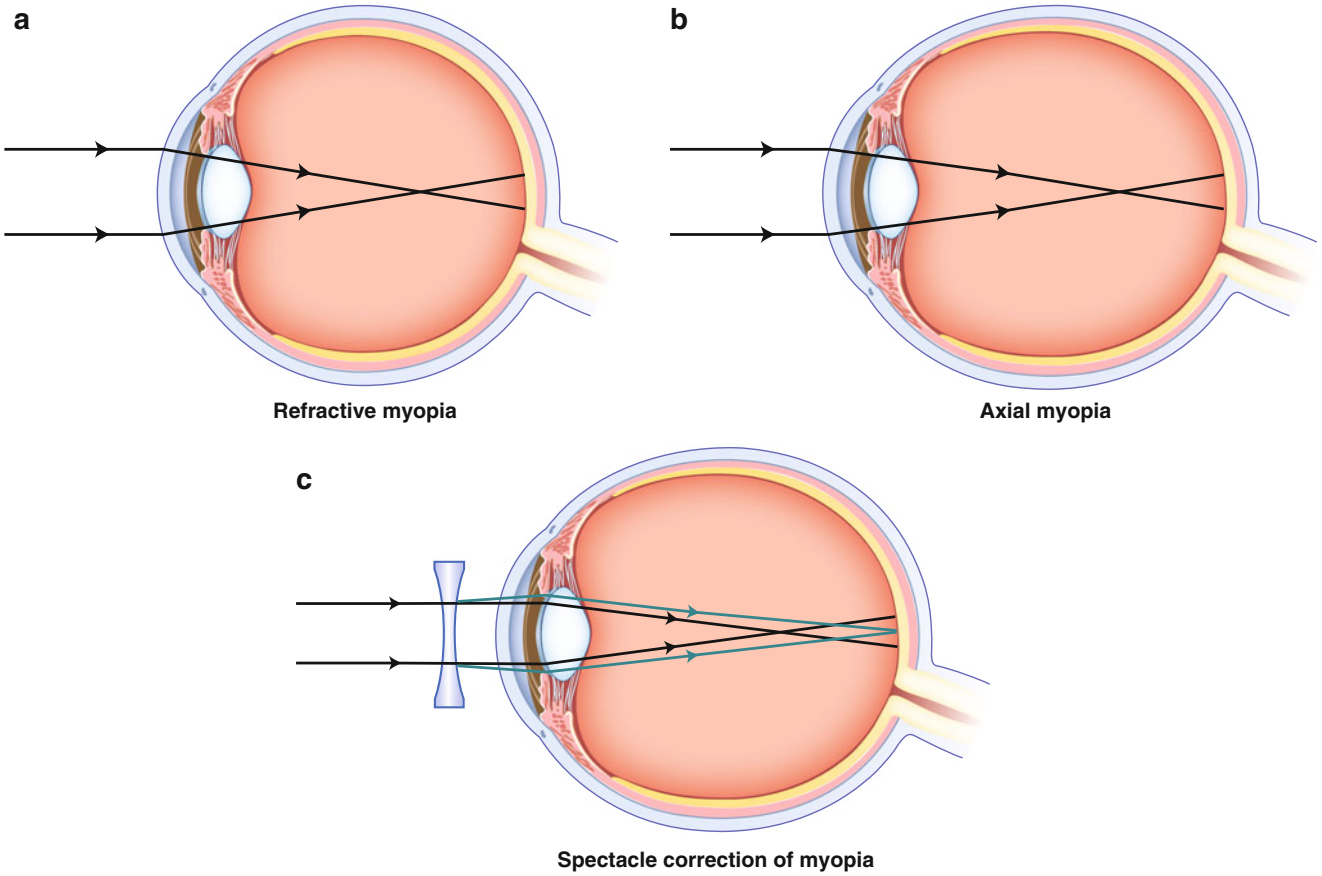

Fig. 4.1 Myopia can be secondary to (**a**) increased refractive power of the cornea and/or lens leading to refractive myopia or (**b**) increased axial length. (**c**) Divergent lenses allow the image to be focused on the retina in both forms of myopia

Normal Growth and Development of the Human Eye

In the human eye, myopia is associated with steep corneal curvature, elongated axial length, or increased lenticular refractive power. At birth, the corneal power is approximately 52 D, flattening to 46 D by 6 months of age and reaching adult curvature of 42–44 D by age 12 years [2]. Newborn ocular axial length is between 15 and 17 mm and rapidly increases in the first 6 months to 19–21 mm. Approximately 2 mm of growth occurs over the next 10 years of life. Lenticular power also changes rapidly in the first 6–12 months of life from 35 diopters to 27 diopters and continues to decrease in a more gradual fashion (24 D–21 D) from ages 2–10 years. Emmetropization refers to the changes in the refractive power of the anterior segment and the axial length of the eye to reach emmetropia [3]. The changes in the optical components during childhood and adolescence are more gradual and can lead to the development of myopia.

Ocular and Systemic Conditions Associated with Myopia

Ocular and systemic abnormalities can lead directly or indirectly to myopia. Collagen and connective tissue disorders such as Stickler syndrome and Marfan syndrome [4] may lead to an elongation of the eye, creating axial myopia. The elevated intraocular pressure in young infants with infantile glaucoma causes global elongation from decreased scleral rigidity leading to axial myopia. Corneal disorders such as keratoconus will create a steepening of the corneal curvature and in early stages may create myopic refractive changes. Lenticular disorders, such as lentiglobus, or spherophakia can induce myopia due to the increase in lens power as a result of the rounded or distorted lens curvatures (Table 4.1).

Retinopathy of prematurity, especially in cases severe enough to require treatment (laser photocoagulation or cryotherapy), has been linked with the development of high myopia [4, 5].

Table 4.1 Differential diagnosis of ocular and systemic conditions leading to myopia

Ocular and systemic conditions associated with myopia	Examples
Pathologic elongation of globe	Infantile glaucoma, Stickler syndrome
Cornea	Keratoconus; corneal ectasia; contact lens warpage
Lens • Ectopia lentis • Spherophakia • Cataract formation	Ectopia lentis: trauma, Marfan syndrome, homocystinuria, sulfite oxidase deficiency, hyperlysinemia, ectopia lentis et pupillae Spherophakia: Marfan syndrome, Weill-Marchesani syndrome, Alport syndrome, Cohen syndrome
Ciliary body edema/shift	Medications: topiramate, antihistamines, sulfonamides Ciliary body effusion: infectious and inflammatory disorders

In a study of eyes that had high-risk pre-threshold ROP, two-thirds of patients developed myopia in the preschool and early school years [5]. Other factors associated with myopia include genetic [6] and environmental factors [7].

Case Examples

Case Study 1

Early Development of Mild Myopia

A 3-year-old boy presents for a routine comprehensive eye exam. His parents have no concerns about his vision or eye health. Both parents developed myopia in childhood. His uncorrected distance visual acuity is 20/40 (using Allen pictures single optotype). His alternate cover testing revealed orthophoria at distance and near fixation, with near stereopsis testing of 40 s arc. There were no motility disorders or restrictions with versions and ductions. His cycloplegic refraction was: OD −0.75 DS and OS −0.75 DS, with corrected visual acuity of 20/20 in each eye. His dilated fundus exam was unremarkable. No glasses were prescribed at this visit as the uncorrected myopia was not affecting this patient's daily living and was not amblyogenic. A follow-up exam in 1 year was recommended.

Case Study 2

Moderate Myopia Associated with Retinopathy of Prematurity

This 18-month-old infant, born at 27 weeks' gestation, had a history of bilateral ROP and had undergone post-laser treatment in both eyes. Parents report no visual concerns. The patient's uncorrected near vision was noted to be central, steady, and maintained (CSM) in each eye. Alternate cover testing revealed orthophoria at near. The cycloplegic refraction was OD −6.50 + 1.00 × 090 and OS −6.00 + 1.00 × 090. Indirect ophthalmoscopy revealed stable retinal scarring from previous laser treatment in the right eye from 7:00 to 12:00 and in the left eye from 12:00 to 5:00. Glasses for the cycloplegic refraction were prescribed at this visit, due to the significant amount of myopia and the tendency for progression.

One of the most common refractive outcomes of advanced ROP is myopia [8], which can occur in cases of regressed or treated retinopathy. A myopic shift rate of 4.7 D/year compared to 0.004 D/year was reported in these groups [9].

Case Study 3

Myopia Associated with Systemic Conditions (Stickler Syndrome)

A 2-year-old boy was referred for evaluation with a history of high myopia (current glasses, −7.50 D OU). He had a history of pulmonary valve stenosis, but no hearing loss or cleft palate. His ears were low-set and he had a flat nasal bridge and malar hypoplasia. His family history was not significant for myopia. His corrected VA was 20/60 in each eye at distance. Retinal examination revealed lattice degeneration with no retinal breaks or tears. Based on the high myopia at a young age, pulmonary valve stenosis, and dysmorphic facial features, he was referred to a geneticist for further evaluation for Stickler syndrome. He was tested for mutations in *COL2A1* and found to have a c. IVS44-2A>G mutation confirming a molecular diagnosis of Stickler syndrome.

Briefly, Stickler syndrome is an autosomal dominant connective tissue disorder leading to orofacial, skeletal, and ocular anomalies. Patients usually have congenital myopia with a range of 8–18 D secondary to axial length. The vitreous is described as "optically empty" with vitreous degeneration and liquefaction. Both typical lattice degeneration and perivascular

(continued)

lattice degeneration may be present, and there is a high risk of early retinal detachment. Glaucoma may also be associated. Therefore, this patient was followed every 4–6 months with a dilated fundus examination with scleral depression, measurement of intraocular pressure, and cycloplegic refraction. His myopia has increased progressively to −13.00 D in each eye, at his last visit at age 10.

Thus, in a young patient with high axial myopia, a diagnosis of Stickler syndrome should be considered. The clinician should inquire as to a history (or family history) of cleft palate, hearing impairment, and arthropathy. Refractive correction and regular dilated fundus examinations to screen for the presence of retinal breaks/detachment at 6-month intervals have been recommended.

Management of Myopia

A cycloplegic refraction is necessary in children, especially under the age of 12 years [8]. Uncontrolled patient accommodation during retinoscopy may lead to an overestimation of the magnitude of myopia. Symmetrical, uncorrected myopia of low magnitude usually results in distance blur, which may be asymptomatic in young, nonschool-aged patients. Myopic correction in nonschool-aged children for refractions less than −1.50 D is rarely needed [4] (Case 1). In contrast, low-grade myopia in school-aged children may warrant correction to meet the visual demands of the patient (Case 2). Correction of myopic anisometropia depends on the age of the patient, and correction should be considered if ≥−4.00 in patients <1 year of age and −3.00 in patients >1 year of age to reduce the risk of amblyopia [4].

In young children, spectacles are the most common form of myopic correction. Contact lenses become an option in older children, although risks of infection must be stressed. Limiting factors for contact lens success in children include ability to insert and remove lens, hygiene, and motivation of parent or caregiver.

Surgical refractive procedures are currently under investigation in a select group of pediatric myopic patients, with preliminary results suggesting good tolerability of the procedure and stability of the refractive error postoperatively [10].

Case 4

School-Aged Myopia

A 12-year-old girl presents with complaints of blurry vision and headaches at school. Uncorrected visual acuities at distance were OD 20/60 and OS 20/50. Alternate cover testing at distance and near (uncorrected) showed orthophoria. Manifest refraction and corrected acuities were OD −1.50 20/20 and OS −1.25 20/20. Cycloplegic refraction revealed OD −1.25 20/20 and OS −1.00 20/20. Dilated fundus exam was normal in each eye. Glasses were prescribed based on the cycloplegic refraction for full-time wear. A follow-up examination in 1 year was recommended.

Interventions To Prevent the Progression of Myopia

Interventions for preventing myopic progression have been studied for decades with a lack of significant evidence for efficacy of various treatment modalities. In the past 5–7 years, several randomized controlled studies have been published about this topic [11–15].

Early studies of spectacles with bifocals (to reduce accommodative response), rigid contact lenses, and soft contact lenses demonstrated minimal effects on reducing the progression of myopia [16]. Studies of atropine use demonstrated the largest, yet still quite modest reduction in myopic progression (up to 1 D less myopia per year [15]). Long-term benefits and outcomes remain to be determined for these treatment modalities. The clinician should be aware, in order to inform and educate families, that in all forms of myopic treatment, the myopia continues to progress but may not progress as rapidly as in the control groups [13–17].

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Management of Astigmatism in Children

5

Jason Lee and Daniele P. Saltarelli

Abstract

Uncorrected moderate to high degrees of astigmatism are risk factors for the development of refractive amblyopia in infants and young children. The magnitude of astigmatism that needs to be corrected to prevent the development of amblyopia is relatively well established and has become the basis of preferred practice patterns for prescribing glasses in the pediatric age group (Donahue SP. Prescribing spectacles in children: a pediatric ophthalmologist's approach. Optom Vis Sci. 2007;84(2):110–4). The critical period during which refractive amblyopia can be prevented or reversed with spectacle correction remains however a topic of ongoing debate. In addition to the issue of amblyopia induced by uncorrected astigmatism, the pediatric eye care provider must be aware of specific eye conditions that lead to progressive regular or irregular astigmatism in childhood. Specific diseases that affect the curvature of the cornea or lens can cause degradation of vision over time and, in some cases, may be related to important systemic diagnoses.

Keywords

Astigmatism • Irregular astigmatism • Refractive error • Refractive amblyopia • Keratoconus • Marfan syndrome

Background

Astigmatism can be subdivided into "regular" and "irregular." In regular astigmatism the shape of the cornea, the lens, or a combination of both causes light to be focused at two separate line foci rather than at a single point. This is most often due to the cornea having two principal curvatures of differing refractive powers; the axes of these corneal curvatures are typically perpendicular to one another. Regular astigmatism can usually be corrected effectively by spectacle correction. Subtypes of regular astigmatism are *with-the-rule* (plus axis at 90° ± 15°), *against-the-rule* (plus axis at 180° ± 15°), and *oblique astigmatism* (all other axes).

Irregular astigmatism arises from corneal or lenticular irregularities from a variety of causes that cannot be corrected with simple cylindrical lenses. Irregular astigmatism can be the result of corneal dystrophies and degenerations, injury to the lens or cornea, and other processes that disrupt the regular state of the cornea or lens. Conditions such as keratoconus, pellucid marginal degeneration, corneal scarring after injury or infection, and lens subluxation are examples of conditions that can result in changes to a person's refractive state such that glasses can no longer effectively provide the patient with their best-corrected visual acuity.

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Table 5.1 American Association for Pediatric Ophthalmology and Strabismus preferred practice patterns for prescribing astigmatic correction

	Refractive error		
Condition	Age <1 year	Age 1–2 years	Age 2–3 years
Astigmatism	≥3.00 diopters	≥2.50 diopters	≥2.00 diopters
Astigmatic anisometropia (without strabismus)	≥2.50 diopters	≥2.00 diopters	≥2.00 diopters

[a]Adapted from the American Association for Pediatric Ophthalmology and Strabismus PPP panel recommendations, 2012
Pediatric Eye Evaluations ppp-2012. Table 3
http://www.aao.org/preferred-practice-pattern/pediatric-eye-evaluations-ppp--september-2012. Accessed maarch 2014.

Corneal topography is very helpful in evaluating irregular astigmatism and often demonstrates non-orthogonality of the steep and flat axes. Thus, a diagnosis of irregular astigmatism can be made when the two following clinical and imaging criteria are met: (1) loss of best-corrected spectacle visual acuity with preservation of visual acuity with rigid gas permeable contact lenses and (2) topographic corneal irregularity. Patients with irregular astigmatism must often resort to specialty contact lenses or surgical procedures to achieve their best visual acuity.

Current Prescribing Recommendations

The American Academy of Ophthalmology's preferred practice pattern (PPP) for infants and young children has provided recommendations for prescribing at the following ages and degrees of astigmatism, as determined by cycloplegic retinoscopy (Table 5.1).

In 2004, a survey was completed by 412 members of the American Association for Pediatric Ophthalmology and Strabismus (AAPOS). Using results from the survey, Harvey et al. compared actual prescribing practices with the AAO PPP recommended guidelines and found close agreement, with some variance in the subcategory of birth to 1 year of age [1]. Most practitioners agree that full correction of astigmatic refractive errors is indicated in infants and toddlers to prevent the development of amblyopia.

There are a few important caveats to bear in mind regarding these prescribing guidelines for astigmatism. First, the guidelines above pertain to the vast majority of astigmatic refractive errors, which are with-the-rule (WTR) or against-the-rule (ATR). Although research is very limited on the refractive thresholds used to prescribe for *oblique* astigmatism—plus axis between 15° and 75° or 105° and 165°—it is probably preferable to correct oblique astigmatism of smaller magnitudes [2]. As an example, a 3-year-old with a cycloplegic refraction (CRx) of $plano + 1.50 \times 045\ OD$ and $plano + 1.50 \times 135\ OS$ is preferably prescribed glasses based on current recommendations. Second, if astigmatic errors of magnitudes less than those listed above are present in conjunction with amblyogenic or visually significant degrees of hyperopia or myopia, they should be fully corrected to provide the most focused image possible. For example, a 2-year-old with a CRx of $-6.00 + 1.00 \times 090\ OU$ should be prescribed the 1 diopter of astigmatism, even though 1 diopter of WTR astigmatism found in isolation does not warrant glasses in a toddler. Finally, older school-aged children with smaller degrees of astigmatism may benefit from spectacle correction if it provides relief of symptoms such as blurry vision or asthenopia. Thus, the preferred practice patterns provide guidelines for astigmatic correction, but additional careful clinical assessment determines the final decision for the prescription of glasses.

Amblyopia

The question of *when* glasses must be prescribed to prevent amblyopia from uncorrected astigmatism is not fully answered. A study by Dobson et al. [3] shows that if astigmatism is left untreated, amblyopia can permanently affect vision as early as 3–5 years of age. A more recent study by the Pediatric Eye Disease Investigator Group indicates that bilateral refractive amblyopia—including amblyopia due to bilateral astigmatism—responds successfully to treatment with spectacles in children aged 3 to <10 years of age, with 73 % of children achieving binocular visual acuities of 20/25 or better within the first year of spectacle wear [4]. These two studies highlight the importance of prescribing the appropriate glasses for infants and toddlers who meet the 2012 panel recommendations, as well as for school-aged children with no previous correction who have >2 D of astigmatism in both eyes.

Case Studies: Regular Astigmatism

Case 1

A 3-year-old girl presents after a failed vision screening at her well-child examination. Parents report no prior concern for her vision.

Relevant Exam Findings:

VA_{sc}	OD *20/50*, OS *20/50 (Lea symbols, matching)*
CRx	OD *plano + 4.00 × 090* VA *20/30*, OS *plano + 4.25 × 090* VA *20/30*

Diagnosis: Moderate to high WTR astigmatism

Treatment: Full CRx prescribed for full-time wear. Follow up 3 months to evaluate visual acuities which improved to 20/25 OU. Interval follow-up for 6 months later demonstrated visual acuities of 20/20 OU.

Case Synopsis

This child has 4 diopters of WTR astigmatism in each eye. Although her parents and she report no signs or symptoms of visual difficulties, this degree of astigmatism needs to be corrected in order to minimize the risk of developing refractive amblyopia. The patient had mild ametropic amblyopia as best-corrected visual acuity was 20/30 OU initially in full cycloplegic refraction. Full-time wear of full cycloplegic refraction led to progressive improvement of visual acuity to 20/20.

Case 2

A 2.5-year-old is referred for "abnormal red reflexes" OU. The patient's mother does not have any concerns for his visually directed behavior and does not observe any eye misalignment. There is no family history of strabismus or amblyopia.

Relevant Exam Findings:

VA_{sc}	*Central, steady, and maintained fixation* OD *and* OS *(no fixation preference detected). Lea matching attempted. Binocular VA 20/60*
CRx	OD *+0.50 + 1.75 × 180*, OS *+0.75 + 1.50 × 180*
Slit lamp exam	*No media opacities OU*
Dilated fundus exam	*Within normal limits OU*

Diagnosis: Moderate ATR astigmatism OU

Treatment: No glasses prescribed. Follow up 4–6 months to recheck. Lea symbols are given to practice at home.

Case Synopsis

The degree of astigmatism found in this case is at the limit of what would be prescribed for a 2.5-year-old child according to the 2012 panel recommendations, and prescribing glasses would be certainly acceptable in this case. The decision to monitor the child closely without glasses was prompted by age-appropriate visual behavior. Had the same prescription been found in an older school-aged child who has been moved to the front of her classroom and/or is symptomatic (e.g., gets regular headaches by the end of the school day), then prescribing the glasses would have been strongly considered.

Case 3

A 3-year-old presents after a failed vision screening at preschool. Her parents report that she likes to sit closely to the TV, and this is their only concern about her vision.

Relevant Exam Findings:

VA_{sc}	OD *20/60*, OS *20/70 (OD tested first)*
CRx	OD *plano + 1.25 × 030* VA *20/40*, OS *plano + 1.25 × 165* VA *20/40*

Diagnosis: Mild degree of oblique astigmatism OU

Treatment: Full CRx given for full-time wear. Follow up in 3 months.

Case Synopsis

Glasses were prescribed for mild astigmatism in this case because of the oblique axes. Oblique astigmatism tends to be more amblyogenic at lower degrees of magnitude. In contrast, the same degree of astigmatism WTR or ATR would generally not be an indication for glasses at age 3 years.

Case Studies: Irregular Astigmatism

Case 4

A 16-year-old presents with progressive decrease in best-corrected vision over the last 3 years together with high degrees of astigmatism and myopia.

Relevant Exam Findings:

VA_{cc}	OD *20/80*, OS *20/70 (glasses)*
CRx	OD *−3.50 + 5.25 × 098* VA *20/80*, OS *−3.50 + 5.50 × 085* VA *20/70*
Keratometry	OD *39.25/44.00 @ 008*, OS *39.25/45.00 @ 173* Note: *2+ mire distortion*
Slit lamp exam	*(-) Vogt's striae, (-) corneal scarring, (-) Fleischer ring OU*
Dilated fundus exam	*Within normal limits OU*

Diagnosis: Keratoconus suspect, high astigmatism OU, moderate myopia OU

Treatment: Referral for topography and contact lens refraction/fitting

At subsequent visits, topography revealed steepening of the inferior corneas of both eyes (Fig. 5.1). Rigid gas permeable contact lenses were fit, with best-corrected vision of 20/30 OD and 20/25 OS.

Case Synopsis

Keratoconus is a bilateral ectatic condition characterized by progressive thinning of the central or inferocentral cornea leading to steepening of the cornea and irregular astigmatism. Rigid gas permeable contact lenses are often the best solution for restoring good vision, especially early in the disease course (Fig. 5.2).

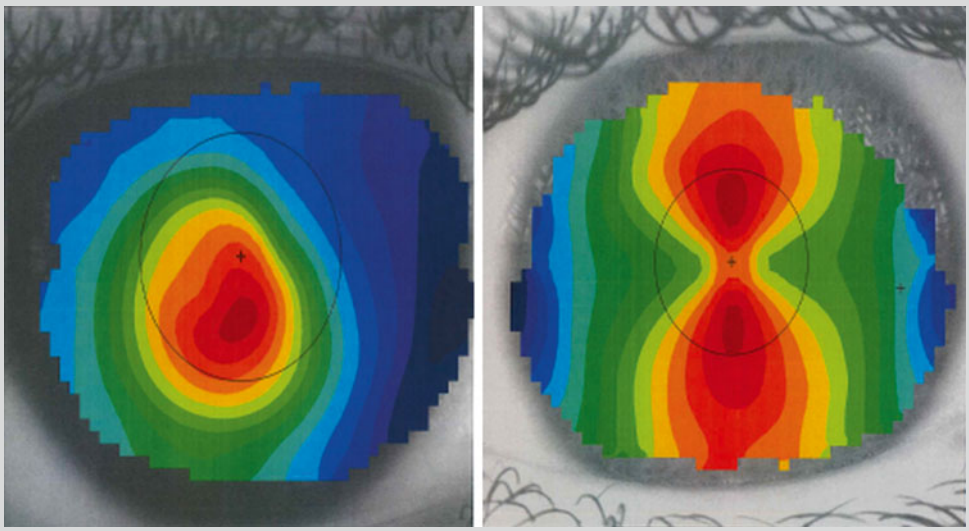

Fig. 5.1 Topography of a keratoconic eye (*left*) compared with a topography of regular astigmatism (*right*)

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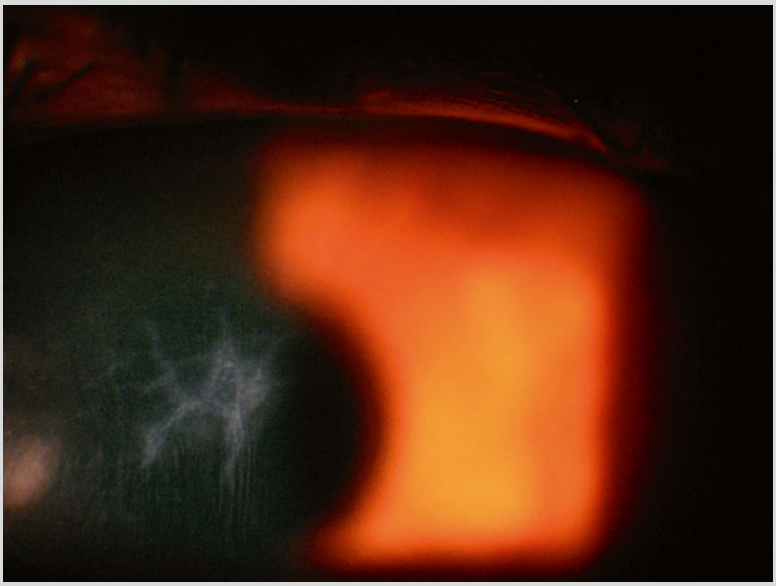

Fig. 5.2 Vogt's striae and apical scarring in a patient with keratoconus

Case 5

A 7-year-old with a history of penetrating trauma and global rupture presents status-post surgical repair of the corneal laceration and lens removal in the left eye. A lens could not be implanted, and the patient reports that the vision is blurry and distorted even with a high plus lens.

Relevant Exam Findings:

VA_{sc}	OD *20/20*, OS *counting fingers at 6 in.*
Corneal topography	OS *severe distortion of the corneal surface, especially upper ½ of cornea. Highly variable keratometry readings surrounding the scar/suture*
Best-corrected VA	OS *20/30-2 (with contact lens)*

Diagnosis: Irregular corneal astigmatism and aphakia OS

Treatment: Left eye fit with custom rigid contact lens

Case Synopsis

Rigid gas permeable contact lenses were attempted in this case due to the highly distorted corneal surface and resultant irregular astigmatism. Corneal scarring is one of the most common causes of irregular astigmatism in the pediatric population and is most often due to trauma after injury or infection. In this case, the patient's irregular corneal astigmatism was optimally corrected with a rigid contact lens, which provides a regular, smooth refracting surface in place of the patient's irregular corneal surface. This patient's options for refractive correction were further limited by the severe anisometropia between his healthy right eye and his aphakic left eye. Secondary intraocular lens implantation was considered to help address this but was not pursued (Figs. 5.3 and 5.4).

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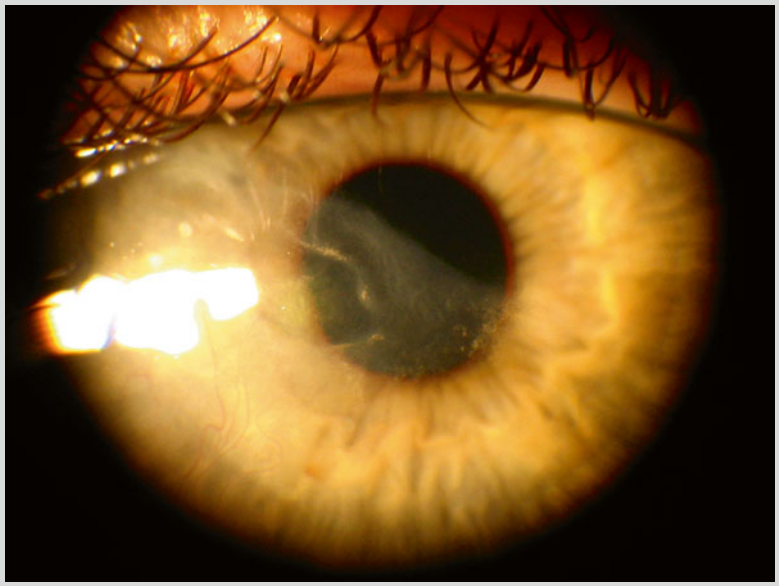

Fig. 5.3 Example of visually significant corneal scarring

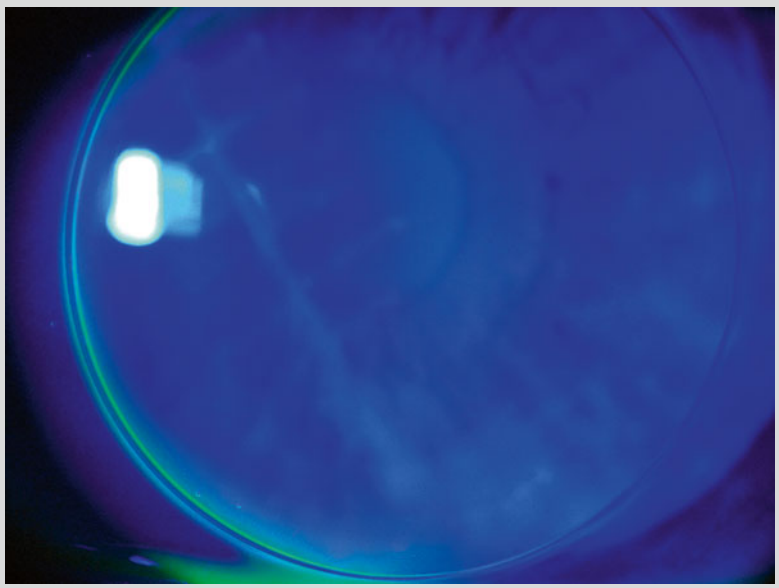

Fig. 5.4 Rigid contact lens over a scar produced from a previous penetrating injury

Case 3

An 8-year-old with Marfan syndrome presents after being lost to follow-up for 4 years.

Review of previous notes:

VA_{sc}	OD *20/80*, OS *20/25*
SLE	OD *mild subluxation of lens*, OS *normal*
CRx	OD $-3.00 + 1.75 \times 120$, OS $+1.00 + 0.75 \times 090$

Diagnosis: Ectopia lentis OD, possible amblyopia OD

Treatment: Glasses prescribed for full-time wear. Patch the left eye 2 h/day. Follow up in 2 months.

Relevant exam findings at follow-up (4 years later):

VA_{cc}	OD *20/60*, OS *20/50*
Slit lamp exam	OU *lens subluxation temporally, OD≫OS*
CRx	OD $-3.00 + 2.25 \times 150$ VA *20/50*, OS *plano* $+ 0.50 \times 075$ VA *20/30*

Diagnosis: Ectopia lentis OU, mild amblyopia OD

Treatment: Glasses prescribed for full-time wear. Follow up 3 months to assess visual acuities in refractive correction. Visual acuity improved to 20/30 OD in refractive correction alone. The patient was followed on an interval basis with cycloplegic refraction annually or sooner if warranted.

Case Synopsis

As many as 60 % of patients with Marfan syndrome suffer from lens subluxation, which results in a wide spectrum of possible refractive errors. Dislocated lenses in Marfan syndrome can be unilateral, but are often bilateral, occurring before the age of 20 years in most patients [5]. Depending on the degree of lens displacement, astigmatism—oblique or irregular—can be present at very high degrees, and most patients will actually obtain better vision through the aphakic portion of their pupil. Cycloplegic refraction should be carefully performed through both the phakic and aphakic portions of their eyes to determine the refractive correction that will restore best-corrected visual acuity. In this case, the child's disease progressed relatively slowly over 4 years—note the shift in axis from 120° to 150° in his right eye—permitting a spectacle corrected acuity of 20/50 in the right eye. Full-time wear of spectacle correction led to reversal of the mild amblyopia present in the right eye. At last follow-up, he has maintained good visual acuities of 20/30 in both eyes (Fig. 5.5).

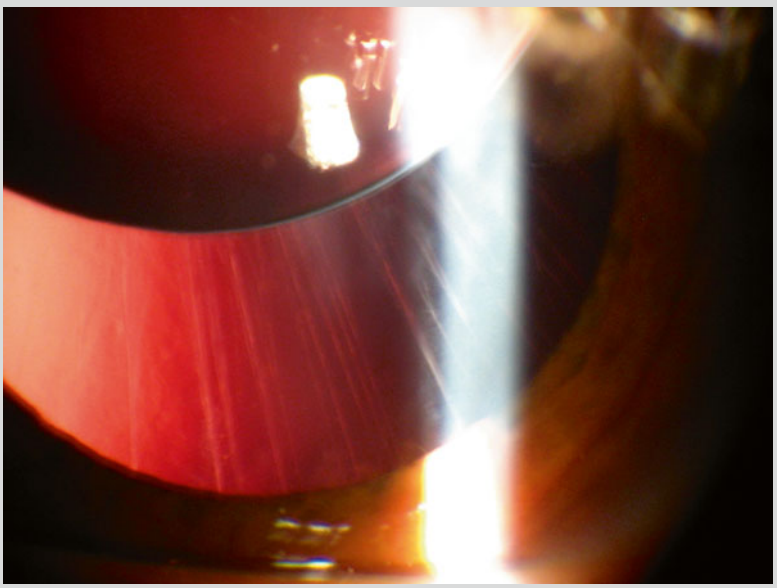

Fig. 5.5 Ectopia lentis, with visible and elongated zonules

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Pediatric Contact Lenses for Medical Indications

6

Daniele P. Saltarelli, Heather L. Cimino, and Virginia Miraldi Utz

Abstract

Infants and children with special refractive needs can benefit greatly from contact lens correction. Ocular conditions that may particularly require contact lens correction include infantile/childhood aphakia, high refractive error including high anisometropia, and post-traumatic or infectious corneal scarring. Careful clinical evaluation and proper education of the patient and parents for the use and care of contact lenses is crucial to a successful contact lens regimen. This chapter will provide a guide to recognize the medical indications for contact lens wear in children, to understand the contact lens design options that meet specific patient needs, and to develop a working knowledge of the basic concepts required to achieve a proper contact lens fit. Emphasis will be placed on the aphakic infant since this is a common application for the medical use of contact lenses in childhood.

Keywords

Contact lens • Aphakia • (Rigid) gas permeable • Silsoft

The Problem

Pediatric patients with special refractive needs may benefit greatly from contact lens (CLs) correction. In the case of infants and children who are left aphakic after cataract surgery, a distinct and immediate need for refractive correction is necessary, and the advantages of contact lens wear over intraocular lens (IOL) implantation in infants are becoming increasingly evident [1]. Results from the Infant Aphakia Treatment Study have demonstrated that visual outcomes using either contact lenses or intraocular lenses (IOLs) in infants with unilateral cataracts operated on under the age of 7 months are the same, although those with IOLs require additional surgeries to clear the visual axis from secondary lens proliferation [1]. The practical benefits of contact lenses over glasses in this situation have already been extensively reported [2, 3]. As an example, a typical contact lens power for a newly aphakic infant would be approximately +30.00 diopters. Glasses with lenses of this power would be extremely thick and heavy to wear, and they would cause significant optical distortion and prismatic effect with even the slightest frame misalignment (Table 6.1) (Fig. 6.1). Furthermore, for the infant or child with monocular aphakia, extreme anisometropia and aniseikonia during spectacle wear may hinder the development of good binocular vision and stereopsis and possibly contribute to the development of amblyopia [5, 6]. In contrast, a contact lens in one or both eyes is considered to be advantageous to spectacle correction by virtue of the superior optical quality provided by CLs (especially at very high powers). The contact lens interacts closely with the refracting surface of the eye, thereby mini-

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Table 6.1 Advantages of contact lens wear over spectacle correction for high refractive errors

(a) Less prismatic effect, distortion, and blur: All refracting systems depend highly on optical centration to deliver the intended and most clearly focused refractive signal. A well-fitted, well-centered contact lens will be much more successful at minimizing off-axis viewing and delivering the intended refractive correction consistently. This is also a function of on-eye stability and the close interaction the contact lens has with the refractive properties of the corneal tear layer
(b) Less aniseikonia (disparate image sizes): In the case of anisometropia, contact lens correction will lessen the magnification effect of high plus prescriptions (and lessen the minification effect of high minus prescriptions). This is especially true in extreme cases of aniseikonia such as unilateral aphakia. *Aphakic glasses produce approximately 25 % image size magnification versus only 7 % for vertex-adjusted contact lenses of the same magnitude, a level more likely to be tolerated by the child* [4]
(c) Less obstruction of peripheral vision: High-powered spectacles will typically not only produce a physical obstruction to peripheral viewing targets (consider frames and lens edging) but also produce optical effects that distort off-axis viewing. These effects are greatest in the periphery and are minimized (if not eliminated) with contact lens wear. *Examples include the following:* • *Pincushion distortion (door appears to bow inwardly)* • *Ring scotoma* • *Prismatic effect of lens edge producing the "jack-in-the-box" phenomenon*
(d) Improved physical comfort and cost considerations: especially for aphakic children, spectacles can be tremendously thick and heavy on the face causing unnecessary discomfort. They can also be quite expensive to manufacture and replace when broken. Contact lenses can be very comfortable when a good fit is achieved and are typically readily replaced when lost or damaged, and frequent replacements (which increase costs) do not have to be incurred if enough time is spent to properly fit the lens and train the parent and/or child on proper lens care techniques

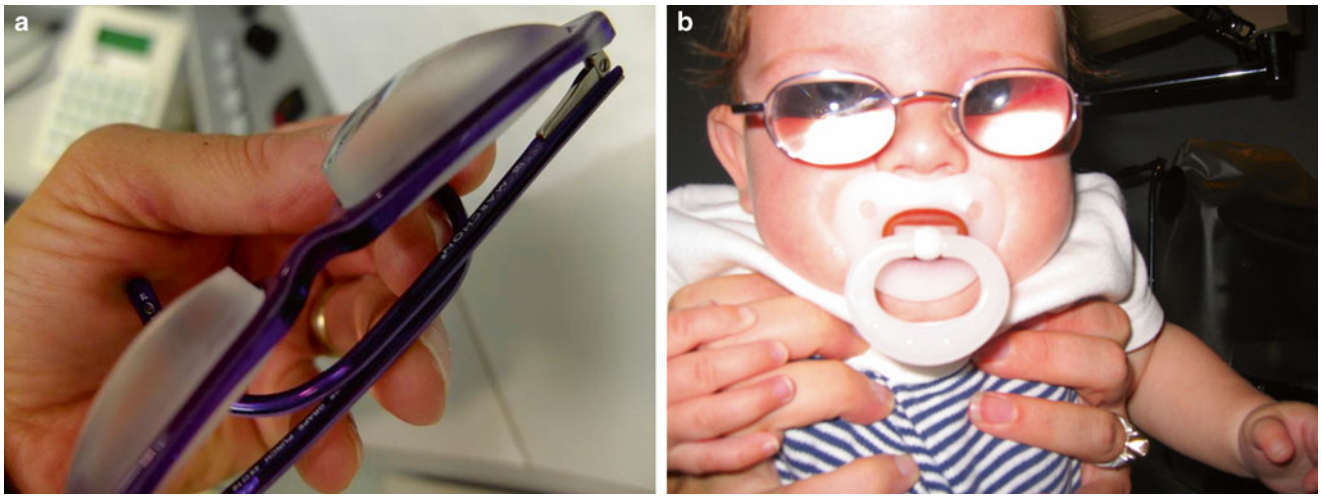

Fig. 6.1 Aphakic spectacle correction. (**a**) Aphakic spectacles can be extremely thick and heavy. Being highly sensitive to centration and vertex distance, they can produce unwanted distortion and prismatic effects. (**b**) Children with bilateral aphakia are more likely to successfully wear high plus spectacles than those with unilateral aphakia but would still benefit from the optical advantages of contact lenses

mizing distortion and providing more consistent image focus [7]. In addition, the power of the lens can easily be adjusted to accommodate the rapid refractive changes of the eye in the first 2–3 years of life [8, 9].

Initial Contact Lens Consultation

In the example of pediatric aphakia, visually significant congenital cataracts are typically removed in the first few weeks of life necessitating the fitting of a contact lens shortly thereafter. A traumatic cataract can occur at any age, and if an intraocular lens cannot be implanted, such patients may also need aphakic contact lens correction. A host of other conditions affecting corneal health including irregular astigmatism and posttraumatic scars can also occur in early childhood, and the patient may benefit tremendously from hard contact lens correction to neutralize irregular astigmatism. Once a patient is considered for contact lenses, the following basic pieces of clinical information should be collected if possible as they can provide a useful guide in the fitting process: (1) cycloplegic refractive error, (2) best-corrected visual acuity with glasses [10], (3) keratometry readings (manual and/or digital), and (4) a thorough evaluation of the corneal surface. In the case of the aphakic infant, many of these elements will simply not be possible to collect in the office and may be more successfully obtained at the time of surgery. Even then, one should be prepared to perform an infant contact lens fitting with little to no preliminary clinical data if required.

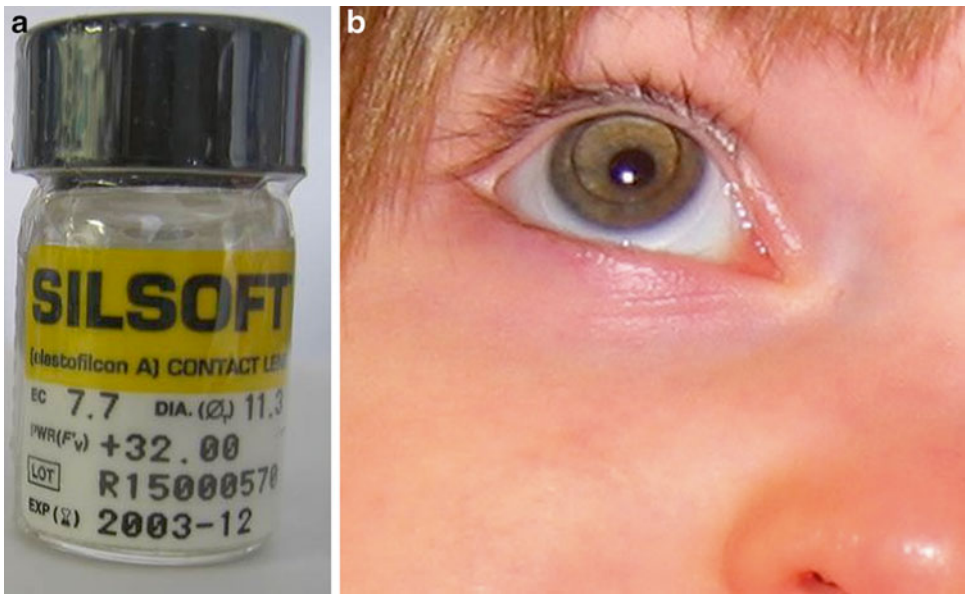

Fig. 6.2 Bausch and Lomb Silsoft® lenses. (**a**) An individually vialed Silsoft lens is packaged ready-to-use and stored in contact lens solution. If using Silsoft®, the initial lens choice for newborns and infants is a lens with a 7.50 mm base curve, a +32.00 diopter power, and an 11.3 mm diameter. This would be recorded as 7.50/+32.00/11.3. Some advocate calculating the lens power *based* on preoperative biometry [11]. (**b**) Silsoft lens on the eye of an aphakic child: notice the central optical zone ideally centered over the pupil and the lens skirt overlapping the limbus onto the sclera

Some advocate the initial contact lens fitting take place at the time of cataract removal in the operating room. Trivedi and Wilson performed regression analysis to determine the initial contact lens power required after surgery, based on the Holladay IOL formula and an A-constant specific for the contact lens (112.176) [11]. In this study, a Silsoft® silicone lens with a base curve of 7.5 mm and diameter of 11.3 mm was used [11], and a +2 D overcorrection was added to the calculated lens power to correct for the near point. This calculated approach to predicting initial lens power may prove helpful in patients in whom CLs are fit after the first postoperative visit in whom obtaining an accurate refraction is limited.

Although it is advantageous to assess the fit of a contact lens with no resistance from the child, this is an artificial situation, and valuable information on lens dynamics may be lost that would otherwise be useful in guiding the fitting process. For example, how does the child react to the lens insertion process? How difficult is it to remove the lens from the eye? How difficult is it to restrain the child, or is it even necessary? Do they react differently with different lens materials? How difficult is it to open the eyelids? Does the lens dislodge easily or recenter well after the child rubs or blinks? Beyond objective lens parameters, these are all equally important elements of on-eye lens dynamics that influence the tolerability of the specific contact lens and/or material and may ultimately contribute to the success and/or failure of contact lens wear. While intraoperative measurements may be helpful in select cases, the authors recommend that a formal lens fitting and evaluation be performed in the early postoperative period. The initial consultation should always include anticipatory guidance on contact lens wear and care for the caretakers as well as a thorough explanation on what to expect during the fitting process and subsequent appointments.

Selecting a Lens Type

Several contact lens materials/designs are available for aphakic correction. The Silsoft® lens from Bausch and Lomb is the most widely used lens in this category because it is FDA approved for use in pediatric aphakia and its extremely high oxygen permeability (Dk) rating which allows it to be safely worn overnight (Fig. 6.2). It is made of a silicone elastomer material, and its greatest advantage clinically is its adherence to the eye once inserted (Fig. 6.2). It is a good lens to use for those with less experience in fitting contacts because of its simplicity, market availability, and proven safety record [12–14].

There are however several disadvantages to the Silsoft® lens that are worth mentioning. Although it is a soft product that seems the logical choice for the newborn eye, there are significant limitations in its utility in the high refractive error range. Above +20.00 diopters, the Silsoft only comes in increments of +3.00 diopters and is only available in powers as high as +32.00 diopters. In this range, it is also only available in three base curve powers (7.50 mm/7.70 mm/7.90 mm), which correspond to only a 2 diopter variation in corneal curvature. These available lenses will be adequate for a majority of newly aphakic children, but not all. Furthermore, this type of lens is prone to lipid and protein accumulation and a film develops that is difficult to remove after a few months of wear. This can be addressed with vigorous cleaning, but eventually necessitates lens replacement, adding to costs. Lastly, the edge profile of the lens cannot be manipulated to improve the fit as it can with custom rigid lens products. For example, the Silsoft® lens edge cannot be manipulated to make it steeper, flatter, thicker, or thinner while maintaining the base curve. It is also only available in a single standard (11.3 mm) diameter.

Despite these deficiencies, the Silsoft® lens still provides a viable option in the contact lens treatment of pediatric aphakia and other conditions requiring high plus correction. It can sometimes be the best selection for a patient even if not fully customizable to the individual eye.

Hard or what is now commonly referred to as rigid gas permeable contact lenses (RGP, or simply GP lenses) provide an equally effective if not improved means of correcting high or irregular refractive errors such as those found in aphakia [15–17]. GP lenses offer the advantage of being completely customizable in terms of base curve, power, diameter, edge profile, material, and a host of other details of lens design. This makes them very advantageous when an acceptable fit cannot be achieved with standard available soft lens products, such as may be the case with very irregular or scarred corneas or situations where there is an abnormally high level of sphere or cylindrical refractive error. For example, in a case of a newborn with aphakia requiring a contact lens correction of +37.75 D, this refractive error would not be available "off the shelf" in Silsoft or any other pre-manufactured soft lens product but could be readily made to order in a GP material of choice.

Most GP lens manufacturers will offer trial lens sets with a range of predetermined power and curve parameters that can be loaned or purchased to assist in the initial fitting process. Specific pediatric designs are also available and are essential to success when fitting the aphakic child. Examples of companies include Lens Dynamics (http://www.lensdynamics.com) and ART Optical (https://artoptical.com).

The Fitting Process

Determine the Base Curve

Regardless of lens type or initial selection of the diagnostic lens, placement of the first lens on the eye should be preceded by a drop of fluorescein (preferably high molecular weight in the case of soft lens products), which will be tremendously useful in assessing the contact lens-corneal fitting relationship. In the case of Silsoft® lenses, fluorescein analysis is most useful in assessing the edge of the lens (see Fig. 6.3a demonstrating fluting). Generally however, a lens that fits well will appear to have an even distribution of fluorescein across the central optic zone or body of the lens, an edge that aligns evenly with the corneal surface in a 360° fashion, adequate movement and recentration of the lens with each blink, and evidence of sufficient tear exchange around the edges of the lens (i.e., adequate edge lift). Some of these details will be more obscure when using soft lens products, in which case centration, corneal coverage, and adequate movement/recentration with blink may be the only factors necessary in the on-eye fit evaluation. In the case of infants, all of this can be assessed accurately and efficiently with the use of a handheld pocket device that illuminates the fluorescein with blue light (Fig. 6.4).

Questions for Readers

(a) A contact lens of BC 7.20 mm and power +29.00 D is noted to be *2 D too steep* (see Fig. 6.5c): note the steep pattern of central fluorescein pooling, the location and size of the air pocket, and the very tight edge and exces-

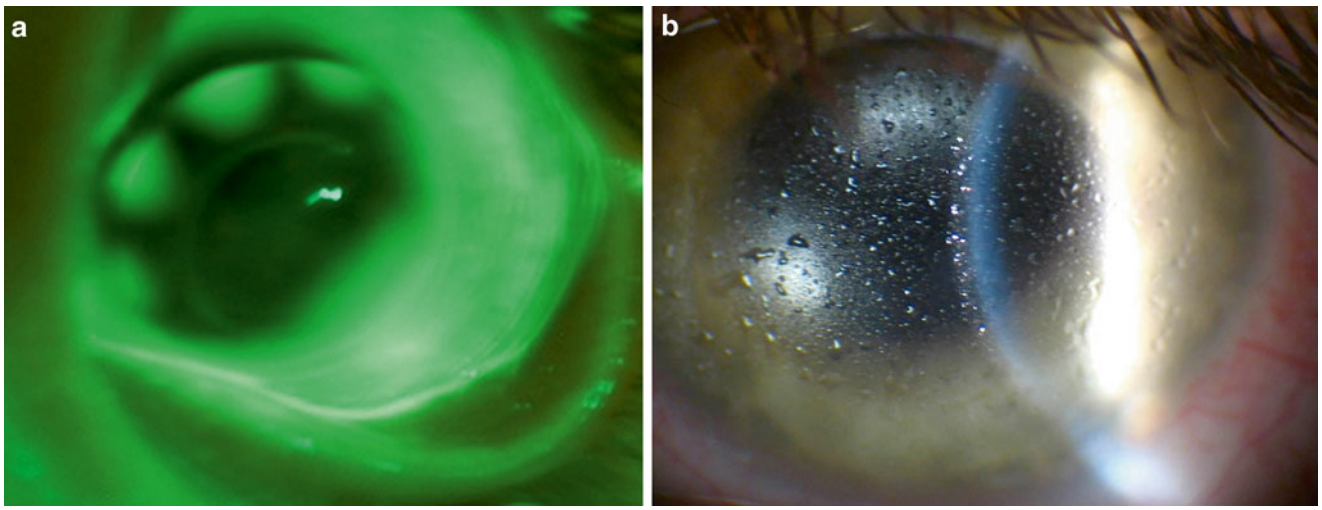

Fig. 6.3 (**a**) Example of a Silsoft® lens that appears to fit well until examined with fluorescein under blue illumination. Note the undulating appearance to the lens edge due to "edge fluting" or liftoff. This lens will move excessively, create more discomfort, and likely spontaneously dislodge from the eye requiring frequent replacements. In a 7.50 mm base curve, there would be no available selection to tighten the fit of the lens (e.g., via steepening the base curve or changing the peripheral lens design as one can do with a gas permeable lens), which is what is needed to solve this problem. (**b**) The parent in this case reported great success with Silsoft® lens wear, and clinically the eye was quiet. Despite this, examination revealed an impressive amount of protein/lipid accumulation of the lens surface, necessitating reinstruction of proper cleaning techniques and more frequent lens replacement

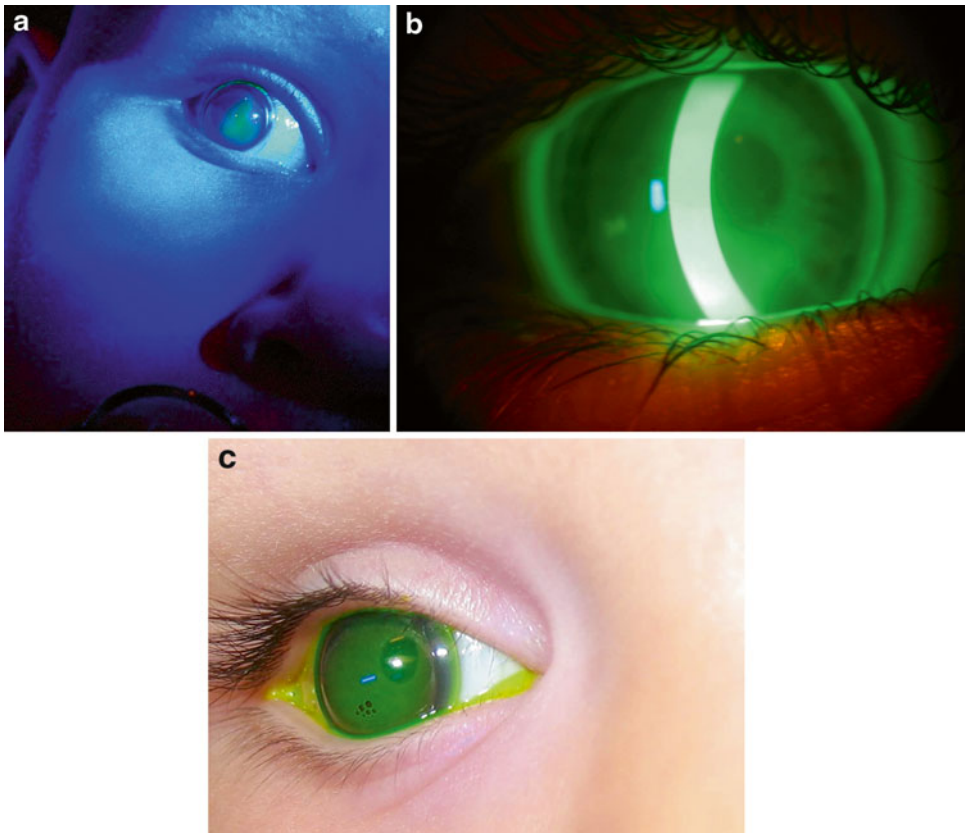

Fig. 6.4 (**a**) Example of a well-fit GP lens on an infant aphakic eye. The fluorescein is evenly distributed across the body of the lens with adequate fluorescein under the edge in a 360° fashion and good lens centration and coverage of the cornea without excessive bearing in the mid-peripheral lens region. (**b**) Example of a GP lens (*base curve* 7.10 mm) that is well centered but fits too steeply across the central optic zone (as evidenced by the pooling of fluorescein and bubble formation) and too tightly along the edge (notice compression and lack of fluorescein at the corneal-limbal interface). In addition, this patient was observed to have inadequate movement with each blink. The first approach to remedy this fit would be to select a flatter *base curve*

sive corneal bearing. To adjust this contact lens, one would select a base curve "2 D flatter." What new BC would have to be selected to achieve a 2 D flatter fit?
Answer: BC 7.60 mm

(b) A contact lens of BC 8.35 mm and +26.50 is noted to be *2 D too flat* (see Fig. 6.5d): note the flat pattern of central touch and the lack of adequate fluorescein across the center of the lens (over the pupil), the excessive fluorescein pooling in the mid-periphery, and the excessive amount of fluorescein under the lens edge. To adjust this contact lens, one would select a base curve "2 D steeper." What new BC would have to be selected to achieve a 2 D steeper fit?
Answer: BC 7.95 mm

The scatterplot in Fig. 6.6 depicts contact lens base curve against age for over 20 newly aphakic children fit in GP lenses [18]. It shows us that most infants <8 weeks of age require an initial base curve selection between 7.00 and 7.50 mm, that there are outliers to this rule, and that base curve flattens as the children age (due to natural corneal flattening with eye growth) [18]. Data such as this can be critical to an efficient fitting process when keratometry and other details are lacking. Similar reference data has also been published for Silsoft lenses [19].

Determine the Refraction

Once the proper contact lens base curve is confirmed, attention should be directed to determining the appropriate contact lens power. This can be done with retinoscopy (with attention to one's working distance) over a diagnostic contact lens of known base curve and power while in place on the eye. The resultant values will need to be vertexed to the corneal plane in order to yield the total dioptric value of the contact lens. It is important to note that any value under ±4.00 D does not require vertexing. The equation for this conversion is

$$Fc = F / (1 - xF), \text{ where}$$

Fc = power corrected for vertex distance
F = original spectacle lens power
x = the change in vertex distance in meters

It is often more efficient to simply refer to a published chart or online resources to make the appropriate vertex conversion (see Table 6.2). Additional resources that may be helpful for vertex conversions are:

https://artoptical.com/lenses/fitting-tools/calculators/vertex-adjustments-calculator/
http://www.gpli.info/conversion-charts/#
http://www.lensdynamics.com/calculator

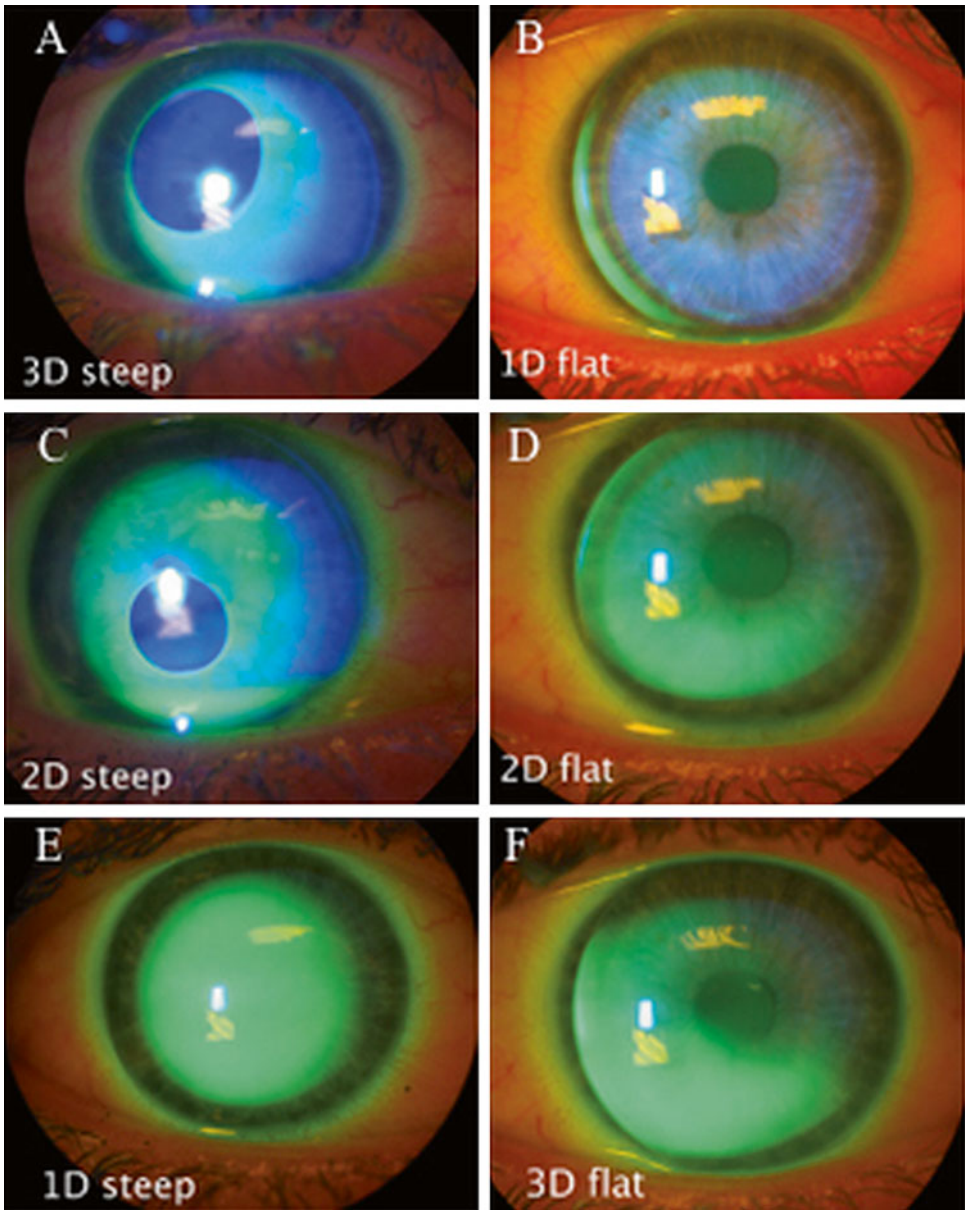

Fig. 6.5 This visual reference provides a very useful guide to directing base curve changes during the fitting process and is very useful in the case of a patient with aphakia fit with GP lenses. When adjusting lenses, one must understand the mathematical relationship between the radius of curvature and dioptric refractive power: *For every 0.05 mm change in base curve, it automatically produces a 0.25 D change in lens power*. In order to determine the appropriate next lens to choose for the patient pictured in Fig. 6.4b, one could estimate that the lens is 1.25 D too steep (it is between the image (**e**) 1 D steep and (**c**) 2 D steep). Changing the base curve 1.25 D flatter is therefore required (i.e., from BC 7.10 to BC 7.35 mm in this case) and should produce a more aligned fit, eliminating the central fluorescein pooling and air, reducing the mid-peripheral corneal bearing, and allowing for adequate movement with each blink. Figure reproduced with permission from Sindt, CW. Contact Lens Spectrum, Issue January 2010

Case example 1: Monocular aphakic infant presenting for evaluation for contact lens:

- Diagnostic CL parameters: BC 7.50 mm/power +19.50 D/diameter 10.4 mm
- On-eye CL over-refraction: +12.50 D (vertexes to roughly +14.75 D at a standard vertex distance of 12 mm)
- Total CL power: +34.25 D (19.50 + 14.75)

Most of a child's visual interest at a very young age is in the very near range, and without the natural lens of the eye in place, normal accommodation is not possible. To overcome this, aphakic newborns and toddlers will need to be intentionally overcorrected in their final contact lens power in order to provide better visual clarity at near. Differing recommendations exist on how to accomplish the overcorrection for a child at any given age. In the Infant Aphakia Treatment Study, a +2.00 overcorrection was provided until the age of 2 years, and thereafter, patients were corrected for emmetropia [20]. Other authors advocate +3.00 D for newborns [9], but essentially the overcorrection is greatest for a newborn and lessens as the child ages and begins to walk. The authors use the following clinical guidelines to determine overcorrection in a child who is aphakic:

- Birth to 2 years of age and not walking: overcorrect by 3.00–2.00 D
- Birth to 2 years of age and walking: overcorrect by 1.50–1.00 D
- >2 years of age: correct for emmetropia at distance; contact lens to be worn in conjunction with bifocal spectacles measuring plano/+3.00 for the aphakic eye(s)

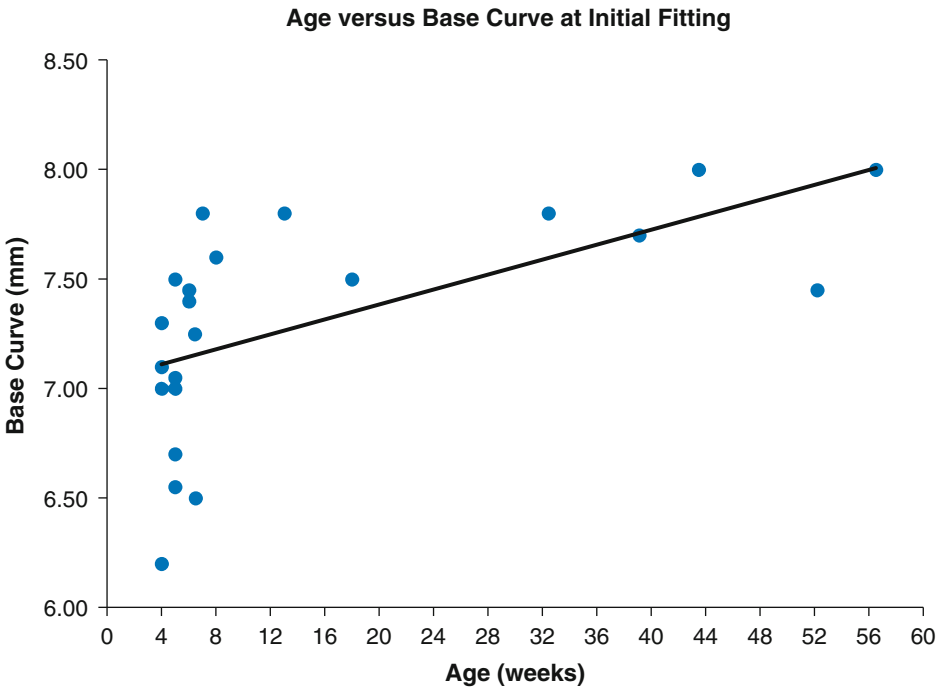

Fig. 6.6 Scatterplot of initial base curves used in the CL fitting of aphakic infants. Significant variability is noted and therefore requires careful measurement and assessment of fit [18]

Table 6.2 Vertex corrected contact lens power as a function of increasing plus-spectacle lens power (left column) across differing vertex distances

	Vertex dist (mm)							
Power (D)	8	9	10	11	12	13	14	15
4.00	4.13	4.15	4.17	4.18	4.20	4.22	4.24	4.26
4.25	4.40	4.42	4.44	4.46	4.48	4.50	4.52	4.54
4.50	4.67	4.69	4.71	4.73	4.76	4.78	4.80	4.83
4.75	4.94	4.96	4.99	5.01	5.04	5.06	5.09	5.11
5.00	5.21	5.24	5.26	5.29	5.32	5.35	5.38	5.41
5.25	5.48	5.51	5.54	5.57	5.60	5.63	5.67	5.70
5.50	5.75	5.79	5.82	5.85	5.89	5.92	5.96	5.99
5.75	6.03	6.06	6.10	6.14	6.18	6.21	6.25	6.29
6.00	6.30	6.34	6.38	6.42	6.47	6.51	6.55	6.59
6.25	6.58	6.62	6.67	6.71	6.76	6.80	6.85	6.90
6.50	6.86	6.90	6.95	7.00	7.05	7.10	7.15	7.20
6.75	7.14	7.19	7.24	7.29	7.34	7.40	7.45	7.51
7.00	7.42	7.47	7.53	7.58	7.64	7.70	7.76	7.82
7.25	7.70	7.76	7.82	7.88	7.94	8.00	8.07	8.13
7.50	7.98	8.04	8.11	8.17	8.24	8.31	8.38	8.45
7.75	8.26	8.33	8.40	8.47	8.54	8.62	8.69	8.77
8.00	8.55	8.62	8.70	8.77	8.85	8.93	9.01	9.09
8.25	8.83	8.91	8.99	9.07	9.16	9.24	9.33	9.42
8.50	9.12	9.20	9.29	9.38	9.47	9.56	9.65	9.74
8.75	9.41	9.50	9.59	9.68	9.78	9.87	9.97	10.07
9.00	9.70	9.79	9.89	9.99	10.09	10.19	10.30	10.40
9.25	9.99	10.09	10.19	10.30	10.40	10.51	10.63	10.74
9.50	10.28	10.39	10.50	10.61	10.72	10.84	10.96	11.08
9.75	10.57	10.69	10.80	10.92	11.04	11.17	11.29	11.42
10.00	10.87	10.99	11.11	11.24	11.36	11.49	11.63	11.76
10.25	11.17	11.29	11.42	11.55	11.69	11.83	11.97	12.11

(continued)

Table 6.2 (continued)

	Vertex dist (mm)							
Power (D)	8	9	10	11	12	13	14	15
10.50	11.46	11.60	11.73	11.87	12.01	12.16	12.31	12.46
10.75	11.76	11.90	12.04	12.19	12.34	12.50	12.65	12.82
11.00	12.06	12.21	12.36	12.51	12.67	12.84	13.00	13.17
11.25	12.36	12.52	12.68	12.84	13.01	13.18	13.35	13.53
11.50	12.67	12.83	12.99	13.17	13.34	13.52	13.71	13.90
11.75	12.97	13.14	13.31	13.49	13.68	13.87	14.06	14.26
12.00	13.27	13.45	13.64	13.82	14.02	14.22	14.42	14.63
12.25	13.58	13.77	13.96	14.16	14.36	14.57	14.79	15.01
12.50	13.89	14.08	14.29	14.49	14.71	14.93	15.15	15.38
12.75	14.20	14.40	14.61	14.83	15.05	15.28	15.52	15.77
13.00	14.51	14.72	14.94	15.17	15.40	15.64	15.89	16.15
13.25	14.82	15.04	15.27	15.51	15.76	16.01	16.27	16.54
13.50	15.13	15.37	15.61	15.85	16.11	16.37	16.65	16.93
13.75	15.45	15.69	15.94	16.20	16.47	16.74	17.03	17.32

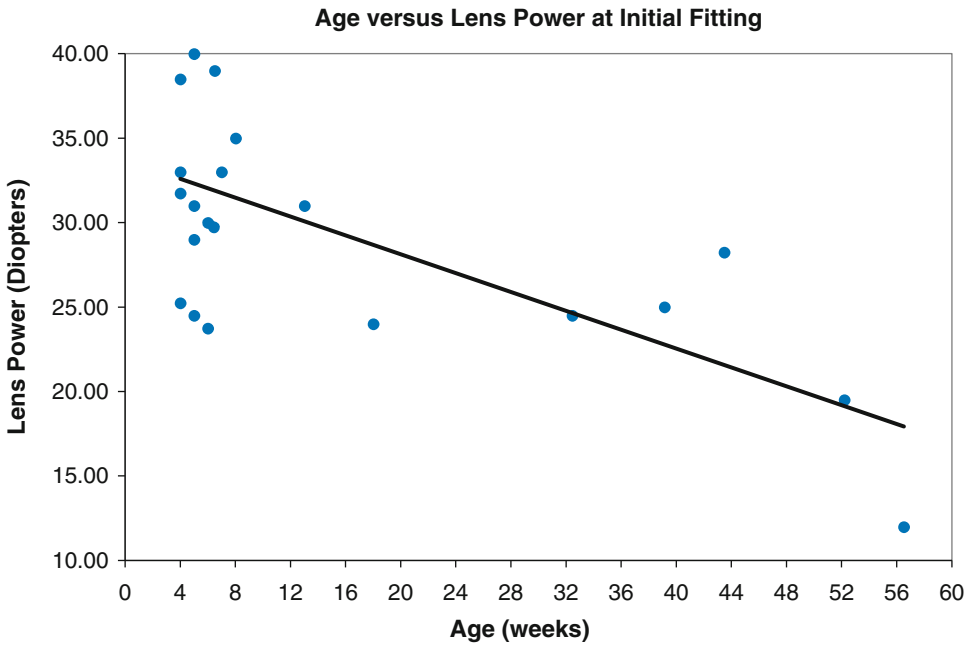

Fig. 6.7 Relationship of age versus lens power at initial CL fitting in a sampling of aphakic patients. Note the variability in initial lens power and subsequent decrease with age in weeks [18]

Therefore, in Case Example 1, if the child fit with this lens was just a few weeks of age, the final contact lens power to be ordered would be +37.25 D (34.25 + 3.00). Once placed on the eye, retinoscopy over this lens should indicate a −3.00 D refractive error. Overcorrection for infants and toddlers in contact lenses is only indicated when managing aphakia.

The scatterplot in Fig. 6.7 plots the contact lens power against age for newly aphakic children fit in GP lenses. It demonstrates that most infants <8 weeks of age require an initial power selection between 30.00 and 35.00 D, that there are outliers to this rule, and that power requirements lessen as children age (due to the natural decrease in refractive error that occurs with eye growth) [9]. Similar reference data has also been published for Silsoft lenses [19].

Determine the Diameter

In general, the diameter of the lens will be the final element to consider during an initial diagnostic fitting. In the case of soft lens products, one can expect the edges of the lens to overlap the corneal limbus and extend several millimeters onto the sclera in a 360° fashion. For custom rigid designs, most lenses will have a smaller diameter than the cornea and not extend past the limbus. Either situation is acceptable, as long as the lens centers well and does not move excessively

Table 6.3 The fitting process: step-by-step approach to evaluating a contact lens fit[a]

Lens parameter	Possible on-eye findings	Possible adjustments	Goal	Notes
(1) Base curve	Too steep: lens will be tight with inadequate movement	Flatten the BC	An even distribution of FL across the body of the lens; no areas of excessive FL pooling under the lens; no areas of corneal bearing other than mild touch in the mid-periphery of the lens; appropriate degree of edge lift to allow for good tear exchange	Recall the relationship between BC and power: 0.05 mm = 0.25 D Soft lens products depend highly on base curve variations and other design features to achieve the optimal cornea-lens fitting relationship
	Aligned	No change required		
	Too flat: lens will be loose with excessive movement	Steepen the BC		
(2) Power	Over-plussed with CL: will see a minus over-refraction	Decrease the power of the final lens accordingly	Neutrality for non-aphakic eyes; age-based overcorrection for near viewing for aphakic eyes less than 2 years of age	Remember to: – incorporate your working distance when determining the CL over-refraction – vertex the result accordingly (if ≥ 4.00 D) before adding to the CL power – overcorrect accordingly for aphakic eyes (add +2 to 3 D to the power of the lens in newly aphakic infants)
	Neutrality on retinoscopy	Apply the appropriate overcorrection if indicated		
	Over-minused with CL: will see a plus over-refraction	Increase the power of the final lens accordingly		
(3) Diameter	Too large: risk of being too tight with inadequate movement, but lens may appear comfortable to patient	Decrease the diameter	Select a lens large enough to provide good corneal coverage, centration, and on-eye stability without being too large that it becomes excessively tight on the eye and inhibits adequate lens movement and/or eliminates tear exchange around the edges	Even a very small change in diameter (e.g., 0.20 mm) can resolve the issue of frequent lens loss in the case of GP lenses Recall that soft products will not offer as many options in diameter and rely predominantly on base curve changes to achieve the ideal fit profile
	Centered	No change required		
	Too small; will observe excessive movement producing high level of lens awareness and greater risk for displacement and loss	Increase the diameter		

[a]*Note*: All contact lens companies provide free phone consultation services which can be very helpful if one is faced with a lens that requires an improved fit but unsure how to optimize the fit. Providing digital photos of the fit to the consultant may also be helpful in this regard

FL fluorescein, *D* diameter, *mm* millimeters

(i.e., the two most common reasons to select a larger diameter lens in the infant and toddler stages). The large diameter of a soft lens is beneficial for centration and stability by providing more surface contact with the eye. Increasing the diameter of a rigid lens will also improve centration and stability by virtue of the increased sagittal depth and the resultant lens steepening effect. Stability and centration work to improve contact lens comfort. Although most soft materials are available in only a single standard diameter, rigid products will offer full customization of diameter, thereby significantly improving one's ability to fine-tune the fitting process. Smaller-diameter lenses may be preferred when trying to limit eyelid interaction and to improve comfort or when dealing with specific entities such as microcornea.

Table 6.3 describes a systematic framework for evaluating fit of contact lenses.

Lens Material Considerations

Especially in the case of infants and young children, contact lenses should be made of highly oxygen permeable materials to allow for maximum oxygen availability to the cornea and the least risk of corneal edema, especially considering the number of hours devoted to sleep at this age. With the advent of more soft and GP materials in the high oxygen permeable range (i.e., Dk > 70 and often beyond 100), one should rarely have a reason for the use of older generation materials in the contact lens treatment of children. GP materials in the high or "hyper" Dk range (e.g., Boston XO2 (Bausch and Lomb) or Menicon Z (Menicon Co.) have been shown to allow for thicker lens designs without the expected decrease in corneal oxygen uptake [21]. As a result of this and other developments in lens manufacturing and design, GP lenses have

actually experienced a resurgence in use due to their increasingly broad clinical application and their impressive track record on safety and efficacy [22–24].

Other Considerations

Parents of infants and toddlers in contact lenses will often find GP lenses easier to manipulate during the insertion and removal process. Especially in the case of a child who is resisting insertion or removal of the lens, GP lenses will not fold or turn inside out in the same way that soft lenses often do. Further advantages of GP over soft lenses include not requiring the use of toric designs when dealing with regular astigmatism of ≤2.50 to 3.00 D, and their ability to resist film deposition even when compliance with lens care recommendations is less than adequate. Perhaps the biggest disadvantage to GP lenses is edge awareness that can make these lenses uncomfortable in comparison to soft edge designs. Edge awareness is a function of the relationship between the eyelid and the lens edge and is the primary reason that many adults cannot tolerate GP lenses and why many practitioners defer to soft lens products for almost all their contact lens patients. Infants and children will often become very comfortable in GP lenses if enough time and attention is devoted to the fitting process and lens design as described herein.

Once the proper contact lens is obtained, attention must be directed to training the caregivers in proper insertion, removal, and lens care techniques. It is usually recommended that a caregiver demonstrate in-office success with this before the lens is dispensed for use, especially in cases involving infants and young children. If needed, there are also training videos that can be used at home to supplement the hands-on knowledge gained in-office (e.g., http://www.cincinnatichildrens.org/health/a/aphakia/). Proper cleaning and storage techniques should also be reviewed prior to dispensing lenses. Most contact lens manufacturers will list the specific lens care solutions that are recommended for their products.

Lastly, once the contact lens fit is established (which may take a few closely spaced visits in the beginning stages), a proper follow-up regimen should be established with no more than 3–4-month intervals between evaluations. At each contact lens follow-up, the following should be assessed:

- *On-eye evaluation of the fit with white light*—The clinician should evaluate general aspects including centration, corneal coverage, adequate movement and recentration with each blink, evidence of material buildup and deposits, and obvious signs of discomfort.
- *On-eye fluorescein evaluation of the fit with blue light*—The clinician should evaluate the "fluorescein pattern" for areas of excessive lens touch/bearing or excessive pooling or pockets of air. One should also evaluate the lens edge for excessive lift contributing to lens awareness/discomfort or inadequate lift resulting in "pinch off," a situation where the edge of the lens creates such a tight seal against the eye that it blocks the movement of tears around the lens edge. Tear exchange around the edge is an important feature of a healthy GP fit and can be realized by observing the flushing movement of fluorescein within the tear layer as the CL translates between blinks.
- *Contact lens power*—If dealing with an aphakic eye, perform retinoscopy over the contact lens and correlate with the intended overcorrection to determine if lens power is sufficient or needs to be updated. Retinoscopy will also provide a good clue to the onset of any media opacities that may redirect the need for further medical or surgical care as is sometimes the case with newly aphakic children.
- *Evaluation of the cornea without the lens*—The clinician should remove the lens and evaluate corneal surface under both white and blue light conditions. Fluorescein evaluation may reveal areas of staining and corneal compromise that were not evident during the on-eye lens evaluation.
- *Off-eye evaluation of the contact lens*—This is an often overlooked, yet very valuable component of the contact lens evaluation. Especially when dealing with aphakic fits, viewing the contact lens behind the slit lamp and/or held up against the ceiling lights can be quite useful at deciphering the overall lens integrity. Tiny edge nicks and irregularities are easily identified in this manner, and especially with Silsoft lenses, the level of haze and/or film formation across the optic zone will become readily obvious.

One should keep in mind that lens loss is an expected component in the contact lens care of infants and young children treated for aphakia. Even under the best circumstances, numerous studies report various rates of lens loss. This understanding should therefore be part of the expectations set forth to parents and caregivers at the outset of contact lens treatment. A plan should also be in place for the efficient replacement of lenses when they do get lost, including the provision of a backup lens with each new order.

There is no question that contact lens wearers have a higher incidence of microbial keratitis, that contemporary contact lens materials and designs have not reduced the overall incidence of keratitis, and extended wear of contact lenses (i.e., overnight wear) is one of several modifiable risk factors that have been consistently reported to increase the risk for infection [25]. With this knowledge, it is prudent to educate families of children in contacts of this risk and for both parent and practitioner to be aware of the symptoms and signs of potentially sight-threatening infections and the need for immediate medical care.

Case Presentations

Case Study 1: Aphakic Infant Fit with Silsoft Lens

History: 4-week-old infant with history of congenital cataract OS removed at 3 weeks of age. Retinoscopy and keratometry values have not been provided.

Choice of diagnostic lens: Silsoft 7.50/+32.00/11.3 (based on the very young age of this child, it's a good choice to start with the steepest and most powerful lens available in this category).

Retinoscopy/on-eye over-refraction: +2.50 D (desired over-refraction: −3.00 D based on age).

Fit assessment: Optic zone is well centered over the pupil; lens overlaps limbus evenly 360° (Fig. 6.1b). Fluorescein evaluation reveals minimal edge fluting, with a subtle but equal distribution of fluorescein across the breadth of the lens.

Plan: Since the over-refraction is +2.50 and you want an overcorrection of −3.00, the eye is actually under-plussed in the current lens. You will need to add +5.50 D to the diagnostic lens power (+2.50 + 3.00) to achieve the desired −3.00 overcorrection. The lens power required will be +37.50 D. Since this is not available in Silsoft, you have two options:

(a) Prescribe the +32.00 D contact lens for the left eye, and prescribe single vision glasses over this (i.e., +5.50 D spectacle lens for the left eye). One may consider prescribing a plano spectacle lens for the sound eye or incorporate refractive correction for that eye if indicated. The one advantage to this option is that glasses provide protection from external injury for both eyes.

(b) Switch to a GP lens. GP lenses are fully customizable, and so the clinician will be able to order the exact power required in all cases. Since lens design profiles are different for GP versus Silsoft lenses, it is advisable to do a diagnostic fitting first if switching to the GP lens. In the current example, it would make sense to start with a 7.50 mm BC diagnostic GP lens and make adjustments as necessary prior to ordering.

Case Comments

The over-refraction (+2.50 D) does not have to be vertexed to the corneal plane. Vertexing is not required for powers under ±4.00 D.

It is clinically easier and more exacting to over-refract a diagnostic CL of known power rather than refract the aphakic eye. With this approach, the refractive error of the aphakic eye will rarely (if ever) be needed to initiate the fitting.

The edge fluting of the Silsoft in this case is acceptable as long as the child appears comfortable and the lens is not dislodging excessively. If it becomes an issue, this may require a change to GP lenses since 7.50 mm is the steepest BC available for Silsoft, and there is no other parameter change available to tighten the fit.

By age 2, this child will need to be fit in a CL without overcorrection for near viewing (i.e., corrected for emmetropia at distance). A bifocal spectacle lenses over the CL-corrected aphakic eye will be required (e.g., plano OD; plano/+3.00 OS).

Case Study 2: Aphakic Infant Fit with GP Lens

History: Premature infant treated for bilateral congenital cataracts, removed in the first week of life. Retinoscopy and keratometry values have not been provided.

Choice of diagnostic lens: GP 7.00/+19.50/10.2 OU (based on the history of prematurity and the young age at fitting, this child will likely have steeper than average corneal curvature for a newborn). Using Fig. 6.6 as a reference, a GP lens with a 7.00 mm BC is a reasonable initial selection for a diagnostic lens. In this example, all lenses in the diagnostic set have a +19.50 D power and 10.2 mm diameter, but this will vary depending on the manufacturer of the lens set.

Retinoscopy/on-eye over-refraction: +13.25 D (desired over-refraction: −3.00 D based on age).

Fit assessment: The lens is staying on the cornea but excessive movement is present. When the CL is centered, there appears to be inadequate fluorescein under the optic zone (i.e., almost central cornea-lens touch) with too much fluorescein in the mid-periphery and excessive edge lift. Using Fig. 6.5b, d, it is estimated that the lens is too flat by 1.50 D.

Plan: Since an over-refraction of +13.25 vertexes to +15.75 at 12 mm (see Table 6.2) and an overcorrection of −3.00 is desired, +18.75 D will need to be added to the diagnostic lens power (+15.75 + 3.00).

(continued)

The lens power required will be +38.25 D (19.50 + 18.75). Recall the 7.00 BC diagnostic CL was determined to be 1.50 D too flat. To adjust for this, a steeper lens of 6.70 BC will need to be ordered (recall 0.05 mm = 0.25 D). This will automatically add +1.50 D to the effective power of the CL, thus creating an unwanted refractive shift. To correct for this, the final lens power required will be changed to +36.75 D (38.25–1.50). The CL to be ordered will be 6.70/+36.75/10.2.

Case Comments

When dealing with very high-powered GP lenses, the clinician may find that the shear bulk of the optic zone prevents complete eyelid closure and contributes to lens displacement due to excessive lid interaction. The clinician can request that the CL manufacturer focus on "debulking" the optic zone if all other lens parameters are acceptable. One can be even more specific by requesting the center thickness of the lens be limited to no more than 0.80 mm.

"SAM/FAP": steeper add minus/flatter add plus. This handy mnemonic is very useful in making CL power adjustments in response to base curve changes, but only in the case of GP lenses. In the current example, the diagnostic CL was steepened in the final order from 7.00 to 6.70. Steepening the lens moves the focal point/plane of the refracting system more anterior relative to the retinal plane. This has to be compensated for by an equal but opposite shift in power if the intention is to maintain focus at the retinal plane (or in this case, at 3.00 D anterior to the retinal plane). In the current example, "SAM" required adding −1.50 to the CL power to achieve this.

Question for Readers

With the changes in BC that were made in both cases (a) and (b) (page X), what compensatory power change would also have to be made in order to maintain the refractive power of the original lenses?

Answers: FAP = +31.00 D (a) and SAM = +24.50 (b)

When dealing with bilateral cases, once the diagnostic fitting is completed for one eye, this will help in figuring the lens parameters needed for the other eye. Although it is always advisable to perform a diagnostic fitting for each eye, circumstances may not permit, and the clinician may need to order the same lens for both eyes based only on the fitting of one. Many times the CLs required for each eye will be very similar, if not identical. At worst, one can make small adjustments at follow-up if required.

Case Study 3: GP Lens Fit for Child with Corneal Scar

History: 5-year-old child with corneal scarring OD after corneal wound repair for penetrating injury. Digital corneal topographies indicate severe distortion of the corneal surface in the area of the scar (Fig. 6.8).

Choice of diagnostic lens: GP only—The irregularities produced by opacities and deformities of the cornea can really distort vision, and soft lens products, due to their lack of rigidity, will not neutralize the optical irregularities in these situations. GP lenses will be advantageous due to the uniformity and rigidity of their back surface and hence their ability to recreate a smooth refracting surface by utilizing the tear layer formed between the cornea and CL.

Retinoscopy/on-eye over-refraction: It is often very difficult to perform a reliable retinoscopy on a damaged cornea due to distortion of the retinoscopy reflex and high levels of irregular astigmatism. If this is the case, simply place a diagnostic GP lens on the eye that fits reasonably well and over-refract. The retinoscopic reflex will be much easier to discern following diagnostic lens placement, producing lower levels of refractive error to neutralize. The over-refraction result can then be incorporated into the lens for the final CL order.

Fit assessment: In general, a CL will always want to center over the steepest part of the cornea. In a normal cornea, this is the central corneal apex. In a damaged cornea, this will often be the scarred area. Even if CL centration is not possible due to the location and steepness of the scarred area, the same general principles of fit evaluation apply, with the added requirements to avoid CL bearing on any part of the scar and to allow for complete CL coverage of the scar.

Plan: As in any case, the clinician should determine the optimal base curve, lens power, and diameter that allows for best acuity and optimal comfort.

Case Comments

Using contact lenses to address corneal scarring and irregularities is a therapeutic measure that is generally underutilized by ophthalmologists, especially for pediat-

(continued)

ric cases. It is not uncommon to realize a corrected visual acuity of 20/20 in a GP CL that was only best corrected to 20/200 in glasses. It is also often impressive to realize significant visual gains from CL wear in individuals for whom the level of corneal scarring was deemed too advanced for further intervention.

Several children fit for contact lenses need to be on medicated eyedrops to treat underlying conditions, and this cannot be discontinued once CL wear begins. When using soft lens products, it is generally advisable to administer drops before lens wear and/or remove lenses prior to drop administration, wait for several minutes, and then reinsert. These precautions can be ignored if using GP materials as there is no risk for solution retention and/or staining of the CL in this situation.

Since discomfort can be more of an issue for GP wearers (especially in unilateral applications), be aware that both "hybrid" designs (larger diameter lenses with a central GP zone surrounded by a peripheral soft edge/skirt) and "piggyback" applications (GP overtop very low powered soft lenses) exist which both work to minimize lens edge awareness. If comfort cannot be achieved via normal CL parameter changes, these alternatives may be considered in select cases. The contact lens manufacturer can be a helpful resource to further guide the fitting process and navigate alternative design options if needed.

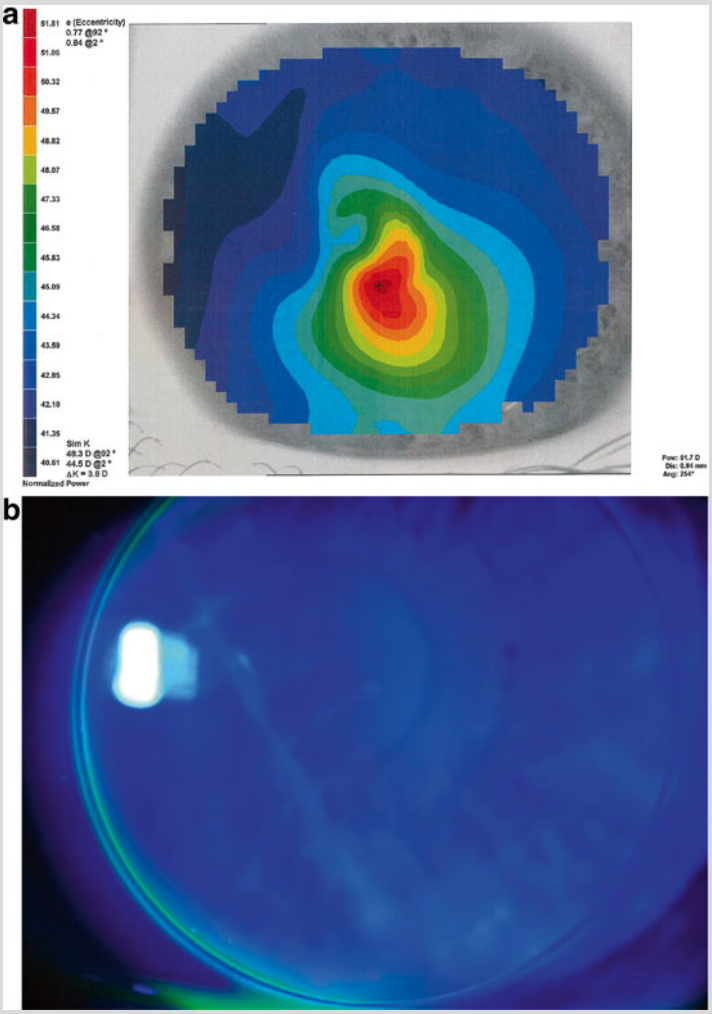

Fig. 6.8 (**a**) Corneal topography prior to contact lens placement. (**b**) GP lens placed over the corneal scar resulted in neutralization of the irregular astigmatism and significant visual improvement from 20/80 (spectacle corrected) to 20/20 (GP corrected)

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Pediatric Refractive Surgery

7

Erin D. Stahl

Abstract

Refractive surgery is performed in children who are at risk for permanent vision loss and have no other conventional options for treatment. Various forms of refractive surgery including corneal laser, phakic intraocular lenses, refractive lens exchange, and refractive lensectomy have been shown to be successful in treating children with debilitating refractive errors. Careful assessment of risks, benefits, and long-term goals of treatment should be considered and discussed with patients and families.

Keywords

Pediatric • Refractive surgery • Anisometropia • Amblyopia • Excimer laser

Introduction

Adult refractive surgery is one of the most common surgical procedures performed in the United States. Laypeople are very familiar with this procedure, and the ease with it can reduce the reliance on glasses and contact lenses. On the other hand, pediatric refractive surgery is so rarely performed that many ophthalmologists and optometrists are not aware that it can be a treatment option. Various techniques of refractive surgery have been performed on children for the past 15 years. Deciding if a child is a candidate for refractive surgery involves many factors and relies on carefully weighing risks and potential benefits of the procedure.

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Case Studies

The following cases will serve as examples of the difficult clinical scenarios and decisions facing a pediatric refractive surgeon.

Case 1

A 17-year-old boy has significant developmental delay and a refraction of −7.00 D in both eyes. He wore glasses until age 10 and then began to remove and break his glasses. Contact lenses were attempted and he could not successfully wear them. From age 10 to 17, he did not wear any refractive correction. He is confined to a wheelchair though he is capable of ambulating and is nonverbal. His mother reports that he holds his hands close to his face and looks at them most of the day at home and school. He was referred for refractive surgery, and photorefractive keratectomy (PRK) was performed in both eyes with a target refraction of plano. His surgery was done under general anesthesia. After the 1-week healing phase, his mother

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reported that he began ambulating independently and began to feed himself at the table. His school reported improvement in behavior and more interaction with others. He no longer holds his hands to his face but interacts with people in the room.

Case 2

A 6-year-old boy has unilateral myelinated nerve fiber layer, myopia of $-11.50+3.00\times90$ refraction, and best-corrected vision of 20/70. He was very compliant with patching for the past 5 years and wore his glasses daily. He was referred for refractive surgery and underwent PRK with a target refraction of −1.00 D in the involved eye. Postoperatively his refraction was −1.00 and with this correction in place, his vision was 20/50. He continued wearing glasses for his residual refractive error and was patched until age 8 and had a final best-corrected vision of 20/50.

Case 3

A 19-year-old boy has bilateral refractive errors of −22.00 D and significant developmental delay. He is nonverbal and could ambulate with the assistance of his parents. He was fearful to be around other people and was generally confined to his house. He had worn refractive correction when he was a young child but had not been compliant with glasses for many years. He was too strong and combative to attempt contact lenses. After thorough informed consent, he was taken to the operating room for unilateral refractive lensectomy. An examination under anesthesia (EUA) was performed, and his aphakic refraction was calculated to be −2.00 D. A thorough retinal exam was also performed and no significant pathology was identified. A refractive lensectomy with anterior vitrectomy was performed, leaving the patient aphakic. His postoperative refraction was −2.00 D and his parents noted a significant change in behavior. He was no longer fearful to leave the house and could ambulate independently. He has had no retinal complications to date.

The cases discussed above show examples of children and young adults who have refractive errors that cannot be corrected with conventional means and as a result have poor vision or risk permanent vision loss. The discussion below will cover which children could be candidates for refractive surgery, the process of surgical decision-making, and challenges unique to refractive surgery in the pediatric population.

Surgical Candidates

The most common indications for pediatric refractive surgery are bilateral high myopia, anisometropic amblyopia, and, less commonly, craniofacial or muscular disorders [1]. Most children with bilateral high refractive errors will happily wear glasses or contact lenses and develop good visual acuity. Some children, especially those with neurodevelopmental disorders, will reject glasses and will not wear contact lenses for a variety of reasons. When these children have a visual impairment in addition to their other disabilities, their level of impairment is compounded. As demonstrated in the cases above and other case reports, treating the refractive error in these children can have a positive impact on their overall behavior and quality of life [2]. It is often impossible to measure visual acuity pre- or postoperatively so the impact of the treatment is measured by functional improvement as opposed to measured improvement in acuity. As surgery is performed under general anesthesia, it is important that the child be healthy enough to undergo elective anesthesia. It is also important for the parents to be well informed about the healing phases of surgery and the necessity of administering topical eye medications at home after surgery. In rare cases, arm restraints may be needed postoperatively to prevent the child from damaging the eye or eyes.

The second most common group of patients, those with unilateral high refractive error and resultant amblyopia, are only .candidates if they have failed conventional treatment. Glasses, contact lenses, and patching therapy must be attempted and failed before pursuing surgical correction. Most children will fully improve with conventional treatment, and only a few will go on to being candidates for surgical correction. Improvement in visual acuity is most rapid and effective when surgery is combined with vigorous postoperative patching therapy. But in many cases the treatment is considered because of poor compliance with patching therapy. Paysse has shown that surgical refractive correction alone (without patching) can still show moderate improvement in best-corrected visual acuity [3]. These children are typically neurodevelopmentally normal making visual acuity testing an important tool in determining treatment success.

The third and least common group of children who could benefit from refractive surgery are those with craniofacial

or musculoskeletal disorders that preclude glasses wear. For children with nasal or ear malformations, spectacle wear can be very difficult. Contact lenses can be attempted, but if unsuccessful, refractive surgery can be used to provide the ability to develop good vision. Children with cerebral palsy, poor muscle tone, or the inability to use the neck muscles often have difficulty wearing glasses as they do not stay in proper position. These children may chronically hold their head in a position where they are looking over or under the frames of their glasses. Even with wraparound frames, some children will repeatedly dislodge their glasses against the head support on their wheelchairs. If these children fail all trials with different glasses frames and contact lenses, they can be candidates for refractive surgery.

Surgical Options

Once a child has been identified as a candidate for refractive surgery, the type of surgery that is most suited to the individual child must be selected. This can be one of the most difficult aspects of treatment as refractive error, target correction, anatomy of the eye, and age of the patient must be considered when planning surgical treatment. The various surgical options will be discussed according to level of refractive error to be treated.

Low to Moderate Myopia and Low Hyperopia

Most children with low hyperopia or myopia are not candidates for refractive surgery. Low levels of refractive error are unlikely to cause amblyopia in the setting of anisometropia, and children who choose not to wear correction can usually function adequately (Fig. 7.1). Excimer laser correction (either LASIK or PRK) is the procedure of choice for refractive errors ranging from approximately +4.00 D to −10.00 D. This is the range where there is maximization of refractive outcomes, stability, and patient satisfaction with corneal laser surgery. Excimer laser treatment can be useful in larger myopic refractive errors (approximately −6.00 D to −10.00 D). A thorough examination of the cornea must include corneal thickness, keratometry or topography, and a visual inspection with the slit lamp. If the patient is not cooperative for this testing, it can be performed under anesthesia at the time of the planned treatment. If the corneal thickness is not adequate, if there is inferior steepening, or corneal scarring, the patient may not be a candidate for corneal laser surgery. LASIK and PRK procedures have both been performed on children [4–7]. LASIK has the benefit of having less postoperative pain and faster visual recovery. PRK has the benefit of not having a risk of flap disruption and thicker residual corneal bed. For these reasons, the majority of pediatric refractive surgeons in the United States choose PRK for their laser treatments. All excimer laser platforms are FDA approved for use in patients older than 18 years of age. All pediatric treatments are off label.

High Myopia

Decisions about treatment options for moderate to high myopia often hinge on age and refractive error. In young patients with >−8.00 D of myopia, laser treatments are sometimes an option when the patient has adequate corneal thickness. If there is a concern about corneal thickness, young myopic patients are often better candidates for phakic IOL (PIOL) implantation. There are two models of PIOL that are FDA approved in the United States for use in adult patients and are capable of treating up to 18 D of myopia. Their use in pediatric patients is considered off

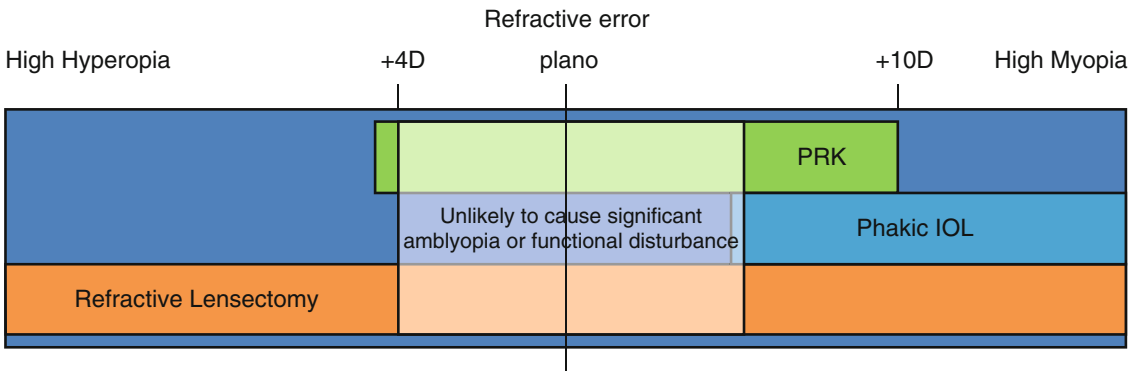

Fig. 7.1 Recommended ranges of refractive error by type of surgery. *Lighter* shaded box shows refractive errors unlikely to cause significant amblyopia

label. Studies have shown that the PIOL technologies provide excellent optical outcomes in patients with high refractive errors [8–10]. As this technology is more invasive than surface refractive procedures, risks involve endothelial cell loss, cataract formation, risk for retinal detachment, and the generally increased risk of intraocular surgery [11, 12]. The patient must have adequate anterior chamber depth so that an IOL is safely implanted. Anterior chamber depth, white-to-white, and axial length must all be measured preoperatively to ensure enough room and adequately size the implant.

In a very highly myopic eye of greater than −20.0 D, a refractive lensectomy with or without IOL placement is a surgical option [13]. The risks of this procedure are considerable as the retina may be very thin and prone to detachment. The patient will also lose accommodation after surgery, and this should be understood by the patient and the parents. Some children who undergo retinal laser for retinopathy of prematurity as infants often have very high myopia due to abnormal lens formation and may not have adequate anterior chamber depth to be a candidate for PIOL; they could also benefit from refractive lensectomy.

Moderate to High Hyperopia

As there is no FDA-approved PIOL for the treatment of hyperopia, highly hyperopic patients have more limited surgical options. Excimer laser treatments are most effective up to +4.00 D. The discrepancy between the limits for hyperopic and myopic treatment results from the relative ease in flattening the central cornea (myopic treatment) as contrasted with the difficulty in achieving a satisfactory optical result with steeping the central cornea (hyperopic treatment). Hyperopic patients outside the range of excimer laser treatments have the option of a refractive lens exchange with IOL implantation.

Challenges of Pediatric Refractive Surgery

As in most aspects of medicine, children are not just small adults when considering refractive surgical procedures. There are many unique challenges that arise when considering refractive surgery for the pediatric population.

Patient Cooperation

Adult laser and intraocular refractive surgeries are for the vast majority outpatient procedures utilizing only topical anesthesia. The patient is instructed to fixate on the operating light or laser target to center the treatment and assist in surgical manipulation. When dealing with a pediatric population, the cooperation of the patient is much more variable. Adolescent subjects will often be able to lay still and fixate on targets as instructed [7], but in surgery performed to prevent amblyopia, children are much too young and require sedation/anesthesia. In the United States, studies have reported the use of brief general anesthesia during excimer laser procedures [14, 15]. Intraocular surgeries have been preformed with general anesthesia in a similar manner to pediatric cataract surgeries.

Another challenge arises when considering the logistics for administering anesthesia during excimer laser treatments. Excimer lasers are cumbersome pieces of equipment and are for the most part immobile. They are usually located in outpatient surgery centers or in the office of refractive surgeons—far from the pediatric anesthesiology needed to perform sedation. Excimer laser technology is also very costly with equipment prices of $100,000 and more. For the most part, this problem has been solved by bringing the laser into a pediatric hospital setting at which refractive procedures are more commonly performed; this limits the number of individuals who can perform the procedure.

A final challenge with pediatric refractive surgery is the potential for flap (LASIK) or epithelial (PRK) complications in the immediate postoperative period. Adult patients can for the most part be trusted not to rub or manipulate their eye in the healing stages postoperatively. Children, especially young children, may manipulate the eye after surgery and cause a flap slip after LASIK requiring additional surgery. After PRK epithelial disruption from manual manipulation may cause delaying healing subsequently increasing the risk for haze formation.

Long-Term Risks for Corneal Changes

The postoperative biomechanical changes in the adult cornea are being elucidated but are not yet fully understood. A more thorough understanding of the maximal tissue ablation and limitations to keratorefractive surgery has been explored and continues to be the subject of intense research in adult refractive surgery. When considering intraocular or cornea-based refractive surgery in children, it is necessary to carefully consider these issues as well. It is known that pediatric eyes have a greater propensity toward the development of postoperative inflammation and that pediatric corneas are thinner than adult corneas. Due to these differences, special concern exists for the development of haze, regression, and ectasia in pediatric treatments.

Desired Postoperative Correction

Planning for refractive surgery in the adult population consists of targeting a plano or monovision refraction depending on the age or activities of the patient. Planning the intended treatment and postoperative refractive outcome in pediatric surgery is more challenging and complicated. For the younger pediatric population undergoing surgery to prevent amblyopia, the desired postoperative refraction is plano. In cases of anisometropia, the treatment goal is often to match the refraction in the other eye. For older children the ideal postoperative refraction has not been established. As most children can tolerate a mild degree of hypermetropia, a mildly hyperopic target may be appropriate in older children who will continue to have a natural myopic progression with growth. Although population studies have examined the growth of the eye and changes in refraction, it cannot be calculated for an individual eye at this time. The key to these calculations is to keep in mind that the refractive error of the child will change with age, and the refractive surgeon must have future options available to handle future refractive needs.

Conclusion

The emerging field of pediatric refractive surgery is an interesting marriage of the rapidly progressing field of refractive surgery and the traditionally ultraconservative field of pediatric ophthalmology. The refractive side offers its advanced technologies, and the pediatric group is charged with making conscientious and practical decisions regarding their use in children. In cases of anisometropic amblyopia and bilateral high myopia, surgeons have found clinical situations in which refractive surgery has been effective, safe, and beneficial.

Overall the field of pediatric refractive surgery shows great promise in its ability to help a small segment of the pediatric population. Maximizing visual potential in these patients who have often failed traditional therapies is the ultimate goal of these endeavors. Emerging techniques and technology may bring even more possibilities for benefit in an expanded population of infants, children, and adolescents.

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Part III

Amblyopia

Practical Management of Amblyopia

8

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Abstract

Amblyopia is the leading cause of unilateral visual loss in children. Fortunately, amblyopia is both preventable by screening for risk factors and treatable, especially if identified at an early age. Amblyopia is classified by etiology into strabismic, refractive, and deprivational. A significant amount of research has been dedicated to further understand the underlying mechanisms of amblyopia and to optimize its treatment. The Pediatric Eye Disease Investigator Group [PEDIG] has been instrumental in spearheading current studies that guide evidence-based management.

In this chapter, we highlight the pathophysiology of amblyopia, advances in screening paradigms, and evidence-based treatment strategies with an emphasis on landmark studies that guide providers in the management of patients with amblyopia. Example cases are presented throughout the chapter to highlight diagnosis and management.

Keywords

Amblyopia • Strabismus • Anisometropia • Isoametropia • Refractive • Deprivational • Penalization • Occlusion • Atropine

Introduction

Amblyopia is a disorder of early visual development in which best-corrected visual acuity (BCVA) is reduced in one or both eyes for reasons that cannot be fully attributed to structural abnormalities of the eye or visual pathways [1]. It occurs as a result of an interruption in cortical visual input during the critical period of visual development and varies in severity depending on timing and etiology.

In the United States, the prevalence of amblyopia is estimated at between 1 and 5 % of the general population [2–4]. Amblyopia is the cause of permanent vision loss in 2.9 % of adults [3]. The risk factors for the development of amblyopia include refractive errors (either anisometropia in monocular cases or large isoametropia in binocular cases), strabismus, and visual deprivation from conditions that impede the visual axis including ptosis and surface or ocular media opacities. Multicenter prospective, randomized amblyopia screening and treatment trials have helped to shape the clinical practices

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of screening, diagnosis, and treatment of amblyopia. This chapter will provide an introduction to etiology and treatment of amblyopia with emphasis on results of studies by the Pediatric Eye Disease Investigator Group trials and their application to patient care. This chapter is not a comprehensive treatise on amblyopia, and the authors will direct the reader to references provided at the end of the text.

Etiology

The development of normal binocular vision relies on the transmission of clear retinal images to the lateral geniculate nucleus and to the visual cortex in the occipital lobe. Amblyopia is a neurodevelopmental disorder that occurs due to de-correlated binocular input to the visual cortex, but the eye structure itself is normal. Amblyopia is the largest cause of monocular blindness in adults and the most common visual deficit in children [3, 5]. Amblyopia affects a host of visual functions including decreased visual acuity, contrast sensitivity, form and motion detection, crowding, and impaired binocularity. Causes of abnormal visual experience include unequal refractive errors or symmetric high refractive errors (anisometropia or isoametropia, respectively), strabismus, and form deprivation by a variety of abnormalities such as ptosis or media opacity (e.g., cataract, corneal opacity, or vitreous hemorrhage). The eye in amblyopia may otherwise be structurally normal, but may also have other malformations or pathology.

Normally, the neurons in the visual cortex respond to stimulation from both eyes.

The input from each eye remains segregated till they reach the visual cortex. In the visual cortex, the inputs terminate in alternating columns in layer IV C called ocular dominance columns. Amalgamation of inputs from the two eyes on a common cell occurs in the cells above and below layer IV C. This pattern of organization is achieved after birth, and the prerequisite is normal binocular visual experience during the first 6 months of life (defined as critical periods) [6].

In the pioneering experiments done by Hubel and Wiesel, they examined visual cortex neuronal responses in animals raised with monocular deprivation from birth to 6 months. They studied the architecture of ocular dominance columns by using tracer injections to label the axonal terminations of the two eyes in the cortex. They found reduced axonal terminations relaying the input from the deprived eye whereas expanded terminations of the normal eye. These shifts in organization of the ocular dominance columns result in reduced number of cortical cells that respond to input from the deprived eye which is the anatomic basis for amblyopia [7]. Although the first locus of dysfunction appears to occur in V1, abnormalities in the downstream extra-striate cortex have been shown by recent studies using neural recordings in animal models of amblyopia [8, 9] as well as psychophysical and functional MRI studies in humans [10–12]. Involvement of striate as well as extra-striate visual cortex can explain the spectrum of visual function abnormalities that involve both the afferent and efferent visual systems and visual perception in amblyopia.

Currently, the goal of amblyopia treatment is to provide a clear retinal image to the amblyopic eye and to increase the cortical visual input from the amblyopic eye to reverse the amblyopia. While ideally treated in early childhood (<7 years of life), visual improvement has been demonstrated in treated patients up to 20 years of age [13, 14] and in some cases, into adulthood [15]. Newer amblyopia treatment strategies including dichoptic motion coherence task [15] and noninvasive brain stimulation of the visual cortex [16, 17] have shown improvement in visual acuity and stereopsis in amblyopic adults. These treatment effects have been successfully quantified using psychophysical and neuroimaging testing.

Amblyopia is defined as the reduction of best-corrected visual acuity to ≤20/40 or a difference of two lines of recognition acuity between the amblyopic and normal fellow eye. In mild to moderate amblyopia, visual acuity ranges from 20/40 to 20/100 in the amblyopic eye, whereas vision ranges from 20/100 to 20/400 in moderate to severe cases. The most severe vision loss occurs in infants with significant form deprivation (e.g., cataracts, media opacities) in the first 3 months of life. Amblyopia is classified by etiology into strabismic, refractive, and deprivational.

Strabismic amblyopia, one of the more common forms of amblyopia, occurs most frequently in patients with constant, non-alternating heterotropias. In such cases, amblyopia results from cortical suppression of visual input from the constantly deviated eye in order to avoid diplopia or visual confusion. In an effort to further assess the characteristics of amblyopia in children, clinical profiles of amblyopia in children ages 3–6 as well as younger than 3 years of age were explored [18]. In children <3 years of age, 82 % of amblyopia was associated with strabismus; 66 % of these children had strabismus at less than 1 year of age [18]. In children ages 3–6 years, 38 % of amblyopia was associated with strabismus, 37 % with anisometropia, and 24 % with a combination of refractive and strabismic causes [18].

Refractive amblyopia is also common and results from uncorrected unilateral or bilateral refractive errors. *Anisometropic* amblyopia develops when unequal refractive errors lead to a chronically defocused image on the retina of one eye. Low-grade anisometropic hypermetropia and astigmatism, especially oblique astigmatism, can result in significant amblyopia (Table 8.1). Isoametropic amblyopia is less common and is the result of large, often equal uncorrected refractive errors (high hypermetropia, astigmatism, or myopia) in both eyes leading to decreased visual acuity in both eyes (Table 8.1).

Deprivation amblyopia is the least common type and occurs secondary to obstruction of the visual axis. This

Table 8.1 Risk factors for refractive and form deprivation amblyopia [19]

Anisometropic risk factors
– Anisometropia (spherical or cylindrical) > 1.5 D
– Oblique anisometropia > 1 D
Isoametropic risk factors
– Hypermetropia: 3.50 D in any meridian
– Myopia > 3.00 D in any meridian
– Regular astigmatism > 1.5 D
– Oblique astigmatism (10° eccentric to 90° or 180°) > 1.0 D
Other risk factors for form deprivation
– Manifest strabismus
– Media opacity ≥ 1 mm in size
– Ptosis ≤ 1 mm margin reflect distance-1 (MRD-1)

obstruction results from ptosis, eyelid lesions (e.g., hemangiomas), corneal opacities, vitreous hemorrhage, or congenital cataracts. Visual loss from an obstructed visual axis is more profound in unilateral than bilateral cases, and the former warrants earlier surgical intervention than the latter.

In some cases, the mechanism of amblyopia may be multifactorial. For example, patients may present with strabismus and anisometropia, with the eye having the higher refractive error often being the deviated eye. In other cases, a cataract, such as an anterior polar cataract, may be associated with significant anisometropia and only mildly impede the visual axis; in this case the anisometropia rather than the cataract may be the cause of the amblyopia. Likewise, eyelid lesions such as a hemangioma or plexiform neurofibroma may induce astigmatism in addition to partially occluding the visual axis.

Lastly, vision loss in a structurally abnormal eye (e.g., one with optic nerve coloboma, optic nerve hypoplasia, retinopathy of prematurity) should not be assumed to be caused only by the structural anomaly, as there may be an additional component of treatable amblyopia caused by anisometropia, strabismus, or occlusion [20–23]. In such cases, a trial of amblyopia therapy is indicated [20–23].

History and Risk Factors Associated with Amblyopia and Strabismus

Children with a family history of strabismus or amblyopia in a first-degree relative are at increased risk for amblyopia [24]. Other factors associated with risk of amblyopia include premature birth, Down syndrome, childhood glaucoma, and ocular and genetic systemic disorders [24]. Some of the risk factors associated with amblyopia are listed in Table 8.1 and are integrated into screening parameters [19]. It is important to obtain historical information of related pre-, peri-, and postnatal factors especially in infants and young children. The clinician should inquire about growth and developmental milestones and any cardiovascular malformations or conditions that may be taken into consideration prior to prescribing amblyopia therapies such as topical atropine, or propranolol for hemangiomas.

Guidelines for Screening for Amblyopia

Guidelines for screening for amblyopia have been developed by the American Association for Pediatric Ophthalmology and Strabismus [25]. Age-based screening and referral criteria are presented in Table 8.2 [26]. Age-based recommendations for automated preschool vision screening have been developed to optimize sensitivity and specificity for detection of refractive amblyogenic risk factors [27]. They include detection of astigmatism >2.0 D, hypermetropia >4.5 D, and anisometropia >2.5 D in patients 12–30 months; astigmatism >2.0 D, hypermetropia >4.0 D, and anisometropia >2.0 D in patients 31–48 months; and astigmatism >1.5 D, anisometropia >1.5 D, and hypermetropia >3.5 D in patients >49 months [27]. Vision screening methods should be based on Cotter et al. [28] as well as AAPOS guidelines [25].

The Clinical Examination

The ophthalmologic examination should be complete, starting with observation of the child for manifest strabismus, anomalous head position, or dysmorphic facial features. Visual acuity should be assessed with age-appropriate testing methods (a detailed description of age-appropriate testing is found in Chap. 1). Importantly, the "crowding phenomenon" or "contour interaction" is often observed in eyes with amblyopia. Because of this phenomenon, visual acuity as measured by single optotypes will overestimate visual acuity. Therefore, whenever possible linear or single optotypes surrounded by brackets or contour interaction lines should be utilized. Fixation preference is also important as measured specifically by the "maintained" component of central, steady, maintained (CSM) in strabismic cases and by the induced tropia test in orthotropic cases (Chap. 1). Dynamic retinoscopy should be completed to assess for hypo-accommodation, which may contribute to persistent amblyopia despite treatment [29]. (Note: Testing is ideally completed with the patient wearing the appropriate refractive correction. See Chap. 73.)

An afferent pupillary defect (APD) is uncommon in amblyopia, and the presence of an APD should alert the clinician to an organic etiology. A complete sensorimotor examination should be completed followed by cycloplegic dilation. Examination of the fundus is extremely important to evaluate for any organic lesions such as optic nerve or macular hypoplasia that can lead to decreased vision [30]. Cycloplegic refraction is obtained and ideally, best-corrected visual acuity subjectively confirmed whenever possible. The relevant findings should be discussed with the parents, and if amblyopia is suspected or diagnosed, anticipatory guidance on natural history and treatment is paramount to maximize adherence.

Table 8.2 American Association for Pediatric Ophthalmology and Strabismus age-based screening and referral criteria for amblyogenic risk factors [26]

Age	Tests	Referral criteria/comments
Newborn to 12 months	• Ocular history • Vision assessment • External inspection of the eyes and lids • Ocular motility assessment • Pupil examination • Red reflex examination	• Refer infants who do not track well after 3 months of age • Refer infants with an abnormal red reflex or history of retinoblastoma in a parent or sibling
12–36 months	• Ocular history • Vision assessment • External inspection of the eyes and lids • Ocular motility assessment • Pupil examination • Red reflex examination • Visual acuity testing • Objective screening device "photoscreening" • Ophthalmoscopy	• Refer infants with strabismus • Refer infants with chronic tearing or discharge • Refer children who fail photoscreening
36 months to 5 years	• Ocular history • Vision assessment • External inspection of the eyes and lids • Ocular motility assessment • Pupil examination • Red reflex examination • Visual acuity testing (preferred) or photoscreening • Ophthalmoscopy	Visual acuity thresholds • Ages 36–47 months: must correctly identify the majority of the optotypes on the 20/50 line to pass • Ages 48–59 months: must correctly identify the majority of the optotypes on the 20/40 line to pass • Refer children who fail photoscreening
5 years and older[a]	• Ocular history • Vision assessment • External inspection of the eyes and lids • Ocular motility assessment • Pupil examination • Red reflex examination • Visual acuity testing • Ophthalmoscopy	• Refer children who cannot read at least 20/32 with either eye. Must be able to identify the majority of the optotypes on the 20/32 line • Refer children not reading at grade level

[a]Repeat screening every 1–2 years after age 5

Case Studies

Herein, we present three cases of amblyopia: strabismic (Case Study 1), anisometropic (Case Study 2), and deprivation (Case Study 3) with a discussion of evidence-based management guidelines.

Case Study 1 (Amblyopia from Strabismus)

An 8-month-old girl presents with crossing of the left eye since the age of 4 months. Patient was born at full term, with normal growth and development. She does not have a family history of amblyopia or strabismus.

She had CSM vision in the right eye and was CSUM in the left eye, with an esotropia of about 45 PD and full ocular motility. Cycloplegic refraction revealed a mild hypermetropic correction of +1.25 D OU. Retinal examination was unremarkable.

Assessment: This patient has a large-angle esotropia, most consistent with infantile esotropia, and a strong right fixation preference. Moderate to severe amblyopia is suspected in the left eye based on fixation behavior and inability to maintain fixation in the left eye under binocular conditions. The hypermetropia is very low and unlikely to contribute an accommodative component to the esotropia.

Management options at this time include:

- Occlusive penalization (e.g., patching the sound eye) for 6 h/day and delaying surgical correction of the esotropia until vision appears to be equal in both eyes
- Surgical correction followed by occlusion therapy for the amblyopia

(continued)

Patching was instituted and glasses were not prescribed for the low hypermetropia [1].

At the follow-up 6 weeks later, at the age of 9.5 months, the family reports that the eyes are still crossing, but the right eye is also crossing now. They report adherence to patching regimen.

Examination shows CSM OD and CSUM (although now holds fixation OS through a blink). She continued to have an esotropia of 45 PD. Surgery was performed and the medial rectus muscles were recessed 6 mm.

Four weeks after the surgery and continuation of patching of the right eye, the eyes were straight at distance and there was a small esophoria at near viewing. Visual acuity tested with Teller cards was equal in both eyes at 20/63. Patching was tapered over the following 2 months. The child continues to be observed and visual acuity checked every 3 months.

Comments

Management of Moderate to Severe Amblyopia Full-time patching is best avoided in infants, because of the fear of occlusion amblyopia. Similarly atropine penalization in this age group is more likely to result in amblyopia of the atropinized eye than in older children.

Six hours of patching is effective in treating severe amblyopia. The amblyopia treatment studies (ATS), specifically ATS 2A [31] and ATS 2B [32], organized and spearheaded by the Pediatric Eye Disease Investigator Group (PEDIG), served to provide guidelines for the management of severe amblyopia (ATS2A) defined as visual acuity of 20/100–20/400 and moderate amblyopia defined as visual acuity of 20/40–20/80 in children ages 3 to less than 7 years of age.

ATS 2A compared 6 h of daily patching to full-time (defined as all, or all but 1 h) patching daily for a 4-month period and found visual acuity in the amblyopic eye improved a similar amount in both groups, thereby suggesting that 6 h of occlusion therapy to be sufficient in the treatment of severe amblyopia [31].

ATS 2B compared part-time (6 h) to minimal (2 h) patching for moderate amblyopia, combined with 1 h/day of near visual activities while patching, and found a similar improvement in visual acuity in both groups [32].

Cessation of Amblyopia Therapy The Amblyopia Treatment Study 2C (ATS2C) [33] evaluated the recurrence of amblyopia at 52 weeks in children <8 years of age who were successfully treated with patching or atropine. Recurrence was defined as a 2 or more logMAR reduction in visual acuity. The study found that amblyopia recurred in 24 % of patients and was more common in those treated with 6–8 h/day of patching. Therefore, for patients who are patched >6 h/day, the treatment should be tapered to 2 h/day prior to cessation [33].

Alternatives to Occlusion Therapy for Amblyopia The first PEDIG amblyopia study (ATS1) [34] compared atropine 1 % to patching for moderate amblyopia (20/40–20/100) in children ages 3 to less than 7 years. Patients enrolled in ATS1 had strabismic, refractive, or combined mechanism amblyopia. The occlusion protocol consisted of 6 h of patching daily or pharmacological treatment with atropine 1 % instilled daily into the non-amblyopic eye. Patients who were randomized to patching had a more rapid improvement in visual acuity; however, by 6 months, the mean visual acuity in each group was within a line difference, and this difference was considered clinically insignificant. This similar visual acuity difference in both treatment groups continued to the 2-year follow-up [35]. On average, however, visual acuity in the amblyopic eye remained two lines worse than the non-amblyopic eye. These findings were consistent at ages 10 and 15 years, with mild residual amblyopia common and outcome similar regardless of initial treatment with patching or atropine [36, 37]. Therefore, atropine 1 % is an acceptable alternative to patching in children 3–7 years of age with moderate amblyopia.

ATS4 compared daily atropine treatment to weekend atropine administration in children ages 3 to less than 7 years [38]. As in ATS1, the amblyopia was secondary to strabismus, refractive error, or both. Atropine 1 % was instilled daily in group 1 vs. twice a week (on Saturday and Sunday) in group 2. At the conclusion of the study, the weekend use and the daily use of atropine had similar effects on visual acuity improvement in the treatment of moderate amblyopia in children ages 3 to less than 7 years.

In moderate to severe amblyopia in patients 3–12 years of age, the weekend use of atropine leads to visual improvement with or without optical penalization and therefore can be considered in this patient group [39]. The authors advocate maximizing patching therapy before resorting to weekend atropine use.

In addition to penalization with patching or atropine, Bangerter filters can be considered for treatment of moderate amblyopia. ATS 10 evaluated the use of Bangerter filters versus standard occlusion with patch-

(continued)

ing for the treatment of moderate amblyopia (20/40–20/80) in children 3 to less than 10 years of age [40]. Two hours of patching daily was compared to the use of a Bangerter filter of 0.3 or 0.2 depending on the level of visual impairment in the amblyopic eye. Bangerter filters can be adjusted according to the intended level of visual deprivation and may be associated with improved compliance with treatment as the filter is applied to the spectacle lens as opposed to the direct application of the patch to the skin. After 24 weeks of treatment, visual acuity improved 1.9 lines in the Bangerter filter treatment group and 2.3 lines in the patching group, suggesting that Bangerter filters were not inferior to patching in children ages 3 to less than 10 years with moderate amblyopia [40].

Can Spectacles Alone Be Used to Treat Strabismic or Combined Strabismic/Refractive Amblyopia? ATS5 included a small observational study of 12 patients with strabismic amblyopia who demonstrated improved visual acuity with refractive correction alone [41]. In a larger study, ATS13 evaluated the use of spectacles alone for the management of strabismic and combined mechanism amblyopia (20/40–20/400) in children ages 3 to less than 7 years [42]. Visual acuity improved more than two lines in the amblyopic eye in 75 % of patients and more than three lines in 54 % of patients, with resolution of amblyopia in 32 % of patients. The treatment had a more significant effect in patients with strabismic amblyopia, with roughly three lines improvement in visual acuity, compared to two lines in patients with combined mechanism amblyopia, thereby suggesting that amblyopia can be treated with spectacle correction alone. While the patient in Case Study 1 did not have significant refractive error, patients with strabismus and significant hypermetropic refractive error may be initially treated with correction of the refractive error without patching.

Should Amblyopia Be Treated Before Surgical Intervention? Although ocular alignment cannot be achieved without surgical intervention in a child with early onset infantile large-angle esotropia, significant refractive errors (e.g., hypermetropia >2.00 D) and anisometropia should be corrected prior to surgical intervention. While some practitioners treat amblyopia prior to surgical intervention, Lam and colleagues demonstrated that corrective surgery before full resolution of amblyopia was safe and effective as long as therapy was continued after surgery [43]. A more recent Cochrane review concluded that the optimal timing of strabismus surgery in relation to amblyopia treatment is unknown, and available evidence is only available from nonrandomized trials [44].

In Case Study 1, amblyopia in the left eye was partially treated prior to surgery. After 6 weeks, the visual behavior and ocular alignment were reevaluated, and surgery was performed to promote binocular development. Future randomized controlled trials may be helpful to clarify the timing of strabismus surgery relative to amblyopia treatment. Most importantly, the family should be educated that amblyopia treatment will likely need to be continued after surgery.

Case Study 2

A 4-year-old boy failed his vision screening at school. His birth and past medical history are unremarkable. There was no family history of amblyopia or strabismus.

Visual acuity (bracketed HOTV) was OD 20/200 and OS 20/20. Strabismus was not present and stereoacuity was 200″. Worth-4-dot showed that he suppressed OD at distance but not at near. His fundus examination was unremarkable. Cycloplegic refraction was OD +5.00 + 1.75 × 105 (20/150) and OS +1.50 + 0.50 × 090 (20/20).

Assessment: This patient has moderate to severe amblyopia (20/100–400) in the right eye secondary to hypermetropic anisometropia. The vision is correctable to only 20/150. He also appears to have monofixation syndrome with central suppression and peripheral fusion with some gross stereopsis (see Chap. 2).

Management options at this time include:

(1) Full correction of cycloplegic refraction
(2) Partial correction of cycloplegic refraction
(3) Optical, occlusive, or pharmacological penalization
(4) A combination of options 1 and 3 or 2 and 3

Because the patient was orthophoric, the patient was prescribed partial correction of his cycloplegic refraction as per the PEDIG protocol [32, 34]: OD +3.50 + 1.75 × 105 and OS plano +0.50 × 090. If he had evidence of accommodative esotropia, the full cycloplegic refraction would have been prescribed. Because visual acuity can improve using refractive correction alone (refractive adaptation) [45, 46], the patient did not receive penalization treatment initially. The family was informed of the possible later need for penalization therapy.

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The patient was followed at 6 weeks intervals, and visual acuity improved and stabilized at 20/50 after 16 weeks of follow-up. At that time, patching 2 h/day, pharmacological penalization with weekend atropine and/or Bangerter filters were discussed. The family elected to use weekend atropine (one drop on Saturdays and Sundays) as the initial treatment [38]. Systemic signs of flushing, dry mouth, hyperactivity, and tachycardia were discussed with family, and they were to call immediately if these symptoms develop (note that systemic sensitivity to atropine is especially common in patients with trisomy 21 and extreme caution in this patient population). The family was asked to discontinue the medication 2 weeks prior to the next follow-up appointment.

Eight weeks later, the family reported adherence to the weekend use of atropine, and the patient was wearing glasses 100 % of the time. Visual acuity was OD 20/40 and OS 20/20. Dynamic retinoscopy (cc) was brisk and sustained OU. Stereopsis was 60″. Worth-4-dot: Distance: fusion and near: fusion. All parameters indicated an improvement of the amblyopia and of binocular function. Full-time refractive correction and atropine 1 % on the weekend in the left eye were continued.

No additional improvement was demonstrated at 8-week follow-up, and treatment was increased to atropine 1 % in the left eye daily. The patient returned for follow-up after 12 weeks of treatment. Visual acuity continued to be OD 20/40 and OS 20/20. Manifest overcorrection with –0.50 lens showed VOD 20/40. (Patients with hypermetropia who are overcorrected may not demonstrate visual improvement, and the clinician must rule out changing refractive error as a cause of failure to improve with amblyopia therapy. This is subsequently followed by cycloplegic refraction.) Stereoacuity was 60 s arc. Worth-4-dot showed distance and near fusion. Cycloplegic retinoscopy was OD +4.75 + 1.75 × 105 (20/40) and OS +1.25 + 0.50 × 090 (20/20).

Visual acuity appeared to have reached a plateau and no improvement since last visit. The current glass prescription was confirmed with cycloplegic refraction; thus changing refractive error was not contributing to failure for vision to improve with daily atropine use.

Continuing the current therapy or adding occlusion therapy was discussed with the parents who thought the patient would not tolerate patching, but may be able to use a Bangerter filter. Subsequently, daily atropine drops were continued and a 0.2 Bangerter filter was empirically selected. However, given the visual acuity in the right eye, 0.4 would have blurred the vision to the 20/50 level in the left eye and is also a reasonable alternative.

After 8 weeks, the family reported compliance with glasses, Bangerter filter, and daily atropine use. Visual acuity OD improved to 20/25 + 1, and OS remained at $20/20^{-1}$. Stereoacuity was now 40″.

Management options at this time were:

(1) Stop atropine drops and Bangerter filter.
(2) Continue with daily atropine penalization.
(3) Continue with Bangerter filter.
(4) Continue with weekend atropine and Bangerter filter.
(5) Continue with daily atropine and Bangerter filter.
(6) Continue with weekend atropine and Bangerter filter 50 % of the time.

After discussion with family, weekend atropine was administered in combination with Bangerter filter 50 % of the time. Although this specific tapering strategy is not evidence based, this patient is probably at high risk for recurrence of the amblyopia, given he is using full-time Bangerter filter and daily atropine (as well as a mild degree of optical penalization with the plano lens).

The patient's vision was maintained at the next 8-week follow-up visit. The Bangerter filter was discontinued at that time, and weekend atropine was continued until follow-up visit 8 weeks later. Visual acuity was maintained at last follow-up visit (2 years after discontinuation of atropine).

Comment

- **Prescribing glasses in patients with anisometropic amblyopia.** (Preferred practice patterns for prescribing refractive correction in the setting of **asymptomatic** anisometropia can be found in Appendix 1.)

In general, optical prescription for amblyopic eyes should be based on the refractive error as determined with cycloplegia with 1 or 2 % cyclopentolate (depending on patient's weight, iris color, and dilation history) [47]. Adjunctive agents such as phenylephrine may also be used [47]. In the ATS5 protocol, symmetric reduction in plus lens power may be necessary to foster acceptance of spectacles by a child. In PEDIG ATS5 protocol for the treatment of anisometropic amblyopia in children with refractive correction [47], the investigators based the spectacle prescription on cycloplegic refraction (cyclopentolate 1 %), and anisometropia, astigmatism, and myopia were fully corrected. In the setting of hypermetropic anisometropia as in Case Study 2, the full cycloplegics error may be symmetrically undercorrected by no more than +1.50 D in both eyes to foster acceptance [47]. If the hypermetropic anisometropic prescription is symmetri-

(continued)

cally reduced, the author will often check dynamic retinoscopy in correction at the follow-up visit, as hypo-accommodation in the amblyopic eye may indicate the need for full cycloplegic refraction to prevent a defocused image at near [29]. Instructions for performing dynamic retinoscopy may be found in Chaps. 69 and 73.

- **How is anisometropic amblyopia treated**?

I. Refractive Correction

Historically, anisometropic amblyopia has been treated with refractive correction combined with occlusion or pharmacologic penalization. However, based on the results of ATS5, initial treatment of anisometropic amblyopia with glasses alone may be utilized [47]. In this study of 3 to <7 year-old patients, amblyopia improved with optical correction alone by >2 lines in 77 % of cases and resolved in 27 % (see PEDIG trial Table 8.3). In children age 3–7 years with anisometropic amblyopia that had not been previously treated, visual acuity improved by 2 or more logMAR units in 77 % of patients and completely resolved in 45 % over the 30-week study period [47]. They also noted that the treatment effect seems to plateau after 15 weeks of spectacle wear [47]. Higher degrees of anisometropia and moderate to severe visual loss at baseline were less likely to improve with refractive correction alone [47]. Refractive correction alone as a primary initial treatment was also explored in patients 7–17 years of age [48]. In this age group, amblyopia improved with refractive correction alone in approximately 25 %; however, most patients required further amblyopic treatment with penalization [48]. Thus, refractive correction alone results in improved visual acuity and may be utilized as the initial treatment for both anisometropic [47, 48] and strabismic amblyopia (Cotter, 2007 #1086). In Case Study 2, this patient was 4 years and had moderate to severe vision loss. He did respond well to refractive correction alone, but required additional penalization therapy consistent with the findings of Cotter and colleagues [47].

If residual visual disparity is still present after refractive correction, most commonly utilized treatment options include part-time patching, Bangerter filters, optical penalization, and pharmacologic penalization with atropine. Other modalities including contact lenses and refractive surgery may apply in a select patient population. Levodopa has been utilized to treat residual amblyopia, but efficacy was not demonstrated in placebo-controlled clinical trials. Emerging therapies are focused on reducing suppression by promoting binocularity, which is lost in the process of amblyopia.

II. Therapies for Moderate Amblyopia (Best-Corrected Visual Acuity (BCVA) 20/40–80)

A. Patching

In ATS2B, patients 3–7 years of age were treated with either 6 h of patching or 2 h of patching combined with 1 h of near visual activities [32]. Initially, the group patching for 6 h/day experienced a more rapid rate of improvement. However, at 4 months, there was no statistical difference in visual acuity between the two groups, with visual acuity of at least 20/32 in the amblyopic eye [32]. One of the inherent difficulties of this study was in assuring compliance to the prescribed therapy, with self-reported compliance likely an overestimation of actual treatment time [32, 57]. Therefore, prescribing 2 h of patching may be equivalent to prescribing 6 h of patching with visual acuity in terms of visual result. Despite these limitations, the patients who were prescribed 2 h/day of patching experience visual improvement with a majority with visual acuity of at least 20/32 at the end of the study [32]. The most common method of patching is with adhesive patches; however, reusable spectacle-mounted covers may be used. Note that if amblyopia does not improve with the spectacle-mounted cover, the patient may be peaking or looking over the cover, thus not adequately treating the condition [58].

B. Pharmacological Penalization with Atropine

1. Daily Atropine

Atropine is a parasympatholytic agent that inhibits the muscarinic acetylcholine receptors leading to inhibition of accommodation and dilation of the pupil, thus blurring the vision especially near the non-amblyopic eye. As discussed in the previous section on strabismic amblyopia, the ATS1 was a randomized trial of children ages 3 to <7 years of age who were randomized to either a minimum of 6 h of patching or daily atropine for 6 months [34]. The visual acuity improved slightly faster in the patching group; however, the visual acuity at 6 months was not statistically significant (3.16 lines in patching group, 2.84 lines in the atropine group) [34]. Thereafter, amblyopia treatment was via investigator discretion. At patient age of 15 years in the ATS1 extended study, both treatment modalities resulted in good visual outcome, with visual acuity of 20/25 in 60 % of amblyopic eyes. Mild residual amblyopia was common, with approximately a 2.1 LogMAR intraocular difference at 15 years of age [36]. Those patients who were enrolled

(continued)

Table 8.3 Select PEDIG trials with published results

	ATS no./study design	No. of patients age range	Study period	Comments/results/application
Moderate amblyopia (BCVA 20/40–80)				
Anisometropic	ATS 5 [47], prospective noncomparative intervention Refractive correction alone	84 (3 to <7 years)	Up to 30 weeks	• VA 20/40–20/250 (moderate and severe included)
				• 77 % improved >2 lines with glasses alone
				• 27 % had resolution with glasses alone
				• Likelihood of resolution was not related to age, but to better baseline VA and lower degrees of anisometropia
				• Optical correction alone may serve as initial treatment for anisometropic amblyopia
Strabismic	ATS 5 [41], prospective interventional case series Refractive correction alone	12 (3 to <7 years)	Up to 25 weeks	• VA improved by >2 lines from glasses alone in 75 %
				• Amblyopia resolved in 25 %
				• Small study, but confirms findings of Stewart et al. [45]
				• Optical correction alone may serve as initial treatment for strabismic amblyopia
	ATS 13 [42], prospective, interventional case series, spectacles for strabismic, or combined mechanism	146 (3 to <7 years)	18 weeks	• All patients had strabismus; some had both strabismus and anisometropia. All given cycloplegic refraction
				• VA improved 2.6 lines, amblyopia resolved in 32 % irrespective of improvement in alignment
				• Higher likelihood of resolution in purely strabismic amblyopia as compared to combined mechanism
				• Optical correction alone results in improved VA in patients with strabismus > combined mechanism
Anisometropic or strabismic or combined mechanism	ATS1 [34]/RCT occlusion vs. atropine	419 (3 to <7 years)	6 months	• Patch 6 h vs. atropine daily
				• BCVA improved in both groups: 3.16 lines in patching; 2.84 lines in atropine
				• VA > 20/30 and improved by >3 lines in 79 % in patching group and 74 % in atropine group
	ATS1 [35]/RCT	419 (starting age, 3 to <7 years)	2 years	• BCVA improved in both groups: 3.7 lines in patching group; 3.6 lines in atropine group
				• Similar improvement with either 6 months atropine or patching 2 years after treatment
	ATS1-ext [37]/RCT	419 (starting age, 3–7 years)	10 years of age	• No difference in BCVA at age 10 between those prescribed atropine or patching
				• Better VA associated with early treatment (age < 5 years)
				• Residual IOD common (2.0 logMAR lines)
	ATS1-ext [36]/RCT	419 (starting age, 3–7 years)	15 years of age	• No difference in BCVA at age 15 between those prescribed atropine or patching
				• BCVA maintained at age 15 years (60 % 20/25 or better)
				• Residual IOD common (2.1 logMAR lines)
				• Atropine daily and patching 6 h/day are effective for treating amblyopia. Residual IOD is common. Response sustained in most patients at age 15 years
	ATS 2B [32]/ RCT 6 h vs. 2 h patching	189 (3 to <7 years)	4 months	• 6 h vs. 2 h of patching
				• VA > 20/32 and/or >3 lines in 62 % of patients in both groups
				• Prescribing 2 h vs. 6 h/day resulted in similar visual acuity gain

(continued)

Table 8.3 (continued)

	ATS no./study design	No. of patients age range	Study period	Comments/results/application
	ATS 3 [48]/RCT efficacy of amblyopia treatment in older children	507 (age 7–17 years)	6 months	• Optical correction/patching/atropine vs. glasses alone compared
				• 7 to <13 years: 36 % 20/25 with treatment vs. 14 % with glasses alone
				• 13–17 years: 14 % 20/25 with treatment vs. 11 % with glasses
				• 25 % of older children improved with glasses alone, although most require further treatment
				• Older children with amblyopia should be treated. Children who have never been treated previously respond better to treatment
	ATS 4 [38]/RCT Atropine daily vs. weekend dosing	168 (3 to <7 years)	4 months	• Atropine dosed daily compared to atropine dosed weekend only
				• 47 % of daily group and 53 % of weekend group either had VA ≥ 20/25 or greater than or equal to sound eye
				• Both dosing regimens result in similar visual gains
	ATS 5 [49]/RCT, 2 h patching after glasses alone	180 (3 to <7 years)	5 weeks	• VA 20/40–400 and in refractive correction for 16 weeks or no improvement on two visits. Randomized to refractive correction vs. patching 2 h
				• Modest improvement in patching group of 1.1 lines vs. 0.5 lines in the refractive correction alone at 5 weeks
				• Patching 2 h/day improves VA after VA fails to improve with glasses alone
	ATS6 [50], RCT Near activities enhance VA improvement	425 (3 to <7 years)	17 weeks	• All pts (moderate and severe) randomized to patch 2 h + near activities or 2 h + distance activities
				• No difference between groups (2.6 lines in distance activity group and 2.5 lines in the near activity group)
				• Severe amblyopes improved by 3.6 lines with 2 h of patching
				• Near activities do not enhance amblyopia treatment
	ATS8 [51], RCT Atropine + optical penalization	180 (3 to < 7 years)	18 weeks	• Randomized to weekend atropine vs. weekend atropine + plano lens for sound eye
				• 2.8 lines improvement in atropine alone and 2.4 lines improvement in atropine + plano lens group
				• No significant difference in VA improvement between atropine only vs. atropine + plano lens
	ATS9 [14], RCT Patching vs. atropine in older children	193 (7–12 years)	17 weeks	• Randomized to patching 2 h/day vs. weekend atropine
				• VA improvement 8.6 letter in patching group vs. 7.6 letter in atropine group (not statistically significant)
				• 1/5 achieved VA of 20/25 or better
				• Weekend atropine and patching 2 h/day resulted in modest VA improvement in older children
	ATS A10 [40], RCT Bangerter filter vs. patching	186 (3 < 10 years)	24 weeks	• Randomized to patching 2 h/day vs. Bangerter filter (0.3 for VA 20/40–63 vs. 0.2 for VA 20/80)
				• VA improved 1.9 lines in Bangerter group and 2.3 lines in the patching group and VA of 20/25 or better in 36 % Bangerter group and 31 % of patching group
				• Lower treatment burden in Bangerter group
				• Bangerter filter or patching can be considered as initial treatment for moderate amblyopia
Severe amblyopia (BCVA 20/100–20/400)				
Anisometropic	ATS 5 [47], prospective noncomparative intervention Refractive correction alone	84 (3 to < 7 years)	Up to 30 weeks	• VA 20/40–20/250 (moderate and severe included)
				• 77 % improved >2 lines with glasses alone
				• 27 % had resolution with glasses alone
				• Likelihood of resolution was not related to age, but to better baseline VA and lower degrees of anisometropia
				• Optical correction alone may serve as initial treatment for anisometropic amblyopia

(continued)

Table 8.3 (continued)

	ATS no./study design	No. of patients age range	Study period	Comments/results/application
Anisometropic or strabismic or combined mechanism	ATS 2A [31]/ RCT part-time vs. full-time patching	175 (3 to < 7 years)	4 months	• 6 h of patching compared to full-time patching (all hours but 1 h/day)
				• VA improvement not statistically significant: 4.8 lines in 6 h patching group; 4.7 lines in the full-time patching group
				• Prescribing 6 h vs. full-time patching results in similar visual acuity gain
	ATS 3 [48]/RCT efficacy of amblyopia treatment in older children	507 (age 7–17 years)	6 months	• Optical correction/patching/atropine vs. optical correction alone compared
				• 14 % achieved 20/40 or better with treatment vs. 0 % with optical correction alone
				• Older pts with severe amblyopia likely need penalization in addition to optic correction. Pts who had never been treated for amblyopia were more likely to respond to therapy
	ATS 5 [49]/RCT, 2 h patching after glasses alone	180 (3 to < 7 years)	5 weeks	• VA 20/40–400 and in refractive correction for 16 weeks or no improvement on two visits. Randomized to refractive correction vs. patching 2 h
				• Modest improvement in patching group of 1.1 lines vs. 0.5 lines in the refractive correction alone at 5 weeks
				• Patching 2 h/day improves VA after VA fails to improve with glasses alone
	ATS6 [50], RCT Near activities enhance VA improvement	425 (3 to < 7 years)	17 weeks	• All pts (moderate and severe) randomized to patch 2 h + near activities or 2 h + distance activities
				• No difference between groups (2.6 lines in distance activity group and 2.5 lines in the near activity group)
				• Severe amblyopes improved by 3.6 lines with 2 h of patching
				• Near activities do not enhance amblyopia treatment
	ATS9 [39], RCT Weekend atropine	60 (3–6 years)	18 weeks	• Trial 1: required >+1.50 in sound eye. Randomized to atropine + full spectacle correction vs. atropine + plano lens
				• VA improved 4.5 lines (atropine + correction) and 5.1 lines (atropine + plano lens group)
				• Improved VA with atropine in pts with severe amblyopia and greatest in younger children, no difference between spectacle correction vs. plano lens
		40 (7–12 years)	17 weeks	• Trial 2: randomized to weekend atropine or 2 h of patching
				• VA improved 1.5 lines in atropine group and 1.8 lines in patching group
				• 2 h of patching or atropine result in modest VA improvement in older children
Bilateral isoametropic amblyopia				
	ATS7 [52], prospective, noncomparative intervention	113 (< 10 years)	52 weeks	• Bilateral isoametropic amblyopia prescribed refractive correction
				• Baseline VA 20/40–80: improved 3.4 lines with glasses
				• Baseline VA 20/100–320: improved 6.3 lines
				• Probability of binocular improvement to 20/25 was 21 % at 5 weeks, 47 % at 13 weeks, 59 % at 26 weeks, 74 % at 52 weeks
				• Most patients improve to 20/25 with refractive correction over the course of year

(continued)

Table 8.3 (continued)

	ATS no./study design	No. of patients age range	Study period	Comments/results/application
Residual amblyopia				
Anisometropic or strabismic or combined mechanism	ATS A11 [53], RCT Treatment of residual amblyopia	55 (planned 240) (3 to < 10 years)	10 weeks	• Eligible: VA 20/32–63 or IOD of 2 lines
				• Randomized to intensive group (6 h of patching + atropine daily) or weaning group (reduced current treatment × 4 weeks → 2 h patching/day or atropine 1×/week → glasses only
				• Poor recruitment, average improvement of 0.5 lines in both groups (intensive and weaning equal)
				• Not widely applicable, intensive treatment did not make a difference in this specific patient population
	ATS 15 [54], RCT Increasing patching from 2 to 6 h for residual amblyopia	169 (3 to < 8 years)	12 weeks	• Pts with stable residual amblyopia 20/32–20/160 randomized to maintaining 2 h of patching or increasing to 6 h of patching/day
				• VA improved 1.2 lines in the 6 h group and 0.5 lines in the 2 h group (significant)
				• 2-line improvement in 40 % in 6 h group and 18 % in 2 h group (significant)
				• Increased patching from 2 to 6 h for residual amblyopia is effective in improving VA
	ATS 16 [55], RCT of addition of plano lens to atropine for residual amblyopia	73 (3 to < 8 years)	10 weeks	• Pts with stable residual amblyopia (20/32–20/16) randomized to continuation of weekend atropine vs. weekend atropine + plano lens for sound eye (augmented)
				• VA improved 0.6 lines in atropine only group and 1.1 lines in the atropine + plano lens
				• Not statistically significant, large confidence interval, need larger study to determine treatment effect
	ATS 17 [56], RCT of levodopa vs. placebo for residual amblyopia	139 (7–12 years)	18 weeks	• Pts with residual amblyopia (VA 20/50–20/400) randomized to 2 h of patching + levodopa vs. 2 h of patching + placebo
				• VA improved 5.8 letters in levodopa group and 3.8 letters in the placebo group
				• No meaningful improvement in VA with levodopa for residual amblyopia

ATS amblyopia treatment study, *RCT* randomized control trial, *No.* number, *IOD* intraocular distance, *BCVA* best-corrected visual acuity, *VA* visual acuity, *pt* patient

in the study at <5 years achieved a better visual outcome than those in the 5–6 year-old range [36]. Again, at 10 years and 15 years of age, there was no statistical difference between patching 6 h/day or atropine 1 % daily in patients with moderate amblyopia treated between the ages of 3 and 7 years [36]. In addition to excellent visual outcome, atropine was better tolerated in terms of social stigma, compliance, and adverse effects of treatment [59]. Because visual outcome relies heavily on compliance to treatment, a lower psychosocial burden with atropine may result in increased compliance.

For older children, atropine is also efficacious in treating amblyopia. The ATS09 was a randomized control study of 7–12-year-olds with moderate amblyopia who were randomized to either 2 h of patching or daily atropine [14]. At 17 weeks, the visual acuity had improved to 7.6 letters in the atropine group and 8.6 letters in the patching group, which was not statistically significant [14]. In contrast to the ATS1, 17 % in the atropine group and 24 % in the patching group had a visual acuity of 20/25 in the amblyopic eye [14], demonstrating that younger age of treatment leads to better visual results. Again, note that the patching regimen was 2 h/day in the ATS09 as compared to 6 h/day in the ATS1 study.

2. Weekend Atropine
   In the ATS4, patients ages 3 to <7 years with moderate amblyopia were randomized to either daily atropine or weekend atropine for 4 months [38].

(continued)

The visual acuity improved an average of 2.3 lines in each group and visual acuity was at least 20/25 or better than or equal to the non-amblyopic eye in 47 % in the daily group and 53 % in the weekend group [38]. Two patients from each group (3 %) experienced a two-line decrease in vision in the sound eye; therefore, it is important to monitor the sound eye for reversal of amblyopia [38]. The author usually has the patient discontinue atropine 2 weeks prior to follow-up appointment to accurately obtain visual acuity and alignment in patients with strabismus.

3. Atropine plus Optical Penalization
   Initial studies suggested that penalization with atropine could be augmented by prescribing less than the full cycloplegic refraction in the sound eye [39, 60]. However, a randomized trial of patients 3 to <7 years of age with moderate amblyopia (ATS8) failed to demonstrate a statistical significance between visual improvement in those patients with atropine only versus atropine plus plano lenses in the sound eye [51]. This study, however, did not specifically address the role of plano lens in patients in whom visual acuity had plateaued with atropine alone. Therefore, the ATS15 explored the role of the addition of plano lenses for residual amblyopia remaining after 12 weeks of atropine treatment [55]. At 10 weeks, the atropine only group had improved by 0.6 lines and the atropine plus plano lenses had improved by 1.1 lines [55]. The effect was not statistically significant; however, the large confidence interval makes meaningful conclusions on treatment efficacy difficult [55]. A larger study is needed to truly evaluate the treatment effect of plano lenses.

C. Bangerter Filter
   In the Bangerter Filter Treatment Study (ATS10A), patients with moderate amblyopia ages 3 to <10 were randomized to either 2 h of patching or Bangerter filter of either 0.2 (visual acuity 20/80 in amblyopic eye) or 0.3 (visual acuity of 20/40–63 in the amblyopic eye) [40]. At 24 weeks, the patients who patched had improved 2.3 lines as compared to 1.9 lines in the Bangerter filter group, which demonstrated noninferiority of the Bangerter filter group [40]. The treatment burden, however, was significantly less in the Bangerter group as measured by the amblyopia treatment index. There is also some emerging evidence that Bangerter filters promote binocularity for mid- and low spatial frequencies [61], which may prove clinically significant for motion-defined perception and multiple-object tracking [62].

D. Contact Lens
   Daily-wear opaque contact lenses have been utilized in nonrandomized, observational studies with reported improvement in visual acuity in patients in whom all other methods of penalization had failed [63, 64]. More recently, high plus lens were used to treat the sound eye in patients with unilateral aphakia in whom all other penalization modalities had failed [65]. There were no safety events reported in any of these cases. However, extreme caution must be exercised when placing contact lenses in the sound eye of an essentially monocular patient, and larger, randomized studies are needed to determine efficacy and safety.

III. Therapies for Moderate to Severe Amblyopia (BCVA Worse Than 20/100)

The treatment of moderate to severe amblyopia is often more difficult than moderate amblyopia because the patient may struggle with normal activities initially with penalization of the sound eye. However, parents should be educated that lifelong vision loss may result if amblyopia treatment is not completed and that as the vision improves, therapy will become increasingly easier.

1. Occlusion
   The ATS2A study compared the efficacy of prescribing full-time patching or 6 h of patching for 3 to <7-year-old patients with severe amblyopia, with average visual acuity of 20/160 at baseline [31]. At 4 months, the vision had improved by 4.8 lines in the 6 h group and 4.7 lines in the full-time group, a difference that was not statistically significant [31]. Compliance with the prescribed regimen was subjectively confirmed.
2. Pharmacologic
   Although patients with severe amblyopia may still have better vision in the sound eye even in the presence of atropine penalization, visual acuity improved with weekend atropine in two randomized control trials of patients with severe amblyopia [39]. In the first study, patients aged 3–6 years with severe amblyopia were randomized to weekend atropine with full refractive correction in the sound eye or weekend atropine and optical penalization with the plano lens in the

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sound eye [39]. Visual acuity improved by 4.5 lines in the refractive correction plus atropine group and 5.1 lines in the plano lens plus atropine group [39]. Interestingly, treatment effect of atropine in this study was similar to that of 6 h of patching (4.8 lines) in the ATS2A [31], although not specifically compared in this trial [39]. In the second trial of atropine for severe amblyopia, patients aged 7–12 years were randomized to either weekend atropine or 2 h of daily patching. Visual acuity improved by 1.5 lines in the atropine group and 1.8 lines in the patching group [39]. Thus, visual acuity can improve with weekend atropine treatment in patients with severe amblyopia, with better visual outcomes if instituted at a younger age [39]. Interestingly, even if the fixation preference at near does not change to the amblyopic eye, visual acuity will still improve in the amblyopic eye [60]. Thus the mechanism for visual improvement with atropine penalization is complex.

IV. Therapies for Older Children >7 Years of Age

Historically, amblyopia identified in older children was not treated as many believed visual maturity to occur by age 7. However, PEDIG systematically assessed response to amblyopia treatment in older children in ATS3 [48]. In this study, patients ages 7–17 years with visual acuity ranging from 20/40 to 20/400 were treated with optical correction and then randomized to treatment with optical correction alone vs. patching 2–6 h a day and atropine [48]. Patients were considered responders if visual acuity improved by two lines or more. Twenty-five percent of patients responded with optical correction alone, and 53 % were considered treatment responders [48]. The response was statistically better in those patients who had not been treated previously. This visual acuity improvement was maintained in 82 % of patients at 1 year, with the cumulative probability of losing visual acuity of >2 lines of 7 % [66]. Since both patching and occlusion were utilized to treat older children in ATS3, a later study sought to determine whether atropine or patching 2 h/day was more effective in this age group in patients with moderate amblyopia [14]. Treatment outcomes were not statistically significant, and, therefore, both are potential strategies in this patient population. Approximately one in five patients improved to 20/25 or better in the amblyopic eye (24 % in the patching group and 17 % in the atropine group) [14].

V. Therapies for Residual Amblyopia

1. Occlusive and Pharmacologic
   In ATS11, patients ages 3 to <10 years with residual amblyopia (20/32–20/63 or intraocular difference of two lines) with plateau of visual acuity with either daily atropine or 6 h daily of patching were randomized to receiving either an intensive course of daily atropine plus 6 h of patching of the sound eye or a weaning regimen of 2 h of patching per day or atropine once weekly [53]. Unfortunately, because of slow recruitment, only 55 subjects of the 250 expected sample size were randomized [53]. At 10 weeks of treatment, there was no statistical difference between the intensive and weaning groups, and interestingly, both groups gained an average 0.5 logMAR of visual acuity [53]. Application of this study to patients with history of less intensive treatment or more severe residual visual acuity should be avoided.
2. Optical
   As discussed in the section on atropine plus optical penalization, the additional use of optical penalization with plano lens did not improve outcomes in ATS15 [55].
3. Levodopa
   Prior studies have evaluated the use of levodopa as an adjunctive treatment of amblyopia, with reporting of visual improvement [67–69]. PEDIG initially conducted a pilot study (ATS14) to evaluate dose, efficacy, and safety of levodopa in combination with occlusive therapy in older patients ages 8–18 years with residual amblyopia [70]. This set the framework for a randomized, placebo-controlled trial of children ages 7–12 years with residual amblyopia (20/50–400) followed for 16 weeks. A total of 139 patients were assigned to placebo, 0.76 mg/kg, or 0.17 mg/kg of levodopa plus 2 h of patching of the non-amblyopic eye. Adjusting for baseline acuity, there was no significant difference among the groups [56]. Therefore, levodopa is not efficacious for treating residual amblyopia at the dosages utilized in the study.

VI. Refractive Surgery in Resistant Cases

The use of refractive surgery in children remains controversial. Keratorefractive surgery in children requires the off-label use of an FDA-approved device. Studies have shown that refractive surgery can be safely performed in children with anisometropic amblyopia who fail conven-

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tional treatment with improvement of stereopsis and visual acuity in most eyes, even in older children [58]. See Chap. 7.

In conclusion, for some children with anisometropic amblyopia, a period of spectacle wear alone can lead to visual improvement and restore normal vision in approximately 25 %. Younger patients with better visual acuity in the amblyopic eye at baseline may do better with refractive correction alone. For those children in whom visual improvement plateaus after a trial of spectacle correction alone, therapy with occlusive or penalization therapy is indicated and is likely to result in additional visual improvement. The patching regimen should be guided by age and visual acuity in the amblyopic eye per the amblyopia treatment studies of PEDIG trials (see Table 8.3).

Case Study 3

A 6-week-old infant is referred by her pediatrician because of an abnormal red reflex in the left eye. Her birth history was unremarkable, with an uncomplicated delivery at 39 weeks. Maternal history during pregnancy was noncontributory. She is otherwise healthy with normal growth and development. There is no family history of any inherited systemic or ocular problems. While visual acuity could not be assessed adequately, the examination revealed a significant nuclear cataract in the left eye that obstructed a view of the fundus. Pupils were equally reactive without an afferent pupillary defect. An ultrasound was obtained that did not reveal any retinal detachment or vitreous opacities. A diagnosis of unilateral congenital cataract was made. The patient underwent an examination under anesthesia with subsequent cataract extraction. Because of the unilaterality of the cataract and the otherwise excellent general health of the baby, no additional tests were ordered (see Chaps. 18 and 19).

After successful cataract extraction, the patient was left aphakic.

One week after surgery, the patient is fitted with a Silsoft contact lens of 32 D with a 7.50 mm base curve (see Chap. 6). Retinoscopy demonstrated a +3.00 overcorrection for near vision. Training for application and removal of the contact lens was provided to the caregivers. Contact lens complications such as microbial keratitis, corneal vascularization, and giant papillary conjunctivitis were extensively discussed with the parents.

The right eye was patched using the stair-case approach described by Gregg and Parks [71] and employed in the protocol of the Infant Aphakia Treatment Study [72]. The sound eye was patched for the first 48 h after placement of the contact lens and then 1 h/day/month of age to allow for binocularity until 8 months. At 8 months, the patient was then patched one-half of waking hours (approximately 6 h/day). The patient was followed at 1 day, 1 week, 1 month, 3 months, and then 3 months thereafter. Intraocular pressure was monitored and within normal limits. The contact lens was assessed by a contact lens specialist and adjusted for growth.

At 1 year of age, the visual acuity was 20/63 in the right eye and 20/80 in the left eye by Teller Acuity (left eye tested first). Intraocular pressure was within normal limits. Patching treatment was continued until visual acuity equalized and then was slowly tapered. Family was educated of need for lifelong follow-up.

Comment

Deprivation amblyopia from a unilateral congenital cataract can occur quickly and can be more profound than that caused by bilateral congenital cataracts, in which the deprivation is bilateral and therefore there is less opportunity for the development of a fixation preference. The cataract should be extracted between 4 and 6 weeks of age and optical correction and amblyopia treatment instituted thereafter [71, 73, 74]. In bilateral cases surgery can be performed as late as 6–8 or more weeks of age [72]. The time interval between the first and second cataract surgery should be no longer than 1–2 weeks [72]. In older children cataracts that occupy the central 3.00 mm or more of the lens are considered amblyogenic and should be removed [75]

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(see Chap. 19). The options for optical correction include spectacles, intraocular lenses (IOLs), and contact lenses. Contact lenses (rigid gas permeables or silicone lenses) remain the preferred method of optically correcting unilateral infant aphakia [76, 77]. Furthermore, as the eye elongates, the refractive power of the lens should be adjusted accordingly. In cases of bilateral aphakia, aphakic spectacles may also be utilized, although they can be heavy and difficult to fit in an infant (see Chap. 6).

According to the Infant Aphakia Treatment study (IATS), there was no visual benefit from the implantation of IOLs in infants less than 7 months of age at the time of cataract extraction when compared to infants who were optically treated with a contact lens [77]. Furthermore, more adverse events and reoperations in order to clear the visual axis were required in the group of infants treated with IOLs [77] (see Chap. 19). In older children, intraocular lenses are commonly used with excellent visual result.

Stimulus deprivation is the rarest form of amblyopia, comprising approximately 3 % of amblyopia cases [78]. Because the disruption in vision often occurs very early in life, most commonly from congenital cataracts, it can be the most difficult to treat. A recent Cochrane Review on occlusive therapies for stimulus deprivation amblyopia failed to find any randomized trials, nor evidence of effectiveness of any treatment [79]. Although amblyopia treatment was not a randomized variable, the IATS demonstrated that occlusion of the fellow eye for 1 h/month of life and half of all waking hours after 8 months throughout is associated with excellent visual outcomes in unilateral aphakia [80–82]. Younger age at surgery and private insurance are associated with better visual outcomes [83]. Frequent reexamination including testing for fixation preference, retinoscopy, and adjustments in refractive corrective lenses are also imperative.

Emerging Therapies

In 2010, Hess and colleagues demonstrated the presence of residual binocular function in adults, prompting the pursuit of amblyopic treatments that reduce suppression and restore binocularity [15]. The basic premise is that binocularity is lost secondary to strabismus or anisometropia with secondary suppression and amblyopia. Dr. Hess' team and others quantified suppression through specialized testing that correlates with visual acuity in the amblyopic eye [84–86]. Thus, binocular treatments focus on improving binocularity through iPod or iPad-based video games to reduce cortical suppression [87, 88]. Artificial binocular viewing conditions are created in which the signal strength to the sound eye is reduced so that it no longer suppresses the amblyopic eye. The more time the eyes work together to combine the information, the greater the improvement of binocular capacity. This treatment was studied in adults with amblyopia with improvements in binocularity including stereopsis [87, 88]. PEDIG investigators will study these methods further through multicenter, randomized control trials to assess efficacy as compared to standard therapies.

Conclusions

The Pediatric Eye Disease Investigator Group should be applauded for their efforts to design randomized, multicenter studies to systematically evaluate the efficacy of various treatment regimens for amblyopia. The Amblyopia Treatment Studies provide a fundamental framework to guide treatment, and an entire textbook dedicated to these trials would be needed to adequately cover the material. We urge the reader to use Table 8.3 as a reference and to read the individual articles whenever possible. Education of the parents or caregivers is paramount to achieve a successful outcome. Because there is incomplete understanding of the multiple variables that affect response to therapy, management should be tailored to the individual patient's response to treatment [23]. Although advances have been made in early screening and treatment paradigms, a mild visual acuity deficit usually remains in amblyopic eyes and there may be some regression, especially in older children. Understanding the precise neurophysiologic mechanisms of amblyopia may provide the insight to develop novel, mechanism-based treatment modalities to improve outcomes.

See Fig. 8.1 for a diagnostic and therapeutic algorithm for patients with amblyopia.

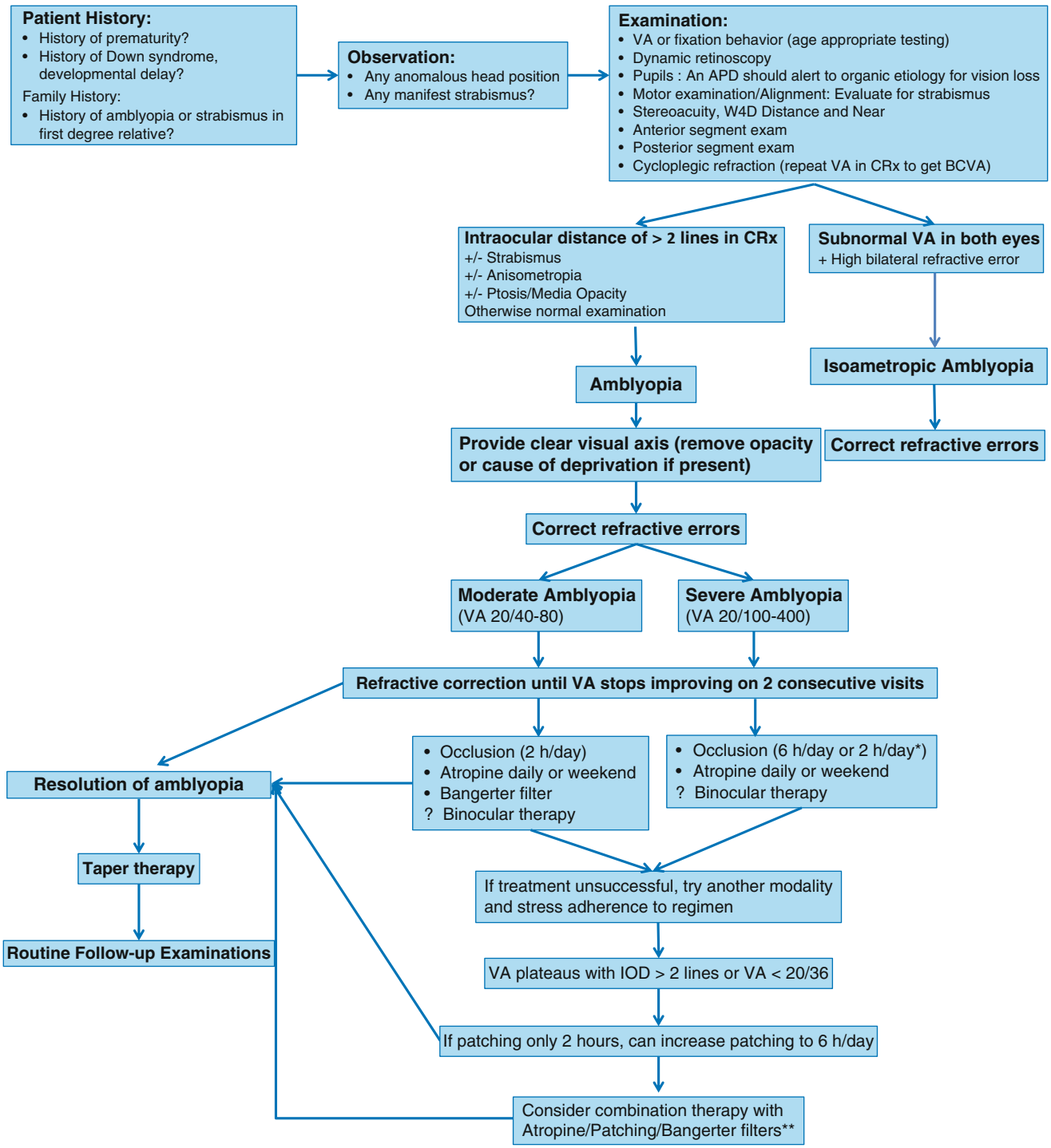

Fig. 8.1 Diagnostic and therapeutic algorithm for patient with amblyopia. Examination should be complete and visual acuity should not be correctable in glasses with normal ocular structures and afferent pathway. Causes of amblyopia include uncorrected anisometropia, strabismus, and occlusion (ptosis, media opacity). The first step is to remove any occlusion or opacity. The second step is to place the patient in refractive correction. Amblyopia may improve or resolve in refractive correction alone. Amblyopia has been classified by severity in the amblyopia treatment studies by the Pediatric Eye Disease Investigator Group (PEDIG) into moderate and severe amblyopia. Prescribed treatment is based on the severity of the amblyopia. Although the results of the ATS serve as a guide for management, factors such as age of patient, social concerns, family's motivation, and best clinical judgment are imperative in the management of amblyopia. *2 h/day of prescribed daily patching was effective in patients 3 to<8 years for initial treatment of severe amblyopia [1]. This may not necessarily be applicable to older patients who have relatively small visual gains with 2 h of patching in the setting of severe amblyopia [2]. **Because of limited data for combined therapy, treatment should be tailored to individual patient presentation. Abbreviations: *APD* afferent pupillary defect, *W4D* worth-4-dot testing, *CRx* cycloplegic refraction, *VA* visual acuity, *BCVA* best-corrected visual acuity, *IOD* intraocular difference

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Part IV

Cornea/Anterior Segment

Diagnosis and Management of Conjunctivitis in Infancy and Childhood

9

Alison E. Smith and Michelle M. Ariss

Abstract

The evaluation of the child with a red eye can be challenging, as the differential diagnosis is broad and the performance of an adequate exam in this age group can sometimes be difficult. Following a paradigm and looking for specific signs and symptoms and historical clues, combined with careful examination facilitates the identification of the underlying etiology.

Keywords

Conjunctivitis • Red eye • Atopic conjunctivitis • Vernal conjunctivitis • Ophthalmia neonatorum

Introduction

Conjunctivitis is one of the most common ocular infections in childhood and accounts for up to 15 % of ophthalmologic and 6 % of primary care physician consultations [1]. A thorough understanding of this group of conditions is necessary to provide optimal eye care to children [2].

The major categories of childhood conjunctivitis are infectious and noninfectious. The two main categories of infectious conjunctivitis are viral and bacterial. Bacteria cause up to 70–80 % of cases in children [3]. Viral cases, most commonly due to adenovirus, vary depending on the serotype. Some serotypes are responsible for epidemic keratoconjunctivitis (EKC) (types 8, 19, and 37), while others cause pharyngoconjunctival fever (types 3 and 7), acute hemorrhagic conjunctivitis (types 11 and 21), or acute follicular conjunctivitis (types 1–4, 7, and 10). Both bacterial and viral conjunctivitides are highly contagious and appropriate isolation should be addressed and discussed with family members in order to help limit spread.

Neonatal conjunctivitis is contracted during passage through the birth canal, or as a result of the infectious agent ascending to the uterus and infecting infants born via cesarean. Neonatal conjunctivitis carries the risk of systemic spread and the possibility of associated meningitis or pneumonitis hence its management may entail hospitalization and systemic treatment.

Noninfectious etiologies of childhood conjunctivitis include atopic keratoconjunctivitis and vernal keratoconjunctivitis.

The characteristics of each of these major groups, including signs, symptoms, and optimal management, are discussed in the following sections, with the purpose of helping to identify the cause and to plan appropriate management of children with acute conjunctivitis.

Bacterial Conjunctivitis

Bacterial conjunctivitis, characterized by mucopurulent discharge and conjunctival injection, is contracted through direct contact with secretions and/or contaminated objects.

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The associated discharge is copious and thick, often green-tinged or yellow-white in color. The discharge is present in the conjunctival cul-de-sac with crusting or matting of the lashes.

The most common pathogens are *Streptococcus pneumonia*, *Haemophilus influenza*, and *Moraxella catarrhalis* and account for roughly 55–68 % of cases in children [4]. The incidence of *Haemophilus* infections has dropped with widespread use of immunizations. Cultures are not necessary before the initiation of treatment, and may yield false positive results. An exception is made for the patient suspected to be infected with *Neisseria* in whom a Gram stain and culture should be obtained as *Neisseria gonorrheae* is vision-threatening with high risk of progression to corneal perforation, and *N. meningitides* may spread systemically and cause meningitis [1]. A hyperpurulent discharge is characteristic of gonococcal conjunctivitis.

While many cases of conjunctivitis are self-limited, the use of topical antibiotics can shorten the course of infection. A study by Gigliotti et al. [5] found that the bacterial pathogen was eradicated at days 3–5 in 70 % patients treated with a topical antibiotics, compared to only 19 % in the placebo group.

A Cochrane Review of studies comparing placebo versus antibiotics for acute bacterial conjunctivitis concluded that although frequently self-limiting, antibiotics did hasten the recovery from infection and the resolution of symptoms in patients with acute bacterial conjunctivitis, thereby supporting their use in the treatment of acute bacterial conjunctivitis.

Various studies have been conducted to identify ideal topical antibiotic agents for the treatment of bacterial conjunctivitis in children. Polymyxin and bacitracin ointment used four times per day is effective in clinically proven cases of *H. influenza* and *S. pneumonia* in patients between the ages of 1 month and 18 years [4]. Increasing antibiotic resistance has resulted in more widespread use of the fluoroquinolones. But when studied by Gigliotti and Williams, fluoroquinolones (specifically moxifloxacin) were not found to be superior to polymyxin B-trimethoprim in the treatment of acute conjunctivitis by day 7–10 of treatment, suggesting that polymyxin B-trimethoprim can be safely used as a first line agent [4].

Although azithromycin was shown to be superior to tobramycin in resolving clinical symptoms at day three of treatment, they were both shown to be equally effective at curing conjunctivitis associated with purulent discharge by day 7 [6].

In cases of *Neisseria* and *Chlamydia*, management should include the systemic administration of antibiotics because of the risks of meningitis and pneumonitis, respectively. Systemic treatment will be discussed in more detail in the section regarding management of neonatal conjunctivitis.

Hence it appears that adequate first line agents include erythromycin or polytrim [7]. If there is no improvement of signs and symptoms after a few days, other agents with broader coverage including bacitracin, fluoroquinolones, or azithromycin can be used. Aminoglycoside drops carry a risk of corneal toxicity and may not be the best first choice [8]. Fluoroquinolones should not be used first because of concerns over emerging resistance. One exception is the contact lens wearer with signs of conjunctivitis. These patients should stop all contact lens wear and discard potentially infected contact lenses. Contact lens wear can be resumed once the infection has subsided and a course of topical antibiotic therapy has been completed.

Viral Conjunctivitis

Case 1 Clinical synopsis: A 5-year-old girl presents to the ophthalmologist's office with a one-day history of red burning right eye. Visual acuity was 20/40 OD and 20/20 OS. Her mother reported that the entire family has had upper respiratory tract infections over the past few weeks. Slit lamp examination of the right eye revealed 4–5 subepithelial infiltrates of the cornea as well as 2+ conjunctival injection. The anterior chamber was quiet. There was no purulent discharge. She was treated for presumed viral conjunctivitis and a suspicion for EKC, with education about effective hand washing and frequent artificial tear use. Because of decreased vision and corneal involvement she received prednisolone acetate 1 % drops four times/day for 5 days. Upon her follow-up visit her vision was back to 20/20 in the affected eye and her ocular discomfort as well as corneal changes had resolved. The steroids were stopped and the patient was educated to follow-up as needed.

Comment Unlike the purulent white discharge of its bacterial counterpart, viral conjunctivitis presents with unilateral or bilateral watery serous discharge from a hyperemic eye. A follicular conjunctival reaction is usually present and can be visualized on slit lamp examination. Eye findings may be isolated or combined with a viral prodrome consisting of lymphadenopathy, fever, pharyngitis, or upper respiratory tract infection. Viral conjunctivitis is highly contagious and, like bacterial conjunctivitis, spreads through direct contact with infected patients, or contaminated surfaces. The most common pathogen identified in viral conjunctivitis is the DNA virus, adenovirus. To date, 68 serotypes of adenovirus have been reported (Human Adenovirus Working Group http://hadvwg.gmu.edu/). Various serotypes account for conjunctivitis as well as other systemic diseases such as gastroenteritis, hepatitis, myocarditis, and pneumonia.

Epidemic Keratoconjunctivitis

A highly contagious type of viral conjunctivitis caused by adenovirus is EKC. Adenoviral serotypes 3, 4, 8, 19, and 37 are associated with EKC. Of these, serotypes 8, 19, and 37 have been reported to cause the most severe conjunctivitis [9]. EKC is associated with systemic symptoms of fever, malaise, respiratory complaints, myalgia, as well as ocular symptoms of redness, photophobia, foreign body sensation, and tearing. Ipsilateral preauricular lymphadenopathy is a common finding with EKC. Associated eyelid swelling and conjunctival hemorrhage may also be present.

Differentiating EKC from other forms of conjunctivitis is the presence of associated corneal abnormalities, which can prompt complaints of blurred or decreased vision. Punctate keratopathy often occurs within a few days of onset of symptoms and can coalesce into focal epithelial keratitis that can persist for roughly 2 weeks or more [10]. Within the subepithelial layer beneath the focal lesions, infiltrates may develop which can leave scars that persist for months to years [11]. These subepithelial infiltrates are the result of an immune response to adenoviral antigens within the corneal stroma.

With the use of confocal microscopy, corneal structural changes have been identified during the course of infection [10]. As reported by Dosso and Rungger-Brandle [10], follicular conjunctivitis and focal keratitis occur within 1 week of symptoms, associated with clusters of dendritic cells and keratocytes in the anterior stroma. Subepithelial infiltrates occur by week 2. A higher number of infiltrates are associated with a decrease in visual acuity. By week 4 of infection, patients are usually asymptomatic, however, confocal microscopy reveals persistence of dendritic cells and keratocytes. By 24 weeks after the onset of symptoms, when epithelial and anterior stromal dendritic clusters have resolved, high reflectivity may persist in the mid stroma, suggesting late stromal wound healing in EKC.

Because of the absence of effective antiviral therapy and the spontaneous recovery in most cases, management of EKC is predominantly supportive with artificial tears and cool compresses, and complete resolution occurs within 3 weeks in most cases [12]. The use of topical steroids should be reserved for more complicated cases associated with pseudomembranes or extensive subepithelial infiltrates and reduced vision; animal models have suggested an increase in replication of the virus as well as duration of infection, most notable in the later phase of infection (days 9–21) if steroids are used continuously for up to 18 days. The alteration of adenoviral replication has been shown with both higher potency steroids such as prednisolone acetate 1 % and low potency steroids such as prednisolone acetate 0.12 % [13]. Topical cyclosporine A has been shown to reduce subepithelial infiltrates, yet promote viral shedding and prolong the duration of infection [14], thereby increasing the risk of spread and of epidemics. Topical NSAIDs appear to have no effect on adenoviral clearance, but can provide relief of symptoms [15].

A rapid test for the detection of the adenovirus in acute conjunctivitis is available and may be helpful in confirming a clinical diagnosis, hence assisting in treatment and patient education [16]. Due to the highly contagious nature of EKC, patients suspected of having this condition should be kept out of school for 1–2 weeks until signs and symptoms have subsided.

Pharyngoconjunctival Fever

Pharyngoconjunctival fever is a specific clinical presentation of adenovirus infection. Typically it manifests with a high fever lasting an average of 4–5 days with pharyngitis, conjunctivitis, regional lymphoid hyperplasia, and other symptoms associated with viral prodrome. It is very common in the pediatric age group. Transmission occurs through contact with infected upper respiratory droplets or fomites, or through swimming pools, in which fecal contamination containing the virus is believed to be responsible. The incubation period averages 8 days. Management follows the same protocol as those previously mentioned for viral conjunctivitis [17].

Allergic Conjunctivitis

Case 2 Clinical synopsis: An 8-year-old boy presents with a 1-month history of chronic red eyes associated with itching. His mother does not report recent upper respiratory tract infections but comments that her son has eczema and seasonal allergies. The key exam features include: normal vision, Horner-Trantas dots, conjunctival papillae and injection in both eyes. The patient was diagnosed with vernal keratoconjunctivitis and effectively treated with initiation of a mast cell stabilizer, one drop daily (olopatadine hydrochloride 0.2 %) and a very short course of steroids (fluorometholone 1 %, 4 times daily for 5 days). There was marked improvement of signs and symptoms within a few days of the initiation of treatment.

Comment Allergic conjunctivitis encompasses more than one condition with the hallmark symptoms of itching and eye rubbing. Under the umbrella of allergic conjunctivitis are the conditions of seasonal allergic conjunctivitis, vernal keratoconjunctivitis, and atopic keratoconjunctivitis. The following section will elaborate specifically on vernal and atopic conjunctivitis.

Vernal Keratoconjunctivitis

Vernal conjunctivitis is a severe form of ocular surface allergy that, if left untreated, can cause permanent visual deficits through scarring of the corneal surface. The word vernal literally means "related to or occurring in the spring." This condition most often affects individuals who live in warm climates and is more prevalent in warm weather months. It is associated with other atopic manifestations such as allergic rhinitis, asthma, or eczema, in approximately one-half of patients. Males are more often affected than females. As with seasonal allergies, many children outgrow the disease as they approach puberty. Vernal keratoconjunctivitis is associated with high tissue levels of IgE and various inflammatory mediators, hence, responds well to mast cell stabilizers.

Symptoms generally include itching with associated eye rubbing, often with redness, eyelid swelling, and mucus discharge. Additional symptoms can include pain, burning, and, if the cornea is involved, photophobia. On slit lamp examination, a papillary reaction can be seen on the conjunctiva. Almost all children have large papillae on the upper tarsal conjunctiva. These giant papillae are the result of IL-4 and IL-13 mediated proliferation of conjunctival fibroblasts, and filled with inflammatory cells and edema.

Other signs include Horner-Trantas dots (eosinophil aggregates), corneal shield ulcers, and blepharospasm. Horner-Trantas dots form as eosinophils collect in crypts at the limbus. They often appear during active VKC and resolve when symptoms subside.

Shield ulcers often occur in the superior cornea, and appear as oval-shaped epithelial ulcers with underlying stromal opacification. They are sterile in nature. Other sight-threatening corneal findings in VKC include neovascularization and scarring. In contrast to vernal keratoconjunctivitis, atopic keratoconjunctivitis nearly always presents with corneal scars and neovascularization and predominately affects the lower lids.

To manage this immune-mediated condition, initial treatment requires the use of mast cell stabilizers and antihistamines. Olopatadine is an anti-allergy agent with selective H1 antihistaminic and mast cell stabilizing properties that works well as a first line dual-mechanism agent therapy [18]. Other agents with these two properties include ketotifen fumarate (Alaway), azelastine (Optivar), pemirolast potassium (Alamast), and epinastine (Elestat). If there is corneal involvement on presentation or limited response to the aforementioned drugs, corticosteroid drops may be indicated. Depending on the severity of the disease, the physician may choose prednisolone acetate 1 % (Pred Forte®), fluorometholone 0.1 % (FML Forte®; FML Liquifilm®), loteprednol 0.2 % (Lotemax®), or rimexolone 1 % (Vexol®). Steroids are frequently given as a high dose short course of 1 drop 4–8 times daily for 1 week, then quickly taper. The use of steroids should be closely monitored for side effects such as glaucoma or cataract formation. Severe cases may also require oral therapy or referral to an allergist for systemic immunomodulation.

Refractory cases or ones associated with corneal epithelial defects may benefit from topical treatment with calcineurin inhibitors. Their use may provide long-term benefits by avoiding side effects associated with chronic steroid use. The two most commonly used medications are tacrolimus (Protopic®) and cyclosporine (Restasis). Ophthalmic cyclosporine has been tested and shown to be effective in treating patients with VKC. Utilization of the drug showed a statistically significant decrease in the signs and symptoms over a 6-week period [19]. An Italian study found similar results and determined that most of the therapeutic effect occurs quickly, within 2 weeks [20].

Although typically sterile, corneal shield ulcers should be treated similarly to other corneal ulcers with culture and coverage with broad-spectrum antibiotics until culture results are obtained.

It is important to educate patients to limit eye rubbing and to use cool compresses for symptomatic relief of itching.

Atopic Keratoconjunctivitis

Atopic conjunctivitis (AKC) is a chronic bilateral allergic ocular disease that is perennial and typically affects older individuals. Most patients have additional atopic manifestations such as dermatitis or eczema. Thus, eczematous skin lesions may be seen on the eyelids as well. Blepharitis and scurf are commonly found on the lashes and patients may have staphylococcal superinfections. In contrast to VKC the lower eyelid is often involved and can appear swollen. Cicatricial entropion may develop secondary to chronic inflammation and conjunctival scarring.

AKC typically presents with more severe corneal findings than VKC as many patients can develop corneal neovascularization, scarring, and corneal thinning, however, many of the same features, such as Horner-Trantas dots and giant papillae, are present. Cataract formation can also be seen in AKC as a result of the condition and the chronic use of topical corticosteroids. While VKC often resolves in the second decade of life, AKC often persists throughout life.

Similar to VKC, pathogenesis is primarily immune-mediated with a proliferation of mast cells and eosinophils. Treatment often requires more potent medications including steroids or immunomodulatory agents. The physician may also need to treat eyelid dermatitis. This can be done with application of a low dose topical steroid to the lids two to four times daily. Topical calcineurin inhibitors as mentioned above can be used as an alternative.

Neonatal Conjunctivitis

Case 3 Clinical synopsis: This is a 3-day-old infant who presents with purulent discharge from both eyes. The patient was born at home to a mother with limited prenatal care. The physician was suspicious of *N. gonorrheae* and immediately obtained a Gram stain and culture in Thayer-Martin media as well as on agar plates. The patient was immediately admitted and treated with IV Ceftriaxone as well as oral erythromycin to cover any co-infection with chlamydia. Cultures grew *N. gonorrheae*. The infectious disease specialist was consulted to evaluate for any other systemic involvement including septic arthritis. The patient was carefully evaluated for resolution of all ocular symptoms. The mother was educated about sexually transmitted disease and plans were made to test her as well as any sexual partners for STDs including HIV.

Comment Ophthalmia neonatorum is a special name given to conjunctivitis that occurs in infants in the first month of life. It occurs in 1.6–12 % of newborns [22]. Chemical conjunctivitis that results from antimicrobial prophylaxis is the most frequent type of neonatal conjunctivitis.

In the USA, perinatal transmission occurs in 30–40 % of cases from maternal cervical infections [21]. Infants can be infected directly through passage in an infected birth canal during vaginal delivery, or bacterial infections can ascend the birth canal and cause chorioamnionitis and resultant fetal infection. Increased risk factors for this transmission include premature rupture of membranes. The two principal and most severe responsible pathogens are *C. trachomatis* and *N. gonorrheae*. Another pathogen transmitted through direct contact includes Herpes Simplex Virus (HSV). Infected newborn generally present with bilateral purulent discharge within the first 5 days of life.

Common bacteria responsible for neonatal conjunctivitis include *C. trachomatis*, *H. influenza*, and *S. pneumonia*e. Less likely to occur because of prophylaxis, but at high risk of causing severe ocular surface complications is *N. gonorrheae.* Helpful clues to identify the inciting agent are day of onset of conjunctival injection after birth and type of discharge.

Chemical conjunctivitis, characterized by bilateral hyperemia, often occurs within the first day of life, and is a result of antimicrobial prophylaxis used at birth, most often silver nitrate, which fortunately has been mostly abandoned in developed countries. Chemical conjunctivitis is often a self-limited condition.

Gonococcal conjunctivitis, characterized by hyperemia and purulent discharge, often occurs within the first week of life. Although it occurs less frequently, gonococcal conjunctivitis is capable of penetrating the cornea, causing ulceration and perforation. Also concerning is the risk of systemic spread of *Neisseria* and resultant meningitis, sepsis, or arthritis. Topical antibiotics may be helpful in cases of corneal involvement, but otherwise are not indicated. Ocular surface irrigation with saline is also helpful in eliminating the bacteria from the ocular surface.

Chlamydia may present up to 2 weeks after birth and the discharge is frequently described as serous in nature. There may also be edema of the soft tissue (eyelids) and conjunctival chemosis. The conjunctiva may form pseudomembranes that bleed when disrupted. Lack of treatment may result in corneal scarring and cicatrization of the conjunctiva. The diagnosis of *Chlamydia*, an obligate intracellular organism, requires culture of conjunctival scrapings, which can be obtained from an everted eyelid. *Chlamydia* cultures should be sent to the laboratory in 2SP (0.2 M sucrose-phosphate transport medium containing 10 μg of gentamicin/mL, 25 μg of vancomycin/mL, and 25 U of nystatin/mL) if possible. There are more rapid assays for *Chlamydia* and in urgent situations nucleic acid amplification may be acceptable However, in sexual abuse cases, culture is the only acceptable result recognized in by law. Treatment of *Chlamydia* conjunctivitis includes oral erythromycin (50 mg/kg per day PO in four divided doses) for fourteen days per the American Academy of Pediatrics and Centers for Disease Control (CDC). Systemic therapy is indicated to fully treat the patient secondary to risk of *Chlamydia* pneumonitis. Erythromycin is effective in only 80–90 % of cases so patients need to be followed closely for complete resolution [22]. The infant's mother and sexual partners need to be evaluated for all STDs including HIV. Co-infection of *Neisseria* and *Chlamydia* is common and infants should be treated for both infections.

The gold standard for diagnosis of gonococcal conjunctivitis is isolation by culture after gram stain. *Neisseria* should be cultured on appropriate selective media (Thayer-Martin or VPN) that inhibit normal flora because they contain antibiotics (vancomycin, colistin, nystatin, and trimethoprim) and facilitate the growth of *Neisseria* species. A diagnosis of gonorrhea mandates hospitalization to evaluate for systemic infection particularly septic arthritis. Treatment should be initiated empirically upon suspicion of infection and consists of a single dose of Ceftriaxone (25–50 mg/kg not to exceed 125 mg, IV or IM).

Prophylaxis for neonatal conjunctivitis in the USA is recommended by the American Academy of Pediatrics and Center for Disease Control and Prevention and consists of erythromycin or tetracycline ointment administered to both eyes within 1 h of birth.

See Fig. 9.1 for red eye flowchart.

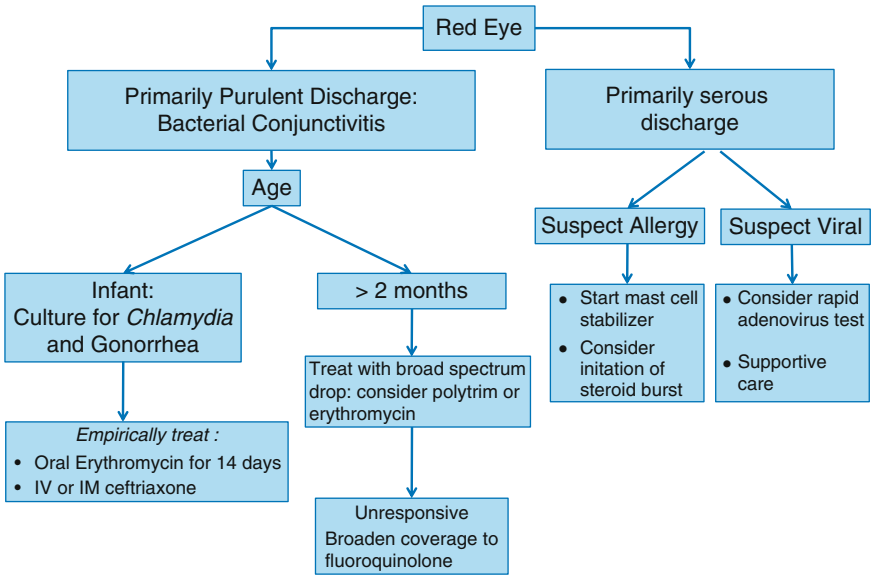

Fig. 9.1 Red eye flow chart

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Diagnosis and Management of Corneal Ulcers in Pediatric Patients

10

Patricia Ann Ple-plakon and Christopher Thomas Hood

Abstract

Pediatric corneal ulcers are potentially devastating ocular conditions of special importance in children due to children's expected longevity and the risk for visual impairment from deprivational and refractive amblyopia. Young patients can present challenges because of their limited ability to provide history and to describe symptoms, and their potential difficulty in cooperating with examination. As in adults, the most common organisms responsible for corneal ulcers in children are bacteria and herpes simplex virus (HSV), and less frequently fungi. Keratitis can also be secondary to ocular rosacea, which due to its low prevalence and sub-acute course may lead to delay in appropriate diagnosis and treatment. Antibiotics, antivirals, and sometimes corticosteroids are employed to eradicate infection and to modulate the host immune response to prevent scarring and permanent visual loss.

Keywords

Pediatric corneal ulcers • Microbial keratitis • Fungal keratitis • Herpes simplex • Ocular rosacea

The Problem

Children present unique challenges in the diagnosis and management of keratitis and corneal ulcers. They may not be able to effectively verbalize their symptoms, and slit-lamp examination may be limited in uncooperative children. As such, a thorough ophthalmic examination with diagnostic testing such as corneal cultures may require sedation in the operating room. Additionally, installation of eye drops may be difficult, potentially confounding whether sufficient appropriate therapy has been administered. Furthermore, pediatric patients can manifest findings of ocular disease differently than adults, often with a more robust inflammatory response that can obscure the clinical picture [1, 2] and lead to misdiagnosis or a delay in appropriate treatment. Also unique to the pediatric population is the risk for both deprivational amblyopia due to corneal opacification and scarring and refractive amblyopia from induced astigmatism, further highlighting the need for close ophthalmic care. Finally, much of the published evidence for treatment of corneal ulcers and keratitis is based on studies performed in adults. In children, potential systemic absorption of topically applied medications as well as appropriate dosing of oral therapies must be considered. Despite the challenges, it is crucial to obtain a thorough history from the child and caregiver, focusing on potential risk factors, and to perform a complete ophthalmic examination.

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Case Studies

Case 1 (Fig. 10.1)

Clinical Synopsis

A 12-year-old girl presented with pain, photophobia, and decreased vision in the right eye for 3 days. She wore soft contact lenses for myopia but otherwise had no significant ocular history. She reported sleeping in her contact lenses and cleaning them infrequently. Slit-lamp examination revealed a round anterior stromal infiltrate with an overlying epithelial defect, consistent with a bacterial corneal ulcer (Fig. 10.1). Diagnostic culture was deferred due to the small size and peripheral location of the lesion. Empiric treatment was initiated with moxifloxacin eye drops every hour around-the-clock. She was followed daily for the first 2 days until there was a significant improvement in her symptoms and resolution of the corneal epithelial defect, at which time the antibiotic eye drops were decreased to 6 times per day for the next week. On final follow-up the patient was left with a 0.5 mm round anterior corneal scar which was not visually significant. The patient and her parents were counseled on the importance of proper contact lens hygiene to avoid future contact lens-related keratitis.

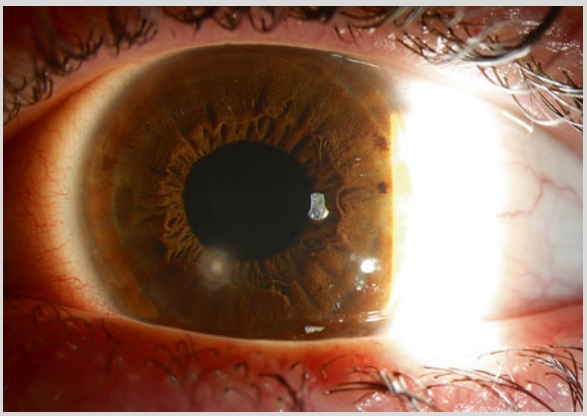

Fig. 10.1 Slit-lamp photograph of 12-year-old girl demonstrating a small anterior stromal infiltrate with overlying epithelial defect, consistent with a contact lens-related bacterial corneal ulcer

Case 2 (Fig. 10.2)

Clinical Synopsis

A 6-year-old patient sustained an injury with a tree branch to the left eye 1 week prior to presentation while on a camping trip. He had progressive worsening of both vision and pain. He had seen multiple primary care providers before presenting to an ophthalmologist 2 weeks later. Slit-lamp photograph of the left eye is shown. After failed treatment with topical ciprofloxacin and moxifloxacin, an examination under anesthesia with corneal cultures was performed. Gram stain demonstrated septate fungal hyphae, and treatment was initiated with topical natamycin 5 % every hour while awake and every 2 h at night. He was initially followed daily until there was improvement in the active infiltrate. Debridement was considered but deferred due to the large epithelial defect. One week later, cultures grew *Fusarium solani*. The frequency of drop administration was decreased over 12 weeks of treatment as his clinical picture improved. Despite eradication of the infection, he developed central scarring and subsequent amblyopia. Due to irregular astigmatism from scarring, he was treated with a rigid gas permeable contact lens in the left eye with some improvement in visual acuity.

Fig. 10.2 Slit-lamp photograph of a 6-year-old boy with a Fusarium corneal ulcer that developed after a tree branch injury. Severe conjunctival injection with a large epithelial defect and underlying feathery infiltrate can be seen. Photo courtesy of Jeffrey M. Goshe, MD

Case 3 (Figs. 10.3 and 10.4)

Clinical Synopsis

A 5-year-old patient with a history of type I diabetes mellitus presented with 7 days of right eye pain, redness, and irritation. She was diagnosed with viral conjunctivitis by her primary care physician but did not improve. Slit-lamp examination with fluorescein revealed a dendritic epithelial defect with terminal bulbs (Fig. 10.3), and she was subsequently diagnosed with HSV epithelial keratitis. Treatment with 400 mg oral acyclovir suspension 4 times daily led to resolution of the dendrite with only minimal corneal scarring. She returned 12 months later with worsening vision in her right eye and exam demonstrated stromal inflammation and haze without an epithelial defect (Fig. 10.4). She was diagnosed with immune stromal HSV keratitis, and was treated with a suppression dose of oral acyclovir and 0.1 % fluorometholone drops 6 times daily, which were tapered off over 8 weeks as the stromal inflammatory response improved. After resolution, she was maintained on a prophylactic dose of oral acyclovir.

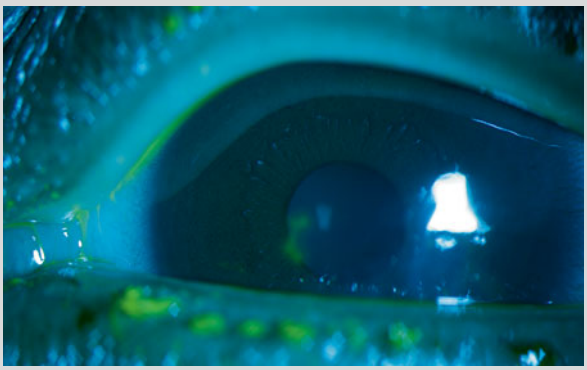

Fig. 10.3 Slit-lamp photograph of a 5-year-old boy with an infectious HSV epithelial keratitis, with a fluorescein staining pattern demonstrating the dendritiform appearance and terminal bulbs

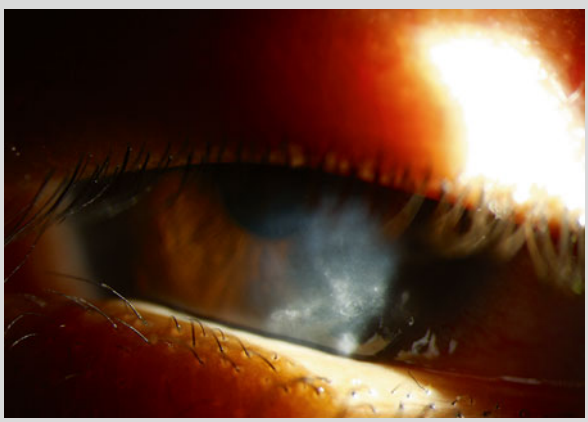

Fig. 10.4 The same patient in Fig. 10.3 developed HSV immune stromal keratitis in the right eye 1 year later. Haze and white blood cells are seen in the anterior corneal stroma underlying a resolved epithelial dendrite

Case 4 (Fig. 10.5)

Clinical Synopsis

A 9-year-old-girl with a 2-year history of waxing and waning photophobia, ocular irritation, and red eyes had been treated by multiple eye care providers with topical antibiotics, lubricants, and anti-allergy eye drops without significant alleviation of symptoms. Slit-lamp examination demonstrated bilateral blepharitis, lid margin telangiectasia, conjunctival hyperemia, and punctate epitheliopathy. Peripheral bilateral corneal scarring and superficial neovascularization were present in both corneas. The patient was diagnosed with rosacea keratoconjunctivitis and systemic erythromycin twice daily was initiated along with topical 0.1 % fluorometholone 4 times daily. She was counseled on eyelid hygiene. With improvement in her signs and symptoms the topical corticosteroids were gradually tapered over 4 weeks, and oral erythromycin was decreased to once daily and maintained for 12 months with resolution of symptoms.

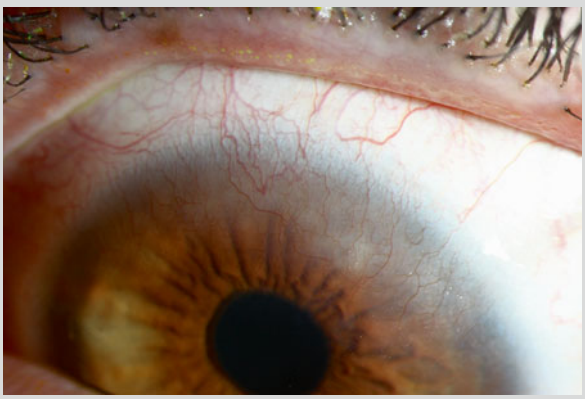

Fig. 10.5 Slit-lamp photograph of a 9-year-old girl with rosacea blepharoconjunctivitis demonstrates lid telangiectasias and obstructed meibomian glands in the upper eyelid. A band of sterile infiltrates and vascularization without an overlying epithelial defect are seen in the superior cornea. Photo courtesy of Jeffrey M. Goshe, MD

Bacterial Keratitis

Risk Factors

Trauma is the most common cause of infectious microbial keratitis in children [3–5]. Other predisposing factors include prior ocular disease, prior ocular surgery, contact lens wear, use of topical corticosteroids, and systemic diseases such as diabetes, leprosy, pulmonary tuberculosis, and xeroderma [3]. Pediatric bacterial keratitis is more common in males [3, 4]. In teenagers, contact lens wear becomes an increasingly predominant risk factor. Overnight wear of orthokeratology lenses also increases the risk of infection [6].

Pathogenesis

To infect the cornea, micro-organisms must overcome the defense mechanisms present in the tear film as well as the ocular surface barrier of intact corneal epithelium. As such, microbial infection often involves trauma to the ocular surface, which allows bacteria to invade and adhere to exposed corneal protein and lipid receptors, leading to corneal penetration and subsequent microbial proliferation. This is followed by white blood cell recruitment, predominantly polymorphonuclear neutrophils (PMNs). Degranulation of PMNs leads to the release of enzymes and toxic metabolic products that attack micro-organisms but also can degrade corneal stroma. Cytokines and chemokines aid in wound healing by modulating the host inflammatory response to prevent additional stromal damage. Corneal wound healing after infection involves a complex interplay between growth factors, cytokines, and extracellular matrix components. The activation of keratocytes and the generation of myofibroblasts lead to neovascularization, scarring, and opacification of the cornea [7].

Diagnosis

A complete medical history and eye examination focusing on characteristic clinical features is essential in making the diagnosis. Predisposing risk factors, specifically a history of ocular trauma or contact lens wear, should be sought, although often none are ascertained. Clinical manifestations vary, but symptoms may include pain of rapid onset, decreased vision, conjunctival injection, photophobia, mucoid discharge, and eyelid edema. Slit-lamp examination classically reveals the presence of a white or yellowish suppurative infiltrate in the corneal stroma with an overlying corneal epithelial defect. White blood cells in the corneal stroma, corneal edema, an anterior chamber reaction, or a layered hypopyon may be present. To determine the underlying etiologic organism in severe or rapidly progressing cases, diagnostic corneal cultures should be performed and may require an examination under anesthesia. Depending on clinical suspicion, smears may be inoculated in blood, chocolate, Sabouraud agar, Lowenstein-Jensen agar, and thioglycolate broth while microscopic slides may be used for staining. Ideally, diagnostic cultures should be obtained before the initiation of treatment if severe keratitis is present. In particular, large or central ulcers or those associated with hypopyon should be cultured to ensure appropriate treatment. Similar to adults, the rate of positive cultures for bacterial ulcers in children has been reported between 52 % and 65 % [8–11], with a microbial spectrum that varies by geographical location. *Staphylococcus aureus* and *Streptococcus pneumoniae* are the predominant Gram-positive micro-organisms, and *Pseudomonas aeruginosa* is the major Gram-negative micro-organism associated with pediatric bacterial keratitis [6, 12–15].

Treatment

The primary aim of therapy is to eradicate infection with antimicrobial agents to prevent scarring and subsequent visual impairment. Initially, frequent topical administration of antibiotics (as often as every hour) allows a high concentration of the drug to be delivered, with minimal risk of ocular and systemic toxicity; the frequency of drop administration can then be decreased according to clinical response. While concerns exist regarding potential effects of systemic absorption due to lower blood volume of children, most topical drug therapies for microbial keratitis are relatively well-tolerated without reported side effects. Frequent administration of topical antimicrobials can be challenging in uncooperative children. Additionally, drug concentration may be reduced if crying ensues after drop application. As a result, ophthalmic antibiotic ointments should be considered in children due to their ease of use and longer surface concentration, although these advantages must be weighed against a more limited spectrum of antibiotic activity. No studies have reported differences in the efficacy of antibiotics in drop versus ointment formulations. In certain cases, an examination under anesthesia may be necessary for best observations, and depending on clinical suspicion, subconjunctival injection of antibiotics with supplemental topical administration can be considered at that time to ensure an adequate initial therapeutic concentration of the treatment agent, although no published studies support the efficacy of this approach.

Appropriate treatment involves taking into account potential risk factors and the most likely causative organism.

While awaiting results of cultures in severe cases, or for empiric treatment of less severe ulcers, topical broad-spectrum antibiotics should be initiated. Therapy may involve monotherapy with a commercially available fluoroquinolone, or with fortified pharmacy-prepared antibiotic drops as frequently as every hour around-the-clock. Common regimens of fortified antibiotic drops that treat both gram-negative and gram-positive infections include cefazolin or vancomycin in combination with an aminoglycoside. In adults, studies have demonstrated similar efficacy of monotherapy with fluoroquinolones versus a combined fortified antibiotic regimen with rates of overall clinical efficacy ranging between 86.2 % and 93 % [16–18]. The type of antibacterial therapy is changed if the ulcer worsens or if a species resistant to the antibiotic regimen is isolated. There should be a low threshold for repeating cultures if the clinical picture does not rapidly improve on empiric therapy. Cases in which patients have unreliable follow-up may require inpatient admission to ensure appropriate compliance.

In some cases, moderating the host inflammatory responses with corticosteroids can be considered once the infection is controlled, but there are risks of decreasing host defenses and promoting corneal melting; no evidence supports the use of corticosteroids in children. In adults, the Steroids for Corneal Ulcers Trial (SCUT) demonstrated no overall benefit, but also no increased risk, for the use of topical corticosteroids in culture positive bacterial ulcers; however, subgroup analysis among those with the most severe ulcers did demonstrate better visual acuity with corticosteroids [19]. As a result, topical corticosteroids may be considered in severe ulcers after initial treatment with antibiotics.

As with adults, surgical intervention for bacterial corneal ulcers is rarely required in children, usually in cases of impending or frank corneal perforation. Options include application of cyanoacrylate glue, therapeutic penetrating or lamellar keratoplasty, conjunctival flap, debridement, and amniotic membrane transplantation.

Outcomes

The large majority of corneal ulcers in children are effectively treated with topical therapy alone [3, 12, 13]. The rate of surgical intervention reported in various case series has varied between 2 % and 74 %, depending on geographic region (urban versus rural settings), associated severe protein-energy malnutrition, and the presence of bilateral keratitis [3, 6, 12–15, 20, 21]. A prior study reported that pediatric microbial keratitis, in contrast to adult keratitis, was more likely bacterial in etiology, less severe, and more likely to resolve with medical treatment alone [22].

Fungal Keratitis

Risk Factors

The most common risk factor for fungal keratitis is trauma, particularly when associated with agricultural material [23, 24]; fungi are also more common in tropical, humid environments. In adults, corticosteroid use is a risk factor because of diminished host defenses against fungi [25–32], although this has not been demonstrated in the pediatric population.

Pathogenesis

Pathogenesis is similar to bacterial infection. Fungi produce extracellular toxins and enzymes that result in corneal destruction [33] and can penetrate an intact Descemet's membrane. Once fungi have reached the anterior chamber, infection may be very difficult to eradicate.

Diagnosis

Clinical signs and symptoms overlap greatly with bacterial infection. Clinical features that suggest fungal keratitis include infiltrates with irregular, feathery margins, the presence of satellite lesions, and an intact epithelium with stromal infiltration, but none of these findings are pathognomonic. Diagnostic corneal cultures are necessary to definitively diagnose fungal infection. The most common filamentous species causing childhood keratomycosis are *Aspergillus*, followed by *Fusarium* and *Alternaria* [13, 34]. Newer imaging modalities, such as confocal microscopy, may offer a non-invasive method to diagnose fungal keratitis [35], but their utility has not been specifically described in children.

Treatment

Antifungal treatment is usually initiated if cultures are positive, fungi are found on confocal microscopy, or if there is a high clinical suspicion; the reasons for this therapeutic paradigm are the prolonged duration of treatment and potential for epithelial toxicity. Polyenes, including natamycin, nystatin, and amphotericin B, disrupt the cell by binding to fungal cell wall ergosterol and are effective against both filamentous fungi and yeast. Amphotericin B is the drug of choice for patients with fungal keratitis caused by yeasts. Antifungal treatments have more limited activity against the organisms compared to anti-bacterial treatments, and also poorer penetration into the cornea [36, 37]. Subsequently,

fungal keratitis is more likely to lead to corneal perforation than bacterial infection [38]. Frequent topical treatment may be combined with corneal epithelial debridement in order to improve penetration into the corneal stroma. Epithelial toxicity may also be observed with use of topical antifungals. Topical natamycin 5 % is the only commercially available antifungal agent and has been used successfully in children [13, 39]. Other effective antifungal drops in children include fluconazole 0.5 % and amphotericin B 0.25 % [12, 15]. Oral antifungal agents should be considered in the management of deep fungal keratitis, as the newer-generation triazoles have excellent intraocular penetration and are effective against a broad spectrum of fungi [40, 41]. Due to potential systemic toxicity and dosing issues in children, the authors recommend that these medications should be prescribed in concert with a pediatrician or an infectious disease specialist. Even with the initiation of appropriate therapy, improvement in clinical signs may initially be difficult to detect with fungal ulcers, and successful treatment requires frequent drug administration for a prolonged period. Corticosteroid drops should not be used in the treatment of fungal keratitis because of the promotion of fungal growth [42, 43]. Surgical options in cases of impending or frank corneal perforation include application of cyanoacrylate glue, therapeutic penetrating or lamellar keratoplasty, conjunctival flaps, debridement, and amniotic membrane transplantation.

Outcomes

Outcomes in fungal keratitis are worse than those in bacterial keratitis, with high rates of corneal perforation, endophthalmitis, and surgical intervention [38]. Prompt recognition and initiation of treatment may improve the outcome.

Viral Keratitis

Risk Factors

Herpes simplex virus-1 (HSV-1) has a seroprevalence in adults between 50 % and 90 %, and is a leading cause of corneal blindness worldwide [44]. Primary ocular infection with herpes simplex usually occurs in children at less than 6 years of age [45, 46], with blepharoconjunctivitis the most common manifestation and keratitis occurring less frequently. Compared to adults, recurrences of keratitis are more frequent in children [13, 46], which increases the risk of stromal involvement [34]. While presentation is unilateral in the majority of cases, bilateral cases are more common in children [47, 48], as well as in those with atopy and immunosuppression [47, 49–52].

Pathogenesis

In addition to overcoming the ocular surface barrier and nonspecific immune mechanisms of the host, viruses also must overcome antibody and T-cell-mediated immune mechanisms. Pathogenesis involves adhesion of the viral particles to the ocular surface with penetration into the cornea, nucleic acid uncoating, transcription and translation of regulatory proteins, nucleic acid synthesis, protein synthesis, virion assembly, and release from the host cell.

Ocular HSV occurs through human-to-human transmission or more frequently through reactivation of latent virus in the trigeminal ganglion, spreading via the mandibular or maxillary branch of the trigeminal nerve to reach the eye. Potential triggers for recurrence may include fever, trauma, stress, and immunosuppression, although the Herpetic Eye Disease Study did not confirm these associations [53].

Diagnosis

The diagnosis of ocular HSV is often made clinically, but because manifestations can be less distinctive in children, laboratory confirmation, including PCR or immunofluorescence assay (IFA), may be employed with reported high sensitivity and specificity [54].

HSV keratitis can be classified based on epithelial, stromal, or endothelial involvement and whether it is infectious, immunologic, or neurotrophic in etiology. Infectious HSV epithelial keratitis begins as epithelial vesicles that arborize to form dendritic ulcers and can coalesce to form a geographic ulcer. The classic appearance is that of a branching lesion with terminal end bulbs, highlighted with fluorescein stain. Immune stromal keratitis, likely a cell-mediated immune response to HSV antigens, presents clinically as focal or patchy diffuse stromal infiltrates, typically with an intact overlying epithelium; however, it can occur simultaneously with infectious epithelial keratitis. With chronicity, lipid keratopathy, superficial and deep corneal neovascularization, or ghost vessels can occur. Disciform endotheliitis primarily involves the corneal endothelium, with resultant edema of the stroma or epithelium in a well-delineated circular (disc-like) configuration. Fine keratic precipitates typically underlie the area of edema, and there is usually only a mild anterior chamber reaction that is out of proportion to the amount of corneal edema. Recurrent epithelial and stromal disease can decrease corneal sensitivity and lead to neurotrophic keratopathy, often manifested as a persistent epithelial defect with rolled edges and anterior stromal haze. Compared to adults, children have more frequent recurrences of HSV keratitis [2, 55], with immune stromal keratitis occurring more frequently [54]. Findings are generally unilateral, although bilateral involvement in the pediatric population occurs from 10 % to 26 % of the time [44, 47, 48].

Treatment

Treatment for ocular HSV is tailored to whether the manifestations are infectious, immunologic, or neurotrophic in nature. For infectious HSV epithelial keratitis, topical or oral antivirals are effective. In children, the recommended dose of oral acyclovir in epithelial keratitis is 12-40 mg/kg/day in divided doses up to 40 kg, and the adult dose of 400 mg 5 times daily in children greater than 40 kg [2]. Oral acyclovir or topical ganciclovir gel is often preferred to topical trifluridine, given the latter's epithelial toxicity. For immune stromal keratitis and disciform keratitis, a lower prophylactic dose of antiviral medications is used in combination with frequent topical corticosteroids, which are tapered based on clinical response. For children with multiple episodes of HSV keratitis the long-term use of oral acyclovir should be considered, based on the significant reduction of recurrences in the HEDS trial in adults [56].

Outcomes

Children with HSV keratitis tend to have poor visual outcomes [47]. Corneal scaring often develops, with a risk for deprivation or refractive amblyopia. Studies have reported approximately half of children with herpetic keratitis develop recurrences within 1–2 years [44, 47, 48], highlighting the importance of prolonged antiviral administration in childhood to suppress viral replication and reduce the risk of recurrences.

Rosacea Keratoconjunctivitis

Risk Factors

Both cutaneous and ocular manifestations of acne rosacea, including rosacea keratoconjunctivitis, are most common in the third to fifth decades of life but can occur in the pediatric population [57]. There is no clear sex predilection, and while it affects all races it is more common in lighter-skinned individuals [58–60].

Pathogenesis

Rosacea keratoconjunctivitis is a chronic inflammatory disease focused on the meibomian glands, leading to meibomian gland dysfunction, thickened secretions, glandular dropout, and ocular surface inflammation [60].

Diagnosis

Rosacea keratoconjunctivitis is uncommon in the pediatric population but can lead to significant vision loss because it can be difficult to recognize, leading to prolonged symptoms and delay in appropriate treatment. There is often a prolonged history of eye redness, irritation, and photophobia that is poorly responsive to topical treatments. The classic cutaneous finding of facial erythema, flushing, telangiectasias, and pustules on the face may not be associated with ocular rosacea in children [39, 58, 59, 61–63], and this condition may be more appropriately termed chronic blepharokeratoconjunctivitis [64, 65]. Currently, there is a lack of uniform diagnostic criteria for rosacea keratoconjunctivitis and blepharitis-related keratitis. Ocular signs may include blepharitis, meibomian gland dysfunction, chalazia, conjunctival hyperemia, punctate epitheliopathy, superficial peripheral corneal vascularization, and corneal subepithelial infiltrates [39, 58, 59, 61–63], typically without an overlying epithelial defect. Keratitis, the most sight-threatening complication of ocular rosacea, occurs in 5 % of patients [66]. It usually presents as an interstitial keratitis, but subsequent breakdown of the overlying epithelium can occur because of infiltration by white blood cells into the subepithelial cornea [66]. Females are more affected than males and presentation is generally bilateral, but may be asymmetric [57, 62].

Treatment

Treatment for this chronic disease is focused on the control of symptoms and prevention of complications, rather than cure. To avoid visually threatening complications, it is important to initiate appropriate treatment before corneal neovascularization and scarring develop. Oral medications that alter gland composition are used long-term in combination with bursts of anti-bacterial and anti-inflammatory drops to reduce surface inflammation and scarring. Oral tetracycline and doxycycline decrease the production of bacterial lipase and subsequent free fatty acids to decrease microbial inflammatory mediators and are effective in older children. Doxycycline may be preferred to tetracycline due to less gastrointestinal side effects [60]. However, both are contraindicated in children younger than 9 years of age because of potential tooth discoloration [39, 57, 67]. In younger children, oral erythromycin can effectively prolong tear break-up time and improve meibomian gland function and punctate keratopathy [64, 65, 67]. An optimal dosing strategy for oral antibiotics is not well-defined, although authors report using 50–80 % of the dose used for infections in children, divided into two daily doses [65, 67]. Corticosteroids

are sometimes necessary to suppress associated inflammation, but should be used judiciously to avoid the potential development of cataracts, glaucoma, and corneal melting [57]. Supplemental treatments include frequent warm compresses to the eyelids and lid scrubs to maximize meibomian gland function. Anti-inflammatory nutritional therapy with flaxseed oil may be an alternative to long-term systemic antibiotics [65].

Outcomes

Children generally respond favorably to systemic doxycycline or erythromycin in addition to lid hygiene and short-term topical corticosteroid and antibiotics [68], although serious visual morbidity can result [65]. To avoid recurrences, prolonged therapy over months is recommended [39, 57, 62, 65], although the ideal dosing strategy in children is not well-established, and close follow-up is necessary to monitor for recurrences.

Conclusion

Pediatric corneal ulcers and microbial keratitis are uncommon but potentially devastating ocular conditions characterized by a more potent and rapid inflammatory response than in adults. Amblyopia from corneal scarring or induced astigmatism is a potentially significant sequela. Addressing and minimizing risk factors, identifying etiologic organisms, and understanding treatment strategies can aid in early recognition and treatment, and ultimately improve patient outcomes.

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Pediatric Herpes Virus Anterior Segment Infections

11

Aaron R. Kaufman and Adam H. Kaufman

Abstract

This chapter is designed as a practical guide for diagnosis and management of anterior segment herpetic disease in children. When these potentially serious infections occur in childhood, the pediatric ophthalmologist frequently coordinates the acute and long-term management. In atypical or severe cases, consultation with a cornea, uveitis, or infectious disease specialist may be necessary. Although complex diagnostic and treatment descriptions are possible, this chapter provides generalized guidance through defined categories of disease with delineated treatment protocols. Herpes simplex virus (HSV) is the primary focus of the chapter, and the text emphasizes pediatric blepharoconjunctivitis, epithelial keratitis, stromal keratitis, endotheliitis, iritis, and neonatal disease. Varicella zoster virus (VZV) infections are also briefly discussed. Treatment flow diagrams and clinical photographs are presented for additional guidance.

Keywords

Pediatrics • Herpes simplex virus • Varicella zoster virus • Blepharoconjunctivitis • Epithelial keratitis • Stromal keratitis • Endotheliitis • Iritis • Acyclovir • Valacyclovir • Famciclovir

Abbreviations

CMV	Cytomegalovirus
CN V	Trigeminal nerve
HEDS	Herpetic Eye Disease Study
HSV	Herpes simplex virus
HSV-1	Herpes simplex virus type 1
HSV-2	Herpes simplex virus type 2
PCR	Polymerase chain reaction
V_1	Ophthalmic nerve (1st branch of the trigeminal nerve)
VZV	Varicella zoster virus

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Introduction

Herpes virus infections are a major cause of ocular disease, and special considerations are necessary in the pediatric population. The majority of pediatric anterior segment herpetic disease involves herpes simplex virus (HSV), although varicella zoster virus (VZV) and cytomegalovirus (CMV) involvement may also be seen. Ocular herpes may be caused by either of the two types of herpes simplex virus, type 1 (HSV-1) and type 2 (HSV-2). HSV-1 typically causes orofacial disease (including ocular disease), and HSV-2 typically causes genital disease, although cases exist where the reverse occurs [1, 2].

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HSV-1 is a globally widespread virus [2, 3]. Seroprevalence of antibodies to the virus is very high. In the USA presence of antibody titers in 14- to 49-year-olds is over 50 % for HSV-1 and about 15 % for HSV-2 [4]. Additionally, polymerase chain reaction (PCR) testing of cadaveric trigeminal nerve (CN V) ganglia has demonstrated that the presence of HSV-1 genome increases with age and is nearly 100 % for ages over 60 [5]. Many individuals do not have a history with identifiable primary herpetic infection yet are seropositive for herpes antibodies. Thus, primary HSV infections may often be asymptomatic. Additionally important for ocular disease, HSV has the insidious ability to both shed and infect asymptomatically [2, 6].

A defining feature of ocular HSV infection is the recurrent nature of the disease. After primary infection with HSV, inactive virus remains in the ganglion of CN V. The latent virus is able to periodically cause disease in the area innervated by CN V. Orofacial herpes may recur in the eye via the ophthalmic nerve (V_1), a branch of CN V, even if the primary infection occurred in areas innervated by the other two branches of CN V (V_2, maxillary nerve; V_3, mandibular nerve). Recurrence of ocular herpes increases risk of corneal scarring and vision loss. The disease appears to have a greater rate of recurrence in children than in adults [7, 8]. The pathophysiologic mechanism for recurrent episodes of ocular herpes is multifactorial and not fully understood [6]. Sunlight, local physical trauma, hormonal changes, and immunological stress (as by fever) are thought to contribute to risk of recurrence of non-ocular herpetic disease [9]. However, with correction for recall bias, the Herpetic Eye Disease Study (HEDS) Group found that none of these factors were a significant cause of recurrent ocular herpes [10]. However, a history of atopic disease has been associated with recurrent herpetic eye disease, possibly secondary to immunologic dysfunction [11–13]. Therefore, the practitioner should inquire about personal and family history of conditions such as asthma, eczema, and seasonal allergies.

Interestingly, only topical antiviral medication has been FDA approved for the treatment of HSV keratitis and only for epithelial keratitis [14, 15]. Evidence-based oral antiviral treatment protocols have been developed for multiple forms of ocular HSV disease from retrospective studies as well as from the prospective studies conducted by the HEDS Group [7, 8, 16–21].

The emphasis of this chapter is HSV, and the various forms of HSV disease of the anterior segment are discussed. VZV disease is also briefly reviewed, but it is much less common in children. CMV is a very rare cause of anterior segment viral disease, and its discussion is beyond the scope of this chapter. Straightforward treatment strategies for pediatric anterior segment herpetic disease will be presented both in text and in flow diagrams.

HSV Clinical Manifestations – Structure of Discussion

This chapter devotes a separate section to each of the various patterns of anterior segment HSV disease. Although the different forms of herpetic disease are discussed separately for clarity of presentation, it is important to note that a child may have multiple forms of herpetic disease either simultaneously (e.g., keratouveitis) or separately in recurrent disease (e.g., epithelial keratitis later followed by stromal keratitis).

HSV Blepharoconjunctivitis and Periocular Disease

Pediatric ocular HSV infection frequently manifests as blepharoconjunctivitis and periocular skin disease. Often, these lesions are associated with a primary herpetic infection [22], although recurrent ocular herpes can also include these features [23]. Figure 11.1 demonstrates ulcerative and vesicular lesions that are typical of eyelid involvement. The eyelid may be swollen and edematous, with discharge and lacrimation [24]. Periocular and eyelid skin involvement may resemble other orofacial herpetic sores. Preauricular lymph nodes may also be enlarged and palpable. Herpetic conjunctivitis manifests as follicular inflammation and is sometimes associated with corneal epithelial involvement [22, 24]. Epithelial herpetic disease is discussed further in the next section. If the epithelial keratitis is near the limbus (marginal keratitis), then the herpetic blepharoconjunctivitis may be mistaken for staphylococcal blepharokeratoconjunctivitis. However, ocular involvement is typically unilateral in herpetic disease and

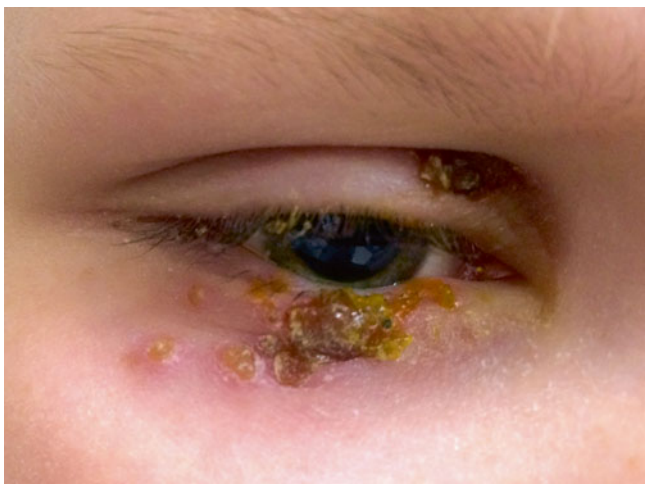
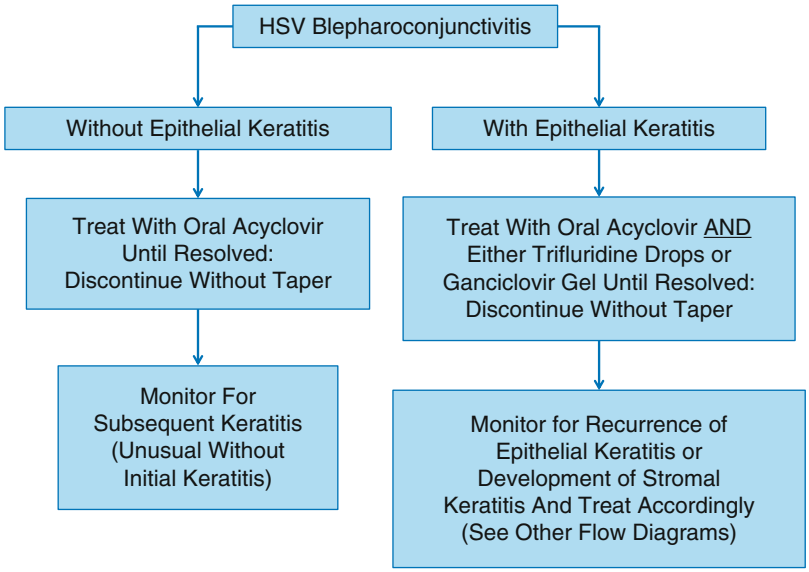


Fig. 11.1 Typical appearance of eyelid involvement in primary or recurrent herpetic blepharoconjunctivitis. Note numerous vesicular lesions, some of which have ulcerated and crusted. Photo courtesy of Allison Babiuch, MD



Flow Diagram 11.1 Treatment overview for pediatric HSV blepharoconjunctivitis

may be bilateral in staphylococcal disease [8]. Additionally, the distinct appearance of HSV skin vesicles and corneal epithelial involvement may assist in differentiating HSV from other infectious entities.

HSV blepharoconjunctivitis may be self-limiting, but oral antiviral treatment can shorten the course and limit corneal exposure to active virus [24]. Younger children and infants may be treated with a short course of oral acyclovir suspension, and older children can be treated with either acyclovir pills or oral suspension [7, 8, 21, 25]. Oral antiviral treatment is generally discontinued after full resolution of the HSV blepharoconjunctivitis or periocular disease. Corticosteroid treatment is not indicated for primary ocular herpes [26]. If the cornea is not involved, prognosis for primary HSV infection is generally good, with minimal effect on final vision [8]. See Flow Diagram 11.1 for the treatment of HSV blepharoconjunctivitis. See Table 11.1 for drug dosage considerations.

Table 11.1 Generalized guidelines for oral antiviral treatment for pediatric HSV ocular disease

Age	Dose (mg/kg)
Neonate	Intravenous acyclovir 10–20 mg/kg 3 times per day
Age < 12 years OR Weight < 40 kg	Oral acyclovir 10 mg/kg 2 times per day (3 times per day for acute treatment)
Age > 12 years OR Weight > 40 kg	Oral acyclovir 400 mg 2 times per day (3–5 times per day for acute treatment)
Older teenager	Oral valacyclovir 1 g/day

Guidelines based on FDA-approved protocols and retrospective studies [8, 21, 25, 33, 40]. Valacyclovir guidelines for pediatric HSV ocular disease have not been developed

HSV Epithelial Keratitis

HSV epithelial keratitis manifests as ulcerative disease. The epithelial keratitis begins with areas of punctate epithelial defects that progress into more severe dendritic ulceration [24]. Dendritic ulcers are named for their tree-like appearance and have linear, branching ulcers with bulb-shaped ends. Dendrites are readily identified by their characteristic appearance and staining pattern. Rose bengal stains the edges and fluorescein stains the base of dendritic ulcers [27]. Geographic ulcers encompass a larger area than dendritic ulcers and may have a shape suggestive of a map. Geographic ulcers represent more advanced epithelial disease and develop when a dendritic ulcer's linear shape expands [24]. The edges of geographic ulcers have a distinctive scalloped shape that differentiates them from corneal abrasions [6]. Geographic ulcers also stain with rose bengal and fluorescein similarly to dendritic ulcers. Epithelial ulcers may cause sensitivity to light, blurriness, or a foreign body sensation [24]. In children, photophobia is easily observed [26]. Pediatric HSV keratitis is typically unilateral; however, atopy and an altered immune system predispose to bilateral disease [7].

Diagnosis of HSV epithelial keratitis is typically based on clinical findings. Figure 11.2 shows a typical HSV dendrite. The distinctive appearance and staining pattern of these ulcers are important diagnostic points. Laboratory testing is generally not necessary when the lesions are typical, but can be useful when the diagnosis is not definitive [24] and should always be utilized in neonates [28]. In particular, HSV culture and PCR are commonly available testing methods that can be utilized to aid in the diagnosis of HSV epithelial keratitis. Serum antibody testing can identify previous HSV infection. It is important to note that viral samples for lab testing should be collected prior to epithelial staining since rose bengal is toxic to HSV [29]. Collecting samples prior to staining will thus reduce false negative test results.

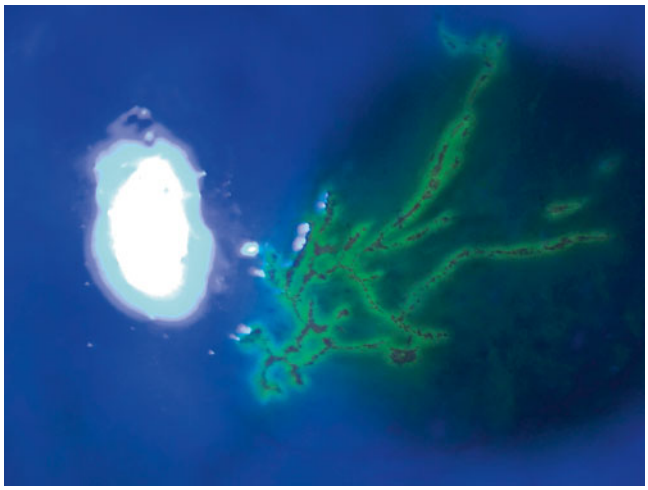


Fig. 11.2 HSV epithelial keratitis with dendritic ulcer. The base of this dendritic ulcer has been stained with fluorescein. The distinctive branching shape of the dendritic ulcer is an important diagnostic point for HSV epithelial keratitis. Photo courtesy of Erich Hinel, OD

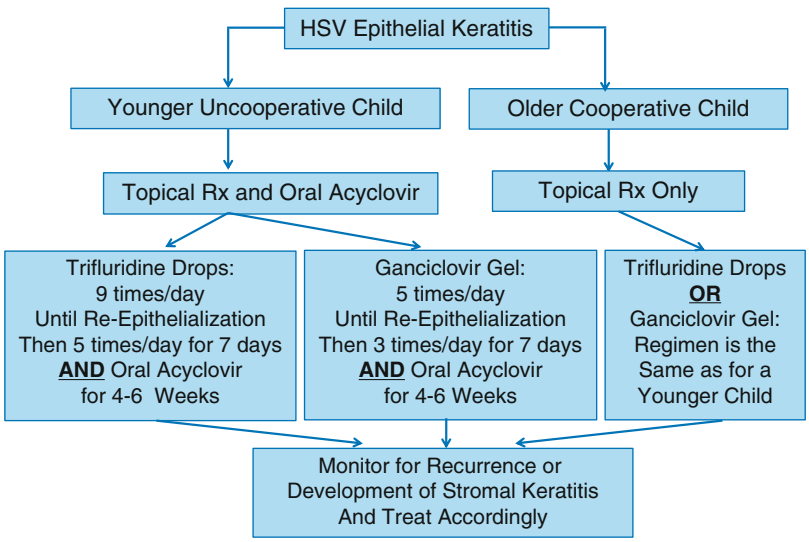
Although HSV epithelial disease may resolve in some cases without intervention [30], medication is utilized to speed resolution, reduce corneal scarring, and diminish stromal inflammation. Since the epithelial ulcers are caused by actively replicating virus, treatment targets the virus itself. Topical antiviral drugs (trifluridine drops, vidarabine ointment [not currently commercially available], or ganciclovir gel) have been shown to be effective in resolving HSV epithelial keratitis [14, 15, 31]. However, instillation of eye drops in small children may be difficult, and tear dilution from crying could prevent an effective dose. Oral acyclovir thus provides an important adjunctive treatment for pediatric HSV epithelial keratitis, and may provide effective treatment without the use of a topical antiviral [21]. See Table 11.1 for acyclovir dosage considerations. Topical corticosteroids are not indicated for HSV epithelial keratitis and may in fact accelerate ulceration [24]. However, topical corticosteroids play a role in the treatment of HSV stromal keratitis. Stromal keratitis is discussed in the next section. Some clinicians recommend debridement of infected epithelial cells to enhance resolution. Historically, corneal debridement has been described as a method to reduce the amount of active virus in the epithelium. However, debridement may be less effective than antiviral therapy and may not significantly improve outcome of antiviral therapy [32]. Additionally, corneal debridement is difficult in children, and may increase discomfort.

Unfortunately, as described in the introduction, HSV epithelial keratitis can recur. After an epithelial ulcer resolves, a faint stromal scar may remain. Recurrent HSV dendritic ulcers may recur near the scar. Epithelial recurrences increase the risk of HSV stromal keratitis, an immune-mediated disease process. Recurrence of HSV keratitis is higher in children and is a major management concern [21]. Thus, monitoring of children with periodic follow-up examinations and educating the parents for signs of recurrence are essential. See Flow Diagram 11.2 for the treatment of HSV epithelial keratitis. See Table 11.1 for drug dosage considerations.

HSV Stromal Keratitis

HSV stromal keratitis classically involves an immune-mediated response to inactive HSV antigen in the corneal stroma [6]. However, complex presentations with mixed patterns of anterior corneal disease and corneal scarring from multiple recurrences are possible [24]. Simple HSV stromal keratitis may present with single or multifocal sub-epithelial inflammatory infiltrates. Recurrent disease may have corneal neovascularization accompanying the inflammatory infiltrates and results in a disease presentation known as

Flow Diagram 11.2 Treatment overview for pediatric HSV epithelial keratitis



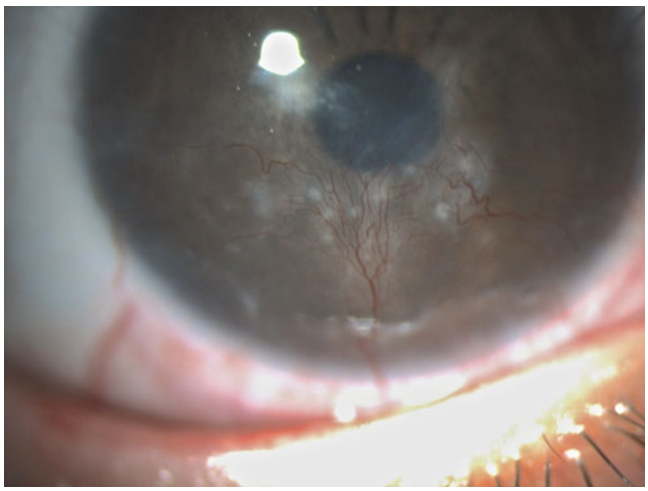
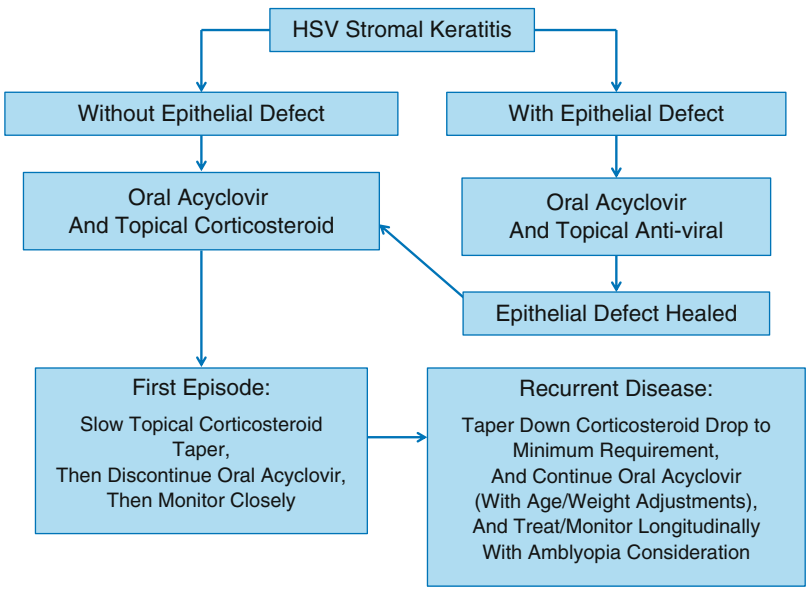


Fig. 11.3 HSV stromal keratitis with interstitial keratitis features. The sub-epithelial haze represents the distinctive stromal infiltrates observed in HSV stromal keratitis. This eye also displays corneal neovascularization associated with recurrent HSV interstitial keratitis. Photo courtesy of Erich Hinel, OD

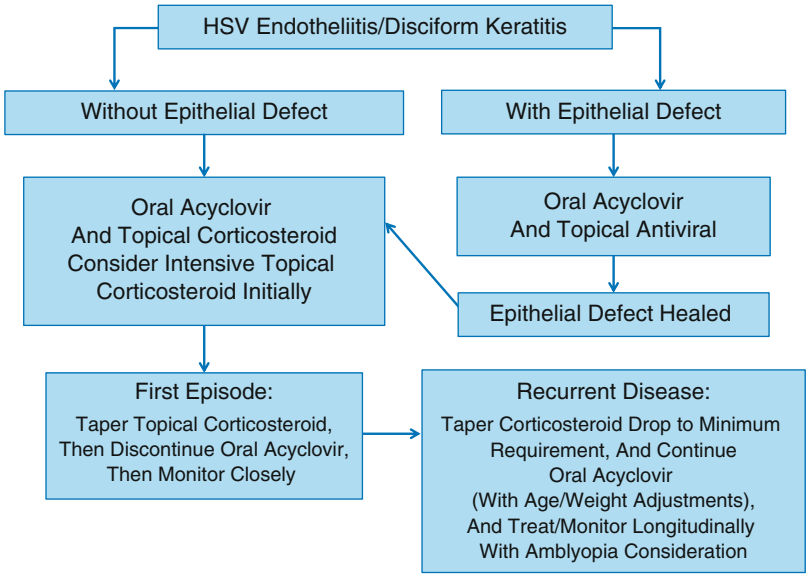
interstitial keratitis. Figure 11.3 demonstrates an active interstitial keratitis with stromal infiltrates and vascularization. Large inflammatory infiltrates with presumed active viral infection may result in necrotizing keratitis. Microbial super-infection of stromal keratitis may have an appearance similar to that of necrotizing keratitis. Stromal keratitis presentation may be further complicated by any combination of epithelial keratitis, endotheliitis, and iritis. Severe cases with necrotizing keratitis, super-infection, or recalcitrant recurrent disease require consultation with a cornea specialist. The majority of HSV stromal keratitis cases in children benefit from longitudinal involvement of a pediatric ophthalmologist due to inherent risk of amblyopia.

Although diagnostic categorization of HSV stromal keratitis and interpretation of evidence-based studies may be difficult, basic treatment protocols have evolved that are applicable to most pediatric cases [7, 8, 18, 21]. Treatment of stromal keratitis in children typically involves the use of topical corticosteroids and oral antivirals. The topical corticosteroid is necessary to treat the stromal inflammation, and the oral antiviral treats any active viral disease in addition to a putative contribution in preventing recurrence [7, 8, 18, 21]. In cases with concomitant epithelial disease, topical treatment is generally added for the first 2 weeks. The topical corticosteroid may be tapered and the oral antiviral discontinued after the first episode. However, longitudinal treatment throughout the amblyogenic period may be required to prevent visually debilitating scarring in the visual axis and resultant amblyopia. Corticosteroid should be tapered to the minimum amount necessary to control inflammation. Frequently, medication management strategies are complex and may require consultation with cornea and pediatric infectious disease specialists. Valacyclovir may be considered for older teenage patients with HSV stromal keratitis since it has been FDA approved for long-term treatment (at the 1 g/day suppressive therapy dose for genital herpes) [33]. Valacyclovir is a pro-drug of acyclovir that has an ester moiety that is removed by esterases to result in the active acyclovir. As a pro-drug of acyclovir, valacyclovir has greater bioavailability and would theoretically be expected to have a similar side effect profile. Famciclovir has also been approved for long-term suppressive therapy of genital herpes (at 250 mg twice a day), so it may also be considered for HSV stromal keratitis in older teenage patients [34]. However, famciclovir is not FDA approved for children. See Flow Diagram 11.3 for the treatment of HSV stromal keratitis. See Table 11.1 for dosage considerations. See the section on "Special Considerations in Treating Children" for additional discussion.

Flow Diagram 11.3 Treatment overview for pediatric HSV stromal keratitis



Flow Diagram 11.4
Treatment overview for pediatric HSV endotheliitis/disciform keratitis



HSV Endotheliitis

Active herpes viral infection may involve the corneal endothelium. Disciform keratitis occurs when there is a localized or "disc"-shaped area of corneal edema anterior to an area of localized endothelial dysfunction. Thus, although the patient may present with obvious stromal edema and haze, the underlying cause is the endotheliitis. The hallmark of endotheliitis is the presence of keratic precipitates that do not respect Arlt's triangle and are present in the area of corneal edema. Clinical presentation of endotheliitis may be complicated by the concomitant occurrence of other forms of HSV disease such as immune stromal keratitis and iritis. The treatment protocol is analogous to stromal disease treatment, although more intensive initial topical corticosteroid may be utilized. This more intensive regimen serves to rapidly reverse the endothelial inflammation to minimize permanent damage to the endothelial cells. See Flow Diagram 11.4 for the treatment of HSV endotheliitis. See Table 11.1 for drug dosage considerations.

HSV Iritis

HSV iritis may occur in an isolated fashion or in combination with keratitis. HSV iritis may be characterized by stellate keratic precipitates, sectoral iris atrophy, and ocular hypertension. The stellate keratic precipitates may be diffuse or may be clustered inferiorly in an Arlt's triangle distribution pattern. Sectoral iris atrophy has been shown to be an important diagnostic marker for herpetic iritis, and HSV iritis in particular [35]. See Fig. 11.4 for a photograph of characteristic iris atrophy after HSV iritis. Diagnosis of HSV iritis is more easily accomplished when HSV keratitis is also present. Suspected isolated HSV iritis may require a laboratory work-up as well as uveitis consultation to rule out other causes of iritis. Additionally, in certain cases, an anterior chamber paracentesis may be indicated to perform PCR analysis of the aqueous to identify a viral cause of the iritis. CMV (in immune-competent individuals) [36, 37] and VZV may also cause iritis in rare instances. Treatment of HSV iritis is similar to treatment of HSV endotheliitis. Importantly, absolute resolution of the iritis is required before attempting to taper the corticosteroid drops. See Flow Diagram 11.5 for treatment of HSV iritis. See Table 11.1 for drug dosage considerations.

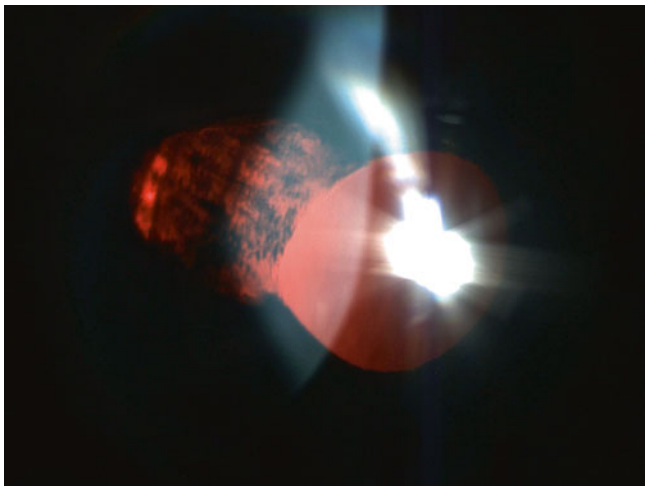
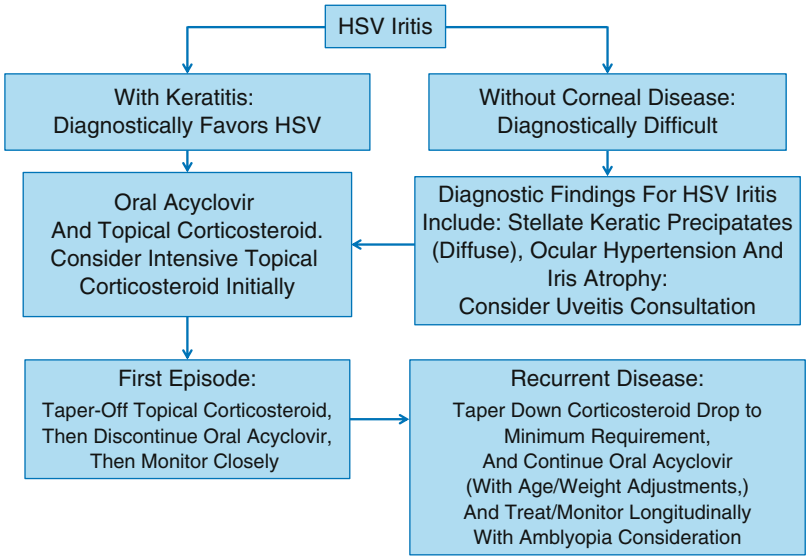


Fig. 11.4 Iris atrophy secondary to HSV iritis. The sectoral iris atrophy shown here is a useful diagnostic marker for HSV iritis. Photo courtesy of Erich Hinel, OD

Flow Diagram 11.5
Treatment overview for pediatric HSV iritis



Neonatal Ocular HSV Infection

Neonatal HSV infection requires emergency admission and treatment, coordinated by the pediatrician and an infectious disease specialist. Incidence of neonatal HSV in the USA has been observed at 10 in 100,000 [38]. Although the incidence of neonatal HSV infection is rather low, the disease poses a high risk. Neonatal HSV infection can progress to disseminated disease or central nervous system involvement, and may result in death of the newborn. Prompt identification of ocular herpes disease in the neonate leads to early diagnosis and treatment of potentially concomitant systemic disease. Treatment of the ocular disease itself is directly important in preserving sight.

Neonatal herpes infections are often contracted during passage through the birth canal of a mother with a genital infection. Because most adult genital infections are HSV-2, 75 % of neonatal herpes infections are caused by HSV-2 [28]. Moreover, most neonates with ocular herpes disease have HSV-2 infection [39]. In mothers with known active genital herpes infection, delivery by Caesarian section decreases the risk of neonatal herpes infection. However, HSV infection may also be transmitted placentally [7] or acquired from caregivers postnatally [3].

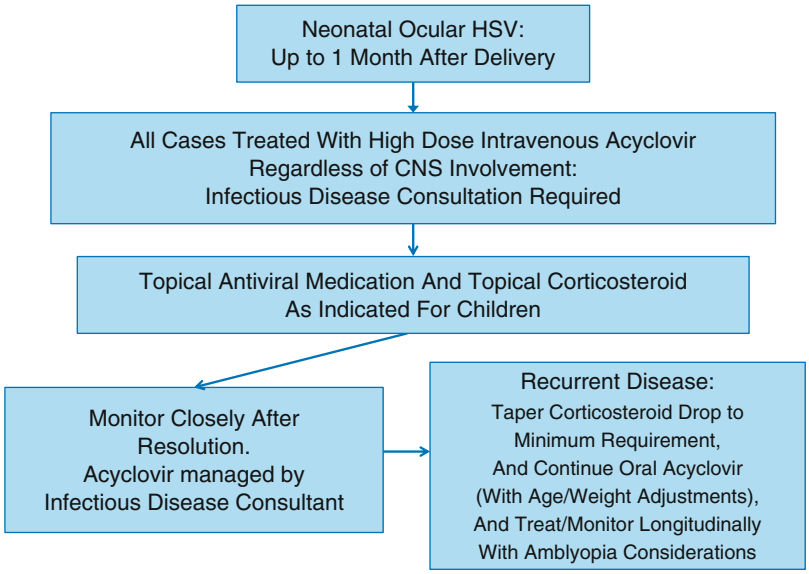
Typical features of a neonatal HSV infection include localized external lesions (skin, eye, and/or mouth), disseminated herpes affecting internal organs, and central nervous system infection (encephalitis). An infected infant may display several of these features. Ocular herpes in the newborn typically appears as periorbital skin vesicles, blepharoconjunctivitis, keratitis, anterior uveitis, chorioretinitis, and congenital cataracts [3, 39]. Importantly, a dilated fundus examination should be performed in any neonate with suspected HSV infection. Since herpes infections may resemble other neonatal infections, laboratory tests (e.g., fluorescein antibody tests, herpes culture, or PCR testing) should be performed in all cases of suspected neonatal herpes [28]. While awaiting lab results, the newborn should be empirically treated with intravenous acyclovir [40]. Infectious disease consultation is critical. Additionally, monitoring for the development of amblyopia is required after resolution of neonatal HSV keratitis. See the section on "Special Considerations in Treating Children" for further discussion of amblyopia.

Overall prognosis of neonatal ocular HSV infection treated with intravenous antiviral therapy is generally good. However, mortality is higher in newborns with disseminated infection or CNS disease [28]. Visual outcome is poorer when corneal herpetic disease causes scarring. Infants must also be monitored closely for evidence of recurrent disease. Infants with recurrent HSV keratitis are typically followed longitudinally by an infectious disease specialist. Additionally, longitudinal follow-up by a pediatric ophthalmologist is important due to the risk of amblyopia development associated with recurrent HSV keratitis. If there is recurrent neonatal ocular HSV infection, higher oral doses of acyclovir may be necessary. See Flow Diagram 11.6 on next page for treatment of neonatal ocular HSV infection. See Table 11.1 for drug dosage considerations.

Varicella Zoster Virus Infections in Children

Chicken pox is caused by VZV, and ophthalmic involvement may rarely occur. The incidence of chicken pox has diminished due to the widely used live attenuated VZV vaccine [41]. Early treatment of chicken pox in normal children with oral acyclovir has been shown to diminish the severity and

Flow Diagram 11.6
Treatment overview for neonatal ocular HSV infection



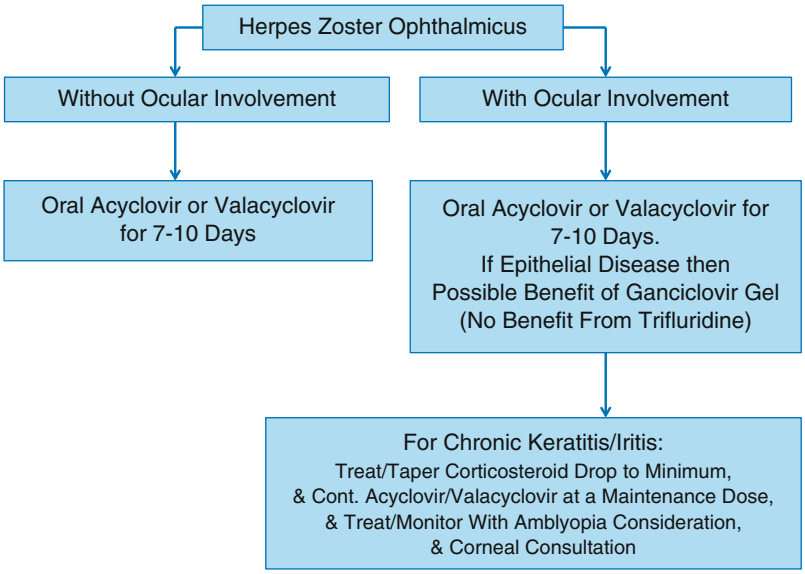
duration of the disease [42]. Both acyclovir and valacyclovir have been FDA approved for chicken pox in children [25, 33]. Children older than 2 years of age who weigh less than 40 kg can be treated with acyclovir 20 mg/kg 4 times per day for 5 days; children weighing more than 40 kg can be given acyclovir 800 mg 4 times per day for 5 days [25]. Alternatively, children between 2 and 18 years of age can be treated with valacyclovir 20 mg/kg for 5 days [33]. Compounding instructions for a pediatric valacyclovir oral solution are included in the current package insert. The anterior segment disease is usually limited to blepharoconjunctivitis or periocular disease, and oral treatment is adequate. Adjunctive ganciclovir gel could theoretically be considered for topical use in the rare instances of chicken pox epithelial keratitis, but this has not been studied. Trifluridine is ineffective against VZV.

The incidence of zoster (shingles) is less common in children than in adults, but there is a higher incidence in immunosuppressed pediatric patients [43]. Herpes zoster ophthalmicus follows the distribution of V_1. Hence, lesions may occur on the adjacent scalp, forehead, upper cheek, nose, eyelids, conjunctiva, cornea, and within the eye. Hutchinson's sign, lesions of the nasociliary dermatome (side, tip, and root of the nose), is associated with ocular involvement [44]. Ocular involvement may occur early in presentation or after resolution of skin vesicles, so slit-lamp monitoring is important. As was previously noted for chicken pox, early treatment of zoster (including herpes zoster ophthalmicus) with oral antiviral medication is considered to diminish severity and duration of disease [45]. FDA-approved recommendations for pediatric zoster are not available [25, 33]. For children, the FDA-recommended dosage for chickenpox treatment should be considered. See prior paragraph for pediatric acyclovir and valacyclovir dosages recommended for chicken pox. Older teenagers may be treated with adult dosages of valacyclovir (1 g 3 times per day for 7 days) [33], acyclovir (800 mg 5 times per day for 7–10 days) [25], or famciclovir (500 mg 3 times per day for 7 days) [34]. As discussed previously, famciclovir is not FDA approved for any disease in children. As with chicken pox, adjunctive ganciclovir gel could theoretically be considered for topical use in zoster epithelial keratitis, but this has not been studied. Treatment of recurrent VZV anterior segment disease is complex and follows patterns largely based on HSV ocular disease. Corneal consultation for treatment of recurrent VZV keratitis and iritis should be considered. See Flow Diagram 11.7 for treatment of herpes zoster ophthalmicus.

Special Considerations in Treating Children

There are a number of additional concerns in management of a pediatric herpes infection. There is significant risk of amblyopia development following herpetic anterior segment disease in children due to astigmatism and/or stromal scarring [26]. Children with herpetic anterior segment disease prior to the age of 9 may develop amblyopia. Consequently, minimization of corneal scarring through monitoring and longitudinal medical treatment is only part of the required formula. Appropriate management in children requires attention to amblyopia risk and discussion of prophylaxis for recurrent disease. Thus, long-term involvement of the pediatric ophthalmologist potentially contributes to improved visual outcome in herpetic keratitis due to the concomitant amblyopia therapy that may be required [8].

The risk of amblyopia associated with herpetic infection is compounded by significantly higher reported rates of



Flow Diagram 11.7
Treatment overview for pediatric herpes zoster ophthalmicus

recurrent disease in children relative to adults [7, 46]. Recurrent episodes of stromal disease lead to increased risk of permanent corneal opacification. Stromal scarring may also be worse in children than in adults due to children having a stronger immune response to HSV as compared to adults [7].

Drug management is also an important consideration with pediatric ocular herpetic disease. As discussed in the section "HSV Epithelial Keratitis," oral antiviral drugs may enhance compliance to treatment regimens and thereby allow for more consistent administration of the intended drug therapy [21]. Administration of topical drugs in children may be challenging, particularly for very young children. Eyedrops will be significantly less effective in a tearing child upset by the drug administration. Application of an ointment or gel several times per day may also be extremely difficult for a parent if the child is uncooperative [26]. Systemic administration of oral acyclovir is thus useful in treating children as either a primary or supplemental antiviral therapy since it is easier to administer to a child [21]. In addition to being easier to administer, oral acyclovir is safe and generally well tolerated by children [46].

Another concern in treating children for anterior segment herpetic eye disease is the difficulty in performing an adequate exam [26]. Both slit-lamp assessment and measurement of visual acuity may be challenging in children [8]. Mobility and photophobia also make evaluation of the child more challenging [21]. Detailed monitoring of the status of the keratitis is essential, and drawings of the area of involvement may be helpful for longitudinal follow-up. Parents must be educated concerning the importance of monitoring for signs of recurrent herpetic disease at home as well as the importance of regular follow-up visits.

Conclusions

Pediatric ophthalmologists participate in the complex and long-term management of herpetic anterior segment disease in children. We presented a structured guidance to the relevant anterior segment herpetic disease processes as well as basic treatment protocols. This chapter is not designed to replace comprehensive reviews or the necessity in some cases for cornea, uveitis, or infectious disease consultations. Rather, it serves as basic guidance for the management of the child with anterior segment herpetic disease. The flow diagrams included in the chapter provide easy to follow protocols that assist in the development of individualized treatment plans.

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The Anesthetic Cornea and Exposure Keratopathy in Infants and Children

12

Viral Juthani and William J. Dupps Jr.

Abstract

Corneal anesthesia and exposure keratopathy are important and often overlooked causes of visual loss in infants and children. Corneal anesthesia may be congenital or acquired, and exposure keratopathy may be secondary to corneal anesthesia or mechanical eyelid abnormalities. The evaluation of any child with corneal anesthesia and exposure keratopathy should begin with a careful history seeking to determine the etiology of the condition. The exam should focus on eyelid position, and health of the conjunctival and corneal surfaces. Treatment depends on the underlying etiology, and can be approached in a step-wise fashion depending on the severity of corneal involvement. Active corneal ulceration should be treated aggressively in order to prevent progression of disease, perforation, and loss of vision. Treatment of pediatric corneal anesthesia and exposure keratopathy may be continued for life; however, with careful attention to the integrity and health of the ocular surface, the long-term prognosis may be quite good.

Keywords

Corneal anesthesia • Neurotrophic keratitis • Lagophthalmos • Exposure keratopathy

The Problem

Exposure keratopathy is an ocular surface condition in which the absence of an adequate tear film results in breakdown of the corneal epithelium. This can result in punctuate disruption of the epithelium, ulceration, secondary infections, corneal thinning, and in severe cases, corneal perforation. The causes of exposure keratopathy in infants and children can be divided into two main categories: exposure that results from primary or secondary corneal anesthesia or hypoesthesia, and exposure caused by mechanical eyelid abnormalities such as lagophthalmos.

Corneal sensation plays a vital role in the maintenance of a healthy corneal epithelium. It is an important stimulus for blinking, reflex tear production, and promotion of epithelial cell proliferation after injury [1, 2]. It is proposed that nerve growth factors and neurotransmitters released by corneal nerve terminals mediate epithelial cell proliferation [3]. Therefore, corneal anesthesia results in a surface that is more vulnerable to injury, delayed epithelial healing, and progression of epithelial keratopathy.

Reduced corneal sensation can be congenital or acquired, and may be complete or partial [4, 5]. Congenital corneal

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Table 12.1 Classification of congenital corneal anesthesia (adapted from Ramaesh et al. [1])

Isolated corneal involvement	Familial
	Isolated
Associated with other ocular conditions	Corneal dystrophies, e.g., hereditary fleck corneal dystrophy, Schnyder crystalline dystrophy, others
	Contralateral anophthalmos and microsomia
Decreased sensation in the distribution of trigeminal nerve without other neurological or systemic deficits	Familial
	Sporadic
Associated with neurological disorders	Möbius syndrome
	Riley–Day syndrome
	Generalized insensitivity to pain and muscle weakness
	Vertebral and other congenital defects
	Cerebellar ataxia, cogwheel ocular pursuits, anal atresia, and abnormal optokinetic nystagmus
Associated with multi-systemic disorders	MURCS (Müllerian duct and renal aplasia, cervical somite dysplasia)
	Goldenhar syndrome (OAVD—oculo-auriculo-vertebral dysplasia)
	Hypo-hydrotic ectodermal dysplasia
	VACTERL association (vertebral, anal, cardiovascular, tracheoesophageal, renal, limb defects)
Congenital insensitivity to pain	–

anesthesia is rare and may be either limited to the cornea or be associated with defective sensations from the first and second divisions of the trigeminal nerve. It may be associated with other ocular conditions, neurological disorders, or even multi-systemic disorders, many of which have important systemic implications. Ramaesh et al. [1] propose a classification system for congenital corneal anesthesia, which is summarized in Table 12.1.

Lagophthalmos is the inability to close the eyelids completely. Although fairly common, the condition can be associated with symptomatic ocular conditions including dry eye syndrome and exposure keratopathy. The causes of lagophthalmos can be divided into three main groups: proptosis, leading to excessive ocular surface exposure, palpebral insufficiency secondary to physiologic, congenital, or acquired conditions, and idiopathic lagophthalmos [6].

Table 12.2 Causes of lagophthalmos (from Latkany et al.)

Proptosis/Greater eye exposure	Physiologic/congenital
	Exophthalmic/endocrine
	Tumor
	Shallow orbits (craniosynostosis)
Palpebral insufficiency/ Shortened tarsal height or reduced tonus	Physiologic/congenital
	Iatrogenic/post-surgical
	Iatrogenic/medicine
	Cicatricial
	Traumatic/hemorrhagic
	Involutional
	Infectious
	Peripheral nerve palsy
	Central nervous system disease/coma
	Periocular myopathy
Idiopathic	–

In the proptotic group, the volume of the orbital contents is greater than the volume of the bony orbit, resulting in protrusion of the globe. There are several causes of increased volume of intraorbital contents including thyroid dysfunction, tumors, and infections [7]. As the globe is forced forward the eyelids may fail to close completely as patients blink and corneal exposure ensues. In another situation, an abnormally small bony orbit relative to the volume of the orbital contents can also result in lagophthalmos and exposure, as seen in the craniosynostoses [8].

Palpebral insufficiency has many causes as listed in Table 12.2. In children, reduced tarsal height in the upper eyelid can be seen after ptosis repair [9]. Eyelid-altering diseases such as Stevens–Johnson syndrome, chemical injury, and chronic conjunctivitis can cause adhesions between the lids and globe, resulting in lagophthalmos [10]. Decreased tone in the eyelids caused by orbicularis oculi muscle dysfunction or disturbance of motor innervation from the seventh cranial nerve can also result in lagophthalmos, as in Bell's palsy, or leprosy [11].

Case Example

Table 12.3 Case 1

Clinical history	15-year-old boy with a history of Apert syndrome. The patient and his parents complained of chronic red eyes.		
Key components of exam		OD	OS
	UCVA	20/40-1	20/50
	Exophthalmometry	23	23
	Eyelid Position	1 mm lagophthalmos OU	
	Conjunctiva	2+ inferior injection OU	
	Cornea	2×3 mm epithelial defect, no infiltrate	3×4 mm epithelial defect, no infiltrate
Management Options	• Lubrication with artificial tear drops/ointment, patching, temporary tarsorrhaphy		
Management	Lubrication with non-preserved tears and erythromycin ointment q2-3 h		
Interval history (2 weeks)	Redness slightly improved		
Key components of exam		OD	OS
	UCVA/BCVA	20/40	20/50
	Conjunctiva	1+ inferior injection OU	
	Cornea	2×3 mm epithelial defect, no infiltrate	2×3 mm epithelial defect, no infiltrate
Management	• Bilateral lateral tarsorrhaphies, non-preserved artificial tears, erythromycin ointment QID		
Interval history (2 weeks)	Improvement in redness and vision		
Key components of exam		OD	OS
	UCVA/BCVA	20/30	20/30
	Conjunctiva	Trace inferior injection OU	
	Cornea	Mild anterior stromal haze, no epi defect	1×1 mm epithelial defect, no infiltrate
Management	• Plan for Le Fort III distraction osteogenesis, bilateral lateral canthoplasties, and bilateral medial and lateral tarsorrhaphies		
Interval history (2 months)	Patient doing well, vision and redness improved		
Key components of exam		OD	OS
	UCVA/BCVA	20/30	20/30
	Eyelid position	Medial and lateral tarsorrhaphies, no lagophthalmos	
	Conjunctiva	White and quiet OU	
	Cornea	Mild anterior stromal haze, no epithelial defect	Mild anterior stromal haze, no epithelial defect

Clinical Synopsis

A 15-year-old patient with Apert syndrome presents with red, prominent eyes. Apert syndrome is a form of acrocephalosyndactyly characterized by congenital malformations of the skull, face, hands, and feet. The patient had several prior craniofacial procedures and presented with bilateral exophthalmos. The patient was noted to have bilateral exposure keratoconjunctivitis and epithelial defects. The patient was treated in a step-wise fashion: initially with aggressive lubrication, then bilateral temporary tarsorrhaphies. He then underwent a Le Fort III distraction osteogenesis by the craniofacial surgery department, bilateral lateral canthoplasty, and bilateral medial and lateral tarsorrhaphies. After surgery, the patient had increased intraorbital volume, improved exophthalmos, good closure of the eyelids, and resolution of the epithelial defects.

Evidence for Effective Diagnosis and Treatment

The evaluation of any child with corneal anesthesia and exposure keratopathy should begin with a careful history seeking to determine the etiology of the condition. Any recent trauma, surgery, or infection should be documented. One should also inquire about a history of Bell's palsy. A family history of corneal anesthesia or lagophthalmos should be elicited. This may be helpful in conditions such as familial congenital corneal anesthesia and familial trigeminal anesthesia. Patients will often present with poor vision, photophobia, or conjunctival injection, and children may be previously misdiagnosed with recurrent conjunctivitis. However, corneal anesthesia may also be relatively asymptomatic, and only diagnosed by clinical suspicion and careful examination.

The examination begins with observation from a distance of the interpalpebral distance as well as the position of the eyelids in a relaxed open and closed position. The patient's ability to reach full appositional closure of the eyelids with each blink should be noted. Eyelid position should also be noted at the slit lamp, as obscure lagophthalmos may only be noted in this way at times. Obscure lagophthalmos occurs when the upper and lower eyelashes meet, preventing full lid closure, or obscuring the examiners view of the true eyelid position. The upper eyelid skin may also overhang the lower lid, giving the appearance of total closure, however the eyelid margins may not appose [6]. Observation of a good Bell phenomenon is also important. In a child with lagophthalmos, an examiner may simply observe for upward rotation of the globe during each blink. If no lagophthalmos is present, one may have a child fixate downward on an object, gently lift the eyelids, and observe the rotation of the globe during each blink. The conjunctiva should be examined for areas of scarring or cicatrization. Prior to administering eye drops, corneal sensation should be evaluated using either a cotton wisp or an esthesiometer. Staining with fluorescein sodium will reveal any punctate epithelial erosions, frank epithelial defects, or ulceration. A punched-out oval or circular epithelial defect is characteristic of neurotrophic keratitis. If cellular infiltration is present, the area should initially be scraped for Gram and fungal stains, and cultured to rule out a secondary infection. A complete neurologic exam should also be performed with special attention to the function of all cranial nerves (Table 12.4).

The treatment of exposure keratopathy depends on its underlying etiology—whether the pathology is primarily related to corneal anesthesia or to lagophthalmos (Fig. 12.1). Although treatment regimens are similar, they will be discussed separately.

In patients with lagophthalmos, treatment varies with degree of corneal involvement. If there is no ulceration and only mild epitheliopathy is present, medical treatment includes preservative-free artificial tears at least 4 times daily and a lubricating ointment at bedtime may be used. If there is moderate to severe corneal involvement, but no ulceration, one should consider the expected duration of the

Table 12.4 Important history and exam elements

History
• Recent trauma, surgery, infections
• History of Bell palsy
• Family history of corneal anesthesia/lagophthalmos
Exam
• Observation of lid position in relaxed open and closed positions
• Observation of Bell reflex
• Examine conjunctiva for cicatrization
• Check corneal sensation prior to administering eye drops
• Staining with fluorescein
• Corneal cultures if cellular infiltration
• Complete neurologic exam

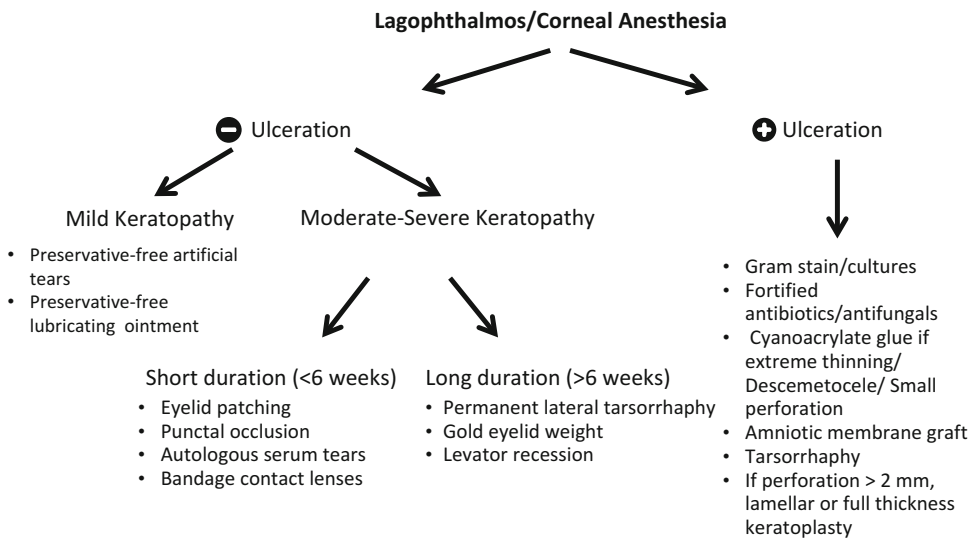

Fig. 12.1 Treatment algorithm for corneal anesthesia or exposure keratopathy from lagophthalmos

lagophthalmos. If the lagophthalmos is expected for 6 weeks or less, options include patching and ointment, frost suture, or temporary tarsorrhaphy. If the duration is expected to be greater than 6 weeks, one can consider a permanent tarsorrhaphy, gold lid weight surgery, levator recession, or full-thickness graft/flap, depending on the etiology. If the lower eyelid is involved, one can consider a lateral tarsal strip, lower lid spacing graft, full-thickness skin graft, collagen or mucous membrane graft, midface lift, or autogenous fascia sling. Temporary measures may be necessary in permanent conditions until more definitive treatment can be performed. If corneal ulceration is present and if there is clinical suspicion for infection, corneal cultures at the base of the ulcer and including material from the most dense portions of an infiltrate are taken whenever possible and should be plated on blood, chocolate, potato dextrose, and Sabouraud agar and in thioglycolate broth. Fungal cultures should be incubated for at least 14 days since fungal species can exhibit very slow growth. Topical antibiotics should be started. Our choice of empiric antibiotics includes fortified vancomycin (25 mg/mL) and fortified tobramycin (15 mg/mL), however antifungal therapies may also be started in areas where fungal infections are common. Once the infiltrate is thought to be sterilized, after at least 48–72 h of high intensity antibiotics, and ideally with knowledge of the pathogenic organism and sensitivities to antimicrobial therapy, further therapies may be used to facilitate re-epithelialization including temporary tarsorrhaphy, amniotic membrane, or bandage contact lens. Although the role of amniotic membrane grafts as an initial treatment in the management of corneal ulceration is not widely accepted, it may be of benefit in select cases, especially where acute infection on chronic ulceration is not suspected. Cyanoacrylate glue alone or with an amniotic membrane placed above may be used in cases of extreme thinning or Descemetocele. Frozen and dried amniotic membrane grafts designed for self-retention can be used and have the potential to be placed in the office setting. However, the authors' preference in recalcitrant cases of persistent epithelial defect with or without ulceration, particularly in pediatric patients more prone to postoperative manipulation and graft dislocation, is to place a thick, cryopreserved amniotic membrane graft anchored with a running circumferential 8-0 vicryl suture using 5 episcleral bites then covered with a large diameter bandage contact lens (for example, Kontur 18 mm).

In cases of anesthetic corneas, the mainstay of treatment is also lubrication with preservative-free artificial tears and lubricating ointment at night. Short-term use of bandage contact lenses can be effective as they can promote epithelial migration and adhesion to the stroma by protecting the ocular surface from the swiping action of the upper eyelid [12]. Anti-inflammatory agents, such as corticosteroids, must be used with caution as they may precipitate stromal lysis and perforation [13]. Tetracyclines have been shown to have anti-collagenase activity and may be effective in cases of stromal necrosis [14]. Autologous serum may also be a valuable adjunct in the treatment of neurotrophic corneas and persistent epithelial defects [15, 16]. Several protocols for production have been published, creating concentrations from 20 % to 100 % of serum. Due to the differences in concentration, storage regimens, and protocols, the efficacy of serum tears has varied between studies. Serum tears are typically unpreserved, but can be stored frozen for 3–6 months [17]. Topical cyclosporine 0.05 % may also be helpful, however it is more commonly used in inflammatory conditions such as atopic or vernal keratoconjunctivitis. Punctal occlusion either with punctal plugs or cauterization of the puncta may also be helpful. Surgical therapies for advanced disease may include tarsorrhaphy and/or amniotic membrane transplantation. In occlusive therapies such as tarsorrhaphy, one must carefully monitor for the progression of amblyopia in the occluded eye. Patching of the non-occluded eye may be necessary and therefore co-management with pediatric ophthalmologists and cornea specialists may be prudent. The balance between maintaining a healthy ocular surface and maximizing visual potential is critical and must be evaluated on a case-by-case basis. The degree and duration of closure may be titrated to the least amount necessary in order to protect the integrity of the globe and prevent visually significant scarring. Use of an adjustable drawstring temporary tarsorrhaphy can be an attractive option in pediatric patients to facilitate examination and titration of the degree of closure as a function of clinical response [18]. Amniotic membranes act as basement membrane scaffold upon which epithelium may migrate and adhere [19]. They may be applied in a single- or multi-layered fashion [20]. Cyanoacrylate glue may be applied with a bandage contact lens for the treatment of small (<1 mm) corneal perforations [21]. If the size of the perforation is larger than 1 mm, a lamellar keratoplasty or penetrating keratoplasty may be necessary, however the success rates of penetrating keratoplasty in anesthetic corneas are low due to stromal neovascularization and scarring of the graft [22].

Overall, treatment of pediatric corneal anesthesia and exposure keratopathy may be lifelong and may fluctuate in complexity, however with meticulous care and attention to the ocular surface, the long-term prognosis may be quite good.

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Peters Anomaly

13

Charline S. Boente and Faruk H. Örge

Abstract

Peters anomaly is an uncommon and extremely heterogeneous ocular malformation that presents at birth with corneal opacification and iridocorneal adhesions. Early management is necessary to address the visual deprivation leading to amblyopia, and the other associated complications, such as cataract and glaucoma; the latter may be absent at birth but should be monitored for development later in life (Lesnik Oberstein et al., GeneReviews™ [Internet], 2014). While some patients with mild involvement can be observed, surgical management with sector iridectomy, iris peeling from the cornea, as well as penetrating keratoplasty (PK) or even Descemet stripping automated endothelial keratoplasty (DSAEK) may be necessary in more severe cases. A significant subset of patients with Peters anomaly have associated systemic malformations that may be life-threatening and need early diagnosis and treatment.

Keywords

Peters anomaly • Corneal leukoma • Amblyopia • Penetrating keratoplasty

Introduction

Peters anomaly was first described in 1906 in a patient with shallow anterior chamber, iridocorneal synechiae, central corneal leukoma, and a defect in Descemet membrane [2]. The disorder has been associated in a minority of patients with mutations in the homeobox genes that regulate anterior segment development, such as Paired Box 6 (*PAX6*), Paired-like Homeodomain 2 (*PITX2*), and Forkhead Box C1 (*FOXC1*) [2]. These mutations result in disruption of the normal process of separation of the lens vesicle from the surface ectoderm or incomplete central migration of mesenchyme forming the corneal endothelium [2]. Some cases are related to a variety of heterogeneous chromosomal abnormalities. Familial isolated Peters anomaly typically exhibits autosomal recessive inheritance, but autosomal dominant cases have been reported [3, 4]. Kivlin–Krause syndrome, which is a distinct autosomal recessive condition with Peters anomaly and short stature and limbs, is also inherited in an autosomal recessive manner [5].

In addition to genetic causes, Peters anomaly may be idiopathic or related to environmental exposures such as prenatal alcohol exposure [6]. The ocular malformations are often accompanied by systemic malformations and in some cases compose a well-defined inherited syndrome such as the recessive syndrome of Peters anomaly with short limbs due to mutations in beta 1,3-galactosyltransferase-like (*B3GALTL*). In the most typical cases, ocular histopathology reveals that the corneal opacity overlies a localized absence of posterior corneal stroma, Descemet membrane, and corneal endothelium, and the peripheral cornea may remain clear [6]. While the clinical presentation may vary widely, it is essential to evaluate the extent of the opacity and its effect on vision so that the appropriate management is instituted early.

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Clinical Manifestations

In a recent study that reviewed the literature on 58 cases of Peters anomaly [2], 56 % of patients were male and 67.2 % of cases were bilateral. 71.8 % of bilateral cases were associated with systemic malformations versus 36.8 % of unilateral cases. The same study found a 53 % overall success rate (defined as clear graft at unspecified times to follow-up) in 15 eyes undergoing penetrating keratoplasty (PK). 87.5 % of patients with Peters I as opposed to 14.2 % in those with Peters II. Peters I and Peters II are defined in a classification scheme that has been proposed to subdivide Peters anomaly into descriptive categories [1, 2, 5]. Peters I refers to the presence of corneal opacification with posterior corneal thinning and iridocorneal adhesions, but without cataracts or glaucoma. In Peters II, there is also a cataract and glaucoma. Peters I and II can be sporadic, AR, or AD and may result in some cases from mutations in *PAX6*, *CYP1B1*, *PITX2*, *PITX3*, *FOXE3*, or *FOXC1*. In Peters plus syndrome (Kivlin–Krause syndrome), which is caused by mutations in the recessive beta 1,3-galactosyltransferase-like (*B3GALTL*) gene, patients have Peters I or Peters II type corneal findings together with systemic anomalies in the form of abnormalities of the extremities such as short limbs, broad distal extremities, broad neck (75 %); abnormal facial features including prominent forehead, short palpebral fissures, long philtrum, ear anomalies (>33 %), cleft lip (45 %), and cleft palate (33 %); as well as congenital heart defects (<33 %), genitourinary anomalies (15 %), structural brain malformations (e.g., agenesis of corpus callosum), congenital hypothyroidism, prenatal polyhydramnios (18.6 %); patients can have autism, as well as developmental delay (80 %) [1]. Please note that about 1/3 or more of all patients with Peters anomaly have systemic abnormalities and do not necessarily have the AR Krause–Kivlin syndrome. In fact this well-defined syndrome is an uncommon cause of Peters anomaly when it is associated with systemic abnormalities. This classification does not take those patients into account.

The differential diagnosis of Peters anomaly includes sclerocornea, which as Peters anomaly, may have absent Descemet membrane and endothelium [5, 6]. Other causes of corneal opacification may include megalocornea, anterior segment dysgenesis, congenital glaucoma, congenital hereditary endothelial dystrophy, congenital anterior staphyloma, corneal ulcer, or epibulbar choristoma [5].

Ocular abnormalities associated with Peters anomaly include ptosis, microcornea, microphthalmia, spontaneous corneal perforation, anterior polar cataracts, glaucoma, aniridia, iris coloboma, polycoria, persistent fetal vasculature, optic nerve hypoplasia, foveal hypoplasia, and posterior segment colobomas [5, 6]. Glaucoma is the most common associated complication, occurring in 50–70 % of eyes, and colobomatous microphthalmia is the most common associated malformation, occurring in 25–59 % of eyes with Peters anomaly [6].

Diagnosis

All patients with suspected Peters anomaly should undergo prompt, comprehensive ophthalmologic and systemic examinations. The ocular examination should include the following components with particular attention to the associated findings (Table 13.1).

Adequate visualization of the anterior segment is essential to determine the degree of ocular involvement and the potential for surgical intervention. Recently, several adjunct techniques have been used to better visualize and characterize anterior segment abnormalities, guiding more specific management strategies. Anterior segment optical coherence tomography (A/S OCT) allows a rapid, non-contact, cross-sectional visualization of corneal opacities, corneal thickness, anterior chamber depth, and allows the detection of irido—or lenticulo—corneal adhesions. This is a useful tool for both initial diagnosis and subsequent follow-up examinations to monitor the progression of the disease at a resolution 10–25 times higher than ultrasound biomicroscopy. High-frequency ultrasound biomicroscopy has a resolution of approximately 50 μm, and has been particularly useful in the setting of corneal opacities to evaluate anterior segment structures up to a depth of 5 mm [7, 8].

It is recommended that patients with Peters anomaly undergo further evaluation for associated systemic anomalies. This is best done in collaboration with the medical genetics team or the pediatrician, involving additional specialists as needed. This evaluation can include an echocardiogram, renal imaging with abdominal ultrasound, and cranial imaging with head ultrasound or CT/MRI to evaluate for associated systemic abnormalities, such as congenital heart defects, genitourinary anomalies, and structural brain abnormalities.

Table 13.1 Abnormalities to look for in cases suspected of having Peters anomaly

Exam component	Possible features to note
External	Microphthalmos, buphthalmos, ptosis, cleft lip/palate, ear abnormalities
Slit lamp	Corneal diameter, presence of sclerocornea, corneal opacity, iris abnormalities, cataract
Corneal thickness	Correlate areas of increased thickness with corneal opacity
Intraocular pressure (IOP)	May be elevated if there is associated glaucoma
Dilated fundus exam (if adequate view)	Persistent fetal vasculature, coloboma, optic nerve or foveal hypoplasia
B-scan ultrasonography	Evaluate structures not visible on DFE
Ultrasound biomicroscopy and anterior segment OCT	Cross-sectional detailed view to determine level and degree of anterior segment involvement

Management and Prognosis

The management of patients with Peters anomaly depends on the estimated degree of visual impairment as well as the severity of anterior segment involvement. Options range from conservative treatment, such as correction of refractive errors and management of amblyopia, to lysis of iridocorneal adhesions or, in more severe cases, penetrating keratoplasty (PK) with cataract extraction and surgical management of glaucoma. With any surgical intervention, aggressive amblyopia therapy and frequent post-operative follow-up visits are essential. Figure 13.1 outlines a suggested algorithm for the management of suspected Peters anomaly.

Corneal Opacity

In cases where the corneal opacity is small, spontaneous clearing of the cornea may occur [6]. However, when the corneal opacity is large and dense enough to cause visual deprivation, more definitive surgical management should be considered, either with a penetrating keratoplasty (PK) or Descemet stripping automated endothelial keratoplasty (DSAEK). If iridocorneal adhesions are present, breaking these adhesions with a relatively simple procedure using viscoelastic can eliminate the chronic traction on the cornea, and with time may lead to some clearing of the corneal opacity. In patients with persistent opacification, additional corneal surgeries may be beneficial. If the opacification is small and slightly off center, a sector iridectomy or enlargement of the pupillary aperture can allow the child to see through the enlarged pupil. A discussion of the details of penetrating keratoplasty in infants is beyond the scope of this chapter.

Keratoplasty in the pediatric population can be challenging, especially in the setting of Peters anomaly where eyes are at increased risk of complications and glaucoma because of associated defects such as microphthalmos, irido-lenticulo-corneal adhesions, or sclerocornea. Reported rates

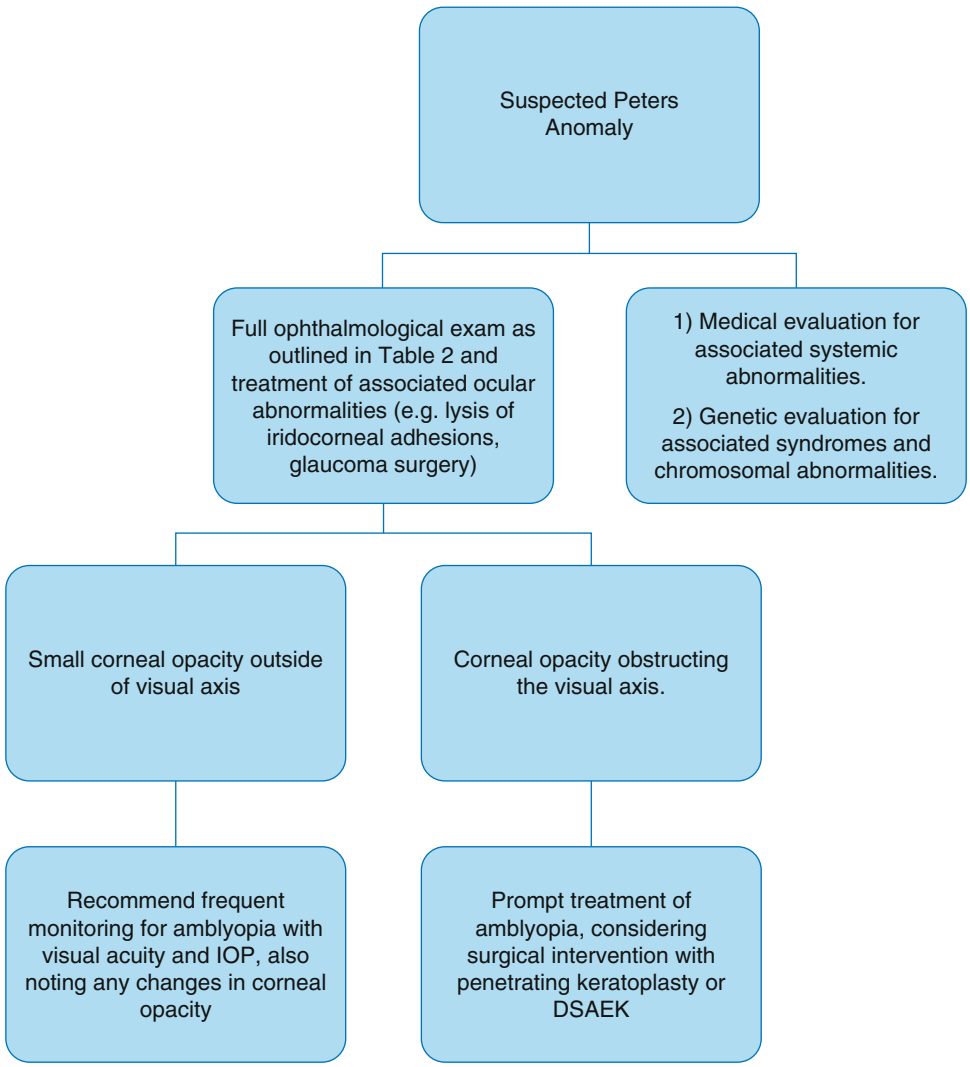

Fig. 13.1 Suggested algorithm in management of patients suspected to have Peters anomaly

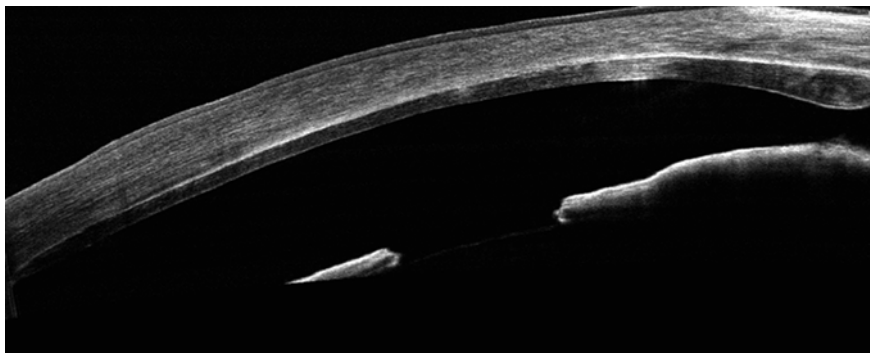

Fig. 13.2 Anterior segment OCT of an infant with Peters anomaly after a superior trabeculotomy at 1 week of age, then anterior synechiolysis at 3 weeks of age. This was followed by DSAEK at 7 months of age. The image shows the endothelial graft centered and attached without iridocorneal touch at the 4-month post-operative visit

of successful penetrating keratoplasty, defined as a clear graft, have varied from 35 % to 100 % at varying follow-up periods [9, 10]. The discrepancy in reported rates may be attributable to differences in disease severity, pre-operative risk factors, and timing and duration of follow-up. One study of 144 penetrating keratoplasties in 72 eyes of 47 patients found the overall probability of graft clarity to be 56 % at 6 months, 49 % at 12 months, 44 % at 3 years, and 25 % at 10 years [11]. The most common cause of graft failure is allograft rejection, with the vast majority occurring in the first year after transplantation [9]. The timing of surgery is debatable, as many studies have not found any apparent correlation between improved visual outcomes and early keratoplasty [10]. Bhandari et al. did advocate for patients with Peters I to be considered for penetrating keratoplasty or optical iridectomy within the first year of life to prevent amblyopia. A higher rate of keratoplasty failure was noted in Peters II patients, so the timing of recommended keratoplasty in those patients is unclear [2]. While the success and survival of the graft is important, one study correlating visual acuity outcome to host and donor factors found that poor visual acuity after PK was related to more severe disease or stromal vascularization, extensive synechiae, larger donor corneal buttons, and corneal surgeries combined with lensectomy and/or vitrectomy [10]. It is important to discuss with families at the time of diagnosis that visual potential may be limited in patients with corneal opacities from Peters anomaly and to explain the importance of regular and consistent follow-up, particularly during the critical period of the patient's visual development.

Recently, DSAEK has been advocated in select cases where corneal involvement is limited to the posterior layers. While very few cases have been reported to derive statistically significant conclusions regarding outcomes, DSAEK in patients with Peters anomaly is promising in cases with detailed characterization of the extent of corneal stromal involvement and ability for close follow-up, particularly with A/S OCT and ultrasound biomicroscopy (Fig. 13.2). Some challenges and shortcomings described have included intraoperative technical difficulty due to corneal haze, irregular thickness, adhesions, shallow anterior chamber, and graft size selection [12]. PK may still be required if the corneal opacity remains significant post-operatively or should surgical complications of DSAEK occur.

Glaucoma

Glaucoma occurs in about 50–70 % of eyes with Peters anomaly [6, 13], and should therefore be investigated in all suspected cases of Peters anomaly. Glaucoma most commonly develops in infancy when the condition is diagnosed, but it may also develop later in life, so long-term monitoring of intraocular pressure should be performed [13]. Diagnosis requires monitoring of signs also seen in congenital glaucoma, such as tearing, photophobia, buphthalmos, and corneal enlargement, but other signs, such as breaks in Descemet membrane, corneal edema, or optic disc cupping, may be difficult to appreciate because of the corneal opacity [13]. The mechanism for elevated IOP in Peters anomaly is not well understood, but is probably related to a developmental abnormality of the trabecular meshwork and Schlemm's canal [13, 14]. Topical IOP lowering medications can be used to initially treat the glaucoma associated with Peters anomaly, but surgery is often required. Published data on outcomes after glaucoma surgery is limited, but one study of 126 glaucoma procedures (including trabeculectomy, trabeculotomy, goniotomy, Molteno shunt implant, cyclodialysis, and cyclocryotherapy) in 34 eyes of 19 patients with Peters anomaly and glaucoma found IOP control, defined as IOP between 7 and 21 mmHg, with or without IOP lowering medications in 32 % of the cases after 1 or more surgical procedures, with median follow-up of 11.0 years [13].

Visual outcomes remain poor in patients with Peters anomaly and glaucoma either from inability to control the IOP or from post-operative complications, most commonly phthisis and/or inoperable retinal detachment. Poor visual outcomes also result from associated ocular malformations such as colobomas or optic nerve malformations, amblyopia, corneal transplant graft failure, or associated developmental or neurologic impairment [2, 13].

Case Example 1

A 2-day-old full-term male infant was noted to have poor red reflexes in both eyes. His prenatal history was unremarkable for any maternal infections, complications, or co-morbidities. In addition, his standard newborn screen consisting of tests for amino acid disorders, fatty acid disorders, organic acid disorders, biotinidase deficiency, congenital adrenal hyperplasia, hypothyroidism, cystic fibrosis, galactosemia, sickle cell and other hemoglobinopathies, and immunodeficiencies were all within normal range. Table 13.2 outlines the exam obtained upon initial ophthalmological consultation (Figs. 13.3 and 13.4).

Table 13.2 Ophthalmology evaluation findings on a 2-day-old full-term male with suspected Peters anomaly

	Testing	OD	OS
Pertinent exam findings	UCVA	Blinks to light	Blinks to light
	Pupils	poor view	poor view
	IOP (mmHg)	26	24
	Corneal diameter (mm)	10	10.5
	Bedside portable slit lamp exam (Fig. 13.3)	4 mm central corneal opacity with peripheral clearing, iris stranding to peripheral edge of corneal opacity	2.5 mm central corneal opacity with peripheral clearing, iris stranding to peripheral edge of corneal opacity
Ancillary testing	Ultrasound biomicroscopy (Fig. 13.4)	Iridocorneal adhesions with irregular corneal thickness and central posterior stromal, Descemet's membrane, and endothelial defects	
Management	Patient was started on cyclomydril OU and betaxolol 0.25 % OU and recommended for genetic testing and further workup of systemic anomalies. Cyclomydril was later switched to atropine 1 % drops for more effective dilation, and the adhesions and corneal haze were noted to have improved.		
Systemic workup	Renal ultrasound: within normal limits bilaterally Cardiac echocardiogram: within normal limits		
Genetic consult and testing	Genetics consultation recommended testing for *FOXC1, PITX2, FOXE3, CYP1B1, and PAX6* sequencing as well as full ophthalmological exam for siblings and parents. All genetic testing was negative. The patient's older brother was also diagnosed with Peters anomaly as an infant. The mother did not pursue ophthalmological testing but did not note any ocular complaints.		
Management	Patient continues to be followed for vision and IOP checks. At 3 months of age the patient was noted to have a visual acuity of central, steady, and maintained OD/OS, IOPs of 9 OD and 9 OS, and the paracentral corneal opacities and temporal iridocorneal adhesions remained stable without obstruction to the central visual axis. The posterior segment is well visualized without any abnormalities noted. Patient is maintained on atropine drops qAM OU, with persistent yet stable appearance of iridocorneal adhesions.		

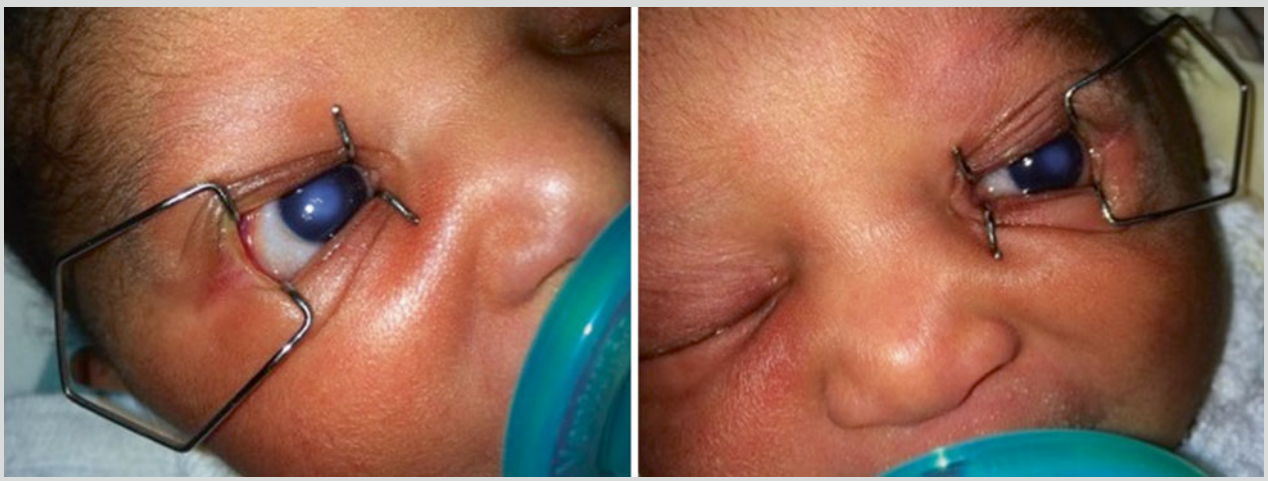

Fig. 13.3 Two-day-old infant evaluated for bilateral corneal leukomas

(continued)

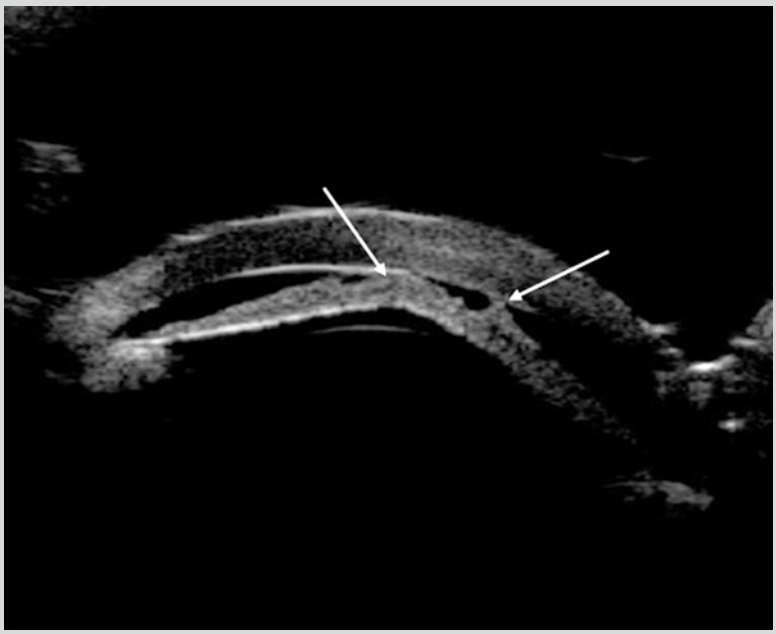

Fig. 13.4 Ultrasound biomicroscopy of the right eye of a 2-day-old patient with bilateral corneal leukomas and a clinical suspicion of Peters anomaly. The cornea has an irregular contour with thickening and haze, and central iridocorneal adhesions are shown (*arrows*)

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Anterior Segment Dysgenesis Syndromes

14

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Abstract

Anterior segment dysgenesis comprises a spectrum of disorders affecting the anterior chamber structures including the cornea, iris, and anterior chamber angle. Importantly, approximately 50 % of patients with anterior segment dysgenesis will develop glaucoma. Conditions with anterior segment dysgenesis include most notably, Axenfeld–Rieger spectrum and Peters anomaly. This chapter will focus on the findings and management of patients with Axenfeld–Rieger spectrum disorders. Classic findings include an anteriorly displaced Schwalbe's line (posterior embryotoxon), iridocorneal adhesions, and pupillary ectopia and corectopia. However, some patients may present with findings of infantile glaucoma. The condition may or may not be associated with systemic findings. Axenfeld–Rieger spectrum disorders are usually inherited in an autosomal dominant manner with disease-causing mutations in *PITX2*, *FOXC1*, and very rarely mutations in *PAX6*. Significant phenotypic heterogeneity is present, and severity and findings may vary significantly among family members with the same mutation. Ophthalmologic management should include maintaining a clear visual axis, monitoring closely for amblyopia, and glaucoma. Patients with anterior segment dysgenesis should be evaluated by a geneticist for evaluation of possible systemic associated abnormalities and appropriate genetic counseling.

Keywords

Anterior segment dysgenesis • Axenfeld–Rieger syndrome • Congenital glaucoma

Introduction

The term anterior segment dysgenesis is used to describe a spectrum of disorders related to abnormal development of the cornea, anterior chamber angle, and iris. Other terms used historically to describe these conditions include anterior chamber cleavage syndrome, mesodermal dysgenesis of the cornea and iris, and Axenfeld–Rieger syndrome. The development of the anterior segment involves complex interactions between neural crest cells, surface ectoderm, neuroectoderm, and mesoderm [1, 2]. Several genes encoding transcription factors have been implicated in the Axenfeld–Rieger spectrum of disorders including *FOXC1*, *PITX2*, and *PAX6*. Both genotypic heterogeneity and variable expressivity lead to a wide spectrum of ophthalmologic and systemic manifestations making classification schemes difficult. Importantly, multi-system involvement may be present and patients should be referred to a clinical geneticist for systemic evaluation.

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Clinical Presentation

Although several conditions have been classified under anterior segment dysgenesis disorders, most patients fall in the Axenfeld–Rieger category of anterior segment dysgenesis. Axenfeld–Rieger spectrum encompasses a broad spectrum of ocular and systemic findings, is typically bilateral and asymmetric, and, as an autosomal dominant disorder, affects males and females equally [2]. Depending on the clinical findings patients may are classified as having:

- Axenfeld anomaly: strands of iris bridging the peripheral part of the anterior chamber angle and attaching to an anteriorly displaced Schwalbe's line (Fig. 14.1)
- Rieger anomaly: Axenfeld anomaly in addition to one or more of the following: iris stromal atrophy, corectopia (Fig. 14.2), polycoria, or pseudo-polycoria
- Axenfeld–Rieger syndrome: ocular findings as described above with accompanying systemic anomalies, such as hypertelorism, maxillary hypoplasia, absent teeth, redundant periumbilical skin (inaccurately referred to as an umbilical hernia), hypospadias, anal stenosis, cardiac defects, hearing impairment, and pituitary abnormalities. Facial, dental, and umbilical anomalies are the most common extraocular manifestations [3].

Posterior embryotoxon, or anteriorly displaced Schwalbe's line, is present in most patients with Axenfeld–Rieger spectrum disorders, but is not entirely unique to this population, and can be an isolated non-pathological finding. It is visible most commonly on the temporal cornea and rarely seen superiorly and inferiorly, as the sclera extends more anteriorly in these regions [3]. Histopathologically, posterior embryotoxon represents dense collagen and ground substance

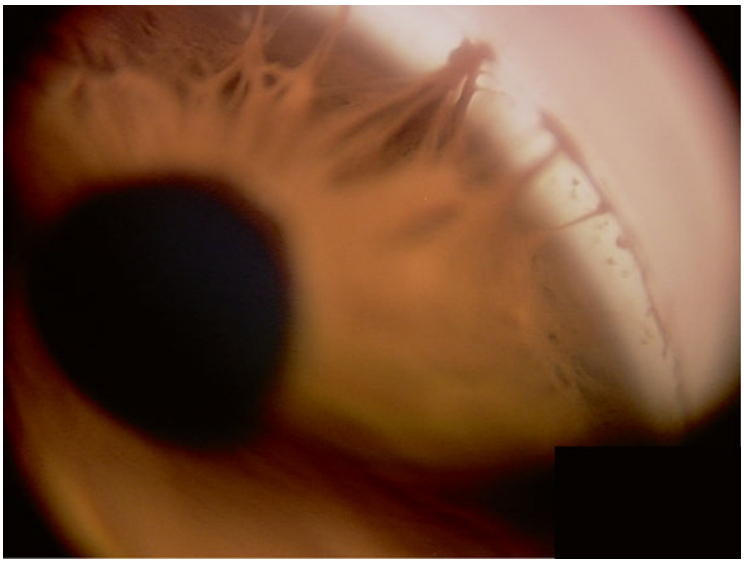

Fig. 14.1 Axenfeld–Rieger spectrum disorder. Corectopia is present with iridocorneal adhesions to an anteriorly displaced Schwalbe's line (posterior embryotoxon)

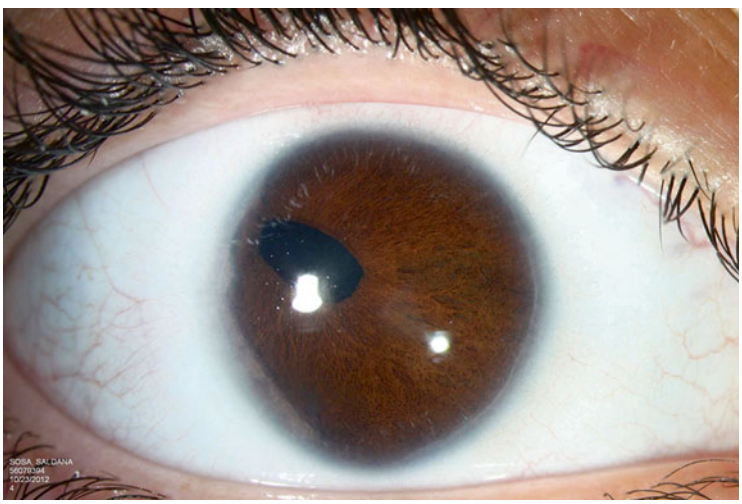

Fig. 14.2 Axenfeld–Rieger spectrum disorder. Iridocorneal adhesions to anterior displaced Schwalbe's line (posterior embryotoxon) with temporally displaced ectopic pupil. Image courtesy of Elias I. Traboulsi, MD, Cleveland, Ohio

Table 14.1 Anterior segment dysgenesis disorders (AD = autosomal dominant; AR = autosomal recessive)

Disorder	Description	Inheritance	Genes
Axenfeld–Rieger syndrome	*as above*	AD	*FOXC1* (6p25) *PITX2*(4q25-27) [5]
Peters anomaly	Unilateral or bilateral central corneal leukoma. Histologically, Descemet's membrane and endothelium are absent at the leukoma. Iridocorneal adhesions, corneolenticular adhesions. – 50 % of patients develop glaucoma [3.4] – Systemic manifestations in 60 %[a]	AD, AR, sporadic, or environmental (e.g., teratogens)	*PAX6* (11p13) *PITX2* (4p25) *CYP1B1* (2p22.2) [4, 5]
Peters plus syndrome	Peters anomaly plus together with short stature, cleft lip/palate, midline defects, cardiovascular, genitourinary anomalies, CNS anomalies, growth and developmental delay [4]	AR	*B3GALTL* (13p12.3) [4, 5]
Iris hypoplasia	Loss of normal crypts and folds of anterior iris, allowing visibility of underlying pigment epithelium. Absence of iris collarette or very peripheral small collarette [3]		
Primary congenital glaucoma	Glaucoma present within the first 6 months to 2 years of life, often with maldevelopment of trabecular meshwork and Schlemm's canal [3, 4][b]	AR	GLC3A locus (*CYP1B1*) GLC3B and GLC3C [4]
Aniridia	Pan-ocular disorder with limbal stem cell deficiency leading to keratopathy, iris hypoplasia, ciliary body hypoplasia, ectopia lentis, cataract, foveal hypoplasia, optic nerve hypoplasia – Glaucoma occurs in 50 % – Referral for systemic work-up crucial as Wilms' tumor associated with sporadic cases secondary to loss of adjacent *WT1* [4]	AD AR (Gillespie syndrome)	*PAX6* (11p13) [5]
Sclerocornea	Bilateral corneal opacification and vascularized cornea. Can be associated with Peters anomaly and cornea plana [3, 4]	AD, AR unknown gene [4]	*FOXE3*[c] *SOX2*[c] *TBX1* gene (22q11.2 deletion syndrome)

AD autosomal dominant, *AR* autosomal recessive
[a]See Chap. 13
[b]See Chap. 42
[c]Usually associated with severe ocular malformations

with an associated monolayer of spindle cells [6]. In the normal adult population, isolated posterior embryotoxon occurs in 8–15 % of people and can be accompanied by Axenfeld anomaly in 6 % in otherwise apparently normal eyes [2].

Conditions often classified under the spectrum of anterior segment dysgenesis disorders are listed in Table 14.1.

Glaucoma in the Anterior Segment Dysgenesis Disorders

Glaucoma develops in up to 50 % of patients with Axenfeld–Rieger syndrome and other anterior segment dysgenesis disorders, and constitutes the greatest ocular morbidity in these patients. Interestingly, although the development of glaucoma appears to be related to the abnormal development of anterior segment structure regulating aqueous humor flow, the risk of developing glaucoma does not appear to be related to the severity of anterior segment abnormalities [3, 4, 6]. Histopathological observations have suggested abnormalities in the trabecular meshwork extracellular matrix and Schlemm's canal as the reason for improper aqueous humor drainage. Other theories to explain the development of glaucoma in anterior segment dysgeneses include maldevelopment of the ciliary body and the inability of anterior segment structures to adequately regulate aqueous flow in response to external stress [4]. Because of the unclear etiology and natural history of glaucoma development, regardless of phenotypic presentation, all patients should be followed for development of increased intraocular pressure through adulthood. Intraocular pressure measurements are generally obtained every 4–6 months.

Other Ophthalmologic Manifestations

In addition to glaucoma and amblyopia, strabismus can also be present in occasional patients, and studies in a murine model have demonstrated anomalous extraocular muscle insertions, in addition to absent extraocular muscles [7].

One case has been described of a patient with bilateral Axenfeld–Rieger syndrome and A-pattern deviation exotropia, DVD, and superior oblique overaction. The DVD and superior oblique overaction were more notable in the left eye, and at the time of surgery, the superior oblique muscle insertion was noted to be more posterior and also composed of a fibrous band along its entire course under Tenon's capsule [8]. The hypothesis to this mechanism is the shared influence of *PITX2* gene expression on the anterior segment and extraocular muscles [8, 9].

Genetics

Axenfeld–Rieger syndrome is an autosomal dominant group of disorders, although sporadic cases do occur [7]. Family members should be examined, as a parent may have an undetected mild form of the disorder. Axenfeld–Rieger syndrome has been described as a result of mutations in genes encoding transcription factors, most notably *FOXC1* (Forkhead Box C1, 6p25) and *PITX2* (Pituitary Homeobox 2, 4q25-27). In patients in whom mutations are identified in either *FOXC1* or *PITX2*, the incidence of glaucoma increases to about 75 % [4]. Importantly, *PITX2* and *FOXC1* duplications lead to an increased risk of glaucoma as compared to other *FOXC1* mutations [10]. The genotypic heterogeneity and variable expressivity contribute to the large phenotypic spectrum observed, adding to the complexity of classifying these disorders.

Diagnosis

When evaluating a patient with suspected anterior segment dysgenesis, attention to particular historical and clinical features may aid in diagnosis. A family history of glaucoma or other systemic anomalies should be elicited. The practitioner should determine whether there is unilateral or bilateral presentation, presence or absence of glaucoma, and associated systemic anomalies. Examination should include visual acuity, cycloplegic refraction, intraocular pressure, and slit lamp exam to meticulously evaluate corneal clarity, anterior chamber depth, presence of corneal adhesions, presence of posterior embryotoxon, iris structure and integrity, and lens opacities. Gonioscopy is necessary to evaluate the anterior chamber angle and to detect any iridocorneal attachments (Fig. 14.1). In infants suspected of having congenital glaucoma secondary to anterior segment dysgenesis, corneal diameter and axial length measurements are helpful for the diagnosis and to guide the response to therapy (Fig. 14.3). A dilated fundus examination should be performed to evaluate the optic nerve and cup to disc ratio (see Chap. 42).

Other diagnostic tools useful in characterizing anterior segment dysgenesis disorders include ultrasound biomicroscopy (Fig. 14.4) to evaluate corneal and anterior chamber structures, as well as anterior segment optical coherence tomography (A/S OCT) to obtain high-resolution images of the anterior chamber angle. These imaging modalities can help to depict the nature and extent of anomalous structural

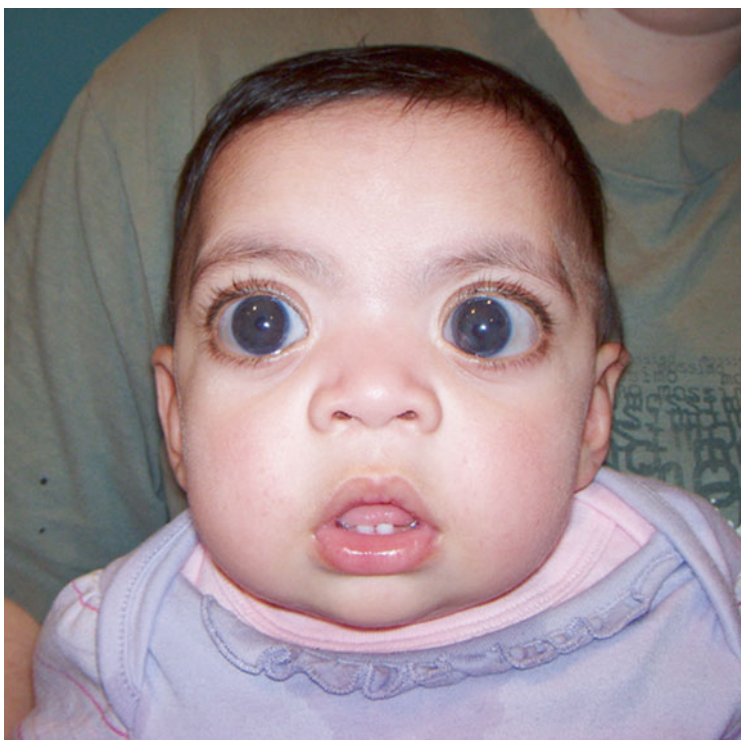

Fig. 14.3 Patient with Axenfeld–Rieger syndrome who presented with buphthalmos from infantile glaucoma. Patient was found to have a *FOXC1* mutation. Characteristic facial features including maxillary hypoplasia and prominent lower lip are present. Systemic manifestations included mild aortic arch hypoplasia and mild to moderate hearing loss

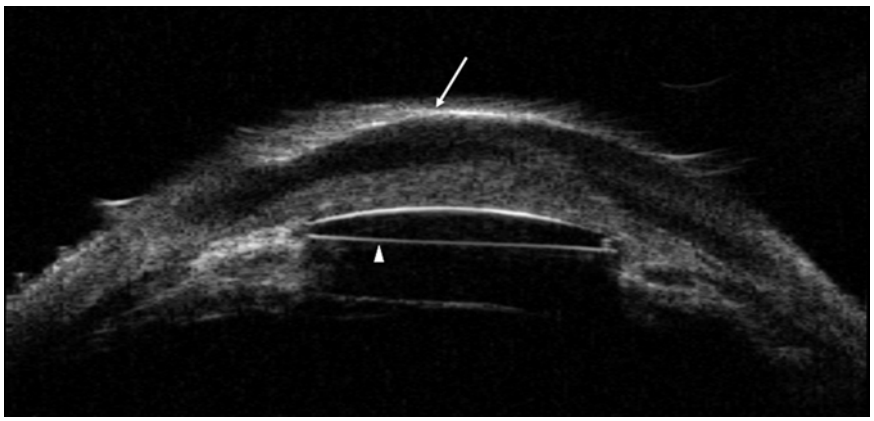

Fig. 14.4 Ultrasound biomicroscopy of a patient with Axenfeld–Rieger syndrome and congenital glaucoma. There is abnormal echogenicity in the cornea (*arrow*), correlating with opacification from band keratopathy. In addition, the anterior chamber is shown to be flat with scar tissue and fibrotic adhesions. Note that the patient had a prior cataract extraction with sulcus intraocular lens placement (*arrowhead*) as well as an Ahmed tube placement for congenital glaucoma (not shown)

relationships within the anterior segment and may be helpful in guiding surgical interventions, especially in patients in whom the cornea is opaque.

A thorough systemic examination should be conducted at the time of diagnosis or if Axenfeld–Rieger syndrome is suspected. Systemic manifestations include hearing loss, dental anomalies, congenital heart disease, redundant periumbilical skin, developmental delay, pituitary abnormalities, and a characteristic facial appearance of hypertelorism and maxillary hypoplasia [11, 12]. Because there are genotype–phenotype correlates that may portend prognosis, genetic counseling and testing should be strongly considered. The patient should also be evaluated by a multidisciplinary team to evaluate for abnormalities in the dental, craniofacial, cardiac, genitourinary, neurologic, endocrine, and musculoskeletal systems.

Management and Prognosis

The main focus of management is to address the risk for glaucoma and secondary amblyopia from any source. Despite its dramatic appearance, the iris abnormalities in Rieger anomaly tend not to cause visual deprivation [7], but if refractive error or strabismus is present, these should be addressed and managed promptly. In patients with Peters anomaly, ultrasound or OCT imaging of the anterior segment can help determine the location and extent of structural anomalies and assist in surgical planning.

Glaucoma management in the pediatric population can be challenging and requires close monitoring and follow-up. Since increased intraocular pressure can occur at any age in Axenfeld–Rieger syndrome, it is critical to follow these patients closely over time and also to differentiate IOP rise in young infants with Axenfeld–Rieger syndrome from that in primary congenital glaucoma, as the response to goniotomy may not be as effective in Axenfeld–Rieger syndrome [3]. In general, trabeculotomy is favored over goniotomy in glaucoma of congenital onset in Axenfeld–Rieger syndrome due to the iris adhesions creating technical difficulties [7]. We have found that direct visualization of the angle structures via an endoscope can further facilitate goniotomy in such cases. Irrespective of the age of onset of glaucoma, medical management should be attempted initially, followed by surgical intervention if there is a poor response to topical antiglaucomatous medications. Long-term outcome data is lacking regarding filtering, shunting, and laser procedures for the management of glaucoma in Axenfeld–Rieger syndrome [7].

In summary, patients with anterior segment dysgenesis disorders require frequent examinations and close follow-up throughout infancy and into adulthood. Often, a coordinated multidisciplinary approach is required involving other subspecialties to minimize associated systemic morbidity in these patients. Further studies on genetic and molecular pathways may prove beneficial to improving our understanding of this disease spectrum for more targeted therapeutic approaches.

Case Example 1 (Table 14.2)

Table 14.2 Case Example 1

Chief complaint	1 day old male born with congenital glaucoma with IOP of 30 OU, cataract OD, and eccentric pupil with iris stranding OD		
Prenatal history	Normal prenatal care, no maternal infections or illnesses		
Birth History	Full term male, well developed, normal spontaneous delivery		
Family history	Older brother with Axenfeld–Rieger syndrome. Older sister with congenital glaucoma OU.		
Initial management	Patient suspected to have Axenfeld–Rieger syndrome and underwent trabeculotomies at ages 10 days and 19 days OU as well as subsequent cataract extraction with posterior chamber IOL placement.		
Follow-up exam		OD	OS
	UCVA	Blinks to light	Blinks to light
	Pupils	eccentric, 6 mm, trace reaction, no APD	4 mm, 2+ reaction, no APD
	IOP (mmHg)	32	13
Interval management	Apparent failed trabeculotomies *x*2 OD, successful OS. Medical management with numerous glaucoma medications including trusopt, timoptic, and xalatan attempted. Despite the maximal medical management, the IOP was not controlled in OD and the patient subsequently received 2 tube shunts and 3 external cycloablation treatments via G-probe. Patient with still poorly controlled IOP was referred to us for further evaluation and treatment.		
Follow-up exam		OD	OS
	Visual acuity	central, steady, maintained	central, steady, maintained
	Cycloplegic refraction	+0.25 + 1.00 090	+0.25 + 1.25 090
	IOP	30	13
	DFE	c/d 0.2, retina attached	c/d 0.2, retina attached
1 month post-op follow-up exam (with portions under anesthesia)		OD	OS
	Visual acuity	central, steady, maintained	central, steady maintained
	Slit lamp examination	Diffuse microcystic edema, 2–3 hazy cornea with poorly defined anterior segment structures	unchanged
	IOP	25	13
	Ultrasound biomicroscopy (UBM)	Iridocorneal adhesions, apparent vitreous strand clogging tube impeding flow	
	B-scan	Posterior vitreous detachment overlying optic nerve only, retina attached	
Further management and findings	Patient with Axenfeld–Rieger syndrome and multiple failed surgeries with still poorly controlled glaucoma OD. Due to poor visualization through the cornea an endoscopic exploration was performed. The ciliary processes were mostly found to be intact despite the history of 3 external cycloablations. In advanced glaucoma and buphthalmos, the structures may be found to be outside the predicted anatomy and unless the treatments are performed via the guidance of the UBM or internal ablation via endoscope; laser treatment can be ineffective, as was seen in this patient. Furthermore, utilizing the endoscope, the clogged shunt was opened via vitrectomy under direct visualization, irrigated with a 30-gauge cannula and the shunt was observed to be patent by observation of tissue distention around the shunt plate. The IOP has been under control with no medications utilized for more than a year postoperatively.		

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Management of the Patient with Hyphema

15

Sarah B. Wierda and Michelle M. Ariss

Abstract

Bleeding into the anterior chamber (hyphema) occurs most commonly after blunt or penetrating injuries, but also in a number of other settings. Complications include elevation of intraocular pressure and its consequences as well as corneal blood staining, and vision loss from associated injuries. The risk of complications is believed to be higher in patients with sickle cell disease. Although there is no consensus on the use of various medications in patients with hyphema, most ophthalmologists agree that cycloplegics, topical steroids, and anti-glaucoma medications are important and prevent complications such as elevated intraocular pressure, posterior synechiae, and possibility of rebleeds. Management of pediatric patients as out or inpatients and the restriction of their level of activity continue to be debated, as is the use of systemic anti-fibrinolytics and oral steroids. It is critical to identify associated ocular, orbital, or other accompanying injuries. The surgical evacuation of blood from the anterior chamber is considered and performed in cases in which the hyphema does not resolve and intraocular pressure is significantly elevated.

Keywords

Hyphema • Trauma • Glaucoma • Injury • Sickle cell • Therapy

Introduction

A hyphema, or blood in the anterior chamber, commonly occurs following blunt or penetrating ocular injuries [1]. While trauma is the most common cause of hyphema, other conditions associated with spontaneous bleeding into the anterior chamber have been identified such as juvenile xanthogranuloma, uveitis [2], leukemia [3], retinoblastoma [4], and Swan syndrome, a condition defined as the development of hyphema months to years after cataract surgery due to an abnormal proliferation of blood vessels at the cataract wound site [5]. Children comprise about 70–75 % of patients who present with traumatic hyphemas [6]. Complications of traumatic hyphemas can lead to permanent vision loss, and include elevated intraocular pressure (IOP) leading to optic nerve damage, secondary hemorrhage, corneal blood staining, and, in children, deprivation amblyopia [1]. It is important to evaluate and to recognize penetrating injuries to the globe in patients with traumatic hyphema so that the appropriate surgical interventions are performed. For details regarding the management of penetrating globe injuries please refer to Chaps. 17 and 30, as the remainder of this chapter addresses the diagnosis and management of traumatic hyphema from non-penetrating ocular trauma.

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Pathophysiology

The impact of a blunt object hitting the eyeball results in distortion of the globe, a decreased antero-posterior diameter with stretching and posterior displacement of the lens-iris diaphragm and scleral expansion in the equatorial zone. This distortion leads to disruption of the arterioles of the ciliary body and iris vessels that results in bleeding into the anterior chamber. The formation of a fibrin clot and the rise in intraocular pressure (IOP) tamponade the bleeding vessel, leading to a cessation of bleeding [1, 6].

One of the most common acute complications of traumatic hyphema is elevation of IOP. The fibrin clot that forms at the site of a vascular tear breaks down into its degradation products, which are cleared from the eye through the trabecular meshwork. Obstruction of aqueous fluid outflow at the site of the trabecular meshwork with the fibrin degradation products and red blood cell components often leads to a rise in intraocular pressure if not counterbalanced by decreased aqueous production from inflammation. If the dissolution of the fibrin clot occurs prior to the healing of the injured blood vessel a secondary hemorrhage may result.

Clinical Features

The timing and mechanism of injury should be recorded. Lacerating and penetrating injuries must be ruled out, and if head trauma or orbital wall fractures are suspected, appropriate imaging studies such as computed tomography (CT) scans or ultrasonography should be obtained. Ocular trauma in the course of children's play activities is the most common cause of hyphema [7], but other situations include sports injuries, airbag, finger or fist to the eye, paintball and with increasing incidence, air-soft pellet injuries [8]. In children, non-accidental trauma should also be considered as a cause of hyphema, and social services alerted in case it is suspected.

Clinical symptoms and signs associated with traumatic hyphema include: decreased vision, photophobia, pain, nausea and vomiting, elevated IOP and injury to adjacent structures including the eyelids, iris, and cornea. Iridodialysis is common. Table 15.1 provides a scheme for grading macrohyphemas [1], microhyphema may be graded using the Standardization of Uveitis criteria scale for grading cells [9].

Table 15.1 Grade of hyphema according to amount of blood in anterior chamber

Grade	Percentage of anterior chamber involvement
Grade 4	Fills the whole anterior chamber. "Eight ball hyphema"
Grade 3	1/2 to nearly entire anterior chamber
Grade 2	Between 1/3 and 1/2 of anterior chamber
Grade 1	Less than 1/3 of anterior chamber
Microhyphema	Circulating red blood cells

All patients of African descent should be screened for sickle cell disease using a sickle prep, followed by a hemoglobin electrophoresis [1, 10]. Patients with sickle cell anemia can have a more complicated course, with increased risk for elevated intraocular pressure, central retinal artery occlusion, optic nerve compromise from mildly elevated IOP, visual impairment, and rebleed [6, 9, 11]. This greater propensity for complications is due to the particular environment of the anterior chamber and the sickled red blood cells. The red blood cells have a greater propensity to sickle in aqueous humor than in venous blood [11]. Sickled red blood cells go on to obstruct the trabecular meshwork, which increases intraocular pressure and also results in an acidic, hypoxic environment that perpetuates additional sickling [11].

Medical Management

Treating pediatric patients in an inpatient versus outpatient setting continues to be a source of debate. While inpatient management of children with traumatic hyphema allows a restriction of the child's activities and a more reliable administration of eye drops, studies have not shown a statistically significant benefit of inpatient vs. outpatient treatment with regard to the rate of secondary hemorrhage (rebleed) or visual acuity outcomes [12].

Regardless of the setting, initial management requires a protective shield to be placed over the eye, restricted activities to prevent secondary hemorrhage, and elevation of the head of the bed to allow settling of the hyphema to the inferior part of the anterior chamber, facilitating a view of the retina and optic nerve. In order to prevent pain associated with ciliary spasm and to reduce posterior synechiae formation, a cycloplegic agent, such as atropine sulfate 1 %, homatropine 2 % or 5 %, or even cyclopentolate 1 % or 2 % is given. Topical corticosteroids are administered to reduce inflammation, and may play a role in the reduction of secondary hemorrhage. Oral corticosteroids have also been used with the thought that they also help to reduce inflammation, stabilize the blood ocular barrier, and slow clot dissolution [6]. Another medication that helps to prevent the dissolution of the clot is aminocaproic acid. Aminocaproic acid is an anti-fibrinolytic that is administered intravenously or topically. It has been shown to reduce the rate of rebleed but can significantly increase the time it takes for the clot to dissolve [13]. Because of the increased time to clot dissolution, this medication is not recommended in hyphemas that fill >50 % of the anterior chamber as a large clot will obstruct the vision [6]. The use of systemic aminocaproic acid has not been shown to improve visual outcomes. It is also possible that the cessation of this medication can result in a higher risk of

Table 15.2 Commonly used medication in the treatment of traumatic hyphema

Medication	Dosage	Reason
Atropine sulfate 1% or other cycloplegics	Daily or as necessary for the individual medication	Cycloplegic to help relieve ciliary spasm and pain
Prednisolone acetate 1 %	Four times daily, but can vary based on grade of hyphema[a]	Reduce inflammation; possibly reduce secondary hemorrhage
Treatment of elevated IOP	Medication and dosage	Cautions/side effects
Beta-blocker	Twice daily	Caution in asthma or heart disease
Carbonic anhydrase inhibitor	Dorzolamide or Brinzolamide 3 times daily topically or Acetazolamide or Methazolamide oral or IV	Can precipitate sickling
Combination medications	Dorzolamide/Timolol (Cosopt) twice daily	See above
Hyperosmotic agents	Latanoprost qHS	Can lead to increased inflammation

[a]If more extensive hyphema or corneal edema from the blunt trauma, may require more frequent dosing. In the setting of concomitant large corneal epithelial defect, judicious utilization as may delay corneal re-epithelialization

secondary hemorrhage [14]. At the time of writing of this chapter we do not believe that anti-fibrinolytics are widely and routinely administered.

In the pediatric population, treatment of IOP requires special consideration. Elevated IOP is often initially treated with an aqueous suppressant, such as a topical β-blocker or carbonic anhydrase inhibitor (CAI), or a combination thereof [1]. It should be mentioned that in sickle cell trait or disease, CAIs, topical or oral, should not be used as they cause a metabolic acidosis, which may worsen sickling. In addition, in very young children, alpha-adrenergic agonists are avoided as they can cause respiratory depression especially in those patients less than 12 years of age. In cases where IOP remains unacceptably elevated, oral or intravenous CAIs or hyperosmotic agents may be required. The following table (Table 15.2) can help to guide initial medical management of patients with traumatic hyphema.

Surgical Management

Evacuation of blood clots or washout of hyphema from the anterior chamber is rarely necessary, but there are specific indications for these procedures. Reasons to consider surgery include corneal blood staining and uncontrolled IOP. Corneal blood staining is most common in patients with rebleeds and results from the combination of elevated IOP, endothelial dysfunction, and anterior chamber hemorrhage. Red blood cells release hemoglobin that is absorbed by the corneal stroma and by keratocytes leading to keratocyte death. Corneal blood staining may be difficult to detect because of apposition of the hemorrhage to the corneal endothelium. Slit-lamp examination is significant for yellow granular changes or haze of the posterior corneal stroma. Blood staining leads to a reduction in corneal transparency that may be permanent. Surgical evacuation is recommended at the earliest detection of blood staining. Empirical guidelines have been suggested for performing anterior chamber washout of hyphemas associated with elevated intraocular pressure and include: (1) an intraocular pressure of 25 mmHG or more for 5 days with a total hyphema; or (2) an intraocular pressure of 60 mmHG or more for 2 days. The surgical guidelines in patients with sickle cell disease differ, as the optic nerves of patients are more susceptible to damage from modest elevations of pressure. The guidelines are: (1) an intraocular pressure above 25 mmHg for greater than 24 h; or (2) repeated spiking of intraocular pressure to above 30 mmHg for 2–4 days [1].

Complications

One of the more common acute complications of traumatic hyphema is an elevation of IOP. However, elevated IOP and glaucoma can also manifest as a late complication due to angle recession, peripheral anterior synechiae formation, or posterior synechiae with iris bombe. Therefore, gonioscopy and a description of angle findings are recommended as soon as the hyphema resolves and 3–6 months after initial injury [1].

In addition to an elevation of IOP, traumatic hyphema can cause corneal blood staining. In the pediatric population this is especially concerning, as it can result in deprivation amblyopia. Corneal blood staining can be minimized by judicious daily follow-up and evacuation of the hemorrhage if IOP consistently elevated as above or at the earliest detection of corneal blood staining. Another serious complication is secondary hemorrhage or rebleed. In such patients, visual prognosis appears to be worse than those without rebleed [6]. The most likely time for secondary hemorrhage are the first 4–7 days after trauma. A higher rate of secondary hemorrhage is more likely in the following populations: African Americans, patients with sickle cell disease or trait, and younger patients, possibly due to the difficulty in maintaining limited activity [6]. Furthermore it has also been reported that high IOP and worse vision at time of initial exam may be associated with an increased probability of secondary hemorrhage [15].

Outcomes and Conclusions

Hyphemas resolve without consequence in the majority of patients who do not have other associated ocular injuries and who do not experience any rebleeds [13]. Visual outcomes in the absence of commotio retinae are good. Patients with sickle cell trait/disease require judicious observation, avoidance of medications that may contribute to sickling, and evacuation of hemorrhage if IOP remains elevated. The use of corticosteroids, cycloplegics, and interventions such as binocular patching, bed rest, or head elevation are done at the discretion of the treating physician and are possibly of benefit to the individual patient [16].

Cases

Clinical Case 1

A 10-year-old Caucasian male presents to the emergency department with left eye pain 1 day after an altercation at school which resulted in a fist to the eye. He reports that vision was blurry when he awoke this morning. Light made his pain worse.

Examination was significant for a visual acuity of 20/20 in the right eye and 20/40 in the left eye. Extraocular movements were full. IOP was OD = 12 mmHg, and OS = 34 mmHg. On slit-lamp examination there was a grade I hyphema in the left eye and dispersed microhyphema in the anterior chamber (Fig. 15.1). The rest of the eye examination was within normal limits.

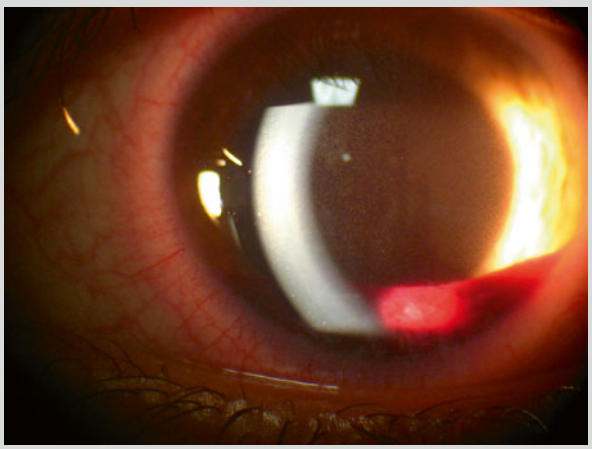

Fig. 15.1 Grade I hyphema of the left eye (occupied <1/3 of the anterior chamber) and dispersed (4+ RBCs) present in the anterior chamber. Note the absence of corneal blood staining. Image courtesy of Daniele Saltarelli, OD, Cincinnati, OH

Management: The patient was started on atropine sulfate 1 % drops twice daily and prednisolone acetate 1 % drops four times daily, along with timolol maleate/dorzolamide combination drops twice daily for the elevated IOP. He was instructed to limit activities, sit whenever possible, and to keep the head of the bed elevated. The risks and consequences of secondary hemorrhage were explained to the parents. The patient was followed daily until resolution of the hyphema. The drops were discontinued over the course of 3 weeks and gonioscopy 3 months post trauma showed no angle recession or peripheral anterior synechiae.

Clinical Case 2

An 8-year-old African American male with sickle cell trait presented to the emergency room 2 days after his brother hit his right eye with an air soft bullet. His mother states that he has had two episodes of emesis upon waking that morning, along with complaints of headache. Examination showed a visual acuity of hand motions in the right eye and 20/20 in the left eye. The pupil could not be visualized OD and was normal OS. The IOP was 62 mmHg in the right eye and 15 mmHg in the left eye. Anterior segment examination was significant for diffuse corneal edema and a Grade 4 hyphema. The left eye was normal. There was no view of the iris or the fundus on the right. A B-scan was obtained OD and showed no evidence of retinal detachment or vitreous hemorrhage.

Management: This patient with sickle cell trait presents with a total, hyphema, significant symptoms, and elevated and severely elevated intraocular pressure. Because of the severely elevated intraocular pressure and contraindications to both systemic agents to rapidly reduce pressure, the patient was immediately taken to the operating room for surgical removal of hyphema. At the conclusion of the case, atropine sulfate 1 %, prednisolone acetate 1 %, and antibiotic drops were placed in the eye; and a patch and shield were applied. The head of the bed was elevated and the patient was placed on a limited activity regimen. The following day visual acuity in the right eye had improved to 20/50 and the anterior chamber was deep with a 3+ microhyphema. Intraocular pressure was 18 mmHg. The patient was started on topical timolol,

(continued)

prednisolone acetate eye drops and cycloplegics, and followed daily. Six days after the initial event the patient returned with an acute decrease in visual acuity to 20/100 and intraocular pressure elevation to 26 mmHg. A rebleed was diagnosed and the patient was maintained on the eye drops with strict adherence to head of bed elevation and limited activity. Over the next couple of days, vision continued to improve and the intraocular pressure continued to decrease. At 3 months post trauma, visual acuity was 20/20, intraocular pressure was 18 in both eyes and the anterior chamber was quiet. Gonioscopy was performed and there was no evidence of angle recession.

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Management of Chemical Ocular Injuries in Pediatric Patients

16

Christine Shieh and Terry Kim

Abstract

Chemical injury to the ocular surface constitutes a hyperacute medical emergency and requires immediate evaluation and treatment. Chemical injury is one of the most common causes of eye injury in the USA in children. Alkali liquids are particularly hazardous, as they can cause saponification resulting in further tissue penetration. Expeditious assessment and treatment is essential to prevent the extensive damage that can quickly result. The management of the sequelae of chemical injury may be challenging as well, ranging from the treatment of corneal thinning or opacification to the management of the damaged ocular surface and limbal stem cell deficiency. Children may also suffer both anisometropia from induced astigmatism and/or deprivational amblyopia from corneal opacification in the injured eye. Patients are at risk for permanent vision loss without close ophthalmologic follow-up. This chapter will address the acute treatment of ocular chemical injuries as well as the management of the sequelae.

Keywords

Ocular chemical injury • Pediatrics • Acids • Alkali

Case Example

Patient Presentation

Phone call: **The mother of a 6-year-old girl thinks her daughter had a drop of bleach splashed in her right eye while the mother was cleaning the bathroom. What should the physician tell the mother?**

Answer: The physician should tell the mother to immediately start irrigating the patient's eye. It is crucial to dilute and remove the offending agent. Ideally, sterile saline, contact lens solution, or artificial tears would be used. However, time is of the essence, so even non-sterile neutral liquids such as milk or water should be considered if the aforementioned options are not available. The patient's eye should be thoroughly irrigated for several minutes before even being brought to see the physician (See Fig. 16.1 and section Presenting Signs and Symptoms and Immediate Action).

(continued)

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Emergency Department The mother has followed your instructions and then brings the patient immediately to the emergency department. The past medical history is positive for Down syndrome and the patient has an allergy to sulfa medication. **What are the next steps in acute management? What must the physician be aware of in treating this patient in the acute setting?**

Answer: The patient's eye should be irrigated again with saline. A brief exam should be conducted, and the pH of the patient's eye should be assessed with pH paper. Continuous irrigation should be performed until the pH of the eye is neutral. A Morgan lens may be helpful in irrigating the eye. The physician also needs to be cognizant of how the medical history of the patient could affect management. In this case, the patient has Down syndrome, and the medical team should be careful not to hyperextend the patient's neck due to possible cervical vertebrae instability noted in this population (See Fig. 16.1) and section on Presenting Signs and Symptoms and Immediate Action).

After examining and treating the patient in the emergency department, the mother inquires as to the patient's prognosis. **What classification schemes address the prognosis of this patient? What must the physician be careful to follow in this patient? What medications are contraindicated?Answer: The most accepted classification schemes to predict prognoses are those of Roper-Hall [1], Pfister [2], and Dua [3]. These classifications are based on a combination of the extent of corneal haze, limbal ischemia, clock hours of limbal and bulbar conjunctival involvement (See section on Classification Schemes and Tables 16.1 and 16.2).**

The patient's vision and intraocular pressure must be carefully followed after the initial emergency room visit. Contraindicated medications include, but are not limited to: tetracyclines (often used to protect against corneal melt, but contraindicated in children due to potential for teeth and enamel hypoplasia) and brimonidine (used to lower intraocular pressure, but alpha-2 agonists have potential for CNS depression) (Fig. 16.2, See section on Medications).

Clinic The patient is 1 month out from her initial presentation and has developed a corneal opacity. The mother asks you if anything can be done. **What should the physician tell her? What risks might surgery present?**

Answer: The physician should attempt to determine the patient's visual acuity, and the significance of the corneal opacity. A careful cycloplegic refraction should be performed to evaluate for secondary regular astigmatism that could be potentially correctable with glasses. A con-

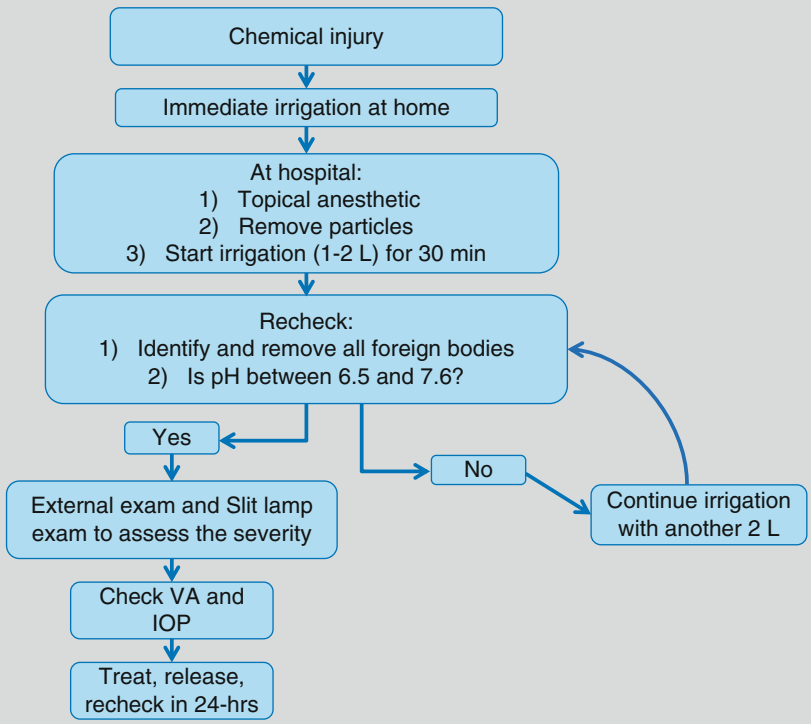

Fig. 16.1 Algorithm for the acute management of chemical injuries to the eye

(continued)

Table 16.1 Roper-Hall modification of the Hughes classification

Grade	Cornea	Limbal ischemia	Prognosis
I	Corneal epithelial damage	None	Good
II	Corneal haze, iris details visible	<1/3	Good
III	Total epithelial loss, corneal stromal haze, iris details obscured	1/3–1/2	Guarded
IV	Cornea opaque, iris, and pupil details obscured	>1/2	Poor

Reproduced with permission from Roper-Hall MJ. Thermal and chemical burns. Trans Ophthalmol Soc UK 1965; 85:631–53

Table 16.2 Dua classification of acute chemical injuries based on clock-hours of limbal and conjunctival involvement and associated prognosis

Grade	Clock hours of limbal involvement	Conjunctival involvement	Prognosis
I	0	0	Very good
II	≤3	<30 %	Good
III	>3–6	>30–50 %	Good
IV	>6–9	>50–75 %	Good to guarded
V	>9–<12	75–<100 %	Guarded to poor
VI	12	100 %	Very poor

While calculating percentage of conjunctival involvement, only involvement of bulbar conjunctiva, up to and including the conjunctival fornices is considered

Reproduced with permission from Dua HS, King AJ, Joseph A. A new classification of ocular surface burns. Br J Ophthalmol 2001;85:1379–83

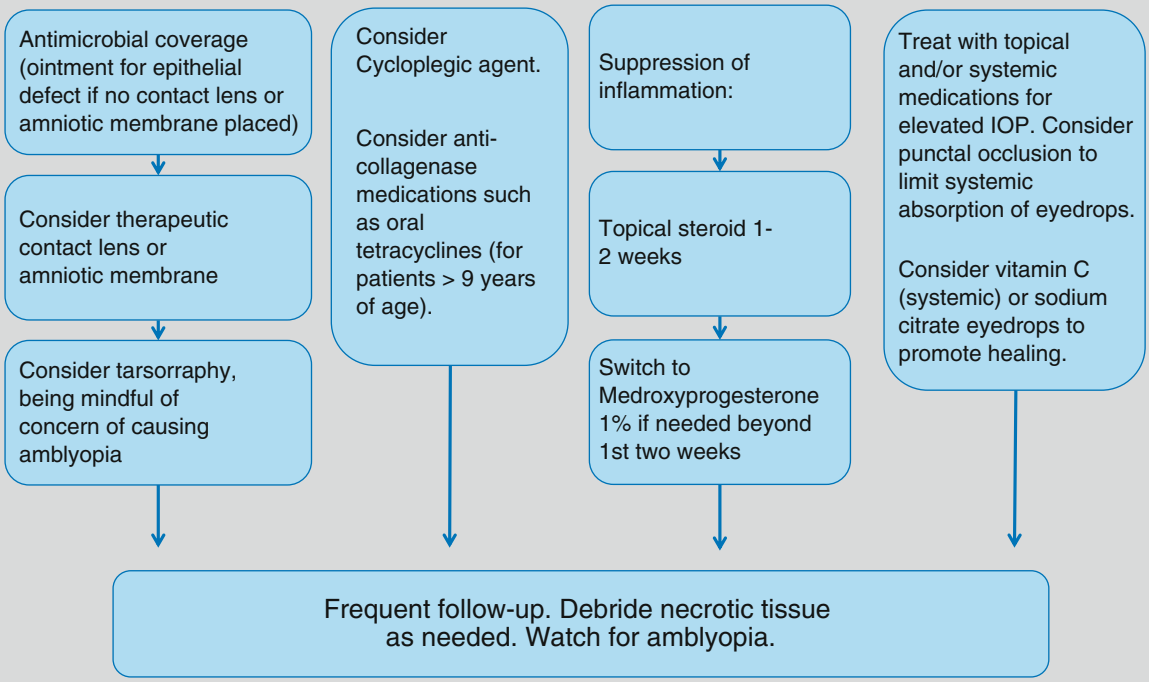

Fig. 16.2 Algorithm for early management of chemical injuries

tact lens over-correction could also be considered to determine if irregular astigmatism can be further neutralized and result in improved acuity. Deprivational amblyopia is a concern in this young child but must be balanced with the risk of transplant rejection or failure. Furthermore, cornea transplants are technically challenging in children and have a high risk of neovascularization and rejection in young patients. The ocular surface must be optimized, sometimes requiring a limbal stem cell transplant prior to transplantation (See Fig. 16.3).

(continued)

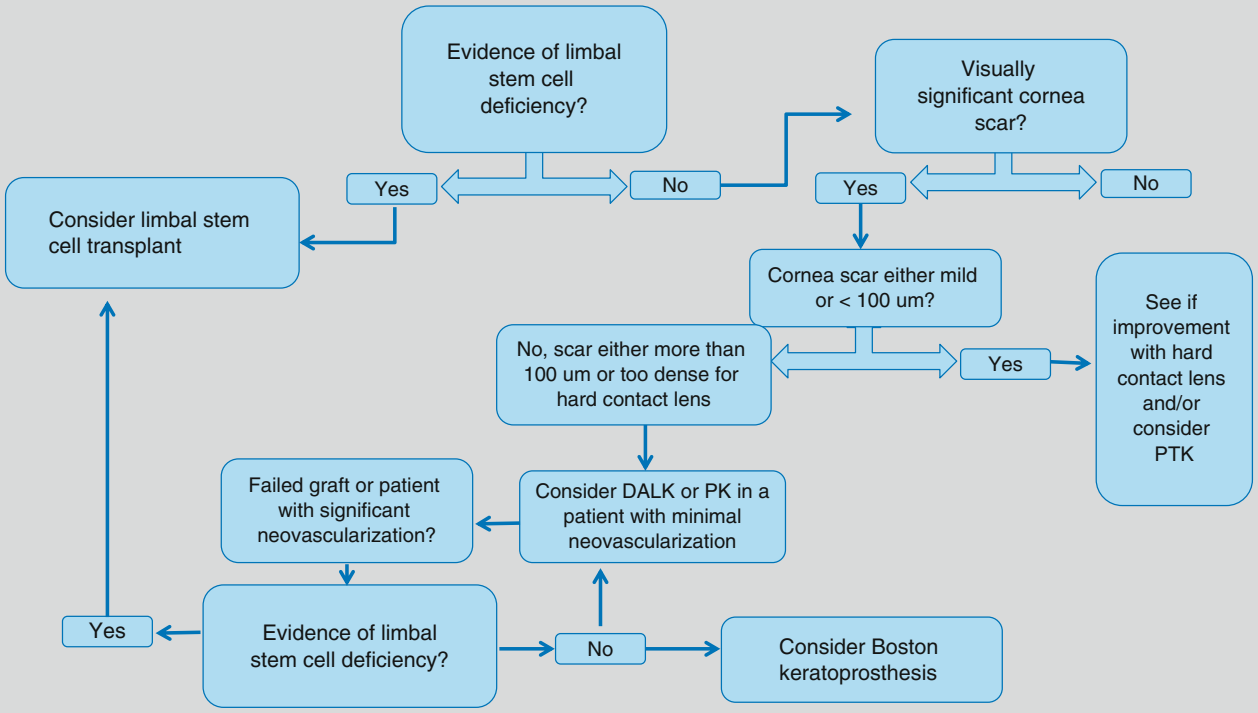

Fig. 16.3 Algorithm for long-term management of chemical injuries

Epidemiology

Ocular injuries constitute the main cause of pediatric monocular visual disability and monocular blindness in the USA. They are much more common in children than in adults [4, 5]. In a large US population-based study examining consumer-product-related pediatric eye injuries treated in emergency departments, chemical conjunctivitis (12.4 % of cases) was the second most common diagnosis, exceeded only by contusions or abrasions in 44.6 % of cases [6]. Gender differences were also examined. Interestingly, while two-thirds (62.5 %) of the pediatric eye injuries were in boys, the injuries were more likely to be related to blunt trauma or lacerations from recreation (sports, toys, vehicles) rather than chemical injuries. This was speculated to be due to the aggressive nature of play among young boys [6]. In contrast, girls were slightly more likely than boys to experience eye injuries from household cleaning chemicals and swimming pools/equipment. The most common consumer products associated with chemical eye injuries were general-purpose cleaners, bleaches, and fireworks [6].

In the same study, while older children (age 2–12) were more likely to sustain traumatic eye injuries, younger children (less than age of 2 years) were more likely to suffer eye injuries from household cleaning chemicals. Almost one-half (46 %) of injuries to infants ages 0–12 months were due to chemical consumer products, with higher reported injuries in older infants, likely due to their increased mobility. Chemical injury was often related to a family member using sprayed chemicals (either residue from a nearby parent or sibling).

It is also important for the ophthalmologist to be informed of potentially hazardous agents unique to their geographical region. Vajpayee et al. conducted a retrospective chart review of case records of pediatric patients with ocular burns who were treated at a tertiary eye care hospital in North India between March 2006 and March 2011 [7]. In this study, lime, in the form of chuna, was the most common

offending agent. Chuna is an alkaline, edible calcium hydroxide paste added to chewing tobacco to increase the penetration of chemical compounds released from tobacco. In contrast to American patients with chemical injury presenting early in the USA, patients in this study were significantly less likely to be brought for treatment immediately after the injury, and 70.2 % of patients presented more than 1 month after the injury.

Lastly, trends in consumer products may also impact emergency room visits. For example, there has been a recent wave of reports of pediatric ocular injury from liquid detergent capsules [8].

Alkali

While studies have shown no clinically significant differences in clinical course and prognosis between severe acid and alkali injuries, the classical teaching is that alkali chemicals are more dangerous due to their lipophilicity and their ability to penetrate the eye faster due to saponification [9]. As alkaline solutions saponify fatty acids in cell membranes, this may lead to rapid tissue penetration and cell lysis [9]. Inflammatory response from the damaged tissues results in the release of proteolytic enzymes. Alkalis can penetrate into the anterior chamber and result in cataract formation as well as damage to the ciliary body and to the trabecular meshwork.

Chemicals implicated in pediatric alkali injuries include: wet and dry cement, fertilizers and refrigerants, airbag contents, as well as cleaning agents such as lime or lye [5, 10]. Firework injuries are unique, because they can result in both chemical injury (due to magnesium hydroxide) and thermal injury. The most common cause of limbal stem cell deficiency (LSCD) is alkali injury, especially with lime [11].

Acids

Strong acids also have the ability to penetrate the cornea as rapidly as alkali agents. Burns caused by hydrofluoric acid can be particularly severe. In addition to the action of the dissociated proton, by which most strong acids ionize completely, hydrofluoric acid has a low molecular weight, which allows it to quickly penetrate into deeper tissues. It also may generate heat from the acid's reaction with the water in the corneal tear film [12].

However, in contrast to alkalis, acids also cause protein binding and precipitation, which neutralizes or buffers the reaction in the corneal epithelium and superficial stroma. This protein precipitation produces the typical ground glass appearance of the epithelium, and acts as a barrier to further penetration [12]. Therefore, acid solutions tend to cause less damage to ocular surface tissues than alkali solutions that are not buffered by the tissues.

Presenting Signs and Symptoms and Immediate Action

Children are often poor historians, so it is necessary to have a high degree of clinical suspicion of chemical injury if a patient presents to the physician with severe pain, epiphora, and/or blepharospasm [9].

Studies have demonstrated that the severity of damage after ocular chemical injury depends significantly on the duration of the chemical contact with the ocular surface and the promptness of medical treatment [4]. This influences the outcome more than any specific therapeutic modality. Because patients may experience irreversible eye damage in 5–15 min, acute chemical injury should be treated immediately with irrigation [4]. If the clinician is contacted over the phone by a patient or a patient's family member about acute chemical injury to the eye, the physician should recommend copious irrigation of the affected eye immediately, by whichever means possible. While irrigation with sterile saline is the first choice, the most important goal is dilution and removal of the chemical, so even flushing the affected eye with non-sterile water is preferred over no action (Fig. 16.1).

In the emergency room, topical anesthetic is used prior to ocular irrigation to decrease discomfort. Given the acidity of topical anesthetics, most having a pH between 4 and 5 [13], the physician has to check the patient's conjunctival fornix pH prior to the instillation of topical anesthetics. The emergency department is generally well supplied with isotonic saline or lactated Ringer's solution, and the Morgan lens may be connected with a hanging bag of saline (Fig. 16.4a, b). The Morgan lens has been used on children as young as 6 months of age. Because chemical irritants may potentially pool between the lens and the conjunctival surface, some physicians advocate irrigation prior to placement of the Morgan lens.

Management requires continual irrigation with the appropriate solution until a neutral ocular surface pH of 7.4 is approached. This usually requires 1–2 L of saline. Most commercially available preparations of normal saline have a pH range between 4.5 and 6.0 [14]. Irrigating the eye with solutions that have a pH less than 6.8 or greater than 8.2 may contribute to corneal pain and swelling [15]. Although Normal Saline (NS) is isotonic and is generally well tolerated during irrigation, the acidic pH of NS may be a potential aggravating factor during copious and prolonged ocular irrigations. Other irrigating solutions may be available in the Emergency Department whose pH is closer to neutral. These solutions

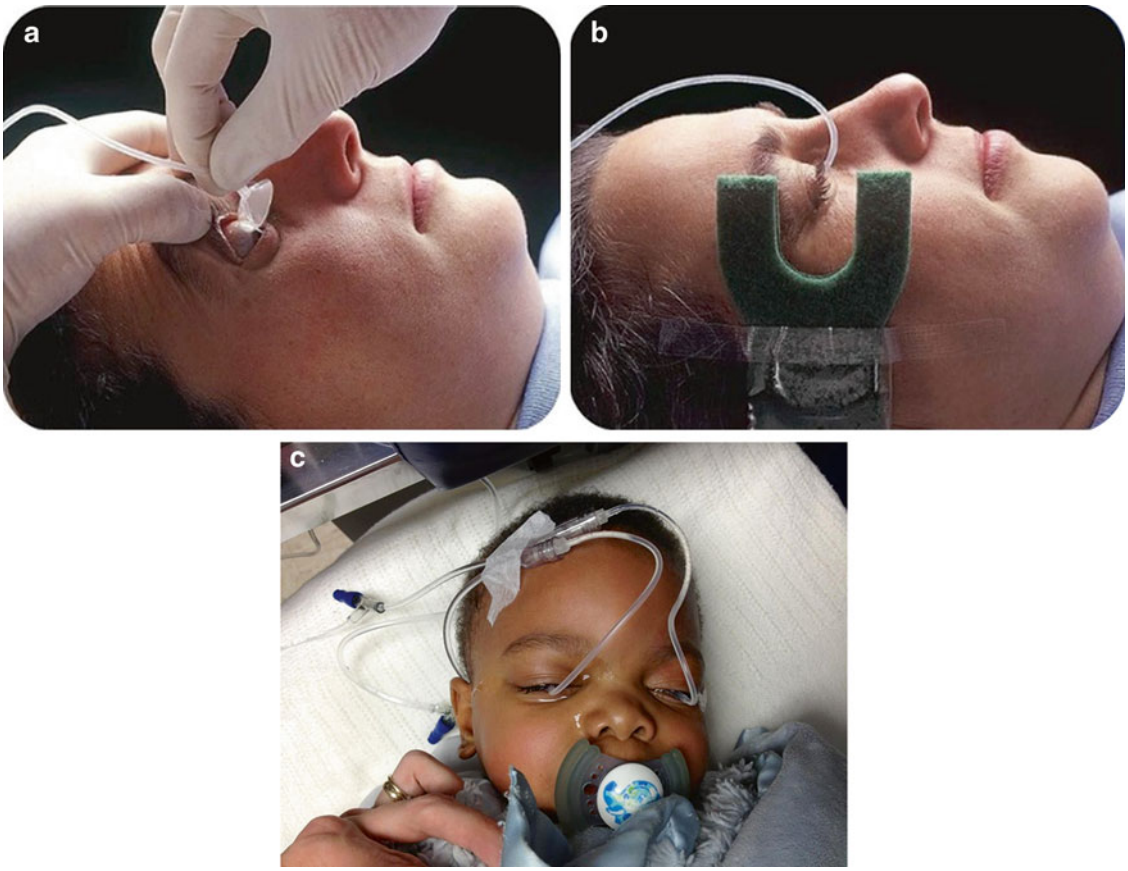

Fig. 16.4 After initial irrigation of the surface, a Morgan® Lens is inserted (**a**) and irrigating solution flows from the IV bag to the ocular surface (**b**). (**c**) 16 month infant with bilateral Morgan® lenses inserted after chemical exposure. Images reproduced with permission from Morgan® Lens MorTan® Incorporated (morganlens.com)

include Lactated Ringers and BSS Plus buffered to neutral pH, and NS with added sodium bicarbonate (used to buffer the solution to neutral pH). Of note, though, BSS plus is about three times more expensive than other irrigating fluids [14].

Irrigation should be continued until physiologic pH has been attained. It is preferable to use pH litmus paper to ascertain that physiologic pH has been reached; if none is available, the physician may use urine pH sticks, which are commonly found in the emergency room department. The normal ocular surface pH is between 6.5 and 7.6 [16].

After extensive irrigation, and using the slit lamp if possible, the physician should carefully remove any debris found in the eye and eyelid fornix. Sweeping the fornices (with a cotton-tip applicator or a glass rod) can aid in this assessment. Upper eyelid double eversion should be performed with Desmarres eyelid retractors. In the pediatric population, it may even be necessary to sedate the patient to ensure both adequate irrigation and examination especially in severe cases of chemical injury. In children with Down syndrome, special care should be given to avoid hyperextension of the neck due to the possible instability between the first and second cervical vertebrae in this population [17].

If the parents know the name of the chemical that was splashed in the eye, and the clinician is unsure of the nature of the composition or effects of the chemical, the local poison control center can be contacted (www.aapcc.org, 1-800-222-1222) to facilitate diagnosis and subsequent treatment.

Classification

There are a number of classification schemes that have been developed to document the extent of anterior segment damage and to predict prognosis. The Roper-Hall classification (Table 16.1) was one of the earliest scales to be developed, and grades the degree of corneal haze and the extent of limbal ischemia to predict prognosis (1). Pfister subsequently developed a classification system based upon photographs demonstrating corneal haze and peri-limbal ischemia (2). Dua proposed a classification scheme based upon clock hours of limbal involvement (as opposed to ischemia) as well as the percentage of bulbar conjunctival involvement (Table 16.2) (3). Limbal ischemia refers to abnormal whitening indicating ischemia in an otherwise

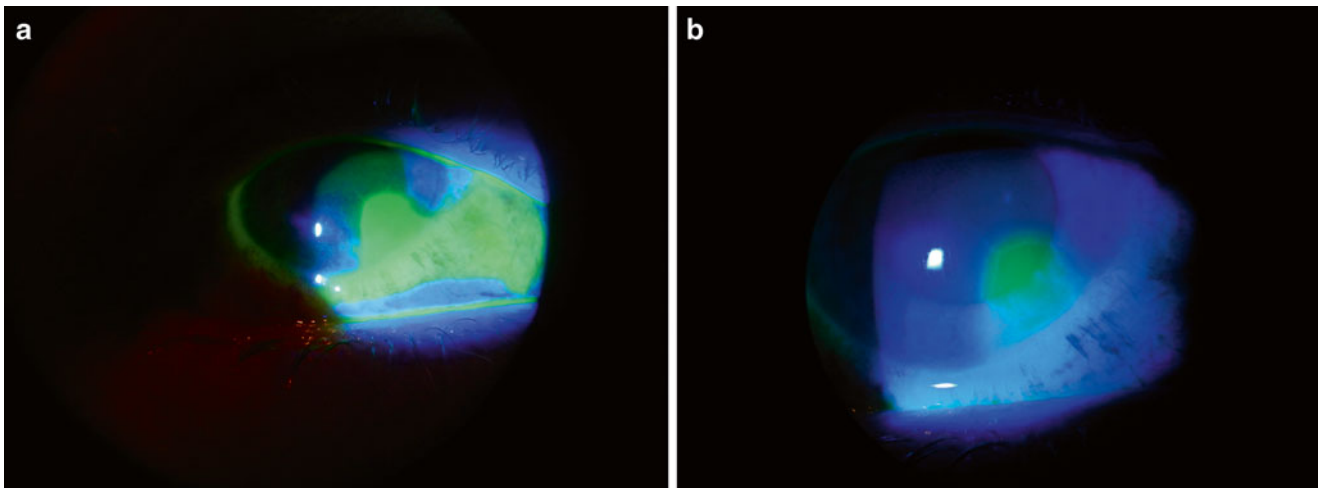

Fig. 16.5 (**a**) Acute chemical injury with peripheral 3×2.5 mm corneal epithelial defect and corneal haze. There is approximately a 25 % conjunctival epithelial defect and 3 clock-hours of limbal involvement. No limbal ischemia is present. This is considered Grade II by the Dua Classification and Grade II by the Roper-Hall Classification. The prognosis for this patient is good. (**b**) Twenty-four hours post injury, the conjunctiva has started to re-epithelialized and a small epithelial defect remains. Images courtesy of Edward Holland, MD, Cincinnati, OH

inflamed eye. In contrast limbal involvement has a broader connotation than limbal ischemia and includes areas where complete loss of limbal epithelium and/or stem cells has occurred without necessarily limbal ischemia. Gupta et al. [18] demonstrated that the Dua classification's evaluation of conjunctival involvement helped predict symblepharon formation. There continues to be controversy as to which classification scheme is superior, with Roper-Hall and Dua being the most frequently utilized in clinical practice [18, 19]. The grading scales are applied to an example in Fig. 16.5.

Regardless of the classification scheme utilized, the clinician should document the extent of corneal, limbal, and conjunctival injury at the initial exam. As the patient is followed, documenting changes may assist in grading the severity and also provide the patient and family with a general idea of prognosis.

Medical Treatment

Due to medicolegal constraints, there have been few trials to establish the safety and efficacy of ophthalmic solutions in children. As a result, many of the topical ophthalmic eye drops used to treat children are not approved by the Food and Drug Administration (FDA). Nevertheless, the FDA recognizes that these topical medications are necessary in certain circumstances. The clinician, should, however, be alert to potential adverse reactions unique to the pediatric population. When in doubt, the clinician should collaborate with a pharmacist and/or a pediatrician.

The spectrum of damage from chemical injury is broad. Damage to the corneal epithelium with injury to Bowman's layer and the anterior stroma may lead to recurrent corneal erosions [12]. Loss of pluripotent limbal stem cells may lead to subsequent conjunctivalization of the cornea and to neovascularization [9]. Furthermore, penetration from either acid or alkali may lead to loss of proteoglycans and subsequent collagen shrinkage and distortion of the trabecular meshwork. This, combined with the release of prostaglandins, may lead to an acute rise in intraocular pressure [12].

A severe inflammatory reaction may result from a chemical injury, due to breakdown of the blood-aqueous barrier. The neutrophils infiltrate tissues within 12–24 h of injury. There may also be a deficiency in ascorbate secretion due to damage to the ciliary body epithelium. Ascorbate is a cofactor in the rate-limiting step in collagen synthesis. Keratocytes are involved in both collagen synthesis and degradation, producing new type I collagen and type I collagenase, a matrix metalloproteinase [12].

To suppress the intense neutrophilic inflammatory response after chemical injury, topical corticosteroids are helpful in limiting damage in the first 1–2 weeks, and are not associated with sterile corneal and scleral melt. However, beyond the 2-week early reparative phase, keratocyte suppression of collagen production may contribute to corneal melting. Topical progesterone (medroxyprogesterone 1 %) is recommended to replace corticosteroids as they are tapered after the second week. Though medroxyprogesterone has weaker anti-inflammatory activity than corticosteroids, it minimally suppresses stromal wound repair and also exhibits anti-collagenase activity [12] (Fig. 16.2 and Table 16.3).

Table 16.3 Stages of corneal wound healing and treatment considerations

Phase	Day	Medications
Acute	0	• Irrigate the eye until neutral pH
Initial	1–14	• **Steroids:** every 1–2 h. May want to consider lower dosing frequency if an epithelial defect is present. • **Topical antibiotic:** moxifloxacin or trimethoprim-polymyxin B • **Ascorbate:** consider systemic ascorbate (see Table 16.4) and/or topical sodium ascorbate 10 % eye drops and sodium citrate 10 % eye drops every 30 min • Cycloplegic eye drops dosing depending on patient age • **Debride any necrotic tissue, consider amniotic membrane** • **Consider oral tetracycline if concern of cornea melt and if patient >8 years for anti-collegenase activity** • **Topical ointment at night**
Early repair	After day 14	• **Steroids:** stop/taper, and switch to medroxyprogesterone • Other medications as per **initial phase,** depending on clinical appearance. • Of note, collegenase activity peaks at day 21, so anti-collegenase medications (tetracycline), may have less effect after this time-frame.

Table 16.4 Dosing of systemic abscorbate (Vitamin C) in pediatric patients

Age	Recommended daily allowance (RDA)
Infants to 1 years old	Would not recommend using in neonates without guidance of pharmacist
1–3 years	15 mg daily
4–8 years	25 mg daily
9–13 years	45 mg daily
14–18 years	Males: 75 mg daily, Females: 65 mg daily

Please note: the use of vitamin C for promoting collagen synthesis is off-label, but the suggested dosing is based on the pediatric recommended daily allowance in vitamin C deficiency. Please consult with your pharmacist as needed

Compiled from Institute of Medicine (IOM), *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*, Washington, DC: National Academy Press, 2000 and Lexicomp—pharmacy database (with permission). Available: http://www.lexi.com/institutions/online.jsp?id=databases

Management of an ocular surface chemical burn should include the initial debridement of necrotic ocular surface tissues (Table 16.3). In younger children, an exam under anesthesia (EUA) may be needed to adequately perform this task. Following debridement, there may be a role in amniotic membrane grafting to promote epithelial regeneration while suppressing peri-limbal inflammation. Amniotic membrane, derived from the innermost layer of the placenta, may be used to hasten epithelialization, restore the conjunctival surface, and reduce ocular surface inflammation [9, 20]. In cases where the lids are involved, anchoring sutures may also be applied to the lid margin in addition to the conjunctiva and episclera. Amniotic membrane grafting may also be performed in cases of partial LSCD to help in vivo expansion of limbal stems. Sutureless amniotic membrane patches with a symblepharon ring are also commercially available, but may pose a challenge in pediatric patients. While some pediatric patients may be able to tolerate the amniotic membrane (either sutured or with a sutureless ring), the clinician may wish to also consider a temporary partial tarsorrhaphy to help protect the eye. The amniotic membrane promotes regeneration of a healthy surface and reduces neovascularization, which leads to improved prognosis should the patient require a corneal transplant [21]. A recent Cochrane review found no conclusive evidence for the placement of amniotic membrane as compared to medical therapy alone in the first 7 days after the injury [22]. However, the clinician may still wish to consider amniotic membrane in the first week for patients with significant damage from chemical injury.

If an epithelial defect is present, the use of a topical antibiotic for antimicrobial prophylaxis is indicated. While systemic fluoroquinolones should be avoided in children due to the risk of tendonitis and tendon rupture, studies have demonstrated that topical fluoroquinolones are safe in pediatric patients, including newborns, to offer broad-spectrum coverage [23, 24]. Although these studies have not specifically examined the presence of tendon rupture, no case reports of the co-incidence of ocular fluoroquinolones and tendon issues have been reported. However, if there is significant thinning and ulceration, fluoroquinolones should be used with caution as there have been a few reports of corneal melting associated with the use of topical fluoroquinolones [25]. Other commonly used antibiotics include trimethoprim-polymyxin B, which provides broad-spectrum antibiotic coverage. Aminoglycosides such as gentamicin and tobramycin have good gram-negative coverage, but they do not provide as broad a spectrum coverage and corneal epithelial toxicity is common after prolonged use [17].

In addition, sodium ascorbate 10 % eye drops and sodium citrate 10 % eye drops may be given twice per hour, and preservative-free artificial tears instilled every 1–2 h. Systemic ascorbate may also be considered to augment depleted amounts (Table 16.5). The clinician should be careful of potential risks in the pediatric population and also be aware of the recommended daily allowance in children (see Table 16.4). Some oral formulations of vitamin C products contain aspartame, which is metabolized to phenylalanine and must be avoided (or used with caution) in patients with phenylketonuria [26]. Liquid formulations of vitamin C must be used with great caution in neonates, as they may contain

Table 16.5 Dosing of acetazolamide and tetracycline/doxycycline in pediatric patients

Medication	Younger age group	Older age group
Diamox: maximum daily dose 1000 mg/day	Children < 12 years: 10–30 mg/kg/day • Immediate release tablet: Divided doses every 6–8 h • Extended release capsules: Divided doses twice daily	Children (≥12 years) and Adolescents: 15–30 mg/kg/day • Immediate release tablet: Divided doses every 6–8 h • Extended release capsules: Divided doses twice daily
Tetracycline	Children > 8 years: 25–50 mg/kg/day in divided doses every 6 h; not to exceed 3 g/day	Adolescents and Adults: 250–500 mg/dose every 6–12 h
Doxycycline	Children ≥ 8 years: Oral/IV 2–4 mg/kg/day divided every 12–24 h Maximum daily dose: 200 mg/day	Adolescents and Adults: Oral/IV 100–200 mg/day in 1–2 divided doses

Please note: the use of these medications in pediatric patients for ocular purposes is off-label, but the suggested dosing is based on the safe pediatric dosing. Please consult with your pharmacist as needed
From: Lexicomp—pharmacy database, with permission. Available: http://www.lexi.com/institutions/online.jsp?id=databases

sodium benzoate, a metabolite of benzyl alcohol [26]. Large amounts of benzyl alcohol have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates with metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction, hypotension, and cardiovascular collapse [26].

Cycloplegic agents cause pupillary dilation and paralysis of the ciliary muscle of the eye. They should be considered for patient comfort and for minimizing the formation of synechiae with a constricted pupil. Cycloplegic agents include: atropine, scopolamine, homatropine, cyclopentolate, and, to a lesser extent, tropicamide [17]. The average duration of action is 2–6 h for tropicamide, 6–24 h for cyclopentolate, 2–7 days for scopolamine, and 1–2 weeks for atropine [17]. Preterm infants are especially vulnerable to toxicity from these cycloplegic eye drops. Systemic atropine toxicity may result from topical atropine. Infants with Down syndrome have both increased sensitivity to cardiac effects and mydriasis to atropine. A single drop of a 0.5 % solution in each eye approaches the toxic dose of atropine for infants. Caution should also be exercised in patients with pyloric stenosis or hiatal hernia associated with reflux esophagitis; avoid use of cyclopentolate in patients with paralytic ileus or severe ulcerative colitis. Cyclopentolate is a commonly used cycloplegic agent in children in the clinic, and its adverse systemic effects include psychosis, seizures, and gastrointestinal disturbances, including necrotizing enterocolitis in premature infants [27].

Cyclomydril, a combination of cyclopentolate 0.2 % and phenylephrine 1 %, is a combination of lower drug concentrations than what is commercially available separately [17]. If an infant or child shows evidence of severe cycloplegic toxicity, the treatment is physostigmine 0.05 %. Children with spastic paralysis or brain damage are at increased risk for rapid rise in body temperature due to suppression of sweat gland activity.

Tetracyclines have been shown to offer protection against corneal melt through the proposed mechanism of matrix metalloproteinase inhibition, suppression of collagenases, and scavenging of reactive oxygen species. However, they are contraindicated by the American Academy of Pediatrics in children younger than 8 years old due to the potential for permanent discoloration of teeth and enamel hypoplasia [28].

If the patient has an elevated intraocular pressure, aqueous suppression is the first choice. Punctal occlusion may be performed to reduce systemic absorption of eye drops. It is important to remember to avoid the use of brimonidine, and other alpha-2 agonists in children younger than 2 years, given the potential for central nervous system depression through decreased sympathetic outflow [14]. The use of alpha-2 agonists may be considered with caution if all other alternative therapies have been exhausted in children above this age range. Parents should be warned to look for signs of lethargy, especially in those patients younger than 6 years [29]. The weight of the child is an important factor, and the clinician should avoid use of alpha-2 agonists in children weighing less than 20 kg [29].

The use of beta-adrenergic antagonists should be considered in cases of elevated intraocular pressure. Timolol is generally well-tolerated, with the gel-forming solutions preferred over the timolol eye drops due to lower systemic absorption from the gel formation in pediatric patients [29]. Timolol and betaxolol are FDA approved for pediatric patients younger than 6 years. However, potential side effects from systemic absorption include: apnea, hypotension, bradycardia, bronchospasm, masked hypoglycemia in patients with diabetes, and depression [17]. Plasma timolol concentrations in children after topical use can be significantly higher than systemic therapeutic levels, and the lowest possible concentration and dosage (timolol 0.1 % or 0.25 %) should be used. Timolol should be avoided in patients with cardiac arrhythmias and asthma/bronchospasm. Betaxolol is a cardioselective beta blocker, with fewer undesirable pulmonary effects than timolol and it may be safer for use in children with asthma or other chronic lung diseases [17].

Carbonic anhydrase inhibitors are potent inhibitors of aqueous production and should be avoided in patients with

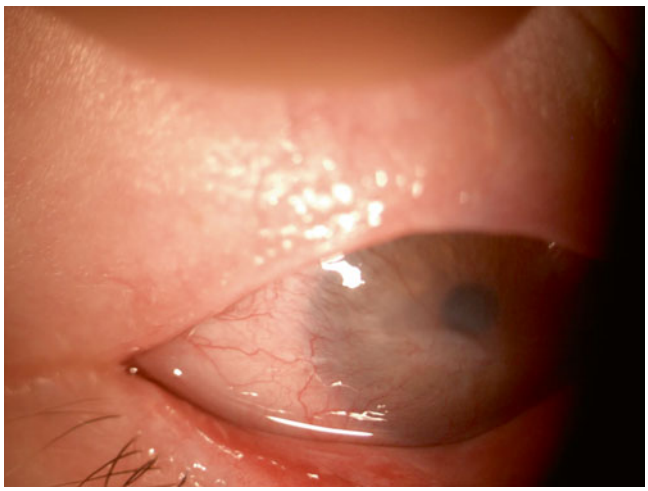

Fig. 16.6 Corneal opacification is the most frequent complication of chemical injury. A vascular pannus extends toward the center cornea

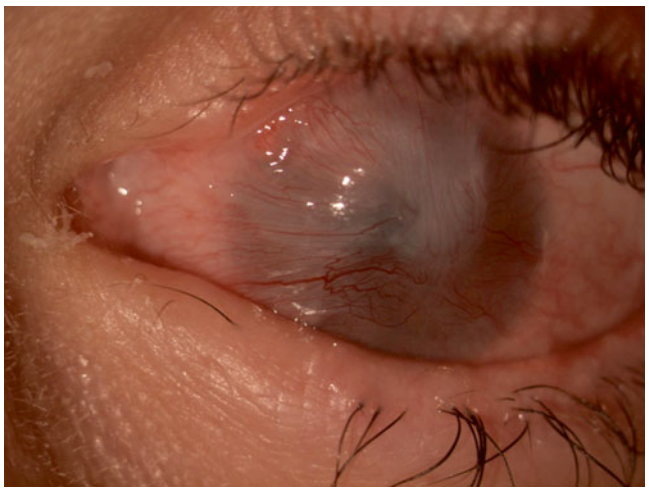

Fig. 16.7 Limbal stem cell deficiency leads to conjunctivalization of the corneal surface

sulfonamide allergies (Table 16.4). Dorzolamide, the topical solution, is relatively well-tolerated. Oral acetazolamide is contraindicated in patients with severe liver or kidney disease, adrenal failure, hypokalemia/hyponatremia, or hyperchloremic acidosis [29]. Also, a high dose does increase diuresis and may increase the incidence of CNS depression. For pediatric patients who will be on the medication longer than a few days, the ophthalmologist may wish to co-manage with a pediatrician, as this medication has been associated with tachypnea, lethargy, metabolic acidosis, and growth retardation in children receiving chronic therapy (possibly due to chronic acidosis) [17]. Rare instances of Steven-Johnson syndrome and blood dyscrasias have also been reported [29]. This medication should not be given to patients on aspirin as salicylate inhibits plasma binding of acetazolamide (leading to higher free acetazolamide levels) and inhibits renal tubular secretion of acetazolamide leading to toxicity. Also, given the prevalence of patients on amphetamines for attention deficit disorder, the clinician should also be aware that oral acetazolamide may decrease the excretion of this medication.

Sequelae and Surgery

Patients will require close follow-up after initial injury, as they are vulnerable to possible sequelae such as: potential corneal ulceration/perforation, corneal scarring, LSCD, conjunctival scarring/symblepharon, dry eye, secondary open angle glaucoma, and exposure due to lid malposition from cicatricial changes.

In the acute phase of recovery, thinning of the cornea may be addressed with tissue adhesive if there is still evidence of active inflammation. Tectonic grafting may be necessary in the setting of a perforated corneal ulcer.

The most common sequela after chemical injury is central corneal opacification (Fig. 16.6). Phototherapeutic keratectomy, while not FDA approved, may be performed for older children with residual scarring if it is limited to the superficial anterior stroma (less than 100 μm), and if the cornea is avascular and of sufficient thickness. Cornea transplantation should be delayed until the ocular surface has been optimized and inflammation has been controlled. This must be balanced by the concern for deprivation amblyopia. Unique to the pediatric population is the concern of deprivation amblyopia in cases of severe corneal scarring. Once the ocular surface stabilizes at approximately 4–8 weeks, lamellar or penetrating keratoplasty should be considered in those patients whose age and severe residual corneal scarring leaves them at risk of deprivation amblyopia. The decision could be extrapolated from the literature on congenital cataract studies [11]. It is useful to remember that while the child's cornea reaches adult size by 2 years of age, the surgery is technically more challenging than in adults due to low scleral rigidity and corneal pliability, and smaller graft sizes are generally required [30]. Corneal transplantation in children under the age of 2 is associated with rapid neovascularization, especially along the sutures. Eye rubbing may lead to epithelial defects, vascularization, and mucus accumulation.

Corneal transplantation is challenging in the pediatric population. There is a high incidence of allograft rejection, reoperation, and complications compared to corneal transplantation in adults. Examination for epithelial problems and signs of rejection (rejection lines, etc) aids in determining the cause of previous failure and in planning for repeat surgery. Even if graft failure does not occur after penetrating keratoplasty, children can mount an exuberant inflammatory response and clearing of the graft may take several months, prolonging the period of deprivation amblyopia. In addition,

significant irregular astigmatism in the corneal graft (which is not uncommon due to the difficulty of suture placement in young, soft eyes) may result in refractive amblyopia [30].

Some surgeons favor the use of keratoprosthesis in pediatric patients with previous graft failures. Boston keratoprosthesis has generally been used in the setting of a failed corneal graft with poor prognosis for further grafting. Potential issues include the need for long-term use of a bandage contact lens and topical antibiotics to prevent tissue necrosis and secondary infection [31]. Complications of a keratoprosthesis placement include infection, corneal melt, glaucoma, as well as formation of a retroprosthetic membrane [32]. Monitoring for postoperative glaucoma is particularly challenging with no reliable method of checking intraocular pressure to date. Some surgeons will place a tube shunt at the time of keratoprosthesis placement in anticipation of this problem.

Oftentimes, severe corneal scarring is accompanied by LSCD (Fig. 16.7). There are a number of methods to try to address LSCD. A popular surgical intervention for unilateral LSCD is conjunctival limbal autograft. It involves the excision of 90–240 degrees of conjunctival limbal tissue from the contralateral healthy eye. Improved ocular surface stability has been reported in 80–100 % of patients undergoing limbal autograft [32]. Potential complications of this procedure to the donor eye include partial LSCD and filamentary keratitis. Allografts may also be used. The downside of allogenic limbal stem cell transplantation is the need for systemic immunosuppression.

Sejpal et al. investigated the clinical outcomes of autologous ex vivo cultivated limbal epithelial transplantation (CLET) in children with unilateral LSCD after ocular surface burns, using a standardized xeno-free protocol of limbal cell culture [11]. This technique avoids the need for systemic immunosuppression. However, post-operative inflammation may play a significant role in the outcome, and higher rates of failure were found in children as compared to other studies of CLET in adult patients [33–35]. In the study, eyes undergoing CLET at or before 4 months from the time of injury had a higher rate of failure. This was attributed to low-grade smoldering inflammation, and the authors recommend CLET be considered only after 4 months from the time of chemical injury. The authors also found that there was a high rate of graft failure and microbial keratitis in eyes where a simultaneous lamellar or penetrating keratoplasty was performed [11]. The authors, therefore, recommend that in eyes where tectonic support in the form of keratoplasty is anticipated that a 2-stage procedure with volume augmentation by keratoplasty be performed initially followed by CLET. Simple limbal epithelial transplantation, a combined modification of the CLET and conjunctival limbal autograft techniques, has been recently described as an alternative [36]. A 2×2 mm strip of donor limbal tissue is excised from the healthy contralateral eye, and cut into 8–10 pieces [36]. These small limbal transplants are then circularly distributed and fixed to amniotic membrane glued to the cornea of the diseased eye, sparing the visual axis [36]. The long-term outcomes are pending.

Eyelid surgery may be necessary if the healing of the ocular surface is inadequate. Surgical interventions such as symblepharon release, tarsorrhaphy (partial or complete depending on the patient's age), oral mucosa graft, and fornix reconstruction should be considered as necessary.

Conclusions

Chemical ocular surface injury in children requires early recognition and prompt treatment. Pediatric patients constitute a unique population, vulnerable to deprivation amblyopia and to potential toxicity from medications. Management of the sequelae of chemical injury poses additional technical obstacles to the surgeon. However, with prompt proper management and follow-up, the physician is able to limit damage to the ocular tissue and to help preserve vision.

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Anterior Segment Trauma (Non-chemical)

17

Michael Eric Gray

Abstract

Pediatric ocular trauma is common, and open globe injuries in particular can have poor visual outcomes. Efforts to improve visual outcomes include prompt recognition and surgical repair of open globe injuries with diligent follow-up for complications. Visual rehabilitation includes treatment of amblyopia, which is common after surgical repair. This chapter will present suggestions on how to recognize pediatric open globe injuries, considerations for ancillary testing, antibiotic prophylaxis, and follow-up care. An example of a pediatric perforating eye injury will be presented, including the child's presentation, surgical repair, and follow-up care.

Keywords

Ocular trauma • Open globe • Post-traumatic endophthalmitis

The Problem

Pediatric ocular injuries are common, accounting for 35 % of the 2.4 million eye injuries that occur in the USA each year. In 2000, pediatric eye injuries resulted in an estimated 7500 hospitalizations, with males accounting for over two-thirds of the cases. Open globe or perforating injuries (full-thickness wounds of the eye wall) accounted for 20.9 % of these hospitalizations [1]. Open globe injuries predictably have a worse visual outcome compared to closed globe injuries. Studies of visual outcomes in children after open globe injuries vary, with estimates ranging from 21 % to 51 % having final acuity of>=20/40. Poor visual outcomes can be related to endophthalmitis, retinal tears/detachment, hemorrhage, and location of wound. A recent Canadian study of 131 cases of pediatric (<18 years) open globe injuries noted slightly better final acuity of>=20/40 in 56.5 % of cases [2]. Seventy-five percent of the children were males, 45 % were<=5 years, and the child's home was the most common location where injuries occurred. Factors associated with worse final visual acuity in this study included age <5 years, retro-limbal involvement, wound length>=6 mm, and blunt force injuries.

One useful tool that provides prognostic information in the setting of ocular injury is the Ocular Trauma Score (OTS) developed by Kuhn et al. [3]. The OTS assigns a raw point value for initial visual acuity and then subtracts points using other diagnoses at initial exam (Table 17.1). Although this scale is not specific to pediatric patients and therefore numerical values cannot be used to predict long-term visual acuity, this score may be useful when counseling patients and families at the time of injury as to prognosis. A higher score indicates less severe injury and likely better visual prognosis.

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Evaluation of the Child with a Suspected Open Globe Injury

In any case of pediatric ophthalmic trauma, there could be other more pressing bodily injuries that take management precedence over ocular trauma. Once other injuries are excluded or deemed not life-threatening, attention should be directed toward obtaining a detailed history of the injury in order to rule out penetrating or perforating injury. A penetrating wound passes into a structure, whereas a perforating wound passes through a structure. For example, a full-thickness corneal laceration perforates the cornea and penetrates the eye. Key historical inquiries include: mechanism of injury (blunt force, motor-vehicle accident, projectile, etc.), presence of eye protection at the time of injury (grinding or sharpening work which can cause small metallic projectiles), timing of injury, velocity of projectile, if the injury was witnessed, and when the child last had anything to eat or drink. Prior ocular history, medical history, and vaccination status (tetanus) are important to obtain as well.

Table 17.1 The Ocular Trauma Score [3]

Variables	Raw points
Initial vision	
NLP	60
LP/HM	70
1/200–19/200	80
20/200–20/50	90
≥20/40	100
Rupture	−23
Endophthalmitis	−17
Perforating injury	−14
Retinal detachment	−11
Afferent pupillary defect	−10

The higher the score, the better the overall visual prognosis

OTS The Ocular Trauma Score

The ophthalmological exam should include measurement of visual acuity, pupil exam with documentation of any relative afferent pupillary defect, external exam of ocular adnexa, and scrutinization for signs of open globe injury. Obvious signs of an open globe include exposed uvea or vitreous, foreign body seen within (Fig. 17.1a, b) or protruding from the eye, and positive Seidel test. Seidel testing is an important part of the examination for possible corneal lacerations. To perform this test, a wet fluorescein strip (or concentrated drop of fluorescein) is applied to the wound ("painting" the area), and a blue light is used to illuminate the ocular surface. The test is positive if clear aqueous is visualized streaming through the concentrated color of the dye. At times the leak can even be seen without the blue light. Less obvious signs suggestive of open globe injury include full-thickness eyelid injuries, conjunctival lacerations or hemorrhage, shallow anterior chamber, iris damage or "peaked pupil" (peak points toward area of corneal, limbal or scleral rupture), hypotony, anterior capsule defect or focal cataract, and retinal tears/detachment (Figs. 17.2 and 17.3).

Some of these history and physical exam elements can frequently be difficult to obtain, especially in young or uncooperative children. If ocular injury is suspected, a brief sedated exam in the emergency room can be performed with the help of emergency department physicians. In cases of suspected open globe injury, however, the ophthalmologist or the emergency physician should avoid using drops or intravenous medications that might increase intraocular pressure, or other maneuvers that might place pressure on the globe and lead to expulsion of intraocular contents (scleral depression, forced duction testing, and careful use of lid speculums). If suspicion on external exam is high for open globe injury but detailed examination is impossible, it might be best to defer further manipulation until the child is in the operating room. In such cases, after initial exam is complete, a metal or other stiff shield should be taped over the eye to the forehead and cheek while awaiting the OR. The patient

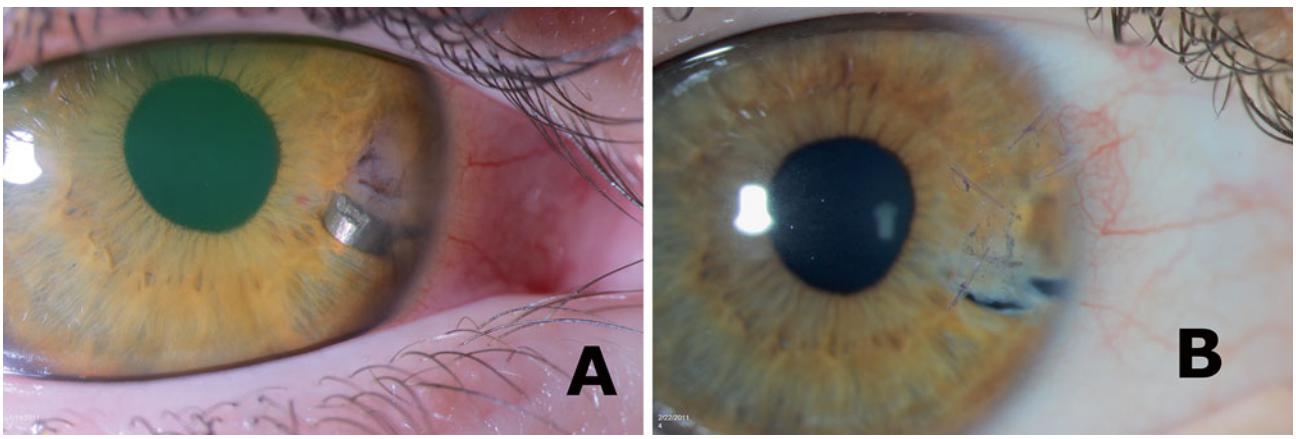

Fig. 17.1 (**a**) Pencil lead has penetrated the cornea and is embedded in iris, in front of lens. (**b**) Same case as in 1a after removal of foreign body (5 mm in length) and corneal wound suture. The patient did not develop a cataract. *Photo courtesy of Elias I. Traboulsi, MD, MEd*

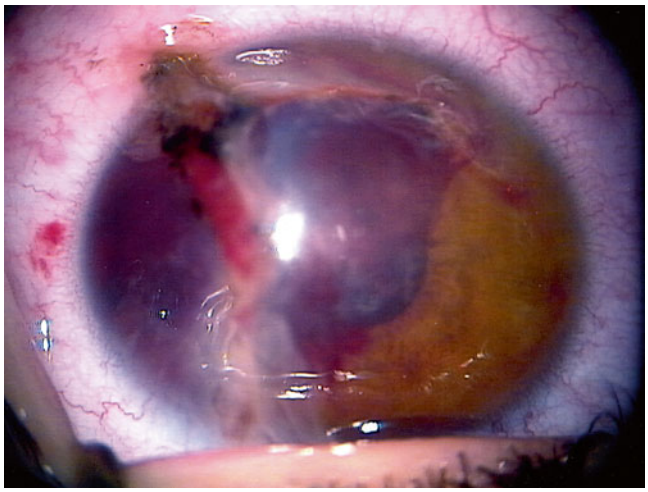

Fig. 17.2 Example of an open globe injury in a 4-year-old child due to a stick. There is a shelved C-shaped corneal laceration. Note peaked pupil, and iris and vitreous prolapse through the wound

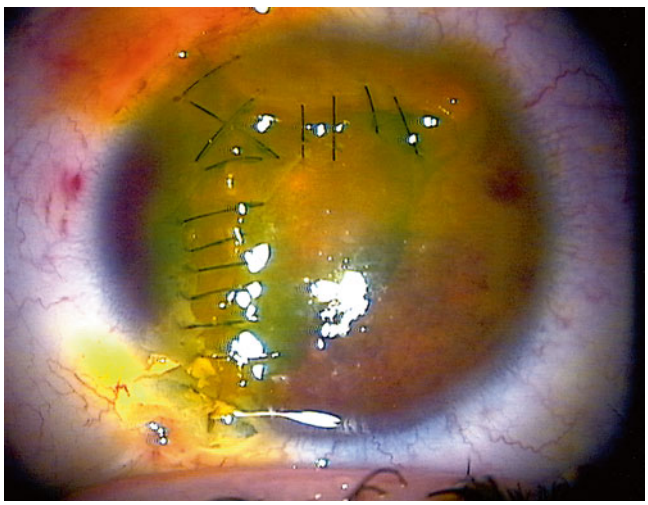

Fig. 17.3 Same eye from Fig. 17.1a immediately at end of repair. Multiple nylon sutures are in place. *Yellow coloring* is from Seidel testing at the end of the case to ensure watertight closure

should remain NPO while the emergency department provides pain control, nausea control, intravenous antibiotics, and tetanus prophylaxis if indicated.

Ancillary Tests

In many cases it can be advantageous to obtain imaging studies to assist in diagnosis and operative planning. When there is concomitant head trauma in addition to orbital/globe trauma, imaging is essential. In nearly all cases in which there is head and orbital trauma, computed tomography (CT) scanning is the preferred modality. CT scan is generally readily available, fast, and can be performed on patients who are connected to life support equipment. In contrast, magnetic resonance imaging (MRI), which requires more time, would be contraindicated in suspected cases of intraocular metallic foreign bodies which can accompany open globe injuries. CT scanning, however, should not be the only diagnostic study used to diagnose an open globe. A study by Joseph et al. found a sensitivity and specificity of 75 % and 93 %, respectively, in diagnosing open globe injury by CT, in the absence of clinical findings [4]. The most common finding in true open globe cases was scleral deformity, followed by altered anterior chamber depth, altered lens position, and vitreous hemorrhage. There were cases, however, of open globe injuries with no positive radiographic findings. Distortion of the vitreous space, absence of the lens, and vitreous hemorrhage were all associated with poor visual outcomes. If possible, the clinician should request thin cuts through the orbits with axial and coronal views to improve resolution and detection of subtle abnormalities. Plain film X-rays can also be used for evaluation of foreign bodies, but generally are not as useful as CT scans.

Table 17.2 Materials for operative repair of open globe

• Microsurgical instruments (ideally an "anterior segment" tray)
• Suture
– 8-0, 9-0, and 10-0 nylon (or silk if nylon not available)
– 8-0 vicryl (polyglactin) suture or similar for conjunctival closure
– 6-0 vicryl (polyglactin) in case extraocular muscles need to be disinserted and reattached
• Ophthalmic viscosurgical device—have multiple tubes ready
• Antibiotics (topical, subconjunctival, and/or intravitreal)
• Eye patch and shield
• Patient consent

Preparation for the Operating Room

Pediatric open globe injuries, as in adults, require prompt treatment for optimal results. Frequently such cases occur after office hours and in the middle of the night, so the ophthalmic operating team may not be available to assist in the procedure. In this situation, it can be helpful to discuss with operating room personnel prior to the patient arriving to ensure necessary supplies are readily available (Table 17.2). The immediate surgical goals include a watertight closure of the wound and restoration of normal anatomy as best as possible. In general, other procedures such as vitrectomy, cataract extraction, and iris repair, can be postponed until a later time. When obtaining informed consent from the patient's guardians, it is important to make sure they understand the goals of the initial procedure and the possible need for additional surgery in the future. A frank discussion regarding visual prognosis, risk of infection, and other possible complications is important for an urgent

trauma case such as an open globe. Techniques for repair of lacerations are beyond the scope of this text.

Antibiotic Prophylaxis

Endophthalmitis is one of the most severe complications of ocular trauma. Reports have suggested 3.4 % of open globe injuries are complicated by endophthalmitis [5]. The incidence is higher in the presence of an intraocular foreign body or if closure is delayed for 24 h or more. In children, studies of post-traumatic endophthalmitis rates are widely variable [6]. *Streptococcus* species are the most common responsible organisms, followed by *Staphylococcus* and *Bacillus*. Although not studied extensively, visual prognosis is predictably poor in cases of post-traumatic endophthalmitis, with a suggestion that *Bacillus* species are particularly devastating. Therefore, most surgeons use some form of antibiotic prophylaxis in cases of open globe injuries, although large randomized studies are lacking [6]. Options for prophylaxis include systemic, topical, subconjunctival, and intravitreal antibiotics. Various combinations and durations of systemic antibiotics have been proposed. A common regimen is comprised of a cephalosporin (e.g., cefazolin) in combination with an aminoglycoside (e.g., gentamicin). Others recommend fluoroquinolones due to their generally excellent broad antimicrobial coverage and high levels of intraocular penetration. Typical duration of treatment includes 1–3 days of intravenous antibiotics, followed by 7–10 days of oral antibiotics. A longer duration of intravenous antibiotics in the setting of an intraocular foreign body can be considered. Note, however, that large scale investigations of the efficacy of systemic antibiotics are lacking, although in a study of 675 patients, all of whom received intravenous and topical antibiotics, the overall incidence of endophthalmitis was very low at 0.9 % [7]. Intravitreal antibiotic prophylaxis is more controversial. Some studies have only shown a benefit in cases with an intraocular foreign body [6, 8]. One regimen could include intravitreal vancomycin and ceftazidime (Table 17.3). We typically treat our pediatric cases with systemic (intravenous followed by oral), subconjunctival, and topical antibiotics. In certain cases we use intravitreal antibiotics (foreign body, contaminated injuries, delayed closure, large wounds).

Table 17.3 Ocular medication concentrations

	Drug	Concentration
Intravitreal	Cefazolin	2 mg/0.1 ml BSS
	Ceftazidime	2.25 mg/0.1 ml BSS
	Vancomycin	1 mg/0.1 ml BSS
	Amphotericin	5 mcg/0.1 ml sterile water
Subconjunctival	Cefazolin	100 mg/0.5 ml NS
	Ceftazidime	50 mg/0.5 ml NS
	Dexamethasone	2 mg/0.5 ml (straight drug)
	Gentamicin	20 mg/0.5 ml (straight drug)
	Triamcinolone	20 mg/0.5 ml (straight drug)

mg milligrams, *mL* milliliters, *BSS* balanced salt solution, *NS* normal saline

Post-Operative Care

Typical post-operative regimens include antibiotic prophylaxis as mentioned above, topical steroid drops, and topical cycloplegic drops. Duration of treatment depends on the clinical response to the medical regimen. In addition to the risk of endophthalmitis, other sequelae that must be identified and treated include traumatic cataract, hyphema, vitreous hemorrhage, iris damage, retinal tears and detachment, and amblyopia. In cases of severe corneal scarring causing irregular astigmatism, a rigid gas permeable lens can be considered for visual rehabilitation, although some cases might eventually benefit from corneal transplantation. Sutures will need to be removed within several weeks to a few months, depending on several factors including number of sutures, extent of wound, and likelihood of follow-up. Loose sutures might need to be removed early, and in many pediatric cases suture removal is done in stages, removing a few at a time. An examination under anesthesia can be performed at the same time as suture removal, providing a good opportunity to examine the child for secondary complications. Deprivation amblyopia can be a major concern, especially in younger patients, so initiating early penalization therapy of

Case Example

A 3-year-old child was evaluated in the emergency department for possible open globe injury in the left eye after accidentally running into a steak knife held by her younger brother. Examination revealed blink to light vision OU (poor cooperation for further testing), and an irregular, sluggish left pupil but no RAPD. There was a left horizontal full-thickness sclero-corneal laceration that was Seidel positive (Fig. 17.4). The anterior chamber was formed, but fundus examination was not possible due to poor view. The patient was taken urgently to the operating room for repair.

During surgery, a conjunctival peritomy was made to explore the full extent of the scleral portion of the wound. Exposed vitreous was trimmed flush with the cornea. The limbus was closed first with 9-0 nylon suture, followed by repair of the corneal laceration with 10-0 nylon sutures. Lastly, the scleral portion of the laceration was closed with 8-0 nylon sutures.

(continued)

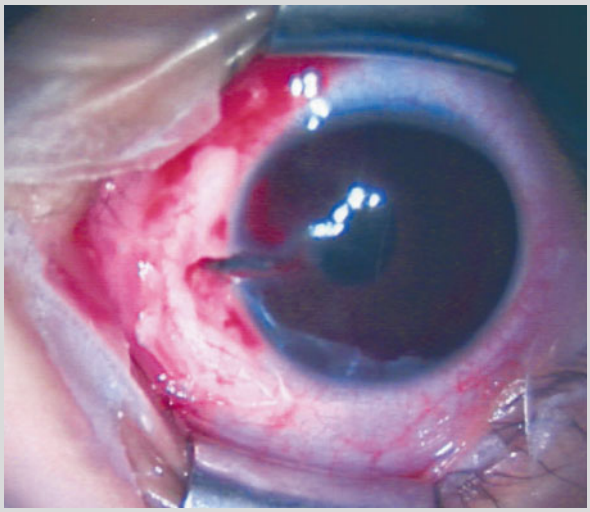

Fig. 17.4 Full-thickness corneoscleral laceration secondary to steak knife injury. The anterior chamber appears shallow and iris is peaked toward the wound

The conjunctiva was closed with 8-0 polyglactin sutures. The wound was Seidel negative at the conclusion of the procedure. Intravitreal injections of cefazolin and vancomycin were given. The patient was treated in the hospital with IV antibiotics that were transitioned to oral antibiotics at discharge 1 day later. Topical antibiotic, steroid, and cycloplegic drops were also used. The patient has been followed since the injury for 1 year, and has been treated with a contact lens for irregular astigmatism, patching therapy for amblyopia, and focal wall-off laser for a self-demarcated macular sparing retinal detachment. Her most recent visual acuity in the left eye was 20/40.

the sound eye is indicated. Failure to recognize and treat amblyopia can result in poor visual outcomes even in children who had "successful" repair with good restoration of ocular anatomy [9]. Spectacle correction for refractive error is also vitally important, and protective lenses should be ordered.

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Part V

Lens/Cataract

Cataracts

18

Laura L. Hanson and Virginia Miraldi Utz

Abstract

Infantile cataracts are important treatable causes of childhood blindness worldwide. While a majority of infantile cataracts are either idiopathic or familial and isolated, some can be associated with systemic conditions including congenital infection, teratogenic exposures, metabolic, and genetic syndromes. In some cases, cataracts may be the presenting signs of these conditions. In general, unilateral cataracts occur in isolation and do not require additional evaluation for systemic disease. Similarly, bilateral autosomal dominant familial cataracts are typically not associated with systemic disease and do not require additional evaluation. Children with bilateral cataracts who do not have a known family history of heritable cataracts require a thorough evaluation for recognized associated conditions, such as chromosomal abnormalities, metabolic disorders, and infectious etiologies. Treatment is dictated by the degree of visual significance of the cataract and frequently involves surgical removal of the opacified lens.

Keywords

Congenital cataract • Infantile cataract • Lens opacity • Amblyopia • Metabolic disorder

The Problem

It is estimated that approximately 1 in 2,500–3,000 infants in the USA are born with a visually significant cataract [1], and cataracts are an important treatable cause of childhood blindness worldwide [2, 3]. The varied presentation, lenticular location, and severity of infantile and developmental cataracts may present a diagnostic challenge to the clinician. Cataracts can be congenital or acquired, bilateral or unilateral, sporadic or inherited, and may have important systemic associations including chromosomal abnormalities, craniofacial and musculoskeletal syndromes, metabolic disorders, maternal infections, or exposure to teratogens (Table 18.1). In addition, location in the lens and morphology of the opacities may be suggestive or diagnostic of a specific disease (Table 18.1).

Early intervention is required so that visually significant cataracts are removed and amblyopia is prevented. Lens opacities that are present within the first 2–3 months of life

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Table 18.1 Inherited causes of cataracts

	Specific disorders	Clinical and/or Diagnostic Pearls for Select Disorders
Chromosomal abnormalities	Trisomy 8	
	Trisomy 13	
	Trisomy 18	
	Trisomy 21	
	Turner Syndrome	
Renal Disorders	Alport Syndrome	– Usually X-linked inheritance – Genes encoding Type IV collagen (*COL4A3, COL4A4, COL4A5*) – Audiology evaluation needed (sensorineural hearing loss) – Renal function evaluation – Anterior lenticonus – Paramacular flecks
	Lowe Syndrome	– X-linked inheritance – Inositol polyphosphate 5-phosphatase OCRL-1 activity in skin fibroblasts (<10 % activity of enzyme) – Type 2 renal tubular acidosis – Associated with infantile glaucoma – Prolonged or delayed bleeding after surgery
Metabolic Disorders Associated with Enzyme Deficiencies	Galactosemia	– Erythrocyte galactose-1-phosphate uridyl transferase (GALT) activity, erythrocyte galactose-1-phosphate concentration, urine galactitol – GALT molecular genetic testing – "oil droplet" cataracts
	Galactokinase deficiency	
	Fabry disease	– X-linked inheritance (*GLA* mutation) – Lysosomal disorder, alpha-galactosidase A deficiency (leukocytes, plasma) – Cardiac, renal, and angiokeratomas of skin, acroparesthesias – Cornea verticillata, conjunctival and retinal vasculature tortuosity
	Refsum disease	– Elevated serum phytanic acid levels secondary to AR mutations in *PHYH* and *PTS2* – Anosmia, hearing loss, peripheral neuropathy, ichthyosis, retinitis pigmentosa
	Wilson disease	– Copper deposition, low ceruloplasmin concentration – Sunflower cataracts (brownish-yellow deposits in the subcapsular cortex) – Kayser–Fleischer rings in cornea, liver disease, neurologic abnormalities
	Hypoparathyroidism	
	Cerebrotendinous Xanthomatosis (CTX)	– AR condition leading to bile acid deficiency. Infantile diarrhea and bilateral juvenile cataracts are the earliest manifestations. – Cholestanol accumulates in the lens (cataracts), CNS (leading to neurologic decline, dementia, seizures), and tendons (xanthomas). Treat with chenodeoxycholic replacement
Congenital Infections	Toxoplasmosis	– Toxoplasma gondii IgM and IgG
	Other (syphilis)	– VDRL or RPR; FTA-Ab or MHA-TP
	Rubella	– Rubella IgM and IgG
	Cytomegalovirus	– Cytomegalovirus IgM and IgG
Ocular Anomalies	Anterior segment dysgenesis	
	Aniridia	– Sporadic aniridia requires systemic and/or molecular evaluation for Wilms' Tumor (*WT1*)
	Persistent fetal vasculature	
	Microphthalmos	
Musculoskeletal Disorders	Myotonic dystrophy	– "Christmas tree" cataracts (refractile polychromatic opacities in the deeper cortex of the lens)
	Albright Syndrome	
Connective Tissue Disorders	Marfan Syndrome	– Refer to cardiology to evaluate for aortic aneurysm

(continued)

Table 18.1 (continued)

	Specific disorders	Clinical and/or Diagnostic Pearls for Select Disorders
	Homocystinuria	– High risk of thromboembolic events
	Ehlers–Danlos	
	Weill–Marchesani	
	Stickler Syndrome	
Craniofacial Malformations	Hallermann–Streiff Syndrome	
	Rubinstein–Taybi Syndrome	

AR autosomal recessive, *CNS* central nervous system

tend to be the most amblyogenic [4]. Amblyogenic cataracts require surgery within the first 6 weeks of life for optimal visual recovery, while bilateral cataracts may be removed within 10 weeks [5–7].

Evaluation

Screening for pediatric cataracts begins with an examination of the red reflex, usually performed by the child's pediatrician. Babies with an asymmetric or abnormal red reflex should be evaluated by a pediatric ophthalmologist. If a lens opacity is identified, its visual significance is then determined. As a general guideline, those that are small (less than 3 mm in diameter) and anterior, or of insufficient density to interfere with vision, do not require surgical intervention (see Chap. 19). Many infants less than 2 months of age have not developed central fixation yet, hence determination of visual significance will depend largely on the size and density of the opacity and the quality of the red reflex and its obscuration by lens opacities. In older pre-verbal children, findings that indicate significant interference with vision include abnormalities in fixation behavior and preference, decreased acuity based on preferential looking techniques such as Teller acuity card testing, and the objection to occlusion of the uninvolved eye in unilateral cases. Clues that are indicative of significant visual impairment (more likely to be associated with moderate to severe amblyopia) include strabismus in unilateral cataract cases and nystagmus in unilateral and bilateral cataracts [8].

The location and morphology of the cataract may aid in the diagnosis of an associated systemic disorder. For example, a sunflower cataract appears as small yellowish-brown opacities in the anterior and posterior subcapsular regions with petal-like spokes extending peripherally, and can be pathognomonic for Wilson disease, a disorder of copper metabolism [9] (Table 18.1). Similarly, in patients with classic galactosemia, intracellular accumulation of galactose and other by-products leads to increased osmotic pressure and fluid influx causing progressive opacification in the nucleus and cortex resulting in an "oil drop" appearance on retroillumination (Table 18.1).

A thorough ophthalmic evaluation is indicated in every patient with any lens opacity and should include slit-lamp examination, and measurement of corneal diameter and intraocular pressure. Examination of the retina and optic nerve should be performed, unless the density of the cataract precludes visualization of posterior pole. In such instances, B-scan ultrasonography can help identify possible vitreoretinal abnormalities, such as persistent fetal vasculature or an intraocular tumor. Cycloplegic refraction should be carefully performed. Some cataracts (e.g., anterior polar cataracts) may not be visually significant by density and size; however, they may induce optical distortions and may be associated with anisometropia, leading to amblyopia if not recognized and appropriate refractive correction prescribed.

A detailed history, including birth and developmental history, past medical and family history, aids in determining if an associated systemic condition is present. Children should also have a complete physical examination by their pediatrician or family doctor (see Fig. 18.1).

Systemic Evaluation

The identification of bilateral cataracts in children who do not have an autosomal dominant, recessive, or X-linked family history of isolated cataracts should prompt additional evaluation with laboratory testing (Fig. 18.1). This includes testing the urine for reducing substance (after ingestion of milk) and amino acids, and enzyme assays to evaluate red blood cell galactokinase and galactose 1-phosphate uridyltransferase [10]. Additional blood tests should include serum calcium, phosphorus, ferritin, and glucose, as well as testing for infectious diseases such as TORCH titers, varicella titers, and VDRL/FTA antibodies for syphilis. Genetic counseling should precede any genetic testing such as karyotyping, microarray, and/or specific genetic testing (see Chap. 33). Depending on the results of the systemic work-up, referral to other subspecialists to manage the systemic manifestations of the disease may be indicated.

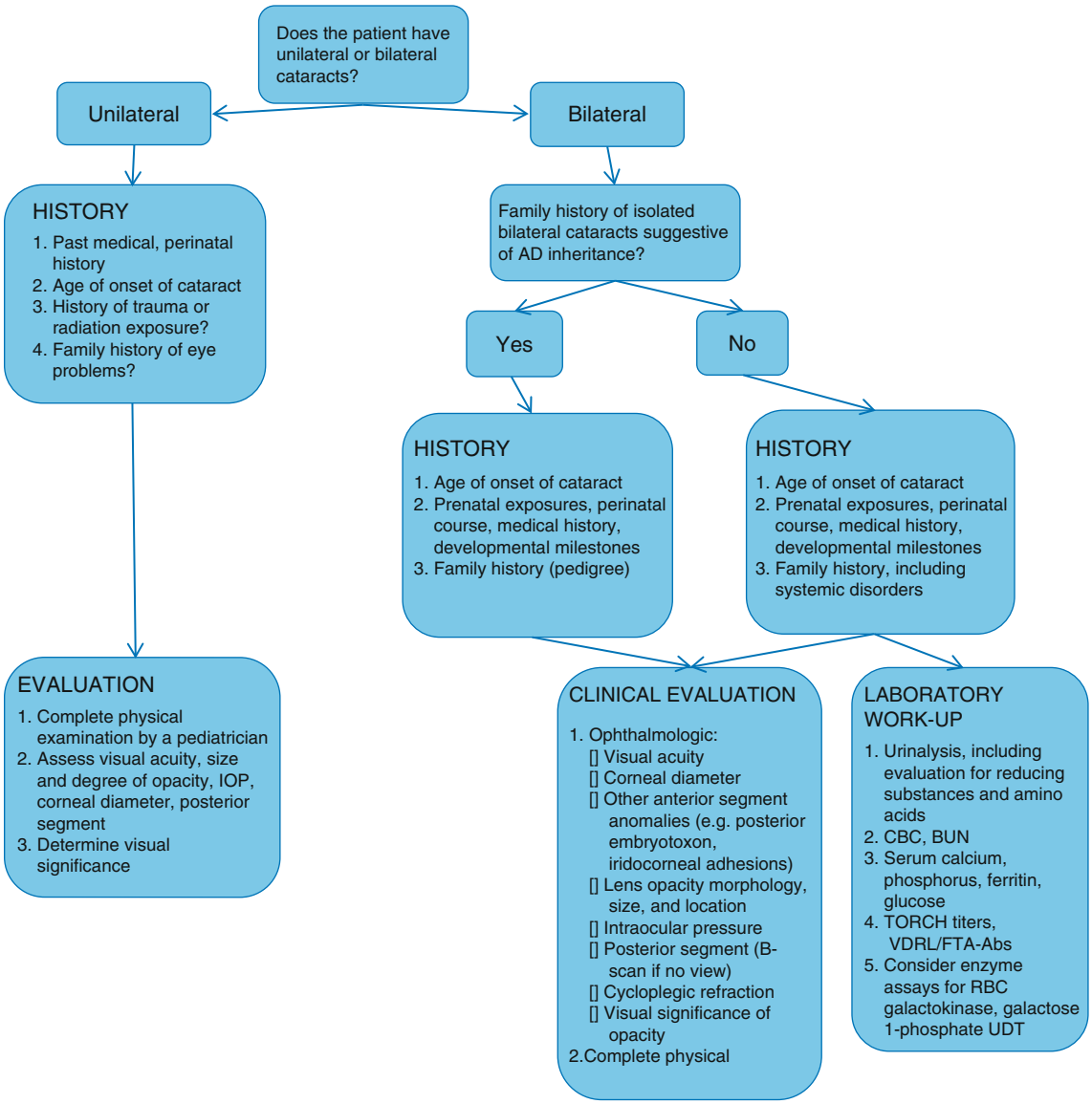

Fig. 18.1 Summary of evaluation of the infant or child with a cataract

Case Examples

The clinical history and cataract location and morphology can aid in the diagnosis of underlying etiology and guide the clinician to further systemic evaluation if indicated. Three illustrative clinical examples are described below.

Case 1 (Table 18.2)

Table 18.2 Case 1: Unilateral congenital cataract

Chief complaint: Abnormal red reflex, left eye HPI: A 10-day-old female was referred by her pediatrician for evaluation of an abnormal red reflex OS. She had an uncomplicated prenatal, perinatal, and postnatal course. Her parents deny any family history of cataract, strabismus, or amblyopia.		
	OD	OS
BCVA	F&F	F&F
Direct ophthalmoscopy	Blunted red reflex OS	
Anterior segment	Dense 3 mm central nuclear and lamellar opacity OS (Fig. 18.2)	
Fundus exam	Normal	Poor view
B-scan	Normal posterior segment structures, retina flat OS	
Assessment	Isolated visually significant cataract, OS	
Plan	Surgical removal of left lens at 4 weeks of age with aphakic correction[a]	
Clinical Course	Patient was fitted with aphakic contact lenses[b] Amblyopia treatment was initiated[c]	

[a]See Chap. 19 for evidence-based discussion of surgical indications, timing, and
[b]See Chap. 6 on prescribing contact lenses in pediatric patients
[c]See Chap. 8 on amblyopia

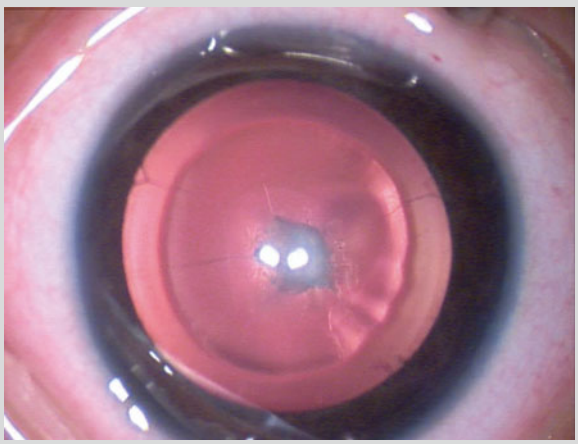

Fig. 18.2 Unilateral congenital posterior polar cataract with subcapsular cortical opacification. Photograph courtesy of W. Walker Motley III, MD

Unilateral congenital cataracts are infrequently associated with systemic disorders, and an extensive work-up is generally not warranted [11, 12]. Findings from The National Study of Congenital Cataracts in the UK found that in 92 % of unilateral cataracts, no underlying systemic association could be identified, and approximately 80 % of unilateral cataracts are considered idiopathic [2]. However, a complete medical and family history should be obtained, and all children with lens opacities should undergo a complete ophthalmic examination, including an assessment of visual function to determine visual significance of the opacity, slit-lamp examination, and posterior segment examination (Fig. 18.1). A thorough evaluation may elicit an etiology that is associated with other ocular conditions, which may have important surgical considerations. For instance, persistent fetal vasculature (PFV) is a common cause of unilateral infantile cataract. Eyes with PFV often display microcornea, thickened posterior capsule, dragged ciliary processes, and the presence of a patent hyaloid vessel ending in the posterior capsule that can be associated with intra-operative vitreous hemorrhage [13]. Other ocular abnormalities associated with unilateral cataract include posterior lenticonus, tumors of the posterior segment, such as retinoblastoma, and anterior segment dysgenesis disorders, such as Peters' anomaly [12]. Congenital rubella infection has been known to cause a unilateral cataract, but the incidence is very low [14].

Case 2 (Table 18.3)

Table 18.3 Case 2: Familial bilateral congenital cataracts

Chief complaint: Evaluate for congenital cataracts HPI: A 6-day-old female was referred by her family physician for a comprehensive exam to evaluate for congenital cataracts. Prenatal and postnatal histories were unremarkable. Family History: • Father with congenital cataracts removed at 6 weeks of age • Paternal aunt and grandfather also had congenital cataracts		
	OD	OS
BCVA	F&F	F&F
Direct ophthalmoscopy	Blunted red reflex OU	
Anterior segment	Central lens opacities 4.5 mm in diameter OU (Fig. 18.3)	
Fundus exam	Poor view	
B-scan	Normal structures, retina flat	

(continued)

Table 18.3 (continued)

Assessment	Bilateral, visually significant cataracts OU
Plan	Surgical removal of lenses at 5 weeks of age with aphakic correction.[a]
Clinical Course	Patient was fitted with aphakic contact lenses to create an over-correction of −3.00 D (For infants < 2 years of age in whom bifocals are not easily utilized, the patients are corrected for a far point of 1/3 (over-correction of −3.00) to 1/2 m (over-correction of −2.00) to allow for near/intermediate focusing.) A general rule of thumb is to have the far point at the patient's fingertips[b].

[a]See Chap. 19 for evidence-based discussion of surgical indications, timing, and intervention
[b]See Chap. 6 on prescribing contact lenses in pediatric patients

Familial congenital cataracts are usually inherited in an autosomal dominant fashion, and are nearly always bilateral, although they may be asymmetric [15]. Rarely, cataracts may follow an autosomal recessive or X-linked pattern of inheritance [16]. Therefore, children with bilateral congenital cataracts in whom there is a strong family history of isolated childhood cataracts do not require a systemic evaluation. Slit-lamp examination of the patient's family members can also be useful in identifying heritable cases, as it may reveal visually insignificant lens opacities (Fig. 18.3).

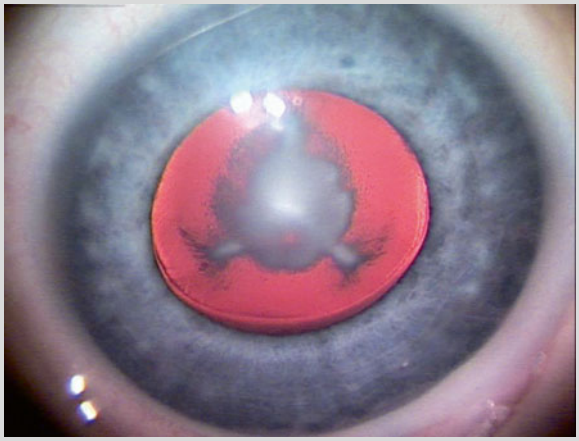

Fig. 18.3 Autosomal dominant congenital lamellar cataract with horseshoe-shaped rider opacities at 4 and 8 o'clock, right eye. A similar opacity was noted in the left eye. Photograph courtesy of W. Walker Motley III, MD

Case 3 (Table 18.4)

Table 18.4 Case 3: Cataracts with associated systemic disorders

Chief complaint: Nystagmus OU HPI: A 2-month-old male was referred by his family physician for evaluation of nystagmus with onset noted within first few weeks of life. He was born full-term via cesarean-section for failure to progress without complication. Medical history was significant for dysmorphic facies, bilateral cryptorchidism, and hypotonia.		
	OD	OS
BCVA	Central, unsteady, unmaintained	Central, unsteady, unmaintained
IOP	12 mmHg	12 mmHg
Direct ophthalmoscopy	Blunted red reflex OU	
Motility	Dissociated rotary nystagmus OU	
Anterior segment	Dense 3 mm central nuclear opacity OU (Fig. 18.4)	
Fundus exam	No view	No view
B-scan	Normal structures, retina flat OU	
Assessment	Nystagmus secondary to bilateral visually significant cataracts OU with dysmorphic facies, bilateral cryptorchidism, developmental delay, and hypotonia.	

(continued)

Table 18.4 (continued)

Plan	1. Bilateral cataracts with systemic manifestations and no family history require systemic laboratory evaluation. a. Laboratory evaluation: urinalysis with evaluation for reducing substances and amino acids, complete blood count, basic metabolic panel, calcium, phosphorus, ferritin, TORCH titers, VDRL/FTA-Ab, enzyme assays for RBC galactokinase, galactose-1-phosphate UDT b. Referral to genetics 2. Surgery for bilateral cataracts
Clinical Course	Laboratory investigation was significant for elevated threonine, proline, lysine, and alanine and Type II renal acidosis. Karyotyping and microarray were normal. He was found to have an *OCRL* mutation leading to termination of the protein product (p.R230X), consistent with X-linked Lowe syndrome. His cataracts were removed 1 week after the initial examination[a], and he was subsequently fitted with contact lenses for aphakic correction[b]. Unfortunately, the deprivational nystagmus persisted.

[a]See Chap. 19 for evidence-based discussion of surgical indications, timing, and technique
[b]See Chap. 6 on prescribing contact lenses in pediatric patients

Approximately 25 % of children with bilateral cataracts have an associated systemic disorder [11]. In the absence of a family history of isolated cataracts, children with infantile or childhood bilateral cataracts should undergo a systemic evaluation for underlying syndromes and disorders (see Table 18.1). These may include chromosomal abnormalities such as trisomy 21, 18, or 13, or metabolic disorders (Table 18.1). Renal disease (such as Lowe syndrome, Alport syndrome), musculoskeletal disorders (myotonic dystrophy, Albright syndrome), and the TORCH infections (toxoplasmosis, syphilis, rubella, cytomegalovirus) are also important causes of infantile or early developmental cataracts in children [10, 12, 18] (Fig. 18.4).

Infantile cataracts are most frequently idiopathic, but their identification and classification—based on laterality, heredity, and other signs of systemic disorders—can be used to create a simplified guide for systemic evaluation. Treatment is dictated by the degree of visual impairment created by the opacity, but generally involves lens extraction with subsequent visual rehabilitation using contact lenses and/or spectacle correction until an intraocular lens can be implanted (see Chap. 19) [19]. The infantile visual system requires consistent, detailed visual input for normal development. Moderate to severe amblyopia that develops in infancy can result in nystagmus, strabismus disorders, and life-long disability. Early identification and corrective treatment of infantile lens opacities is crucial in maximizing visual potential in infants and children vulnerable to amblyopia.

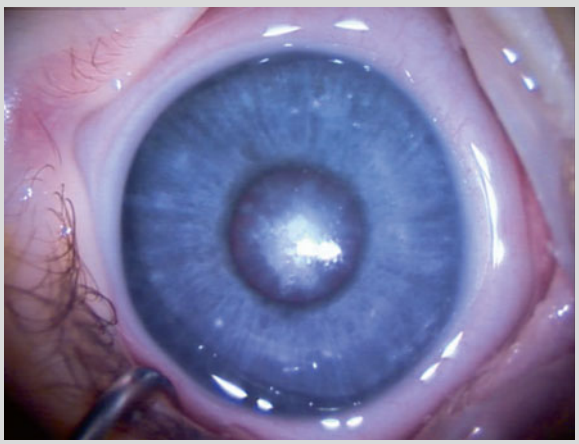

Fig. 18.4 Congenital cataract of the right eye associated with Lowe syndrome. Multiple gray-white, wedge-shaped opacities in all cortical layers are present. Although not readily apparent in this photo, the lens is discoid shaped and proposed to be secondary to defective formation and degeneration of posterior lens fibers [17]. A similar cataract was noted in the left eye. Photograph courtesy of W. Walker Motley III, MD

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Management of Infantile and Childhood Cataracts

19

Courtney L. Kraus, Rupal H. Trivedi, Brita S. Deacon, and M. Edward Wilson

Abstract

Pediatric cataracts are an important cause of decreased vision in children. Managing cataracts in childhood presents an assortment of distinct challenges. Visual prognosis depends upon a multitude of factors, including etiology, surgical variables, and postoperative rehabilitation. Morphology, location, and the age of onset can greatly assist the pediatric ophthalmologist in determining the suspected etiology. Surgical timing and approach must be tailored for each child's unique presentation. Finally, parents and caregivers play an incredibly important role in vision outcomes. A thorough and candid discussion must take place to ensure everyone is actively engaged in the postoperative management of the aphakic or pseudophakic child.

Keywords

Infantile cataracts • Congenital cataracts • Examination • Pediatric cataract surgery • Surgical timing • Preoperative considerations • Visual rehabilitation • Informed consent

Identification and Classification of Pediatric Cataracts

Presentation

A cataract may be discovered early in life when parents or caregivers notice a white spot in the child's eye. A photograph may reveal an abnormal or asymmetric red reflex. The primary care physician or nurse may detect a blackening or asymmetry of the red reflex on Bruckner testing at a well-child visit. Behavioral changes such as visual inattentiveness, clumsiness, or hesitancy in unfamiliar environments may be noticed. Observation of nystagmus, strabismus, or asymmetry of the size or appearance of one eye relative to the other (e.g., microphthalmos) may draw concern. Other physicians or healthcare workers (e.g., physical or occupational therapists) who examine the child can be additional sources of referrals. At times, the evaluation is scheduled preemptively because of a family history of childhood cataracts or because the child has one of a growing number of systemic conditions or syndromes that may be associated with cataracts (Table 19.1).

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Table 19.1 Systemic associations of infantile cataracts

Systemic associations	
Prenatal factors	Intrauterine infection (toxoplasmosis, syphilis, rubella, cytomegalovirus, HSV, VZV); fetal alcohol syndrome
Metabolic and endocrine	Galactosemia, mannosidosis, Wilson disease, neonatal hypoglycemia, hypoparathyroidism, diabetes mellitus, Fabry disease
Chromosomal	Trisomy 21, 13, or 15; Turner syndrome
Dermatologic	Congenital ichthyosis; hereditary ectodermal dysplasias; infantile poikiloderma; Cockayne syndrome
Renal	Lowe syndrome; Alport syndrome
Musculoskeletal	Myotonic dystrophy; Conradi syndrome
Rheumatologic	Juvenile idiopathic arthritis; other uveitis (psoriatic, HLA-B27, etc)
Other	Craniofacial and mandibulofacial syndromes; neurofibromatosis; trauma

Questions related to the child's growth and development can be helpful, with a failure to meet milestones potentially suggesting visual impairment. With significant bilateral congenital cataracts, patients may exhibit developmental delays that are brought to the pediatrician's attention before the cataracts are detected.

Obtaining a history of symptoms can be a challenge, especially with a preverbal child. The young age of presentation of most infantile and childhood cataracts makes questions related to decreased vision, increased blur or glare, or changes in depth perception difficult. Even in an older child, particularly in cases of unilateral cataracts, poor vision may go unnoticed. Asking the parents, "Does your child appear to see well?" can provide some clue as to visual acuity status. Caregivers may notice changes in the attention or function of the child. Questions pertaining to strabismus, "Do the eyes look straight or does one seem to cross, drift, or be lazy?" may provide additional clues.

Examination

The examination of a child with a cataract differs in many ways from that of an adult patient. Visual acuity and slit-lamp examination provide valuable information about the cataract, but are not always attainable. Several other components of the exam become equally, if not more, important.

Visual acuity in a child can be recorded using a Snellen chart, LEA symbols, or HOTV matching; success with these methods is possible in children as young as 2, therefore attempts should be made if the child seems capable. Turning this portion of the exam into a game: challenging the child to "get the next smallest line even though it is so tiny" or "playing the fun matching game" may improve success. In the pre- or nonverbal, developmentally delayed, or uncooperative child, grating visual acuity assessed by preferential looking, or objection to covering one eye more than the other can provide a strong indication of an eye fixation preference, indicating poor vision in the other eye. This is particularly useful information in cases of unilateral or asymmetric cataracts.

Assessment of the red reflex provides arguably the most information about the nature and visual obstruction caused by a cataract. Using the retinoscope, subtle abnormalities in the red reflex can be appreciated. The examiner can quickly and relatively unobtrusively determine the relative nature of the opacification. Cataracts that prevent performing retinoscopy generally can be considered visually significant. Retinoscopy can be performed to ascertain refractive error. High myopia may suggest form deprivation and an axially elongated eye. Anisometropia and astigmatism may be detected in eyes with cataracts that do not need surgical removal. Failure to detect and correct these refractive abnormalities can lead to amblyopia.

Measurement of strabismus and characterization of nystagmus, if present, should be performed. Detailed examination of the cataract and dilated fundoscopic exam may have to wait until the time of surgery, especially in cases of dense bilateral cataracts.

At the time of surgery, keratometry, intraocular pressure (IOP), corneal pachymetry, corneal diameter, and gonioscopy should be performed. Using the operating microscope, pupillary membranes, iridocorneal or lenticulocorneal adhesions, and the presence of a stalk may be detected for the first time. These should be noted as they all carry prognostic information. A-scan ultrasound or optical biometric measurements are performed to allow the determination of globe axial length (AL). This measurement then helps with the selection of intraocular lens (IOL) power, evaluates the interocular AL difference, and when repeated over time, allows for a direct measure of long-term eye growth. Ultrasound biometry performed in the operating room may be obtained with either contact or immersion methods. Immersion A-scan has been shown to be superior to contact biometry in children [1]. In older children, AL measurement and keratometry may be obtained in the clinic.

Additional Tests

Supplementary testing, including laboratory tests, systemic workup, referral to a clinical geneticist or developmental pediatrician, and/or examination of parents/siblings, may be indicated in certain circumstances. For cases with a clear etiology, a laboratory workup is typically unnecessary. For bilateral cataracts without a clear cause, a selective workup to rule out associated conditions may be indicated (see Chap. 18).

The pediatric ophthalmologist should pay particular attention to prenatal history and the results of a complete physical exam. Epidemiological reviews suggest that up to 12 % of non-traumatic cataracts may be due to potentially preventable causes [2]. Associated findings may suggest TORCH (Toxoplasmosis, *Other* [syphilis, varicella], Rubella, Cytomegalovirus, Herpes) infections and serologies should be sent. Other tests such as blood glucose, calcium, and phosphate may rule out metabolic disorders such as diabetes and hypoparathyroidism. Urine tests for reducing substances can rule out galactosemia. The presence of protein or amino acids and an abnormal pH detect Lowe syndrome.

Karyotyping, in conjunction with genetic consultation and ocular examination of parents and siblings, may provide further information about the etiology of cataracts and should be considered in select circumstances.

Classification of Cataracts

Classification (Table 19.2) of cataracts by type, location, morphology, partial versus complete, and unilateral versus bilateral can give the physician important information about prognosis, guide treatment decisions, and help indicate etiology (Fig. 19.1).

Non-familial bilateral cataracts, even if the eyes are asymmetrically affected, may be due to an undiagnosed systemic disease and the aforementioned symmetric workup is warranted. The location of the opacity plays a key role in estimating the degree of visual impairment induced by the cataract. A general rule is the more posterior and more central the opacity, the more amblyogenic it is. Complete cataracts are universally visually significant. Considerations for a partial cataract include whether it obstructs the pupil in ambient lighting conditions; whether it complicates retinoscopy or prevents fundoscopic examination; and whether it leads to decreasing vision, significant glare, or worsening amblyopia.

Table 19.2 Morphological classification of infantile cataract

Cataract type	
Fetal 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
Cortical	Anterior and/or posterior cortical opacity not involving the fetal nucleus and often associated with posterior capsule plaque
Persistent fetal vasculature	A combination of one or more of the following: retrolental membrane with or without visible vessels, patent or nonpatent persistent hyaloid vessel, or stretched ciliary processes
Isolated posterior capsule plaque (posterior polar)	Opacity of the posterior capsule without overlying opacity in the cortex or nucleus
Posterior lentiglobus	Posterior bowing of the posterior capsule with or without a preexisting posterior capsule defect
Total	Entire lens white

A total cataract denotes opacity of the entire lens. It may be completely opaque at the time of initial presentation or may develop from lamellar or nuclear cataracts. Total cataracts are frequently bilateral and may progress from gray or translucent to uniform and complete whiteness.

A cortical cataract traditionally involves one or more layers of the lens. It is defined as an anterior and/or posterior cortical opacity not involving the fetal nucleus and often associated with posterior capsule plaque [3]. This opacity may be dense enough to create a central opacity, or translucent and visually insignificant [4]. Cortical cataracts are typically bilateral, but may be asymmetrical.

A congenital nuclear cataract is defined as an opacity of the entire embryonic or fetal nucleus. Bilaterally present nuclear opacities are the most common autosomal dominant inherited form of cataract [5].

Anterior polar cataracts can be unilateral or bilateral; when bilateral, they are usually symmetric, dot-like opacities (Fig. 19.2). Anterior pyramidal cataracts are the more severe form and demonstrate a pathognomonic pyramidal shape rising towards the cornea [6].

Unilateral or bilateral thinning and posterior bowing of the posterior lens capsule is classified as posterior lentiglobus. This type of lens change is usually unilateral and is characteristically not associated with microphthalmia or microcornea. If bilateral, asymmetric thinning and bowing may be appreciated. These cataracts characteristically show a peripheral distortion in the red reflex. Opacification may occur or a high degree of astigmatism may be induced, with or without cataract [7]. Rarely, the thin posterior capsule in posterior lentiglobus will spontaneously rupture. In these instances, the history is often of an acute onset of a pure white total cataract in one eye without any significant trauma to the eye.

Persistent fetal vasculature (PFV) cataracts represent a spectrum of disease that includes persistent pupillary membrane, persistence of the posterior fetal sheath of the lens, a Mittendorf dot, a persistent hyaloid artery, Bergmeister's papilla, macular abnormalities, optic nerve hypoplasia and dysplasia, and malformations of the size and shape of the globe. Elongated ciliary processes and a membrane of variable thickness can suggest this diagnosis (see Chap. 18).

Traumatic cataracts usually present with a clear history of eye injury with or without treatment for hyphema, retinal detachment, or ruptured globe. These cataracts can take on many forms, subcapsular opacities with fibrotic capsular plaques being among the more common [8].

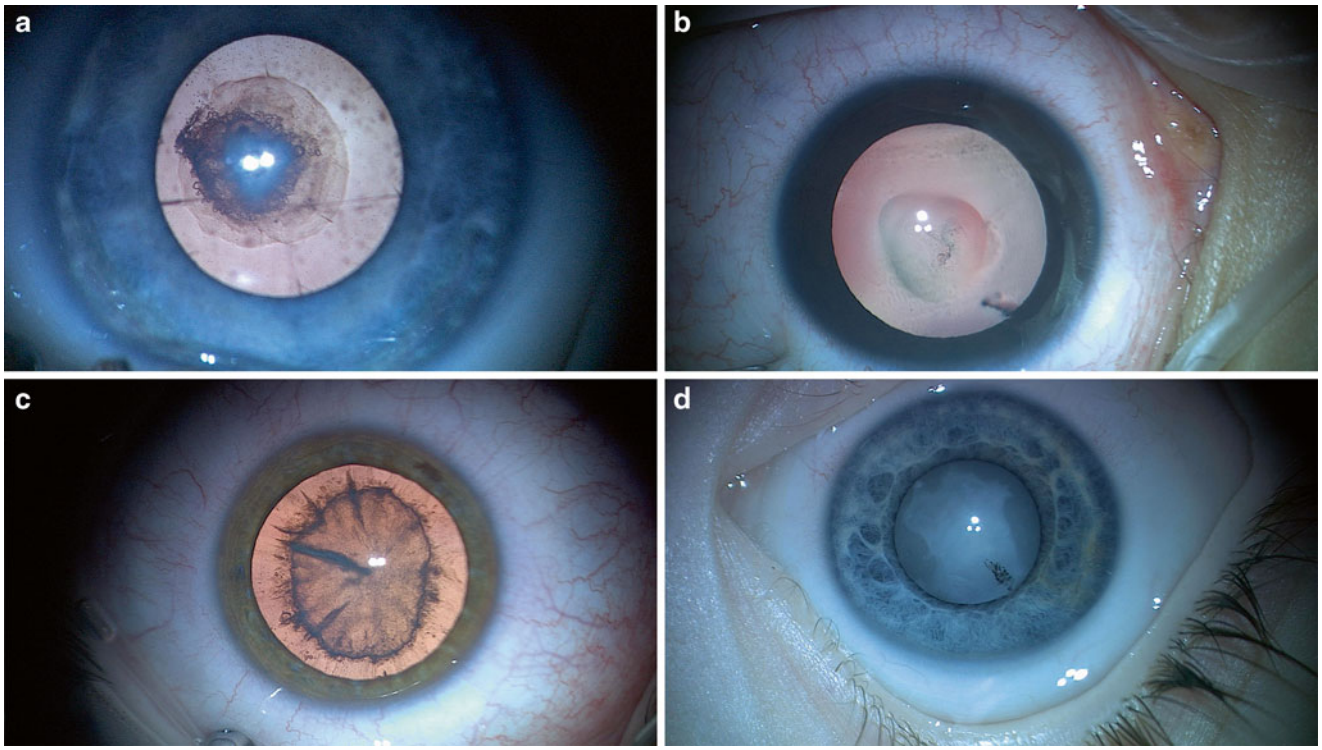

Fig. 19.1 (**a**) Fetal nuclear cataract primarily involving the posterior portion of the nucleus with posterior capsular bulging into the anterior vitreous; (**b**) posterior lentiglobus; (**c**) cortical cataract; (**d**) dense white cataract, dense hyaloid stalk identified intraoperatively

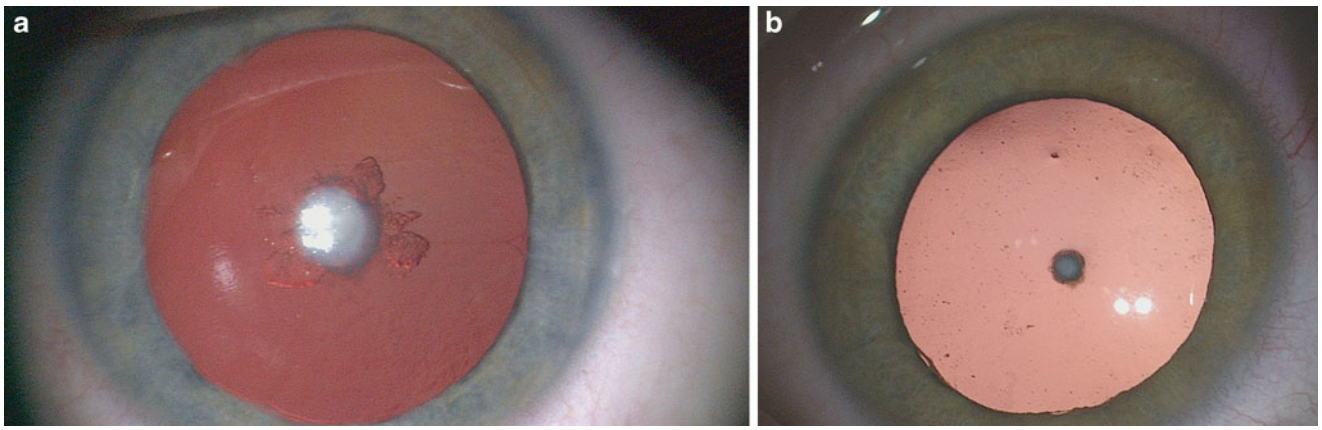

Fig. 19.2 (**a**) Visually significant anterior polar cataract; (**b**) typical anterior polar cataract

Indications for Surgery

Considerations Prior to Surgical Intervention

The decision to remove a cataract, especially one that is partial, must be made with consideration to the loss of the natural, youthful ability to accommodate. The reduction in acuity or the amblyogenic potential of the opacification must be significant enough to justify this sacrifice. If observation is elected, the pediatric ophthalmologist must follow the child closely.

If the cataract has presented or developed such that it interferes with examination of the fundus or distorts and blackens the retinoscopic reflex creating an inability to obtain an accurate refraction, then it is likely visually significant and surgical removal should be considered.

When a cataract coexists with amblyopia, the timeline and necessity of surgery can be challenging to determine. In children who have been given their appropriate spectacle correc-

tion, completed any necessary amblyopia therapy, and have reached a plateau in visual improvement, surgery may be indicated. For verbal children, cataract surgery is considered if visual acuity has dropped below 20/50 or 20/60; if the child is intolerant to glare; or if she/he is resistant to amblyopia therapy with documented deteriorating visual function. In nonverbal children, more weight is placed on visual behavior or on the assessment using preferential looking techniques, especially in unilateral cases. A demonstrated eye preference, intolerance or resistance to covering one eye more than another, or poor saccades of one eye compared to the other when vertically spaced animal fixation toys are sequenced on and off, or other tests of preferential looking, all suggest an eye preference and in cases of unilateral or asymmetric cataract may push the physician towards surgery.

Cataract Morphology

Certain types of cataract mandate surgical removal for the best possible visual rehabilitation, while others are more likely to be observed [9]. Especially in the pre- or nonverbal child, cataract morphology can lend support to a decision to operate.

Anterior polar and *cortical cataracts* are more likely to be managed without surgery. Patients with total, nuclear, and PFV cataracts are significantly more likely to require surgery [10].

Non-traumatic total cataracts involving the entire lens are not very common in industrialized countries [11]. When present, they can have a profound effect on visual development. Bilateral cases may present with deprivation nystagmus, while unilateral cases present with dense amblyopia. Therefore, early surgery is often indicated. Reasonable outcomes can be achieved with optimal surgical and postoperative management [12].

The visual prognosis of patients with cortical cataracts, especially partial opacities, is probably better than that of other morphological types. Many cases can be managed conservatively and surgery in early infancy is rarely necessary [13].

Fetal nuclear cataracts are a common form of infantile cataract, although exact incidence rates vary. Nuclear involvement has been reported to be in as few as 10 % of reviewed cases [9]. In the Infant Aphakia Treatment Study, nuclear cataracts were present in 54 % of eyes and associated with a posterior capsule plaque in all cases [3]. The higher proportion of nuclear cataract was attributed to a cohort that included infants up to only 7 months of age and with monocular cataracts only. Even with the presence of a posterior plaque, surgery and visual rehabilitation can be quite successful.

Anterior polar cataracts are often not visually significant [4]; however, they may be associated with astigmatic refractive errors that can cause amblyopia and strabismus [14]. For this reason, close follow-up and correction of refractive error is necessary to avoid amblyopia. *Anterior pyramidal cataracts*, while sharing a location with the former, more dot-like anterior polar cataracts, are more likely to show spread into the subcapsular cortex and need surgery [4].

With *PFV cataracts* visual rehabilitation is possible, although more challenging [15]. Preoperative findings such as microphthalmia, retinal detachment, retinal or optic nerve abnormalities predict a much higher likelihood of a poor visual outcome (defined as <20/400) [16]. However, especially in those studies including a broader definition of PFV cataract, good visual outcomes can be achieved with surgery and diligent postoperative management [17].

Surgical and Post-Surgical Issues

Age and Surgical Timing

Deciding on the timing of surgery is most critical for cataracts presenting in early infancy. Cases of dense unilateral cataracts diagnosed at birth, 4–6 weeks of age is the preferred age of intervention. Postponement of surgery until 30 days of age or more decreases the anesthesia-related risks and often allows term infants to be healthy enough for discharge to home after surgery. After 6 weeks of age, waiting may adversely affect visual outcome [18, 19].

In bilateral cataracts diagnosed at birth, good visual outcomes can be achieved if the child is operated before 10 weeks of age [20]. Surgery on the first eye can be offered at 4–6 weeks of age, and the second eye surgery one week later. At the time of surgery for the second eye, the surgeon can perform a postoperative examination of the first eye. It is important to keep the time interval to a minimum between the two surgeries. Occlusion between operations is not generally recommended as long as prolonged delay between surgeries is avoided.

Some surgeons prefer to operate on both eyes of infants at the same time and under one anesthesia. This immediate sequential surgery option is more often chosen when systemic medical conditions place the patient at greater than normal risk during general anesthesia. Each eye is treated as a separate case with fresh instrumentation and a new surgical preparation and drape.

For older children, the timing of surgery is not as crucial. In children beyond the amblyopic age, surgery can often be decided based on convenience and other logistical issues.

Surgical Technique

The surgical approach to the pediatric cataract follows many of the same steps and general sequence of adult cataract surgery. However, characteristics of the patient, the lens, the scleral and corneal rigidity, the formed posterior vitreous,

and higher propensity for postoperative inflammation render it in many ways very different. What follows is the authors' technique for pediatric cataract surgery; variability exists among surgeons for certain steps and preferences.

Preoperative preparation of the patient begins with topical antibiotics and dilating cocktail. A fourth-generation fluoroquinolone and dilating drops are placed topically at 5-minute intervals for a total of 3 applications. A pediatric combination drop contains 2 mL 2 % cyclopentolate, 0.5 mL 10 % phenylephrine, and 0.5 mL tropicamide. Povidone iodine, diluted to a 5 % solution, is applied to the skin, lashes, and eye before surgery. An additional drop is placed at the conclusion of surgery.

Surgical incisions are different in the pediatric eye. Due to reduced scleral rigidity and a greater propensity for anterior chamber collapse, smaller incisions are preferred. Two paired stab incisions in the clear cornea near the limbus allow for the passage of the irrigating handpiece and either the aspiration handpiece or vitrector. We generally prefer 10:00 and 2:00 o'clock positions, operating from a superior approach. This allows for the wounds to be protected by the brow and the Bell's phenomenon in the more trauma-prone child. One of these incisions can then be enlarged with a keratome if an IOL is to be implanted. Corneal incisions should be sutured as they do not self-seal as in adults. We recommend closure with a 10-0 synthetic absorbable suture.

The *anterior capsulotomy* in pediatric cataract surgery can be accomplished through a manual continuous capsulorhexis (CCC) or vitrectorhexis. Manual CCC is preferred when the surgical plan includes primary IOL implantation; vitrectorhexis can be used in infants when the surgical plan does not include primary IOL implantation. Use of small incision capsulorhexis forceps that fit easily through a paracentesis will allow for maintenance of the anterior chamber and keep the incisions small enough to maintain a tight fit when bi-manual irrigation and aspiration are done later in the procedure. Remember that the anterior capsule in children is highly elastic and therefore the vector forces should be directed more towards the center of the pupil than in an adult. Filling the anterior chamber with a highly viscous ophthalmic viscosurgical device and frequently re-grasping the leading edge are recommended. For a vitrectorhexis, begin by placing the vitrector port facing posteriorly in contact with the anterior capsule. Engage the capsule and enlarge the round capsular opening in a spiral fashion to the desired size and shape. Use caution to avoid leaving any right angles, which would be prone to radicalizing when stressed by lens removal.

Lens removal in children differs from that of an adult; due to the soft, "gummy" quality of the pediatric lens. Phacoemulsification is unnecessary for pediatric lens removal. Instead, the lens is removed using irrigation/aspiration and, when necessary, vitrectomy handpieces. We prefer the bi-manual approach with separate irrigation and aspiration. When using the vitrector, bursts of cutting can be used to ease aspiration of the more "gummy" cortex of young children. Thorough lens removal is essential to pediatric cataract surgery. Any residual cortical material is highly mitotically active and has great potential to grow and become a visual axis opacification (VAO).

Creation of a *posterior capsulectomy* is necessary in young children as posterior capsule opacification (PCO) occurs rapidly when the posterior capsule is left intact and PCO can be quite amblyogenic. A primary posterior capsulectomy and anterior vitrectomy maximize the likelihood of a longstanding clear visual axis. As a rough guideline, we perform a primary posterior capsulectomy and anterior vitrectomy on children below age 5 years. Children 5–8 generally are assessed on a case-by-case basis; those that tolerate slit-lamp examination and IOP checks generally can be assumed to be able to tolerate a neodymium: yttrium aluminium garnet (Nd-YAG) laser capsulotomy, should the need arise. In children over age 8, the posterior capsule is generally left intact unless a posterior capsule plaque is present or the child is developmentally delayed or has been diagnosed with autism spectrum disorder.

At the *conclusion of surgery*, intracameral antibiotics (a 1:1 dilution of preservative free moxifloxacin [Vigamox®] and balanced salt solution) and steroid are injected. As mentioned above, a drop of dilute povidone iodine is placed on the eye. An antibiotic-steroid ointment and atropine drop are placed on the eye. If the child has been left aphakic, we place a SilSoft contact lens at the time of surgery and omit the ointment. A fox shield and patch are placed over the eye.

Management of After-Cataract and Posterior Capsule Opacification

Frequent examinations of the child must occur following surgery, not only to monitor IOP, refractive error, and need for and response to amblyopia therapy, but also to ensure that a clear visual axis is maintained. Lens proliferation into the visual axis is more commonly observed the younger the patient is at the time of cataract surgery, and in those cases where an IOL is placed [21]. These children often require an additional intraocular surgery to remove the proliferated lens epithelial cells and clear the visual axis—a procedure that is relatively straightforward, and not often associated with any additional complications [22].

Generally, for children older than 5 years of age, and if they are able to cooperate for slit-lamp examination, cooperation is possible for Nd-YAG laser capsulotomy in the office. In children above 5–6 years of age with an intact posterior capsule and an AcrySof® IOL implantation, a visually significant PCO may develop most commonly at 18–24 months after surgery, but this can occur earlier.

Parental Counseling and Informed Consent

As soon as cataract surgery is proposed for a child, the informed consent process is initiated. A well-communicated informed consent is as essential as the surgery itself. The ophthalmologist must be able to explain to the patient's parents or legal guardians (and to the child as well, if appropriate) the nature of the problem and indications for surgery.

All options for managing the cataract and the optical rehabilitation should be explained using terms the family can understand. With increasing frequency, parents arrive at appointments having conducted hours of internet queries. While not all of the information is scientifically based, the access to information has led to more knowledgeable and inquisitive parents and patients. The surgeon should be prepared for lengthy discussions. The extra time invested results in a better-informed family that will be more likely to comply with the frequent follow-ups, medications, patching, glasses wear, components that are essential for a successful outcome.

No matter how well informed the family is, the surgeon should nonetheless advise parents about the treatment details, alternatives, and meaningful risks of the proposed surgery. A request for a second opinion may arise during the discussion, and the surgeon should be open to facilitating the request.

In the specific instance of pediatric cataract surgery, the informed consent discussion should include the criteria used by the surgeon to decide that the cataract is visually significant; the details of the surgical procedure being proposed (i.e., whether a posterior capsulectomy and anterior vitrectomy will be performed and whether an IOL will be placed); whether the surgery will result in the postoperative need for glasses, contact lens, and/or patching for amblyopia; and the importance of postoperative follow-up and medications as well as the importance of avoiding trauma to the recently operated eye. A general discussion of operative and postoperative risks should include a discussion of VAO, IOL malposition, abnormalities of the size and shape of the pupil, and variability in the postoperative residual refractive error. Endophthalmitis and retinal detachment are rare after pediatric cataract surgery, but are of such significance to vision, that they should be mentioned as part of the informed consent. Complicating conditions that may not appear for years after the surgery should also be mentioned including aphakic/pseudophakic glaucoma, deprivation amblyopia, strabismus, and changing refractive error. Ideally, these conditions should be discussed at the time of the preoperative patient education.

The informed consent discussion should include relevant issues related to the placement of an IOL. Parents should be made aware that IOL implantation in children is considered an "off label" or "physician-directed" use. However, they should also be made aware that IOL implantation at the time of cataract surgery has become the treatment of choice for a large majority of surgeons depending upon age of the child and other considerations. Before moving forward with IOL implantation, it is important to discuss the major pros and cons of the available options with the parents/legal guardian.

When the parents understand the reasons for, goals of, and the advantages and potential complications of cataract surgery, they are more likely to comply with the treatment plan. They should be informed that surgery is only one part of the treatment plan, and that following cataract surgery, a child will require regular scheduled care for the first decade of life and then every 1–2 years. Changing refraction will require frequent follow-up examinations and changes in prescription. Finally, the parents need to be aware that glaucoma may develop many years after cataract surgery. Parents need to understand that their child may need serial examinations under anesthesia until the child is cooperative enough to be fully examined in the office.

In short, an informed consent becomes far more than just a discussion of risks, benefits, and alternatives. Parents must understand that a successful visual outcome depends on their ability to maintain adequate optical correction and follow through with amblyopia therapy. A perfectly timed intervention and a perfectly executed surgery can be rendered unsuccessful if parents do not understand or comply with postoperative instructions, glasses, or patching. Parents need to also understand that cataracts can be accompanied by abnormal development in many parts of the eye. Early recognition, proper surgical and medical treatment, and parental compliance render the highest possible chance of an excellent visual outcome but they do not guarantee it. Without this understanding, poor outcomes may bring on guilt in the parents and blame towards the doctors. This is especially true with unilateral infantile cataracts where visual outcomes are more difficult to predict at the initial informed consent discussion. Optimism and encouragement from the doctors promote parental compliance even when success is difficult. However, the doctor also has the responsibility to know when to reduce or to discontinue treatment if and when no progress is made. Parents must always be praised for their efforts and made to feel thankful for even a partial visual recovery.

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Persistence of the Fetal Vasculature: Varieties and Management

20

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Abstract

The spectrum of persistence of the fetal vasculature (PFV) is broad and includes anterior segment as well as vitreal and retinal abnormalities. The great majority of cases are unilateral and not associated with other systemic abnormalities. Some patients can be observed and the ocular abnormalities are inconsequential; others require surgical interventions such as lens extraction, anterior vitrectomy, and occasionally posterior vitreoretinal maneuvers. Rarely, patients have very small eyes with disorganized vitreous and a very poor visual outcome; in such cases, the lens is often removed to avoid angle closure glaucoma and phthisis bulbi. Accurate diagnosis and appropriate management are associated with acceptable outcomes in a majority of cases.

Keywords

Persistent fetal vasculature • Persistent hyperplastic primary vitreous • Pupillary membrane • Embryology • Cataract • Cloquet canal • Malformation

Introduction

Persistence of the fetal vasculature (PFV) refers to a spectrum of ocular abnormalities characterized by deformations and malformations of ocular structures that result from failure of some of the ophthalmic fetal vasculature to regress and form an accompanying fibrotic response. Abnormalities of regression of fetal vasculature in any location in the eye, especially in the anterior vitreous and around the iris, result in the clinical spectrum of PFV, which includes what was previously referred to as persistent hyperplastic primary vitreous (PHPV), persistent tunica vasculosa lentis, as well as other discrete ocular findings, such as inconsequential remnants of the pupillary membrane, and Mittendorf dot on the back of the lens. In 1997, Goldberg proposed integrating the numerous clinical variations of failed regression of the embryonic vasculature involving the anterior and posterior segment under the umbrella term of PFV [1]. The etiology of PFV remains unclear but factors that interfere with regression and absorption of fetal structures and blood vessels are evidently at play. These factors probably include genetic and environmental components.

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Clinical Presentation

Signs

The presentation of patients depends on the severity of the variety of PFV. In those with iris and pupillary abnormalities (Fig. 20.1), the diagnosis may be made shortly after birth because of the flagrant appearance of the anterior segment. Those with a small eye and severe anterior and posterior

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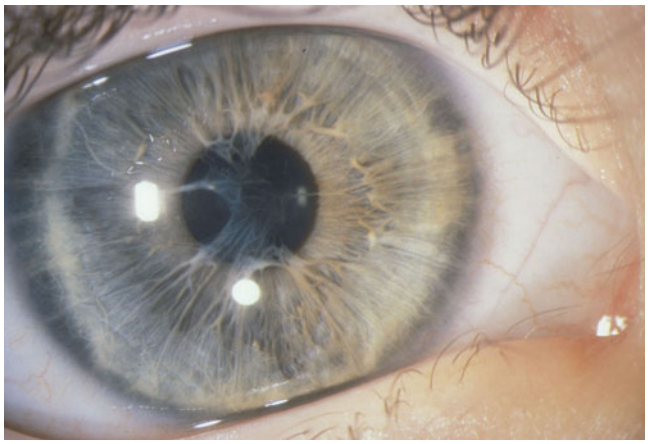

Fig. 20.1 Remnants of the pupillary membrane. Some attach to the anterior lens capsule

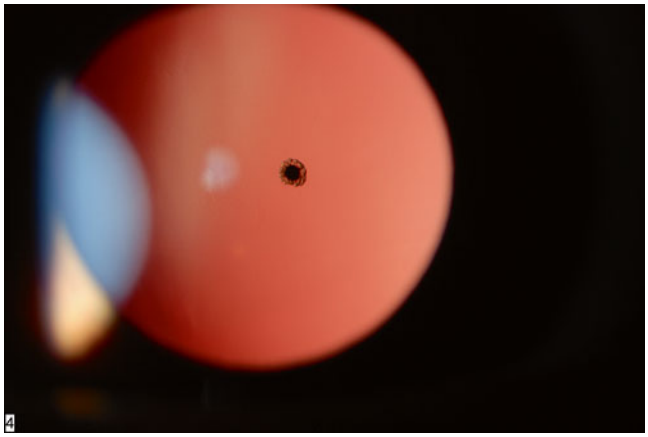

Fig. 20.2 Small posterior capsular opacity lightly nasal to center of the lens—Mittendorf dot

abnormalities are likewise diagnosed shortly after birth. Others, in whom the size of the eye is normal and abnormalities are restricted to the posterior aspect of the lens or the posterior pole of the eye, may escape early detection, especially if the red reflex is not carefully evaluated by the pediatrician or primary caregivers and may present much later with strabismus or through a failed vision screening examination. Finally, patients with very mild variants such as very small remnants of the pupillary membrane, Mittendorf dots (Fig. 20.2) or Bergmeister papilla (Fig. 20.3) may be identified on routine eye examinations at any age.

The breadth of clinical findings due to the extent of residual fetal vasculature has led to a tripartite classification system (Table 20.1). Anterior PFV refers to malformations and secondary complications due to involvement of the anterior chamber, iris, and lens by the partially regressed tunica vasculosa lentis and hyaloidal vascular system. As such, it includes cases of congenital cataract, remnants of the pupillary membrane (Fig. 20.2), and some cases of localized coloboma of the lens (Fig. 20.4). The latter are due to interference with the formation of the zonule in a sector of the lens by an irido-hyaloid vessel that has not regressed and exerted localized deformational pressure on developing zonular apparatus. Patients previously referred to as having PHPV generally have unilateral microphthalmia, cataract caused by fibrosis

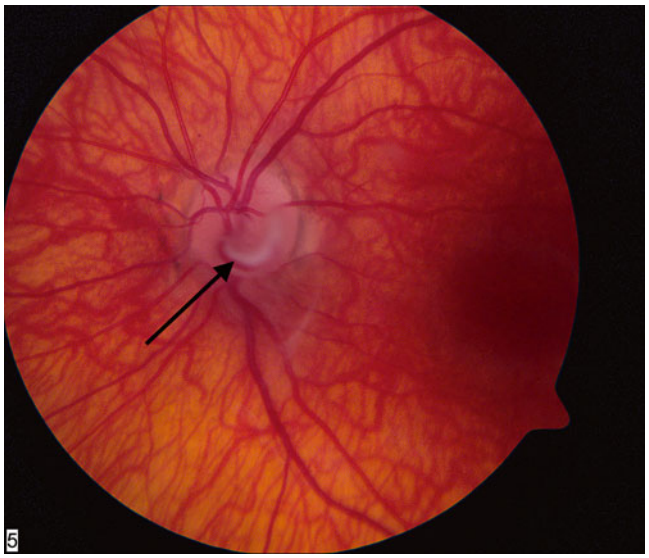

Fig. 20.3 Small posterior remnant of the regressed hyaloid system at the disk (*arrow*)—Bergmeister papilla

Table 20.1 Clinical varieties of persistent fetal vasculature with corresponding anterior, posterior, and combined categories (modified from Ceron et al. [4])

PFV variety	Anterior	Posterior	Combined
Persistent pupillary membrane	x		±
Coloboma of the lens	x		
Mittendorf dot/brittle star formation	x		±
Elongated ciliary processes	x		±
Shallow anterior chamber	x		±
Intracapsular and retrolental fibrovascular membrane	x		±
Microphthalmos with vitreous stalk and lens abnormalities (PHPV)	x	x	x
Cataract	x	x	x
Leukocoria	x	x	x
Intralenticular hemorrhage	x	x	±
Coloboma of the lens	x		
Bergmeister papilla		x	±
Retinal fold		x	±
Optic nerve hypoplasia/dysplasia		x	±
Hypoplastic macula; pigment maculopathy		x	±
Vitreous membranes and stalk		x	±

PFV persistent fetal vasculature, *PHPV* persistent hyperplastic primary vitreous

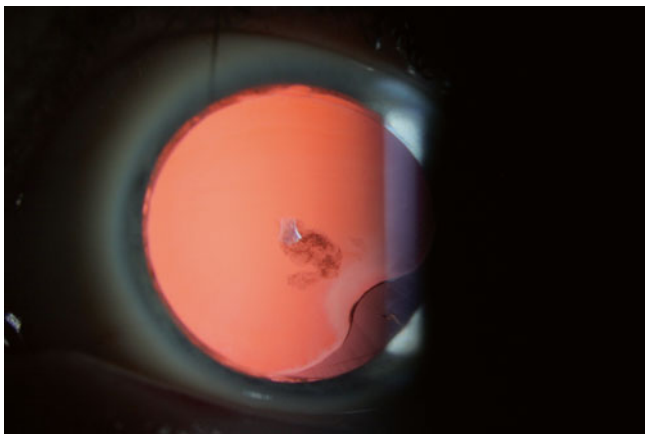

Fig. 20.4 Notched equator of the lens at 4 o'clock with absent zonules (coloboma of the lens). There also is a small central capsular opacity

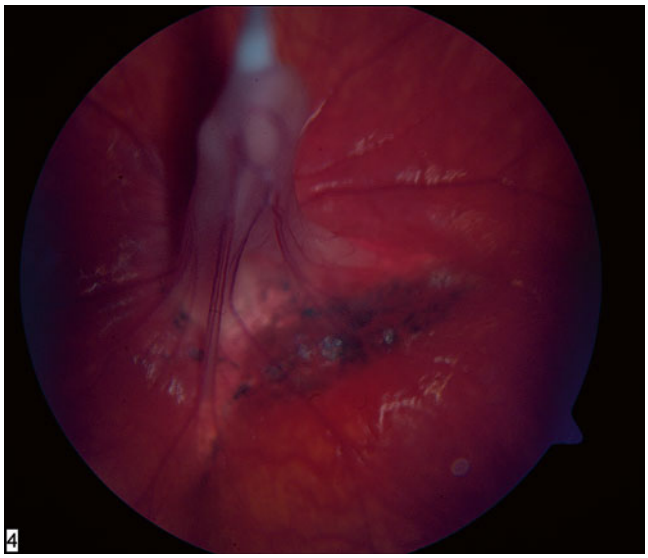

Fig. 20.5 Posterior PFV at the disk the stalk protrudes forward. The traction has resulted in pigmentary changes near the dysplastic disk

in and on the posterior capsule of the lens, and dragging of the ciliary processes toward the center of the posterior lens capsule. Persistence of the fetal vasculature posteriorly classically causes changes to the lens, optic nerve, and/or retina, resulting in optic nerve dysplasia, retinal folds, and/or posterior stalks (Fig. 20.5). Patients with combined forms of PFV demonstrate features of both categories, and almost always have microphthalmia, cataract, leukocoria, and sensory strabismus. More than 60 % of patients with PFV fall under the combined PFV category [2, 3]. Persistent fetal vessels from the iris that lead to adhesions to the corneal endothelium cause focal areas of corneal opacification, as seen in some cases of peripheral Peters' anomaly [1]. Similarly, abnormal blood vessels causing malpositioning of the iris stroma can cause congenital ectropion uvea or radial fibrous bands that deform the iris. Incompletely regressed irido-hyaloidal vasculature can cause focal zonular and lenticular maldevelopment, leading to what has been referred to as lens coloboma, and occasionally lens subluxation [1].

Associated Syndromes

In its strict definition, PFV is a unilateral, idiopathic, and non-inherited condition. However, the similarity of PFV to other vascular and malformative ocular diseases that occur in heritable systemic diseases such as Trisomy 13, Norrie disease, Walker–Warburg syndrome, incontinentia pigmenti, and oculo-dento-osseous syndrome has led to the inaccurate use of the PFV terminology in the context of heritable conditions.

Pathogenesis

Embryology

Development of the eye begins within the first few weeks of embryogenesis and is highly dependent on the growth of a luxuriant, but transient anastomotic network of blood vessels that develops posteriorly to anteriorly. Three weeks after fertilization, the future hyaloidal artery, arising from the ophthalmic artery, enters the eye inferiorly by means of the fetal fissure and grows through the vitreous compartment toward the posterior aspect of the fetal lens, forming the posterior tunica vasculosa lentis. This structure nourishes the developing optic cup posteriorly, and anastamoses anteriorly with the annular artery via irido-hyaloidal vessels to create the anterior tunica vasculosa lentis, which develops alongside the pupillary membrane in the iris stroma by the 6th to 7th week of gestation (Fig. 20.6).

This complex vascular network is most extensive between the 8th and 12th weeks of development, and slowly begins to regress in the 2nd trimester, with almost complete involution at birth. In most cases, the anterior portion involutes at 8 months, while the posterior portion of the system typically regresses later, although the anterior and posterior hyaloidal systems may persist independently or together [4]. As this vasculature develops and regresses, the vitreous is also continually changing. The primary vitreous develops from embryonic mesenchymal cells and contains the hyaloidal vasculature described above. The secondary vitreous begins to develop in the 9th week of gestation from the inner retinal cells, depositing centrally from the ocular wall. In normal development, the secondary vitreous compresses the primary vitreous into what is known as Cloquet canal, leading to regression of the vascular structures. Normal growth of the eye depends in part upon expansion of the secondary vitreous,

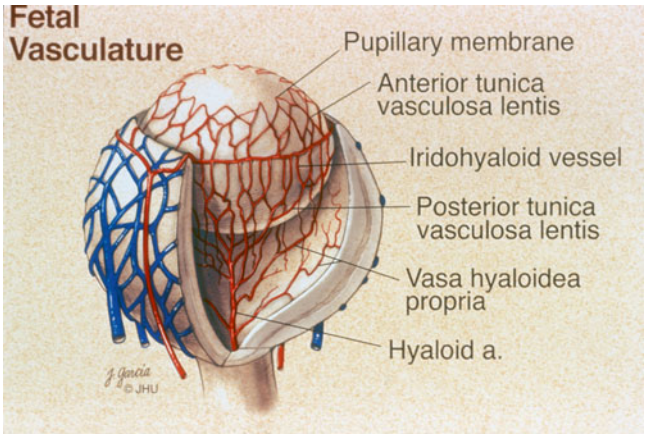

Fig. 20.6 Anastomotic relationships of key components of the fetal vasculature. Reproduced with permission from Ref. [1]

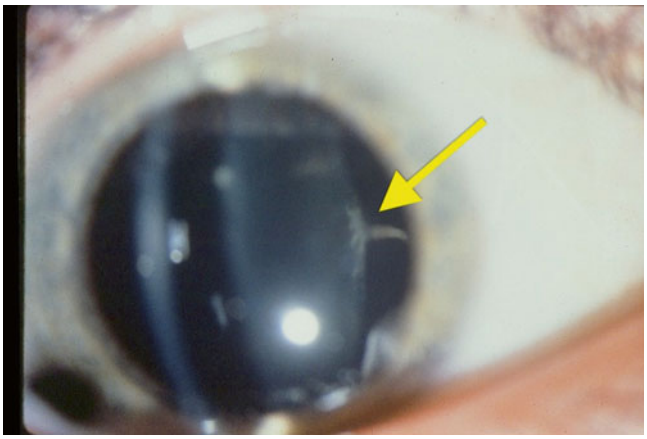

Fig. 20.7 The anterior end of the hyaloid remnant divides as it attaches to the back of the lens forming a so-called starfish (*arrow*)

which explains why many eyes with PFV are microphthalmic. By the 23rd week of gestation, well-formed fibrils running from the ciliary epithelium to the lens are identifiable, better known as zonules, or the tertiary vitreous [5].

Incomplete regression of the fetal vasculature occurs in 3 % of normal full-term babies and in 95 % of premature babies, leading to small remnants such as the Mittendorf dot—a small remnant on the posterior aspect of the lens, brittle star (Fig. 20.7) sign—a multi-pronged opacity that connects the hyaloid remnant to the back of the lens, Bergmeister papilla—a small veil on the surface of the optic disk, and persistent pupillary membranes that float in the anterior chamber or adhere to the anterior surface of the lens [3].

Molecular Genetics

Despite the clinical descriptions of the broad spectrum of clinical phenotypes of PFV, the molecular mechanisms leading to the persistence of the fetal vasculature have been elusive. Although it has been hypothesized that regression of the hyaloidal vessels is regulated by a complex pathway of angiogenic and apoptotic signals, only recently have attempts successfully uncovered pieces of the puzzle. Recent work in animal models strongly implicates the *arf* (alternative reading frame) protein, and p53 in the pathogenesis of PFV [6]. In mouse eye development, the *arf* tumor suppressor gene promotes hyaloidal vessel regression, indicating that its deficiency could cause persistence of the fetal vasculature [6, 7]. Similarly, p53 is key in a critical apoptotic pathway, leading to the hypothesis that mutations in p53 lead to incomplete regression due to failure of appropriate apoptosis [8, 9]. The WNT signaling pathway is also an important signaling system and involves a number of proteins, including norrin (pathogenic to Norrie disease), and frizzled-4 receptor (FZD4, linked to pathogenesis of FEVR). Mutations in the genes coding for these proteins have been described in a limited number of unilateral and bilateral cases of PFV, providing supportive evidence that inhibition of apoptotic signaling leads to persistence of the fetal vasculature, as well as to other related syndromes such as Norrie disease, FEVR, and ROP [10, 11].

Clinical Genetics

The majority of cases of PFV are sporadic and non-heritable. Studies in dogs and cats, as well as case reports in humans, indicate the possibility of rare autosomal recessive, X-linked, and dominant variants [4, 7, 8, 12, 13]. Linkage analysis in cases of autosomal recessive PFV suggests that a possible candidate gene is located on chromosome 10q11-q21 [4, 7]. Similarly, two case reports of PFV in the absence of other congenital anomalies and with a family pedigree suggestive of AD transmission have been described, but no candidate genes were identified [8, 12].

Differential Diagnosis

Retinoblastoma is a retinal tumor of children, caused by mutations in the *RB1* gene located on chromosome 13. Retinoblastoma is predominantly identified in children age 6 months to 2 years who present with leukocoria and a retinal mass. Occasionally, differentiating retinoblastoma from PFV can be challenging. The eye in retinoblastoma is not microphthalmic and has no cataract, and ultrasonography or computed tomography typically reveals calcification in retinoblastoma but not in PFV.

Coats' disease is a congenital, non-hereditary disease of the retinal vasculature, associated with vascular leakage, retinal exudates, and retinal detachment, usually occurring in

males. When Coats' disease is strongly suspected, some advocate sending samples of subretinal fluid for analysis of presence of fatty exudates, ghost cells, and cholesterol crystals. Coats' disease can be distinguished from PFV by the presence of extreme subretinal exudation, and large areas of telangiectasia and retinal neovascularization.

Familial exudative vitreoretinopathy (*FEVR*) is a congenital, inherited disease of the retina caused by failure of peripheral retinal vascularization. Although it mimics retinopathy of prematurity, as well as Coats' disease and peripheral uveitis, FEVR occurs in full-term babies without a history of oxygen supplementation. FEVR is usually distinguished from PFV by evidence of family history and bilateral, though sometimes markedly asymmetric, disease.

Norrie disease is a rare X-linked recessive disease, also known as oculo-acoustico-cerebral degeneration, presents as a variable triad of retinal malformation or dysplasia, deafness, and mental retardation. It often has retinal findings that mimic PFV, including retinal folds, retrolental mass, microphthalmia, cataracts, and secondary glaucoma, but it is usually distinguished from PFV by its X-linked inheritance, bilaterality, and systemic manifestations.

Retinopathy of prematurity (*ROP*) if diagnosed late with end-stage findings such as total retinal detachment and posterior membranes can mimic PFV. However, it is usually distinguished by its bilaterality and occurrence in premature, low birth weight infants exposed to high levels of oxygen supplementation.

Ocular toxocariasis is an infectious disease of the retina caused by ingestion of Toxocara cysts, in which patients commonly present with a large glial mass coming off of the optic nerve. Late stage disease can present with retinal folds, or total retinal detachment. Because infection depends upon ingestion of feces of infested dogs, it usually presents in children who are older and more mobile (aged 4–8 years) than the typical patient with retinoblastoma.

Retinal detachment in the newborn and infant population is rarely a spontaneous event. More commonly, it is associated with a predisposing disease such as those listed above. However, in the absence of other identifiable causes of a retinal detachment, spontaneous detachment could mimic PFV, but would be readily distinguishable based on the clinical context, and absence of other ophthalmic findings such as those described in Table 20.1.

Diagnostic Methods

The key to the diagnosis of PFV is a careful and thorough clinical examination with appropriately selected testing modalities. Although most cases of PFV can be diagnosed on the basis of clinical exam alone, there are a variety of supplemental tests that may prove helpful in cases with challenging presentations. B-scan ultrasonography is critical if the view into the posterior segment is poor (Fig. 20.8). Anterior segment OCT can provide important information about the ciliary body and structures under the peripheral iris. In select cases, fluorescein angiography may be a useful test to identify patent irido-hyaloidal vessels. Although computed tomography is rarely necessary to make the diagnosis of PFV, radiographic scans through the orbit can detect the presence of calcification, the absence of which is more suggestive of PFV. Additionally, color-flow doppler sonography can be used to characterize the vascularity of PFV stalks [14].

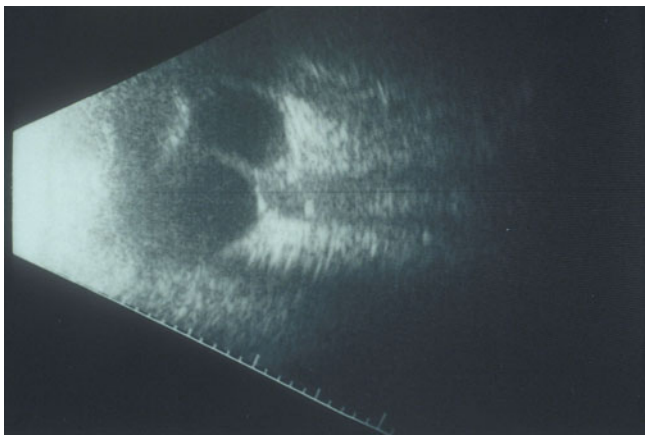

Fig. 20.8 B-scan of an eye with combined posterior and anterior PFV. There is apparent localized detachment at the optic nerve head forming a tent that attaches via a thick membrane/hyaloid remnant to the posterior aspect of the lens

Treatment

The management of PFV has evolved as the understanding of the disease and its various forms has improved. Each case requires an individual assessment of the goals for visual rehabilitation, as well as risks of any and all interventions, including observation.

Without treatment, all eyes with PFV that obscures a view of the fundus develop severe amblyopia, along with the associated risk of strabismus. One feared scenario likely due to growth of the lens is progressive shallowing of the anterior chamber, leading to angle closure in these small eyes, elevation of intraocular pressure, infarction of the ciliary body, vitreous hemorrhage, retinal detachment, and phthisis bulbi. In the 1970s, natural history collected on patients with PFV showed that enucleation was a common endpoint for these eyes due to intractable glaucoma and phthisis [3]. It is for these reasons that many advocate at least lens removal in certain cases of PFV, even if the prognosis for visual improvement is dismal.

Surgical Intervention

The decision to proceed with surgery usually depends upon the severity of presentation, as well as the patient's age, and visual prognosis. Common indications for surgery include a visually significant cataract, shallowing of the anterior chamber, intralenticular hemorrhage, traction on the ciliary body, and elevated intraocular pressure. Important considerations for surgical planning include awareness of the fact that the pars plana is not as well developed in an infant as it is in an adult, as well as cognizance of the strength of vitreoretinal adhesions, and the thick leathery consistence of the posterior lens capsule.

One of the utilized surgical options employed for patients with isolated posterior, and for the rare combined severe cases of PFV is a closed pars plana vitrectomy, lensectomy, and membranectomy. Patients with predominantly anterior PFV, including those with lens involvement and just a thin strand that bridges the optic nerve to the back of the lens, however, are best managed with a lensectomy via a limbal approach. Both techniques have the advantages of good visualization through a clear cornea. Factors thought to increase intraoperative and post-operative complications include the width of the fibrovascular stalk, presence of blood flow in the stalk, combined type of PFV, and microphthalmia [15]. Surgeons should be prepared to deal with thickened and difficult to cut posterior capsules and with ciliary processes that are pulled toward the center of the contracted posterior capsule. A few maneuvers are worth mentioning that facilitate the attainment of a large clear pupillary axis. After the anterior capsule is opened and the cortex removed, any blood vessels in the posterior capsule are cauterized using an intraocular cautery (Fig. 20.9); the posterior capsule is stabbed with an MVR blade; it is then divided into small segments using curved intraocular scissors and the capsular fragments are removed with the vitrector. The posterior capsule is divided radially all the way to the equator and in-between the ciliary processes in multiple quadrants (Figs. 20.10 and 20.11), and the segments are then removed using the vitrector [16]. For a video demonstration visit (https://vimeo.com/4405171). Post-operative management is similar to that for patients who have had cataract extraction and routinely includes anti-inflammatory medications, antibiotics, patching to prevent amblyopia, and aphakic correction, either with contact lenses or spectacles.

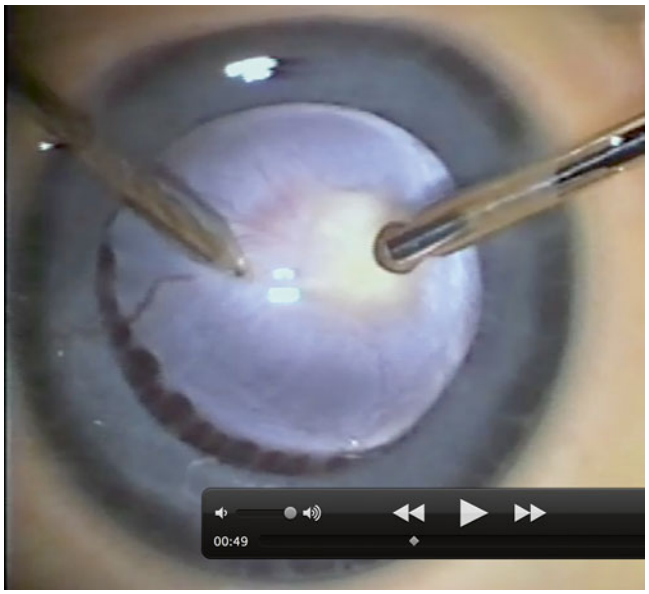

Fig. 20.9 Intraoperative photograph shows fibrotic posterior capsule with intracapsular blood vessels. Intraocular cautery cauterizes one of the larger vessels. The other instrument provides irrigation. The ciliary processes are pulled inferiorly toward the posterior capsule

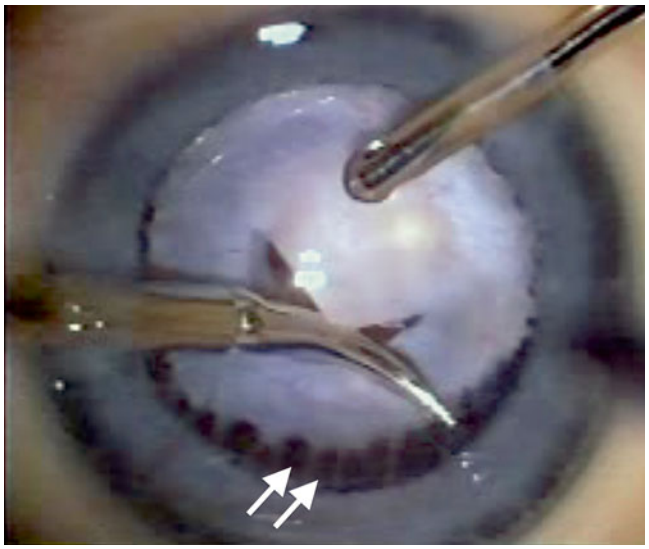

Fig. 20.10 Intraocular scissors are used to divide thick fibrotic posterior capsule all the way to the edge of the capsule between ciliary processes. Double arrows indicate elongated ciliary processes

Outcomes

Visual outcomes correlate strongly with the type and severity of the PFV, as well as the age at presentation [17]. In general, patients with anterior PFV fare better than those with combined or posterior forms of the disease. Those who are diagnosed and managed at a younger age tend to obtain better functional and anatomic outcomes. Patients who undergo surgery with the hope of obtaining good vision require dedicated families committed to long-term amblyopia therapy, including aphakic correction and patching. In the absence of these interventions, prognosis for good vision is guarded.

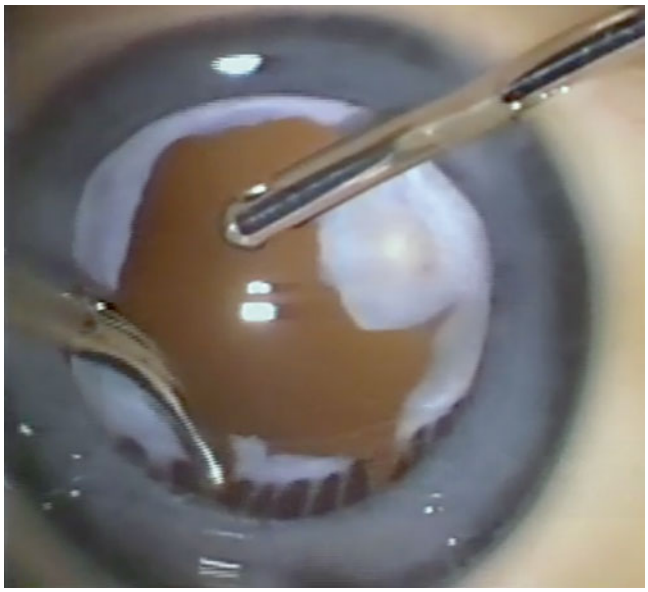

Fig. 20.11 More advanced stage of surgery shown in Figs. 20.8 and 20.9. An additional cut is taken between ciliary processes and a large part of the posterior capsule has been removed. This maneuver is repeated several times until the tight capsular ring is divided and the ciliary processes fall back in place and most of the capsule is removed

Illustrative Case

A 6-day-old newborn was referred to Ophthalmology for assessment of a cataract in the left eye. On examination, the cornea was noted to be slightly small at 9.5 mm in diameter, with mild ectropion uveae at 9 o'clock, a moderately deep anterior chamber, and a dense cataract with no view to the posterior pole. B-scan ultrasonography revealed a faint opacity extending from the disk to the anterior vitreous, but no retinal traction or detachment. The child was taken to the OR for lensectomy and removal of the retrolental stalk at 6 weeks of age. A clear corneal anterior surgical approach was undertaken. The anterior capsule was opened using the vitrector and an MVR blade. The capsulotomy was enlarged and the cortical material irrigated and aspirated. The posterior capsule was found to be white and thickened, and upon incision, a retrolental vessel was visualized and cauterized with intraocular cautery. The posterior capsule was divided using intraocular scissors and the vitrector. No complications were encountered. The patient's aphakia was corrected using a contact lens and patching was instituted. At the age of 3 years visual acuity in the operated eye was 20/50.

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Evaluation and Management of the Patient with Subluxated Lenses

21

Elias I. Traboulsi

Abstract

Patients with subluxated lenses present a number of diagnostic and therapeutic challenges. In addition to ascertaining the effect of the lens subluxation on vision and planning the appropriate treatment, one must determine whether there is an associated underlying systemic disorder or whether the subluxation is the result of an inherited purely ocular disease or the result of an injury or malformative process. Underlying systemic disorders can have serious cardiac and other organ involvement and need to be managed by a team of subspecialists best coordinated by a clinical geneticist. Ophthalmic management includes the correction of errors of refraction, the screening for and sometimes the treatment of glaucoma, the therapy of associated amblyopia and strabismus, and, in some cases, lens extraction and the management of the resulting aphakia. This chapter provides an algorithm for the diagnosis and management of such patients as well as some information on the clinical findings and genetics of associated systemic and ocular diseases.

Keywords

Ectopia lentis • Dislocated lenses • Marfan syndrome • Homocystinuria • Weill-Marchesani syndrome • Ectopia lentis et pupillae • Lens extraction • Genetics • Fibrillin • ADAMTS

Introduction

The lens is suspended to the ciliary body by the zonule, which is composed of a large number of zonular fibers that bridge the ciliary processes to the equatorial region of the lens. The zonule allows the lens to change its contour as the ciliary body contracts and relaxes, facilitating the accommodation process. The zonule is rich in fibrillin, which, in turn, is rich in cysteine and has a large number of disulfide bonds. It is therefore abnormal in Marfan syndrome (MFS), in which fibrillin is mutated, and in diseases of sulfate metabolism such as homocystinuria and sulfite oxidase deficiency. Also, mutations in members of the *ADAMTS* family of genes lead to ectopia lentis in the setting of diseases such as Weill-Marchesani syndrome (WMS) and others (Table 21.1). Tectonic changes in the zonule and its partial or total disruption by structural, biochemical to traumatic processes, lead to displacement of the lens from its normal position and to changes in its curvature and refractive power. Vision is subsequently reduced, and in the child, ametropic or derivational amblyopia may develop.

Ectopia lentis refers to any displacement of the crystalline lens away from its position in the center of the visual axis. If it remains attached, it is referred to as subluxated, and when it is totally loose, dislocated. The zonule exerts uniform circumferential traction on the lens capsule and suspends the lens behind the iris in a central position. If the zonular fibers are abnormal, they can stretch or break. If the fibers are stretched in one sector, the lens moves in the opposite direction. If all the fibers are stretched, dissolved, or missing, the lens in the young child will assume a rounded shape

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Table 21.1 Inherited and developmental disorders associated with ectopia lentis

Disease OMIM#	Defective gene or enzyme	Inheritance	Type and prevalence of ectopia lentis
Disorders of collagen metabolism			
Stickler syndrome 108300	*COL2A1*	AD	Uncertain about type of subluxation Rare
Kniest dysplasia 156550	*COL2A1*	AD	Uncertain about type of subluxation 15 %
Spondyloepiphyseal dysplasia congenital 183900	*COL2A1*	AD	Uncertain about type of subluxation Rare
Osteogenesis imperfecta congenita	*COL1A1* and *COL1A2*	AR/AD	Uncertain about type of subluxation Rare
Disorder of fibrillin formation			
Marfan syndrome 154700	*FBN1*	AD	Zonules are stretched. Edges of lens are irregular. Most move superiorly but could be in any direction 60–70 %
Simple ectopia lentis 129600	*FBN1*	AD	As in MFS >90 %
Simple ectopia lentis/ectopia lentis et pupillae	*ADAMTSL4*	AR	Variable degrees of subluxation and configuration of the lens contour. Remnants of the pupillary membrane in some
Weill-Marchesani syndrome, recessive 277600	*ADAMTS10*	AR	Most zonules are absent. Lens is loose and spherophakic. Blocks pupil as it moves forward >90 %
Weill-Marchesani syndrome, dominant	*FBN1*	AD	Uncertain about type and prevalence of subluxation
Shprintzen-Goldberg syndrome 182212	*FBN1*	AD	Uncertain about type and prevalence of subluxation
Developmental disorders			
Aniridia 106210	*PAX6*	AD	Uncertain about type of subluxation 10–20 %
Congenital glaucoma 601771	*CYP1B1*	AR	Rare. Probably due to stretching of globe
Persistence of fetal vasculature (PFV, PHPV)		Not inherited	Rare. Probably due to interruption of zonular fibers by persistent vessels and pull on zonular fibers by contracting posterior capsular membrane/fibrosis
Other connective tissue diseases			
Craniofacial dysmorphism with ocular coloboma, absent corpus callosum, and aortic dilatation (Temtamy syndrome) 615140	*C12ORF57*	AD	Uncertain about type and prevalence of subluxation
Craniofacial dysostosis with ectopia lentis and anterior segment dysgenesis (Traboulsi Syndrome) 601552	*ASPH*	AR	Progressive disruption of zonular fibers leads to pupillary block and its consequences All
Spondyloepimetaphyseal dysplasia with joint laxity (SEMDJL) 271640	*B3GALT6*	AD	Uncertain about type of subluxation Rare
Ectopia lentis, cataracts, axial myopia, and retinal detachments 614292	*LEPREL1*	AR	Uncertain about type of subluxation Rare
Metabolic disorders			
Homocystinuria 236200	Cystathionine beta-synthase deficiency	AR	Zonules disappear and leave a frill at lens equator. Lens subluxates anteriorly causing pupillary block. Could end in anterior chamber All untreated
Hyperlysinemia 238700	Lysine: alpha-ketoglutarate reductase deficiency	AR	Uncertain about type and prevalence of subluxated lenses

(continued)

Table 21.1 (continued)

Disease OMIM#	Defective gene or enzyme	Inheritance	Type and prevalence of ectopia lentis
Sulfocysteinuria 272300	Sulfite oxidase deficiency	AR	Uncertain about type and prevalence of subluxated lenses
Molybdenum cofactor deficiency types A and B 252150 and 252160	Combined deficiency of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase	AR	Uncertain about type and prevalence of subluxated lenses
Miscellaneous disorders			
Ectopia lentis et pupillae 225200	*ADAMTSL4*	AR	Lens has irregular edges with sectors of absent or stretched zonular fibers. Remnants of the pupillary membrane are almost always present and could be extensive. Lens could have cortical opacities 95 %
Megalocornea 309300	*CHRDL1*	XR	Uncertain about characteristics of lens subluxation Rare
Cohen syndrome 216550	*COH1*	AR	Progressive stretching of zonules with age leading to progressive myopia and some irido- and phakodonesis Very common

Some of the cells in this table are not filled because the information is not available

(spherophakia), and this will lead to a significant (up to 20 D) degree of myopia. Irregular contour of the lens from sectoral irregularities in zonular tension leads to lenticular astigmatism that can be quite severe, measuring up 7 or 8 diopters or even more. Iridodonesis or movement of the iris with ocular movements results from loss of the posterior support that the lens and zonules provide to the iris diaphragm. Iridodonesis is more conspicuous with increasing degrees of lenticular displacement.

Differential Diagnosis of Ectopia Lentis

Dislocation of the lens can be the result of trauma, and a history of eye injury should always be sought in children presenting with ectopia lentis, especially if it is unilateral. Bilateral lens subluxation is almost always of genetic origin. It is present in about 60 % of patient with Marfan syndrome [1]. Dominantly inherited isolated ectopia lentis is caused by *FBN1* mutations and is in a way a form of Marfan syndrome with predominant ocular phenotype [2, 3]. Patients with Weill-Marchesani syndrome have lenses with very little if any intact zonular fibers and the lenses are spherophakic. Most patients have mutations in *ADAMTS10* [4], but some are due to mutations in *FBN1* [5]. The contrasting habitus of MFS (tall stature, long hands and feet, thin build, lax joints and skin) and WMS (short stature, thick skin, short hands and feet, muscular build) [6] help to differentiate the two syndromes on a clinical basis. Ectopia lentis can also result from mutations in *ADAMTS17* and *ADAMTSL4*, with a phenotype that is Weill-Marchesani-like in nature but without skin, joint, and cardiac anomalies in the first and recessive isolated ectopia lentis in the second [7, 8].

Ectopia lentis can also be a component of developmental malformation syndromes affecting the eye such as aniridia or persistent fetal vasculature (PFV) or a manifestation of a metabolic disorder such as homocystinuria. It has also been reported in rare inherited multisystem disorders such as Cohen syndrome and Traboulsi syndrome. The following sections briefly review the clinical features of these conditions.

Case Presentation

A 2 8/12 year-old girl was referred because she sat close to the television and drew with her face very close to the paper. Her past medical history was non-revealing, and her general physical examination did not show signs of Marfan syndrome or any of the other conditions associated with ectopia lentis. Her visual acuity was 20/200 OD and 20/100 OS. Her refraction was −10.50 +7.50×80 OD with which she saw 20/100 OD and 20/60 OS. Her IOP was normal in both eyes. The slit-lamp examination revealed anteriorly displaced Schwalbe's line in both eyes, extensive remnants of the pupillary membrane in both eyes, and bilateral subluxated lenses OD>OS (Fig. 21.1). Glasses were prescribed as well as patching of her left eye. Although a clinical diagnosis of *ectopia lentis et pupillae* was

(continued)

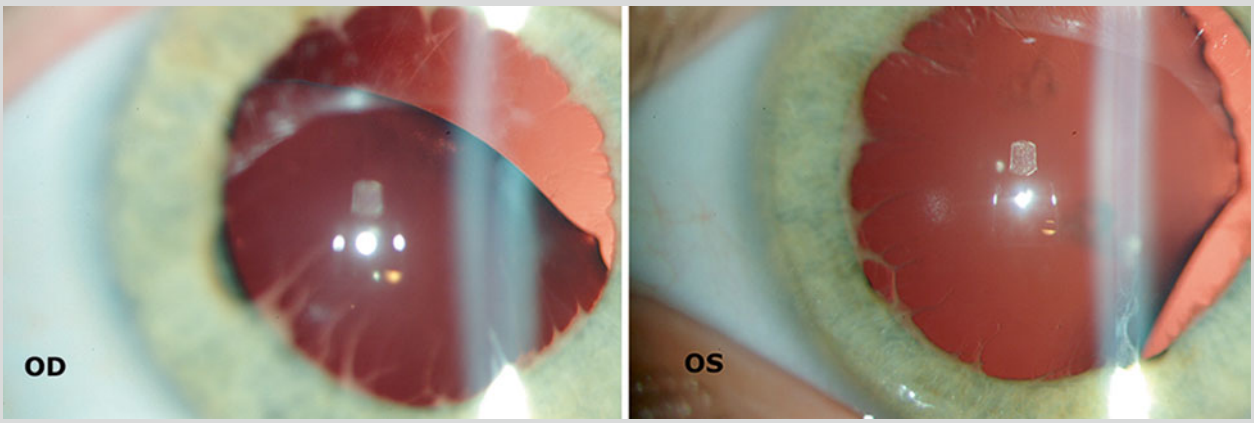

Fig. 21.1 *Right* (OD) and *left* (OS) eyes of patient with *ectopia lentis et pupillae* described in case report. Note remnants of the pupillary membrane OD>OS and small paracentral posterior subcapsular cataract OS

made, it was decided to have her examined by the pediatric cardiologist to make sure she did not have any of the cardiac problems associated with Marfan syndrome. That examination did not reveal any abnormalities. She did well with her glasses and appeared to function much better. Her vision improved to 20/50 OD and 20/30 OS over the course of 6 months and to 20/40 OD and 20/25 OS 1 year later. The prescription in the left eye changed slightly but that of the right eye was stable. She was noted to have a small posterior subcapsular cataract in the left eye. Three years later her vision was 20/30 OU with −9.50 +5.50×85 OD and −4.50 +3.50×80 OS. The slit-lamp findings had not changed. Over the next several years, she developed amblyopia in her right eye that was reversed with patching, and her IOP measured in the low 20s on a few occasions but no treatment was given. At the age of 15, she continues to have excellent vision in her left eye at 20/25 and 20/40 in the right eye. Her intraocular pressure remains in the normal range and no surgery has been performed.

Synopsis: This is a case of subluxation in which management with careful refraction and amblyopia treatment resulted in the development and maintenance of normal vision. A systemic diagnosis was investigated by appropriate referral early in the course of disease and was unrevealing. Because the subluxation has minimally progressed, if at all, this patient can be observed.

Simple (Isolated) Ectopia Lentis

In autosomal dominant ectopia lentis, the characteristics of lens subluxation are indistinguishable from those of patients with the Marfan syndrome and cases are due to mutations in *FBN1* [9–11]. Some family members of patients with dominant ectopia lentis will show signs of Marfan syndrome.

Recessive simple ectopia lentis can result from mutations in *ADAMTSL4* [7]. Autosomal recessive inheritance of subluxated lenses should suggest the diagnosis of *ectopia lentis et pupillae*, homocystinuria, Weill-Marchesani syndrome, or the entity of craniofacial dysostosis, dislocation of the lens, and anterior segment dysgenesis (Traboulsi syndrome).

Ectopia Lentis et Pupillae

This is an autosomal recessive, purely ocular disease characterized by congenital subluxation of the lens [12, 13]. Pupils may be eccentric, miotic, and difficult to dilate in some patients, with the lens and pupil displaced in opposite directions. Most often there are remnants of the pupillary membrane that assists in the diagnosis (Fig. 21.1). Glaucoma and retinal detachment can occur spontaneously or following lens extraction [12]. The decision to extract subluxated lenses in this condition is difficult to make. Every effort should be made to perform an excellent refraction and prescribe the appropriate glasses, deferring surgical interventions if at all possible. Patching is used to treat amblyopia if necessary. The subluxation is generally stable over prolonged periods of time.

Ectopia lentis et pupillae is caused by mutations in *ADAMTSL4* [7, 14]. The ADMTSL4 protein binds to FBN1 and promotes microfibril assembly in the zonules [15, 16]. It is unclear how mutations in ADAMTSL4 lead to the iris and pupillary abnormalities in ectopia lentis et pupillae.

Ectopia Lentis, Axial Myopia, Cataract, and Retinal Detachment

Khan and coworkers described lens subluxation and/or juvenile lens opacities in four sisters from a consanguineous family [17]. None of the patients had systemic abnormalities

and FBN1 sequencing was normal. Two of the four sisters who had cataract surgery developed bilateral postoperative retinal detachments, and one had documented lens instability during cataract surgery. The patients had a novel homozygous recessive mutation in *LEPREL1* (c.292delC; p. Gly100Alafs*104). Mutations in this gene had been reported in patients with cataracts and possible lens subluxation [18].

Marfan Syndrome

This disease is named after the French pediatrician Antoine Marfan [19]. It results from an abnormality in fibrillin 1, a major component of the lens zonule and of connective tissues [20].

Marfan syndrome most prominently affects the skeleton, the heart, and the eye. Common and major clinical manifestations include subluxation of the crystalline lens; dilatation of the aortic root and aneurysm of the ascending aorta; and skeletal abnormalities such as kyphoscoliosis, an upper segment/lower segment ratio 2SD below mean for age, and pectus excavatum [21–23]. Additional signs such as myopia, mitral valve prolapse, arachnodactyly, joint laxity [24], tall stature, pes planus, striae distensae, pneumothorax, obstructive sleep apnea, and dural ectasia may also be present [25]. In order to make a clinical diagnosis, patients have to satisfy a number of criteria outlined first in the 1986 Berlin criteria [22] and later revised in Ghent [26] and one last time in 2014 [27]. Detailed ophthalmological, cardiac, and skeletal evaluations should be performed in patients in whom the diagnosis is suspected [21, 28]. The advent and availability of *FBN1* molecular testing has significantly increased diagnostic precision. Patients with homocystinuria may have a body habitus indistinguishable from that of patients with the Marfan syndrome, and the exclusion of the former using biochemical testing is a required criterion for the clinical diagnosis of Marfan syndrome [26]. Advances in the medical and surgical management of patients with Marfan syndrome have resulted in a significant increase in survival [29].

About 25 % of cases of Marfan syndrome result from fresh mutations in *FBN1* [10, 30, 31]; the rest are due to inherited mutations in the same gene [9, 32, 33]. The clinical manifestations of MFS result from altered morphogenetic and homeostatic programs induced by altered transforming growth factor-beta signaling. Transforming growth factor-beta neutralizing antibodies or losartan (an angiotensin II type 1 receptor antagonist) prevents and possibly reverses aortic root dilatation, mitral valve prolapse, lung disease, and skeletal muscle dysfunction. Losartan®, a drug widely used to treat arterial hypertension in humans, is currently used for the prevention of some of the clinical manifestations in Marfan syndrome [34, 35]. Most Marfan syndrome families have unique *FBN1* mutations [36]. In a study of 1013 probands with *FBN1* mutations and Marfan syndrome, Faivre et al. [37] found a higher probability of ectopia lentis in patients with missense mutations substituting or producing a cysteine.

Ocular abnormalities in the Marfan syndrome can be correlated to the pattern of distribution of fibrillin in the eye [38, 39]. Fibrillin fibers that are normally present around the equatorial region of the lens and on the anterior capsule were found to be abnormal and disrupted in patients with the Marfan syndrome [40]. Subluxation of the crystalline lens is the most diagnostic ocular abnormality in Marfan syndrome and is found in about 60 % of patients. It varies from mild superior and posterior displacement of the lens to significant subluxation that places the equator of the lens in the pupillary axis. It is critical to examine the patient at the slit lamp after the pupil has been as dilated as possible. The patient is asked to look down as the lens is examined in retroillumination; if the lens is displaced superiorly, there will be a gap between the visible inferior edge of the lens and the iris, the equatorial region will be crenated, and the zonules will be clearly visible. The lens is rarely totally dislocated into the vitreous cavity and this occurs mostly in older individuals. The lens is (almost) never dislocated into the anterior chamber. Although superior and temporal displacement of the lens is most common, inferior, nasal, or lateral subluxation can also occur. The zonular fibers are stretched and may be reduced in number (Fig. 21.2).

Lens subluxation may not be noted in the first few years of life and progresses thereafter. Microspherophakia was present in only two of 160 patients [41]. In microspherophakia, the lens has a small diameter and assumes a globular configuration that results in very high myopia [39]. Cataracts develop 10–20 years earlier in patients with the Marfan syndrome than in the general population.

The corneal curvature is flatter than normal in most patients with the Marfan syndrome with average keratometric values of 41.38 ± 2.04 diopters, as compared to 43.44 ± 0.19 diopters for normal males and 44.00 ± 0.19 diopters for normal females. Corneal thickness has been reported as normal in one study [41]. Sultan et al. noted that the cornea was thin and that reduced pachymetric readings highly correlated with ectopia lentis [42]. In a study of 62 patients who met the clinical diagnostic criteria for Marfan syndrome and 98 controls, we found that Marfan patients had significantly lower keratometry and central corneal thickness (CCT) values than controls. We proposed that values less than 42 D could be used as a clinical diagnostic criterion for Marfan syndrome [43].

Other abnormalities include a very deep anterior chamber, with prominent iris processes to Schwalbe's line, a thin and velvety iris and a pupil that may be difficult to dilate, especially in the more severely affected patients. 19.2 % of 573 patients with the Marfan syndrome have strabismus, with a majority having exotropia [44]. Amblyopia in patients with the Marfan syndrome responds well to optical correction and visual penalization, sometimes despite years of

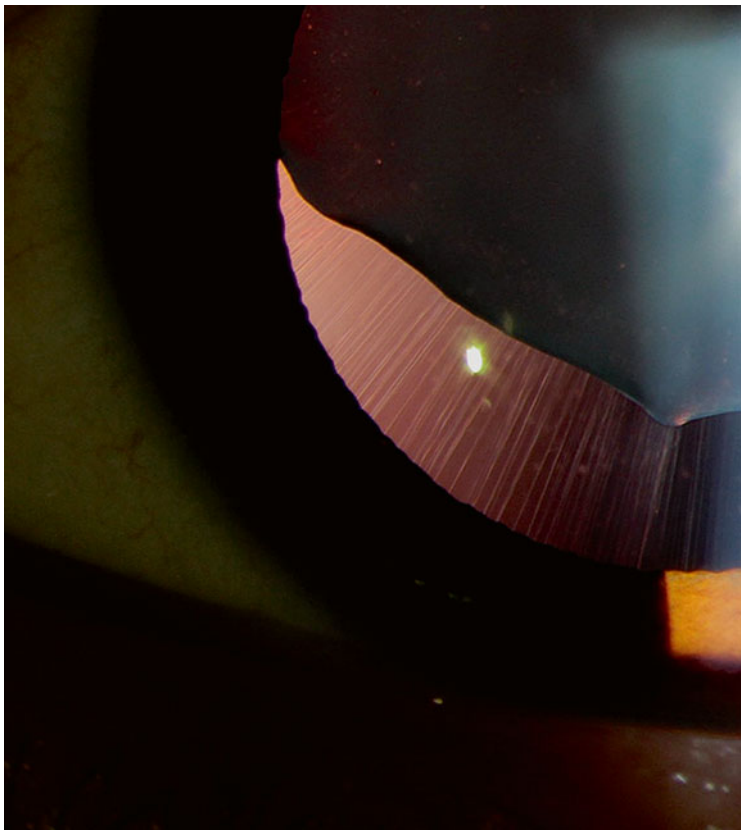

Fig. 21.2 Stretched and rarified zonules in a patient with superiorly subluxated lens

uncorrected high errors of refraction. The vitreous is well formed in the majority of patients with the Marfan syndrome. When the lens is extracted in children, one almost never has an intraoperative problem with the lens sinking back into the vitreous. The retinal appearance is generally normal [41]. Retinal detachment may occur spontaneously or may follow lens extraction [45]. Open angle glaucoma is more common in patients with Marfan syndrome than the general population [46]. Pupillary block is extremely rare.

Infants and children with the Marfan syndrome can present major therapeutic orthopedic and cardiovascular challenges [47, 48]. Treatment consists of the prevention of cardiac complications using beta-blocking agents [49] and more recently losartan®, an ATI antagonist that arrests the progression of aortic dilatation [34]. Patients often require surgical repair of the ascending aorta and other valvular disorders, as well as a number of orthopedic procedures, the discussion of which is beyond the scope of this book. Prenatal diagnosis of the Marfan syndrome is possible using ultrasonography if the fetus is severely affected. Direct gene sequencing may allow prenatal or preimplantation diagnosis [50].

Weill-Marchesani Syndrome

The Weill-Marchesani syndrome is a rare autosomal recessive condition but autosomal dominant cases have been described. Patients are short, brachycephalic, and have short stubby spade-like hands (Fig. 21.3) and feet, microspherophakia, and subluxated lenses [51–53]. The recessive form and dominant form are caused, respectively, by mutations in ADAMTS10 or in FBN1, and the resulting clinical presentations are not easily distinguishable [4–6]. Mutations in ADAMTS17 cause a syndrome that resembles WMS [8].

The lens is small and round and tends to move into and block the pupil leading to glaucoma [54]. Myopia results from spherophakia and the lens diameter may be very small and the lens can thicken by 25 % [55]. The anterior chamber is usually shallow, predisposing to angle closure glaucoma. Patients with WMS should undergo a peripheral laser iridotomy to prevent the development of pupillary block. Lens extraction may become necessary in those with mobile lenses that continue to cause significant problems.

Homocystinuria

Untreated patients with this autosomal recessive disease have mental retardation, coarse fair hair, a Marfanoid body habitus, and a thromboembolic diathesis. They can be misdiagnosed with the Marfan syndrome because of their slender body habitus and the presence of lens dislocation.

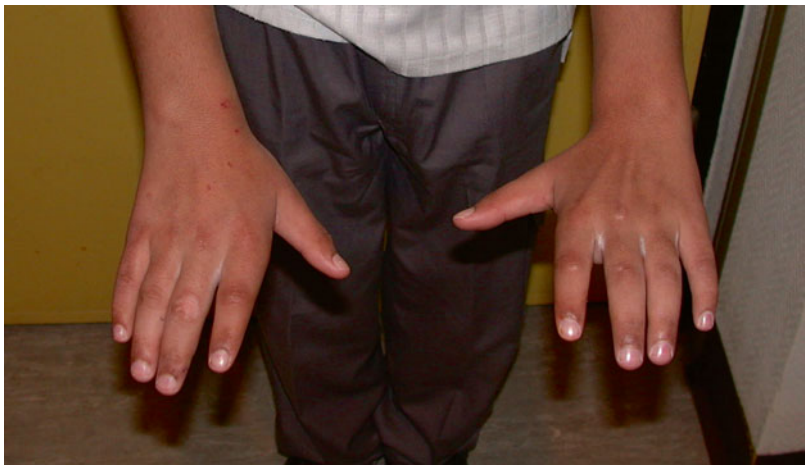

Fig. 21.3 Spade-like hands of patient with Weill-Marchesani syndrome. Note short and stubby fingers

Accumulation of homocysteine may be responsible for the arteriosclerosis, abnormal platelet adhesiveness, and frequent cerebral thrombosis. It has also been proposed that the accumulated homocysteine interferes with collagen and elastin cross-linking hence leading to the observed connective tissue defects and ectopia lentis.

There are two major subtypes. The most common type results from mutations in cystathionine-ß-synthetase deficiency. 50 % of patients with this type respond to vitamin B6 supplementation with clearing of their urine of homocysteine. Mental retardation occurs mostly in vitamin B6 nonresponders [56]. The less common variety is caused by reduced activity of 5-methyltetrahydrofolate-homocysteine methyltransferase.

All untreated patients with homocystinuria develop dislocation of both lenses: 40 % by the age of 5 years. The lenses dislocate completely in an inferior or inferonasal direction [57]. Anterior movement of the unrestrained lenses leads to pupillary block and to glaucoma leading to patients to present with a red eye and cloudy cornea. There are usually no zonular remnants [58]. High myopia results from microspherophakia. Cystic and pigmentary changes are present in the retinal periphery of some patients.

Molybdenum Cofactor Defects and Sulfite Oxidase Deficiency

Ectopia lentis develops in the first year or two of life in this group of metabolic diseases characterized by severe neurologic abnormalities [59, 60]. Patients have a molybdenum-containing cofactor deficiency that results in deficient activities of three enzymes that require this cofactor: sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase [61, 62]. Mutations in either *MOCS1* or *MOCS2* cause identical clinical presentations [63]. In addition to dislocated lenses, patients have convulsions, feeding difficulties, and mental retardation.

Hyperlysinemia

There is only one patient with hyperlysinemia who was reported to have dislocated lenses [64], and the association has been considered fortuitous by some authors [65]. We will not give more details of this condition in this chapter.

Craniofacial Dysostosis with Ectopia Lentis, Anterior Segment Dysgenesis, and Glaucoma (Traboulsi Syndrome)

This autosomal recessive condition was reported in several Lebanese Druze families and a few other patients from around the world. Patients have a characteristic facial appearance, craniofacial dysmorphism, and severe ocular anomalies that include totally dislocated lenses, anterior segment dysgenesis, severe glaucoma, and progressive spontaneous thinning and perforation of the perilimbal sclera with bleb formation [66–68]. The disease is caused by mutations in *ASPH* that code for aspartyl/asparaginyl β-hydroxylase which is specific to the aspartic acid and asparagine residues that fall within the consensus motif (CX[DN]4X[FY]XCXC) in EGF domain-containing proteins [69]. Virtually all of the genes implicated in syndromic or isolated forms of ectopia lentis (*FBN1*, *ADAMTSL4*, *ADAMTS10*, and *ADAMTS17*) encode proteins that harbor EGF domains; hence a disruption of this hydroxylase activity is postulated to lead to the lens dislocation and other ocular and facial abnormalities in this syndrome. The management of the ocular abnormalities in this syndrome is extremely challenging.

Cohen Syndrome

I include the autosomal recessive Cohen syndrome in this chapter because it is common in the Amish and in communities in which consanguinity or a closed gene pool is present.

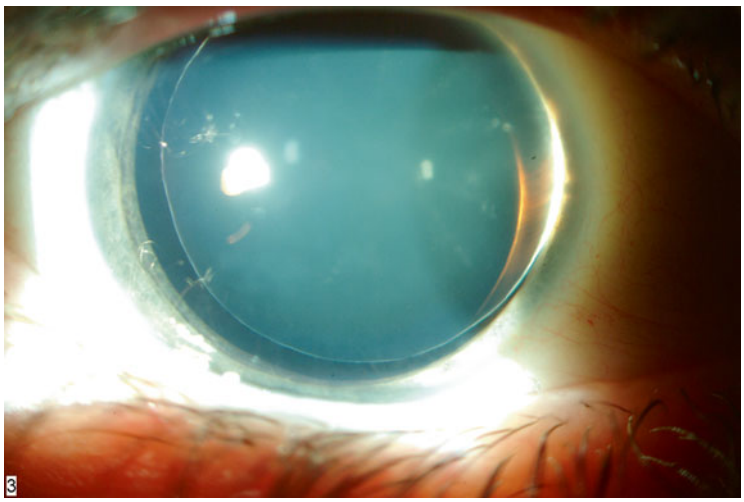

Fig. 21.4 Spherophakic lens in a patient with Cohen syndrome. One can see the contour of the whole lens. The pupil is widely dilated

Although there is no flagrant ectopia lentis, especially in very young children, adolescents and young adults develop progressive lenticular myopia, phako- and iridodonesis [70]. The lens remains round (Fig. 21.4), indicating that all the zonules relax equally, leading to spherophakia. Patients with Cohen syndrome also develop cataracts and care must be taken during surgery because of the phakodonesis. Some patients have also developed retinal detachments [71].

Management of the Patient with Ectopia Lentis

Medical Management

It is critical to determine whether one is dealing with an isolated ocular problem from trauma, for example, or from mutations in genes such as *ADAMTSL4* that cause ectopia lentis et pupillae, or if the subluxated lens is part of a systemic disease in which case, the management goes beyond treating the ocular complications and involves therapies and interventions by other specialists. In case there is any doubt, patients should be referred to clinical geneticists who would coordinate the necessary consultations to rule out Marfan syndrome or other conditions. Even the ophthalmic management depends on the underlying etiology since surgical interventions should take into consideration the underlying and associated medical issues such as cardiac problems in patients with MFS and a predisposition to thrombosis in patients with homocystinuria.

All patients with dislocated lenses without a clear history of trauma should undergo quantitation of urine and serum amino acids to rule out homocystinuria. An episode of anterior dislocation of the crystalline lens in a patient with presumed Marfan syndrome should suggest the diagnosis of homocystinuria.

Patients with homocystinuria receive supplementation with 50–1000 mg/day of oral vitamin B6, which clears the urine from methionine in vitamin B6 responders. Nonresponders do not receive further vitamin supplementation and are started on a diet low in methionine, and they also receive cystine supplements. Betaine supplementation facilitates the conversion of serum homocysteine to methionine and significantly reduces the symptoms of homocystinuria. Neonatal screening, detection of homocystinuria at birth, and appropriate therapy will prevent the development of mental retardation, myopia, and lens subluxation. Platelet anti-aggregation agents such as dipyridamole and acetylsalicylic acid are given to prevent vaso-occlusive or thromboembolic events. A normal life span is expected in vitamin B6 responders. Patients with other types of homocystinuria have shortened survival depending on the type of mutation, severity of the disease at diagnosis, and the time of institution of therapy.

From an ophthalmic perspective, patients can be refracted through the phakic or aphakic part of the pupil, if the edge of the lens is visible in the pupillary area, and the glasses or contact lenses are prescribed accordingly. If optical correction is difficult, most often from intermittent movement of the lens in and out of the visual axis or if the lens edge interferes with refraction and vision, or if the degree of astigmatism is extremely high, lens extraction may become necessary. Frequent measurements of the intraocular pressure are necessary because of the increased prevalence of glaucoma in patients with ectopia lentis et pupillae. Periodic ultrasonographic examination of the eye or visual field testing is indicated in the occasional patient with severely miotic and non-dilating pupils. Laser and surgical iridoplasty have been used to visualize the fundus and to permit retinoscopy.

In patients with WMS and in those with homocystinuria, a peripheral iridectomy/iridotomy should be performed to prevent or relieve pupillary block. Lens extraction may be

necessary to control intraocular pressure elevation in some patients. Although mydriatics are preferred over miotics for the relief of pupillary block, cycloplegics have been reported to induce pupillary block in patients with the Weill-Marchesani syndrome [72]. Trabeculectomy may be successful in controlling intraocular pressure.

Management of the Dislocated Lens

If the crystalline lens dislocates into the anterior chamber, the pupil is dilated and the patient is placed in a supine position to reposition the lens behind the pupil. Digital pressure on the cornea may be a helpful maneuver. Miotics are then prescribed, and a peripheral laser iridotomy is performed. In some patients, and with the passage of time, the pupillary sphincter infarcts and miotics become ineffective in keeping the lens behind the iris. Lens extraction may then become necessary. Because of the increased risk of thromboembolic phenomena with general anesthesia, local anesthesia is preferred if surgery is inevitable. Intravenous hydration is instituted prior to surgery. Harrison et al. [73] studied 45 patients with ophthalmic complications of homocystinuria. 84 surgical procedures were performed on 40 of these patients. 82 procedures were done under general anesthesia. Lens dislocation into the anterior chamber was the most frequent indication for surgery (50 %) followed by pupillary block glaucoma (12 %).

Careful and repeated phakic or aphakic refractions are necessary to achieve the best possible vision. Patients with subluxated lenses that are bisecting the pupillary aperture should try both aphakic and phakic corrections before lens extraction is considered because of the risk of retinal detachment, especially in elongated globes. If lens extraction is planned, automated suction/cutting lensectomy is preferred and may be performed through the limbus or the pars plana, depending on the surgeon's preference. The vitreous is well formed and the lens does not sink back toward the retina (personal observations). The indications for and techniques of clear subluxated lens removal in patients with the Marfan syndrome have been the subject of controversy. A cataractous lens that obscures the visual axis evidently needs to be removed. This can be achieved using endocapsular or extracapsular techniques [74, 75]. Intracapsular lens extractions should be avoided. Removing clear subluxated lenses that bisect the visual axis or that render refraction very difficult is gaining wide acceptance especially if diligent efforts at refracting the patient through the phakic or aphakic portions of the pupil have been undertaken. Sufficient time, in the order of several months, should be allowed for the patient to adapt to new corrective refractive method before a decision to perform a lensectomy is taken. Limbal (the author's preferred approach) or pars plana lensectomy can be performed safely in patients with the Marfan syndrome, and that these procedures result in a clear pupillary axis, which allows a stable refraction and excellent vision [76, 77]. Patients with an increased axial length may be at higher risk of retinal detachment following lens extraction [41], although no statistics are currently available that address this specific issue. Transscleral fixation of the intraocular lens has been used in adults when capsular support is inadequate [78]. Anterior chamber lenses are considered safe and effective by some [79]. In the pediatric population, many, including the author of this chapter, feel that intraocular lenses of any type have unpredictable and potentially hazardous outcomes, including late dislocation even if sutured to the sulcus or iris. I consider aphakic correction with glasses or contact lenses to be a safer alternative. Iris claw lenses have been used and are currently studied as a modality to treat aphakia in children.

Concluding Pearls

- Look at the patient's body habitus, it will give you a clue to the underlying systemic disease and will allow appropriate referral to geneticist and multispeciality team.
- Examine the anterior segment and the subluxated lens carefully; the anatomy of the lens can point to the diagnosis.
- Do not rush into removing a subluxated lens. Refraction will be difficult but feasible and corrective lenses may allow the avoidance or deferral of surgery.
  - Perform both phakic and aphakic refraction and subjectively manifest whenever possible.
- While multiple surgical approaches and refractive correction of aphakia are possible, simple ones are probably the safest.
- Involve the clinical geneticist in the management of the patient with subluxated lenses as they are the experts in the diagnosis of systemic inherited disorders.

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Part VI

Uveitis

Uveitis Associated with Juvenile Idiopathic Arthritis

22

Francesco Pichi, Paola Carrai, and Careen Lowder

Abstract

Juvenile idiopathic arthritis (JIA) is the most common systemic disease causing uveitis in childhood, with a prevalence of 10 per 100,000 persons. JIA often takes a severe inflammatory course, and its complications often endanger vision. Regular ophthalmologic examinations should be performed starting as soon as JIA is diagnosed. Of the patients who develop uveitis associated with JIA, 75–80 % of patients are females and antinuclear antibodies are found in 70–90 %. The risk for vision loss is higher if uveitis begins in the preschool years. Severely affected patients should be treated in tertiary centers by uveitis specialists to optimize their long-term outcome. Multidisciplinary, individualized treatment is needed because of the chronic course of active inflammation and the ensuing high risk of complications that can endanger vision. Topical corticosteroids should be given as the initial treatment. Systemic immunosuppression is needed if inflammation persists despite topical corticosteroids, if new complications arise, or if the topical steroids have to be given in excessively high doses or have unacceptable side effects. If the therapeutic effect remains inadequate, conventional and biological immune modulators can be given in a stepwise fashion until therapeutic response is attained. Treatment lowers the risk of uveitis and its complications and thereby improves the prognosis for good visual function.

Keywords

Juvenile idiopathic arthritis • Anterior uveitis • Ocular complications • Immunosuppression

Introduction

Juvenile idiopathic arthritis (JIA), an umbrella term encompassing the most common chronic rheumatic diseases in childhood, is broadly defined by the International League of Associations for Rheumatology (ILAR) as arthritis of unknown etiology that begins before the age of 16 years and persists for at least 6 weeks, with other known conditions excluded [1]. In an effort to develop mutually exclusive disease categories of idiopathic childhood arthritis, seven categories within the JIA classification have also been defined (Table 22.1).

The prevalence of JIA is approximately 1 per 1000 children and remains an important cause of disability in the pediatric age group with prognostic implications that often extend into adulthood [2–7]. The disease is more common in girls than boys, with a ratio 3:2. Prolonged disease course also occurs more frequently in girls.

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Table 22.1 International league of associations for rheumatology classification of juvenile idiopathic arthritis [1]

Subtype of JIA	Features	Association with uveitis
Systemic subtype (still disease)	• Average age <5 years • High-grade fever, multiple extra-articular manifestations (rash, hepatosplenomegaly, lymphadenopathy)	Uveitis in 5 % of cases
Polyarticular JIA (RF negative)	• Arthritis affecting ≥5 joints in the first 6 months with a negative RF • It can be asymmetrical or symmetrical with large and small joints involved	High risk (70 %) of uveitis in asymmetrical disease
Polyarticular JIA (RF positive)	• Arthritis affecting ≥ 5 joints in the first 6 months with a positive RF titer on two occasions • There is symmetrical involvement of small joints—particularly the hands and wrists with swelling and stiffness • Systemic features such as fever, enlarged liver and spleen, lymphadenopathy, serositis, and pericardial effusions can be present	Uveitis 10 %
Oligoarticular subtype	• ≤ 4 affected during the first 6 weeks of the disease • Frequently, low titers of antinuclear antibodies (ANA) are present, and rheumatoid factor is almost always absent	Highest association with uveitis, 70–80 % of cases
Psoriatic subtype	• Children have both arthritis and psoriatic cutaneous disease or a family history of psoriasis in a parent or sibling • Typical signs of psoriatic arthritis include nail changes and widespread swelling of a toe or finger called dactylitis	Associated with uveitis in 10–20 % of cases
Enthesitis-related subtype	Causes inflammation of tendons and ligaments at sites of attachment to bone	Acute, recurrent, unilateral, anterior uveitis in older boys who are HLA-B27 positive
Undifferentiated arthritis	Any arthritis of unknown cause, with symptoms continuing at least 6 weeks, that does not meet criteria for any one type of JIA or involves symptoms that span two or more types	Unknown

Pathogenesis

The underlying etiology involves immune dysregulation and targeting of autoantigens within the synovial membrane of involved joints. The disease is characterized by synovial proliferation and infiltration by inflammatory cells, with increased synovial fluid and pannus formation. The persistence of synovial pannus may lead to damage of cartilage and bone with subsequent functional disability. The cause of immune dysregulation is unknown. The condition is not inherited as a single-gene Mendelian disorder. However, susceptibility likely has a genetic component, with specific HLA subtypes conferring a greater risk. In some cases, individuals may have a genetic tendency to develop JIA, but develop the condition only after exposure to an infection or other unknown trigger [8].

Ocular Manifestations

Uveitis is the most common ocular manifestation that children with JIA develop. The uveitis associated with JIA is typically anterior (involving the iris and ciliary body), nongranulomatous, chronic, and asymptomatic. It is bilateral in approximately 80 % of cases, and often unilateral disease progresses to bilateral involvement. Risk factors for the development of uveitis are presented in Table 22.2.

Eye inflammation is usually asymptomatic and nonpainful. On rare occasions, a child might complain of blurred vision and light sensitivity or family members may note that his/her eyes might look red or cloudy. Unfortunately, the disease does not cause obvious symptoms in about 50 % of patients [9]. Even low-grade uveitis may lead eventually to ocular damage, including band keratopathy, maculopathy (macular edema, macular cysts, epiretinal membrane), glaucomatous optic neuropathy, and cataract formation from chronic inflammation and corticosteroid therapy.

Cataract, glaucoma, and macular edema account for a majority permanent visual loss among these patients [9]. Risk factors for complications include male gender, presence of uveitis prior to arthritis, short duration between uveitis and arthritis onset, ocular complications present upon initial ophthalmologic visit, specifically abnormally high or low intraocular pressure, and posterior synechiae [9] (Table 22.2). Therefore, the knowledge of these factors can help to optimize management of children with uveitis and improve direct screening and therapy.

The more severe and widespread the arthritis, the less likely the child is to develop uveitis [10]. The average age of onset of uveitis in patients with JIA is 6 years. Table 22.3 lists the recommended screening schedule from the American Academy of Pediatrics [9]. The period of highest risk is within the first 4 years of diagnosis of arthritis, but it can occur 1 year before or as late as 15 years after the arthritis.

Table 22.2 Risk factors for developing uveitis and risk factors for visual morbidity

	Risk factors for uveitis development	Risk factors for visual complications
ANA	ANA positivity	None
Disease duration	None	Short duration between arthritis diagnosis and uveitis diagnosis
Age at onset	Young age at arthritis onset	Young age at uveitis onset
JIA subtype	• Oligoarticular JIA • Pauciarticular JRA • Psoriatic JIA • Enthesitis-related JIA • Other arthritis	None
Gender	Females	Males
HLA	HLA B27, HLA DR11	None
Relationship between uveitis and arthritis	None	Uveitis before arthritis
First ophthalmology visit	None	Ocular complications at first examination

JIA juvenile idiopathic arthritis, *HLA* human leukocyte antigen

Table 22.3 American academy of pediatrics frequency of screening ophthalmologic examination for children with juvenile idiopathic arthritis [9]

Type	ANA	Age at onset, year	Duration of disease, year	Risk category	Eye examination frequency, months
Oligoarthritis or polyarthritis	+	≤6	≤4	High	3
	+	≤6	>4	Moderate	6
	+	≤6	>7	Low	12
	+	>6	≤4	Moderate	6
	+	>6	>4	Low	12
	−	≤6	≤4	Moderate	6
	−	≤6	>4	Low	12
	−	>6	NA	Low	12
Systemic disease (fever, rash)	NA	NA	NA	Low	12

ANA antinuclear antibody, *y* years, *NA* not applicable

Because uveitis may already be present at time of diagnosis and is usually asymptomatic, it is recommended that the first ophthalmologic exam be performed within a month of diagnosis (Table 22.3). A child is considered to be at a higher risk for uveitis if he/she is ANA seropositive, of oligoarticular or polyarticular JIA subtype, has early age of arthritis onset (≤6 years), and has <4 years duration of arthritis (Table 22.2). Once the diagnosis of uveitis is made, frequency of exams is based on response to therapy and complications.

Systemic Treatment

With the development of newer therapeutic agents and combination treatment approaches, the goals of therapy for children with JIA have universally become more ambitious, targeted to limit all signs of disease activity and to achieve normalization of both short-term and long-term functional outcomes. As a result, increasing numbers of children with JIA are now experiencing prolonged periods of disease quiescence and, in some cases, complete clinical remission [9]. Adherence to treatment in JIA requires collaboration on the part of parents, child, and practitioners. Adherence to treatment may be associated with better outcomes, and nonadherence may be responsible for more hospital admissions due to disease exacerbation in children who have a chronic disease [2]. Clinicians need to assess adherence in order to evaluate the impact of treatments. They must be aware of possible divergence between parents and children regarding adherence in order to gain a better understanding of adherence and factors associated with it. Compliance with recommended therapy is a difficult construct to measure. There is no gold standard measure for the determination of adherence to treatment in JIA, and parents and professionals often overestimate it [3–5]. Most often, in children with JIA, the level of adherence is determined by direct questioning of the parents who function as proxy reporters for their children (who in turn may have difficulty in completing assessment instruments). This is especially true in the case of young children [6, 7, 11, 12]. However, such information may not only be incomplete, but it may be entirely inaccurate because parents may not be fully aware of the difficulties an individual child may have in adhering to the treatment regimen. Studies have shown that adolescents are less adherent than younger children often because of their growing autonomy [11, 13, 14]. Similarly, children and adolescents who take responsibility for their own treatment may be more reliable informants on adherence than their parents. Clinicians may need to seek information from both the children and their parents in order to gain better insight into issues of adherence in children and adolescents with JIA.

Poor parental adherence to treatment regimens may compromise potential benefits of conventional treatments [7, 11, 12]. Some parents believe that the deleterious side effects of medications outweigh the potential benefits and are reluctant to comply with treatment [11, 13, 14]. Therefore, there may be a complex relationship between chronicity and severity and poor adherence with recommended therapeutic regimens. Poor communication and limited parental comprehension of the medical condition have also been shown to be associated with diminished adherence [17]. Methods for measuring adherence to treatment such as provider estimates and patient/caregiver reports are considered to be feasible but may overestimate adherence [15]. A theoretical model

proposed by the World Health Organization (WHO) includes the following 5 dimensions/groups of factors that may be related to adherence: social and economic factors (e.g., age, socioeconomic status, distress, coping), health-care team and system-related factors (e.g., patient-provider relationship, perception of adherence by the provider), condition-related factors (e.g., severity, duration of disease), therapy-related factors (e.g., complexity of the regimen, side effects), and patient-related factors (e.g., knowledge, attitudes, beliefs, perceptions, and expectations) [3, 16–18]. For the ophthalmologist, compliance to treatment can be assessed by looking for ocular complications of an active uveitis, such as band keratopathy, synechiae, and cataract formation. This model can be useful while planning the multidisciplinary approach to a JIA pediatric patient.

Treatment of Uveitis

The therapy of JIA-associated uveitis starts with **topical steroids**, such as prednisolone acetate 1 %. Regional (sub-Tenon) injection of steroids (triamcinolone acetonide) and systemic steroids (prednisone) are often used simultaneously in the initial care of a patient with JIA-associated iridocyclitis. In the treatment of JIA, the use of systemic corticosteroids is typically reserved only for JIA coinciding with active systemic features (including severe cytopenias, serositis, and macrophage activation syndrome). In addition, low-dose systemic steroids may be used in severe polyarthritis (particularly RF positive) as a therapeutic bridge until other disease-modifying agents take effect. Patients are also placed on mydriatic agents to prevent the formation of posterior synechiae in the setting of a small pupil.

Ocular Complications of JIA-Associated Uveitis and Their Treatment

Approximately 20–60 % of children with JIA uveitis suffer from severe vision-compromising complications secondary to uveitis; these include cataract, glaucoma, band keratopathy, posterior synechiae, and hypotony [19]. Up to 65 % of children are asymptomatic early while uveitis is active, and about 45 % of patients are discovered to have complications from uveitis at their initial visit. Increased duration of eye inflammation leads to a greater likelihood of ocular damage and complications. JIA-associated uveitis can lead to long-term visual impairment and ocular complications, with persistent visual morbidity extending into adulthood [20].

Cataracts, or lens opacities, are among the most frequently observed ocular complications of JIA. 9 % and 80 % in children with JIA-associated uveitis patients have new onset cataracts [19, 20]. Several retrospective series have described risk factors for cataract development in JIA; these include (1) posterior synechiae, or adhesion of the capsule to the iris of the lens, on initial examination; (2) systemic steroid therapy; (3) topical steroid therapy exceeding three drops per day; and (4) active, ongoing inflammation. Children with JIA-associated uveitis who have undergone cataract surgery have had worse visual outcomes and a more complicated postsurgical course compared with children with uveitis secondary to other causes (i.e., idiopathic), likely due to more severe intraocular inflammation and younger age [20]. Studies have demonstrated that control of ocular inflammation by immunosuppressive therapy peri- and postoperatively leads to improved outcomes. Hence, it is important that uveitis be quiescent, typically for at least 3 months prior to surgery. Cataract surgery can be challenging due to limited surgical exposure from posterior synechiae and fibrinous membranes overlying the anterior lens capsule. Posterior synechiae, or adhesions from the iris to the lens, requires synechiolysis prior to cataract extraction. Viscoelastic may be used to dissect the iris adhesions from the lens, but in other situations, a blunt spatula (i.e., cyclodialysis spatula or iris sweep) or vitreous microscissors are needed to accomplish this task. However, special care should be taken to avoid manipulating the iris, as perturbation of iris pigment cells contributes to postoperative inflammation. One frequently finds a membrane across the whole pupillary area that needs to be peeled of the lens before a capsulotomy can be performed. In some patients intraocular scissors are necessary. Iris hooks may also be needed in some patients to retract the iris peripherally to gain visualization of the cataractous lens. Moreover, the management of postoperative complications such as uncontrolled inflammation, early posterior capsular opacification, glaucoma, cystoid macular edema (CME) [20], epiretinal membrane, hypotony, and phthisis bulbi requires meticulous care. Controversy remains regarding the placement of an intraocular lens (IOL) due to various complications (e.g., synechiae from fibrin deposition, pupillary membrane formation, hypotony, secondary cataract formation) and the possible need for IOL explantation [21] if the visual axis is compromised by IOL pigmentation or secondary fibrinous membranes. However, recent studies have demonstrated favorable overall outcomes [21]. Of the studies reporting favorable outcomes with IOL implantation, several key factors are emphasized: control of inflammation for at least 3 months prior to surgery, systemic immunomodulatory therapy, and pre- and postoperative steroids in most cases.

In patients with long-standing uveitis, *band keratopathy* (i.e., the deposition of calcium in the subepithelial space) may warrant ethylenedi-amine tetra-acetic acid (EDTA) chelation prior to or after cataract surgery [20, 21]. This may be especially relevant in circumstances in which dense band keratopathy precludes a view adequate for cataract extraction.

Following cataract extraction, patients should be monitored carefully for the development of cystoid *macular edema* (CME). Macular edema is the second most sight-threatening

complication in JIA-associated uveitis [22] and occurs in 3–47 % of patients. It is reported that macular edema is the cause of legal blindness in 8 % of children affected by active uveitis. Pathogenesis of CME in inflammatory disorders is still unclear, but malfunction of blood-retinal barrier plays a central role and several inflammatory and vasoactive peptides are probably involved [22]. Cataract extraction in eyes affected by uveitis may represent one of the most important factors in triggering CME (44 % of JIA patients after cataract surgery). Macular edema usually occurs 4–12 weeks after cataract surgery, since cataract extraction stimulates ocular inflammation by releasing pro-inflammatory mediators, for example, prostaglandins, which diffuse throughout posterior chamber and provoke macular edema [19]. However, this complication may be also interpreted as the result of vitreous traction during surgery [20]. Microvascular factors are involved and probably enhanced by inflammatory factors and by sex hormones. Sex hormone changes have been demonstrated to modulate inflammation. Several studies provided evidence of the modulatory effect of the estrogens on the CD4 cell subpopulation designed Th1 and Th2 [22]. Studies on behavior of noninfective uveitis during pregnancy showed uveitis recovery during mid- and late pregnancies and flare up in postpartum period, like in other autoimmune diseases. Further studies about the interactions of neuroendocrine, immunologic, and microvascular factors involved in JIA-associated macular edema are necessary to prevent cystoid macular edema in young affected patients. Cystoid macular edema is diagnosed by optical coherence tomography or by fluorescein angiography. Cystoid macular edema is best managed with consultation with a vitreoretinal or uveitis specialist familiar in treating uveitic CME. Treatment of cystoid macular edema often involves judicious use of topical, periocular steroids, intravitreal steroids, or, as in the Case Study 1, a dexamethasone implant. Other treatment modalities, especially if CME occurs after cataract surgery, involve topical or oral nonsteroidal anti-inflammatory drugs. Appropriate systemic immunomodulatory treatment may also lead to improvement of CME.

Case Study

An 8-year-old girl with a previous diagnosis of oligoarticular JIA on methotrexate and adalimumab was referred for 6 relapses of her anterior uveitis in the past year and macular edema. Her right eye had anterior synechiae and her right eye with 360° of posterior synechiae nearly occluding the pupil with a band keratopathy (Fig. 22.1); both eyes had 2+ cells in the anterior chamber and the left eye had macular edema on optical coherence tomography (OCT) (Fig. 22.2a). She was not compliant with both topical and oral steroids during her relapses; it was decided to inject a sustained-release dexamethasone implant (Ozurdex®) in her vitreous cavity (Fig. 22.3). Although its use is off-label in anterior uveitis, pharmacodynamic studies have demonstrated that it reaches adequate concentrations in the anterior chamber [23, 24]. Two weeks after the injection, the anterior chamber was completely quiet and the macular edema had completely resolved (Fig. 22.2b). This improvement persisted for 8 months; therefore, a second implant was planned for the right eye, and the girl has been off systemic steroids for the last 10 months.

Comment

In approximately 30 % of cases, JIA-associated iridocyclitis is not satisfactorily controlled by conventional anti-inflammatory treatments, and iridocyclitis recurs whenever steroids are withdrawn despite the long-term use of an oral nonsteroidal anti-inflammatory drug (NSAID). At this stage, once-a-week oral or subcutaneous **methotrexate** therapy (0.3–0.5 mg/kg per week; typically, 7.5–25 mg per week) should be considered. The dosage of methotrexate can usually be increased to a maximum of 40 mg weekly to control the iridocyclitis if the standard starting dose is not adequate. MTX has become the most commonly used disease-modifying antirheumatic drug in the treatment of JIA. Traditionally a second-line agent (following local or oral steroids), MTX is now also recommended as initial treatment for patients with oligoarthritis/polyarthritis with high disease activity and/or poor prognostic features and for JIA with predominant joint manifestations. It is currently FDA approved for the treatment of severe and active polyarticular JIA (children ≥2 years old) [25]. When comparing the efficacy of MTX in JIA subgroups, studies suggest that patients with extended oligoarthritis demonstrate the best clinical response [26, 27]. MTX is a folic acid analog and a potent inhibitor of dihydrofolate reductase, inhibiting both purine and pyrimidine biosyntheses. In the low doses used to treat JIA, the primary effects of MTX are thought to be secondary to the accumulation and anti-inflammatory properties of adenosine, rather than its action as an antimetabolite [28–30]. The side effects of MTX are typically mild and reversible and most commonly include nausea, vomiting, abdominal discomfort, elevation of liver transaminases, and oral ulcers. The administration

(continued)

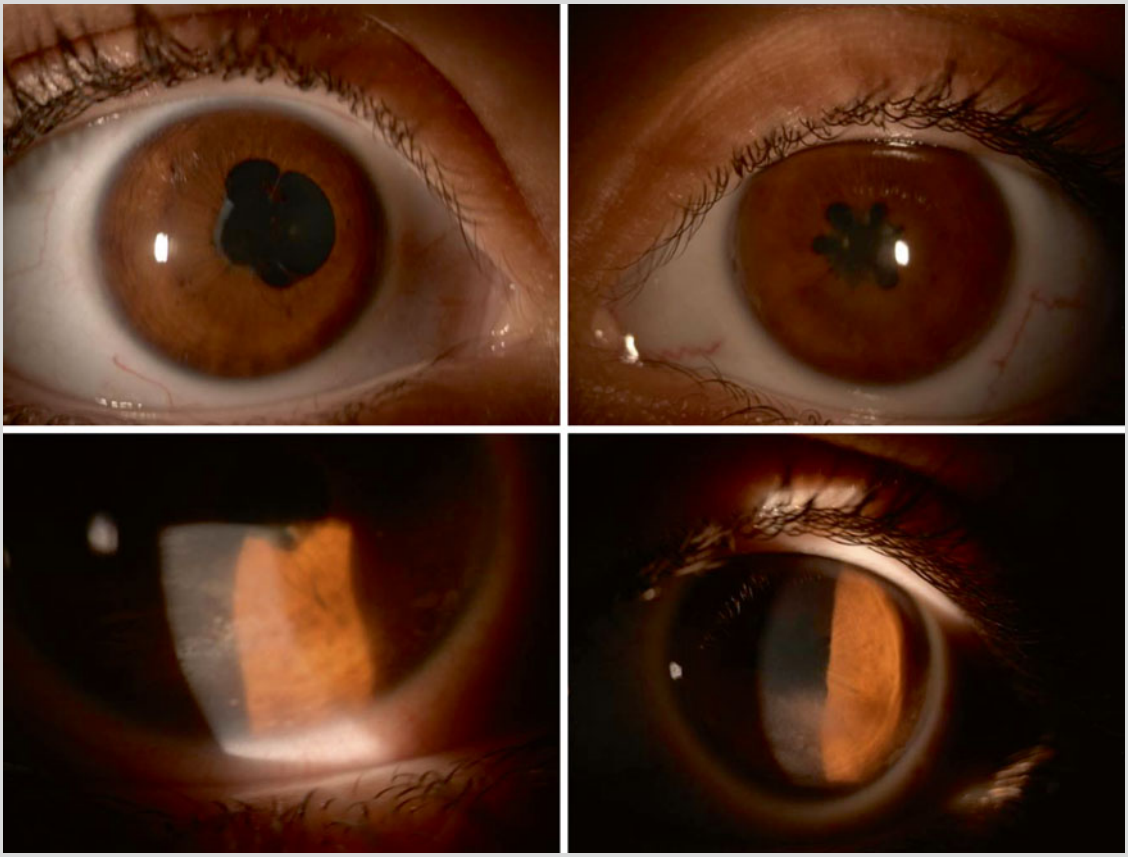

Fig. 22.1 *Right* (**a**) and *left* (**b**) eye of a young patient with JIA-associated uveitis showing synechiae; (**c**, **d**) higher magnification shows bilateral band keratopathy

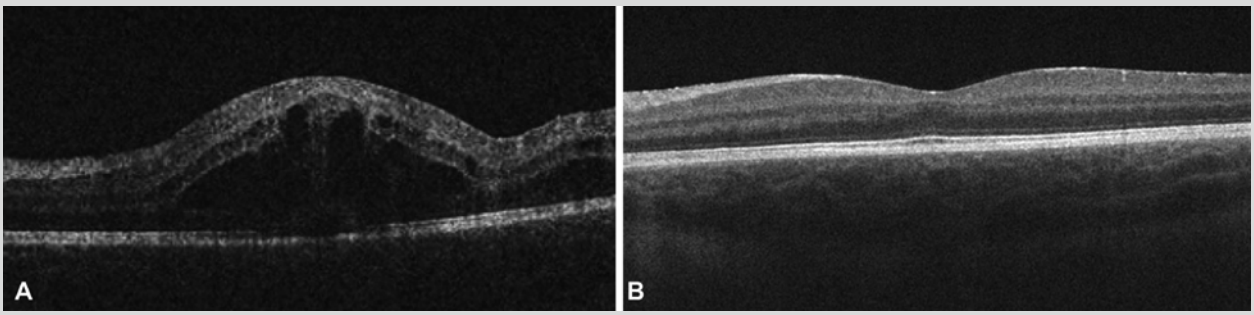

Fig. 22.2 Spectral domain optical coherence tomography (SD-OCT) of the left eye of the patient showing cystoid macular edema (**a**) and a complete disappearance of the same after sustained-release dexamethasone intravitreal implant (**b**)

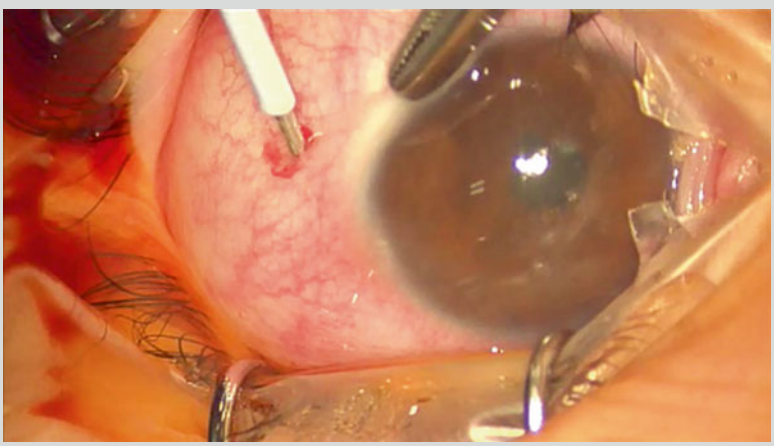

Fig. 22.3 Injection of a sustained-release dexamethasone implant in the vitreous chamber of the patient leads to control of anterior segment inflammation and resolution of the macular edema

(continued)

of low-dose daily folic or weekly folinic acid is associated with a reduction of these side effects and has not been shown to have any adverse effects on MTX efficacy [31, 32]. MTX is teratogenic (category X) and associated with spontaneous abortions. Contraception must be emphasized in adolescent females of child-bearing potential who are placed on the medication.

When methotrexate treatment fails or is not tolerated, other immunomodulators, such as azathioprine (1–2 mg/kg per day), cyclosporine (2–5 mg/kg per day), mycophenolate mofetil (mg/m [2] body surface area bid), or chlorambucil (0.10–0.16 mg/kg per day), may replace methotrexate or be used adjunctively to achieve the goal of total quiescence of ocular inflammation. However, the frequency of failure of methotrexate treatment is less than 17 %.

Physicians more commonly rely on combinations of traditional disease-modifying antirheumatic drugs (e.g., MTX) with newer **biologic agents** in children with refractory disease. The first class of biologic agents approved for use in JIA was directed against TNF-α (**TNF-α inhibitors**). This pro-inflammatory cytokine, also known as cachexin, is produced by activated phagocytes and primarily involved in the recruitment of inflammatory cells, endothelial activation, induction of fever, production of acute phase reactants, and promotion of metabolic changes. Current guidelines suggest the use of TNF inhibitors as a second- or third-line agent in patients with JIA who continue to have persistent disease activity despite an adequate trial of initial therapeutic agents. According to these recommendations, TNF inhibitors should be initiated sooner in patients with poor prognostic features, polyarticular disease, and active sacroiliac disease [10].

The biologic agents used in the treatment of patients with JIA are summarized in bullet points below. The specific agent may or may not be useful in the management of uveitis. We provide the details on these agents to give the pediatric ophthalmologist information that is encountered while patients with JIA are under his/her care.

- Etanercept, a fully human, dimeric fusion protein, consists of the human p75 TNF receptor fused to the Fc region of human IgG1. With actions analogous to the naturally occurring soluble TNF-a receptor, etanercept binds to TNF-α in circulation, preventing interaction with its cell surface receptor and subsequently the inflammatory response that would follow. In 1999, etanercept became the first biologic agent approved by the FDA for the treatment of moderate to severe polyarticular JIA. Administration is given at a dose of 0.8 mg/kg/week or 0.4 mg/kg twice weekly subcutaneously (max = 50 mg/week), with initial clinical response expected by the third or fourth injection. The most common adverse event includes transient local skin reactions and minor infections. In general, etanercept is not recommended as a primary immunomodulatory agent in patients with uveitis associated with JIA.
- Infliximab is a chimeric (murine-human) monoclonal IgG1 antibody that binds to soluble TNF-α and membrane-bound TNF-α, leading not only to neutralization of TNF but also to antibody-dependent cytotoxicity of TNF-producing cells. It is administered via intravenous infusion, with dosing and frequency varying based on clinical response. Infliximab is typically reserved as a second- or third-line agent in patients who have failed etanercept (their efficacy is comparable to infliximab for joint disease but the latter may cause infusion-related reactions and particularly the development of granulomatous opportunistic infections, such as tuberculosis) or as a primary biologic agent in the treatment of JIA-related uveitis.
- Adalimumab is a fully humanized monoclonal IgG1 antibody that binds both soluble and membrane-bound TNF-α. It received FDA approval for the treatment of polyarticular JIA (children ≥ 4 years old) in 2008. Adalimumab is administered subcutaneously in a fixed dose of 20 mg every other week in children ≤ 30 kg and 40 mg every other week in children > 30 kg. Similar to infliximab (but with less risks of side effects), adalimumab appears to be efficacious for the treatment of JIA-related uveitis [33].
- Golimumab is a fully humanized monoclonal IgG1 antibody to TNF-α in the circulation and on the cell surface. It is FDA approved for adult RA and psoriatic arthritis [34, 35]. Case series have also suggested benefit in refractory JIA-related uveitis [36]. In children with JIA and inadequate response to MTX, a dose of 30 mg/m [2] (max = 50 mg) subcutaneously once a month is recommended. The side effect prolife is similar to adalimumab.

Another class of biologic agents used in JIA therapy is **IL-1 inhibitors;** IL-1b is a pro-inflammatory cytokine that shares many biologic functions with TNF-α, including induction of fever, activation of endothelial cells and macrophages, and production of acute phase reactants. IL-1b plays an important role in the underlying pathogenesis of JIA and may contribute to bone damage and erosions. Anti-TNF agents, although widely effective for many subtypes of JIA, appear to be less effective in the treatment of systemic JIA. By contrast, these patients have been shown to have a very favorable response to IL-1 inhibition, including anakinra, canakinumab, and rilonacept.

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Another important pro-inflammatory cytokine, IL-6, has also been implicated as a central cytokine in the underlying pathogenesis of systemic JIA, and in 2011, an **IL-6 inhibitor**, tocilizumab, was approved by the FDA for the treatment of systemic JIA. It is a humanized, monoclonal antibody against the IL-6 receptor, competing with natural soluble and membrane-bound IL-6 receptors, reducing cell signaling. Tocilizumab is administered at a dose of 12 mg/kg (children < 30 kg) or 8 mg/kg (children ≥ 30 kg) every 2 weeks, via intravenous infusion. Serious adverse events have included infusion reactions (including anaphylaxis), gastrointestinal hemorrhage, serious infections, macrophage activation syndrome, bronchitis, gastroenteritis, and pulmonary hypertension. Neutropenia and mild elevations in liver transaminases have also been reported.

An alternate approach to management, particularly in refractory JIA, has been to target direct lymphocyte activation and cellular functions. This line of therapy is typically reserved for patients who have previously had inadequate response to initial therapies, including one or more anti-TNF agents.

- Abatacept is a fully human, soluble fusion protein composed of the Fc region of IgG1 and the extracellular domain of cytotoxic T-lymphocyte antigen 4. It competitively binds to CD80/86 on antigen-presenting cells as an inhibitory signal, preventing T-cell activation. Abatacept received FDA approval for the treatment of polyarticular JIA in 2008 and is currently recommended for patients ≥ 6 years old who have received a trial of anti-TNF therapy for 4 months and still have moderate or high disease activity [37]. Abatacept is administered via intravenous infusion at a dose of 10 mg/kg for patients under 75 kg. It is generally well tolerated, only minor infections, infusion events, and local injection reactions.
- Rituximab is a chimeric, monoclonal mouse-human antibody to the CD20 B-cell receptor. Current guidelines suggest the use of rituximab for the treatment of polyarticular JIA in patients who have had inadequate response to anti-TNF agents and abatacept, particularly in those who are rheumatoid factor positive [9]. Serious adverse events include infusion reactions and anaphylaxis; thus, premedication with antihistamines, acetaminophen, and/or corticosteroids is typically recommended. Other side effects include hypogammaglobulinemia, infection, and progressive multifocal leukoencephalopathy.

Conclusions

Therapeutic advances in the treatment of JIA are occurring at a rapid rate. With these advances, physical and functional outcomes have improved immensely. The establishment of research consortia between the pediatric rheumatology and the ophthalmology community has allowed for large controlled studies and enabled a somewhat better understanding of the safety and efficacy of these therapeutic agents in children, but larger, longer safety studies are needed. It has also become evident that the underlying pathogenesis of JIA differs not only from adult RA but also among JIA subsets. Current research efforts are directed at understanding the underlying biologic mechanisms in each of these subsets in an effort to better individualize patient management.

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Noninfectious Intermediate and Posterior Uveitis

23

E. Mitchel Opremcak

Abstract

The diagnosis and management of noninfectious intermediate or posterior uveitis in children presents several unique challenges. The history and review of systems can be limited, and there are few outward signs for parents to observe. Subsequently, the diagnosis is often delayed. Both examination of the eye and treatment of posterior disease via the delivery of periocular steroids may require general anesthesia. Children receiving oral corticosteroids must be carefully monitored for side effects on growth and development. Immunomodulatory therapies such as methotrexate or cyclosporine can be used safely in children and are often added to spare steroid dose. While pars planitis, sarcoidosis, sympathetic ophthalmia, Vogt–Koyanagi–Harada syndrome, tubulointerstitial nephritis and uveitis syndrome, Adamantiades–Behcet's disease, polyarteritis nodosa, and APMPPE can occur in children, the majority of cases of intermediate, posterior, and panuveitis are idiopathic.

Keywords

Intermediate uveitis • Panuveitis • Posterior uveitis • Macular edema • Corticosteroids

The Problem

The diagnosis and management of uveitis in children presents several unique challenges. The history and review of systems are often limited in preverbal children and in children without ocular complaints. Noninfectious intermediate and posterior uveitis rarely have outward signs for the parents to observe, and consequently, the diagnosis is often delayed. This delay results in more advanced disease and higher complication rates than those associated with uveitis in adults. Vision is often impaired in these forms of uveitis and if untreated will also be complicated by amblyopia. Examination of the eye and fundus in an uncooperative patient may be impossible in the office and may need to be completed under anesthesia to document the severity, extent, and location of the disease. Fundus photography is often quite useful in children with posterior uveitis as photographs "freeze-frame" the retina for easier study.

Furthermore, the medical management of posterior and IU in children is more challenging than in adults. Socioeconomic factors and family dynamics can be problematic with regard to overall understanding of the seriousness of the disease and its consequences. Irregular follow-up visits and noncompliance with the treatment plan are major reasons for poor visual outcomes in children with IU, posterior uveitis, and panuveitis. Parents may have difficulty delivering eye drops effectively. In the office, periocular steroid injections can be impossible to administer to children under 10 years of age. Oral corticosteroids may be needed initially to control disease, but bone growth retardation is a unique and an ever-present concern in childhood. Many of these diseases are chronic and require long-term immunomodulatory therapies (IMT), such as methotrexate or cyclosporine, to avoid side effects of systemic steroids. It is

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important to note that if a medical regimen had been working and the inflammation recurs, the dosage may need to be adjusted upward to account for rapid growth and increased body weight during the childhood years.

Background, Differential Diagnosis, and Case Presentations

In most series, children account for less than 10 % of all uveitis cases [1]. Anterior uveitis is responsible for around 47 % of all reported cases. Intermediate uveitis accounts for 25 %, with a range of 12–28 %, [2–5] posterior uveitis for 6–24 %, and panuveitis for 6–24 % depending on the series [2–5]. Cataract, glaucoma, and band keratopathy can occur in any form of uveitis, but they are more common in anterior uveitis. Cystoid macular edema (CME), epiretinal membranes (ERM), retinal detachment, vitreous hemorrhage, and disc edema are more common with IU, posterior uveitis, and panuveitis [2–5]. In a retrospective analysis of 116 Italian children with intermediate uveitis (97 % idiopathic), the incidence of ocular complications associated with intermediate uveitis is 0.131/eye-year [6]. Macular edema or dense vitreous haze at presentation were risk factors for vision loss, with the most frequent cause of visual loss from CME (64 %) and cataract (21 %) [6]. While most ophthalmologists feel comfortable treating anterior forms of uveitis, deeper forms are often referred for retina and uveitis consultation. If a systemic disease is discovered during the work-up of a child with uveitis such as sarcoidosis or polyarteritis nodosa, a pediatric rheumatologist is often needed to help manage the underlying disease. Even with local ocular diseases such as sympathetic ophthalmia or pars planitis, a rheumatologist is often needed to assist in pediatric oral medication dosing and monitoring for side effects.

Table 23.1 lists the differential diagnosis for noninfectious intermediate uveitis, posterior uveitis, and panuveitis. While pars planitis, sarcoidosis, sympathetic ophthalmia, Vogt–Koyanagi–Harada syndrome (VKH), tubulointerstitial nephritis and uveitis syndrome (TINU), Adamantiades–Behcet's disease (ABD), polyarteritis nodosa, and acute posterior multifocal placoid pigment epitheliopathy (APMPPE) can all occur in children, the majority of cases of intermediate, posterior, and panuveitis are idiopathic. At tertiary referral centers, up to 100 % of IU, 53 % of posterior uveitis, and 51 % of panuveitis cases are reported as idiopathic [4].

Table 23.1 Differential diagnosis for noninfectious intermediate, posterior, and panuveitis in children

Intermediate uveitis
• Pars planitis • Sarcoidosis and Blau syndrome • Tubulointerstitial nephritis and uveitis syndrome
Posterior uveitis
• Sarcoidosis and Blau syndrome • Adamantiades–Behcet's disease • Polyarteritis nodosa • Vogt–Koyanagi–Harada syndrome • Sympathetic ophthalmia • Tubulointerstitial nephritis and uveitis syndrome • Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
Panuveitis
• Vogt–Koyanagi–Harada syndrome • Sympathetic ophthalmia • Sarcoidosis and Blau syndrome • Tubulointerstitial nephritis and uveitis syndrome (TINU)

Initial evaluation should consist of a dilated examination, and in some cases, ancillary imaging can be used to document the extent of disease including representative fundus photos, fluorescein angiography, spectral-domain optical coherence tomography, and ultrasonography. Basic laboratory investigation for intermediate and posterior uveitis includes: serum angiotensin-converting enzyme (ACE), lysozyme, syphilis serologies, Lyme serologies, QuantiFERON, and chest x-ray. Additional laboratory testing is guided by the clinical presentation and differential diagnosis.

Pars Planitis and Case Example 1 (Table 23.2)

Idiopathic intermediate uveitis or pars planitis has also been called chronic cyclitis and peripheral uveitis. The etiology of pars planitis is unknown but thought to be an autoimmune disease targeting type II collagen found in the vitreous gel [7–9]. Pars planitis accounts for 20–25 % of all pediatric uveitis [4, 7]. There is no gender or racial predilection, nor are there known HLA associations. Retinal vasculitis and granulomatous inflammation of the peripheral retina and vitreous base are found on pathologic examination. True cyclitis or choroiditis are rarely found [10].

Patients with pars planitis present with bilateral (80 %), painless, chronic, blurring of vision and floaters [7, 8]. Children rarely complain of these symptoms and pars planitis is often found on routine eye examinations and are otherwise healthy. As such, visual acuity at presentation is worse than in adults at presentation [1, 11]. The eye is typically "white and quiet," making it difficult for parents to recognize signs of the disease. In children, biomicroscopic examination of the eye reveals a mild,

(continued)

Table 23.2 Case 1

Clinical history	8-year-old male referred complaining of "blurred vision and dots" in his right eye over the summer. He was sent to a uveitis specialist by his pediatric ophthalmologist		
Key components of exam		OD	OS
	BCVA	20/60	20/20
	Intraocular pressure	12 mm Hg	12 mm Hg
Anterior segment examination		Within normal limits	Within normal limits
Posterior segment examination	Vitreous	2+ cells; snowball formation (Fig. 23.1a)	1+ cell
	Optic nerve	C/D 0.2, no edema	C/D 0.2, no edema
	Macula	Normal foveal reflex	Normal foveal reflex
	Vessels	Normal course and caliper	Normal course and caliper
	Periphery	Within normal limits	Within normal limits
Assessment	Laboratory work-up completed to evaluate for infectious and noninfectious etiologies (complete blood count, ESR, CRP, FTA-Ab, RPR, Lyme serology, toxoplasmosis serology, QuantiFERON, ACE/lysozyme). Chest x-ray was completed to evaluate for findings associated with sarcoidosis or tuberculosis		
Management	After infectious etiology was ruled out, sub-Tenon kenalog was given by uveitis specialist (see discussion)		
Interval history (6 weeks)	Reports improved vision and resolution of floaters		
Key components of exam		OD	OS
	BCVA	20/20	20/20
	Intraocular pressure	12 mm Hg	12 mm Hg
Posterior segment examination	Vitreous	Resolution of cell and vitreous snowballs (Fig. 23.1b)	Resolution of cell
Management	Patient followed routinely every 3 months for recurrence of symptoms and signs		

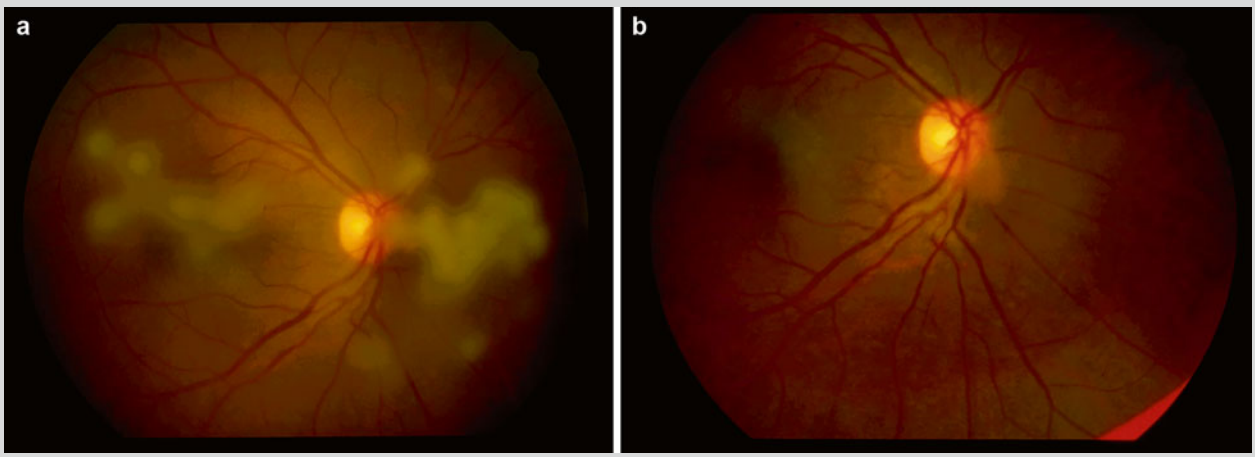

Fig. 23.1 (**a**) Fundus photograph of an otherwise healthy 8-year-old male referred in for uveitis consultation. He had been complaining of "blurred vision and dots" in his right eye over the summer. His VA was 20/60 OD and 20/20 OS. Biomicroscopic examination found 2+ cells and "snowball" formation in the vitreous cavity OD and 1+ cell in the vitreous cavity OS. Laboratory testing was normal. A diagnosis of pars planitis was made. (**b**) Fundus photograph of the same eye 6 weeks following sub-Tenon's injection of 40 mg triamcinolone under anesthesia. Note the clearing of the vitreous snowballs. VA improved to 20/20 OD

nongranulomatous anterior uveitis more often than adults [11]. Importantly, the majority of the cells in intermediate uveitis are found in the vitreous. Diffuse forms of pars planitis have inflammatory cells and "snowball" formation without pars plana exudation [8]. The exudative form has, in addition to vitreous cells, inferior vitreous base and pars plana "snowbanking." Inactive pars planitis will show a more distinct "collagen band." Snowbanking and collagen band formation are often difficult to see in children as scleral depression is required. In many cases, this can only be done under anesthesia. Perivasculitis, disc edema (50 %), cataract (50 %), synechiae formation, band keratopathy, glaucoma, retinal detachment, and vitreous hemorrhage can all occur in patient with pars plani-

(continued)

tis. Cystoid macular edema is the most common cause of permanent vision loss. Chronic optic disc edema (3–50 %) and peripheral retinal neovascularization with secondary vitreous hemorrhage are more common in pediatric cases. Cataracts develop in up to 50 % of patients due to either inflammation or from the use of corticosteroids usage [12]. Lensectomy without intraocular lens (IOL) implantation has historically been thought to be the safest option in children with chronic, active disease with regard to preventing uveitis recurrences and secondary IOL complications [13]. Aphakia, however, presents a challenge with regard to contact lens use and amblyopia. With the advances in ophthalmic surgery, the placement of an IOL in children with cataract and uveitis has been reported and may be considered with caution in eyes with well-controlled inflammation [14].

The diagnosis is made by ocular examination. Fluorescein angiography may be used to diagnose CME in older children. Ocular coherence tomography (OCT) is a noninvasive way to detect CME and is often well tolerated in children of all ages. Lyme disease, sarcoidosis, syphilis, and multiple sclerosis [9] can present as an intermediate uveitis in children and should be considered in the differential diagnosis of pars planitis [7, 8]. Occasionally, a patient with toxocariasis may present with an intermediate uveitis and an inferior white mass resembling a pars plana snowbank. Most of these conditions in the differential diagnosis will have other systemic complaints and findings on physical examination.

For treatment, it is important to distinguish old, inactive cells from active inflammatory cells. Active cells are white and plump and are evenly distributed throughout the vitreous. Active disease may also have snowballs and snowbanking, and their presence is an indication for treatment [8]. Inactive and old cells trapped in the vitreous gel are brown, crenated, and unevenly distributed throughout the vitreous gel. Inactive pars planitis may also have a distinct collagen band. In this setting, medical treatment is not necessary. Children with pars planitis may respond to topical corticosteroids alone, and this should be the first line of treatment [7, 8, 15]. Every hour dosing with a slow taper may be a challenge for both parent and child but is the optimal approach. If topical therapy does not completely control the inflammation, a "step ladder" treatment approach is pursued. Periocular corticosteroid injections should be the next treatment modality. Sub-Tenon's triamcinolone, 40 mg every 3–6 weeks, will control a large percentage of pediatric pars planitis (Fig. 23.1a, b). This can be performed successfully in the office in some older and cooperative children. Commonly, periocular steroid injections need mask anesthesia and need to be performed in the operating room. Patients who are unresponsive or intolerant to periocular steroid injections can benefit from oral prednisone pulses. Ideally such courses should be less than 3 months in duration. For children who fail to respond to oral steroids or have numerous recurrences, pars plana vitrectomy with or without pars plana cryopexy should be offered. Several studies have reported success with vitrectomy in managing children with pars planitis [16]. The last step in this treatment ladder is systemic immunomodulatory therapy (IMT). Methotrexate, cyclosporine, and mycophenolate mofetil are fairly well tolerated in children. About 10 % of patients experience a single, self-limited episode of pars planitis, 30 % experience multiple recurrences over several years, and 60 % develop chronic disease [8]. In up to 20 % of patients, visual acuity is 20/200 or less due to fixed macular cystic edema.

Sarcoidosis

Sarcoidosis is a multisystem, noncaseating, granulomatous disease of unknown etiology. The disease can cause many patterns of ocular inflammation [7, 8, 15]. All races are affected but African-Americans are ten times more likely than Caucasians to develop sarcoidosis. There are two types of pediatric sarcoidosis, an early onset form in children under 4 years of age and a later onset form in those older than 8 [17]. The early onset form occurs primarily in Caucasians with less pulmonary involvement. Blau syndrome is a familial, autosomal dominant granulomatous pediatric disease with a clinical presentation identical to sarcoidosis [18]. The susceptibility locus is mapped to chromosome 16p12-q21 (*CARD15/NOD2*) [19]. Both sarcoidosis and Blau syndrome affect multiple organ systems. Children may present with fever, weight loss, fatigue, and shortness of breath. The upper and lower respiratory tracts are most commonly involved in sarcoidosis (83 %) but not in Blau syndrome. Lymph nodes (76 %), skin (22 %), liver, and spleen are also commonly affected. Ophthalmic manifestations occur in 19–54 % of patients [7, 8, 15].

All parts of the eye may be involved. The inflammation may be nongranulomatous or granulomatous. The disease may start acutely and evolve into a chronic condition. Intermediate uveitis with snowball formation, retinitis, choroiditis, retinal vasculitis, and choroidal granulomas are all observed in both sarcoidosis and Blau syndrome. The definitive diagnosis is established by tissue biopsy demonstrating the presence of noncaseating granuloma in the affected tissue. Chest radiograph or CT shows hilar adenopathy in 90 % of late onset sarcoidosis. Serum lysozyme, angiotensin-converting enzyme, and calcium may all be elevated.

Sarcoidosis should be considered in the differential diagnosis of all forms of uveitis. Tuberculosis may present in a similar manner and should be considered in this setting. While the clinical course is unpredictable, in most cases, sarcoidosis will eventually "burn out." Active sarcoid uveitis responds well to topical, regional, and systemic corticosteroids. Oral prednisone is often required for an extended period of time but should be given at very lose doses (1–10 mg/day). Methotrexate can be used in sarcoidosis to spare oral corticosteroid use and is well tolerated in children [7, 8, 15].

Sympathetic Ophthalmia and Case Example 2 (Table 23.3)

Table 23.3 Case 2

Clinical history	6-year-old male referred for uveitis in the right eye with history of being stabbed in the left eye with scissors 2 years prior status-post vitrectomy and two corneal transplants		
Key components of exam		OD	OS
	BCVA	20/400	LP
Anterior segment examination	Conjunctiva	2+ injection	2+ injection
	Cornea	Mutton fat keratic precipitates	Opacified corneal transplant
	Anterior chamber	3+ cell/2+ flare	No view
	Iris	Posterior synechiae	No view
	Lens	2+ cataract	No view
	Intraocular pressure	5 mm Hg	0 mm Hg
Posterior segment examination	Vitreous	3+ cell	No view
	Optic nerve	C/D 0.2, disc edema	No view
	Macula	Cystoid macular edema	No view
	Vessels	Vascular tortuosity	No view
	Periphery	Dalen–Fuchs nodules	No view
Assessment	Sympathetic ophthalmia in the right eye secondary to penetrating injury and multiple subsequent surgeries in the left eye		
Management	The inflammation was controlled systemically with cyclosporine A and prednisone. After 3 months of inflammatory control, the visually significant cataract was removed via vitrectomy and treated with aphakic correction with visual acuity returning to 20/20 OD. At the age of 21, he still requires cyclosporine and low-dose prednisone. With each attempt to taper, he develops disc edema, CME, and diffuse panuveitis		

Sympathetic ophthalmia (SO) is a bilateral, granulomatous panuveitis that occurs following ocular injury [7, 8, 15]. SO is thought to be an autoimmune disease precipitated by an injury to an eye with uveal tissue exposure. Disruption of the blood–eye barrier, exposure to ocular autoantigens, and an adjuvant effect of contaminating bacteria may sensitize the immune system. The incidence is estimated at 1.9/1000 nonsurgical penetrating injuries and 1/10,000 surgical cases. Histopathologic examination in SO shows a diffuse, non-necrotizing, granulomatous inflammation of the eye that spares the choriocapillaris.

Childhood cases often involve accidental injury with scissors or pencils. Most cases (70 %) will occur within 3 weeks to 3 months of the injury and the onset of inflammation in the inciting eye [7, 8]. Children will present with photophobia, redness, and pain. Mild cases will have a diffuse nongranulomatous uveitis with Dalen–Fuchs nodules (35 %) and optic nerve involvement (Fig. 23.2). With disease progression or in severe cases, a granulomatous panuveitis with mutton fat keratic precipitates (KPs), posterior synechiae and multifocal chorioretinitis will be noted. The diagnosis is a clinical one. Vogt–Koyanagi–Harada syndrome (VKH) can exhibit similar ocular findings, but typically, VKH has no history of injury and has more systemic manifestations.

SO can be prevented by removing a potentially inciting eye after severe injuries, and in cases where there is no hope of visual recovery, comfort, or a cosmetically acceptable eye. In this setting, if the injured eye is removed within 2 weeks, the development of SO is unlikely [20,

(continued)

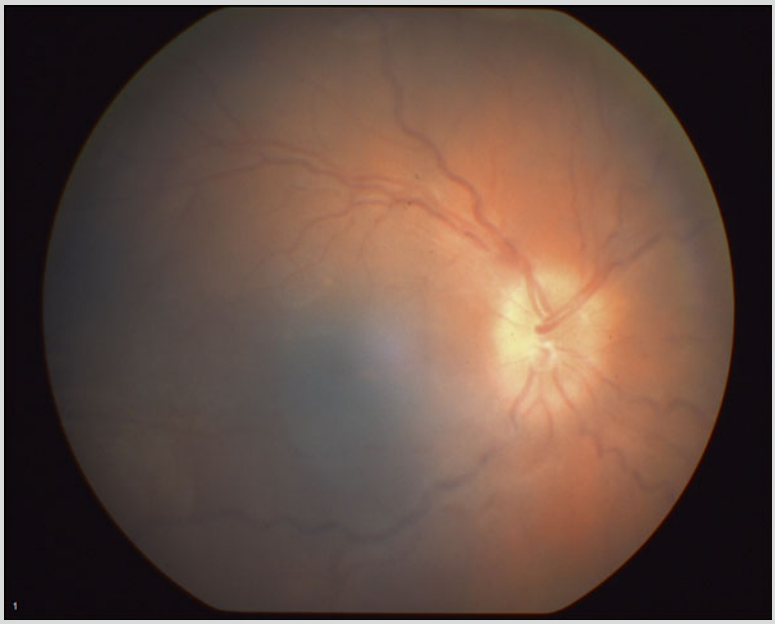

Fig. 23.2 Fundus photograph of a 6-year-old male referred in for uveitis consultation. In April of 1999, he was stabbed in his left eye with scissors and had two corneal transplants and vitrectomies. His right eye became inflamed and was on oral prednisone and topical prednisolone. His vision was 20/400 OD and LP OS. Intraocular pressures were 5 mmHg OD and 0 mmHg OS. There was no view of the fundus OS. The right eye had posterior synechiae, cataract, vitritis, disc edema, and Dalen–Fuchs nodules. He was started on cyclosporine which controlled the uveitis. At the age of 21, he has maintained 20/20 VA OD but requires continuous treatment with cyclosporine and low-dose prednisone. With each attempt to taper, he develops decreased vision, diffuse uveitis, disc edema, and CME

21]. Advances in ophthalmic surgery have made it less likely to remove an injured eye as more complex trauma repairs are accomplished. Oral and local corticosteroids have been the mainstay of therapy for SO. Initial doses are 1–1.5 mg/kg prednisone daily with a slow taper. The addition of other IMT such as cyclosporine, methotrexate, or mycophenolate mofetil is often opted for in children to reduce the dose of corticosteroids. SO may be recurrent and chronic disease is seen in 60 % of cases.

Tubulointerstitial Nephritis and Uveitis

Tubulointerstitial nephritis and uveitis syndrome (TINU) is a self-limiting disease in children characterized by nephritis and uveitis [22]. Most cases (75 %) occur in girls with a median age of 15 years. Patients will present with fever, fatigue, and flank tenderness. Laboratory testing reveals proteinuria, hematuria, and elevated BUN and creatinine. Renal biopsy will demonstrate inflammation in the renal interstitium. The renal disease resolves spontaneously or with corticosteroids use. The ocular disease may be more persistent. The uveitis may become recurrent or chronic and can be anterior, posterior, intermediate, or take the form of a panuveitis. The disease may be granulomatous or nongranulomatous in nature. Retinal complications include CME, ERM, and chorioretinal scarring. Most cases are responsive to topical, regional, or systemic corticosteroids. A few children have been reported to require methotrexate, cyclosporine, or mycophenolate mofetil in steroid-resistant cases [23].

Vogt–Koyanagi–Harada Syndrome and Case Example 3 (Table 23.4)

Table 23.4 Case 3

Clinical history	16-year-old white female referred for decreasing vision OU She had no significant PMH. Review of systems was significant for headache, tinnitus, vertigo, and complete body alopecia including her eyelashes and eyebrows. Her identical twin sister was asymptomatic		
Key components of exam		OD	OS
	BCVA	20/400	20/400
Anterior segment examination	Conjunctiva	2+ injection	2+ injection
	Cornea	Mutton fat keratic precipitates	Mutton fat keratic precipitates
	Anterior chamber	3+ cell/2+ flare	3+ cell/2+ flare
	Iris	Posterior synechiae	Posterior synechiae
	Lens	Clear lens	Clear
	Intraocular pressure	5 mm Hg	5 mm Hg
Posterior segment examination (Fig. 23.3a)	Vitreous	3+ cell/2+ haze	3+ cell/2+ haze
	Optic nerve	C/D 0.2, disc edema	C/D 0.2, disc edema
	Macula	Exudative retinal detachment	Exudative retinal detachment
	Vessels	Within normal limits	Within normal limits
	Periphery	Dalen–Fuchs nodules	Dalen–Fuchs nodules
Assessment	Ocular and systemic findings support a diagnosis of VKH. Basic infectious and immunologic labs were ordered, although suspicion for alternative diagnosis was low		
Management	After infectious etiology ruled out, she was initially treated with 40 mg triamcinolone OU and started on cyclosporine and prednisone		
Interval history	Visual acuity improved to 20/20 in the right eye and 20/40 in the left eye. Two years later, she developed bilateral choroidal neovascular membranes (CNVM) treated with focal laser photocoagulation as that was the only option for treatment at that time. Left eye showing CNVM and the "sunset glow" fundus following resolution of her exudative retinal detachments (Fig. 23.3b)		

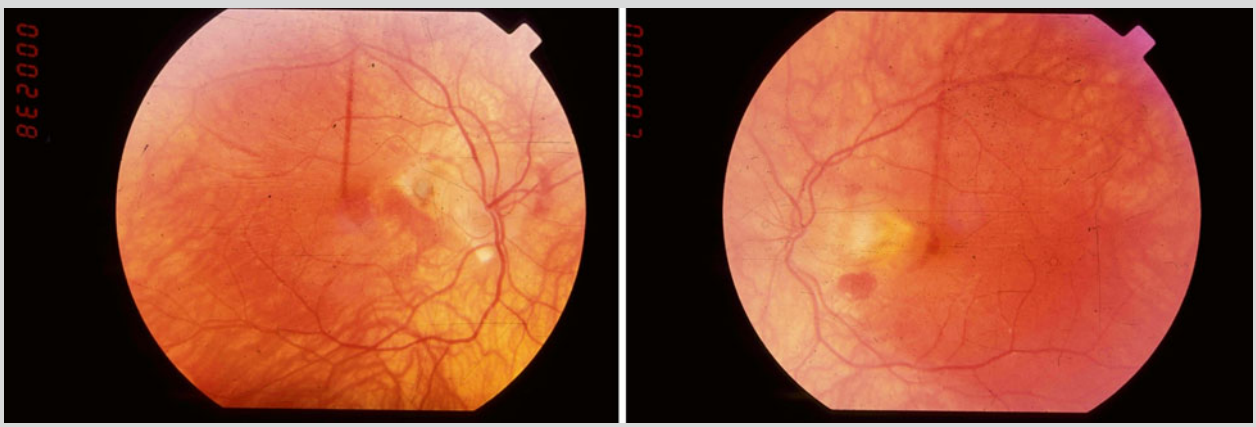

Fig. 23.3 (**a**) Fundus photograph of a 16-year-old white female referred in for loss of vision OU. She presented with bilateral exudative retinal detachments and 20/400 acuity OU. She had headache, tinnitus, vertigo, and complete body alopecia including eyelashes and eyebrows. She had an identical twin sister who was asymptomatic. She was treated with bilateral sub-Tenon's injection of 40 mg triamcinolone and started on oral prednisone and cyclosporine. Her uveitis was controlled and VA improved to 20/20 OD and 20/40 OS, but she developed bilateral choroidal neovascular membranes (CNVM) 2 years later that were treated with focal laser photocoagulation. (**b**) Left eye showing the CNVM and the "sunset glow" following resolution of her exudative retinal detachments

(continued)

Vogt–Koyanagi–Harada syndrome (VKH) consists of a diffuse, granulomatous uveitis associated with CNS, vestibule-auditory, and cutaneous abnormalities [7, 8, 15]. Components of the syndrome were described by Vogt in 1906, Koyanagi in 1929, and Harada in 1926. The etiology is unknown but is believed to be autoimmune in nature. VKH affects all races and both sexes but is more common in darker skinned individuals and is rare in children [24]. There is a bilateral granulomatous panuveitis that occurs without a history of injury or surgery. On histopathology, the inflammation involves the choriocapillaris and is associated with an exudative retinal detachment.

Patients present with headache, stiff neck, hearing loss, vertigo, and tinnitus. Skin involvement includes poliosis, alopecia, and vitiligo. Ocular manifestations can be divided into anterior and posterior findings. Vogt and Koyanagi described the anterior granulomatous uveitis with the dermatologic and vestibule-auditory findings. Perilimbal vitiligo (Sigiura's sign), posterior synechiae, cataract, and glaucoma are common. Harada described headache and meningeal findings with vitritis, multifocal chorioretinitis, disc edema, and exudative retinal detachments. With resolution of the uveitis, the fundus can develop extensive scarring and/or a "sunset glow" appearance (Fig. 23.3a, b). The diagnosis is clinical. Patients with the complete syndrome will have all clinical elements present. Those with incomplete forms will have the characteristic ocular findings but without either dermatologic, auditory, or CNS findings. Fluorescein angiography reveals a characteristic multifocal pattern of punctate hyperfluorescence with an exudative retinal detachment. In children an ultrasound can be helpful showing exudative retinal detachments and choroidal thickening.

VKH responds well to regional and oral corticosteroids. The disease is chronic and often requires cyclosporine, mycophenolate mofetil, methotrexate, or biologic agents to reduce the steroid dosage and side effects. Vision loss is commonly due to retinal scarring and glaucoma.

Other Rare Noninfectious Posterior and Panuveitis Syndromes in Children

Adamantiades–Behcet's disease (ABD) is a systemic necrotizing vasculitis with protean manifestations [7, 8, 15]. The etiology is unknown but appears to have an autoimmune component. There is a possible genetic and HLA association with HLA-B51. ABD occurs primarily after puberty and is rare in children. Reported pediatric cases were diagnosed at a mean age of 13 in one series. Oral ulcers (96–100 %), genital ulcers (70 %), and skin rash (90 %) were noted with the ocular findings (60 %). Conjunctivitis, uveitis, disc edema, retinal vasculitis, panuveitis, and optic atrophy were all found in the pediatric cases. Treatment includes oral corticosteroids and other IMT agents.

Polyarteritis nodosa (PAN) is multisystemic disease associated with a necrotizing vasculitis of medium to small arteries [7, 8, 15]. PAN is more common in males. It is rare in children with a peak age of onset between 7 and 11 years. Patients present with fatigue, arthralgias, weight loss, and testicular pain. Iritis, scleritis, and retinal vasculitis are noted on ocular examination. Treatment requires both corticosteroids and other IMT as untreated cases have an 80–90 % 5-year mortality rate.

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is an inflammatory disorder of the retina of unknown etiology [7, 8, 15]. APMPPE is rare in children. The average age of onset is 29 years with a range of 15–40 years. A viral-like prodrome can occur in 50 % patients followed by a bilateral, asymmetric loss of vision. Ocular examination shows multiple, large, yellowish-white, plaque-like lesions in the posterior pole. Fluorescein angiography shows the lesions blocking early and staining late. In most cases there is no treatment needed as the disease is self-limiting and carries a good prognosis with 80–90 % of cases recovering 20/30 or better visual acuity.

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Infectious Uveitis

24

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Abstract

Infectious etiologies are implicated in many cases of pediatric uveitis. Common causes of infectious uveitis in children include toxoplasmosis, toxocariasis, and the herpes viruses. Tuberculosis is a less common cause of uveitis and is more often encountered in developing countries. Toxoplasmosis is the most common cause of posterior uveitis in children. In one recent study, 58 % of children with posterior uveitis had ocular toxoplasmosis. Infectious posterior uveitis in children can have particularly devastating visual outcomes, both because of anatomic damage and the induction of amblyopia. If an infectious etiology is suspected in uveitis, therapy should be directed against the causative organism prior to initiating steroid therapy or systemic immunosuppression.

Keywords

Uveitis • Infectious uveitis • Pediatric • Toxoplasmosis • Toxocariasis • Herpes • Cytomegalovirus • Syphilis • Histoplasmosis • Tuberculosis • Necrotizing retinitis • Rubella • Cat-scratch disease • Endogenous endophthalmitis

Abbreviations

AIDS	Acquired immunodeficiency syndrome
ARN	Acute retinal necrosis
CMV	Cytomegalovirus
CMVR	Cytomegalovirus retinitis
CNV	Choroidal neovascularization
CSD	Cat-scratch disease
DUSN	Diffuse unilateral subacute neuroretinitis
ELISA	Enzyme-linked immunoassay
FHI	Fuchs heterochromic iridocyclitis
FTA-ABS	Fluorescent treponemal antibody
HSV	Herpes simplex virus
HZO	Herpes zoster ophthalmicus
PCR	Polymerase chain reaction
PHPV	Persistent hyperplastic primary vitreous
POHS	Presumed ocular histoplasmosis syndrome
PVR	Proliferative vitreoretinopathy
RPR	Rapid plasma reagin
TP-PA	Treponema pallidum particle agglutination
VDRL	Venereal Disease Research Laboratory
VEGF	Vascular endothelial growth factor
VZV	Varicella zoster virus

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Parasitic Infections

Toxoplasmosis

Toxoplasmosis accounts for approximately 50 % of all posterior uveitis in children [1–4]. The causative organism, *Toxoplasma gondii*, is an obligate intracellular protozoan, of

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which cats are the definitive host. Humans become intermediate hosts after ingesting the cyst or bradyzoite form, which may be found in cat feces, raw meat, vegetables, or contaminated drinking water. The encysted organism then migrates to muscular or neural tissue, where it ruptures, releasing the active, or tachyzoite form [2].

Maternal-fetal transmission accounts for up to 40 % of clinical infections, the severity of which is affected by the gestational age of the fetus at the time of transmission. Fetal infection is most severe during the first trimester, and can result in hydrocephalus, intracerebral calcifications, and seizures [2, 3]. Congenital infection was previously thought to account for most cases of ocular toxoplasmosis; however, recent studies suggest that a majority of patients with ocular toxoplasmosis acquire the infection postnatally [1, 2].

Congenital toxoplasmosis typically presents with chorioretinal scars that may be detected on routine screening [2]. Macular lesions were traditionally considered to be indicative of congenital toxoplasmosis (Fig. 24.1), but it is now accepted that this finding does not reliably distinguish between congenital and postnatal infection [5]. Acquired disease may be suspected in patients with active retinitis without adjacent retinochoroidal scars [2] (Fig. 24.2). Retinal disease can reactivate after both congenital and postnatally acquired infections. Classically, these recurrences manifest as active "satellite lesions" adjacent to a preexisting retinochoroidal scar, with overlying vitritis that may be minimal (Fig. 24.3) or severe ("headlight in the fog"). Other associated findings may include disc edema, macular edema, and occlusive retinal vasculitis [5].

Ocular toxoplasmosis is typically a clinical diagnosis based on the appearance of the retinochoroidal lesion. Serologic tests may be used as supportive evidence, but are limited in utility as they can only reliably identify individuals with recent *T. gondii* infections [1, 2]. Serum anti-toxoplasma antibody titers can be detected by several serologic tests, including enzyme-linked immunoassay (ELISA), indirect fluorescent antibody test, Sabin-Feldman test, complement fixation test, and indirect hemagglutination test. Anti-toxoplasma IgM can suggest a recently acquired infection, and anti-toxoplasma IgA may also be present in active disease [2]. Anti-toxoplasma IgG presents within 1–2 weeks of infection and may persist for life, and therefore does not correlate with disease activity [6]. Analysis of intraocular fluid for antibody titers or polymerase chain reaction (PCR) to detect parasitic DNA may also assist in establishing a diagnosis of ocular toxoplasmosis [2, 7].

Toxoplasmosis is typically self-limited in immunocompetent individuals and the ocular infection usually resolves within a few months. Treatment is offered, however, in order to reduce the risks of ocular damage. Some clinicians treat only immediately vision-threatening disease in adults, but most treat all active disease in children [2, 8].

Most drugs used to treat ocular toxoplasmosis act against the tachyzoite, not the encysted, bradyzoite form of the organism. One treatment combination includes oral pyrimethamine (2 mg/kg/day for 3 days followed by 1 mg/kg/day) and sulfadiazine (25–50 mg/kg/dose four times daily). Folinic acid (10–25 mg daily) may be administered in con-

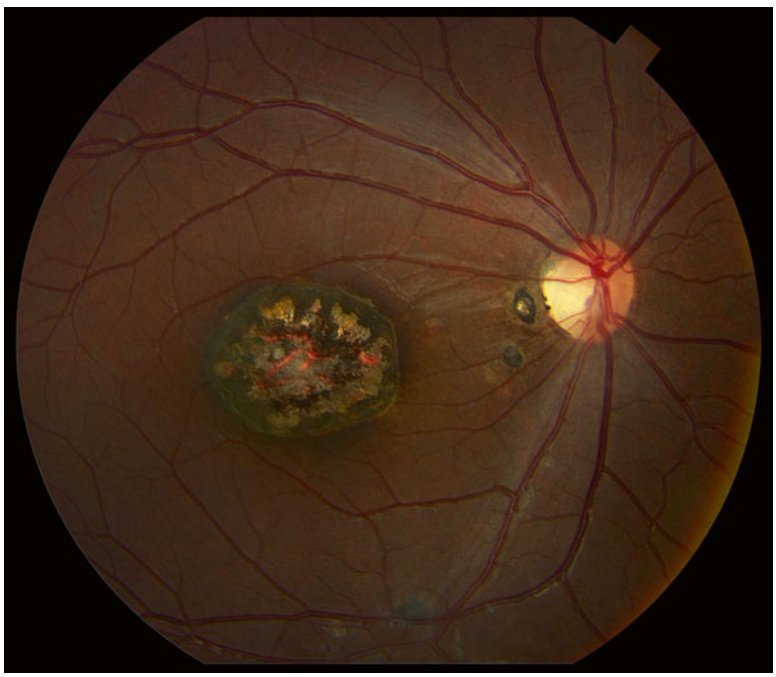

Fig. 24.1 Large chorioretinal macular scar in a case of congenital toxoplasmosis

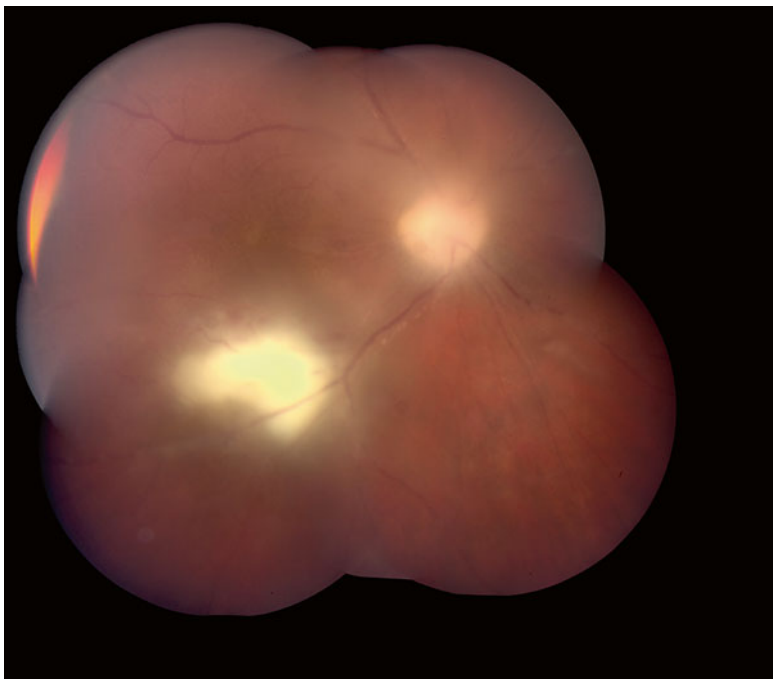

Fig. 24.2 Acquired toxoplasmosis. Note the active retinitis without an adjacent chorioretinal scar

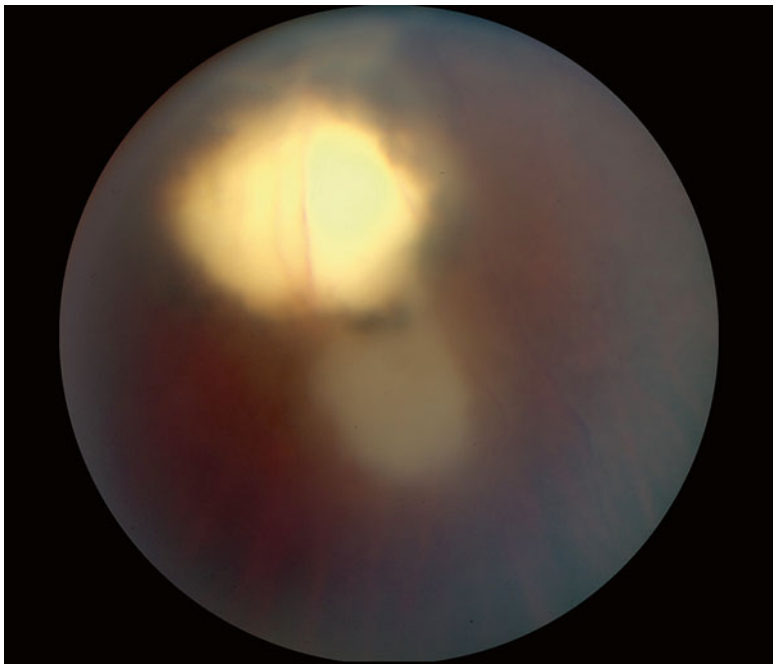

Fig. 24.3 Active inflammation adjacent to an old chorioretinal scar in a patient with reactivated toxoplasmosis

junction with pyrimethamine to prevent bone marrow suppression. Clindamycin (5–7.5 mg/kg/dose four times daily) may also be added. Newer medications such as azithromycin and atovaquone have demonstrated cysticidal effects in animal models; however this has not been demonstrated in humans and dosing recommendations for children have not been established [5, 9]. In patients with significant inflammation, oral corticosteroids may be started after initiation of antimicrobial therapy [5].

The visual prognosis depends on several factors, including the presence of macular or optic nerve involvement, and other complications of the disease such as amblyopia, macular edema, macular dragging secondary to a peripheral lesion, glaucoma, choroidal neovascularization, or retinal detachment.

Toxocariasis

Toxocariasis is a nematode infection caused by *Toxocara canis* or *Toxocara catis*, of which dogs and cats are the definitive hosts. The type and extent of clinical disease depend upon the migration pattern of the worm within the host, as well as the hosts' immune response [10].

These roundworms live in the intestinal tract of dogs or cats; humans acquire the infection after unintentional ingestion of eggs found in contaminated food or soil. The eggs then hatch into larvae in the duodenum and reach the portal circulation to cause infection [11]. Migration of the larvae into the posterior segment of the eye induces an intense inflammatory response resulting in the clinical manifestations of ocular toxocariasis.

Toxocara larvae do not develop below 50 °F, making the soil in warm climates more supportive for survival of the eggs [10, 11]. Outdoor parks are typically contaminated with *T. canis* eggs, putting children who play in these areas at higher risk of infection [11, 12]. A history of playing in sandboxes, on playgrounds, or being in contact with dogs and puppies can often be helpful in exposing risk.

Ocular toxocariasis accounts for approximately 9.4 % of all pediatric uveitis cases [13, 14]. In one study of school children, the prevalence of consultant-diagnosed toxocara eye disease was 6.6 cases per 100,000 children [15]. Ocular toxocariasis is unilateral in >90 % of cases and infection most commonly affects the pediatric population, with an age range of 2–14 years. The most common presenting signs include decrease in vision, strabismus, and leukocoria [12, 16].

Clinically, ocular toxocariasis presents in one of the three ways. Peripheral granulomas account for approximately one half of cases, and present as a white mass in the periphery [12, 16]. If there is still active inflammation, the mass may appear hazy and ill defined. As inflammation resolves, the elevated mass is typically surrounded by variable amounts of RPE pigmentary change. There may be associated retinal folds with subretinal and pre-retinal membranes extending to the macula or optic nerve (Fig. 24.4). Traction of these membranes can lead to severe vision loss and retinal detachment [10, 14]. Posterior pole granulomas are less common than peripheral ones, and present as elevated white lesions often with associated dense vitritis and tractional retinal folds. Less commonly ocular toxocariasis can present as a chronic painless endophthalmitis or dense vitritis. This presentation is more common in younger children (ages 2–9) and is often associated with the development of cyclitic membranes, retinal detachment, anterior chamber reaction, and, in severe cases, hypopyon [2, 14, 17]. Toxocariasis should be included in the differential diagnosis of conditions causing leukocoria in children, including retinoblastoma, Coats' disease, and persistent hyperplastic primary vitreous (PHPV). Shields et al. reported that 16 % of pseudoretinoblastoma eyes were actually infected with ocular toxocariasis [18].

The diagnosis of ocular toxocariasis is mainly clinical; laboratory testing thus far has proven unreliable. Serum ELISA for toxocara antibodies does not differentiate between previous exposure and current active disease, as Toxocara IgG can remain in the serum for many years [10]. In addition, the seroprevalence of toxocara antibodies is very high: 4–31 % in developed countries and up to 86 % in tropical regions [15]; thus, positive ELISA for toxocara is not diagnostic for ocular disease. In addition, false-negative test results may occur as only small amounts of antibody are released in the eye at the time of infection, with even lower serum levels [19, 20]. It is, therefore, essential that serum antibody tests are interpreted with caution, and only in the context of the clinical disease. Testing stool for ova and parasites is not useful in this disease, and unlike systemic toxocariasis, peripheral eosinophilia is not a feature of ocular

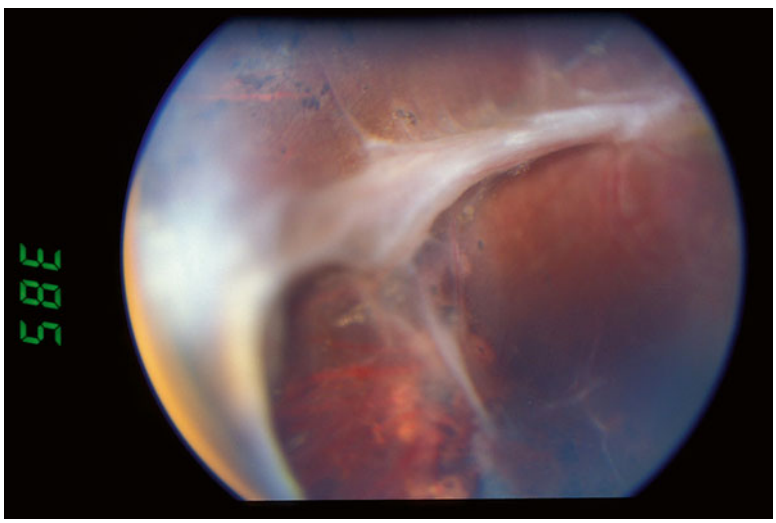

Fig. 24.4 Fundus photograph of a patient with a peripheral toxocara lesion. Note the peripheral elevated mass with adjacent RPE pigmentary change and extensive subretinal and pre-retinal membranes

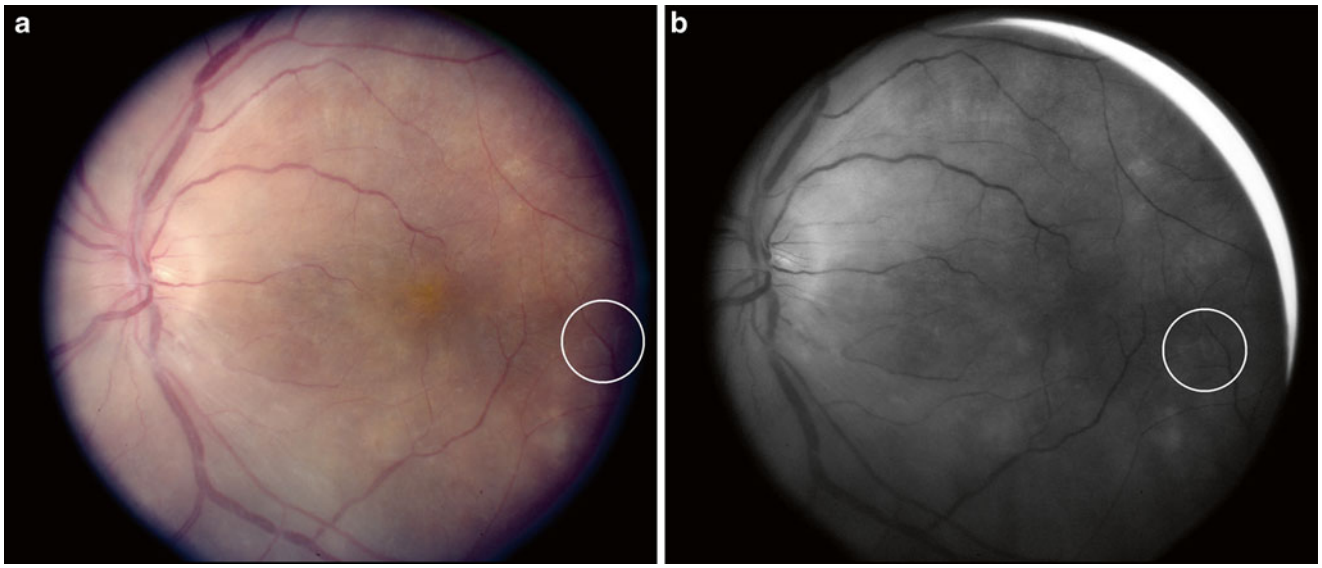

Fig. 24.5 Color fundus photograph (**a**) demonstrates subretinal worm along with vascular attenuation and diffuse RPE changes. There is also mild optic nerve edema. Red-free photo (**b**) taken minutes later demonstrates migration of the worm in the subretinal space

disease. Sampling the aqueous humor to identify toxocara antibodies can aid in the diagnosis in difficult clinical cases in which there is high clinical suspicion and negative or equivocal serum ELISA testing [19, 21]. However, this testing is not commercially available in the USA.

Treatment for ocular toxocariasis is aimed at reducing the immune response and preventing sequelae of inflammation. As the organism is presumed to be dead when the patient presents [22], the mainstay of treatment in cases with dense vitritis includes periocular or systemic corticosteroids rather than antihelminthic agents [22]. Cycloplegic agents may be added in the presence of a significant anterior chamber reaction. Surgical intervention has been successful in managing complications by relieving macular traction, repairing retinal detachments, and removing fibrotic vitreal membranes [16, 23, 24]. Visual improvement after pars plana vitrectomy was obtained in 50 % of cases in one study [23]. More importantly, prevention can be achieved through education regarding regular deworming of pets and the practicing of good hygiene.

Diffuse Unilateral Subacute Neuroretinitis

Diffuse unilateral subacute neuroretinitis (DUSN) is caused by a motile worm in the subretinal space. *Baylisascaris procyonis* and *Ancylostoma caninum* have been implicated in DUSN cases in the USA [25, 26]. *Ancylostoma caninum*, a smaller sized dog hookworm, is associated with cases described in the Southeastern USA and Latin America [25]. *Baylisascaris procyonis* is a much larger worm whose host is the raccoon and is more common in the Midwestern and Northern USA [17, 26]. Ocular infection in children occurs following ingestion of soil contaminated with larvae or eggs which hatch in the intestines and migrate via the bloodstream to the subretinal space.

DUSN most commonly affects healthy children and occurs in two clinical phases. In the acute phase, it presents as an insidious onset of unilateral decrease in vision or scotoma. The findings on examination include vitritis, papillitis, and multiple crops of gray-white lesions at the level of the retina and choroid [27]; in 40 % of cases, the live worm may be identified in the subretinal space [14, 28] (Fig. 24.5). Occasionally there may be associated vasculitis [28–30]. The retinal lesions may fade over time only to recur in another nearby location. Without treatment, worm by-products cause a local toxic effect on the retina leading to extensive retinal pigment epithelial changes [31], arteriolar attenuation, and optic atrophy. Late stages of disease are correlated with an 80 % chance of vision worse than 20/200 [32].

Electroretinographic changes occur early in the disease with evidence of damage to both cone and rod systems. The b wave is more severely reduced than the a wave, thus creating a negative ERG. Serological testing, blood smears, and stool evaluations are not helpful in diagnosing DUSN [27]. Detection of the worm in the subretinal space on dilated fundus examination is the preferred confirmatory test.

Direct application of laser photocoagulation using 200–500 μm, 0.2–0.5-s duration, can effectively destroy the nematode [14]. If the worm is located in the macula, bright light aimed directly at it may induce it to migrate, providing a much safer location to apply photocoagulation. When

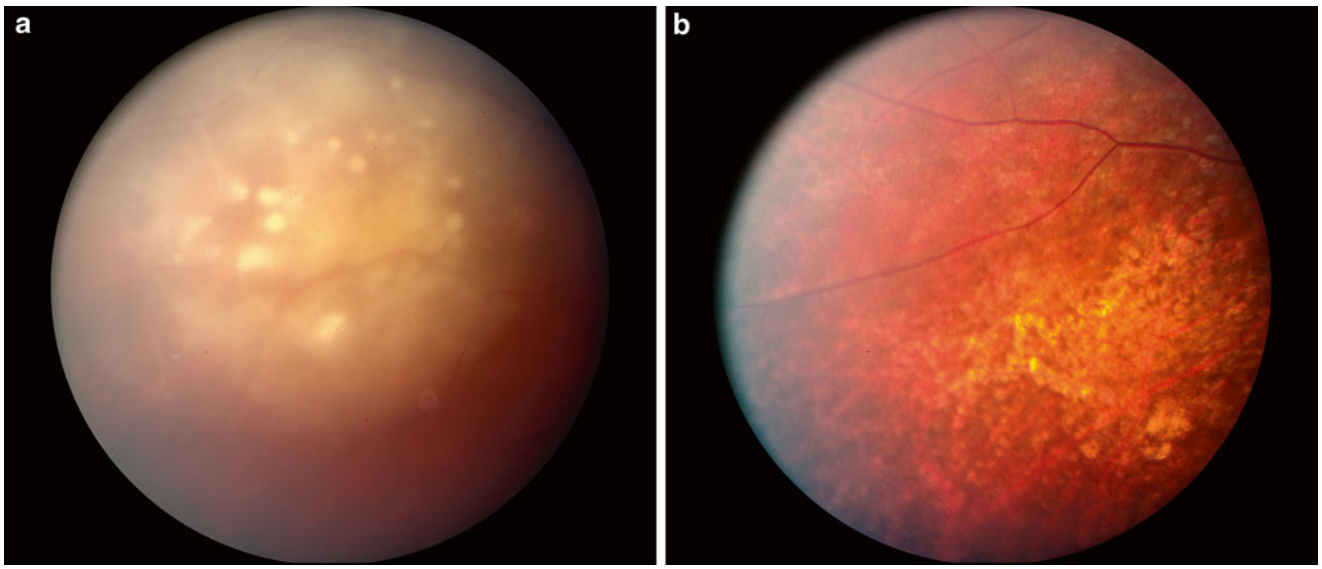

Fig. 24.6 Active syphilitic retinitis in an HIV-positive patient (**a**). Note the characteristic retinal infiltrate with superficial precipitates. Salt-and-pepper appearance of resolved retinitis (**b**) after therapy with IV penicillin

performed at an early stage in the disease course, laser treatment may improve vision and reduce inflammation [33, 34]. Once deep retinal atrophy has ensued, visual recovery is unlikely. A few studies support the use of once-daily 400 mg oral albendazole in the treatment of DUSN [30, 35]; however this has not consistently been proven, and the gold standard remains the use of laser photocoagulation [30].

DUSN should be considered in any patient with unilateral vision loss associated with vitritis, papillitis, and retinal lesions. Given the devastating visual consequences of delayed diagnosis, a careful search for the worm should be performed on every visit and, if located, treated promptly with photocoagulation.

Bacterial Infections

Syphilis

Syphilis is a systemic disease caused by the spirochete *Treponema pallidum*. It is most commonly transmitted during sexual contact, but can also occur by direct contact with infectious lesions. Congenital infection may occur transplacentally even during periods of seronegativity of the mother [2, 36].

Clinical manifestations during early congenital syphilis may include rash, hepatosplenomegaly, lymphadenopathy, and skeletal abnormalities. The most common form of uveitis in congenital syphilis is a chorioretinitis. Once inactive, it gives the fundus a "salt-and-pepper" appearance. Other ocular manifestations of congenital syphilis include anterior uveitis or interstitial keratitis, which may not present until late childhood or adolescence [2, 37]. Acquired ocular syphilis in children or adolescents presents similarly to that of adults (Fig. 24.6), and can potentially involve any ocular structure. Ocular inflammation may appear at any stage of acquired syphilitic infection and can involve the anterior or posterior segment, and may be unilateral or bilateral, and granulomatous or non-granulomatous. Because syphilis can manifest in nearly any ocular structure, it is imperative to rule out syphilis as an etiology during the work-up of any unexplained ocular inflammation [37].

Serologic tests to diagnose syphilis include non-treponemal tests and treponemal tests. Non-treponemal tests include the Venereal Disease Research Laboratory (VDRL) and rapid plasma reagin (RPR), and treponemal tests include the fluorescent treponemal antibody absorbed (FTA-ABS), *T. pallidum* particle agglutination (TP-PA), and the microhemagglutination (MHA) test. Testing for syphilis requires that both treponemal and non-treponemal tests be obtained, as non-treponemal tests may become negative over time [38, 39]. Non-treponemal tests may also produce false-positive results due to autoimmune disease, pregnancy, or infection with rickettsial or other spirochetal infections [37]. Patients with ocular syphilis should have a cerebrospinal fluid examination and be referred to an infectious disease specialist. Intraocular syphilis should be treated as neurosyphilis, regardless of the results of lumbar puncture [40]. Treatment of neurosyphilis in adults includes intravenous aqueous penicillin G 18–24 mU/day for 14 days, or procaine penicillin G 2.4 mU/day intramuscularly plus probenecid 500 mg intramuscularly four times a day for 10–14 days. Children with

congenital syphilis or neurologic involvement should be treated with intravenous aqueous penicillin G 200,000–300,000 units/kg/day, administered as 50,000 units/kg every 4–6 h for 10 days [41]. Any patient diagnosed with syphilis should also have HIV testing, as studies have demonstrated that up to 83 % of patients with posterior manifestations of ocular syphilis are coinfected with HIV [38].

Cat-Scratch Disease

Cat-scratch disease (CSD) is caused by the facultative intracellular gram-negative rod *Bartonella henselae*. It typically occurs in immunocompetent patients under 20 years old, and is more common in males [42]. Transmission occurs through the bite or scratch of an infected cat. Systemic manifestations include a mild-to-moderate influenza-like illness with painful lymphadenopathy [42]. The eye is commonly affected, and clinical manifestations may vary.

The most common ocular complication of CSD is Parinaud oculoglandular syndrome, which presents with a follicular conjunctivitis and is associated with regional lymphadenopathy and fever. On examination, there is unilateral conjunctival injection, epiphora, and discharge. Conjunctival lesions may be present on the palpebral or bulbar surfaces and ulceration with necrosis of the epithelium is common. Other organisms reported to cause Parinaud oculoglandular syndrome include tuberculosis, syphilis, and sporotrichosis [42, 43].

Other ocular manifestations of CSD include neuroretinitis, retinitis and choroiditis, retinal infiltrates, retinal vasculitis and vascular occlusions, and disc edema [42–44]. Neuroretinitis with macular star formation has classically been considered the most common intraocular finding associated with CSD; however recent reports suggest that isolated lesions in the outer retina and choroid may be more common than previously reported [42, 44, 45].

Diagnosis of CSD is based on clinical findings that can be supplemented with laboratory tests. Serologic tests include indirect fluorescence assay and ELISA. Polymerase chain reaction may also be useful; however its sensitivity is lower than that of serological tests [42].

In immunocompetent patients, CSD is often a self-limiting disease, and therefore treatment may be reserved for those with severe infections or for immunocompromised patients. However, there are reports that demonstrate a benefit to antibiotic therapy in those with CSD retinitis. Doxycycline (100 mg orally twice daily) combined with rifampin (300 mg orally twice daily) has been used successfully. Doxycycline should be avoided in patients younger than 12 years of age due to the risk of tooth discoloration [42].

Lyme Disease

Lyme disease is a multisystem infection caused by the spirochete *Borrelia burgdorferi*, which is transmitted to humans by the *Ixodes* tick [2, 46]. The preferred host for the adult tick in the USA is the white-tailed deer [46]. Most cases of Lyme disease in the USA occur in the Mid-Atlantic and Northeastern regions.

Lyme infection is described by its three distinct stages. Stage 1 involves the classic target lesion of erythema migrans, flulike symptoms, and lymphadenopathy. Transient mild bilateral conjunctivitis and episcleritis can be seen in early disease [46]. Stage 2 infection occurs days to weeks later and is characterized by cardiac and neurological involvement. Bell's palsy may occur during this stage [47]. The third stage manifests with chronic fatigue, painful episodes of arthritis, and neurological symptoms such as ataxia, encephalomyelitis, and dementia [46]. Ocular manifestations of Lyme disease generally occur in the later stages and can include optic neuritis, cranial nerve palsies, interstitial keratitis, and uveitis [48]. Most commonly, uveitis presents as a bilateral intermediate uveitis associated with granulomatous iridocyclitis, typically associated with peripheral snowbanking and exudates [46, 47]. Posterior uveitis has also been reported in the form of a diffuse choroiditis with cystoid macular edema and exudative retinal detachment [49]. Retinal vasculitis has also been reported [48, 50]. Bilateral keratitis occurs in approximately 4 % of children with chronic Lyme arthritis [51].

Diagnosis of Lyme disease can be challenging as *B. burgdorferi* is extremely difficult to culture. A clinical history describing a tick bite in an endemic area followed by characteristic rash is suggestive of infection; however, most patients do not recall being bitten by a tick. A fourfold increase in serial IgM antibody levels in a patient with a clinical history consistent with Lyme disease increases the probability that Borrelia infection is the cause of symptoms [52]. In the acute phase, most patients have not yet mounted a sufficient antibody response and tests will be falsely negative [52, 53]. The sensitivity of an ELISA done at least 5 weeks after disease onset approaches 90 %; however positive results must be confirmed with Western blot [52]. False-positive ELISA results are common, and can occur with autoimmune disease and Rocky Mountain spotted fever, or as a result of immunologic cross-reactivity with treponemal antibodies in cases of syphilis or relapsing fever [53–55].

Severe posterior uveitis associated with Lyme infection should be treated with IV antibiotics such as ceftriaxone (100 mg/kg/day IV × 21 days) or penicillin G (250,000 units/kg/day IV daily × 21 days). Topical corticosteroids and mydriatics can be used for anterior segment inflammation [47]. Mild ocular disease not involving the posterior segment can

be treated with oral antibiotics such as doxycycline or amoxicillin.

Lyme infection is a rare cause of uveitis. More commonly patients will experience mild conjunctivitis or cranial nerve palsies. Clinical diagnosis depends on a suggestive history followed by elimination of other more likely causes. Serum testing is not diagnostic and should be interpreted with caution. Confirmed cases of uveitis should be treated with appropriate intravenous antibiotics.

Intraocular Tuberculosis

Nearly one-third of the world's inhabitants are infected with *Mycobacterium tuberculosis* but only 10 % of those will develop active disease. Worldwide tuberculosis prevalence among children was estimated at 530,000 cases in 2012, approximately 6 % of the 8.6 million cases worldwide [56]. Tuberculosis (TB) is characterized by multiple foci of granulomatous inflammation most commonly affecting the lungs, although it may spread to any solid organ [57]. Ocular involvement was found in 1.39 % of 1005 cases of pulmonary and extrapulmonary TB in a study from India [58]. Most patients with tuberculous uveitis however present without concurrent systemic disease [59–61]. Ocular TB carries risks of significant visual morbidity and is associated with a 30 % enucleation rate [62].

In patients in endemic areas, the ocular signs most predictive of tuberculous uveitis include broad-based posterior synechiae, retinal vasculitis with or without choroiditis, and serpiginous-like choroiditis [63]. In nonendemic areas, posterior uveitis with multiple choroidal granulomas is the most common clinical presentation of intraocular tuberculosis, followed by anterior uveitis and panuveitis, although retinal vasculitis and neuroretinitis, scleritis, and serpiginous-like choroiditis are also described [57, 61, 64, 65].

Tuberculous choroidal granulomas are grayish white to yellow nodules with indistinct borders, occasionally associated with overlying serous retinal detachment [66]. As the infection resolves, the margins become more distinct with a pigmented border resulting in an atrophic scar [67]. Liquefaction necrosis can occur as the bacilli multiply and caseation becomes present within the granuloma, leading to the development of subretinal abscesses [68]. Plaque-like choroidal lesions displaying an advancing border represent the serpiginous-like choroiditis associated with tuberculous uveitis [69]. Less commonly, a large solid tuberculoma may mimic a choroidal tumor [70].

Retinal vasculitis typically presents as an obliterative periphlebitis with retinal hemorrhages and areas of nonperfusion [64, 65]. Anterior uveitis is generally granulomatous, with mutton fat keratic precipitates, iris nodules, and, rarely, tuberculous granulomas in the anterior chamber angle [63].

Diagnosis of intraocular tuberculosis is complicated by the challenge of ocular sampling for microbiological confirmation of disease. Recommended diagnostic criteria for presumed ocular tuberculosis include clinical findings consistent with intraocular TB infection, as well as positive testing such as tuberculin skin testing, interferon gamma release assay, radiologic findings, or cultures from extrapulmonary sites of infection, a positive response to a therapeutic trial of four anti-tuberculin medications, as well as exclusion of other causes of intraocular inflammation [61, 67]. Additional tests to confirm the diagnosis include identification of the organism in ocular fluid either by culture or PCR; however the yield is very low and testing carries the risk of morbidity [71, 72]. Cultures of *M. tuberculosis* on Lowenstein-Jensen media can take as long as 8 weeks [67] and the sensitivity of polymerase chain reaction in vitreous samples is less than 50 % [71].

The recommended treatment for ocular tuberculosis involves the use of various combinations of specific antituberculous medications including isoniazid, rifampin, ethambutol, and pyrazinamide. Therapy should include a multidrug regimen continued for at least 8–9 months [57, 60, 73]; ocular disease may require longer therapy than is required for pulmonary disease [61]. These medications carry risks of systemic toxicity; thus management should be done in conjunction with a pediatric infectious disease specialist. Sequestered organisms have been identified in the retinal pigment epithelium of enucleated specimens and are likely responsible for disease reactivation [74]; thus relapses of posterior segment disease should also be treated with specific anti-mycobacterial therapy.

Ocular tuberculosis may be associated with significant morbidity. In cases without systemic evidence of disease or microbiological confirmation of infection, a high index of suspicion is required to make the diagnosis and prevent delay in treatment.

Viral Infections

Herpes Simplex Keratouveitis

Herpes simplex is a ubiquitous DNA virus responsible for the pathogenesis of many ocular infections. Herpes simplex virus (HSV) type 1 is most commonly acquired during childhood via contact with infected saliva or mucous membranes, while type 2 can be acquired by exposure to active lesions during vaginal delivery or through transplacental spread [75]. The virus then becomes latent in the corresponding sensory ganglia where it may reactivate later [76]. Ophthalmic infection is generally a manifestation of virus reactivation in the trigeminal ganglion.

HSV uveitis is a challenging disease to manage in children due to the added risk of amblyopia secondary to corneal scarring and astigmatism in patients with associated corneal involvement. Herpes simplex keratitis and uveitis are typically unilateral in adults, with the exception of individuals with atopic disease, but may present bilaterally in children [77].

The diagnosis of herpes simplex keratouveitis is easily made in a patient with a typical dendritic epithelial lesion. However, making the diagnosis of herpes simplex iridocyclitis without evidence of keratitis can be more challenging. A careful history should include a search for exposures, coexisting atopic or dermatologic disease, recent vaccination, and a history of prior herpetic disease [78]. Examination may reveal inflammatory cells in both the anterior chamber and anterior vitreous owing to iris and ciliary body inflammation. The uveitis is often granulomatous with pigmented keratic precipitates not confined to the inferior cornea and iris nodules, and may be associated with a hypopyon or hyphema [78–81]. Iris transillumination defects are common due to ischemic atrophy of the iris pigment epithelium [78, 80, 82] (Fig. 24.7). Distortion of the pupil may occur due to a combination of localized sphincter damage and the presence of posterior synechiae [78, 79, 82], and the pupil is often larger in the involved eye [83]. The condition is commonly associated with elevated intraocular pressure at presentation [78, 82], helping to differentiate it from other causes of acute anterior uveitis, where ciliary body inflammation typically results in a reduction in IOP. The disease may run a chronic or recurrent course, and prophylactic treatment may be indicated. Confirmation of diagnosis can be made by PCR detection of viral DNA in aqueous humor samples [84].

The recommended treatment for herpes simplex keratouveitis in children involves the use of systemic antiviral medications. Oral acyclovir is dosed from 12 to 40 mg/kg/day in divided doses depending on the renal health of the child and disease severity [85]. Oral valacyclovir has higher bioavailability with less frequent dosing, is well tolerated, and has been shown to be effective in children. Dosing recommendations in the pediatric population have not yet been established; however adult dosing (1 g twice daily) can be given to older children [86]. Early trials with famciclovir demonstrated favorable results in children aged 1–12 years, but further studies are warranted and no pediatric formulation is available [87]. Cycloplegics may be added to improve comfort and prevent development of posterior synechiae, and topical antihypertensive agents may be required o control intraocular pressure. If there are no corneal epithelial defects, topical corticosteroids can be added [88]. The addition of topical steroids in herpetic disease should only be used with simultaneous topical or systemic antiviral coverage. Prolonged antiviral treatment can be used to reduce recurrences.

Varicella Zoster and Herpes Zoster Ophthalmicus

The varicella zoster virus (VZV) belongs to the family of herpes viruses and is responsible for two distinct clinical entities: varicella (chickenpox) and herpes zoster (shingles). Since the introduction of the childhood VZV vaccine, many children no longer experience wild-type chickenpox infection and varicella-related morbidity has declined dramatically [89].

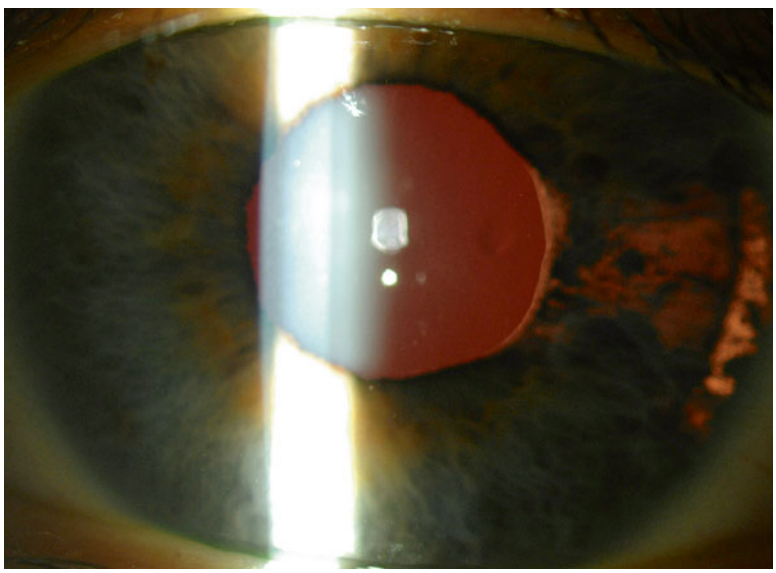

Fig. 24.7 Slit-lamp photograph demonstrating sectoral iris transillumination defect in a patient with HSV anterior uveitis

Intraocular inflammation may occur in the setting of systemic varicella infection or as part of VZV reactivation during an episode of shingles. Ocular manifestations of systemic varicella infection are less common than those that occur during zoster reactivation and may include eyelid lesions, conjunctivitis, disciform keratouveitis, and anterior uveitis [90–93]. Approximately 12–25 % of children with active chickenpox lesions develop a mild anterior uveitis [90]. Ocular involvement does not correlate with the presence of eyelid lesions or the severity of the chickenpox infection [93].

Herpes zoster reactivation (shingles) is more frequent with advancing age or immunosuppression. However, childhood cases have been reported. Risk factors for herpes zoster in children younger than 10 years of age include varicella acquired in the first year of life or VZV exposure in utero from maternal gestational infection [94]. In children older than ten, infection typically occurs in the setting of immunosuppressive medications, human immunodeficiency virus infection, or malignancy [94, 95]. Ocular involvement during herpes zoster infection occurs in 60–71 % of cases involving the ophthalmic division of the trigeminal nerve [96]. Hutchinson's sign describes involvement of the nasociliary branch, with skin lesions developing on the tip of the nose, and is a strong predictor of intraocular inflammation and poorer visual outcome [97].

Herpes zoster ophthalmicus (HZO) can involve any portion of the eye causing blepharoconjunctivitis, episcleritis, scleritis, sclerokeratitis, uveitis, retinal necrosis, optic neuritis, or oculomotor palsies, and is typically more severe than ocular disease that occurs during primary varicella infection [95, 96].

Uveitis occurs in 30–50 % of cases of HZO, and often presents 1–2 weeks after the onset of skin or corneal lesions, but can also manifest without evidence of prior or concurrent epithelial or stromal disease [82]. Anterior uveitis is similar to that observed in herpes simplex infection, and examination may demonstrate keratic precipitates, synechiae, pupil distortion from sphincter atrophy, and iris transillumination defects [96]. Hyphema has also been reported as a complication of herpes zoster uveitis [98], and intraocular pressure is often elevated. Since necrotizing retinitis may develop, every patient with HZO requires a dilated fundus examination. Diagnosis can be made based on the medical history and the presence of the typical dermatomal rash; however a small number of patients demonstrate zoster sine herpete and have only ocular disease with no skin lesions [99]. In difficult cases, viral culture from corneal scrapings or aqueous PCR can be helpful [100].

Ocular involvement in primary varicella can be self-limited or may require a short course of cycloplegic and topical steroids. Most cases heal without complications and the prognosis is good [90]. Conversely, herpes zoster ophthalmicus is much more difficult to treat and the course may be prolonged. Treatment of HZO involves use of oral antivirals such as acyclovir, valacyclovir, and famciclovir. For children weighing less than 40 mg, oral acyclovir can be given as 20 mg/kg/dose four times daily. For children weighing over 40 kg, 800 mg four times daily is effective. Pediatric dosing for oral valacyclovir and famciclovir has not yet been elucidated [9]. Topical corticosteroids are used for isolated stromal or nummular keratitis and for anterior uveitis. Anterior uveitis often persists for weeks or months and may respond to topical corticosteroids, cycloplegics, and topical antihypertensives, although systemic antiviral therapy is usually required. Long-term therapy often is needed due to residual damage caused by the inflammatory reaction. Surgical management may be required for lid abnormalities, corneal scarring, glaucoma, or cataract development [96]. Persistent corneal hypoesthesia has been found in 90 % of children with HZO and is a long-term risk factor for neurotrophic complications [101].

Necrotizing Retinitis

Acute retinal necrosis (ARN) was first described in 1971 by Urayama and associates as a severe vaso-occlusive retinal necrosis [102]. Histopathological identification of the herpes virus in the retina of patients with ARN was made in 1982, paving the way for directed therapy [103]. Acute necrotizing herpetic retinitis is an uncommon cause of pediatric uveitis; thus keeping a high clinical index of suspicion is crucial to diagnosis.

In contrast to ARN in adults, where varicella zoster is the most common etiology [104], ARN in the younger population is more frequently associated with reactivation of herpes simplex type 2 [105, 106]. Retinal necrosis has been reported following congenital HSV 2 encephalitis and meningitis; however in most cases no previous neonatal infection exists, and perinatal contact with maternal lesions is thought to be the source [107].

Acute retinal necrosis in children may be accompanied by fever in addition to the typical symptoms of blurred vision, photophobia, floaters, and pain [106, 107]. The fellow eye may become affected in 36 % of patients, weeks to months later [108]. Granulomatous anterior uveitis often accompanies posterior disease, and therefore examination of the peripheral retina is essential to avoid misdiagnosis.

The diagnostic criteria for ARN established by the Executive Committee of the American Uveitis Society include (1) one or more foci of retinal necrosis with discrete borders in the peripheral retina (Fig. 24.8), (2) occlusive arteriolar vasculopathy, (3) circumferential spread, (4) vitreous and anterior chamber inflammatory reactions, and (5) rapid progression of disease without treatment. An important characteristic that differentiates this condition from other

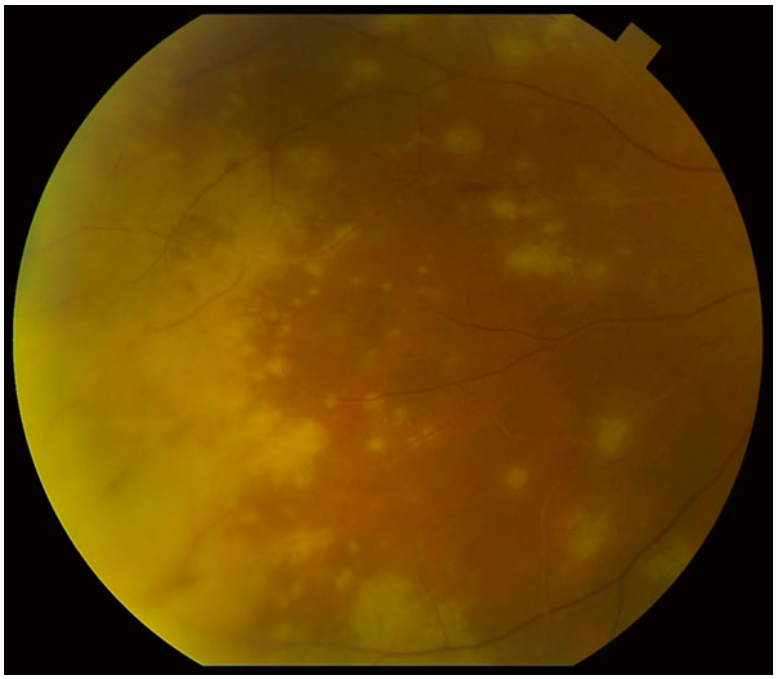

Fig. 24.8 Peripheral areas of confluent retinal whitening with occlusive vasculitis in acute retinal necrosis

entities is that the lesions do not follow the retinal vascular architecture [109].

Acute retinal necrosis must be considered in any patient who presents with peripheral retinitis and retinal vasculitis; a prompt diagnosis is necessary given the rapid progression of disease and risk of permanent vision loss. Clinical diagnosis may be supported with confirmation of viral etiology by PCR. PCR of aqueous or vitreous specimens is highly sensitive and can confirm clinical suspicion as well as determine the responsible virus [110].

Prompt treatment with systemic antiviral medication is essential to hasten resolution in the affected eye and prevent contralateral infection. Presently, there is no single standard of care for ARN, and many options for antiviral treatment exist. A common strategy is to initiate therapy with intravenous acyclovir or valacyclovir for 10–14 days, followed by extended therapy with oral acyclovir [9, 108, 111]. For children able to take adult dosing, sole therapy with oral valacyclovir (1–2 g three times daily) or famciclovir (500 mg three times daily) can be given due to their greater bioavailability and intraocular penetration [9, 112, 113]. Adjunctive therapy should be considered for foveal threatening disease, and includes the use of intravitreal antivirals such as ganciclovir (2 mg/0.05 ml) and foscarnet (1.2 mg/0.05 ml) [9, 111, 114]. Meghpara et al. showed that in patients with moderate retinal involvement in ARN (25–50 % retinal involved) intravitreal therapy can stabilize or improve visual acuity [115]. In pediatric cases of ARN that are resistant to acyclovir, intravenous foscarnet (40–60 mg/kg/dose every 8 h) has been shown to be beneficial; however precise dosing calculations should be made by a pediatric infectious disease specialist [116]. Systemic corticosteroids may be added after antiviral therapy is initiated, in order to decrease reactive inflammatory tissue damage; dosing should be adjusted based upon clinical severity.

The predominant complication of ARN is rhegmatogenous retinal detachment, occurring in 60 % of pediatric cases in one series [107]. Thus, a thorough peripheral examination in search for retinal holes should be performed at every visit. Prophylactic laser barricade has been shown in some studies to reduce the risk of retinal detachment, although this recommendation has not been consistently supported [111, 117–119]. Surgical repair retinal detachment may be complicated by the posterior location of breaks, presence of multiple large holes in necrotic retina, and proliferative vitreoretinopathy (PVR). Repair often requires vitrectomy with silicone oil and/or scleral buckle [108]. Despite aggressive management, the development of epiretinal membranes, optic atrophy, macular scarring, and PVR may limit final visual acuity [107].

Cytomegalovirus

Cytomegalovirus (CMV), a member of the herpes virus group, is the most common congenital viral infection in the USA [120], and can result in intrauterine growth retardation, microcephaly, hepatosplenomegaly, hearing impairment, and mental retardation [121, 122]. Ophthalmologic abnormalities are common in CMV infection and include visual impairment from optic atrophy or cortical visual impairment, macular scars, and chorioretinitis [120, 123]. CMV retinitis

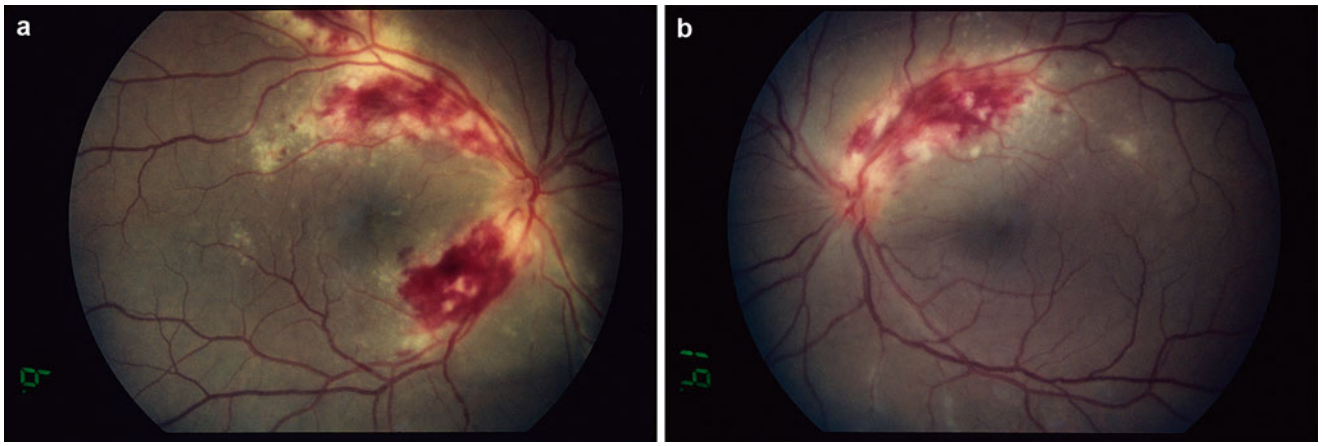

Fig. 24.9 (**a** and **b**) Bilateral cytomegalovirus (CMV) retinitis in an immunosuppressed patient demonstrating retinal necrosis and hemorrhages along the distribution of retinal vessels in the posterior pole

(CMVR) has been reported in up to 25 % of symptomatic congenital CMV patients [122, 124].

CMV is a common viral cause of retinitis in immunocompromised individuals, such as those with acquired immunodeficiency syndrome (AIDS) or in those who are iatrogenically immunosuppressed after solid organ transplantation [2]. Between 20 and 40 % of adults with AIDS may be affected with CMVR, while it has only been reported in approximately 5 % of children with AIDS [125–127]. Similarly, it is rare in children with other systemic etiologies of immunosuppression, although it has been reported in patients with severe combined immunodeficiency syndrome and renal or bone marrow transplantation, and those undergoing chemotherapy for acute lymphocytic leukemia [126, 128].

CMV retinitis may begin as retinal whitening and necrosis along retinal blood vessels, often with associated hemorrhage (Fig. 24.9). Multifocal, granular lesions and vasculitis may also occur. Full-thickness necrosis can result in retinal thinning, multiple large retinal holes, and retinal detachment [2].

The clinical presentation of CMVR in children differs from that of adults. Young children may be unable to describe visual changes, such that retinitis is detected only during screening examination performed because of extraocular CMV or HIV infection. This delay in diagnosis may contribute to the higher proportion of bilateral, macula-involving retinitis at initial presentation in children, and subsequent poor visual outcome. Baumal et al. found that CMVR was bilateral in 89 % of immunocompromised children at diagnosis, whereas only approximately one-third of adults with AIDS have bilateral CMVR at initial presentation [126, 129].

CMV retinitis is typically a clinical diagnosis; however PCR of anterior chamber or vitreous fluid may be helpful. Treatment induction can be achieved with intravenous ganciclovir (5 mg/kg every 12 h), intravenous foscarnet (60 mg/kg every 8 h), or oral valganciclovir. Dosing of valganciclovir in pediatric patients has not yet been agreed upon [9, 126]. Induction therapy is generally continued for 2–3 weeks. Decisions regarding dosing maintenance or suppressive therapy should be made in conjunction with a pediatric infectious disease specialist. Intravitreal ganciclovir (2 mg/0.05 ml) and foscarnet (1.2 mg/0.05 ml) may also be used as adjunctive therapy in children with retinitis who have failed to completely respond to or do not tolerate systemic therapy [9, 126, 130, 131].

Rubella

Congenital Rubella syndrome is classically characterized by a combination of cardiac, ocular, and hearing defects. The rate of in utero transmission and severity of fetal infection is largely correlated with gestational age at the time of maternal infection. Ocular disease may occur in up to 78 % of children. Typical findings include pigmentary retinopathy, cataracts, microphthalmia, and glaucoma [132].

In addition, the rubella virus has been implicated in the etiology of Fuchs heterochromic iridocyclitis (FHI) [133–136]. Typical findings in FHI include iris heterochromia, unilateral anterior uveitis with stellate keratic precipitates, anterior stromal iris atrophy, and the development of posterior subcapsular cataract [137]. Antibodies to the rubella virus have been detected in the aqueous humor of patients diagnosed with FHI and may represent chronic infection [133, 135, 138]. FHI has become less common in the USA with the introduction of rubella vaccination [136].

Fungal Infections

Histoplasmosis

Presumed ocular histoplasmosis syndrome (POHS) is a distinct ocular syndrome that develops following systemic infection with *Histoplasma capsulatum*, a dimorphic fungus

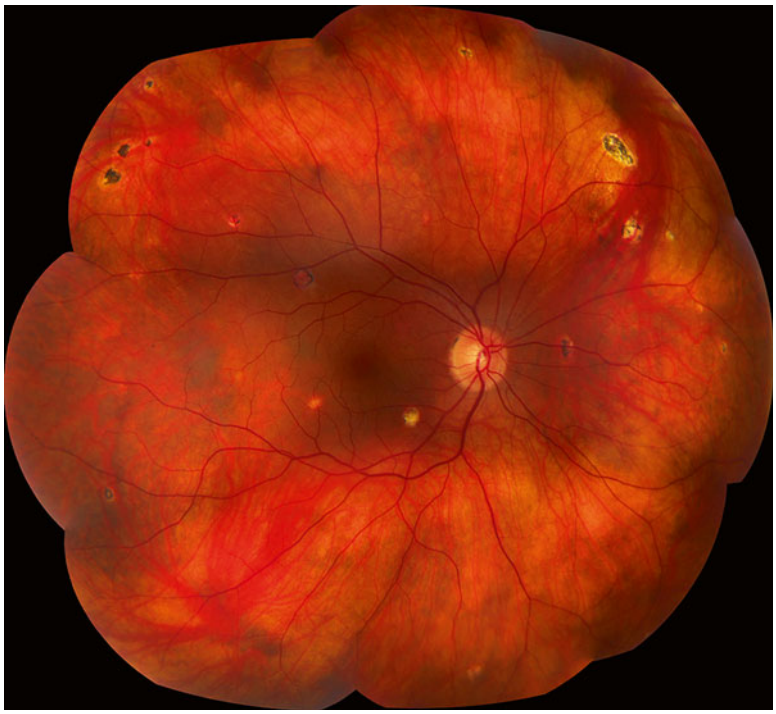

Fig. 24.10 Montage of right fundus of a patient with POHS. Note the mild peripapillary atrophy and scattered punched-out lesions in the posterior pole and periphery. Also note clear media and lack of vasculitis

that is endemic to the Ohio and Mississippi River Valleys [139–141]. Humans become infected by inhalation of spores, which then spread hematogenously to the spleen, liver, and uveal tract. Acute infection is typically self-limited and may be asymptomatic or resemble a viral illness [139]. POHS typically presents between the ages of 20 and 50; however cases have been reported in teenagers [139]. POHS is diagnosed clinically by identifying typical ophthalmoscopic findings including peripapillary atrophy and multiple, atrophic, choroidal scars ("histo spots") in the absence of vitritis (Fig. 24.10). The choroidal scars represent the dissemination of the organism to the choroid, resulting in choroidal granulomas; resolving granulomas then develop into focal areas of choroidal and RPE atrophy, leaving multiple, "punched-out" lesions [139].

The majority of patients with POHS are asymptomatic. However, the development of choroidal neovascularization (CNV) is a well-known sight-threatening complication that may occur at sites of atrophic scars, as a result of focal breaks in Bruch's membrane [140, 141].

Treatment for POHS is targeted at the CNV. Antifungal medication is not indicated as the organism is not present in the atrophic lesions [139]. Intravitreal anti-vascular endothelial growth factor (VEGF), photodynamic therapy, local corticosteroid injection, and photocoagulation have all been successfully used to treat CNV due to POHS.

Endogenous Endophthalmitis

Infectious endophthalmitis is a rare complication of septicemia, penetrating globe trauma, or intraocular surgery [142]. Endogenous infection, resulting from hematogenous spread of microorganisms to the eye, is the least common cause of infectious endophthalmitis in children. It accounts for only 0.1–4 % of all cases, with the highest incidence in India and the lowest in the USA [143, 144]. Risk factors for endogenous endophthalmitis in the pediatric and neonatal age group include prematurity, bacteremia, candidemia, prolonged hospitalization, and the presence of indwelling catheters [143, 145]. The most common etiology of fungal endophthalmitis is *Candida albicans*, and common causes of bacterial endophthalmitis include *Pseudomonas* species, group B *Streptococci*, and *Klebsiella* [145–147]. Although the incidence of endogenous endophthalmitis in children is rare, the ophthalmologist should have a high index of suspicion in susceptible patients, as delays in diagnosis can lead to poor visual outcomes. Patients may present with fulminant features such as eyelid edema, conjunctival injection and chemosis, and hypopyon, or the infection may affect only the posterior segment, manifesting as vitritis or retinal infiltrates [146]. Management of endogenous endophthalmitis includes parenteral antimicrobials, intravitreal injections, and vitrectomy [146].

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Pediatric Masquerade Uveitis

25

Francesco Pichi, Paolo Nucci, Paola Carrai, and Careen Lowder

Abstract

Several noninfectious and neoplastic processes that are not autoimmune diseases may commonly masquerade as uveitis, leading to delays in appropriate treatment. Careful history and examination in concert with appropriate ancillary investigations and histopathologic evaluation of tissue specimens are required in order to make the correct diagnosis. This chapter evaluates neoplastic and nonneoplastic conditions which may be considered masquerades. Diagnostic strategies, therapy, and prognosis are reviewed in detail.

Keywords

Masquerade syndromes • Neoplasm • Retinoblastoma • Juvenile xanthogranuloma • Uveitis

Introduction

The term masquerade syndrome first appeared in the ophthalmic literature in 1967 to describe a conjunctival carcinoma that had presented as chronic conjunctivitis [1]. Since then, the masquerade syndrome label has been applied to a group that either mimic uveitic conditions or cause secondary uveitis and may represent as many as 5 % of patients referred for a uveitis evaluation [2, 3].

Determining the underlying cause of masquerade pediatric uveitis is a diagnostic challenge as a wide array of conditions may present with cells in the intraocular space. Conditions include endogenously or exogenously triggered immune-mediated conditions, infiltration by malignant cells, as well as a number of other conditions that may be confused with uveitis. The importance of determining the underlying cause cannot be overemphasized. Expeditious diagnosis of ocular disease may lead to early diagnosis of a systemic disorder, especially in cases of malignancy, and can result in potentially life-saving or life-prolonging intervention.

Malignant Masquerade Syndromes

These entities primarily mimic inflammation, although there may be a secondary inflammatory response in rare or advanced cases. Differentiating chronic pediatric uveitis from more esoteric conditions may be difficult.

Retinoblastoma Retinoblastoma is the most common childhood intraocular malignancy and has a reported incidence of 1 in 15,000 [4]. The most frequent presenting sign of retinoblastoma is leukocoria, followed by strabismus. However, a small percentage of cases present with a uveitic-like

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appearance, with tumor cells in the anterior chamber (0.5–3 %) sometimes forming a pseudohypopyon (0.25 %) [5–7]. Patient with the relatively rare variant of unilateral diffuse infiltrating retinoblastoma usually present around 6 years of age [8]. Patients are often mistakenly diagnosed with uveitis. Clinical signs may include conjunctival chemosis, pseudohypopyon, increased intraocular pressure, and vitritis. The pseudohypopyon typically shifts with changes of head position. An important morphological clue is that, in contrast to the typically yellowish hypopyon of inflammation, the pseudohypopyon of retinoblastoma is usually white. Confusion is most likely to occur if visibility of the fundus is limited by anterior chamber exudate, vitreous hemorrhage, or inflammation [9, 10].

Case Study 1

A 10-month-old boy was referred to our service with suspected anterior uveitis. The patient's past medical and family history was unremarkable. Slit lamp examination was significant for hyperemic conjunctiva and sclera, corneal endothelial precipitates and nodules, 4+ flare with marked cellularity in the anterior chamber, and a 1 mm hypopyon. Multiple large, fluffy, white nodules were observed on the iris surface, on the corneal endothelium, and in the angle (Fig. 25.1a). The intraocular pressure was 30 mmHg and infiltration of the irido-corneal angle with

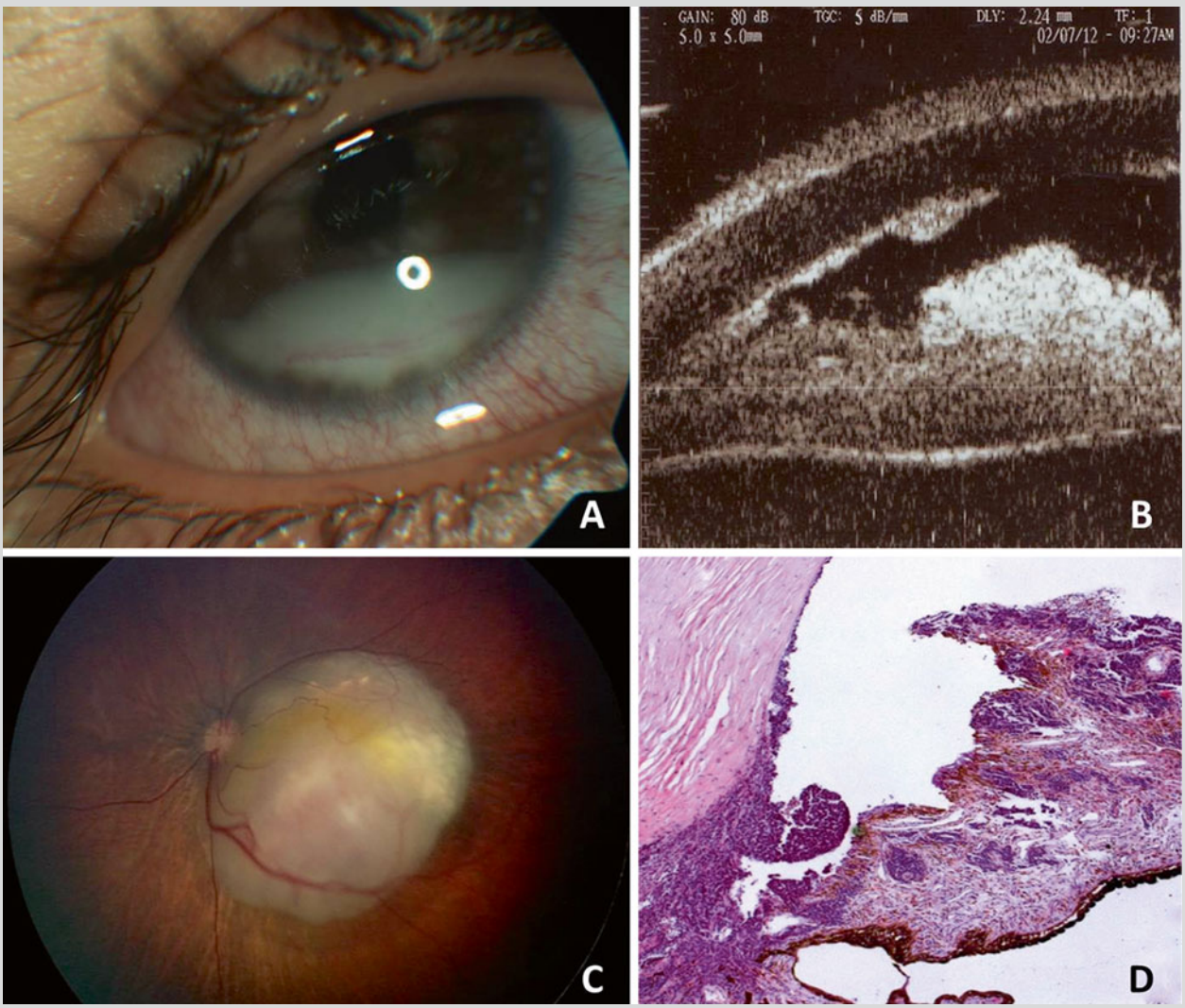

Fig. 25.1 Case 1: Retinoblastoma invading the anterior chamber (**a**) as demonstrated by ultrasound biomicroscopy (**b**). The primary tumor is involving the optic nerve and the macula (**c**), leading to enucleation of the eye and pathology examination (**d**)

(continued)

tumor cells was also detected on gonioscopy. There were posterior synechiae and multiple deposits were present on the anterior capsule of the lens. The contralateral eye was normal. Ultrasound biomicroscopy (UBM) examination demonstrated abnormal hyperreflectivity indicative of the presence of retinoblastoma, with a thick hyperechoic cornea, hyperechoic endothelial nodules, tumor cells in the anterior chamber, ciliary body infiltration, and iris nodules (Fig. 25.1b). On dilated fundoscopy a Reese class IIb retinoblastoma involving the posterior pole was detected (Fig. 25.1c). On histopathological examination a diffuse infiltrating retinoblastoma involving posterior iris, iridocorneal angle, corneal endothelium, ciliary processes, pars plana, and anterior was detected (Fig. 25.1d).

Comment Unlike endophytic or exophytic retinoblastoma of the retina, most of these diffuse retinoblastomas do not show calcifications on X-ray or ultrasound [11]. Imaging studies, including CT and ultrasonography, often fail to reveal calcifications and may show diffuse retinal thickening. In such cases, a diagnostic aspiration of aqueous humor may be required [8]. Because this is a highly aggressive tumor rarely encountered in adults, posterior biopsy techniques for diagnostic purposes may increase the risk of inadvertent tumor spillage and have little role in the evaluation of children with refractory uveitis [12]. Likewise, needle aspiration biopsies carry a significant risk of possible tumor spread through the needle tract. Needle-aspiration biopsies should therefore be reserved for select cases, where the diagnosis cannot be made otherwise. Patients with this suspected condition should be managed by an experienced ophthalmic oncologist at large tertiary eye centers. The diagnostic procedure should be performed by an ocular oncologist through clear cornea to avoid spillage of tumor cells. Cytological examination of the aspirated fluid is often diagnostic, showing round cells with hyperchromatic nuclei and scanty cytoplasm. Elevated aqueous lactate dehydrogenase levels may also support the diagnosis of retinoblastoma in equivocal cases, but the specificity of this test in retinoblastoma versus uveitis is uncertain.

Leukemia Rarely, patients with primary or recurrent leukemia including acute lymphoblastic leukemia, acute myeloid leukemia, and chronic myeloid leukemia subtypes may present with anterior chamber cells and hypopyon composed of malignant leukemic cells. Primary presentation of acute lymphoblastic leukemia solely as refractory uveitis has also been reported and therefore this diagnosis must be considered in any unusual or atypical uveitis [13]. In 1–2 % of patients, this presentation may occur as the first or only sign of recurrence of leukemia and therefore early diagnostic anterior chamber paracentesis is recommended for any child with signs of uveitis and a prior history of leukemia [14–17]. Negative hematologic evidence of recurrent leukemia does not rule out an ocular relapse in patients with a history of acute lymphoblastic leukemia and has sometimes led to a delay in diagnosis and treatment of the relapse [18].

Lymphoma The third most common form of childhood malignancy is lymphoma [19]. Twenty percent of patients with primary central nervous system lymphoma have ocular manifestations at diagnosis [13]. When present, there may be signs of vitreous and anterior chamber cells in an otherwise non-inflamed eye. Systemic non-Hodgkin's lymphoma may also present with a hypopyon, but these ocular findings usually occur after onset of lymphadenopathy and constitutional symptoms. Multiple vitreous biopsies may be required to make the diagnosis [20]. Nodular iris lesions may also occur, mimicking sarcoidosis [21].

Nonmalignant Masquerade Syndromes

These entities are characterized as a secondary inflammatory process.

Juvenile Xanthogranuloma Juvenile xanthogranuloma (JXG) is a benign, non-Langerhans cell histiocytic skin disorder that affects children during the first 2 years of life [22]. It usually regresses spontaneously within 3–6 years [23]. The characteristic raised, reddish-yellowish skin papules appear in infancy or early childhood with a predilection for the facial skin. The eye is the most commonly involved extra-cutaneous organ, but the incidence of such involvement is only 0.3–0.5 % [24]. Of reported patients with ocular JXG, 41 % have had multiple cutaneous lesions [24]. However, the disease may present solely in the eye in 5 % of cases [24] without the characteristic skin lesions. Skin lesions may develop after the ocular findings, with a delay of as much as 8–10 months [24]. When only ocular involvement of JXG is present, the clinical diagnosis is often difficult. Ocular JXG lesions typically involve the iris, where they appear as yellowish nodules. Iris involvement may also present as diffuse thickening with a muddy color. In cases of

diffuse involvement of the iris, heterochromia may be observed [22]. Iris lesions are vascular, tending to bleed and to cause spontaneous hyphema; the hyphema, in turn, may be complicated by secondary glaucoma and corneal opacification. Rarely, JXG involves the choroid, ciliary body, retina, or optic nerve [25–27]. There has been one report of posterior segment involvement only that was treated as a refractory uveitis and not properly diagnosed as JXG until the blind, painful eye was enucleated [28]. Epibulbar lesions can be found at the corneoscleral limbus, conjunctiva, episclera, or orbit [22]. The skin of the eyelids may be involved, in which case the globe is usually spared.

Case Study 2

A 9-month-old boy was referred for diagnosis and management of a spontaneous hyphema. Two weeks prior to presentation of the hyphema, the child had a subconjunctival hemorrhage that resolved and "muddy brown" iris discoloration was noted (OD). On examination, fibrin and a small hyphema were present in the anterior chamber. Iris details could not be visualized, but heterochromia was present along with a yellow-brown iris lesion (Fig. 25.2a). The patient had numerous yellowish skin lesions on his face and trunk that had mostly disappeared over the preceding months. A persistent skin lesion from his neck (Fig. 25.2b) was biopsied, but no characteristic Touton giant cells were present. The patient developed a second small hemorrhage in the anterior chamber. An examination under anesthesia revealed a small blood clot on the inferior iris overlying a yellowish-brown tumor (Fig. 25.2a). Two to three small nodules were present on the nasal iris but could only be detected using the microscope. The lens was clear with fibrin clot on the anterior capsule. Although the iris tumors atrophied with oral steroid therapy and iris color returned to normal, a flat, tan lesion was still present on the inferior half of the iris 5 months after treatment was completed.

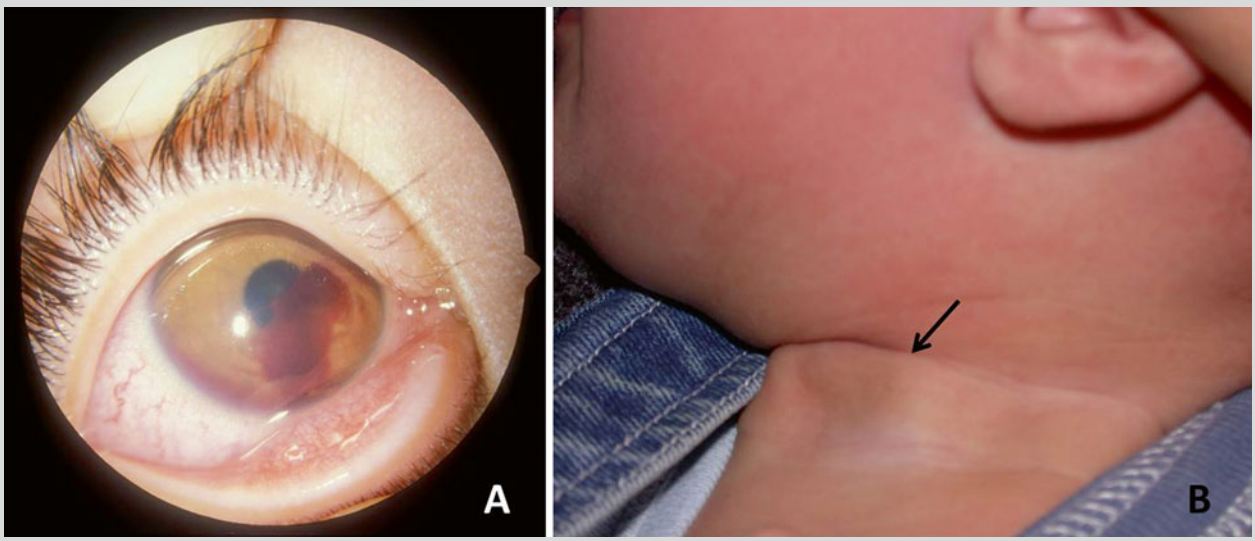

Fig. 25.2 Case 2: Juvenile xanthogranuloma with a yellow-brown iris lesion and an hyphema (**a**), associated with neck skin lesions (**b**) [courtesy of Elias I. Traboulsi]

Case Study 3

A 7-month-old girl was referred for heterochromia of the left eye and nodules in the inferior part of the iris (Fig. 25.3), with a possible diagnosis of sarcoid-related anterior uveitis. A detailed examination under general anesthesia revealed diffuse thickening of the temporal iris with muddy coloration and yellowish nodules in the inferior portion; fundus examination was unremarkable. One of the lesions was biopsied, and a diagnosis of JXG was made.

Comment Differential diagnosis for ocular JXG is wide, ranging from juvenile idiopathic arthritis to retinoblastoma,

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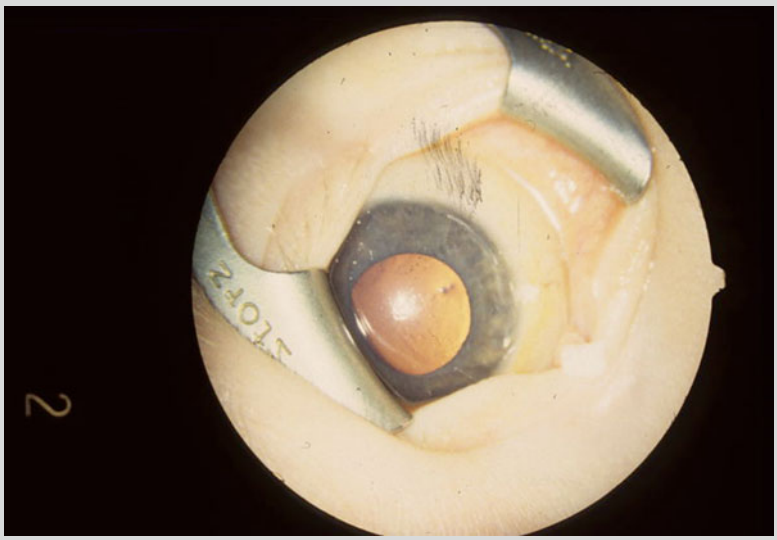

Fig. 25.3 Case 3: Juvenile xanthogranuloma

medullo-epithelioma, and leukemia. An array of laboratory diagnostic techniques is often required to make a final diagnosis. Ocular JXG can be diagnosed by a skin biopsy if the characteristic skin lesions are present. Otherwise, an anterior chamber paracentesis may aid in the diagnosis by revealing foamy histiocytes [29]. Iris biopsy may be required and may be diagnostic in cases where paracentesis is equivocal or uninformative [25]. Simple iris JXG lesions may regress with topical, periocular, or systemic steroid therapy [30, 31]. However, some cases are refractive to corticosteroids and may require therapy with local irradiation or immunosuppressive drugs [32–35]. Early tissue diagnosis is critical in JXG since untreated intraocular lesions can result in blindness. Involvement of the retina is a rare complication of JXG that may lead to chronic retinal detachment and portends a poor ocular prognosis.

Orbital Pseudotumor Orbital pseudotumor in the pediatric population, unlike in adults, may be associated with anterior uveitis. Uveitis may be the only presenting sign in children and therefore imaging studies for signs of orbital pseudotumor may be considered in cases of persistent childhood uveitis [36]. Bilateral posterior scleritis, anterior uveitis, and hypothyroidism associated with orbital pseudotumor have also been reported [37].

Occult Intraocular Foreign Body Children with occult intraocular foreign bodies may present with uveitis because children may be too young to be able to report their initial injury or they may fear punishment for the behavior that led to the injury. A high index of suspicion for penetrating injury must be maintained to intervene in these cases if treatment is to be effective and vision preserved [38]. Removal of the intraocular foreign body within 24 h provides the best opportunity for preserving vision and avoiding progression to infectious endophthalmitis [39]. The inflammation from an intraocular foreign body may not always be infectious. Metal fragments with high copper content can result in severe inflammatory reactions, and there are rare cases of intraocular fly larvae masquerading as severe uveitis [40–42].

Retinal Detachment Although a high prevalence of rhegmatogenous retinal detachment has been reported in patients with panuveitis and infectious uveitis, it is the primary uveitic condition that places these patients at risk for rhegmatogenous retinal detachment [43]. However, in childhood, two major risk factors for rhegmatogenous retinal detachment in childhood include myopia greater than four diopters and trauma [44]. A small subset of pediatric and young adult patients with rhegmatogenous retinal detachment have been reported to have a uveitis masquerade syndrome caused by photoreceptor outer segments within the anterior chamber and associated with high intraocular pressure [45].

Case Study 4

An 8-year-old girl was referred to our clinic with a previous diagnosis of idiopathic pars planitis in the right eye, which did not improve despite aggressive topical and oral steroid treatment. On clinical examination, she had a deep and quiet anterior chamber, and snowballs in the inferior vitreous (Fig. 25.4a), consistent with the primary diagnosis. However her BCVA was LP in the right eye, IOP was slightly elevated (24 mmHg), and fundus examination was very hazy due to hemovitreous, and all of these findings suggested an alternative pathological entity masquerading as an intermediate uveitis. An ultrasound was performed (Fig. 25.4b) and revealed a complete retinal detachment with a subretinal hyperechogenic blood clot. When the parents were presented with this new and definitive diagnosis, and the necessity of a surgical intervention, they remembered that their daughter accidentally bumping her head against a door a week before, 2 days prior to the visual decline in the right eye.

Comment Masquerade syndromes should be strongly considered in any child with atypical uveitis. A flowchart for the diagnosis of pediatric uveitis masquerade is hereby presented (Fig. 25.5). In such cases, evaluation by a specialist in uveitis or ocular oncology is recommended. If retinoblastoma or medullo-epithelioma cannot be ruled out on clinical grounds, obtaining intraocular material for diagnosis should be considered.

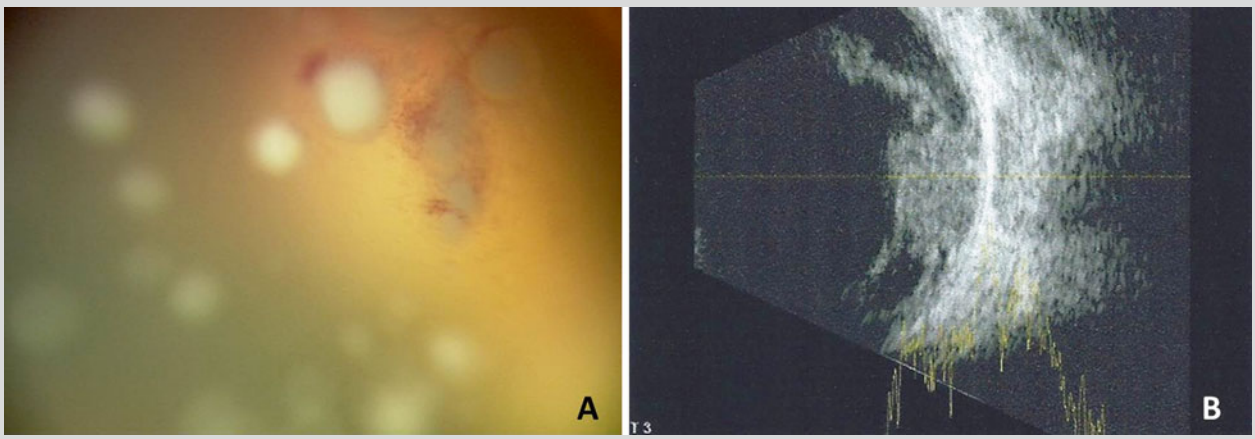

Fig. 25.4 Case 4: Retinal detachment causing snowballs in the inferior vitreous (A) and visible on ultrasound (B) with an associated hyperechoic blood cloth

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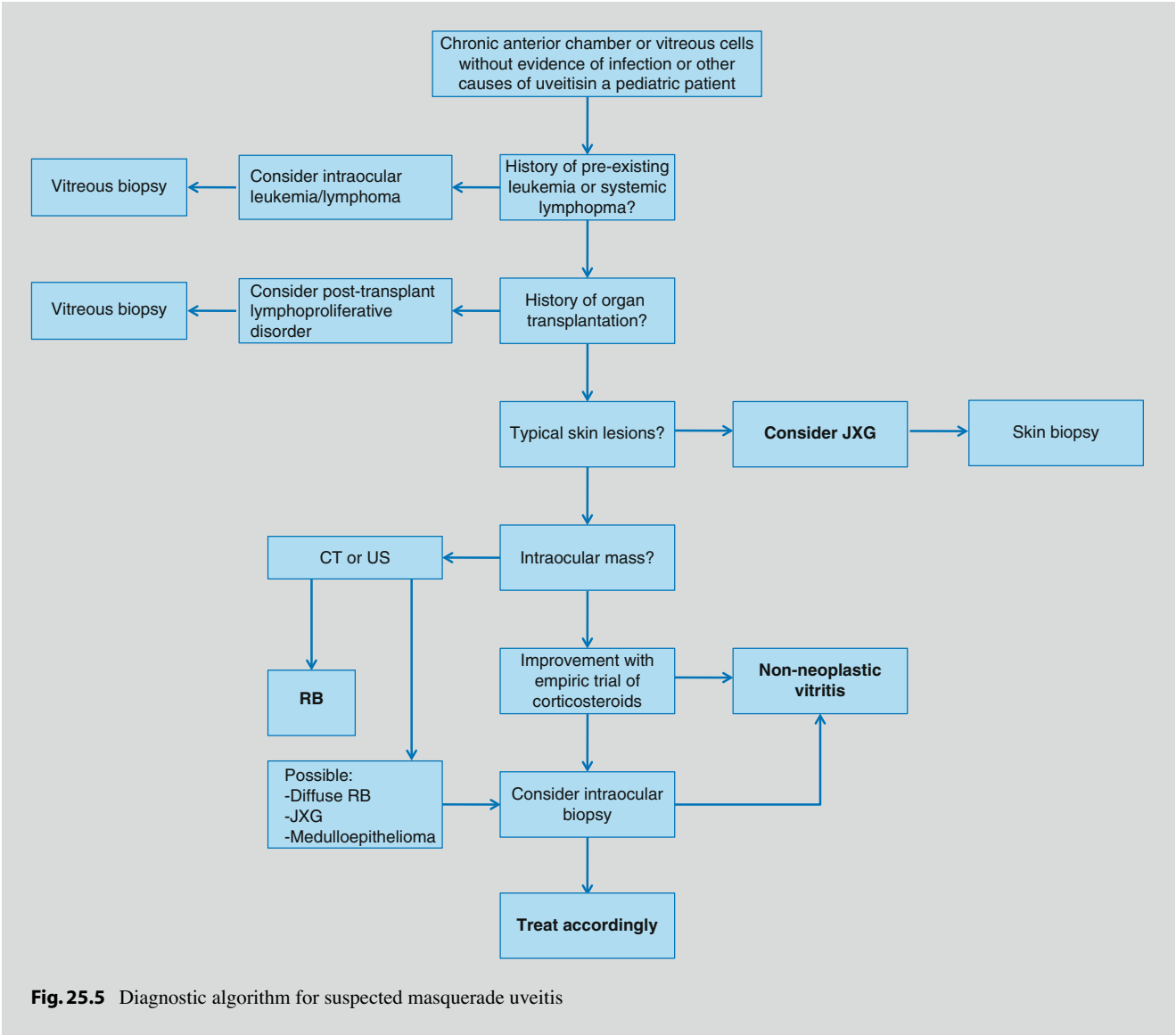

Fig. 25.5 Diagnostic algorithm for suspected masquerade uveitis

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Part VII

Diagnostic Testing of the Posterior Segment

Retinal Imaging for Pediatric Patients

26

Robert Andrew Sisk and Brian G. Zamora

Abstract

Retinal imaging is useful in diagnosis, prognosis, medicolegal documentation, and medical decision making for treatment. Imaging can also provide structural and functional information not discernable solely by physical examination, especially in patients with unexplained vision loss or hereditary retinal diseases. Spectral domain optical coherence tomography can reveal macular ultrastructural defects via an in vivo "optical biopsy." Scanning laser ophthalmoscope-based imaging platforms are gaining popularity over traditional flash fundus photography for ease of use, speed of image acquisition, simultaneous multimodal imaging, and ultra-wide-field capabilities. Patients 3 years and older can usually cooperate with outpatient imaging not requiring intravenous access. Most kinds of retinal imaging and full-field electroretinography can be obtained during examination under anesthesia if the procedures are too invasive and painful, or preclude cooperation of an awake patient. Although imaging is a powerful tool, it is intended to supplement, not replace, a thorough history and physical examination for medical decision making.

Keywords

Fluorescein angiography • Fundus autofluorescence • Fundus photography • Indocyanine green angiography • Portable • RetCAM • Retina • Retinal imaging • Spectral domain optical coherence tomography • Ultrasonography

The Problem

Purpose of Retinal Imaging

Retinal imaging is employed for diagnosis, disease monitoring, and prognosis, and to facilitate decisions about treatment. In highly medicolegal risk populations, such as children or victims of crime or abuse, imaging may also augment the written medical record to justify diagnostic assertions or treatment decisions and to serve as legal evidence for domestic or criminal cases.

Diagnosis

Retinal imaging, like any other clinical test, is intended to supplement rather than to replace a thorough history and physical examination. Pediatric patients pose particular

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challenges in this regard due to their limited ability to communicate and cooperate. Although imaging provides enormous diagnostic power, the information gained is of little use, and may even be dangerous, if taken outside the context of the clinical setting and indication for the testing. A well-formulated differential diagnosis prior to testing is critical for the correct interpretation of findings. The testing should refine the pretest probability of the presumptive diagnosis.

Monitoring for Disease Progression and Prognosis

Although meticulous written records are practical for patient care and expected for justification of coding and financial remuneration for rendered services, they rely on the subjective appraisal of the examining physician. Even the best of examiners cannot match the objectivity of photographic documentation. It behooves practitioners to utilize reproducible, quantitative information such as retinal imaging to improve precision and accuracy of recorded information. Retinopathy of prematurity and ocular oncology are practical examples where accuracy of documentation has major ramifications in delivering appropriate care.

Considerations when Performing Retinal Imaging

Many factors influence the feasibility and utility of retinal imaging of pediatric patients including patient age, physical or intellectual disability, examination setting, and medicolegal risk. Recognizing and navigating these issues successfully will build trust between patients and patients' families and their providers. A skilled photographer who can capture attention pleasantly and playfully facilitates image acquisition in younger or intellectually limited patients. The photographer should be very comfortable with acquiring images in older patients before attempting the procedures with younger, less cooperative patients.

Patient Age

Patient cooperation and available time for image acquisition are frequently directly proportional to patient age in patients without intellectual disability. Procedures that require greater cooperation therefore are more practical in older, awake patients. However, successful optical retinal imaging can be performed in awake patients as young as 2 years of age. Ultrasonography (U/S) can be performed in patients of all ages, although extended or detailed studies may be impractical in less cooperative patients in an office-based setting. Spectral domain optical coherence tomography (SDOCT) and infrared imaging, which utilize infrared light, are more tolerable to patients than the intense blue light from fundus autofluorescence (FAF) or fluorescein angiography (FA). Eye-tracking software can reduce artifactual capture in patients with limited cooperation either due to young age or reduced monocular visual function. Regardless of imaging modality, alleviating patient fear and anxiety with continuous verbal reassurance and instructions will improve patient performance. Engaging parents to comfort the child and hold the head steady is preferred over office staff.

Physical or Intellectual Disability

Retinal pathology is frequently associated with systemic disease. Therefore the photographer should be comfortable working with children with physical or intellectual disabilities, who may require greater time and patience for image acquisition. While equipment can be adjusted and support staff can be enlisted to facilitate this in ambulatory patients, examination under anesthesia (EUA) is often more practical, especially in patients with nystagmus, movement disorders, or behavioral problems.

Examination Setting

Retinal imaging can be performed on pediatric patients in a variety of settings: outpatient ambulatory, inpatient, and under anesthesia. Portable imaging systems add flexibility to the choice of examination setting but typically produce images of lower quality than traditional, office-based units that are routinely used for adults. Portable digital, light-based imaging systems, due to limitations in equipment architecture for examining a supine patient, also frequently utilize a contact system to enhance image quality and provide ultra-wide-field images, making their routine ambulatory use impractical except in infants.

Medicolegal Risk

In cases of high medicolegal risk, high-quality fundus photographs are preferred over detailed retinal drawings, although both are admissible. A greater volume of documentation is preferred, and this may require an EUA if patient or parental cooperation is a limiting factor. Redundant information from multiple imaging modalities can bolster diagnostic assertions that have legal implications.

Practical Tips

- Perform testing from least to most noxious (U/S < IR < SDOCT < FAF < FA/ICGA).
- Image the eye suspected to have pathology first.
- Avoid bright lights prior to acquiring images with FAF and FA.
- If the likelihood of obtaining useful images in an awake patient is low, plan to obtain them under anesthesia.
- If other procedures are planned under anesthesia (lasers, surgery, full-field electroretinography, etc.), it may be preferable to defer imaging until the time of those procedures in order to limit patient discomfort and have those images available to guide application of treatment.

Imaging Modalities (Table 26.1) and Selected Cases

Fundus Camera

A fundus camera uses the optical principles of monocular indirect ophthalmoscopy to capture an upright, magnified image of the fundus for documentation of vitreoretinal status. The retina is illuminated by a ringed flash of light, and the light reflected from the retina passes through the aperture of the ring and is captured on either film or digital media.

Fundus cameras are described by their angle of view. The normal angle of view is about 30°. Wide-angle fundus cameras capture images between 45° and 140° and provide proportionately less retinal magnification. A narrow-angle fundus camera has an angle of view of 20° or less, but can provide a more magnified and detailed view of the fundus. The angle of view should be selected based upon the pathology of interest and should be communicated clearly to the photographer beforehand.

Fundus cameras can be upright or portable. The upright fundus camera requires the patient to maintain the face upright and to follow instructions for appropriate positioning of the eye. This may not always be feasible in a pediatric patient, limiting the upright fundus camera's use in certain pediatric populations.

Portable fundus cameras allow the photographer more freedom to capture images in patients unable to be imaged by upright fundus camera, such as patients in the inpatient setting or during EUA. Most portable models have a base that can interface with a computer, hard drive, or printer to allow for the transfer of captured fundus images from the device.

Practical Tips

- Portable systems that utilize a gel-based contact lens system for retinal imaging can also be used to perform anterior segment imaging, including direct gonioscopy, by adjusting the focusing distance.
- When preparing to image the fundus with portable systems, adjust the focus for sharpness at a distance, and then make incremental changes until a clear fundus image is achieved.
- Always use two hands to steady portable imaging devices, resting one on the patient's head to avoid injury.
- Darkly pigmented fundi may be particularly difficult to image with portable systems, but red-free filters may improve utility when documenting retinal vascular status (i.e., retinopathy of prematurity). Fluorescein angioscopy (indirect ophthalmoscopy after dye instillation) may be helpful to look for dye leakage and visualize where retinal vessels terminate.
- Smaller pupils will produce two common artifacts: (1) a dark spot in the center of the image and (2) a white ring from the light source. Aiming the camera head adjacent to the desired fundus target will displace the dark artifact to visualize the desired landmark (Fig. 26.1 and Table 26.2).

Fluorescein Angiography

Fluorescein angiography (FA) is an imaging modality that uses serial fundus photography or a confocal scanning laser ophthalmoscope (cSLO) with specialized filters following intravenous injection of a fluorescent dye (sodium fluorescein) to study the circulation of the retina and

Table 26.1 Specific imaging modalities for the office setting

Modality	Ages	Portability	Common uses	Examples
Fundus photography	3+	Yes	Baseline and serial fundus comparisons	Non-accidental trauma
Fluorescein angiography	8+	Yes	Studies of retinal and choroidal vasculature	Exudative retinopathy, sickle cell retinopathy
Indocyanine green angiography	8+	No	Choroidal lesions and inflammation, retinal white dot syndromes	Circumscribed choroidal hemangioma
Infrared imaging	3+	No	Melanocytic lesions, fundus documentation in uncooperative patients	Choroidal nevi Choroidal nodules of NF1
Fundus autofluorescence	4+	No	Disorders of retinal pigment epithelium and photoreceptors	Stargardt disease
Spectral domain optical coherence tomography	3+	Yes	Vitreoretinal interface disease, disorders of exudation, defining anatomic correlates for unexplained vision loss	X-linked retinoschisis, retinitis pigmentosa
Ultrasonography	Any	Yes	Mass lesions, eye trauma, media opacities limiting fundus evaluation by other methods	Vitreous hemorrhage Intraocular foreign body

Abbreviations: *NF1* neurofibromatosis type 1

(continued)

Table 26.2 Case 1 (to complement Fig. 26.1)

Chief complaint: Non-accidental trauma HPI (bullet points if able) 4-month-old female presented in distress with bilateral retinal hemorrhages from domestic violence		
	OD	OS
BCVA	NCUSUM	CSM
Significant anterior segment findings	Normal	Normal
Significant posterior segment findings	Preretinal hematoma obscuring macula OD; multiple blot intraretinal hemorrhages diffusely OD>OS	
Assessment	Non-accidental trauma/shaken baby syndrome with retinal hemorrhages OU and dense, amblyogenic preretinal hematoma OD	
Plan	Alert admitting attending of suspicion of child abuse to prompt other necessary examination and testing Vitrectomy with evacuation of preretinal hematoma OD, including ILM peeling	

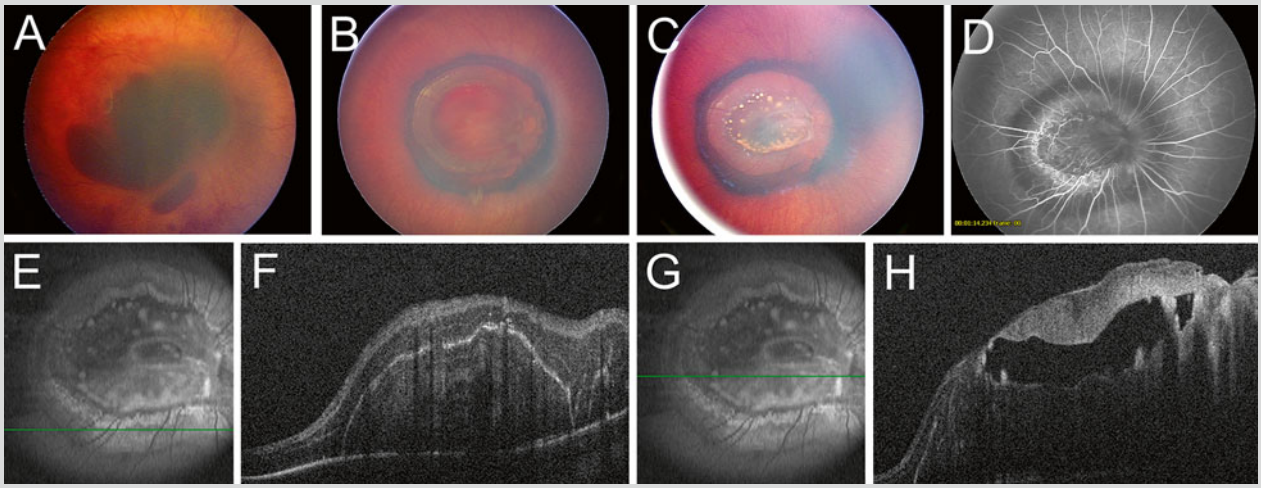

Fig. 26.1 (**a**–**c**) Portable fundus camera image (Retcam 3®, Clarity Medical Systems, Pleasanton, CA) of the right posterior pole of a 4-month-old female victim of domestic violence with preretinal and subretinal hematoma of Terson's-like shaken baby syndrome. In the acute stage (**a**), the macula was not visible, and the hematoma was clearly amblyogenic. Note the artifact of central darkness due to poor pupillary dilation. Due to medical instability, vitreoretinal surgical intervention was delayed, and a posterior tractional complex with RPE hyperplasia was observed with liquefaction of the preretinal hematoma (**b**). Note the white ring artifact from the circular light source of the portable fundus camera. Vitrectomy with internal limiting membrane peeling was performed. Endolaser was applied to areas of peripheral ischemia identified by fluorescein angiography performed preoperatively under anesthesia. Postoperatively, subretinal hemorrhage appeared to be displaced from the fovea, yet the macula remained elevated (**c**), raising concern for a full-thickness macular hole with central rhegmatogenous retinal detachment. The small pupil made visualization centrally with the portable fundus camera difficult, so the lens was tilted eccentrically, producing peripheral white ring artifact and countercoup white and dark artifacts. (**e**–**h**) However, portable spectral domain optical coherence tomography images (SDOCT, Envisu C2300, Bioptogen, Inc, Durham, NC) revealed subretinal (**e**, **f**) and intraschisis (**g**, **h**) hemorrhages and serous fluid without a full-thickness or inner retinal defect. The vitreoretinal interface of intact ILM (**f**) is not observed in areas where ILM was peeled (**h**). The handpiece for the portable SDOCT unit can be microscope mounted or covered with sterile draping to perform intraoperative imaging

choroid. Eighty percent of injected fluorescein is protein bound, primarily to albumin, and is not available for fluorescence; the remaining 20 % is unbound and circulates in the vasculature and tissues of the retina and choroid, where it can be visualized. Sodium fluorescein emits at a wavelength of 520–530 nm (yellow-green) after excitation by light in the 465–490 nm (blue) spectrum.

In pediatric patients, the usefulness of FA is limited by the ease of administration of fluorescein dye. Venipuncture may be difficult in patients under 8 years of age. Oral administration of 10 mL of 10 % sodium fluorescein, usually mixed with juice and drunk through a straw to improve palatability, can provide late images at 20 min, but does not provide transit images. Fortunately, newer portable fundus cameras are capable of fluorescein angiography during an EUA.

Practical Tips

- For children receiving intravenous fluorescein (7.7 mg/kg), round up to the nearest 0.5 mL and follow with a

(continued)

3 mL saline push. Dye is eliminated quickly with minimal recirculation phase in neonates, so it's crucial to capture the transit images when looking for non-perfusion.
- Ultra-wide-field upright and portable systems can be utilized to evaluate peripheral retinal non-perfusion.
- For portable systems with gel-based contact systems, minimize pressure on the globe by the camera head, especially in infants, as it will limit perfusion of dye into the retinal circulation. If pulsing or occlusion of the central retinal artery is observed, reduce pressure.
- The lens used for FA on portable systems has a shorter focal length than that used for fundus photography. Readjust focus with the white light aimed at the distance prior to switching to the blue light source.
- Video FA may be particularly useful for documenting vascular anomalies that leak early, but these files consume a significant amount of computer memory. When data storage space is almost exhausted, it may impair video recording or slow still image acquisition substantially. A secure external or network drive is a good solution for institutions with high usage.

Indocyanine Green Angiography

Indocyanine green angiography (ICGA) has more narrow application in retinal practice compared to FA, such as choroidal vascular lesions and tumors, central serous chorioretinopathy, and inflammatory disorders of the outer retina, RPE, and choroid. The dye must be administered intravenously and requires an upright fundus camera, which further limits its usefulness among pediatric patients.

Infrared Imaging

Infrared imaging is frequently utilized by cSLO systems as a registration image for SDOCT. For patients who cannot tolerate fundus photography or detailed slit lamp macular evaluation, infrared imaging may provide preliminary information to justify additional testing. Infrared light produces hyperintensity of melanocytic lesions. Retinal edema and hemorrhages appear hypointense. The middle retinal defect in acute macular neuroretinopathy is best visualized by infrared imaging.

Fundus Autofluorescence

Fundus autofluorescence (FAF) uses an upright fundus camera or cSLO with excitation and barrier filters to detect fluorophores that may occur naturally in the eye or accumulate as a by-product of a disease process without the introduction of a fluorescent dye. Fluorophores are molecules that possess fluorescent properties when exposed to light of an appropriate wavelength and, in the eye, include calcium and lipofuscin (Fig. 26.2 and Table 26.3). Fundus camera-based FAF systems require special filters that also function with fluorescein angiography. CSLO systems use blue laser excitation (488 nm) and a 500 nm barrier filter.

FAF interpretation requires high-resolution images to be clinically useful. Computerized image averaging and white balancing can increase resolution of FAF images of cSLO systems to exceed the quality obtained by fundus camera-based systems. However, the excitation beam may be less tolerable than a camera flash for photophobic patients and those with limited ability to cooperate. Nonmydriatic ultra-wide-field cameras can capture lower resolution FAF images in less than a second, making them more practical in uncooperative or photophobic patients, and when more peripheral pathology needs further investigation.

Practical Tips
- For cSLO-based systems, FAF must be acquired prior to FA. Otherwise FAF images will represent late FA images rather than intrinsic autofluorescence.
- Ultra-wide-field autofluorescence can be particularly useful in evaluating retinal dystrophies and differentiating retinoschisis from retinal detachment.

Spectral Domain Optical Coherence Tomography

SDOCT is a very powerful, noninvasive, noncontact imaging modality that utilizes long-wavelength light and the concept of interferometry to rapidly produce in vivo, micrometer-resolution, cross-sectional images (tomograms) of the retina, similar in appearance to histologic specimens, allowing for measurements of retinal thickness, segregation of the different retinal layers, and detection of any structural abnormalities, tractional forces, or fluid accumulation from exudation (Fig. 26.3 and Table 26.4). Most commercial models are upright, but portable models are available.

Reflectivity readings of individual tissues may be represented in positive or negative forms in grayscale, or in colored representation. Multiple B-scans can be averaged to reduce noise and improve image resolution or to create volumetric measurements and three-dimensional representations (C-scans). Devices with two laser sources can perform eye-tracking functions to reject misaligned B-scans or can perform simultaneous capture of multiple imaging modalities, including FA and ICGA, for precise localization and correlation of anatomic defects.

Table 26.3 Case 2 (to complement Fig. 26.2)

Chief complaint: 6-week blurred vision, metamorphopsia, and scotoma OD (patient claimed OS) HPI: Long-standing, stable reduced vision OD from macular laser years ago. Few weeks of photopsias OS. Recent upper respiratory illness preceded symptoms		
	OD	OS
BCVA	20/80	20/80
Significant anterior segment findings	Normal No cell or keratic precipitates	Normal No cell or keratic precipitates
Significant posterior segment findings	Chorioretinal atrophy involving fovea OD, gray-white wreath around fovea OS, peripheral multifocal round, clustered areas of chorioretinal scarring OU	
Assessment	Multifocal choroiditis OU post-macular laser OD; probable white dot syndrome (multiple evanescent white dot syndrome)	
Plan	Autofluorescence and indocyanine green angiography; observe for resolution	

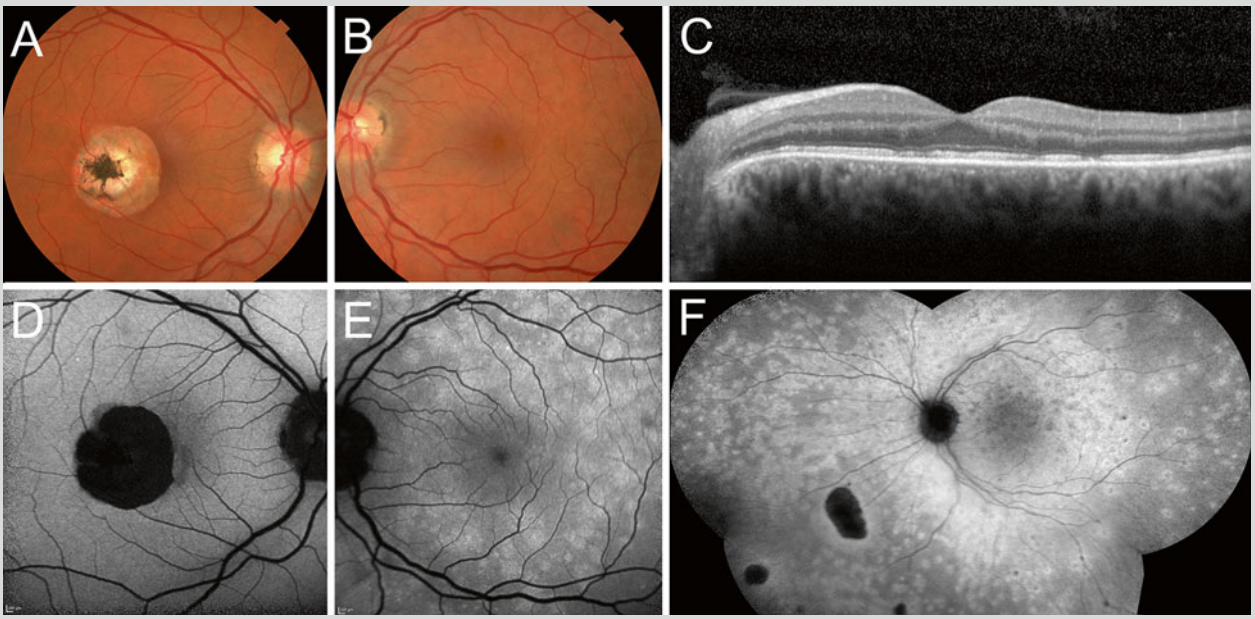

Fig. 26.2 (**a**, **b**) Fundus photographs (Topcon TRC-50X, Topcon Medical Systems, Inc, Oakland, NJ) of the right and left maculae, respectively, of a female with prior multifocal choroiditis OU and secondary extrafoveal choroidal neovascularization OD treated by focal retinal photocoagulation. The chorioretinal scarring from that laser expanded over time to involve the fovea, leaving the patient functionally monocular. Fundus photographs demonstrate a subtle gray-white wreath surrounding the fovea OS (**b**) when compared to OD (**a**). (**c**–**e**) Multimodal imaging (Heidelberg Spectralis® HRA-OCT, Heidelberg Engineering, Carlsbad, CA), including SDOCT, demonstrates focal disruptions of the inner segment ellipsoid band (formerly called the inner segment-outer segment junction) without RPE or choroidal abnormalities, which excluded reactivation of multifocal choroiditis. (**d**, **e**) Fundus autofluorescence (FAF) images (30°) of the right and left maculae, respectively, showed no new alterations of lipofuscin turnover OD and multifocal, nummular, patchy, overlapping foci of hyperautofluorescence. (**f**) Montage indocyanine green angiography image of the left eye demonstrated diffuse hypercyanescent lesions of acute multiple evanescent white dot syndrome (MEWDS) and hypocyanescent, inactive, peripheral lesions of prior multifocal choroiditis

Practical Tips

- Set the zero-delay line close to the area of pathology to achieve the best resolution. Enhanced depth imaging allows detailed imaging of the outer retina, RPE, and choroid.
- Utilize specific protocols rather than a one-size-fits-all approach. For diseases that increase or reduce macular thickness, utilize cube scans that provide volumetric data. For vitreoretinal interface disease, use radial scans that may detect fine vitreoretinal adhesions.
- For patients with poor cooperation, a rapid acquisition 5-line horizontal raster protocol may be useful. Some may tolerate raster scans with vertical orientation better than horizontal orientation.
- Many upright SDOCT devices are capable of performing multiple additional functions, including FA, ICGA, FAF, IR, red-free, and microperimetry. Choose the instrument that best meets your clinical practice needs and provides adequate technical support and training for your staff.

Table 26.4 Case 3 (to complement Fig. 26.3)

Chief complaint: Reduced visual acuity, exotropia OD HPI (bullet points if able) 4-year-old male referred with abnormal macula and iris neovascularization OD. He had developmental delay, autism, and bone marrow failure s/p transplant		
	OD	OS
BCVA	UCSUM	CSM
Significant anterior segment findings	Corectopia, posterior synechiae, peripheral anterior synechiae, iris neovascularization, nuclear cataract	Normal
Significant posterior segment findings	Preretinal and vitreous hemorrhage, epiretinal membrane, macular dragging, and vitreomacular traction OD, retinal neovascularization and extensive retinal capillary dropout OU, proliferative stalk off optic disc resembling remnant of persistent fetal vasculature OS	
Assessment	Dyskeratosis congenita with retinal neovascularization OU, tractional retinal detachment OD, and neovascular glaucoma OD	
Plan	Vitrectomy with membrane peeling OD, then cataract extraction and pars plana placement of Baerveldt glaucoma drainage device OD; laser ablation of peripheral avascular retina OU	

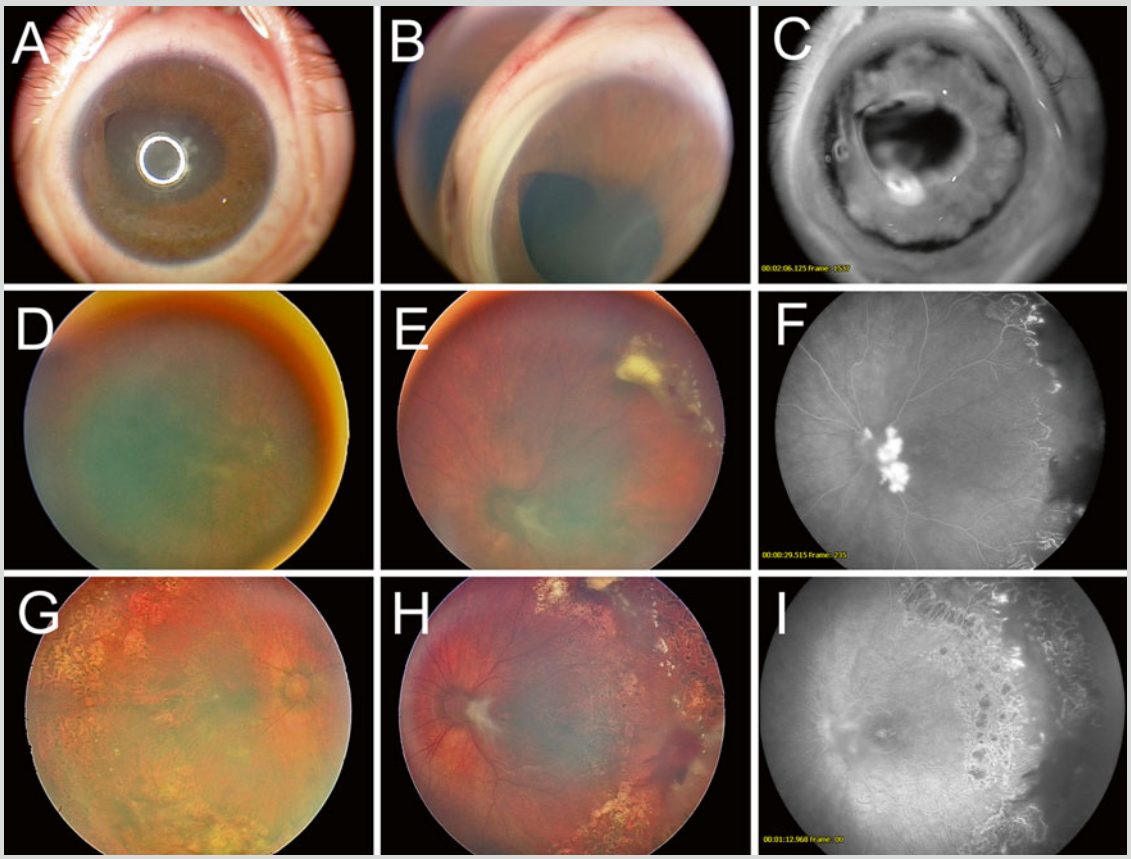

Fig. 26.3 (**a**) Portable fundus camera non-contact anterior segment imaging of corectopia in the right eye of a 4-year-old with dyskeratosis congenita (DKC). (**b**) Direct gonioscopy was performed utilizing the coupling ophthalmic gel to evaluate for angle neovascularization and high peripheral anterior synechiae. (**c**) Diffuse iris neovascularization (hyperfluorescent) and high peripheral anterior synechiae (hypofluorescent) were more evident by fluorescein angiography than by ophthalmoscopy. (**d**, **e**) Pretreatment fundus photographs of the right and left eyes, respectively. The right macula was dragged temporally and the temporal arcades were dragged towards the horizontal midline by a broad epiretinal membrane. View was limited by cataract and limited pupillary dilation, producing a dark, central artifact. A prepapillary fibrotic mass and an irregular, postequatorial line of exudation were seen OS. (**f**) Fluorescein angiography (FA) demonstrated neovascularization of the optic disc and peripheral fundus, extensive peripheral capillary dropout bordered by capillary remodeling and dilation, and peripheral veno-venous collateralization. These findings resembled familial exudative vitreoretinopathy and are typical of DKC. Laser was applied guided by fluorescein angiography to ablate areas of peripheral avascular retina in both eyes to treat pathologic neovascularization, and vitrectomy with membrane peeling was performed OD to address the dense epiretinal membrane. (**g**, **h**) Posttreatment fundus photographs of the right and left eyes, respectively, demonstrate chorioretinal scarring from laser OU. Quality of fundus imaging of the right eye was enhanced by removal of a cataract. (**i**) Fluorescein angiography OS showed regression of neovascularization at the optic disc in response to adequate laser ablation of peripheral avascular retina

(continued)

- Portable devices require extensive hands-on training to master compared to upright systems. Adjustments must be made for refraction and axial length. Improper settings reduce image quality and create bowing artifacts on raster scans. Stability is enhanced with microscope mount, which also enables intraoperative use. Certain operating microscopes now integrate real-time SDOCT technology.

Ultrasonography

Ultrasonography allows visualization of ocular structures by recording the reflections or echoes of ultrasonic pulses directed into the eye. A-scan (quantitative) ultrasonography displays one-dimensional data in the form of amplitude of echoes based on reflectivity of tissues plotted as vertical height against distance, and can be used to determine depth, size, and ultrasound characteristics of a lesion or mass in the eye. B-scan (topographic) ultrasonography displays two-dimensional data as a cross-sectional image of the eye, in which amplitude of echoes is represented by signal brightness on a grayscale image. This provides localization of lesions and can have A-scan overlay. Clinically, ultrasonography is used to identify and characterize lesions and/or masses within the eye and to detect retinal, posterior vitreous, and choroidal detachments. Ultrasound biomicroscopy can be used to visualize anterior segment structures, the ciliary body, and the vitreous base, if posterior segment lesions extend anteriorly.

Practical Tips

- Individual B-scans that may be difficult to capture by foot pedal in uncooperative patients can be recovered by reviewing frames from video ultrasonography.
- Always have the A-scan overlay turned on during B-scan assessments, as it may be difficult to ascertain from the B-scan image alone whether a mid-vitreous line represents retinal detachment, vitreous hemorrhage, or vitreous membranes.
- Retinal detachment terminates at the optic nerve. Choroidal detachments respect the vortex veins.

Synopsis of Utility of Retinal Imaging in Presented Cases

Retinal imaging can guide both medical and surgical management, as demonstrated from the cases presented. In the first case, failure of amblyogenic preretinal hemorrhage to clear spontaneously prompted surgical intervention. The funduscopic appearance of persistent postoperative macular elevation in an eye with preexisting subretinal hemorrhage and high risk for macular hole due to internal limiting membrane peeling raised suspicion for a rhegmatogenous macular detachment. SDOCT imaging was invaluable for confirming the absence of a full-thickness defect as well as demonstrating persistent intraschisis and subretinal hemorrhage and fluid. No further intervention was taken for this eye with poor visual prognosis.

The second case was particularly interesting because the patient believed her new visual symptoms were emerging from the right eye with inactive multifocal choroiditis and reduced baseline vision due to extensive of chorioretinal scarring into the fovea from prior laser for choroidal neovascularization. However, her photopsias and recent upper respiratory infection in the setting of a subtly whitened macula suggested a white dot syndrome, and multiple evanescent white dot syndrome (MEWDS) was confirmed by fundus autofluorescence and indocyanine green angiography. More importantly, reactivation of multifocal choroiditis, which would necessitate local or systemic steroid treatments, was excluded.

- The versatility of the portable fundus camera was displayed in the third case. Non-contact anterior segment imaging recorded corectopia, and direct gonioscopy coupled by lubricating ocular gel (GenTeal gel ophthalmic, Novartis, New York, NY) was used to evaluate for high peripheral anterior synechiae. Funduscopic evaluation of the retinal capillary system can be challenging, especially in pediatric patients. FA clearly delineated areas of perfused retina from areas with capillary dropout, identified areas of vascular remodeling and neovascularization, and served as a real-time map for application of laser photocoagulation by comparison with the monitor. SDOCT can also demonstrate inner retinal thinning and loss of lamination in areas of confluent retinal capillary dropout. Unfortunately, iris neovascularization was extensive and overwhelmed the fundus fluorescence during FA, making FA limited to transit images. In our patient, this was further complicated by reduced pupillary size and cataract associated with ischemia, which prevented SDOCT imaging preoperatively. After laser ablation of avascular retina and removal of cataract, FA confirmed the adequacy of the ablative treatments in both eyes.

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Use of Optical Coherence Tomography in the Eyes of Children

27

Jared E. Duncan, Sharon F. Freedman, and Mays Antoine El-Dairi

Abstract

OCT has found its niche within virtually all ophthalmic subspecialties, be it glaucoma, retina/vitreous, or anterior segment. OCT's role in the diagnosis, management, and treatment of pediatric eye disease continues to evolve. Monumental gains have been made in our understanding of various physiologic principles and pathological processes as a result of this relatively new technology. While not intended to be an exhaustive catalogue of the opportunities afforded by OCT, this chapter should provide the well-rounded pediatric ophthalmologist with the appropriate framework to better appreciate this new technology and its role in pediatric eye disease.

Keywords

Optical coherence tomography • Pediatric optic neuropathies • Pediatric glaucoma • Pediatric retinal diseases

Definition

Optical coherence tomography (OCT) has become an invaluable tool for ophthalmologists to diagnose a variety of posterior and anterior segment conditions [1]. OCT is a recently developed, noninvasive imaging technology that uses optical waves and inferometry to create in vivo high-resolution (3–15 μm) tomograms of biological (such as eye, skin, dental, vascular, and cardiac tissue) [2] and non-biological tissues [3]. Its use of optical waves limits its utility to tissues that can be visualized through clear media [1]. Each type of tissue requires a different wavelength for proper imaging, which for the retina is about 840 nm for most standard SD-OCT devices and 1050 nm for swept-source devices [1].

The earliest commercial form of OCT, time domain-OCT (TD-OCT), was limited by its relatively slow acquisition times and poor resolution. Newer devices, specifically spectral domain OCT (SD-OCT), provide better axial image resolution and much faster scan acquisition. Swept-source OCT (SS-OCT), a very recent innovation, provides even faster acquisition times and is now mostly available on research systems [4]. Numerous commercially available OCT machines use similar imaging protocols and are employed by ophthalmologists in a variety of settings.

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Posterior Segment OCT Protocols

Retinal Scans

High-Resolution Scans

Cross-sectional scans allow for exceptional visualization of the posterior segment. Abnormalities of the vitreo-retinal interface (vitreomacular attachment and traction), preretinal areas (epiretinal membranes, neovascularization, and fibrovascular tissue), retinal layers (macular holes, edema, schisis, thickening, folding, atrophy, degeneration), and subretinal space (subretinal fluid, pigment epithelium detachment, choroidal neovascularization) can be diagnosed using OCT. It is also a powerful tool for imaging areas deep to the retina, including the retinal pigment epithelium and choroid (Fig. 27.1).

Macular Maps

Macular maps are a customizable feature that can be generated by integrating multiple single-line macular scans. A topographical map centered on the foveal center is created. Most machines will provide the retinal thickness according to the ETDRS macular map that displays the average thickness values in three concentric rings. The foveal area corresponds to the innermost 1 mm diameter, the inner ring to 3 mm diameter, and the outer ring to 6 mm diameter. Volumetric analysis provides a quantitative and repeatable method to evaluate optic nerve or retinal disease progression.

Enhanced Depth Imaging

Enhanced depth imaging (EDI) compensates for the poor penetration of the infrared light beam used for routine retinal imaging. It allows for better imaging of those layers deep to the retina, such as the choroid and the retrolaminar optic nerve [5]. Low-coherence swept-source lasers can image deeper structures such as the lamina cribrosa and details of choroidal vessels.

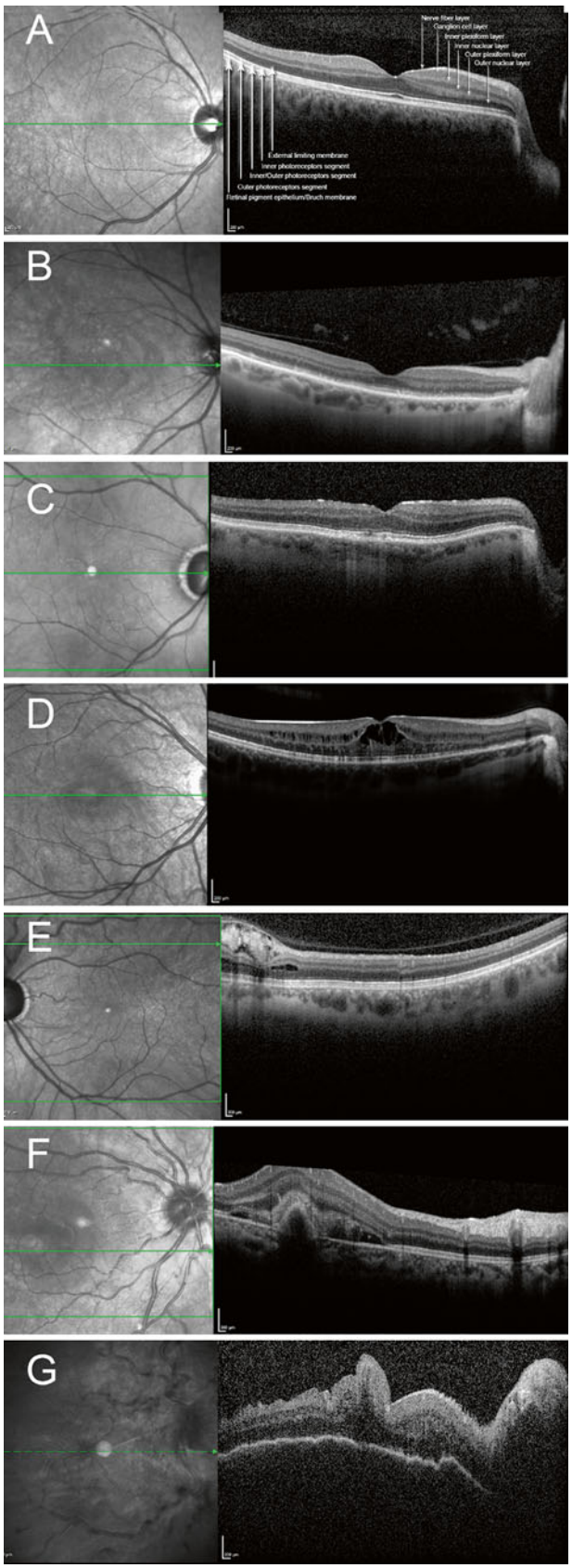

Fig. 27.1 Examples of retinal OCT. (**a**) Normal retinal scan through the macula of a 9-year-old child. (**b**) Thinning of the photoreceptor layer due to vitamin A toxicity in an adult. (**c**) Perimacular photoreceptor changes due to hydroxychloroquine toxicity in an adult. (**d**) Cystoid macular edema in a child with uveitis. (**e**) Localized peripapillary schisis in the outer nuclear layer, in a child with a history of uveitis and optic nerve edema. (**f**) Pigment epithelial detachment with subretinal fluid in a child with uveitis. (**g**) Choroidal folds in a child with postoperative ocular hypotony

Retinal Nerve Fiber Layer Scan

Quantitative analysis of the retinal nerve fiber layer (RNFL) and macula initially gained popularity among glaucoma experts due to its numerical interpretation of the integrity of the axons forming the optic nerve rim. Specifically, the peripapillary RNFL measurement is a circular scan of 3.4–3.5 mm (machine dependent) that is centered on the optic nerve head. By capturing the axons of the vast majority of retinal ganglion cells, its importance for accurately assessing the health of the RNFL cannot be overemphasized. The peripapillary RNFL is an indirect measure of all the retrobulbar optic nerve axons and is easily obtained by this quick and accurate, noninvasive technology. RNFL measurements were shown to correlate with severity of glaucoma and response to treatment [6–12]. Not surprisingly, this technology has been used to study optic nerve damage from various causes including optic neuritis, compressive lesions [13–19], genetic optic neuropathies [20, 21], and others [22–25]. RNFL measurements can also be used as a marker for successful treatment in a variety of conditions such as optic neuritis. More recently, the RNFL measurements have been shown to mirror the integrity of not only the optic nerve and retina, but that of the brain as well [18, 26–28].

The majority of commercially available OCT machines do not have an integrated, pediatric normative database. However, pediatric RNFL data are not significantly different from those of young adults. One should keep in mind that RNFL values in children vary with refractive error, axial length, and race [29–34]. Due to the inherent limitation of patient cooperation, acquisition of quality images, especially in younger children, has thus far reduced the utility of OCT in diagnosing pediatric posterior segment disorders (see Chap. 26). New innovations in the form of handheld SD-OCT should help to alleviate this problem (see Chap. 26).

Optic Nerve Head Map

The optic nerve head map is similar to the macular map but is instead centered on the optic nerve. It is useful for qualitatively assessing the peripapillary area, especially if a lesion is suspected (e.g., peripapillary choroidal neovascularization, Fig. 27.2). By using the EDI protocol on the optic nerve, one may also identify buried optic nerve head drusen (Fig. 27.3) [35, 36]. The identification of hyper-reflective material suggestive of drusen underneath the optic nerve does not rule out papilledema, as up to 55 % of pediatric patients with papilledema may also have this finding [55].

OCT in Optic Neuropathies

Glaucoma

OCT has been used extensively in the monitoring of ONH damage from glaucoma [37–44]. Measurements from the RNFL macular thickness and macular maps were shown to correlate with the severity of cupping in pediatric glaucoma [29, 45, 46] and have acceptable reproducibility [31, 32]. However, this technology's application to pediatric glaucoma is still imperfect. As mentioned previously, pediatric normative values have yet to be integrated into most commercial machines [33, 34, 47, 48]. We know that normative

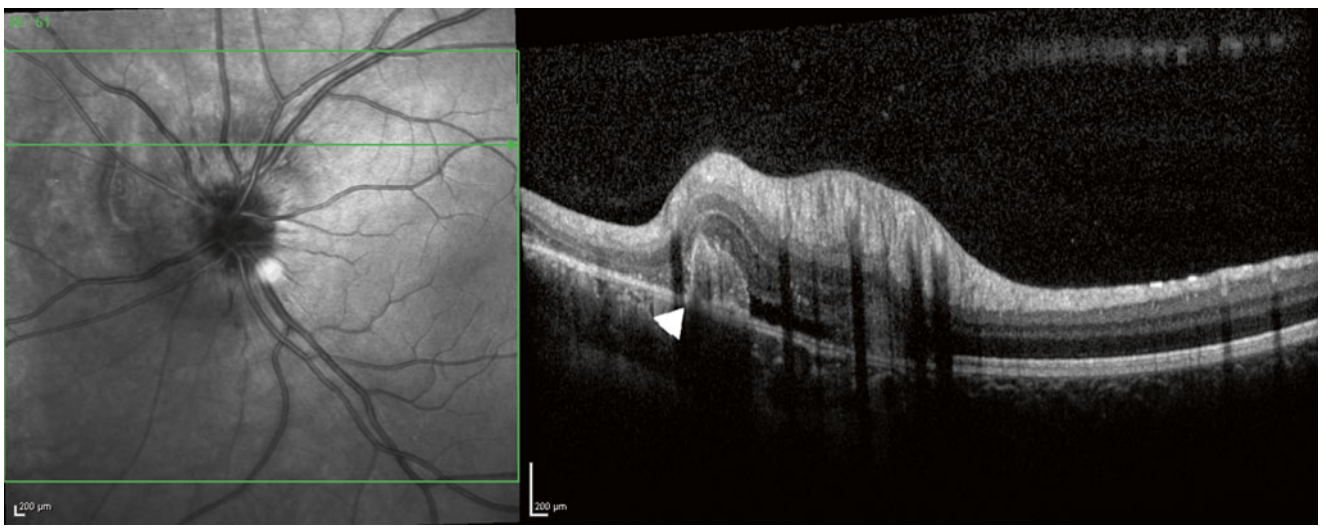

Fig. 27.2 Nasal peripapillary choroidal neovascular membrane in the left of a 12-year-old girl with optic nerve head drusen

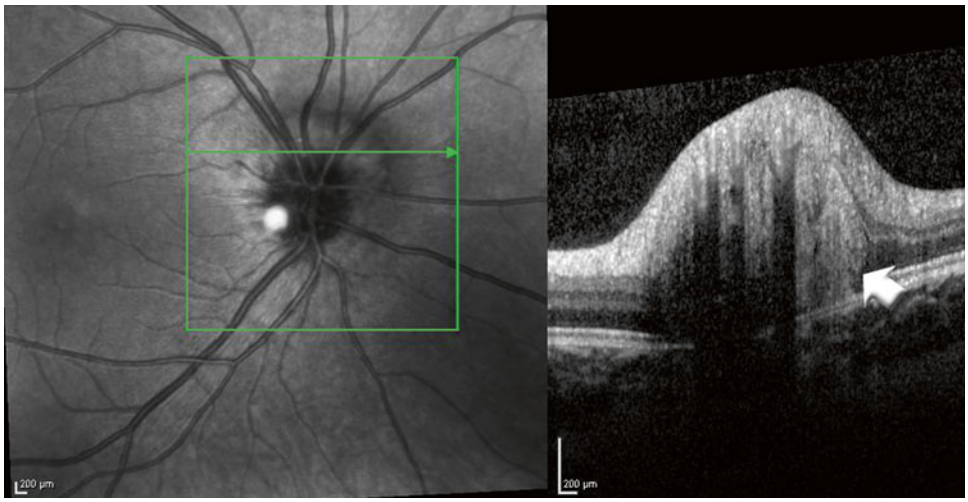

Fig. 27.3 Optic nerve head scan showing buried hyperreflective optic nerve head drusen

values for these OCT parameters vary with age (RNFL slowly decreases with age), race (blacks have thicker average and superior quadrant RNFL than whites), and axial length (longer axial length associated with thinner RNFL) [30] and data about the longitudinal reproducibility of SD-OCT values in a growing child are still lacking [31, 32] (Fig. 27.4).

Optic Nerve Edema

Papilledema

OCT can reliably diagnose and grade papilledema, more so than even an expert panel [49]. RNFL scanning protocols [50, 51] and the optic nerve head map with automated software segmentation of the retinal layers can provide a total disc volume [52]. Some investigators use linear scans through the optic nerve to look at the deformation of Bruch's membrane in the papillary area. [An upward angle of Bruch's membrane is suggestive of increased intracranial pressure.] This may help to differentiate pseudopapilledema from true papilledema (Fig. 27.5) [53]. Finally, OCT can identify retinal changes from papilledema that are predictive of final visual outcome [54, 55] (Fig. 27.6).

Optic Neuritis

In the acute phase of optic neuritis, OCT may show thickening of the RNFL even if no edema is seen on funduscopic examination [56, 57]. As optic atrophy becomes evident with time, the RNFL becomes thin and it correlates with final visual outcome [16, 56–60]. In the setting of adult-onset multiple sclerosis, the RNFL measurement inversely correlates with disease activity and is currently being used as one of the biomarkers for treatment efficacy in clinical trials [18, 19, 28, 61, 62].

Imaging of the retina in optic neuritis-induced optic atrophy may reveal cystic lesions in the inner nuclear layer [63]. These are seen in other types of optic atrophy and are thought to be due to schisis at the level of the inner nuclear layer [63, 64] (Fig. 27.7).

Neuroretinitis

In neuroretinitis, OCT initially shows RNFL thickening due to optic nerve edema, foveal contour changes, photoreceptor changes and thickening, and subretinal fluid and exudates [65]. The presence of these retinal changes in cases of suspected optic neuritis should prompt a work-up for neuroretinitis even if a macular star is not observed (Fig. 27.8).

Optic Nerve Head Drusen

Imaging the optic nerve head with the EDI protocol can help differentiate pseudopapilledema from true papilledema by revealing the buried drusen (appearing as a hyperreflective body underneath the nerve) or by looking at the angle formed by the edge of the RPE (an inward angle suggests high intracranial pressure) [35, 36, 66] (Fig. 27.8).

A decreased average RNFL in the setting of an optic nerve heard drusen is suggestive of partial optic atrophy and the presence of a visual field defect [67]. Finally, the drusen may cause peripapillary choroidal neovascular membranes that can be easily detected by OCT [68, 69].

Atrophic Nerves

Optic atrophy will manifest as thinning on the RNFL scan and the macular map. Sometimes cystic lesions in the inner nuclear layer can be seen on the macular scan, which have been

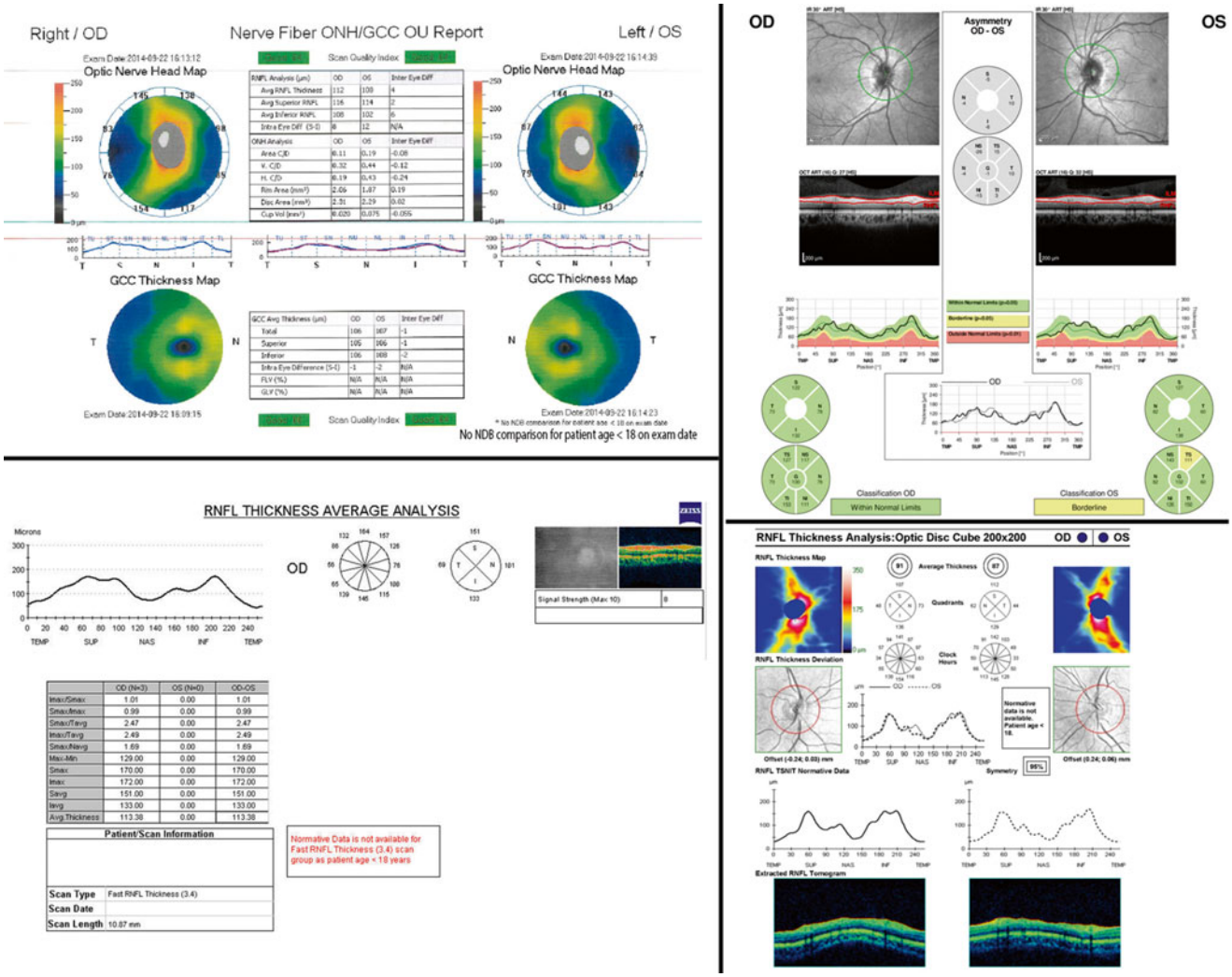

Fig. 27.4 Retinal nerve fiber layer output of four different children on four different commercial OCT machines. *Top left* Optovue; *top right* Spectralis; *bottom left* Stratus; *bottom right* Cirrus. Optovue, Stratus, and Cirrus do not color code the output for patients younger than 18 years due to the lack of an internal pediatric normative database. Spectralis output has a pediatric normative database but it applies to Caucasian eyes only

reported in various types of optic atrophy and are not indicative of the cause of atrophy [70–72]. When atrophy is secondary to papilledema, it is difficult to decipher resolution of edema from superimposed atrophy and sometimes the RNFL may appear falsely reassuring when there is a combination of both pallor and atrophy in the same nerve (Fig. 27.9).

Compressive Lesions

Optic atrophy caused by compressive lesions of the anterior visual pathways can be measured by OCT [73–76]. Furthermore, the average RNFL value can be predictive of visual recovery after resection of the inciting compressive lesion [77, 78]. OCT can be used in conjunction with MRI for monitoring optic pathway gliomas (Fig. 27.10) [73, 74, 79, 80] (see Chap. 39).

Macular scans can occasionally predict a homonymous visual field defect in children who are unable to perform standardized, automated visual fields. The macular map will show homonymous thinning of the maculae that respects the vertical midline (Fig. 27.11) [81–83].

Optic Nerve Hypoplasia

Optic nerve hypoplasia will be associated with sectoral thinning of the RNFL that corresponds to the missing segment of the nerve [84]. Sometimes, macular scans will show absence of the innermost retinal layers (ganglion cell and nerve fiber layer) (Fig. 27.12).

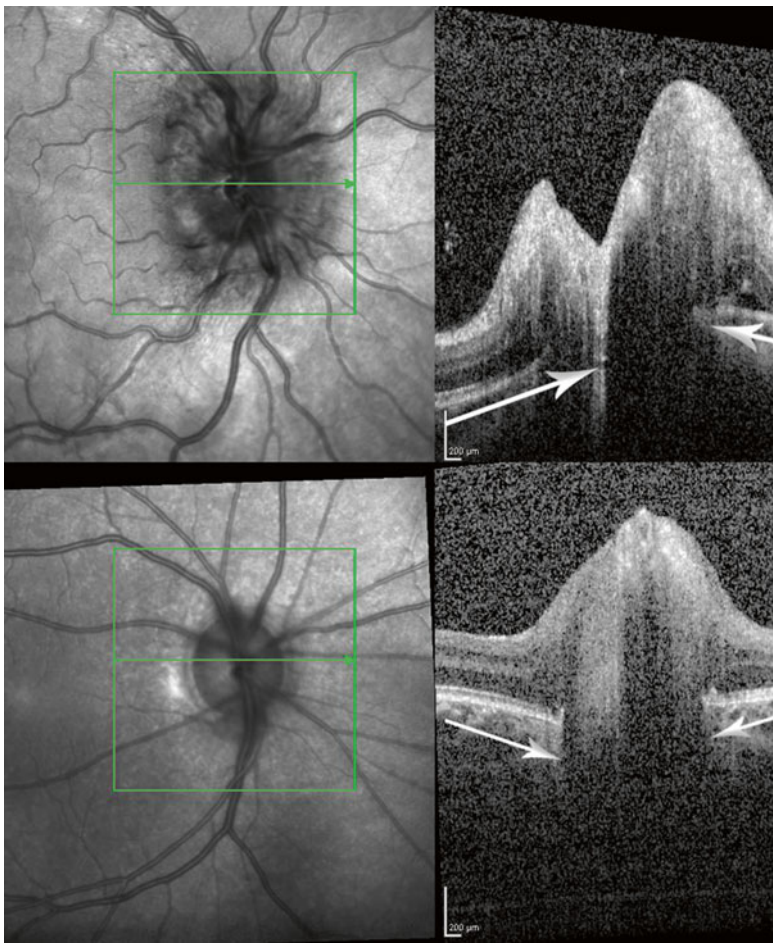

Fig. 27.5 *Arrows* indicating the angle formed by Bruch's membrane at the level of the optic nerve. *Top*: Membrane curving upward in a child with idiopathic intracranial hypertension, opening pressure was 38 mm H_2O. *Bottom*: Bruch's membrane curving downward in a child with optic neuritis, and opening pressure of 16 mm H_2O

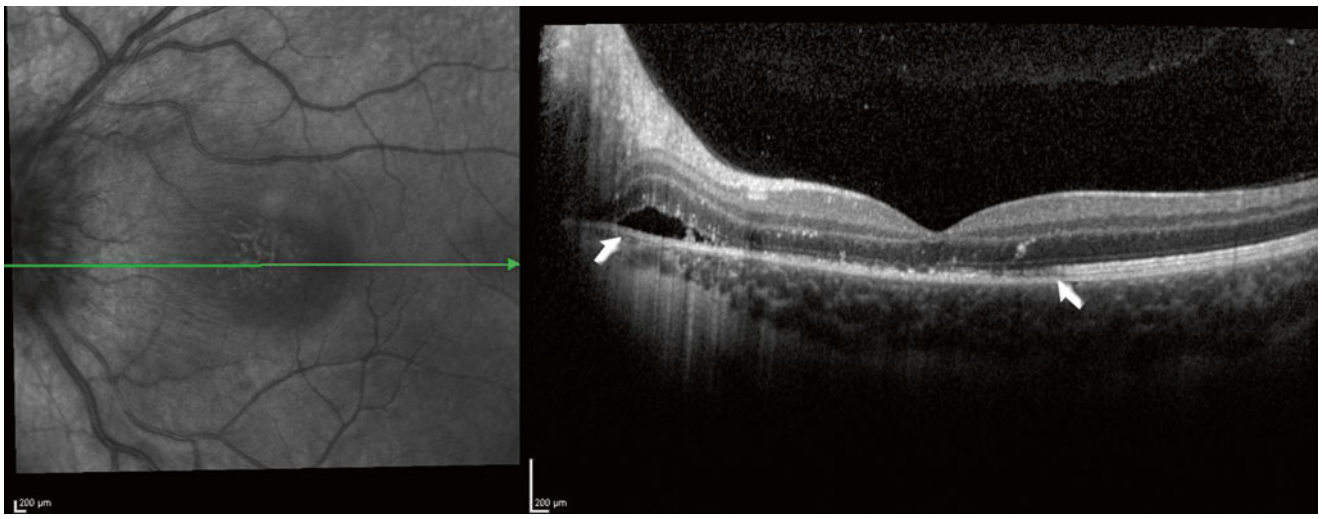

Fig. 27.6 Subretinal fluid and photoreceptor changes in a child being treated for papilledema due to idiopathic intracranial hypertension

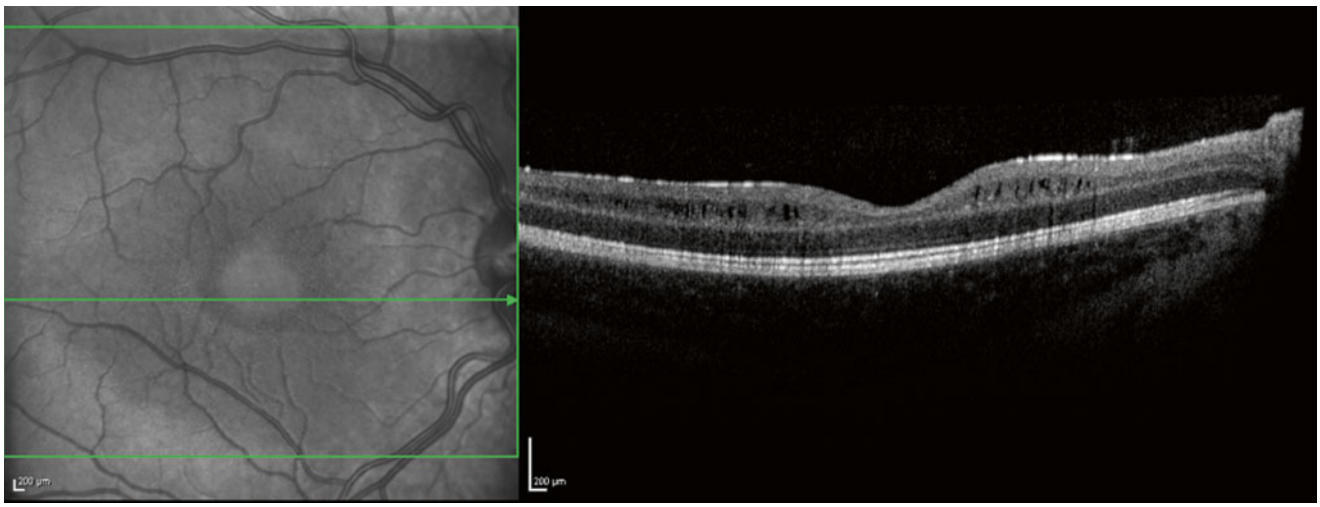

Fig. 27.7 Cystic changes in the inner nuclear layer in the setting of partial optic atrophy (note severe thinning of ganglion cell layer) due to optic neuritis

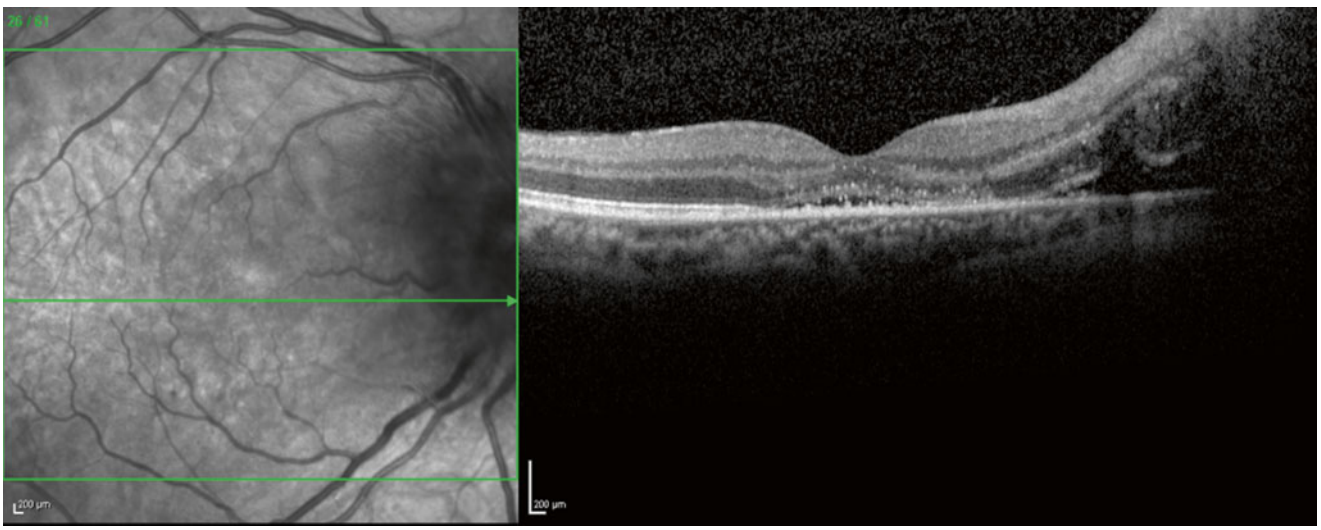

Fig. 27.8 Macular OCT showing subretinal fluid and photoreceptor changes in an eye with acute neuroretinitis

OCT in Genetic Retinopathies

Outer retinal pathology is well visualized by OCT. The pattern of RPE or photoreceptor changes can be pathognomonic for certain disease pathology. Below are examples of known genetic retinopathies and their corresponding OCT findings (see Chap. 34).

Stargardt Disease

OCT findings in Stargardt disease include an initial disruption of the outer segment ellipsoid band accompanied by later progression of foveal photoreceptor outer segment loss. This creates foveal cavitation with RPE preservation and distinct external limiting membrane thickening [85, 86]. Additionally, loss of the foveal ellipsoid zone has been

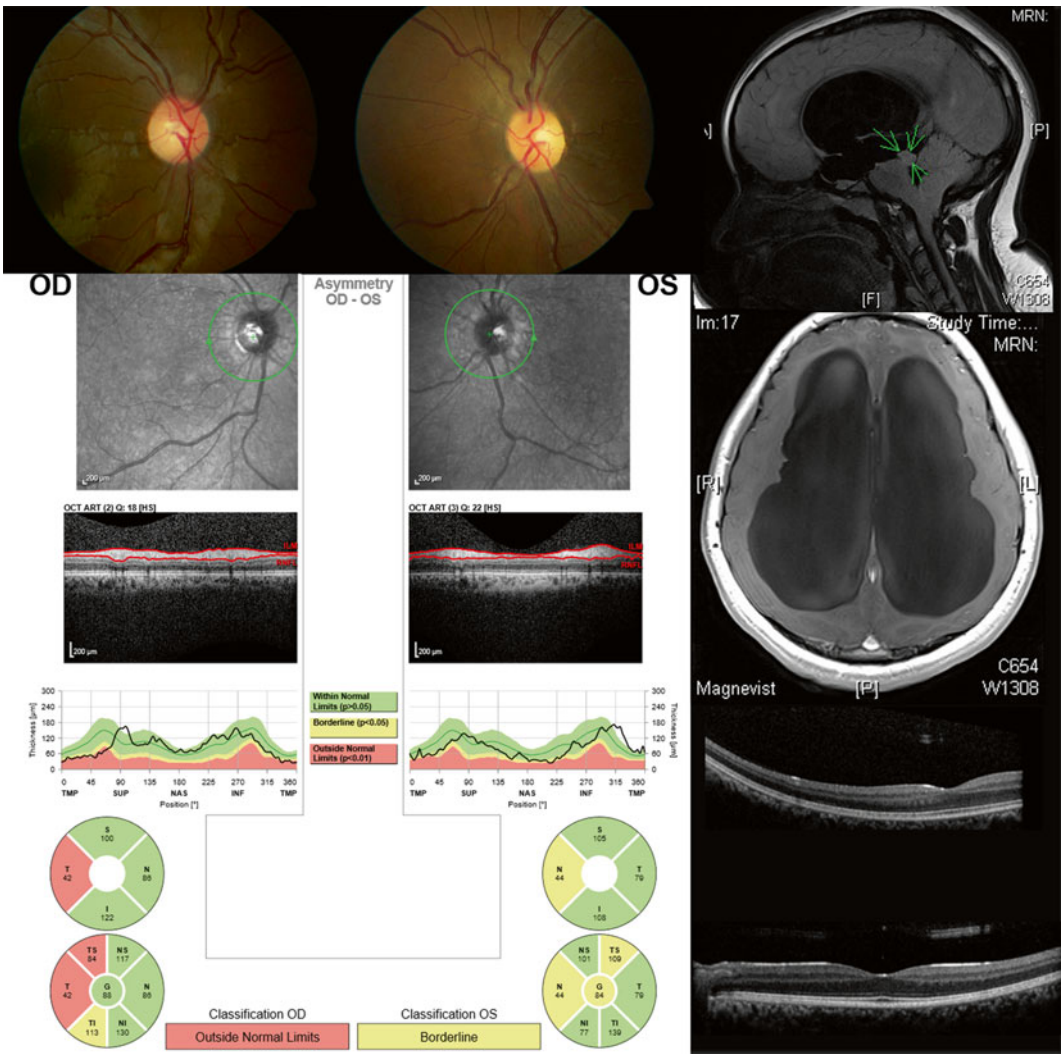

Fig. 27.9 Optic atrophy superimposed on papilledema due to obstructive hydrocephalus, and counting fingers vision in both eyes of a 16-year-old African-American girl. OCT RNFL shows an average retinal nerve fiber layer higher than 80 μm in both eyes (almost normal). Macular OCT shows almost complete absence of the macular ganglion cell cells (*bottom right*)

observed in a small cohort of patients with juvenile Stargardt disease [87]. The distinctive retinal flecks in Stargardt disease can also be characterized by SD-OCT into five different types based on their location in the retina. Although no significant correlation between fleck type and visual acuity is observed, this characterization may prove important for evaluating the sequential changes in Stargardt disease [88] (Fig. 27.13).

Juvenile X-linked Retinoschisis

Juvenile X-linked retinoschisis is a disease with characteristic retinal schisis cavities. These are easily apparent on SD-OCT images, and have been documented in various layers of the neurosensory retina [89]. Foveomacular schisis is seen most frequently in the inner nuclear layer. Interestingly, subclinical extramacular schisis cavities can be seen in up to 45 % of eyes and are equally prevalent in any of the inner retinal layers. SD-OCT images have also been obtained on female carriers of X-linked retinoschisis and no schisis cavities were documented [90]. SD-OCT reveals age-dependent morphologic features of the cavities: younger patients typically exhibit cystic retinal elevation, whereas older patients show collapsed retinoschisis with retinal thinning [91] (Fig. 27.14).

Cone Rod Dystrophy

Cone rod dystrophy is a disease that causes deterioration of the cone photoreceptors located in the outer layers of the retina. One study of patients with cone rod dystrophy noted

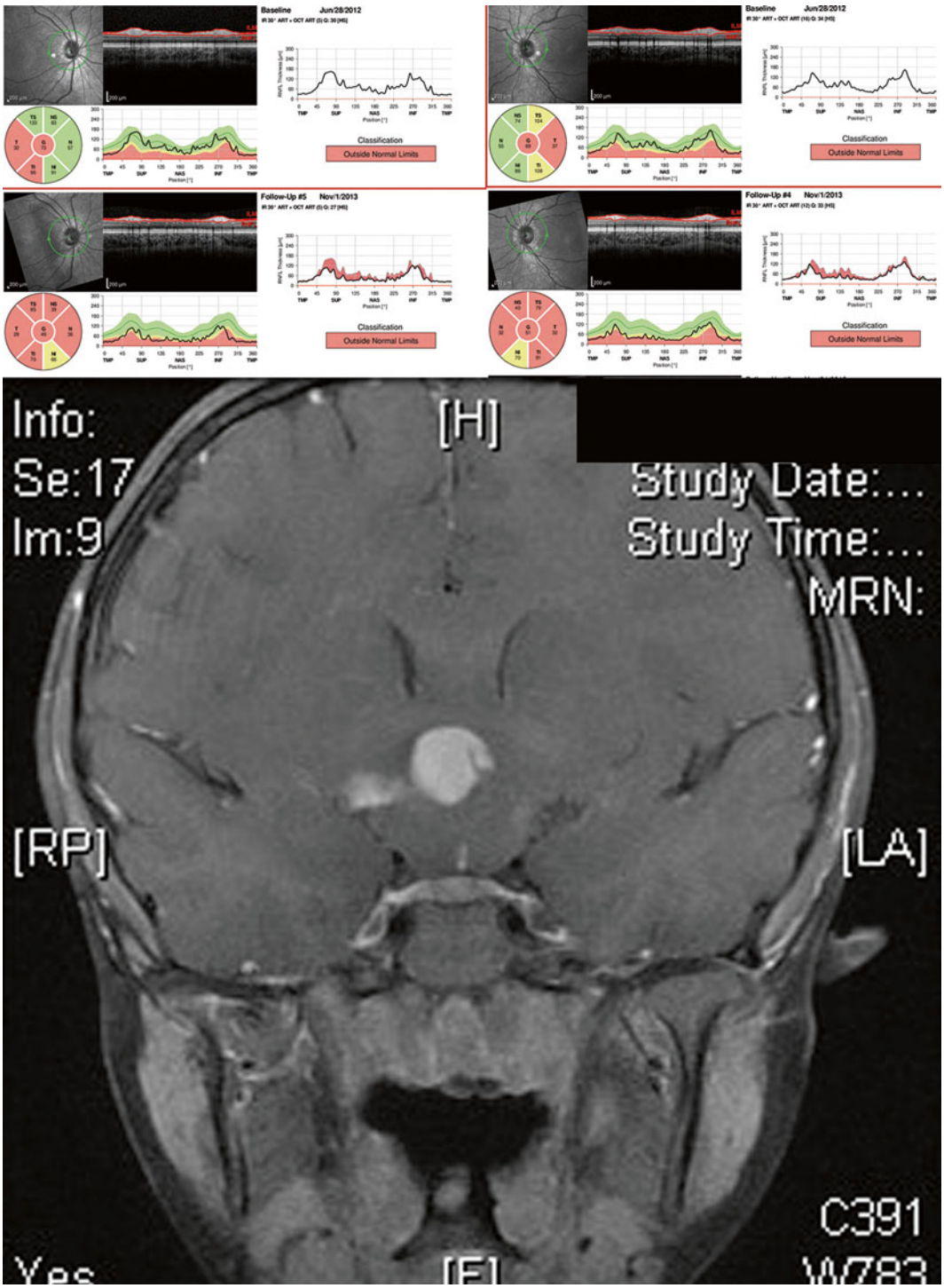

Fig. 27.10 Retinal nerve fiber layer OCT showing worsening optic atrophy in both eyes that paralleled the growth of a chiasmal glioma

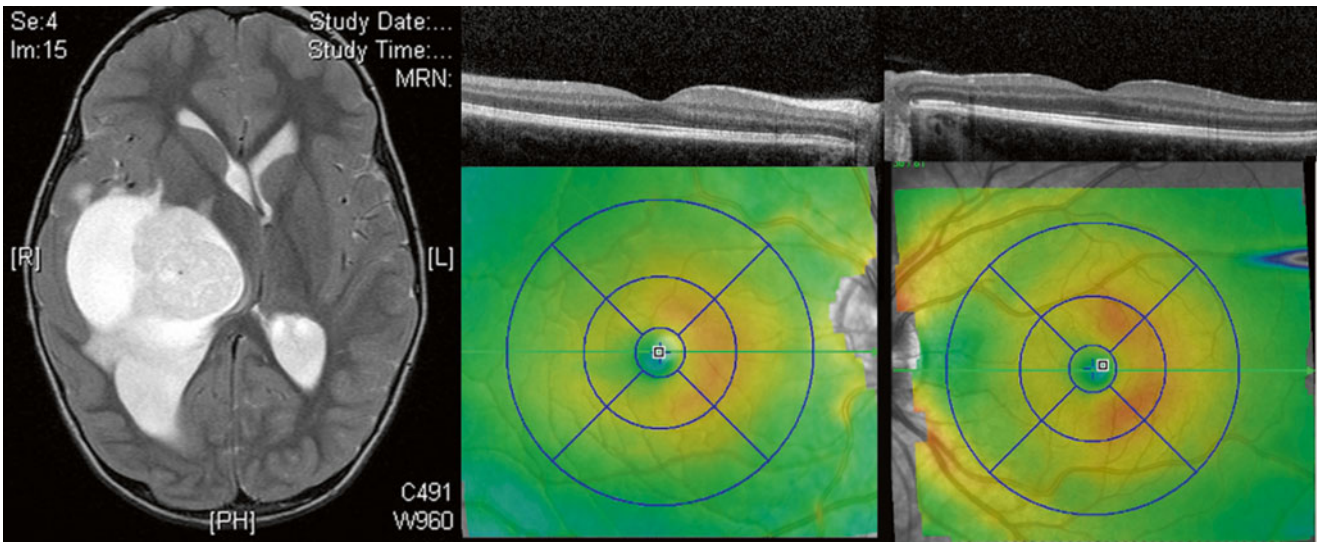

Fig. 27.11 Homonymous thinning of the right macula (temporal thinning of right eye, nasal thinning in left eye) that respects the vertical midline in a child with a right-sided brain tumor causing a left homonymous visual field defect (note the homonymous thinning of the ganglion cell layer, *top right*)

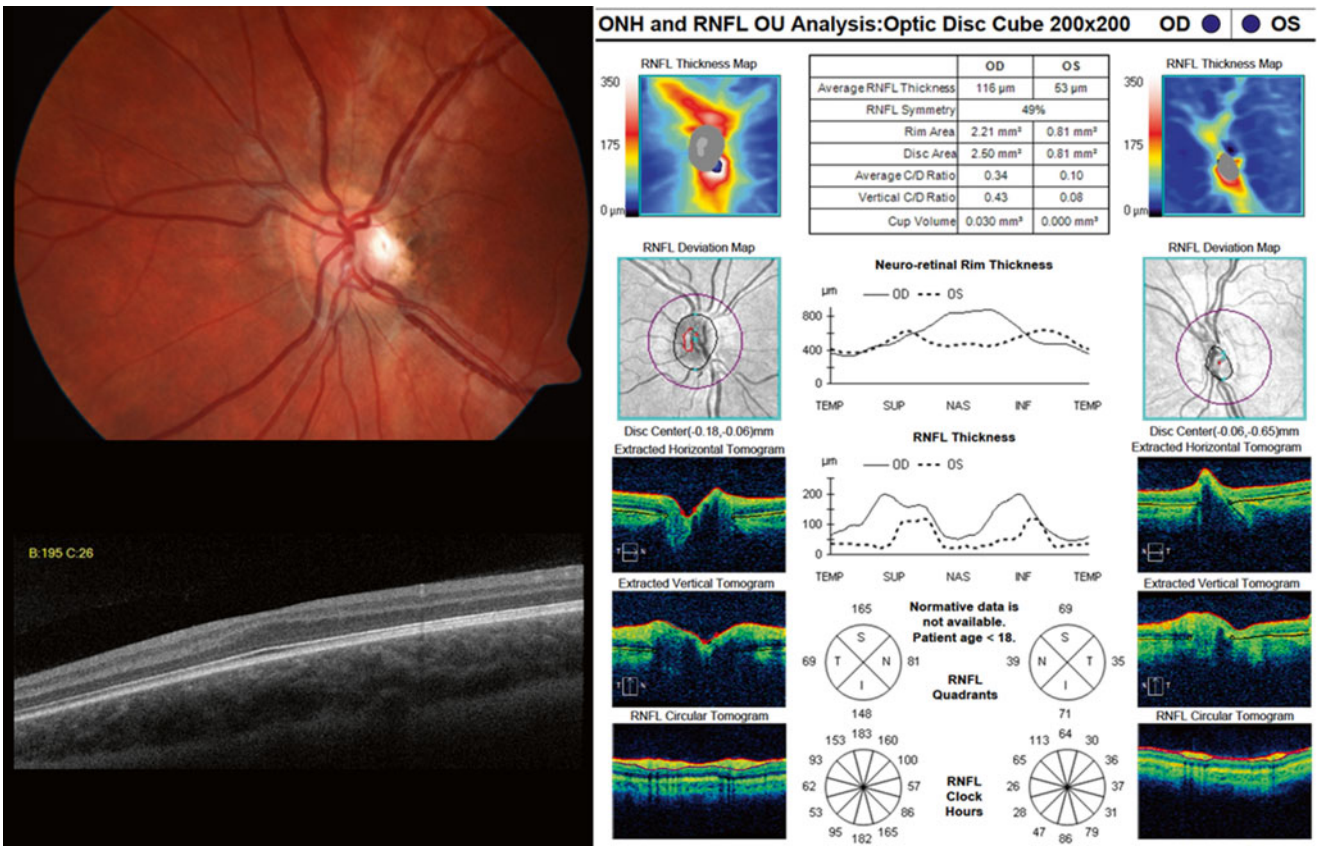

Fig. 27.12 Left optic nerve hypoplasia: Retinal nerve fiber layer (RNFL) scan shows superior sectoral thinning of left eye. RNFL scan cannot distinguish acquired optic atrophy from optic nerve hypoplasia. Also note associated foveal hypoplasia. Image courtesy of Elias I. Traboulsi

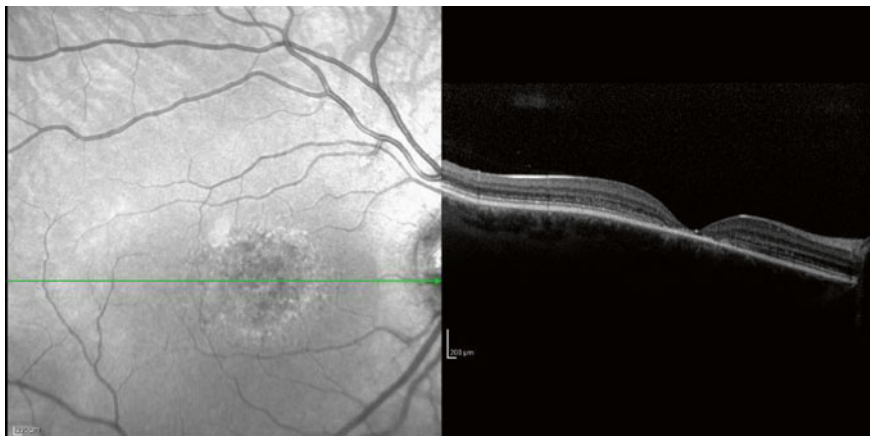

Fig. 27.13 Macular SD-OCT of the right eye of a child with Stargardt disease showing disruption of the ellipsoid zone accompanied by foveal photoreceptor outer segment loss

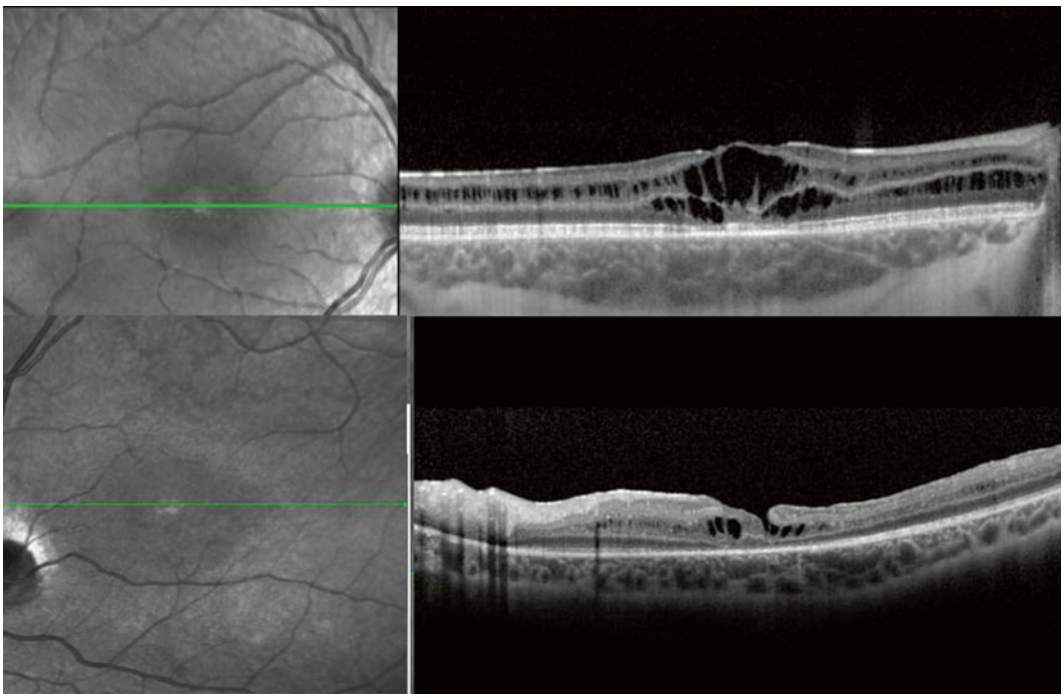

Fig. 27.14 Macular scans in juvenile X-linked retinoschisis showing schisis cavities in inner nuclear and outer nuclear layers in early disease (*top*). A case with more advanced disease showing thinning of inner retina, pseudomacular hole, schisis in the outer nuclear layer, and central photoreceptor loss (*bottom*)

nearly universal loss of the external limiting membrane and ellipsoid zone on foveal SD-OCT. These same investigators observed a complete absence of the foveal interdigitation zone in all patients with cone rod dystrophy [92] (Fig. 27.15).

Leber Congenital Amaurosis

Patients with Leber congenital amaurosis usually present in infancy with manifest nystagmus, thus limiting the utility of OCT due to fixation instability. However, one group was able to acquire adequate images in a small cohort of LCA patients with the *LRAT* mutation. These SD-OCT images were notable for disrupted retinal lamination, outer-retinal "debris," and an unidentifiable photoreceptor layer in two cases. In addition, the retinal nerve fiber layer in three patients exhibited a characteristic saw-tooth pattern [93]. This was not found in a separate study of patients with the more common *RPE65* mutation [94]. This study noted photoreceptor loss in foveal and extrafoveal retina. Additional studies involving OCT and the more common *RPE65* mutation are lacking (Fig. 27.16).

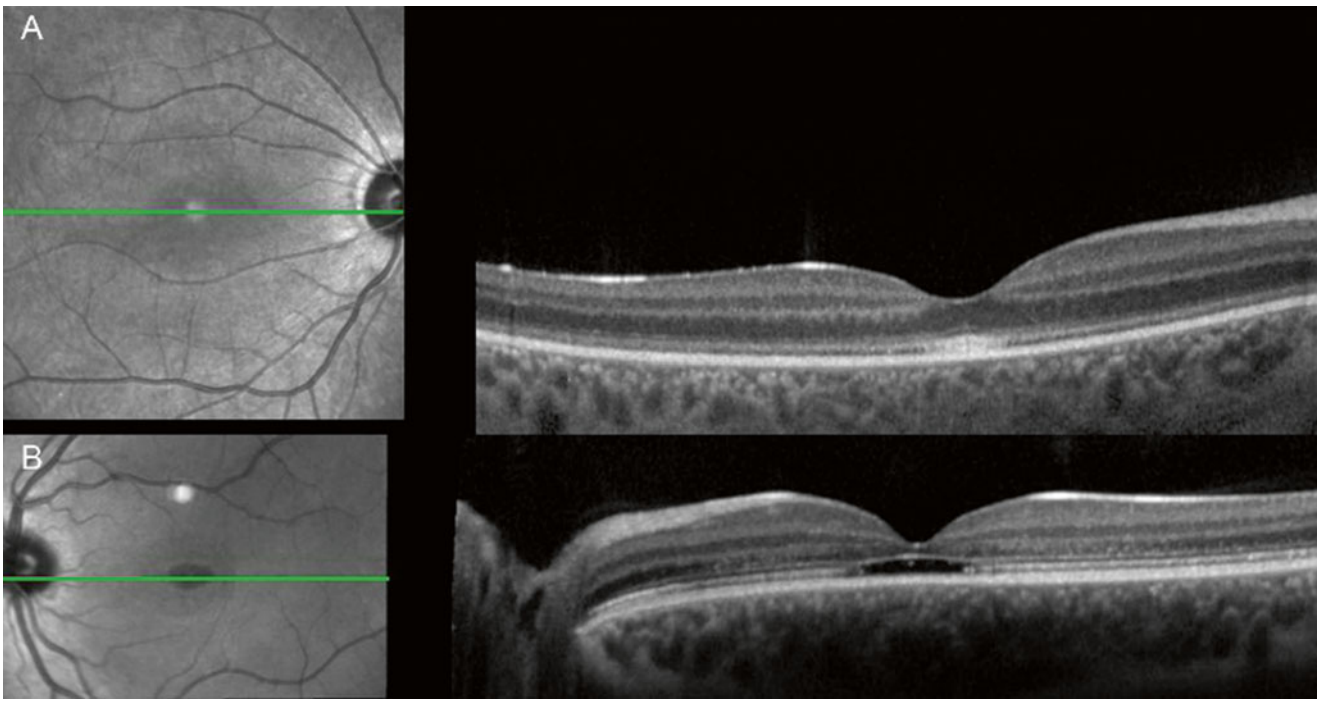

Fig. 27.15 Foveal OCT in cone rod dystrophy showing thickening of photoreceptors in early disease (*top*) and advanced disease showing loss of the external limiting membrane and ellipsoid zone (*bottom*)

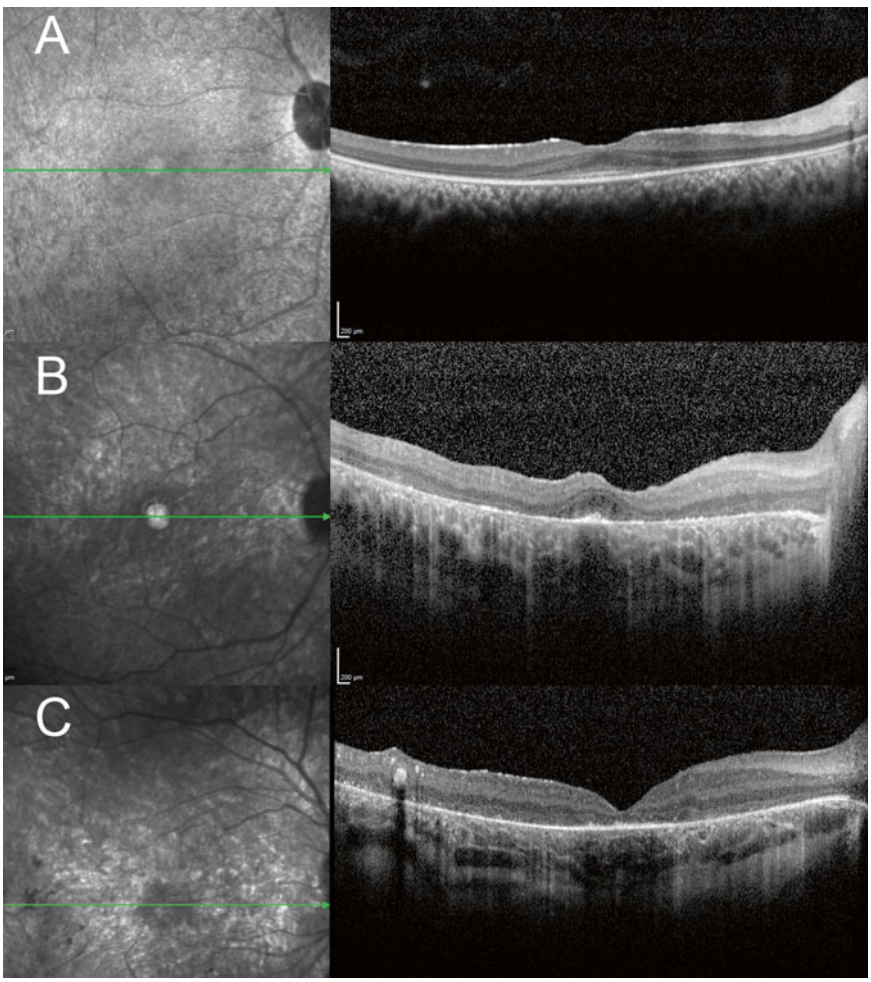

Fig. 27.16 SD-OCT in Leber congenital amaurosis: (**a**) Extrafoveal photoreceptor loss (LCA DQB1 mutation). (**b**) Disruption of retinal lamination, and central outer-retinal debris (LCARDH12 mutation). (**c**) Foveal and extrafoveal photoreceptor loss with saw-tooth pattern

Best Disease

Ophthalmoscopic features of Best disease (vitelliform dystrophy) are usually striking and proceed in a predictable stepwise fashion that is defined by their funduscopic appearance. However, the visual consequences of the disease are quite variable and often depend on the clinical stage. SD-OCT may be beneficial in correlating retinal structure and pathology to visual acuity. One study looked at the evolution of the vitelliform lesion using SD-OCT. The previtelliform lesion was characterized by a slight thickening of the interdigitation zone. This then evolved to form a vitelliform lesion described as a dome-shaped hyperreflectivity in the subretinal space. The "pseudohypopyon" stage revealed a partial reabsorption of the hyperreflective material that was replaced by a fluid component. Progression to the subsequent vitelliruptive stage ("scrambled egg" in appearance) revealed a near-complete replacement of the hyperreflective material by a fluid component. Finally, the atrophic stage had a diffuse loss of photoreceptor and other sensory retinal layers [95, 96] (Fig. 27.17).

Rod Cone Dystrophy (Retinitis Pigmentosa)

Retinitis pigmentosa is a broad term used to describe a group of heterogenous, inherited disorders with symptoms such as night blindness and constricted visual fields. Most have retinal pigmentary changes such as bone spicules and many go on to develop cystoid macular edema. Using OCT, several studies associate the presence of an ellipsoid zone with better visual acuity and a thicker fovea [97, 98]. Another publication evaluated the prevalence and characteristics of cystoid spaces in retinitis pigmentosa. Using SD-OCT, these authors found that the prevalence of cystoid spaces was 22.5 %. The vast majority of these spaces were located in the inner nuclear layer and in areas where the external limiting membrane was preserved, indirectly supporting the involvement of Muller cells in the pathogenesis of retinitis pigmentosa-associated CME [99] (Fig. 27.18).

Choroideremia

This hereditary retinal degeneration features deterioration of the choriocapillaris and the deeper layers of the retina, especially the retinal pigment epithelium and the photoreceptors. OCT was used to document the disappearance of the interdigitation layer between the RPE and the photoreceptors. In this zone, a distinct loss of cone photoreceptors was observed [100]. Patients with choroideremia frequently demonstrate outer retinal tubulations on SD-OCT images. These tubulations manifest as round or ovoid structures with hyperreflective borders at junctions of intact and atrophic outer retina [101] (Fig. 27.19).

Batten Disease

Batten disease (Jansky-Bielschowsky disease) is the classic example of a group of progressive neurodegenerative disorders of childhood known as neuronal ceroid lipofuscinoses. It

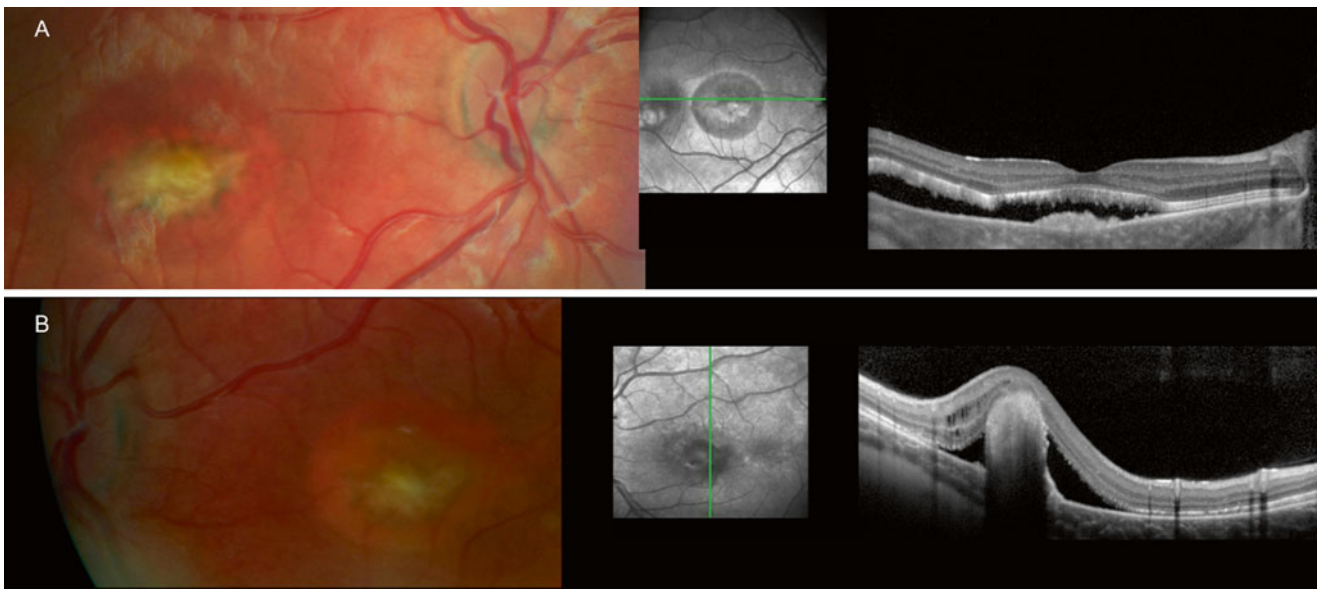

Fig. 27.17 OCT in Best vitelliform dystrophy. (**a**) Central exudative vitelliform lesion, subretinal fluid, and thickening of both the ellipsoid zone and the retinal pigment epithelium/Bruch's membrane complex. (**b**) Dome-shaped hyperreflective vitelliform lesion in the subretinal space

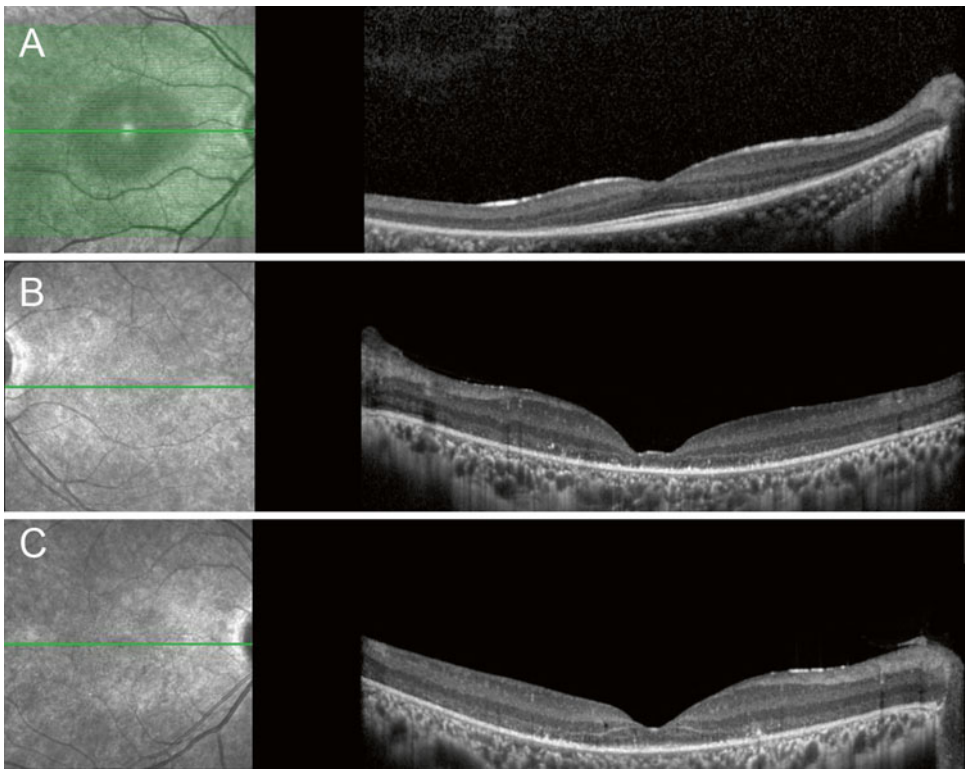

Fig. 27.18 OCT in retinitis pigmentosa. (**a**) Mild disease sparing the fovea and perifovea. (**b**) Diffuse photoreceptor loss. (**c**) Diffuse photoreceptor loss and one cystic lesion in the inner nuclear layer

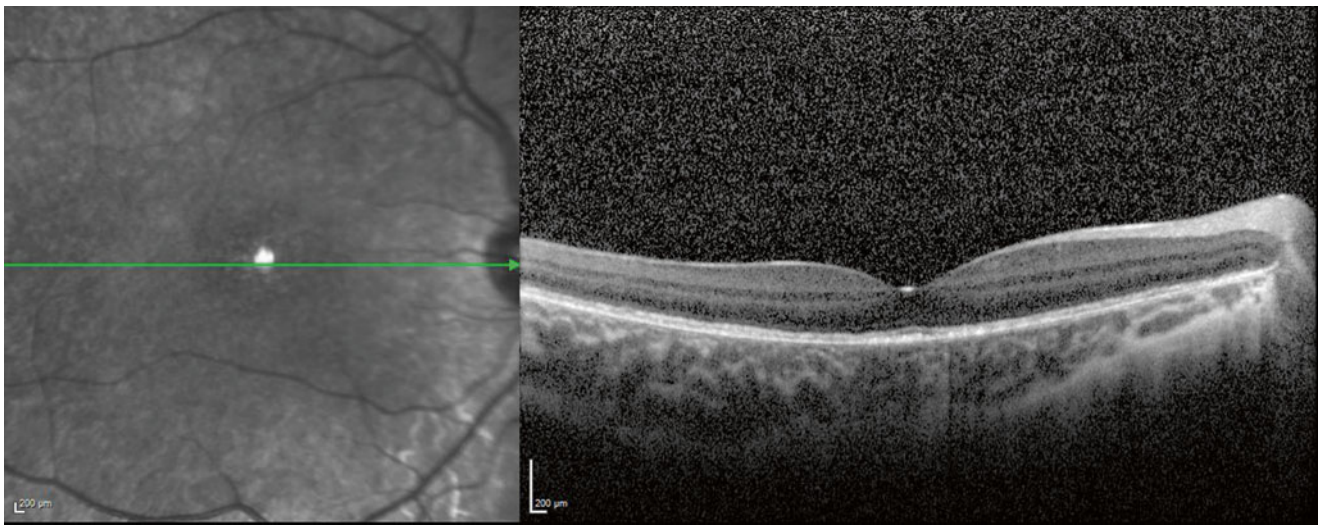

Fig. 27.19 OCT in choroideremia showing degeneration of retinal pigment epithelium and photoreceptors

results in the accumulation of autofluorescent material in lysosomes, ultimately leading to neuronal cell death. Ocular manifestations include retinal degeneration and optic atrophy. OCT can be used to correlate pathological changes in the eye with neurological function. In one study, in the early stages of the disease, characterized by better neurological function, patients had normal SD-OCT images or only subtle disruptions of the outer retina. As the disease progressed, neurological function became severely impaired, and SD-OCT images demonstrated severe outer retinal atrophy, bulls-eye maculopathy, and/or deposition of hyperreflective material throughout the entire fundus [102] (Fig. 27.20).

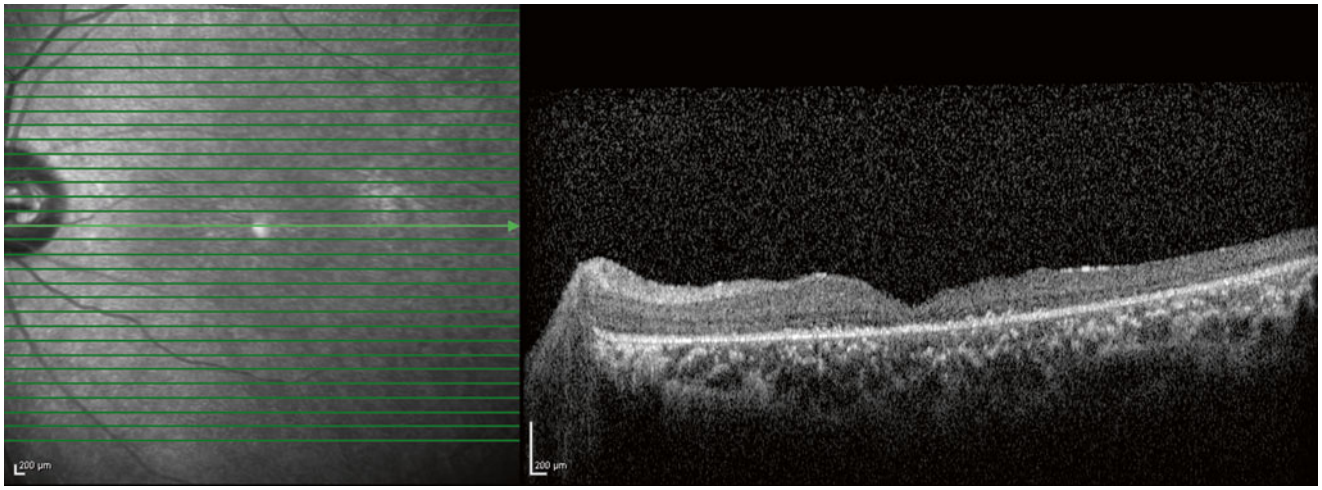

Fig. 27.20 OCT in advanced Batten disease in a 7-year-old child showing severe outer retinal atrophy. Note thinning of ganglion cell layer and retinal nerve fiber layer as well

Foveal Hypoplasia

Diagnosing and grading foveal hypoplasia can be accomplished by OCT: the inner retinal layers are seen to extend across the fovea without thinning at the fovea to form a foveal pit. This is associated with increased foveal thickness, loss of the normally thickened photoreceptor nuclear layer at the fovea [103], decreased macular volume due to the loss of retinal nuclear layers [103–105], hyporeflectivity of the photoreceptors at the fovea, increased transillumination of the choroid layer, and hyperreflectivity of the choroid space [106]. Although the grade of foveal hypoplasia and visual acuity may not always correlate [106, 107], the size of the photoreceptor outer segment at the fovea can predict visual acuity in albinism [108] (Fig. 27.21).

OCT in Infants

Bioptigen has developed a customized protocol for safe imaging in smaller eyes [109]. Acquired OCT images reveal a photoreceptor layer that is absent near birth owing to the immaturity of foveal cones. Cones continue to slowly develop over the first 24 months of life and mature into childhood [110, 111] (Fig. 27.22) (please also see Chap. 26).

OCT in Retinopathy of Prematurity

Handheld SD-OCT has recently found its niche in the neonatal intensive care unit in the recent years. This imaging modality has helped delineate the microanatomic changes that accompany the maturation of the human neonatal fovea as well as abnormalities that often present in the maculae of prematurely born infants being screened for retinopathy of prematurity [110, 112]. SD-OCT is superior to indirect ophthalmoscopy and fundus photography in detecting retinal abnormalities such as cystoid macular edema and epiretinal membranes [4, 113]. SDOCT can detect pre-retinal fibrovascular tissue (popcorn) in zone I [113] (Fig. 27.23). As a useful paradigm for detecting plus disease, SD-OCT can measure vessel tortuosity in three dimensions. In addition, the new Doppler flow imaging feature allows for the documentation of increased blood flow [4].

Anterior Segment OCT

Anterior segment OCT (AS-OCT) allows for images of the cornea (transverse resolution of 60 μm and axial resolution of 18 μm) [114]. AS-OCT can be used for diagnosing corneal pathology and for delineation of glaucoma drainage devices and intraocular lens implantation. It can also be used to measure

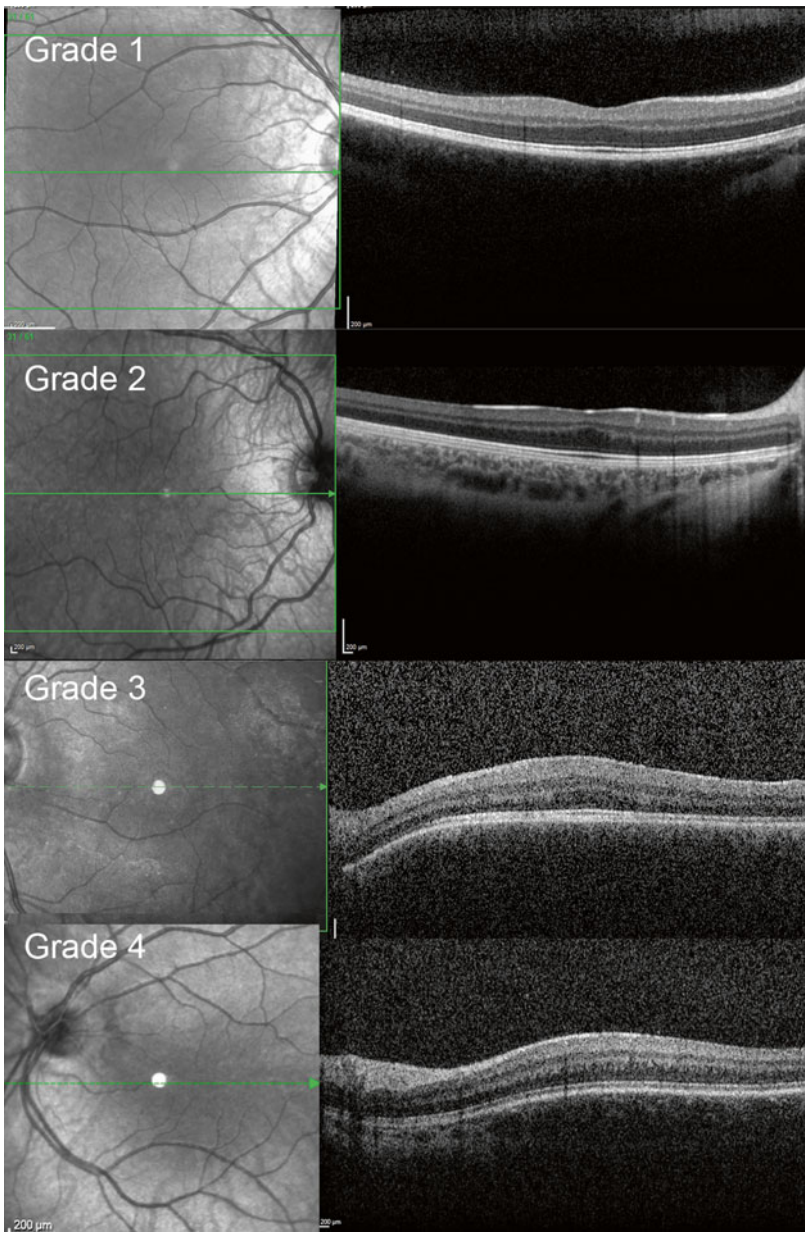

Fig. 27.21 Macular OCT in different grades of foveal hypoplasia in four different children, based on grading by Holmstrom et al. [103]. *Grade 1*: Lack of extrusion of plexiform layers. Shallow foveal pit is formed, outer segment lengthening present, outer nuclear layer widening present. *Grade 2*: Lack of extrusion of plexiform layers, foveal pit is absent. Outer segment lengthening present, outer nuclear layer widening present. *Grade 3*: Lack of extrusion of plexiform layers, foveal pit is absent, outer segment lengthening absent. Outer nuclear layer widening present. Image quality poor due to nystagmus. *Grade 4*: Lack of extrusion of plexiform layers, foveal pit is absent, outer segment lengthening absent, outer nuclear layer widening present. Image quality poor due to nystagmus

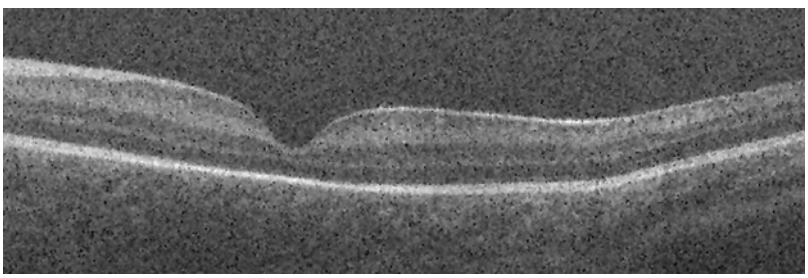

Fig. 27.22 OCT in premature infant at 39 weeks. The inner retinal layer has migrated out of the foveal center, and ellipsoid zone is starting to develop at the peripherally and approaching fovea. Ellipsoid zone and external limiting membrane are not visualized in the foveal center. Photo courtesy of Duke Advanced Research in SDOCT Imaging Laboratory (DARSI Lab)

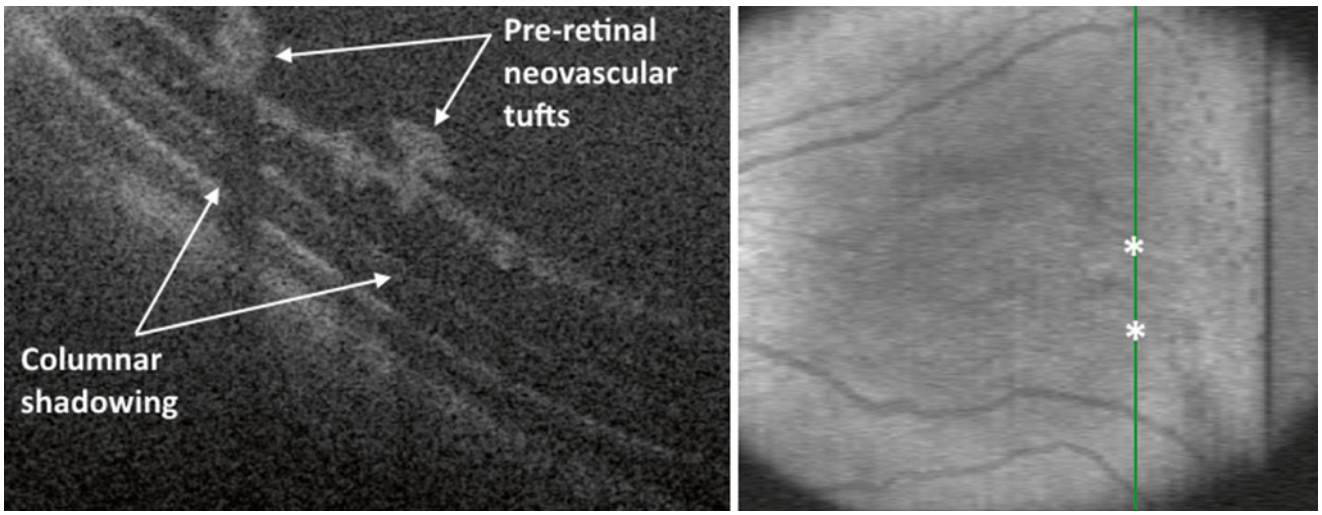

Fig. 27.23 Popcorn in retinopathy of prematurity showing pre-retinal vascular tufts. Photo courtesy of Duke Advanced Research in SDOCT Imaging Laboratory (DARSI Lab)

the anterior chamber depth, corneal thickness, and anterior chamber angle. Unfortunately, current commercial units cannot yet reliably image Schlemm's canal or image any structure posterior to the iris such as the ciliary body [114, 115].

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Electroretinography in Pediatric Retinal Dystrophies

28

James Lin, Luz Amaro-Quireza, and Stephen H. Tsang

Abstract

The use of full-field electroretinography (ERG) is crucial to the diagnosis and understanding of retinal dystrophies in pediatric patients. It is also important to elucidate the etiology of nystagmus in infants, ruling in or out the presence of a retinal etiology. Congenital retinal dystrophies can be categorized by their effect on rods or cones, and further by whether they are stationary or progressive. Here we describe the procedure of performing an ERG in the pediatric patient and use the aforementioned classification method to outline the characteristics of some of the retinal dystrophies, including the use of ERG in their diagnoses.

Keywords

Congenital stationary night blindness • Achromatopsia • Leber congenital amaurosis • Retinitis pigmentosa • Cone dystrophy

Introduction

Inherited retinal dystrophies in children can be broadly divided into two categories: those that start primarily in rods or those that involve cones first. While most of these dystrophies are progressive, some are stationary, an important distinction to make, as patients are young and an accurate diagnosis permits the prediction of their visual prognosis.

Full-field ERG, the most commonly used electroretinographic test, uses a full-field light stimulus usually generated in a Ganzfeld stimulator (Fig. 28.1). ERG recordings with skin corneal or skin electrodes can be used to aid in the diagnosis of childhood retinal dystrophies and to differentiate between rod, cone, and bipolar cell disorders. Localized dysfunctions such as those caused by lesions or small scotomas may not be detected with full-field ERG.

Indications for ERG in Children

ERG can be a useful diagnostic tool to determine the visual potential of a patient, especially useful in children who are preverbal or in those in which reliable histories cannot be obtained. It provides objective functional data to further assess patients who present with symptoms of nyctalopia, photophobia, photopsias, field defects, or decreased visual acuity. In an abnormal-appearing fundus it can be used to

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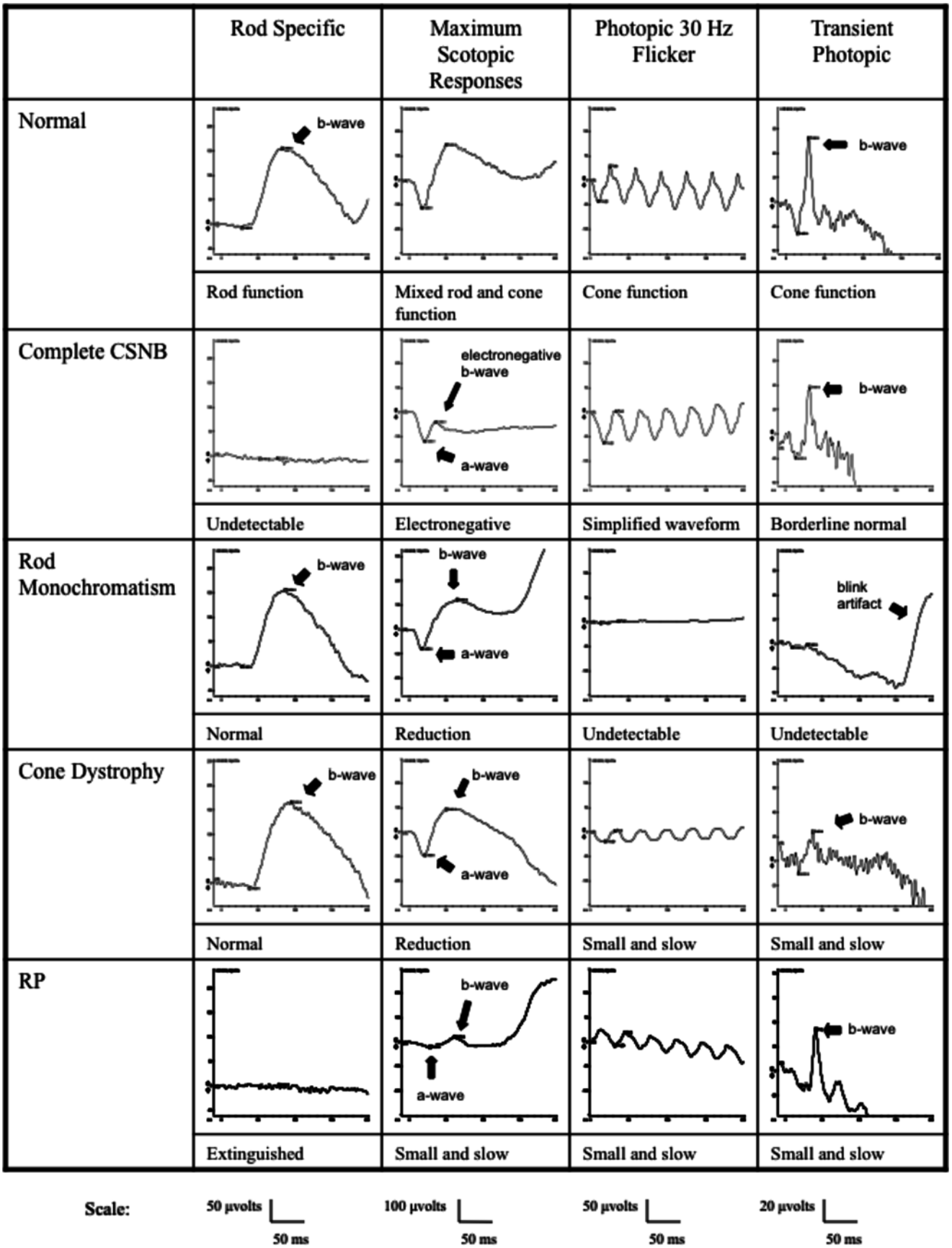

Fig. 28.1 Summary of classic electrophysiological findings in retinal dystrophies. Reproduced with permission of *Retinal Physician*, PentaVision, LLC

quantify the function of rods and cones, and to determine the existence of retinal disease particularly when symptoms are incompatible with ERG testing. In patients with a family history of inherited retinal disease, ERG can be used to determine an individual child's risk. ERG can also be utilized in children presenting with nystagmus to determine whether the cause of the nystagmus is from retinal or intracranial visual pathway origin.

Procedure

The protocol for full-field ERGs includes five different tests to be performed. The standards set by the International Society for Clinical Electrophysiology of Vision (ISCEV) should be followed when performing an ERG.

1. After 20 min of dark adaptation, the electrodes are applied under dim red light in order to prevent rod photoreceptor activation. Rather than using eye patches or a mask, the electrodes may be applied before adaptation begins if dark adaptation occurs in a darkroom.
2. After dark adaption and electrode application, the four standard tests are performed in the following order.
   (a) The first two tests are performed directly following dark adaption, consisting of light flashes against a dark background. This enables the detection of the rod response.
   (b) The latter two tests are performed against a light background, which filters out the rod response and allows the isolation of the cone response.

The first test is the scotopic or dark-adapted dim ERG that measures rod responses. The stimulus is dim (0.01 cd s m^{-2}) in order to prevent cone stimulation, which allows for the isolation of the rod response. Second is the scotopic or dark-adapted bright ERG that measures combined maximal rod and cone function. This uses a bright stimulus (3.0 cd s m^{-2}) to stimulate both rods and cones. After the second test, the patient is light adapted for 10 min. The third test is the light-adapted or photopic bright ERG to measure the cone response. Lastly, the fourth test is the photopic bright flicker ERG at 30 Hz. It is important that fixation is monitored during each test to ensure proper measurement and that artifacts from eye movement or blinking be removed from the data before averaging the results.

Two crucial components are necessary in obtaining an ERG: electrodes and a light stimulus.

For full-field ERGs, the standard light stimulus is the Ganzfeld stimulator, which is a spherical device with an opening for the patient's head to ensure even distribution of the light stimulus. The setup for an ERG includes a reference electrode that is placed on the skin in the middle of the forehead. Grounding electrodes for each eye are placed on the earlobes. Topical anesthetic is sometimes used to facilitate electrode insertion and minimize discomfort during the test.

Two different types of recording electrodes can be used. *Burian-Allen* electrodes, which consist of a contact lens with a conducting surface around the edge, provide the strongest signal. These electrodes reduce the amount of noise created by eye movements and blinking, but are not ideal for pattern ERGs or multifocal ERGs as they blur the patient's vision and require sensitivity to geographic distribution of the stimulus. The *Dawson-Trick-Litzkow* (DTL) electrode is a cheaper more comfortable alternative that consists of a fine, single-thread silver wire that spans the eye, and is placed on the surface of the cornea. As they are less irritating, DTL electrodes are better suited for long tests; however they promote greater eye movement and thus have a 20–30 % weaker signal compared to contact lens electrodes. The *Hawlina-Konec* electrode (HK) or metal loop electrode consists of a metal loop that is shaped to fit into the conjunctival fornix. The metal is coated with Teflon to increase comfort, but patches are not insulated to ensure recording sensitivity. HK electrodes are not as sensitive to eye movement compared to DTL electrodes, but they also produce a weaker response amplitude. The cotton wick electrode is another alternative that is applied onto the cornea. Because it is made of cotton, this eliminates recording artifacts from the photovoltaic effect, in which light striking metal generates a voltage potential. However, as they are more difficult to use, cotton wick electrodes are not widely utilized in clinical practice. Because the DTL, metal loop, and cotton wick electrodes do not interfere with central vision, they are ideal for use in full-field ERGs.

Particularly in infants and uncooperative children, sedation or anesthesia during testing may be used. However, anesthesia may depress ERG responses and it is potentially dangerous in children, particularly in those with systemic cardiovascular defects. This risk precludes its choice as a first-line approach in this population. Instead, the use of skin electrodes has been determined to be a safe method of performing ERGs in pediatric patients. The waveform morphologies of corneal and skin electrode responses are similar, although the average amplitudes measured by skin electrodes are 30 % lower compared to contact lens electrodes (Fig. 28.2). However, this is often sufficient to distinguish progressive from stationary disorders.

Stationary Rod Dysfunction

Conditions characterized by stationary rod dysfunction include congenital stationary night blindness (CSNB), which can be assessed using full-field ERG testing. CSNB is inherited and affects rod pathways, which are responsible for night vision. The pathophysiology involves a signaling deficit between rod cells and their postsynaptic bipolar cells, but variants affecting rod phototransduction exist as well. X-linked inheritance is most common followed by other

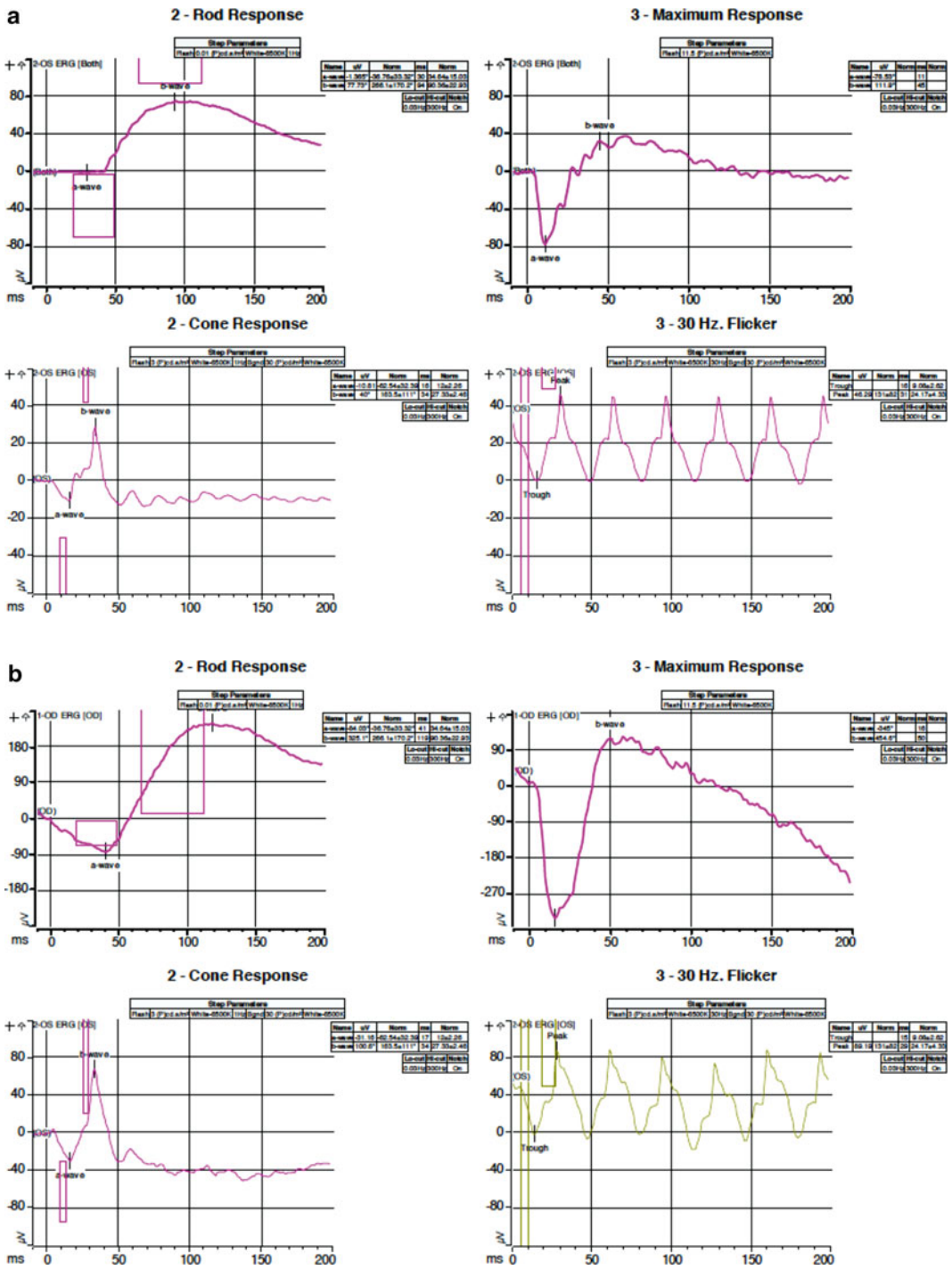

Fig. 28.2 Comparison of normal ERG tracings of child using (**a**) skin electrodes and (**b**) DTL electrodes

patterns including autosomal dominant and autosomal recessive. Patients who have X-linked or autosomal recessive CSNB often have reduced visual acuity and myopia, whereas those with autosomal dominant forms do not. Additionally the autosomal recessive and X-linked recessive forms present in infancy with nystagmus, strabismus, and reduced vision, while the autosomal dominant form presents with normal visual acuity in teenage years with symptomatic night blindness.

While the fundus exam is normal, CSNB causes variable ERG changes. Some patients show only rod-specific scotopic reduction, while others show a more classic electronegative b-wave on the maximum scotopic test. The transient photopic b-wave may also be delayed (Fig. 28.1).

Furthermore, patients with the negative ERG pattern can be divided into complete and incomplete types. Complete CSNB typically affects the ON-pathway; incomplete CSNB has dysfunction in both the ON- and OFF-pathways. Those

with complete types have poor rod function, whereas those with the incomplete type have some rod function but an elevated dark-adaptation threshold. Incomplete CSNB can demonstrate normal SD-OCT and fundus autofluorescence images, which can be distinguished from progressive entities such as retinitis pigmentosa that demonstrate a ring of increased autofluorescence around the macula on fundus autofluorescence and sometimes loss of the inner ellipsoid band on SD-OCT.

Stationary Cone Dysfunction

Patients with achromatopsia have an absence of color discrimination and may be referred to as "monochromats" because they see shades of gray. Patients may be classified into three separate groups: (1) typical rod monochromats (complete achromats) who lack all retinal sensitivity mediated by cone pigments; (2) atypical rod monochromats (incomplete achromats) who have some residual cone function and thus better visual acuity and color vision; and (3) S-cone monochromats who have rod and blue-cone function, along with the best visual acuity in this category of diseases. Rod monochromats have symptoms similar to those with progressive cone dystrophies such as photophobia, decreased visual acuity, and poor color perception. Despite a normal fundus appearance, they have characteristic full-field ERG findings including an extinguished cone function response, reduced maximum response, and relatively normal scotopic rod response (Fig. 28.1). In contrast, atypical achromatopsia is believed to originate in the post-bipolar cell transmission of color vision and patients can have photopic ERG responses. S-cone monochromatism is less severe and demonstrates X-linked recessive inheritance, whereas the other types of achromatopsia are autosomal recessive.

Findings in animal models and in human studies have suggested that achromatopsia may be a progressive degeneration; some studies in humans demonstrate that cone ERG function deteriorates over time. Fundus autofluorescence can be used to provide a modality to topographically visualize progression of disease. The foveal external limiting membrane is the first structure to develop hyper-reflectivity, which may be an early sign of cone degeneration in those who have an intact outer retina.

Progressive Rod Dysfunction

Leber Congenital Amaurosis and Retinitis Pigmentosa

Leber congenital amaurosis (LCA) is a group of early-onset progressive retinal dystrophies characterized by poor visual fixation in the first months of life, with a sensory nystagmus and amaurotic or sluggish pupils. Keratoconus may develop in some patients, possibly induced by eye-poking behavior (the oculodigital reflex). The appearance of the posterior segment is highly variable, ranging from mild pigmentary mottling, mild vascular attenuation, maculopathy, white dots in the periphery, or even a retinitis pigmentosa-like fundus. The most important diagnostic indication for this disease is a severely reduced or undetectable full-field ERG in the first year of life. Inheritance is generally autosomal recessive, although dominant forms exist as well.

Rod-cone degenerations such as retinitis pigmentosa (RP) are characterized by progressive photoreceptor loss with cone death secondary to rod death. Patients often have diminished or loss of night vision, followed by reduced daytime visual acuity and visual field defects. Cone loss generally begins in the periphery and progressively encroaches around the macula, with resultant tunnel vision. This visual constriction can be monitored with autofluorescent fundus imaging, and the degree of visual dysfunction can be assessed with the full-field ERG.

Phenotypically, patients with RP present with pigmentation of the peripheral retina, and patients with early-stage disease show reduced to severely decreased or even extinguished scotopic rod response corresponding to early loss of rods. The optic nerve becomes progressively pale and the retinal blood vessels become attenuated. As the disease progresses, the maximal ERG, 30-Hz flicker, and photopic responses also diminish as cone cells are lost (Fig. 28.1).

Progressive Cone Dysfunction

Cone dystrophies are progressive and symptoms include decreasing visual acuity and color vision, while peripheral fields typically remain normal. Late stages of the disease may show bull's eye maculopathy. They can be inherited in an autosomal dominant, autosomal recessive, or X-linked recessive pattern. Diagnostic findings on ERG can be an abnormal photopic response and a normal or near-normal rod-isolated response (Fig. 28.1).

Conclusion

Full-field ERGs are essential in the diagnoses of retinal dystrophies by providing an objective way to measure photoreceptor function in children. The diagnosis and its associated inheritance and progression patterns are especially valuable in determining the visual outcome of the pediatric patient. This information can then lead to genetic counseling that would be of great social and financial importance to the family. Earlier diagnosis would allow for prompt intervention by social agencies to provide educational and occupational services that would benefit the livelihoods of the child and family.

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Part VIII

Posterior Segment Disorders

Retinopathy of Prematurity

29

Michael B. Yang

Abstract

Retinopathy of prematurity (ROP) is a proliferative disorder involving the developing vasculature of premature infants that can result in retinal detachment and blindness. Timely screening for ROP and prompt treatment of severe ROP can decrease the prevalence of unfavorable retinal structural and poor visual outcome. The criteria for treatment of ROP has evolved from classic threshold ROP, as defined in the Multicenter Trial of Cryotherapy for ROP, to type 1 prethreshold ROP, as defined in the Early Treatment of ROP randomized trial, with incremental improvement in the overall treatment outcome. The mode of treatment has also transitioned from the use of cryotherapy to laser photocoagulation. The mouse model of oxygen-induced retinopathy has elucidated the pathogenesis of ROP and led to new interventions and screening approaches. Pharmacotherapy using the intravitreal injection of bevacizumab, an antibody to vascular endothelial growth factor, appears to be superior to laser photocoagulation for type 1 ROP in zone I but equivalent to laser therapy for type 1 ROP in zone II. However, the systemic risks associated with bevacizumab are uncertain. New screening algorithms based on the rate of postnatal growth of at risk infants are being developed in order to reduce the percentage of infants screened while maintaining efficacy. Digital fundus photography has a high degree of accuracy for the detection of treatment warranting ROP. Validation studies for the reliability and accuracy of telemedicine for ROP are under way.

Keywords

Retinopathy of prematurity • Screening • Laser • Cryotherapy • VEGF • Bevacizumab • Algorithms • Telemedicine

Abbreviations

AP-ROP	Aggressive posterior ROP
BEAT-ROP	Bevacizumab eliminates the angiogenic threat of ROP randomized trial
BW	Birth weight
CHOP	Children's Hospital of Philadelphia
CRYO-ROP	Multicenter trial of cryotherapy for ROP
EGA	Estimated gestational age
e-ROP	Telemedicine approaches to evaluating acute-phase ROP study

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ETROP	Early treatment for ROP randomized trial
G-ROP	Postnatal growth in ROP studies
ICROP	International classification of ROP
IGF-1	Insulin-like growth factor 1
IVB	Intravitreal injection of bevacizumab
PMA	Postmenstrual age
RM-ROP2	Risk models for ROP version 2
ROP	Retinopathy of prematurity
VEGF	Vascular endothelial growth factor
WINROP®	Weight insulin-like growth factor I, neonatal ROP algorithm

Background

Retinopathy of prematurity (ROP) is a proliferative disorder involving the retinal vasculature of premature infants that can result in retinal detachment and blindness. Retinal vessels develop from the optic nerve beginning at 14–15 weeks of gestation and proceed peripherally to fully vascularize the retina to the ora serrata nasally and temporally by 32 weeks and approximately 40 weeks postmenstrual age (PMA), respectively [1].

In the currently accepted model of ROP pathogenesis (Table 29.1), the vascularization of the retina is dependent upon both insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF) and may be divided into two phases [2, 3]. In phase I, premature birth disrupts the normal retinal vascularization process by depriving the premature infant of IGF-1, which is normally derived from the placenta and amniotic fluid in utero. VEGF, in the absence of IGF-1, is not sufficient to promote maximum retinal angiogenesis. In addition, VEGF expression is downregulated by the relatively higher oxygen environment outside the womb. Consequently, normal retinal vascularization during phase I is diminished.

Several weeks after birth, during phase II of ROP, the metabolic demand of the maturing retina increases. Relative hypoxia of the avascular retina develops and results in an up-regulation of VEGF. However, the higher levels of VEGF alone are not effective in promoting vascularization of the retina unless sufficient IGF-1 is also present. In the premature infant, low IGF-1 levels are associated with poor nutritional intake and poor weight gain [4]. As the infant gains weight postnatally over several weeks, IGF-1 levels also rise to a threshold level which then has a permissive effect on VEGF-stimulated retinal angiogenesis. If retinal vascular development up to this point has been sufficiently blunted by the previously low expression of VEGF and IGF-1, extraretinal neovascular proliferation may occur. This abnormal proliferative process may regress if retina vascularization continues such that hypoxia is diminished and VEGF expression reduced. But the persistence of hypoxia can result in continued fibrovascular proliferation and ultimately lead to a retinal detachment.

Table 29.1 Simplified model of the pathogenesis of retinopathy of prematurity

In utero (normal vessel growth)	Premature birth (vessel growth stops)	Maturing retina (becomes hypoxic)	Retinal neovascularization[a]
IGF-1 normal	↓ IGF-1	Slow ↑ IGF-1	↑ IGF-1 to "threshold"
VEGF normal	↓↓ VEGF	↑↑ VEGF	↑↑ VEGF

IGF-1 insulin-like growth factor 1, *VEGF* vascular endothelial growth factor (adapted from Hellstrom et al. 2001) [3]

[a]Subsequently, the retinal neovascularization either regresses with the normalization of vitreous levels of VEGF, or the proliferative process continues and can result in a retinal detachment.

Clinical Appearance and Classification of ROP

Timely screening for and prompt treatment of severe ROP can prevent the development of unfavorable retinal structural outcome and visual loss. The International Classification for ROP (ICROP), first developed in 1984 and revised in 2005 [5, 6], enabled clinicians and researchers to describe ROP using a common scheme, which also facilitated the conduct of clinical trials. ROP is classified on the basis of location (zones I–III), severity (stages 1–5), and the extent or number of clock hours of involvement. In general, the more posterior the location, the greater the extent of involvement, and the higher the stage, the more severe the ROP.

As shown in Fig. 29.1, the zones defined by ICROP are as follows:

- Zone I is a circle centered upon the optic nerve with a radius that is twice the disc to macula distance.
- Zone II is the region outside of zone I and inside a circle centered upon the optic nerve with a radius defined by the distance from the optic disc to the nasal ora serrata.
- Zone III is the remaining temporal crescent provided that the nasal retina is fully vascularized to the ora serrata for at least 2 clock hours.

The stages of ROP are defined as follows:

- Stage 0—immature vascularization
- Stage 1—demarcation line
- Stage 2—ridge (demarcation line with height and width)
- Stage 3—extraretinal fibrovascular proliferation
- Stage 4—partial retinal detachment
  - 4A—not macula involving
  - 4B—macula involving

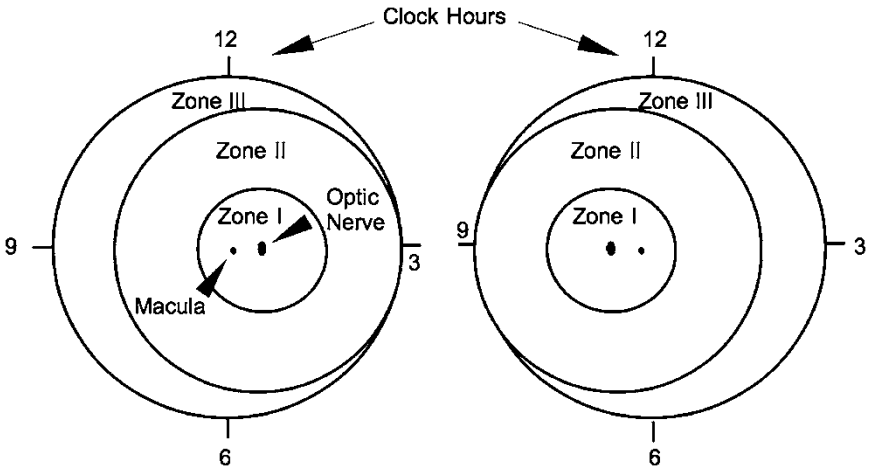

Fig. 29.1 Zones for the classification of retinopathy of prematurity. Adapted from the International Classification of Retinopathy of Prematurity [5, 6]

Table 29.2 Subgroups of severe retinopathy of prematurity

Category	Definition
Threshold ROP	≥5 contiguous or ≥8 cumulative clock hours of stage 3 in zone I or II with plus disease
Prethreshold ROP	Zone I stage 1, 2, or 3[a] with or without plus disease, zone II stage 2 with plus disease, or zone II stage 3[a] with or without plus disease
Type 1 prethreshold	Zone I stage 1, 2, or 3[a] with plus disease, zone I stage 3 without plus disease, or zone II stage 2 or 3[a] with plus disease
Type 2 prethreshold	Zone I stage 1 or 2 without plus disease or zone II stage 3 without plus disease

[a]The extent of stage 3 involvement in eyes with plus disease is less than for threshold ROP. Threshold and prethreshold ROP were defined in the Multicenter Trial of Cryotherapy for ROP; [8] type 1 and type 2 prethreshold ROP were defined in the Early Treatment for ROP randomized trial [9]. *ROP*, retinopathy of prematurity

- Stage 5—total retinal detachment, which is funnel shaped and described based on the anterior and posterior configurations as open-open, open-closed, closed-open, or closed-closed.

In addition, plus disease, which usually develops with stage 3 ROP but may occur with other stages of ROP, is defined as venous dilation and arteriolar tortuosity in the posterior pole. Currently, the diagnosis of plus disease requires at least two quadrants of vessel dilation and tortuosity consistent with a standard reference photograph [6]. However, there is a subjective element in the examiner's perception of vessel dilatation and tortuosity and, consequently, in the diagnosis of plus disease [7]. Care should be taken to differentiate plus disease from pre-plus disease in which the posterior vessel abnormalities are insufficient to warrant the diagnosis of plus disease [6].

Besides the standard zone-stage-plus disease combinations, subgroups of ROP have been defined in various clinical trials [6, 8, 9]. As shown in Table 29.2, these include classic threshold ROP and prethreshold ROP (types 1 and 2). In addition, aggressive posterior ROP (AP-ROP) describes a severe, rapidly progressing form of ROP that occurs mostly in zone I but may also appear in posterior zone II. It is characterized by a severity of plus disease out of proportion to the observed peripheral retinopathy. The typical progression from stage 1 to 3 ROP does not occur. Instead, a "deceptively featureless" flat neovascularization may occur at the junction of vascularized and nonvascularized retina, where a circumferential vessel often appears. If not treated promptly, AP-ROP usually progresses to a total retinal detachment [6].

ROP examination pearls are detailed in Appendix J.

Screening for ROP

The details of the currently recommended screening guidelines for ROP in the USA are provided in Appendix K [10]. Premature infants ≤1500 g birth weight (BW) or ≤30 weeks of estimated gestational age (EGA) are identified for screening. The recommended timing of initial screening for ROP and the subsequent intervals of screening are also described in Appendix K. Recent studies suggest, however, that postnatal weight gain, which is associated with postnatal IGF-1 levels, is an important predictor of infants developing severe ROP [2–4]. Different screening algorithms based on postnatal weight gain have been developed in an attempt to reduce the percentage of infants screened while maintaining efficacy. The Weight, Insulin-like growth factor I, Neonatal ROP algorithm (WINROP®), developed in Sweden and Boston, has a sensitivity of 98.6 % in detecting type 1 prethreshold ROP when assessed in a multicenter cohort of premature infants [11]. The Children's Hospital of Philadelphia (CHOP) ROP algorithm [12] is being evaluated in the postnatal growth in ROP studies (G-ROP) to determine if a sensitivity >99 % can be achieved for the detection of type 1 prethreshold ROP and whether the approach is cost effective.

Remote screening for ROP using wide-angle digital fundus photography, i.e., telemedicine, has a high degree of accuracy and already complements standard ROP examinations in many institutions [13]. The multicenter Telemedicine Approaches to Evaluating Acute Phase ROP study (e-ROP) will provide important data regarding the validity, reliability, feasibility, and cost-effectiveness of digital retinal imaging by comparing it with diagnostic examinations by ophthalmologists performed on the same eyes.

Major Clinical Trials

The CRYO-ROP Study

The Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP, 1986–1987) evaluated cryotherapy of the peripheral avascular retina for the treatment of classic threshold ROP as defined in Table 29.2 [8]. Cryotherapy, performed within 72 h of diagnosis, resulted in a 39.5 % reduction in the incidence of unfavorable retinal structural outcome at 3 months as compared with observation. During the 15 years of follow-up of the CRYO-ROP study, the beneficial effects of cryotherapy in reducing the proportion of eyes with unfavorable structural and visual outcome, as compared with observation, have remained consistent [14]. Subsequently, in the 1990s, cryotherapy was gradually replaced by laser therapy, which seemed to yield better structural and functional outcomes [15]. Ablation of the avascular retina has been found to reduce the expression of retinal VEGF mRNA, which has a critical role in the abnormal proliferative process in ROP [16].

The ETROP Study

The CRYO-ROP study showed that eyes with threshold disease in zone I had a particularly high rate of progressing to an unfavorable retinal structural outcome despite treatment (78 % for cryotherapy versus 94 % for observation) [8]. This led investigators to consider whether treatment at a lower severity of disease, namely prethreshold ROP (Table 29.2), prior to the onset of threshold ROP would improve outcome. In the Early Treatment for ROP (ETROP) randomized trial, a multiple logistic regression formula was used to categorize the prethreshold ROP eyes of infants enrolled in the ETROP study as either high or low risk [9, 17]. The formula, also known as risk models for ROP version 2 (RM-ROP2), was developed using information regarding untreated prethreshold ROP eyes from the CRYO-ROP study that developed an unfavorable retinal structural outcome at 3 months. It was comprised of prognostic variables that included "baby" characteristics, such as birth weight, gestational age, race, location of birth, and multiple birth status, as well as eye characteristics, such as the age at which the initial detection of ROP occurred or the interval of time between the onset of ROP and prethreshold ROP. Using this formula, high-risk prethreshold ROP eyes in ETROP were randomized to early treatment within 48 h of diagnosis or to conventional management in which treatment occurred only if the eyes progressed to classic threshold ROP [9]. By contrast, low-risk prethreshold ROP eyes were reexamined and reassessed for risk at the appropriate intervals and triaged accordingly. At 9 months after treatment, early treatment had reduced the proportion of eyes with unfavorable retinal structural outcome and with unfavorable visual acuity from 15.6 % to 9.1 % and from 19.5 % to 14.5 %, respectively, as compared with conventional management [9].

While the results for the early treatment of high-risk prethreshold ROP eyes were compelling, the ETROP investigators also performed a post hoc analysis in which they evaluated the eye outcome of early treatment versus conventional management for various zone-stage-plus disease combinations of high-risk prethreshold ROP. Based on these results, they recommended the early treatment of those zone-stage-plus disease combinations defined as type 1 prethreshold ROP and conventional management of those combinations defined as type 2 prethreshold ROP (Table 29.2) [9]. It should be emphasized that the ETROP was not designed to evaluate the benefits of early treatment versus conventional management of type 1 or type 2 prethreshold ROP but rather of high-risk prethreshold ROP as calculated by RM-ROP2. Even though the early treatment of type 1 prethreshold ROP may have become the de facto standard of care, there has been controversy with some clinicians advocating early treatment for only zone I type 1 prethreshold ROP [18–21]. To their credit, the ETROP authors acknowledged that the type 1 versus type 2 prethreshold ROP distinction was in part for the benefit of those clinicians who did not wish to use the RM-ROP2 formula to determine if a prethreshold ROP eye was at high risk. Moreover, rather than mandating treatment at the onset of type 1 prethreshold ROP, they saw the development of type 1 prethreshold ROP as opening a time window of opportunity until the onset of threshold ROP, during which early treatment should be seriously considered [21].

The BEAT-ROP Study

The mouse model for the pathogenesis of ROP had suggested that the injection of anti-VEGF antibodies into the vitreous could be used to reverse the manifestations of oxygen-induced retinopathy [22]. The Bevacizumab Eliminates the Angiogenic Threat of ROP (BEAT-ROP) randomized trial compared the intravitreal injection of 0.625 mg

bevacizumab (IVB) with laser treatment for type 1 prethreshold ROP [23]. With respect to the proportion of eyes that developed a recurrence of neovascularization by 54-week PMA, IVB was superior to laser for the treatment of type 1 prethreshold ROP in zone I (6 % vs. 42 %, $p=0.003$) but not different from laser for the treatment of type 1 prethreshold ROP in zone II (5 % vs. 12 %, $p=0.27$). In addition, IVB-treated eyes showed progressive vascularization of the immature retina beyond the original vascular-avascular junction at the time of therapy, an area that would otherwise have been destroyed by laser photocoagulation. Since recurrence of neovascularization generally occurred later in eyes receiving IVB as compared with laser treatment (16.0 ± 4.6 vs. 6.2 ± 5.7 weeks), infants treated with IVB should be monitored for a longer period of time than those receiving laser therapy. However, there is currently no consensus on the intervals and duration of posttreatment follow-up examinations or on the use of laser as an adjunctive treatment in eyes previously treated with IVB, which have had regression of neovascularization, but nevertheless still possess persistent avascular areas in the peripheral retina.

With respect to safety, BEAT-ROP was not sufficiently powered to evaluate the risk of mortality [23]. Thus, it was not possible to determine if the number of infant deaths in the group receiving IVB was significantly higher than the group receiving laser therapy (5 vs. 2). However, in animal and human studies, bevacizumab appears to escape from the eye as indicated by either an elevation in the serum concentration of bevacizumab or a reduction in the level of VEGF in the peripheral circulation after IVB [24, 25]. These findings are concerning as VEGF is important in the development of the brain, lungs, kidney, and bones. Since the current dose of IVB is theoretically capable of neutralizing all VEGF in the vitreous in excess of 5000-fold [24], it may be possible to reduce the dose of IVB without loss efficacy for the treatment of type 1 prethreshold ROP while lowering the infant's systemic exposure to the drug. A forthcoming Phase 1 trial by the Pediatric Eye Disease Investigator Group is designed to answer this question.

Case Studies

Case Study 1

The RetCam® (Clarity Medical Systems, Pleasanton, CA) fundus photographs in Fig. 29.2 are from a Caucasian male premature infant, who was born at 24-week EGA with 650 g BW. The infant was screened initially at 32-week PMA and found to have immature vascularization (stage 0) in zone I of both eyes. By 35-week PMA, the patient had developed plus disease and significant arteriovenous shunting. Flat neovascularization with hemorrhage as well as circumferential vessels along the border of the vascular-avascular junction were present in both eyes. The findings fulfilled the definition of either type 1 zone I ROP or AP-ROP. Both eyes were treated with laser photocoagulation within 24 h. In the ensuing weeks, the plus disease and flat neovascularization completely regressed leaving a favorable retinal structural outcome.

Key Points

- It may be debated whether plus or pre-plus disease is present in Fig. 29.2. Excessive pressure on the eye during RetCam® photography can compress retinal vessels and thus damp or mask the presence of extraretinal neovascularization or plus disease [26].
- Even though the ETROP study allowed for treatment within 48 h of diagnosis, consideration should be given to treating zone I disease, especially AP-ROP within 24 h.
- After treatment, one should see, at the very least, *no progression* at the 1-week posttreatment examination and significant regression of plus disease and neovascularization by week 2. If the treated ROP appears to be worsening and no untreated areas of avascular retina are available for supplemental laser treatment, consideration should be given to intravitreal bevacizumab as adjunctive therapy.
- Based on the results of BEAT-ROP, this patient would have been a candidate for treatment with bevacizumab [23]. The potential systemic risks associated with IVB, the need for longer follow-up examinations due to late recurrence of neovascularization, and the potential need for subsequent laser therapy should be explained to the parents as part of the consent process.
- After IVB, one should expect a dramatic improvement in the plus disease as early as 1–2 days with significant regression of extraretinal neovascularization within a few days to 1 week.

(continued)

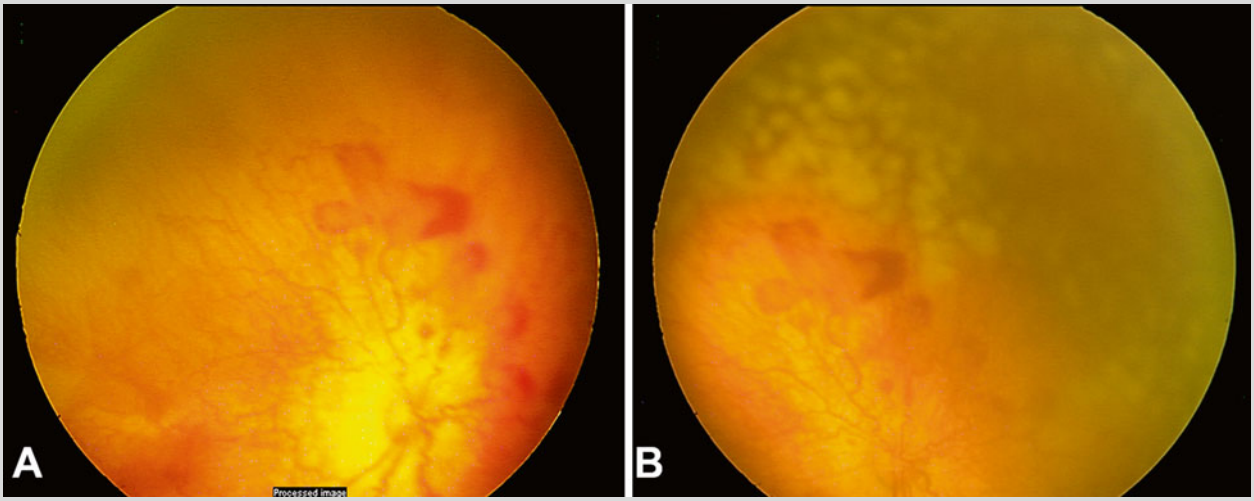

Fig. 29.2 Right eye of an infant with aggressive posterior ROP in zone I immediately (**a**) before and (**b**) after laser treatment

Case Study 2

The fundus photograph in Fig. 29.3 was from an African-American female premature infant who was of twin birth and born at 26-week EGA with 690 g BW. At 37-week PMA, both eyes developed stage 3 ROP in mid-zone II but without plus disease. By 39-week PMA, the stage 3 ROP in both eyes had progressed to involve all 12 clock hours (360°) of retina but still without plus disease. This was an unusual case because based on the revised ICROP guidelines, the patient did not have type 1 prethreshold ROP at this point. No treatment was offered until 40-week PMA when plus disease developed, which converted the eye status simultaneously to type 1 prethreshold ROP as well as classic threshold ROP. Laser photocoagulation was performed in both eyes with subsequent complete regression of disease.

Key Point

- Again, it may be argued that this patient has pre-plus, instead of plus, disease. However, given the presence of 12 clock hours of stage 3 neovascularization, this patient would likely have progressed to unequivocal plus disease soon afterward. Then the large extent of stage 3 present would have increased the risk for unfavorable outcome after treatment, though the patient's black race may somewhat lessen that risk [8].

Additional ROP examination and treatment pearls are given in Appendix J.

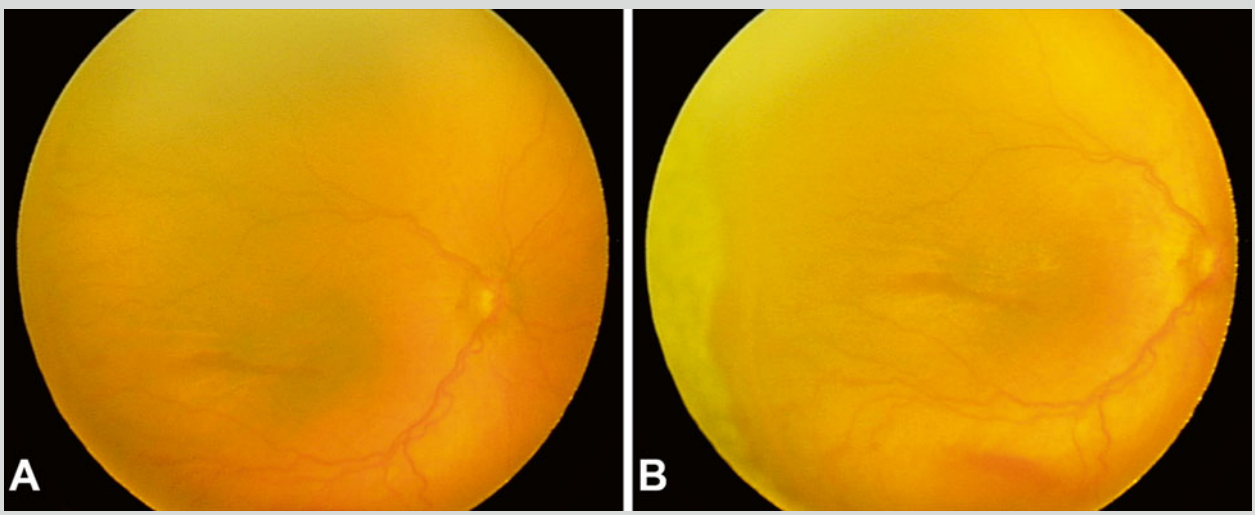

Fig. 29.3 Right of a patient with 360° of stage 3 neovascularization with plus, or possibly pre-plus, disease immediately (**a**) before and (**b**) after laser treatment

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Management of Pediatric Posterior Segment Trauma in Children

30

Nathanial Clarks Sears and Jonathan Eliot Sears

Abstract

Posterior segment trauma in children has particular clinical features and carries unique implications unlike those in adults. The critical history associated with the injury may be difficult to obtain, and the examination of the patient is almost always challenging. In addition, the response of the eye to injury and the visual outcome differ from older patients because of the adherence of the posterior hyaloid and the risk of amblyopia. A basic understanding of these challenges can improve the outcome of intervention.

Keywords

Trauma • Children • Pediatrics • Retina • Posterior segment • Intraocular foreign body • Vitrectomy • Cyclodialysis cleft

Ocular Trauma in Children

Ocular trauma is a leading cause of monocular blindness in children. After strabismus, trauma is the leading diagnosis for ophthalmological intervention and approaches 15 % of all eye procedures in children [1, 2]. Ocular Trauma Scores (OTS) were originally developed in the 1990s as a tool to predict outcomes and involved type of injury, presenting acuity, presence of relative afferent pupillary defect (RAPD), and zone of injury [3]. An attempt to modify the original classification for adults to one that can be used in children takes into account the difficulty in obtaining accurate vision and RAPD testing in young patients, by decreasing the importance of visual acuity measurements and the inclusion of additional findings such as age of the patient and time to surgery (Table 30.1) [4]. Zone I includes the cornea and limbus, zone II is 5 mm posterior to the limbus, and zone III, which includes the macula and optic nerve, is posterior to zone II. Despite minor controversy between these trauma scales, both concur that involvement of the posterior segment (zone III) portends grave consequences to a child's vision. The authors then used the formula $\{2\times(\text{age}+\text{zone})-\text{corresponding pathologies}\}$ to generate a raw score; the higher the score the better the prognosis. In this small study, a score above 45 predicted some visual function of 0.1–0.5 log scale.

Posterior segment trauma in children can be roughly divided into four groups: blunt trauma, penetrating and perforating trauma, intraocular foreign body (IOFB), and non-accidental trauma. Blunt trauma often has manifestations that affect the anterior segment, such as iridodialysis and cyclodialysis. The latter is important to recognize as chronic cyclodialysis clefts often lead to hypotonous optic neuropathy and macular edema and can be difficult to discern in a patient who is uncooperative for gonioscopy. In addition, blunt trauma can create any of five types of retinal breaks that include retinal dialysis in most commonly the inferotemporal or superonasal quadrant, horseshoe tear, operculated tear, giant retinal tear, or macular hole. Because most of the energy associated with blunt injury is distributed within the eye, the retinal tissues are especially

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Table 30.1 The pediatric ocular trauma score [4]

Variables	Raw points
Initial visual acuity (LogMAR)	
NLP	10
LP	20
Counting fingers	30
0.1–0.5	40
0.6–1.0	50
Age of the pediatric patient	
0–5	10
6–10	15
11–15	25
Wound location	
Zone 1	25
Zone II	15
Zone III	10
Concomitant eye pathology	
Iris prolapse	−5
Hyphema	−5
Organic/unclean injury	−5
Delay of surgery (>48 h)	−5
Traumatic cataract	−10
Vitreous hemorrhage	−20
Retinal detachment	−20
Endophthalmitis	−30

at risk for macular commotio retinae and sclopetaria [5]. Children especially should be examined for traumatic superonasal dialysis.

Penetrating and perforating injuries are not uncommon in children and are often accidentally self-inflicted as in the case of scissors, screwdrivers, or knives. The most important feature of these injuries is the associated risk of endophthalmitis, which must be considered if the entry site is posterior to the limbus. Primary wound closure and subsequent referral to pediatric retinal physicians should be prompt but intraocular injection of antibiotics (vancomycin 1.0 mg/0.1 ml, inject 1 mg; and ceftazidime 2.0 mg/0.1 ml, inject 2.0 mg) may be administered through the pars plana. The vitreous cavity can be safely accessed 3–4 mm posterior to the limbus in any child except those with congenital disorders such as PFV where often pars plana is attenuated or nonexistent. In the setting of primary closure and referral, the timing of referral is critical. As a general rule, the timing of posterior segment repair has two conflicting tensions, such that increased time from injury to repair increases the ease of which the posterior hyaloid could be separated from the retina. However, a delayed surgical intervention must be counterbalanced by the success of visual rehabilitation [6]. In general the rapid cicatricial response of the pediatric eye transforms what initially may be a repairable retinal detachment to a nonrepairable one in a very short time period. Therefore immediate referral for retinal evaluation is always advised.

The removal of an intraocular foreign body can be the most challenging and simultaneously gratifying surgical intervention. Careful attention to history details, preoperative CT scan, and judicious timing of surgery are critical for the best possible outcome, which is obviously dependent on the path of the projectile and the extent of the induced damage. Equally important is the history of the IOFB in regard to the possibility of it being sterile (as in the case of high-speed metal) or non-sterile, such as the tip of a carbon pencil or vegetable matter.

Metallosis bulbi occurs through damage to intraocular tissue through toxic effects of retained metal IOFB. The mechanism of damage is through electrolytic disassociation of solid metal that leads to chemical reaction of the metal ions with surrounding tissues. The oxidation that ensues releases autolytic enzymes from lysosmal compartments. IOFBs that are less than 85 % copper cause chalcosis. If the IOFB is greater than 85 % copper then an acute sterile endophthalmitis ensues, which is different than chalcosis. In fact, most metallosis (except IOFBs that are >85 % copper) develops slowly over months to years. Therefore, prevention of metallosis does affect the acute surgical management. Siderosis can cause a diffuse brown haze to the cornea late, heterochromia, brownish discoloration of the lens, RPE degeneration, and a supranormal b-wave followed by 100 % loss of all amplitudes. Chalcosis creates a Kayser-Fleischer ring, green iris heterochromia, sunflower cataract, and refractile properties within the macula. The ERG can be extinguished with prolonged chalcosis.

Between 5 and 30 % of patients are reported to develop endophthalmitis or retinal detachment associated with IOFB [7]. Traditionally, the extraction of an IOFB has been declared an emergent procedure but recent data derived from the military conflict in Iraq showed no difference in occurrence of endophthalmitis when surgical removal of the IOFB was delayed [8]. However, there are important considerations in regard to this data. First, 96 % of injured individuals with delayed surgery received either immediate intravitreal or intravenous antibiotics. Second, the majority of the IOFBs in the Iraq study were high-speed metallic projectiles and might be considered sterile. Therefore, in the setting of a child, who might need sedation or even intubation for appropriate imaging, it makes sense to follow evaluation with intervention to limit repeated anesthesia, and if the removal of the IOFB is delayed, administration of intravitreal antibacterial agents as described above is preferable, along with antifungal agents such as amphotericin B (1–10 μg per 0.1 ml, inject 0.1 ml or voriconazole, 5 μg per 0.1 ml, inject 0.1 ml) if vegetable matter is suspected. IOFBs that are small and track through the lens outside the visual axis may not

always create a visually significant cataract in children [9]. Often, a small lens disruption can be observed until a planned lens extraction with intraocular lens placement can be performed at a later date, as opposed to a possibly unnecessary surgery in the toddler in whom unilateral aphakia might induce amblyopia.

Finally, non-accidental trauma or shaken baby syndrome (SBS) can create significant challenges for an ophthalmologist. Not all retinal hemorrhages are of traumatic origin in infants, and can be the result of subdural hemorrhage and Terson's syndrome or infectious etiologies or blood dyscrasias with leukostasis [10]. However, the presence of premacular hemorrhage in the setting of trauma should alert the physician to consider non-accidental injury and trigger the appropriate investigation. Multilayered retinal hemorrhages are found in 85 % of children with SBS; some believe that the presence of macular schisis is consistent with SBS. Preretinal and nerve fiber layer hemorrhage that is bilateral and accompanied by seizures or evidence of injuries to other organs, bones, or parts of the body are more likely to be non-accidental in nature. SBS is often defined as the triad of subdural and retinal hemorrhages with acute encephalopathy [11]. The mechanism of injury is hypothesized to result from shearing damage to the cerebral bridging veins at the sites of their attachments to the walls of the sagittal sinuses.

The approach to a discussion of this with the family should always involve the hospital protective services and pediatricians. Such discussions should aim to provide reassurance that parents who love their children cooperate willingly with authorities who are prepared to protect their children to uncover the mechanism of injury. The ophthalmologist is not present to decide on the origin of the trauma, but merely to document the findings immediately. The hemorrhages can clear within weeks. It is rare that eye findings are the only manifestation in cases of abusive head trauma.

Case 1

A 9-year-old male was looking down the barrel of a paint ball gun when the gun discharged. Visual acuity at presentation was Hand Motion at 1 ft. Intraocular pressure was 21 mmHg. External and slit lamp exam revealed periorbital ecchymoses and 360° of subconconjunctival hemorrhage. The cornea was intact with punctate endothelial trauma manifested by stromal edema with a ground glass appearance. The pupil was dilated and immobile, and the lens out of the visual axis. View of the posterior segment was obstructed by dense vitreous hemorrhage. Surgical exploration revealed no scleral rupture; subsequent vitrectomy/lensectomy demonstrated extramacular commotio retinae that resulted in superior retinal/RPE scar. One month postoperatively, intraocular pressure was 1 mmHg. Ultrasound biomicroscopy revealed a cyclodialysis cleft between 4:30 and 6:30 (Fig. 30.1). The cleft was closed using 3 radial 9-0 prolene sutures. Two weeks later the pressure was 18 mmHg; 1 year later visual acuity with contact lens was 20/30 and eye pressure stable at 16 mmHg.

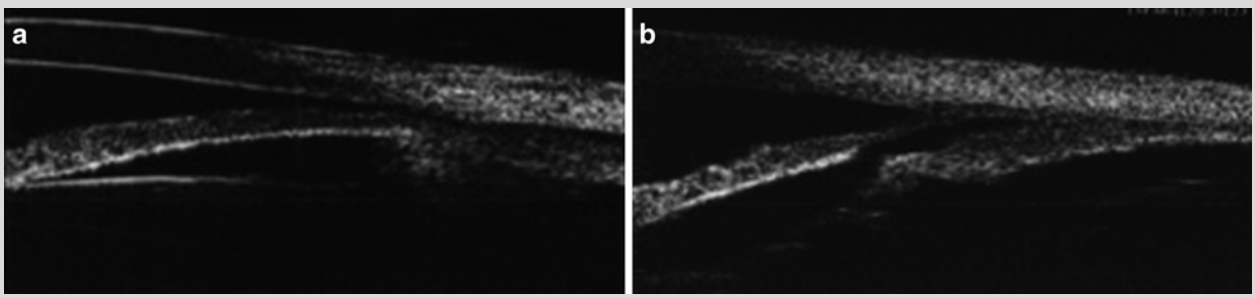

Fig. 30.1 Ultrasound biomicroscopy shows the presence of a cyclodialysis cleft (*white arrows*) prior to (**a**) and after closure with an external radial suture (**b**)

Case 2

A 6-year-old female was helping her father repair a screen door when she fell on a 6 in. flat screwdriver that perforated the globe 1 mm posterior to the surgical limbus at 12:00 exiting the globe at the superior equator. At presentation her vision was HM with an intraocular pressure of 8 mmHg. Initial repair included closure of the entry site and placement of a scleral buckle by the referring doctor. One month post-injury she was diagnosed with severe phacodonesis, retinal incarceration, and retinal detachment. Pars plana lensectomy, vitrectomy, retinectomy, endolaser, silicone oil placement, and removal of silicone oil 3 months later were performed to treat retinal detachment associated with PVR C3,4 (proliferative vitreoretinopathy in both the subretinal space [C3] and anterior contraction of the hyaloid and retina to the vitreous base [C4]). Two years later, visual acuity with contact lens wear and amblyopia management was 20/200 (Fig. 30.2).

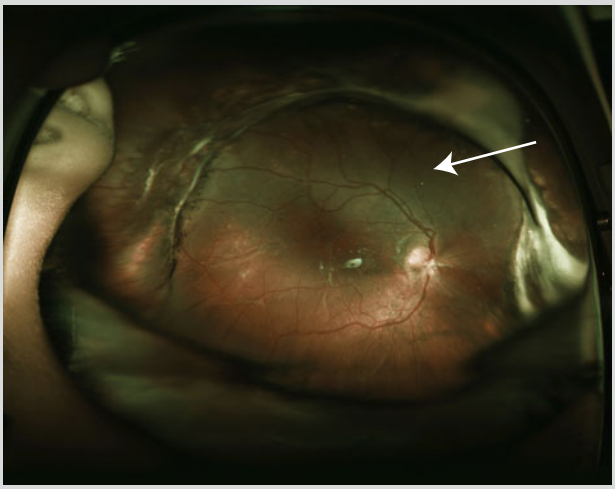

Fig. 30.2 Fundus photograph of retina after scleral buckle, pars plana vitrectomy, and lensectomy with silicone oil tamponade. The mechanism of injury was a screwdriver that perforated the globe at the limbus and exited through the superonasal equator. A retinectomy relieved retinal incarceration (*arrow*)

Case 3

A 15-month-old infant was sitting on a porch as her father mowed the lawn with a rotary mower. Immediately after he inadvertently ran over a braided wire dog leash, she began to cry, rubbing her left eye. She was brought to the emergency department at a remote hospital where she was diagnosed with a corneal abrasion and prescribed topical ciprofloxacin for 3 days. Three weeks later the mother noted that the left pupil was slightly dilated and her blue iris darker than the companion eye. Upon referral visual acuity was fix and follow both eyes with equal pressure of 12 mmHg. Anterior segment exam revealed a small black scleral spot anterior to the inferior rectus insertion (Fig. 30.3a). Dilated fundus exam revealed an intraocular wire (Fig. 30.3b) left eye. Pars plana vitrectomy and removal of intraocular wire (Fig. 30.3c) were completed the day of referral with thermal treatment around the retinal/choroidal wound nasally. Three years later, visual acuity was 20/50 by Teller card with a refraction of +1.50 sph RE and −0.50 sph LE, pressure normal, and retina attached. Glasses were prescribed.

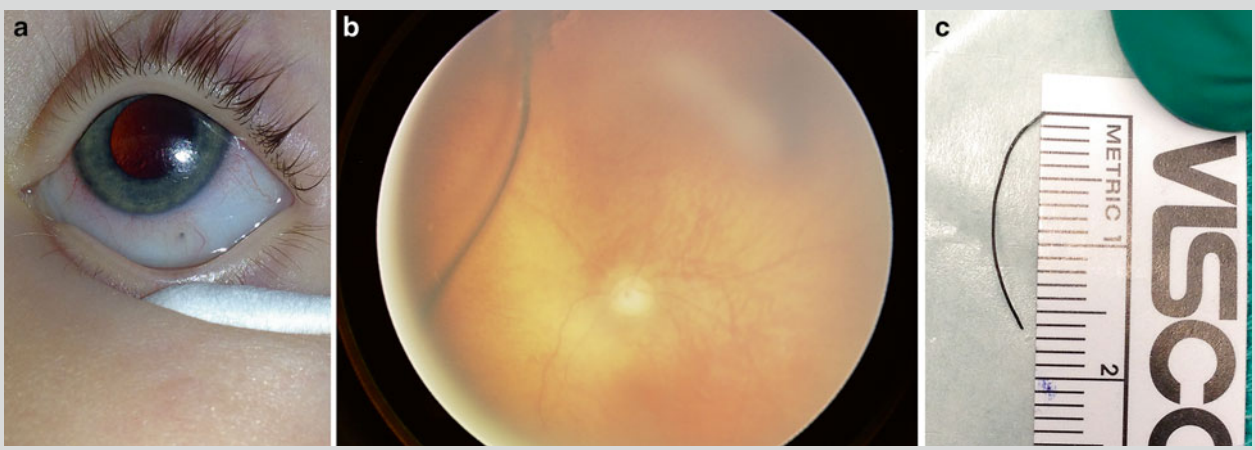

Fig. 30.3 External photo (**a**) of an occult intraocular wire diagnosed upon referral 3 weeks after injury. The wire (**b**) is seen emanating from the inferior pars plana to the nasal retina and is under tension. The fovea is below the disc in this frame. Picture of the wire (**c**) after removal

Case 4

A 6-month-old infant was admitted to the emergency room with a diagnosis of seizures. The mother reported that the father called her at work concerned that the baby was not accepting a bottle feed. She immediately returned home and transported the child with the father to the emergency department, where the patient was immediately sedated with intravenous benzodiazepine and admitted to the NICU. The child had a history of severe upper respiratory tract infection 1 week earlier with concern for RSV. There were no rashes, petechiae, or bruises. MRI under sedation revealed diffuse intracerebral hemorrhage. Ocular examination revealed a sedated and intubated infant with normal anterior segment exam. Dilated fundus exam revealed bilateral diffuse intraretinal hemorrhages extending from the macula to the ora serrata, Roth spots, and premacular subhyaloid hemorrhage (Fig. 30.4). While a complete infectious work-up was pending, the fundus findings were consistent with non-accidental trauma. The father admitted to shaking the baby after the results of the dilated exam were communicated to a detective. Two weeks later, follow-up MRI demonstrated cerebral liquefaction and the dilated eye exam showed clearing of retinal heme. Fluorescein angiography 1 month later showed peripheral nonperfusion. Laser indirect ophthalmoscopy was applied to ischemic retina to prevent vasoproliferative traction retinal detachment and exudation.

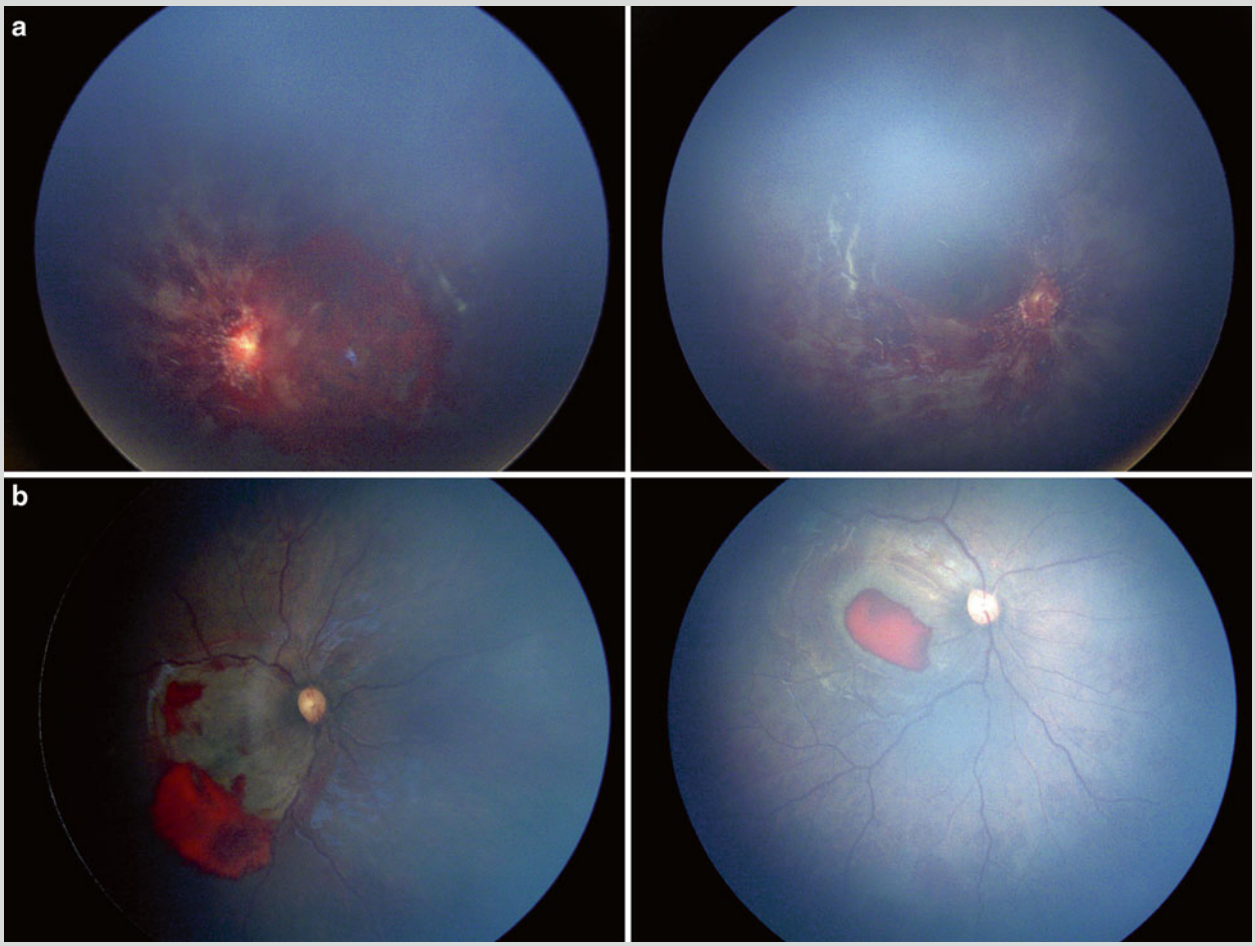

Fig. 30.4 Fundus photographs 1 day after hospital admission for seizures (**a** and **b**). Note the preretinal subhyaloid hemorrhage in the macula, and presence of intraretinal nerve fiber layer heme in 4/4 quadrants with Roth spots. Follow-up fundus photos 2 weeks later show boat-shaped heme in the macula and clearing of intraretinal heme (**c** and **d**). Fluorescein angiogram 1 month later revealed peripheral ischemia that required laser ablation to prevent traction retinal detachment secondary to neovascularization

(continued)

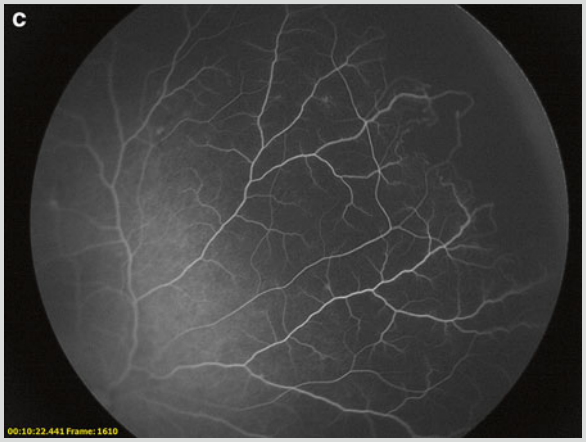

Fig. 30.4 (continued)

Summary

Diagnosis and management of posterior segment trauma in children require adequate evaluation. This may require exam under anesthesia to make certain that globe penetration and perforation, or occult intraocular foreign body, are not present. Lens trauma does not always require prompt lensectomy. Close coordination of surgical intervention with pediatric ophthalmology to lessen the risk of amblyopia is critical. Protective glasses are mandatory at all times. Any premacular hemorrhage, even if unilateral, in the setting of trauma, warrants consideration of non-accidental trauma. Follow-up wide-field angiography is vital to determine the need for laser therapy to prevent retinal detachment from neovascularization and subsequent ROP like traction and exudation within 1–3 months of non-accidental trauma.

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Non-accidental Trauma: Abusive Head Trauma

31

Sonia B. Dhoot, Jennifer B. Pierce, Mary E. Moffatt, and Michelle M. Ariss

Abstract

Abusive head trauma, sometimes referred to as "shaken baby syndrome," is a potentially lethal event that is difficult to diagnose and to manage. The victim is a baby or a very young child usually referred to the pediatric ophthalmologist to look for ocular evidence of abuse in the form of retinal hemorrhages and to appropriately document these findings. Less commonly, and if retinal hemorrhages are discovered on fundus examination of any child, it is always important to maintain a high index of suspicion for possible non-accidental trauma as the etiology for the findings.

Keywords

Child physical abuse • Abusive head trauma • Retinal hemorrhages

The Problem

Child abuse is a prevalent problem in society today. The National Child Abuse and Neglect Data System (NCANDS) reported that referrals to Child Protective Services (CPS) in the United States in 2012 were 6.3 million children, of whom about 700,000 cases were determined to be substantiated by CPS investigation and 1640 died from child maltreatment [1]. Annual rates probably underestimate the cumulative number of children who are confirmed to be maltreated, with a cumulative prevalence of one in eight American children by 18 years of age [2].

Child maltreatment encompasses a broad range of offenses, including all forms of neglect, physical injury, sexual abuse, emotional mistreatment, and death. *Abusive head trauma* occurs when shaking, mechanical blunt trauma, or both types of injury are inflicted upon a child's head by a caregiver. "Shaken baby syndrome" refers to a subset of children with abusive head trauma who have injuries characterized by repetitive acceleration-deceleration forces upon a baby's head resulting in a unique complex of ophthalmologic and intracranial findings. The broader classification, abusive head trauma, encompasses all types of abusive injury to the child's head and is preferred over specific, mechanistic-based terms [3]. Abusive head trauma is the leading cause of traumatic death in infants and is associated with severe irreversible brain injury and overall poor prognoses in survivors [4–6].

Diagnosis

Considerable challenges can complicate the evaluation and diagnosis of children with abusive head injury, and a multidisciplinary team is needed to make an accurate diagnosis [7]. The perpetrators are unlikely to give an accurate injury

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history; therefore, it takes a high index of suspicion to initiate the evaluation of non-accidental trauma.

The most common finding in abusive head trauma is subdural hemorrhage, occurring in 90–95 % of fatal injuries. Retinal hemorrhages are present in 85–100 % of fatal cases [8–14]. Subdural bleeding is thought to result from displacement of the brain relative to the dura, causing tears in bridging veins that course from the surface of the brain to the dura mater. This requires substantial force and rarely results from accidental trauma [6, 15–17]. Subarachnoid hemorrhage, axonal injury, and hypoxic ischemic brain injury are frequently seen as well [9]. Children present clinically with symptoms of irritability, vomiting, seizures, apnea, altered mental status, or for care of other inflicted injuries, such as bruises, fractures, or abdominal injuries [18–21].

Abusive injuries occur in all age groups, but most commonly occur in patients less than 3 years old, with the majority presenting between birth and 1 year of age [1, 22, 23]. A diagnosis of abusive head trauma should be considered in situations in which inconsistent stories are told by different family members, when the history does not adequately explain the type or severity of injury (e.g., when a simple short-distance fall is given as the explanation for a child who is critically ill or deceased) or when the mechanism of injury is inconsistent with the child's developmental abilities (e.g., a 1-month-old child who allegedly rolled off a bed) [24]. Once the suspicion has been raised, the physician is mandated by law to report the concern to child protective services, law enforcement, or another designated governmental agency for further investigation.

While only an estimated 4–6 % of non-accidental trauma cases present initially to an ophthalmologist, a complete ophthalmologic exam helps in the diagnosis of many more cases [25]. Often children are asymptomatic from an ophthalmological perspective, unless both eyes have significant visual compromise. Ophthalmologic consultation is indicated for all children ages 0–5 years who are victims of traumatic brain injury or have unexplained altered mental status to perform indirect ophthalmoscopy through a pharmacologically dilated pupil [25]. Ophthalmology consultation is preferably performed within the first 24 h of presentation [10]. Forensically, significant retinal hemorrhages are unlikely to be found in the absence of traumatic brain injury on diagnostic neuroimaging [26]. Monitoring for acute changes in the child's neurological status does not preclude examination. Short-acting mydriatics may be used for the initial exam, and in cases of severe neurologic impairment in which the pupillary examination is critical, the examination can be performed on each eye individually. The ophthalmologist is crucial in assisting in the diagnosis as abusive injuries create retinal hemorrhages in the same distribution and extent as those caused by acceleration-deceleration injuries. On dilated fundus exam, hemorrhages are observed in the preretinal or subhyaloid (scaphoid or boat shaped), nerve fiber layer (flame or splinter shaped), deep layers (dot and blot), or subretinal layers. The hemorrhages tend to be distributed in the posterior pole and macula, but are often so extensive that the entire fundus, including the peripheral retina to the ora serrata, is involved. Intraretinal hemorrhages with white centers are frequently seen and considered nonspecific as they are often seen in other medical conditions such as endocarditis. When documenting the exam in these patients, it is crucial to include the number, depth, and location of hemorrhages. Key descriptions such as "hemorrhages too numerous to count," "macular schisis cavities," and "extending to the ora serrata" are highly sensitive for retinopathy secondary to a shaking mechanism (Fig. 31.1). Peripheral retinal hemorrhages are considered a more sensitive finding for acceleration-deceleration injury as seen in abusive head trauma [27]. Retinal photography is not required, but is strongly encouraged to most accurately document findings. If photography is not possible, manual drawings with detailed descriptions are appropriate [28].

The traumatic retinoschisis that occurs may involve either the nerve fiber layer or deeper retinal layers. Hemorrhagic macular schisis cavities are very sensitive signs of abusive head trauma and result from repeated acceleration-deceleration forces causing vitreoretinal traction; they are almost exclusively associated with abusive head trauma [10, 28]. They can be distinguished from subhyaloid hemorrhage by the finding of an associated hypopigmented or hemorrhagic circumlinear line representing the edge of the schisis cavity. Rhegmatogenous retinal detachments or traumatic retinal breaks are rare, but vitrectomy is often needed for persistent, non-clearing vitreous hemorrhage. Permanent vision loss typically is secondary to traumatic retinoschisis, traumatic optic neuropathy, or cortical visual impairment and occurs in approximately 20 % of patients with eye involvement [13]. Vitreous hemorrhage that is more dense or traumatic retinoschisis present in deeper retinal layers (instead of in the nerve fiber layer) is associated with worse visual outcomes [13].

For children previously in good health and who die without explanation and for children who die from abusive injury, post-mortem examination of the eyes and orbital tissues dissected en bloc by an ocular pathologist should be performed to determine if retinal hemorrhages and/or retinoschisis are present. The presence of hemosiderin within orbital fat, muscles, or cranial nerve sheaths indicates previous hemorrhage into these structures and may be of diagnostic use [25, 26].

In addition to retinal hemorrhages, blunt force to the child's face or eyes can cause external and anterior segment findings including periorbital ecchymoses, orbital fractures, globe rupture, subconjunctival hemorrhages and/or chemosis, and hyphema [29]. The presence of subconjunctival hemorrhage or other signs of eye injury in infants and young children who

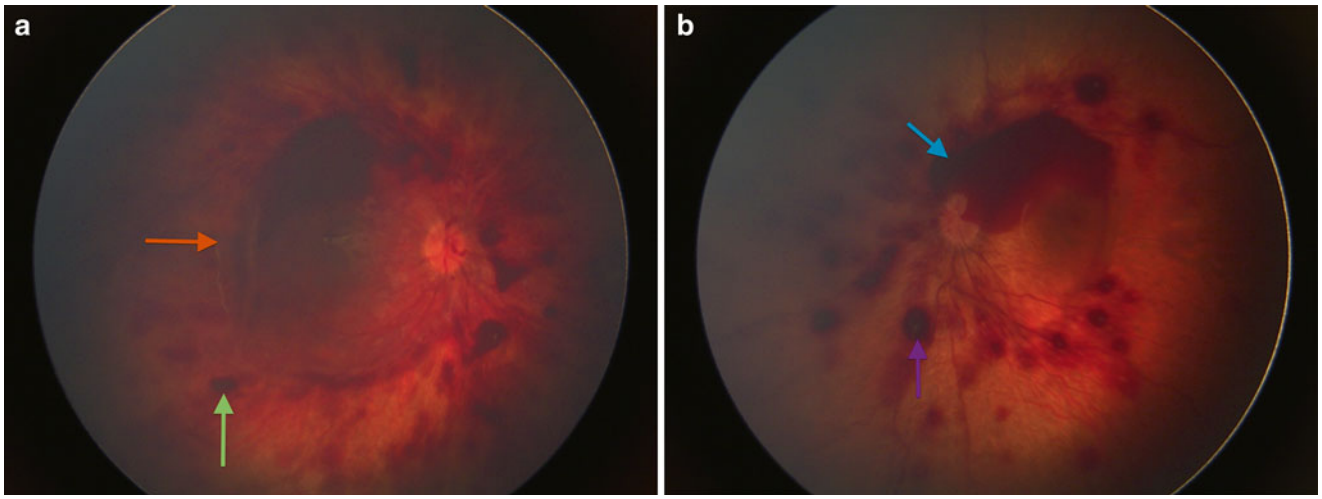

Fig 31.1 (**a**) Color fundus photograph of the right eye. The optic nerve appears normal, with good color and no edema. There is preretinal hemorrhage extending from the superior arcade down into the inferior arcade and involving the macula. A schisis cavity can be seen involving the superotemporal macula with a retinal fold at the temporal edge of the schisis (*orange arrow*). There are also multiple intraretinal dot-blot hemorrhages (*green arrow*) throughout the posterior pole and midperiphery, too numerous to count. (**b**) Color fundus photograph of the left eye. There is questionable optic nerve pallor of the left eye along with a large subhyaloid hemorrhage obscuring the superior portion of the optic nerve (*blue arrow*) and extending along the superior arcade and macula. There are multiple intraretinal hemorrhages, some with a white center (most prominently inferonasally; see *purple arrow*) extending throughout the posterior pole

Table 31.1 Screening for occult injury in the evaluation of suspected child abuse

Systemic screening	Recommended modality
Neuroimaging for neurologically asymptomatic head trauma [32, 33]	*CT or MRI of the head* • All children < 6 months of age with suspected physical abuse • Children 6 to 24 months of age with suspected physical abuse, rib fractures, multiple fractures, and facial injury
Screening for occult abdominal trauma [34, 35]	*Measurement of AST, ALT, and lipase* • Children < 5 years of age with suspected physical abuse *Abdominal CT (with oral and intravenous contrast)* • If AST/ALT > 80 IU/L • OR Lipase > 100 U/L
Screening for occult fractures [36, 37]	*Skeletal survey (per published guidelines)* • All children < 2 years of age with suspected physical abuse • Children aged 2 to 5 years of age with suspected physical abuse should be considered on case by case basis

do not have a history of eye trauma should raise concern for non-accidental injury and prompt further evaluation [30]. Table 31.1 provides a summary of recommended systemic evaluation in cases of suspected child abuse. Cataracts and lens subluxation may also occur, but are more commonly seen after either repeated injuries or a previous injury [31].

Differential Diagnosis

The constellation of extensive retinal hemorrhages, schisis cavities, and intracranial hemorrhages, in the absence of a sufficiently traumatic accidental injury history, generally solidifies a diagnosis of abusive head trauma [38–40]. However, in cases with a non-classic distribution of retinal hemorrhages, alternative diagnoses must be considered. The list of possible causes of retinal hemorrhages in young children is extensive and includes accidental trauma, coagulation disorders, meningitis, sepsis, vasculitis, metabolic disorders, leukemia, increased intracranial pressure, reperfusion retinopathy secondary to extensive cardiopulmonary resuscitation, and birth trauma [10, 12, 41]. The majority of these conditions should be easily differentiated based on historical, clinical, and laboratory evaluation.

While accidental trauma may result in retinal hemorrhages, it is very rare to find diffuse, multilayer involvement with extension to the periphery as seen in non-accidental cases. Rather, significant accidental head injury can be associated with small numbers of predominately intraretinal hemorrhages confined to the posterior pole [42, 43]. However, in some cases of abusive head trauma, the distribution of retinal hemorrhages may be limited as in accidental trauma, and thus, this pattern or retinal hemorrhages does not exclude a diagnosis of non-accidental trauma. Some children who sustain short falls and have an epidural hematoma that requires neurosurgical evacuation have had retinal hemorrhages documented. In general, however, simple short-distance

falls have not been associated with retinal hemorrhages [44]. Single case reports of significant fatal crush injuries to the heads of young children have had detailed postmortem examinations of the eyes that revealed bilateral extensive hemorrhages and perimacular folds [45, 46].

Retinopathy after extensive cardiopulmonary resuscitation has been reported in the literature, as have retinal hemorrhages due to elevated intracranial pressure. However, such cases are rare and result in few hemorrhages confined to the posterior pole [10, 40, 47]. Severe hemorrhagic retinopathy has not been described in the setting of coagulopathy alone, but disseminated intravascular coagulation or other significant bleeding dyscrasias could theoretically contribute to retinal hemorrhages. However, in addition to extensive bilateral retinal hemorrhages, one would expect widespread visceral hemorrhages as well [10]. Birth trauma is well known to cause hemorrhages in the retina [48]. Retinal hemorrhages have been found in about 25 % of spontaneous vaginal deliveries and about 35 % of instrumented deliveries, especially deliveries via vacuum extraction or vacuum extraction combined with forceps use [49]. The majority of birth-related retinal hemorrhages resolve rapidly over the first 2 weeks of life. Only rarely do more severe birth-related retinal hemorrhages persist to 6 weeks postdelivery [31, 50].

Because of this broad differential diagnosis, it is important to provide accurate documentation of ocular findings [28]. Extensive hemorrhagic retinopathy as seen in abusive head trauma is not typical of other causes of retinal bleeding, and a detailed description of findings can help to distinguish between non-accidental trauma and other causes. Documentation should include a description of the type, number, pattern, and extent of retinal hemorrhages. Information regarding how to document the exams is outlined in Table 31.2. It is also important to provide specifics regarding laterality and/or asymmetry of hemorrhages.

Currently, the standard of care for documentation relies heavily on fundus photography, which is an imperfect method. Not all centers have access to retinal fundus cameras, good quality photographs are often difficult to obtain in infants secondary to poor dilation or an inability to stabilize their ocular movements, and photographs do not often extend to the ora serrata. Therefore, a more standardized method for documentation is necessary.

Bhardwaj et al. suggest using the terms mild (less than ten hemorrhages) versus severe to describe the extent of retinopathy. The definition of severe included any patient with greater than ten hemorrhages and therefore encompasses a wide range of disease. They also recommend using an anatomic classification by describing two zones, one centered on the fovea and one peripheral to it. However, these zones are not clearly delineated and would therefore be subject to a great deal of interobserver differences [51].

Longmuir and his colleagues also suggest using a graphics program that traces retinal hemorrhages on the photographs to determine total surface area covered by hemorrhages. It has its advantage in that it would be easily reproducible among multiple examiners. However, it still relies on the availability of photography. It is also limited in that it does not take into account the presence or absence of schisis cavities and the type and location of the hemorrhages [52].

Further efforts are currently being made to attempt to develop an international classification system for documenting the retinopathy, similar to the one that exists for retinopathy of prematurity [53].

Table 31.2 Documentation of retinal hemorrhages

Layers	Macular exam	Location	Number
• Preretinal	• Retinoschisis	• Peripapillary	• Mild (<10)
• Nerve fiber layer	• Folds	• Macular	• Moderate (10–25)
• Deep retina		• Perivascular	• Too numerous to count
• Subretinal		• Posterior pole	
		• Midperiphery	
		• Far periphery	

Table constructed based on information derived from Wade, M. Clinical Update: Shaken Baby Syndrome: Making an Accurate Diagnosis, EyeNet Magazine. May 2014

Case Study

The patient is a 5-month-old boy who was admitted to the Pediatric Intensive Care Unit (PICU) with a head injury, new-onset seizure, and altered mental status requiring endotracheal intubation and mechanical ventilation. The child was previously healthy, with no prior history of seizure or altered mental status. The patient's parents indicated that the child was well and acting normally prior to him being left with the babysitter. While at work, mother received a phone call from the babysitter, who reported that the baby was being transported by ambulance to the hospital after he suddenly stopped breathing. Emergency medical personnel responding to the home found the infant with altered mental status and shallow respirations. En route to the emergency department, the infant was noted to have generalized tonic-clonic seizure activity lasting one minute. Upon arrival to the emergency department, the baby was intubated due to a Glasgow Coma Score (GCS) of 8. Secondary survey revealed no external signs of injury. Computed tomography of the head revealed bilateral thin

(continued)

subdural hemorrhages. He was admitted to the PICU for further evaluation and management.

The parents reported that the infant is not yet crawling and is unable to sit independently, but he can roll over. There was no history of any significant injury; the baby had fallen off the couch several days prior to admission, with no immediate symptoms present after the fall. The Child Abuse Pediatrics Team was consulted and recommended a skeletal survey and ophthalmology consultation. The skeletal survey was negative for any acute or healing fractures.

At the time of his eye exam, the baby was sedated, and visual acuity was therefore unattainable. He had 1+ eyelid edema of both of his upper eyelids, 1–2+ chemosis of the conjunctiva of his left eye, and the rest of his anterior segment was unremarkable. Dilated indirect ophthalmoscopy revealed multiple retinal hemorrhages, too numerous to count, involving the preretinal and intraretinal layers and extending to the ora serrata in both eyes. Hemorrhagic macular schisis cavities were present bilaterally (Fig. 31.2).

Further evaluation for medical conditions that could have contributed to his presentation was negative; the child had no indication of a bleeding diathesis on screening laboratory studies [54]. Based on the constellation of bilateral thin-film subdural hemorrhages along the convexities of the cerebral cortex, extensive bilateral retinal hemorrhages, and bilateral hemorrhagic retinoschisis, combined with the absence of any medical cause for these findings, and the absence of any history of significant accidental trauma, a diagnosis of child physical abuse was made.

A repeat skeletal survey was performed 14 days after the initial study and revealed healing posterior rib fractures.

The infant was followed monthly in the ophthalmology clinic to monitor for resolution of the retinal hemorrhages and ensure the development of optimal visual function.

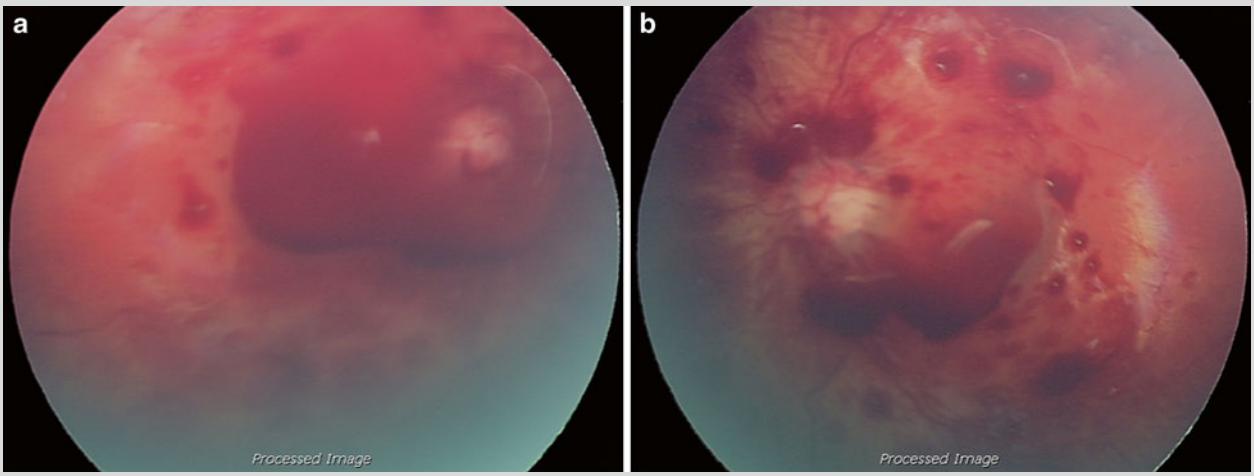

Fig. 31.2 (**a**) Color fundus photograph of the right eye. Preretinal hemorrhage obscures a clear view of the optic nerve and macula. There are multiple white-centered hemorrhages throughout the posterior pole. (**b**) Color fundus photograph of the left eye. The optic nerve is surrounded by preretinal hemorrhage. This preretinal hemorrhage partially obscures the macula: however, a macular schisis cavity is visible (note circumlinear hypopigmented edge). There are prominent white-centered hemorrhages along the superior arcade and temporal to the macula. Images courtesy of Laura S. Plummer, M.D

Prognosis and Management

There is strong correlation between the severity of brain injury and the severity of retinal hemorrhages in abusive head trauma; therefore, ophthalmologic findings may be useful prognostic indicators [10, 13, 14]. Some studies have additionally demonstrated that reactivity of the pupils in patients subject to abusive head trauma is a very reliable marker for mortality; those with nonreactive pupils are significantly more likely to die than those in whom pupils are reactive [13]. The mechanism for the nonreactivity of the pupils is not well understood, but may be related to optic nerve trauma or brain injury.

Retinal hemorrhages may resolve within days to months, depending on the severity and extent [10]. Those associated with abusive head trauma are often extensive and therefore may resolve more slowly. Management of hemorrhagic retinopathy most commonly involves supportive care and monitoring for late complications [10, 41]. The majority of patients will exhibit gradual resolution with no significant retinal or visual sequelae. Even those with macular retinoschisis typically do well; although schisis cavities can persist

indefinitely and lead to irreversible vision loss, they most often result in minimal or no impairment [10, 41]. Close ophthalmologic follow-up is indicated, especially when vitreous hemorrhage or macular schisis is present or when there is asymmetric ocular pathology [28]. Follow-up is based on extent of retinal hemorrhages present on initial examination. For example, if hemorrhages are too numerous to count and retinoschisis is present, the patient should be reevaluated within a week as a vitreous hemorrhage can leak from the macular schisis cavity. Deprivation amblyopia can develop and adversely affect visual outcomes. However, permanent visual impairment is frequently related to cortical brain damage rather than retinal hemorrhages, but can occur due to optic nerve injury or retinal detachment [10, 28].

Conclusions

Abusive head trauma is a significant and potentially lethal problem affecting young children, with mortality rates approaching 20 % [55, 56]. Unfortunately, the diagnosis can be difficult in some cases, especially when obvious signs of external injury are absent. It is important for clinicians to maintain a high index of suspicion for abuse; a full ophthalmologic examination performed by an ophthalmologist can be extremely helpful in the evaluation of any infant and young child suspected of having abusive head injury.

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Screening for Vigabatrin (Sabril®) Retinal Toxicity in Children

32

Scott E. Brodie

Abstract

Vigabatrin (Sabril®) is used as a drug of last resort in the treatment of refractory seizures. It is associated with a high risk of visual field defects due to retinal toxicity, which in some cases are irreversible. In the USA, regular ophthalmic assessment of patients on vigabatrin treatment is mandatory. While visual field testing is the preferred monitoring modality in older children and adults, it is not practical for infants and small children. In many cases, vigabatrin treatment may be continued even after the detection of retinal toxicity to maintain adequate seizure control. We present a case where visual field and ERG recovered over several months after drug cessation.

Keywords

Vigabatrin (Sabril®) • Retinal toxicity • Monitoring • ERG

The Problem

Vigabatrin (γ-vinyl-GABA, Sabril®) is an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. It is indicated for the treatment of complex partial seizures and for infantile spasms and is thought to be particularly effective in the treatment of seizures due to tuberous sclerosis [1]. Infantile spasms frequently occur secondary to inherited diseases with visual implications (including Aicardi syndrome, incontinentia pigmenti, Sturge-Weber syndrome, and other neurometabolic diseases) [1]. The drug was introduced in 1989 in the UK [2], and it has been widely available in Europe and Canada for many years.

Reports of irreversible visual field constriction in patients taking vigabatrin emerged in 1997 [3]. Subsequent investigations demonstrated evidence of frequent retinal dysfunction in patients taking the medication, at frequencies ranging from 10 to 50 % [4–6], and multifocal ERG testing shows a strong correlation between visual field constriction and reduced peripheral retinal function [6, 7]. Large series have reported a correlation between the likelihood of visual dysfunction and dose and duration of vigabatrin therapy [8–10]. However, in some cases, toxicity is reported after only weeks of treatment, and therefore, no dose or duration is known to be safe [11].

ERG studies have suggested a retinal origin for the visual field defects seen in patients on vigabatrin therapy, and the typical pattern of peripheral field loss is likewise suggestive of a retinal origin. While retinal nerve fiber layer thinning has been observed in these patients, optic nerve toxicity, which would more likely present with central or ceco-central scotomas, has not been reported. The mechanism of vigabatrin retinal toxicity appears to be due to the excitotoxic effect of elevated GABA levels on retinal neurons, due to the blockage of enzymatic degradation of GABA by the drug. Reductions in cellular taurine levels have also been implicated [12, 18].

Concerns over retinal toxicity engendered a cautious approach to vigabatrin use in the USA. The drug was available in the USA for many years only on a case-by-case compassionate use basis. In 2009, the FDA convened an expert panel to review the literature and make appropriate recommendations for approval of the drug [13]. In August 2009, vigabatrin was approved by the FDA

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for treatment of infantile spasms and refractory complex partial seizures in adults, but only by means of a restricted distribution program with rigorous requirements for monitoring of visual function [13, 14]. Ophthalmologic assessment was required at baseline (within 4 weeks after starting vigabatrin therapy), every 3 months while on therapy and about 3–6 months after discontinuation of therapy. The specific modes of visual assessment were left to the discretion of the examiner, but, as indicated on the official reporting form, may include visual acuity, kinetic perimetry, static perimetry, optical coherence tomography (OCT), and electroretinography (ERG). No specific instructions were given for the monitoring of infants or children [14].

The prescribing information cites a risk of visual field loss for patients on vigabatrin of "30 % or more" and indicates that the risk in children is not known, but could be higher. Yet, the value of ophthalmologic monitoring in the mitigation or prevention of visual field loss has remained unproven. Even if it were possible to detect incipient vigabatrin retinal toxicity at a stage when cessation of the drug would substantially reduce the risk of visual field loss, in many cases, the morbidity and/or mortality associated with the seizure disorder or infantile spasms may outweigh the visual morbidity. Vigabatrin is approved as a second-line drug to be used only when adequate seizure control cannot be attained with less toxic medications or as a first-line drug for treatment of infantile spasms, for which there is no other approved therapy [15]. Indeed, peripheral visual field loss may be judged by parents to be a lesser evil than severe neurodevelopmental delay due to intractable seizures.

A practice pattern for monitoring vigabatrin toxicity was suggested by the author in 2011 [16]. It includes ophthalmological assessment at baseline and every 3 months, with clinical evaluation of vision by the best possible method with which the infant or child cooperates. Special attention is given to the examiner's ability to elicit refixation saccades with peripheral stimulation of the retinas with an appropriate target. Dilated fundus examination is performed at each assessment, with attention to possible wrinkling of the internal limiting membrane (ILM) and atrophy of the nerve fiber layer as seen in blue- or red-free light.

After a discussion of the pros and cons of electrophysiological testing with the parents and/or patient, ERG testing may be utilized as a supplemental procedure to provide objective documentation of retinal function. Adequate Ganzfeld ERGs can usually be obtained from infants up to 18–24 months of age using only topical anesthesia and a handheld Ganzfeld stimulator. Abnormalities of essentially all the ERG amplitude parameters have been reported in cases of vigabatrin retinal toxicity, especially the amplitudes of the responses to single-flash and 30-Hz flicker stimulation under photopic (light-adapted) conditions, which reflect primarily cone function. The author's preference has been to follow primarily the peak-to-peak amplitude of the response to photopic 30-Hz flicker, as the repetitive nature of this response facilitates the distinction between signal and noise. Older children, including nonverbal teenagers, may be unable to cooperate with ERG testing and may require an examination under general anesthesia for adequate recordings.

Visual field testing remains the "gold standard" to screen for vigabatrin toxicity in patients who can perform the test reliably—usually only those over the age of 10 years. Goldmann kinetic perimetry is much preferred over the usual Humphrey visual field protocols, such as the 30-2 or 24-2, as these protocols do not probe the region outside of 30° eccentricity, where the visual field abnormalities in vigabatrin patients are most likely. (See case study below.)

ERG testing every 6 months appears to be adequate, unless other evidence of visual deterioration is noted. It may be convenient to alternate ERG testing with clinical ophthalmic assessments in order to comply with the mandate for evaluation at 3-month intervals. We emphasize that there is no consensus as to a "standard of care" for vigabatrin screening. ERG testing is only one option, which may be of greatest value for patients in whom developmental delays or other neurologic complications limit the utility of simpler clinical visual assessment.

Recent reports have suggested that thinning of the retinal nerve fiber layer, as indicated by spectral domain OCT, may also be of value in screening for vigabatrin retinal toxicity, particularly in adults [17]. While this modality may not be practical for awake infants, the advent of handheld OCT instruments may allow such assessment as part of examinations under anesthesia.

An age-specific summary of screening recommendations is provided in Table 32.1.

The following case history will serve to illustrate the possible benefits of screening for vigabatrin retinal toxicity in children:

Table 32.1 Age-based vigabatrin retinal toxicity monitoring guidelines

Infants	Fixation pattern
	Visual fields by confrontation
	Dilated fundus examination
	ERG—can usually be completed **without** an EUA
Age 18 (?24)–48 months	Fixation pattern
	Visual fields by confrontation
	Dilated fundus examination (may be done during EUA)
	ERG—will likely require EUA
Age 48–120 months	Visual acuity—use pediatric picture optotypes as appropriate
	Visual fields by confrontation
	Dilated fundus examination
	ERG—may be performed on awake children if cooperative
Age >120 months	Visual acuity
	Formal perimetry—Goldmann perimetry preferred
	Dilated fundus examination
	Spectral mode OCT
	ERG only if patient cannot perform formal perimetry

EUA examination under anesthesia, *ERG* electroretinogram, *OCT* optical coherence tomography

Case Study

An infant was referred for ERG testing to monitor for vigabatrin toxicity. On initial examination, the patient was able to fix and follow OU and was able to initiate saccades to a toy held in the peripheral visual fields. The fundus examination was within normal limits. In addition to the recommended screening examination, the family elected to undergo full-field ERGs, which were of good quality, and showed normal responses. Follow-up ERG recordings over the next 2 years were unchanged. The patient remained on vigabatrin treatment, but was lost to follow-up for the next 5 years. Seven years after the initial ERG recordings, he returned for further screening evaluation.

Visual acuity was 20/20 in both eyes and visual fields were full to confrontation. Ophthalmoscopy did not reveal any wrinkling of the ILM and optic nerve was healthy OU. In the intervening 5 years, ERG amplitudes had decreased by about 50 % and remained at this level over the next 3 years (Fig. 32.1).

The patient was examined at 3-month intervals, and visual acuity, fundus examination, and ERG remained unchanged over the next 3 years. He was able at age 11 to complete a Goldmann visual field (Fig. 32.2).

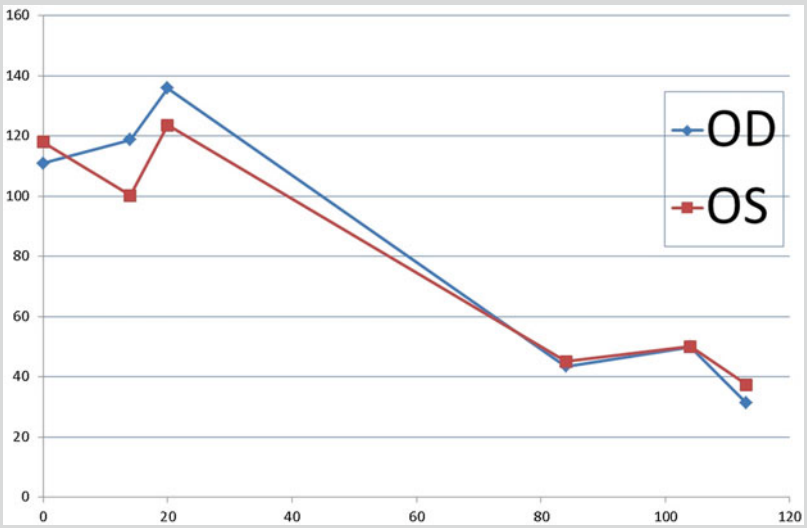

Fig. 32.1 Photopic 30-Hz flicker amplitudes (in μV) over 120 months since initial ERG studies. Patient had remained on vigabatrin treatment but was lost to follow-up for 5 years after three initial ERG studies

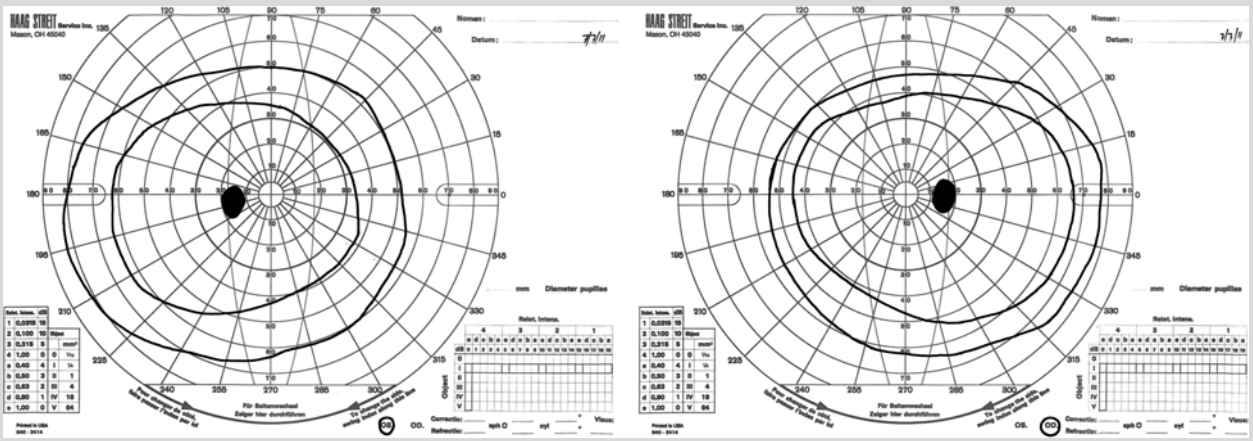

Fig. 32.2 Goldmann visual fields at age 11

(continued)

At the next examination at age 12, the Goldmann visual fields and ERGs remained unchanged. At age 13, the clinical examination remained unchanged. However, the ERGs became nearly extinguished, and mild peripheral constrictions were noted in the Goldmann visual fields (Fig. 32.3).

After consultation with the patient's pediatrician and neurologist, vigabatrin was discontinued, and adequate seizure control was established with topiramate (Topamax®). Five months later, substantial recovery of both ERGs and Goldmann visual fields was evident (Fig. 32.4):

Clinical Synopsis: A patient on vigabatrin treatment has been followed for over 12 years, with steadily diminishing ERG amplitudes. At age 13, visual field constriction was first noted. Vigabatrin treatment was discontinued, and recovery of ERG amplitudes and normalization of the visual fields were documented 5 months later.

This case is unusual for the lengthy follow-up period, as well as the ability of the patient to perform reliable visual field testing—most pediatric patients on vigabatrin lack the ability to perform this test. Nevertheless, notwithstanding the consensus that visual field loss due to vigabatrin toxicity is in general irreversible [10], this case would suggest at least the occasional potential for recovery of visual function in children on vigabatrin upon discontinuation of the drug, especially if vigabatrin can be withdrawn when only minor visual field abnormalities have developed.

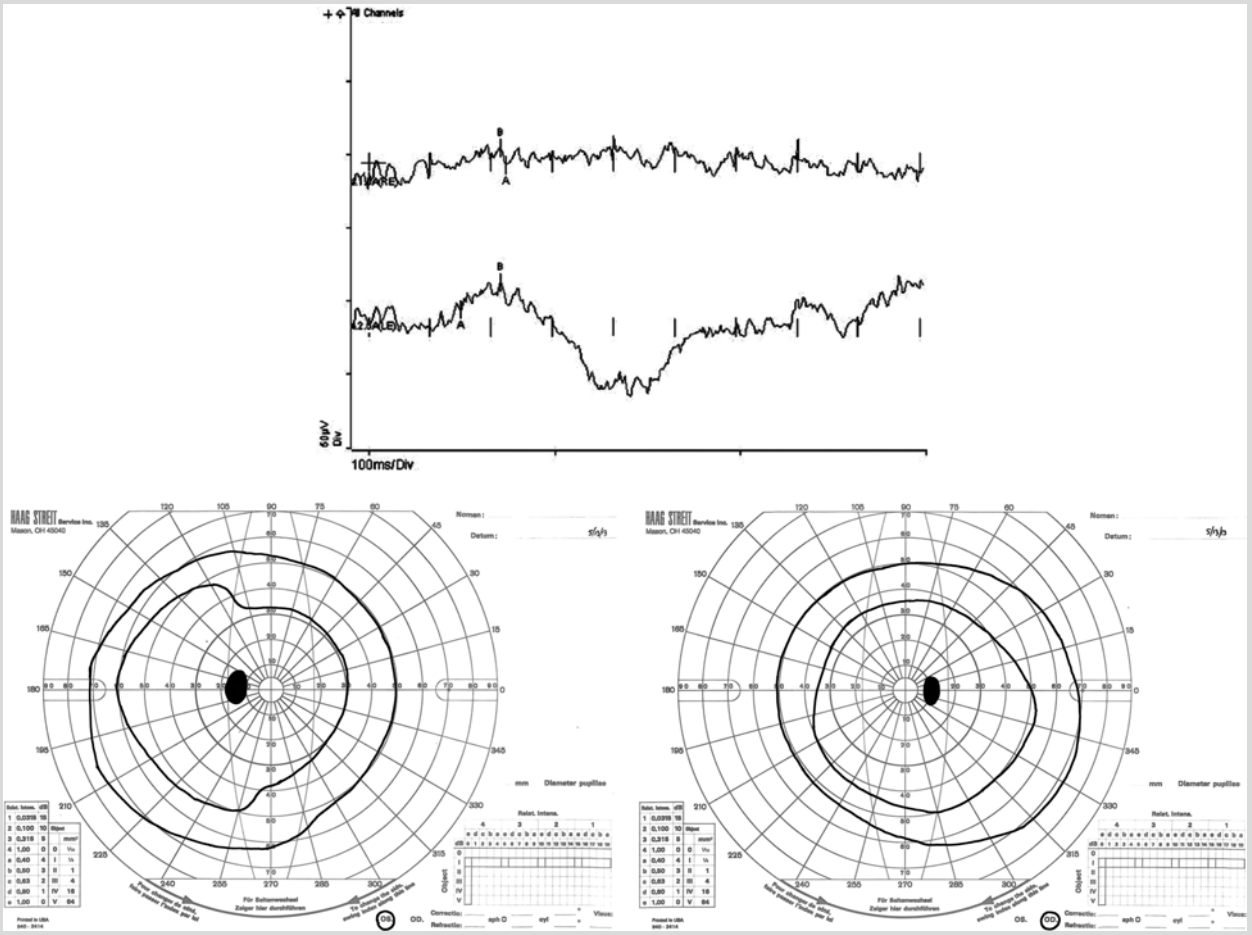

Fig. 32.3 Photopic 30-Hz flicker ERGs (*top*, right eye; *bottom*, left eye) and Goldmann visual fields obtained at age 13

(continued)

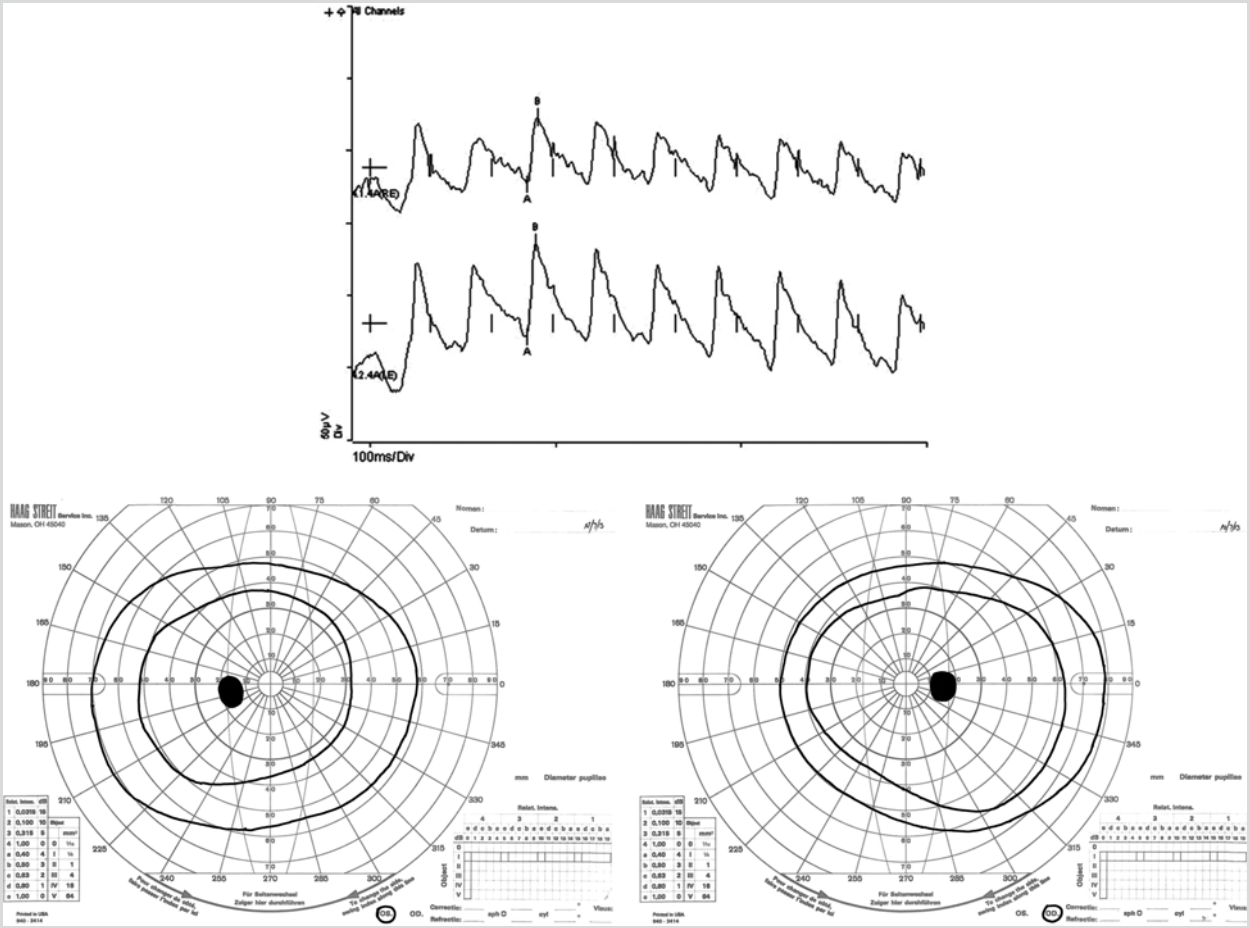

Fig. 32.4 Significant improvement of (**a**) photopic ERG 30-Hz flicker response and (**b**) Goldmann visual field 5 months after cessation of vigabatrin treatment

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Part IX

Inherited Disorders

Genetic Counseling and Testing

33

Meghan J. Marino and Elias I. Traboulsi

Abstract

The understanding of the genetic basis of ophthalmic and systemic diseases has greatly improved over the last few decades. With the advent of new and effective genetic testing options and the increasing importance of these tests for appropriate diagnostic and therapeutic management of patients, the need for specialists in genetics has become more critical. The appropriateness of tests for individual patients needs to be understood, and the tests need to be judiciously selected. The incentives for obtaining genetic testing include confirmation of a clinical diagnosis, direct medical management, and the determination of recurrence risks.

Keywords

Genetic • Testing • Counseling

Genetic Testing

There have been rapid changes in genetic testing technology in the past few years. Additional changes are expected to occur at a rapid pace and will alter the way physicians and genetic counselors approach genetic testing in clinic. Therefore, this chapter serves as an overview of genetic testing as it is performed at the time this book is written. It is imperative for clinicians and counselors ordering genetic tests to remain current on testing technology and to recognize the benefits, limitations, and recommendations for the various types of available testing modalities. The Centers for Medicare and Medicaid Services (CMS) regulates all laboratory testing performed on humans in the USA through the Clinical Laboratory Improvement Amendments (CLIA). The objective of the CLIA program is to ensure quality laboratory testing and provide federal standards for sites offering testing on human specimens [1]. Laboratories offering genetic testing must be CLIA certified in order to provide a patient or their clinician with a formal test report. A research laboratory may or may not be CLIA certified. Laboratories that are not CLIA certified are not permitted to provide results in the form of a report, nor can research results be used for the treatment or management of a patient. Research results may be confirmed, though, in a CLIA laboratory and can then be utilized in clinical care and the results relayed to the patient. Clinicians and counselors should perform their own research on the various labs offering testing and consider the following factors for each patient and testing situation.

Cost

The cost of a genetic test can vary drastically depending on many factors. The price for single gene analysis (usually

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Sanger sequencing) largely depends on the size of the gene. There can also be large fee differences between laboratories. Multiple gene testing panels can be performed with either Sanger sequencing or next-generation sequencing (NGS) with the latter being much less expensive, but with more limitations. Another factor that may impact cost is whether or not a laboratory is billing the patient or their insurance company directly or billing the institution or hospital at which the sample is obtained and submitted. Insurance coverage is dependent on the CPT codes of the test and the ICD9 code for the disease and is oftentimes based on medical necessity. It is helpful to obtain prior authorization or a predetermination of benefits for patients so as to ensure a test will be covered. Highlighting how the testing will impact the patient's medical management is essential for getting approval for genetic testing.

Testing Methodology

Sanger sequencing was developed by Frederick Sanger in the 1970s [2] and is still considered the gold standard of genetic testing today. It allows one to read the entire DNA sequence of a gene. It will detect missense, nonsense, and frameshift mutations [3, 4]. Large deletions or duplications cannot be detected and require a different type of analysis such as microarray [5]. Targeted mutation (allele-specific) analysis is oftentimes a faster and less expensive test. However, it only provides data on specific sequence variations or mutations within a gene, hence only works in cases in which one is looking for one or a few specific mutations. For example, the same mutation in *EFEMP3* causes dominant radial drusen in all patients with this condition; hence a single targeted mutation analysis would be appropriate in any such case and would have an extremely high degree of sensitivity in confirming the clinical diagnosis on a molecular level. This approach is also useful if a family is known to harbor a certain mutation and one wants to test an individual within that family for his/her carrier status. Next-generation sequencing (NGS) is a more recent technology that allows sequencing of DNA and RNA much faster and at a lower cost than Sanger sequencing [3, 6]. NGS is often used when multiple genes are tested simultaneously (panel tests) for genetically heterogeneous conditions such as retinitis pigmentosa. Gaps or low areas of sequencing coverage need to be filled in with Sanger sequencing. Whole-exome sequencing (WES) allows one to analyze all the exons of the genome that are protein encoding and that represent ~20,000 genes and account for ~2 % of all human genetic material [7, 8]. WES cannot detect mutations in introns nor can it detect large deletions, duplications, or triplet repeat disorders. WES is appropriate for (1) patients who have an undiagnosed genetic disorder and in whom all other genetic testing options have been exhausted without securing a molecular diagnosis, (2) patients with multiple diagnoses whose constellation of findings does not seem to fit into one condition and the cost of testing for the various possible conditions would be more expensive than WES, and (3) patients diagnosed with disorders characterized by significant genetic and phenotypic heterogeneity [7, 8].

Turnaround Time

The turnaround time of a test (from the date the sample is submitted to the lab to the date the result is received by the treating team) is important to discuss with the patient and a factor to consider when selecting a test and laboratory. One must also consider the level of anxiety of the patient, whether the results will alter the management of the patient, and if the results impact the outcome of a pregnancy.

Laboratory Reputation

Some institutions offer various genetic tests in house. Other times a sample will have to be sent out to another laboratory for analysis. A great resource for determining which labs offer the test of interest is the Genetic Testing Registry through the National Center for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/gtr/). This website allows one to search by gene or genetic condition and enables filtering by different parameters (i.e., CLIA-certified laboratories, laboratories in the USA, testing methodology). Choosing a laboratory for genetic testing can be very easy if there is only one laboratory that offers the test. It can also be difficult when multiple laboratories offer the same test. Factors to consider when choosing a laboratory are:

- Is it CLIA certified?
- What information does the laboratory report include?
- Is the laboratory director reachable and receptive to questions?
- Does the laboratory have a genetic counselor on staff?
- How does the laboratory classify variants of unknown significance?
- What is the method for reclassifying variants of unknown significance and contacting clinicians?
- Does the laboratory offer segregation analysis and is there an additional fee?

Family History

The drawing of a detailed pedigree is imperative to determine the likely inheritance pattern, which in turn guides the

choice of genetic testing. A detailed complete pedigree is also useful in providing the patient/family with information on recurrence risks. One should use caution when using absolutes as genetic information is communicated to patients. For example, there is always potential for de novo mutations. Additionally, some recessive conditions have a higher carrier frequency in a certain population, so a pedigree may appear dominant, when in fact the genetic condition is a recessive one (pseudodominant inheritance).

Clinicians and genetic counselors should also be familiar with the underlying purpose of ordering a genetic test. Is the purpose of the test to diagnose a patient's condition or identify the etiology of their signs and symptoms (diagnostic testing)? Or is there a genetic disease already known in the family, and is the patient curious to know if they will one day develop the same condition (predictive testing)? Controversy remains surrounding predictive or presymptomatic genetic testing, especially in minors for conditions that no prevention or treatment is available. A genetic counselor can help in these cases to further explore the risks, benefits, limitations, and patient motives for testing.

Recommendations for Genetic Testing

A number of organizations have published guidelines and policy statements on genetic testing for certain conditions or scenarios for testing. These have been researched and reviewed at the time this book was written and include the following:

1. Chromosomal microarray (CMA) for copy number variants (CNVs) is recommended as a first-tier test when one or more of the following are present (*American College of Medical Genetics (ACMG) Practice Guideline, 2010*) [9]:
   (a) Multiple anomalies not specific to a well-delineated genetic syndrome
   (b) Apparently non-syndromic developmental delay
   (c) Autism spectrum disorders
2. The American Academy of Pediatrics (AAP) and the American College of Medical Genetics (ACMG) do not support routine carrier testing or screening for recessive conditions when carrier status has no medical relevance during adolescence [10].
3. Predictive genetic testing may be performed on a child with a positive family history for a specific genetic condition, particularly if early surveillance or treatment may affect morbidity or mortality [11, 12].
4. The American Academy of Ophthalmology (AAO) released guidelines on genetic testing for eye diseases [13]. To summarize, these guidelines state:
   (a) Genetic testing should be performed by a clinician or genetic counselor familiar with such testing.
   (b) Avoid direct-to-consumer testing.
   (c) When possible, use CLIA labs as they are permitted to provide test results in the form of a formal report.
   (d) Use the patient's personal and family history to order the most specific test for the patient. Consider genotype-phenotype correlations when available.
   (e) Avoid genetic testing for conditions that do not have a well-defined molecular association, such as multifactorial conditions like age-related macular degeneration.

The above recommendations are not exhaustive, and clinicians should be kept current on practices and guidelines.

Genetic Counselors as Healthcare Professionals

Genetic counseling is the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease [14]. Genetic counselors are taking an increasingly important role as genetic testing becomes more available and complex [15]. Genetic counselors are healthcare professionals with specialized graduate degrees and experience in both medical genetics and counseling. They are trained to provide a critical service to individuals and families by helping them identify their risks for certain disorders, investigate family health history, interpret information, and determine if testing is needed.

Genetic counselors are available at most major medical centers and in many states are licensed healthcare providers. They can also be easily located by searching the NSGC website, www.nsgc.org.

The Process of Genetic Counseling

Every genetic session is slightly different since they are tailored to the specific patient needs and reason(s) for referral. During a genetic counseling session, the patient is educated on the basics of genetics and principles of inheritance, focusing on the inheritance pattern most likely present in the patient/family. If a genetic condition has already been diagnosed in a patient, the counselor is able to review the natural history of the disorder, discuss management and prevention options, and provide the patient with appropriate resources and referrals. They can also assist patients and their families by investigating possible participation in suitable research trials.

Genetic counseling is considered a process. Throughout the session, counseling is offered to promote informed decisions and adaptation. The genetic counselor is also trained to consider socioeconomical, ethnic, and cultural differences and to ensure the patient is receiving care in accordance with his/her beliefs and values.

Case Examples

Case Example 1

A 10-year-old boy carries a clinical diagnosis of Axenfeld-Rieger syndrome. He initially presented at 2 months of age and found to have posterior embryotoxon OD and posterior persistent fetal vasculature (PFV) with retinal detachment OS. Medical history review was significant for bilateral hydrocele repair and circumcision with hidden penis repair at 8 or 9 months of age. Audiogram at the age of 5 years was remarkable for mild bilateral neurosensory hearing loss. At 6 years of age, he was evaluated for bilateral toe walking and left hip/thigh pain. A diagnosis of bilateral Legg-Calve-Perthes disease vs. multiple epiphyseal dysplasia was considered. At age 11, an echocardiogram showed mild aortic valve regurgitation with a normal and tri-commissural aortic valve and a left aortic arch with an aberrant right subclavian artery. On ophthalmologic examination, his visual acuity was 20/20 OD and NLP OS. Confrontation visual field of his right eye was full. The intraocular pressures were normal. An anteriorly displaced Schwalbe's line OD was noted on slit lamp examination (Fig. 33.1). The fundus and optic nerve were normal OD. His father, younger brother, and paternal uncle were also affected. Given the dominant nature of inheritance and the clinical history, genetic testing of the *FOXC1* gene was pursued. Sanger sequencing of *FOXC1* was normal. Subsequent targeted exon array comparative genomic hybridization (CGH) analysis was performed, which detected a heterozygous deletion of one copy of the *FOXC1* gene. Deletions of this size are not detectable by Sanger sequencing. In order to determine the extent of this deletion, genome-wide microarray analysis was performed. This testing showed an interstitial deletion of at least 642 kb on chromosome 6p25.3. This region encompassed three genes and a portion of a fourth. Only the *FOXC1* gene in this region has been associated with a known clinical disorder—Axenfeld-Rieger syndrome type 3 (OMIM 602482).

This result allowed targeted genetic testing in this patient's younger brother (who was also positive for the same gross deletion). This prompted systemic evaluation of the affected brother and prevention of morbidity associated with the findings. Other patients with 6pter-p24 deletions have been also reported to have hip dysplasia [16], so the test also contributed to the elucidation of the etiology of the dysplasia.

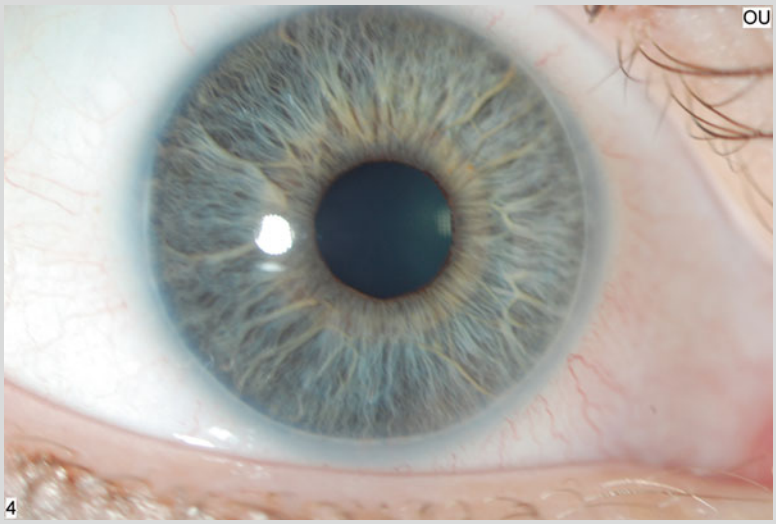

Fig. 33.1 360° prominent and anteriorly displaced Schwalbe's line in a patient with Axenfeld-Rieger spectrum of anterior segment dysgenesis

Case Example 2

A 6-year-old Caucasian male was evaluated for a suspicion of amblyopia OS since 4 years of age. This was treated with patching. His vision had decreased in both eyes , and etiology was unknown. On clinical examination, his visual acuity was 20/40 OU. His confrontation visual fields were full and color vision was full. His slit lamp and fundus examinations were both normal. His medical history was unremarkable. His family history was significant for a maternal grandfather with retinoschisis. An OCT was obtained and was consistent with a diagnosis of juvenile X-linked retinoschisis (Fig. 33.2). His central subfield thickness was 559 OD and 532 OS. He was started on dorzolamide.

Genetic testing was obtained via Sanger sequencing of the *RS1* gene as this was the most likely candidate gene based on constellation of findings. He was hemizygous for a mutation c.626G>A, p. Arg209His) in exon 6 of the *RS1* gene. His mother was also tested and was found to be a heterozygous carrier of this mutation. This means that any other male children of hers will have a 50 % chance of inheriting this mutation and being affected with the condition. Targeted mutation analysis could be performed to determine whether future male offspring are affected. Testing such as this could be performed preconceptually, prenatally, or after a baby is born—depending on the beliefs and motives of the parents.

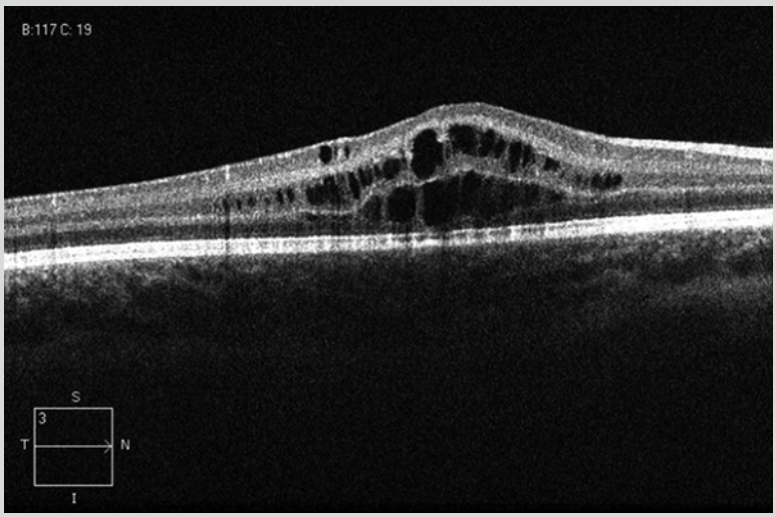

Fig. 33.2 OCT image of the fovea in the right eye from a patient with juvenile X-linked retinoschisis

Case Example 3

An 11-year-old girl presented for evaluation of her retinal dystrophy. She had initially been diagnosed at the age of 6 years with Leber congenital amaurosis (LCA) vs. achromatopsia. Genetic testing at the time was obtained for LCA. The analysis utilized consisted of allele-specific testing that investigated 62 segments of 8 genes associated with LCA. This testing was negative, but in view of the limited testing methodology, LCA could not be ruled out. She had nystagmus. Her medical and family histories were otherwise unremarkable. Her visual acuity was 20/125 OD and 20/100 OS. Fundus exam was significant for mild disc pallor and very mild pigmentary mottling in the macula (Fig. 33.3). Retinal blood vessels appeared normal.

An ERG was performed and was consistent with a cone-rod dystrophy. Fundus autofluorescence was significant for bilateral foveal hyperfluorescence, consistent with a diagnosis of cone or cone-rod dystrophy. Given the stability of her visual acuity and her ERG results, a diagnosis of achromatopsia appeared to be more likely.

Given the genetic heterogeneity of achromatopsia and the lack of genotype-phenotype correlations, genetic testing was pursued via a NGS panel of five achromatopsia genes. She was found to have two novel variations in the *CNGB3* gene, a frameshift mutation c.1600_1601insTT and a missense variant, c.1700G>A, p.G567E. The missense variant

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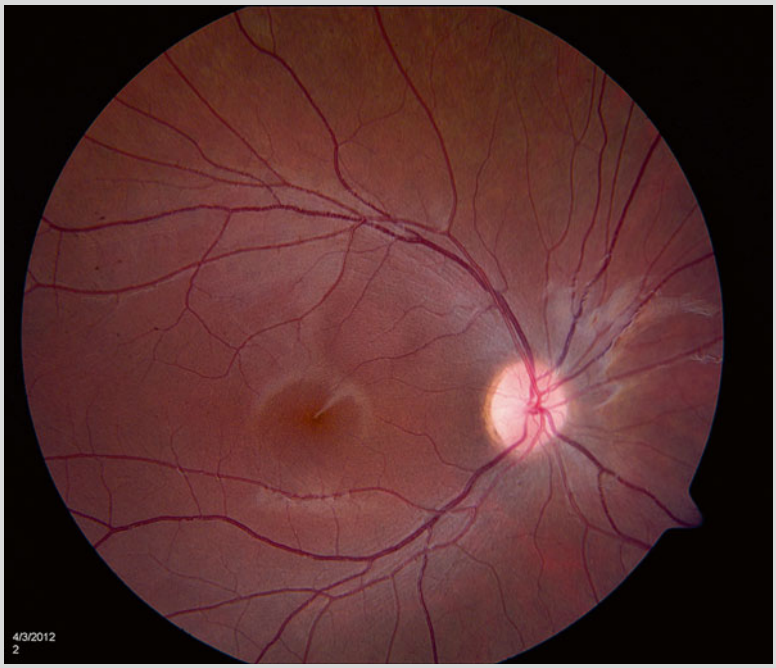

Fig. 33.3 Fundus image of patient with achromatopsia due to compound heterozygous *CNGB3* mutations. Note mild disk pallor but very mild if any pigmentary changes

was predicted to be pathogenic. Her parents were tested and found to each carry one of the two mutations, confirming that the variants were in trans (on separate alleles). This was important to confirm since achromatopsia due to *CNBG3* mutations is autosomal recessive. If both mutations were in cis (inherited together on the same gene copy—i.e., both mutations from the same parent), it would not be sufficient to cause disease. Additionally, determining which parent carried which mutation could allow for carrier testing of other family members. Achromatopsia is a relatively stable retinal dystrophy, whereas LCA is a more severe and progressive condition. The molecular confirmation of a clinical diagnosis of achromatopsia allowed the provision of important diagnostic and prognostic information.

Case Example 4

An 11-month-old male patient of Ashkenazi Jewish ancestry was evaluated by his pediatrician for persistent fatigue. He was noted to be extremely pale and a heart murmur was detected. Blood work showed a hemoglobin g of 1.9 (reference range, 10.8–15.5 g/dL); mitochondrial DNA test Southern blot performed on blood (lymphocytes) showed a 5 kB deletion spanning the ATPase 6 gene to the *ND5* gene. This deletion is associated with both Pearson syndrome (PS) and Kearns-Sayre syndrome (KSS). The deletion encompassed several of the genes that encode for mitochondrial complex I, III, and V subunits, as well as several of the transfer RNAs. The typical features of Pearson syndrome include a sideroblastic anemia and exocrine pancreatic failure, along with lactic acidosis, failure to thrive, and developmental delays. His deletion was de novo. At 5 years of age, he was noted to have some pigmentary changes in his retina. He developed neuropathy with sensory ataxia around age 9. At the age of 10 years, he presented for an ophthalmology exam for follow-up. He was noted to have chronically progressive external ophthalmoplegia and ptosis (Fig. 33.4). His visual acuity was 20/25 OD and 20/30 OS. Dilated fundus exam was significant for optic nerve pallor, pigmentary changes in the macula, vascular attenuation, and peripheral pigmentary changes (Fig. 33.5). Goldmann visual fields also showed progressive constriction. He underwent ptosis repair at age 11 and received hearing aids at age 12. At age 13, his visual acuity was 20/50 OD and 20/80 OS. His fundus appearance was relatively stable.

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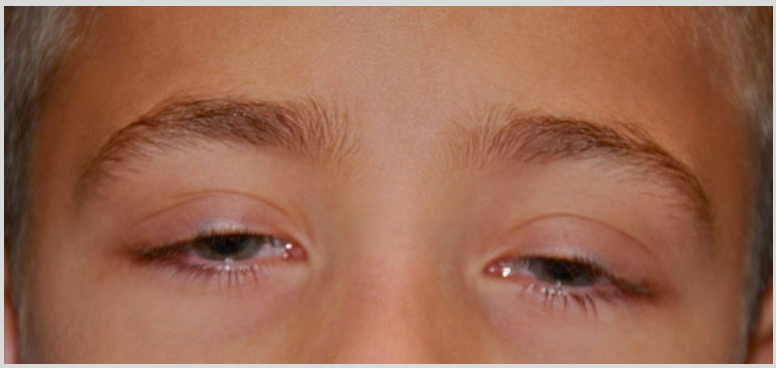

Fig. 33.4 Chronic progressive external ophthalmoplegia and bilateral ptosis in a patient with Pearson syndrome and Kearns-Sayre syndrome

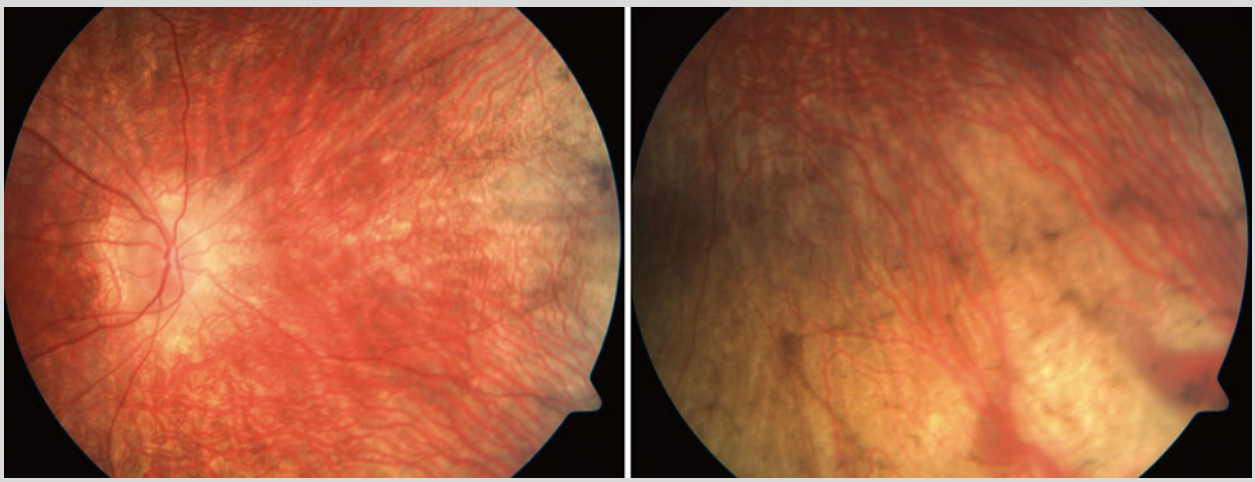

Fig. 33.5 Fundus images of a patient with a mtDNA deletion. Pale optic nerves are observed in addition to peripheral areas of atrophy as well as pigmentary changes compatible with retinopathy of Kearns-Sayre syndrome

Glossary

CGH array Comparative genomic hybridization—fluorescence hybridization technique used to screen for chromosomal deletions and duplications along whole genomes [17]. This test is indicated when a deletion or duplication is suspected or to determine the actual size of a deletion when one is detected in a gene. (Please see Case Study 1.) This test is also an appropriate first-tier test when a child has multiple congenital anomalies that are not consistent with a unifying genetic syndrome.

CNV Copy number variation—the presence or absence of a DNA segment, ranging from 200 bp to 2 Mb [18].

Compound heterozygous When a person has two mutated alleles and the mutations are different. One is inherited from one parent and the second from the other parent.

De novo Refers to a mutation that was not present in either parent but arose in one of the two gametes. It can be passed on to the patient's children since it is present in all of the patient's cells.

Hemizygous Males have one X chromosome and one Y chromosome. A male who has a mutation in a gene located on the X chromosome is said to be hemizygous (since he only has one X) for that mutation.

Heterozygous When a person has one mutated allele.

Homozygous When a person has two mutated alleles and the mutations are the same.

Next-generation sequencing (NGS) All NGS platforms perform sequencing of millions of small fragments of DNA in parallel. Bioinformatic analyses are used to piece together these fragments by mapping the individual reads to the human reference genome [6].

Predictive testing (often synonymous with presymptomatic testing) Is performed on individuals who have a family history of a genetic disease and are at risk for being affected. This term applies to those who are currently asymptomatic and can include newborns, adolescents, or adults.

Sanger sequencing Determining the sequence of nucleotides in a fragment of DNA [18].

SNP Single nucleotide polymorphism—variants or single base changes at one DNA location, present in a significant number of a population, and not causing a change in a protein or in a disease process.

SNP array The hybridization of fragmented single-stranded DNA to arrays containing hundreds of thousands of unique nucleotide probe sequences. Each probe is designed to bind to a target DNA subsequence [19]. This method of genetic testing allows for detection of copy number variations. This test is similar to a CGH array; however, SNP arrays can also detect copy-neutral loss of heterozygosity such as uniparental disomy.

Targeted exon array *comparative genomic hybridization* **(CGH)** A rapid, cost-effective, highly sensitive, and accurate approach for the detection of single- and multi-exon deletions or duplications, particularly in cases where direct sequencing fails to identify a mutation [20]. A targeted exon array is different from a standard CGH array as it only detects deletions or duplications of targeted exons or genes—not the entire genome.

Whole-exome sequencing (WES) A diagnostic approach used to identify the molecular etiology of an individual's suspected genetic disease. The technology analyzes all the exons of the genome that are protein encoding and that account for ~2 % of all human genetic material [7]. WES is indicated for (1) patients who have an undiagnosed genetic disorder and in whom all other genetic testing options have been exhausted without securing a molecular diagnosis, (2) patients with multiple diagnoses whose constellation of findings does not seem to fit into one condition and the cost of testing for the various possible conditions would be more expensive than WES, and (3) patients diagnosed with disorders characterized by significant genetic and phenotypic heterogeneity.

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Retinal Dystrophies: Clinical Work-Up and Selected Examples

34

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Abstract

Childhood retinal dystrophies may be isolated or represent one sign of serious systemic diseases. Because of the variety of ways they manifest themselves, retinal dystrophies may be overlooked or misdiagnosed. A thorough patient history, family history, ophthalmologic examination, ancillary testing, and complete review of systems and physical examination are imperative to detect and to accurately diagnose disease. The diagnosis can be confirmed using genetic testing in a large proportion of cases. This chapter discusses a practical approach to the diagnosis and management of patients with a suspected retinal dystrophy and provides case examples of a few disorders. The reader is also referred to the chapter on genetic counseling in this book for additional discussion and other case examples.

Keywords

Achromatopsia • Bardet-Biedl syndrome • Fundus flavimaculatus • Leber congenital amaurosis • Gene therapy • Retinal dystrophy • Rod monochromatism • Stargardt disease

Introduction

There are several situations in which a retinal dystrophy should be highly suspected in children and infants. One specific example is in the infant with nystagmus. Achromatopsia, Leber congenital amaurosis (LCA), oculocutaneous albinism, cone-rod dystrophy, bilateral severe optic nerve hypoplasia, and congenital stationary night blindness, for instance, may present in this manner. If a retinal dystrophy is suspected in such a patient, and physical findings do not rule out albinism and optic nerve hypoplasia, an electroretinogram (ERG) should be obtained. The findings on the ERG will help guide subsequent genetic testing. It is also important to differentiate between children with isolated ophthalmic disease from those in which the retinal dystrophy is only one of several manifestations of an underlying systemic disease. Various inherited conditions, such as mitochondrial disorders (e.g., Kearn-Sayre disease), ciliopathies (e.g., Bardet-Biedl syndrome (BBS), Usher syndrome), neurologic and metabolic disorders (neuronal ceroid lipofuscinosis [Batten disease], Refsum syndrome, gyrate atrophy, abetalipoproteinemia, and Cockayne syndrome), among others, are associated with a retinal dystrophy. It is imperative that these diagnoses are correctly identified, as some may be amenable to early treatment (see Fig 34.1). Here are key questions to ask the patient and guardians:

Key Questions in Medical and Vision History

1. Age of onset of signs and/or symptoms?
2. Symptoms worsening or stable (progression)?
3. Trouble navigating in dark surroundings (nyctalopia)?

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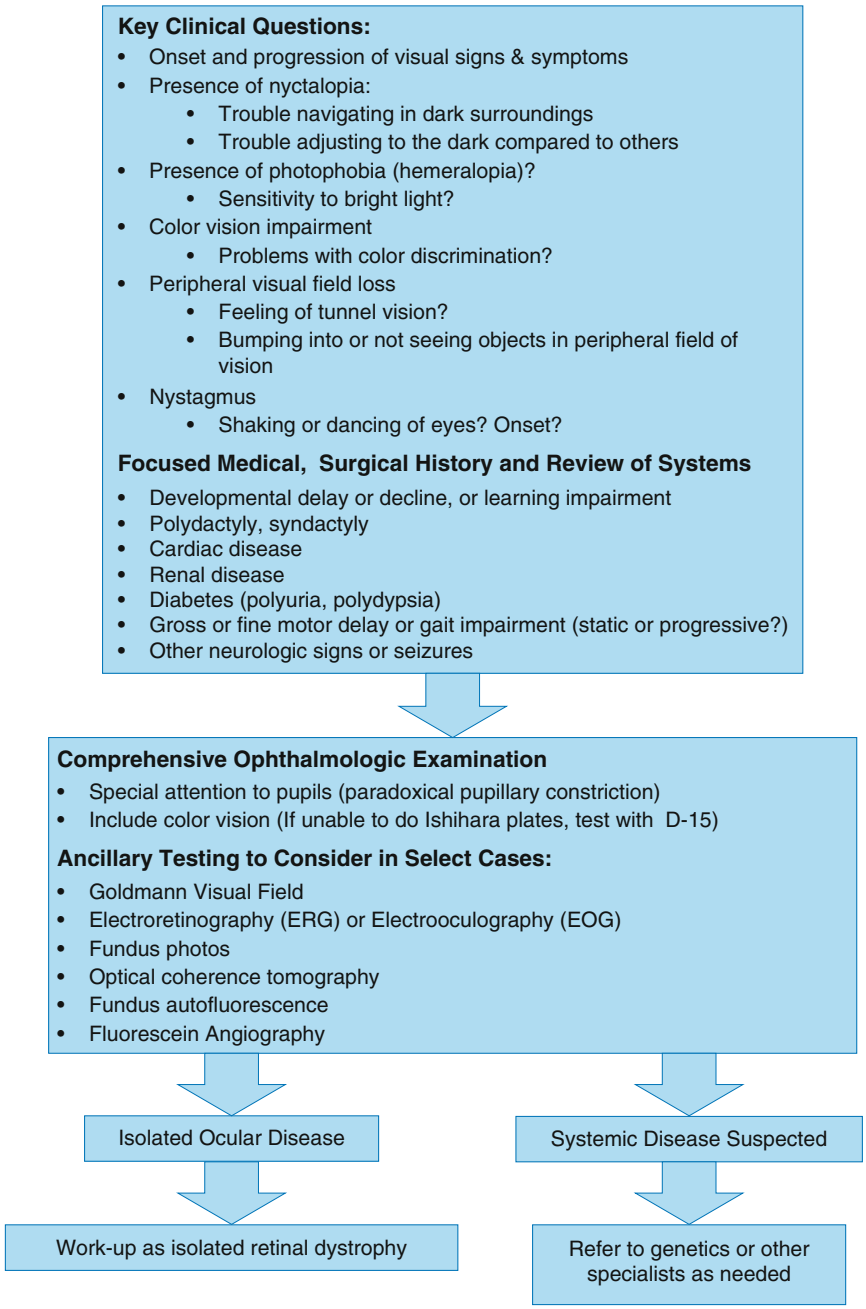

Fig. 34.1 Algorithm for the evaluation of the patient with a retinal dystrophy

4. Trouble adjusting to a darker environment (dark adaptation)?
5. Sensitivity to bright light (photodysphoria)?
6. Difficulty discriminating colors (color vision impairment)?
7. Feeling of tunnel vision (peripheral visual field loss)?
8. Shaking or abnormal movements of eyes (nystagmus)?

Focused Medical/Surgical History and ROS

1. Difficulty with schoolwork or learning (developmental delay)?
2. Loss of milestones (neurological regression)?
3. Extra/abnormal finger or toe or other malformations (polysyndactyly)?
4. Cardiac abnormality (cardiomyopathy)?
5. Kidney problems (renal disease)?
6. Polyuria or polydipsia (diabetes)?
7. Hearing loss (deafness)?
8. Problems with walking or balance (neuromuscular disease)?
9. Peculiar and very restricted diet (vitamin A deficiency)?
10. Family members with similar symptoms (family history)?

The presence of night blindness points to a rod dysfunction, while light sensitivity and difficulties discriminating colors are more suggestive of cone disorders. Peripheral visual loss is associated with LCA, cone-rod dystrophies, and retinitis pigmentosa, while central visual loss is more consistent with cone dystrophies and Stargardt disease.

Ancillary tests are critical to the attainment of a clinical diagnosis. Fundus photographs, fundus autofluorescence, optical coherence tomography, ERG, and occasionally EOG and fluorescein angiography can provide very specific clues to a particular disease and assist in guiding genetic testing.

Because of the very large number of retinal dystrophies and systemic disorders associated with retinal degeneration, this chapter focuses on just a few of the more common types that are encountered in children. The reader is referred to other specialized texts for more detailed descriptions of these conditions and to the chapter on genetic counseling in this textbook.

Achromatopsia (Rod Monochromatism)

Case 1 (Table 34.1)

Table 34.1 Case 1

Clinical History	11-year-old female with a history of a retinal dystrophy, nystagmus, poor vision, severe photophobia, and relatively stable visual acuity in recent years. PMH and FH were noncontributory		
Base Exam		OD	OS
	BCVA	20/125	20/100
	Versions	Full	Full
	CRx	−2.75 + 2.25 × 100	−2.75 + 2.50 × 085
Fundus Exam		OD	OS
	Disc	Pallor	Pallor
	Macula	Mild macular pigmentary mottling	Mild macular pigmentary mottling
	Vessels	Normal	Normal
	Periphery	Limited (severe photophobia)	Limited (severe photophobia)
Previous Genetic Testing	Negative for Leber congenital amaurosis (LCA)		
Subsequent Genetic Testing	Two novel variations in the *CNGB3* gene identified		
Diagnosis	Achromatopsia		
Treatment	– Currently no effective treatment for achromatopsia – Tinted lenses may be worn to alleviate photophobia		

The patient is an 11-year-old female with a history of a retinal dystrophy, nystagmus, poor vision, and severe photophobia from very early in life. She has had a stable visual acuity of 20/100 for the last few years. She had mild bilateral optic nerve pallor and macular pigmentary mottling while the peripheral retina (Figs. 34.2, 34.3, and 34.4) appeared relatively normal. Previous genetic testing for LCA was negative. Subsequent testing for achromatopsia (*CNGA3*, *CNGB3*, *PDE6C*, and *PDE64*) revealed two novel pathogenic variations in the *CNGB3* gene, and these were deemed to cause her retinal dystrophy—diagnosis: achromatopsia.

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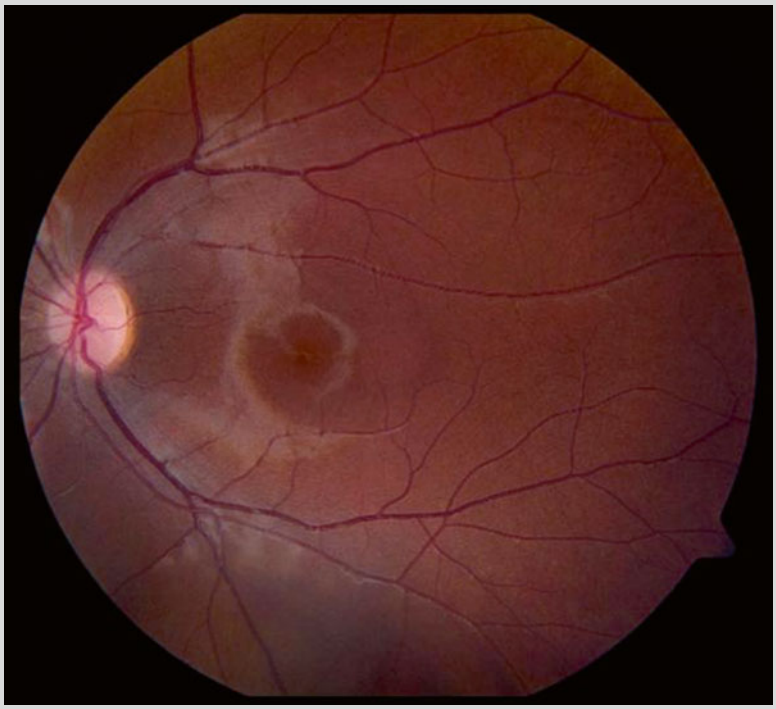

Fig. 34.2 Color fundus photo of an 11-year-old achromatopsia patient with mild optic nerve pallor and subtle macular pigmentary mottling of the left eye

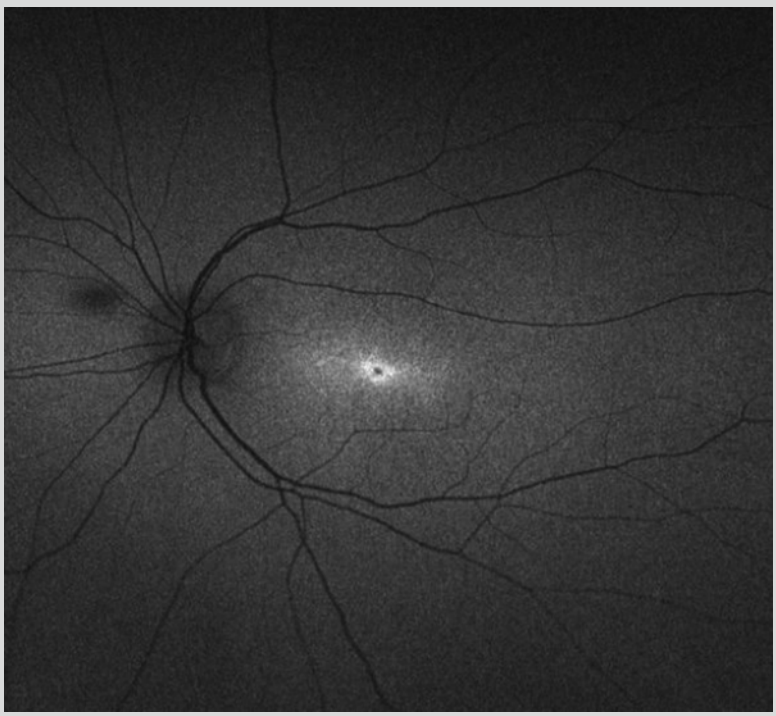

Fig. 34.3 Fundus autofluorescence (FAF) of the achromatopsia patient demonstrating increased perifoveal autofluorescence in the left eye

Comment: Achromatopsia, also known as rod monochromatism, is a nonprogressive hereditary disorder characterized by an absence of cone function with normal rod function. It has an estimated prevalence of 1 in 20,000 to 50,000 [1]. A higher prevalence (about 10 %) is seen on the island of Pingelap in the Eastern Caroline Islands of Micronesia secondary to a founder mutation in *CNGB3* [2, 3]. Poor central vision, color blindness, congenital nystagmus, and photophobia are present from birth. Although the lack of color vision is a defin-

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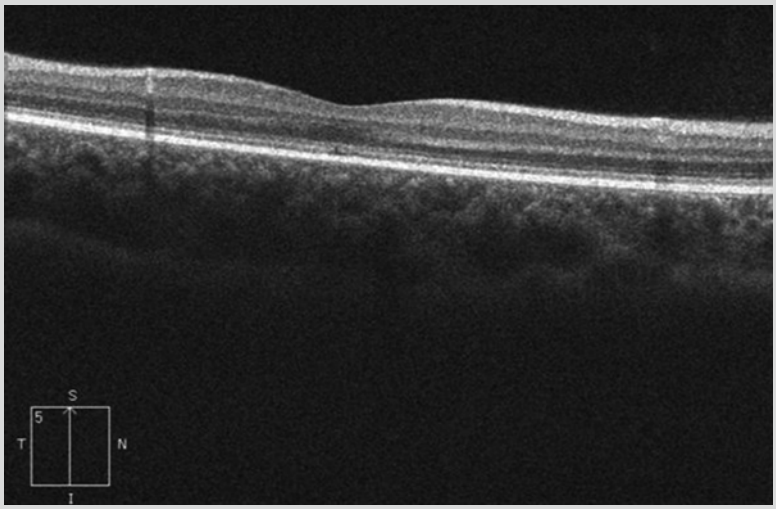

Fig. 34.4 SD-OCT of the achromatopsia patient showing subtle disruption of the IS/OS junction within the fovea and a shallow foveal depression

ing feature, variable degrees of abnormal color perception may be observed in some patients as they age [1]. As a result, achromatopsia can be categorized as complete/typical (no color perception) or, less commonly, incomplete/atypical (some degree of abnormal color perception) [1]. In the complete form visual acuity is usually <20/200, while in the incomplete form the visual acuity may be better (in the range of 20/80) [2, 3]. A "bull's eye" maculopathy or granular macular pigmentation is usually present. However, the macula can appear entirely normal. Hyperopia is a common feature of the complete form in which extrafoveal cones are reduced in number, while a normal number of cones with abnormal morphology are found in the fovea [1].

The photopic ERG is usually non-recordable in achromatopsia, while the scotopic ERG is normal, but may eventually become subnormal. On dark adaptation testing, the cone segment is abnormal and may even be absent while the rods exhibit normal function. Visual field testing may reveal central scotomas, but peripheral visual fields remain intact. Foveal hypoplasia, inner/outer segment loss, RPE disruption, and an optically empty foveal cavity are characteristic findings on optical coherence tomography (SD-OCT) [2–4]. The fluorescein angiogram may be normal or reveal window defects in areas of pigmentary change.

Achromatopsia is typically inherited in an autosomal recessive fashion and linked to five genes including *CNGA3*/*ACHM3*, *CNGB3*/*ACHM3*, *GNAT2*/*ACHM4*, *PDE6C*/*ACHM5*/*COD4*, and *PDE6H* (Table 34.2). *CNGB3* is the most commonly (50 %) involved gene [2, 3]. Mutations in *CNGA3* account for about 30 % of all cases of achromatopsia and slightly higher than that in patients of European descent (40 %) [2, 3].

Table 34.2 Genetic types of achromatopsia [1–5]

Gene	Locus	Mutation frequency (%)	Gene product
CNGA3/ACHM2	2q11.2	30	Alpha subunit of cone cGMP-gated cation channel
CNGB3/ACHM3	8q21.3	50	Beta subunit of cone cGMP-gated cation channel
GNAT2/ACHM4	1p13.3	<2	Alpha subunit of cone transducin
PDE6C/ACHM5/COD4	10q23.33	<2	Alpha subunit of cone-specific phosphodiesterase
PDE6H	12p12.3	0.3	Gamma subunit of cone photoreceptor cyclic guanosine monophosphate phosphodiesterase

There is currently no effective treatment for achromatopsia. Tinted spectacle or contact lenses may be worn to alleviate the intense photophobia [2, 3]. In patients with complete achromatopsia, red filter lenses are thought to offer the most amount of alleviation. Red filters reduce photophobia by allowing the passage of long-wavelength light, which is less stimulatory to rods, while blocking short-wavelength light. In patients with residual cone function, red tinting may interfere with color discrimination by blocking light within the visible spectrum. Consequently, reddish-brown lenses are preferred for patients with incomplete achromatopsia [6].

Bardet-Biedl Syndrome

Case 2 (Table 34.3)

Table 34.3 Case 2

Clinical History	15-year-old female with a history of a retinal dystrophy, poor vision, obesity, hyperlipidemia, renal disease, polydactyly, and retrognathia. PMH was noncontributory. She has a family history of "blindness" in a second cousin		
Base Exam		OD	OS
	BCVA	20/60	20/60
	Versions	Full	Full
	Alignment	LXT 4 (at distance)	
	CRx	−0.75 + 1.75 × 085	−2.75 + 2.00 × 095
Fundus Exam		OD	OS
	Disc	Normal	Normal
	Macula	Pigmentary mottling	Pigmentary mottling
	Vessels	Mild attenuation	Mild attenuation
	Periphery	Pigmentary mottling	Pigmentary mottling
Genetic Testing	Two heterozygous sequence variants in *BBS1* identified		
Diagnosis	Bardet-Biedl syndrome (BBS)		
Treatment	Currently no effective treatment for BBS		

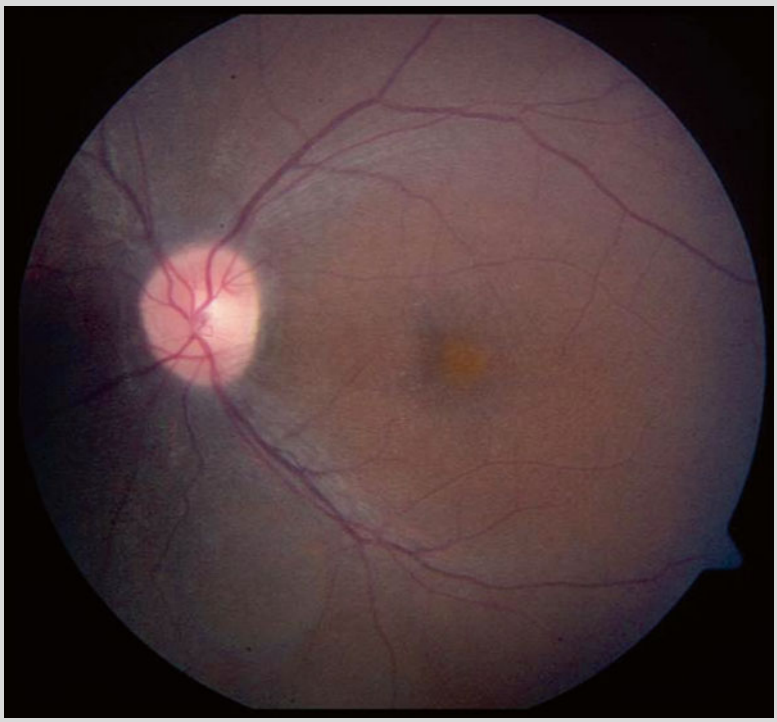

Fig. 34.5 Color fundus photo of a 15-year-old Bardet-Biedl syndrome (BBS) patient with diffuse retinal pigmentary mottling, which is most prominent within the fovea, and mild vascular attenuation of the left eye. No significant optic nerve pallor is present

The patient is a 15-year-old female with a history of a retinal dystrophy, reduced visual acuity, obesity, hyperlipidemia, renal disease, polydactyly, and retrognathia. Her fundus examination revealed bilateral diffuse retinal pigmentary mottling and mild vascular attenuation, but no significant optic nerve pallor (Figs. 34.5, 34.6, and 34.7). Genetic testing confirmed the clinical diagnosis of BBS, and she was found to have two heterozygous pathogenic sequence variations in *BBS1*.

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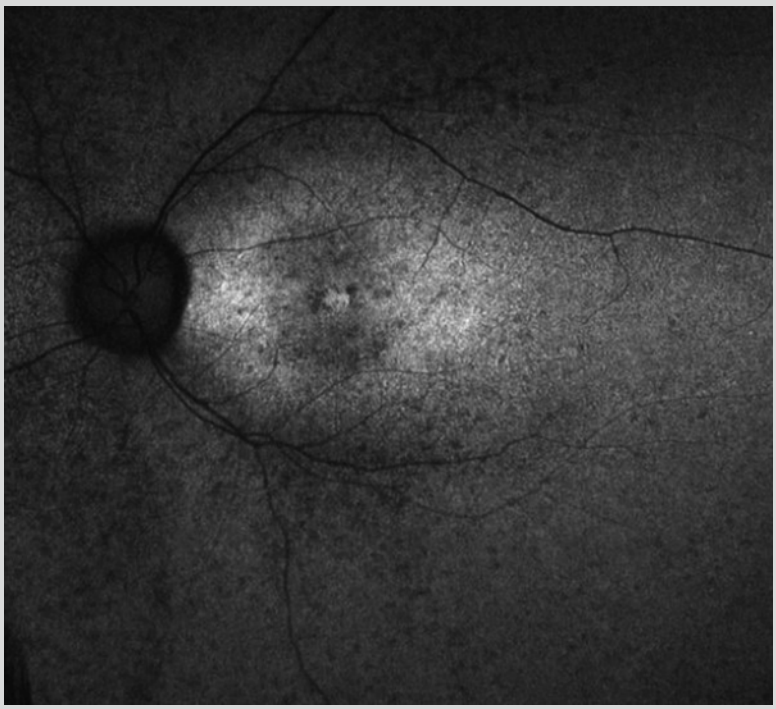

Fig. 34.6 FAF of the BBS patient reveals increased foveal autofluorescence surrounded by an inner perifoveal ring of decreased autofluorescence and an outer perifoveal of increased autofluorescence in the left eye. In addition, there is generalized mottling of both increased and decreased autofluorescence within the macula that extends beyond the arcades into the mid-periphery

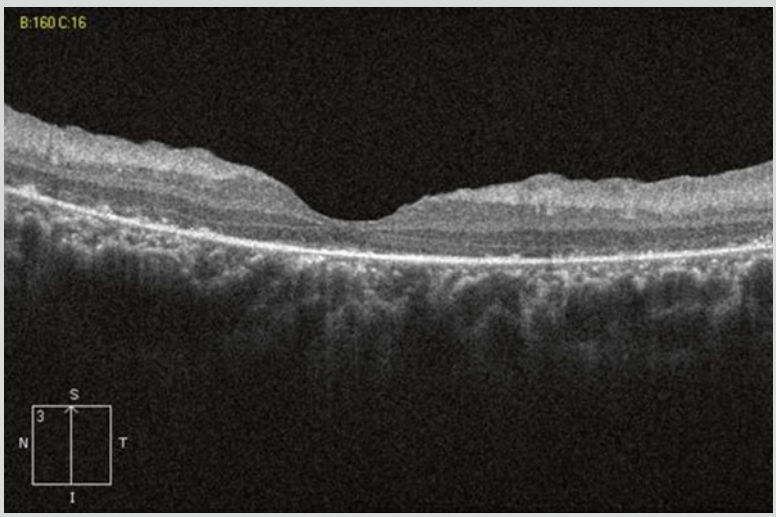

Fig. 34.7 SD-OCT of the BBS patient shows abnormal foveal contour and gross perifoveal retinal thickening. There is severe distortion of the outer retina, including disruption of the IS/OS junction and hyperreflective deposits at the level of the RPE

Comment: BBS has a worldwide prevalence of 1 in 100,000. It is more common among the Bedouin of Kuwait, occurring in 1 in 13,500 individuals. A similarly high prevalence is seen in Newfoundland [2, 3, 7]. The salient clinical characteristics of BSS are retinal degeneration, postaxial polydactyly, learning difficulties, and renal/genital tract abnormalities [8].

The clinical diagnosis of BBS requires the presence of 4 of 6 major criteria or 3 of 6 major criteria plus 2 of 11 minor criteria [9] (Table 34.4).

More than 80 % of patients with BBS have a pigmentary retinopathy with early macular involvement [7]. Parents usually notice night blindness around 8 years of age, although onset of visual impairment is variable [9]. A salt-and-pepper-like retinopathy or one with frank bone spicules may also be observed. Polydactyly and syndactyly are present in 75 % and 14 % of BBS patients, respectively. Early in the disease course of BBS minimal pigmentary changes may be observed in the setting of "normal" vision. However, severe vision loss occurs in almost all patients by 30 years of age, with more than 90 % having a vision of 20/200 or less by this age [7]. Severe color abnormalities and profoundly constricted visual fields also occur. Nystagmus is rarely (5 %) observed in BBS patients but could be an early sign of the disorder. Anosmia, resulting from the involvement of the ciliated

(continued)

Table 34.4 Clinical diagnostic criteria for BBS [9].

Major criteria (frequency, %)	Minor criteria (frequency, %)
Rod-cone or cone-rod dystrophy (90–100)	Speech delay (54–81)
Obesity (72–92)	Developmental delay (50–91)
Polydactyly (63–81)	Brachydactyly, syndactyly (46–100)
Genital anomalies (59–98)	Dental anomalies (51)
Learning difficulties (50–61)	Ataxia/poor coordination (40–86)
Renal abnormalities (20–53)	Diabetes mellitus (6–48)
	Anosmia/hyposmia (60)
	Cardiopathy (10)
	Deafness (11, 12)
	Congenital heart disease (7)

Table 34.5 Genetic types of BBS and their protein products

Type	Locus	Gene	Gene product
1	11q13.2	*BBS1*	BBS1 protein
2	16q12.2	*BBS2*	BBS2 protein
3	3q11.2	*BBS3/ARL6*	GTPase
4	15q24.1	*BBS4*	BBS4 protein
5	2q31.1	*BBS5*	Flagellar apparatus-basal body protein DKFZp7621194
6	20p12.2	*BBS6/MKKS*	Part of chaperonin complex/BBSome assembly
7	4q27	*BBS7*	BBS7 protein
8	14q31.3	*BBS8/TTC8*	Tetratricopeptide repeat domain 8
9	7p14.3	*BBS9/PTHB1*	Parathyroid hormone-responsive B1 protein
10	12q21.2	*BBS10*	BBS10 (C12ord58) chaperonin
11	9q33.1	*BBS11/TRIM32*	E3 ubiquitin ligase
12	4q27	*BBS12*	BBS12 protein
13	17q22	*BBS13/MKS1*	Meckel syndrome type 1 protein
14	12q21.32	*BBS14/CEP290/NPHP6*	Centrosomal protein 290 kDa
15	2p15	*BBS15/WDPCP*	Protein involved in regulation of septin localization and ciliogenesis
16	1q43	*BBS16/SDCCAG8*	Serologically defined colon cancer antigen 8
17	3p21.31	*BBS17/LZTFL1*	Leucine zipper transcription factor-like 1
18	10q25.2	*BBS18/BBIP1*	BBSome protein
	3q11.2	*ARL6*	ADP-ribosylation factor-like 6
	9q34.3	*INPP5E*	Inositol polyphosphate-5-phosphatase E
	20p12.2	*MKKS*[a]	McKusick-Kaufman syndrome protein

[a]Mutations in MKKS also cause McKusick-Kaufman syndrome with hydrometrocolpos, polydactyly, and cardiac defects [7]. BBS proteins assist microtubule-related transport and cellular organization processes

olfactory epithelia, may also be present in BBS [7]. The ERG is non-recordable or significantly reduced with elevated dark adaptation thresholds [7].

All BBS types are inherited in an autosomal recessive fashion. Table 34.5 lists the BBS genes and the functions of some of the proteins they encode for.

There is currently no effective treatment for BBS. Early low vision evaluation with implementation of specific interventions can ease adaptations and guide IEP in the school setting (see chapter on Low Vision).

Leber Congenital Amaurosis

Case 3 (Table 34.6)

Table 34.6 Case 3

Clinical History	8-year-old female with a history of a retinal dystrophy. PMH and FH were noncontributory.		
Base Exam		OD	OS
	BCVA	20/60-2	20/200
	Versions	Full	Full
	Alignment	Small X(T)	
	WRx	+3.00 + 2.50x095	+2.75 + 2.75x085
Fundus Exam		OD	OS
	Macula	Pigmentary mottling	Pigmentary mottling
	Vessels	Vascular attenuation with PPRPE	Vascular attenuation with PPRPE
	Periphery	Pigmentary mottling	Pigmentary mottling
Genetic Testing	Two heterozygous variations in the *CRB1* gene identified		
Diagnosis	Leber congenital amaurosis (LCA)		
Treatment	– An effective treatment for LCA has not yet been established – A gene therapy trial is currently under way for patients with LCA harboring mutations in *RPE65*		

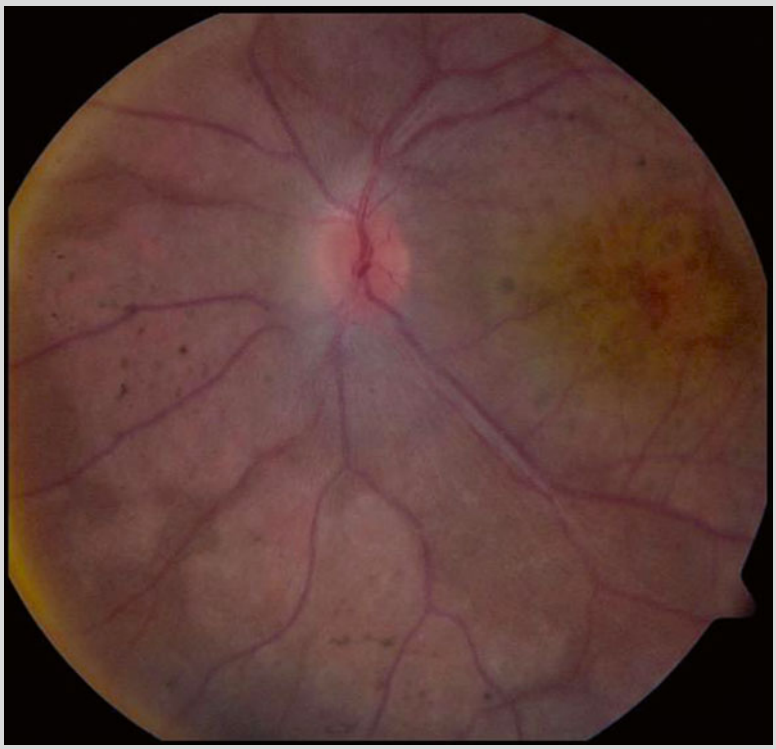

Fig. 34.8 Color fundus photo of an 8-year-old Leber congenital amaurosis (LCA) patient with RPE atrophy and pigmentary mottling within the macula and extending along the retinal vessels of the left eye. Vascular attenuation is also present

The patient is an 8-year-old female with a history of a retinal dystrophy and poor visual acuity (20/60-2 OD and 20/200 OS). On dilated ophthalmoscopy there was bilateral pigmentary mottling in the posterior pole with preservation of the para-arteriolar retinal pigment epithelium (PPRPE) and vascular attenuation (Figs. 34.8, 34.9, and 34.10). Genetic testing was significant for two heterozygous mutations in the *CRB1* gene that were determined to be disease-causing sequence variations, confirming the clinical diagnosis of LCA.

Comment: LCA refers to a group of hereditary retinal disorders with onset in early childhood or at birth. ERG reveals non-recordable photopic and scotopic waveforms in the great majority of cases. Patients typically have nystagmus, severe-to-profound visual impairment, poorly reactive pupils, nyctalopia, or photophobia (50 %). LCA has a prevalence of 1 in 30,000 to 80,000 people. Visual acuity ranges from 20/200 to CF, and rarely LP or NLP, but could be better in some cases, and may depend on the underlying genetic defect. The fundus changes in LCA

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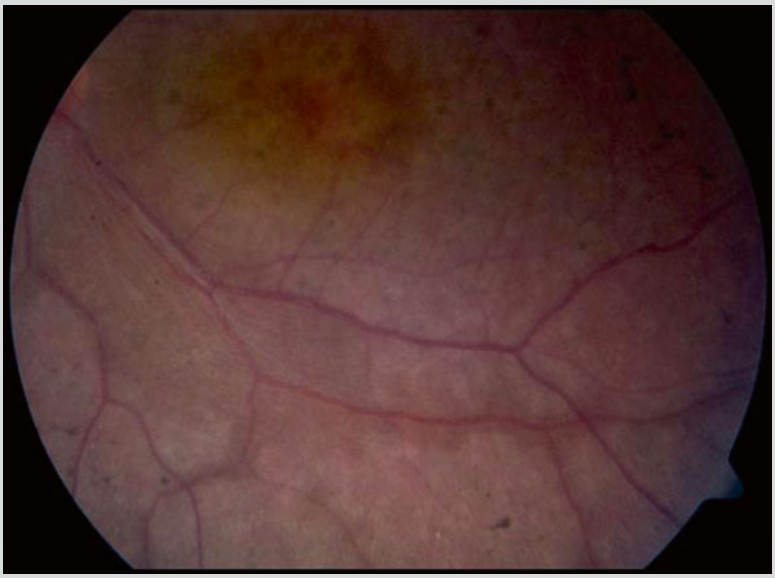

Fig. 34.9 Color fundus photo of the LCA patient highlighting preservation of the para-arteriolar retinal pigment epithelium (PPRPE), which is characteristic of mutations in *CRB1*, along the inferior arcade of the left eye

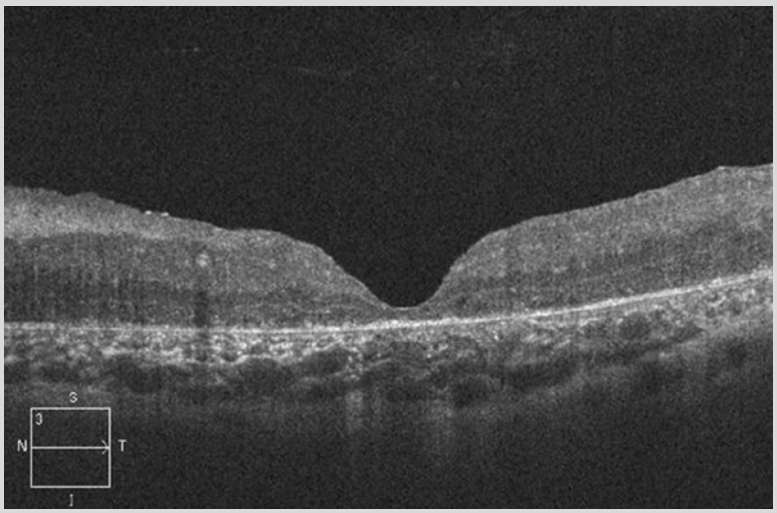

Fig. 34.10 SD-OCT of the LCA patient shows a grossly abnormal foveal contour with retinal thinning within the fovea and adjacent perifoveal thickening. There is apparent loss of the outer retina, including the photoreceptors and IS/OS junction

are quite variable. For example, the retina may appear normal early in life and in patients with *GUCY2D* mutations. A "salt-and-pepper" retinopathy, progressive retinal pigment epithelial granularity, vascular attenuation, optic nerve atrophy, pseudopapilledema, tapetal sheen, yellow flecks, nummular pigmentation, macular colobomas, chorioretinal atrophy, choroidal sclerosis, choroidal atrophy, PPRPE, preretinal fibrosis, Coats-like reaction, or a retinitis pigmentosa-like appearance have all been described. The fundus appearance may guide molecular diagnosis. For example, PPRPE is associated with mutations in *CRB1*, as in the case presented above [10]. LCA is also associated with high hyperopia in a significant proportion of patients, the oculodigital sign of Franceschetti, keratoconus, and posterior subcapsular cataracts. The presence of developmental delay, deafness, seizures, skeletal abnormalities, and renal/muscular abnormalities in some patients should prompt the search for an underlying systemic disease such as a ciliopathy.

Classically, the ERG is non-recordable before the age of one. In addition, visual fields are severely constricted. Outer nuclear layer, outer segment, and photoreceptor loss with resultant retinal thinning are observed on OCT [11]. Intraretinal cystoid spaces may also be detected on OCT in association with mutations in *CRB1* (Fig. 34.11) [12], and may respond to treatment with topical dorzolamide. Fundus autofluorescence shows a variety of patterns that depend on the underlying genetic defect and the stage of the disease [13, 14].

LCA is most commonly inherited in an autosomal recessive fashion with a high degree of phenotypic and genotypic variability (Table 34.7). Rarely, heterozygous

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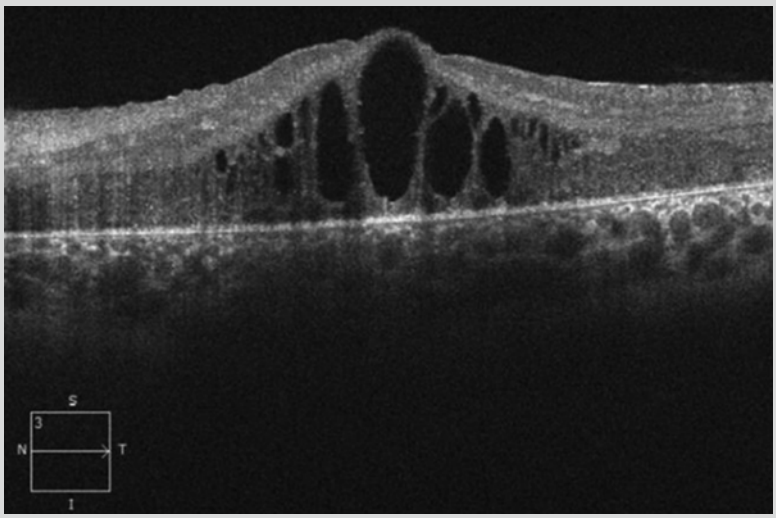

Fig. 34.11 SD-OCT exhibiting intraretinal cystoid spaces within the fovea of another LCA patient with mutations in *CRB1*

Table 34.7 Summary of the different genetic types of LCA (adapted from Table 34.1, pg. 492, of the Genetic Diseases of the Eye [2, 3])

Symbol	Locus	Gene	Mutation frequency (%)	Gene product	Clinical findings
LCA 1	17p13.1	*GUCY2D*	11.7	Retinal guanylate cyclase	Very poor vision, normal-appearing fundus, severe photophobia
LCA 2	1p31.3-p31.2	*RPE65*	6	Retinoid isomerase	Nyctalopia, transient vision improvement, relatively good vision early in life
LCA 3	14q31.3	*SPATA7*	Unknown	Unknown (possible ciliary transport)	Poor vision, retinal atrophy, attenuated vessels
LCA 4	17p13.1	*AILP1*	5.3	Rod PDE chaperone	Very progressive phenotype with atrophic maculopathy, keratoconus, cataracts, optic disc pallor, poor vision, nyctalopia
LCA 5	6q14.1	*LCA5*	1.8	Lebercilin (10), expressed in cilia	Coloboma-like macula, ciliary defect, transient improvements in vision reported
LCA 6	14q11.2	*RPGRIP1*	4.2	Protein transport	Severe vision loss, initially normal retinal appearance, progress to pigmentary retinopathy
LCA 7	19q13.33	*CRX*	1	Photoreceptor development	Severe vision loss, infantile nystagmus, some dominant cases
LCA 8	1q31.3	*CRB1*	9.9	Muller cell-photoreceptor interaction	PPRPE, Coats-like response, thickened and disorganized retina on OCT
LCA 9	1p36.22	*NMNAT1*	Unknown	Unknown	Adenylyltransferase activity
LCA 10	12q21.32	*CEP290*	15	Protein transport	Most common in patients with European descent; extremely poor vision in most, olfactory disturbances
LCA 11	7q32.1	*IMPDH1*	8.3	Guanine synthesis	Rare, diffuse RPE mottling, no pigmentary deposits
LCA 12	1q32.3	*RD3*	0.1	GUCY2D chaperone	Poor vision, atrophic macular lesion, rare
LCA 13	14q23.3	*RDH12*	2.7	All trans retinol in photoreceptor, in retinoid cycle	Rapid loss of vision, rapidly progressive maculopathy, fundus pigmentary fishnet or reticular pattern, prominent macular luteal pigment, Coats-like response
LCA 14	4q32.1	*LRAT*	0.5	Retinyl esters in retinoid cycle	Clinically like juvenile RP, similar appearance to *RPE65*
LCA 15	6p21.31	*TULP1*		Photoreceptor ciliary transport (tubby-like protein 1) (12)	Slow decline in vision, onset of VF defect around age 2, nyctalopia, yellow perifoveal annular ring, more likely to have juvenile-onset RP

(continued)

Table 34.7 (continued)

Symbol	Locus	Gene	Mutation frequency (%)	Gene product	Clinical findings
LCA 16	2q37.1	*KCNJ13*		Inwardly rectifying potassium channel Kir7.1 (12)	
LCA 17	8q22.1	*GDF6*		Member of the transforming growth factor-beta (TGFB1) superfamily	
	3q	*IQCB1*		IQ motif-containing protein B1 (12)	Lobular pattern of hypo- and hyperpigmentation outside the retinal arcades, associated with renal disease (14)
	11q13	*CABP4*		Calcium-binding protein 4 (12, 13)	Photophobia, minimal fundus changes, some have decreased foveal reflex (13)
	14q22.3	*OTX2*		Orthodenticle homolog 2 (12)	Poor vision, nyctalopia, fine, granular RPE pigmentation (15)
	1p36.22	*NMNAT1*		Nicotinamide nucleotide adenylyltransferase 1 (12)	Severe vision loss, macular coloboma (15)
		MERTK1			

mutations in the *CRX* and *IMPDH1* genes result in autosomal dominant inheritance [2, 3].

An effective treatment for LCA has not yet been established, but gene therapy trials are under way and nearing the end for patients with mutations in *RPE65*. Adeno-associated viral (AAV) vectors carrying *RPE65* DNA have been successfully utilized to deliver normal copies of the RPE65 gene in laboratory animals and in early phases of human gene therapy trials [15]. Ongoing clinical trials for gene replacement or other types of therapy in LCA can be found at http://clinicaltrials.gov.

Stargardt Disease

Case 4 (Table 34.8)

Table 34.8 Case 4

Clinical History	11-year-old male with a history of a retinal dystrophy and poor vision since early childhood. PMH and FH were noncontributory.		
Base Exam		OD	OS
	BCVA	20/200	20/250
	Versions	Full	Full
Fundus Exam		OD	OS
	Disc	Mild temporal ON pallor	Mild temporal ON pallor
	Macula	Large area of foveal atrophy with diffuse white fleck-like lesions in the posterior pole	
	Vessels	Normal	Normal
	Periphery	Extension of fleck-like lesions into the mid-periphery	
Genetic Testing	Two heterozygous mutations in the *ABCA4* gene identified		
Diagnosis	Stargardt disease		
Treatment	– No current treatment for Stargardt disease – Avoidance of vitamin A supplementation is recommended in order to reduce lipofuscin accumulation – Patients with the *ELOVL4* mutation may benefit from DHA supplementation		

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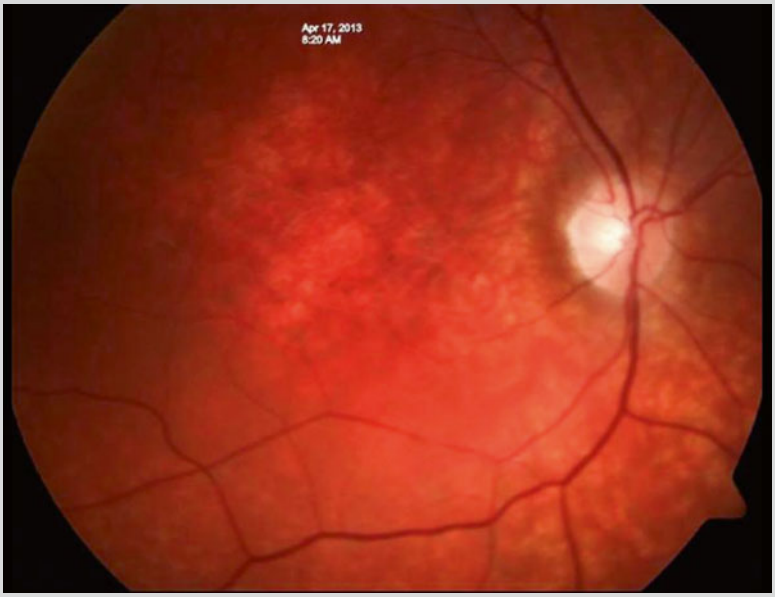

Fig. 34.12 Color fundus photo of a 14-year-old Stargardt disease patient with multiple fleck-like lesions scattered throughout the posterior pole, macular atrophy, and mild temporal optic nerve pallor of the right eye

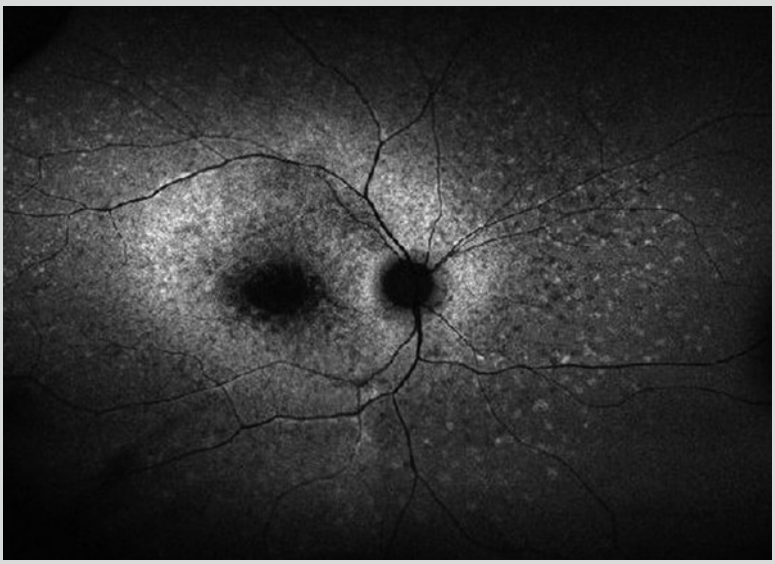

Fig. 34.13 FAF of the Stargardt disease patient displaying decreased foveal autofluorescence surrounded by generalized perifoveal increased autofluorescence that extends peripapillary in the left eye. There is also diffuse mottled increased and decreased autofluorescence present throughout the posterior pole

The patient is a 14-year-old male with a history of a retinal dystrophy and poor vision since early childhood. His most recent visual acuity was 20/200 OD and 20/250 OS. On dilated fundus examination multiple fleck-like lesions were seen scattered throughout the posterior pole and mid-periphery of both eyes. In addition, a large area of atrophy was present in the fovea bilaterally. Mild temporal optic nerve pallor was also noted (Figs. 34.12, 34.13, and 34.14). Genetic testing confirmed the clinically suspected diagnosis of Stargardt disease. Two heterozygous mutations in the *ABCA4* gene were identified.

Comment: Stargardt disease is the most common juvenile hereditary macular dystrophy with a prevalence of 1 in 10,000 [16, 17]. The age of onset can range from 5 years to 80 years of age, with a majority of patients presenting within the first two decades of life without gender predilection [2, 3]. In addition to variability in onset of disease, the clinical presentation and course of progression are vastly heterogeneous. Patients usually present with decreased central vision and in some cases the fundus can appear normal. The degree of central vision loss may be out of proportion to the macular changes, resulting in the dismissal of many cases as having functional vision loss. Fluorescein angiography or fundus autofluorescence imaging will reveal changes in the retina of such individuals and clinch the diagnosis. Characteristically,

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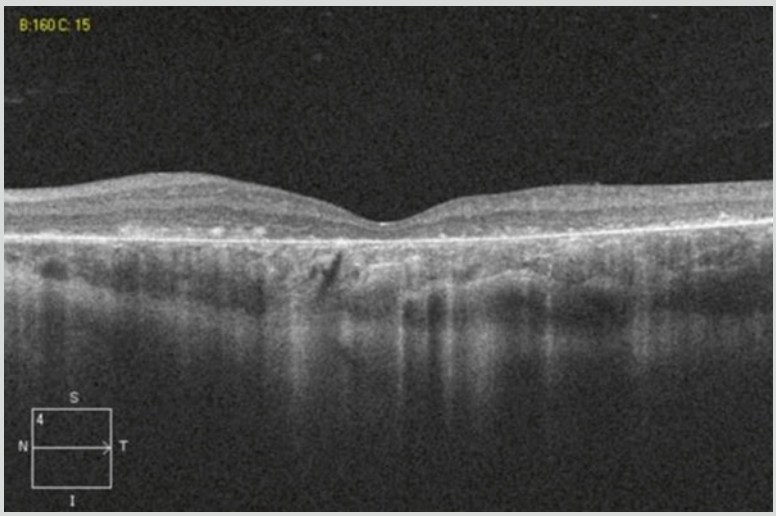

Fig. 34.14 SD-OCT of the Stargardt disease patient shows diffuse thinning and distortion of the fovea. There are distinctive hyperreflective deposits at the level of the inner RPE and outer retina

yellow pisciform flecks are scattered throughout the posterior pole. These lesions are "fish-tail" shaped and at the level of the retinal pigment epithelium (RPE). The flecks represent groups of enlarged RPE cells packed with a granular substance, which is thought to be lipofuscin [2, 3]. A disease spectrum exists, ranging from fundus flavimaculatus, occurring without a macular dystrophy in adulthood, to Stargardt disease, which presents in late childhood/adolescence. The current preferred terminology for all cases is Stargardt disease. Some patients have a bull's eye maculopathy with a "beaten bronze" appearance. Peripheral pigmentary changes may develop with age, and will lead to what has been called cone-rod dystrophy. Mild-to-moderate color vision abnormalities may develop as the disease progresses, and some patients may complain of increasing difficulties with night vision. Ancillary testing with retinal imaging, visual field, and electroretinography (ERG) may aid in the diagnosis and characterization of the retinal phenotype (Table 34.9).

Peripheral visual fields are normal in early stages. With time, a relative central scotoma, that often becomes absolute, may develop [17]. Fundus imaging with fluorescein angiography, fundus autofluorescence, and SD-OCT can be helpful in the diagnosis of Stargardt disease (Table 34.9).

The classic dark or "silent" choroid sign on fluorescein angiography is secondary to blockage of choroidal fluorescence by RPE that is packed with lipofuscin and occurs in 62–86 % of patients [2, 3, 17]. The flecks demonstrate early blockage and late hyperfluorescent staining. Other findings include window defects in areas of the macular atrophy and other hyperfluorescent spots that are not associated with the clinical flecks. On FAF, areas of decreased autofluorescence (AF) correlate with RPE loss. Yellowish flecks, on the other hand, correspond to areas of increased AF [16]. The macula may contain mottled areas of decreased AF or it can appear normal with a relatively preserved autofluorescence signal [16]. Photoreceptor loss, corresponding to atrophic macular areas with decreased foveal thickness, is seen on OCT [19]. A better visual prognosis is observed in the presence of an intact photoreceptor layer (preserved ellipsoid zone) in the setting of inner retinal atrophy. The retinal flecks correspond to hyperreflective deposits in the inner RPE and the outer nuclear layer on OCT. The ERG can be normal; however a significant number of patients or more may have photopic abnormalities. In patients with a cone-rod dystrophy phenotype, the scotopic ERG is also

Table 34.9 Ancillary tests in Stargardt disease [2, 3, 16–18]

Visual Field	– Normal early – Relative central scotoma, that often becomes absolute, may develop
FA	– Classic dark or "silent" choroid sign secondary to blockage by lipofuscin (62–86 % of patients) – Flecks demonstrate early blockage and late hyperfluorescence – Hyperfluorescent spots that are not associated with the clinical flecks – Window defects in areas of macular atrophy
FAF	– Increased and decreased AF corresponding to flecks and RPE loss, respectively – Macula may appear normal or contain mottled areas of decreased AF
OCT	– Photoreceptor loss (corresponds to macular atrophy with decreased foveal thickness) – Flecks appear as hyperreflective deposits at the level of the inner RPE or outer retina
ERG	– Can be normal – 1/3 have photopic abnormalities – Abnormal scotopic response in cone-rod dystrophy phenotype – Multifocal ERG subnormal within the macula
EOG	– Abnormal in up to 75 %

(continued)

Table 34.10 Genetic types of Stargardt disease [2, 3, 16]

Type	Gene	Locus	Inheritance	Gene product
STGD1	*ABCA4*	1p22.1	Autosomal recessive	Retina-specific adenosine triphosphate (ATP)-binding cassette transporter (ABCR)
STGD3	*ELOVL4*	6q14.1	Autosomal dominant	Photoreceptor-specific component of polyunsaturated fatty acid elongation system
STGD4	*PROM1*	4p	Autosomal dominant	Pentaspan transmembrane glycoprotein, prominin-1

abnormal. The multifocal ERG is subnormal within the macula in all patients. The EOG is abnormal in up to 75 % of cases.

Stargardt disease is inherited predominantly in an autosomal recessive mode, but an autosomal dominant subset exists [2, 3]. Recessive Stargardt disease is caused by mutations in the *ABCA4* gene on chromosome 1p21-p22. Retina-specific adenosine triphosphate (ATP)-binding cassette transporter (ABCR), which is encoded by *ABCA4* [16], is present in the rod and cone outer segment rims. ABCR is responsible for the extracellular transport of all-trans-retinol produced in light-exposed photoreceptor outer segments. Mutations in the *ELOVL4* (elongation of a very-long-chain fatty acid-like 4) gene on chromosome 6q14 cause autosomal dominant Stargardt disease. *ELOVL4* encodes a photoreceptor-specific component of the polyunsaturated fatty acid elongation system (Table 34.10).

The visual prognosis is quite variable. Half of the patients have vision in the range of 20/200–20/400, while 25 % of patients maintain a visual acuity of 20/40 or better in at least one eye [2, 3]. However, a certain subset, especially those patients with onset of symptoms in the first decade of life, may develop profound vision loss [18]. A significant proportion of patients labeled as having recessive cone-rod dystrophy have mutations in *ABCA4,* the gene responsible for Stargardt disease, again demonstrating the phenotypic variability. Prognostic factors related to poorer visual outcome include earlier disease onset, larger number [>/= 2] of identifiable mutations in *ABCA4* [18], and specific select genotypes. The autosomal dominant form is often less severe.

There is currently no effective treatment for Stargardt disease. Some studies in murine model of Stargardt disease suggest that vitamin A supplementation may contribute to lipofuscin accumulation. As a result, we instruct patients to avoid vitamin A supplementation. In the autosomal dominant form, there is also an inverse relationship between functional ELOVL4 activity and docosahexaenoic acid (DHA) levels in red blood cell lipids. Evidence exists that DHA may slow the progression of photoreceptor and RPE cell death. Therefore, patients harboring the *ELOVL4* mutation could potentially benefit from DHA supplementation. Gene therapy trials for Stargardt disease are under way and can be found at http://clinicaltrials.gov.

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Inherited Vascular Disorders

35

Johane Robitaille

Abstract

Peripheral avascularity of the retina at birth that is not related to prematurity is a nonspecific finding that can occur in a variety of syndromes or in isolation. The majority of these conditions are hereditary (autosomal dominant, autosomal recessive, X-linked recessive, and X-linked dominant). A thorough review of systems and evaluation by a clinical geneticist is warranted. This is particularly important for newly diagnosed cases, even in the absence of a family history, as many of these conditions can manifest a high degree of intra-familial variability. Eye examinations should be performed on parents and siblings and may require intravenous fluorescein angiography (IVFA) to evaluate for subtle manifestations of the disease. The corroboration of disease manifestations in relatives portends management implications in both patients and affected family members and enhances the accuracy of genetic counseling for families at risk of having future affected children. Genetic testing should be offered based on the clinical presentation to confirm the diagnosis and identify relatives at risk. The management including interval surveillance and decision to treat is predominantly based on age of the patient, extent and severity of the disease, and the presence of complications.

Keywords

Developmental retina vascular disease • Blindness prevention • Genetic counseling • Familial exudative vitreoretinopathy • Norrie disease • Coats disease • Persistent fetal vasculature • Incontinentia pigmenti • Osteoporosis • Microcephaly • Retinal dysplasia

Identifying the Cause of the Vascular Disorder

A number of conditions may result in developmental retinal vascular disorders, either in isolation or as part of a syndrome. The initial management involves determining the underlying etiology while identifying immediate treatment needs to prevent complications that may lead to poor visual outcomes. A review of systems should be elicited, as well as a family history of similar eye disease or of blindness. Physicians should inquire specifically about a history of bone fractures, microcephaly, developmental delays and other neurological problems, hearing loss, progressive muscle weakness, a history of skin lesions in the first year of life with subsequent scarring, and dental anomalies.

A complete eye examination should be performed in the patient and relatives at risk, starting with parents and siblings. IVFA is necessary to evaluate for mild disease that may be missed on ophthalmoscopy, to delineate the area of avascular retina and to highlight the vascular abnormalities [1]. In addition, many conditions can manifest highly asymmetrical disease, with features only appreciated using IVFA in an otherwise presumed "normal" eye using ophthalmoscopy alone.

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Determining unilaterality versus bilaterality is key in identifying the correct differential diagnosis (Tables 35.1 and 35.2).

Physicians should inquire about siblings and/or offspring (including the possibility of current or future pregnancy) and note their ages. Young children at risk should be examined promptly, even if the proband is still undergoing work-up to identify the cause of the disease, as they are at particular risk for the development of blinding complications that can be prevented if managed early [2]. The family should be referred to medical genetics for a thorough assessment of systemic features to enhance the accuracy of the diagnosis, prognosis, and genetic counseling. Genetic testing can be arranged based on the clinical presentation.

Differential Diagnosis (Tables 35.1 and 35.2)

Bilateral cases should be considered hereditary unless proven otherwise. Unilateral presentation does not rule out an underlying hereditary condition, although it is much less likely. Unilateral cases without a family history or associated systemic disease, especially in boys, are likely to represent Coats disease. Coats disease is a non-hereditary condition, with approximately 70 % of cases occurring in males. Physicians should review the ocular features and IVFA, looking for aneurysmal dilatations that are typically found in Coats disease.

Table 35.1 Differential diagnosis for unilateral avascular retina and associated complications

Systemic disease	Ocular features	Diagnosis
None	Aneurysmal dilatations	Coats disease
None	Persistent hyaloid vasculature	Persistent fetal vasculature
Present	Follow differential diagnosis in Table 35.2	

In cases in which retinal detachment or the presence of fibrovascular scar tissue precludes the assessment of the retinal vasculature, and depending on the ocular features, it may be necessary to rule out the cicatricial consequences of toxocara endophthalmitis or an occult intraocular foreign body

Table 35.2 Differential diagnosis for avascular retina and associated complications

Systemic features	Special notes on ocular features	Diagnosis	Gene(s)
None		FEVR	*NDP, FZD4, LRP5, TSPAN12, ZNF408*
Decreased bone density with increased risk of bone fractures	Severe ocular phenotype, typically presenting as retrolental fibrovascular mass	FEVR	*LRP5*
Developmental delay, hearing loss		Norrie disease and FEVR	*NDP*
Microcephaly, characteristic facies, developmental delay, lymphedema	Chorioretinopathy prominent feature but may be absent	Microcephaly-lymphedema-chorioretinal dysplasia/chorioretinal dysplasia, microcephaly, and mental retardation	*KIF11*
Bone demineralization with bone deformities, microcephaly	Severe ocular phenotype, typically presenting as retrolental fibrovascular mass	Osteoporosis pseudoglioma syndrome	*LRP5*
Blistering skin lesions in first year of life, teeth abnormalities, developmental delay, seizure disorder, microcephaly		Incontinentia pigmenti	*IKBKG* or *NEMO*
Progressive muscle weakness, sensorineural hearing loss	Acquired vaso-obliteration reported	Facioscapulohumeral dysplasia	*D4Z4*
Syndromes featuring retinal dysplasia as a nonspecific ocular feature	Nonspecific retinal dysplasia	For example Walker-Warburg syndrome	Causative gene depending on specific syndrome

Acquired capillary closure with subsequent avascular areas of retina with or without neovascularization in the mid-periphery, as can be seen in Eales disease and sickle cell disease, may present with features that overlap with developmental vascular disorders. In cases where retina detachment or presence of fibrovascular scar tissue precludes the assessment of the retinal vasculature and depending on the ocular features, it may be necessary to rule out juvenile X-linked retinoschisis

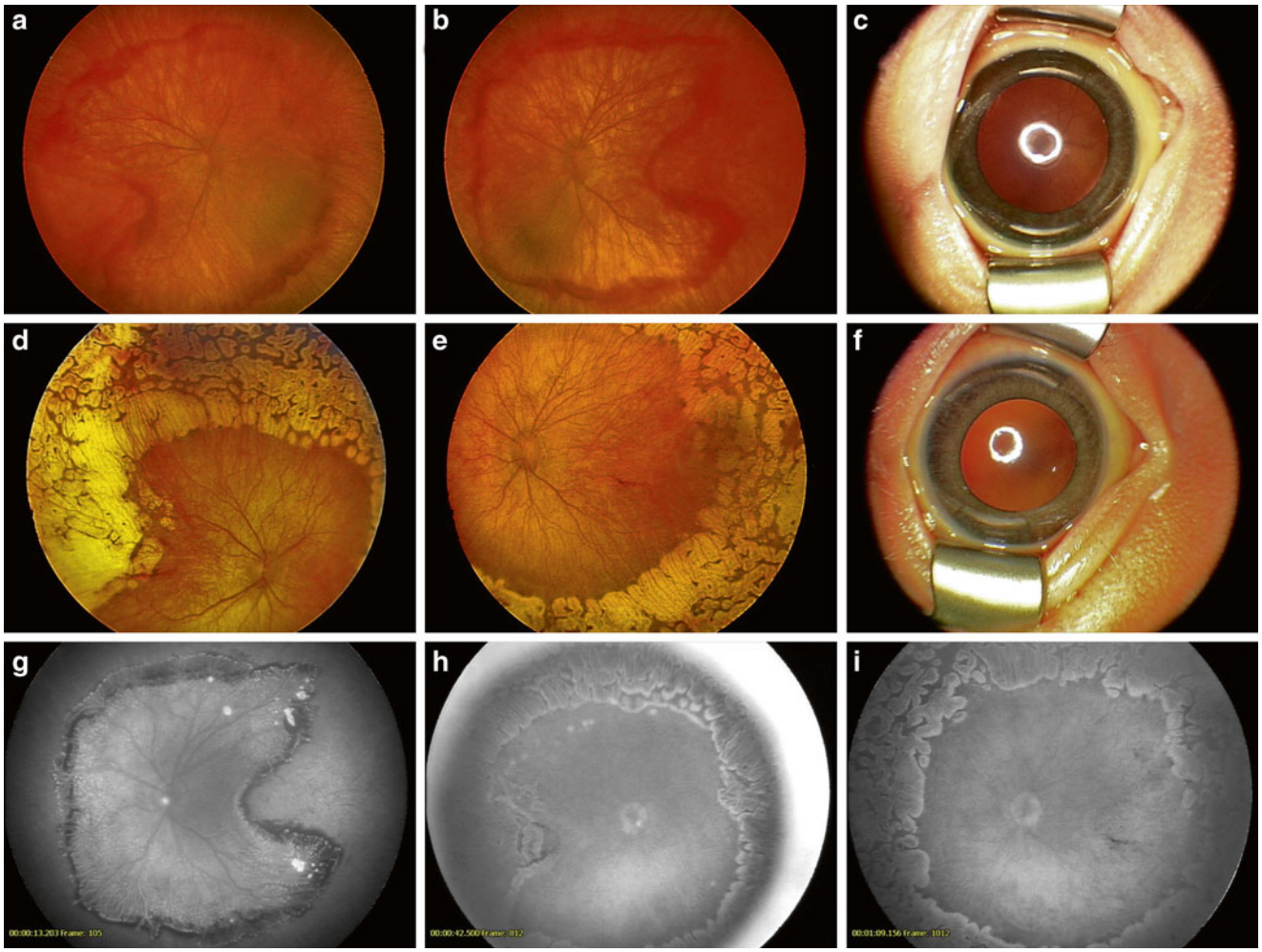

Fig. 35.1 Fundus photography (RetCam 3, Clarity Medical Systems, Pleasanton, CA) of infant with Norrie disease delivered preterm at 34 weeks. (**a**, **b**) Fundus photographs of the *right* and *left* eyes demonstrating incomplete retinal vasculogenesis with hemorrhagic border, dilation, and incomplete vascularization of the fovea. (**c**, **d**) Sixteen weeks posttreatment images demonstrating regression of the retinal neovascularization and hemorrhage, except at untreated border of retinal vascularization temporally in both eyes. Reprinted with permission from Robert A. Sisk, Robert B. Hufnagel, Sindura Bandi, et al. Planned Preterm Delivery and Treatment of Retinal Neovascularization in Norrie Disease. Ophthalmology vol 121/no 6, p 1312, 2014

Bilateral cases with or without a family history are likely to represent familial exudative vitreoretinopathy (FEVR). FEVR is a heterogeneous disorder, and to date five genes have been identified that account for approximately 50 % of cases of FEVR: *NDP* [3], *FZD4* [4], *LRP5* [5, 6], *TSPAN12* [7, 8], and, more recently, *ZNF408* [9]. In general, the ocular phenotypes resulting from disease caused by each of the genes overlap significantly, and genetic testing is necessary to distinguish the subtype and confirm the diagnosis. FEVR is usually found in isolation, with the exception of disease caused by *LRP5* mutations that may be associated with decreased bone density and an increased risk of developing bone fractures [10, 11], and in X-linked recessive cases in which relatives with FEVR or Norrie disease have been reported in the same family, i.e., caused by the same mutation in the *NDP* gene (example case of Norrie disease, Fig. 35.1) [12]. Genetic counseling and follow-up of EVR cases caused by *NDP* mutations should take into consideration the possible development of additional clinical features of Norrie disease in the first decades of life and the potential for newborns at risk to develop Norrie disease even when older relatives only show signs of EVR.

Cases

Case Example 1

A boy was examined at 4 years of age when he presented with non-central, unsteady, and unmaintained fixation in both eyes and bilateral retinal folds in conjunction with peripheral avascular areas of retina documented by IVFA. He did not have a mutation in the known FEVR genes, but was found to have a mutation in *KIF11* (p.A218Gfs*15). He was subsequently noted to have microcephaly, and despite normal development to date he will be at risk of having an affected child that may have severe developmental delay as part of the spectrum of KIF11-related disease (see Table 35.2). The parents did not carry the mutation.

This case demonstrates the importance of making an accurate diagnosis and the role of genetic testing to confirm the diagnosis. Details of this case are described in a recent study [13].

Management Approach

There are no specific guidelines to determine who should be treated and the method of treatment versus observation alone. However, the presence of certain factors can guide the decision to intervene including the age of the patient, the extent of avascular retina and abnormal vasculature, and the presence, location, and/or extent of exudates and neovascularization. For instance, a child less than 3 years of age with a large area of avascular retina is at particular risk of rapidly developing blinding complications as opposed to an adult with avascular retina and no proliferative or vitreoretinal tractional changes. In particularly severe cases, complications can occur in utero or within weeks of birth, hence the need to identify and screen young children at risk, including arranging for an eye examination in newborns at risk as soon as possible after birth. Disease threatening to involve the macula with potential for subsequent scarring should also be treated promptly. Treatment options include laser, cryotherapy, anti-VEGF agents, and surgery, depending on the ocular findings and the best judgment of the treating vitreoretinal specialist. Prophylactic treatment of the avascular retina with laser should be considered in young children who have lost vision in the fellow eye or who cannot travel to a medical facility for recommended follow-up examinations.

When a decision is made to observe, the frequency of examinations is based on the same criteria that determine the need to treat. A newborn with avascular retina should be evaluated more frequently in the first year of life with slow taper to yearly examinations during the childhood years. A follow-up schedule for incontinentia pigmenti was proposed by Holmström and Thorén [14], who suggested eye examinations at least monthly for the first 3–4 months of life, decreasing to 3-month intervals for 1 year, and then twice a year up to 3 years, beyond which the examination intervals are based on the clinical findings. O'Doherty et al. [15] added that if the retina is normal after an examination under anesthesia, it will remain normal and follow-up can be done in clinic biannually. This is especially true if IVFA is normal. However, if the retina is abnormal, the authors recommend more frequent retinal examinations: every 2 weeks for the first 3 months, monthly for the following 6 months, and every 3 months for 1 year. These guidelines are reasonably applicable to all conditions that can result in developmental vascular abnormalities of the retina.

Case Example 2

A 2-month-old infant male presented with bilateral congenital retinal folds. His parents failed to show peripheral avascular zones on fundus examination and IVFA was normal. The mother was found to have a peripheral retinal tear and possible retinal hole in areas of lattice degeneration that were treated with laser. The review of systems and family history were unremarkable, and the family was referred to medical genetics. No systemic abnormality was found, and he was diagnosed with FEVR. Genetic testing of the known FEVR genes at the time revealed *FZD4* mutation p.I114T in both the infant and his mother.

The family underwent genetic counseling and elected to have a second child. Arrangements were made to examine the child on the day he was born. Hemorrhages initially blurred the fundus details but 3 days later the hemorrhages cleared sufficiently to enable the detection of bilateral temporal areas of avascular retina with a large exudative retinal detachment involving the macula in the right eye. Bilateral vitreous bands extended from both maculas to the inferotemporal aspect of the lens, suggesting an impending exudative detachment in the left eye. Confluent treatment of the avascular retina with a diode laser was performed

(continued)

the following day, and the vitreous bands disappeared, leaving a partial fold in the right eye and the macula intact in the fellow eye. The visual acuity at age 8 was 1/50 OD and 6/19 OS. In the absence of early diagnosis and treatment, the disease likely would have progressed to bilateral congenital retinal folds, such as was the case for the older brother who at age 11 had a vision of 1/25 OD and 1/30 OS.

This case illustrates the high intra-familial variability common in these conditions, and the importance of accurate genetic counseling and early management of ocular complications to improve visual outcomes. Details of this case study are part of a previous publication [2].

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The Phakomatoses

36

Virginia Miraldi Utz and Elias I. Traboulsi

Abstract

The phakomatoses are a heterogeneous group of hereditary disorders in which loss of function of a tumor-suppressor gene leads to tumor formation of the skin, central nervous system, viscera, and eyes. Patients may initially present with ocular manifestations, and accurate diagnosis and expeditious referral for systemic evaluation are paramount, and in some cases, life saving. This chapter discusses the ophthalmologic manifestations of neurofibromatosis 1 and 2, tuberous sclerosis complex, von Hippel-Lindau disease, and familial adenomatous polyposis (Gardner syndrome).

Keywords

Phakomatoses • Neurofibromatosis • NF1 • NF2 • Tuberous sclerosis • Von Hippel-Lindau • Familial adenomatous polyposis • Gardner syndrome

Introduction

The phakomatoses (Greek *phakos*, meaning birthmark) are a heterogeneous group of hereditary disorders classically characterized by hamartomas of the skin, central nervous system, viscera, and eye. However, some associated lesions may be classified histopathologically as choristomas or true neoplasms (Table 36.1) [1]. With advances in molecular diagnosis and better understanding of the pathophysiologic basis of these disorders, the authors elected to include only those disorders with the following genetic and pathophysiologic criteria:

1. Autosomal dominant inheritance pattern
2. Gene identified
3. Mechanism involves cellular proliferation secondary to loss of function of a tumor-suppressor gene and its respective protein product

The molecular, diagnostic criteria and major ophthalmologic findings and management for each disorder will be discussed and case examples presented (Table 36.2).

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Table 36.1 Tissue definitions

Hamartomas: overgrowths of mature tissue normally present in the involved site (Mnemonic: *H*amartomas are *H*ome) Examples: Sakurai-Lisch nodules, retinal astrocytic hamartomas, hemangiomas, retinal hemangioblastoma
Choristomas: benign tumors derived from tissue not normally present in the tumor's location Examples: dermoid, lipodermoids, teratomas
Neoplasms: new, abnormal tissue that grows by cellular proliferation more rapidly than normal tissue and may demonstrate partial or complete lack of structural organization

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Table 36.2 The phakomatoses: gene, protein, diagnostic criteria, select ocular manifestations and key histopathology

Disorder	Gene	Protein	Clinical diagnostic criteria	Select ocular manifestations	Key histopathology
Neurofibromatosis 1 (NF1, von Recklinghausen disease) (OMIM 162200)	17q11.2	Neurofibromin	*>2 of following*: – ≥6 café au lait spots[a] – ≥2 neurofibromas or one plexiform neurofibroma – Freckling in the axillary or inguinal regions – Optic pathway glioma – ≥2 iris hamartomas (Sakurai-Lisch nodules) – Osseous lesion such as sphenoid wing dysplasia or thinning of the long bone cortex with or without pseudoarthrosis – A first-degree relative meeting the above criteria	*Orbital and adnexal* – Orbitotemporal neurofibromas[b] *Eye* – Prominent corneal nerves – Iris ectropion[b] – Iris hamartoma (Sakurai-Lisch nodules) – Retinal hamartomas – Choroidal hamartomas *Neuro-ophthalmologic* – Glaucoma – Optic pathway gliomas *Refractive* Ametropia	*Sakurai-Lisch nodules*: Condensation of spindle cells (hamartomas) on anterior iris *Plexiform neurofibroma*: disorderly proliferation of Schwann cells an endoneural fibroblasts in mucinous matrix *Choroidal hamartoma*: increased melanocytes, ovoid bodies (resemble tactile corpuscles, composed of Schwann cell processes) *Optic nerve glioma*: spindle-shaped astrocytic processes with eosinophilic filaments (Rosenthal fibers)
Neurofibromatosis 2 (NF2) (OMIM 101000)	22q12.2	Merlin or schwannomin	– Bilateral eighth nerve masses – A first-degree relative with NF2 and either unilateral eighth nerve mass or two of the following: neurofibroma, meningioma, glioma, schwannoma, early PSC	*Eye* – Lenticular opacities (e.g., PSC) – Retinal hamartoma – Combined hamartoma of the retina and RPE (CHRRP) – Epiretinal membrane (ERM) *Neuro-ophthalmologic* – Optic nerve sheath meningioma – Cranial nerve palsies	*Optic nerve sheath meningioma*: Bland meningothelial cells arranged in a whorls and may contain calcified psammoma bodies
Retinal angiomatosis (von Hippel-Lindau, VHL) (OMIM 193300)	3p25-26	Protein VHL (pVHL)	*Isolated cases*: – ≥2 hemanioblastomas (retinal or CNS) – Single hemangioblastoma with a visceral manifestation (pheochromocytoma, renal epididymal cysts, renal carcinoma) *Familial*: – Single hemangioblastoma or visceral complications	– Retinal hemangioblastoma – Optic nerve head hemangioblastomas	*Retinal hemangioblastoma*: endothelial-lined channels separated by vacuolated foam cells (explains characteristic exudation and leakage on IVFA)

Tuberous sclerosis complex (TSC) (Bourneville disease) (OMIM 191100 and 613254)	9q34 16p13.3	TSC1 (hamartin) TSC2 (tuberin)	*Major features*: – Facial angiofibromas or forehead plaque – Nontraumatic ungula or periungual fibroma – Hypomelanotic macule (>3) – Shagreen patch [Wood lamp] – Multiple retinal nodular hamartomas – Cortical tuber – Subepedymal nodule – Subependymal giant cell astrocytoma – Cardiac rhabdomyoma – Lymphangiomyomatosis – Renal angiomyolipoma *Minor features*: – Randomly distributed pits in dental enamel – Hamartomatous rectal polyps – Bone cysts – Cerebral white matter radial migration – Gingival fibromas – Nonrenal hamartomas – Retinal achromic patch – "Confetti" skin lesions – Multiple renal cysts *Definite: 2 major or 1 major + 2 minor* *Probable: 1 major + 1 minor* *Possible: 1 major or 2 or more minor*	*Eye* – Astrocytic hamartomas 1. Flat, translucent peripheral fundus 2. Elevated, nodular, calcific "mulberry-like" lesion (juxtapapillary) – Peripheral depigmented or hypopigmented lesions	*Astrocytic hamartoma*: retinal astrocytes with small oval nuclei, long processes, varying degrees of calcification
Gardner syndrome (OMIM 175100)	5q21-22	APC	No formal criteria, but following findings: – Familial adenomatous polyposis – Osteomas – Soft tissue tumors – POFLs	*Eye* POFLs: multiple (>3–4) hyperpigmented pleomorphic (round, comma, pencil shaped), flat lesions, usually bilateral *Orbit* Orbital osteoma Epidermoid cyst of eyelid	*POFLs*: hyperplastic RPE cells containing melanin and lipofuscin that may be a monolayer or extend from Bruch's membrane to occupy the full thickness of the retina. Lesions are best classified as adenomas

PSC posterior subcapsular opacity, *CNS* central nervous system, *IVFA* intravenous fluorescein angiography, *POFLs* pigmented ocular fundus lesions

[a]>0.5 cm in diameter in prepubertal children or >1.5 cm in diameter in postpubertal individuals

[b]Associated with ipsilateral glaucoma in the involved eye

Neurofibromatosis Type 1

Neurofibromatosis type I (NF1) is a multi-system disorder characterized by the presence of café-au-lait spots, axillary and inguinal freckling, Sakurai-Lisch nodules of the iris, cutaneous and CNS neurofibromas, and optic pathway gliomas (Table 36.2) [2, 3]. Mutations in the *NF1* gene located on chromosome 17q11.2 encoding neurofibromin lead to NF1, with an incidence of 1 in 3000–5000 live births [4]. A wide spectrum of ophthalmologic manifestations can be present in patients with NF1 and involve the skin, periorbita, anterior segment, posterior segment, and optic pathway [5, 6]. Specific ophthalmologic findings of diagnostic and clinical significance for the pediatric ophthalmologist include high incidence of ametropia (refractive error) [7], Sakurai-Lisch nodules, glaucoma [8, 9], orbitotemporal neurofibromas, and optic pathway gliomas [5].

Iris Hamartomas (Sakurai-Lisch Nodules)

Sakurai-Lisch nodules are one of the major diagnostic criteria in NF1. They are present in 33 % of NF1 patients at 2.5 years of age and increase with age to approximately 95–100 % in patients over 30 years of age [10]. In the pediatric population, they are fairly specific for NF1, although lesions can occur rarely in normal individuals. Clinically, the hamartomas appear as raised, dome-shaped elevations with color ranging from white and yellow to tan depending on the background color of the iris (Fig. 36.1a, b) [11]. For example, in patients with brown irides, the lesions may appear cream colored, while in light irides, they may appear brown. Lisch nodules have a distinct appearance; however, they must be distinguished from other iris lesions (Table 36.3).

Table 36.3 Differential diagnosis of Sakurai-Lisch nodules

Iris nevi
Iris nevi associated with iridocorneal endothelial syndrome
Iris mammillations (in melanosis of the iris)
Brushfield spots (Down syndrome)
Inflammatory, granulomatous nodules (Koeppe, Busacca, Berlin)
Iris cyst
Iris melanoma
Retinoblastoma
Leukemic infiltration of the iris
Juvenile xanthogranuloma
Iris foreign body

Histopathologically, the lesions consist of a condensation of spindle cells or melanocytes on the iris surface [11]. The lesions can sometimes be visualized without magnification, but the absence can only be confirmed by slit-lamp examination (*Clinical Pearl: Tangential, broad beam illumination for viewing lesions at slit lamp*).

Orbitotemporal Neurofibromas (Plexiform Neurofibromas)

Orbitotemporal neurofibromas (plexiform neurofibromas) are infiltrative, potentially vision-threatening lesions that usually begin early in childhood. Initially, the eyelid may appear thicker and mildly ptotic. However, as the lesion progresses, the eyelid margin assumes an S-shaped configuration with indistinct margins (Fig. 36.2). In a study by Avery and colleagues, amblyopia was present in 62 % of patients with these lesions [12]. Amblyopia was the result of the following: (1) anisometropia (global lengthening, induced astigmatism from mechanical distortion of globe

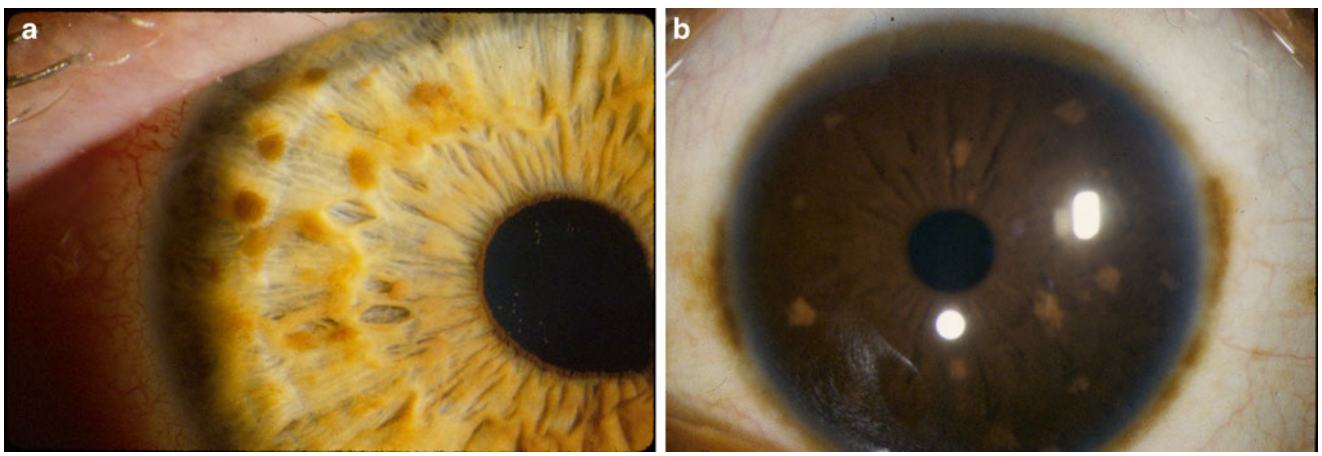

Fig. 36.1 Sakurai-Lisch nodules. (**a**) Numerous brown Sakurai-Lisch nodules on a lightly colored iris. (**b**) Numerous tan Sakurai-Lisch nodules on a darkly pigmented iris

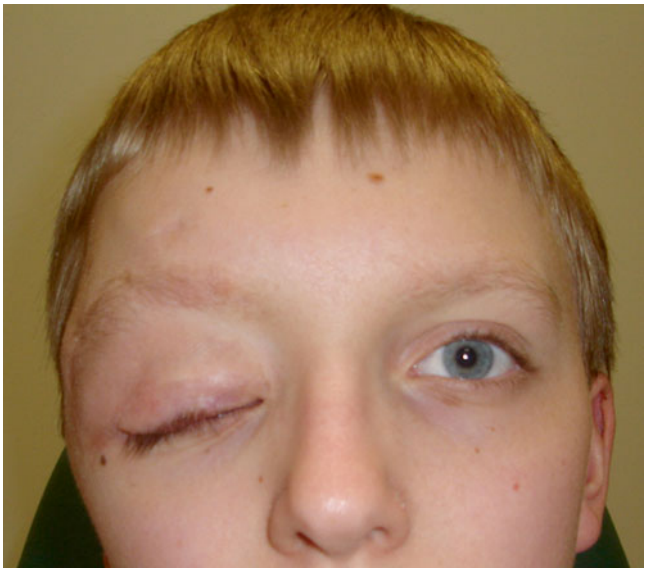

Fig. 36.2 Orbitotemporal neurofibroma in patient with NF1. Note the S-shaped configuration of the right eyelid. The orbitotemporal neurofibroma now obscures the visual axis. This likely will require surgical intervention, although complete excision is rare and recurrences are common.

and/or cornea), (2) obscuration of the visual axis, and (3) restrictive strabismus or a combination of these factors [12]. Although the mechanism is difficult to discern, some authors report a higher rate of glaucoma ipsilateral to the neurofibroma. Avery and colleagues propose that patients with plexiform neurofibromas should have an examination every 6 months with a quantitative visual acuity testing, motility evaluation, intraocular pressure measurement, and cycloplegic refraction; the clinical exam and rate of progression guide the frequency of clinical follow-up [12]. The authors suggest that a 3D MRI analysis may be helpful to determine therapeutic intervention [12].

The infiltrative nature of plexiform neurofibromas usually precludes complete surgical excision. Surgical debulking and frontalis suspension procedures are indicated for visually significant ptosis and allow the patient to develop binocular vision [13–15]. However, the condition is usually progressive and may require multiple surgical procedures.

Optic Pathway Gliomas

Optic pathway gliomas are low-grade pilocytic astrocytomas that occur in 15–20 % of patients with NF1 [16–18]. Although behavior of these tumors may be non-progressive and indolent, approximately one-third to one-half of patients will display clinical symptoms, including vision loss and precocious puberty [16, 19]. The incidence of OPG is highest in patients less than 6 years of age [16, 17, 20]; however, new symptomatic OPGs may arise in older children [21]. Children with symptomatic OPGs usually present with decreased visual acuity, pupillary abnormalities, decreased color vision, proptosis, or optic nerve pallor [20].

Because young children usually do not complain of vision loss, periodic examination is crucial and evidence-based screening guidelines have been developed by the OPG Task Force [20] and updated in 2007 [22] (Table 36.4). Screening examinations should include visual acuity, confrontation visual fields, pupil examination, motility, color vision, anterior segment, and dilated fundoscopic evaluation and be performed yearly until age 8 and then every other year until age 25 [22]. Visual evoked potentials (VEPs) have been advocated by some authors to screen and to monitor for progression or response to treatment in patients with known OPG [23, 24]. However, the task force found that visual acuity, visual field, and color vision are more representative of visual function, and the evidence does not support utilization of VEPs as a screening tool [22]. While not advocated as a screening tool in asymptomatic individuals, VEP may be a helpful ancillary study for following patients with OPG on neuroimaging in whom reliable visual information cannot be obtained.

More recently, spectral domain optical coherence tomography (SD-OCT) has been employed to screen for optic pathway gliomas. Parrozzani and colleagues compared visual acuity, fundoscopic examination, and SD-OCT in 57 patients with NF1 ages 2–15 years and found that retinal nerve fiber layer analysis was superior in detecting OPG [25]. Gu and colleagues demonstrated that decreased ganglion cell layer-inner plexiform thickness (GCL-IPL) (<5th percentile) could discriminate among patients with and without vision loss [26]. Avery and colleagues have investigated the use of circumpapillary RNFL measurements using a handheld SD-OCT in infants and children under sedation and demonstrated reproducibility of measurements [27]. Therefore, like VEP, SD-OCT of RNFL and/or GCL-IPL may be helpful in patients followed for OPG in whom reliable visual acuity cannot be obtained.

Evidence supporting the efficacy of routine screening with neuroimaging is also lacking [22]. However, at some institutions, neuroimaging is performed systematically to screen for OPGs usually between 1 and 3 years of age. If any of the parameters of the clinical examination suggest decline in visual function, MRI imaging is warranted (Table 36.4) [22].

In patients in whom NF1-associated OPG is newly identified, Fisher and colleagues recommend that patients undergo neuro-ophthalmologic evaluations every 3 months for the first year, every 6 months for the next to years, and yearly thereafter [28].

There is little consensus regarding indications for treatment, although early treatment with chemotherapy is considered for vision loss and/or radiologic tumor progression. Radiographic progression has been defined by change in

Table 36.4 Evidence-based recommendations for screening and monitoring of OPG in patients with NF1

Screening for asymptomatic children with NF1 for OPG
1. Baseline screening neuroimaging is not warranted. 2. All children with NF1 <8 years should undergo an annual[a] ophthalmologic examination with the following components: (a) Visual acuity (VA): tested with preferential looking tests (Teller acuity), LEA, HOTV, or Snellen acuity depending on age, cooperation, and literacy. Visual acuity should be comparable to age-based norms (20/40 or better in children ≤3 years, 20/30 age 4 years, 20/25 age 5 years, 20/20 age ≥6 years). A 2-line difference between eyes should prompt imaging if VA cannot be explained by refractive error or amblyopia from anisometropia or strabismus. (b) Visual field testing by confrontation (kinetic or automated perimetry can be performed as adjunct). (c) Pupils (d) Anterior segment examination (eyelids, iris): Consider IOP measurements if iris ectropion present or ipsilateral orbitotemporal neurofibroma present (e) Ocular motility (f) Fundoscopic exam (optic nerve, fundus) 3. Role of VEPs, pattern-reversal VEPs, and flicker VEPs is debated in literature. Evidence is lacking to support routine use in screening and following patients with known OPG. 4. Role of SD-OCT for screening and monitoring progression is unknown. May be helpful adjunct be used in specific circumstances in which tests of visual function cannot be reliably obtained.
Evaluation of patient with suspected OPG
If ophthalmologic abnormality is detected, MRI of brain is warranted.
Longitudinal follow-up in patients with OPG identified
1. Ophthalmologic evaluations should be performed 3 months for the first year, every 6 months until age 8, then yearly thereafter. More frequent examinations should be performed as the clinical progression dictates. 2. MRI can be performed on the same interval, or based on recommendations from neuro-oncologist.

Compiled from references Listernick et al. [22] and Fisher et al. [28]

[a]Some institutions will do biannual examination in young children to compensate for variability in the child's examination performance

tumor size or enhancement pattern, whereas clinical progression has been defined by new neurologic symptoms, endocrinologic abnormality, or vision changes [22]. Ophthalmologic progression is defined by the task force as a two line (0.2 logMar) for recognition acuities or one octave decline in preferential looking pattern (Grant Liu MD, personal communication). In a recent retrospective multicenter study by Fisher and colleagues, the authors sought to determine the visual outcomes of patients undergoing early (treatment initiated within 4 months of diagnosis of OPG) chemotherapy for NF1-associated OPG. Whereas previous studies have suggested that vision loss from OPG is irreversible [29, 30], 32 % of patients in this study who received early chemotherapy actually had improvement of visual acuity, which is useful in counseling families [28]. Approximately 40 % remained stable and 28 % declined, with tumor location as the most consistent prognostic factor for poor visual outcome, with tumor involving the optic tracts/radiations associated with progression despite chemotherapy [28]. Other factors that conferred a poor prognosis included optic pallor at the time of treatment and age <2 years or >5 years [28]. (A complete discussion of diagnosis, management, and visual outcomes may be found in Chap. 39 Optic Pathway Gliomas.)

Summary

The ophthalmologic examination is exceedingly important in the diagnosis of NF1 and the monitoring for serious complications such as optic nerve gliomas. Guidelines have been established by multidisciplinary teams to screen and to monitor for progression of OPG (Table 36.4). Please see Case Study 1 in Chap. 39 Optic Pathway Glioma.

Neurofibromatosis Type 2

Neurofibromatosis type 2 (NF2) is much less common than NF1 with prevalence of 1 in 30,000–40,000 [31, 32]. NF2 is caused by mutations in a gene located on 22q that encodes merlin or schwannomin [33]. NF2 is characterized by bilateral acoustic neuromas and CNS meningiomas, schwannomas and ependymomas, cataracts, and retinal abnormalities (see Table 36.2 for diagnostic criteria). Like NF1, NF2 is highly penetrant with considerable phenotypic variability in terms of clinical severity of disease and tumor location [32]. Two clinical subtypes have been proposed: (1) severe [Wishart] subtype: onset less than 20 years of age, many CNS tumors and schwannomas, and rapid clinical progression and (2) mild [Gardner] subtype: onset in third decade, very few tumors other than schwannomas, and more benign clinical course [34]. Patients with frameshift or nonsense mutations are more likely to have a severe phenotype in terms of onset and tumor burden as compared to those with missense mutations [35–37]. In contrast to adults who usually present with eighth nerve schwannomas, children are more likely to present with non-eighth nerve-related symptoms such as vision loss (from retinal or optic nerve abnormalities), diplopia from paretic strabismus, or mononeuropathy such as facial nerve palsy [38, 39].

Ophthalmologic findings are present in 83 % of patients with NF2 [40]. Ocular findings include cataracts [40, 41], combined hamartomas of the retina and retinal pigment epithelium (CHRRPEs) [40, 41], and epiretinal membranes [40–42]. Some authors have suggested that patients presenting with retinal abnormalities early in life may have a more severe (Wishart) phenotype [35, 42–44]. Patient may also present with neuro-ophthalmologic abnormalities including strabismus, nystagmus, and optic nerve involvement [45].

See Table 36.5, Case Study 1.

Table 36.5 Case study 1

A 6-month-old infant was referred by her pediatrician for esotropia and pendular nystagmus of the left eye present since approximately 3 months of age. Patient was the product of a full-term birth and had no significant past medical history.
Pertinent examination findings:
VA: OD: CSM OS: UCUSUM
Pupils: 4 → 2 mm OU, trace RAPD OS
Sensorimotor: LET′ = 40 PD (Modified Krimsky)
High-frequency, low-amplitude pendular nystagmus OS
Extraocular movements: full
Anterior segment: within normal limits
Posterior segment: OD: within normal limits OS: elevated gray pigmented lesion of the macula with hypopigmented borders. The temporal arcades are dragged towards the fovea, which is displaced nasally. The underlying RPE is irregularly hyperpigmented (Fig. 36.3).
Differential diagnosis
- Combined hamartoma of the RPE and retina
- Retinoblastoma
- Choroidal melanoma
- Choroidal nevus
- Melanocytoma
- Adenoma
- Adenocarcinoma

What ocular diagnostic studies are needed?
An examination under anesthesia should be performed with ultrasonography and fundus photography to document size and extent. Ultrasonography usually reveals a plaque-like lesion of RPE and retina without choroidal excavation or scleral extension. Optical coherence tomography may be utilized to evaluate for an epiretinal membrane that may be amenable to surgical intervention. Fluorescein angiography may also be considered and will usually demonstrate early hypofluorescence in the region of hyperpigmentation. In the arterial-venous phase, microaneurysms and fine networks of tortuous or dilated vessels may exhibit leakage.
Follow-up:
The patient was examined under anesthesia and findings were consistent with a combined hamartoma of the RPE and retina. The surgeon referred the patient to a human geneticist to evaluate for neurofibromatosis type 2. The patient had genetic testing and had a mutation in the gene for NF2. He was followed for several years and later developed signs and symptoms of vestibular schwannomas.

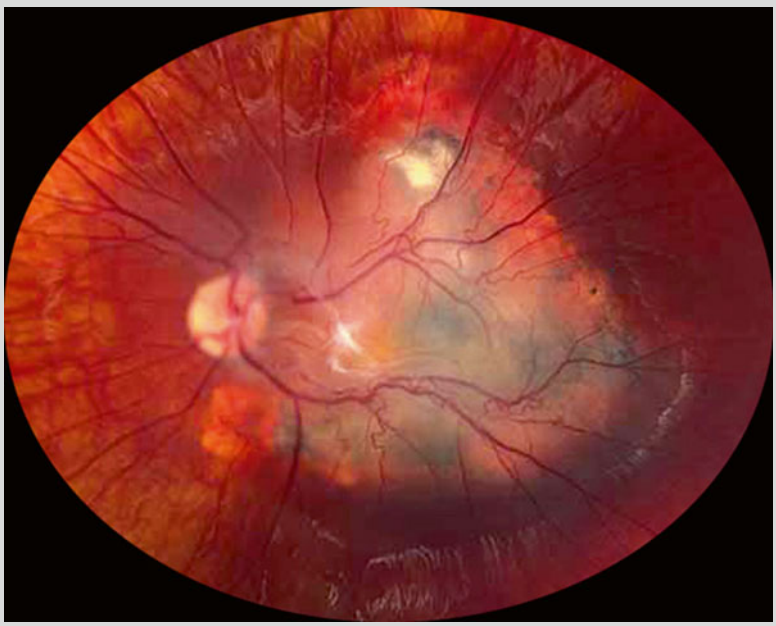

Fig. 36.3 Combined hamartoma of the RPE and retina with associated retinal traction, vascular tortuosity, and telangiectasias. Image courtesy of Drs. James Augsburger and Zelia Correa. Cincinnati, OH

Cataracts

Approximately 65–80 % of patients with NF2 develop childhood or juvenile-onset lenticular opacities [39, 40]. While a majority are posterior subcapsular cataracts [46], posterior polar and cortical opacities have been reported [47, 48].

Retinal Abnormalities

(a) Combined hamartomas of the retina and RPE

Combined hamartomas of the retina and RPE (CHRRPE) are darkly pigmented, elevated lesions associated with retinal traction and tortuous vessels [49]. Histopathologically, these lesions are composed of disorganized retina and hyperplastic and hypertrophic RPE cells with or without a vascular component; gliosis often occurs on the surface with concomitant vitreoretinal interface abnormalities. CHRRPEs may be located adjacent to the optic nerve or may simulate a macular scar [40]. Peripapillary CHRRPEs may be indistinguishable from optic disc drusen [40]. Importantly, CHRRPE may be the presenting manifestation of NF2 [50].

(b) Vitreoretinal interface abnormalities

Epiretinal membranes (ERMs) have been described in patients with a more severe systemic phenotype, with prevalence ranging from 13 to 80 % [44]. ERMs associated with NF2 have characteristic ophthalmoscopic, SD-OCT, and histopathologic features. Although ERMs are usually solitary and located in the macula, peripheral or multiple ERMs may be present. Unlike secondary or acquired ERMs, ERMs in NF2 are usually congenital in origin. Fundoscopically, the lesions have a spiculated appearance with curled edges. In contrast to acquired ERMs, the fibers project vertically into the cortical vitreous (Fig. 36.4). Sisk and colleagues described the SD-OCT features in four pediatric patients with NF2-associated ERMs and identified the following features: (1) ERM extended anteriorly into the vitreous without a posterior vitreous detachment (PVD), (2) loss of foveal contour, (3) preservation of the retinal lamination including preservation of the inner ellipsoid band, and (4) absence of cystoid macular edema [42]. Histopathologic studies by McLaughlin and colleagues demonstrated that ERMs in NF2 are likely of Müller cell origin [17]. Importantly, the ophthalmologic manifestations were recognized before neurologic signs and led to the diagnosis in three of the four patients. All patients had >2 CNS lesions, and three of the four patients eventually required neurosurgical intervention for CNS tumors [42]. Thus, the presence of ERMs in childhood may be of both diagnostic and potentially prognostic importance.

Neuro-Ophthalmologic Findings

Neuro-ophthalmologic findings include optic disc edema, optic atrophy, motility disturbances and strabismus, and peripheral or vestibular nystagmus [39, 43]. Ocular motor paresis was present in 10 % of children with NF2 [40]. Optic nerve sheath meningiomas can also lead to progressive vision loss [51, 52]. While generally uncommon in the pediatric population, 28 % of patients with optic nerve meningiomas will be diagnosed concomitantly with NF2 and the meningioma is hence the presenting manifestation of the disease [53]. Approximately 50 % of patients with NF2 develop intracranial meningiomas that may present with ophthalmologic manifestations including cranial nerve palsies or may lead to vision loss via direct compression or increased intracranial pressure. In a recent survey by Bosch and colleagues of 14 patients with childhood onset and follow-up, ophthalmologic manifestations included disc edema, optic atrophy, motility disturbances (10/14), and pupillary dysfunction (5/14) [39]. Formal evidence-based guidelines for ophthalmologic follow-up have not been established. Janse and colleagues suggested yearly ophthalmologic screening examination for patients with an affected parent and patients with suspected NF2 who do not meet clinical diagnostic criteria [54]. Bosch and colleagues recommend that affected pediatric patients have once- or twice-yearly ophthalmologic examinations [39]. If findings are present, interval follow-up should be consistent with course and likelihood of progression.

Summary

Ophthalmologic manifestations are common in pediatric patients with NF2. The presence of retinal lesions (CHRRPE or ERM) may be associated with a more severe systemic clinical course. In contrast to adult patients who present with hearing loss secondary to acoustic neuromas, pediatric patients commonly present with neuro-ophthalmologic or motility disturbances. The presence of neuro-ophthalmologic signs, optic nerve edema, or pallor should prompt neuroimaging as optic nerve and intracranial meningiomas are more common in patients with NF2. Yearly ophthalmologic examination is recommended for patients with NF2.

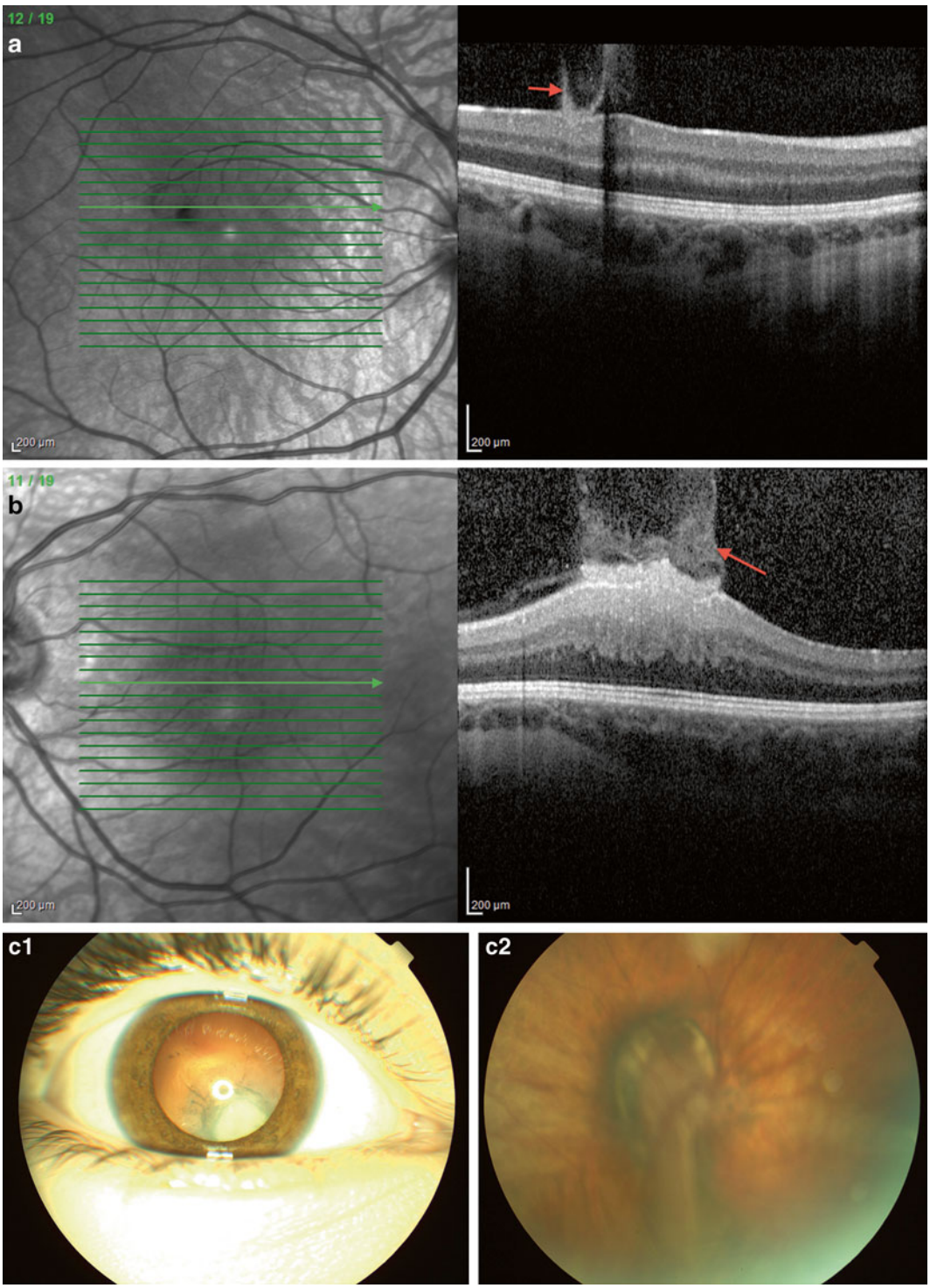

Fig. 36.4 Siblings with NF2 and associated vitreoretinal interface abnormalities. (**a** and **b**) SD-OCT horizontal raster scans of bilateral epiretinal membranes and corresponding infrared reference images. *Arrows* denote the vertical projection of fibers into the cortical vitreous through discontinuities in the internal limiting membrane, characteristic of congenital ERMs in NF2, which are believed to be Muller cell hamartomas. Other findings include absence of a posterior vitreous detachment, loss of foveal contour with relative preservation of retinal lamination pattern, and absence of cystoid macular edema. (**c1** and **c2**) The second sibling had persistent fibrovascular vitreous present in the right eye, a finding uncommonly seen associated with NF2 (unpublished data, Sisk). (**c1**) Anterior segment photo demonstrating posterior lenticular opacity connected to fibrovascular stalk and (**c2**) its extension to the disc. The congenital epiretinal membrane in the left eye has vertical projects off of the disc in addition to the macula that could have formed off of the hyaloid artery before it regressed. Images courtesy of Dr. Robert Sisk, Cincinnati, Ohio

Retinal Angiomatosis (von Hippel-Lindau)

Von Hippel-Lindau disease is an autosomal dominant multisystemic disorder caused by mutations in the *VHL* tumor-suppressor gene (3p25-26) [55]. The most common clinical manifestations include hemangioblastomas of the CNS and retina, renal cell carcinoma, pheochromocytoma, pancreatic islet cell tumors, and epididymal cystadenomas (Table 36.2) [56], with renal cell carcinoma as the leading cause of mortality [57, 58]. The incidence of VHL disease is 1 in 36,000 with age-dependent penetrance of 95 % by the age of 60 years [59]. For individuals with VHL disease, VHL disease-causing mutation, or at-risk relatives with unknown molecular status, the following surveillance guidelines are summarized in Table 36.6.

See Table 36.7, Case Study 2.

Table 36.6 Surveillance guidelines for patients with VHL disease, a disease-causing mutation, or relative at risk with unknown molecular status

Age	Recommended testing and interval
Ages 0–4 years	• Annual neurologic examination • Annual ophthalmologic evaluation with dilation • Audiology testing • Blood pressure screening
Age 5–14 years of age	• Annual neurologic examination • Annual ophthalmology examination with dilation • Annual plasma-metanephrine and plasma-normetanephrine • Annual audiology examination • 1 MRI of CNS • 1 Ultrasound (US) of abdomen (kidneys, adrenal glands, pancreas, liver)
>15 years of age	• Annual neurological examination • Annual ophthalmology examination with fluorescein angiography • Every 2 years: MRI scan of the CNS including inner ear • Annual US of abdomen (kidneys, adrenal glands, pancreas, liver) • Annual plasma-metanephrine, plasma-normetanephrine, and plasma-chromogranin A • Annual audiologic examination

Compiled from Gene Reviews (http://www.ncbi.nlm.nih.gov/books/NBK1463/), National clinical guideline for diagnosis and surveillance in Denmark [60], Cambridge Screening Protocol [61]

Table 36.7 Case study 2

An otherwise healthy, 15-year-old girl presented for evaluation of an optic nerve lesion in the right eye noted on routine examination for glasses. She has no significant past medical history. Her father passed away at age 40 from a brain tumor, but family history is otherwise unremarkable.
Pertinent examination findings:
Best corrected visual acuity: OD: 20/20 OS: 20/20
Wearing Rx: OD: −2.00 + 0.50 × 090 OS: −2.50 + 0.50 × 090
Pupils: 5 → 2 mm, no APD
Anterior segment: within normal limits
Intraocular pressure: 16 mmHg OU
Posterior segment:

	OD	OS
Vitreous	Clear media	Clear media
Optic nerve	Pink, thin neuroretinal rim, C/D 0.8 (*v*) × 0.6 (*h*). Disc size 2.5 mm 1 DD, juxtapapillary elevated, vascular lesion (Fig. 36.5a)	Pink, thin neuroretinal rim, C/D 0.8 (*v*) × 0.7 (*h*), Disc size 2.30 mm
Macula	Normal foveal reflex, 1/10 DD hyperpigmented flat lesion superotemporal to fovea	Normal foveal reflex
Vessels	As described above, peripheral exudate nasal to the lesion	Normal
Periphery	Pre-equatorial exudate	Small vascular tumor with dilated feeding arteriole and draining venule (Fig. 36.5b)

(continued)

Table 36.7 (continued)

Fluorescein angiography was completed and was significant for early hyperfluorescence of the feeding vessels and staining of the late phases, with some leakage. The patient was diagnosed with retinal hemangioblastomas and the patient was referred to an ocular oncologist for further management and the lesions were treated with argon green laser photocoagulation (Fig. 36.6a, b). What systemic associations should be considered? What should the work-up include? The presence of a single hemangioblastoma should prompt systemic evaluation, and in this case, with multiple lesions, a systemic diagnosis of VHL is likely. The patient should be referred to a human geneticist and neurologist for comprehensive evaluation. MRI of the brain should be completed along with an ultrasound of the abdomen, plasma catecholamines, and audiologic examination. The patient's first-degree family members should also undergo comprehensive evaluation including ophthalmologic examination. The family should meet with a genetic counselor prior to molecular confirmation of diagnosis.

Although likely physiologic cupping related to larger disc size, the practitioner might consider baseline testing such as pachymetry, gonioscopy, visual field, and OCT, especially if there is a family history of juvenile glaucoma.

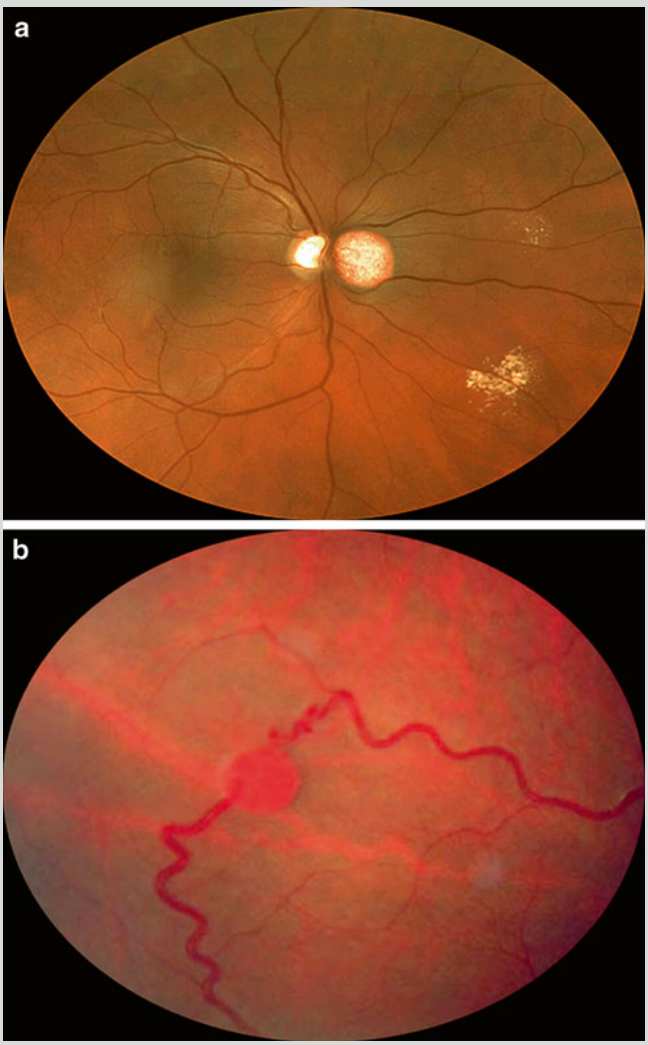

Fig. 36.5 (**a**) Juxtapapillary, endophytic hemangioblastoma with peripheral exudate. (**b**) Peripheral hemangioblastoma with dilated feeding arteriole and draining venule. Images courtesy of Drs. James Augsburger and Zelia Correa, Cincinnati, OH

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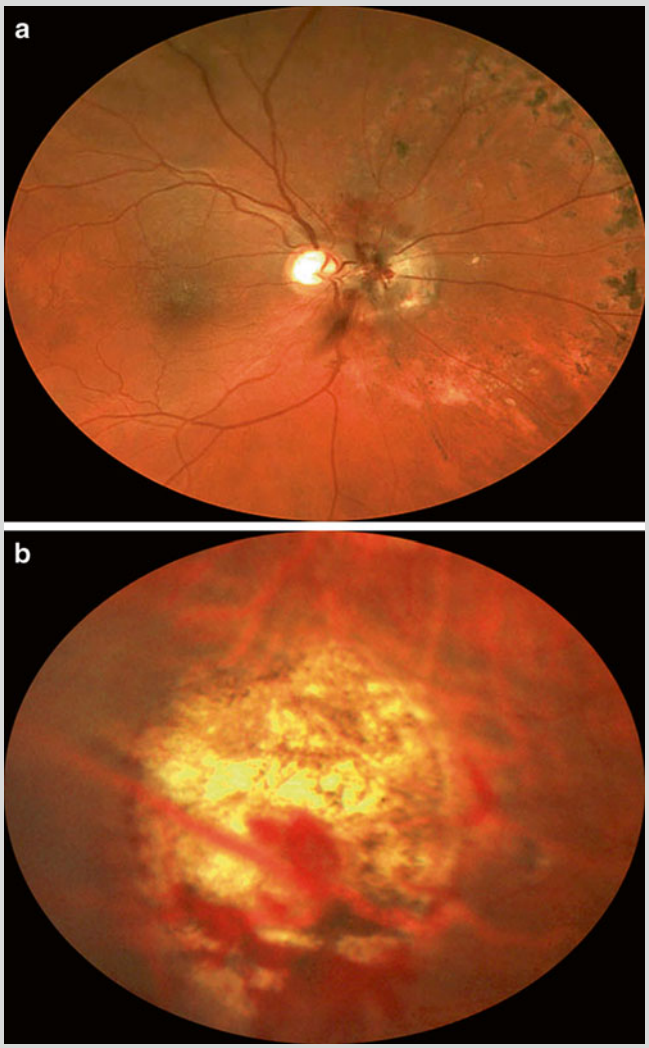

Fig. 36.6 (**a**) Juxtapapillary hemangioblastoma status-post 2 treatments with green argon laser photocoagulation. The peripheral exudate has subsequently resolved. (**b**) Peripheral hemangioblastoma status-post argon laser photocoagulation. Images courtesy of Drs. James Augsburger and Zelia Correa, Cincinnati, OH

Retinal and Optic Nerve Head Hemangioblastomas

Retinal and optic nerve head hemangioblastomas are one of the earliest manifestations of VHL with mean age at presentation of 25 years [62], approximately a decade before patients present with cerebellar hemangioblastomas. However, these lesions may be visible by ophthalmoscopy by late childhood [63]. Between 25 and 80 % of patients with retinal hemangioblastomas have VHL [64]. Therefore, all patients with retinal hemangioblastomas and their first-degree relatives should be screened for VHL. Genotype-phenotype correlates have been described for ocular involvement with missense mutations in the alpha domain having a higher likelihood of ocular involvement than missense mutations in the beta domain [65].

Hemangioblastomas may be multiple in one-third of patients and bilateral in 50 % of patients [57]. Hemangioblastomas are classified as either endophytic or exophytic [66]. Endophytic tumors arise from the superficial retina or optic disc and extend into the vitreous [66]. Early lesions may appear as minor, reddish vascular malformation, while the mature tumor characteristically is reddish, elevated, and well circumscribed with a pair of markedly dilated artery and vein running between the lesion and the optic disc. Exophytic lesions are less common and arise from the outer retinal layers and are usually located in the peripapillary or juxtapapillary area [66]. They may be misdiagnosed as unilateral optic nerve edema, papillitis, or choroidal neovascularization [66]. The vascular tumor may be accompanied by lipid exudation and circumferential subretinal fluid and may cause traction on the

adjacent retina. After careful examination of the fundus, fluorescein angiography is essential to accurately diagnosis and to determine the extent of these lesions. Fluorescein angiography demonstrates early hyperfluorescence especially of the feeding vessels with staining in the late phase and variable leakage [66, 67]. A-scan ultrasonography demonstrates medium-to-high internal reflectivity. B-scan ultrasonography may be useful in determining the tumor dimensions and presence of subretinal fluid. Histopathology reveals vascular thin-walled, endothelial-lined channels separated by vacuolated, "foamy" stromal cells. Because the tumor endothelial cells are fenestrated, exudation may be present.

Treatment of retinal hemangioblastomas depends on their size, location, and the presence of exudate, subretinal fluid, and/or retinal traction, with consideration of visual acuity. Small tumors (<500 μm) that do not pose a threat to vision can be observed [68]. For larger tumors with associated fluid and traction or that are likely to lead to visual compromise, treatment modalities include laser photocoagulation, cryotherapy, photodynamic therapy, proton-beam therapy, and brachytherapy [68–73]. Adjunctive vitreoretinal surgery is sometimes needed in cases of rhegmatogenous or tractional retinal detachment. Intravitreal VEGF inhibitors have recently been employed as primary or adjunctive therapy in some cases with variable results. Therefore, the role of VEGF inhibitors in retinal hemangioblastomas is unclear [74–76].

The risk of severe visual impairment depends on number of tumors, location, size, and secondary fluid and or traction on the retina [77, 78]. Factors associated with adverse outcomes include large tumor size at presentation, early onset of tumors, and the presence of visual symptoms [78]. Ophthalmologic examination with scleral depression should be performed on a yearly basis and fluorescein angiography performed in patients older than 15 years as early detection and treatment can improve visual outcome (see Table 36.6) [60, 61].

Summary

Retinal and optic nerve hemangioblastomas are some of the earliest manifestations of VHL disease. Imaging modalities such as fluorescein angiography and ultrasonography can aid in the diagnosis of these lesions. Importantly, the presence of these lesions should prompt comprehensive screening for VHL disease in both the patient and first-degree relatives.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) or Bourneville disease is an autosomal dominant multi-systemic disorder involving the skin, eye, CNS, and other visceral organs. The prevalence ranges from 1/6000 to 1/10,000 [79]. Tuberous sclerosis is caused by mutations in *TSC1* on chromosome 9q34 and *TSC2* located on chromosome 16p13.3 encoding tumor growth-suppressor proteins, hamartin and tuberin, respectively [80–82]. The classic Vogt's triad includes adenoma sebaceum, mental deficiency, and epilepsy. This constellation of findings is present in only one-third of patients and significant phenotypic heterogeneity is present [83] (see Table 36.2 for diagnostic criteria).

Adenoma sebaceum consists of clusters of hamartomatous angiofibromas that often have a butterfly distribution over the nasal and malar surface. Other cutaneous manifestations include ash-leaf spots (sharply demarcated leaf-shaped area of skin depigmentation that fluoresces under a Wood lamp present at birth or early infancy), shagreen patch (waxy, confluent, hyperpigmented raised patches usually located in lumbosacral area), periungual fibromas, and café au lait spots.

Central nervous system manifestations are present in all patients, although variable in severity. Seizures occur in 60 % of patients and are often difficult to control [83]. Infants may present with refractive infantile spasms requiring medications such as vigabatrin to control the spasms (see Chap. 32 on Vigabatrin). Neuroimaging may reveal cortical hamartomas, subependymal nodules, subependymal giant cell astrocytomas, and infrequently malignant astrocytomas. Obstruction of the foramen of Munro by tumor extension may lead to obstructive hydrocephalus, and patients may present with symptoms of increased intracranial pressure and papilledema. Visceral manifestations include renal cysts, renal angiomyolipomas, pulmonary lymphangiomyomatosis, and cardiac rhabdomyomas. Systemic surveillance involves cranial CT/MRI every 1–3 years in pediatric patients, renal ultrasonography every 1–3 years, neurodevelopmental and behavioral evaluations, echocardiography if indicated, and high-resolution CT in women at least once after age 18 or if pulmonary symptoms are present [84].

The most common ocular manifestations of TSC are retinal and optic nerve head astrocytic hamartomas that occur in approximately 35–40 % of patients [85, 86]. These tumors constitute one of the major diagnostic criteria (see Table 36.2). Aronow and colleagues demonstrated that those with retinal findings are more likely to have concomitant subependymal giant cell astrocytomas, renal angiomyolipomas, cognitive impairment, and epilepsy than those patients without retinal findings [85]. In addition, retinal findings were more likely to be present in those patients with *TSC2* mutations [85]. Two morphologic subtypes of hamartomas have been described (Fig. 36.7a–c):

1. More common, relatively flat lesion with indistinct margins, often gray-white to translucent in appearance located in the peripheral fundus: These lesions are often present in young children and may be difficult to detect ophthalmologically.

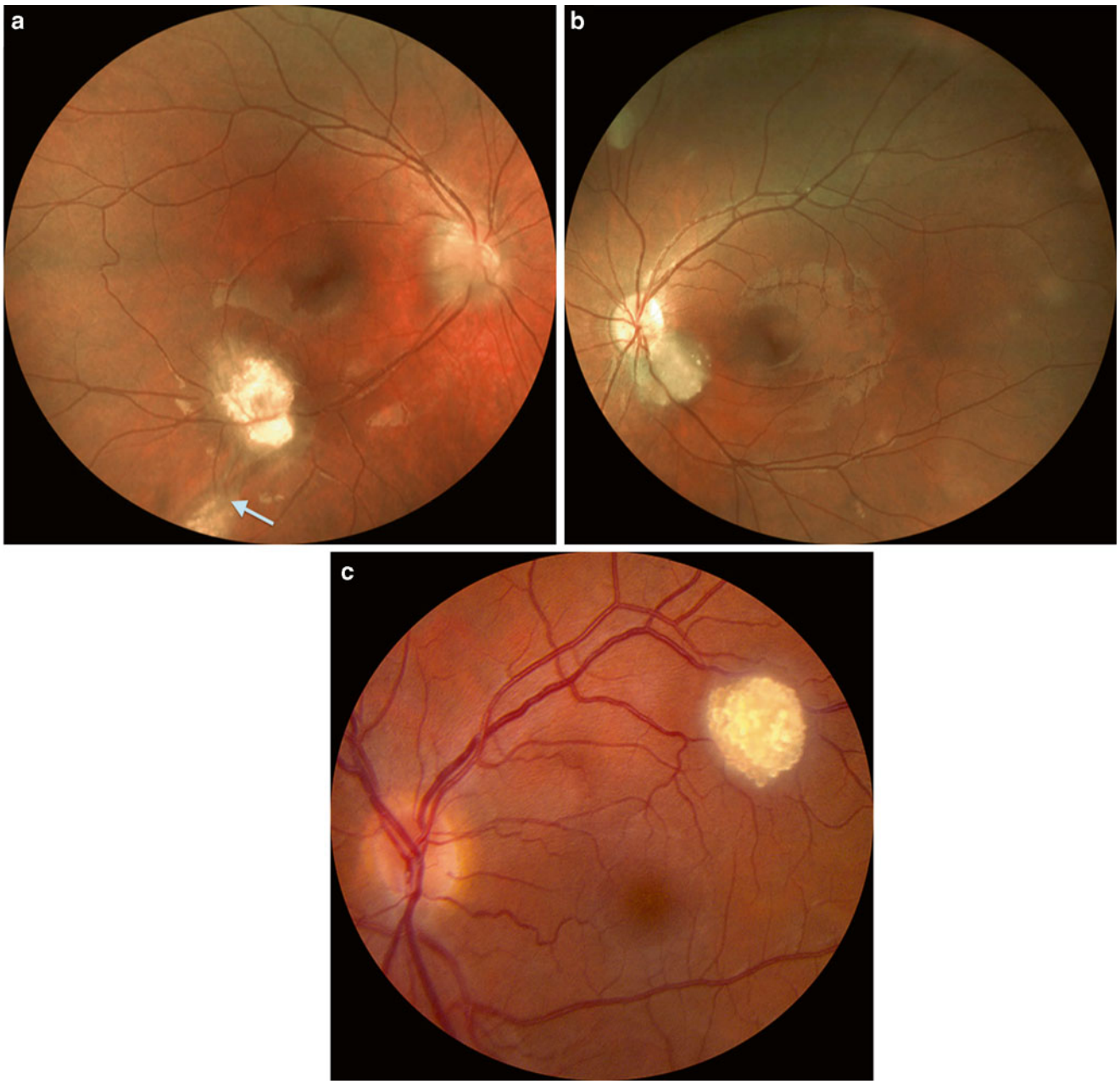

Fig. 36.7 (**a**) Fundus photograph of the right eye in a patient with TSC. The optic nerve astrocytic hamartoma is translucent in appearance, although borders are relatively well-demarcated and is intermediate to the two subtypes described. The peripheral lesion demonstrates calcification and some elevation. The inferior edge (*arrow*) is more reminiscent of the first subtype, as it obscures the course of vessel. (**b**) Fundus photograph of the left eye in a patient with TSC. A juxtapapillary astrocytic hamartoma, and similar to **a**, the lesion has characteristics of both subtypes of astrocytic hamartoma. (**c**) Classic astrocytic hamartoma demonstrating "mulberry appearance" or "fish egg" appearance. Images courtesy of Drs. James Augsburger and Zelia Correa, Cincinnati, OH

Clinical Pearl: Evaluate course of the retinal vessels and scrutinize points at which vessel is obscured by tissue.

2. Sharply demarcated, elevated lesion with irregular surface ("mulberry" or cluster of "fish eggs" appearance): Lesions are opaque and yellow-white as a result of calcification and are typically located adjacent to the optic nerve or posterior pole. The term "giant drusen" is often applied to astrocytomas of the prelaminar part of the disc; however, true drusen of the optic disc are composed of hyaline bodies.

Histopathologically, retinal astrocytomas are glial tumors of the retinal nerve fiber layer composed of retinal astrocytes with small oval nuclei and long processes and varying degrees of calcification. Most astrocytic hamartomas change very little with time [87, 88]. However, Shields and colleagues described four pediatric patients with TSC who had progressive enlargement of a juxtapapillary astrocytic hamartoma with optic nerve invasion, exudative retinal detachment, and neovascular glaucoma eventually requiring enucleation [89]. In contrast to the histopathology described above, these lesions were similar to CNS subependymal giant cell astrocytomas, exhibiting large, plump cells with eosinophilic cytoplasm, some mitotic activity, calcification, and necrosis [89]. Therefore, serial examinations are necessary to ensure stability of lesions. Other ophthalmologic findings include achromic patches, hypopigmented lesions and hamartomas of the iris or choroid [90], and eyelid angiofibromas.

Summary

The ophthalmologic examination may aid in the diagnosis of patients with clinical findings suggestive of TSC, as astrocytic hamartomas of the retina and/or optic nerve are part of the major diagnostic criteria. There are no formal recommendations for ophthalmologic surveillance. The presence of retinal lesions, CNS findings that may increase the risk of obstructive hydrocephalus, or a diagnosis of infantile spasms on vigabatrin (see Chap. 32 on Vigabatrin) may prompt more frequent ophthalmologic follow-up.

Encephalofacial Angiomatosis (Sturge-Weber Syndrome)

A detailed discussion of Sturge-Weber syndrome is not included given that it does not share inheritance pattern and pathophysiology with the other entities included in this chapter. A discussion is included in the infantile glaucoma chapter (see Chap. 42 on Childhood Glaucoma).

Familial Adenomatous Polyposis (Gardner Syndrome)

Familial adenomatous polyposis (FAP) is characterized by hundreds to thousands of pre-cancerous colonic polyps that inevitably lead to malignancy without treatment with colectomy. Gardner syndrome refers to the combination of FAP and extracolonic manifestations that include dental anomalies, osteomas, fibromas, other malignancies [91, 92], and pigmented ocular fundus lesions (POFLs) [93, 94]. Epidermoid cysts are the major cutaneous manifestation and are primarily located on the face, scalp, and extremities [95]. More recently, several case reports have documented the presence of primary cerebellopontine angle craniopharyngiomas in patients with Gardner syndrome, although the association is not well defined [96–98]. Gardner syndrome is caused by mutations in the APC gene located on chromosome 5q21-q22 [99]. Interestingly, Olschwang and colleagues found that POFLs are only present in patients who harbor mutations in exons 10–15 of the APC gene or deletion of the APC gene [100].

Pigmented ocular fundus lesions (POFLs) associated with Gardner syndrome are usually multiple, small (<1 mm), flat, round, hyperpigmented lesions located in the equator or midperiphery (Fig. 36.8). However, several other morphologic variants have been described including larger, ovoid lesions that appear grayish brown to black with varying degrees of hypopigmentation and/or lacunae formation. Larger lesions tend to be located in the posterior pole and may have a hypopigmented halo or tail [101]. Other lesions may be tear shaped, pencil shaped, or coffee bean shaped. The lesions are bilateral and multiple. Traboulsi and colleagues have demonstrated that the presence of four or more POFLs is a highly specific (>90 %) and relatively sensitive (70–80 %) clinical marker to identify family members at risk for the disease [102, 103].

POFLs are congenital [104] and therefore are an early manifestation of a potentially fatal disease. The findings of POFLs should prompt systemic evaluation and screening for hepatoblastoma by liver ultrasound and measurement of serum alpha-fetoprotein concentration (until age 5), yearly colonoscopy starting at age 10, and esophagogastroduodenoscopy beginning at age 25 or prior to colectomy [105]. Panoramic X-rays of the mandible can be used to detect osteomas [106].

POFLs must be carefully distinguished from other pigmented lesions of the RPE including congenital hypertrophy of the retinal pigment epithelium (RPE), choroidal nevus or melanoma, melanocytoma, congenital grouped pigmentation of the retinal pigment epithelium, bilateral diffuse uveal melanocytic proliferation (BDUMP), paving stone degeneration, and sunburst lesions of sickle cell disease (Table 36.8).

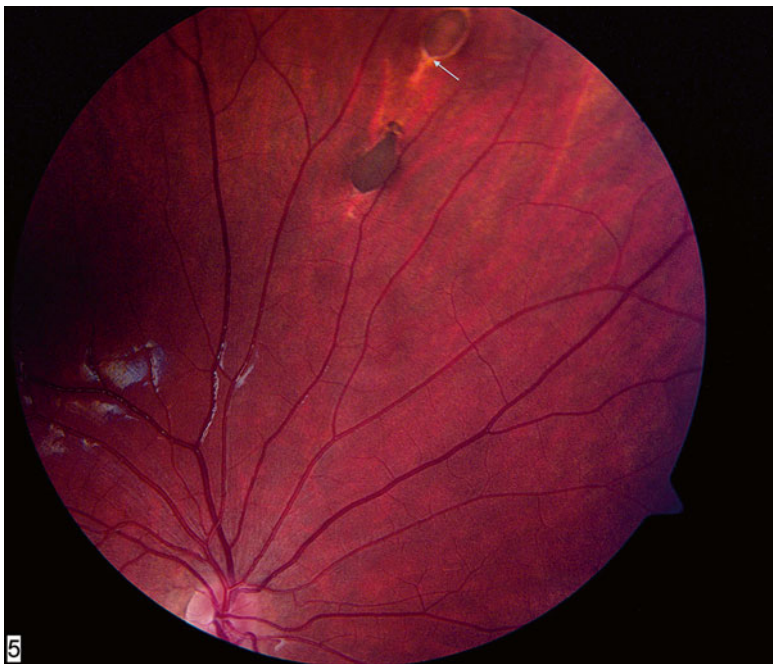

Fig. 36.8 Pigmented ocular fundus lesions associated with Gardner syndrome. The lesions in this patient are ovoid and of variable pigmentation. The more peripheral lesion has a hypopigmented halo and tail (*arrow*).

Table 36.8 Characteristic features of POFLs in Gardner syndrome as compared to congenital hypertrophy of the retinal pigment epithelium (CHRPE), and congenital grouped pigmentation of the retinal pigment epithelium (see Fig. 36.9)

	CHRPE	Grouped pigmentation of RPE	POFLs in Gardner syndrome
Number	Single, but up to 2 or 3	Numerous	More than 3 or 4
Location	Mostly peripheral	Throughout the fundus; sectoral	Throughout fundus
Size	Variable	Variable; smaller ones close to nerve; larger ones in periphery	Variable; larger ones close to nerve or posterior pole
Appearance	Generally round; can have scalloped borders; can have depigmented lacunae or be totally depigmented	Roundish; gray, light brown or dark brown	Round, pencil shaped, coffee bean shaped, may have hypopigmented tail or halo
Other features	Flat; monolayer of large RPE cells	Flat; monolayer of large RPE cells	Flat or multilayered; "adenomas"

Adapted from Ref. [107]

CHRPE congenital hypertrophy of the retinal pigment epithelium, *RPE* retinal pigment epithelium

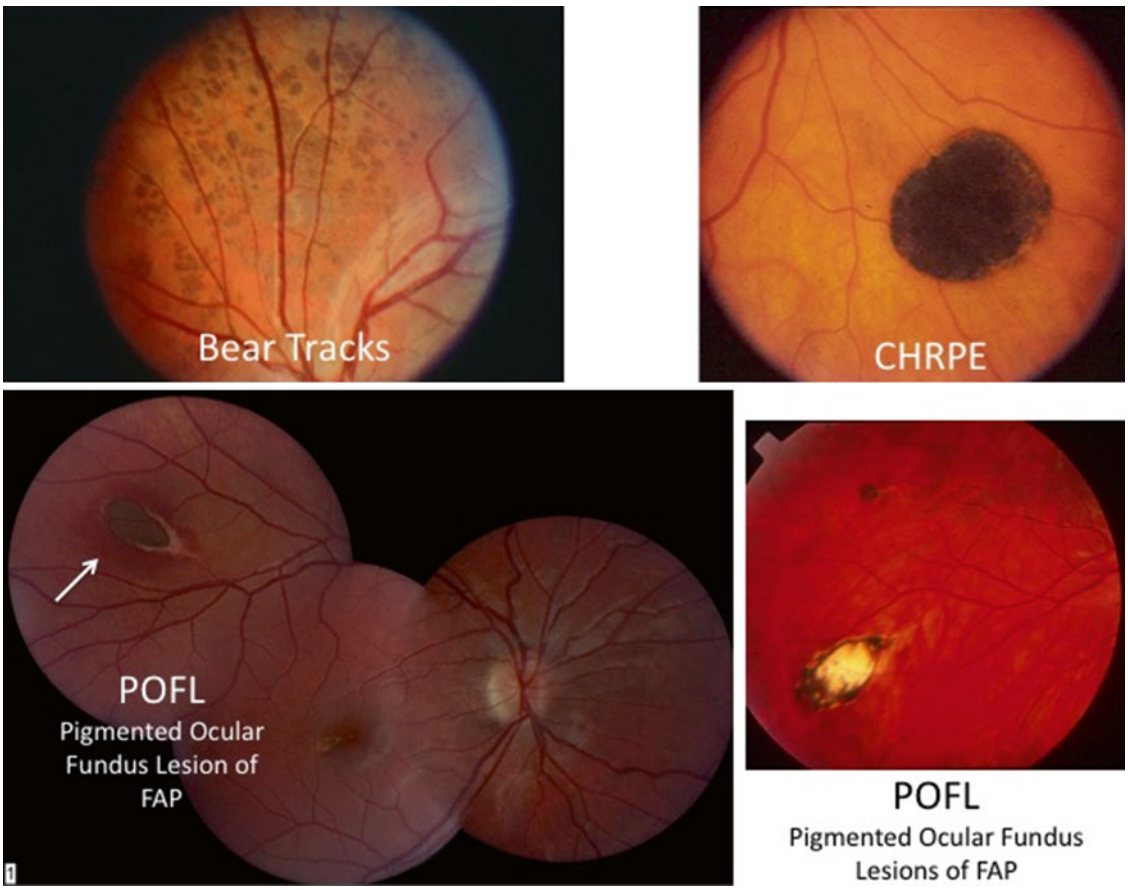

Fig. 36.9 Comparison of pigmented lesions involving the retinal pigment epithelium (RPE) (**a**). Grouped pigmentation of the RPE (bear tracks), (**b**). Congenital hypertrophy of the retinal pigment epithelium (CHRPE), and (**c** and **d**) pigmented ocular fundus lesions (POFLs)

Summary

The presence of greater than 3–4 POFLs is highly specific for Gardner syndrome and should prompt systemic evaluation for colonic polyps and other extracolonic manifestations of the disease. These lesions must be carefully distinguished from other pigmented lesions of the fundus (Table 36.8).

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Retinoblastoma

37

Carlos A. Medina, Priyanka Kumar, and Arun D. Singh

Abstract

This chapter considers general aspects and clinical features of retinoblastoma, an intraocular malignancy of primitive neuroendocrine origin that primarily affects young children. In the United States, the age-adjusted incidence of retinoblastoma is approximately 11.8 per million children aged 0–4 years, which represents 6.1 % of all childhood cancers under age 5 years. Depending on the classification of the tumor, globe-sparing treatment may be advised and should be performed by a clinician with experience in the treatment of retinoblastoma. A number of treatment options are available including local or systemic chemotherapy, chemoreduction, photocoagulation, thermotherapy, cryotherapy, brachytherapy, and enucleation. Treatment selection is complex and should be personalized to every case through a multidisciplinary approach. Genetic counseling is integral to the management of retinoblastoma patients.

Keywords

Leukocoria • Retinoblastoma • Retinocytoma • Retinoma • Tumor • *RB1*

Introduction

Retinoblastoma is an intraocular malignancy of primitive neuroectodermal origin that primarily affects young children [1]. Although there is no racial predisposition for the development of retinoblastoma, incidence varies across countries, regions, and ethnic groups due to fluctuations in birth and infant mortality rates [2]. In the United States the age-adjusted incidence rate of retinoblastoma is approximately 11.8 per million children aged 0–4 years. This has remained stable for the last 30 years and represents 6.1 % of all childhood cancers under age 5 years [3, 4]. Approximately 90 % of cases are diagnosed in patients less than 3 years of age.

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Although Pawius described retinoblastoma as early as 1597, it was not until 1926 that the American Ophthalmological Society officially accepted the term retinoblastoma [5].

Genetics

In 1971 Knudson proposed a "two-hit" hypothesis to explain the events needed for development of retinoblastoma based on his observations about the pattern of inheritance. He concluded that one mutant "tumor suppressor" gene inherited as a dominant trait (first hit) with inactivation of the second normal allele occurring in susceptible tissues (second hit) led to unregulated proliferation of cells [6]. There are at least four possible cells of origin including the retina stem cell, differentiated neuron or glial cell, retinal progenitor cell or newly post-mitotic cell committed toward a particular retinal fate [7]. In hereditary retinoblastoma, the initial hit is a germinal mutation that is inherited and is found in all cells. The second hit develops in the retinal progenitor cells leading to the development of retinoblastoma (Fig. 37.1).

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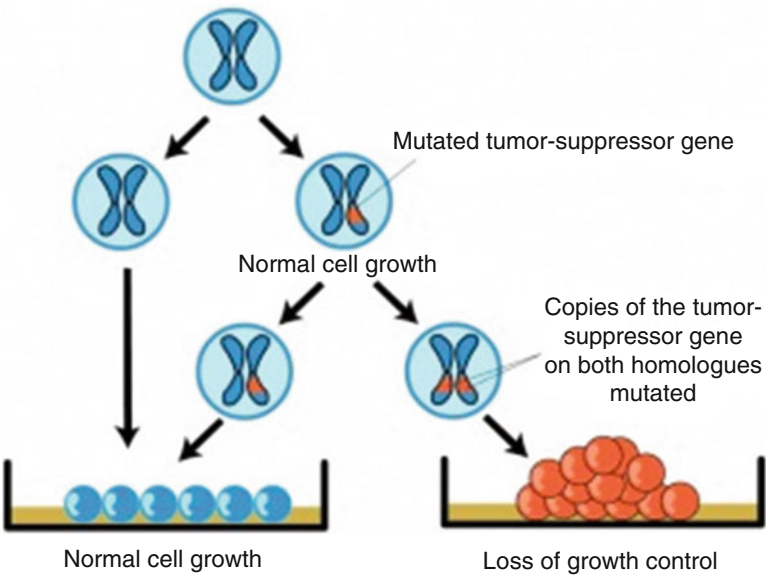

Fig. 37.1 Retinoblastoma and the RB1 gene. Source: http://lengfeldgen677s09.weebly.com/ (This web page was produced as an assignment for Genetics 677, an undergraduate course at UW-Madison)

Because of the mutation of one of the two alleles and the involvement of the *RB1* gene in other cancers, hereditary cases are predisposed to the development of non-ocular tumors such as osteosarcoma. In contrast, non-hereditary retinoblastoma occurs when an individual born with two normal copies of the *RB1* gene subsequently acquires mutations in both copies of the *RB1* gene in retinal cells only. Thus, given the localization of the loss of *RB1* function to the eye, patients with non-heritable retinoblastoma do not carry the risk of a second ocular or non-ocular tumor.

Knudson's "two-hit" model was eventually confirmed after the *RB1* gene was cloned and isolated to the long arm of chromosome 13 at locus 14 (13q14.2). Recent work has uncovered the importance of the *RB1* gene in cancer biology and established its role in the development of other tumors such as lung and breast cancer. It is now recognized that the RB1 protein interacts with an E2F transcription factor to regulate the cell cycle at the G1 checkpoint in all dividing cells [8–11].

Patients diagnosed with retinoblastoma can be categorized as having familial, sporadic heritable or sporadic non-heritable disease. Less than 10 % of retinoblastoma patients have a family history of retinoblastoma. The average age of diagnosis for a patient with a known family history is approximately 4 months of age. In these patients, every cell has an *RB1* gene mutation, and therefore, they are at risk for non-ocular cancers. The remaining 90 % of all retinoblastomas are sporadic. Of these, 60 % have unilateral disease and no germline mutations (sporadic non-heritable) while the remaining 40 % have a new onset germline mutation (sporadic heritable). Patients with no family history and unilateral disease are usually diagnosed at an average age of 24 months. Patients with bilateral disease are diagnosed sooner, on average 14 months of age.

Germline cases, either familial or sporadic, represent approximately 1/3 of retinoblastoma cases [12]. These patients tend to have bilateral and multifocal tumors although about 15 % of unilateral cases occur in individuals with germline mutations. Of note, some patients may present initially with unilateral disease but subsequently develop tumor in the other eye [12]. If a patient has bilateral retinoblastoma, it must be assumed that they carry a germline mutation.

As mentioned above, it is important to determine the germline mutation status of a patient as those with germline mutations carry a risk for non-ocular tumors including primitive neuroendocrine tumors in the brain such as pinealoblastoma. Pinealoblastoma is identical to retinoblastoma from an embryologic, pathologic and immunologic standpoint, and its presence in a patient with bilateral retinoblastoma is often referred to as "trilateral retinoblastoma." Approximately 5–15 % of patients with hereditary retinoblastoma develop pinealoblastoma, which constitutes approximately 3 % of all children with retinoblastoma [13]. Pinealobastoma usually occurs during the first 4 years of life with a mean age of diagnosis between 23 and 48 months. Because of the poor prognosis of trilateral retinoblastoma, prospective screening with MRI of the brain and orbits as often as every 6 months for 5 years has been advocated for all patients with germline mutations [14].

Genetic counseling is integral to efficient management of retinoblastoma. Transmission is autosomal dominant inheritance with 90 % penetrance. Therefore a bilateral retinoblastoma patient has a 45 % chance of having an affected child. *RB1* mutation analysis should be obtained for family counseling purposes and in any case where the results will affect future management. The National Society of Genetic Counselors (www.nsgc.org) and Gene Tests (www.genetests.org) can be used to find qualified genetic counselors,

medical genetics clinics or laboratories offering *RB1* analysis. Prenatal and pre-implantation genetic diagnostic methods are also available.

Clinical Features

Leukocoria is the most common presenting sign of retinoblastoma, and is present in up to 60 % of patients (Table 37.1). Other important signs include strabismus, cataract, and decreased or loss of vision. Presenting features vary depending on the extent and location of the tumor at the time of diagnosis. Early and small tumors are likely to be missed unless ophthalmoscopic examination is performed. More advanced tumors, such as those causing reduced visual acuity or involving the macula, may present with strabismus. Vitreous hemorrhage, mydriasis, and "cellulitis" are extremely rare presenting findings in retinoblastoma. Microphthalmos is generally only present in cases with a deletion of 13q14 that involves more than just the *RB1* gene. The presence of microphthalmos and retinoblastoma is highly characteristic of a deletion case [15].

Stepwise Evaluation of Patients with Retinoblastoma

A practical stepwise approach to evaluate the child suspected to have retinoblastoma includes obtaining a detailed history, thorough office examination, focused ophthalmic ultrasonography, and an examination under anesthesia, if needed (Fig. 37.2).

Most clinicians prefer to carry out a detailed examination under monitored anesthesia care because preschool age children are rarely fully cooperative with an office exam. Intraocular pressure, corneal diameter, and tumor size and location should be documented. Fundus photography is highly recommended at baseline and follow-up examinations. Ophthalmoscopy of small tumors reveals a translucent, gray to white intraretinal tumor with dilated retinal feeder vessels. Larger tumors may contain foci of calcifications that give the tumor its characteristic chalky white appearance. Tumors may be exophytic, growing beneath the retina with an associated retinal detachment and subretinal seeds (Fig. 37.3), or endophytic and growing above the retinal surface and into the vitreous cavity (Fig. 37.4). Vitreous seeding is more commonly observed in endophytic tumors. These seeds may enter the anterior chamber where they can aggregate on the iris to form nodules or settle inferiorly and form a pseudo-hypopyon. Secondary glaucoma and rubeosis iridis occur in about half of these cases. Rarely, retinoblastoma may be diffuse infiltrating type (Fig. 37.5). These cases are sometimes difficult to diagnose as they present with dense vitreous cell in the absence of a frank mass. As a result, they are often mistaken for pediatric uveitis of unknown etiology.

In the United States, retinoblastoma rarely presents at the time of diagnosis with systemic metastasis or intracranial extension. However, when left untreated, retinoblastoma most commonly escapes the eye by invading the optic nerve into the subarachnoid space. Tumor cells may also erode through the sclera into the orbit. Patients with extraocular extension usually present with proptosis and a clinical picture suggestive of "cellulitis" (Fig. 37.6). If tumor cells are present in the anterior chamber, these may gain access to the trabecular meshwork and draining vessels and conjunctival lymphatics. These patients should be assessed for palpable cervical and pre-auricular lymph nodes [6, 15].

Table 37.1 Common presenting features of retinoblastoma [15]

Leukocoria	56 %
Strabismus	20 %
Red painful eye	7 %
Poor vision	5 %
Asymptomatic	3 %
Orbital cellulitis	3 %
Unilateral mydriasis	2 %
Heterochromia iridis	1 %
Hyphema	1 %

Differential Diagnosis

The diagnosis of retinoblastoma is a clinical one based on a comprehensive history, clinical examination and ancillary testing. Intraocular biopsy is absolutely contraindicated because of the possibility of extraocular spread from the biopsy site. It is important to rule out a number of other retinal tumors that closely resemble retinoblastoma, including retinoma and retinocytoma.

Retinomas are tumors that resemble treated retinoblastoma and often have a component that resembles a chorioretinal scar [1, 16]. Retinocytomas are benign manifestations of the *RB1* gene mutation and are thought to be a benign variant of retinoblastoma [17]. The incidence of retinocytoma is unknown and the majority of patients are asymptomatic. The ophthalmoscopic appearance of retinocytoma resembles that of retinoblastoma that has undergone regression. The presence of a translucent grayish retinal mass, with calcifications, retinal pigment epithelial changes, and chorioretinal atrophy are common diagnostic features of retinocytoma. Calcification is present in over half of the cases. Although retinocytomas can undergo malignant transformation, they usually do not exhibit growth when observed over weeks to months. Feeder retinal vessels are usually absent or sclerosed. Other retinal tumors such as astrocytic hamartoma,

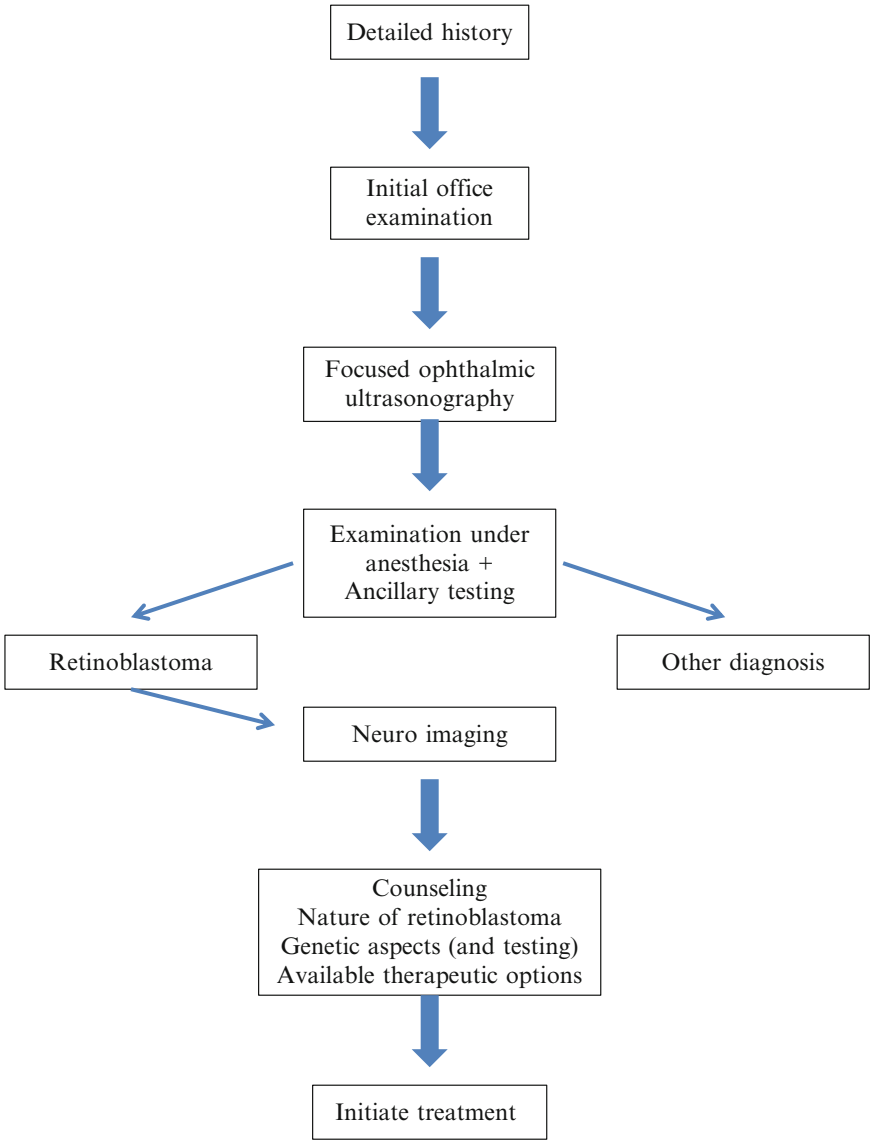

Fig. 37.2 Stepwise evaluation for retinoblastoma. This approach is merely a guide that can be modified as needed based upon clinical setting. Reproduced with permission from Marr BP, Singh AD. Retinoblastoma diagnosis and management. Clinical Ophthalmic Oncology—Retinoblastoma. Singh AD, AL Murphree, BE Damato. (Eds). Springer, Heidelberg 2014

medulloepithelioma, combined hamartoma of the retinal pigment epithelium (RPE) and retina, and retinal capillary hemangioma should be considered in the differential diagnosis of retinoblastoma. Other non-neoplastic diagnostic possibilities include persistent fetal vasculature, Coats' disease, ocular toxocariasis, retinopathy of prematurity, familial exudative vitreoretinopathy, Norrie disease, incontinentia pigmenti, endogenous endophthalmitis, congenital cataract, congenital toxoplasmosis, chorioretinal coloboma, morning glory disc anomaly, myelinated nerve fibers and scar tissue formation secondary to trauma.

Diagnostic Imaging

Ultrasonography, whether obtained in the office setting or during an exam under anesthesia, is extremely useful, as it can easily demonstrate pathognomonic features of the tumor. A-scan typically shows high internal echoes within the tumor and rapid attenuation. B-scan may show a rounded or irregular intraocular mass with numerous highly reflective granules consistent with intraocular calcification (Fig. 37.7). Ultrasonography may also be used in combination with fundus photography or ophthalmoscopy to document tumor response to treatment.

Fluorescein angiography is particularly useful for imaging small intraretinal tumors. It may show minimally dilated feeding vessels with mild tumor hypervascularity and staining in the venous phase. Larger tumors usually demonstrate more significant hypervascularity and late staining.

MRI is the preferred imaging modality, offering better soft tissue resolution and imaging of both the brain and pineal region while avoiding radiation exposure. Retinoblastoma usually appears in T2-weighted images as a lesion that is moderately hypointense compared to the vitreous (Fig. 37.8). A systemic metastatic evaluation is only indicated in children

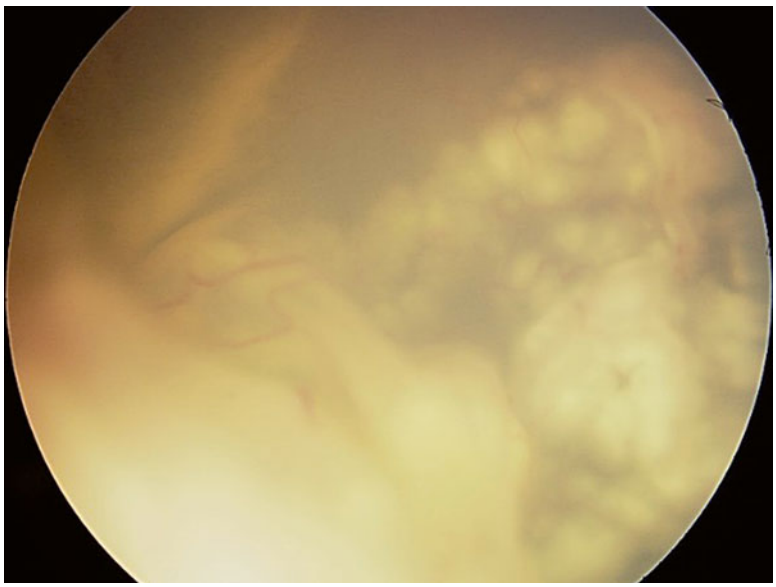

Fig. 37.3 Exophytic retinoblastoma growing beneath the retina with an associated retinal detachment and sub retinal seeds

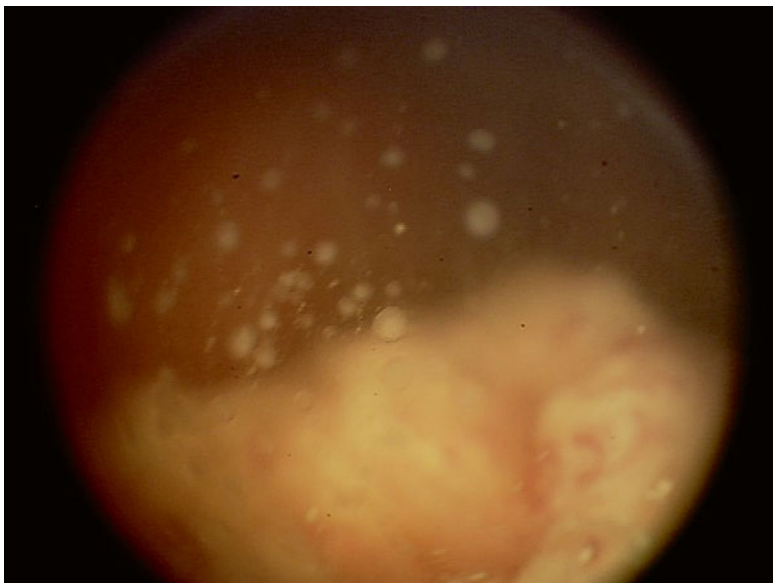

Fig. 37.4 Endophytic retinoblastoma growing above the retinal surface and into the vitreous cavity with vitreous seeding

with evidence of neurologic abnormalities that suggest brain extension, extrascleral extension, high-risk features of massive choroidal invasion, or retrolaminar optic nerve extension on histopathologic examination of the enucleated globe. If any of these characteristics is present, systemic workup should include a bone marrow biopsy as well as lumbar puncture.

Non-ocular Tumors

In the United States, more patients with retinoblastoma die from second non-ocular malignancies than from the original disease. Non-ocular tumors are frequently observed in patients with heritable retinoblastoma who survive childhood without developing trilateral retinoblastoma. This group is composed of all familial cases, all bilateral cases and about 15 % of unilateral cases [1]. The most common type of non-ocular tumors are solid non-hematopoietic tumors, with osteosarcomas accounting for one-third of these malignancies. Soft tissue sarcomas and cutaneous malignant melanomas are the next most common non-ocular tumors. The incidence of a second cancer in patients with germ line *RB1* mutations is approximately 1 % per year of life. Radiation exposure is a known risk factor for the development of secondary malignancy and should therefore be avoided if possible. If radiation is inevitable, delay in radiation therapy should be the main goal.

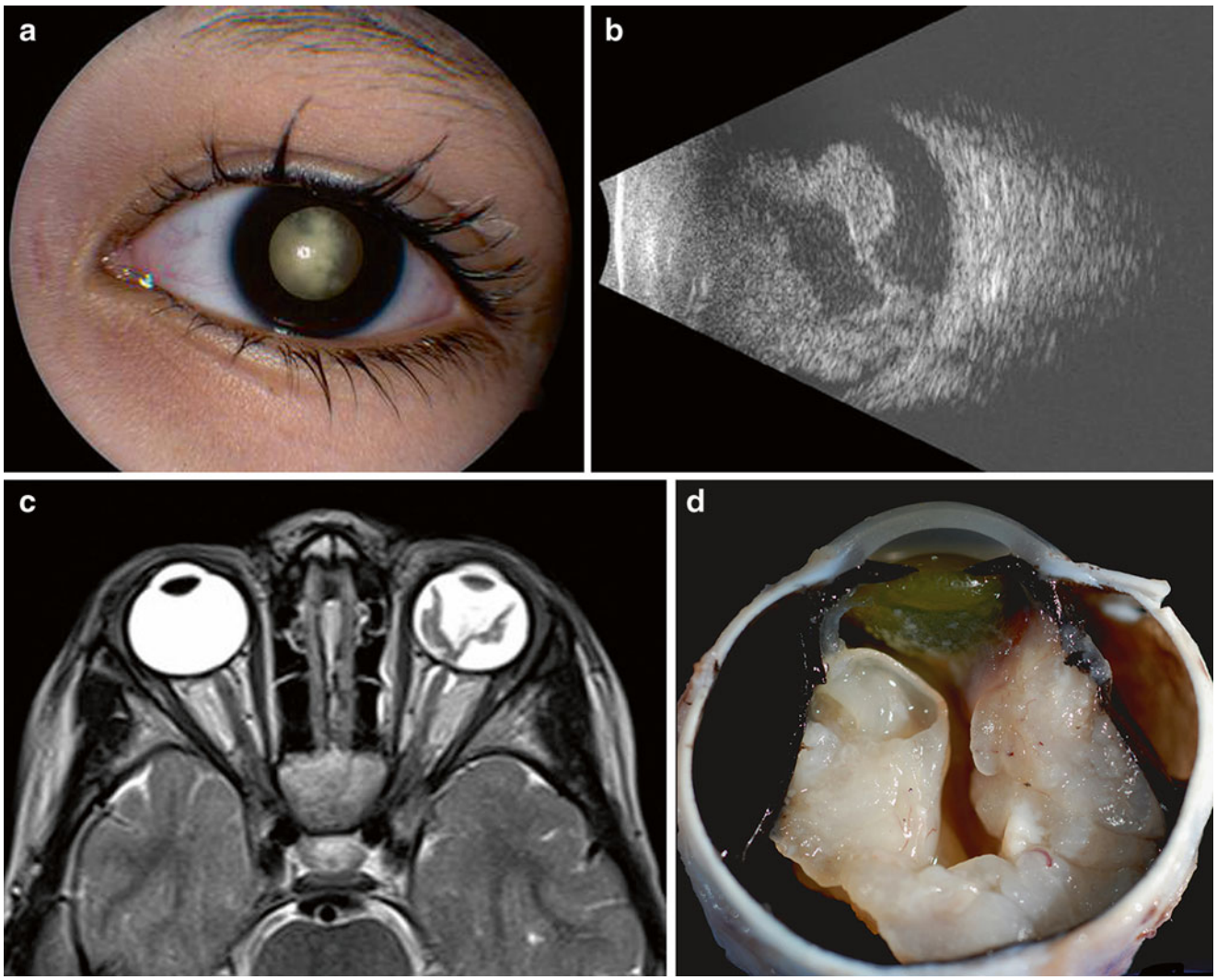

Fig. 37.5 Diffuse variant of retinoblastoma. External photograph demonstrating the appearance of diffuse retinoblastoma (**a**), B-scan ultrasonography revealed irregularly thickened retinal detachment with vitreous cells (**b**). Typical features of retinoblastoma including intraocular mass and intraocular calcification were not present. Magnetic resonance imaging confirmed enhancing thickened retina (**c**). Enucleated globe with diffuse infiltrating retinoblastoma (**d**). Reproduced with permission from: Turell ME, Hayden BC, Schoenfield LR, Singh AD. Intraocular Tumors. Ophthalmic Ultrasonography. Singh D and Hayden BC (Eds). Elsevier Saunders, London, 2012, Chapter 11

Classification

Several classification systems have been developed for retinoblastoma. In the 1960s Algernon Reese and Robert Ellsworth introduced a pre-operative grouping system, which quickly became the most widely used for clinical classification of the tumor. The Reese-Ellsworth classification takes into account the number, size, and location of intraocular tumors as well as the presence of vitreous seeding. This classification system groups tumors based on the probability of eye preservation when treated with external beam radiation alone. Nowadays, treatment commonly consists of chemotherapy combined with focal treatment rather than external beam radiation. This change in treatment modalities, in addition to the absence of prognostic information on patient survival or preservation of vision, fueled the creation of a number of newer classification systems of which the International Classification for Intraocular Retinoblastoma is most popular (Table 37.2) [18, 19].

Management

Retinoblastoma was associated with near-certain death just over a century ago. Today although survival rates in developed societies are higher than 90 %, retinoblastoma contin-

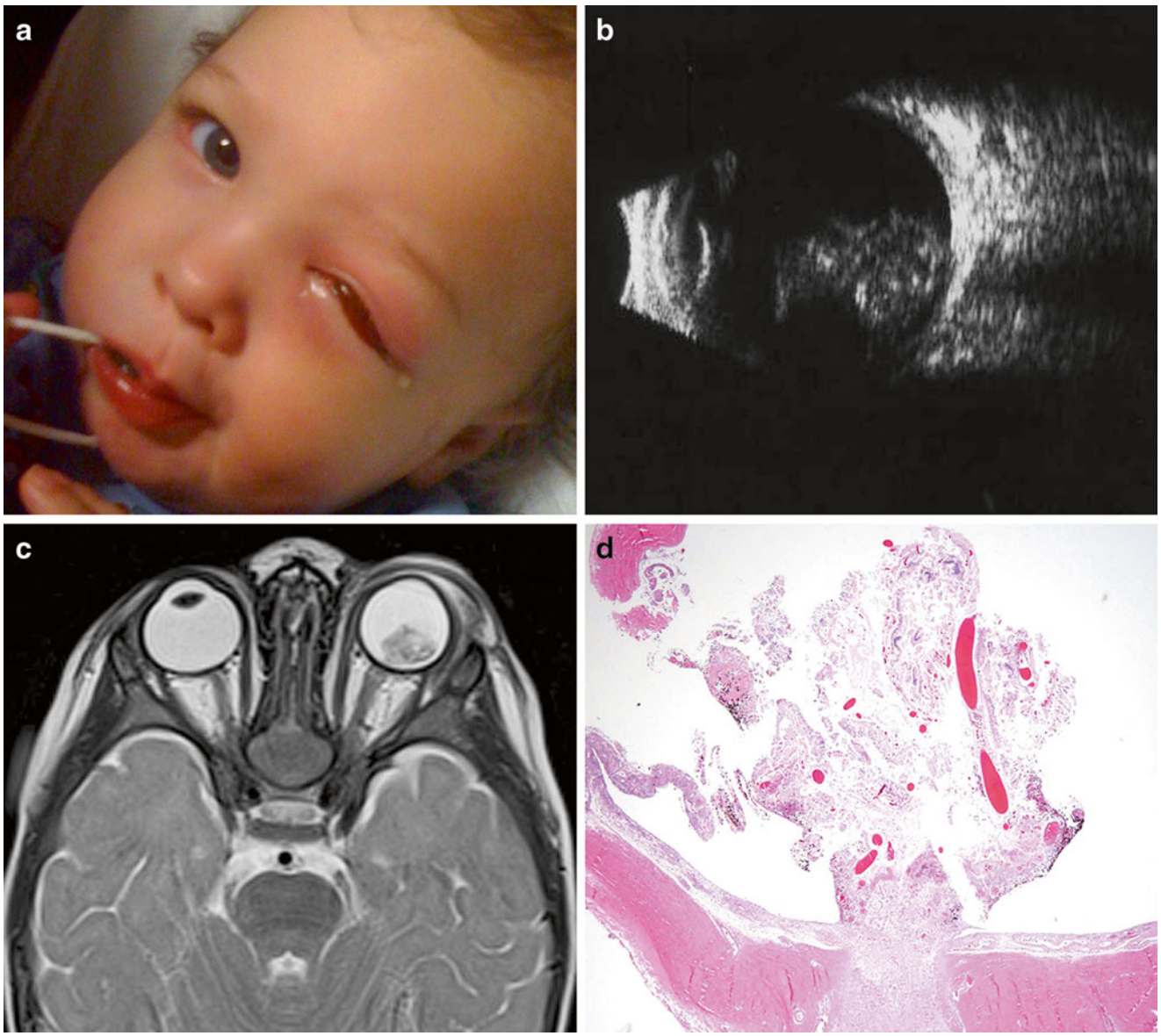

Fig. 37.6 Retinoblastoma presenting as orbital cellulitis. External appearance (**a**). B-scan ultrasonography reveals a large intraocular mass extending from the optic disk. Multiple hyperechogenic intensities are present throughout the mass consistent with calcium deposition (**b**). T2-weighted axial magnetic resonance image reveals an intraocular mass emanating from the optic nerve and retina of the left eye (**c**). Retrobulbar stranding as well as preseptal edema are evident as well. Histopathologic section (hematoxylin–eosin, original magnification ×40) of the enucleated globe consists of fibrin, detached and degenerating retina, inflammatory cells, prominent vascularity, a small amount of necrosis, and calcification (**d**). Reproduced with permission from: Sachdeva R, Schoenfield L, Marcotty A, Singh AD. Retinoblastoma with autoinfarction presenting as orbital cellulitis. J AAPOS. 2011;15:302–4

ues to represent a therapeutic challenge in developing societies in Asia, Latin America, and Africa where survival rates lower than 50 % have been reported [1]. Delayed diagnosis due to patient-related factors or physician-related factors are responsible for the disparity in mortality between countries. Thus, early detection and subsequent reduction in systemic dissemination is the main goal for increasing survival.

The treatment of retinoblastoma is complex and requires a multidisciplinary team approach. An ophthalmic oncologist with expertise in retinoblastoma management should be consulted early in the management as prompt referral is of paramount importance in obtaining satisfactory outcomes. Treatment selection should consider the extent of disease based on the number, extent, and location of the tumors, as well as the status of the contralateral eye (Table 37.3).

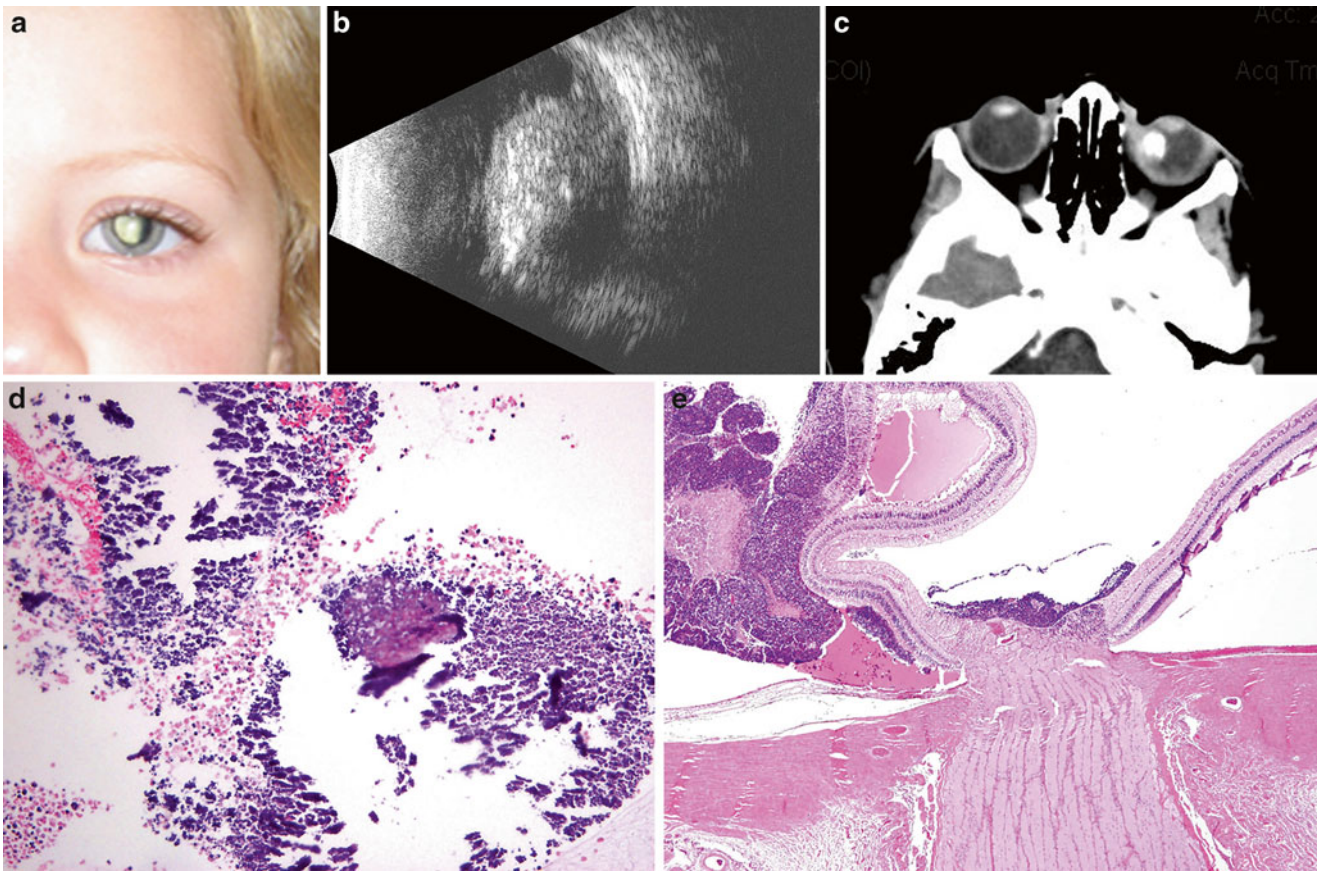

Fig. 37.7 Intrinsic calcification. A 3 year old girl with left sided leukocoria (**a**). B scan ultrasonography confirmed the mass with intrinsic calcification (**b**). Prior to referral, CT scan had also revealed an intraocular mass with calcification (**c**). Enucleation was performed. The tumor was necrotic with calcification (**d**) without optic nerve extension (**e**)

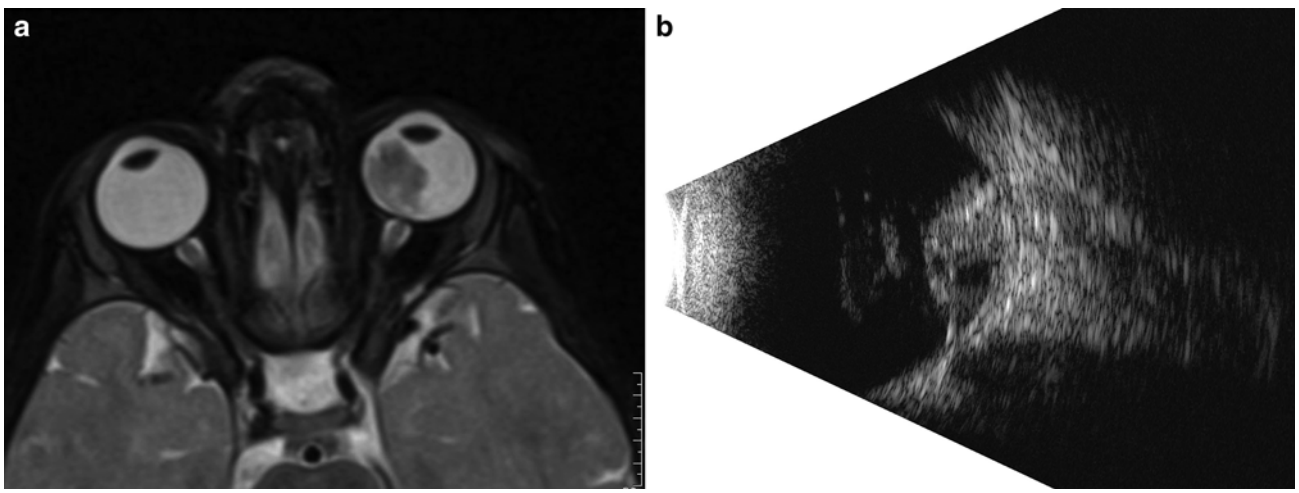

Fig. 37.8 Two year old girl with Group E retinoblastoma. Since there was no view of the optic disc, MRI was performed to exclude retrolaminar optic nerve extension, extrascleral/orbital extension, and presence of pinealoblastoma. MRI (T-2) shows hypointense mass in the left globe with normal optic nerve (**a**). Orbit and brain was normal. Corresponding B scan ultrasonograph (**b**)

Table 37.2 International classification for intraocular retinoblastoma

Group	Criteria
Group A (very low risk)	All tumors are 3 mm or smaller, confined to the retina and at least 3 mm from the foveola and 1.5 mm from the optic nerve. No vitreous or subretinal seeding is allowed.
Group B (low risk)	Eyes with ***no*** vitreous or subretinal seeding and discrete retinal tumor of any size or location. Retinal tumors may be of any size or location not in group A. Small cuff of subretinal fluid extending **≤5 mm** from the base of the tumor is allowed.
Group C (moderate risk)	Eyes with ***focal*** vitreous or subretinal seeding and discrete retinal tumors of any size and location. Any seeding must be local, fine, and limited **so as to be theoretically treatable with a radioactive plaque.** Up to **one quadrant of subretinal fluid** may be present.
Group D (high risk)	Eyes with ***diffuse*** vitreous or subretinal seeding **and/or massive, nondiscrete endophytic or exophytic disease**. Eyes with more extensive seeding than Group C. Massive and/or diffuse intraocular disseminated disease may consist of 'greasy' vitreous seeding or avascular masses. Subretinal seeding may be plaque-like, includes exophytic disease and >1 quadrant of retinal detachment.
Group E (very high risk)	Eyes that have been **destroyed anatomically or functionally** with one or more of the following: Irreversible neovascular glaucoma, massive intraocular hemorrhage, aseptic orbital cellulitis, tumor anterior to anterior vitreous face, tumor touching the lens, diffuse infiltrating retinoblastoma, phthisis or pre-phthisis.

Table 37.3 First line treatment according the laterality and group as determined by Internal Retinoblastoma Classification System

Group	Unilateral		Bilateral
Group A	Posterior to equator	TTT	TTT
	Anterior to equator	Cryotherapy	Cryotherapy
Group B	IV chemotherapy + FOCAL		IV chemotherapy + focal
Group C	Plaque brachytherapy		IV chemotherapy + focal
	IA chemotherapy + focal		IA chemotherapy + focal
	IV chemotherapy + focal		Plaque brachytherapy
Group D	Enucleation		IA chemotherapy + focal
	IV chemotherapy + focal		IV chemotherapy + focal
	IA chemotherapy + focal		Enucleation
Group E	Enucleation		Enucleation

This table is only a guideline. Actual treatments may vary depending upon institutional preference, experience, and availability of treatment
Bilateral assumes symmetric bilateral involvement. In presence of asymmetric disease, treatment of each may be considered individually. Usually, treatment of more advanced eye (such as use of intravenous chemotherapy) will influence decision of treating less affected eye
TTT transpupillary thermotherapy
Focal: TTT or cryotherapy or plaque brachytherapy
At present, intravitreal chemotherapy is considered only for recurrent/or persistent vitreal/sub retinal seeds in conjunction with treatment of retinal tumor (source of the seeds)

The primary goals listed in order of priority should be preservation of life, then the eye, and finally vision, all whilst minimizing secondary effects of the treatment. It is important to remember that patients diagnosed when the tumor(s) are intraocular have survival rates exceeding 95 %, while those patients diagnosed with retinoblastoma with extraocular spread have a survival rate lower than 50 % [12]. Although a detailed description of each treatment modality is beyond the scope of this chapter, a brief overview of the most commonly employed treatment modalities is outlined below.

Enucleation

Enucleation continues to be the treatment of choice for significantly advanced retinoblastoma (Group E) and eyes without visual potential (Fig. 37.9). This is particularly true in the setting of unilateral and non-germ line disease since enucleation is curative in the majority of cases.

Here is a brief step-by-step description of the procedure: After the operative eye is prepped and draped, a 360° conjunctival/sub-Tenon peritomy is performed to separate these

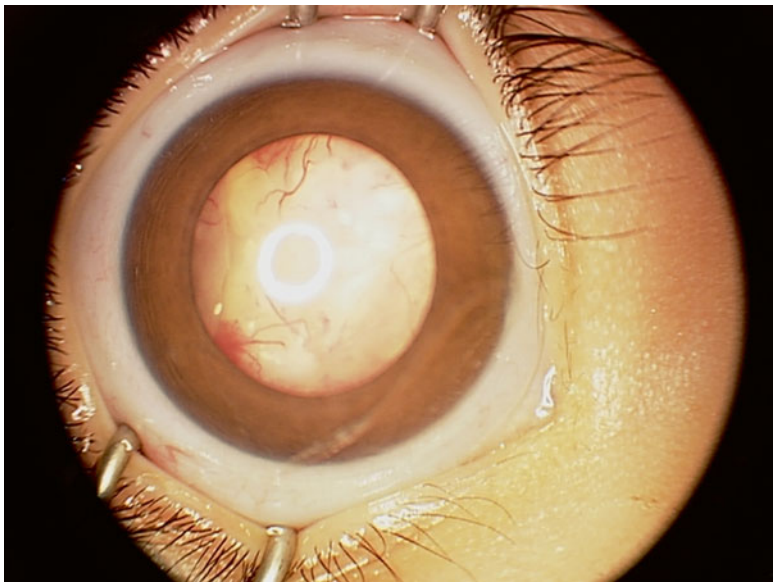

Fig. 37.9 Unilateral Group E retinoblastoma. Enucleation continues to be the treatment of choice for significantly advanced retinoblastoma (Group E) and for eyes without visual potential

layers from the sclera. The four rectus muscles are isolated and 6-0 polyglactin double-armed sutures are passed through the tendon of each muscle to allow for later reattachment to the orbital implant. The muscles are then disinserted from the globe. The superior oblique and inferior oblique muscles are then isolated and disinserted from the globe. With tension held on the globe, the optic nerve is identified and then cut, with a goal to submit as long of a segment of the nerve as possible. Hemostasis is then achieved with a combination of mechanical pressure, neurosurgical cottonoids soaked in epinephrine, and thrombin as needed. The orbital implant is then sized and inserted into the orbital socket, and the four rectus muscles are reattached to the center of the implant. Tenon and conjunctiva are then closed in a multi-layered fashion. During enucleation, particular care should be taken to avoid perforation or penetration of the globe to minimize the risk of extraocular extension. Important findings regarding the specimen that need to be communicated in any pathology report include the presence and extent of choroidal, scleral and optic nerve invasion, as well as the mitotic activity of the cancerous cells.

Chemotherapy

(a) *Intravenous*: The foundation of systemic chemotherapy protocols has generally been a combination of carboplatin and vincristine with or without etoposide. Current regimens incorporate various combinations of these three drugs, with a primary goal of reducing tumor size (i.e. chemoreduction) so that conservative methods such as thermotherapy, cryotherapy and brachytherapy may be subsequently employed (Fig. 37.10). Intravenous chemotherapy may decrease the risk of development of trilateral retinoblastoma. Intravenous treatment is usually administered every 3–4 weeks for four to nine cycles while serial examinations under anesthesia are performed to monitor tumor response. Common side effects of carboplatin include but are not limited to neutropenia, anemia, thrombocytopenia, and brittle hair. Vincristine use is commonly associated with alopecia, fatigue and constipation. The side effect profile of etoposide is similar to carboplatin and vincristine but also includes nausea and vomiting. Of note, however, one of the surprising side effects of systemic chemotherapy that has been reported is the incidence of hearing impairment. Two long-term studies report a 5–20 % incidence of deafness in children with retinoblastoma treated with systemic chemotherapy, with younger children appearing to be more sensitive to the effect [30]. The visual outcomes following intravenous chemotherapy are excellent and comparable to external beam radiation for patients with bilateral disease [20]. For these reasons, intravenous chemotherapy is the most common primary, eye conserving approach for treating intraocular retinoblastoma in developed countries.

(b) *Intra-arterial:* Recently, selective intra-arterial infusion of chemotherapy (IAC) to the retinal circulation has emerged as an important new modality for treating eyes with advanced intraocular retinoblastoma (Group C–E) (Fig. 37.11) [21, 22]. In this procedure, a balloon catheter is inserted in the femoral artery, past the internal carotid artery and guided just past the origin of the

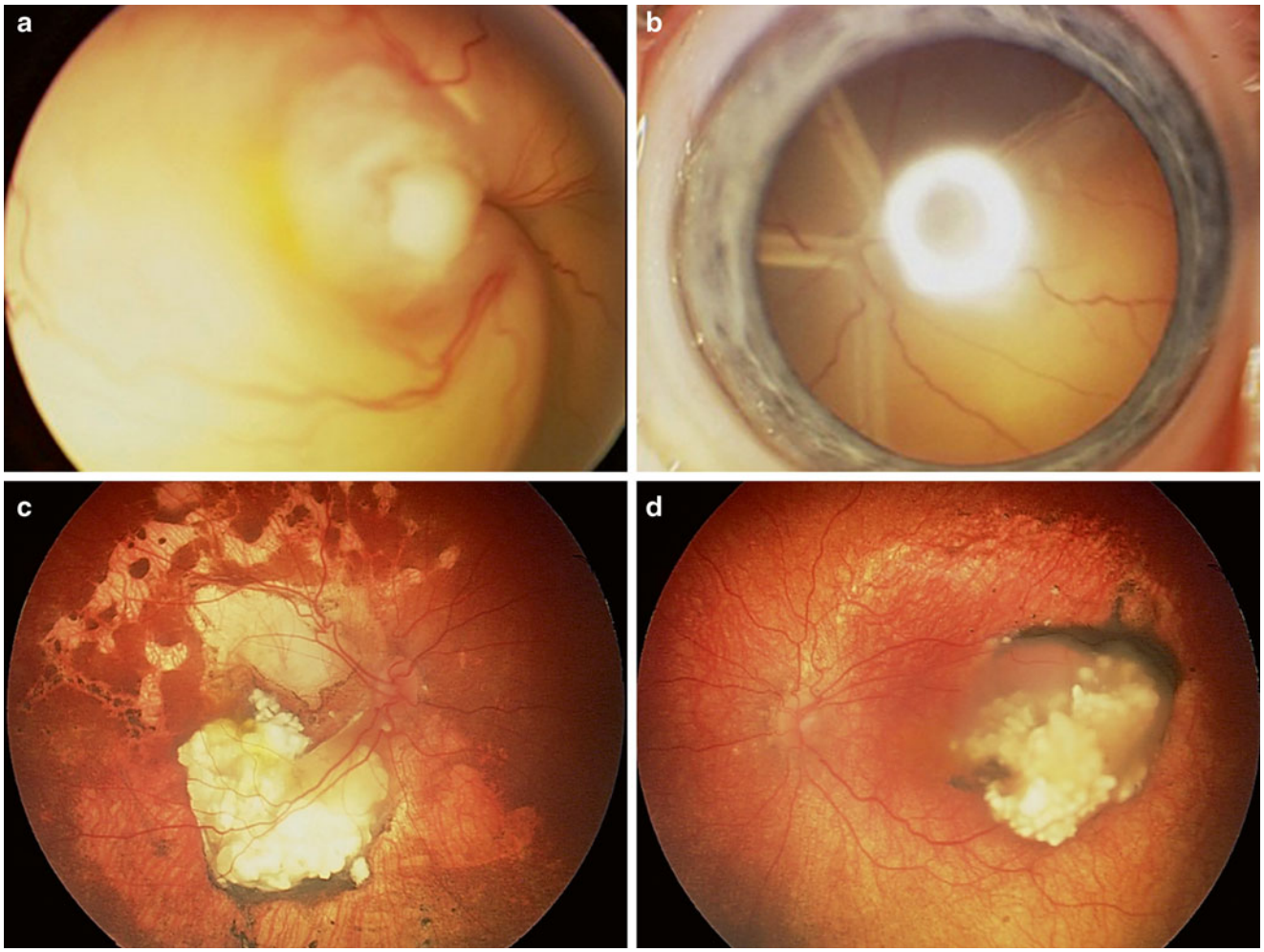

Fig. 37.10 Bilateral Group E retinoblastoma. Initially treated with six cycles of intravenous carboplatin, vincristine, etoposide (**a** and **b**). Despite encouraging initial response (**c** and **d**) there were multiple recurrences requiring thermotherapy and cryotherapy OU and plaque radiation therapy OS. Following additional recurrence OS was enucleated and OD controlled with intra-arterial chemotherapy

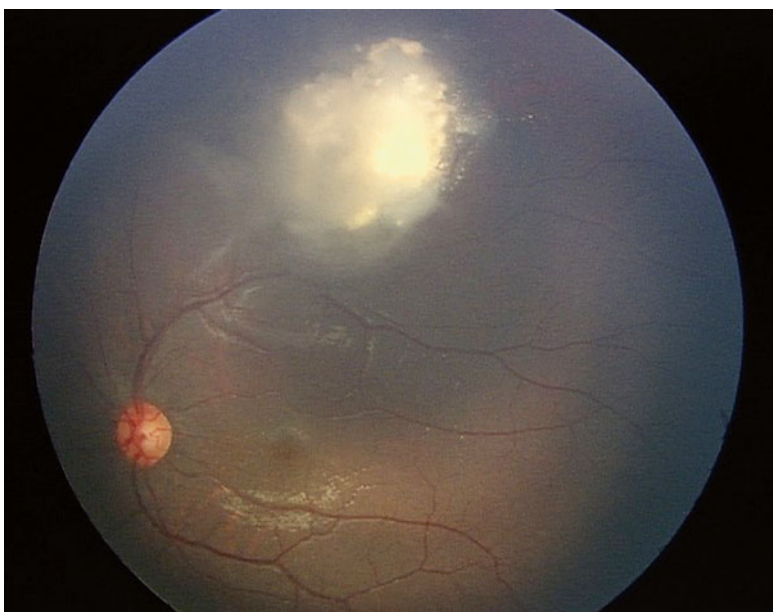

Fig. 37.11 Group D retinoblastoma. Unilateral sporadic retinoblastoma with normal optic disc and macula. Such a case can be treated with intra-arterial chemotherapy because of presence of diffuse vitreous seeds

ophthalmic artery. The balloon is then inflated and melphalan injected into the arterial vasculature. Other agents including carboplatin and topotecan (alone or in combination) have also been used. Local complications have been reported and range from periocular edema to more serious complications such as retinal artery occlusion and vitreous hemorrhage [23]. Fortunately, neurologic complications related to the catheterization process appear to be rare with this technique and published reports document none of the systemic side effects associated with systemic chemotherapy infusion, such as anemia requiring blood transfusions, neutropenia/neutropenic fever, or GI toxicity [30].

(c) *Periocular*: Administration of periocular chemotherapeutic agents (carboplatin, etoposide, and vincristine) are currently used and are small molecules that enter the eye easily via a trans-scleral delivery system. Studies in primates have shown this technique achieves higher vitreous concentrations than intravenous administration [24]. However, side effects are not insignificant, with reports of optic atrophy and periocular tissue scarring causing restriction in ocular motility, as well as periorbital edema and redness occurring in over one third of patients [25, 26].

(d) *Intravitreal:* Intravitreal injections have recently gained popularity since they have the potential to achieve exponentially higher concentrations of drug into the vitreous space, while maintaining low concentrations in the plasma. Intravitreal chemotherapy may be considered as salvage therapy in eyes with residual intravitreal seeding following intra-arterial or intravenous chemotherapy (Group D and E). Extraocular seeding through the needle tract, retinal toxicity, and other safety concerns persist and therefore, intravitreal chemotherapy should be considered only for select cases.

Cryotherapy

Cryotherapy is particularly useful for small peripheral tumors up to 3.0 mm in diameter and 2.0 mm in thickness (Group A). Posterior tumors can also be treated with a concomitant conjunctival cutdown so that the probe can be extended posteriorly. Standard cryotherapy usually requires application of the triple freeze-thaw technique in one or two sessions. The control rate is as high as 90 % with small tumors (<3 mm) with minimal complications, such as redness, swelling or mild discomfort at the site [27].

Laser Therapy

Both photocoagulation (532 nm argon laser) and thermotherapy (810 nm diode laser) may be used for treatment of retinoblastoma. Although usually used to treat small peripheral or posterior tumors, laser therapy can effectively address tumor recurrences, as well as larger tumors after systemic chemotherapy (Fig. 37.12). Photocoagulation usually requires multiple sessions while thermotherapy may be effective in a single session. Moreover, thermotherapy employs a longer wavelength than photocoagulation, with resultant deeper tissue penetration and possible direct cytoxic effects. It is useful as sole therapy for tumors that are less than 3 mm in diameter (Group A). The reported success rates go up to 92 % with minimal side effects if used appropriately [28].

Plaque Radiation Therapy (Brachytherapy)

Brachytherapy with either iodine-25 or ruthenium-106 continues to be an excellent treatment modality for retinoblastoma. Radiation exposure to adjacent tissue is limited, and

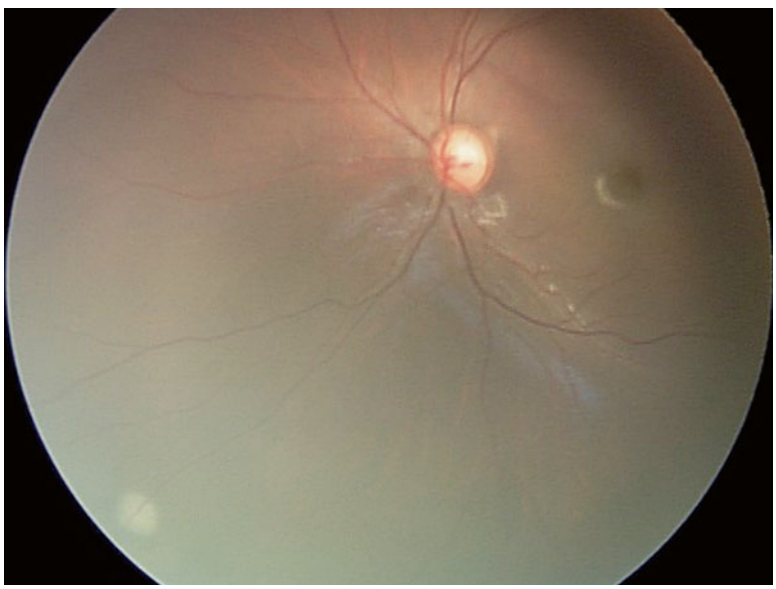

Fig. 37.12 Group A retinoblastoma detected in 3 month old child undergoing prospective screening because of presence of familial germline mutation. Appearance immediately after transpupillary thermotherapy

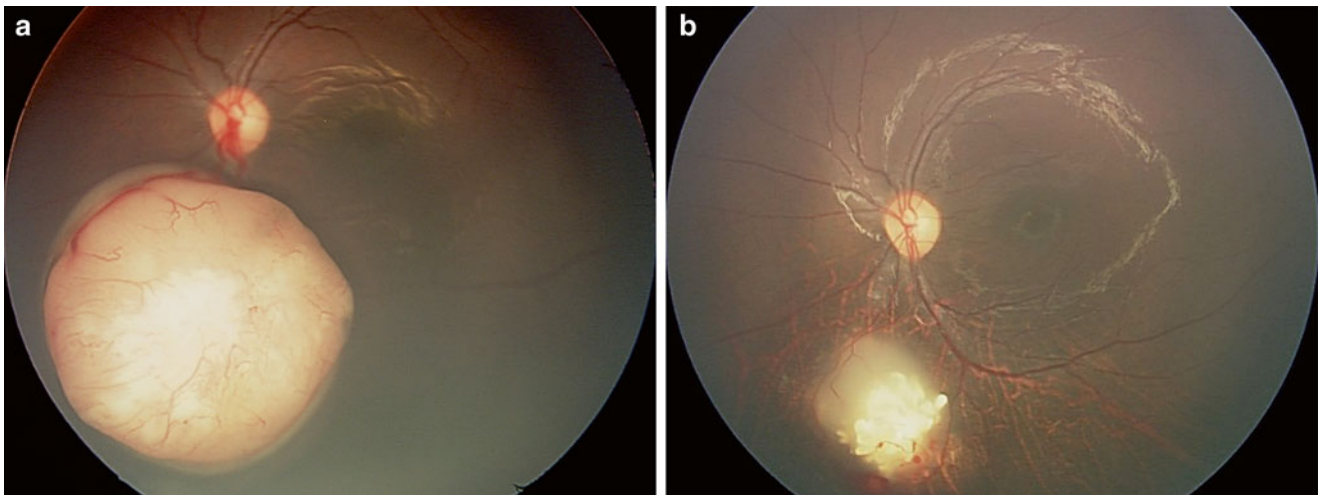

Fig. 37.13 Group C retinoblastoma. Left eye of the child shown in Fig. 37.8. Appearance before (**a**) and 8 weeks after plaque radiation therapy (**b**, iodine-125 plaque, 45 Gy/48 h)

there is no increased risk of second non-ocular cancers or orbital hypoplasia such as that seen with external beam radiotherapy. It may be used for tumors up to 16 mm in greatest basal dimension and 8 mm in height (Group C) and is particularly indicated in unilateral tumors as well as for tumors that have failed chemoreduction or other focal treatment modalities (Fig. 37.13) [29].

Radiation Therapy

Although external beam radiotherapy remains an excellent option for preserving vision in patients with retinoblastoma, most clinicians believe that current chemotherapy regimens offer a better safety profile than radiotherapy. Local control rates of tumor recurrence with external beam radiation therapy are excellent, and are reported to be over 90 %. The typical dose is approximately 40–45 Gy distributed over 4–6 weeks. Radiation therapy complications include midface hypoplasia as well as radiation retinopathy, neuropathy and cataract. More importantly, radiotherapy significantly increases the risk of secondary malignancy. The use of proton beam radiotherapy has also been advocated although long-term follow up and results have not been established. External beam radiotherapy is still indicated for tumors with extraocular extension or evidence of tumor at the surgical transection margin of the optic nerve at the time of enucleation (see "Enucleation" section above in italics).

Future Developments

As portable non-mydriatic imaging hardware and sophisticated image analysis software become economical and readily available, future efforts should be directed at developing automated systems for early detection of disease by population screening. Prompt consultation with a specialist either in person or via tele-ophthalmology, may help ascertain a diagnosis and treatment plan. Although current treatment modalities are very successful at treating early disease, improvements in drug delivery are needed. Data from ongoing trials will further allow us to elect the appropriate treatment modality for each individual case and establish evidence based treatment algorithms.

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Part X

Optic Nerve Disorders

Optic Nerve Malformations

38

Palak B. Wall and Elias I. Traboulsi

Abstract

Optic nerve malformations are common causes of visual impairment and are increasing in incidence. When examining the optic nerve, it is crucial to pay close attention to features that can differentiate one malformation from another. Associated conditions can include anatomic abnormalities of the brain, endocrinopathies, cerebrovascular abnormalities, renal disease, hearing loss, and many other genetic syndromes. Many of these conditions can lead to significant morbidity and mortality without prompt diagnosis and treatment. In addition, diagnosis is important to determine the risk of other ocular issues such as refractive error, strabismus, amblyopia, choroidal neovascularization, and retinal detachment.

Keywords

Optic nerve • Malformations • Optic nerve hypoplasia • Optic nerve coloboma • Morning glory disc anomaly • Optic pit • Myelinated nerve fibers

Optic Nerve Hypoplasia

Optic nerve hypoplasia (ONH) is defined by a congenital occurrence of reduced number of optic nerve fibers resulting in a small optic nerve. Optic nerve aplasia is an extreme form of optic nerve hypoplasia. The prevalence of ONH in England in 2006 was 10.9 in 100,000 births [1], but there has not yet been a study estimating the prevalence in the USA. On examination, the optic nerve is small. The double-ring sign is believed to represent the extension of retina and retinal pigment epithelium (RPE) over the outer portion of the lamina cribrosa. The outer ring is the junction between sclera and lamina cribrosa, and the inner ring is the termination of the RPE (Fig. 38.1) [2]. The retinal veins are frequently tortuous, probably as a result of the loss of tectonic support by the nerve fiber layer. The ratio of the distance from the center of the disc to the macula and the disc diameter can be helpful in determining if there is optic nerve hypoplasia. Optic nerve hypoplasia should be considered when the ratio is greater than 3 [3]. OCT demonstrates the reduced retinal thickness, particularly the inner layers, and foveal hypoplasia in many patients (Fig. 38.2) [4]. Visual acuity varies depending on the severity of the hypoplasia, but typically remains stable over time. In more severe cases, an afferent pupillary defect may be detected in the eye with ONH. Patients with ONH may have congenital nystagmus. Strabismus is more common when the condition is unilateral [5]. Eighty percent of cases are bilateral and two-thirds are asymmetric [6].

Optic nerve hypoplasia is associated with a number of conditions including prematurity [7], developmental delay, and autism [8]. Table 38.1 lists systemic and environmental associations of ONH. Most cases of ONH are not inherited and can be a result of environmental factors. There is an association with recreational and prescription drugs, alcohol,

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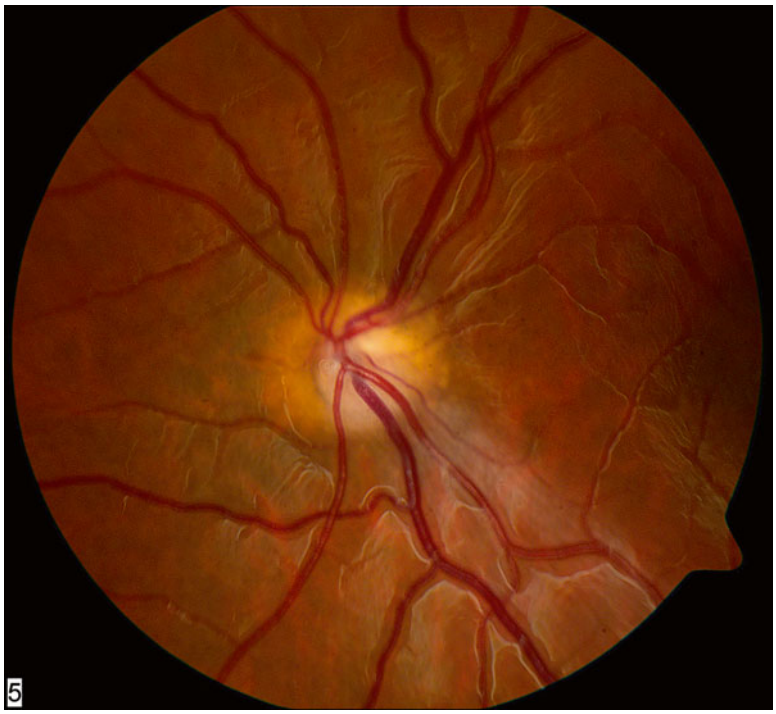

Fig. 38.1 Optic nerve hypoplasia. Note double-ring sign and tortuosity of retinal veins

tobacco, and viral infections [9]. A large Swedish study using interviews in the first trimester of pregnancy showed a correlation with young maternal age, primiparity, and alcohol use [10]. Another study did not show a link between optic nerve hypoplasia and drug or alcohol use [11]. The drugs that have been reported to be associated with ONH are listed in Table 38.1. There are very few genetic associations, but rarely, mutations in *PAX6* have been implicated with autosomal dominant inheritance [12]. Superior segmental hypoplasia with a corresponding inferior visual field defect may occur in children of mothers with type I (insulin-dependent) diabetes mellitus [13].

Patients with ONH have a higher risk of hypothalamic and pituitary dysfunction. There is a wide range in reported prevalence of hypopituitarism, ranging from 66 to 71.7 % [6, 14], and it may be higher with bilateral disease. Hypopituitarism is usually due to hypothalamic dysfunction. The most common deficiency is of growth hormone, followed by thyroid hormone, then adrenocorticotropic hormone, and lastly antidiuretic hormone leading to diabetes insipidus. Retinal veins are more tortuous in patients with ONH and growth hormone deficiency [15]. There is an association and co-occurrence of absence of the septum pellucidum, endocrinopathies, and optic nerve hypoplasia which has classically been referred to as "septo-optic dysplasia" or "de Morsier syndrome." More recent data suggests that hormonal abnormalities are independent of an absent septum pellucidum [16]. Other anatomic abnormalities tend to be more predictive of endocrinopathies such as an absent corpus callosum, gyrus dysplasia, and cortical heterotopia. In light of this recent data, there has been a departure from using the previous terminology of septo-optic dysplasia. Twelve percent of patients with mitochondrial cytopathies have ONH presumed to be the result of excessive apoptosis of ganglion cells during development [17]. Figure 38.3 illustrates the multiple pathways and possible underlying etiologies leading to optic nerve hypoplasia.

Eyes with ONH are more likely to have astigmatism, and amblyopia is common [18]. All patients with ONH should have a cycloplegic refraction with spectacles and occlusion therapy when indicated. Patients with ONH should also undergo brain MRI and be referred to pediatric neurology and pediatric endocrinology.

Morning Glory Disc Anomaly

An excavated, enlarged optic disc characterizes the morning glory disc anomaly (MGDA). The retinal vessels radiate from the optic disc in a spoke-like fashion and are increased in number. The disc can have a funnel-like appearance and may have a central glial tuft (Fig. 38.4). Patients typically present with leukocoria or strabismus, and vision is typically poor ranging from 20/200 to counting fingers, but can be as good as 20/30. MGDA is more common in females [19]. Although it is usually unilateral, there are a few cases of bilateral MGDA. Transient visual loss and changing appearance of the anomaly may be caused by heterotopic smooth muscle in the posterior sclera contracting [20].

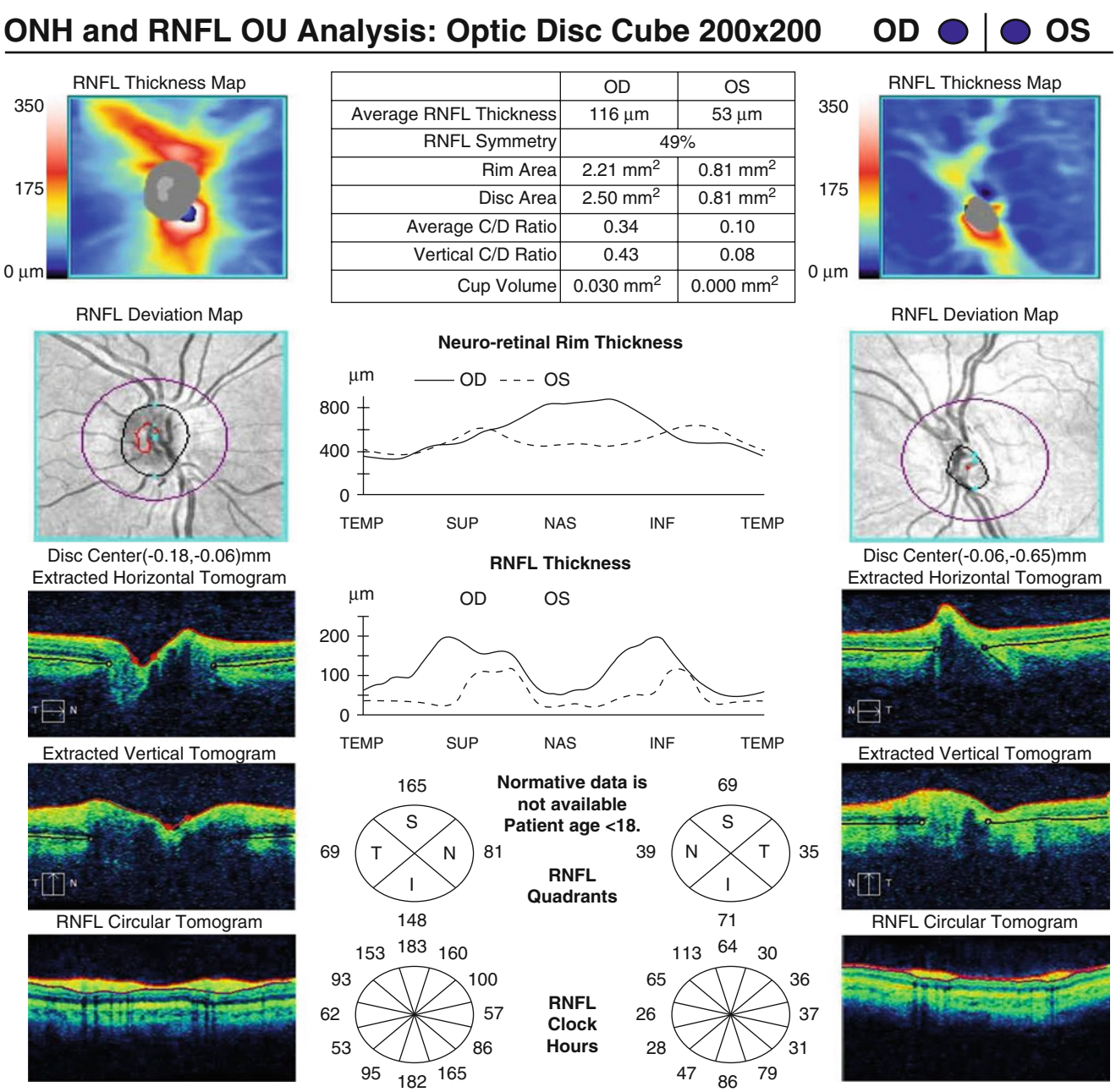

Fig. 38.2 OCT of optic nerve head in a case of left ONH. Note thin nerve fiber layer at the nerve head

One-third of patients with MGDA will develop a retinal detachment [21]. Some suggest that the fluid enters the subretinal space through microbreaks in the peripapillary retinal tissue [22, 23], while others propose that the fluid is cerebrospinal fluid entering through an abnormal communication between the subarachnoid space and subretinal space [24]. The detachments are difficult to treat, and success rates have been low with optic nerve sheath fenestrations and with surgical repair. In one case report, triamcinolone was used with some success in a patient with recurrent and refractory retinal detachments, but no further support for this treatment was found in our literature search [25].

There are several systemic associations with MGDA. It has been associated with trans-sphenoidal encephalocele, which is a type of basal cephalocele. Endocrine abnormalities may occur as a result of hypothalamic and pituitary axis dysfunction [26]. MGDA is also associated with Moyamoya disease, which is characterized by narrowing or aplasia of vertebral or carotid arteries or branches thereof. This can lead to strokes or seizures. Altogether, cerebrovascular abnormalities are common and present in 45 % of patients with MGDA. PHACES syndrome (*P*osterior fossa abnormalities and other structural brain abnormalities, *H*emangioma(s) of the cervical facial region, *A*rterial cerebrovascular anomalies,

Table 38.1 Genetic and environmental associations of optic nerve hypoplasia

Genetic associations	Environmental associations
13q- syndrome	Alcohol
Aarskog syndrome	Carbamazepine
Aicardi syndrome	Isotretinoin
Albinism	Phenytoin
Aniridia	Quinine
Blepharophimosis syndrome	Valproic acid
Borjeson-Forssman-Lehmann syndrome	Maternal insulin-dependent diabetes mellitus
CHARGE syndrome	
Chondrodysplasia punctate, Conradi-Hunermann type	
Cornelia de Lange syndrome	
Duane syndrome	
Ectopia lentis et pupillae	
Eye-muscle-brain syndrome	
Fetal alcohol syndrome	
Focal dermal hypoplasia (Goltz syndrome)	
Frontonasal dysplasia	
Goldenhar syndrome	
Lethal X-linked microcephaly	
Nevus sebaceous of Jadassohn	
Noonan syndrome	
Smith-Lemli-Opitz syndrome	
Trisomy 8	
Walker-Warburg syndrome	

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Cardiac defects, aortic coarctation, and other aortic abnormalities, *E*ye anomalies, *S*ternal defects, and/or *S*upraumbilical raphe), a neurocutaneous syndrome involving posterior fossa abnormalities, facial hemangiomas, and cardiac anomalies, is also associated with MGDA and posterior staphyloma [27]. Due to the gravity of the associated conditions, an MRI and MRA of the brain are recommended in all patients with MGDA. There are no consistent associated genetic mutations with MGDA.

Optic Nerve Coloboma

The embryonic fissure normally closes between the sixth and seventh weeks of gestation. When it fails to close completely, the result can be a coloboma that involves the optic nerve head (Fig. 38.5). It can extend anteriorly to the choroid, retina, ciliary body, and iris, constituting what is referred to as typical chorioretinal colobomas that are generally associated with microphthalmia. In contrast to MGDA, the retinal vessels in optic nerve colobomas have a normal course and caliber and form normal arcades unless the coloboma is very large. Visual acuity is highly variable and depends on the degree of foveal involvement. Refractive errors are common and can lead to anisometropia and subsequently amblyopia. Choroidal neovascularization can occur in patients with optic nerve colobomas. Both serous and rhegmatogenous retinal detachments are possible.

There are many systemic associations with optic disc coloboma. CHARGE syndrome involves coloboma, heart defects, choanal atresia, growth retardation and development, genitourinary abnormalities, and ear abnormalities. It is caused by mutations in *CHD7* in two-thirds of cases and is inherited in an autosomal dominant fashion [28]. Other syndromes associated with optic nerve coloboma and microphthalmia/coloboma (Table 38.2) include Walker-Warburg syndrome, Goltz focal dermal hypoplasia, Goldenhar sequence, and linear sebaceous nevus syndrome. These are usually large and bilateral, and extend anteriorly to involve the retina and choroid [29].

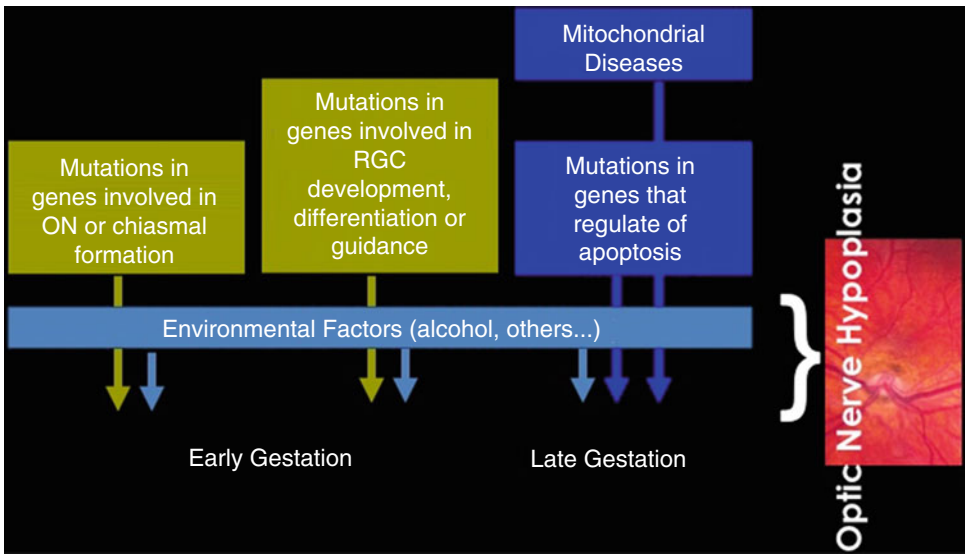

Fig. 38.3 Different pathways and their timing in eye development leading to optic nerve hypoplasia. Multiple etiologies may be at play in certain patients

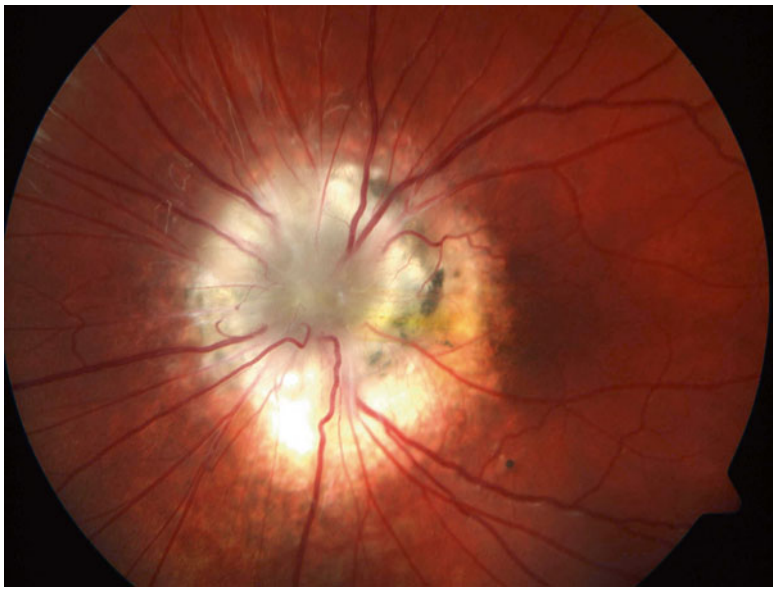

Fig. 38.4 Morning glory disc anomaly. Note enlarge scleral opening, central tuft of glial tissue, and straight course of blood vessels out of nerve head

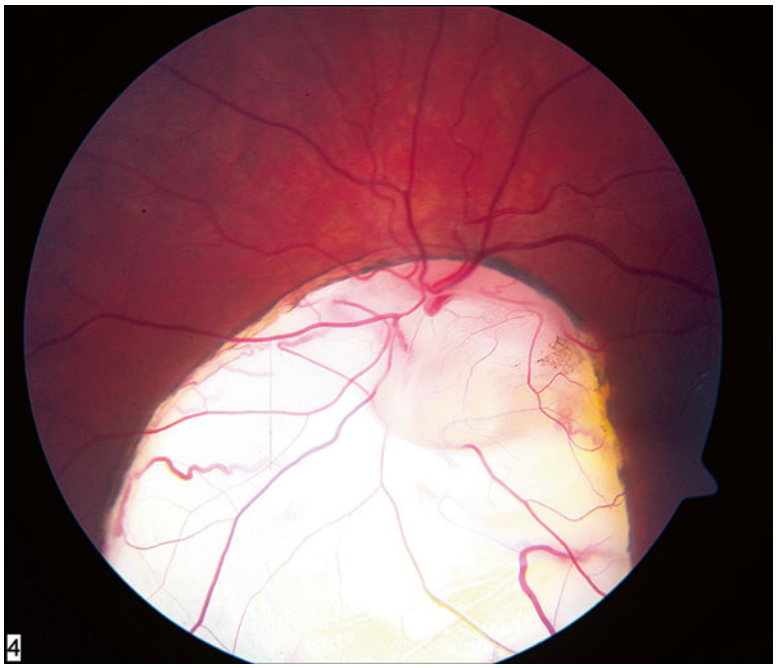

Fig. 38.5 Typical inferior chorioretinal coloboma involving the optic nerve head and resulting from failure of closure of embryonic fissure

Papillorenal Syndrome

Patients with this syndrome have optic nerve malformations similar to coloboma, but share features of optic pit, and morning glory disc anomaly. The renal pathology is also varied and can include hypoplasia, hypodysplasia, multicystic dysplastic kidney, oligomeganephronia, and horseshoe kidney. These abnormalities can lead to renal failure. Mutations in *PAX2* cause the papillorenal syndrome and are autosomal dominant [30]. High-frequency hearing loss is present in 10 % of patients with papillorenal syndrome; this is likely due to *PAX2* also being involved in cochlear development [30].

Optic Pit

An optic pit is a localized defect in the optic nerve head. Optic pits are typically unilateral and can occur anywhere on the optic nerve head (Fig. 38.6). Although previously thought to be most common temporally, a recent population-based study showed that optic pits are most commonly located inferiorly, followed by centrally, and then temporally [31]. The prevalence is 0.19 % of the general population and increases with age. The prevalence appears to be higher in patients with normal tension glaucoma at 2.8 %, suggesting that optic pits could also be acquired in some patients. Visual

Table 38.2 A practical classification of colobomatous microphthalmia

Isolated
Colobomatous microphthalmia (AD)
Microphthalmia with cyst
Microphthalmia with ocular anomalies
Microphthalmia with cataract (AD, AR)
Microphthalmia with myopia and corectopia (AD)
Microphthalmia with ectopia lentis
Microphthalmia with congenital retinal detachment (AR)
Persistent hyperplastic primary vitreous (sporadic)
Aicardi syndrome (XL)
Microphthalmia with mental retardation
Microphthalmia with mental retardation (AD, AR, XR)
Microphthalmia with mental retardation and congenital spastic diplegia (Sjogren-Larsson)
Microphthalmia with craniofacial malformations
Facio-auriculo-vertebral sequence
Hallermann-Streiff syndrome
Amniotic band syndrome
Transverse facial cleft
Microphthalmia with cleft lip/palate
Microphthalmia with microcephaly
Microphthalmia with microcephaly and retinal folds (XR, AR)
Microphthalmia with hydrocephalus and congenital retinal non-attachment (Warburg syndrome)
Linear nevus sebaceous of Jadassohn
Microphthalmia with malformations of the hands and feet
Microphthalmia with polydactyly
Waardenburg's anophthalmia syndrome (AR)
Subgroup of CHARGE association (bifid thumbs)
Microphthalmia with multiple congenital anomalies (syndromes)
CHARGE association
Lenz microphthalmia syndrome (XL)
Oculo-dento-osseous dysplasia (AD, AR)
Cryptophthalmos or Frasier syndrome (AR)
Cerebro-ocula-facial syndrome or COFS (AR)
Goltz syndrome or focal dermal hypoplasia (XL)
Lowe syndrome (XL)
Microphthalmia with linear skin defects (Al-Gazali syndrome) (XL)
Meckel-Gruber syndrome (AR)
Basal cell nevus syndrome or Gorlin-Goltz (AD)
Congenital contractural arachnodactyly (AD)
Rubinstein-Taybi syndrome (AD)
Cross syndrome (AR)
Fanconi syndrome (AR)
Diamond-Blackfan syndrome (AR)
Epidermal nevus syndrome
Branchio-oculo-facial syndrome (AD)
SOX2 syndrome
Microphthalmia in chromosomal anomalies
Trisomy 13 (Patau)
4p- (Wolf-Hirschhorn)
18q-
18r
Trisomy 18 (Edward)
Cat-eye syndrome (marker 22)
Numerous other chromosomal aberrations
Microphthalmia and intrauterine insults
Maternal drug intake: thalidomide, alcohol, isotretinoin, others
Maternal vitamin A deficiency
Maternal fever or radiation exposure
Maternal uncontrolled phenylketonuria
Intrauterine infections: CMV, EBV, varicella, herpes simplex, rubella, toxoplasmosis
Amniotic band syndrome

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defects are common, but central vision is usually normal if there is no associated maculopathy. Optic pits can be inherited in an autosomal dominant pattern.

Serous retinal detachments occur in 52 % of patients and are most common in patients who have temporal optic pits [32, 33]. It is likely that patients with temporal optic pits are more often symptomatic and therefore present more frequently. Ocular coherence tomography can show subretinal fluid, schisis cavities, or a combination of the two [34]. The detachments can resolve without intervention; however, if they are persistent they can be difficult to treat. Jain and Johnson reviewed current treatment options which can include pharmacologic agents such as corticosteroids or acetazolamide, laser photocoagulation, macular buckling, and vitrectomy with or without internal limited membrane peeling. Their preferred method of treatment for serous retinal detachments associated with cavitary optic disc anomalies was juxtapapillary laser photocoagulation followed by pars plana vitrectomy and gas tamponade [35].

Peripapillary Staphyloma

This very rare condition is characterized by a well-defined optic disc in the bottom of a deep excavation (Fig. 38.7). The excavation is typically deeper than what one would see with MGDA and can be demonstrated on B-scan ultrasonography (Fig. 38.8). The margins of the excavation are usually pigmented. Unlike MGDA, there is no central glial tuft and the course of the retinal blood vessels is fairly normal. The condition is usually unilateral and isolated. Patients are myopic or emmetropic. An enlargement of the blind spot is present, and visual acuity depends on the level of foveal involvement but is generally poor. Kim et al. published a case series of 19 patients with peripapillary staphyloma [36]. Only two

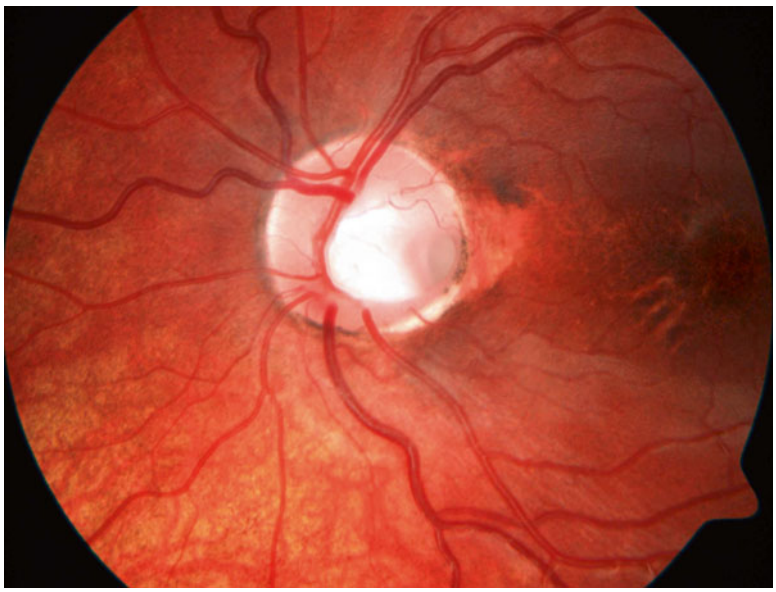

Fig. 38.6 Temporal gray small optic pit. Foveal changes are the result of chronic serous detachments associated with the optic pit

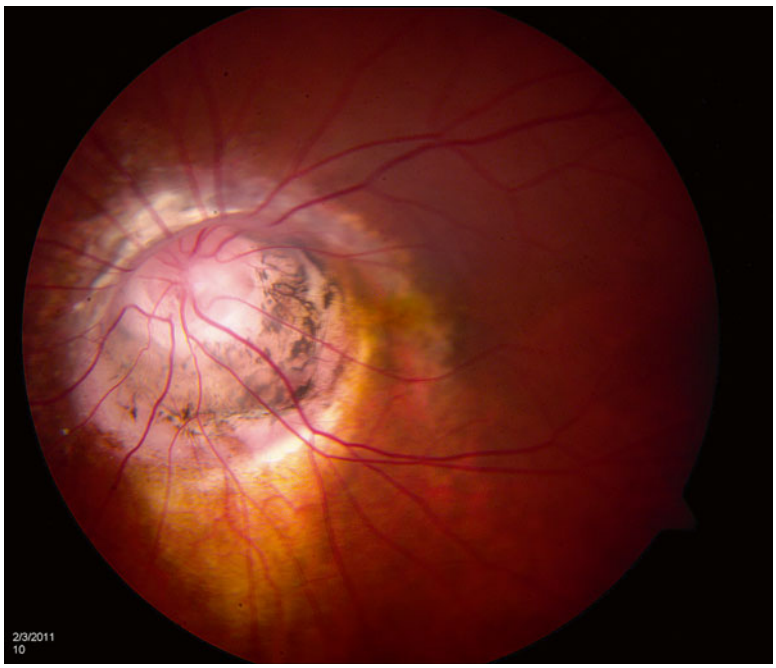

Fig. 38.7 Peripapillary staphyloma. Note normal appearance of optic nerve head in the depth of the posterior scleral defect shown in Fig. 38.8

patients had vision better than 20/200. Seven patients had greater than six diopters of myopia.

The proposed mechanism for formation of peripapillary staphyloma is a halt in differentiation of the posterior sclera from para-axial mesoderm in the fifth month of gestation [37]. Because the sclera forms anterior to posterior, this leads to a defect in sclera posteriorly. Once normal intraocular pressure is established, the area with the scleral defect is pushed posteriorly and becomes excavated in shape. Like MGDA, contractility can be noted in peripapillary staphyloma as well. This malformation can also be associated with trans-sphenoidal encephalocele, PHACE, linear nevus sebaceous syndrome, 18q- (de Grouchy syndrome) [38].

Tilted Disc Syndrome

A tilted disc has an oblong, oval appearance with the superotemporal disc being elevated and the inferonasal disc recessed. This can be associated with situs inversus of the

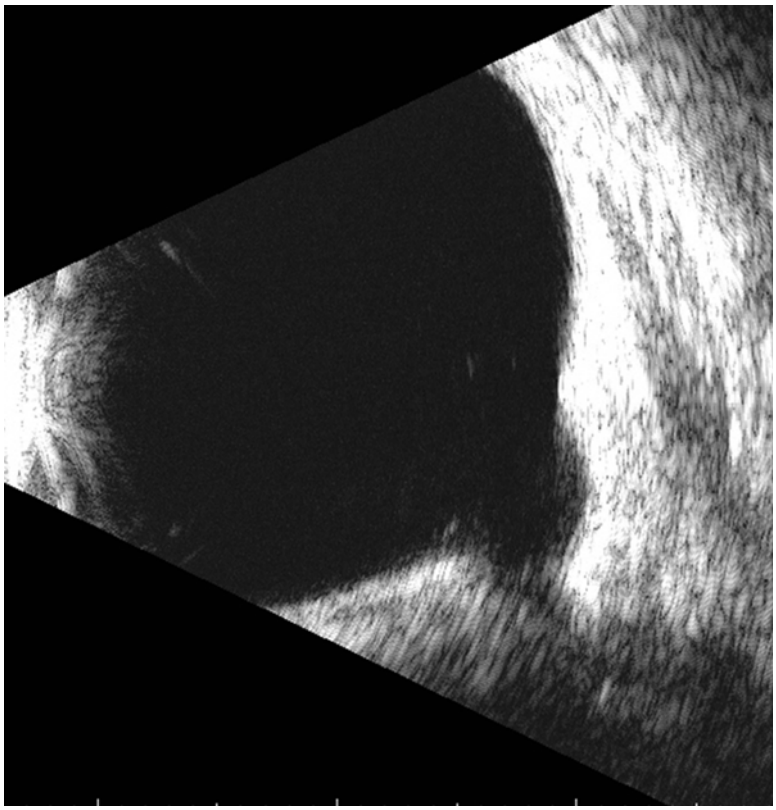

Fig. 38.8 B-scan ultrasound showing posterior defect associated with peripapillary staphyloma

retinal vessels. Hypopigmentation of the inferonasal fundus may be present as well as a scleral crescent. Myopic astigmatism is common in patients with tilted disc syndrome. The most commonly associated visual field defect is an incomplete bitemporal hemianopsia that does not respect the vertical midline. Vuori et al. showed that this defect can be improved by testing with the full myopic correction. Prevalence ranges from 0.36 % [39] to 3.5 % [40].

Complications of tilted disc syndrome include parafoveal choroidal neovascularization (CNV) and serous macular detachment. Park et al. showed that eyes with tilted discs had a significantly greater myopic progression than age-matched controls that started with the same spherical equivalent refractive error [41]. This indicates that a tilted disc may be a prognostic indicator for progressive myopia. Rare associations include trans-sphenoidal encephalocele, congenital tumors of the visual pathway, X-linked congenital stationary night blindness, Ehlers-Danlos syndrome, and familial dextrocardia [38].

Optic Disc Drusen

Optic disc drusen are the most common cause of pseudopapilledema (Fig. 38.9). They are caused by proteinaceous deposits that accumulate as a result of abnormal axonal metabolism and subsequently become calcified [42]. The deposits are usually present bilaterally. The prevalence is approximately 2 % of the general population [43]. Visual field defects are common and can be present in children [44]. The drusen may be more subtle during childhood and become more prominent with age. Systemic associations include pseudoxanthoma elasticum [45] and retinitis pigmentosa [46].

Diagnosis can be made with a variety of imaging modalities. Drusen will be hyperechoic with shadowing on B-scan ultrasonography (Fig. 38.10). Autofluorescence photography has been shown to be as effective as B-scan in detecting drusen [47]. Optic disc drusen can also be detected with optical coherence tomography, particularly with enhanced depth imaging [48]. Drusen are visible on CT scan as well. Because drusen are typically buried in children, they frequently can be mistaken for optic disc edema. Performing testing such as a B-scan when presented with a child with optic disc edema may prevent unnecessary and expensive testing such as brain imaging and lumbar puncture [49]. It is always important to look at the whole clinical picture before making the determination whether further testing is necessary as patients with optic disc drusen can still have concurrent papilledema. The clinician should also evaluate for spontaneous venous pulsations, the absence of which strongly suggests a diagnosis of increased intracranial pressure.

Nonarteritic anterior ischemic optic neuropathy is the most common cause of acute vision loss in patients with optic disc drusen [50]. This can happen at a young age and is

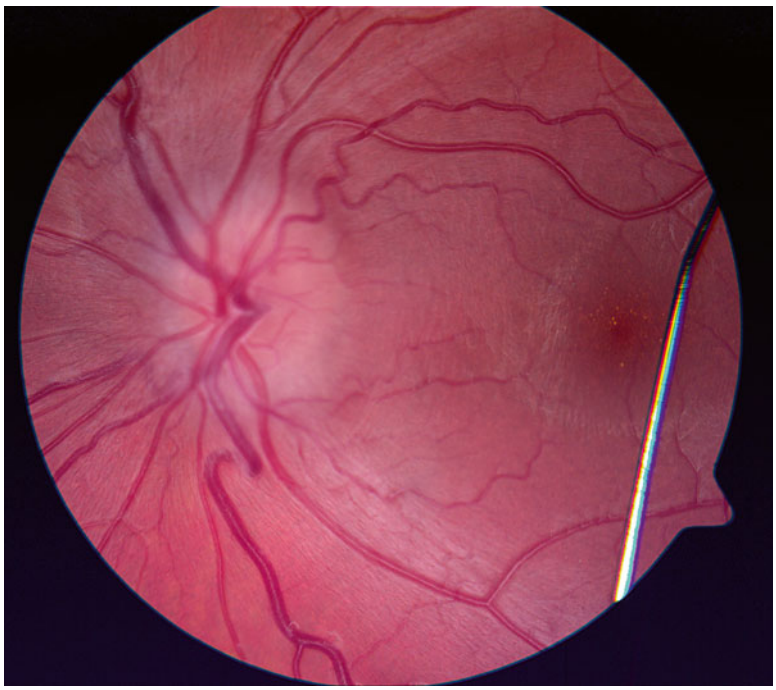

Fig. 38.9 Optic nerve elevation (pseudopapilledema) from buried optic disc drusen

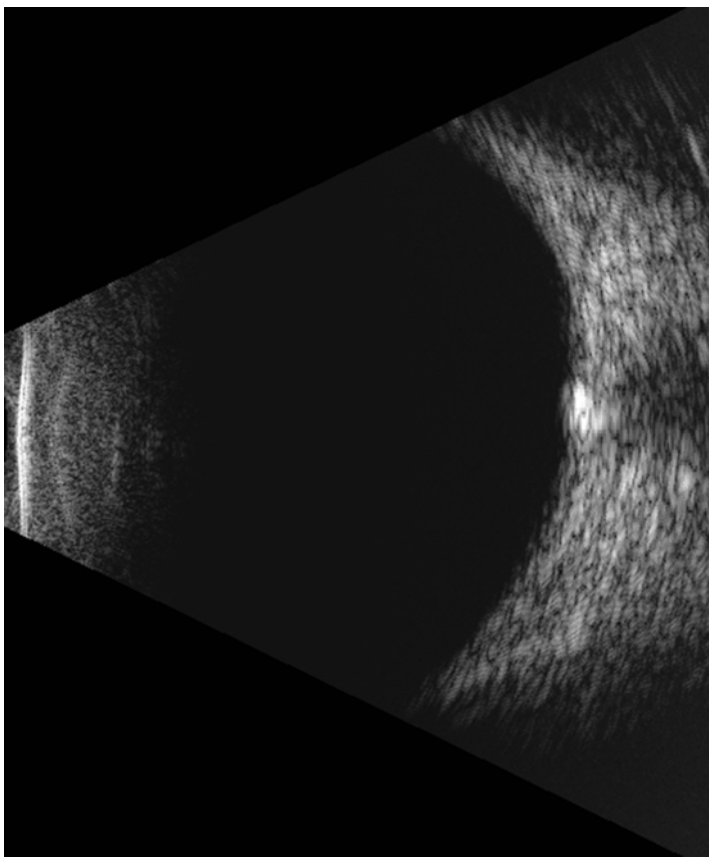

Fig. 38.10 B-scan ultrasound reveals calcified optic nerve head drusen in eye shown in Fig. 38.9

exacerbated by dehydration and high altitude. Choroidal neovascularization can also occur and cause subretinal hemorrhage. This can be treated with laser, photodynamic therapy, surgical excision, or anti-VEGF injection [51].

Myelinated Nerve Fibers

Myelination of optic nerve fibers begins at the lateral geniculate body and extends toward the globe, stopping at the lamina cribrosa. Occasionally myelinated fibers can be found in the retinal nerve fiber layer. This condition is present in 0.57–0.98 % of the population, is bilateral in 7.7 %, and is more common in females than males [52, 53].

Myelinated nerve fibers are typically diagnosed based on the dense white appearance on ophthalmoscopy with feathered edges following the course of the nerve fiber layer. They appear white on red-free imaging and dark on autofluorescence and fluorescein angiography due to blocking of normal fundus autofluorescence and fluorescein, respectively. On OCT, the retinal nerve fiber layer appears thickened [54]. Studies have shown that the myelinated nerve fibers are not directly connected to the optic nerve fibers [52]. This finding has led to the theory that the myelination is a result of anomalous oligodendrocyte-like glial cells that migrate to the retina in utero during a period when the lamina cribrosa loses its barrier function [55].

There is an association with unilateral high myopia and severe amblyopia (Fig. 38.11). Strabismus is also common. The amblyopia can be dense and difficult to treat, especially with more extensive myelination [55]. A syndrome of myelinated nerve fibers, vitreoretinal degeneration, high myopia, and skeletal malformations has been identified [56]. There is also an association with Gorlin (basal cell nevi) syndrome and retinal vascular abnormalities [57, 58].

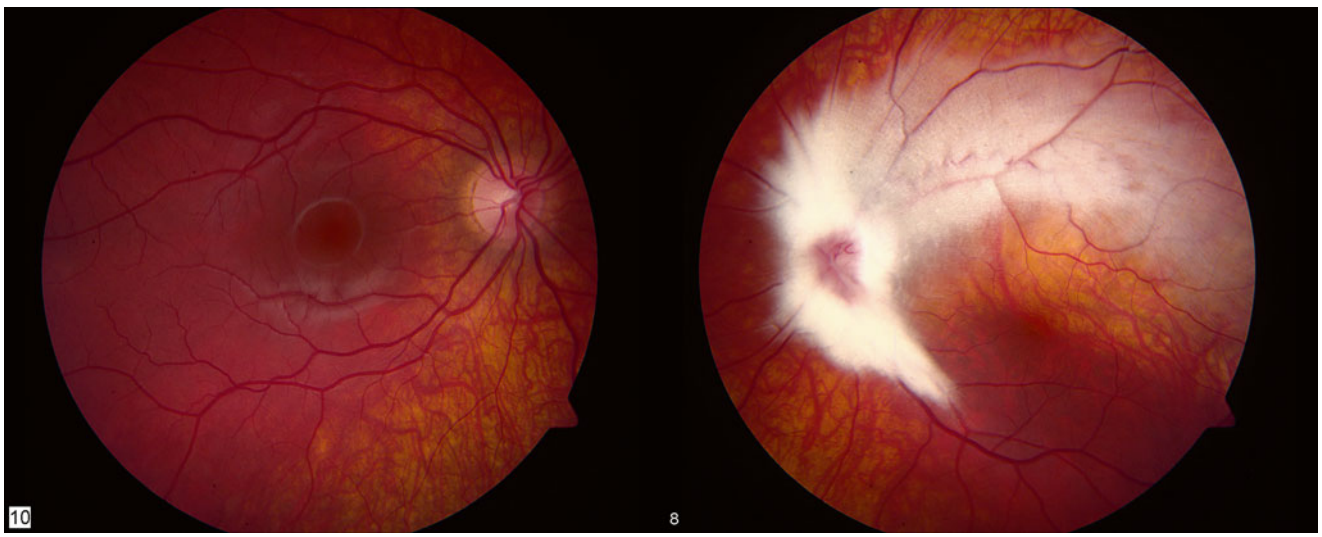

Fig. 38.11 Left eye of patient with unilateral myelinated nerve fibers associated with high myopia and amblyopia

Table 38.3 Summary of important clinical associations of optic nerve malformations

Malformation	Important clinical associations	Consultations/tests	Genetically determined
Optic nerve hypoplasia	Pituitary dysfunction	Pediatric neurology	Rarely
	Fetal alcohol syndrome	Pediatric endocrinology	
		MRI	
Morning glory disc anomaly	Moyamoya disease	MRI and MRA	Very rarely
Peripapillary staphyloma	Basal encephalocele		
Optic nerve coloboma	Numerous syndromes	Clinical genetics	Commonly
Optic nerve dysplasia/coloboma	Papillorenal syndrome	Pediatric nephrology	*PAX2* mutations
		Clinical genetics	
Optic pit	Macular detachment	Vitreoretinal specialist	Very rarely
Myelinated nerve fibers	Few syndromes	Clinical genetics if syndrome is suspected	Very rarely
Optic nerve head drusen	Retinitis pigmentosa, rarely	Ophthalmic genetics	Rarely
			Can be autosomal dominant

Conclusions

The diagnosis of optic nerve malformations relies mostly on clinical recognition of morphological appearance and sometimes on ocular imaging. Associations are common and some are specific for individual malformations. The identification of comorbidities allows the appropriate management of patients who may have very serious associated CNS and other abnormalities (Table 38.3).

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Evaluation and Management of Optic Pathway Gliomas

39

Gena Heidary

Abstract

Optic pathway gliomas (OPGs) are low-grade neoplasms that may be associated with profound vision loss, endocrinologic deficits, and neurologic dysfunction. OPGs occur sporadically or in association with the neurocutaneous disorder neurofibromatosis type 1 (NF1). There is ample debate regarding the most effective way for ophthalmologists to screen patients with NF1 for the presence of these tumors. Furthermore, the decision to treat and the criteria that serve as a basis for this treatment remain topics of significant discussion amongst the multidisciplinary team managing these patients including pediatric ophthalmologists, neuro-ophthalmologists, neuro-oncologists, neurosurgeons, and geneticists. Prospective natural history data are needed to develop consensus recommendations for a screening protocol for OPGs, the criteria for treatment of OPGs, and risk factors for poor visual outcomes.

Keywords

Optic pathway glioma • Neurofibromatosis type 1 • Pediatric brain tumor

Introduction

Optic pathway gliomas (OPGs) are low-grade neoplasms that affect the precortical visual pathways extending from the optic nerve, optic chiasm, and optic tracts to the optic radiations [1]. These tumors constitute an important cause of acquired vision loss from brain tumors in children. OPGs develop both in association with the neurocutaneous disorder, neurofibromatosis type 1 (NF1), as well as sporadically. The focus of this chapter is to review current literature regarding screening recommendations for symptomatic OPGs, management of OPGs from the ophthalmic perspective, and current treatment considerations. Two representative cases have been selected to emphasize these key elements.

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Case Examples

Clinical Synopsis

Case 1 (Table 39.1) exemplifies the management of an optic pathway glioma in the setting of a known diagnosis of NF1. A young boy with progressive vision loss and an acquired hypotropia was treated with a combination of chemotherapy as well as patching therapy to address the compounding element of strabismic amblyopia induced by the tumor. Vision recovered although not to baseline.

Case 2 (Table 39.2) highlights the presentation of a sporadic optic pathway glioma. A boy presented with progressive vision loss in the right eye and bitemporal hemianopia on visual field testing. Upon diagnosis of a sporadic OPG, chemotherapy was initiated. There was both visual and radiographic improvement. Subsequently, due to continued progression of the disease both by visual assessment and neuroimaging findings, the patient has undergone multiple courses of chemotherapy.

(continued)

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Table 39.1 Case 1

Clinical history	2 year 9-month-old boy with NF1 and recently diagnosed OPG involving both optic nerves presents for his 3-month follow-up exam. Prior visual acuity by LEA optotypes was 20/25 OD and 20/25 OS		
	Recent interval enlargement of optic pathway glioma on MRI		
Key components of exam		OD	OS
	BCVA by LEA	20/30	20/100
	CRx	+1.25	+1.25
	Ductions/versions	Full	Limited supraduction (−2)
	Sensorimotor exam	Left hypotropia 20 PD	
	Pupils	Relative afferent pupillary defect OS	
	Visual fields by confrontation	Full	Equivocal responses OS
	Posterior segment	Optic nerve edema	Optic nerve edema
Impression	Mixed mechanism of visual decline OS both from progression of OPG and from strabismic amblyopia from mechanical restriction by tumor on supraduction OS		
Management	• OPG treatment with chemotherapy for tumor progression		
	• Patch OD to address contribution of strabismic amblyopia to vision loss		
	• Follow-up in 4 weeks		
Interval history (1 month)	Chemotherapy was initiated including vincristine and carboplatin. Patient tolerated patching up to 2 h per day OD		
Current age: *2 years 10 months*			
Key components of exam		OD	OS
	BCVA by LEA	20/30	20/50
	Ductions/versions	Full	Limited supraduction (−2)
	Sensorimotor exam	Left hypotropia 20 PD	
	Pupils	Relative afferent pupillary defect OS	
	Visual fields by confrontation	Full	Full
	Posterior segment	Improved optic nerve edema	Improved optic nerve edema
Impression	Improved VA and optic nerve edema		
Management	• Continue with chemotherapy for OPG treatment		
	• Continue with patching OD		
	• Follow-up in serially every 3 months to evaluate visual function		
Interval history (serial eye exams every 3 months over the year following)	Completed 1 year of chemotherapy with stabilization of visual function and radiologic stability of tumor. Patient continued to patch up to 2 h per day OD		
Current age: 4 years			
Key components of exam		OD	OS
	BCVA by LEA	20/30	20/50
	Ductions/versions	Full	Improved supraduction (−1)
	Sensorimotor exam	Left hypotropia 10 PD	
	Pupils	Relative afferent pupillary defect OS	
	Visual fields by confrontation	Full	Full
	Posterior segment	Mild optic atrophy	Mild optic atrophy
Impression	Stable VA with stable optic neuropathy secondary to OPG and continued vulnerability of visual function because of OPG and strabismus		
Management	• Continue with patching OD		
	• Discussion of management of strabismus ongoing with consideration of surgery		
	• Continue with serial eye exams to ensure no progression after cessation of chemotherapy		
Teaching points	• Pediatric patients are vulnerable to vision loss from the OPG but also from secondary effects of the OPG		
	• Attention to fundamental issues including management of strabismus and refractive error should always be considered in addition to treatment of the primary process		

Table 39.2 Case 2

Clinical history	A 10-year-old otherwise healthy boy with no history of NF1 presented with progressive vision loss of the right eye over the course of 6 months. This prompted neuroimaging and an OPG centered at the optic chiasm was identified. He comes for an eye exam in anticipation of treatment		
	Past ocular history: Myopia, congenital dyschromatopsia		
Key components of exam		OD	OS
	BCVA by Snellen	20/60	20/20
	CRx	−3.25 sph	−3.00 + 0.50 × 180
	Ductions/versions	Full	Full
	Sensorimotor exam	Normal	
	Pupils	Normal without relative afferent pupillary defect	
	Color	Red/green dyschromatopsia	Red/green dyschromatopsia
	Visual fields (Humphrey visual fields 24-2)	Temporal hemianopia	Temporal hemianopia
	Posterior segment	Minimal optic atrophy temporally	Minimal optic atrophy temporally
Impression	Optic neuropathy involving right nerve and optic chiasm with impairment of central acuity and visual fields		
Management	• Discussion of treatment options with multidisciplinary team		
	• Chemotherapy regimen of vincristine and carboplatin initiated		
Interval history (6 weeks)	Tolerating chemotherapy well		
Current age: *10 years*			
Key components of exam		OD	OS
	BCVA by Snellen	20/25	20/20
	Ductions/versions	Full	Full
	Sensorimotor exam	Normal	
	Pupils	Normal without relative afferent pupillary defect	
	Visual fields (Humphrey visual fields 24-2)	Marked improvement	Minimal improvement
	Posterior segment	Minimal optic atrophy temporally	Minimal optic atrophy temporally
Impression	Improved VA and visual field exam with chemotherapy		
Management	• Continue with chemotherapy for OPG treatment		
	• Follow-up in serially approximately every 2–3 months to evaluate visual function		
Interval history (serial eye exams every 2 months over the year following, then extended to every 3 months)	Completed 1 year of chemotherapy. Over this year, VA improved to 20/20 in each eye and visual fields improved with residual superotemporal changes OD and superotemporal changes OS		
Current age: 12.5 years	10 months following completion of chemotherapy, at follow-up exam, substantial visual decline OD and visual field worsening OD were noted coincident with progression on neuroimaging		
Key components of exam		OD	OS
	BCVA by Snellen	20/150	20/20
	Ductions/versions	Full	Full
	Sensorimotor exam	Normal	
	Pupils	Relative afferent pupillary defect OD	
	Visual fields (Humphrey visual fields 24-2)	Profound defect	Superotemporal defect, stable
	Posterior segment	Optic atrophy	Optic atrophy
Impression	Evidence of a junctional scotoma consistent with radiologic impression of expansion of tumor component involving right optic nerve		
Management	• Re-initiation of chemotherapy		
	• Serial follow-up		
Interval history (serial eye exams every 6 weeks to monitor treatment response)	Marked improvement in visual function		
Current age: 14 years			

(continued)

Table 39.2 (continued)

Key components of exam		OD	OS
	BCVA by Snellen	20/25	20/20
	Ductions/versions	Full	Full
	Sensorimotor exam	Normal	
	Pupils	Relative afferent pupillary defect OD	
	Visual fields (Humphrey visual fields 24-2)	Marked improvement of visual field defect	Superotemporal defect, stable
	Posterior segment	Optic atrophy	Optic atrophy
Impression	Substantial improvement of visual function of right eye with stable changes in left eye		
Management	• Continuation of chemotherapy		
	• Close serial follow-up		
Teaching points	• Non-NF1-associated OPGs are more likely to progress than NF1-associated OPGs		
	• Vigilant follow-up is needed as relapses or visual progression are likely after cessation of treatment		

Background

OPGs arise from the supportive glial tissue of the visual pathway and account for up to 5 % of tumors that affect the central nervous system in children [2]. Histologically, OPGs are classified as low-grade astrocytomas (World Health Organization grade I or II) [3]. In spite of their low-grade designation, some OPGs may be locally aggressive causing significant vision loss, endocrinologic dysfunction, and neurologic abnormalities such as obstructive hydrocephalus [4, 5]. Therefore a careful understanding of the natural history, diagnosis, and treatment considerations for OPGs is crucial for the pediatric ophthalmologist or pediatric neuro-ophthalmologist.

Clinically, it is useful to differentiate NF1-associated and non-NF1-associated OPGs as the presentation and course are distinct between these two groups, with more favorable visual outcomes associated with NF1 [6, 7]. In the setting of NF1, OPGs occur in approximately 15–20 % of patients and become symptomatic in up to approximately 50 % of those affected [8, 9]. Mean age at presentation in NF1-associated OPGs has been reported to range from 4 to 6 years [7, 9, 10]; in the non-NF1-associated tumors, there is a broad range of age at diagnosis from 0.34 to 17 years [10]. Although it was previously believed that NF1-associated OPGs were uncommon after age 6, more recent studies have demonstrated late-onset tumors in patients with NF1 throughout adolescence [11–13].

Involvement of the optic pathway may extend from the optic nerve to the optic radiations. The involvement of both optic nerves is an exclusive feature of NF1 [10, 14]. Nystagmus, papilledema, and diencephalic syndrome or failure to thrive are more commonly seen in non-NF1-associated OPGs [10], whereas proptosis and vision loss may be features of both NF1 and non-NF1-associated OPGs [10, 14].

Diagnosis of OPGs

The diagnosis of an optic pathway glioma is established with neuroimaging, and the preferred method is MRI involving the brain and the orbits. In children, CT imaging is deferred in an effort to minimize exposure to radiation. Features suggestive of an optic nerve/pathway glioma include thickening and tortuosity of the optic nerve and thickening of the optic pathway (Fig. 39.1) [15–17]. On T2-weighted MRI, NF1-associated optic nerve gliomas may appear to have a heterogeneous signal intensity with a higher signal surrounding an inner core of lower signal intensity with the opposite finding on T1-weighted imaging. This has been attributed to perineural gliomatosis [18, 19]. There may be an associated exophytic component to the glioma, which may have cysts that wax and wane. Spontaneous regression of optic nerve gliomas has been reported but is considered a rare occurrence [4, 20]. On gadolinium-enhanced MRI, the optic pathway glioma may enhance heterogeneously [21]. Because the neuroimaging findings are characteristic, diagnostic biopsy typically is not performed.

Screening for OPGs

In the setting of non-NF1-associated OPGs, neuroimaging would have been performed to establish the diagnosis when a child presents with symptoms, and therefore the issue regarding a baseline screening MRI is not relevant. Conversely, whether or not to obtain a baseline neuroimaging study to screen patients with confirmed NF1 remains controversial and protocols vary by institution. At Boston Children's Hospital (BCH), patients with NF1 generally do not undergo a baseline neuroimaging study, but rather participate in routine ophthalmic screening (discussed below). The decision not to perform screening neuroimaging is

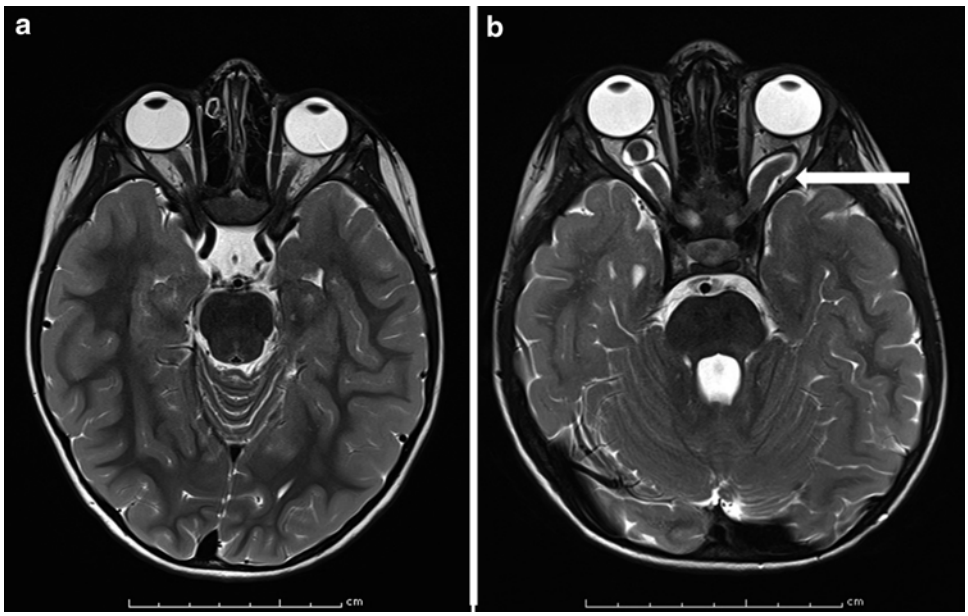

Fig. 39.1 T2-weighted axial magnetic resonance imaging studies demonstrating normal optic nerves (**a**) and bilateral optic nerve gliomas in a child with neurofibromatosis type 1 (**b**, *white arrow*). Note the thickening and tortuosity of the nerves in the patient with optic nerve gliomas

consistent with the NIH Task Force Recommendations published in 1997, which suggest that such screening does not improve visual outcomes in patients [22]. Further, because in NF1 the majority of optic nerve gliomas remain asymptomatic, their identification may create undo anxiety and concern for the patient and family. Importantly, prior normal neuroimaging does not preclude the development of OPGs at a later date [8, 11, 23–25]. With this in mind, it then becomes unclear with what frequency a screening MRI should be done and for what duration. Prospective data of a large number of patients are needed to develop a clearer understanding of the role of screening with neuroimaging for OPGs in NF1.

Ophthalmic Screening for OPGs

At BCH, each patient with a new diagnosis of NF1 undergoes routine, required comprehensive ophthalmic examinations to screen for the presence of an OPG. In children under 8 years of age, consensus recommendations are for at least yearly ophthalmology examinations [26]. However at BCH, youngest children are examined every 6 months to better ensure that no child's vision loss is missed and to account for the inherent variability in the pediatric ophthalmic examination with respect to patient cooperation. By 8 years of age and thereafter, the consensus recommendation is for an eye exam every 2 years [26]; however, at BCH, such older patients are examined on a yearly basis.

Careful assessment for afferent dysfunction including an age-appropriate, quantitative visual acuity assessment, visual field testing by confrontation or formally with Goldmann visual fields or automated perimetry, color vision when able, documentation of pupillary function, and a dilated fundus exam documenting optic nerve appearance is performed. Signs of the presence of an OPG include optic nerve edema or pallor. In addition, patients are evaluated for efferent dysfunction associated with optic pathway gliomas including nystagmus and strabismus. The presence of proptosis may be a harbinger of an optic nerve glioma.

Use of optical coherence tomography of the optic nerve head as an adjunct to the eye exam is rapidly emerging as a new frontier for screening patients with NF1 for evidence of optic pathway disease. Several important studies have documented a relationship between retinal nerve fiber layer thinning and optic nerve gliomas prior to the onset of vision loss [27, 28]. Most recently, it has been suggested that ganglion cell layer thinning most closely approximates vision loss when comparing visual acuity testing to the measurements obtained on OCT imaging [29]. Avery et al. described the use of handheld OCT as a method for identifying the youngest patients who may be at risk for vision loss [30].

The role of visual evoked potentials (VEPs) as a screening tool to identify children who harbor OPGs remains controversial. In their recent review of pattern reversal VEPs (pVEPs) in NF1, Van Mierlo et al. discussed the high false-positive rate of pVEPs [31]. Iannaccone et al. examined 16 children with NF1 and normal neuroimaging and found that ten of these children had abnormal VEPs [32]. Although other authors have found promising results with respect to the high sensitivity of VEPs in identifying patients who harbor OPGs, the practical limitations of access to VEP testing, lack of universal normative data, and difficulty in interpretation of fluctuations on VEP testing make this a limited tool at present [33].

At BCH, if a child is suspected of visual dysfunction or if the eye exam is so limited such that an assessment of visual function cannot reliably be made, neuroimaging is then performed to evaluate for an OPG including MRI of the brain and orbits with and without gadolinium.

In patients with or without NF1 in whom a newly diagnosed OPG has been identified, a recommended timeline for

ophthalmic evaluation is every 3 months during the first year; the examinations may be more frequent depending on the presentation and the results of the ophthalmological exam [26]. After the first year and depending on the stability of the visual exam, the interval between ophthalmic exams may be extended to every 6 months in children with NF1 but may be again more frequent in those without NF1 depending on the clinical course. Often during adolescence, the interval of eye exams for children with known NF1-associated OPGs may take place yearly because of the lower risk of progression [34]. In a cohort of 43 children with NF1-associated OPGs, time to vision loss occurred between 1 and up to 6 years from the time of diagnosis, emphasizing the importance of maintaining routine ophthalmologic follow-up [34]. The interval between MRI studies is less standardized and often will be determined per institution protocol.

Management and Treatment of OPGs

Currently, there are no consensus guidelines defining when treatment of an OPG is indicated, as many tumors will remain indolent and asymptomatic, particularly in children with NF1 [35]. Natural history studies of NF1 and non-NF1 associated OPGs suggest that progression requiring treatment is more likely in the absence of NF1 [10, 14, 35]. In a multicenter retrospective review of patients treated for NF1-associated OPGs, Fisher et al. found that the indications for treatment were most frequently dependent on vision loss and tumor progression [36]. However, indications for treatment also depended on presence of visual field loss, optic nerve pallor, proptosis, and size and location of tumor [36].

With respect to visual acuity, loss of two lines or more of vision from the age appropriate norm is often used as a guideline for progression. With regard to visual fields, there is less consensus as to what constitutes progressive disease, and defining this threshold is more difficult because of the inherent limitations in obtaining formal visual fields in young children with OPGs. Nevertheless, general guidelines of visual field progression include a change from a full visual field to any visual field loss and/or progression from a visual field involving one quadrant to involvement of a hemifield.

In NF1-associated OPGs, the location and extent of tumor appear to be important risk factors for poor prognosis, with worse vision associated with more posterior OPGs [34]. Importantly, tumor progression on MRI does not necessarily correlate with vision loss but may warrant more frequent eye exams to ensure visual stability. Kelly and Weiss retrospectively evaluated 54 patients with and without NF1-associated OPGs and found that tumor enlargement on neuroimaging had a poor sensitivity and specificity in predicting vision loss and that vision loss had a poor sensitivity and specificity for predicting tumor progression. Their study stresses the important role that the ophthalmic exam has in helping to guide management decisions as a complement to neuroimaging [37].

Treatment options include observation, chemotherapy, surgical debulking of large tumors, radiotherapy, and treatment of associated findings such as hydrocephalus with the appropriate neurosurgical shunting procedures. The protocol for treatment will vary by institution.

With respect to NF1-associated OPGs that require treatment, chemotherapy is currently used first and commonly includes vincristine and carboplatin [38, 39]. Radiotherapy is no longer recommended as a primary treatment in children with NF1 because of the increased risk of secondary tumors, subsequent neurocognitive dysfunction, and susceptibility to the development of the vasculopathy moyamoya disease [40, 41]. When there is profound proptosis and associated exposure keratopathy in a blind eye with an optic nerve glioma, enucleation may be performed. Finally, large OPGs involving the chiasm/hypothalamic region may require surgical debulking [26]. The approach again will be guided per institution protocol and individualized to the patient.

Importantly, patients' tumor may enlarge and continue to grow in spite of treatment and in spite of initial stability after cessation of first-line therapy. Nicolin et al. evaluated a heterogeneous group of patients with OPG, with and without NF1, and who had received single or multimodal treatment and found an overall progression-free survival rate of 48 % in those patients who required treatment, with a mean duration of 29.4 months to second progression [10]. In their NF1 and non-NF1 cohort of 68 patients being treated for an OPG, deHaas et al. found that 65 % of patients experienced a "relapse" requiring modification of current treatment or resumption of treatment on the basis of clinical or radiographic progression [42]; similarly, Laithier et al., also with a heterogeneous cohort of OPG patients, found that 67 % of their patients experienced a "relapse" [43]. Therefore, vigilant ophthalmic follow-up must ensue to monitor for visual progression during and after completion of treatment.

Visual Outcomes

Reports on visual outcomes in the setting of optic pathway gliomas are heterogeneous and often include children who harbor both NF1- and non-NF1-associated OPGs as well as children who may have been treated in a multimodal fashion making definitive conclusions regarding treatment efficacy difficult. In a series of 54 patients with NF-1-associated OPGs, the majority of whom (68.5 %) were managed with observation, Thiagalingam et al. found that 31.5 % of patients had profound visual impairment and 16.7 % showed moderate vision loss at most recent follow-up [13]. In another study of non NF1-associated OPGs in which the majority of patients received chemotherapy, radiotherapy, or both, Campagna et al. found that 56 % of children continued to show visual decline at the most recent follow-up 6 years after initial tumor diagnosis [44].

Several studies have focused on visual outcomes after treatment with chemotherapy alone. In a ten-center retrospective study of children with NF1-associated OPGs treated with chemotherapy, Fisher et al. found that amongst 88 children, visual acuity improved or remained stable in 72 % of cases, and deteriorated while on treatment in 28 % of subjects [36]. Moreno et al. performed a meta-analysis of eight studies that included 174 subjects to evaluate the effectiveness of chemotherapy; the analysis did not specify whether children had NF1 or not [45]. The authors found that vision improved following chemotherapy in 14.4 % of patients and stabilized in 47.1 % of patients. Progressive vision loss occurred in 38.5 % of children in spite of treatment [45]. The disparity may reflect the heterogeneity of the subjects with and without NF1 in the meta-analysis.

Summary

OPGs represent an important cause of visual morbidity in children. The role of the ophthalmologist in the management of these patients cannot be overemphasized. Often the findings on a comprehensive eye examination will identify the first signs of an OPG and the multidisciplinary work-up that ensues will be initiated on the basis of the ophthalmic findings. Once an OPG is diagnosed, the ophthalmologist will play an important role in monitoring patients for visual progression and highlight those children in whom treatment may be warranted. Finally since the risk for visual progression continues throughout childhood and adolescence and may occur in spite of prior treatment, the importance of continued and vigilant ophthalmic follow-up must be stressed with the child and family (see Fig. 39.2).

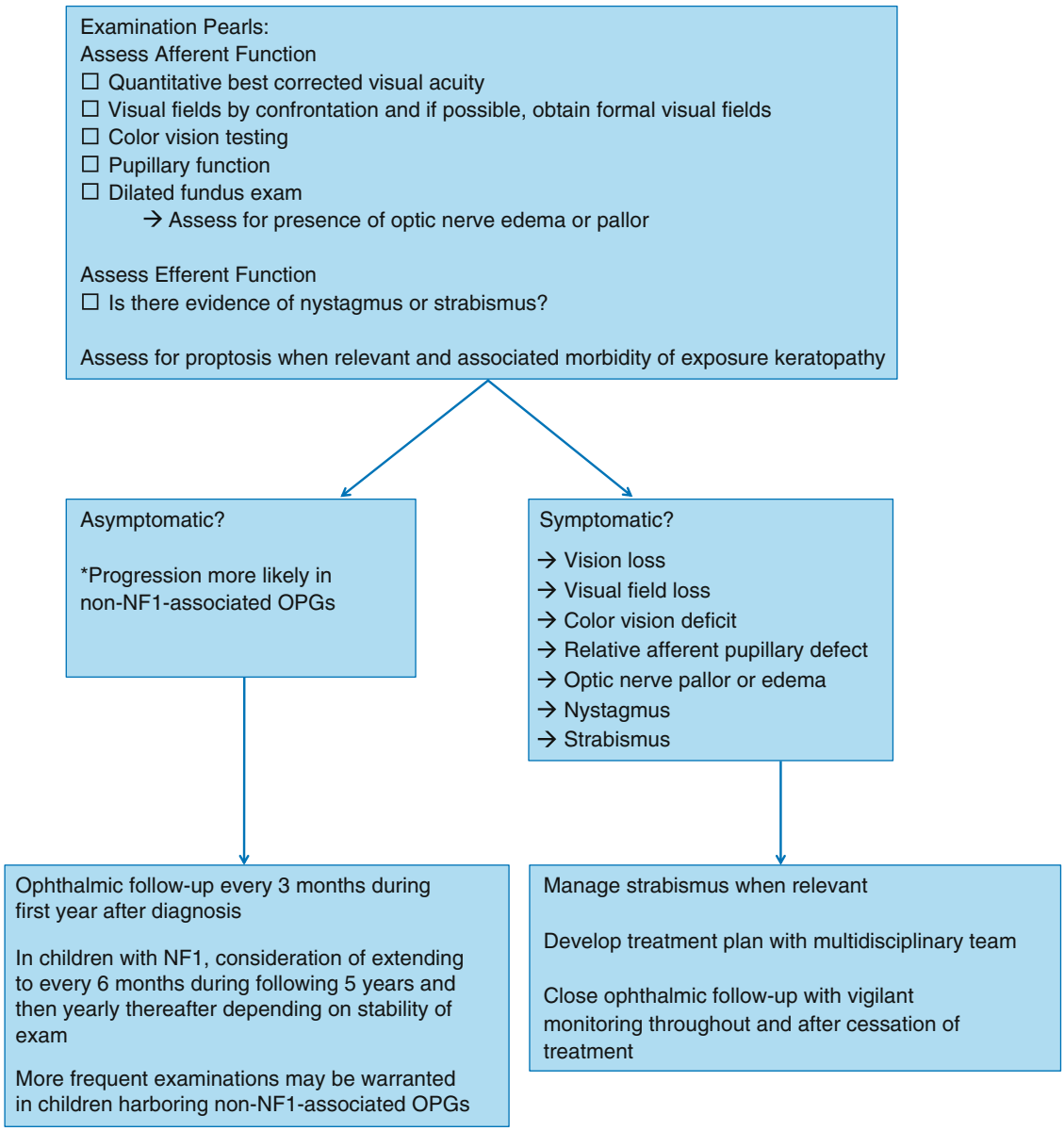

Fig. 39.2 Algorithm for newly diagnosed optic pathway glioma (flowchart)

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Pediatric Pseudotumor Cerebri Syndrome

40

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Abstract

Patients with pseudotumor cerebri syndrome (PTCS) have elevated intracranial pressure of unclear etiology. This diagnosis requires the presence of normal brain parenchyma on neuroimaging and normal cerebrospinal fluid composition without evidence of infection or neoplasm. PTCS can be a highly morbid complication of obesity; however, the diverse clinical spectrum of pediatric PTCS is becoming increasingly recognized. With appropriate management, the prognosis for vision and other symptoms, such as headache and double vision, is excellent for mild cases; however, patients with more severe disease and progressive vision loss may suffer permanent visual impairment.

Keywords

Pseudotumor cerebri syndrome • Intracranial hypertension • Vision loss • Papilledema

List of Abbreviations

APD	Afferent pupillary defect
BMI	Body-mass index
CDC	Centers for Disease Control and Prevention
CSF	Cerebrospinal fluid
GH	Growth hormone
ICP	Intracranial pressure
LP	Lumbar puncture
OD	Right eye
OR	Odds ratio
OS	Left eye
OU	Both eyes
PTCS	Pseudotumor cerebri syndrome

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The Problem

Patients with pseudotumor cerebri syndrome (PTCS) have elevated intracranial pressure (ICP) of unclear etiology. This diagnosis of exclusion requires the presence of normal brain parenchyma on neuroimaging and normal cerebrospinal fluid (CSF) composition without evidence of infection or neoplasm. Headache and visual disturbances are common presenting complaints, and many patients display visual field defects on examination. With appropriate management, the prognosis for vision and other symptoms is excellent for mild cases; however, patients with more severe disease and progressive vision loss may suffer permanent visual impairment.

In general terms, PTCS is classified as either primary or secondary. Primary PTCS is also referred to as idiopathic intracranial hypertension. In the adult population, the typical patient with primary PTCS is a female of reproductive age who is overweight and/or has a history of recent weight gain. Primary PTCS is certainly seen in the pediatric population, although its epidemiology is complex and is characterized by a multi-faceted relationship between obesity, pubertal status, and gender. Adolescents with PTCS are more frequently obese and female, suggesting that the risk factors for developing PTCS in this age group may be similar to those in adults [1]. Young, prepubertal children, on the other hand, are less likely to be obese, are equally male and female, and may present without symptoms of headache or visual blurring [2, 3]. Ongoing studies are examining the relative influence of gender, age, and key pubertal stages on the changing epidemiology of pediatric PTCS [4]. These observations highlight the need for vigilance by the medical provider, not only for overweight and obese children, but also for young, thin children who may present with atypical or no symptoms.

Secondary PTCS refers to a clinical diagnosis of PTCS attributable to one of a variety of identifiable cases, including venous sinus thrombosis, medications, and medical conditions other than obesity alone. Some of the most common causes of secondary PTCS include withdrawal from chronic corticosteroids, marked anemia, exposure to tetracycline-related antibiotics, and synthetic growth hormone or vitamin A-derivative medications [5, 6]. Together, these cases appear to lack a unifying pathophysiologic mechanism; however, further research into the pathophysiology of PTCS may identify common themes.

Diagnosis of PTCS

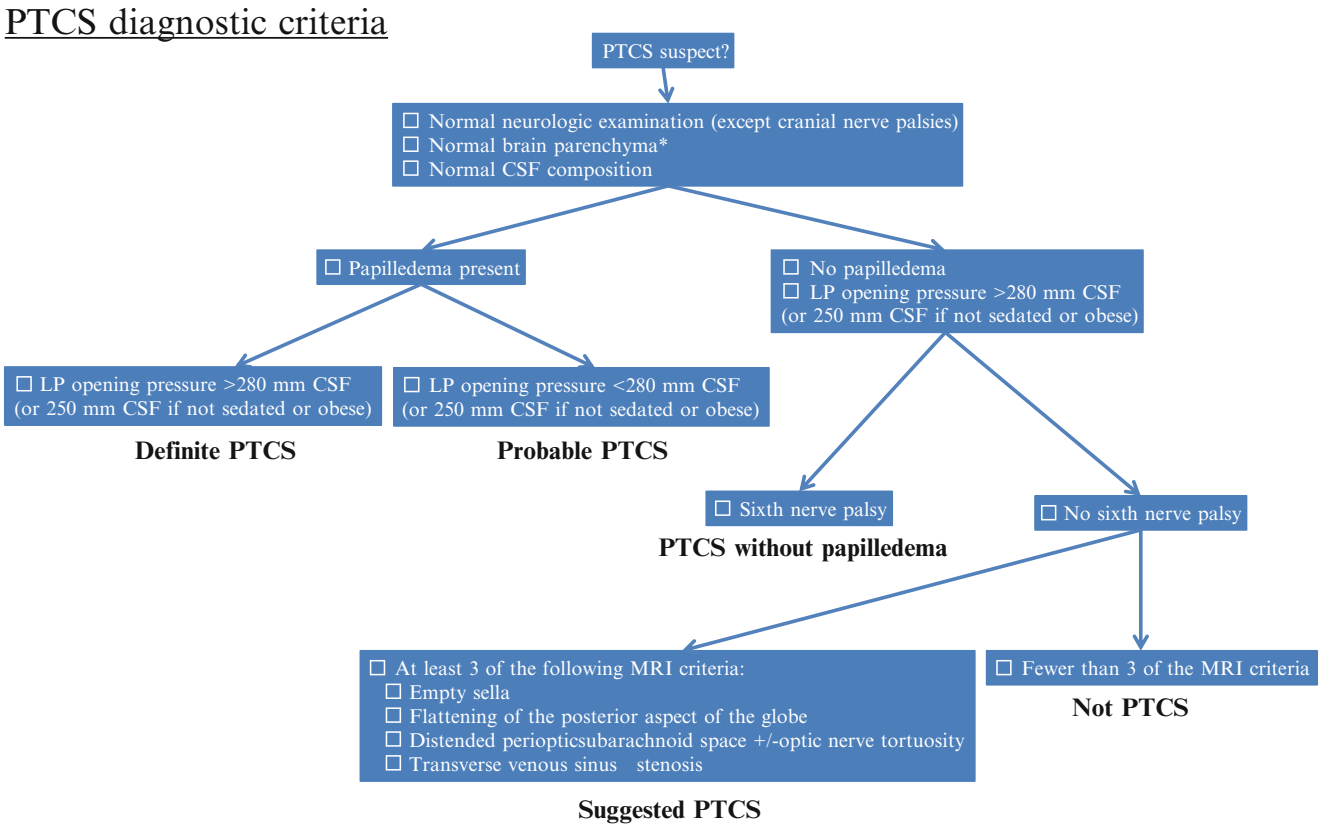
The recently updated diagnostic criteria for PTCS are illustrated in Fig. 40.1 [6]. The accurate diagnosis of PTCS is, first, based on the presence or absence of papilledema. In contrast to optic disc edema, papilledema is a term specifically reserved for optic nerve head swelling due to raised ICP. A careful dilated fundus examination is typically sufficient to identify papilledema; however, orbital ultrasound, including a 30° test by an experienced ultrasonographer, may be a useful adjunctive test. In the presence of papilledema or if clinical suspicion remains high in the absence of papilledema, the diagnosis of PTCS requires the presence of normal brain parenchyma on contrast-enhanced neuroimaging (MRI or CT). In patients typical of PTCS (e.g., female and obese), an MRI-venogram is not routinely necessary, but should be considered for those patients at high risk for cerebral venous sinus thrombosis. Venous imaging is a requisite for all atypical patients. Next, a lumbar puncture is necessary to document elevated intracranial pressure. CSF composition should be normal, with necessary CSF analyses including cell count, cytology, and concentrations of glucose and protein.

Thus, in the presence of papilledema, key diagnostic requirements include (1) normal brain parenchyma on neuroimaging with contrast-enhanced MRI or CT, (2) normal venous imaging with MRI- or CT-venogram in select cases, and (3) normal CSF composition on lumbar puncture (including cell count, protein and glucose concentrations, and cytology). As outlined in recently revised diagnostic criteria for PTCS [6], with elevated ICP, a diagnosis of *definite PTCS* can be made. If a normal ICP is measured, a diagnosis of *probable PTCS* can be made.

In the absence of papilledema, key diagnostic requirements include (1) normal brain parenchyma on neuroimaging with contrast-enhanced MRI or CT and (2) elevated ICP and normal CSF composition on lumbar puncture. With these features, in the presence of unilateral or bilateral sixth nerve palsy(ies), the diagnosis of *definite PTCS* can be made [6]. However, without a sixth nerve palsy, the diagnosis of *suggested PTCS* can be made if critical neuroimaging features are observed [6] (Fig. 40.2). These critical neuroimaging features include distension of perioptic subarachnoid space with or without optic nerve tortuosity, flattening of the posterior aspect of the globe, an empty sella and transverse venous sinus stenosis (Chart 1; 6). As a group, the required neuroimaging features are highly suggestive of PTCS.

Treatment of PTCS

There are no randomized clinical trials to allow for evidence-based recommendations in the treatment of PTCS in children. A recent multicenter, randomized, placebo-controlled study of acetazolamide vs. placebo in adult subjects with idiopathic intracranial hypertension with mild visual loss, all of whom were also managed with low-sodium weight-reduction diets, illustrated that patients treated with acetazolamide plus diet



*As seen on contrast-enhanced MRI neuro-imaging for typical patients (female and obese), plus MR-venography for atypical patients (male or non-obese female);or contrast-enhanced CT if MRI is not obtainable.

Fig. 40.1 PTCS diagnostic criteria flowchart.

experienced more visual improvement (based on visual field scores) compared to those treated with diet alone [7]. The primary goal of treatment of PTCS is to prevent vision loss and relieve symptoms of elevated ICP (e.g., headache). The two mainstays of treatment are (1) medications to lower ICP and (2) weight loss. Surgical interventions are typically reserved for progressive vision loss despite maximal medical therapy or when there is severe visual loss at presentation. The two most commonly used surgical procedures are optic nerve sheath fenestration and CSF shunting (i.e., lumboperitoneal or ventriculoperitoneal). Severe vision loss may also be treated with high-dose intravenous methylprednisolone (250 mg four times a day) for 5 days, followed by an oral prednisone taper, all in combination with acetazolamide (a carbonic anhydrase inhibitor) and ranitidine (H_2 blocker) [8]. A lack of immediate clinical recovery with this regimen would be a further indication for surgical intervention. Carbonic anhydrase inhibitors, like acetazolamide, reduce CSF production and provide effective management of PTCS [9]. The recommended starting dose for acetazolamide is 15–25 mg/kg/day divided into 2–3 doses; and may be gradually increased up to 100 mg/kg (up to 2 g/day in children and 4 g/day in adolescents) as needed. Common side effects include paresthesia, metallic taste, gastrointestinal upset, and loss of appetite. Metabolic acidosis is a well-recognized adverse effect but is typically asymptomatic and well tolerated, and generally does not require screening blood work or treatment [10]. Alternatives to acetazolamide include furosemide (a loop diuretic [11]), topiramate (an antiepileptic drug [12]), and spironolactone (an aldosterone antagonist [13]). When associated with being overweight or obese, weight loss is an additional key treatment in the management of PTCS. Based on studies in adult patients [4, 14, 15], patients are advised to lose 6–10 % of their body weight to manage the disease acutely and prevent its recurrence.

Treatment is guided by the patient's specific clinical presentation. As mentioned, surgical interventions are typically reserved for progressive vision loss despite maximal medical therapy or when there is severe visual loss at presentation. The extent of vision loss is guided by a complete clinical eye examination. Unless there is evidence of macular exudates or macular edema, acute papilledema does not cause reduction in central or color acuities or pupillary abnormalities. In contrast, if left untreated, chronic papilledema can cause clinical

evidence of an optic neuropathy (with loss of central and color acuities and slowed pupillary responses). Thus, the severity of vision loss at presentation is best assessed by the extent of visual field loss (as determined by visual fields on confrontation or automated visual fields). Optic disc and fundus photos have proven useful to follow patients during their recovery. Follow-up intervals will logically vary depending on the severity of vision loss. If severe and/or progressive, requiring either optic nerve sheath fenestration or CSF shunting procedures, patients should be followed at least weekly until clinical stability has been documented. If there is mild-to-moderate vision loss, follow-up intervals typically occur every 4 weeks initially, increasing to every 12 weeks once visual recovery has been made, weight loss initiated, and medications being tapered. The duration of treatment is based on the clinical resolution of papilledema. We do not routinely obtain OCT measurements of the retinal nerve fiber layer to follow patients over time but rather base resolution of papilledema on serial clinical examinations and disc photos.

Clinical Cases

Case 1 (Fig. 40.2)

Table 40.1

Clinical history	17-year-old young woman
	2-week history of headaches and 3-day history of blurred vision OD
Key components of exam	BMI 36.3 kg/m^2 (98th percentile)
	Snellen acuity: 20/20 OD and OS
	Trace right afferent pupillary defect (APD)
	Ductions full
	Constricted visual fields to confrontation and by automated perimetry (Fig. 40.2a)
	Dilated fundus examination: moderate disc edema OU (Fig. 40.2b)
Key diagnostic tests required	MRI: Normal brain parenchyma, flattening of the posterior aspect of globes and perioptic dilation of the optic nerve sheaths (Fig. 40.2c)
	MRV: Normal, without venous sinus thrombosis
	LP: Opening pressure 650 mm CSF, normal constituents
Acute management	Urgent optic nerve sheath fenestration OD
	Acetazolamide 500 mg by mouth three times a day
	Close follow-up
Interval history	4 days following optic nerve sheath fenestration OD
	Improved headaches and vision
Ongoing management	Continue acetazolamide 500 mg by mouth, three times a day
	Evaluation by clinic endocrinologist for secondary causes of PTCS and screen for obesity-related complications
	Work with clinic nutritionist to encourage weight loss
Interval history	4 months following presentation and initial intervention there is improved headaches and vision
	Ongoing weight loss
Key components of exam	Snellen acuity: 20/20 OD and 20/20 OS
	Mild right APD
	Improved visual fields to confrontation and automated visual fields (Fig. 40.2d)
	Moderate diffuse disc pallor OD and mild disc pallor OS
Ongoing management	Continue acetazolamide 500 mg by mouth three times a day until resolution of disc edema OU
	Continue weight loss strategies

(continued)

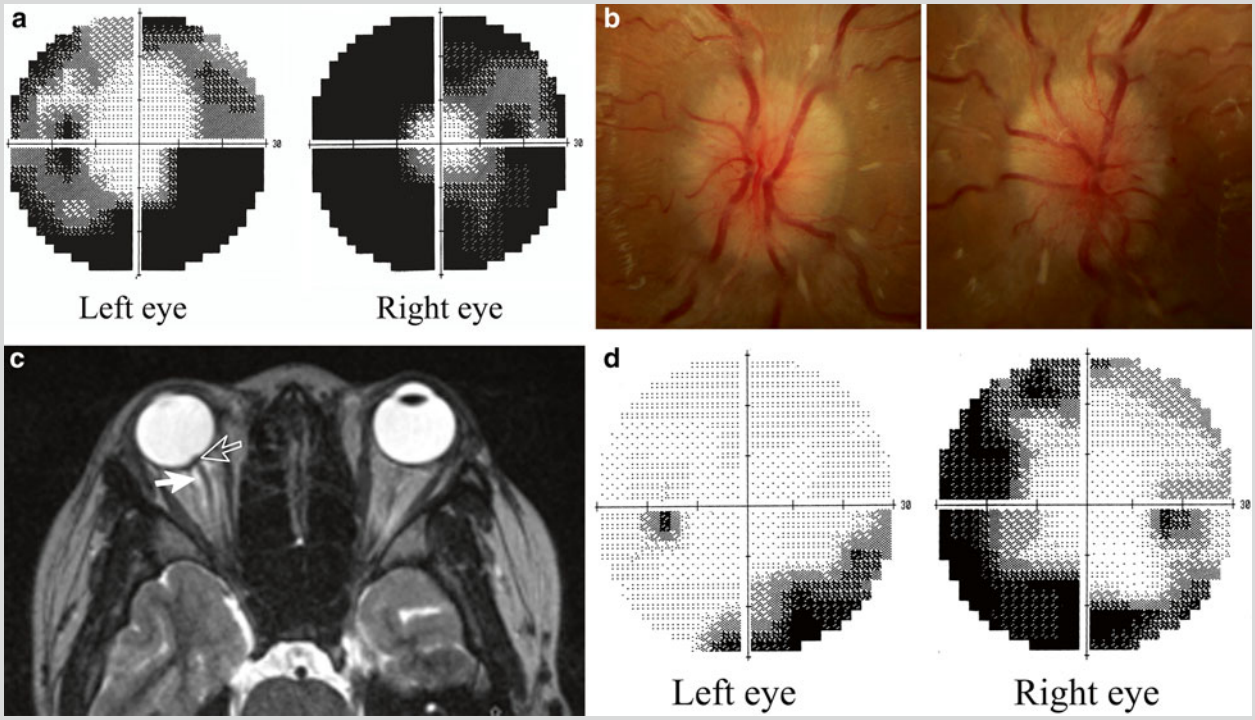


Fig. 40.2 Clinical and radiographic features of primary pseudotumor cerebri syndrome. (**a**) Humphrey visual fields (30-2) illustrate bilateral enlarged blind spots and constricted visual fields OU (right eye>left eye). (**b**) Severe bilateral disc edema, disc hyperemia, engorged veins, and peripapillary cotton wool spots. (**c**) MRI brain showed normal brain parenchyma. As illustrated on T2-weighted axial image, there were radiographic features of raised intracranial pressure, namely flattening of the posterior aspect of globes (*open arrow*) and perioptic dilation of the optic nerve sheaths (*white arrow*). In the presence of clinical observed disc swelling, these radiographic features are not required to confirm a diagnosis of definite or probable PTCS. These are two of the four radiographic features required to establish a diagnosis of suggested PTCS. (**d**) Repeat Humphrey visual fields (30-2) illustrate improved visual field loss

Clinical Synopsis

A 17-year-old student had a 2-week history of headaches and a 3-day history of blurred vision in her right eye. Examination revealed a BMI of 36.3 kg/m^2 (98th percentile), normal visual acuity, and diffuse constriction of the visual fields on automated perimetry. Fundus examination revealed moderate, acute-on-chronic disc edema in both eyes (right>left). Her MRI brain was normal. Lumbar puncture revealed an opening pressure of 650 mm CSF with normal CSF constituents.

Comment: This is a case of primary PTCS occurring in the setting of obesity in an adolescent young woman. For patients between 2 and 20 years of age, the CDC definitions of overweight and obesity are based on BMI percentile. Cutoff values for overweight and obesity are between the 85–95th percentile and ≥95th percentile, respectively. In a recent large retrospective review, obesity was a risk factor for pediatric PTCS in children >11 years of age, with an OR of 8.33 [1]. PTCS can present with severe vision loss, which may require optic nerve sheath fenestration to relieve compression of the optic nerve. Additional treatment with oral acetazolamide is suggested to maintain a lowered ICP, particularly on the non-operated optic nerve. Weight loss management strategies are initiated in the early phases of PTCS management, by enlisting the expertise of a nutritionist to provide practical guidance regarding meal planning and identification of any barriers to achieving weight loss targets. Having patients with PTCS be seen by an endocrinologist early on in the management of PTCS will expedite screening for weight-related health complications.

Case 2

Table 40.2

Clinical history	9-year-old girl
	Rare headaches
Key components of exam	BMI 14.41 kg/m^2 (12.9th percentile)
	Snellen acuity: 20/20 OD and OS
	No RAPD
	Ductions full
	Visual fields to confrontation and by automated perimetry
	Dilated fundus examination: moderate disc edema, with disc hemorrhages OU
Key diagnostic tests required	MRI: Normal brain parenchyma
	MRV: Normal, without venous sinus thrombosis
	LP: Opening pressure >360 mm CSF, normal constituents
Management	Initiate acetazolamide (15 mg/kg divided three times a day)
	Evaluation by clinic endocrinologist to evaluate for secondary causes of PTCS
Interval history (3 months)	Headaches resolved
Key components of exam	Snellen acuity: 20/20 OD and OS
	No RAPD
	Ductions full
	Visual fields to confrontation and by automated perimetry
	Dilated fundus examination: resolving disc edema
	Tanner I breasts, early Tanner II pubic hair
	Endocrine evaluation unrevealing
Management	Slowly wean acetazolamide

Clinical Synopsis

A 9-year-old girl was found to have disc edema on a routine eye examination. She had experienced only rare headaches. Examination revealed a normal height and weight, normal visual acuity, and visual fields on automated perimetry. Fundus examination revealed moderate, acute disc edema, with peripapillary hemorrhages (right>left). MRI was normal. Lumbar puncture revealed an elevated opening pressure with normal CSF constituents. Evaluation by a pediatric endocrinologist confirmed prepubertal status. Screening for secondary causes of PTCS was unrevealing.

Comment: Pediatric PTCS does occur in the young, prepubertal population. Younger children with PTCS, particularly less than age 9, are less likely to be obese than older children [2]. Retrospective studies that have defined pubertal status with broad age-dependent definitions (and not by actual Tanner staging) have illustrated that a presumed prepubertal onset of PTCS is seen equally in male and females and is not influenced by obesity, in contrast to a postpubertal onset [3, 16]. Young, thin, and/or male patients with a new diagnosis of PTCS all deserve an endocrinologic evaluation. At our institution, pediatric patients with a new diagnosis of PTCS are seen by a pediatric endocrinologist and screened for endocrine abnormalities, anemia, malabsorption syndromes, and vitamin deficiencies.

Case 3

Table 40.3

Clinical history	13-year-old boy, DiGeorge's syndrome (22q11.2 deletion)
	Presents with no specific visual concerns and a history of chronic headaches
	Relevant past medical history: severe obesity, growth hormone deficiency (started recombinant GH 5 months prior), hypoparathyroidism, hypothyroidism, chronic inhaled steroids (for asthma)
Key components of exam	BMI 41 kg/m^2 (>99th percentile)
	Snellen acuity: 20/20 OD and 20/25 OS
	No RAPD
	Disc elevation. Cupless, crowded discs with anomalous vessels
Key diagnostic tests required	Orbital ultrasound: fluid sign on B-scan
	LP: opening pressure of 210 mm CSF, normal constituents
Management	Stop recombinant GH
	Acetazolamide 500 mg by mouth three times day
	Weight loss management, working with clinic endocrinologist and nutritionist
Interval history (9 months)	Mild headaches
Key components of exam	BMI 38 kg/m^2 (>99th percentile)
	Cupless optic nerves, no disc elevation
	No visual field changes
Management	Continue acetazolamide
	Continue weight loss strategies
Interval history (12 months)	BM 34 kg/m^2 (99th percentile)
Key components of exam	Small cupless but flat optic nerves
Management	Slowly wean acetazolamide
	Continue weight loss strategies
	May consider eventual resumption of low-dose GH

Clinical Synopsis

At presentation, the patient was 13 years old with DiGeorge (22q11.2 deletion) syndrome and severe obesity, along with hypoparathyroidism and hypothyroidism. He also had growth hormone (GH) deficiency for which he was prescribed exogenous GH. Papilledema was noted months later on routine surveillance, and GH was stopped. LP opening pressure was within normal limit with normal CSF constituents. With the initiation of acetazolamide and medically managed weight loss, he did not incur vision loss and his papilledema resolved over time.

Comment: This is a case of probable secondary PTCS. There are many causes of secondary PTCS. There is a clear relationship between recombinant GH treatment and PTCS: signs and symptoms are seen after the start of treatment, are relieved after discontinuing the medication, and, in many cases, return with its re-challenge [17]. The frequency of PTCS in children being treated with recombinant GH is increased by 23–100 times above that seen in the general pediatric population [18, 19]. In the present case, other factors contributed to the development of PTCS, including severe obesity and additional endocrinopathies. Thyroid and parathyroid dysfunction have both been associated with pediatric PTCS.

Case 4

Table 40.4

Clinical history	16-year-old boy with sudden onset of constant, 7/10 right-sided headache, with associated right upper lid ptosis, photophobia, and phonophobia
	He also has "nighttime" headaches, awakening him from sleep
	No visual symptoms, but endorses pulsatile tinnitus
Key components of exam	BMI 26 kg/m^2 (90th percentile)
	Snellen acuity: 20/20 OD and OS corrected
	Pupils: equally reactive without APD
	Visual fields full to confrontation
	Ductions: full
	No papilledema
Key diagnostic tests required to evaluate for possible PTCS without papilledema	Contrast-enhanced MRI brain
	MRV
	Lumbar puncture
Results of diagnostic tests	MRI brain: normal; myopic globes
	MRV: normal
	LP: opening pressure of >360 mm CSF, normal constituents
Differential diagnosis can this title of "Differential Diagnosis" be centered within the cell?	
Headache syndrome—Cluster headache, hemicrania continua/paroxysmal hemicrania, chronic migraine	*Pseudotumor cerebri without papilledema*—but does not fulfill current diagnostic criteria
Therapeutic trials	
Management of headache	Management to lower ICP
Prednisone = not effective	LP = provided relief from headache × 1 day
Verapamil = not effective	Acetazolamide = caused side effects, not helpful
Topiramate = not effective	Furosemide = slightly helpful
Indomethacin = not effective	Spironolactone = slightly helpful
Greater occipital nerve block = not effective	Weight loss to 25 percentile = not effective
IV DHE = transient mild effect	
Zonisamide = modest effect	
Botox = minimal improvement	

Clinical Synopsis

This is a case of a child with constant, unilateral headache without papilledema who was found to have elevated opening pressure by lumbar puncture. Current criteria for the diagnosis of PTCS without papilledema were not met.

Comment: This case illustrates that some children with headaches have increased CSF opening pressure. Without a sixth nerve palsy or neuroimaging features of elevated ICP, they do not fulfill the current definitions of PTCS without papilledema. Some of these children may respond better to treatments for PTCS than to treatments for primary headache disorders [20].

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Optic Neuritis in Children

41

Mays Antoine El-Dairi and M. Tariq Bhatti

Abstract

Optic neuritis is rare in children. It may be an isolated event or a manifestation of a systemic recurrent or chronic demyelinating disease such as acute demyelinating optic neuropathy, neuromyelitis optica, or multiple sclerosis. In this chapter, we review the clinical manifestations of pediatric optic neuritis, its differential diagnosis, the tools used for diagnosis, as well as its treatment and long-term management.

Keywords

Pediatric optic neuritis • Demyelinating disorders in children

Case Study 1

History

A 13-year-old Caucasian girl presents with 3 days of left eye pain worse on eye movement, and 1 day of blurry vision in the left eye. She states that the vision in the left eye is "dimmer" and colors are "muted." Other than a history of mild intermittent asthma, she is healthy and her family and social histories are non-revealing.

Examination

Visual acuity was 20/20 in the right eye, and 20/200 in the left eye. Pupillary examination revealed no anisocoria and a left relative afferent pupillary defect (RAPD). Intraocular pressures were 14 in the right eye and 15 in the left eye. Extraocular muscles were full with notable pain of the left eye with movement. She was able to identify 10/10 Ishihara plates with her right eye but only 3/10 with the left. She also reported that the red top of the medication bottle looked more "pinkish" when viewed with the left eye compared to the right eye. Slit lamp exam was normal with no anterior chamber or anterior vitreous cell. Ophthalmoscopy showed no abnormalities in the right eye, and revealed a mildly swollen left optic nerve (grade 2) with no peripapillary hemorrhages and no macular edema (Fig. 41.1).

Differential Diagnosis

The differential diagnosis of an acute optic neuropathy in children includes idiopathic, inflammatory, metabolic, compressive, neoplastic, infectious, ischemic, traumatic, and genetic disorders (Table 41.1) [1].

(continued)

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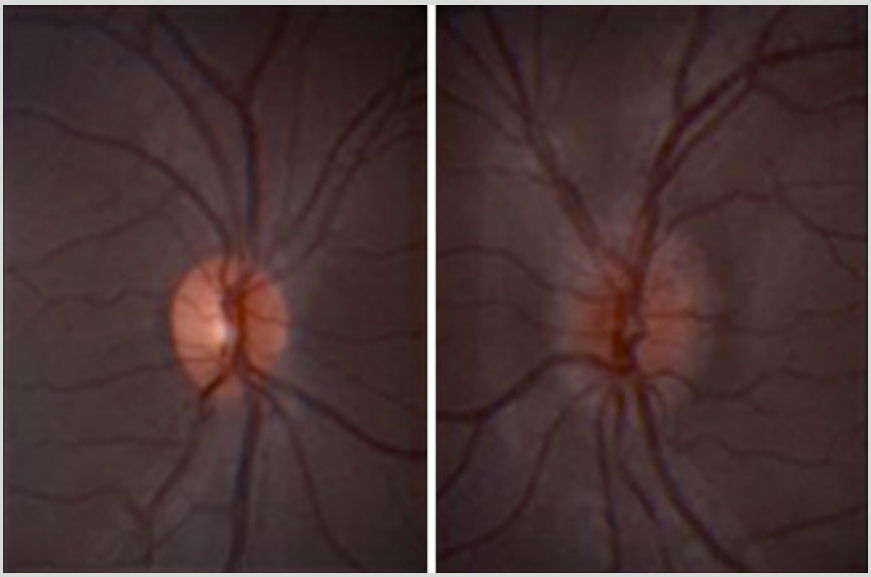


Fig. 41.1 Right and left optic nerves of our patient showing grade 2 swelling of left optic nerve

Table 41.1 Differential diagnosis of optic neuropathies in children

	Selective disease entities	Optic nerve appearance early
Demyelinating	Isolated demyelinating optic neuritis	Normal or mild swelling
	Multiple sclerosis (MS)	
	Neuromyelitis optica (NMO)	
	Acute demyelinating encephalomyelopathy (ADEM)	
Inflammatory	Orbital pseudotumor	Normal or swelling, possible retinal findings
	Sarcoidosis	
	Granulomatosis with polyangiitis	
	Systemic lupus erythematosis	
	Behçet's disease	
Neoplastic/compressive	Lymphoma	
	Leukemia	Swelling or pallor likely retinal findings
	Optic pathway glioma	
	Schwannomas	
	Optic nerve sheath meningioma	
	Craniopharyngioma	
	Pituitary tumor	
	Aneurysm	
Traumatic	Traumatic optic neuropathy: severe trauma to eye/head	Normal or swelling, possible retinal findings
Infectious	Neuroretinitis	Neuroretinitis: swollen with macular exudates in a stellate pattern. Retrobulbar: normal or swelling
	Retrobulbar infectious optic neuropathy	
Metabolic/toxic	B12 or folate deficiency	Pale
	Ethambutol or linezolid toxicity	Normal vs. mild swelling
Increased intracranial pressure	Obstructive hydrocephalus, venous sinus thrombosis, medications (vitamin A, estrogen, tetracyclines, growth hormone), malignant hypertension, meningitis, pseudotumor cerebri	Swelling (papilledema)
Hereditary	Leber hereditary optic neuropathy (LHON)	Pseudo optic nerve edema, peripapillary telangiectasias
	Dominant optic atrophy	Temporal pallor with excavation of cup
	Wolfram disease	

(continued)

Compressive lesions often manifest with chronic or subacute vision loss with a normal or pale optic nerve (optic nerve head pallor typically develops 4–6 weeks after the onset of an insult). Traumatic causes can generally be excluded by a detailed history. Infectious etiologies include neuroretinitis due to *Bartonella henselae*, the causative agent of cat scratch disease, syphilis, Lyme disease, tuberculosis, toxoplasmosis, and toxocariasis. Neuroretinitis is characterized by a swollen optic nerve associated with subretinal fluid and a macular star (Fig. 41.2). However, the macular star may not be apparent on presentation [2]. Leber hereditary optic neuropathy (LHON) is a mitochondrial genetic disorder that predominantly affects young males. The vision loss is usually painless, with either bilateral simultaneous or sequential optic neuropathies. Funduscopic examination can be normal or occasionally demonstrate optic disc edema with telangiectatic vessels on and around the optic nerve. The swollen nerve does not exhibit leakage on fluorescein angiogram (Fig. 41.3).

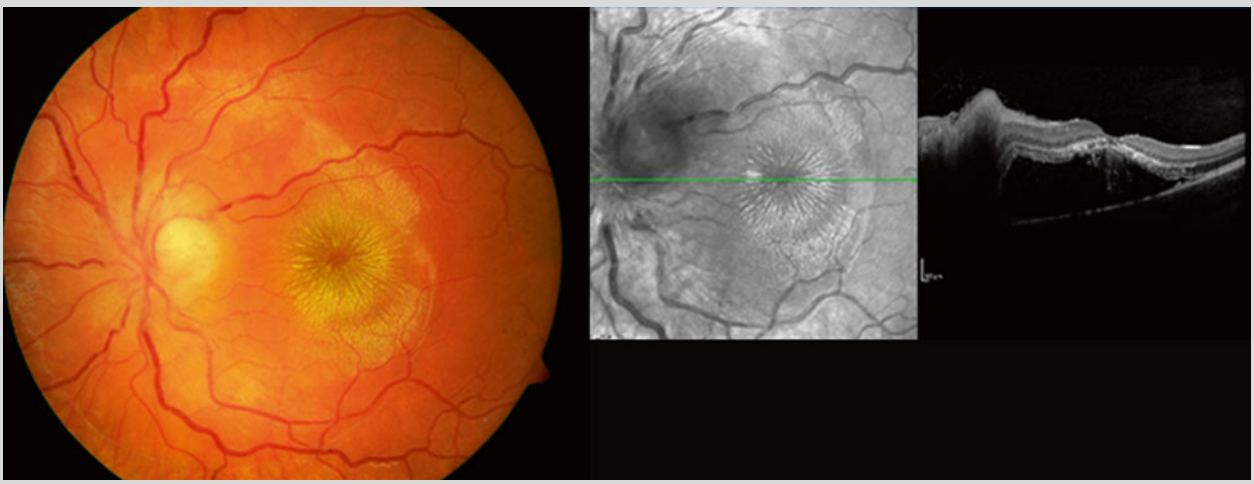


Fig. 41.2 *Left pane*: Fundus photograph of case of neuroretinitis with optic nerve head edema and macular star. *Right pane*: Macular OCT scan showing subretinal fluid

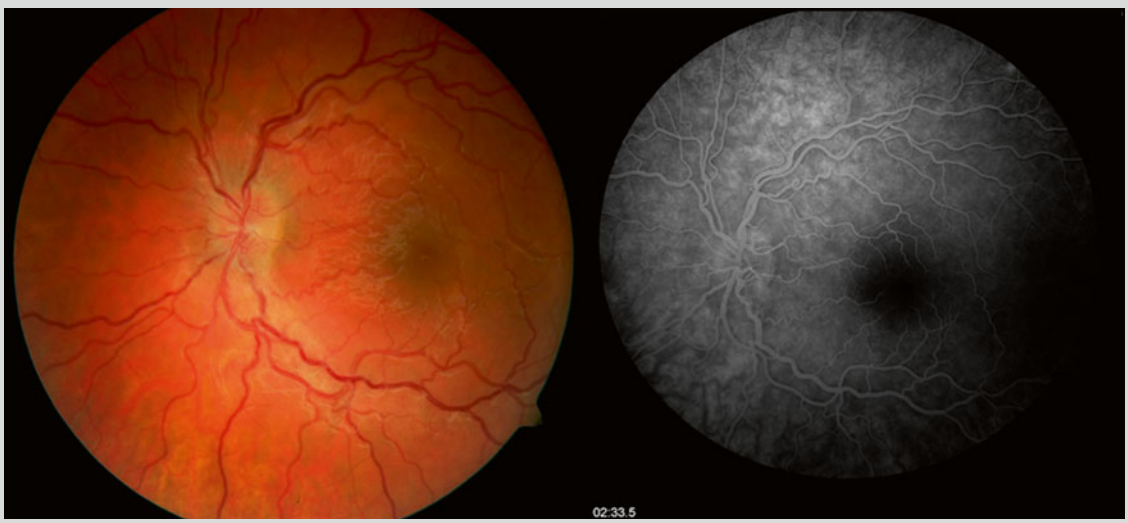


Fig. 41.3 Optic nerve head photo (*left*) and late phase of fluorescein angiogram (*right*) of a 16-year-old boy with acute decreased vision due to Leber hereditary optic neuropathy (LHON). Note temporal telangiectatic vessel and lack of fluorescein dye leakage from optic nerve indicating pseudo-optic disc edema

Clinical Impression: Acute Inflammatory Demyelinating Optic Neuritis

Acute inflammatory demyelinating optic neuritis (DON) is an idiopathic monophasic or chronic/recurrent demyelinating condition that can be associated with acute demyelinating encephalomyelitis (ADEM), neuromyelitis optica (NMO), multiple sclerosis (MS) (Table 41.2), or other inflammatory conditions such as sarcoidosis.

On presentation, the visual loss due to DON is often severe (<20/200 in 90–95 % of children) [3, 4] and frequently bilateral (33–86 %) [3–13]. Headaches, eye pain, or eye pain on eye movements are reported in up to 30 % of cases [3]. Although an RAPD should be invariably present in unilateral or bilateral asymmetric cases [9], it is reported in only 67 % of children, probably due to the difficulty of the examination or the frequency of bilateral disease [12]. Color vision is impaired in approximately 50 % of the cases [12], and the pattern of dyschromatopsia is usually consistent with an acquired red-green deficiency [5]. Optic nerve edema is seen in one-half to three-quarters of cases [3, 10, 14, 15].

Diagnostic Evaluation of Suspected DON

All patients with an acute optic neuropathy require a detailed history, including details of previous illnesses, neurological deficits, family history, and medication list. The authors recommend a thorough neuro-ophthalmic examination including assessment of vision, color vision, pupils, motility, proptosis (with Hertel exophthalmometer measurement), and slit-lamp biomicroscopy to evaluate for anterior chamber and anterior vitreous for inflammatory cells (anterior uveitis or pars planitis can present in a similar fashion to a subacute DON). Aside from a optic nerve edema, the remainder of the examination should be normal in idiopathic DON.

Ancillary Ophthalmic Testing

In a child suspected of having an optic neuropathy, we recommend formal visual field testing and optical coherence tomography (OCT) when possible.

What Kind of Visual Field Testing to Order?

Automated visual fields can be performed with reasonable reliability in children older than 8 years of age and whose

Table 41.2 Diagnostic criteria of acute demyelinating encephalomyelitis, neuromyelitis optica, and multiple sclerosis

Acute demyelinating encephalomyelitis (ADEM)	Neuromyelitis optica (NMO)	Multiple sclerosis (MS)
Polysymptomatic presentation that must include encephalopathy	Optic neuritis or transverse myelitis and at least 2 of the following 3:	Dissemination in space:
Defined as:	• MRI evidence of a continuous spinal cord lesion ≥3 segments	• ≥1 T2 lesion in at least 2 out of 4 areas in the central nervous system: periventricular, juxtacortical, infratentorial, and spinal cord. Enhancement with gadolinium is not a requirement for dissemination in space
• Behavioral change	• Onset MRI non-diagnostic for MS	Dissemination in time:
• Alteration in consciousness	• Positive NMO IgG (aquaporin-4 antibody)	• A new MRI lesion on follow-up with reference to baseline irrespective of the time difference between the two MRIs. The lesion could be the simultaneous presence of a gadolinium-enhancing and a non-enhancing lesion at any time
• Complete or partial clinical or radiological improvement after the initial event		• The simultaneous presence of a gadolinium-enhancing and a non-enhancing lesion at any time
• No prior history of a demyelinating event		• If the first demyelinating event is diagnostic of ADEM, then a second non-ADEM is still not diagnostic of MS, and at least a second non-ADEM event or a change in MRI scan more than 3 months after the second event/s is/are required for the diagnosis of MS
• No other etiologies can explain the event		
Course		
• Usually **monophasic**: Fluctuating clinical or radiological findings can occur up to 3 months from initial presentation		
• **Recurrent** ADEM: Recurrence of the same clinical and radiological findings 3 or more months after the initial ADEM		
• **Multiphasic** ADEM: New clinical event 3 or more months after the initial one that meets the criteria for ADEM and involves new anatomic areas		

MRI magnetic resonance imaging, *CSF* cerebrospinal fluid

central vision is better than 20/200 (without using eccentric fixation). The authors find that the Humphrey visual field (HVF) (Carl Zeiss Meditec, Inc, Dublin, Ca) SITA fast 24-2 protocol or Octopus visual field analyzer (Haag-Streit AG) Tendency Oriented Perimetry (TOP) protocol with foveal threshold "*on*" provides the best reproducible information in children. For younger children and those with dense central scotomas, Goldmann visual field testing is more reliable. Although formal visual field testing may not provide added information to assist in the initial diagnosis, it will establish a baseline extent of field loss, and detect any subtle abnormalities in the contralateral (asymptomatic) eye.

Visual defect patterns in idiopathic DON can vary and include central (40 %), cecocentral (10 %), or peripheral constriction (15 %) [3, 5]. Our patient's visual fields are presented in Fig. 41.4.

What Kind of OCT to Order?

While OCT is not imperative in clinical practice to diagnose DON, it is useful to exclude other diseases such as retinal pathologies that are too subtle to be detected on a routine examination. There are multiple OCT machines and various optic nerve and macular protocols. Please refer to Chap. 27 for more information about OCT. For suspected DON, the authors recommend a retinal nerve fiber layer protocol which can identify subtle swelling of the involved optic nerve or subtle atrophy of the contralateral optic nerve, as well as a macular scan to help identify an early neuroretinitis or macular edema that may not be detectable on clinical examination (Fig. 41.5).

Our patient's OCT images are presented in Fig. 41.6.

Does a Visual Evoked Potential Need to Be Performed?

A visual evoked potential (VEP) can be very helpful in confirming an optic neuropathy in nonverbal children. The VEP signal is initially absent or shows diminished amplitude in about 83 % of eyes with acute DON [12]. Although Flash VEP is easier to perform in children, its sensitivity in cases of mild optic neuritis is poor. The latency of the flash VEP and pattern reversal VEP will show a delay in the acute phase of optic neuritis that later recovers with time [16].

Neuroimaging: What Kind of Magnetic Resonance Imaging to Order?

A cranial magnetic resonance imaging (MRI) is recommended to exclude a compressive lesion and to evaluate for cerebral white matter lesions, assisting in the staging for the future risk of multiple sclerosis (MS). The administration of contrast is recommended because it will detect lesions resulting in disruption of the blood–brain barrier (i.e., acute inflammation, neoplasm, and infection). In addition, a contrasted orbital MRI with fat suppression can help distinguish DON from orbital pathology (Fig. 41.7).

A computed tomography scan is not advisable in pediatric DON because it is associated with radiation exposure and it has a much lower sensitivity for detecting subtle white matter lesions and optic nerve pathology compared to MRI.

The presence of cord lesions on a cervical spine MRI is indicative of MS, ADEM, or NMO (Fig. 41.8). The spine MRI can be obtained in the same setting of the cranial MRI if there is a high suspicion for optic neuritis and if sedation/anesthesia is required to perform the MRI.

Our patient's MRI is presented in Fig. 41.9.

What Laboratory Studies Should Be Performed?

In children with first episode of DON, we recommend screening for sarcoidosis with angiotensin-converting enzyme (ACE) levels, syphilis, cat scratch, and Lyme disease with serology (depending on whether they live in an endemic area). Screening for NMO spectrum disorders with NMO antibodies (a.k.a. aquaporin 4 antibodies) and myelin-oligodendrocyte glycoprotein (MOG) antibodies [17] is recommended in cases of severe vision loss on presentation, irreversible progressive visual loss, or recurrent visual loss [18]. It should be noted that normative values for NMO antibodies, MOG antibodies, and serum ACE are not well established in children. We reserve further, more extensive work-up for cases that do not respond well to initial treatment, or in cases with recurrent or steroid dependent DON.

Is a Lumbar Puncture Needed?

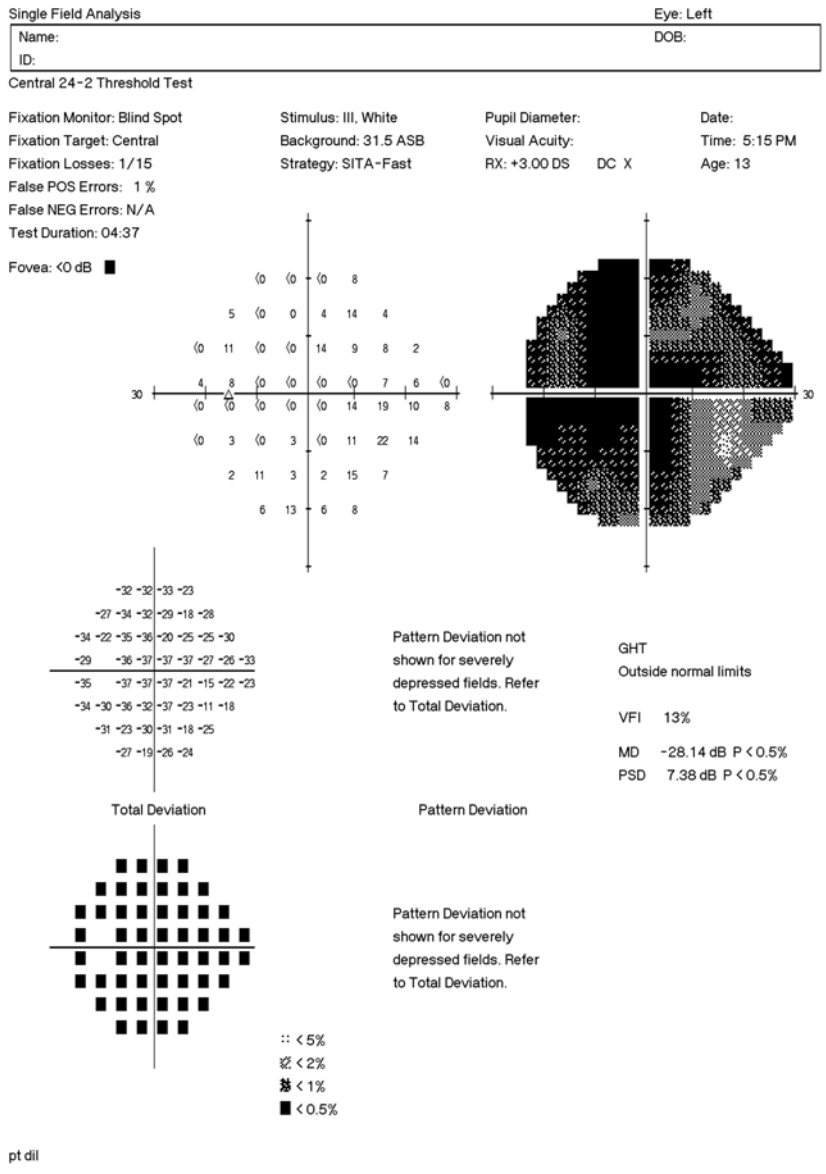
A lumbar puncture is recommended to rule out infectious or infiltrative etiologies. The detection of oligoclonal bands in the CSF is often seen in MS and less commonly in NMO.

Diseases Associated with DON

Acute DON can be an isolated idiopathic disease (a.k.a. clinically isolated syndrome) or can be a manifestation of a more widespread central nervous system (CNS) demyelinating disorder such as ADEM, NMO, or MS (Table 41.2).

Acute Disseminated Encephalomyelitis

ADEM is an inflammatory demyelinating disease of the CNS that commonly affects children between the ages of 6 and 10 years and usually presents 1–6 weeks after a viral illness or a vaccination [19, 20]. ADEM frequently presents with mental status changes and multiple neurological symptoms [21]. DON associated with ADEM is often bilateral [21]. MRI shows multiple white matter lesions that display a pattern of enhancement that is similar in all lesions. Lumbar puncture produces a cerebrospinal fluid (CSF) with



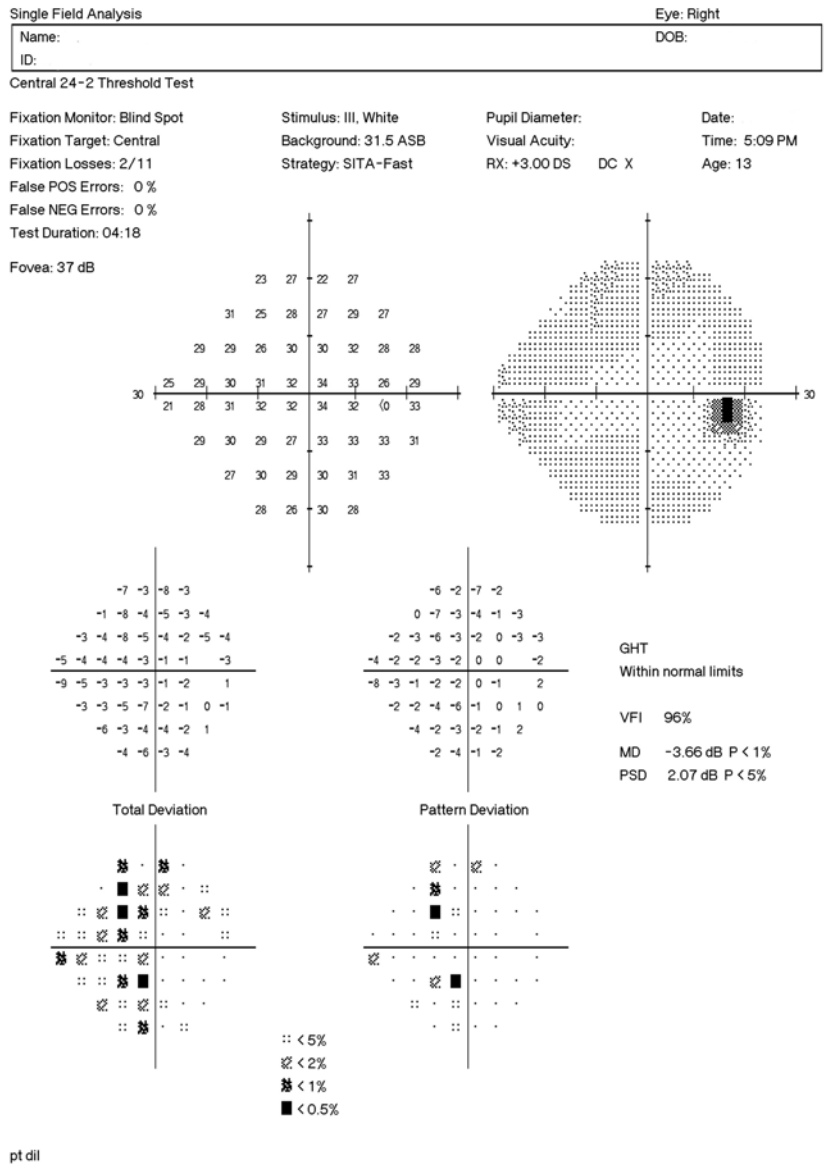


Fig. 41.4 HVF 24-2 SITA fast visual fields of our patient with acute left optic neuritis. Right visual field is normal with normal mean deviation and normal foveal threshold of 37 dB. Left visual field shows generalized severe depression with foveal threshold <0 dB

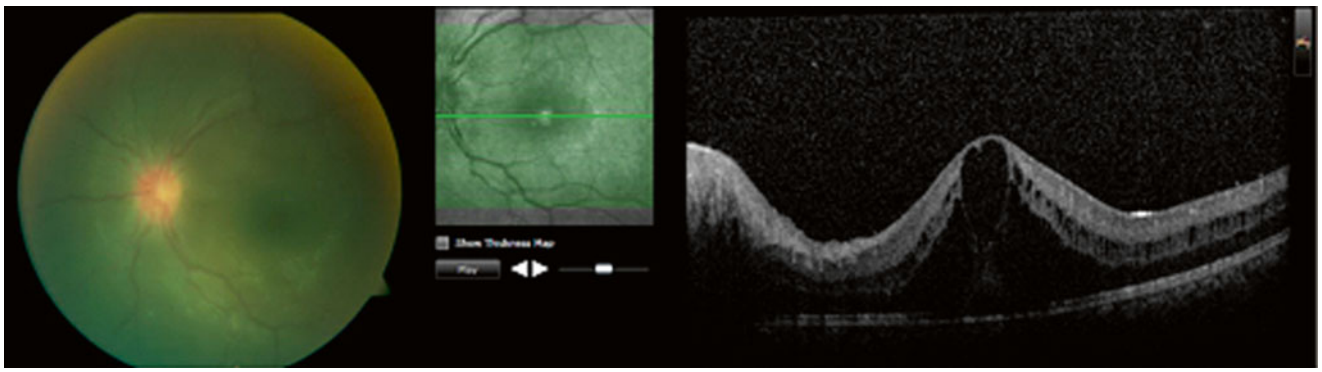


Fig. 41.5 Left macula of child shown in Fig. 41.1 looked normal on fundus examination but OCT showed macular edema and submacular fluid

pleocytosis and oligoclonal bands in the acute phase that disappear later in the course of the disease [21]. ADEM is often a monophasic illness; however recurrent and multiphasic forms of the disease are recognized by the international MS society [22].

Neuromyelitis Optica

NMO or Devic disease is a rare disorder that most commonly affects females. It can present in children or adults and is characterized by longitudinally extensive transverse myelitis (LETM defined as a lesion in the spinal cord >3 vertebrae segments in length), DON, or both. The attacks can be either simultaneous or sequential, occasionally separated by several years [23]. Some patients may have neurologic symptoms indicating brainstem or hypothalamic dysfunction such as nausea, vomiting, vertigo, or cranial neuropathies. NMO relapses are usually severe and the neurologic prognosis without treatment is poor. NMO in a child can result in significant physical and visual disability within about 13 years of the disease's initial presentation [24, 25]. The diagnostic criteria for NMO include the presence of optic neuritis or myelitis with 2 out of 3 of the following findings (provided these findings cannot be explained by another demyelinating disorder such as MS) [26]:

1. MRI not diagnostic of MS.
2. LETM.
3. Positive NMO (aquaporin-4) antibodies.

MOG antibodies can be detected in cases of NMO spectrum disorders [17].

Multiple Sclerosis

In adults, the relationship between DON and MS is well established [27]. The risk of MS is stratified based on the presence or absence of cerebral white matter lesions on MRI. According to the prospective adult Optic Neuritis Treatment Trial (ONTT), and after 15 years of follow-up, patients with a normal brain MRI had a 25 % risk of developing MS compared to those patients with ≥1 or more lesions the risk of MS whose risk was >70 % [27]. To date, there has not been a similar study in children.

The current data regarding the association between MS and DON in children is based on collections of multiple retrospective studies [3–5, 8–15, 28–37], with a reported rate of conversion ranging from 0 to 33 %. The diagnosis of MS relies on the McDonald criteria which were revised in 2010 [38]. The diagnosis of MS in children requires the documentation of multiple CNS demyelinating attacks that are separated in time and space; however, the events must not meet criteria for ADEM (evidence of encephalopathy or altered consciousness). If a child presents with an ADEM-like first clinical attack, the confirmation of MS requires 2 or more non-ADEM demyelinating attacks (a total of 3 attacks separated by time), or 1 additional non-ADEM demyelinating attack associated with a subsequent clinically silent lesion(s) on MRI [39]. The largest (79 patients) retrospective study on pediatric DON with the longest follow-up time of 22 years reported a conversion rate to clinically definite MS of 13 % at 10 years, 19 % by 20 years, 22 % by 30 years, and 26 % by 40 years [14].

Pediatric DON studies have been inconsistent on the subject of whether bilateral or unilateral disease is predictive of a future development of MS. The meta-analysis performed by Waldman et al. [40] did not show a correlation between either bilateral or unilateral ON and the development of MS. However, the study found that bilateral ON is more likely to occur in younger children; that the risk of MS was higher in older children (for every 1-year increase in age, the odds of developing MS increased by 32 %) [40]; and that the presence of cerebral white matter lesions on the initial MRI was associated with an increased risk of MS [40]. These results were similar to a pediatric clinically isolated syndrome (CIS) study conducted by Mikaeloff et al.

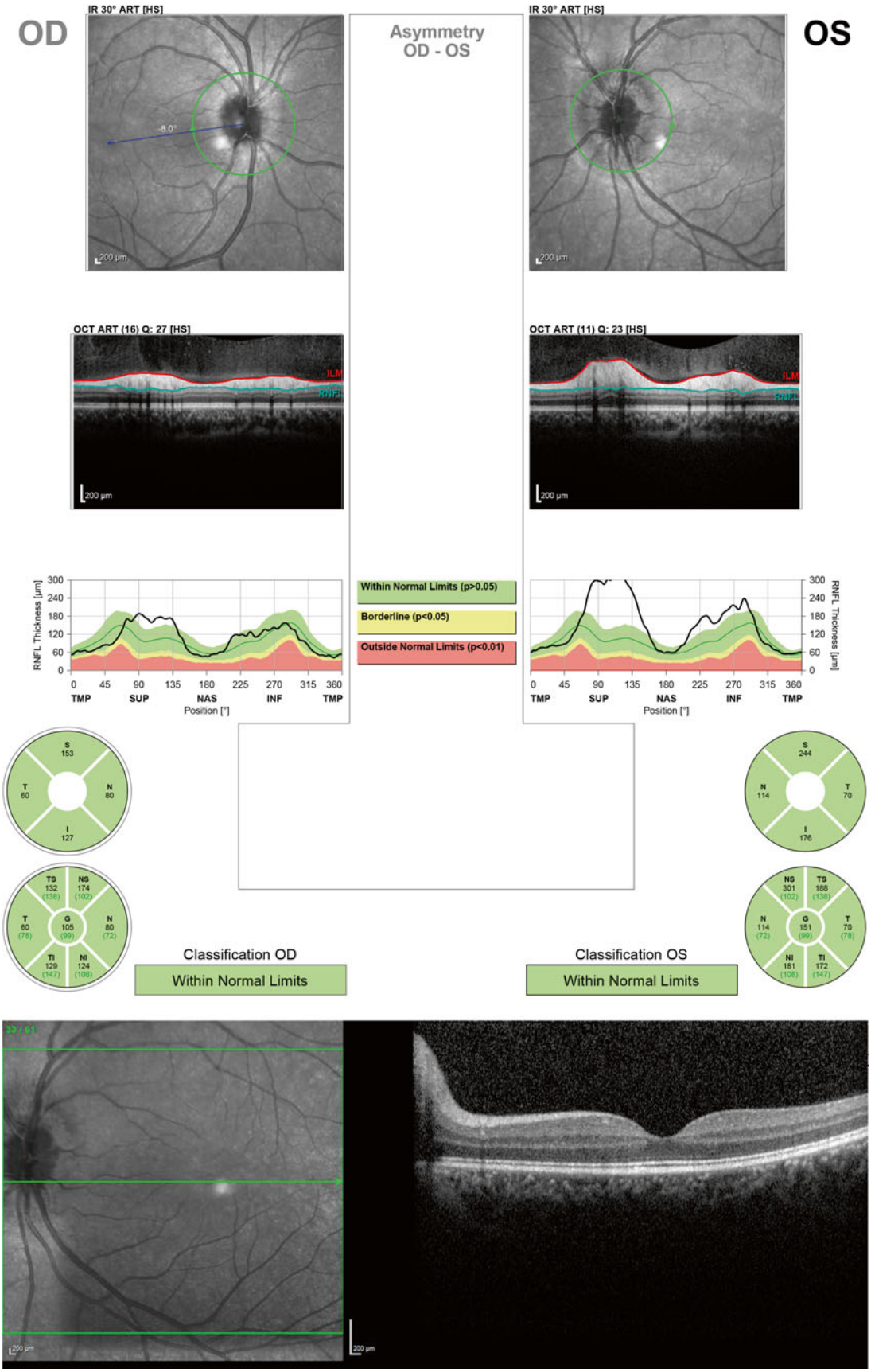


Fig. 41.6 Spectral domain optical coherence tomography of our patient with acute left DON. The retinal nerve fiber layer is slightly thickened (average 151 µm in left eye compared to 105 µm in the normal right eye), macular scan shows normal photoreceptors and no subretinal fluid

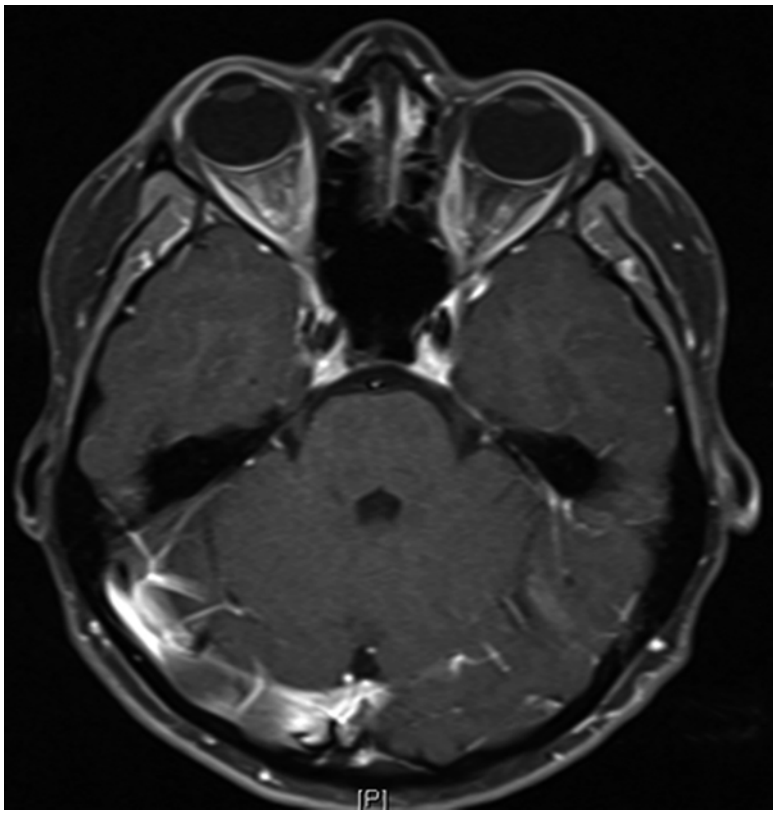


Fig. 41.7 Axial, T1-weighted, post-contrast MRI of orbits with fat suppression showing enhancement of intra-orbital fat in the right eye of a 15-year-old girl with herpes simplex viral orbital cellulitis

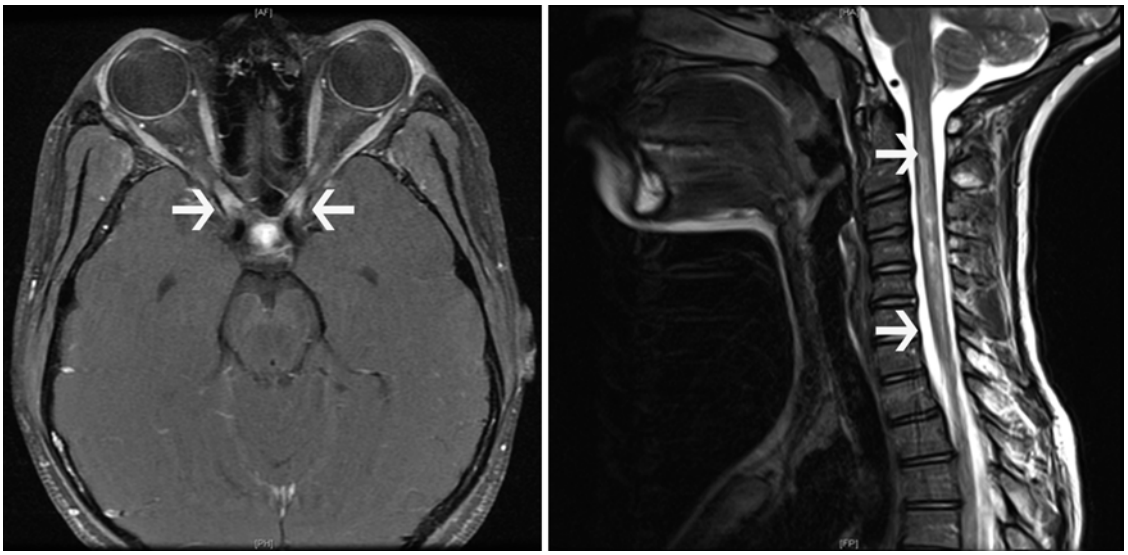


Fig. 41.8 11-year-old girl with neuromyelitis optica. *Left*: Axial, T1-weighted, post-contrast MRI orbits with fat suppression showing bilateral enhancement of the intracranial portions of the optic nerves (*arrows*). *Right*: Sagittal, cervical spine, T2-weighted MRI shows long-segment white matter lesion (*arrows*) consistent with longitudinally extensive transverse myelitis

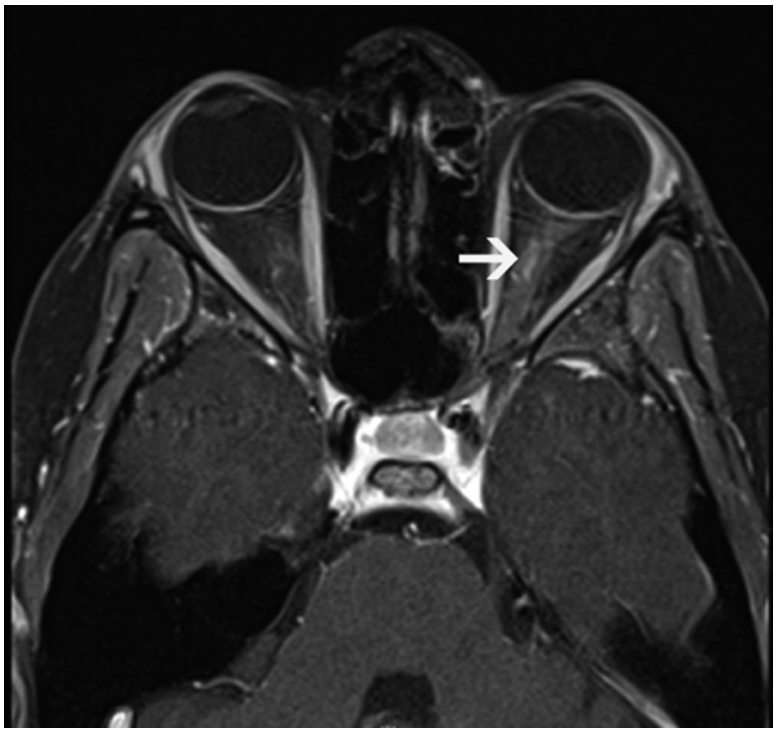


Fig. 41.9 Axial, T1-weighted, post-contrast MRI of orbits with fat suppression showing enhancement of intra-orbital portion of left optic nerve (*arrow*) in our patient with acute left optic neuritis

which showed that age of onset >10 years or an abnormal brain MRI was predictive of the future development of MS (occurring an average time of 2.9 ± 3.4 years after the episode of CIS) [41]. An episode of DON with a normal MRI is a CIS.

Treatment of DON

There are no current guidelines for the treatment of acute idiopathic DON in children. Most clinicians follow the results of the adult ONTT and administer intravenous methylprednisolone (IVMP) 1000 mg daily or 30 mg/kg/day for 3 days followed by a 15-day oral prednisone taper (the authors use 1 mg/kg for 10 days, 0.2–0.3 mg/kg on day 11, 0.1–0.15 mg/kg on day 12, skip day 13, and 0.1–0.15 mg/kg on day 14) to hasten recovery (there is no data to suggest that the final outcome of steroids alters the final visual outcome) [42]. Treatment protocol is the same for cases of established ADEM or MS.

In cases of established or suspected NMO, IVMP is usually administered for 5 days (1000 mg/day or 30 mg/kg/day), and if the vision worsens or fails to recover, further treatment with intravenous immunoglobulin (IVIG), 2 g/kg/day, or plasmapheresis can be offered [43].

Clinical Course of DON

Improvement of vision usually starts within 3 weeks, and continues up to 6 months, and sometimes a year [3]. Visual recovery is excellent, with the vast majority of children recovering a visual acuity of 20/20, but optic nerve pallor persists. As many as 15 % of patients have a vision of <20/200 and approximately 7 % of patients have an acuity of 20/50 to 20/100. Younger children (<6 years of age) appear to have a better visual prognosis than older children [4].

Long-Term Management of DON

The long-term management of DON is dependent upon the likelihood on the development of NMO or MS in the future. There are no pediatric CIS studies similar to the ones performed in the adult population [44].

DON with Normal Brain MRI

Most experts recommended a physical examination every 3 months by a pediatrician or pediatric neurologist. There is no consensus regarding the need of a follow-up MRI [18], but the authors will usually obtain an MRI a year after the initial diagnosis.

DON with Abnormal Brain MRI

If the initial brain MRI is consistent with MS, a pediatric neurologist would discuss management options with the family, and treatment is usually strongly recommended. Although, to date, there have been no randomized clinical trials for disease-modifying therapies in children with MS [45], current accepted long-term therapy in children includes β-interferon, glatiramer acetate, and combinations with steroids or intravenous immunoglobulins (IVIG) [46]. Safety in children has still not been established for emerging MS adult therapies.

DON with Suspected NMO

Maintenance treatment with mycophenolate mofetil, IVIG, rituximab, low-dose steroids, and sometimes azathioprine is recommended and is effective in preventing recurrences [24, 47].

Summary and Conclusions

Pediatric DON may be a presenting sign for a more generalized CNS demyelinating disorder or represent a single isolated idiopathic event. Long-term management of children with DON requires a team approach with a pediatric neurologist and occasionally a pediatric rheumatologist, oncologist, or infectious disease specialist. Many outstanding questions regarding the long-term outcome of idiopathic DON should be answered after the completion of the long-awaited multicenter pediatric optic neuritis clinical trial [48].

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Childhood Glaucoma

42

Eniolami O. Dosunmu and Sharon F. Freedman

Abstract

Childhood glaucoma comprises a group of vision-threatening diseases that can have a far-reaching impact on the life of an affected individual. Glaucoma in children is often difficult to manage, and it is important to understand the underlying etiology to help guide treatment. The diagnosis of glaucoma in children necessitates an understanding of underlying risk factors. A systematic approach to the evaluation of the patient, taking into account the history, examination findings, the use of diagnostic tests, and an understanding of systemic or other local disease factors, will help the treating ophthalmologist to diagnose and treat this group of disorders. The logic of a recent classification system, along with proposed algorithms, will help to delineate and to simplify the diagnostic and treatment modalities.

Keywords

Glaucoma • Intraocular pressure • Goniotomy • Trabeculotomy • Glaucoma drainage device • Buphthalmos • Childhood glaucoma • Primary congenital glaucoma • Pediatric glaucoma

Introduction

Childhood glaucoma, also referred to as pediatric glaucoma, comprises a heterogeneous group of disorders. In this chapter, the terms pediatric glaucoma and childhood glaucoma will be used interchangeably. Glaucoma in the pediatric population is rare; however, it is a potentially blinding condition that must be recognized promptly and treated appropriately. Pediatric glaucoma often requires both medical and surgical approaches to its treatment. Vision loss may occur even when glaucoma has been successfully treated, as a result not only of anatomic ocular changes including high myopia, astigmatism, and anisometropia but also from secondary amblyopia and strabismus. Prompt and accurate recognition of glaucoma in children, timely and appropriate intervention, and a team approach that includes the active involvement and education of the parents/caregivers are essential for its successful management.

Classification of Childhood Glaucomas

Several schemes have been developed and utilized for the classification of childhood glaucoma [1–3]. Recently, there has been an international effort to create a widely accepted classification system. Clinicians who treat pediatric glaucoma collaborated, initially through the recently formed Childhood Glaucoma Research Network (CGRN) and then more formally at the World Glaucoma Association (WGA) 2013 Consensus on Childhood Glaucoma, to define this

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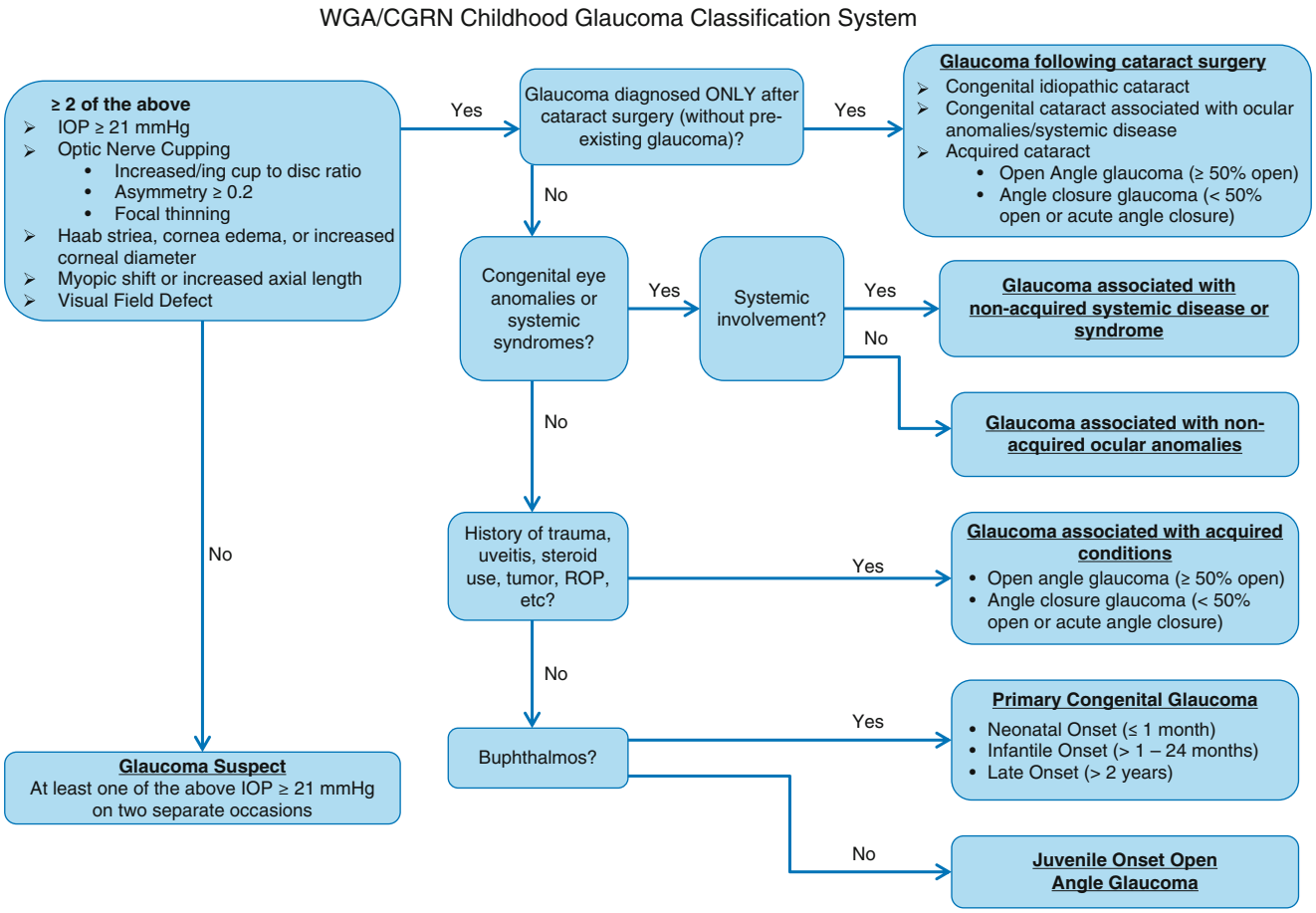

Fig. 42.1 Childhood Glaucoma Research Network/World Glaucoma Association (CGRN/WGA) Childhood Glaucoma Classification System. The algorithm was modified and reproduced, with permission, from *Childhood Glaucoma*, 9th Consensus Report of the World Glaucoma Association. Kugler Publications, Amsterdam, The Netherlands, 2013

group of disorders and to create the classification scheme shown in Fig. 42.1 [4]. Childhood glaucomas are classified as either *primary* or *secondary*. Additional details are then provided within each of these categories. This chapter broadly discusses the classification and diagnosis of childhood glaucomas and presents illustrative cases that demonstrate the evaluation, accurate diagnosis, and treatment of representative patients from each category of this group of diseases. Aphakic glaucoma and juvenile open-angle glaucoma are discussed in Chaps. 43 and 44, respectively.

The Primary Childhood Glaucomas

Primary Congenital Glaucoma

Primary congenital glaucoma (PCG) is a childhood glaucoma that occurs in the absence of other ocular or systemic findings. It is the most common of all primary childhood glaucomas [1–5]. It constitutes 1–5 % of all glaucomas with prevalence rates ranging from 1/1250 to 1/22,000 depending on the population and prevalence of consanguineous unions in the population of interest [5, 8, 9]. In the United States, it probably occurs in about 1/10,000 live births.

Diagnosis

Using the World Glaucoma Association (WGA) Consensus [4] criteria, two or more of the five criteria listed in Table 42.1 must be met for the diagnosis of glaucoma to be made.

Clinical Evaluation

In a child with suspected PCG, the child should have a complete ophthalmologic examination and may require an examination under anesthesia to accurately assess. A complete examination (in most children an examination under anesthesia is necessary) should include the following:

1. Measurement of intraocular pressure (IOP): Multiple modalities may be helpful including Tonopen, Perkins tonometer, and pneumotonometer. These measurements should be obtained during the induction of anesthesia to

Table 42.1 Criteria for the diagnosis of primary congenital glaucoma

Criterion
Intraocular pressure (IOP) >21 mmHg (the examiner makes the final decision on the IOP if measured under anesthesia given the possible effects of anesthesia on the measured IOP)
Optic disk cupping, cup-to-disk asymmetry of ≥0.2 when the disks are of similar size, or focal rim narrowing
Corneal findings: Haab striae, corneal edema or diameter ≥11 mm in a newborn, >12 mm in child less than age 1, and >13 mm at any age
Progressive myopia or myopic shift coupled with an increase in ocular dimensions outside the range of the dimensions expected for normal growth
A reproducible visual field defect that is consistent with a glaucomatous optic disk neuropathy and no other identified causes for the visual field defect

prevent lowering of the IOP by anesthetic agents (with the exception of ketamine which may increase IOP).

2. Examination of the anterior segment with measurement of:
   (a) Corneal diameter.
   (b) Central corneal thickness (CCT) by pachymetry (documents edema). Unlike adult glaucoma, the IOP should not be corrected for CCT. There is no established correlation with IOP and CCT in primary congenital glaucoma (PCG).
   (c) Slit lamp examination: Evaluate for Haab's striae (breaks in the Descemet membrane). Evaluate for the presence of keratic precipitates (which would support an alternative diagnosis). Evaluate for the presence of anterior segment dysgenesis, such as an anteriorly displaced Schwalbe's line (posterior embryotoxon), iris hypoplasia, or corectopia, again these findings supporting an alternative diagnosis.
3. Gonioscopy: In PCG, the iris insertion is more anterior than that of a normal infant angle, and translucency of the uveal meshwork may make the ciliary body band, trabecular meshwork, and scleral spur indistinct.
4. Axial length: Biometry with an A-scan should be completed to assess for axial length as elevated IOP causes globe elongation from decreased scleral rigidity resulting in axial myopia. (See Appendix on measurement of axial length.)
5. Dilated fundus examination should include measurement of the cup-to-disc (C/D) ratio and photo images obtained, if at all possible, to document the extent of cupping.
6. Cycloplegic refraction should be performed to detect the extent of myopia and anisometropia. If a cycloplegic refraction was not obtained in the clinic setting, a miotic agent should be administered prior to the start of any angle surgery, so as to protect the integrity of the lens.
7. Automated visual field testing is completed depending on the patient's age and ability but can be used in the long-term follow-up.
8. Optical coherence tomography (OCT) of the optic nerve head. This test is often used to detect retinal nerve fiber layer thickness. The use of OCT in glaucoma is discussed extensively in Chap. 27.

Clinical and Genetic Aspects of PCG

The underlying etiology of PCG is believed to be a decreased outflow of aqueous humor through the trabecular meshwork [3, 4, 6, 7]. PCG can have (1) neonatal onset at ≤1 month of life; (2) infantile onset, >1 month to age 24 months; and (3) late onset, after age 2 years [1, 4].

While most cases of PCG are sporadic disease, the majority follow an autosomal recessive inheritance pattern, with the majority mapping to the GLC3A locus on chromosome 2p21 and resulting in mutations in the *CYP1B1* gene (Table 42.2). In certain populations, the incidence is higher due to consanguinity [5, 8, 9]. (For a more extensive discussion of the genetics of primary congenital glaucoma, the reader is referred to the following chapter: Sharafieh R, Child A, Sarfarazi M. Molecular genetics of primary congenital glaucoma. In Genetic Diseases of the Eye, Traboulsi EI, Ed. Oxford University Press, 2011.)

Treatment of PCG

Surgical Treatment

Surgical intervention is the definitive treatment for PCG, with medical therapy a temporizing measure before, and sometimes an adjunctive measure after, appropriate surgical intervention [2–4, 6, 7, 10–13].

Surgical intervention in PCG begins with angle surgery techniques that address the limitation to aqueous outflow at the trabecular meshwork [10–13]. Goniotomy and trabeculotomy are the two surgical approaches for angle surgery. Traditional goniotomy requires the presence of a view of the angle to be successfully accomplished. Goniotomy can also be accomplished via an endoscopic route, in the presence of corneal edema [14]; however, this procedure does require advanced surgical technique, and there is no data comparing endoscopic to traditional goniotomy. Trabeculotomy can be accomplished in eyes with and without a gonioscopic view of the angle structures. Goniotomy and traditional trabeculotomy allow for treatment of part of the angle (usually 180°), with a repeated surgical approach allowing for treatment of more of the angle. A suture or illuminated microcatheter can be utilized to facilitate 360° cannulation of the Schlemm canal [11, 13] and therefore a 360° trabeculotomy. High success rates for angle surgery have been reported in several series. Further analyses of the various studies have demonstrated that the success rate is also influenced by the age at onset of the glaucoma [11]. The success rate of angle surgery in neonatal-onset PCG is lower in comparison to the success rate of angle surgery in infantile-onset PCG. It has been reported that only approximately 50 % of all patients with PCG do well with only standard angle surgery in the

Table 42.2 Genetic basis of primary congenital glaucoma

Glaucoma type/locus	Inheritance	Gene	Locus
PCG/GLC3A	Autosomal recessive	*CYP1B1*	2p21
PCG/GLC3B	Autosomal recessive	Not identified yet	1p36
PCG/GLC3C	Autosomal recessive	*LTBP2*	14q24

long term [11, 13]. Trabeculectomy with mitomycin C and placement of glaucoma drainage devices (GDDs) are used in the treatment of refractory cases of PCG, when angle surgery has failed. Trabeculectomy with mitomycin C has been found to have a success rate of 52–59 % at approximately 24 months in childhood glaucomas [15–17]. Analysis of these patients found that the success rate was increased in older children, with the children under age one having a higher rate of failure [15, 16]. Beck et al. compared trabeculectomy with mitomycin C to placement of a GDD in children under the age of 2 years. In that study, the cohort of patients who underwent placement of a GDD had a higher success rate for IOP control than those having trabeculectomy—87 % versus 36 %, respectively, at one year, with the rates dropping to 53 % and 19 %, respectively, at year six [18]. Studies have demonstrated favorable success rates for treatment of childhood glaucomas using a GDD, with reported success varying by patient composition and length of follow-up [19–22]. In one study, success rate of placement of GDDs was found to be 92 % at one year in patients with PCG and 42 % at 10 years [19]. Multiple GDDs can be placed in the same eye if needed to control the IOP [23]. Diode cyclophotocoagulation (CPC), either transscleral or endoscopically applied, can be used as an adjunctive treatment for IOP control or as a treatment option for uncontrolled IOP in selected cases [24, 25]. Often times, in the case of refractory glaucomas, repeat treatment is needed [24, 25].

Medical Treatment

Medical management is used adjunctively in the treatment of PCG. Topical beta-blockers are a reasonable first-line treatment, lowering IOP by aqueous suppression. However, care must be taken when beta-blockers are administered to premature and young infants, or to those with asthma/reactive airways or to those with a contraindication to beta-blockade, given the risk of systemic side effects of bradycardia and bronchospasm [4, 26–30]. Carbonic anhydrase inhibitors (CAIs) are another first- or second-line treatment that have demonstrated efficacy in the pediatric population [4, 28–32]. CAIs can be used either topically (dorzolamide and brinzolamide) or systemically (acetazolamide); like beta-blockers, they also reduce aqueous production. The systemic formulation can result in metabolic acidosis with possible resultant tachypnea and decreased oral intake with resultant poor weight gain or even weight loss. Alpha-2 adrenergic agonists (brimonidine, apraclonidine) both decrease aqueous production and may increase uveoscleral outflow. Although these drugs are effective in reducing IOP, one must use caution when they are used in small children (approximately <6 years/50 lb for brimonidine and <1 year/20 lb for apraclonidine). The side effects of alpha-2 agonists include central nervous system depression, bradycardia, hypotension, and apnea [28–30, 33–35]. Brimonidine has a higher incidence of systemic side effects compared with apraclonidine [36]. Prostaglandin analogs increase the uveoscleral outflow. This class of medications has been found to be effective for IOP lowering, systemically safe, and to be more effective in older children with certain forms of glaucoma such as juvenile open-angle glaucoma [4, 28–30, 37, 38]. Miotics are not currently widely used in the treatment of pediatric glaucomas [4]. In selected cases, such as the use of pilocarpine during angle surgery, miotics can still serve an important role in the medical management of pediatric glaucoma. Echothiophate has also been found to be of use in selected cases of aphakic glaucoma, but its limited availability limits its usefulness [4].

Case Studies of Primary Congenital Glaucoma

The following five case studies will illustrate the clinical presentation, diagnosis, and short-term and long-term management of PCG. Importantly, primary congenital glaucoma is a lifelong disorder with significant visual morbidity if the disease progresses. The families must be educated on a continual basis on the natural history of the disease process, importance of adherence to medication regimens, and necessity of interval follow-up. In addition to glaucoma, visual morbidity can result secondary to amblyopia from anisometropia and/or irregular astigmatism secondary to Haab's striae. Therefore, management must include amblyopia treatment.

(continued)

Case 1

History/presentation: a 5-day-old female infant presents for evaluation of "cloudy eyes" and concern for cataracts. Prenatal history and family history are noncontributory.

Key examination findings:
Visual acuity:
OU: Wince to light (WTL)
Anterior segment examination (portable slit lamp):
OU: Corneas are cloudy appearing with 2+ corneal edema; corneal diameter estimated 11.5 mm.
Intraocular pressure (IOP) using Tonopen® while the child was feeding and calm:
OD: 50 mmHg
OS: 60 mmHg
Central corneal thickness (CCT):
OD: 964 μm
OS: 930 μm
Retinoscopy:
OU: Myopic reflex. Corneal changes limited a definitive end point on refraction.
Cup-to-disk (C/D) ratio:
OU: Estimated to be cupped >0.6 in both eyes (hazy view) using a 20D lens

Management (homegoing): Patient was started on dorzolamide 2% and timolol 0.25%, each eye twice daily (bid), and latanoprost at bedtime (qhs). The clinical significance of the findings, need for early surgical intervention, and long-term prognosis was extensively discussed with the parents.

Management plan: Surgical intervention within the week, pending clearance from anesthesia—examination under anesthesia with gonioscopy and likely angle surgery to both eyes.

Clinical Synopsis

This child meets the diagnostic criteria for *primary congenital glaucoma* (*PCG*)—with IOP ≥ 21 mmHg, increased optic nerve cupping, corneal changes, and a myopic reflex [4]. This child has glaucoma presenting at birth and thus falls into the *neonatal-onset* group, which responds less well to angle surgery than infantile-onset disease. The decision was made to proceed with angle surgery [2–4, 6, 7, 10–13] as the initial surgical intervention. Although the success of angle surgery with neonatal-onset PCG is less than with infantile-onset disease, many surgeons still favor angle surgery prior to more aggressive interventions such as glaucoma drainage implantation in these young infants, as the primary procedure. If surgical intervention was to be delayed in this child, one could consider the use of oral acetazolamide (dosed at 10–15 mg/kg/day divided into three daily doses) as adjunctive therapy. However, this needs to be compounded, as it is not available commercially given the age and size of the child, and one must be aware of the metabolic acidosis and tachypnea that can occur, as anesthesia needs to be alerted to this, in preparation for surgery [28–32].

In the above patient, who underwent angle surgery, the IOP responded well in both eyes decreasing to 20 mmHg and to 15 mmHg with addition of topical timolol 0.25 %. In the course of 6 months, the pressures in the right eye increased, despite addition of topical dorzolamide and latanoprost, to 30 mmHg, and a pediatric GDD was placed in the right eye with good results. At age 9 months, the pressures were 16 mmHg in the right eye and 14 mmHg in the left. Cycloplegic retinoscopy demonstrated high myopia (−8.00 D), and the patient was placed in refractive correction.

Case 2

History/presentation: a 5-month-old male found to have corneal haze at his well-child visit with his pediatrician. He was also found to have myopia and elevated IOP of mid-20s and was referred for evaluation of PCG. Prior to referral, patient was started on topical dorzolamide 2%.

Key examination findings: At an examination under anesthesia (EUA)
IOP obtained using Tonopen® immediately after induction of anesthesia:
OD: 26 mmHg
OS: 25 mmHg
Anterior segment examination (portable slit lamp):
OD: Cornea was enlarged with 1+ corneal edema and Haab striae inferiorly (see Fig. 42.2); corneal diameter measured 12.75 mm; iris demonstrated stromal hypoplasia.
OS: Cornea was enlarged with 1+ corneal edema; corneal diameter measured 12.75 mm; iris demonstrated stromal hypoplasia.
Axial length:
OD: 22.05 mm
OS: 21.79 mm

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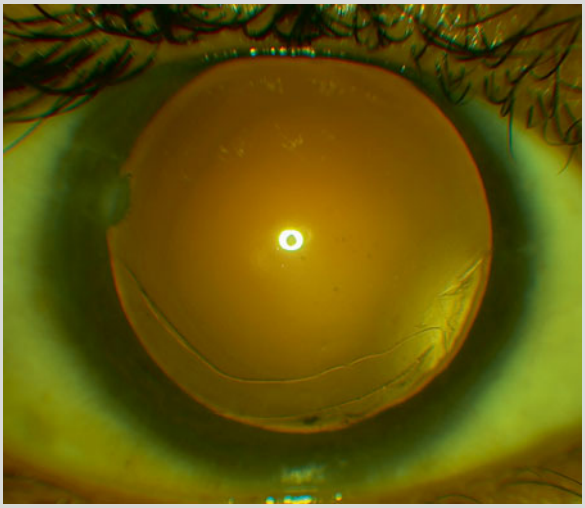

Fig. 42.2 Anterior segment photograph of child with Haab striae located inferiorly (demonstrated by retroillumination)

Gonioscopy:
OU: Open angle with indistinct structures
Central cornea thickness (CCT)
OD: 750 μm
OS: 720 μm
Optic nerve examination using direct ophthalmoscopy and indirect ophthalmoscopy with a 20D lens:
OU: Demonstrated cupping of both optic nerves of approximately 0.4.

Diagnosis: Infantile-onset PCG of both eyes, given the enlarged corneal diameters, hazy corneas, Haab striae, elongated axial lengths, and reported IOPs of mid-20s prior to initiation of medical therapy, and current IOP measurements.

Management options: Surgical intervention—angle surgery.

Management: Temporal (or nasal) goniotomy to both eyes (immediate); likely also second, nasal (or temporal), goniotomy to both eyes (6 weeks later).

Interval history (age 8 months): Now of all topical medications, corneas are clear, and parents are happy.

Key examination findings (in clinic):
IOP obtained using Tonopen® in a sleeping baby:
OD: 16 mmHg
OS: 15 mmHg
Anterior segment examination (portable slit lamp):
OU: The corneas were clear in both eyes with approximate corneal diameter of 12.75 mm in both eyes; inferior Haab striae in the right eye.
CCT:
OD: 575 μm
OS: 550 μm
Gonioscopy (At EUA):
OU: Open clefts nasally and temporally in both eyes
Axial lengths:
OD: 22.10 mm
OS: 21.80 mm
C/D ratio estimated using the 20D lens:
OU: 0.3

Management plan: Continue to follow with routine ophthalmology appointments to follow the IOP and to monitor for amblyopia. At this time, there is no indication for topical or systemic medications. No amblyopia treatment is indicated at this time. Patient education is provided to parents. This patient will be seen in 8 weeks for follow-up as detailed above and also for a cycloplegic refraction.

Clinical Synopsis

This is a patient with a diagnosis of *infantile-onset PCG*. At the time of clinical presentation, the IOPs were in the low to mid-20s, and the differential diagnosis also included a primary corneal disease. An EUA was performed to evaluate for other diagnostic markers of PCG, which were subsequently found at the EUA [4]—the patient's axial length was longer than normal for age-matched controls [39, 40]. Normal cornea diameter for a newborn is 9.5–10.5 mm and 10.5–11.5 mm at the age of 1 year [4, 40]. The authors have found that the use of more than one instrument (instrument decision is based on availability and ease of use of the examiner) to confirm the IOP measurements, especially when the cornea is edematous, is helpful. It is important to obtain the IOP immediately after induction of anesthesia, as most sedative and anesthetic agents reduce the IOP. Given that the IOP can be altered by the anesthetic agent, evaluation for the other diagnostic criteria of glaucoma is important [4, 41]. The decision was made to proceed with surgical intervention. In this case, despite the corneal haze, which was located centrally, a view to the angle was easily obtained, and the decision was made to proceed with goniotomy. This child did well with goniotomy; however, studies have demonstrated that approximately 30–90 % (data depends on the patient study and patient population) of patients with PCG do well with standard angle surgery in the long term, with children with infantile onset doing better than those with neonatal onset [3, 11].

Case 3

History/presentation: a 13-month-old male diagnosed with unilateral elevated IOP, buphthalmos, and corneal edema, right eye—in the setting of tearing and photophobia. He was initially treated as orbital cellulitis due to apparent lid swelling and proptosis on the affected side. Family history is positive for an aunt with PCG. There is no known history of consanguinity. IOP and symptoms did not improve with topical medications prior to referral.

Key examination findings: The clinical findings at presentation and a positive family history of PCG warranted an EUA.

IOP obtained using a Tonopen® immediately following induction:
- OD: 26 mmHg
- OS: 13 mmHg

Anterior segment examination (portable slit lamp):
- OD: Cornea demonstrated Haab striae that involved the visual axis (Fig. 42.3); corneal diameter measured 13.0 mm
- OS: Within normal limits (WNL). Corneal diameter of 11.75 mm

Central corneal thickness:
- OD: 750 μm
- OS: 613 μm

Axial length:
- OD: 23.22 mm
- OS: 21.79 mm

Gonioscopy:
- OD: Open angle with indistinct structures
- OS: Open angle to the scleral spur

Diagnosis: PCG—infantile onset

Management options:
- Angle surgery
  - Goniotomy
  - Trabeculotomy

Management: Nasal goniotomy to the right eye (immediate) and temporal goniotomy in 6 weeks

Interval history (2 months): Patient is doing well according to his parents.

Key examination findings:

Visual acuity:
- OD: Central, steady, and unmaintained (CSuM)
- OS: Central, steady, and maintained (CSM)

IOP obtained using Tonopen® while child is being bottle fed:
- OD: 16 mmHg
- OS: 12 mmHg

Cycloplegic refraction:
- OD: −3.00 + 3.50 × 145
- OS: +1.50 + 0.75 × 095

Following his response to the surgical treatment, he was placed in refractive correction for the induced myopia and astigmatism, and amblyopia treatment with patching was initiated.

Clinical Synopsis

This child has unilateral *infantile-onset PCG* and presents with two symptoms from the classic triad of PCG—blepharospasm, epiphora, and photophobia. This patient also highlights how comparing the axial lengths, IOP, corneal diameter, and CCT between the two eyes was instrumental in confirming the diagnosis. These markers were also used to follow his clinical response to treatment. Successful treatment included not only lowering IOP in the right (affected) eye through his surgical intervention but also correction of the induced myopia, astigmatism, anisometropia, and amblyopia. Even with correction of the above, he went on to develop dense amblyopia, given the Haab striae that involved the visual axis (Fig. 42.3).

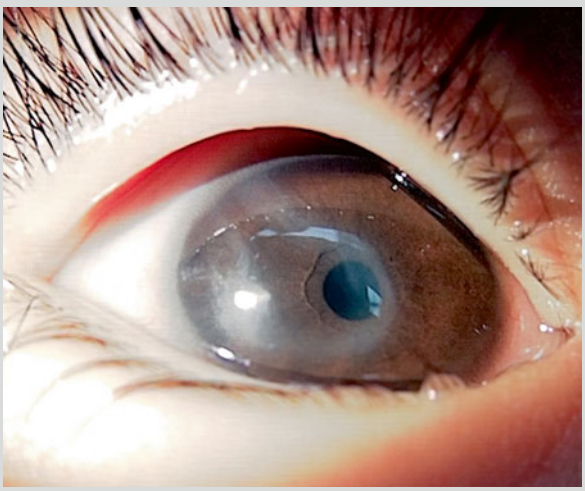

Fig. 42.3 Anterior segment photograph obtained using the Lytro® camera. Photograph demonstrates Haab striae involving the visual axis, resulting in amblyopia

Case 4

History/presentation: an 8-year-old girl with a history of infantile-onset PCG diagnosed at age 7 months. She is status post nasal and temporal goniotomies in both eyes at age 7 and 8 months with excellent response. She has been followed closely over the years, and medical therapy with combination of the dorzolamide/timolol was added for elevated IOP at age 6 years, with excellent IOP response. In the past year, her IOP in the left eye was noted to increase from her baseline 14–15 mmHg to 25 mmHg necessitating the addition of latanoprost and brimonidine. She proceeded to show mild progression of the cup-to-disc ratio to 0.4 from her 0.25 baseline in the left eye. The optic nerve change was confirmed on stereoscopic photographs of her optic nerves from 2 years prior.

Additional key examination findings:
Visual acuity with correction:
OD: 20/20
OS: 20/20
Glasses:
OD: −1.50 + 0.75 × 080
OS: −2.00 + 1.00 × 100
IOP obtained using Goldmann applanation tonometry (GAT):
OD: 14 mmHg
OS: 24 mmHg
Gonioscopy:
OD: Open clefts in the right eye from her previous goniotomy surgeries
OS: Closed clefts from previous goniotomy surgeries

Management options:
- Addition of systemic acetazolamide
- Trabeculectomy with mitomycin C
- Placement of a glaucoma drainage device (GDD)

Management: Trabeculectomy with mitomycin C to the left eye.

Interval history (2 months later): Following revision of the trabeculectomy, the measured IOP in the left eye was 14–15 mmHg without the use of topical medications.

Clinical Synopsis

This patient did well with controlled IOP in both eyes for almost 8 years after angle surgery for infantile-onset PCG, before she needed further surgical intervention in her left eye. This case emphasizes the need for long-term, careful follow-up of all PCG patients, even after initially successful surgery. PCG is often managed with a combination of medical and surgical therapies. The decision was made to proceed with a trabeculectomy with mitomycin C [15–17], following a detailed discussion with her parents; however, implantation of the glaucoma drainage device would also have been a suitable surgical approach in this patient case as well [18–22].

Case 5

Past medical history and presentation: an 8-year-old boy with a history of PCG, both eyes, being referred for elevated IOP of 48 mmHg, left eye. The patient has had multiple surgeries for glaucoma in the past.

Surgical history: Right eye—five previous surgeries—one angle surgery, two combined angle and filtering surgery, cataract surgery, and implantation of a GDD with progression of glaucoma to light perception (LP) vision. Left eye—three previous glaucoma surgeries—two combined angle and filtering surgery (trabeculotomy-ectomy) and one trabeculectomy with mitomycin C.

Interval history: In the past 6 weeks, bleb-related endophthalmitis (secondary to a leak from the previous trabeculectomy site) of the left eye now s/p vitrectomy with intravitreal fortified antibiotic injections. Past 2–3 weeks: Increasing IOP left eye, not responding to topical dorzolamide 2 %/timolol 0.5 % combination, and oral acetazolamide, prompting referral.

At presentation:

Key examination findings:
Visual acuity (uncorrected): Patient did not have refractive correction at presentation.
OD: Light perception (LP) in the right eye (baseline for several years)
OS: 20/100 with effort left eye
IOP obtained using Goldmann applanation tonometry (GAT) in a very cooperative patient:
OD: 8 mmHg
OS: 41 mmHg
Anterior segment examination (table top slit lamp):
OD: White and quiet conjunctiva, with a moderate-sized bleb overlying the superotemporal plate;

(continued)

dense band keratopathy of the cornea; deep and quiet anterior chamber; surgically altered with iridectomy; and pseudophakia with dense posterior capsular opacification

OS: Trace + conjunctival injection with a flat bleb superonasally, marked conjunctival scarring from 0900 to 0500; cornea demonstrated superior and inferior Haab striae circumferential with the limbus; anterior chamber was deep with only one cell per high-power field; iris was surgically altered with iridectomies; lens demonstrated faint amount of anterior capsular pigment.

Posterior segment (table top slit lamp and indirect ophthalmoscopy):

OD: No view, right eye secondary to the band keratopathy and the posterior capsular opacification (B-scan confirms clear vitreous, flat retina, no masses)

OS: Rare cells in the anterior vitreous and pigmentary changes of the macula

Optic nerve examination:

OS: Optic disc with inferior thinning and a cup-to-disc (C/D) ratio of 0.70

Gonioscopy:

OD: No view and secondary to band keratopathy

OS: Open to anterior trabecular meshwork (TM) with peripheral anterior synechiae (PAS) scattered for 360°

Central corneal thickness (CCT):

OD: 682 μm

OS: 582 μm

Cycloplegic retinoscopy:

OS: −3.50 sphere

Optical coherence tomography (OCT) of the retinal nerve fiber layer (RNFL):

OS: Inferior thinning and average thickness of 75 μm

Automated visual field (AVF): Unreliable, high false negatives and positives. Total depression.

Baseline optic nerve photographs obtained. Limited quality given the media.

Management: Interim plan—change acetazolamide from immediate release formulation to sustained release formulation to prevent dramatic IOP changes. Add brimonidine three times daily to the left eye and continue other medications. Start refractive correction with glasses. Discuss monocular precautions.

Definitive plan: EUA and Placement of glaucoma drainage device in the inferonasal quadrant of the left eye

Key examination findings at EUA:

IOP obtained using Tonopen®:

OD: 12 mmHg

OS: 34 mmHg

Axial length:

OS: 32 mm

Interval history (postoperative month 1):

Visual acuity with his refractive correction:

OD: LP

OS: 20/60

IOP obtained using GAT:

OD: 24 mmHg

OS: 11 mmHg

Interval history (postoperative months 2–7): IOP increased in both eyes necessitating the addition of dorzolamide/timolol bid, brimonidine bid, and latanoprost qhs.

Key examination findings at postoperative month 7:

Visual acuity:

OD: LP

OS: 20/60

Anterior segment examination (table top slit lamp):

OD: Unchanged from baseline

OS: Inferonasal tube in excellent position with no corneal tube touch, and good bleb noted inferonasally (confirmed using B-scan)

IOP obtained using GAT:

OD: 25 mmHg

OS: 21 mmHg

C/D ratio obtained using the Superfield lens:

OS: 0.75

AVF:

OS: Reliable. Superior > inferior arcuate defects (close to central vision)

OCT RNFL:

OS: Average thickness of 68 μm

Management options:

- Addition of systemic acetazolamide
- Placement of a second GDD
- Diode cyclophotocoagulation

Management: Placement of a second GDD in the superotemporal quadrant

(continued)

Clinical Synopsis

This case is that of an advanced PCG. There are several points this case highlights:

1. It is important to fully educate parents on the expectations of the disease process, and it is important to do that often, especially given the progression of the PCG in this patient.
2. The use of diagnostic testing for management of glaucoma in pediatric patients is demonstrated. The OCT, AVF, and ultrasounds were used in this case. It should be noted that normative data in children has only been recently acquired in the past decade. In the case where one does not have normative data, the child can serve as his/her own control, and baseline imaging can be used for comparison at a future date [42–44].
3. It is important to perform an ultrasound of a non-seeing eye at least once every 1–2 years, if you have no view to the posterior pole, to ensure that there are no masses.
4. Always educate the parents on the need for compliance with all medications. This patient was on a lot of medications, which were needed for IOP control. However, compliance with multiple medications can be difficult over time.
5. In cases of refractory glaucoma, placement of glaucoma drainage device is recommended [19–22]. The first tube was placed inferonasally where there was the least amount of scarring; this also provided the advantage of not placing the tube in close proximity to the location of the patient's recent trabeculectomy site, which was the nidus for the endophthalmitis. The second tube was placed in the superotemporal quadrant with care taken given the marked amount of scarring in this area during surgery.
6. In the inferonasal quadrant, the bleb over the plate may be difficult to visualize; in this scenario, one can use the B-scan with the probe placed 180° tangentially away from the plate to visualize the fluid overlying the plate. See Fig. 42.4.

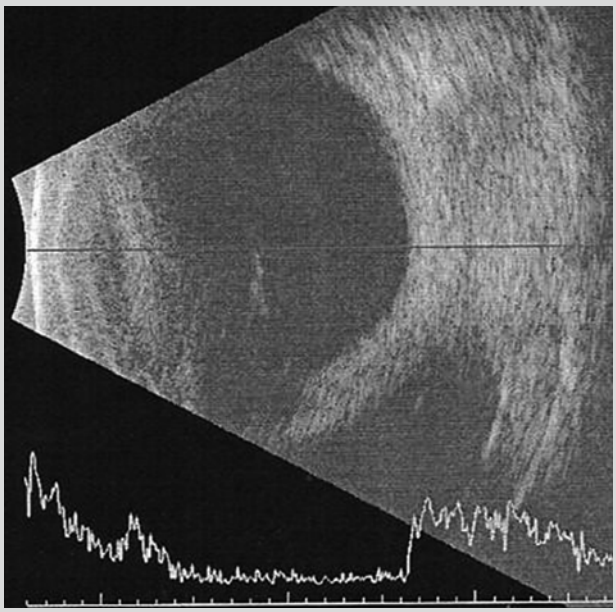

Fig. 42.4 B-scan ultrasound image of an inferonasal Ahmed valve demonstrating fluid overlying the plate. Given the location of the valve, this amount of fluid was not easily appreciated clinically

7. With the discontinuation of systemic medications, the IOP in the right eye increased. Topical medications were initiated for comfort purposes and were successful. If this was not successful, a limited application of cycloablation could have been considered in the right eye. In this patient's case, if cycloablation is considered, care should be taken to avoid excessive treatment, given the miniscule but probably real risk of sympathetic ophthalmia. This child has undergone five previous surgeries in the right eye, and cycloablation has been reported to increase the risk of sympathetic ophthalmia in the fellow eye [45–47].

See Fig. 42.5 for a suggested approach to the management of PCG.

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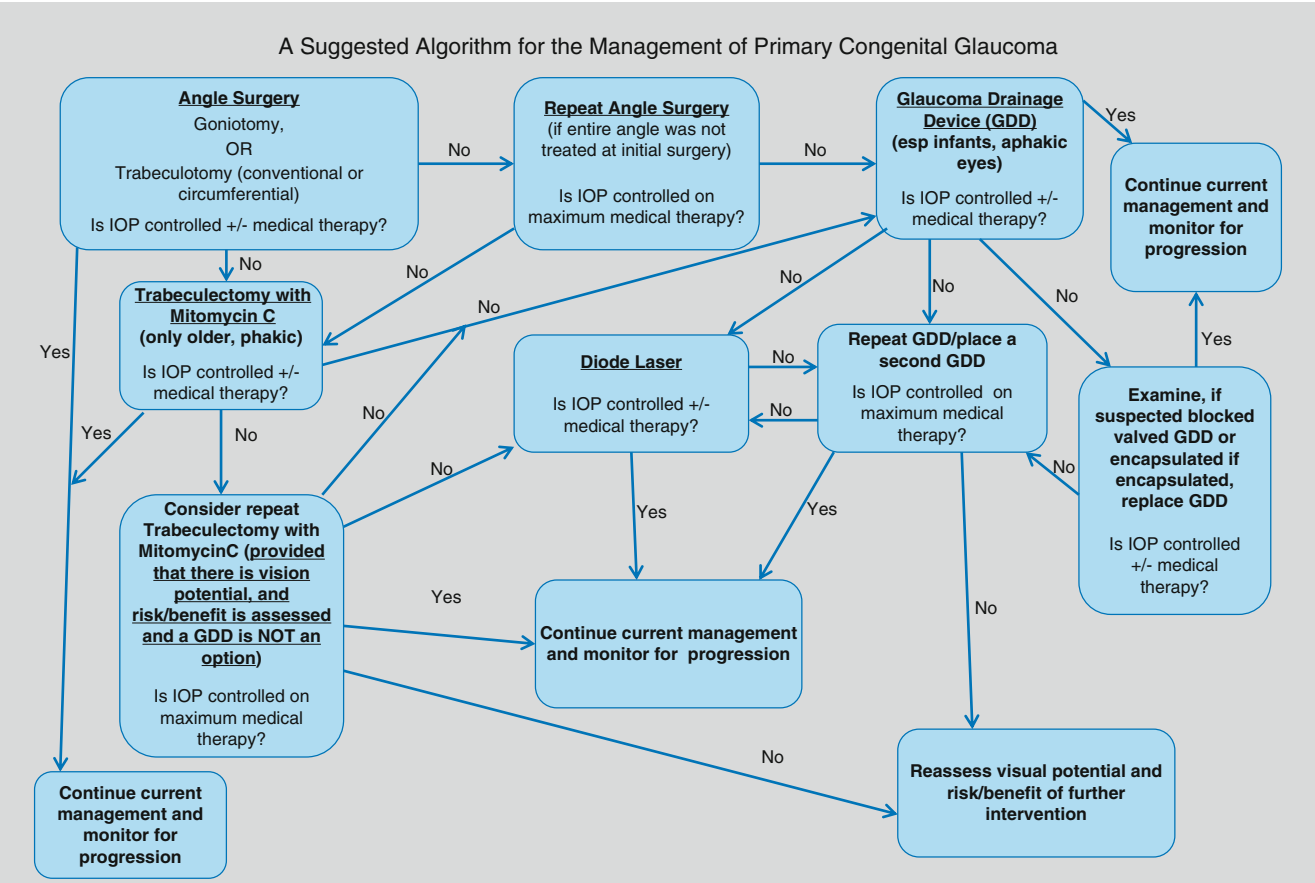

Fig. 42.5 Algorithm for management of PCG. The algorithm was modified and reproduced, with permission, from *Childhood Glaucoma*, 9th Consensus Report of the World Glaucoma Association. Kugler Publications, Amsterdam, The Netherlands, 2013

Juvenile Open-Angle Glaucoma

Please refer to Chap. 44 for a detailed discussion on juvenile open-angle glaucoma.

Secondary Childhood Glaucomas

The rest of this chapter will address secondary causes of glaucoma in children. While information on secondary childhood glaucoma is given in various other chapters in this book, we will present several cases that illustrate their diagnosis and management and provide commentary on each case.

Case Studies of Secondary Childhood Glaucoma

Case 6

Clinical history: a 16-year-old with known Sturge-Weber syndrome presents for an ophthalmic examination. There are no concerns. Past medical history is significant for seizures that are controlled on antiepileptics and a stroke in childhood with a mild left lower extremity deficit that was treated with physical therapy.

Key clinical findings:
Visual acuity (uncorrected):
OU: 20/20
External examination: Left V1 distribution of vascular malformation involving the upper eyelid
Pupils: 1+ afferent pupillary defect, left eye

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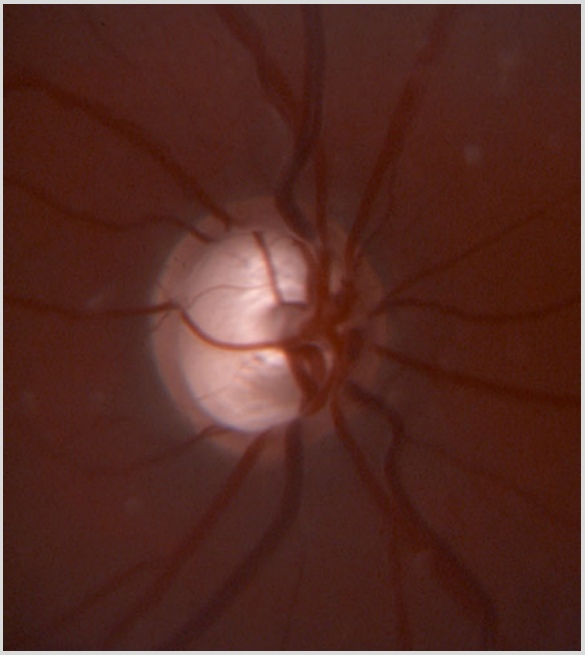

Fig. 42.6 Optic disc photograph demonstrating cupping of the optic nerve and choroidal hemangioma in a child with Sturge-Weber-associated glaucoma. Note the darker fundus pigmentation secondary to the choroidal hemangioma

Anterior segment examination (table top slit lamp):
OU: WNL with no Haab striae or corneal enlargement with the exception of prominent episcleral and scleral vessels, left eye
Posterior segment examination (table top slit lamp and indirect ophthalmoscopy):
OD: WNL
OS: Choroidal hemangioma
C/D ratio:
OD: 0.1
OS: 0.85 (see Fig. 42.6)
IOP obtained using GAT:
OD: 11 mmHg
OS: 38 mmHg
Gonioscopy:
OU: Open to ciliary body band
AVF:
OD: No defects
OS: Prominent superior and inferior arcuate defects sparing the central vision
Baseline OCT RNFL:
OD: 100 μm
OS: 60 μm with thinning superiorly and inferiorly

Management options:
- Medical management
- Surgical management: Placement of a GDD

Management: Start topical medical therapy with dorzolamide/timolol, latanoprost, and brimonidine.

Interval history (5 weeks later): Tolerating medications well

Key examination findings:
IOP obtained using GAT: OS, 26 mmHg

Management: Placement of glaucoma drainage device that was ligated to prevent sudden decrease in IOP following placement. Continue current medications while awaiting dissolution of suture ligating tube.

Interval history (10 weeks later): Glaucoma drainage valve is open, and patient with steroid response while on topical steroids for postoperative care. IOP increased to 30 mmHg on topical steroids and is now 13 mmHg on latanoprost alone.

Interval history (1 year): IOP slowly increased to 18 mmHg and topical dorzolamide/timolol was added with IOP of 10–12 mmHg. AVF stable, OCT RNFL stable, and optic nerve stable.

Clinical Synopsis

Diagnosis is *glaucoma associated with non-acquired systemic disease/syndrome*, in this case Sturge-Weber-associated glaucoma, using the new classification scheme (Fig. 42.1). Major clinical features of Sturge-Weber syndrome (encephalotrigeminal angiomatosis) include clinical findings of nevus flammeus (port-wine stain) of the face, intracranial calcifications, choroidal hemangiomas, and glaucoma. Sturge-Weber-associated glaucoma has a bimodal distribution—at birth and later in childhood or early adulthood [48, 49]. In this case, the anterior segment findings (no corneal enlargement or Haab striae) confirmed that there was no previous birth/childhood presentation of glaucoma that self-arrested. Sturge-Weber glaucoma at birth is usually best treated with angle surgery (and usually supplemented by medications as well), as it is thought that elevated IOP is due, at least in part, to developmental abnormalities of the anterior chamber angle (similar in presentation to primary congenital glaucoma) [48, 49]. Later in childhood and adulthood, elevated IOP is attributed mainly to elevated episcleral venous pressure and is treated first medically. If refractory to medical treatment, outflow surgery is recommended, usually the implantation of a glaucoma drainage device (GDD) [48–50], although some surgeons do perform trabeculectomy, the risks of choroidal hemangioma-related misadventures such as choroidal hemorrhage notwithstanding.

Case 7

Clinical history: a 10-year-old male patient presents for a one-day Emergency Department follow-up of a corneal abrasion of the left eye, sustained while playing soccer with friends. He reports that his eye feels better today. Past medical history and family history are noncontributory.

Key examination findings:
Visual acuity:
OD: 20/20
OS: 20/25
Anterior segment examination (table top slit lamp):
OU: Cornea: prominent posterior embryotoxon with iridocorneal adhesions located nasally and temporally in both eyes, otherwise clear right cornea, and a few punctate epithelial erosions on the left cornea; Anterior chamber: deep and quiet, both eyes; Iris: blue irises with hypoplasia, iridocorneal adhesions, and inferonasally displaced pupils. There was an anteriorly displaced Schwalbe's line in both eyes.
C/d ratio obtained using a Superfield lens:
OU: 0.50
IOP obtained using GAT:
OD: 20 mmHg
OS: 20 mmHg
Gonioscopy:
OU: Unable to tolerate
Baseline OCT RNFL: No areas of thinning
Baseline optic nerve photos obtained
Baseline AVF: Limited reliability, with nonspecific areas of depression
Both birth parents were present, and neither one demonstrated any of the above noted findings. A review of systems and limited systemic examination were unrevealing—in particular there were no malar hypoplasia, no identifiable dental issues, no known cardiac or genitourinary abnormalities per history, and no redundant periumbilical skin.

Management: Explained that the corneal abrasion is healed. Explained the other noted findings of anterior segment dysgenesis, and the association with glaucoma as well as systemic associations. With a negative family history and with a negative review of systems and medical history, a genetics referral was recommended to ensure no systemic manifestations.

Interim history (2 months later): Genetics evaluation—this likely represents a sporadic mutation given the negative family history or less likely an autosomal recessive inheritance. The child's complete and thorough examination did not demonstrate any other systemic anomalies related to the ocular findings.
Management: Given the findings, the child has a 50 % risk of glaucoma throughout his life. Careful interval follow-up is recommended.

Interim history (4 months later):
Key examination findings:
IOP obtained using GAT:
OU: 20 mmHg
Optic nerves are stable compared with stereoscopic photos obtained at the last examination.

Management: Discussed the risk of glaucoma again with family and the need for continued surveillance into adulthood. The patient will be examined in 4 months; gonioscopy will be performed when child is able to tolerate the examination. If the C/D is stable and the IOP stable at the next appointment, we will consider 6-month appointments.

Clinical Synopsis

This child's presentation is consistent with an *Axenfeld-Rieger* (*AR*) *spectrum disorder*. This carries a lifetime 50 % risk of glaucoma necessitating the need for lifelong screening [51–53]. The patient is at an age where he can participate in the clinical discussions; however, this will be repeated to him several times. If no glaucoma has developed while he is still under the care of a pediatric ophthalmologist, he will fully understand the need for continued follow-up as an adult. Using the classification system (Fig. 42.1), this secondary glaucoma is a *glaucoma associated with non-acquired ocular anomalies*. It is important to rule out systemic conditions associated with these findings. In this patient, there were no obvious systemic findings during the ophthalmology clinic evaluation. A formal genetics evaluation with a detailed physical examination is necessary. Examination of the family often helps in the diagnosis. AR is predominantly inherited in an autosomal dominant manner [51–53], but there is marked variance in the expressed phenotypes, raising the need to examine family members, as even they may not be aware of the changes. This case most likely represents a sporadic mutation. If this patient progresses to develop glaucoma, the first-line treatment would be medical. This patient has not tolerated gonioscopy at this time; however, given the marked iridocorneal adhesions, it is certain that angle surgery will not be recommended for this patient, in the event that surgical intervention is needed. The authors would recommend glaucoma-filtering surgery or placement of a GDD. A more extensive discussion of Axenfeld-Rieger spectrum disorder can be found in Chap. 14.

Case 8

Clinical history: a 5-year-old girl who presented from her pediatrician urgently for evaluation of a two-day history of left eye pain associated with a reported decrease in vision, nausea, and emesis.

Key examination findings:
Child in moderate discomfort in father's arms.
Visual acuity: A vision is not obtainable given the patient's discomfort. Moderate photophobia as patient groans to any light.
IOP obtained by palpation:
OD: Soft
OS: Hard
Anterior segment examination (portable slit lamp):
OD: Grossly WNL
OS: Limited views demonstrated a cloudy cornea of the left eye and a shallow anterior chamber.
B-scan:
OS: Demonstrated a clear vitreous and a flat retina and choroid

Management: The decision was made to proceed with an immediate EUA, and the child had refused any food or liquids in the past 18 h and was cleared by anesthesia.

Key examination findings at the EUA:
IOP obtained using Tonopen® at induction:
OD: 14 mmHg
OS: 45 mmHg
Anterior segment examination (portable slit lamp):
OD: WNL
OS: Lids demonstrated some superficial abrasions—likely self-inflicted; conjunctiva: 3+ injection; cornea with 2+ edema with microcystic epithelial changes; anterior chamber: shallow in the left eye with a fibrinous membrane over the pupil. The cornea of the right eye was examined again and no findings to suggest previous chronic inflammation such as keratic precipitates (KP) were appreciated.
CCT:
OD: 580 μm
OS: 750 μm
Gonioscopy:
OD: Open to scleral spur
OS: No angle structures identified
Ultrasound biomicroscopy:
OD: WNL
OS: Confirmed the fibrinous membrane, normal-appearing lens, and normal-appearing ciliary body processes

Management: The patient was dilated with atropine intraoperatively and given systemic acetazolamide.

Key examination findings (intraoperative):
Anterior segment examination (portable slit lamp):
OS: The cornea was noted to clear as the pupil dilated. The fibrinous membrane occluding the pupil was released with the pharmacologic dilation for approximately 180°, and the anterior chamber was noted to visibly deepen. The pupil dilated, and posterior synechiae for 4 clock hours remained.
Posterior segment examination (indirect ophthalmoscopy):
OU: Examination was within normal limits, without any masses, or retinal lesions to suggest any acute infectious processes. Scleral depression did not demonstrate any snow balls or snow banks, and the vitreous was clear in both eyes.
C/D ratio using a 20D lens:
OD: 0.10
OS: 0.15

Management: The working diagnosis at this time was an inflammatory condition causing pupillary block and acute angle closure glaucoma. Diagnostic blood work was obtained including a complete blood count (CBC), basic metabolic panel with differential, antinuclear antibody (ANA), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), human leukocyte antigen B27 (HLA-B27), and a urinalysis. Given the fibrinous membrane and no evidence of an infectious process, an injection of subconjunctival dexamethasone was given. Postoperative medications: prednisolone acetate (PF) six times daily, dorzolamide/timolol twice daily, and atropine twice daily, to the left eye.

Interval history (postoperative day #1): No subjective complaints of pain. Parents report that she opened both eyes later in the evening of the postoperative day and tolerated all meals.

Key examination findings:
Visual acuity:
OD: 20/25
OS: 20/40
IOP obtained using Tonopen® in a cooperative child:
OD: 12 mmHg
OS: 17 mmHg
Anterior segment examination (table top slit lamp):
OD: WNL and no anterior segment cells
OS: Clear cornea; anterior chamber: deep with retracted fibrinous membrane and 2+ cells (16–25 cells/high-power field (HPF))

(continued)

Management: Continue current topical medical regimen. Rheumatology referral placed.

Interval history (2 weeks later): ANA-positive oligoarticular juvenile idiopathic arthritis (JIA) diagnosed.

Interval history (3 months later): Uveitis responded to topical therapy; however, arthritic disease progressed. Patient was started on methotrexate (MTX). She was tapered off of all topical medications.

Interval history (2 months later): She continues to have joint complaints.

Key examination findings:
Visual acuity:
OU: 20/20
IOP obtained using Tonopen®:
OD: 16 mmHg
OS: 35 mmHg
Anterior segment examination (table top slit lamp):
OD: Anterior chamber 0.5+ cells (1–5/HPF)
OS: 1+ cells (6–15/HPF)

Management: Patient was started on topical PF to both eyes (twice daily OD, four times daily OS) and started on dorzolamide/timolol to the left eye. Discussed finding with rheumatology, and adalimumab was started.

Interval history (10 weeks later): Joint disease controlled now

Key clinical findings:
Visual acuity:
OD: 20/20
OS: 20/25
Anterior segment examination (table top slit lamp):
OD: WNL with no inflammation
OS: Trace anterior chamber cells 0.5 cells (2/HPF)
IOP obtained using Tonopen®:
OD: 12 mmHg
OS: 28 mmHg
C/D ratio measured using the Superfield lens:
OD: 0.10
OS: 0.25

Management options:
- Addition of topical apraclonidine (with caution to parents)
- Addition of systemic acetazolamide
- Surgical intervention

Management: Goniotomy to the left eye (nasal angle only)

Interval history (1 month postoperative): Doing well on topical dorzolamide/timolol in the left eye only
Visual acuity:
OD: 20/20
OS: 20/20
IOP obtained using GAT:
OD: 13 mmHg
OS: 15 mmHg
Anterior segment examination (table top slit lamp):
OU: Anterior chamber—deep and quiet
C/d ratio measured using the Superfield lens:
OD: 0.10
OS: 0.25

Clinical Synopsis

Uveitic glaucoma can often have different clinical presentations [4]. In this case, it presented as an acute angle glaucoma secondary to the fibrin membrane. JIA is the most commonly identified cause of uveitis in children. In this patient, the glaucoma was initially secondary to an acutely closed angle; however, later in the course of her disease, there was an inflammatory-related increased resistance to outflow [4, 54, 55]. Treatment with topical steroids often compounds the elevation in the IOP. The role of systemic steroid-sparing immune-modulating agents is very important, as steroid-related IOP elevation cannot be ruled out until uveitis is controlled and topical steroids discontinued [4, 54]. Management of uveitic glaucoma must address the etiology of the uveitis first. However, this is oftentimes not sufficient. Medical and surgical therapies are often needed to control the glaucoma. Angle surgery has been demonstrated to be effective in the control of uveitic glaucoma. Placement of GDDs also controls uveitic glaucoma [54, 56, 57]. In the above case, if the glaucoma was not controlled with the goniotomy, a repeat goniotomy would have been considered, versus placement of a GDD, especially if the angle was largely open (versus with many peripheral anterior synechiae present) and the eye phakic [58]. Using the classification scheme (Fig. 42.1), uveitic glaucoma is a *glaucoma associated with acquired conditions*.

Case 9

Clinical presentation: 6-year-old African-American boy presents to the Emergency Department following an unwitnessed fight with his younger brother. He complains of right eye pain.

Key examination findings:
Visual acuity:
OD: Hand motion (HM)
OS: 20/25
Anterior segment examination (portable slit lamp):
OD: Cornea clear; anterior chamber: 5 mm layered hyphema with 4+ free-floating red blood cells (RBCs) and no view to the posterior pole
OS: WNL
IOP obtained using Icare®:
OD: 60 mmHg
OS: 18 mmHg
B-scan:
OD: Intact posterior segment of the eye, clear vitreous, and flat retina.

Management: Sickle cell prep obtained in the Emergency Department. Immediate admission to the hospital for nausea and pain control. Start topical timolol 0.5 %, atropine 1 %, and prednisolone 1 % drops. Other medications withheld pending results of sickle cell prep.

Interval history (1 h): Sickle prep is positive for hemoglobin C and hemoglobin S. IOP of 50 mmHg. Patient continues with eye pain.

Interval history (4 h): Patient continues with elevated IOP and pain (improved), and nausea is controlled by intravenous antiemetics. IOP of 50 mmHg.

Management: Anterior chamber washout, right eye.

Interval history (postoperative day #1):
Key examination findings:
Visual acuity:
OD: 20/50
OS: 20/20
IOP obtained using Tonopen®:
OD: 10 mmHg
OS: 16 mmHg
Anterior segment examination (table top slit lamp):
OD: Anterior chamber with 2+ RBCs
OS: WNL
C/D ratio measured using Superfield lens:
OU: 0.25

Management: Topical PF four times daily, atropine two times daily, right eye, strict bed rest, head of bed elevated 30°, and eye shield at all times

Interval history (POD#2): Mother reports that he was "very busy" when he got home.

Key examination findings:
Visual acuity:
OD: 20/70
OS: 20/20
IOP obtained using Tonopen®:
OD: 12 mmHg
OS: 16 mmHg
Anterior segment examination (table top slit lamp):
OD: Anterior chamber, deep with 3 mm layered hyphema
OS: WNL

Management: Emphasized the need for strict bed rest to mother. She verbalizes understanding.

Interval history (POD#3–10): Patient continued to be very active when mother was not watching and rebled on two occasions. On POD#11, despite maximum medical therapy, his IOP increased to 40 mmHg, in the right eye.

Management options:
- Placement of GDD
- Repeat AC washout
- Combination of both procedures

Management: Urgent placement of a GDD (valved) in the right eye with an anterior chamber washout

Interval history (postoperative day #1 s/p GDD—POD#30): IOP remained controlled and the hyphema cleared.

Key examination findings: POD#30
Visual acuity:
OD: 20/25
OS: 20/20
IOP obtained using Tonopen®:
OD: 12 mmHg
OS: 13 mmHg
Anterior segment examination (table top slit lamp):
OD: AC was deep and clear, and lens clear.
C/D ratio measured using Superfield lens:
OD: 0.25
Gonioscopy:
OD: Open to ciliary body band with three quadrants of angle recession with increased TM pigment
OS: Open to ciliary body band

(continued)

Clinical Synopsis

Acute glaucoma in the setting of a hyphema. This is another example of a *glaucoma associated with acquired conditions*. This hyphema was complicated by the sickle cell disease, and standard hyphema protocols were not effective in the management of the hyphema [59–61]. In sickle cell disease, the sickling of the cells often leads to large elevations in IOP. It is important to screen patients for sickle cell in patients with ethnicities at risk for hemoglobinopathies. Management of sickle cell-related hyphema requires urgent surgical intervention if the IOP remains elevated, as elevated IOP can lead to optic nerve compromise (even modest elevations can compromise the optic nerve in sickle cell or SC disease). Medical management is often limited as carbonic anhydrase inhibitors (CAIs) precipitate sickling, alpha-agonists are contraindicated in children and they can cause vasoconstriction, and prostaglandins can promote inflammation. Early surgical intervention is recommended to prevent optic nerve damage [4, 59]. The decision to place a GDD versus a simple washout was made given his recurrent and very high IOPs in the setting of multiple rebleeds. The risk of repeated high IOPs with fairly rapid optic nerve damage, given the sickle cell disease, was very high in this particular case. A simple washout may have been effective; however, this particular patient may have required multiple washout procedures. In hindsight, in families where compliance with the activity restrictions and/or follow-up cannot be assured, admission to the hospital with careful observation by nursing staff may be needed.

Case 10

Clinical history: an 8-month-old child presents for evaluation of white spot in the right eye associated with an esotropia. More detailed history revealed that the parents had noted the white change at age 3 months; however, due to a number of factors, the child did not present for care till age 8 months.

Key examination findings:

Visual acuity:

OD: Uncentral, unsteady, and unmaintained (uCuSuM)

OS: CSM

Anterior segment examination (portable slit lamp):

OD: Immediately posterior to the lens was a white dome appearing mass that was found to occupy the anterior half of the vitreous cavity. The anterior chamber was narrow secondary to the change but not occluded.

OS: WNL

Posterior segment examination (indirect ophthalmoscopy):

OD: Dome-shaped white-colored lesion occupying one third of the vitreous cavity

OS: WNL

B-scan ultrasound:

OD: Dome-shaped hyperechoic mass consistent with the clinic examination. No other focus was noted.

IOP obtained using Icare®:

OD: 24 mmHg

OS: 12 mmHg

Detailed family history was negative for retinoblastoma or other known tumors.

Interval history (1 day): A diagnosis of unilateral retinoblastoma was made. Patient was evaluated by Ocular Oncology and Pediatric Hematology and Oncology. Management options of enucleation versus intra-arterial chemotherapy were discussed. The family wanted to do their best to keep the eye and wanted to proceed with intra-arterial chemotherapy. Systemic work-up demonstrated that this was confined to the eye only.

Interval history (4 days): Patient presents following 12 h of pain, nausea, and emesis and no oral intake.

Key examination findings: Injected right eye with a flat anterior chamber and elevated IOP of 45 mmHg.

Management: Immediate enucleation, right eye

Clinical Synopsis

This is a case of an acquired glaucoma in the setting of a tumor that resulted in an acute angle closure. Chapter 37 discusses management of retinoblastomas. Given the rapid change in the child's baseline, the concern for rapid growth of the tumor with potential for systemic spread, the eye was enucleated. The child returned to her normal baseline and has done well since. This is another example of a *glaucoma associated with acquired conditions*.

Surgical Complications of Glaucoma Surgeries

Pediatric glaucoma surgery is considered, by many, to be very challenging. There are several factors that can positively and negatively impact the success of surgery, and potential complications are discussed in detail with the family prior to intervention. The chances of success decrease with subsequent surgical interventions, so it is important for the surgeon to be cognizant of the potential complications and to judiciously and diligently monitor for early and late complications.

Angle surgery is the primary intervention for PCG. When performing goniotomy (traditional), visibility of the angle and its structures is of utmost importance. Preoperative antiglaucoma medications and hypertonic sodium chloride can enhance corneal clarity, and some surgeons (authors excepted) will debride the corneal epithelium to enhance the angle view. Knowledge of the anatomy of the angle is important to avoid incising the incorrect anatomical landmark [6, 7]. It is important to obtain adequate miosis, so as to protect the lens, and thus not create an iatrogenic cataract. If needed, especially in cases where an EUA was performed to establish the diagnosis, intracameral uses of acetylcholine to aid pupillary constriction are recommended. The authors would recommend deferring dilation, when possible, prior to angle surgery. In the WGA consensus report, some surgeons utilize viscoelastic or an anterior chamber infusion to stabilize the anterior chamber depth and minimize risk of damage to anterior segment structures. Using a 25-gauge needle for the entry and goniosurgery will also maintain the chamber without additional maneuvers [4]. If a viscoelastic device is used, the surgeon must take meticulous care to ensure this is removed to avoid an IOP spike. When the knife or needle that was used for the goniotomy is withdrawn from the eye, care should be taken to ensure that the edge does not engage with the cornea endothelium, the iris, or the lens where it can cause damage to those structures. All corneal incisions must be closed with sutures to ensure no wound leaks and reduce the risk of infection.

Trabeculotomy does not require a clear cornea; however, the surgeon should consider the location of the conjunctival and scleral flap carefully, as scarring of conjunctiva may be of significance if the child needs further surgery, which is often the case in PCG [4]. Care must be taken to obtain careful hemostasis of the scleral bed, so that when the surgeon is carefully dissecting for the location of the Schlemm canal, the field is clear for the proper identification of the egress of aqueous, which is often admixed with some heme. Care should be taken to be sure the Schlemm canal has been positively identified, since standard trabeculotome-trabeculotomy can create a false passage into the cornea or beneath the iris root, while the Prolene suture or illuminated microcatheter can be directed into the suprachoroidal space and hence posteriorly beneath the retina [62, 63] or too anteriorly into the anterior chamber; the Descemet detachment can sometimes occur when the suture or catheter is pulled forcefully, if care is not taken [4]. In the circumferential trabeculotomy, especially in cases using an illuminated microcatheter, the authors have found that care should be taken not to pull the "loop" of catheter forcefully out from the anterior chamber, as the last 30° of the canal is opened, as this may result in the incarceration of the iris in the catheter material, and this subsequently leads to prolapse of iris material. The anterior chamber must be maintained when the Schlemm canal is being opened, so as to avoid iatrogenic damage of the lens or excessive reflux hyphema with anterior chamber shallowing and IOP reduction [4]. The scleral flap must be closed securely, to avoid the inadvertent creation of a trabeculectomy. Even in experienced hands, the location of the Schlemm canal can be difficult to locate in some eyes, especially with buphthalmos.

Filtering surgery using trabeculectomy in children always carries the risk of failure from scarring given the aggressive inflammatory response children mount. This can be countered with the use of antimetabolite agents but at the cost of increased risk of thin, avascular bleb formation, with later bleb leak and bleb-related infection [15]. The patient and the parents must be aware of these vision-threatening risks and report immediately if any suggestive symptoms or signs develop in filtered eyes.

Glaucoma drainage devices are frequently used in children. Proper consideration should be given preoperatively to the intended location, type, and size of the device to be placed, as well as to plan "B" and later plans should the initial surgery prove inadequate to control refractory cases. For example, if it is anticipated that the child will need more than one device, the surgeon should consider placing the device with a smaller surface area in a quadrant with less space (i.e., inferonasal), thus allowing the placement of the larger device in a more accessible quadrant such as the superotemporal quadrant. In addition, the location of the tube inside the eye is of critical importance. Care must be taken to avoid endothelial injury, iris trauma, or lenticular damage. The tube can also be occluded by iris tissue, as well as by residual lenticular material in the aphakic eye, and more commonly by vitreous, in the aphakic eye [4, 19, 21]. In the above circumstances, there is a risk for a sudden elevation in the IOP and in the latter for a retinal detachment given the potential traction on the retina. The surgeon must also monitor for complications of hypotony, tube migration either anteriorly or posteriorly, erosion of the tube or plate [4, 19–22], and encapsulation (excessive thickening) of the bleb wall around the reservoir or of fibrovascular tissue ingrowth into the Ahmed valve chamber [23]. The plate of the GDD should be well secured to the globe, and the Baerveldt plate should be placed posterior to the rectus

muscles to avoid anterior migration of the plate, although some surgeons intentionally place these anterior to the rectus muscles [22]. Another complication is strabismus, which is often related to limitation of eye movement in the presence of a glaucoma drainage device and surrounding bleb [64].

Complications that the surgeon can encounter when using cycloablation include inflammation, hypotony (as multiple treatment is often needed), cataract formation, phthisis, conjunctival scarring, scleromalacia, retinal detachment, and sympathetic ophthalmia, and there is risk of vision loss [24, 25, 45–47].

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Aphakic/Pseudophakic Glaucoma

43

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Abstract

Aphakic/pseudophakic glaucoma is a secondary glaucoma that occurs following the removal of a cataract. It is a serious consequence of cataract surgery in some patients and requires early diagnosis and prompt treatment. The presence of glaucoma may significantly impede visual rehabilitation of the affected eye, and if left untreated, can lead to significant vision loss. This chapter will discuss the timing of the onset of aphakic/pseudophakic glaucoma, diagnostic criteria, risk factors, and the medical and surgical management of this condition.

Keywords

Glaucoma • Intraocular pressure • Aphakia • Aphakic glaucoma • Pseudophakia • Pseudophakic glaucoma • Trabeculotomy • Glaucoma drainage device • Cataract surgery

Definition of Aphakic/Pseudophakic Glaucoma

The recent updated classification of childhood glaucomas was presented in Chap. 42 [1], and the importance of prompt recognition and appropriate treatment to prevent vision loss was affirmed. Visually significant cataracts in infants and children require expedited management and removal (see Chap. 19 on Pediatric Cataracts) to prevent vision loss from amblyopia. However, elevated intraocular pressure (IOP) and glaucoma commonly occur following surgery, with higher risk in selected subgroups and incidence rising for years following cataract removal. This type of secondary glaucoma has been termed "glaucoma following removal of childhood cataract" in the new classification system [1], but is also commonly called "aphakic or pseudophakic glaucoma," for eyes without and with an intraocular lens implant (IOL), respectively. We will use the latter terminology in this chapter for brevity and familiarity. This diagnosis is given only if there was no glaucoma present prior to the removal of the cataract [1]. Chapter 42 on childhood glaucomas discusses the diagnostic criteria for glaucoma and glaucoma suspect set forth in the 9th Consensus Report of the World Glaucoma Association [1], and these apply to the aphakic/pseudophakic glaucoma patients as well. Using the World Glaucoma Association (WGA) Consensus [4] criteria, two or more of the following must be met for the diagnosis of glaucoma to be made:

- Intraocular pressure (IOP) >21 mmHg (the examiner makes the final decision on the IOP if measured under anesthesia given the possible effects of anesthesia on the measured IOP).
- Optic disc cupping, cup to disc asymmetry of ≥0.2 when the discs are of similar size, or focal rim narrowing.

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- Corneal findings: Haab striae, corneal edema or diameter ≥11 mm in a newborn, >12 mm in child less than age 1, and >13 mm at any age.
- Progressive myopia or myopic shift coupled with an increase in ocular dimensions outside the range of the dimensions expected for normal growth.
- A reproducible visual field defect that is consistent with a glaucomatous optic disc neuropathy, and no other identified causes for the visual field defect.

The risk of developing aphakic/pseudophakic glaucoma is lifelong, with incidence rising with increase in the duration of time following cataract removal. It is a serious complication following cataract removal, and several studies have reported its incidence and associated risk factors [1–11]. Aphakic/pseudophakic glaucoma has an approximate frequency of 20 % and has a median onset of 5.2 years following cataract removal [3, 5]. Various risk factors have been considered in the development of glaucoma after childhood cataract surgery, including age and corneal size at surgery, type of cataract and associated ocular features such as persistent fetal vasculature (PFV), primary IOL placement versus aphakia, time elapsed since surgery, and need for additional intraocular surgeries being prime among them [2–11]. Of these risk factors, only primary implantation of an IOL is a modifiable risk factor controlled by the surgeon. Published reports have varied in their findings of whether primary implantation of an IOL is protective (or not) against aphakic/pseudophakic glaucoma [5–8]. However, it must be noted that the differing study results are limited by their retrospective nature, varying definitions of glaucoma and glaucoma suspect, varying follow-up times, and the lack of randomization [5–8]. The Infant Aphakia Treatment Study (IATS) was a national, prospective randomized study evaluating treatment of unilateral congenital cataract in infants operated between 1 and 6 months of age, using either aphakic contact lenses (CL) versus primary implantation of an IOL [12, 13]. The IATS provided, for the first time, prospective and randomized data on the risk of glaucoma following removal of a congenital cataract in eyes left aphakic versus those randomized to receive a primary intraocular lens implant; the risk of aphakic/pseudophakic glaucoma was not statistically different between the two groups at 12 months following surgery [3]. The study size was limited, and further analysis of the 5-year IATS data will help to validate this finding.

Management of Aphakic/Pseudophakic Glaucoma

Treatment of aphakic/pseudophakic glaucoma varies and depends on the child's age at the time of diagnosis, the time since cataract removal, as well as the severity of the glaucoma. Prompt diagnosis is imperative. Checking intraocular pressure and a high suspicion level for glaucoma must be part of the routine postoperative care. IOP should be routinely obtained, and other findings of glaucoma should be assessed with regularity in the aphakic/pseudophakic eye. In some practices, this is as often as every 4 months. In some infants, examinations under anesthesia (EUAs) may be indicated in order to properly screen for glaucoma, especially if the child does not allow tonometry in the office setting. Rebound tonometry, which allows for IOP measurements without the use of topical anesthetic, has been found to be well tolerated and to correlate well with Goldmann applanation tonometry [14, 15], although readings are often approximately 2–3 mmHg higher than the latter [14, 15]. It has also been found to reduce the need for frequent examinations under anesthesia [16].

In most aphakic/pseudophakic glaucoma cases, the first-line treatment modality is medical, with surgical intervention if medical treatment fails to control the elevated intraocular pressure. Early diagnosis lends itself to medical treatment; however, if the glaucoma is advanced, surgical treatment may be the first line in order to protect vision.

Medical therapy includes topical medications and systemic medications. Please see Chap. 42, on Childhood Glaucomas, where medical therapy is discussed in more detail.

Surgical treatment options for aphakic/pseudophakic glaucoma include angle surgery (trabeculotomy and goniotomy), placement of a glaucoma drainage device (GDD), trabeculectomy with mitomycin C, and cycloablation of the ciliary processes using diode cyclophotocoagulation (CPC). Studies documenting the success rate of angle surgery for aphakic/pseudophakic glaucoma are limited in number. In one small retrospective study (14 eyes, 11 patients), the success rate was found to be approximately 42.8 % after one angle surgery at 4.7 years, increasing to 57.1 % if angle surgery is repeated [17]. Another study demonstrated only a 16 % success rate in a long-term study of a large number of aphakic patients with a mean follow-up period of 8.6 years [18]. In a subset of refractory aphakic glaucoma patients, the use of a 360° trabeculotomy facilitated by an illuminated micro-catheter has been demonstrated to have reasonable success [19]. Angle surgery tends to have a higher rate of success in younger as compared to older children, and should be performed when the angle is largely open and lacking high peripheral anterior synechiae (PAS). Placement of a GDD is often the surgical treatment option for older children with aphakic/pseudophakic glaucoma and in cases of refractory aphakic/pseudophakic glaucoma [20–23], with one study reporting a success rate of 90 % at 1 year and 55 % at 10 years [21] (Figs. 43.1 and 43.2). GDDs are valved (Ahmed®) or non-valved (Baerveldt®, Molteno®). The valved GDDs allow for regulation of aqueous outflow based on the IOP, and non-valved GDDs need to be ligated for a period of

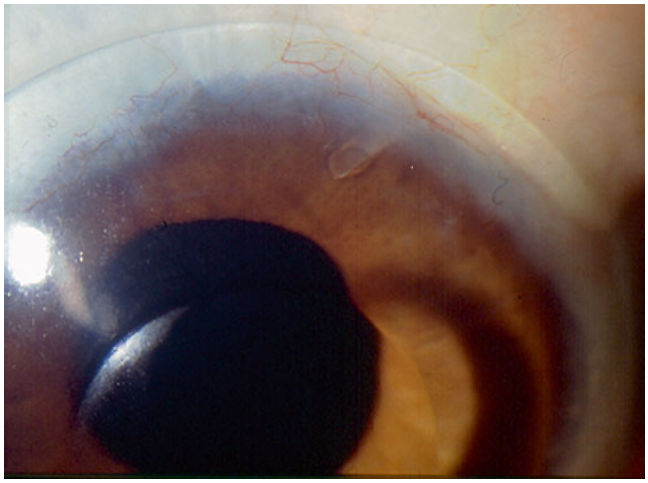

Fig. 43.1 Anterior segment photograph of an aphakic child's eye demonstrating a glaucoma drainage device tube in the anterior chamber and ongoing use of aphakic contact lens

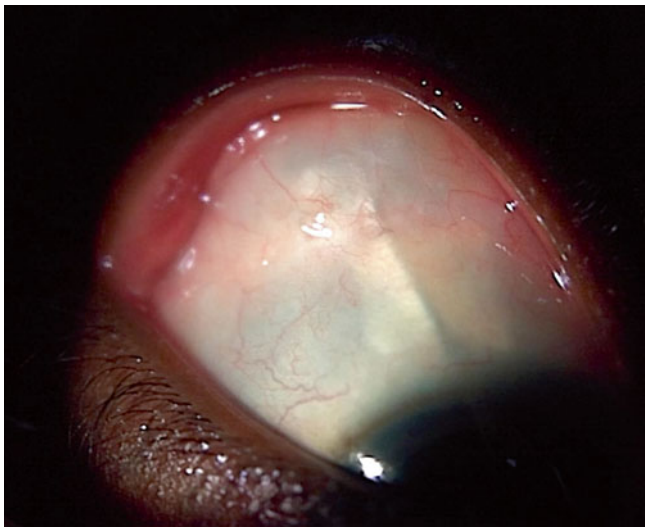

Fig. 43.2 Anterior segment photograph obtained using the Lytro® camera. Photograph demonstrates an Ahmed GDD placed in the superotemporal quadrant with the overlying bleb. Courtesy of Inna Marcus, MD

approximately 6 weeks following placement to prevent hypotony while a fibrous capsule forms around the plate [24]. GDDs can be placed into the anterior chamber or in the anterior vitreous via the pars plana [25], allowing for protection of the endothelium when the anterior chamber is shallow. Trabeculectomy with mitomycin C has a lower success rate in aphakia and young children than in other types of childhood glaucomas, with reported success rates of 24.6 % in a cohort of aphakic patients with a mean follow-up period of 8.6 years [18]. Beck et al. compared trabeculectomy with mitomycin C to GDDs in children with glaucoma under the age of 2 years and found a success rate of 19 % at 6 years for the patients treated with trabeculectomy with mitomycin C, compared with a success rate of 53 % at 6 years in the GDD group [26]. Cyclodestructive procedures are also effective in treating refractory glaucomas. Cyclodestructive procedures can be performed via a transscleral route, or via an endoscopic route in the aphakic or pseudophakic eye. Studies have reported success rates of 38 % at 6 months [27], with increase in the success rate following retreatment to 72 % at 1 year [28], using the transscleral route. A study of patients with aphakic/pseudophakic glaucoma treated via the endoscopic route with an average number of 1.5 treatments found a success rate of 53 % at 3.6 years [29]. Cyclodestructive procedures can also be utilized after incomplete IOP control following GDD implantation [30].

Case Studies

Case Study 1

History/Presentation: 8-year-old male with history of bilateral congenital cataracts, diagnosed at his well-child visit at age 1 month. He is status post cataract extraction in both eyes between 2 and 3 months of age and returns for a routine 6-month follow-up examination. Patient is managed optically in aphakic contact lenses (CL) without any new concerns.

Key Examination Findings:
Visual acuity in aphakic CLs:
OD: 20/20
OS: 20/25
Intraocular pressure (IOP) obtained using Goldmann applanation tonometry (GAT) in a very cooperative patient:
OD: 29 mmHg
OS: 28 mmHg
Anterior segment examination (portable slit lamp):
OU: Clear cornea, deep anterior chamber, flat iris plane with round pupil
Gonioscopy was not tolerated by the patient
Central corneal thickness (CCT):
OD: 720 μm
OS: 698 μm
Cup to disc (C/D) ratio estimated by using a Superfield lens at the slit lamp:
OD: 0.25
OS: 0.30

(continued)

Management Options:
- Start one topical medication for the IOP. In this case, it would be reasonable to start the patient on a topical beta-blocker once daily, or, if contraindicated due to asthma/respiratory issues, a topical carbonic anhydrase inhibitor or topical prostaglandin analog.
- Repeat measurements in 6 weeks without initiating treatment to confirm IOP measurements.

Plan: Start a topical medication to address the IOP. A review of the medical records demonstrated a previous C/D ratio of 0.1 in the right eye and 0.1 in the left eye, therefore the C/D measured today represented a change from his baseline. Obtain baseline optical coherence tomography (OCT) of the retinal nerve fiber layer (RNFL) and optic nerve head stereoscopic photos and consider baseline automated visual field (AVF) within the next year or two, as an 8-year-old will likely not produce a reliable test. In addition, his optic nerves appear healthy and ancillary testing is all within normal limits, and no visual field defect is suspected at this point.

Interval History (6 weeks): Patient tolerated the medication well without any noted side effects. This patient was started on timolol 0.5 % solution once daily in the morning, preferably applied to the eyes before contact lenses are placed to enhance penetration. The gel-forming solution is relatively contraindicated given his contact lenses.

Key Examination Findings:
Visual acuity in aphakic CLs:
OD: 20/20
OS: 20/25
IOP obtained using Goldmann applanation tonometry (GAT) in a cooperative patient:
OD: 14 mmHg
OS: 15 mmHg

Interval History (1 year): Patient continues to tolerate the medication well, and parents are compliant with their administration.

Key Examination Findings:
Visual acuity in aphakic CLs:
OD: 20/20
OS: 20/25
IOP via Goldmann applanation tonometry (GAT) in a cooperative patient:
OD: 13 mmHg
OS: 16 mmHg
Gonioscopy
OU: shows an open angle to scleral spur with patchy trabecular pigmentation in both eyes
C/D ratio:
OD: 0.25
OS: 0.30

Cycloplegic refraction: A change of -0.50 D in the OD and -0.75 D in the OS from the previous year.
OCT RNFL with no interval changes compared with the baseline testing. Visual field testing was attempted but was unreliable due to many fixation losses.

Management: Continue current medical management, with follow-up examination every 4 months to monitor IOP and optic nerve status.

Clinical Synopsis

This is a case of *aphakic glaucoma*, according to the definitions set out in this chapter. Several studies have reported that the time to onset of the glaucoma can vary; however, all the studies have demonstrated that long-term follow-up is imperative in this patient population [1–11]. In this patient, the only clearly identifiable risk factor, outside of the aphakia, is the young age at time of cataract extraction. The patient has done well with medical therapy [31, 32], which is the first line of treatment for aphakic/pseudophakic glaucoma (and glaucoma suspects), as long as there is no angle closure (and in this case we presume an open angle due to the deep anterior chamber and flat iris plane described above).

Case 2

History/Presentation: 6-month-old male with a history of a unilateral congenital cataract of the left eye diagnosed at age 1 month. He is status post cataract extraction with primary mechanical posterior capsulotomy and anterior vitrectomy to the left eye without IOL implantation at age 6 weeks. He presents acutely for evaluation of tearing, photophobia, and a change in the appearance of the cornea noted by his parents.

Key Examination Findings:
Visual acuity:
OD: Wince to light (WTL), central, steady, and maintained (CSM)
OS: Wince to light (WTL), unable to cooperate for further evaluation

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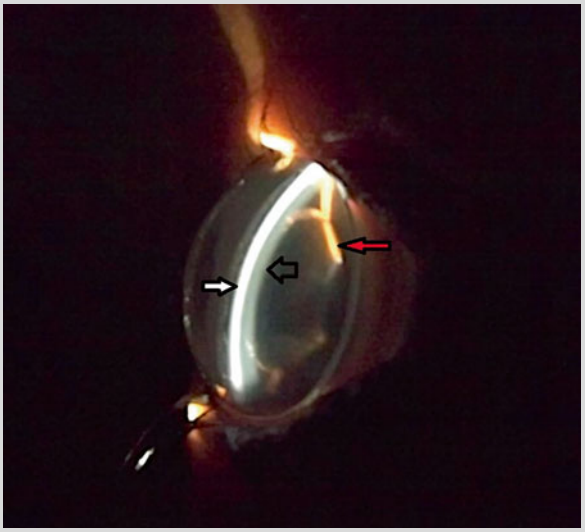

Fig. 43.3 Anterior segment photograph taken through a Koeppe Gonioscopy lens. Photograph demonstrates iris bombe (*red arrow*) with an anteriorly displaced vitreous (*black arrow*) against the corneal endothelium (*white arrow* highlights the cornea). The photograph was obtained using a Lytro® camera. Courtesy of Inna Marcus, MD

IOP obtained using the Tonopen® with the baby taking a bottle:
OD: 18 mmHg
OS: 45 mmHg
Anterior segment examination (portable slit lamp):
OD: Within normal limits
OS: Cloudy cornea, with the iris against the cornea, with a configuration consistent with iris bombe

Management Options:
- Start topical timolol 0.25 % (given patient's young age), dorzolamide 2 %, oral acetazolamide (dosed at 10–15 mg/kg/day divided into three daily doses).
- Surgical intervention in the next 24–48 h once cleared from an anesthesia standpoint.

Surgical Intervention:
- Examination under anesthesia of the left eye demonstrated prolapsed vitreous into the anterior chamber, causing the pupillary block (Fig. 43.3).
- Surgical peripheral iridectomy (PI) and further anterior vitrectomy was performed, with intraoperative flattening of the iris plane and deepening of the anterior chamber.

Interval History (1 week): Patient on topical atropine 1 %, timolol 0.25 %, dorzolamide 2 %, and topical antibiotic/steroid combination with good tolerance and no recurrence of symptoms.

Key Examination Findings:
Visual acuity:
OD: WTL
OS: WTL
IOP obtained using the Tonopen® with the baby taking a bottle:
OD: 10 mmHg
OS: 15 mmHg
Anterior segment examination (portable slit lamp):
OD: Within normal limits (WNL)
OS: Deep chamber with a clear cornea, patent PI in the left eye with flat iris plane, round pupil, and absence of vitreous noted anterior to the pupillary plane

Interval History (1 month): Doing well in aphakic CL and patching well. He is tolerating topical dorzolamide 2 % and timolol 0.25 %.

Key Examination Findings:
Visual acuity:
OD: Central, steady, and maintained (CSM)
OS: Central, steady, and unmaintained (CSUM)
IOP obtained using the Tonopen® with the baby sleeping:
OD: 10 mmHg
OS: 13 mmHg

Interval History (5 months): IOPs remained stable and at postoperative month #4, the topical dorzolamide 2 % and timolol 0.25 % were discontinued. Patient returns today for examination and for IOP check off topical medications.

Key Examination Findings:
Visual acuity:
OD: CSM
OS: CSUM
IOP obtained using the Tonopen® with the baby in a happy and calm disposition:
OD: 11 mmHg
OS: 13 mmHg

Management: Continue patching, return for examination in 8 weeks.

Clinical Synopsis

This is a case of *aphakic glaucoma associated with angle closure*. The treatment of the glaucoma in this case must address the etiology of the acute closure—forward movement of the formed vitreous, causing pupillary block. The patient was continued on topical medications for a period of 3 months until treatment

(continued)

was discontinued given the controlled IOP and stable examination. The patient was followed at intervals suitable for follow-up of the IOP, visual development, and contact lens assessment.

Case 3

History/Presentation: 10-year-old girl with a history of bilateral congenital cataracts. She is status post cataract extraction between age 5 and 6 months, secondary to a delay in diagnosis. She was diagnosed with aphakic glaucoma at 9 years old and managed on topical dorzolamide/timolol combination, latanoprost, and brimonidine. She presents for consideration of surgical intervention in the setting of uncontrolled IOP.

Key Examination Findings:
Visual acuity in aphakic CLs:
OD: 20/50
OS: 20/80
IOP via Goldmann applanation tonometry (GAT):
OD: 30 mmHg
OS: 28 mmHg
Anterior segment examination (table top slit lamp):
OU: Clear cornea with a diameter of 12 mm, shallow anterior chamber, and aphakia
Gonioscopy:
OU: Angle is open to the trabecular meshwork only, with multiple peripheral anterior synechiae
C/D ratio measured using a Superfield lens:
OD: 0.45
OS: 0.50

Management options:
- Addition of systemic acetazolamide
- Trabeculotomy
- Trabeculectomy
- Placement of glaucoma drainage device (GDD)
- Endoscopic diode laser cyclophotocoagulation

Management: Based on medically uncontrolled intraocular, a non-valved GDD with the tube in the pars plana (due to the shallow anterior chamber) following a complete vitrectomy in the left eye was performed. Given the healthy nerve and lack of acute need for IOP reduction and need for long-term control of the IOP, a non-valved GDD was implanted. The axial length was noted to be 23.6 mm at EUA before the surgery, confirming that the eye was long enough for a Baerveldt model 250 mm^2 to be placed without modification. Review of her medical records demonstrated a previous C/D ratio of 0.25 OD and 0.3 OS.

Interval History (2 months): Patient did well following initial surgical intervention.

Key Examination Findings:
Visual acuity in aphakic CLs:
OD: 20/50
OS: 20/80+
IOP obtained using GAT:
OD: 28 mmHg
OS: 15 mmHg
Anterior segment examination (table top slit lamp):
OD: Unchanged from previous examination
OS: Well-placed GDD with patent tube located in the pars plana and with a moderate bleb overlying the plate

Interval History (5 months): Patient underwent an identical procedure to the right eye, which was well tolerated. She is now on dorzolamide/timolol combination twice daily in both eyes.

Key Examination Findings:
Visual acuity in aphakic CLs:
OD: 20/50+
OS: 20/80+
IOP obtained using GAT:
OD: 14 mmHg
OS: 13 mmHg

Clinical Synopsis

This is a patient with *aphakic glaucoma* that was initially controlled with medical treatment; however, over time medical management was insufficient for the control of the glaucoma. The decision was made to proceed with a GDD in the pars plana [22, 25]. No angle surgery was proposed given the presence of an abnormal angle with peripheral anterior synechiae, as well at the patient's age suggesting she may not respond as well to angle surgery. Placement of the tube in the pars plana was preferred to the anterior chamber placement given the shallow anterior chamber and likely corneal damage from proximity to GDD tubes on a long-term basis.

Case 4

History/Presentation: 5-year-old male with history of bilateral congenital cataracts removed at the age of 6 weeks. He is status post placement of secondary posterior chamber IOLs in both eyes at age 4 years. He was subsequently found to have elevated IOP in both eyes, with progression to glaucoma in the left eye based upon increased optic nerve cupping in that eye. He is currently on topical dorzolamide/timolol combination, apraclonidine, and latanoprost.

Key Examination Findings:
Visual acuity:
OD: 20/30
OS: 20/25
IOP obtained using GAT:
OD: 21 mmHg
OS: 38 mmHg
Anterior Segment Examination (table top slit lamp):
OU: Clear cornea, deep anterior chambers, clear corneas, and posterior chamber IOL in position with clear opening in the posterior capsule.
Gonioscopy:
OU: Open to the ciliary body band in both eyes.
C/D ratio:
OD: 0.3
OS: 0.5
CCT:
OD: 650 μm
OS: 670 μm

Management Options:
- Addition of systemic acetazolamide, in the interim
- 360 illuminated catheter-assisted trabeculotomy
- Placement of a GDD

Management: Because of the patient age and clinical parameters of a deep angle and no synechiae, we elected to perform a 360°, illuminated catheter-assisted trabeculotomy.

Interval History (4 months): Patient is tolerating topical dorzolamide/timolol in both eyes and latanoprost in the right eye well.

Key Examination Findings:
Visual acuity:
OD: 20/30
OS: 20/25
IOP obtained using GAT:
OD: 20 mmHg
OS: 15 mmHg
C/D ratio:
OD: 0.3
OS: 0.5

Clinical Synopsis

This is a case of *pseudophakic glaucoma* in the left eye, while the right eye remains technically a glaucoma suspect based on the IOP [1]. His baseline C/D ratio has remained unchanged in the right eye, and he has no other findings for a diagnosis of glaucoma at this time. In his left eye he has elevated IOP and an increased cup to disc ratio necessitating surgical intervention. Given the high IOP, his medical therapy was maximized by the addition of systemic acetazolamide to his topical therapy, as an interim management [33]. The decision was made to proceed with angle surgery (trabeculotomy), using the illuminated micro-catheter, given that this treats the entire angle and has reasonable success reported in refractory aphakic/pseudophakic glaucoma [17, 19]. In aphakic eyes, there is a risk for vitreous hemorrhage, but the posterior chamber IOL decreases the risk in this child. In this case, placement of a GDD, in the presence of adequate anterior chamber depth would have also been an acceptable surgical alternative; a vitrectomy would not have been needed since the posterior chamber IOL would keep vitreous from coming forward to block the anterior chamber tube of the GDD.

Case 5

History/Presentation: 12-year-old girl with a history of a congenital cataract of the right eye, status post removal at age 6 weeks with posterior capsulotomy/anterior vitrectomy. She is also status post placement of a secondary sulcus IOL at the age of 3 years. She was noted to have elevated IOPs at age 10 years and has been managed with topical dorzolamide/timolol combination, brimonidine, and latanoprost; however, she continues to have elevated IOP. She has also been documented to have a change in the C/D ratio prompting referral for surgical evaluation.

Key Examination Findings:
Visual acuity:
OD: 20/100
OS: 20/20
IOP obtained using GAT:
OD: 24 mmHg
OS: 12 mmHg

(continued)

Anterior segment examination (table top slit lamp):
OD: Clear cornea, but small at 10 mm in the OD (vs. 11.5 mm OS). Anterior chamber is moderately shallow in the right eye despite a flat iris plane, and well-centered IOL.
OS: WNL. Corneal diameter of 11.5 mm
C/D ratio measured using a Superfield lens:
OD: 0.45
OS: 0.10
CCT:
OD: 690 μm
OS: 550 μm
Axial Length:
OD: 21.50 mm
OS: 23.15 mm

Management: A non-valved GDD (Baerveldt) was placed in the ciliary sulcus of the right eye, between the iris and the IOL, with the tube tip extending just into the pupillary aperture. Axial length was obtained to ascertain that her eye would tolerate the plate size, given her microcornea in the right eye. In this case, the posterior edge of the GDD plate was trimmed to limit the anteroposterior length of the plate. An alternative would have been to place the plate closer to the limbus than the standard 8 mm.

Interval History (1 year): Doing well and tolerating topical dorzolamide/timolol combination in the right eye.

Key Examination Findings:
Visual acuity:
OD: 20/80 slowly
OS: 20/20
IOP obtained using GAT:
OD: 14 mmHg
OS: 11 mmHg
C/D ratio measured using a Superfield lens:
OD: 0.45
OS: 0.1

Clinical Synopsis

This is a case of *pseudophakic glaucoma*. The decision was made to proceed with placement of a non-valved GDD (Baerveldt) [22], with the tube placed into the ciliary sulcus given the shallow anterior chamber. In addition, given the IOP of 24 and C/D ratio of 0.45, there was sufficient time to await dissolution of the ligature that was placed on the non-valved GDD. The placement of the tube anterior to the IOL but posterior to the iris provides for protection of the cornea from the tube.

Case 6

History/Presentation: 5-year-old with a history of a unilateral congenital cataract of the left eye. The patient is status post cataract extraction at age 2 months and presents for evaluation of elevated IOP of the left eye. Additional history reveals that patient is very intolerant of the use of CL and does not wear phakic-aphakic glasses well; thus his amblyopia treatment is limited. Patient is currently on dorzolamide/timolol combination twice daily to the left eye and latanoprost once daily to the left eye.

Key Examination Findings:
Visual acuity:
OD: 20/20
OS: 20/150
IOP obtained using Tonopen®:
OD: 12 mmHg
OS: 30 mmHg
Anterior segment examination (table top slit lamp):
OD: WNL
OS: Clear cornea, aphakia with an intact capsular support for 360, and prolapsed wisps of vitreous into the anterior chamber with a flat iris plane
C/D ratio:
OD: 0.15
OS: 0.55
Gonioscopy obtained at the EUA:
OU: Open to the scleral spur
Axial Length:
OD: 22 mm
OS: 24 mm

Management options:
- Trabeculotomy
- Placement of a GDD (pars plana tube) with complete vitrectomy
- Placement of a GDD (anterior or posterior chamber tube) concomitantly with placement of a posterior chamber (likely sulcus) IOL and anterior vitrectomy

Management: Placement of a GDD (valved or non-valved) with concomitant placement of a secondary IOL in the left eye and anterior vitrectomy.

Interval History (3 months): Doing well. Patient is now able to patch for his amblyopia therapy. Parents are happy they do not have to struggle with CL.

(continued)

Key Examination Findings:
Visual acuity:
OD: 20/20
OS: 20/80 slowly
IOP obtained via GAT:
OD: 11 mmHg
OS: 15 mmHg
C/D ratio:
OD: 0.15
OS: 0.55

Clinical Synopsis

This patient presented with *aphakic glaucoma* and responded well to the placement of both a GDD and an IOL with anterior vitrectomy [34]. In this case, management of his amblyopia was also important, as the patient was intolerant of his aphakic CL and spectacle correction. Placement of the secondary IOL allowed for placement of the GDD without the need for an extensive vitrectomy that would have been required, if the eye was left aphakic, given anterior location of vitreous at the pupil. In addition, the IOL allowed for placement of the GDD's tube either in the anterior chamber or in the ciliary sulcus. Lastly, placement of the IOL at the time of the GDD also aided with the treatment of his amblyopia. The child was able to discontinue the use of the poorly tolerated aphakic CL.

Case 7

History/Presentation: 17-year-old male with a history of an acquired traumatic cataract in the right. The patient is status post cataract surgery with primary placement of an IOL in the capsular bag at the age of 10 years. Postoperative week #4, he was noted to have a decentered IOL secondary to poor capsular support. The patient was monitored. At age 15, he developed acute eye pain and was found to have acute angle closure glaucoma in the setting of a dislocated posterior chamber IOL.

Interval history: Patient is now status post removal of the dislocated IOL followed by placement of a large one-piece polymethyl methacrylate (*PMMA*) IOL in the ciliary sulcus. Postoperatively the IOP was managed with topical medications; however, by age 16, the IOP was again elevated. This patient is very active in sports, is diligent about wearing sports goggles, but does not want any procedures that can be seen on the "outside" of his eye.

Key Examination Findings:
Visual acuity:
OD: 20/80
OS: 20/20
IOP obtained using GAT:
OD: 32 mmHg
OS: 14 mmHg
Anterior Segment Examination (table top slit lamp):
OD: Clear cornea; anterior chamber with adequate depth and no cells; iris is irregular at the pupillary margin; sulcus lens in proper position
OS: WNL
C/D ratio measured using a Superfield lens:
OD: 0.45
OS: 0.10
Gonioscopy:
OD: Open to the anterior-mid trabecular meshwork with increased trabecular meshwork pigment, areas of peripheral anterior synechiae (PAS) scattered throughout.
OS: Open to scleral spur

Management options:
- Placement of a GDD
- Trabeculotomy
- Trabeculectomy
- Diode laser Cyclophotocoagulation (CPC)

Management: Endoscopic CPC, for nine clock hours, via a pars plana approach with limited anterior vitrectomy given the previously dislocated IOL (and desire not to disturb the current sulcus IOL) was performed. This patient did not want any procedures that would have external changes—eliminating a GDD and trabeculectomy. The changes to the angle reduce the success of a trabeculotomy.

Interval history (6 months): IOP responded to endoscopic CPC; however, over time the IOP continued to increase, necessitating that he returned to the use of all his topical medications (dorzolamide/timolol, brimonidine, and latanoprost).

Key Examination Findings:
Visual acuity:
OD: 20/80
OS: 20/20
IOP obtained using GAT:
OD: 25 mmHg
OS: 12 mmHg
C/D ratio:
OD: 0.5
OS: 0.1

(continued)

Management Options:
- Placement of a GDD
- Trabeculectomy
- Additional Endoscopic or transscleral CPC

Management: A GDD (an Ahmed valve) was placed in the superotemporal quadrant. The Ahmed has a smaller surface area compared with the Baerveldt, and this would be less noticeable in the superotemporal quadrant (Figs. 43.1 and 43.2). The addition of a GDD to an eye that has undergone previous CPC has an additive effect on IOP control.

Interval History (6 months): Patient reports that he is doing well, and is glad to be on only one topical medication.

Key Examination Finding:
Visual acuity:
OD: 20/80
OS: 20/20
IOP obtained using GAT:
OD: 15 mmHg
OS: 11 mmHg

Clinical Synopsis

This patient presented with *multiple mechanisms* likely playing a role in his glaucoma. He had an acute closed angle from a dislocated intraocular lens, which was initially addressed surgically. However, his glaucoma progressed following the lens dislocation. The patient also presented some limitations to the options available for care. In this young, very active patient, and who will need the use of an antimetabolite for a successful trabeculectomy, the risk of a postoperative endophthalmitis is high. A trabeculotomy in the setting of PAS will not be as successful, and a 360° trabeculotomy may not be possible in the setting of PAS. A GDD would be better tolerated; however, the patient initially did not want to consider the placement of any devices, or surgeries that could potentially be noted externally. Given the above, the decision was made to proceed with endoscopic CPC, via a pars plana approach to increase the rate of success, as the ciliary body processes would be directly visualized [29]. Transscleral CPC would have also been an alternative, but it would have required higher energy levels and less ability to directly visualize and confirm treatment of the ciliary processes [27, 28]. This patient did well with the endoscopic CPC for a few months; however, his IOP was not controlled long term. For good IOP control, CPC procedures often need to be repeated [27–29]. Following the increased IOP on maximal medical therapy, a GDD was again recommended and was discussed in detail with the patient. A GDD in combination with cyclodestructive procedures has been demonstrated to have increased effectivity [1, 21, 30]. The patient was amenable to placement of a GDD and did well postoperatively (Figs. 43.1 and 43.2).

Summary

All children, especially young infants who undergo cataract extraction, are at a lifelong risk of aphakic/pseudophakic glaucoma, and this is higher for those who undergo surgery in infancy. Prompt diagnosis and treatment are critical in their care. Figure 43.4 provides a suggested algorithm for the treatment of the patient with aphakic/pseudophakic glaucoma.

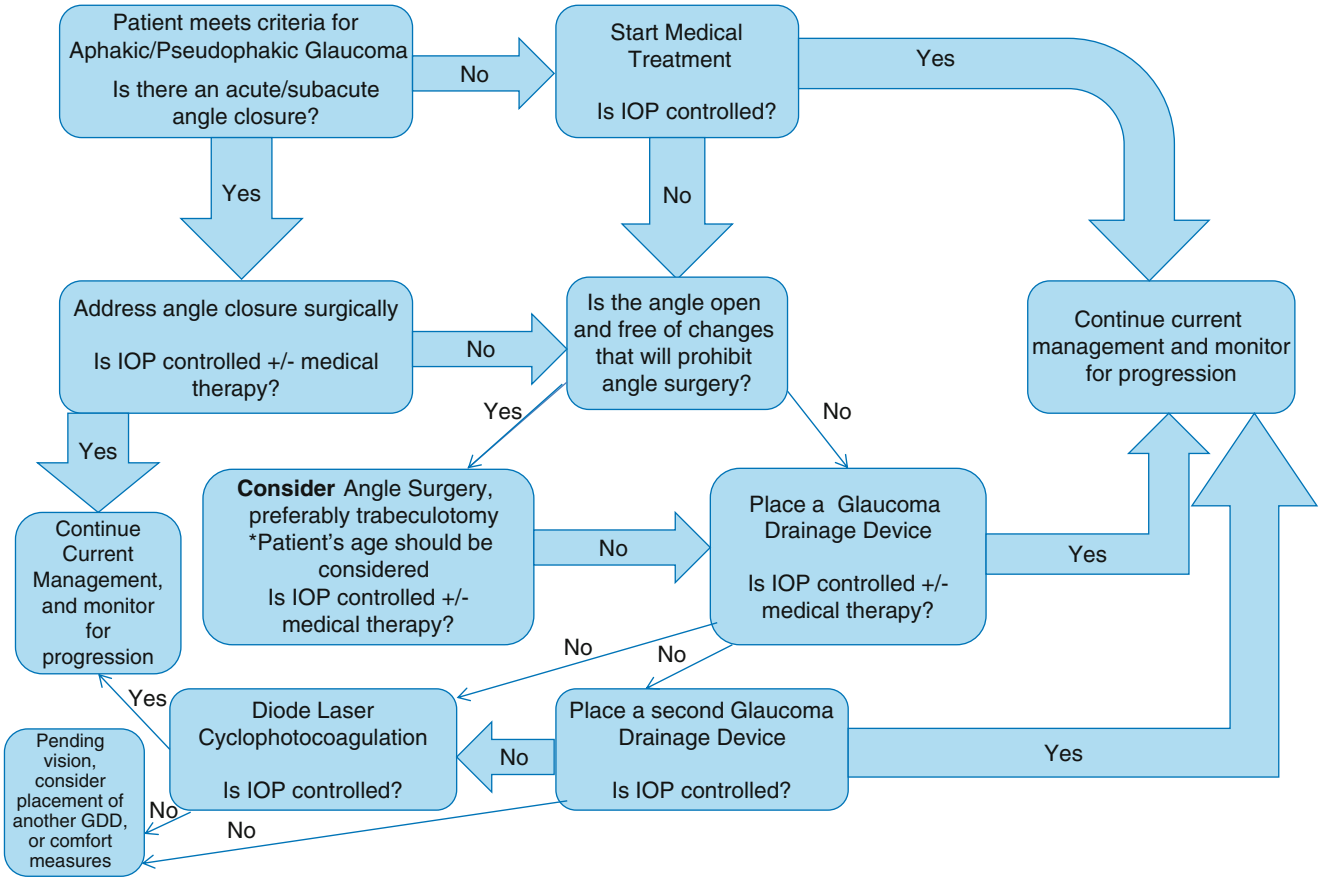

Fig. 43.4 Suggested algorithm for management of aphakic/pseudophakic glaucoma. The algorithm was adapted, with permission, from *Childhood Glaucoma*, 9th Consensus Report of the World Glaucoma Association. Kugler Publications, Amsterdam, The Netherlands, 2013

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Diagnosis and Management of Juvenile Open-Angle Glaucoma

44

Allison E. Babiuch and Yasmin S. Bradfield

Abstract

Juvenile open-angle glaucoma (JOAG) is a rare subset of primary open-angle glaucoma (POAG) characterized by an early age of onset, severe elevation in intraocular pressure, and an autosomal dominant pattern of inheritance. Diagnosis is often delayed as the patient does not exhibit ocular findings typical of congenital glaucoma, including buphthalmos, tearing, and photophobia. JOAG is difficult to manage with medications and often requires surgical intervention. The preferred surgical intervention is either an aqueous tube shunt or filtration surgery, both of which lead to successful reduction of intraocular pressure.

Keywords

Glaucoma • Juvenile • Trabeculectomy

Introduction

Juvenile open-angle glaucoma (JOAG) is a rare form of glaucoma defined as having an onset between the age of 3 years and early adulthood. JOAG is clinically distinct from infantile glaucoma, which develops before the age of 3 years and results in enlargement of the globe from increased intraocular pressure in the youngest patients. Juvenile glaucoma accounts for 2.0–13.3 % of pediatric glaucoma patients in the United Kingdom, Canada, and the United States and as much as 17 % in China [1, 2].

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Affected individuals usually have a strong family history of glaucoma that follows an autosomal dominant pattern of inheritance with variable penetrance. Five GLC1 loci have been associated with JOAG (GLC1A, GLC1J, GLC1K, GLC1M, and GLC1N). Mutations in the myocilin/trabecular meshwork-inducible glucocorticoid response (*MYOC*) gene at GLC1A locus on chromosome 1q21–q31 were identified as responsible for JOAG in 36 % of cases and account for only 2–4 % of adult-onset POAG [3–5]. Some cases of JOAG result from mutations in cytochrome P450, family 1, subfamily B, polypeptide 1 (*CYP1B1*), the gene linked to congenital glaucoma [6]. There can be phenotypic overlap from mutations in these genes.

Clinical Findings and Work-Up

Patients are often asymptomatic and do not have the classic triad of symptoms evident in infantile glaucoma: buphthalmos, tearing, and photophobia. On examination, Haab

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striae, megalocornea, and systemic findings are typically absent. At the time of diagnosis, patients with JOAG often have marked bilateral increase in intraocular pressure, optic nerve cupping, and visual field loss. Gonioscopy reveals normal-appearing angle structures. As in POAG, elevations in IOP are thought to result from impaired outflow of aqueous humor through the trabecular meshwork into the Schlemm canal. Myopia is common in individuals with JOAG [7].

The work-up for children with JOAG includes pachymetry, gonioscopy, measurement of IOP, dilated eye examination with assessment of cup-to-disk ratio, visual field testing, and optical coherence tomography (OCT). IOP can be measured with applanation or with electronic handheld devices such as the Tono-Pen®. Younger patients may have larger average differences in measurements using these two methods, and a higher IOP is measured in the office setting [8]. If the child is too young or uncooperative, an exam under anesthesia is necessary. Automated visual field testing is preferred so that changes in visual fields can be followed and compared, but Goldmann visual fields can be obtained for younger children who are unable to complete automated testing. Numerous studies have demonstrated that OCT can be used as an objective tool for diagnosing and monitoring disease progression in children [9–11]. OCT measurements are reproducible over time despite normal changes in axial length as the child grows (see Chap. 27 "Use of Optical Coherence Tomography in the Eyes of Children").

Treatment

The neuropathy of JOAG is usually severe and rapidly progressive as compared to that of adult-onset POAG. IOP is often >30 mmHg and does not respond well to medications. Treatment is challenging. One starts with IOP lowering medications, but filtration or aqueous drainage device surgery is often required. Angle surgery is generally not helpful [12]. The Dallas Glaucoma Registry studied 376 eyes of 239 childhood glaucoma patients, of whom 10 (4 %) had primary juvenile glaucoma. The mean cup-to-disk ratio was 0.71 and mean IOP was 16.4 mmHg; notably this average IOP reflects IOP at the latest visit, rather than initial IOP prior to treatment. Thirty-seven percent of patients with JOAG required surgery compared to 92.6 % of patients with congenital glaucoma. In the JOAG population, tube shunts were the most common surgery performed. Intraocular pressure was controlled with medications alone in 63.2 % of patients with JOAG, requiring an average of 2.5 medications. Best-corrected visual acuity was 20/40 or better in 13 eyes (77 %) [13]. In one series of 60 eyes of 41 JOAG patients who underwent trabeculectomy without mitomycin C (MMC), the probability of complete success, defined as IOP >5 and <21 mmHg without medications, was 92 % at 1 year, 89 % at 3 years, and 80 % at 5 years [14]. Trabeculectomy has been found to lead to similar results with or without mitomycin C (MMC); however, there are higher rates of hypotony maculopathy with the use of MMC [15]. Reversal of cupping has been noted postoperatively in patients with juvenile glaucoma, but whether that correlates with the return of healthy, functional tissue is yet to be determined [16].

Genetic Testing

Genetic testing may be considered for children with symptomatic glaucoma as well as presymptomatic children with a family history of glaucoma. If genetic testing reveals a mutation in the *MYOC* gene, the patient's siblings and parents should undergo a complete eye examination as well as genetic counseling and molecular testing [17]. Children who are presymptomatic with a known family history of *MYOC* genetic mutation may be monitored clinically, but genetic testing is preferred to determine their exact risk. Results from genetic testing may help in family planning and presymptomatic surveillance of siblings who carry the mutation, but does not alter clinical management of the affected patient. Referral to a geneticist for counseling is also advised as there is variability in phenotypic expression (see Chap. 33 on "Genetic Counseling and Testing").

Genome-wide association studies and gene-specific linkage analysis within pedigrees will identify other candidate and modifying genes involved in JOAG and lead to a better understanding of gene-specific disease mechanism. With increased recognition of the heritability of open-angle glaucoma and its possible linkage to JOAG, appropriate families may be recommended to undergo earlier screening and lead to earlier diagnosis and better prognosis of JOAG.

The following case study exemplifies diagnosis and management of a patient with juvenile open-angle glaucoma (see Flow Chart Fig. 44.1).

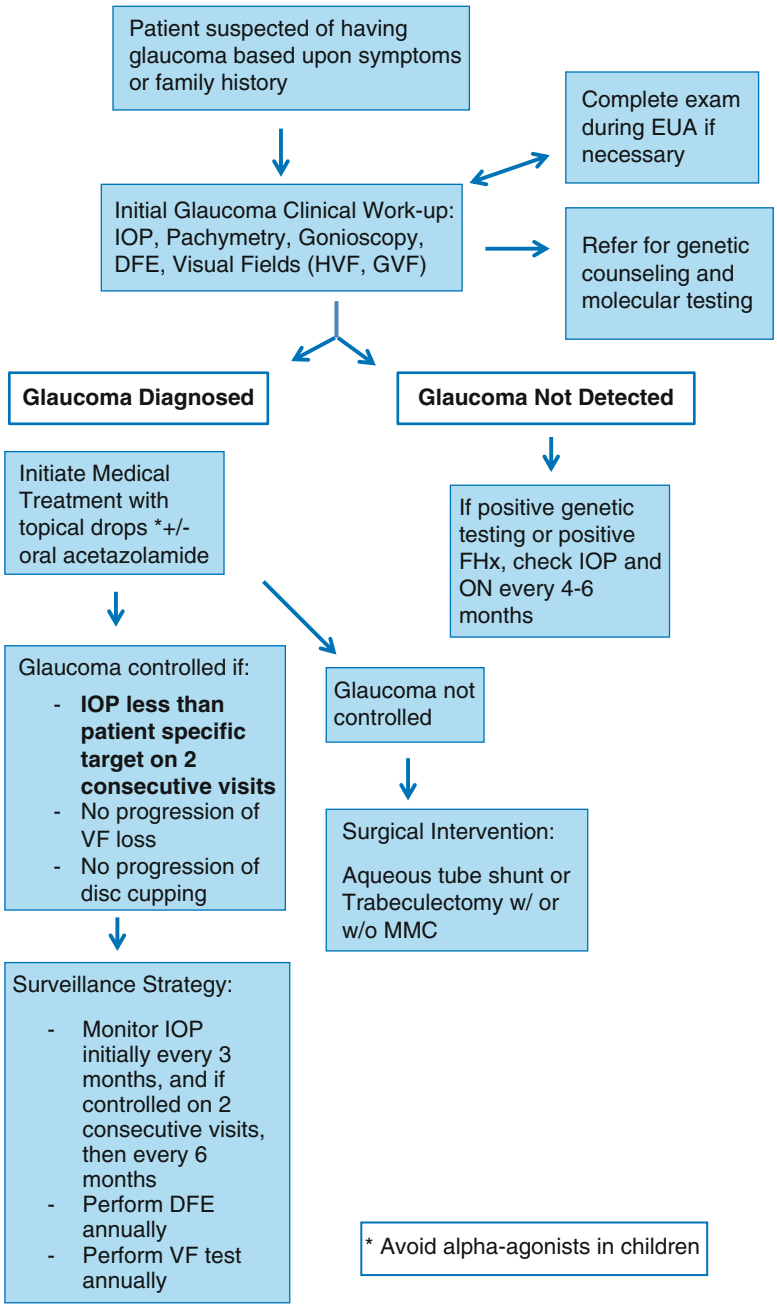

Fig. 44.1 Diagnostic and management algorithm

Case Study 1

An African American female who is 6 and 1/2 years old was referred by her local optometrist for evaluation of optic nerve cupping OU. Her mother took her to the optometrist to check if she needed glasses. The patient was otherwise healthy and past medical and ocular history and medications are unremarkable. Pertinent review was negative for asthma (inhaled steroids), systemic steroid treatment, and ocular trauma. There is no family history of congenital, juvenile, or adult-onset glaucoma.

Initial Examination

UCVA:	OD: 20/70; OS: 20/40
	PH OD: 20/25; PH OS: 20/25

Sensorimotor:
- Ductions and versions full bilaterally
- Orthophoria on cover testing and alternate cover testing

Pupils: PERRL, no RAPD

(continued)

Intraocular Pressure (Goldmann Applanation):
OD: 33, 34 mmHg
OS: 35, 35 mmHg

Anterior segment:

	OD	OS
Eyelids	Normal	Normal
Conjunctiva	Normal	Normal
Cornea	Normal diameter, no Haab striae, no posterior embryotoxon	Normal diameter, no Haab striae, no posterior embryotoxon
Anterior segment	Deep, no cell or flare	Deep, no cell or flare
Iris	Normal iris stroma	Normal iris stroma
Lens	Clear	Clear

Gonioscopy: unable to cooperate with testing.
Pachymetry: OD: 556 OS: 540
Visual field (24-2): high fixation losses, unreliable
Posterior segment:

	OD	OS
Vitreous	Clear media	Clear media
Optic nerve	Superotemporal thinning, no pallor	Inferior rim thinning, no pallor
	C/D 0.8 (Fig. 44.2)	C/D 0.6 (Fig. 44.2)
Macula	Normal	Normal
Vessels	Normal	Normal
Peripheral Retina	Normal	Normal

Cycloplegic Refraction:
OD: −1.00 sph
OS: −0.50 + 0.50 × 090

Her mother's optic nerve had a cup-to-disk ratio of 0.3 right eye and 0.4 left eye.

Working Diagnosis: Juvenile open-angle glaucoma OU.

Plan: She was prescribed 0.5 % timolol eye drops in both eyes twice daily. Optic nerve photographs were taken for future comparison. She was also given a prescription for glasses. She was scheduled to return for intraocular pressure assessment and visual field testing in 1 month.

Follow-Up Examination: Reports compliance with timolol 0.25 % twice daily.

BCVA: 20/20 OU.
HVF 24-2 SITA Standard: Reliable parameters (Fig. 44.3)
OD: inferior arcuate defect
OS: superior arcuate defect
Intraocular pressure (Goldmann applanation):
OD: 33 mmHg.
OS: 35 mmHg.
Assessment: poor response to timolol 0.25 %.
Plan: Latanoprost eye drop in each eye at bedtime and instructed to change the timolol to timolol-dorzolamide eye drops twice daily in each eye. She was to follow up for IOP check in 1 month.

Follow-Up Examination (Pertinent Exam Findings):
Intraocular pressure (Goldmann applanation):
OD: 30 mmHg.
OS: 33 mmHg.
Assessment: poor response to medical management, surgical intervention indicated.

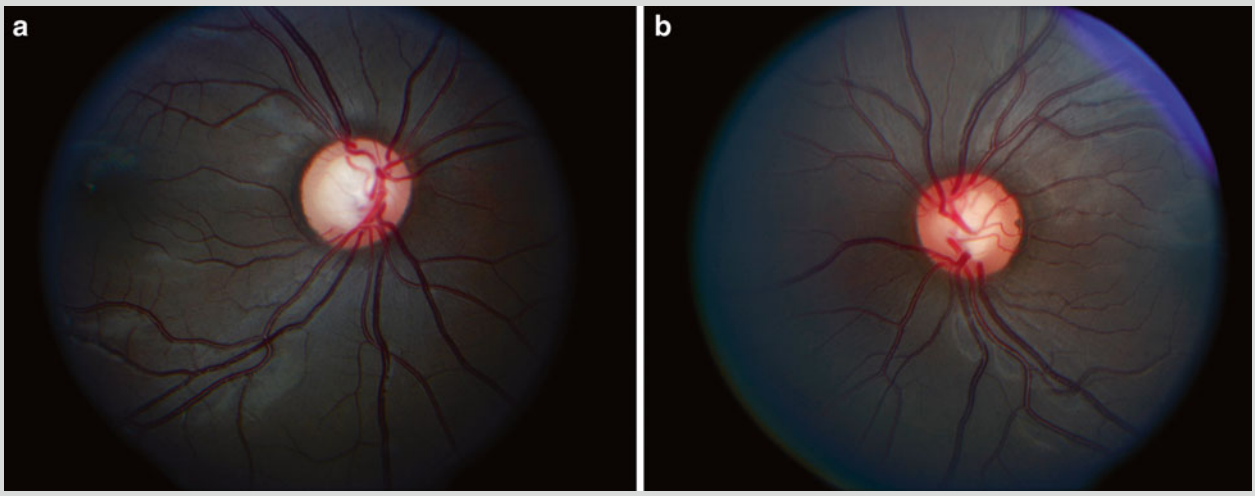

Fig. 44.2 Optic nerve of right (**a**) and left (**b**) eyes, demonstrating a cup-to-disk ratio of 0.8 and 0.6, respectively

(continued)

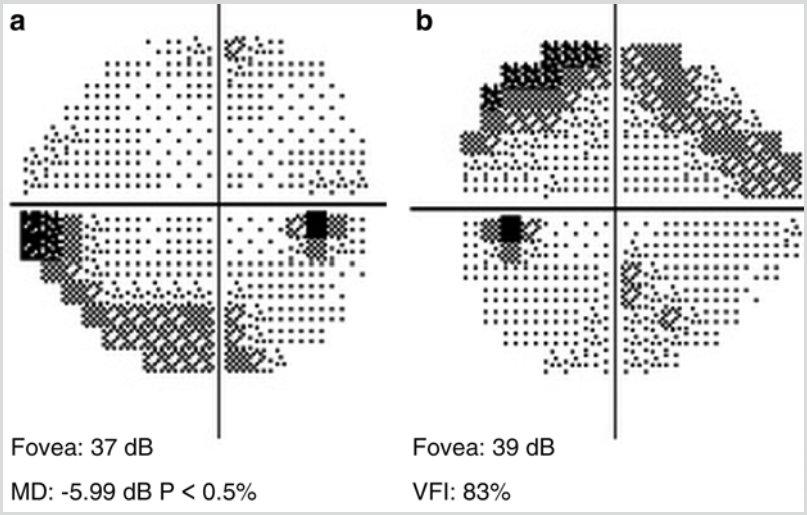

Fig. 44.3 Humphrey Visual Field 24-2 SITA Standard of the right and left eye. (**a**) The right eye demonstrates an inferior arcuate defect. (**b**) The left eye demonstrates a superior arcuate defect

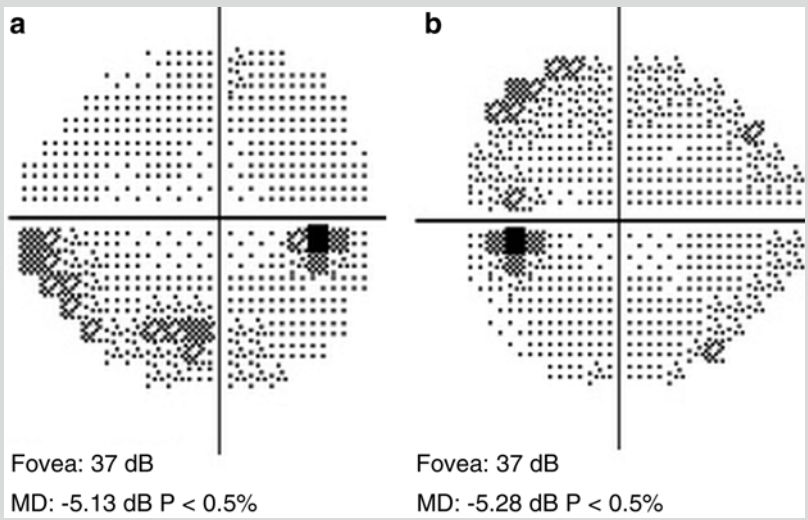

Fig. 44.4 Humphrey Visual Field 24-2 SITA Standard of the right and left eye (**a**) The right eye again demonstrates an inferior arcuate defect that is less dense compared to initial testing (Fig. 44.3a). (**b**) The left eye again demonstrates a superior arcuate defect that is less dense as compared to initial testing (Fig. 44.3b)

Plan: exam under anesthesia with gonioscopy and trabeculotomy OU.
Under anesthesia, gonioscopy confirmed open angles in each eye with no evidence of peripheral anterior synechiae or other angle abnormalities. 180° trabeculotomy completed without complication.

One-Week Postoperative Follow-Up Appointment:
Intraocular pressure (Goldmann applanation):
OD: 23 mmHg.
OS: 24 mmHg.
Assessment: reduction in IOP but above IOP goal.
Plan: add timolol 0.5 % one drop twice daily.

Postoperative Follow-Up Appointment (2 Months):
Intraocular pressure (Goldmann applanation):
OD: 16 mmHg.
OS: 22 mmHg.
Visual field 24-2 (SITA Standard) (Fig. 44.4):
OD: inferior arcuate defect.
OS: improved superior arcuate defect.
Optic nerve: unchanged (Fig. 44.5).
Assessment: still above IOP goal (goal < 21 mmHg).
Plan: follow-up in 6 months. Add latanoprost one drop at bedtime to both eyes.
Follow-up 8 years after initial presentation.
Intraocular pressure (Goldmann applanation):
OD: 15, 17 mmHg.
OS: 17, 17 mmHg.
Visual field (Fig. 44.6) and optic nerve (Fig. 44.7) remained stable.

(continued)

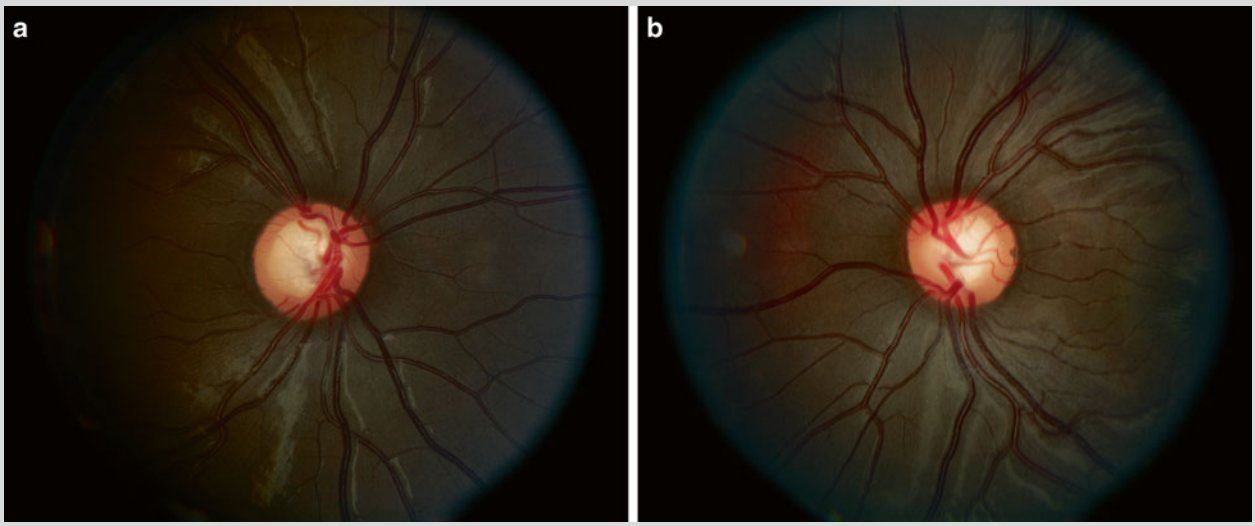

Fig. 44.5 Optic nerve of right (**a**) and left (**b**) eyes, demonstrating a cup-to-disk ratio of 0.8 and 0.6, respectively. There has been no progression as compared to initial presentation in Fig. 44.2

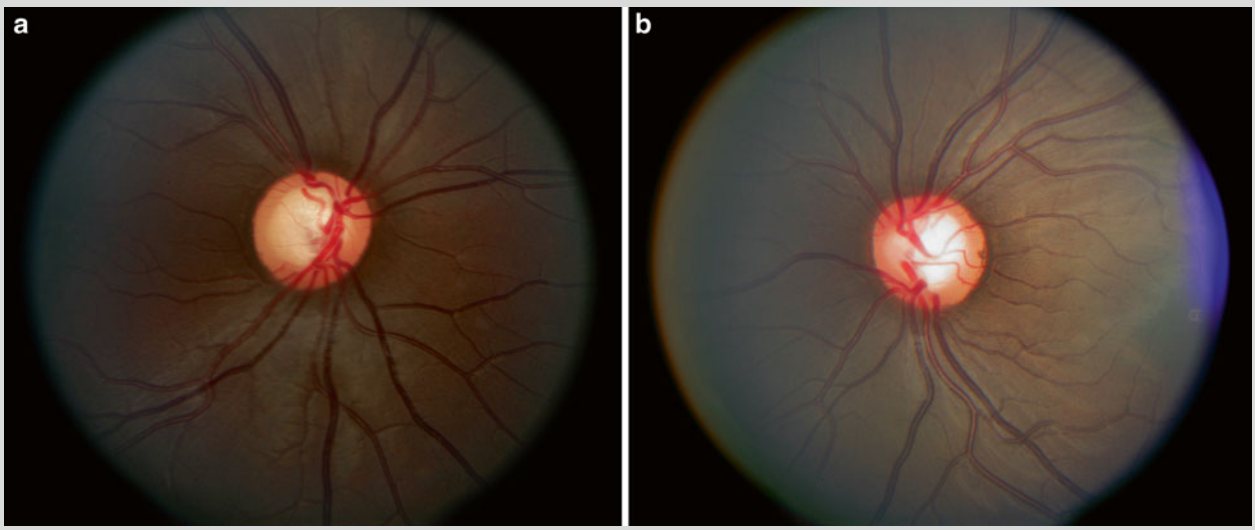

Fig. 44.6 Optic nerve of right (**a**) and left (**b**) eyes 8 years after initial presentation, demonstrating a cup-to-disk ratio of 0.8 and 0.6, respectively. There has been no progression as compared to initial presentation in Figs. 44.2 and 44.5

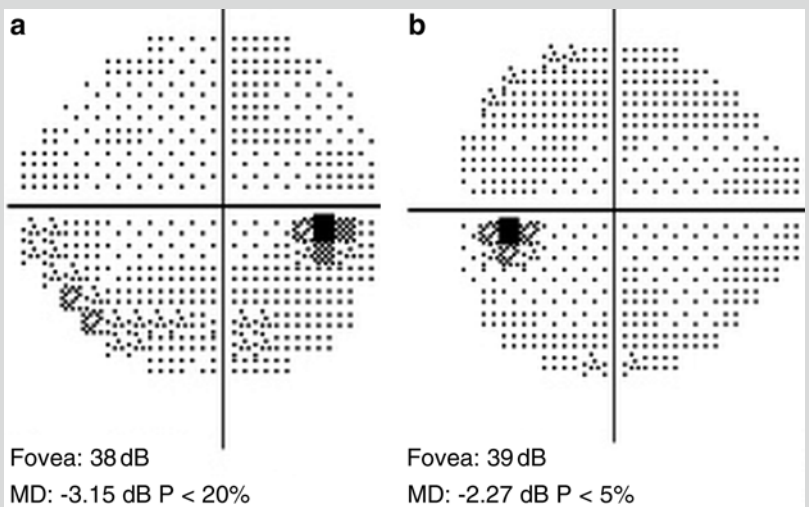

Fig. 44.7 Humphrey Visual Field 24-2 SITA Standard of the right and left eye 8 years after initial presentation. (**a**) The right eye appears relatively full again and demonstrates inferior arcuate defect that is stable in appearance as compared to that shown in Fig. 44.4a. (**b**) The left eye relatively full and stable in appearance as compared to that shown in Fig. 44.4b

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Part XI

Strabismus, Neuro-paralytic Disorders

Diagnosis and Management of Infantile Esotropia

45

Christopher Gappy

Abstract

Infantile esotropia presents as a large-angle esodeviation during the first 6 months of life. Diagnosis is made with a thorough history and complete ophthalmologic examination. Patients usually exhibit alternate fixation and cross fixation. Associated findings include dissociated vertical deviation, inferior oblique overaction, latent nystagmus, and smooth pursuit asymmetry. Treatment aims at providing normal ocular alignment early in life (6 months–2 years of age) to help promote binocularity and subsequent surveillance to prevent amblyopia. A successful result of treatment is good ocular alignment and peripheral binocular vision, although rare patients achieve some level of stereopsis. Treatment often involves bilateral medial rectus recessions, but additional surgical interventions early or later in life may be necessary.

Keywords

Infantile esotropia • Congenital esotropia • Strabismus • Amblyopia • Monofixation syndrome • Dissociated vertical deviation • Inferior oblique overaction • DVD • ET

The Problem

Infantile (or congenital) esotropia is a large-angle, constant esodeviation that is present before 6 months of age. Infantile esotropia is a more appropriate term than congenital esotropia, given that the strabismus is not necessarily and, in fact, rarely present at birth [1]. The incidence in the general population is estimated to be 0.5 % [2]. Features of infantile esotropia include a constant large-angle deviation (>30 prism diopters), alternating fixation, and cross fixation. Commonly associated abnormalities that may not be present on initial presentation include dissociated vertical deviation, inferior oblique overaction, latent nystagmus, and smooth pursuit asymmetry. Cross fixation refers to a visual pattern of behavior in which the patient looks to the left field of vision with the adducted right eye and to the right field of vision with the adducted left eye and does not have to abduct either eye, resulting in a simulation of abduction deficits. Cross fixation can be overcome by occlusion of one eye or by performing a doll's head maneuver to demonstrate ability of the lateral rectus muscle to abduct the eye. Most children have no associated medical conditions, but up to 30 % have developmental comorbidities, such as prematurity, cerebral palsy, hydrocephalus, or a history of maternal smoking during gestation [3]. Because of the early onset of ocular misalignment, infantile esotropia disrupts binocular visual development [4]. The attempt to correct this disruption and promote binocular function in a timely manner is what drives early treatment of infantile esotropia.

There are two competing theories regarding the cause of infantile esotropia. Worth's sensory theory states that an anatomical deficit in the fusion center of the brain causes esotropia, and therefore binocular vision can never be restored [5]. Chavasse's theory, on the other hand, describes esotropia as a mechanical problem and argues that some fusion can be restored through early intervention [6]. This latter theory and encouraging results in some patients are the basis for advocates

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of early surgery that aims at correcting the esotropia between 6 months and 2 years of age. Both theories may describe subcategories of infantile esotropia [7]. Costenbader suggested that infantile esotropia may be a manifestation of hyperopia with overconvergence [1]. Tychsen showed that maldevelopment of the visual cortex coincided with and is a likely cause of infantile esotropia [8]. Wright advocates that infantile esotropia may be the delayed maturation of the sixth nerve [4].

The treatment aims are to achieve normal ocular alignment and some level of binocular vision. Marshall Parks described a subnormal level of binocular vision, measured by level of stereoacuity, as the monofixation syndrome [9]. A microtropia of less than 10 prism diopters with peripheral fusion helps maintain good ocular alignment. Patients with a microtropia have a central suppression scotoma and some have measurable stereopsis. Monofixation is considered a successful outcome of infantile esotropia treatment. The Worth 4-dot test can demonstrate monofixation even in the absence of a measurable esotropia, showing a suppression response at distance but a fusion response at near [10]. Overall, the treatment goal of infantile esotropia is to retain or improve binocularity. The following cases will help illustrate these points.

Case Examples

Case 1 (Table 45.1)

Table 45.1 Case 1

Chief complaint: "Eye crossing." **HPI:** • 4 month old male presents with eye crossing. • Began at 1 month of age. Unchanged since then. Constant. • Mainly right eye, but sometimes left eye • Vision normal per history • No other contributory past ocular or medical history.		
	OD	OS
UCVA	Fix and follow (no preference)	Fix and follow (no preference)
Motility	Full ductions and versions	Full ductions and versions
Deviations (At distance without correction) (Figures 45.1a and b)	35 ET 35 ET / 35 ET / 35 ET 35 ET	
Deviations (At near without correction)	35 ET'	
Cycloplegic Retinoscopy	+1.25 +0.75 x 105	+1.25 + 0.75 x 075
Assessment	Esotropia, likely infantile.	
Plan	1. Recommend BMR recession 5.0 mm for 35 ET.	
Interval history (3 months later)	Had EOM surgery. Now post op week #6. 7 months old.	
	OD	OS
UCVA	CSM (no preference)	CSM (no preference)
Motility	Full ductions and versions	Full ductions and versions
Deviations (At distance without correction)	6 ET 6 ET / 6 ET / 6 ET 6 ET	
Deviations (At near without correction)	8 ET'	
Assessment	Esotropia s/p BMR recessions with good post-op alignment in monofixation range.	

(continued)

Plan	1. Observe alignment for now. 2. Routine interval follow-up	
Interval history (2 years later)	Eyes have remained straight since surgery.	
	OD	OS
UCVA (Allen Line)	20/30	20/30
Motility	Full ductions and versions	Full ductions and versions
Deviations (At distance without correction)	4 ET 4 ET 4 ET 4 ET 4 ET	
Deviations (At near without correction)	6 ET'	
Stereopsis	+ fly, 1/3 animals.	
Worth 4 Dot	Suppression at distance. Fusion at near.	
Cycloplegic Retinoscopy	+1.00 sphere	+1.00 sphere
Assessment	Esotropia s/p BMR recessions with monofixation syndrome and some stereopsis.	
Plan	1. Continue to observe alignment. 2. F/U yearly.	

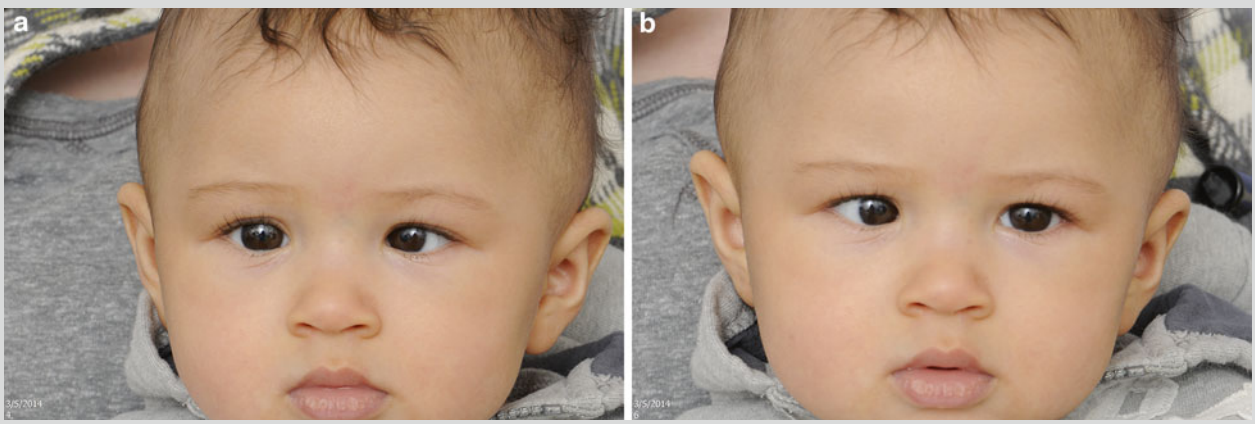

Fig. 45.1 Patient with infantile esotropia. This patient spontaneously alternates fixation: (**a**) right eye fixating and left eye deviating and (**b**) left eye fixating and right eye deviating

Clinical Synopsis

This is a 4-month-old boy with a large-angle esodeviation that manifested shortly after birth. The patient spontaneously alternated fixation without a fixation preference. Cover testing revealed a 35 prism diopter esotropia at distance and near. Cycloplegic retinoscopy revealed minimal refractive error, and an accommodative component to the esotropia was excluded. Bilateral medial rectus recessions of 5.0 mm were performed with a satisfactory result. Follow-up examinations demonstrated an alignment within monofixation range with some stereopsis.

Case 2 (Table 45.2)

Table 45.2 Case 2

Chief complaint: "Eye crossing." **HPI:** • 8-month-old female presents with eye crossing. • Began at birth. Unchanged since then. Constant. • Either eye will cross. Occasionally, one eye "floats up." • Vision normal per history • No other contributory past ocular or medical history.		
	OD	OS
UCVA	CSM (no preference)	CSM (no preference)
Motility	2+ inferior oblique overaction	1+ inferior oblique overaction
Deviations (At distance without correction) (Figures 45.2A and B)	45 ET 45 ET, small LHT | 45 ET | 45 ET, RHT 45 ET	
Deviations (At near without correction)	45 ET'	
Cycloplegic Retinoscopy	+0.50 +1.00 x 90	+0.50 +1.00 x 90
Assessment	1. Esotropia, likely infantile. 2. Bilateral inferior oblique overaction	
Plan	1. Recommend BMR recessions 5.75 mmfor 45 ET with bilateral inferior oblique myectomies.	
Interval history (3 months later)	Had EOM surgery. Now post op week #6. 11 months old.	
	OD	OS
UCVA	CSM (no preference)	CSM (no preference)
Motility	Full ductions and versions	Full ductions and versions
Deviations (At distance without correction)	8 ET 8 ET | 8 ET | 8 ET 8 ET	

(continued)

Deviations (At near without correction)	8 ET'	
Assessment	Esotropia s/p BMR recessions, BIO myectomies with good post-op alignment in monofixation range.	
Plan	1. Observe alignment for now. 2. Routine interval follow-up	
Interval history (2 years later)	Eyes have remained straight since surgery.	
	OD	OS
UCVA (Allen Line)	20/25	20/25
Motility	Full ductions and versions	Full ductions and versions
Deviations (At distance without correction)	8 ET 8 ET 8 ET 8 ET 8 ET	
Deviations (At near without correction)	8 ET'	
Stereopsis	+ fly, 0/3 animals.	
Worth 4 Dot	Suppression at distance. Fusion at near.	
Cycloplegic Retinoscopy	+0.25 +0.50 x 090	+0.25 +0.50 x 090
Assessment	Esotropia s/p BMR recessions, BIO myectomies with monofixation syndrome and some stereopsis.	
Plan	1. Continue to observe alignment. 2. Follow-up yearly.	

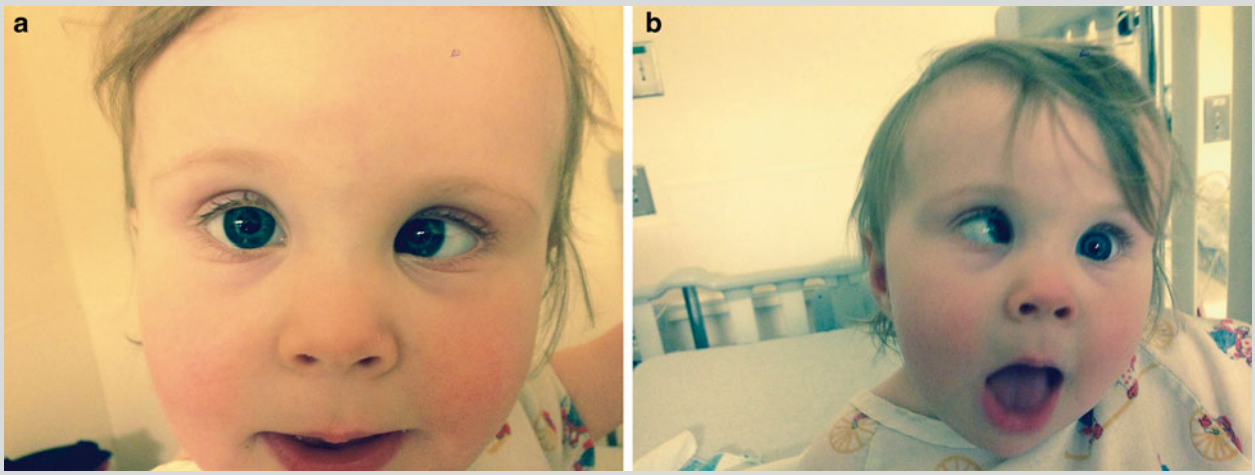

Fig. 45.2 Preoperative images of patient with infantile esotropia with (**a**) right eye fixating and left eye with esodeviation and (**b**) left eye fixating with right esodeviation and hypertropia secondary to inferior oblique overaction

Clinical Synopsis

This is an 8-month-old patient with a large-angle esodeviation that was noted at birth by the parents. Examination revealed no fixation preference and a large-angle esodeviation with associated inferior oblique overaction in both eyes. Cover testing revealed a 45 prism diopter esotropia at distance and near. Cycloplegic retinoscopy revealed minimal refractive error, and an accommodative component to the esotropia was excluded. Bilateral medial rectus recessions of 5.75 mm and inferior oblique myectomies were performed. Follow-up measurements indicated a postoperative outcome within the monofixation range with some recovery of stereopsis.

Evidence for Effective Diagnosis and Treatment

Diagnosis Transient misalignment of the eyes is common shortly after birth. However, exotropia is usually seen, whereas esotropia is rare [2]. A constant esodeviation at birth or soon after should be investigated. A diagnosis of infantile esotropia is made based on the clinical manifestations. A history with a full ophthalmic examination, including a dilated fundus exam and cycloplegic refraction, is required. The following clinical findings help to diagnose infantile esotropia:

(a) Many children with infantile esotropia **alternate fixation** between the two eyes. They may also **cross fixate**, using the adducted eye to view the opposite field of gaze. For instance, the child will use the right eye in adduction to view the left visual field. Amblyopia, however, can still be present or develop in 40–72 % [2, 11]. The Congenital Esotropia Observational Study (CEOS) found that amblyopia frequently develops and needs to be screened during evaluation [12].

(b) The angle of deviation is often **large**, between 40–60 prism diopters or higher [1, 7, 13]. It can be comitant (same measurements in all positions of gaze), although it is difficult to measure at distance in very young children. Alternate prism and cover testing is the gold standard, but this may also be difficult in this age group. Therefore, the Krimsky method is often used. The deviation is **constant**. The CEOS determined that smaller or intermittent deviations of <40 pd in infants first examined at <20 weeks of age could be spontaneously resolved [14].

(c) Children with infantile esotropia usually have **refractive errors** normal for their age [1]. Normal amounts of hyperopia are found in the infantile form of esotropia, whereas high hyperopia is generally found in accommodative types of esotropia. The CEOS found that 23 % of children with congenital esotropia had a refractive error above +3.00 D [12].

(d) **Dissociated vertical deviation** (DVD) is the slow upward deviation of one eye, without a corresponding and concomitant downward shift of the other eye. DVD is now recognized as part of a wider spectrum of ocular movement disorders that are present in the context of infantile strabismus and referred to as dissociated strabismus complex; while the direction of most dissociated deviation is vertical, some are horizontal and, if that is the predominant direction, are referred to as dissociated horizontal deviations (DHD). It can be manifest or latent, present only when the eye is occluded. It can be bilateral but is often asymmetrical. The incidence is between 46 and 92 % of patients with infantile esotropia [13, 15]. It generally manifests later than the esodeviation, sometimes up to early adulthood. The incidence of DVD may be declining possibly because of earlier surgery and better binocular fusion [16].

(e) **Inferior oblique overaction** (IOOA) is characterized by the elevation of the eye in adduction, while the other abducting eye is relatively hypotropic to the first one. If one covers the abducting eye, the elevated adducting eye will go down and so will the abducting eye under cover, obeying Hering's law. IOOA can be unilateral or bilateral and asymmetric. The presence of IOOA can lead to and be associated with a V-pattern esotropia (larger esotropia in downgaze) and fundus excyclotorsion. Like DVD, inferior oblique overaction may only become evident later in the course of esotropia.

(f) **Latent nystagmus** is a horizontal jerk nystagmus elicited when one eye is occluded. The CEOS identified latent nystagmus in 1 % of patients at the initial/baseline presentation (1–3 months of age) and 3 % at the outcome exam (4 to <5months) [12]. The presence of latent nystagmus makes patching therapy in amblyopia difficult because fixation with the amblyopic eye may actually worsen as the nystagmus is elicited.

(g) **No limitation of abduction** is present in infantile esotropia. Full abduction can be elicited with occlusion of one eye or the doll's head maneuver. True limited abduction is a sign of Duane syndrome or sixth nerve palsy.

(h) **Smooth pursuit asymmetry** is present in infantile esotropia. Smooth pursuit asymmetry is normal in all children up to 5 months of age. Temporal to nasal pursuits are accurate, and nasal to temporal pursuits are delayed. However, this asymmetry continues into adulthood in infantile esotropia, likely due to the early disruption of binocularity [17].

When evaluating a patient with esotropia, obtaining a thorough history is essential, including past medical history, birth history, and family history. The CEOS found that infantile esotropia is often familial [12]. Fixation preference and the induced tropia test can help assess for amblyopia. Ductions and versions should be evaluated during examination. Occlusion or the doll's head maneuver may be necessary to elicit full abduction. Alternate and prism cover testing or the Krimsky method can be used to measure or estimate the angle of strabismus. Measurements during distance fixation can be attempted; however, near measurements using prism and cover test or the Krimsky method are often easier to obtain in infants. A dilated fundus exam and cycloplegic refraction are necessary and can provide clues to possible associated conditions or to alternative diagnoses.

See Table 45.3 for a list of differential diagnoses.

Table 45.3 Differential diagnoses of infantile esotropia

Pseudoesotropia
Duane's retraction syndrome
Cranial nerve VI palsy
Accommodative esotropia
Sensory esotropia
Moebius syndrome
Nystagmus blockage syndrome

Management Amblyopia and any degree of significant (>+2.50 D) hyperopia should be treated first in patients with infantile esotropia. Amblyopia is treated with occlusion therapy or other forms of penalization with the end goal of demonstrating alternate maintained fixation. When high hyperopia is present, children can be treated with a trial of glasses with the full cycloplegic refraction to rule out an accommodative component. Correction of refractive error is generally attempted hyperopia is greater than +2.50 D [18]. Smaller amounts of hypermetropia may also be corrected at the discretion of the treating ophthalmologist.

Treatment The goal of treatment is orthotropia, with the hope of attaining some degree of sensory fusion. Monofixation syndrome, as described earlier, is considered a successful result of treatment, and it may help to maintain acceptable ocular alignment later in life [9].

Performing surgery prior to 2 years of age in an attempt to obtain some binocular fusion is widely accepted [10]. Earlier surgery has been advocated by some authors, as the critical period of binocular vision is at 3–4 months [19, 20]. The CEOS suggests that esotropia that is constant and greater than 40 prism diopters is unlikely to spontaneously resolve after 4 months of age [14]. Therefore, surgery is generally performed after 4 months of age and most commonly between 6 months and 2 years of age. Some have advocated surgery even earlier than 6 months of age, because the likelihood of attaining any degree of stereopsis declines with increasing age [21]. However, there are arguments for delaying surgery as well, including anesthesia risks, difficulty obtaining consistent or accurate measurements on young children, and the possibility of spontaneous resolution.

Primary surgery can be either bilateral medial rectus recessions or a unilateral recess–resect procedure [22, 23]. If there is an undercorrection and additional surgery is needed, bilateral lateral rectus resections or a unilateral recess–resect on the other eye can be performed. Bilateral medial rectus recessions are preferred, as they appear to result in less incomitance. Unilateral recess–resect procedures are done more often on the amblyopic eye in cases with dense amblyopia. See Table 45.4 for suggested surgical dosages [24, 25]. Other surgeries include three or four muscle surgeries for large esotropia [26, 27] or larger bilateral medial rectus recessions [28]. These should be done cautiously as they may lead to early or late overcorrections. DVDs may require surgical intervention if they are large or if they manifest frequently. Superior rectus recessions are widely used, but some use anteriorization of the inferior oblique, especially if there is concomitant inferior oblique overaction. Inferior oblique overactions are treated with recessions or myectomies when inferior oblique overaction is significant or when a hypertropia is present.

Table 45.4 Surgical table for esotropia

Deviation (in prism diopters)	Medial rectus recession (mm)	Lateral rectus resection (mm)
15	3	4
20	3.5	5
25	4	6
30	4.5	7
35	5	8
40	5.5	9
50	6	10
60+	6.5	10

For bilateral procedures, perform ***x*** mm recessions (or ***y*** mm resections) on both eyes. For unilateral procedures, perform ***x*** mm recession on the medial rectus and ***y*** mm resection on the lateral rectus. Based on author's experience and teachings from mentors [24, 25]

Botulinum toxin has been used to induce an incomitant deviation that may lead to a face turn and theoretically promote fusion [4]. However, multiple injections are needed and results are more variable. Risks and side effects of botulinum toxin include temporary ptosis, a temporary effect from the toxin; exotropia, risk of globe perforation; and repeated anesthesia exposure [29].

Younger patients are followed frequently in the postoperative period. Overcorrections after surgery can occur and require additional surgery in the form of an advancement of the already recessed medial rectus muscles or bilateral lateral rectus recessions. Residual esotropia can respond to the correction of any hypermetropia after a cycloplegic refraction [30], as should any accommodative component. If the esotropia persists, additional surgery can be performed, either in the form of bilateral medial rectus re-recessions or bilateral lateral rectus resections. Amblyopia should be evaluated at every visit and treated promptly. Neurologic improvement in motor skills and psychosocial benefits, have been observed in some children after strabismus surgery [31–33]. Figure 45.3 provides a summary of evaluation and management of a patient with infantile esotropia.

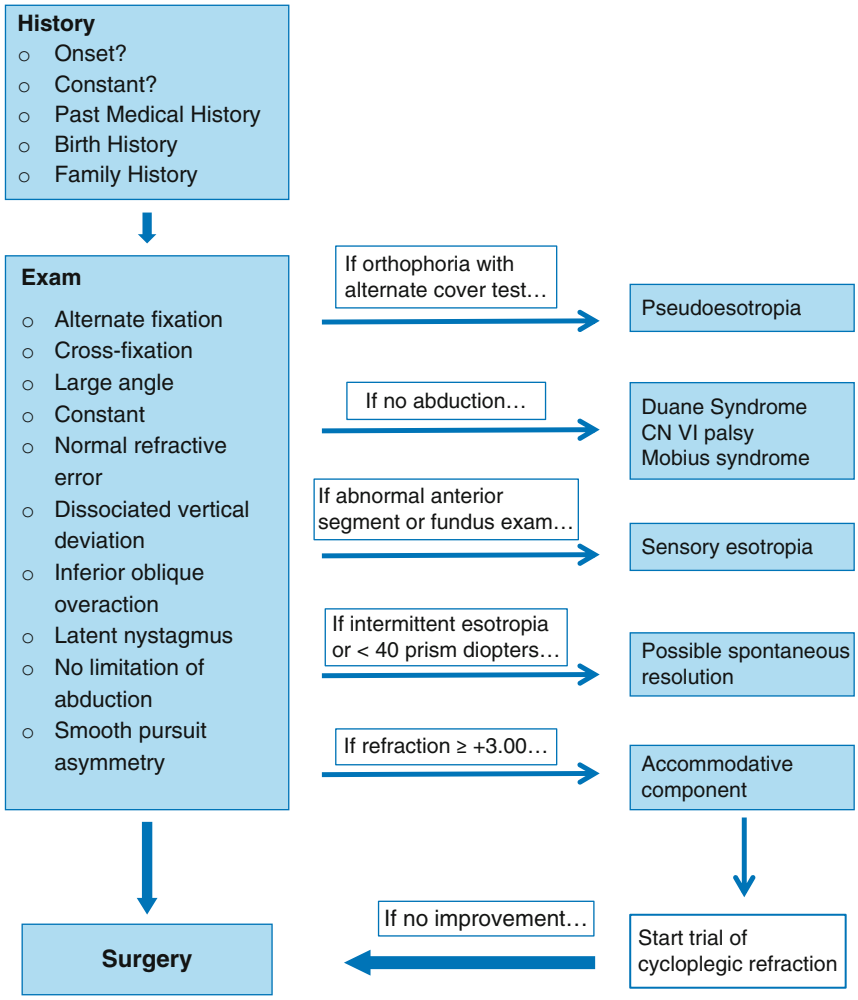

Fig. 45.3 Algorithm for evaluation and treatment of infantile esotropia

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Diagnostic Challenges in Acquired Non-accommodative Esotropia

46

G. Robert LaRoche

Abstract

The sudden onset of an esotropia in childhood can be a challenging diagnostic dilemma for the ophthalmologist, especially when the child is healthy, the refraction is near normal and the family history is negative. Because of the possibility of a neurological cause, many will resort to neuroimaging in the setting of a normal full clinical examination and prior to initiating a treatment such as surgical correction. This chapter will examine the diagnostic challenges of such cases as well as examination findings that can help guide the clinician to the appropriate diagnostic evaluation and therapy.

Keywords

Neurogenic esotropia • Suppression • Diplopia • Magnetic resonance imaging

Introduction

Acquired non-accommodative childhood esotropia is acquired esotropia that is *not* related to the accommodative effort of an uncorrected or partially corrected hyperopia nor to a response to accommodation for near targets. Affected children typically present with an esotropia that developed rather acutely and are found to have refractive errors close to or within the normal range for their age. The angle of strabismus is also generally comitant. The onset and lack of relation to accommodation present a diagnostic challenge in that the clinician must decide whether a neurological investigation is necessary because of the possible neurogenic nature of the strabismus. Previous reports in the literature refer to this presentation as "acute acquired comitant esotropia" [1]. Beside the description in the literature of seemingly simple clinical groupings [1], one can find numerous case and series reports as well as various recommendations on the need for diagnostic imaging [2]. The classical grouping descriptions are typically: (1) esotropia following disruption of binocularity; (2) unexplained rapidly progressive acute onset esotropia, said to be of the "Franceschetti" type; and (3) the acute onset esotropia associated with mild myopia of "Bielschowsky". All three groups usually have a normal or near normal sensory status before the development of their strabismus. This observation is most relevant in consideration of both the diagnosis and treatment in these cases, as will be discussed below. However, specific cases may fail to fit into one of these categories and the possibility of a potential neurogenic cause leaves clinicians uncomfortable before setting a definitive management plan, including surgery [4]. Hence, in this chapter, the indications for neuroimaging investigations in cases of acquired childhood non-accommodative esotropia will be discussed. This discussion will serve as an evidence-based guide, and we will try to avoid leading the reader to blanket recommendations such as imaging all patients. This would be an easy solution, but certainly not practical, and would add unnecessary risks in younger patients who need sedation for an MRI, and clearly not be reasonable in the setting of our responsibility to use healthcare resources appropriately and avoid unnecessary tests.

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Illustrative Cases

Case 1

A 4-year-old girl with a family history of hyperopia on the mother's side but without strabismus or amblyopia is referred by the family optometrist with a 3-month history of intermittent esotropia at near initially, followed by what has now been a constant esotropia for 1 month. On careful history, she did close one eye while playing with her toys at the onset of the problem. She currently denies diplopia. She is otherwise healthy and has not changed her usual activities.

Case 2

A 5-year-old boy is sent for a second opinion after an unsuccessful routine surgery for an acquired esotropia that had started 6 months previously. The residual esotropia returned to almost the same amount as before the surgery. The child's refractive error is 0.75 D of myopia, and because of the recurrence and the angle being worse at distance, an MRI of his brain and orbits was ordered.

Case 3

A 4 year-old boy is referred by the emergency room physician for evaluation of an esotropia noticed by the parents for the first time 3 weeks prior. The child likely had diplopia as shown by his regular closure of one eye. He had an otherwise normal examination and, by history, had become an increasingly picky eater since his return from a vacation at his grandparents' cottage 3 weeks ago. His 6-year-old brother wears hyperopic glasses to "keep his eyes straight".

A Gold Standard Examination

The examination of young children is challenging, and testing can be inconsistent making differentiation of benign from the ominous in cases of acquired paediatric esotropia difficult. Indeed, the clinician must be acutely attuned to diagnostic or at least suggestive clues of a possible organic or neurological cause; these include pupillary signs, small differences of strabismic angle on side gazes or distance and near disparities, certain characteristics of the sensory adaptation to the strabismus or changes in development, behaviours or anomalies on a screening neurological examination (Table 46.1). Only a full and satisfactory examination can reliably yield such information and can be considered a gold standard. As a corollary to this, failure to obtain a *full* clinical evaluation will unfortunately require supplemental investigations when there is any degree of suspicion, and this will include neuroimaging in cases of acquired non-accommodative esotropia. This is an unfortunate situation in that the majority (>90 %) [2] of cases are not caused by organic causes.

Afferent Defects and Strabismus

It is imperative to ensure that the examination of any child with strabismus is **always** complete enough to fully determine the status of the visual system, including the afferent system. The finding of poor vision or other signs of disruption of the visual afference can help determine the possible sensory origin of an acquired esotropia. These include an afferent pupillary light response defects, the presence of optic nerve anomalies such as pallor or oedema, or secondary monocular nystagmus. Causes of sensory esotropia in children are numerous and can include retinoblastoma, posterior uveitides like toxoplasmosis and toxocara canis, post-traumatic injuries including cataract or central retinal scars, and many more. On the other hand, a straightforward anisometropic amblyopia can also present as a childhood-acquired esotropia. The sensory genesis of these cases of acquired esotropia is generally diagnosed promptly and is rarely much of a diagnostic conundrum for the trained clinician.

Table 46.1 Clinical differential diagnostic and suggestive signs of neurogenic acquired non-accommodative esotropia in children

Benign acquired esotropia	Neurogenic esotropia
Stable deviation during and between examinations	Variable deviation with hydrocephalus, Arnold-Chiari
Comitant	Lateral incomitance on measurements
No "A" or "V" incomitance	"V" pattern in bilateral VI
Same near and distance	Typically larger ET at distance in VI
No nystagmus (only small fixation nystagmus on ophthalmoscopy)	Clinically visible upgaze, or downbeat, or abduction nystagmus
Diplopia at onset	Diplopia persists
Suppression	Fragile suppression if present
Ability to fuse	Unable to maintain fusion
Normal neurological exam	Papilloedema, pupils and others
Little if any balance or activity changes	Neurological symptoms can include balance, appetite or personality changes

Efferent Problems and Strabismus

In addition to extraocular motor anomalies including the resulting esotropia, neurogenic esotropia can also be accompanied by pupillary response abnormalities (anisocoria, light-near disparity, hypo-accommodation) depending on the pathway disruption involved. Efferent defects can also include gaze deficits, nystagmus, auditory and vestibular function deficits, as well as additional cranial nerve dysfunctions and long tract deficits including motor and sensory pathways. These motor and pupillary findings may also be accompanied by symptoms and signs of increased intracranial pressure as well as other neurologic deficits depending on the severity and location of the CNS disruption. Positive findings necessitate neurological investigation including proper neuroimaging.

In the case of acquired neurogenic childhood esotropia, a sixth cranial nerve palsy is often high in the differential diagnosis (see Chap. 48 on "Sixth Nerve Palsy in Children"). Classically, the lateral gaze incomitancy with secondary deviation is present, but sometimes signs of mild bilateral VI are the only findings. In asymmetric bilateral cases, a greater esotropia is expected on the side of more significant gaze limitation. Other findings associated include abduction deficits, possibly some nystagmus by fixation duress, a "V" pattern incomitancy; however, in the instance of mild bilaterality, only a divergence deficiency, with an exclusively distance esotropia, is found. In some patients, however, the esotropia has been reported as comitant without an apparent abduction deficit. Various intracranial neoplasms have been implicated in acquired childhood comitant esotropia. Astrocytoma of the cerebellum and the corpus callosum, medulloblastoma of the cerebellum and various tumours of the hypothalamic region have all been implicated [2]. What remains unclear is the mechanism by which these varied locations of neoplastic processes can cause a comitant deviation, especially those with only few, if any, of the associated oculomotility signs described above, even in the late stages of the disease, including a complicating hydrocephalus. The Arnold-Chiari malformation (type II) has also been associated with childhood-acquired esotropia. The deviation is predominantly comitant and is characteristically variable, as are the many other possible signs and symptoms in this entity, notably, for example, headaches, loss of balance and vertical downbeat nystagmus with oscillopsia. The involvement of the fourth ventricule with an associated variable hydrocephalus has been implicated in this phenomenon: the variability of the pressure on the herniating neural structures by the foramen magnum could induce a variable mild VI paresis, hence, a variable esotropia with little incomitancy. However, the likelihood of finding other neurological signs is very high in such cases. All the above motor diagnostic signs can be rather subtle in cases of neurogenic acquired childhood esotropia, and they will understandably be even more difficult to detect in uncooperative children.

The Neuromotility Assessment

The clinical signature of acquired neurogenic esotropia can include signs of multiple paretic processes in addition to those signs of associated efferent defects mentioned above. Therefore, in addition to a good pupillary examination, the mere clinical observation of oculomotor movements, including ductions, versions or saccades, is rarely sufficient or reliable for a critical assessment towards a clear diagnosis in many cases. This is true especially in younger children who might not cooperate fully. Recording of saccades could be suggested [5–6], but few have access to this diagnostic modality, and again cooperation can be a problem for this investigation. While videos and still photos are helpful, ultimately, only careful prism and cover test measurements can be relied upon to give the information needed. For example, a subtle sixth cranial nerve paresis can only be detected by the measurement of a slightly greater angle of esotropia at distance accompanied by a small V pattern incomitancy. These can occur without any apparent abduction deficit or even lateral gaze incomitancy. However, they constitute solid findings that will indicate the true neurological nature of an acquired esotropia.

The search for other associated extraocular motor deficits is also paramount, and again, a careful orthoptic assessment can help. For example, good lateral gaze measurements can confirm the possibility of a sixth nerve dysfunction, as will a three-step test (See Fig. 49.1, Chap. 49 on "Diagnosis and Management of Fourth Nerve Palsy in Children") confirm fourth cranial nerve problem. Variation or progression of carefully measured angles from one visit to the next highlights the importance of repeating examinations within a short follow-up interval if suspicious findings are present. Children with ocular myasthenia can present with such variations, while a progressive neurogenic esotropia will either get worse, be variable or become accompanied by other signs or symptoms.

Sensory Adaptation to Strabismus

In order to understand the usefulness of the sensory evaluation of an acute non-accommodative childhood esotropia, we need to understand the strabismus disease process when there is no associated neurological cause. In these cases of "benign" acute esotropia, the strabismus occurs in children with normal binocularity including bifoveolar fixation and good sensory fusion leading to normal stereopsis. A few, like in the general population, will have an unsuspected microtropia with relatively good sensory fusion but more apt to be disrupted by various extraneous factors like monocular visual disturbance, systemic illness, stress, etc. The deviation here is generally comitant both at near and at distance. The rare cases of myopic acute esotropia (Bielschowsky type) will initially show an esotropia at distance only. Nevertheless, there is no significant A or V pat-

tern in these cases and there is no abduction deficit or nystagmus. The correction of the patient's myopic or hyperopic refractive error will only marginally change the amount of esotropia. The exception is in the case of a decompensated microtropia with induced break of binocularity. In this instance, the refractive correction, even if only modest, can improve the esotropia significantly and actually eliminate it completely. On sensory adaptation testing, in all the cases just described, the acquired deviation will, within a few weeks, generally become associated with the well-known phenomenon of image suppression in young children with an immature visual system. The perceived image originates from the deviating eye and is eliminated to prevent confusion and diplopia. This suppression becomes alternating depending on which eye is fixating. However, the suppression mechanism is ineffective if the angle of strabismus is variable or if it increases over a short time, resulting in a diplopia. In most cases of childhood acute acquired esotropia, a timely realignment of the images will result in the restoration of stable binocular vision and recovery of stereopsis if present prior to onset of the esotropia. All these pathophysiological phenomena just described are typical of "benign" acute non-accommodative childhood esotropia occurrences where there is no neurological cause involved. This is **not** the scenario in neurogenic cases. Indeed, in most of these, there will be a persistent diplopia and an absent suppression and a loss of fusional ability even when the separate diplopic images are realigned. The explanation for this could be a central disruption of fusion but this is still conjectural at best [3]. Nevertheless, because of this key difference, the assessment of suppression and fusional potential in cases of acute non-accommodative childhood esotropia is clearly warranted to help determine the true cause of the strabismus.

Review of the Cases

In **Case 1** presented at the beginning of this chapter, there was an alternating esotropia of 25 prism dioptre (PD) at distance that increased marginally to 30 PD at near. The child's refraction was +2.75 in each eye with a slightly larger cylinder at a different meridional angle in one eye. Corrected visual acuity was 20/25 OD and 20/30-3 OS. Her examination was otherwise normal, including pupils, optic nerve appearance, extraocular motility, *and* cranial nerves V, VII, VIII, IX, XI and XII, in addition to normal vestibular function and upper limb proprioception—all tested by the ophthalmologist at her first visit. She was re-examined 4 weeks later with her full refractive error corrected and was found to only show a small residual left esotropia of 2–3 PD (described as a "flick ET" in the chart) both at near and distance but with an additional esophoria of 8 PD at near. Motility was normal. Notably, her deviation was never measured larger at distance than near, nor did she had a "V" pattern alphabetical incomitancy, two signs of VI cranial nerve paresis. VA was 20/20 and 20/25, stereo was 200 sec arc, and the rest of her examination had not changed. In addition, her fixation on ophthalmoscopy as measured by a visuscope was slightly off the fovea, and there was a fine irregular unilateral very small amplitude "nystagmus" on the side of the poorer VA. A 4 PD base out test was positive for suppression on the left side on binocular viewing of a distance target. In the end, the patient was diagnosed with a decompensated microtropia secondary to uncorrected minimal hyperopia and anisometropia. She had fusion with stereo, but central suppression of the microtropic eye, fusional amplitudes as demonstrated by her residual esophoria at near, and she had no neurological anomalies on examination. Neuroimaging was not indicated or performed.

Case 2 originally presented with an acute esotropia and minimal myopia but no other abnormalities. He could fuse and did achieve good stereopsis on the synoptophore and on free space testing (Titmus®). The child was diplopic at times when the angle of deviation was larger, especially at distance. He underwent surgical correction of the deviation as measured on two occasions a few months apart. He was cooperative for the examination and healthy without neurological symptoms or signs. Unfortunately, his esotropia recurred post-operatively. His surgeon obtained an MRI, which was normal. Prior to ordering imaging, a full examination should have been completed. In the absence of any neurological symptoms or signs, a prism adaptation test could have been considered. It was nevertheless performed and revealed an additional "fusionable" angle of 25 PD. The patient underwent surgery for the full measured angle and recovered well with recovery of full binocularity. This case illustrates the need for a full orthoptic assessment to uncover the total magnitude of the latent angle of strabismus and to correct it prior to surgical intervention. It is also interesting that the child had an effective suppression for his initial distance angle but had diplopia at his larger angle when fully dissociated after his second surgery. These are both normal pathophysiological phenomenon of normosensorial acquired strabismus in children. (The reader can refer to Chaps. X and 2 on "Extraocular Motor Examination" and "Sensorial Adaptation Testing, respectively".)

In **Case 3**, the patient underwent a comprehensive examination with dilation and cycloplegic refraction demonstrating hyperopia of +3.25 D in each eye. The ocular examination was normal and the motility was normal; the esotropia was comitant, measuring 25 PD at distance and 30 PD at near. The child was re-examined 6 weeks later wearing his full correction and found to have a residual esotropia of 20 PD at near and distance with normal motility (versions and ductions). He underwent surgical correction with resolution of

the esodeviation. However, he presented with new headaches and papilloedema on the second post-op visit 3 months later. The question that arises in this particular case is: what clinical clues were possibly available before surgery that could have indicated the presence of a brain tumour? In retrospect, the child never had a screening neurological examination, and one may argue that it was indicated considering the history of recent behavioural change and loss of appetite observed by the family as the same time as the onset of the esotropia. Both symptoms are subtle indices easily identifiable in retrospect, but only a reasonable degree of suspicion would bring this to the attention of the clinician. The pupils were "difficult to examine" and an orthoptic note mentions: "diplopia present", "no suppression" and "no fusion ability on synoptophore". We find here the indications of an incomplete ophthalmological examination as well as the presence of warning signs in the abnormal sensory response to a childhood strabismus. These are all red flags and should have been enough to trigger further investigations including neuroimaging. Finally, based on this example, one could argue that in all cases of acquired esotropia, a pre-operative fundus examination of the disks before proceeding with strabismus surgery is a worthy additional safeguard; this has in fact become our current practice.

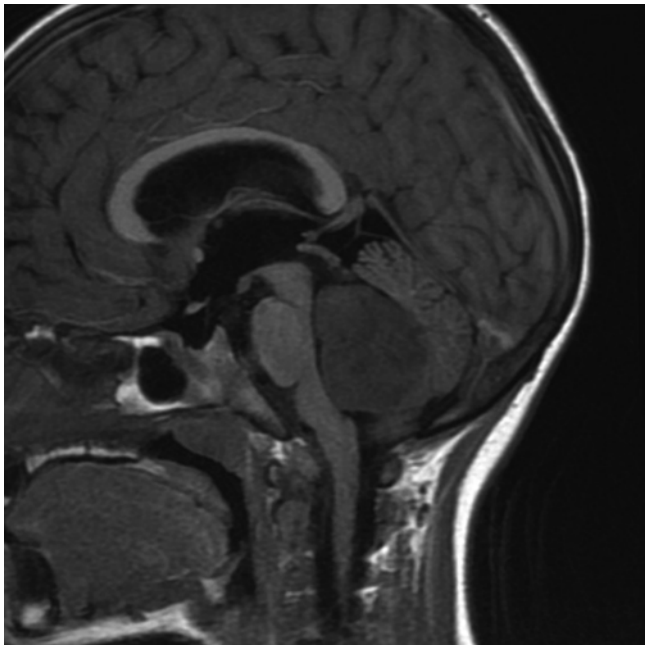

Fig. 46.1 MRI image of posterior fossa medulloblastoma that can reach large proportions before causing severe neurological signs and symptoms. It can present as an acquired comitant non-accommodative esotropia with few other subtle clues

Comparing the Cases

What sets these three scenarios apart is the presence of a central nervous system organic cause in the third case, the treatment of which obviously falls outside the realm of ophthalmology. Indeed, the child had a posterior fossa medulloblastoma (Fig. 46.1) requiring surgical resection and radiation therapy but was instead initially treated with a unilateral horizontal two muscle surgery. The other two cases are typical acquired esotropia with slightly different clinical presentations and with specific treatment needs. However, they could have easily been mistaken for cases with a more dire diagnosis unless some important clinical characteristics were identified, thereby preventing unnecessary costly and stressful investigations.

Concluding Comments

While the decision threshold for neuroimaging needs to be low in cases of acquired childhood esotropia, the majority of cases are "benign" and not caused by an ominous neurological process and can be treated satisfactorily with optical, orthoptic or surgical means. However, to insure the rare organic cases are not missed, a systematic ophthalmologic examination with attention to afferent and efferent abnormalities, gaze incomitancies and distance-near disparities, response to sensory adaptation testing and neurologic examination can help to differentiate benign from neuropathologic processes. Once a truly complete clinical evaluation is successfully completed, and only then, a handful of cases of acquired childhood esotropia will need neuroimaging in the face of uncertainty. In cases where the initial examination is inconclusive, a repeat examination with short interval of follow-up should be considered.

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Management of Accommodative Esotropia

47

Monte A. Del Monte

Abstract

Accommodative esotropia in its many forms is a common type of childhood strabismus. It presents first with intermittent esodeviation and then, if undiagnosed and untreated, progresses to a large constant esotropia that threatens normal development of binocular vision, stereopsis, and even visual acuity with the development of amblyopia. Therefore, early detection of intermittent eye crossing by parents and primary care physicians is required followed by rapid referral to eye care practitioners knowledgeable in the proper diagnosis and medical as well as surgical treatment of this condition to allow for optimal visual and cosmetic benefit. The referral ophthalmologist or optometrist must know the typical presenting history, signs, and symptoms. A complete pediatric eye exam is required including most importantly a cycloplegic refraction, the results of which, with the other clinical findings, are required for proper diagnosis and treatment. A trial of spectacles, with or without bifocals, to correct the full hyperopic refractive error is necessary to confirm the diagnosis and determine ongoing treatment options. If spectacles adequately align the eyes allowing best possible vision and binocular vision development, then proper ongoing follow-up is required until visual and ocular maturity. But if not, then strabismus surgery should be performed. Most experienced strabismus surgeons prefer bilateral medial rectus recession to treat the esotropia in residual refractive or non-refractive accommodative esotropia, but the exact surgical dosing is controversial. This chapter will review the latest information on this topic, emphasizing clinical pearls and a new surgical protocol for treatment that has proved very useful in the treatment of these challenging, yet rewarding patients.

Keywords

Accommodative esotropia • Strabismus • Esotropia • Strabismus surgery

Introduction

Accommodative esotropia is the most common form of esotropia in early childhood, accounting for up to 50 % of all childhood esodeviation [1]. While infantile esotropia syndrome is often present early, before 6 months of age, accommodative esodeviation does not usually become noticeable to others until after 1 year of age, with crossing in most patients first noticed by family and primary care physicians between 1 and 4 years old (although some cases of fully refractive accommodative esotropia have been seen in infants as young as 2–4 months of age [2]). Refractive accommodative esotropia is caused, in most cases, by larger than normal amounts of hyperopia in early infancy, which result in the development of initially intermittent esotropia due to the larger amount of accom-

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modative convergence associated with accommodating for the higher hyperopia or to a dysregulation of the amount of accommodative convergence required in some patients with more normal amounts of hyperopia. The children are usually orthophoric at birth in spite of the increased hyperopia, as they have no need to accommodate to see fine detail during the first months of life. As the infant has increasing visual need to see more clearly, the increasing associated accommodative convergence required when accommodating for clear vision causes initially intermittent and later constant esodeviation. The child is presumed to have to choose between clear but double vision (or suppression) when accommodating vs. blurry but single vision if accommodation is relaxed. As the child becomes older, the need for a clear focused image becomes more important and the accommodative esodeviation increases in frequency and magnitude (depending on the degree of hyperopia or dysregulation of accommodative convergence) until it becomes constant. In the author's experience and in the literature, the constant esotropia associated with untreated accommodative esodeviation for as little as 2–4 months can result in loss of binocular vision and stereopsis and increased risk of strabismic and possibly refractive amblyopia [3]. Early referral by pediatricians and family practitioners to an ophthalmologist for evaluation and treatment of suspected esotropia is therefore very important.

Whereas children with infantile esotropia syndrome often present early with a large esodeviation of >40 PD and later with associated inferior oblique overaction, dissociated strabismus complex, and latent nystagmus, those with accommodative esotropia generally present later with an intermittent small to moderate esodeviation noted with attention, which increases without treatment to a larger constant deviation of up to 50–60 PD. Diagnosis must first be established by ruling out other organic causes of esotropia, such as structural abnormalities, reduced vision, amblyopia, Duane syndrome, or sixth cranial nerve palsy. Then a cycloplegic refraction is required to document the full amount of hyperopic refractive error. Most normal newborn infants will demonstrate small amounts of hyperopia, with spherical equivalent of plano to +2.00 or +3.00 diopters. Hyperopia of greater than this amount raises the suspicion of a refractive accommodative etiology, with many patients demonstrating over +5.00 or +6.00 D of hyperopia (although some have only minimally increased in hyperopia).

The first step in the diagnosis and treatment of accommodative esotropia is to determine if full-time wear of the full hyperopic cycloplegic correction will realign the eyes with evidence of binocular vision and fusion. Some children initially resist wearing glasses, possibly because they have difficulty relaxing the large amounts of tonic accommodation they require for clear vision. In those patients, "atropine relaxation," with prescription of 0.5 or 1 % atropine drops OU daily for 5–7 days, will promote acceptance of glasses wear. Repeat evaluation of visual acuity, alignment, and binocular vision/stereopsis is then completed after the child has been wearing the glasses regularly for at least 4 weeks. Successful alignment with orthophoria, a small esophoria of < 10 PD or monofixational small intermittent esotropia within 6–8 PD of orthophoria, usually with demonstrable improvement in binocular vision and stereopsis is consistent with a diagnosis of fully refractive accommodative esotropia and successful treatment with glasses alone.

Accommodative esotropia with high accommodative convergence to accommodation (AC/A) ratio (also called accommodative non-refractive esotropia) is another form of acquired esotropia in young children. Children with accommodative esotropia and a high AC/A ratio present at 2–6 years of age with a near angle of esodeviation which is greater than the distance angle by more than 10 PD (clinical method) or an AC/A ratio calculated by the gradient method of greater than 5 [4]. These children may have only a very small angle or even no esodeviation at distance viewing, with or without glasses, to correct a generally small degree of hyperopia but demonstrate a larger near deviation outside the angle where binocular vision is possible. Associated findings such as inferior oblique overaction, dissociated strabismus complex, and latent nystagmus are much less common than in infantile esotropia. The most common treatment for these children is the prescription of glasses to correct all or enough of the cycloplegic refractive error to align the eyes at distance, with the addition of a +2.50 or +3.00 D bifocal to allow for fusion at near fixation. A flat top "D" style of bifocal with the line fit high just below or bisecting the pupil in primary gaze is prescribed to encourage use. Most children adapt to this treatment and realize the benefit of binocular vision and stereopsis at near to spontaneously seek the bifocal for near accommodative targets. This can easily be confirmed by noting a chin elevation to use the bifocal when a small

accommodative target is presented at near before the upper segment of the lens. After use of the bifocal becomes automatic and the child approaches the preteens or teens, where cosmesis is more important, a progressive or blended bifocal can be used.

Controversy exists on the appropriate ongoing medical and/or surgical treatment of accommodative esotropia after diagnosis is established. As noted previously, most pediatric ophthalmologists agree that the optimal initial treatment of these children is spectacle correction of all or nearly all of the hyperopia to "relax the excessive accommodation" and realign the eyes. If satisfactory alignment with maximal binocular function is obtained with spectacles with or without bifocals, then observation is indicated to document continued successful alignment, binocular visual function, and binocular visual development without surgery. Parents often ask why surgery cannot be performed to eliminate the need for glasses. I have found that a discussion of the natural history of accommodative esotropia and the likelihood of the hyperopia naturally decreasing from 5 to 15 years of age as well as the possibility of improving fusional divergence by slowly weaning the spectacles can often eliminate the need for glasses without surgery. In fact, if surgery is done too early and the child later outgrows the hyperopia naturally or needs to wear glasses or contact lenses for visual improvement in the presence of very high hyperopia, a consecutive exotropia may occur because of reduced accommodative effort requiring further eye muscle surgery! Most families understand this logic and agree to continue glasses use if successful alignment is possible with glasses or contact lenses alone.

If the child is not realigned after wearing the glasses for 4–6 weeks, then strabismus surgery is recommended to correct the residual angle of esodeviation outside the monofixation range (>8–10 PD) for distance or near fixation (while wearing the full hyperopic correction +/− a bifocal if needed) to allow for maximal binocular vision development and to prevent amblyopia.

There is controversy concerning the optimal dose of surgery. This chapter will discuss this controversy and review a new surgical protocol for surgical dosing that has proved very successful to me in treating these patients.

The Problem

Strabismus surgeons generally agree that bilateral medial rectus recession is the procedure of choice for residual accommodative refractive or non-refractive esotropia, but the surgical dose remains a subject of controversy. Traditionally, standard surgery has been based on residual deviation at distance after full hypermetropic correction [5]. However, this has resulted in an unacceptably high rate of undercorrection—as much as 49 % [6]—and reoperation rates ranging from 9 [7] to 43 % [7, 8]. In response to the high rates of undercorrection with standard surgery, augmented surgery has been advocated to increase the surgical dose. Strabismus surgeons have proposed a number of different protocols for surgical augmentation (see below). Most select specific patient characteristics or test results on which to base the augmentation. However, no consensus has been established as to which dosage augmentation is optimal.

Over the past 25 years we have used a protocol for augmented surgery based on the average of near deviation with correction (through the upper segment if there is a bifocal) and distance deviation without correction. We have been interested in assessing the factors influencing the success and effectiveness of this surgical protocol. Our rationale for selecting this surgical protocol is physiologically based on the following two parameters with a goal of maximizing the chance for surgical correction with a single procedure with minimal chance for overcorrection or undercorrection. We chose the near deviation with correction because even if overcorrection occurs, we still have the option of decreasing the amount of hyperopic correction in the glasses to realign the eyes. However, we would not want to correct more than the distance deviation without correction beyond which even complete glasses removal would still require additional surgical intervention. Hence, the near deviation with correction and distance deviation without correction gives us a safe range within which manipulation of the refractive correction is possible to achieve orthophoria or monofixational alignment with all its advantages to the developing visual system. For example, if a patient has the following alignment: Distance without glasses = 50 PD, Near without glasses = 60 PD, Distance with glasses = 20 PD, Near with glasses = 30 PD, our target angle would be an average of 50 and 30 PD = 40 PD.

Case Examples

Case 1 (Tables 47.1 and 47.2)

Table 47.1 Case study 1

Clinical history	3-year-old girl with history of intermittent crossing of left eye for the past 8 months		
Key components of exam		*OD*	*OS*
	UCVA	20/40 (Allen)	20/50
	Ductions/versions	Full	Full
	Alignment Dsc	50 ET	
	Alignment Nsc	60 ET	
	Cycloplegic retinoscopy	+5.00	+6.00
	Stereo	Negative fly titmus	
Diagnosis	Probable accommodative esotropia with mild left amblyopia		
Management	Rx with +4.75 D OD, +5.75 OS Follow-up in 2 months		
Interval history (2 months)	Patient refused glasses, then relaxed into them with atropine 1 % OU q daily for 1 week. Now wears well		
Key components of exam		*OD*	*OS*
	UCVA/BCVA *Rx confirmed	20/30	20/30–3
	Alignment Dsc/cc	55 ET/20 ET	
	Alignment Nsc/cc	70 ET/20 ET	
	Stereo	Negative randot	
Management	Schedule surgery for target angle = 35 PD (recess medial rectus 5 mm OU)		
6 weeks post-op visit			
	Alignment Dsc/cc	25 ET/5 E	
	Alignment Nsc/cc	30 ET/6 E	
	Stereo	100 s Titmus	
Management	Continue current glasses		
Interval history (4 months)	Patient wears glasses well, removes only for sleep and baths, loves her glasses!		
Key components of exam		*OD*	*OS*
	UCVA/BCVA *Rx confirmed	20/25 (Allen)	20/25 (Allen) *Tested first
	Alignment Dsc/cc	25 ET/orthophoria	
	Alignment Nsc/cc	30 ET/orthophoria	
	Stereo	60 s Titmus	
Management	Excellent functional and cosmetic alignment, continue current glasses. Amblyopia resolved with glasses alone so no need for patching. Follow-up every 6 months and test with −1.00 clip-ons to see if can wean plus		

Table 47.2 Calculation of surgical dosage for case study 1

	With full distance correction	Without correction
Distance viewing	20 ET	50 ET
Near viewing	20 ET	60 ET

Target angle = Near with distance correction (20) + Distance without correction (50) ÷ 2 = 35 PD (Plan: recess medial rectus muscle OU − 5 mm)

Clinical Synopsis

Case 1 is a 3-year-old child with a typical presentation of acquired intermittent esotropia at 28 months of age, becoming progressively larger in magnitude and almost constant. Exam reveals a mild left amblyopia secondary to mild anisohyperopia OS with high hyperopia in both eyes. Spectacle correction was prescribed for the full

(continued)

hyperopic correction –0.25 D OU. Glasses compliance was initially poor but improved following atropine relaxation. Follow-up examination after wearing the glasses well for 5 weeks revealed residual accommodative esotropia outside the monofixation range with glasses. The esotropia with and without glasses at both distance and near was measured and a target angle of correction of the average of near with distance correction and distance without correction was used to calculate surgical dosing using standard surgical tables (See Appendix 9 Surgical Planning and Numbers). Examination 6 weeks after surgery revealed an excellent surgical result with spontaneous resolution of amblyopia and monofixational stereo, which was stable throughout follow-up.

Case 2 (Tables 47.3 and 47.4)

Table 47.3 Case study 2

Clinical history	A 4-year-old boy with history of intermittent crossing of left eye since 2.5 years old. ET diagnosed by local optometrist and glasses dispensed		
Key components of exam		*OD*	*OS*
	VAcc	20/25 (Single Snellen)	20/25
	Wearing	+5.50	+5.75
	Ductions/versions	Full	Full
	Nsc/cc	70 ET/35 ET	
	Dsc/cc	60 ET/20 ET	
	Cycloplegic RNS	+6.50 + 0.50 × 90	+6.75
	Stereo	Negative fly Titmus	
Diagnosis	Accommodative ET with high AC/ratio, only partially corrected with current glasses. Moderate residual ET, no stereo		
Management	Rx with +6.25 + 0.50 × 90 OD; +6.50 OS with +3.00 add OU Follow-up in 2 months		
Interval history (2 months)	Good compliance with new glasses—"alignment improved"		
Key components of exam		*OD*	*OS*
	BCVa	20/25–2	20/25–3
	Alignment Nsc/cc/bifocal	70 ET/25 ET/10 ET	
	Alignment Dsc/cc	55 ET/18 ET	
	Stereo	Negative randot	
Impression	Partially accommodative ET with high AC/A ratio confirmed. Still outside monofixation range with best correction/bifocal		
Management	Schedule surgery for target angle = 40 PD (Recess medial rectus 5.5 mm OU)		
6 weeks post-op visit			
	Alignment Nsc/cc/bifocal	20 ET/15 XT/20 XT	
	Alignment Dsc/cc	12 ET/12 XT	
	Stereo	100 s Titmus	
Management	Test with −1.00 and −2.00 over Weaken glasses and remove bifocal: Rx: +4.25 + 0.50 × 90 OD; +4.50 sphere OS with +1.50 bifocal OU		
Interval history (2 months)	Patient wears glasses well, "eyes much straighter," uses bifocal well		
Key components of exam		*OD*	*OS*
	BCVa	20/25 Snellen	20/25
	Alignment Nsc/cc	18 ET/E(T)5	
	Alignment Dsc/cc	12 ET/orthophoria	
	Stereo	60 s Titmus	
Management	Continues with excellent alignment at distance and near with excellent stereo. Will be followed at 6 month intervals in orthoptic clinic with trial of −1.00 clip-on lenses to see if he will tolerate weaning over the next 10–12 years		

(continued)

Table 47.4 Calculation of surgical dosage for case study 2

	With full correction	Without correction
Distance viewing	18 ET	55 ET
Near viewing/distance correction	25 ET	70 ET
Near viewing/bifocal	10 ET	

Target angle = Near with distance correction (25) + Distance without correction (55) ÷ 2 = 40 PD (Plan: recess medial rectus muscle OU – 5.5 mm)

Clinical Synopsis

This 4-year-old boy has a history of intermittent esotropia first noted at 2.5 years of age. He was initially seen by his local optometrist who documented ET and high hyperopia and glasses were prescribed. He was followed for 6 months with improvement in alignment with his glasses but with residual esotropia, especially with near work, his parents brought him for a second opinion. Examination revealed moderate hyperopia and esotropia that was partially corrected at distance by his glasses. But he continued to have a larger esotropia at near secondary to a high AC/A ratio in spite of glasses that corrected all but 1.0 diopter of his hyperopia. The power of his lenses was increased to the full cycloplegic hyperopic correction and added a +3.00 flat top D bifocal fit high for the high AC/A ratio. He returned 6 weeks later with marked improvement in his distance ET but continued to have moderate ET at near, not corrected with the bifocal. He underwent strabismus surgery to correct the residual non-accommodative esotropia using the augmentation protocol, target angle of correction being the mean of the near ET through the upper segment of his spectacles and the distance ET without correction. With this dosing he initially developed a small overcorrection. He was tested in the office with −1.00 and −2.00 clip-on lenses over his current glasses and he demonstrated best alignment and stereo with −2.00 over his glasses and could tolerate reduction of his bifocal to +1.50. He has continued to do well with these glasses. The plan is to wean him off first his bifocal and then his distance hyperopic correction in small 1.0 D steps as tolerated between 5 and 15–16 years of age to be completed when puberty is completed. In general, little additional weaning is possible after this time and if residual esodeviation is still present and the hyperopia is low enough to allow comfortable vision without glasses or contact lenses, then strabismus surgery could be considered in selected cases.

Surgical Approach for the Treatment of Residual Esotropia in the Setting of Accommodative Esotropia

Surgical treatment of residual accommodative esotropia after spectacle correction of full or nearly full hyperopic refractive error has been unsatisfactory with relatively high rates of undercorrection reported previously in the literature.

A number of protocols for surgical dosing have been presented in the literature for the treatment of residual esotropia after refractive correction of accommodative esotropia. Table 47.5 summarizes the findings of several published studies using a number of protocols for surgical dosing. Marshall Parks recommended adding 1 mm to recession of each medial rectus to the dose for the distance esotropia with correction if a high AC/A is present [9]. Jotterand and Isenberg advocated a target angle equal to half the sum of the distance non-accommodative angle and the distance angle measured without correction [10]. In 12 patients augmented medial rectus recessions of 0.8 mm ± 0.2 were performed using the formula, and in 8 patients who had previous medial rectus recession, bilateral lateral rectus resection was augmented by 1.7 ± 0.8 mm. With a mean follow-up of 26 months, 13 patients (65 %) were within ±10 PD of orthophoria and 4 (20 %) were undercorrected. Wright published the results using a target angle determined by averaging the near deviation with full hyperopic correction and near deviation without correction [11]. In a retrospective review of 40 patients using this augmentation followed for at least 1 year, 88 % had postoperative deviations of ET/XT ≤ 10 PD but the other 12 % were exotropic in original glasses. Reducing or eliminating glasses could correct 4/5 of these overcorrected patients, but others have suggested that patients with significant overcorrection requiring reduction of significant plus to obtain realignment are unstable on long-term follow-up. West and Repka reported success in eight patients with a high AC/A ratio when surgical dosing was based on the distance angle and 25 based on the near angle measured with distance correction, the near angle patients dosed with a variable augmentation of 1.0–6.5 mm (mean 3.1 mm) per eye [12]. Eighty percent success in motor alignment was reported in the near angle augmented surgery group. Kushner used the near angle with full hyperopic distance correction in a group of patients with partially accommodative esotropia with a high accommodative convergence/accommodation (AC/A) ratio and reported retrospective 15-year follow-up results on a cohort of 22 patients from a

Table 47.5 Compares characteristics and results the present protocol with other published studies

Author	Success criteria	Success (%)	Overcorrect (%)	No of subjects	Target angle
Jotterand and Isenberg 1988 [10]	ET ≤ 10	65	15	20	Average of Dcc, Dsc
Multicenter prism adapt 1990 [19]	Deviation ET/XT ≤ 8	83	3.3	61	Full prism adapted angle
Wright 1993 [11]	Deviation ET/XT ≤ 10	88	12	40	Av of Nsc, Ncc
West and Repka 1994 [12]	Deviation ET/XT ≤ 10	80	8	25	Ncc augmented (AC/A >10)
Kushner 2002 [13] (15 years. f/u)	ET<10	86	4.5	22	Ncc
Leo and Del Monte 2006 [16]	ET ≤ 10	88.5	3.4	87	Av of Ncc, Dsc

It is noteworthy that the present study has the highest number of subjects. Despite more stringent criteria (any initial exodeviation was considered a failure), the success rate obtained compares favorably with other studies. In addition, the overcorrection rate is low

previously reported prospective clinical trial [13]. Eighty-six percent retained satisfactory alignment with only 6/19 needing optical correction for alignment although eight more needed to wear glasses for vision. In his study, only one patient needed bifocals for near alignment and all patients showed some sensory fusion, 8/19 with 40 s of stereo and another 8 with 60–200 s.

Other surgical procedures have also been recently reviewed for the treatment of residual accommodative esotropia. Akar, Birsen et al. reported on the results of treatment of residual accommodative esotropia with a high AC/A ratio with Faden operations with (365/473) or without (108/473) symmetric medial rectus recessions [14]. Successful alignment was achieved in 76.9 % at 1 month after surgery and 71.3 % at last follow-up visit with mean follow-up of 4.8 years. Ellis, Pritchard et al. reported in the 2011 Richard G. Scobee Memorial Lecture on retrospective results comparing augmented medial rectus recession (58 patients), slanted medial rectus recessions (27 patients), and medial rectus recession with posterior fixation suture (22 patients) [15] in reducing the distance/near disparity, not actually eliminating esodeviation. At all follow-up periods the patients with slanted recessions showed the greatest reduction in distance/near disparity and the most stable alignment. These authors noted that augmented recessions and slanted recessions were safer and more easily performed and recommended and that slanted recessions are preferred for treatment of residual accommodative esotropia with convergence excess.

Although other methods have been described and reported to be effective in certain forms of residual accommodative esotropia present after full hyperopic spectacle correction, the author has developed and described here a novel surgical protocol for surgical dosing in these patients that physiologically adjusts the amount of augmentation in any individual patient based on the proportion of the esodeviation correct by the spectacles; more augmentation when the greater non-refractive accommodative convergence is present and less when the glasses correct most of the esodeviation. This protocol has proven very effective in correcting a large cohort of patients with residual non-refractive over convergence (residual accommodative esotropia), with a prolonged success rate that compares favorably with other published studies. The protocol has proven safe with a low overcorrection rate and excellent binocular development. Here follows are the details of the protocol and the results achieved in a large number of patients.

Results of a New Protocol for Surgical Treatment

A novel protocol for surgical dosing was developed to be more physiological than simple standard augmentation and relatively easy to apply. We published the surgical results in a cohort of consecutive patients treated at the Kellogg Eye Institute/University of Michigan Mott Children's Hospital using this protocol [16]. This was a retrospective review of all patients operated upon by the author between 1990 and 2000 using this protocol. Inclusion criteria were residual esotropia after full hypermetropic correction, surgery after 6 months of age, postoperative follow-up for at least 6 months, and no associated palsy. Patients with A or V patterns from overacting oblique muscles were included as they are commonly seen in this group of patients in clinical practice. In addition, patients with Down syndrome or developmental delay who met other inclusion criteria were also included in the study. Preoperative details recorded included patient's sex, age, duration of symptoms, and socioeconomic status determined by type of insurance. Preoperative sensory status was assessed using the Titmus test at 33 cm. Preoperative alignment was determined at 6 m and 33 cm. The AC/A ratio

Table 47.6 Shows the guidelines used throughout the study for determining the amount of medial rectus recession

Esotropia (PD)	Recession of each MR (mm)
15	3
20	3.5
25	4
30	4.5
35	5
40	5.5
50	6
60	7

is determined by the gradient method wearing full correction. All patients underwent cycloplegic refraction. Bilateral medial rectus recessions for target angle determined after two stable measurements were performed using a fornix incision. All medial rectus muscles were directly sutured to the sclera and the "hang-back" technique was not used. The target angle, as determined according to the protocol, was the average of near deviation in primary gaze with correction (distance correction if a bifocal was present) and distance deviation without correction. Table 47.6 shows the surgical table [17] used throughout the study for determining the amount of MR recession.

Postoperative data were collected from medical records for visits that took place 2 months, 6–9 months, and 2 years after the initial surgery. Postoperative sensory status was assessed using the Titmus test at 33 cm. Postoperative alignment was determined using the simultaneous prism and cover test at 6 m and 33 cm. The spectacle correction worn by the patient was recorded. Any improvement in sensory status was considered success. Success in alignment was defined as orthophoria or esotropia or intermittent exotropia of less than or equal to 10 prism diopters with or without glasses. Any initial exotropia was considered failure.

Eighty-seven consecutive patients were initially reviewed who met all inclusion criteria with all records available and underwent bilateral medial rectus muscle recession according to the protocol over a period of 8.5 years from July 1996 to Dec 2004. Preoperatively, the mean distance deviation without correction was 36.0 PD, the mean near deviation without correction was 45.5 PD, the mean near deviation with correction was 33 PD, and the mean near deviation with correction was 30.0 PD, 31 % wore bifocals for a mean AC/A ratio or 8.2 with 43.7 % having an AC/A ratio >10. Gross stereopsis was present in 30 %, fine stereopsis in 20 %, and no stereopsis in 50 %. The mean target correction was 33 PD.

Two months following surgery, without manipulation of glasses, 77/87 patients (88.5 % of patients) had successful alignment with ET ≤ 10 PD (any XT was considered a failure) and 70 % had an improvement of stereopsis. Interestingly, surgery was augmented enough such that ten patients (13 %) had successful alignment with unchanged visual acuity without glasses. three patients (3.45 %) were initially overcorrected. Two patients had a trial of reduced hyperopic correction without benefit and required reoperation at 16 and 24 months post-op. The other responded and no additional horizontal surgery was required. Seven patients (8.05 %) were under corrected ≥ 10 PD at distance or near in original glasses. With the addition of bifocals in two patients and improved compliance with glasses in two more, four additional patients achieved early success (94.3 %). One patient refused additional treatment and two needed reoperation at 4 and 14 months post-op.

Successful alignment was still present in 86.7 % of 75 patients at 6–9 months post-op and 94 % of 50 patients who were still being followed at least 2 years after surgery, continued to be aligned at distance and near, 14 % with no glasses, 48 % with appropriate distance glasses, and 38 % with glasses containing a bifocal averaging +2.66 D.

Follow-Up Pearls

A major goal of the long-term follow-up of patients with successful surgical realignment is further weaning of spectacle bifocal and hyperopic correction to eventually maintain at least monofixational alignment without bifocals (so contact lenses are an alternative) or even without any hyperopic spectacle correction at all. We found that possible using our novel surgical dosing protocol and the following spectacle weaning technique. Weaning is attempted at each visit after stable fusion has been established with current correction, in some patients as early as 3–4 years of age but certainly by 6–8 years. The technique is as follows: After complete motility measurements are completed with and without current glasses at distance and near, a −1.00 clip-on lens is applied over the current spectacles and visual acuity and motility measurements repeated after several minutes to allow adjustment of accommodation to the new demand. If the child remains esophoric or demonstrates only intermittent esotropia of less than 5–6 PD without loss of vision or stereo, the spectacle correction can be reduced by up to 1.0 D and new lenses prescribed. Ideally the bifocal is weaned first in 1.0 D steps to allow the use of contact lenses in early teens if desired. When the bifocal is gone, then an attempt to wean the distance hyperopia can be initiated. Beware, however, if a preteen or early teen child reports decreased vision with his/her glasses or is noted to look over them frequently. This finding, especially in the child with relatively mild hyperopia, suggests the glasses have become "overplus" (too hyperopic) as emmetropization has occurred. In this setting, recheck the vision with the −1.0 D clip-ons or repeat cycloplegic refraction often reveals the current glasses to be too strong and in that

case the distance hyperopia must be reduced to less than the full cycloplegic hyperopia to encourage spectacle use rather than weaning the bifocal first as desired.

Patients and their parents often ask what is the likelihood of weaning out of bifocals or distance hyperopic correction while still maintaining satisfactory alignment and binocular vision. The answer depends on the size of the esodeviation, the amount of hyperopia, and the child's age. In our study cohort, maximum weaning must usually be accomplished by the end of puberty, 14–15 years for girls and 15–16 for boys. After that, strabismus surgery can be considered in selected cases if further weaning out of bifocals or entirely from spectacles is desired. Successful elimination of glasses was possible in about 50 % of patients starting with less than 4.0 D hyperopia but only 10 % of those with over 4.0 D. In our study utilizing a weaning strategy as discussed above, at last visit only 8 % continued to require full cycloplegic correction ranging from +1.75 to +6.5 D while 16 % tolerated removal of the bifocals, 22 % tolerated reduction of distance Rx as well as removal of the bifocal and 54 % (with final cycloplegic refraction ranging from −1.75 to +3.75 D) were completely weaned out of spectacles for alignment control [16]. Using a similar planned weaning strategy in a small retrospective pilot study with only ten patients, Hutcheson et al. [18] reported a similar 60 % success in weaning spectacles. However, their study was too small to provide further information on factors predictive of success.

Summary

Accommodative esotropia is a common form of childhood strabismus that requires specialized knowledge concerning appropriate diagnosis, treatment, and follow-up to achieve optimal success, in many cases without surgery. The goals of treatment either medical or surgical are to promote bifixation or monofixational alignment with good fusional amplitudes, refined stereopsis, and normal visual acuity in both eyes. Glasses can be eventually weaned as long as alignment is maintained. This chapter provides a comprehensive approach to the medical and surgical management of accommodative esotropia. While many approaches to surgical dosages have been published, the author presents a pragmatic approach that has proved successful in his practice and that of others.

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Sixth Nerve Palsy in Children

48

Scott E. Olitsky and Timothy P. Lindquist

Abstract

Sixth nerve palsy is a cause of incomitant esotropia that increases in the field of action of the paralytic lateral rectus muscle. Acquired palsies are much more common than congenital, and etiologies include trauma, neoplasm, elevated intracranial pressure, infection, and inflammation, as well as other miscellaneous and idiopathic causes. Due to the high association of sixth nerve palsy with brain tumors in children, neuroimaging is generally indicated. Sixth nerve palsies must be distinguished from entities such as Duane retraction syndrome and Möbius syndrome, both of which possess distinct clinical features that are not present in isolated sixth nerve palsy. Partial or complete recovery of acquired sixth nerve palsies are common, compelling observation until at least 6 months of stable misalignment prior to surgical intervention. Conservative management seeks to avoid amblyopia if the palsy occurs during the period of visual development or to relieve diplopia if it occurs after visual maturation. The goal of surgical management, often utilizing muscle transposition procedures, is to restore binocularity in primary gaze and provide the greatest field of single binocular vision.

Keywords

Sixth nerve palsy • Lateral rectus palsy • Esotropia • Muscle transposition • Incomitant strabismus

Introduction

Paralytic strabismus, a motor imbalance caused by paresis or paralysis of one or more extraocular muscles, is characterized by a variable ocular deviation that depends on the direction of gaze and the fixating eye; the deviation is greatest in the field of action of the paretic muscle and increases in magnitude when the patient fixates with the paretic eye. Older children and adults with acquired paralytic strabismus usually have diplopia with or without an anomalous head position. It is important to distinguish paralytic strabismus from comitant forms of strabismus in order to institute the appropriate diagnostic and therapeutic interventions. Acquired paresis or paralysis may indicate a systemic or neurological abnormality. The treatment of paralytic strabismus, especially in patients with diplopia, may be challenging and the results may not be totally satisfactory; hence, the physician must carefully educate the patient and family to maintain realistic expectations in terms of the goals of treatment.

The distribution and etiology of third, fourth, and sixth nerve palsies in adults at the Mayo Clinic have been

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extensively reviewed by Richards and co-workers [1]. In their series of 4278 cases, abducens nerve palsy was the most common, followed by oculomotor nerve (26.8 %) and trochlear nerve (15.4 %) palsies. Thirteen percent of patients had multiple cranial nerve involvement. The most common etiologies included: undetermined, head trauma, neoplasm, vascular, and aneurysm. In contrast, a similar study of pediatric patients demonstrated that the most common cranial nerve affected was the trochlear nerve (36 %), followed by the abducens (33 %) and the oculomotor nerve (22 %). Multiple nerve palsies accounted for 9 % of cases in this series. The most common etiology was congenital for third and fourth nerve palsy, undetermined for sixth, and trauma for multiple nerve palsies [2].

In other large series of abducens nerve palsies, neoplasm or removal of neoplasm was the most frequent cause followed by increased intracranial pressure (ICP), idiopathic, trauma, congenital, post-viral, and inflammatory [3, 4]. In another series of 12 patients in whom patients with papilledema or other neurologic signs were excluded, neoplasm was the most common etiology especially in older children [5]. Thus, in contrast to adults in whom microvascular insults are the most common etiology for sixth nerve palsies, noplasm, and disorders of the central nervous system are relatively common in children, hence the need for careful clinical examination and neuroimaging.

In this chapter, we will discuss the anatomic course of the sixth nerve, etiology, and differential diagnosis of congenital and acquired sixth nerve palsies in the pediatric population, examination findings, diagnostic testing, and management.

Anatomical Course of the Cranial Nerve VI (CN VI) Abducens Nerve

The nucleus of CN VI is located in the caudal pons and is composed of two populations of cells: motor neurons that innervate the lateral rectus and interneurons of the contralateral medial longitudinal fasciculus that pass to the contralateral third nerve nucleus. Thus, a sixth nerve nuclear lesion will result in an ipsilateral horizontal gaze palsy. Fibers of cranial nerve VII (CN VII) loop around the CN VI nucleus, and therefore, pontine lesions may cause both CN VI and VII paralyses. CN VI exits ventrally from the pons and continues into the subarachnoid space along the clivus and perforates the dura mater below the crest of petrous portion of the temporal bone. It then passes through the inferior petrosal sinus and beneath the petroclinoid (Gruber) ligament into Dorello's canal, where it enters the cavernous sinus. Within the cavernous sinus, unlike the other cranial nerves that are situated in the lateral wall, the sixth nerve lies within the body of the sinus near the carotid artery. CN VI then enters the orbit through the superior orbital fissure within the annulus of Zinn to innervate the lateral rectus muscle. The tethering of CN VI to the petroclinoid ligament as well as structural and vascular anatomic relationships to the sixth nerve makes it more susceptible to increased intracranial pressure. The anatomic locations where CN VI is most susceptible to injury are depicted in Fig. 48.1.

Clinical Examination

Acute sixth nerve palsies cause an esotropia in primary position that increases in the field of action of the paretic lateral rectus muscle. The palsy may be unilateral or bilateral. Patients with a unilateral palsy maintain binocular vision by adopting a lateral gaze preference away from the side of the palsy with a head turn toward the palsied muscle. The distance deviation is usually greater than one measured at near fixation, and the deviation is greatest when the patient fixates with the paralytic eye (secondary deviation). The child may appear to have a lateral gaze palsy as he/she may try to avoid diplopic field of gaze. Motility can be assessed by doll's head or spinning the patient to determine isolated abduction deficit. In contrast, a patient with a bilateral CN VI palsy will not adopt a head turn unless the paresis is asymmetric.

A history of trauma, neoplasm, recent infection, or vaccination should be elicited. A thorough review of systems with attention to other focal neurologic deficits or new onset of headaches should be completed. Specific features that raise suspicion for increased intracranial pressure include emesis upon awakening, a headache that awakens the child in the night or upon supine positioning, wooshing in the ears, and/or transient visual obscurations. The clinical examination should be complete and include visual acuity, pupils (assess for afferent or efferent pupillary abnormalities), and motility examination. The motility examination includes ductions, versions, and deviation in nine gaze positions with careful attention to the fixating eye while completing the measurements at distance and near. Ophthalmoscopy after pupillary dilation should be performed to evaluate for optic disk edema. All cranial nerves should be examined as this may help to localize the lesion. For example, if facial weakness is present, this may be consistent with a pontine or early fascicular lesion (e.g., pontine glioma) or congenital condition such as Möbius syndrome.

Etiology

Congenital Sixth Nerve Palsy

Congenital sixth nerve palsy is rare [6–10]. In newborns, a transient lateral rectus paresis may be rarely noted, with resolution by 6 weeks of age [11, 12]. Most infants with a sig-

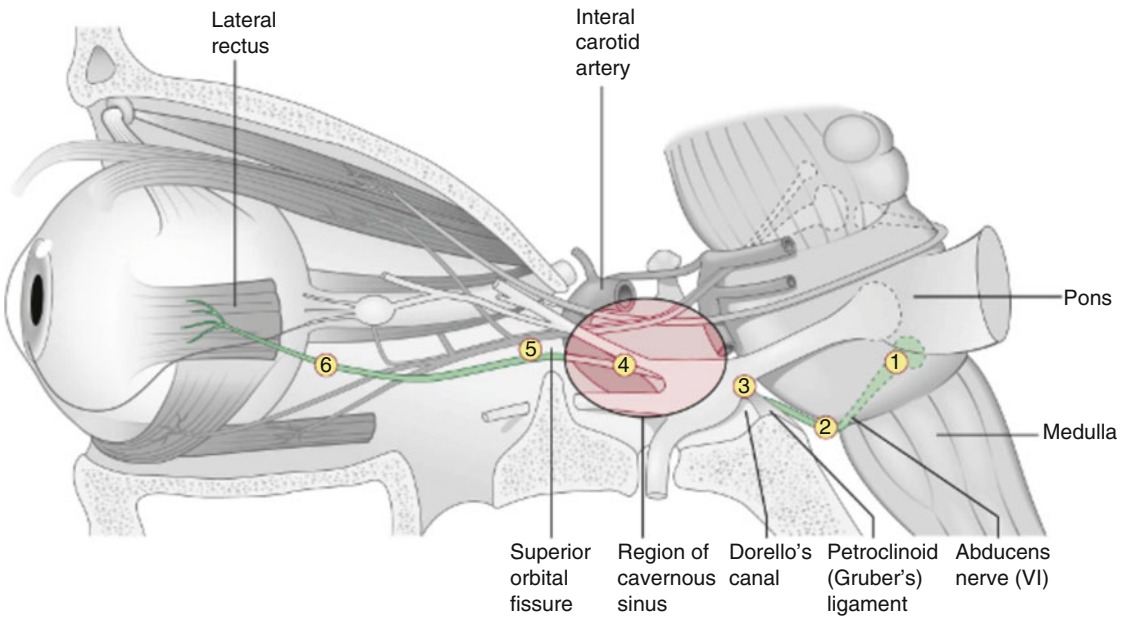

Fig. 48.1 Origin and course of the sixth nerve. Anatomic correlates of etiologies of sixth nerve palsies. (1) Brain stem syndromes. (2) Stretch and compression of the sixth nerve in the subarachnoid space from increased intracranial pressure (downward displacement of brain stem results in stretching of the sixth nerve as it is tethered between the pons and Dorello's canal). (3) Infectious or inflammatory processes affecting the petrous bone impinging on the sixth nerve (Gradenigo's syndrome or Pseudo-Gradenigo's syndrome). (4) Cavernous sinus may involve multiple cranial nerves. (5) Inflammation or infection of orbit may involve multiple cranial nerves. (6) Isolated sixth nerve palsy (usually post-viral). Figure reproduced with permission by Peter Kaiser, MD, Figure 4–20 in Trattler WB, Kaiser PK, and Friedman NJ. Review of Ophthalmology, 2nd Edition. Elsevier-Saunders, 2012

nificant esotropia and what appears to be an abduction deficit usually have congenital esotropia with a cross-fixation pattern; this type of deviation can be distinguished from a sixth nerve palsy by demonstrating full abduction using a doll's head maneuver or by occluding one eye and presenting a target in a position that forces the child to abduct one eye or the other. Other causes of impaired abduction in infants include Duane retraction syndrome and Möbius syndrome. In the former, there is concomitant globe retraction and narrowing of the eyelid fissure or an upshot or downshoot in adduction (see Chap. 52 on Duane Syndrome). In Möbius syndrome, patients also have facial weakness in addition to a sixth nerve palsy and other anomalies including cleft palate, micrognathia, and dental anomalies. A history of poor feeding in infancy is often elicited secondary to weakness of the facial muscles.

Acquired Sixth Nerve Palsy

Several studies of sixth nerve palsies in children have found neoplastic disorders or their neurosurgical removal as the most common cause of acute sixth nerve palsies [2–5, 10, 13]. Other causes include trauma, elevated intracranial pressure of non-tumor etiology such as idiopathic intracranial hypertension or hydrocephalus, congenital and inflammatory disorders, post-infectious or viral, and other miscellaneous and idiopathic causes [2–5, 14].

While serious CNS abnormalities may be associated with sixth nerve palsies, "benign" sixth nerve palsies deserve special mention. Isolated benign sixth nerve palsies may be related to infectious or immunologic processes. For example, Knox and co-workers described a group of children in whom a sixth nerve palsy followed nonspecific viral illness [15]. Several investigators have described recurrent benign sixth nerve palsies, though these cases are thought to be associated with prior immunization or viral illness and are likely mediated by an immune reaction and subsequent inflammation [16–18]. Yousuf and Khan performed a meta-analysis of the clinical features of benign sixth nerve palsies reported in the literature and found that patients less than 14 months of age tended to experience recurrences [19]. A review by Mahoney and Lee found that most recurrent cases were temporally related to vaccination, but they did not find a relationship between young age and recurrence as in the former study [13]. Findings suggestive of a benign etiology include acute onset, history of recent viral illness or immunization, complete absence of abduction (whereas in increased ICP or progressive tumor progression, the palsy is more likely to be initially partial), no other cranial nerve involvement, or symptoms of increased intracranial pressure. Usually, complete resolution is observed in 3–6 months [20]; in some

cases, however, complete resolution is not observed especially in cases of multiple recurrences [17, 21]. In cases where complete resolution does not occur after an initial episode, or if additional neurologic symptoms develop, neuroimaging should be considered to ensure that an occult tumor is not present.

A rare form of CN VI paralysis occurs in the context of what is referred to as Gradenigo's syndrome, in which otitis media is associated with petrositis and edema of its dura or possibly thrombosis in the contiguous venous sinuses that compresses the sixth nerve against the petrosphenoidal ligament (Gruber's ligament) and as the nerve passes between the ligament and the dura of Dorello's canal (Fig. 48.1) [22]. This syndrome is characterized by sixth nerve palsy with associated facial pain, facial paralysis, and ipsilateral decreased hearing. The duration of this type of sixth nerve palsy is typically brief, lasting 3–6 weeks, as symptoms subside quickly with antibiotic therapy. Gradenigo's syndrome has become rare with the increased and effective use of antibiotics. Causes of pseudo-Gradenigo's syndrome in the pediatric population include cerebellopontine angle tumor (usually associated with fifth, sixth, seventh nerve palsies, ipsilateral decreased hearing, and papilledema) and petrous bone fracture (associated with CN V–VIII lesions, ipsilateral decreased hearing, cerebral spinal fluid otorrhea, and bruising over the mastoid bone).

Bilateral Sixth Nerve Palsy

Many of the causes of acute unilateral sixth nerve palsies can lead to bilateral sixth nerve palsies and include trauma, infections (meningitis, Lyme disease) [23], inflammation (Miller Fisher variant of Guillain-Barré) [24], increased intracranial pressure (usually partial), and structural (Chiari I malformation) and posterior fossa tumors (pontine glioma, medulloblastoma, cerebellar astrocytoma). Posterior fossa tumors cause unilateral or bilateral sixth nerve palsy by either direct compression or increased intracranial pressure from obstructive hydrocephalus. In cases of bilateral sixth nerve palsy, diplopia is present and a face turn is usually absent unless the abduction deficit is asymmetric. Visually immature patients must be monitored very closely for amblyopia.

Management of Patients with Sixth Nerve Palsy

In the case of the child with an acute sixth nerve palsy with or without other neurologic signs, a referral for neurologic evaluation including neuroimaging should be considered because of the high incidence of intracranial pathology associated with sixth nerve palsy in children [3–5]. If the evaluation is negative, the patient should be reexamined at regular intervals and the parents advised to observe for new signs and symptoms.

Initial management of unilateral sixth nerve palsy should be conservative. A majority of patients will recover spontaneously within 6 months [25]. Patients may adopt a compensatory face turn or simply occlude one eye to alleviate the diplopia. Young children who do not develop a compensatory face turn should have their eyes alternately occluded to prevent the development of amblyopia and suppression. During alternate patching, children can be given their full hyperopic correction to prevent the development of accommodative esotropia. In the case of acute sixth nerve palsy, botulinum injection into the ipsilateral medial rectus has been suggested to permit binocular vision in primary position during recovery [26–29]. This does, however, not appear to alter the recovery rate [30, 31]. Patients who initially present with bilateral palsies or a unilateral complete palsy with inability to abduct past the midline are less likely to recover within 6 months [32]. After observing the patient for 6 months for possible return of sixth nerve function, surgical treatment is considered. One has to remember that successful treatment of sixth nerve palsies may require multiple surgeries and use of postoperative prismatic correction [33].

A graded medial rectus recession and lateral rectus resection for the appropriate amount of esotropia may be performed in patients with some ability to abduct and some preservation of an abducting saccade. In those with a complete lateral rectus paralysis and a large esotropia, a transposition procedure is necessary with concomitant or subsequent medial rectus recession. Some authors have suggested that recessions of up to 12 mm may be necessary [10]. Resecting the lateral rectus in the setting of total paralysis is of limited utility.

A muscle transposition procedure may be necessary to restore alignment in primary position and to improve abduction. Several muscle transfer techniques have been popularized. The *Hummelsheim* procedure consists of transposing the lateral halves of the vertical recti to the lateral rectus [34]. A resection of the transposed halves of the tendon can be added to increase the effect of this procedure [35]. The augmented Hummelsheim procedure may be less effective in improving abduction than a full tendon transposition with posterior fixation suture [36]. The *Jensen* procedure involves splitting the vertical and lateral recti, tying the upper half of the lateral rectus to the lateral half of the superior rectus muscles, and doing the same with the inferior rectus [37–39]. A full tendon transposition of the vertical rectus muscles is utilized by many surgeons [40]. To

augment the effect of a full muscle tendon transposition, Foster introduced the lateral fixation suture [41]. In this procedure, a nonabsorbable suture is placed in the sclera 16 mm posterior to the limbus and adjacent to the lateral rectus muscle, incorporating one fourth of the transposed vertical rectus muscle. Foster found that the addition of a lateral fixation suture improved the tonic abducting force of the transposition procedure without compromising adduction. Akar and colleagues performed this technique on 50 eyes and demonstrated improvement of esodeviation by 99 %, abduction by 59 %, and useful binocular field of single vision in 71 % [42].

In addition to the transposition procedure, weakening of the ipsilateral medial rectus is often required to decrease the adduction force. There is an increased risk of anterior segment ischemia when three or more rectus muscles are operated on simultaneously, especially in older patients with poor circulation. Partial tendon transfers (Jensen and Hummelsheim) may decrease this risk. However, anterior segment ischemia has been reported even in young children using these modified, vessel-sparing techniques [43]. The use of intraoperative botulinum injection into the medial rectus combined with vertical rectus transposition surgery has been shown to be effective and eliminates the need to disinsert a third rectus muscle [40, 44, 45]. Transposition of only the superior rectus has been described, which also allowed for simultaneous MR recession in patients with severe abduction limitation [46]. Combining superior rectus transposition and MR recession improved esotropia, head position, abduction limitation, and stereopsis without inducing torsional diplopia. Two patients with complex sixth nerve palsies developed a vertical deviation in primary gaze using this technique [46].

Recently, a new technique was described in which a transposition without tenotomy was performed placing a suture in the muscle 10–12 mm from the insertion to draw the lateral third of each vertical rectus muscle to the respective temporal quadrant where it was then sutured to the sclera [47]. Additional studies are required to evaluate the efficacy of this approach.

Management of the patient with bilateral sixth nerve palsies is very similar to that of unilateral sixth nerve palsy. Unfortunately, these patients cannot overcome the diplopia with a compensatory face turn; therefore, surgical intervention or occlusion is necessary to relieve diplopia. It is important to note that in children, occlusion can be amblyogenic; hence, alternating the occluded eye is necessary to avoid amblyopia. If the deviation fails to resolve by 6 months and stability is observed, surgery may be warranted to attempt restoration of single binocular vision.

Case Study 1

A previously healthy 4-year-old presented with acute onset of "crossing." On initial observation, the patient has a right gaze preference and left face turn. The child complains of diplopia.

What Historical Questions Should be Elicited?

- Is there any history of trauma, recent viral illness, or immunization?
- Are there any headaches, change in sleep habits, or eating? Are there any focal neurologic deficits?

The patient did have his second dose of the measles, mumps, and rubella (MMR) 2 weeks prior. The clinical history is otherwise unremarkable.

Key Examination Findings

Visual acuity (uncorrected, HOTV linear)
OD: 20/20
OS: 20/20

Pupils: Equally reactive OU, no afferent pupillary defect
Sensorimotor examination:
Versions and ductions (Fig. 48.2): −4 abduction deficit left eye
Alignment:
Distance (sc):

	ET=35 PD	
ET=5 PD	ET=35 PD	ET=45 PD
	ET=35 PD	

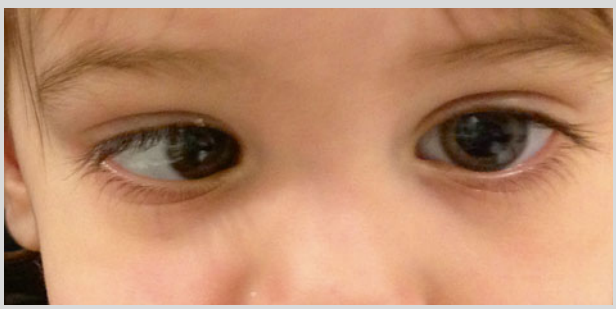

Fig. 48.2 Complete sixth nerve palsy in the left eye. Patient is unable to abduct the left eye past midline. All other versions and ductions were otherwise full

(continued)

Near (sc): ET′=25 PD
Stereoacuity: 60 s arc in preferred gaze position (nil in primary)
40 degree left head turn, right gaze preference

Cycloplegic refraction: +2.50 sph OU
Fundus examination: Healthy nerves, no edema, C/D 0.1 OU
Cranial nerves: CN II-XII intact with exception of VI

Assessment: Acute onset of sixth nerve palsy in setting of recent MMR vaccination. The patient is otherwise well and does not have any concomitant palsies or other focal neurologic deficits grossly. In addition, the patient does not have any optic disk edema or signs of increased intracranial pressure.
What are the next investigations that could be considered?

Management:
(1) Neuroimaging: Benign sixth nerve palsy is a diagnosis of exclusion.
Because of the high association of CN VI with CNS malignancies in the pediatric population, neuroimaging is needed (MRI with and without contrast). If this patient presented with papilledema and signs of increased ICP, MRI and MRV should be considered to evaluate for venous thrombosis. The MRI in this case was within normal limits.
(2) Lumbar puncture: If there was a concern for infection (e.g., meningitis) or increased ICP (e.g., pseudotumor cerebri syndrome), lumbar puncture could be performed following neuroimaging. Because this child was clinically well and the imaging unremarkable, the decision was made to not perform a lumbar puncture.
(3) Prevention of amblyopia: The clinician should encourage family to allow patient to maintain the adopted head position because he is fusing in this field of gaze. The patient should return for follow-up in 2–3 weeks to monitor for progression and/or amblyopia.

Interval history (4 weeks later): Patient is no longer turning his head as much.

Key Examination Findings

Visual acuity (uncorrected, HOTV linear)
OD: 20/20
OS: 20/20
Pupils: Equally reactive OU, no afferent pupillary defect
Sensorimotor examination:
Versions and ductions (Fig. 48.2): −3 abduction deficit left eye
Alignment:
Distance (sc):

	ET=40 PD	
ET=10 PD	ET=40 PD	ET=50 PD
	ET=40 PD	

Near (sc): ET′=25 PD
Strong right fixation preference (the left eye is unmaintained)
Stereoacuity: Nil
Worth 4-dot test: Suppression OS at distance and near
20 degree left head turn, right gaze preference

Assessment: Acute onset of partial sixth nerve palsy in setting of recent MMR vaccination with development of amblyopia OS.
Plan: Begin patching the right eye 2 h per day. Follow-up 3–4 weeks.
Interval history (4 weeks, 8 weeks after onset of sixth nerve palsy): Patient does not have head turn or double vision.

Key Examination Findings

Visual Acuity: (uncorrected, HOTV linear)
OD: 20/20
OS: 20/20
Pupils: Equally reactive OU, no afferent pupillary defect
Sensorimotor examination:
Versions and ductions: −0.5 OS
Alignment:
Distance (sc):

	ET=flick	
Ortho	ET=flick	ET=4–6 PD
	ET=flick	

Near (sc): Ortho
Stereoacuity: 40 s arc
Assessment: Resolving sixth nerve palsy and recovery of vision in the left eye with amblyopia therapy.

Comment: In hindsight, it may have been beneficial to alternately patch upon presentation. However, the patient was fusing in the adopted head position and the decision was made to observe. Neuroimaging was performed and was unremarkable. In most cases, the abduction deficit completely resolves by 3–6 months, and therefore, surgical intervention is rarely performed unless a significant deviation is present after 6 months. If the deviation fails to resolve or other neurologic symptoms are present, one must consider repeat neuroimaging.

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Diagnosis and Management of Fourth Nerve Palsy in Children

49

Cajal K. Patel and Reecha S. Bahl

Abstract

The fourth cranial nerve (the trochlear nerve) innervates the superior oblique (SO) muscle, which intorts, depresses, and abducts the eye. Palsy of the trochlear nerve can be acquired or congenital. While trauma, microvascular insult, increased intracranial pressure, compression, and stroke are well-known causes of acquired fourth nerve palsy, the pathophysiology of the congenital form is more complex. Correction in the amblyogenic age group is imperative if amblyopia develops although many children are able to compensate for the deviation. In an effort to fuse, some develop head tilts, which at a young age can lead to torticollis. Older individuals with well-controlled congenital palsy can decompensate overtime and develop diplopia. Management of these patients depends on the etiology, degree of deviation, development of amblyopia, presence of diplopia, and laterality. This chapter discusses diagnostic and management guidelines of acquired and congenital fourth cranial nerve palsy.

Keywords

Trochlear nerve palsy • Cranial nerve 4 • Bilateral palsy • Torticollis • Strabismus

Background

The fourth cranial nerve (the trochlear nerve) innervates the superior oblique (SO) muscle, which intorts, depresses, and abducts the eye. This motor nerve is unique in that it has the greatest intracranial length and is the only cranial nerve to exit from the dorsal aspect of the brainstem.

Palsy of the trochlear nerve can be acquired or congenital. While trauma, microvascular insult, increased intracranial pressure, compression, and stroke are well-known causes of acquired fourth nerve palsy, the pathophysiology of the congenital form is more complex. It can result from a developmental abnormality of the nucleus or peripheral nerve, or the SO muscle and tendon may be absent. Congenital cases are more commonly unilateral and asymptomatic because children often develop high vertical fusional amplitudes ranging from 2 to greater than 15 prism diopters (normal < 2 PD) [1]. In addition, the manifest hypertropia is commonly intermittent. Patients may also adopt a head tilt to the contralateral side to adjust for associated hypertropia and excyclodeviation. Old photographs may help to identify cases of congenital palsy as these patients may have a history of a long-standing head tilt [2]. Older children and adults with congenital SO palsy who exceed their fusional amplitude ("decompensate") may present with diplopia, whereas young children are more likely to develop suppression and amblyopia in the setting of non-fusing, manifest hypertropia [2] . In those patients with a persistent head tilt, tilting the head to the opposite side can

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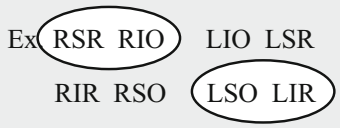
RSR RIO LIO LSR

RIR RSO LSO LIR

Draw out the figure above. Think of muscle functions to help draw out the figure correctly (for example, the oblique muscles abduct and the rectus muscles adduct).

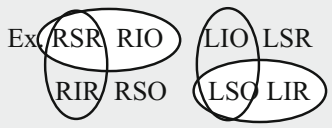
Step 1. Cover/uncover test in primary position to determine which eye is hypertropic.

Example: If the left eye is hypertropic, that indicates that the two muscles on the bottom-left row may be weak, causing the eye to drift up. Conversely, it may indicate that the two muscles on the top-right row are weak, causing the right eye to actually be hypotropic relative to the left eye. Circle the muscles that are suspected to be weak on either side.



Step 2. Cover/uncover test on lateral gazes to determine which gaze makes the hypertropia worse.

Example: If the hypertropia is worse on right gaze, that indicates the two muscles in the right column of either eye may be weak.



Step 3. Cover/uncover test on head tilt to determine which side makes the hypertropia worse.

Example: If the hypertropia is worse on tilting the head to the left or toward the left shoulder, then the two muscles diagonally oriented to the left in each eye could be weak.

The one muscle that remains a possibility in all three steps is the affected muscle. Remember that the figure above illustrates the muscle functions with the examiner facing the patient.

Fig. 49.1 The three-step Parks-Bielschowsky test

elicit a hypertropia not initially apparent. The three-step Parks-Bielschowsky test is a useful method to identify the affected muscle (Fig. 49.1). Care must be taken to differentiate decompensated congenital fourth nerve palsy from acute acquired palsy, as the latter may be due to a serious underlying problem and requires further evaluation. Imaging studies are often indicated if acquired palsy is suspected [3].

Management

Congenital Fourth Nerve Palsy

As patients with congenital fourth nerve palsy often have high vertical fusional amplitudes, they are often asymptomatic, with good vision and stereopsis. Some may adopt a head tilt to compensate for excyclotorsion. Over time, this can lead to facial asymmetry, with the smaller side of the face being contralateral to the palsied muscle [4]. Surgery to correct an abnormal head position may be considered as early as one year of age in those with a significant tilt to allow for binocular fusion in primary position. Early surgery is also associated with better outcomes [5].

Young patients with torticollis are commonly referred for evaluation of extraocular muscle as a cause for their head position. Reconstructive surgery to elongate the neck muscles, while appropriate in some cases of nonocular torticollis, should be avoided in the setting of fourth nerve palsy. Additionally, physical therapy is only appropriate if performed together with or after surgical management of the fourth nerve palsy, as forcing the head into primary position for fixation may break the child's fusion and cause suppression and amblyopia.

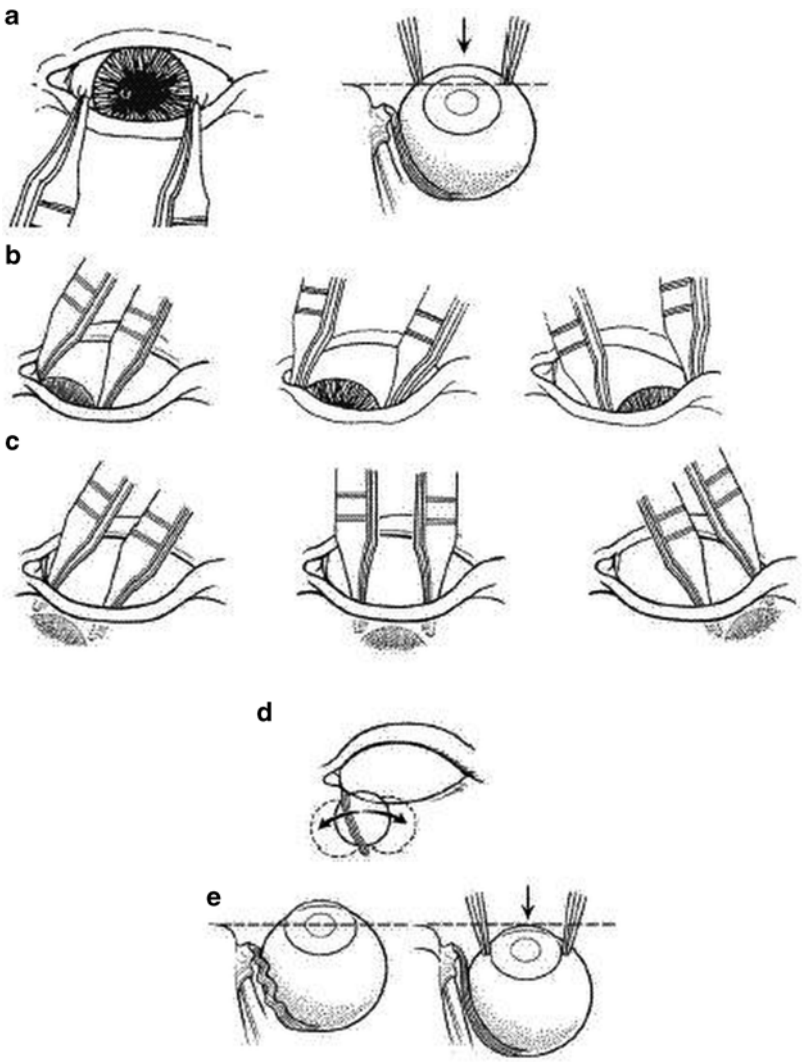


Fig. 49.2 Superior oblique traction test: (**a**) The eye is grasped at the limbus with two forceps at the 3 o'clock and 9 o'clock positions, and the eye is retropulsed into the orbit. (**b**) A "pop" sensation is observed as the eye goes over the normal superior oblique tendon when the eye is guided from nasal to temporal. (**c**) The eye may be guided so that the cornea disappears behind the upper lid during the maneuver in the setting of a lax or loose superior oblique tendon. The path of the globe as it passes over a normal tendon (**d**) and lax tendon (**e**) is also depicted. Figure reproduced with permission from Helveston, E. Surgical Management of Strabismus 5th Edition [6]

If amblyopia is present, occlusion therapy can improve vision in the amblyopic eye (see Chap. 8 on Practical Management of Amblyopia). Surgical realignment can be performed once vision and measurements are stable. In some patients, particularly those with a constant manifest hypertropia, amblyopia treatment may fail to improve acuity, as whenever both eyes are uncovered, vision in the constantly deviated eye is suppressed. In these cases, one may proceed with surgical realignment despite the associated risk of regression or overcorrection with the hope that improved alignment may allow visual improvement with additional amblyopia therapy.

The surgical procedure selected depends on preoperative characteristics as well as intraoperative forced duction testing via the superior oblique traction test (Fig. 49.2) [6]. The Knapp classification (Fig. 49.3) can be useful in guiding surgical management [7]. In the setting of unilateral SO palsy, the surgical management is guided by the magnitude of the hypertropia, as well as by the pattern of the hypertropia and the presence or absence of SO laxity on intraoperative forced

Classic Knapp Classification

Class I	Hypertropia worse on adduction and upgaze
Class II	Hypertropia worse on adduction and downgaze
Class III	Hypertropia worse on abduction
Class IV	Hypertropia worse on abduction and downgaze
Class V	Hypertropia worse on downgaze abd-/adduction
Class VI	Bilateral superior oblique palsy
Class VII	Traumatic palsy and/or ipsilateral Brown's syndrome

Fig. 49.3 Knapp classification of superior oblique palsy

duction testing (Fig. 49.2). If the hypertropia is worse in the field of action of the inferior oblique (IO) (on adduction and upgaze to the contralateral side), which would be classified as class I, then IO weakening is preferred [7, 8]. This is particularly efficacious for patients with small deviations and when the SO tendon is not lax on intraoperative forced duction testing [3, 9]. When selecting an IO weakening procedure, the surgeon may elect to either recess or myectomize the inferior oblique. Recent studies have found both to be equally successful [10].

If the hypertropia is worse in the field of action of the superior oblique (on downgaze to the contralateral side), which is classified as class II, then an SO strengthening procedure, such as a tuck or resection, may be preferred [7, 8]. This is particularly true for patients with severe congenital fourth nerve palsy and superior oblique tendon laxity elicited on forced ductions [3]. Regardless of whether fundus torsion is present on examination, patients in whom head tilt is the presenting feature or those with tendon laxity may be corrected solely with an SO tendon tuck or resection [11, 12]. Although SO tendon tucks are avoided in patients without laxity, a "small" or "soft" tuck can reasonably be performed with careful assessment of intraoperative post-procedure forced ductions to prevent restriction on downgaze [8, 9]. Superior oblique strengthening can be particularly successful if a significant hypertropia on downgaze or reading position is present.

Although effective, SO strengthening procedures are less predictable than IO weakening procedures. They can also increase the risk of developing restriction on downgaze and Brown syndrome, which is a restriction of elevation in adduction [11, 12]. At the time of surgery, ocular movements should be assessed with forced duction testing before and after the procedure to ensure equal ductions and prevent over- or under-correction [8]. In cases of small tropias, some surgeons may elect to perform a contralateral inferior rectus recession with nasal transposition rather than an SO tuck, but only in cases of minimal esodeviation on downgaze, as this can exacerbate the esodeviation [8].

Patients with long-standing superior oblique palsy and spread of comitance should be evaluated for ipsilateral superior rectus tightness via forced ductions. Long-standing hypertropia may result in a tight ipsilateral superior rectus and is best treated with recession of restricted superior rectus muscle [12]. These patients may demonstrate larger than expected hypertropias in downgaze.

In most cases, single muscle surgery such as inferior oblique recession or myectomy is often sufficient to correct head position and alignment in patients with tropias of less than 15–20 prism diopters (PD) in primary position [2] (Fig. 49.4). In patients with greater than 15–20 PD deviations, surgery on two muscles may be necessary, while those with hypertropia of greater than 35 PD may require three-muscle surgery [2, 8, 13]. Most surgeons will perform an ipsilateral inferior oblique recession and either a superior oblique strengthening procedure if there is evidence of laxity, a contralateral inferior rectus recession, or an ipsilateral superior rectus recession in patients with large hypertropias and those with a hypertropia that is larger in downgaze, indicating a tight superior rectus muscle, especially in long-standing cases [2, 8].

If IO weakening and SO strengthening are performed simultaneously, the patient is at higher risk for overcorrection. For this reason, this type of simultaneous procedure should be reserved for select cases, such as those with large hypertropias in primary position or in downgaze with the surgeon performing a generally "soft" or small tuck (8–10 mm) to prevent overcorrection [7].

Acquired Fourth Nerve Palsy

Older children and adults may present with diplopia from decompensated congenital fourth nerve palsy. It is however crucial to rule out acquired causes for the palsy in these patients. Obtaining a thorough history is important to discern risk factors such as vasculopathy or trauma. A long-standing head tilt is suggestive of a congenital cause and old photographs should be reviewed [2]. An assessment of vertical fusional amplitudes may help to differentiate patients with congenital fourth nerve palsy from those with an acquired palsy, as patients with a congenital palsy will have large vertical fusional amplitudes (up to 15 PD), whereas acquired cases usually demonstrate normal vertical fusional amplitudes (<2 prism diopters) [1].

If a fourth nerve palsy occurs without a history of trauma in a patient over 50 years of age with vasculopathic risk factors, observation may be appropriate; however, the deviation usually improves over 3–6 months in these patients [14]. Many physicians order imaging studies in these cases regardless to rule out an intracranial mass or stroke. Surgery may be considered when measurements stabilize after at least 6 months of observation.

A fourth nerve palsy may also be acquired in the setting of trauma. The fourth nerve has the longest route in the intracranial cavity placing it at a higher risk for damage. It is also the only cranial nerve that exits dorsally from the midbrain. Many of these patients are imaged to rule out intracranial damage and, as previously noted, should be monitored for 3–6 months until measurements stabilize prior to surgical intervention.

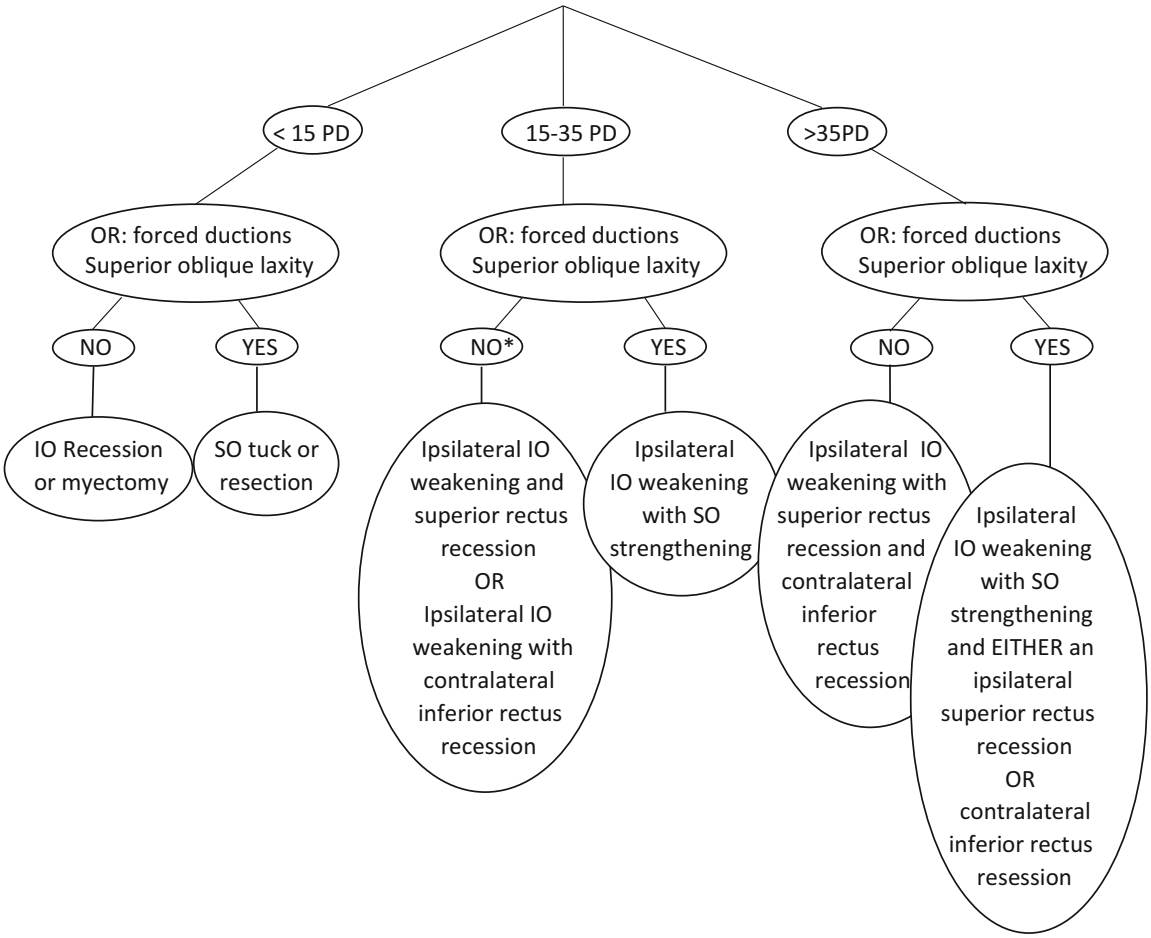


Fig. 49.4 Surgical management of unilateral fourth nerve palsy flow chart. Some clinicians would start with an inferior oblique myectomy and proceed to recessing the ipsilateral superior rectus or contralateral inferior rectus if the IO weakening procedure is insufficient in controlling the deviation and eliminating the head tilt

Bilateral Fourth Nerve Palsy

Bilateral congenital fourth nerve palsies are rare. Most cases of bilateral fourth nerve palsy are acquired and occur in adults, particularly following head trauma. Patients with bilateral fourth nerve palsy tend to have greater than 10 degrees of excyclotorsion as measured using double Maddox rods, bilateral fundus torsion, V-pattern esotropia, minimal head tilt, and alternating hypertropias (right hypertropia on left gaze and left hypertropia on right gaze) from secondary IOOA [15]. The degree of excyclotorsion can be very difficult to measure in young children due to poor cooperation as well as a tendency for suppression of the deviated eye. However, fundus torsion may be objectively observed using the indirect ophthalmoscope. In adults, torsion in both unilateral and bilateral cases can be measured with double Maddox rods. Torsion greater than 10 degrees is highly suggestive of a bilateral fourth nerve palsy, whereas unilateral cases usually have less than 5 degrees of excyclotorsion

In bilateral cases or class VI palsy using the Knapp classification, the Harada-Ito procedure is recommended to correct the excyclotorsion [6, 16]. In this procedure, the anterior one-third of the SO tendon is advanced laterally and anteriorly from its insertion in an attempt to improve incyclotorsion [17]. The anterior third of the SO tendon contributes to incyclotorsion, whereas the posterior tendon is more involved in depression. If a hypertropia is present in addition to the excyclotorsion, IO weakening and/or the other surgical procedures described earlier in the chapter may be performed to correct the hyperdeviation. The surgeon must always consider the possibility of bilateral palsy during preoperative assessment, as occasionally surgery on one side may unmask a palsy on the opposite side, and require additional surgical procedures [18].

The following cases are presented to help illustrate and guide the evaluation and management of patients with fourth nerve palsy.

Case Examples

Case 1 (Table 49.1)

Table 49.1 Case 1

Clinical history	2-year-old boy with a history of left head tilt Past medical history: noncontributory Family history: noncontributory, negative for strabismus			
Key components of exam		OD	OS	
	Uncorrected visual acuity	Central-steady-maintained	Central-steady-maintained	
	Ductions/versions	IO overaction; SO underaction	Full	
	Near alignment	Right head tilt: 14Δ RHT′ Left head tilt: 6ΔRHT′		
		8Δ RHT	10Δ RHT′	15Δ RHT
		8Δ RHT	10Δ RHT′	15Δ RHT
		8Δ RHT	10Δ RHT′	18Δ RHT
	Distance alignment	Right head tilt: 12Δ RHT Left head tilt: 4Δ RHT		
		8Δ RHT	8Δ RHT	12Δ RHT
		8Δ RHT	8Δ RHT	10Δ RHT
		8Δ RHT	8Δ RHT	15Δ RHT
	Cycloplegic refraction	+2.00 sphere	+1.75 sphere	
	Dilated fundus examination	Fundus torsion, otherwise normal (Fig. 49.5)	Normal	
Management options	Ipsilateral inferior oblique recession or myectomy Ipsilateral superior oblique tuck Contralateral inferior rectus recession			
Management	Superior oblique tendon laxity confirmed on forced ductions intraoperatively; right superior oblique tuck performed			
Interval history (3 months) *Current age: 2 years*	Resolution of the anomalous head position			
Key components of exam		OD	OS	
	Uncorrected visual acuity	Central-steady-maintained	Central-steady-maintained	
	Ductions/ versions	1+ IO overaction	Full	
	Alignment (distance and near)	Orthophoria		
Management	Monitor/observe			
Interval history (12 months) *Current age: 3 years*	Patient continues to maintain normal head position in return			
Key components of exam		OD	OS	
	Uncorrected visual acuity (LEA)	20/30	20/30	
	Ductions/versions	1+ IO overaction	Full	
	Alignment	Flick RH′ at near and flick RH′ at distance		
	Cycloplegic refraction	+2.50 sphere	+2.25 sphere	
Management	Monitor/observe			

(continued)

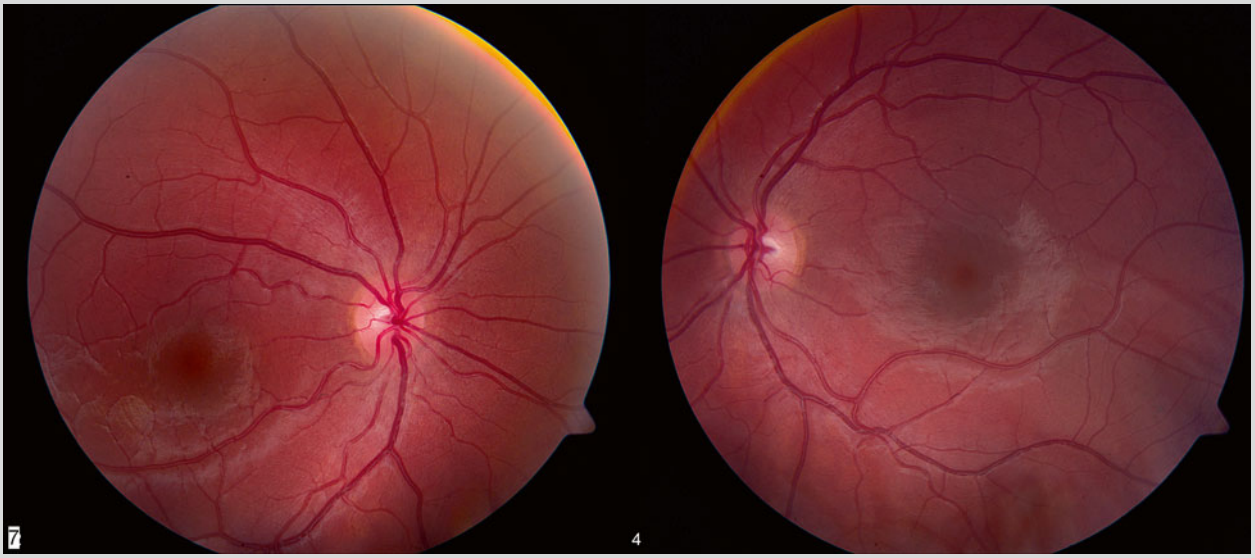


Fig. 49.5 Right excyclotorsion visible on dilated fundoscopy secondary to superior oblique palsy

Clinical Synopsis

An otherwise healthy 2-year-old boy is evaluated for left torticollis since infancy. He had 15 degrees of left head tilt and facial asymmetry with mild left microsomia. With the head forced in primary position, the patient has a right hypertropia of 8 PD that increases to 15 PD on right head tilt. Duction and version testing suggest a right SO weakness and right IO overaction. Dilated fundus examination reveals mild right fundus excyclotorsion (Fig. 49.5). Surgical management is advised. Intraoperative forced ductions confirm a lax superior oblique tendon for which the patient undergoes an ipsilateral superior oblique tuck. Following this procedure, the head tilt and misalignment improve to flick right hypertropia and remain stable at the 1-year postoperative visit.

Case 2 (Table 49.2)

Table 49.2 Case 2

Clinical history	6-year-old female failed vision screening. Parents observe that eyes appear misaligned			
Key components of exam		OD	OS	
	Uncorrected visual acuity (Snellen)	20/20	20/60	
	Ductions/versions	Full	IO overaction; SO underaction	
	Stereo acuity	Nil		
	Alignment (near)	Right head tilt: 8Δ LHT′ Left head tilt: 16Δ LHT′		
		18Δ LHT′	12Δ LHT′	12Δ LHT′
		16Δ LHT′	12Δ LHT′	12Δ LHT′
		16Δ LHT′	12Δ LHT′	12Δ LHT′
	Alignment (distance)	Right head tilt: 8Δ LHT Left head tilt: 18Δ LHT		
		20Δ LHT	14Δ LHT	14Δ LHT
		16Δ LHT	14Δ LHT	14Δ LHT
		16Δ LHT	14Δ LHT	14Δ LHT
	Cycloplegic refraction	+0.75 sphere	+0.75 sphere	
	Dilated fundus examination	Normal	Fundus torsion, otherwise normal	

(continued)

Table 49.2 (continued)

Management	Start part-time patching of the right eye 6–8 hours daily			
Interval history (3 months) *Current age: 6 years*	Good compliance with patching			
Key components of exam		OD	OS	
	Uncorrected visual acuity	20/20	20/30 (tested first)	
	Stereopsis	Denies fly		
	Ductions/versions	Full	IO overaction; SO underaction	
	Alignment (near)	Right head tilt: 8 LHT′ Left head tilt: 16 LHT′		
		18Δ LHT′	12Δ LHT′	12Δ LHT′
		16Δ LHT′	12Δ LHT′	12Δ LHT′
		16Δ LHT′	12Δ LHT′	12Δ LHT′
	Alignment (distance)	Right head tilt: 8 LHT Left head tilt: 18 LHT		
		20Δ LHT	14Δ LHT	14Δ LHT
		16Δ LHT	14Δ LHT	14Δ LHT
		16Δ LHT	14Δ LHT	14Δ LHT
Management options	Continue patching or surgical intervention			
Management	Continue patching and reassess in 3 months			
Interval history (3 months) *Current age: 6 years*	Patient′s family reports good compliance with patching			
Key components of exam		OD	OS	
	Uncorrected visual acuity	20/20	20/20 (tested first)	
	Stereopsis	Denies fly		
	Ductions/versions	Full	IO overaction; SO underaction	
	Alignment (near)	Right head tilt: 8 LHT′ Left head tilt: 16 LHT′		
		18Δ LHT′	12Δ LHT′	12Δ LHT′
		16Δ LHT′	12Δ LHT′	12Δ LHT′
		16Δ LHT′	12Δ LHT′	12Δ LHT′
	Alignment (distance)	Right head tilt 8 LHT Left head tilt 18 LHT		
		20Δ LHT	14Δ LHT	14Δ LHT
		16Δ LHT	14Δ LHT	14Δ LHT
		16Δ LHT	14Δ LHT	14Δ LHT
Management options	Surgical options: • Ipsilateral inferior oblique recession or myectomy • Ipsilateral superior oblique tuck (if evidence of laxity on forced ductions)			
Management	Left inferior oblique myectomy			
Interval history (12 months) *Current age: 7 years*	Good ocular alignment and no anomalous head position			
Key components of exam		OD	OS	
	Uncorrected visual acuity	20/20	20/20	
	Stereopsis	60 s arc		
	Ductions/versions	Full	Full	
	Alignment (near and distance)	6–8 LH′ at near and at distance		
Management	Monitor			

(continued)

Clinical Synopsis

A 6-year-old child fails a vision screening at school. There is no history of trauma, and she is otherwise healthy. She has a left hypertropia, associated with decreased vision on the same side. She also has a right head tilt, which is observed in pictures from several years prior. She is patched to treat the amblyopia and her vision improves. Once vision is stable, she undergoes a left IO myectomy, with good postoperative alignment and recovery of stereopsis.

Case 3 (Table 49.3)

Table 49.3 Case 3

	24-year-old male presents with complaints of diplopia following sports-related head injury. He stated the two images were vertically oriented with one image appearing tilted			
Clinical history	PMH: negative past ocular history – denied			
Key components of exam		**OD**	**OS**	
	Visual acuity (Snellen)	20/20	20/20	
	Ductions/versions	SO underaction on adduction	SO underaction on adduction	
	Stereo acuity	Full	Full	
	Alignment (near)	Primary position: 4 RHT′		
		Left head tilt: 10Δ LHT′		
		Right head tilt: 12Δ RHT′		
	Alignment (distance)	Left head tilt: 12Δ LHT		
		Right head tilt: 12Δ RHT		
		16Δ LHT	6Δ RHT 14 Δ XT	20Δ RHT
		12Δ LHT	6Δ RHT	14Δ RHT
		18Δ LHT	6Δ RHT 6Δ ET	20Δ RHT
		Double Maddox rod: 18 degrees excyclotorsion		
	Refraction	Plano	Plano	
Management	Observation; occlude eye as needed to alleviate bothersome diplopia			
Interval history (3 months)	Mild improvement in diplopia			
Key components of exam		OD	OS	
	Visual acuity	20/20	20/20	
	Ductions/versions	SO underaction on adduction	SO underaction on adduction	
	Alignment (near)	Primary position: flick RHT′		
		Left head tilt: 6Δ LHT′		
		Right head tilt: 6Δ RHT′		
	Alignment (distance)	Left head tilt: 8Δ LHT		
		Right head tilt: 8Δ RHT		
		12Δ LHT	4Δ RHT 10Δ XT	16Δ RHT
		8Δ LHT	4Δ RHT	10Δ RHT
		14Δ LHT	4Δ RHT 6Δ ET	16Δ RHT
		Double Maddox rod: 15 degrees excyclotorsion		
Management	Not affecting daily activities. Reassess in 3 months			
Interval history (3 months)	Minimal improvement since last visit. Patient continues to complain of vertically oriented double vision, with the second image appearing tilted			

(continued)

Table 49.3 (continued)

Key components of exam		OD	OS	
	Uncorrected visual acuity	20/20	20/20	
	Ductions/versions	SO underaction on adduction	SO underaction on adduction	
	Alignment (near)	Primary position: flick RHT′		
		Left head tilt: 6Δ LHT′		
		Right head tilt: 6Δ RHT′		
	Alignment (distance)	Left head tilt: 8Δ LHT		
		Right head tilt: 8Δ RHT		
		12Δ LHT	4Δ RHT 10Δ XT	16Δ RHT
		8Δ LHT	4Δ RHT	10Δ RHT
		14Δ LHT	4Δ RHT 6Δ ET	16Δ RHT
		Double Maddox rod: 15 degrees excyclotorsion		
		Unable to fuse with prism adaptation test, as second image continues to be tilted		
Management options	Surgical options: bilateral inferior oblique recession or myectomy; bilateral superior oblique tuck; bilateral or unilateral superior oblique Harada-Ito procedure			
Management	Harada-Ito procedure performed on right side			
Interval history (1 month)	Good ocular alignment, no complaint of diplopia			
Key components of exam		OD	OS	
	Uncorrected visual acuity	20/20	20/20	
	Ductions/versions	Full	Full	
	Alignment (near and distance)	Ortho in primary position		
		Left head tilt: 3Δ LHT		
		Right head tilt: 3Δ RHT		
		Double Maddox rod: 2 degrees excyclotorsion		
Management	Monitor			

A 24-year-old male presented with complaints of [vertical/tilted] diplopia after a sports-related head injury. He was playing football when he was thrown to the ground hitting the back of his head. He was evaluated and discharged from the ED after being ruled out for an acute intracranial process. On exam, he was found to have alternating hypertropia with contralateral gaze and ipsilateral head tilt. He additionally complained that the second image appeared tilted. The degree of torsion was measured with double Maddox rods. The patient stated both horizontal lines appeared tilted off axis. The extent of torsion was measured to be 18 degrees. To ensure stability of the deviation following trauma, the patient was managed with supportive care with monocular occlusion to eliminate the diplopia. The patient was evaluated again 3 months later and found to have some improvement in his alternating hypertropia. At 6 months, however, the patient was still symptomatic with minimal improvement in measured deviation. The degree of torsion was measured again and found to be 15 degrees. Because symptoms were mainly secondary to the torsional component, a modified Harada-Ito procedure was then performed after which the patient noted significant improvement in his diplopia.

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Cranial Nerve III Palsy in Children

50

Kathryn P. Winkler and Reecha S. Bahl

Abstract

Oculomotor (CN III) palsy results from dysfunction of this nerve along its pathway from the midbrain to the extraocular muscles (EOMs) it innervates – medial, superior, and inferior recti, inferior oblique, levator palpebrae superioris, and sphincter pupillae. In the pediatric population, most cases are congenital. Acquired cases are often the harbingers of serious sometimes life-threatening underlying disease; hence, imaging studies to rule out serious etiologies, such as neoplastic and vascular pathology, should be considered. The management of pediatric CN III palsy includes the identification and treatment of the underlying etiology if possible, the reduction of complications such as amblyopia, the improvement of binocular fusion, and the restoration of the best possible appearance. Strabismus surgery for third nerve palsy is complex and often requires the manipulation of multiple EOMs. It only rarely restores a large field of binocular fusion. The surgical approach depends on surgeon preference, muscles involved, and the extent of involvement of each muscle (complete versus partial paralysis). Surgical options include horizontal rectus resection and recession for the associated exotropia, as well as rectus muscle and superior oblique muscle transposition. When necessary, ptosis surgery is usually performed after strabismus surgeries are completed.

Keywords

CN III palsy • Third nerve palsy • Oculomotor palsy • Knapp procedure • Ptosis • Frontalis sling • Exotropia • Hypotropia

Introduction

Oculomotor (CN III) palsy in childhood is rare. It is congenital in about 50 % of cases, in which it may or may not be associated with other neurologic abnormalities [1]. Acquired CN III palsy in a child may be the sign of a serious sometimes life-threatening underlying disease. Dysfunction along any part of the third nerve from its origin in the midbrain to the muscles it innervates may result in a partial or complete palsy. Muscles innervated by CN III include the medial rectus, superior rectus, inferior rectus, and inferior oblique as well as the levator palpebrae superioris. In addition, the oculomotor nerve carries parasympathetic fibers that control pupillary constriction along its inferior division.

The nucleus for CN III is located in the midbrain and consists of multiple subnuclei for the respective innervated muscle. Each subnucleus innervates the ipsilateral muscle with the exception of the superior rectus nucleus, which innervates the contralateral muscle. Also of note, both levator palpebrae muscles are innervated by a single central nucleus.

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Prevalence and Etiology

In a study by Miller and colleagues [1] in which approximately three million medical records were reviewed, only 28 patients with CN III palsy under the age of 20 years were identified. Another population-based study out of Rochester, Minnesota, over a 15-year time period found a total of 36 cases of cranial nerve palsies, of which only eight were CN III palsies [2].

Most studies have found that congenital CN III palsy is the most common type in children [1–5]. Congenital CN III palsies are most often due to a developmental anomaly or to birth trauma [4]. Bilateral congenital CN III palsies are often associated with congenital cranial dysinnervation disorders (CCDD) such as congenital fibrosis of the extraocular muscles (EOMs), in which genetic mutations lead to abnormal development of CN III, IV, or VI and the associated EOMs, thereby causing complex strabismus [6]. Unilateral congenital CN III palsy has been associated with neurofibromatosis 2, posterior fossa malformations-hemangioma-arterial anomalies-cardiac abnormalities-eye abnormalities-sternal cleft and supraumbilical raphe syndrome (PHACES syndrome), septo-optic dysplasia, and other rare neurologic abnormalities [6].

Trauma is the most common cause of acquired CN III palsy in children and represents about 40 % of acquired cases [1, 7]. Most often, the injury is due to blunt trauma to the skull commonly associated with motor vehicle collisions. Occasionally, the injury occurs in the setting of cranial surgery/neurosurgery [1, 5, 8]. When associated with other cranial nerve palsies, CN III palsy is most likely due to trauma [7]. Neoplastic causes include leptomeningeal sarcoma, rhabdomyosarcoma, lacrimal gland tumor, lymphoma, glioma, meningioma of the cavernous sinus, neuroectodermal tumor, lipofibroma of the orbit, and orbital hemangioma [1, 3, 5, 8]. Typically CN III palsy is a late sign of an intracranial tumor [4]. Infectious and inflammatory etiologies vary widely and include meningitis (viral and bacterial); encephalitis; viral infection, including upper respiratory infections; and chickenpox [1, 3, 4, 7]. Aneurysms are among the most feared etiologies in adults, but are much less common in the pediatric population. It is, however, important to have a high index of suspicion in children who are at increased risk for aneurysms, such as those with polycystic kidney disease, coarctation of the aorta, and Ehlers-Danlos syndrome [8]. Other vascular abnormalities that may present with CN III palsy include vasculitis such as Kawasaki disease, vascular malformations, and cavernous sinus thrombosis [6]. The diagnosis of an ophthalmoplegic migraine is one of exclusion [1, 8]. An overview of the most common causes of CN III palsy in children is given in Table 50.1.

Table 50.1 Causes of CN III palsy in children

Etiology	Percentage of cases
Congenital	38–50 % [1–5]
Trauma	17–37 % [1–5]
Neoplasia	10–17 % [1–5]
Infection/inflammation	5–13 % [1, 3, 4]
Aneurysm/vascular infection/inflammation	6–8 % [1, 3]
Ophthalmoplegic migraine	2–7 % [1, 5]

Diagnosis

A detailed clinical history and evaluation of clinical features is the initial and most critical step in diagnosing a CN III palsy and initiating the work-up to determine its etiology. The patient or his/her family members may report the onset of a droopy eyelid, pupillary changes, and/or changes in the eye movements or eye position. An older, verbal child may vocalize complaints of binocular horizontal, vertical, or oblique diplopia. Children may not experience diplopia due to cortical suppression of one image. Clinical features to note on examination include partial or complete ptosis as well as extraocular movement deficits, including isolated or complex limitation of adduction, elevation, and depression of the involved eye. The classic presentation of a complete CN III palsy is an eye that is turned "down and out," describing an exotropia and hypotropia. A partial CN III palsy may involve any combination and degree of limitation involving the superior rectus, medial rectus, inferior rectus, and/or inferior oblique. A careful pupillary exam may or may not reveal pupil involvement, which can range from a completely dilated and nonreactive pupil to a normally sized and reactive pupil. It is equally important to question the patient's parents about any associated neurologic or systemic abnormalities.

Once a diagnosis of CN III palsy is made using historical and clinical features, the investigation of an etiology is pursued. Selecting the appropriate imaging modality in the pediatric patient involves considerations of the amount of radiation exposure as well as the need for sedation/anesthesia. Computerized tomography (CT) scans are widely available with a short duration of examination, but expose the pediatric patient to radiation [9]. This imaging modality is preferred to evaluate for bony abnormalities, screen for orbital masses, and evaluate the extraocular muscles [9]. Magnetic resonance imaging (MRI), on the other hand, is radiation-free but may be less widely available, requires a longer exam, and often requires sedation [9]. This imaging modality is best used to evaluate soft tissue structures and intracranial abnormalities.

Studies of congenital CN III palsies that are not associated with progressive neurologic or other systemic diseases have

shown that if the clinical findings are stable, there is no need for imaging [1]. In one study Miller examined 13 patients with congenital CN III palsy, none of whom had associated neurologic abnormalities [1]. However, in another series by Balkan and Hoyt, seven of ten patients with congenital CN III palsy had associated neurologic abnormalities [10]. Hamed et al. found that 10 out of 14 cases of congenital CN III palsy had associated neurologic disorders, mostly brainstem lesions [11]. Once congenital CN III palsy cases are diagnosed, they must be closely observed. Any associated neurologic or systemic findings or a progression or change in the clinical findings should prompt further investigation, including MRI [9, 12].

Acquired CN III palsies in the pediatric population are more often an ominous sign of underlying disease [4, 12]. With few exceptions, acquired CN III palsies in children should be imaged with MRI [12]. Fever and neck stiffness should prompt an investigation for meningitis, including a lumbar puncture [8]. Other modalities of investigations should be sought as appropriate. While the need for repeat imaging remains controversial, some suggest that patients without a clear etiology of an acquired CN III palsy should be reimaged every 2 years to ensure identification of neoplastic or vascular abnormalities that may initially be subtle [8]. Angiographic evaluation (MRA or CTA) is only performed if historical clues suggest the presence of an aneurysm. If there is a negative MRA/CTA but an extremely high clinical suspicion for aneurysm, the gold standard remains catheter angiography, keeping in mind that this procedure is associated with significant morbidity and mortality. Consider a discussion with a neuroradiologist prior to imaging if the appropriate choice of modality is not readily evident on clinical examination.

Management

Of the cranial nerve palsies in children, CN III palsy has the poorest prognosis for spontaneous recovery [4]. The goals of management in the setting of pediatric CN III palsy include diagnosis and treatment of the underlying etiology, reduction of complications, improvement of binocular fusion, and restoration of the best possible appearance.

Amblyopia is present in 31–50 % of children with CN III palsy [1, 3, 5, 8]. Most often the amblyopia is strabismic, but could be deprivational and/or anisometropic, due to ptosis. Management includes part-time occlusion, correction of refractive errors, and strabismus surgery and ptosis repair. Amblyopia treatment is most effective when initiated early in patients with congenital CN III palsy [5].

Aberrant regeneration, or misdirected regrowth of nerve fibers, occurs in 43–46 % of pediatric patients with CN III palsy [1, 5, 8]. It may be present at birth in patients with congenital CN III palsy or may develop weeks or months following acquired dysfunction [4, 8]. Unfortunately, once aberrant regeneration occurs, there is no intervention that can reverse this complication. Aberrant regeneration oftentimes improves the strabismic deviation, but it may complicate surgical intervention.

Strabismus surgery is commonly considered in the setting of pediatric CN III palsy, even though it often entails a difficult or complicated repair. Manipulation of multiple extraocular muscles may be necessary, thereby increasing complications, including ocular ischemic syndrome. Strabismus surgery should be considered in acquired CN III palsies that do not improve or resolve within 9–12 months and are nonprogressive [3, 4]. Congenital or complete CN III palsy will likely not resolve, but a period of at least 6 months before operating has been suggested [3]. The surgical approach depends on several factors including surgeon preference, muscles involved, and the extent to which each muscle is involved (complete versus partial). For horizontal misalignment in the setting of partial medial rectus paralysis, a large ipsilateral lateral rectus recession and medial rectus resection are often performed initially [3, 4]. Modified Knapp procedure (transposition of the ipsilateral medial and lateral rectus muscles vertically, usually superiorly toward the superior rectus in the setting of CN III palsy) has been used with some success for vertical misalignments [3, 13]. Superior oblique transposition has also been suggested in some studies for treatment of underactive inferior oblique causing incyclotorsion or in the case of a totally paretic medial rectus [4, 14–17]. A superior oblique transposition procedure involves fracture of the trochlea allowing release of the superior oblique tendon followed by advancement and attachment of the tendon to the sclera near the insertion of the medial rectus muscle. Complete CN III palsy, with only the superior oblique and lateral rectus muscles functional, will present a much more complicated and difficult surgical dilemma and will often require more than one surgical intervention [3]. Given the paralysis of multiple muscles in CN III palsy, while strabismus surgery may achieve an acceptable appearance, it only rarely restores a subjectively acceptable or usable field of binocular fusion and must be clearly communicated to families during the informed consent process prior to surgery [3, 5].

Ptosis surgery should be considered only after strabismus surgeries are completed and if there is little risk of corneal exposure after the surgery [6]. Ptosis repair usually requires frontalis sling suspension secondary to poor levator function, but can occasionally be managed with more conservative approaches such as levator resection or mullerectomy when some residual function is present. In the older patient without suppression, ptosis repair may lead the diplopia to become more symptomatic as the eye is uncovered.

A more conservative approach in the instance of a family who is more hesitant to consider surgical intervention includes part-time occlusion to prevent amblyopia and the use of prisms if they help with diplopia [4].

Case Examples

Case 1

This newborn male presented with a right-sided complete CN III palsy. Patching was implemented early to prevent amblyopia. The patient underwent two strabismus surgeries and one surgery for ptosis repair. Near orthotropia was achieved in primary position, though with continued substantial limitation in motility and a persistent strong visual preference for the left non-paralytic side (see Table 50.2).

Table 50.2 Case 1

Clinical history	14-day-old male born at 38 weeks gestational age presents with right eyelid drooping noted since birth. He is also found to have brain malformations on ultrasound prenatally and at 10 days of age. Past medical history: as noted Family history: noncontributory			
Key components of exam		OD	OS	
	Uncorrected visual acuity	Reacts to light	Reacts to light	
	Margin to reflex distance (MRD1)	−3 mm poor Bell's response	2 mm normal Bell's response	
	Versions/ductions	Limitation in elevation and adduction	Full	
	Pupil exam	5 mm round with trace reaction	4 mm → 2 mm round and reactive + hippus	
	Alignment (modified Krimsky)	Nsc: 10Δ right hypotropia, 60Δ right exotropia in primary position		
		15 RHoT 45Δ RXT	17Δ RHoT 60Δ RXT	15Δ RHoT 65Δ RXT
		10Δ RHoT 45Δ RXT	10Δ RHoT 60Δ RXT	10Δ RHoT 70Δ RXT
		6Δ RHT 45Δ RXT	6Δ RHT 60Δ RXT	5Δ RHT 65Δ RXT
	Dilated fundus exam	Normal		Normal
Diagnostic testing	MRI brain: right frontotemporal open-lip schizencephaly (direct communication from ventricular system into the subarachnoid space), absence of septum pellucidum, band migrational anomaly/heterotropia and cortical dysplasia/polymicrogyria (abnormal cortical thickening) (see Fig. 50.1)			
Assessment and management	1. High risk of amblyopia, right eye, secondary to strabismus and ptosis → Initiation of 2 h/day patching of the left eye 2. Complete CN III palsy with pupillary involvement, right eye, with large exotropia and hypotropia, as well as complete ptosis → Encourage patient's family to follow up with neurologist and geneticist → Defer surgical intervention for primary deviation and ptosis repair per family wishes			
Interval history (6 months) *Current age: 6 months*	Patching was initiated. No interval improvement of eyelid drooping, but patient was noted to raise brows in attempt to compensate and has adopted a chin-up position. Patient followed by neurologist for brain anomalies. Genetic work-up was negative for identification of causative gene mutation or abnormality			
Key components of exam		OD	OS	
	Uncorrected visual acuity	Central-steady-not maintained	Central-steady-maintained	
	Marginal reflex distance (MRD1)	−3 mm	2 mm	
	Alignment	Continued 10Δ right hypotropia, 60Δ right exotropia in primary position Unchanged from previous examination		
Assessment and management	Continued complete right-sided CN III palsy with right-sided amblyopia: 1. Continue patching 2. Surgical intervention: Parents agreed to proceed with right superior oblique tendon transposition 3. Observe ptosis until strabismus is addressed surgically			

(continued)

Table 50.2 (continued)

Interval history (6 months) *Current age: 12 months*	Postoperative healing went well. Continued patching			
Key components of exam		OD		OS
	Uncorrected visual acuity	Central-steady-not maintained		Central-steady-maintained
	Marginal reflex distance (MRD1)	−3 mm		2 mm
	Versions/ductions	Limitation in elevation and adduction		Full
	Alignment (modified Krimsky)	Nsc: 2Δ right hypotropia, 8Δ right exotropia in primary position		
		3Δ RHoT 3Δ RXT	4Δ RHoT 8Δ RXT	4Δ RHoT 12 RXT
		2Δ RHoT 6RXT	2Δ RHoT 8Δ RXT	2Δ RHoT 12 RXT
		1Δ RHT 6RXT	1Δ RHT 8Δ RXT	1Δ RHT 12 RXT
Assessment and management	Complete right-sided CN III palsy with right-sided amblyopia, status post RSO tendon transposition: 1. Discussion with family for further strabismus surgery or ptosis repair. Family opted for conservative management 2. Increase patching of left eye to 4 h daily			
Interval history (12 months) (long interval for patching, no?) *Current age: 24 months*	Family has continued patching			
Key components of exam		OD		OS
	Uncorrected visual acuity	Central-steady-not maintained		Central-steady-maintained
	Marginal reflex distance (MRD1)	−3 mm		2 mm
	Versions/ductions	Limitation in elevation and adduction		Full
	Alignment (modified Krimsky)	Nsc: 2Δ right hypotropia, 10Δ right exotropia in primary position		
		3Δ RHoT 3Δ RXT	4Δ RHoT 10Δ RXT	4Δ RHoT 12 RXT
		2Δ RHoT 6 RXT	2Δ RHoT 10Δ RXT	2Δ RHoT 12 RXT
		1Δ RHT 6 RXT	1Δ RHT 10Δ RXT	1Δ RHT 12 RXT
Assessment and management	Complete right-sided CN III palsy with right-sided amblyopia, status post RSO tendon transposition: 1. Discussed further strabismus interventions and ptosis repair with family. The family opted for surgical intervention: right lateral rectus recession and right medial rectus resection 2. Continue patching left eye 4 h per day			
Interval history (6 months) *Current age: 30 months*	Healing well postoperatively. Has continued to patch 4 h per day			
Key components of exam		OD		OS
	Uncorrected visual acuity (LEA)	20/800		20/25
	Marginal reflex distance (MRD1)	−3 mm		2 mm
	Alignment (modified Krimsky)	Nsc: 2Δ right hypotropia, 3Δ right exotropia in primary position		
		3Δ RHoT 2Δ RXT	4Δ RHoT 3Δ RXT	4Δ RHoT 5 RXT
		2Δ RHoT 2 RXT	2Δ RHoT 3Δ RXT	2Δ RHoT 5 RXT
		1Δ RHT 2 RXT	1Δ RHT 3Δ RXT	1Δ RHT 5 RXT

(continued)

Table 50.2 (continued)

Assessment and management	Complete right-sided CN III palsy with right-sided amblyopia, status post RSO tendon transposition as well as RLR recession and RMR resection: 1. Increase patching to 6 h per day, as tolerated 2. Satisfactory ocular alignment: Observe from strabismus perspective Ptosis management: Proceed with frontalis sling repair		
Interval history (6 months) *Current age: 36 months*	Healing well postoperatively. Family is only able to patch the left eye 2 h per day secondary to progressive issues with patient cooperation		
Key components of exam		OD	OS
	Uncorrected visual acuity (LEA)	20/600	20/25
	Marginal reflex distance (MRD1)	1 mm	2 mm
	Alignment (modified Krimsky)	Nsc: 2Δ right hypotropia, 3Δ right exotropia in primary position Unchanged from previous examination	
Assessment and management	Complete right-sided CN III palsy with right-sided amblyopia, status post RSO tendon transposition, RLR recession and RMR resection, and right upper lid frontalis sling suspension: 1. Optimal postoperative alignment established 2. Good lid position established 3. Continued amblyopia: Advise patching 6 h daily as tolerated. Consider bifocal treatment for hypo-accommodative effort		

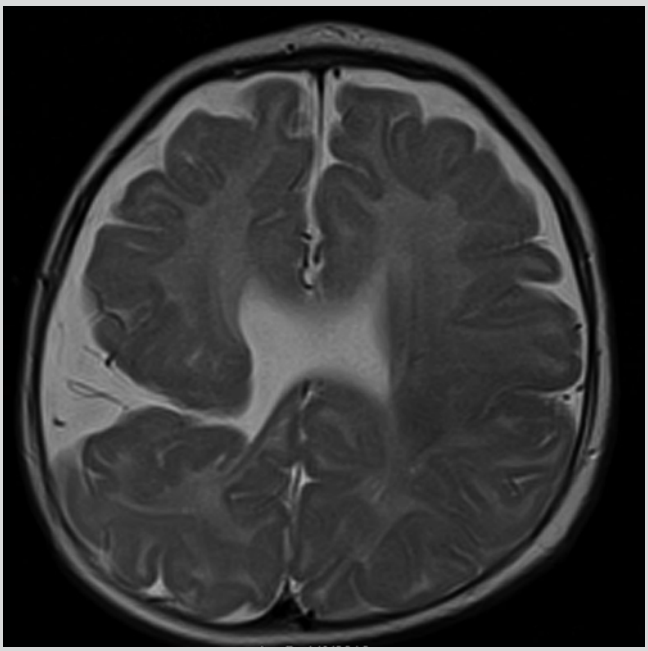

Fig. 50.1 MRI brain: right frontotemporal open-lip schizencephaly (direct communication from ventricular system into the subarachnoid space), absence of septum pellucidum, band migrational anomaly/heterotropia, and cortical dysplasia/polymicrogyria (abnormal cortical thickening)

Case 2

This 15-year-old male presented with a partial, pupil-involving CN III palsy after trauma with closed head injury. This is the most common cause of acquired CN III palsies in the pediatric population. Spontaneous resolution occurred after 4 months, although aberrant regeneration was noted. Spontaneous resolution, while rare, is possible following traumatic CN III palsy [18]. Over 50 % of these patients tend to develop aberrant regeneration [7] (see Table 50.3).

Table 50.3 Case 2

Clinical history	15-year-old male presents in the emergency department after motor vehicle accident. He was a restrained passenger and his head hit the dashboard. The patient complains of oblique binocular diplopia and drooping eyelid on the left side. Past medical history: noncontributory Family history: noncontributory			
Key components of exam		OD		OS
	Best-corrected visual acuity (Snellen)	20/20		20/25
	Marginal reflex distance (MRD1)	3 mm		−1 mm
	Ductions/versions	Full		Limitation in elevation and adduction
	Pupil exam	5 mm → 3 mm Round and reactive		6 mm → 5 mm Round and reactive
	Alignment	8Δ left hypotropia, 25Δ left exotropia in primary position		
		10Δ LHoT 35Δ LXT	10Δ LHoT 25Δ LXT	10Δ LHoT 17 LXT
		8Δ LHoT 35 LXT	8Δ LHoT 25Δ LXT	8Δ LHoT 20Δ LXT
		6Δ LHT 30 LXT	6Δ LHT 25Δ LXT	6Δ LHT 20 LXT
	Dilated fundus exam	C/D: 0.4 (pink/sharp) Normal fundus exam		C/D: 0.4 (pink/sharp) commotio retinae involving the inferior midperiphery
Diagnostic testing	CT brain – negative for acute intracranial process. MRI/MRA brain was negative for brain abnormalities			
Assessment and management	1. Left-sided pupil-involving, incomplete third nerve palsy → Observation 2. Horizontal and vertical binocular diplopia secondary to #1 → Occlude left lens on glasses for bothersome diplopia 3. Ptosis, right eye → Observation 4. Commotio retinae, left eye → Observation, with repeat dilated fundus examination 1–2 weeks later			
Interval history (2 months) *Current age: 15 years*	Patient initially managed diplopia with tape over the left lens of his spectacles. Over the two-month interval, however, his diplopia improved occurring only intermittently, which he was able to fuse			

(continued)

Table 50.3 (continued)

Key components of exam		OD		OS
	Best-corrected visual acuity (Snellen)	20/20		20/20
	Marginal reflex distance (MRD1)	3 mm		1 mm
	Ductions/versions	Full		−1 restriction of adduction, otherwise full; lid elevates with attempted down gaze
	Pupil exam	5 mm → 3 mm Round and reactive		5 mm → 3 mm Round and reactive
	Alignment	6Δ intermittent left exotropia in primary position with good-fair control		
		8 Δ LXT	6 Δ LX(T)	5 Δ LX(T)
		8 Δ LXT	6 Δ LX(T)	5 Δ LX(T)
		8Δ LXT	6 Δ LX(T)	5 Δ LX(T)
Assessment and management	Traumatic partial CN III palsy with near-complete resolution but with aberrant regeneration: observation			
Interval history (4 months) *Current age: 16 years*	Patient doing well. No longer has any diplopia			
Key components of exam		OD		OS
	Uncorrected visual acuity (Snellen)	20/20		20/20
	Marginal reflex distance (MRD1)	3 mm		2 mm
	Versions	Full		Full
	Lids/lashes	Normal		Lid elevates with attempted down gaze
	Alignment	Orthotropia in all cardinal gazes		

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Management of Exotropia in Childhood

51

Andreas Marcotty and Virginia Miraldi Utz

Abstract

Exotropia is an outward deviation of the eye that may be constant or intermittent. Exotropia may be present in infancy (infantile or congenital exotropia) or may become manifest later in childhood or adulthood. Intermittent exotropia, the most common form, can be classified into (1) basic (distance = near deviation), (2) divergence excess (distance > near), (3) pseudodivergence excess (distance angle appears greater than near deviation) secondary to tenacious proximal fusion or a high accommodative convergence/accommodation (AC/A) ratio, and (4) convergence insufficiency (near > distance). This chapter will focus primarily on the diagnosis and management of intermittent exotropia. Subjective and objective assessment of the magnitude and patient's control of the deviation guides management, which can be medical or surgical. Some controversy exists as to the most effective form of treatment and the optimal timing of interventions to promote and to maintain binocular visual development.

Keywords

Exotropia • Intermittent exotropia • Consecutive exotropia

Background

In exotropia one eye is deviated laterally either constantly or in an intermittent fashion. Intermittent exotropia is frequently observed in normal neonates and tends to resolve by 2–4 months of age [1]. The incidence of exotropia in the USA is 1.2 % [2], less frequent than esotropia [3]. Intermittent exotropia is the most common form of exotropia in the general population [4, 5]. The angle of deviation tends to remain the same or gradually worsens. Rarely is there a total resolution of intermittent exotropia [6, 7].

Exotropia can be broadly classified into the following:

- **Pseudoexotropia:** Patient appears exotropic secondary to wide interpupillary distance or a positive angle kappa (e.g., in a patient with macular dragging from retinopathy of prematurity, familial exudative vitreoretinopathy

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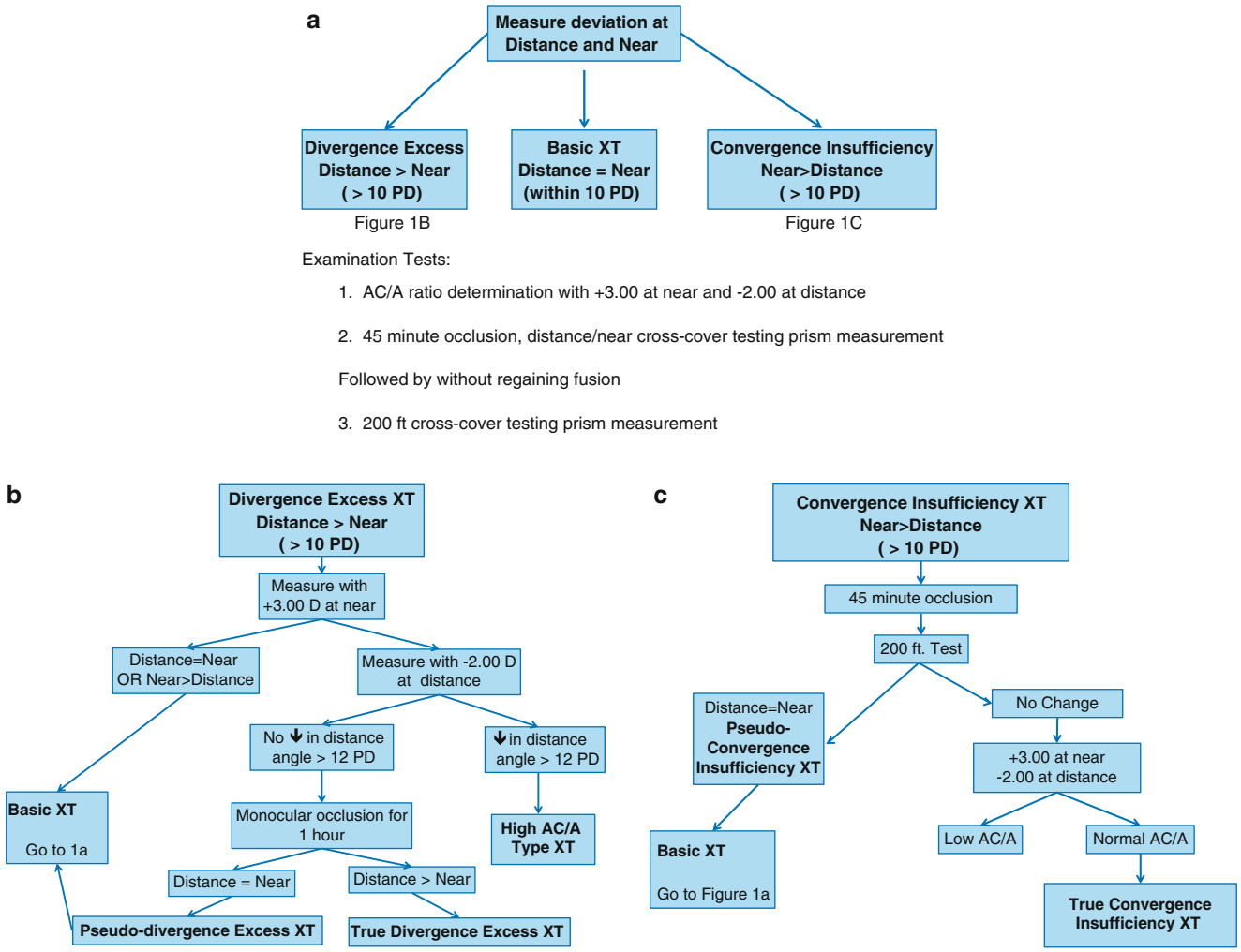

Fig. 51.1 Pattern determination in intermittent exotropia. (**a**) Initial measurements at distance and near allow the deviation to be classified as divergence excess, basic exotropia, or convergence insufficiency exotropia. (**b**) Diagnostic algorithm for the evaluation of divergence excess exotropia. The algorithm allows the practitioner to distinguish between true divergence excess exotropia and pseudodivergence excess from tenacious proximal fusion or high AC/A ratio. (**c**) Diagnostic algorithm for the evaluation of convergence insufficiency exotropia

(FEVR), or toxocariasis). The distinction between exotropia and pseudoexotropia is achieved using the cover test.

- **Exophoria:** An outward deviation that is controlled by fusion. Exophoria does not occur spontaneously. There is no suppression or loss of binocular vision.
- **Infantile exotropia:** Patients present before 6 months of life with a large-angle constant deviation. Systemic or neurologic impairment as well as craniofacial disorders is more likely to be associated with congenital exotropia than with infantile or congenital esotropia [8]. Early surgical intervention is indicated in most cases. Patients may also develop inferior oblique dysfunction, latent nystagmus, and dissociated strabismus complex from early disruption in binocularity.
- **Intermittent exotropia**: The exodeviation occurs spontaneously and is present intermittently.
  - Early signs include closure of one eye in bright sunlight or exodeviation when the patient is fatigued, ill, or inattentive.
  - With the eyes aligned, the patient will most often have normal stereopsis and near-normal vision in both eyes. When the eyes are not aligned, a suppression scotoma develops in the deviated eye under binocular viewing conditions, or, occasionally, diplopia may be present.
  - Intermittent exotropia can be divided into a number of subtypes depending on distance and near measurements of the deviation (see Fig. 51.1a–c).
- **Sensory exotropia**: The eye drifts outwardly as a result of poor vision from any of a variety of conditions that reduce the vision in one eye relative to the other (e.g., refractive errors, media opacity, optic nerve and pathway abnormalities, retinal pathology).

Table 51.1 Examples of scales for assessing control of intermittent exotropia

Intermittent exotropia control scale (IXTCS) [19]	Modified Newcastle score [15]	
5 = Constant exotropia 4 = Exotropia > 50 % of the 30 s period before dissociation 3 = Exotropia < 50 % of the 30 s period before dissociation 2 = No exotropia unless dissociated, recovers in > 5 s 1 = No exotropia unless dissociated, recovers in 1–5 s 0 = No exotropia unless dissociated, recovers < 1 s (phoria)	**Home control: XT or monocular eye closure seen:**	Score
	Never	0
	≤50 % of time when fixating at distance	1
	>50 % of time when fixating at distance	2
	>50 % of time fixating at distance and seen at near	3
	Clinical control:	
	Near:	
	Immediate realignment after dissociation	0
	Realignment with aid of blink or re-fixation	1
	Remains manifest after dissociation/prolonged fixation	2
	Manifest spontaneously	3
	Distance:	
	Immediate realignment after dissociation	0
	Realignment with aid of blink or re-fixation	1
	Remains manifest after dissociation/prolonged fixation	2
	Manifest spontaneously	3
	Total NCS = Home + Near + Distance	

s seconds, *XT* exotropia, *NCS* Newcastle score

Clinical Evaluation

The severity of intermittent exotropia is determined by (1) the angle of exodeviation, (2) the ability of the patient to control the exodeviation, and (3) the level of stereoacuity. A complete evaluation of the deviation at distance (nine positions of gaze) and at near with prism and alternate cover testing should be completed [9–11]. A far distance test (100–200 ft) may help to demonstrate a latent deviation or a larger deviation than the one measured at 20 ft. Near and distance testing with +3.00 lenses and with −2.00 lenses, respectively, can confirm an abnormality in the accommodative convergence to accommodation (AC/A) ratio (Fig. 51.1a–c). Multiple evaluations on different visits should be performed to ensure stability of the measured angle, as test-retest data indicate that the angle of deviation at distance may vary by 3.4 PD (for angles <20 PD) and by 7.2 PD (for angles >20 PD). The multiplicity of examinations is important for monitoring the change in the strabismus angle over time and in deciding the surgical dosage [12]. Interestingly, there is not a strong correlation between the angle of deviation and the ability of the patient to control the exotropia. To assess control, several scoring systems have been developed [13–18] including the intermittent exotropia control scale (IXTCS) [19] and the modified Newcastle control score (NCS) [15, 16] (Table 51.1). Recent work by Hatt and colleagues suggests that assessing the degree of control should be performed by averaging the results of three different measurements using the IXTCS [18]. Lastly, deterioration of distance stereoacuity may indicate a worsening of control and an increasing severity of the exotropia [20]. However, results of stereoacuity testing must be interpreted with caution as significant fluctuation occurs within a single day [21].

In addition to evaluation of motility and alignment, examination should include cycloplegic refraction, and any myopic or significant hypermetropic error should be corrected before a surgical decision is made (Fig. 51.2) [22].

After completion of the examination, if the ophthalmologist determines that the deviation is poorly controlled (Table 51.1), an intervention is often instituted as loss of binocular vision and amblyopia may result [23]. There continues to be some debate as to the roles of medical interventions, the indications for and timing of surgical interventions, and the specific surgical approach selected.

Traditionally, medical management consists of part-time occlusion regimens [24, 25], minus lens therapy [26–28], or prism therapy [29].

Part-Time Occlusion

Part-time occlusion regimens may result in temporary improved control of the exotropia, especially if there is a definite fixation preference without amblyopia; however, long-term benefit is limited [5, 24]. Some authors discourage disruption of binocularity with alternating patching regimens. A Cochrane review failed to provide conclusive evidence of the effectiveness of alternate patching [30]. This issue has recently been investigated by the multicenter *P*ediatric *E*ye *D*isease *I*nvestigator *G*roup (PEDIG) in the *Intermittent Exotropia Study 2* (*IXT2*), *A Randomized Clinical Trial of Observation versus Occlusion Therapy for Intermittent Exotropia* [31, 32]. Patients ages 3 to <11 years were randomized to either occlusive therapy (one eye or alternate patching) for 3 h/day versus observation for 6 months. Interestingly, very little decompensation occurred in

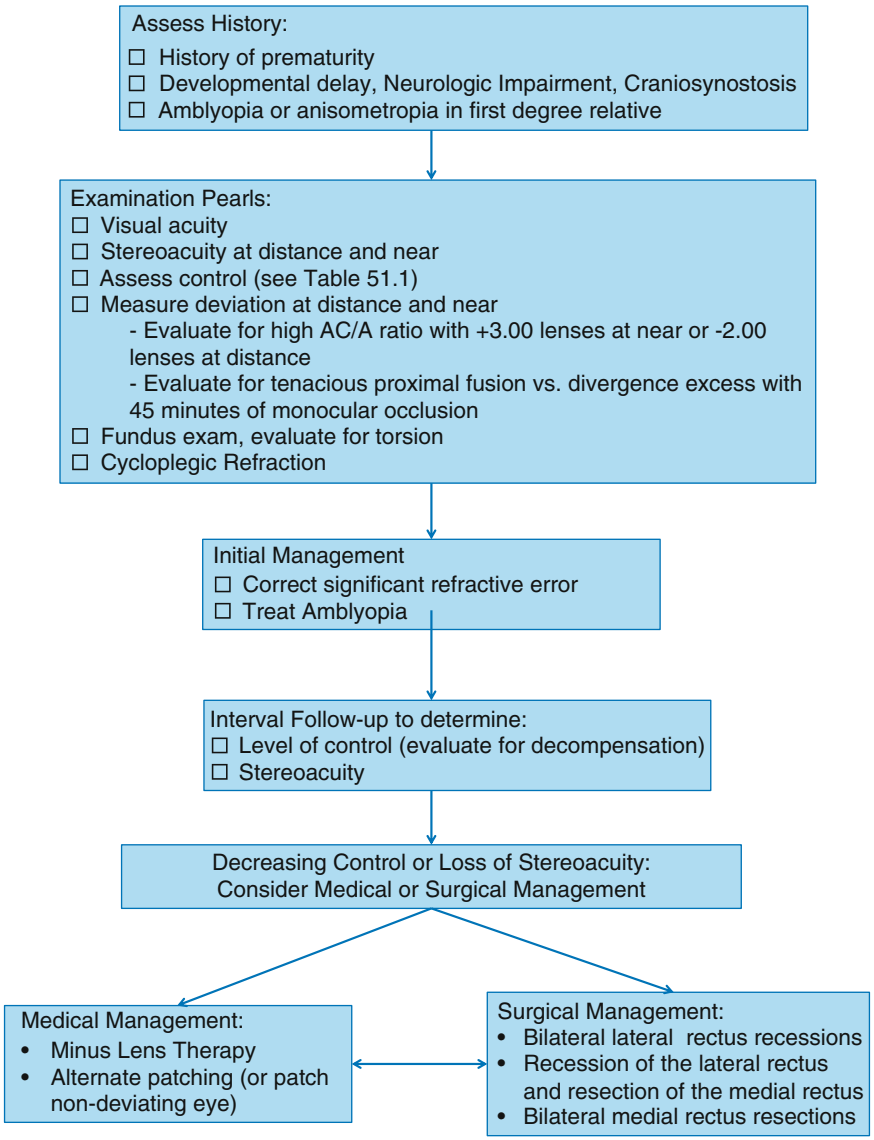

Fig. 51.2 Algorithm for clinical evaluation and management of patients with intermittent exotropia

either group over a 6-month period. There was no statistical difference between the observational and patching group in terms of control of the exodeviation; however, fewer patients in the patching group decompensated [33].

Minus Lens Therapy

Increasing the myopic correction, termed "over-minus," may increase accommodative convergence and theoretically improve the control of the exodeviation. However, it may be difficult for a children to wear glasses that they do not necessarily need for vision, and asthenopic symptoms may develop. Again, the evidence in terms of long-term success of this intervention is limited [26, 27]. In the specific case of patients with high AC/A ratio, there may be a higher risk for a postoperative esotropia at near viewing. Utilizing "over-minus" lenses for distance combined with bifocals can minimize the risk of overcorrection for near and delay or eliminate the need for surgical intervention [26, 28, 34].

Surgical Intervention

The greatest controversy perhaps concerns the timing of surgical intervention. Constant exotropia should be treated in a child once the measured deviation is stable. In a young child, there is a degree of urgency to performing the surgery, as binocular vision cannot develop in the setting of a constant or near-constant deviation. A number of authors have advocated early surgical intervention in children with intermittent exotropia to prevent the progression to constant exotropia and to preserve binocularity [6, 35–37]. Others have not found significant decompensation of the exodeviation nor

loss of binocularity with observation [36, 38]. More recently, in a 2-year observational study, Buck et al. noted rare deterioration into a constant exotropia, with most children not requiring a surgical intervention [39]. These observations are supported by the IXT-2 trial, in which neither the observational nor the patched group experienced significant decompensation (Pediatric Eye Disease Investigator, 2014 #48). Other investigators have also noted a similar lack of worsening in the magnitude or control of the deviation over longer periods of observation [36].

The postoperative goals for ocular alignment are also debated. Historically, the surgical treatment includes a deliberate overcorrection of the exotropia to a small-angle esotropia, with an alignment immediately after surgery within 10–15 prism diopters of esotropia [40]. This postoperative misalignment carries a risk of loss of binocular vision if the infant is in the critical period of vision development [41]. If the overcorrection persists for more than 2 months, the patient may require full cycloplegic refraction, the prescription of any hypermetropic correction and base-out prisms to match or to mildly under correct the overcorrection [42]. Such patients may require additional surgery for their esotropia, although it is preferable to delay the reoperation for up to 6 months, as the overcorrection may continue to improve. Thus, the timing and goals of surgical correction have potential complications that must be balanced with the risks of no surgical intervention. This should be considered seriously before embarking on surgery.

Lastly, if a decision is made to treat the exotropia surgically, the choice of the procedure is also met with some controversy in the literature. Surgical choices include bilateral lateral rectus recessions, unilateral lateral rectus recession and medial rectus resection, and bilateral medial rectus resections. Previous authors' preferences have been based on the pattern of deviation or the distance/near measurement disparity in measurements [43, 44]. The choice of surgery is also currently partly under investigation by the PEDIG group in the *Intermittent Exotropia Study 1 (IXT1), A Randomized Trial of Bilateral Lateral Rectus Recession versus Unilateral Lateral Rectus Recession with Medial Rectus Resection for Intermittent Exotropia (http://clinicaltrials.gov/ct2/show/NCT01032603)* [45].

A recent study suggests that there may be no need to prefer recessions over resections or vice versa in the management of strabismus [46]. Randomized, controlled trials will hopefully clarify the natural history, timing, and selection of the best intervention. Please see Fig. 51.2 for an algorithm to evaluation and management of patients with intermittent exotropia.

Case Study 1

A 2-year-old boy presents with occasional drifting of his eyes. Prenatal, birth, and developmental history is unremarkable. His father has a history of exotropia treated by surgery in childhood.

Key Examination Findings

Visual Acuity:

Central, steady, and maintained (CSM) in each eye

Sensorimotor Examination:

Versions and ductions: Full OU

Alignment:

Distance (sc)

	25X(T)	
25X(T)	25X(T)	25X(T)
	25X(T)	

Near (sc): X(T)' = 18

Classification: Basic subtype (less than 10 PD difference between distance and near deviation (see Fig. 51.1a–c)

Control (Table 51.1):

IXTCS score: 1 (recovers in 1–5 s)

NCS = 3 (1 + 1 + 1)

Stereoacuity: Unable to test

Cycloplegic refraction: +1.50 OU

Dilated fundus examination: Unremarkable, no torsion

Assessment: This patient has intermittent exotropia with relatively good control by both IXTCS and NCS.

Management options at this time include:

- Observation
- Medical intervention: Over-minus lenses or alternate patching
- Surgical intervention

Plan: Because the deviation is well controlled, observation was elected in this case. As long as the deviation occurs infrequently, this patient has an excellent chance of maintaining binocularity. The parents were educated to monitor closely for frequency of deviation as well as to have the patient focus on a near target if the deviation was observed. Follow-up was scheduled in 6 months.

Six-month interval history (current age: 2.5 years): Deviation occurring less frequently at home by parental report. Examination remains unchanged.

Twelve-month interval follow-up (current age: 3 years): No change in deviation at home; it occurs primarily right before nap or bedtime.

(continued)

Key Examination Findings

Visual acuity (LEA symbols, bracketed):
OD: 20/25
OS: 20/25

Sensorimotor Examination:
Versions and ductions: Full OU
Alignment:

Distance (sc):

	20X(T)	
20X(T)	20X(T)	20X(T)
	20X(T)	

Near (sc): X(T)' = 15

Classification: Basic subtype (less than 10 PD difference between distance and near deviation; see Fig. 51.1 a–c)

Control (Table 51.1):
IXTCS score: 1 (recovers in 1–5 s)
NCS = 1 (1 + 0 + 0)

Stereoacuity
Distance: 40 s arc (Distance Randot test)
Near: 40 s arc (Near Randot test)

Cycloplegic refraction: +0.50 OU

Assessment: Well-controlled, intermittent exotropia

Plan: Observation, monitor deviation, control, and stereoacuity. Follow-up in 6 months

Synopsis: This patient presented with intermittent exotropia with a family history of strabismus. A comprehensive examination was completed with assessment of the magnitude and pattern, control of deviation by the IXTCS and NCS, and stereoacuity (when able) completed at each visit. Because the deviation was well controlled, the clinician elected to observe. If the control of the deviation should decompensate at subsequent visits, medical management with over-minus lenses and/or alternate patching could be prescribed. However, both of these modalities have not been shown in clinical trials to be more efficacious than observation. Surgical intervention for this well-controlled deviation was not indicated and this patient developed full stereoacuity further indicative of a well-controlled deviation.

Case Study 2

A 2-year-old boy presents with outward drifting of the left eye that is frequently noted (>50 % of the time at distance, not noted when fixating on objects close to him). Prenatal, birth, and developmental history is unremarkable. His father has a history of exotropia treated by surgery in childhood.

Key Examination Findings

Visual Acuity:
Central, steady, and maintained (CSM) in each eye
Sensorimotor Examination:
Versions and ductions: Full OU
Alignment:

Distance (sc):

	25X(T)	
25X(T)	25X(T)	25X(T)
	25X(T)	

Near (sc): X(T)' = 10 PD
Near (+3.00): X(T)' = 10 PD
Distance (−2.00): X(T) = 25 PD
Monocular occlusion x 45 min, Distance: X(T) = 30 PD
Near: X(T)' = 25 PD
Classification: Pseudodivergence excess intermittent exotropia secondary to tenacious proximal fusion (see Fig. 51.1a–c)
Control (Table 51.1):
IXTCS score: 3 (Exotropia <50 % of the 30 s period after dissociation)
NCS = 4 (2 + 1 + 1)

(continued)

Stereoacuity: Unable to test
Cycloplegic refraction: +1.50 OU
Fundus examination: Unremarkable

Assessment: This patient has intermittent exotropia with poor to moderate control by both IXTCS and NCS.

Management options at this time include:
- Observation
- Medical intervention: Over-minus lenses or alternate patching
- Surgical intervention

Plan: The deviation does not appear well controlled (especially by parental report) and the authors elected to initiate alternate patching (2 h/day). The IXT-2 study did not demonstrate a statistical difference between alternate patching versus observation over a 6-month period. However, fewer patients in the patching group decompensated. Based on this study, either observation or patching could be utilized to manage this patient. Over-minus lenses could also be considered and the efficacy of this intervention is currently being evaluated by the IXT-3 randomized pilot study.

Three-month interval history (current age 2.25 years): Parents report that deviation is occurring >50 % at distance and near. Parents report adherence to alternate patching regimen but no improvement.

Key Examination Findings
Visual Acuity:
OD: CSM
OS: CSM
Sensorimotor Examination:
Versions and ductions: Full OU
Alignment:

Distance (sc):

	30X(T)	
30X(T)	30X(T)	30X(T)
	30X(T)	

Near (sc): X(T)' = 25

Classification: Basic intermittent exotropia (Fig. 51.1a–c)
Control (Table 51.1):
IXTCS score: 5 (mostly tropic during the exam at distance, intermittent at near)
NCS = 9 (3 + 2 + 3)
Stereoacuity: Unable to measure because of patient age

Assessment: Decompensating intermittent exotropia, now poorly controlled

Management Options
- Surgical intervention
- Over-minus lenses + alternate patching
- Observation

Plan: Because the deviation is manifest during the examination, the patient is unlikely to maintain binocularity without further surgical intervention. The patient has decompensated in the setting of alternate patching and over-minus lenses are unlikely to be tolerated. Either a bilateral lateral rectus recession or unilateral lateral rectus recession and medial rectus resection could be considered.

Interval history (age 2, 1/3 years): 1-week status post bilateral rectus recession

Key Examination Findings
Visual Acuity:
OD: CSM
OS: CSM
Sensorimotor Examination:
Versions and ductions: Full OU
Alignment:
Distance (sc): ET = 12 PD
Near (sc): ET' = 15 PD
Stereoacuity: Unable to measure because of patient age

Assessment: Overcorrected at distance and near 1 week postoperatively

Plan: Because the patient is in the amblyogenic age group, the patient was reevaluated 3 weeks later.

Interval history (age 2, 1/3 years): Parents see less crossing at home

Key Examination Findings
Visual acuity: (LEA single optotype)
OD: 20/50
OS: 20/50

(continued)

Sensorimotor Examination:
Versions and ductions: Full OU
Alignment:
Distance (sc): Orthophoria
Near (sc): E(T)' = 2–4 PD
Stereoacuity: Unable to measure because of patient age

Assessment: One-month status post bilateral lateral rectus recession with resolving initial overcorrection. No evidence of amblyopia at this time.

Plan: Monitor closely, reevaluate in 8–10 weeks.

Synopsis: This patient presented with poorly controlled intermittent exotropia with a family history of strabismus. A comprehensive examination was completed with assessment of the magnitude and pattern, control of deviation by the IXTCS and NCS, and stereoacuity (when able) completed at each visit. Between the first and second visits, the pattern changed from a pseudodivergence excess pattern secondary to tenacious proximal fusion to basic exotropia (Fig. 51.1a–c). Because the control was moderate to poor at the initial visit, a trial of alternate patching was initiated. At the follow-up visit, the deviation had further decompensated and was manifest and likely to limit binocularity. The decision was made to undergo surgical intervention. The patient was initially overcorrected and observed closely to ensure that the esodeviation resolved and that amblyopia did not develop.

Case Study 3

A 4-month-old infant with "lazy left eye" since birth. Prenatal and birth history is unremarkable. Parents do not have any developmental concerns. No significant past medical history

Key Examination Findings
Visual Acuity:
OD: F&F (fixes and follows)
OS: F&F (fixes and follows)
Sensorimotor Examination:
Versions and ductions: Full OU
Alignment:
Distance (sc):

	40XT	
40XT	40XT	40XT
	40XT	

Near (sc): XT' = 40PD
Strong right fixation preference, but does occasionally spontaneously alternate fixation
Control (Table 51.1): Manifest deviation, not intermittent
Stereoacuity: Unable to test
Cycloplegic refraction: +6.50 OU.
Fundus examination: Small, crowded hyperopic nerves, C/D 0.05. No fundus torsion or other abnormalities.

Assessment: This patient has congenital exotropia with a strong right fixation preference in the setting of high hypermetropia.

Management options at this time include:
- Observation
- Medical intervention:
  - Refractive correction
  - Over-minus lenses (in this case, we subtracted −1.00 from CRx)
  - Alternate patching
- Surgical intervention

Plan:
Partially correct refractive error and prescribe +5.50 sph OU.
Because of the strong right fixation preference and suspected amblyopia in the left, initiate patching right eye 2 h/day.
Discuss with pediatrician as high association with CNS abnormalities and developmental delay.

Interval history (age 7 months): Adherent to glasses wear and patching right eye 2 h/day. Parents report both eyes now drift and that they see drifting 100 % of the time. There is some gross and fine motor developmental delay and MRI was ordered by the pediatrician and was unremarkable. Early intervention for delayed gross and fine motor developmental delay initiated.

(continued)

Key Examination Findings
Visual Acuity:
OD: CSM
OS: CSUM
Current Prescription:
+5.50 sph OU

Sensorimotor examination: Unchanged in refractive correction. Spontaneously alternates fixation, with small right fixation preference with binocular viewing

Assessment: Congenital exotropia with correction of refractive correction and improvement of amblyopia in the left eye

Plan: Surgical intervention with either a bilateral lateral rectus recession or a left lateral rectus recession and left medial rectus resection

Interval history (age 8 months): 1-week status post bilateral lateral rectus recession

Key Examination Findings
Visual Acuity (cc):
OD: CSM
OS: CSM
Current prescription: +5.50 sph
Sensorimotor examination:
Versions and ductions: Full OU
Alignment:
Distance (cc): ET = 12 PD
Near (cc): ET' = 18 PD
Stereoacuity: Unable to measure because of patient age

Assessment: Overcorrected at distance and near 1-week postoperatively.

Plan: Because the patient is in the amblyogenic age group, the patient was reevaluated 3 weeks later.

Interval history (age 10 months): Parents are still observing crossing at home.

Key Examination Findings
Visual Acuity:
OD: CSM
OS: CSUM
Current prescription: +5.50 sph
Sensorimotor examination:
Versions and ductions: Full OU
Alignment:
Distance (cc): ET = 10 PD
Near (cc): ET' = 15 PD
Strong right fixation preference
Stereoacuity: Unable to measure because of patient age
Cycloplegic refraction: +7.00 sph OU

Assessment: Early consecutive esotropia following bilateral lateral rectus recession for congenital exotropia, strong right fixation preference (suspected recurrence of amblyopia in the left eye), high hypermetropia

Plan: Prescribe full cycloplegic refraction and initiate patching, 2 h/day of the right eye. Follow-up in 6 weeks

Key Examination Findings
Visual Acuity (Teller Acuity Cards, 58 cm)
OD: 4.0 cycles/degree
OS: 4.0 cycles/degree
Current prescription: +7.00 sph
Sensorimotor examination:
Versions and ductions: Full OU
Alignment:
Distance (cc): ET = ortho
Near (cc): ET' = 2–4 PD
Stereoacuity: Unable to measure because of patient age

Assessment: Resolution of consecutive esotropia with full cycloplegic refraction. Amblyopia improved in the left eye.

Plan: Maintain current refractive correction. Taper patching of the right eye to 1–2 h/day.

Synopsis: A more uncommon presentation is of a 4-month-old with constant exotropia. At this age, the exotropia might convert to an intermittent type with patching and observation. Constant or congenital exotropia is uncommon and the timing of surgical intervention will be influenced by this distinction. Identification of high

(continued)

refractive errors and management with appropriate lenses may change the pattern of deviation [22]. If the deviation remains constant despite patching, prior to undertaking a surgical treatment, MRI imaging of the CNS may need to be performed, as there is a higher incidence of occult CNS abnormalities in children with infantile XT [4]. Using standard strabismus tables, a surgical treatment is then performed. The patient has a small-angle esotropia following surgery that warrants close interval observation for the development of amblyopia.

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Duane Retraction Syndrome

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Ashley Abraham, Elias I. Traboulsi, and Michelle M. Ariss

Abstract

Duane retraction syndrome is a unilateral or bilateral condition characterized by abnormal innervation to the extraocular muscles that results in limitation of eye movement and co-contraction of muscles that are normally antagonists (Duane, Arch Ophthalmol 34:133–59, 1905). Depending on the pattern of dysinnervation, a variety of anomalous ocular motility patterns arise. Patients can have limited adduction, abduction, or both. Co-contraction of opposing muscles results in globe retraction. Patients may present with esotropia, exotropia, or orthotropia, and many have a compensatory head posture. There may also be associated upshoot or downshoot movements on attempted adduction or abduction. Classic type I Duane syndrome is often attributed to an absence of the abducens nucleus and nerve on the affected side with anomalous innervation of the lateral rectus muscle by a branch of the oculomotor nerve (Parsa et al., Am J Ophthalmol 125:399–401, 1998; Demer et al., Invest Ophthalmol Vis Sci 48:5505–11, 2007; Denis et al., J AAPOS 12:91–3, 2008; DeRespinis et al., Surv Ophthalmol 38:258–88, 1993). Most cases are sporadic, although familial cases have been reported, usually in an autosomal dominant pattern. An important consideration in the clinical management of patients with limited abduction is the differentiation of Duane syndrome from a cranial sixth nerve palsy, which would necessitate further neurologic evaluation. Surgical intervention is indicated in cases of large primary gaze deviation, significant torticollis, marked upshoots or downshoots, or significant globe retraction. Many patients are able to adapt to their limited motility and do not require surgery.

Keywords

Duane syndrome • Retraction • Strabismus • Esotropia • Exotropia

Introduction

Duane retraction syndrome is characterized by limited horizontal ocular motility (abduction, adduction, or both) accompanied by palpebral fissure narrowing and globe retraction on attempted adduction [1]. In the early half of the 1900s, authors theorized that an anomalous medial rectus muscle insertion was responsible for Duane syndrome, while others reported a fibrotic lateral rectus muscle to be the cause. While these abnormalities are observed in some patients, they are not a consistent feature [5]. Subsequent autopsy studies revealed an absence of the abducens nucleus and

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abducens nerve with anomalous innervation of the lateral rectus muscle by branches of the oculomotor nerve [6]. This was further substantiated by the use electromyography, which showed co-contraction of the medial and lateral rectus muscles on attempted adduction, resulting in palpebral fissure narrowing and globe retraction on the affected side [7, 8]. With the advent of magnetic resonance imaging (MRI), documentation of a hypoplastic or absent abducens nucleus has been confirmed in patients with Duane syndrome [2–4]. Collectively, these studies establish the cause of Duane retraction syndrome to be a paradoxical innervation of the lateral rectus muscle. The syndrome is currently classified as a congenital cranial dysinnervation disorder [9]. Of all the congenital cranial dysinnervation disorders, Duane syndrome is the most common and accounts for about 1 % of all strabismus patients [5]. Although most cases are sporadic, an estimated 5–10 % are reported to be familial, often with an autosomal dominant inheritance pattern [10]. Duane syndrome tends to be unilateral and to predominantly involve the left eye, although it may be bilateral [11]. There is a higher incidence in females compared to males but there appears to be no racial predilection [5, 12].

Clinical Types of Duane Syndrome

Duane retraction syndrome is generally classified into three subtypes based on limitation of extraocular motility [13]. Patients with type I Duane ET have poor abduction with no limitation of adduction (Fig. 52.1). Those with type II Duane XT have poor adduction with slight limitation of abduction (Fig. 52.2). Finally, those with type III have a combination of poor abduction and adduction. Globe retraction and palpebral fissure narrowing with adduction occurs in all three categories. In one study, patients with type I accounted for 83 %, type II for 11 %, and type III for 2 % of cases [14]. Esotropia is commonly associated with type I while in type II exotropia is most common. Patients with type III may be esotropic, exotropic, or orthotropic in primary gaze [5, 15]. There have been multiple retrospective and prospective studies of Duane syndrome patients [14, 16–19]. It is not uncommon for the condition to be diagnosed in childhood (1/3 of cases) or adulthood (1/3 of cases) [18, 19]. About two-thirds of patients are female. More than 80 % of cases are unilateral, and the left eye affected in two-thirds of unilateral cases. The vast majority of patients have good visual acuity

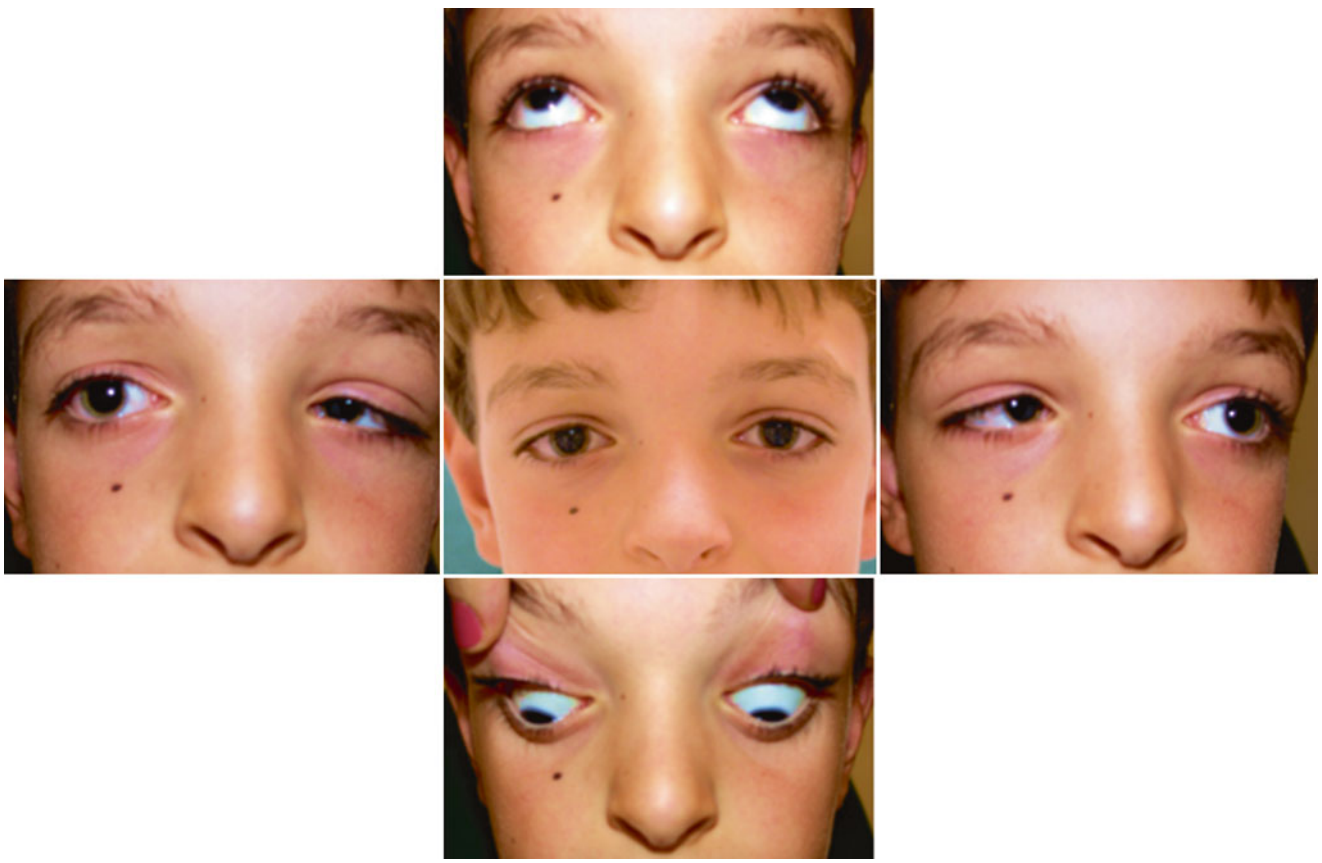

Fig. 52.1 Patient with left type I Duane syndrome. Note the absence in esotropia in primary gaze, the limitation of abduction of the left eye, and the narrowing of the palpebral fissure on right gaze

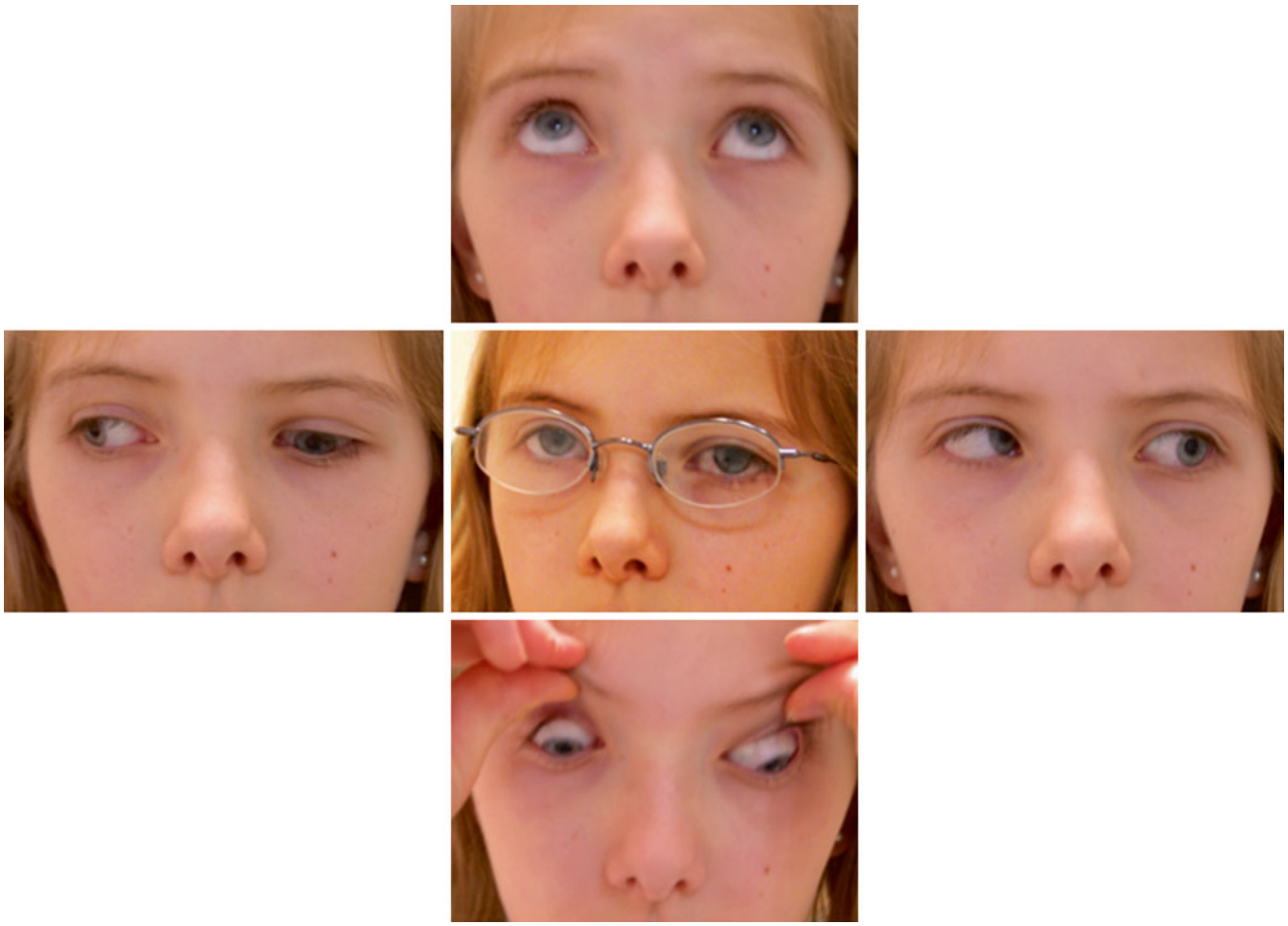

Fig. 52.2 Patient with left type II Duane syndrome. She has a right face turn and fixates in left gaze. There is limitation of adduction as well as downshoot of the left eye on right gaze. A more pronounced left exotropia is present in downgaze

in both eyes, and amblyopia occurs in only approximately 10 % of patients from anisometropia or concomitant esotropia or exotropia. Some patients have been reported to have Duane syndrome and Marcus Gunn Jaw winking [20], providing additional evidence for aberrant innervation. Marcus Gunn Jaw-Winking is caused by trigemino-oculomotor synkinesis of the jaw and levator muscles, leading to eyelid elevation or depression with jaw movement.

Many patients have additional abnormal vertical eye movements or alignment, including A and V patterns from over-elevation or over-depression in attempted adduction, as well as upshoots and downshoots usually in adduction (Figs. 52.3 and 52.4). Patients often adopt a compensatory head turn in order to maintain binocular single vision. For example, a patient with a left type I Duane syndrome and limited abduction will turn his/her head to the left to maintain single binocular vision in right gaze. Significant torticol-

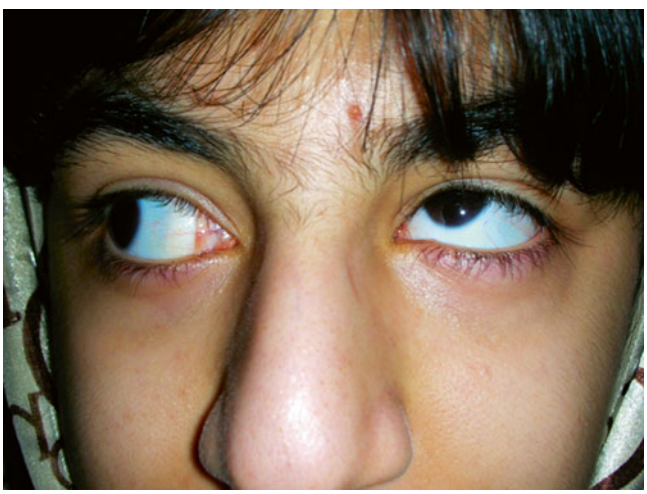

Fig. 52.3 Patient with left type II Duane syndrome with prominent upshoot of the left eye in adduction

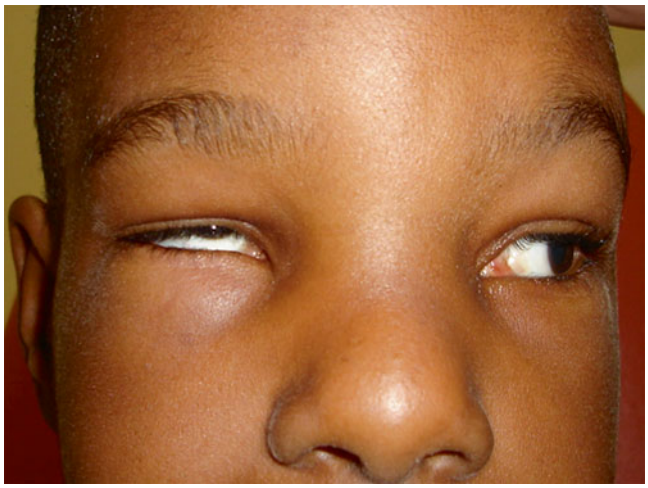

Fig. 52.4 Patient with poorly classifiable right Duane syndrome with significant globe retraction and upshot of the right eye in adduction

Table 52.1 Differential diagnosis for Duane retraction syndrome

Condition	Clinical findings
Abducens nerve palsy	Limited abduction
	Esotropia
	Head turn toward side of the lesion
Möbius syndrome	Abducens nerve palsy
	Facial nerve palsy
	Limitations of abduction and/or adduction
Congenital oculomotor apraxia	Inability to generate normal horizontal saccades
	Head thrust during horizontal tracking
Infantile esotropia	Full extraocular motility. Adduction fixation preference may limit ability to observe abduction movements

lis, strabismus, and anisometropia are the predominant risk factors for the development of amblyopia in patients with Duane syndrome [5, 21]. Bilateral cases are especially associated with a greater risk of amblyopia, which occurs in about 10 % of all cases of Duane syndrome. Bilateral cases also tend to have a lower rate of compensatory head turn and an increased incidence of vertical deviations and other congenital anomalies [11, 21]. Additional rare ocular anomalies included nystagmus, ptosis, microphthalmia, coloboma, heterochromia iridis, and congenital cataract.

When considering the diagnosis of Duane syndrome, it is important to differentiate it from other common causes of strabismus (Table 52.1). Key findings that suggest Duane syndrome include: (1) retraction of the globe and narrowing of the palpebral fissure in attempted adduction and (2) upshoots and downshoots on attempted adduction. In contrast to a muscle palsy, the strabismus is relatively modest despite a profound limitation of duction in the field of gaze of the involved muscle.

Genetics, Accompanying Syndromes, and Other Malformations

While Duane syndrome is often present as an isolated anomaly, approximately 30 % of individuals will have other congenital anomalies, particularly of the ear, heart, kidney, upper limbs, and skeleton [10]. Of 186 cases studied by Pfaffenbach et al. [18], 33 % had at least one, 17 % at least two, and 8 % at least three additional congenital anomalies. Congenital ear anomalies occur in 5 % of patients and include malformed pinnae and/or inner ear and auricular appendages. Sensorineural deafness is present in 6.5 %, genitourinary anomalies in 4 %, and cardiac anomalies in 2 % of patients [18]. Other notable associations include Okihiro syndrome, Goldenhar syndrome, radial ray dysplasia, Holt–Oram Syndrome, Wildervanck syndrome, and Klippel–Feil deformity of the spine [10, 18]. Duane syndrome occurs commonly in infants exposed to teratogens such as thalidomide in the womb [22].

Between 2 and 8 % of patients with Duane syndrome have at least one family member with the same condition [14, 17, 18, 23, 24] or with other types of strabismus [19]. Only one isolated Duane syndrome gene has been identified to date. After initial mapping studies by Apputukan et al. that mapped the gene to chromosome 2q31 in a family with a varying phenotype of unilateral and bilateral Duane syndrome [25], and its confirmation by another two studies [26, 27], Miyake et al. identified mutations in the a2-chimaerin (*CHN1*) gene in patients with isolated Duane syndrome [28].

Table 52.2 provides an overview of conditions associated with Duane syndrome.

Management of Patients with Duane Syndrome

The management of Duane syndrome begins with obtaining a comprehensive history. Specific questions regarding family history of strabismus and review of systemic and neurologic symptoms are essential in aiding the diagnosis. Patients with suspected or documented systemic abnormalities should be directed to the appropriate specialists for evaluation and treatment. All patients should have a hearing test.

Examination

Ophthalmic exam should include a thorough evaluation of ocular motility in all directions of gaze, noting horizontal limitation of movement and the presence of accompanying vertical deviations or paradoxical eye movements. Primary gaze deviation, abnormal head posture, globe retraction, and palpebral fissure narrowing in adduction should also be

Table 52.2 Genetic conditions associated with Duane syndrome

Condition	Clinical findings	Genetics
Duane-radial ray syndrome (DRRS), OMIM#607323	Duane anomaly, deafness, radial dysplasia, renal dysplasia. Hearing loss, dysmorphic facies, and cardiac, renal, and vertebral anomalies are variably expressed	*AD*
Temtamy et al. in 1975 [29] and Okihiro et al. in 1977 [30]		*Mutations in SALL4* gene, a zinc finger transcription factor, have been identified in affected individuals [31, 32]
		Mutations in the *SALL4* gene also cause Duane/Holt–Oram, acro-renal-ocular, and IVIC syndromes [32–34]
Duane/Holt–Oram syndrome	Duane syndrome with congenital cardiac anomaly (secundum ASD or VSD) with a spectrum of limb anomalies from absent or anomalous thumb to phocomelia or ectromelia (limb deformities)	AD
OMIM#142900		Mutations in the *SALL4* gene have cause Holt–Oram syndrome with Duane syndrome [35]
Acro-reno-ocular syndrome (AROS)	Duane syndrome, radial ray anomalies, and kidney malformations [36]	AD
		Mutations in the *SALL4* gene cause AROS, and this syndrome is allelic to DRRS and IVIC syndrome [34, 35, 37]
IVIC/oculo-acoustic-radial syndrome (Instituto Venezolano de Investigaciones Cientificas)	Eye movement abnormalities, radial ray defects, hearing impairment, and thrombocytopenia [34, 38, 39]	AD
		A *SALL4* gene c.2607delA is the causative mutation for IVIC syndrome and IVIC is allelic to DRRS and AROS [34]
Townes–Brocks with Duane syndrome	External auricular anomalies, sensorineural deafness, imperforate anus, and radial ray anomalies	*AD*
OMIM#107480		*Mutations in SALL1* [54]
Wildervanck syndrome (cervico-oculo-acoustic syndrome)	Duane anomaly, Klippel–Feil anomaly, and perceptive deafness [59]	*Sporadic*
		AD

AD autosomal dominant, *OMIM* Online Mendelian Inheritance in Man

noted. If tolerated, forced duction testing may provide additional information. A high suspicion should be maintained for type III Duane syndrome with limitations of both adduction and abduction, as such patients may be diagnosed with type I (more frequently) or type II and may undergo unilateral single-muscle surgery only to discover that the antagonist is also tight, and patients end up with the opposite ocular deviation in the operated eye.

Nonsurgical Management

Nonsurgical management of patients with Duane syndrome involves regular eye examinations to monitor for the development of amblyopia or anisometropia. If amblyopia is present, standard treatment with occlusive therapy, penalization, and corrective lenses should be prescribed. In rare cases, the use of prism glasses may be used to improve a mild head turn. The use of botulinum toxin has also been reported as a safe alternative to surgery in selected patients [40].

Surgical Management

While most patients are able to adapt to their limited motility and do not require surgery, surgical intervention is indicated in cases of large primary gaze deviation, significant torticollis, marked upshoots or downshoots, or significant globe retraction. The main goals of surgical treatment of Duane syndrome are the elimination of the abnormal head turn, the correction of strabismus without causing an overcorrection or additional limitation of movement, and the improvement of globe retraction, upshoot, and downshoot in patients in whom the latter are prominent [5, 41, 42].

A number of surgical procedures have been reported to be effective in achieving the above goals including ipsilateral rectus muscle recession [43], bilateral medial rectus recessions, vertical rectus muscle transpositions, lateral posterior fixation sutures, and weakening of the oblique muscles.

Ipsilateral Recession of a Single Rectus Muscle

This is probably the most commonly utilized successful method of treatment for patients with Duane type I and type II, with predominantly very good results [43–46]. Face turns are reduced or eliminated in most patients, and stereoacuity improved in some. As a representative study, Natan and Traboulsi found that 63 % of patients who undergo recession of a single rectus muscle achieve a good outcome, defined as a combination of minimal or no abnormal head position, less than 10^{Δ} of strabismus in primary gaze, and the maintenance of good stereoacuity [43]. Ninety-three percentage of their patients achieved a head turn less than 10°. A minority of

patients develops limitation of adduction or other unexpected outcomes such as an exotropia or other paradoxical eye movements after medial rectus recession. Such patients illustrate the complexity of abnormal extraocular movement innervation in patients with Duane retraction syndrome and the limitation of the clinical classification. In some patients, the predominant limitation to ocular motility preoperatively is one of abduction with esotropia. After the recession of the medial rectus, increased innervation for adduction is required, concurrently increasing innervation to the lateral rectus and leading to increased globe retraction on attempted adduction, limited abduction and adduction, and upshot and/or downshoot from increased innervation to the vertical rectus muscles [43, 47].

Bilateral Medial Rectus Recession

Kraft recommended bilateral medial muscle recession for all cases with esotropia greater than 20$^{\Delta}$, especially in the presence of severe retraction [41]. Using this technique Kraft reported that 37 of 42 patients had no clinically significant postoperative head posture [48]. Farvadin et al. performed bilateral medial rectus muscle recession in all patients with unilateral esotropic Duane syndrome, including those with esotropia <20$^{\Delta}$. Eighty percent were orthophoric and the rest had a residual esotropia of 5–10$^{\Delta}$. Abnormal head position was completely eliminated or was less than 5° in all patients [42]. Greenberg and Pollard reported poor outcomes using bilateral medial rectus muscle recession in four patients with Duane syndrome type I and a small-angle primary position esotropia [49]. Archer pointed out that recession of the contralateral medial rectus muscle decreases both innervation to the medial rectus muscle and aberrant innervation to the lateral rectus muscle in the affected Duane syndrome eye, leading to an undercorrection in Greenberg and Pollard's patients [50]. Archer does not agree with the benefits of contralateral medial rectus recession for unilateral esotropic Duane's syndrome as was proposed by Farvadin et al. [51]. Saunders et al. proposed large recessions or posterior fixation sutures on the medial rectus of the contralateral eye that would create matching duction limitation, allowing wider diplopia-free field postoperatively [52].

Unilateral Recession of the Medial and Lateral Rectus Muscles

We have used this method in patients with type III Duane syndrome and severe co-contraction. Limited adduction and abduction could ensue; hence, one should be cautious and only recess the medial and lateral about 5 mm each.

Vertical Muscle Transpositions

In a report of five cases, Foster recommended vertical muscle transposition augmented with lateral fixation [53]. While the majority of his patients had no residual head turn, 20 % developed a vertical deviation in primary position. Foster recommended against medial rectus recession at the same time as primary transposition or as a secondary procedure in those who had augmented transposition surgery, because of significant limitation of adduction and of late overcorrections. He cited expansion of the diplopia-free fields as an added advantage of this surgery compared to simple rectus recession. Using augmented and non-augmented vertical transposition, Velez et al. reported significant improvement of head turn as well as improvement in abduction and expansion of the size of binocular single visual field up to 65° [54]. Despite these encouraging results, 12.5–18 % of patients required additional medial rectus muscle recession or botulinum toxin injection. Ten percentage of augmented cases developed adduction limitation, and two patients developed vertical deviations [54]. These results were substantiated by other studies from Rosenbaum's group [55, 56]. The need for additional surgeries and the occurrence of postoperative vertical deviations and rare cases of anterior segment ischemia after vertical muscle transposition surgery in combination with medial rectus muscle recession have been reported [57].

Concomitant Recession of the Medial Rectus and Transposition of the Superior Rectus Muscles

Mehendale et al. performed concomitant recession of the medial rectus and transposition of the superior rectus in patients with severe limitation of abduction in 10 patients with Duane syndrome and 7 with sixth nerve palsy. They reported improved esotropia, head position, abduction limitation, and stereopsis without inducing torsional diplopia [58]. The same Boston group compared this technique to recession of a single or both medial rectus muscles, but the study was retroactive and the choice of the procedure was biased by the severity of the abduction deficit [59]. Kekunnaya et al. present the content of a symposium on the management of Duane syndrome in a review paper [60].

Horizontal Muscle Resection

In general, resections are avoided in patients with Duane syndrome as the results are often unpredictable and may worsen the co-contraction, palpebral narrowing, and vertical deviation.

Summary

While the majority of patients with Duane syndrome can be managed by observation or a simple horizontal muscle recession, some have a complex pattern of dysinnervation and co-contraction, and their surgical management should be individualized, sometimes requiring more than one intervention. A variety of approaches have been advocated and are currently under investigation and clinical trial among practitioners.

It is important to remember the possible systemic associations of Duane syndrome and to involve the appropriate clinical subspecialists in the care of patients with extraocular abnormalities.

Case Examples

Case 1 (Table 52.3)

Table 52.3 Case 1

Case 1				
Clinical history	8-month-old male referred to the eye clinic by his pediatrician for a "lazy eye"			
	PMH: none			
	FH: negative			
Key components of exam		**OD**	**OS**	
	UCVA	CSM	CSM	
	Ductions/versions	Full	Inability to adduct	
	Primary gaze position (Nsc, modified Krimsky)		XT = 15 PD	
		XT = 45 PD	XT = 15 PD	Ortho
			XT = 15 PD	
		Orthophoria in preferred left gaze position		
	Other	Palpebral fissure narrowing, globe retraction on attempted adduction, 10° right head turn (left gaze preference)		
	CRx	+3.00 sph	+3.00 sph	
Diagnosis management	Type II Duane syndrome			
	Observation with regular eye exams to screen for the development of amblyopia or refractive errors			

Synopsis

This is an otherwise healthy 8-month-old infant with small (10°) right face turn and left gaze preference. On motility examination, a total adduction deficit is present on the left. In the preferred head position, the patient is orthophoric with increasing exotropia on right gaze. In right gaze, the palpebral fissure narrows and there is globe retraction on attempted adduction of the left eye. These features are consistent with Duane type II. The differential diagnosis for a patient with an adduction deficit includes partial third nerve palsy, although one would expect other findings such as ptosis, other extraocular muscle dysfunction, and/or pupillary abnormalities. Because of the orthophoria in this adopted head position, the patient is likely to develop excellent binocularity despite the exotropia in primary gaze. Because the anomalous head position is small, this can be observed. The patient should have interval follow-up to ensure no progression of the deviation or suppression of the left eye.

Case 2 (Table 52.4)

Table 52.4 Case 2

Case 2	
Clinical history	2-year-old female presents to the eye clinic because of increased "crossed eyes" and head turn
	PMH: Type I Duane syndrome diagnosed at 12 months of age
	FH: negative

(continued)

Table 52.4 (continued)

Case 2				
Key components of exam		**OD**	**OS**	
	UCVA	CSM	CSM	
	Ductions/versions	Full	Inability to abduct	
	Primary gaze position (Dsc)		ET = 15 PD	
		Ortho	ET = 15 PD	ET = 35
			ET = 15 PD	
		Orthophoria in preferred right gaze position		
		Nsc: ET′ = 35 PD, $ET'_{+3.00}$ = 15 PD		
	Head posture	25° left head turn (right gaze preference), palpebral fissure narrowing on adduction		
	CRx	+6.00	+7.00	
Management	Prescription of hypermetropic correction for prevention of ametropic amblyopia and to rule out accommodative component of esotropia			
Interval history (4 months, age 28 months)	Wearing glasses consistently. Head turn still present, but less crossing noted at home			
Key components of exam		**OD**	**OS**	
	VA with correction (LEA single optotypes)	20/40	20/40	
	Ductions/versions	Full	Inability to abduct	
	Primary gaze position (Dcc)		LET′ = 8 PD	
		Ortho	ET′ = 8 PD	LET′ = 30
			LET′ = 8 PD	
		Ncc: ET′ = 8 PD		
	Head posture	15° left head turn (right gaze preference), palpebral fissure narrowing on adduction		
Management	Observation with interval follow-up			
	Continuation of glasses			

Synopsis

This is a case of a 2-year-old with type I Duane syndrome. This was distinguished from a sixth nerve palsy because of concomitant eyelid fissure narrowing and enophthalmos upon adduction of the affected eye as well as small angle of esodeviation in primary relative to the motility limitations. In addition, she has high hypermetropia, and glasses were initially prescribed leading to reduction of the esodeviation in primary position. This suggests that an accommodative component was present in addition to the Duane syndrome. The patient is managed conservatively at this time because of minimal esodeviation and small face turn.

Case 3 (Table 52.5)

Table 52.5 Case 3

Case 3				
Clinical history	12-month-old female presents to the eye clinic because her parents are concerned that she no longer turns her head to look at objects			
	PMH: Duane syndrome diagnosed at 10 months of age			
	FH: negative			
Key components of exam		**OD**	**OS**	
	UCVA	CSM	CSNM	
	Ductions/versions	Full	Inability to abduct	
	Primary gaze position (Nsc, modified Krimsky)		LET′ = 35 PD	
		LET′ = 25 PD	LET′ = 35 PD	LET′ = 45
			LET′ = 35 PD	
	Other	Palpebral fissure narrowing on adduction		
		No compensatory face turn		
	CRx	+3.00 sph	+3.50 + 4.00 × 180	
Management	Start amblyopia treatment with occlusion or penalization therapy. Correction of refractive error to rule out accommodative component			
	Consider surgical intervention to correct strabismus in primary gaze position once amblyopia improves			
Interval history (3 months, 15-month-old)	Patient is in glasses and has been patching right eye with good compliance			
Key components of exam		**OD**	**OS**	
	VA (in correction) (Teller acuity at 55 cm)	20/94	20/94	
	Ductions/versions	Full	Inability to abduct	
	Primary gaze position (Nsc, CT/ACT)		ET′ = 20	
		Ortho	ET′ = 20	ET′ = 35
			ET′ = 20	
	Other	Palpebral fissure narrowing on adduction		
		25° left face turn, right gaze preference		
	CRx	+3.00 sph	+3.50 + 4.00 × 180	
Management	Esotropia is outside of monofixation in primary and significant face turn. Surgical intervention indicated. Options for surgical intervention include left medial rectus recession (6.0 mm) or transposition of the left superior and inferior rectus to the lateral rectus. Because this patient is in the amblyogenic age group and there is a small risk of vertical deviation following transposition as well as goal to minimize time under anesthesia, a left medial rectus recession of 6.0 mm was performed			
Interval history (1-month postoperative exam)	Parents report improved alignment and head position after surgery			
Key components of exam		**OD**	**OS**	
	VA (in correction) (Teller acuity at 55 cm)	20/94	20/94	
	Ductions/versions	Full	Inability to abduct	
	Primary gaze position (Nsc, CT/ACT)		ET′ = 4	
		Ortho	ET′ = 4	ET′ = 20
			ET′ = 4	
	Other	Palpebral fissure narrowing on adduction		
		5° left face turn, right gaze preference		
Assessment/plan	Improved postoperative alignment and anomalous head position. Reevaluate in 3 months			

Synopsis

This is a case of Duane type I in which amblyopia in the left eye developed. There may have also been an accommodative component that was addressed with the full cycloplegic refraction. Occlusive penalization therapy was completed and in combination with refractive correction resulted in improved alignment. However, the esodeviation in primary gaze and head turn were significant to warrant surgical intervention. She underwent a left medical rectus recession with improved postoperative alignment.

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Management of Strabismus in Thyroid Eye Disease

53

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Abstract

Strabismus associated with thyroid eye disease results in significant impairment of daily activities and a decreased quality of life. Eye muscle surgery restores good ocular alignment and relieves diplopia in primary and reading gaze positions in more than 80 % of cases. Patients frequently undergo orbital decompression prior to eye muscle surgery. The most common patterns of strabismus include unilateral and bilateral inferior rectus restriction causing limited upgaze and unilateral or bilateral medial rectus tightness causing esotropia and limitation of abduction. Determining the amount of recession for tight muscles is difficult, and the response to a given amount of recession does not follow the nomograms that are utilized for nonrestrictive strabismus; this leads to the necessity of using adjustable suture techniques or other methods that allow for the positioning of the recessed muscle insertions based on intraoperative findings. The management of patients with TED and strabismus poses significant surgical challenges that are addressed in this chapter. General principles of evaluation are presented, and surgical techniques, pitfalls, and outcomes are described.

Keywords

Graves' disease • Thyroid eye disease • Strabismus • Surgery

The eyeballs were visibly enlarged, to such a degree the eyelids were unable to close and the white of the eyes could be seen in the breadth of several lines around all of the cornea.

Robert James Graves (1835)

Introduction

Graves' disease is the most common cause of unilateral and bilateral proptosis in adults and affects 16 women and 3 men per 100,000 individuals in Olmsted County, USA [1]. There is a bimodal distribution of cases occurring in the age groups 40–44 years and 60–64 years in females and 45–49 years and 65–69 years in males [2]. Graves' disease is the most common cause of hyperthyroidism worldwide. Terms that describe the ophthalmic involvement are thyroid-related

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orbitopathy (TRO), thyroid eye disease (TED), and Graves' orbitopathy (GO).

Graves' disease is quite uncommon in children with an estimated incidence of 3 per 100,000 prepubescents [2], but when a child is affected, TED occurs in the same proportion between sexes but has milder clinical manifestations compared to adults. Children with TED have lid retraction and lid lag, soft tissue swelling, and proptosis. EOM fibrosis and optic neuropathy are almost unheard of [3, 4]. Children with Graves' disease are treated with antithyroid medications for prolonged periods of time. Occasionally, and in severe cases, surgery or radioiodine ablation of the thyroid gland is required. Orbital decompression is almost never required due to the relatively mild nature of the disease [5]. Adolescents, especially those who smoke, can have a more severe orbitopathy with diplopia and strabismus.

While the majority of patients with Graves' disease do not develop an orbitopathy, about 20 % have some degree of orbital involvement, with 6 % having moderate to severe active orbitopathy and 1 % sight-threatening disease [6]. The active phase of TED involves orbital and periorbital inflammation of connective tissues and fat. This inflammatory phase is eventually self-limited, and the swelling of orbital tissues resolves after the inflammatory phase ceases [7]. About 5 % of patients with TED who have significant diplopia in the post-inflammatory phase require strabismus surgery [8–12]. Orbital decompression is frequently used to treat severe cases of TED, either in the acute phase to treat compressive optic neuropathy or later to alleviate the proptosis and disfigurement that accompanies this condition.

The major emphasis of this chapter is to discuss the diagnosis and management of restrictive strabismus and diplopia from inflammation and fibrosis of the muscles in patients with Graves' disease.

Etiology of Thyroid Orbitopathy

The risk factors for TED and its progression after radioactive iodine ablation in Graves' disease include female sex, smoking [13], severe hyperthyroidism, and poor control of hyperthyroidism after radioactive iodine ablation. High levels of thyroid-stimulating hormone receptor (TSH-R) antibodies, especially TSH-R-stimulating antibodies, also increase the risk of progression. Smokers have a 1.3× increased risk of developing clinical orbitopathy and a 3.1× increased risk of developing proptosis; also, current smokers seem to have a higher risk for orbitopathy than former smokers [14]. Smoking negatively influences the response of the orbitopathy to treatment with radiotherapy and high-dose steroids [13]. A euthyroid status seems to be associated with a milder disease course [15].

Kazim et al. provide an excellent review of the pathophysiology of thyroid orbitopathy [16]. In Graves' disease, antibodies to thyrotropin receptors bind to the receptors and stimulate the thyroid gland to produce more T3 and T4. This results in enlargement of the thyroid gland and to signs and symptoms of hyperthyroidism in some patients. Orbital fibroblasts share the thyroid antigen and are also stimulated by the anti-thyrotropin receptor antibodies, initiating a proliferative and inflammatory process in the adipose tissue of the lid retractors, lacrimal gland, orbit, and extraocular muscles. A number of other cell-surface receptors are activated and lead to an inflammatory response with overproduction of hyaluronan that accumulates in the orbit and extraocular muscles (EOMS), causing many of the clinical features of TED [16–18]. Genetic factors also predispose to autoimmune diseases such as TED [19, 20].

General Principles in the Treatment of TED

The goals of therapy of TED are (1) to treat ocular surface disorders from exposure related to proptosis and eyelid retraction; (2) to anticipate, prevent, or manage compressive optic neuropathy; (3) to manage diplopia and strabismus from EOM involvement, or as a consequence of orbital decompression; and (4) to restore the best possible appearance by surgically treating proptosis and eyelid retraction. Medical and surgical interventions are utilized to achieve these goals. Control of the hyperthyroid state can be reached using medications or thyroid ablation followed by thyroid hormone replacement therapy. Lubricants are utilized to treat ocular surface disorders. Orbital decompression addresses the proptosis and optic neuropathy; prisms or strabismus surgery is utilized to manage persistent diplopia and ocular misalignment; and eyelid surgery treats the secondary effects of the disease on the position and structure of the lids.

Corticosteroids and Other Immunosuppressants

High-dose intravenous corticosteroids are used for the acute management of patients with optic neuropathy and active orbital inflammation. While these agents reduce the inflammation and the accompanying congestive orbitopathy, they do not have an effect on orbital and EOM fibrosis. Many patients who receive intravenous steroids will also require decompression surgery [21–28].

Radiation Therapy

A technology assessment group commissioned by the American Academy of Ophthalmology assessed the effec-

tiveness of radiation therapy in the treatment of thyroid orbitopathy by reviewing the available literature on the subject prior to 2008 [29]. This group concluded that there was evidence of reduced inflammation and a slight improvement in motility after radiation therapy. However, radiation therapy is associated with short- and long-term risks of radiation retinopathy. It is contraindicated in diabetic patients and those with small-vessel disease. Perry and Feldon [30] commented that there was not enough evidence to support the efficacy of orbital radiotherapy in patients with TED; these authors believe that this type of treatment does not offer clear clinical benefit in most cases, that it carries risks of microvascular complications, and that it does not specifically target the underlying pathophysiologic features of the disease. They recommend orbital radiotherapy only in the extremely small subset of patients with compressive optic neuropathy refractory to maximal decompression that is technically feasible or acceptable to the patient [30].

Evaluation of the Patient with TED

Ophthalmic Signs and Symptoms

The most common signs and symptoms of Graves' disease with orbital involvement are eyelid swelling, eyelid retraction (believed to be more characteristic than proptosis), and ocular surface-related symptoms such as irritation and foreign body sensation. Patients with severe orbitopathy can have severe and persistent retrobulbar pain.

The increased volume of the orbital contents leads to increased pressure in the orbit and secondary decrease in venous and lymphatic drainage from the orbit [31]. The increased orbital pressure can lead to optic nerve compression at the orbital apex as the orbital compartment becomes extremely crowded, resulting in an optic neuropathy that can be associated with visual field and visual acuity loss. Optic neuropathy occurs in less than 5 % of patients with TED, and its early signs and symptoms include abnormalities of color vision sometimes in the face of a normal-appearing optic nerve head. More advanced neuropathy is characterized by optic nerve swelling with retinal striae and more extensive visual field defects. Optic neuropathy can occur in the absence of significant proptosis.

Thyroid orbitopathy is present for an average of 2 years (range 0–5 years) prior to the start of diplopia. While irritation, tearing, and pressure sensation associated with lid retraction and proptosis are the most common symptoms and signs in patients with TED, diplopia is the most disabling and occurs in up to 40 % of adults with thyroid orbitopathy [32]. Selective or generalized EOM enlargement and fibrosis lead to limitation of eye movements and diplopia. Most commonly the inferior and medial recti are involved, causing hypotropia and esotropia, respectively. Bilateral involvement may result in limited upgaze with or without diplopia secondary to inferior rectus restriction. This leads patients to assume a chin elevation posture to maintain their eyes in downgaze, avoiding diplopia in primary and upgaze. Similarly, but much less commonly, patients with very asymmetric disease that involves the horizontal muscles can have a lateral face turn position. Some patients with Graves' disease have concomitant myasthenia gravis and develop paradoxical ptosis and limited eye movements as well as slow saccades from weak rather than tight muscles [33].

General Ophthalmic Examination of the Patient with Strabismus and TED

Important historical information to be obtained from patients with TED and diplopia are (1) age of onset and of diagnosis of the disease; (2) treatments received, including thyroid ablation surgery, radioactive iodine, immunosuppressants, radiation therapy to the orbit, orbital decompression surgery, and ocular surface lubrication; and (3) stability of the diplopia over recent months as well as time duration since orbital decompression if it has been performed. As a general rule, the patient needs to have stable ocular deviation and general medical status, as well as no evidence of active orbital inflammation at the time of strabismus surgery. Six months or more would have preferably passed since orbital decompression surgery, although shorter periods may be appropriate in selected cases with significant disability.

It is critical to perform a complete ophthalmic examination of patients with TED, especially if they have not been evaluated by an oculoplastic surgeon or neuro-ophthalmologist who specializes in the care of such patients. While the pediatric ophthalmologist and strabismologist may be asked to take care of the diplopia, she/he has to make sure that the other ophthalmic issues have been addressed.

The orbits and eyelids are inspected and palpated, exophthalmometry performed, and measurements recorded. Photographs are useful in documenting the external appearance of the patient, the extent of eyelid involvement, as well as the magnitude of eye excursions. The eye excursions can also be estimated in the office in degrees from primary gaze, one eye at a time with the other occluded. This allows a semiquantitative assessment of worsening or improvement. Figure 53.1 shows an example annotation of eye movements from primary gaze. Note limited elevation and abduction of this right eye. Notation is made of any eyelid retraction.

The ocular surface is carefully examined using the slit lamp and the appropriate staining methods to assess for the presence of keratopathy.

Patients with TED are also predisposed to an increase in IOP because of compression of the globe by the enlarged and

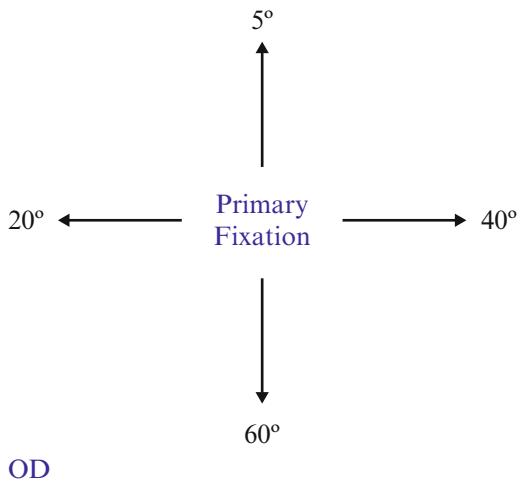

Fig. 53.1 Quantitating ductions using extent of eye movement in degrees. This is done with the patient looking straight ahead with one eye occluded. The examiner estimates the eye movements from primary fixation in degrees. This patient's right eye can only abduct 20° and elevate 5° from central fixation. A similar diagram is made for the movements of the left eye. Measurements are repeated after surgery and improvements noted

tight muscles. This increase in IOP is potentiated in upgaze as tight inferior rectus muscles press against the globe. Hence, IOP should be checked in primary as well as in upgaze.

To investigate optic nerve function, pupillary reactions are checked, best-corrected visual acuity is recorded, color vision is tested, and the nerve head is inspected for the presence of swelling or pallor. Visual field testing and/or OCT of the optic nerve head should be performed. Automated perimetry is commonly utilized in patients with TED. Visual evoked potentials can be used as a complementary diagnostic modality and can improve the detection of the disease at an early stage [34]. If any degree of optic neuropathy is suspected or documented, a neuro-ophthalmologist or oculoplastic surgeon who specializes in the management of patients with TED should be consulted as urgent medical or surgical therapies may be necessary.

Grading of Disease Severity

TED can be graded clinically using a variety of scales; some grade disease severity and others its activity. Most scales have not clearly differentiated between signs of acute inflammation and those of the subsequent cicatricial phase.

The CAS (clinical activity score) system assigns one point to each of seven signs or symptoms indicative of inflammation (Table 53.1) [35]. The VISA classification uses vision, inflammation, strabismus, and appearance to grade severity and change in clinical activity (Table 53.2) [36].

Table 53.1 Clinical assessment score (CAS) system parameters for clinical activity score

Clinical finding	Score
Retrobulbar pain	0–1
Pain on eye movement	0–1
Eyelid erythema	0–1
Conjunctival injection	0–1
Chemosis	0–1
Swelling of the caruncle	0–1
Eyelid edema	0–1
Total	0–7

A total of 0–2 indicates inactive Graves' orbitopathy; a total of 3–7 indicates active orbitopathy

Table 53.2 Parameters for VISA inflammatory score

Clinical finding	Score
Orbital pain (none, at rest, with gaze)	0–2
Chemosis	0–2
Eyelid edema	0–2
Conjunctival injection	0–2
Total	0–8

VISA vision, inflammation, strabismus, and appearance. A total score of <5/8 indicates mild Graves' orbitopathy; a score of >4/8 indicates moderate-to-severe orbitopathy. Chemosis is graded as 1 if the conjunctiva lies behind the gray line of the eyelid and 2 if it extends anterior to the gray line. Eyelid edema is scored as 1 if it is present but not causing the tissues to overhang and as 2 if it causes a roll in the eyelid skin, including festoons in the lower eyelid. The pain score is 0 = no pain, 1 = pain with movement, and 2 = pain at rest

The scoring systems and their individual components are used to guide the management of the individual problems associated with TED. For example, a VISA score of <4/8 with no other clinical findings is indicative of mild disease that can be managed conservatively, whereas a score of >5/8 indicates moderate-to-severe disease necessitating more aggressive therapy such as intravenous corticosteroids or decompression surgery. The European Group on Graves' Orbitopathy released a consensus statement in 2008 that included a refinement of the recommendations for the management of TED; the group recommended the initial stratification of patients into mild, moderate-to-severe, or sight-threatening categories, as well as a determination of disease activity (Table 53.3) [37, 38].

Laboratory Testing

Serum levels of TSH-R antibodies and thyroid-stimulating immunoglobulin (TSI) should be determined. TSI is a bioassay that detects lower levels of TSH-R antibodies and helps to differentiate Graves' disease from Hashimoto thyroiditis, in which it is negative [39]. Antibody levels correlate well

Table 53.3 Classification of patients with TED by severity status

Severity status	Description
Sight threatening	Patients with dysthyroid optic neuropathy and/or corneal breakdown. This category requires immediate intervention
Moderate to severe	Patients without sight-threatening TED whose eye disease has enough impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Patients in this category usually have one or more of the following: lid retraction >2 mm, moderate-to-severe soft tissue involvement, exophthalmos >2 mm above normal for race and sex, or inconstant or constant diplopia
Mild	Patients whose symptoms of TED have only a minor impact on daily life and are insufficient to justify immunosuppressive or surgical treatment
	Patients in this category usually have one or more of the following: minor lid retraction <2 mm, mild soft tissue involvement, exophthalmos <3 mm above normal for race and sex, transient or no diplopia, or corneal exposure responsive to lubricants

with clinical disease activity [40], and serial measurements during the inflammatory phase may be useful in clinical decision making [41].

Imaging

The evaluation of EOMs in TED is complex and requires clinical examination as well as imaging of the orbits. Bilateral orbital involvement is discovered in more than 50 % of patients in whom the disease appears to be clinically unilateral in nature. By determining which muscles are enlarged, additional information can be obtained that may assist in surgical planning, for example, a very large ipsilateral Superior Rectus (SR) to a hypotropic eye that is going to undergo an inferior rectus recession, and one can predict a late overcorrection and avoid it either by limiting the amount of inferior rectus recession or concomitant superior rectus recession [42]. The typical appearance of EOMs in TED is one of diffuse muscle enlargement that characteristically spares the tendons (Fig. 53.2a, b). Mean values for volume of normal EOMs on CT scanning have been determined [43]. One or more EOMs may be enlarged and the disease may be significantly asymmetric. CT orbital findings in TED are listed in Table 53.4.

CT scanning is generally preferred by orbital surgeons because the bony anatomical landmarks are clearly identified and this helps in planning orbital decompressive surgery. The use of MRI avoids orbital irradiation, although this may theoretically help in TED. Furthermore, MRI provides excellent visualization of the orbital apex—if the fat around the optic nerve is apparent, compressive optic neuropathy is unlikely.

B-scan ultrasonography is another imaging modality that is of some help; it requires technicians/operators who are very experienced in targeting the muscles and measuring them in cross section [45].

Orbital Decompression

Orbital decompression in TED has been used to relieve optic nerve compression that leads to vision loss, as well as for the reduction of proptosis that causes exposure keratopathy or is very disfiguring. Strabismus and diplopia can follow orbital decompression in up to 30 % of cases; this occurrence may depend at least in part on the technique of orbital decompression. Exophthalmos usually precedes diplopia. This time course sometimes confounds discussions of the role orbital decompression plays in the development of diplopia, as an estimated 6.7 % of all patients with TED undergo decompression surgery [1]. The natural history of diplopia in TED is such that a certain number of these were likely to develop whether or not the patient had an orbital decompression early in the course of their disease. The effect of orbital decompression on strabismus in TED has been widely studied over the years. The incidence of new diplopia following orbital decompression may be as high as 41–73 % [46]. Subdividing patients into those with normal versions on motility examination and no diplopia prior to decompression (type 1) and those with motility problems prior to decompression (type 2), Nunery and colleagues [46] found that the incidence of new diplopia after decompression was only 4 % for type 1 patients, but 50 % for type 2 patients. Of the type 2 patients who already had primary position diplopia, there was significant worsening of both esotropia and vertical deviations after decompression (Fig. 53.3a–c). Shorr and associates [47] had similarly found that more severely diseased orbits were more likely to have significant strabismus after decompression and that endoscopic techniques produce similar results [48]. Prior orbital decompression was not found to have an effect on the outcome of strabismus surgery in a study by Mourits and associates [49] in which fixed sutures were employed, and 13 of 27 patients had prior orbital decompression. Single binocular vision was obtained in 71 % of patients after one surgery and a total of 89 % after two surgeries.

Nicholson et al. [50] did not confirm the results of Dal Canto et al. [51] in a larger series from the same institution that patients who develop diplopia after orbital decompression have better outcomes than those who do not undergo decompression. They did, however, confirm their finding, supported elsewhere in the literature [52], that patients undergoing orbital decompression tended to require more muscle recessions per surgery. Patients with a history of diplopia that followed decompression surgery had a higher rate

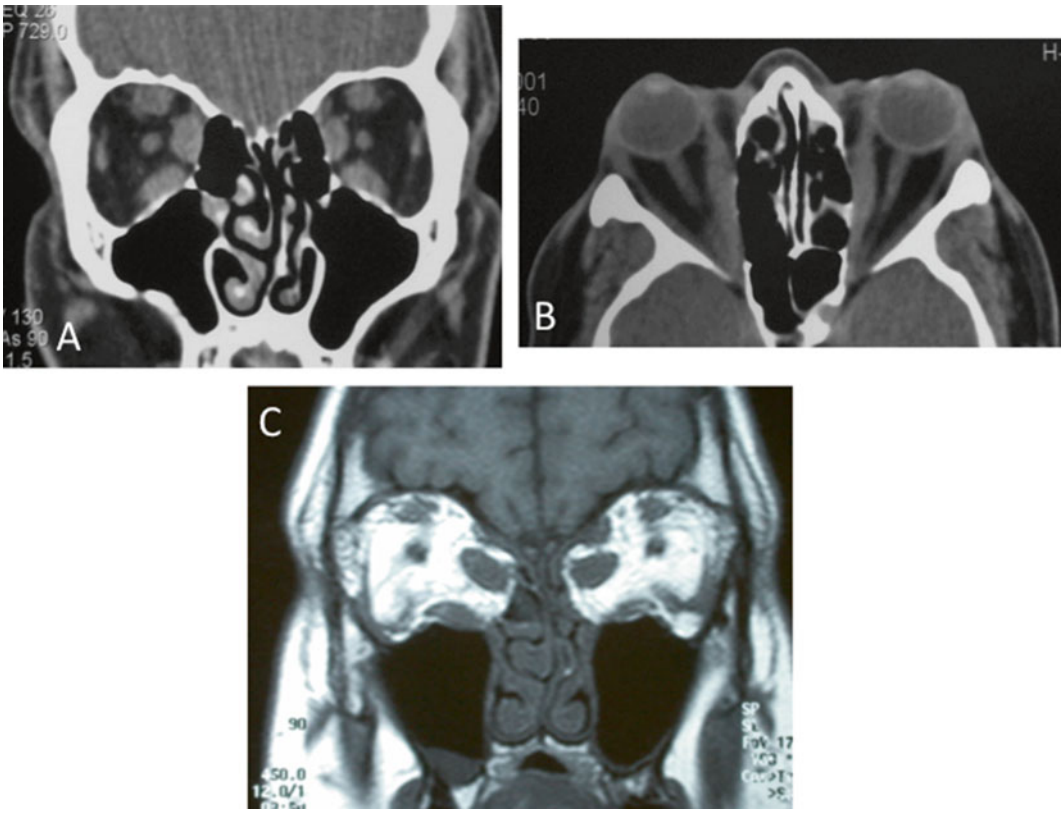

Fig. 53.2 (**a**) Bilateral enlargement of the medial, superior, and inferior recti in this patient with Graves' disease. (**b**) Note enlargement of the belly and sparing of the tendinous region of the medial rectus muscle. (**c**) The medial rectus muscles and the inferior rectus muscles have been displaced into the cavities produced by the orbital decompression procedure

Table 53.4 Computed tomographic (CT) findings in TED [44]

CT finding
Increased volume of the extraocular muscles (spindle-like thickening >4 mm)
Rectus muscle involvement (inferior > medial > superior)
Vascular engorgement
Sinus involvement
Slight bowing of the medial orbital wall into the sinus ("Coca-Cola bottle sign")
Compression of the optic nerve by enlarged extraocular muscles and rarely by lacrimal gland enlargement

of an excellent outcome than did patients who developed diplopia independently of orbital decompression ($p = 0.04$) [51]. It is possible that patients without diplopia prior to decompression may have less severe extraocular muscle disease and normal muscle contractility, allowing for better surgical results. Although more muscles required surgical intervention in patients who underwent orbital decompression, these patients did not require more reoperations than patients who did not have previous orbital decompression.

Examination of the Patient with TED and Strabismus

Careful attention to ductions, versions, and strabismus measurements [53] allows the assessment of all eye movements in all gazes and the determination of the most affected fields of gaze, facilitating surgical planning that alleviates diplopia in primary gaze and improves comitance. This leads to the largest and most useful field of single binocular vision possible for the patient with TED and strabismus.

Ductions and versions generally yield similar results as far as determining which muscle(s) are most affected by the fibrosis that follows inflammation resulting in restriction and limited movement. Ductions and versions can be recorded using the −4 to +4 designation (usually utilizing the minus numbers only to indicate an eye that is restricted from moving in a particular gaze) or percentages of expected full rotation of the globe. One of us (EIT) prefers estimating ductions in degrees from primary gaze. While precise measurements can be obtained using generally unavailable instruments [54], it can be estimated by careful observations and practice

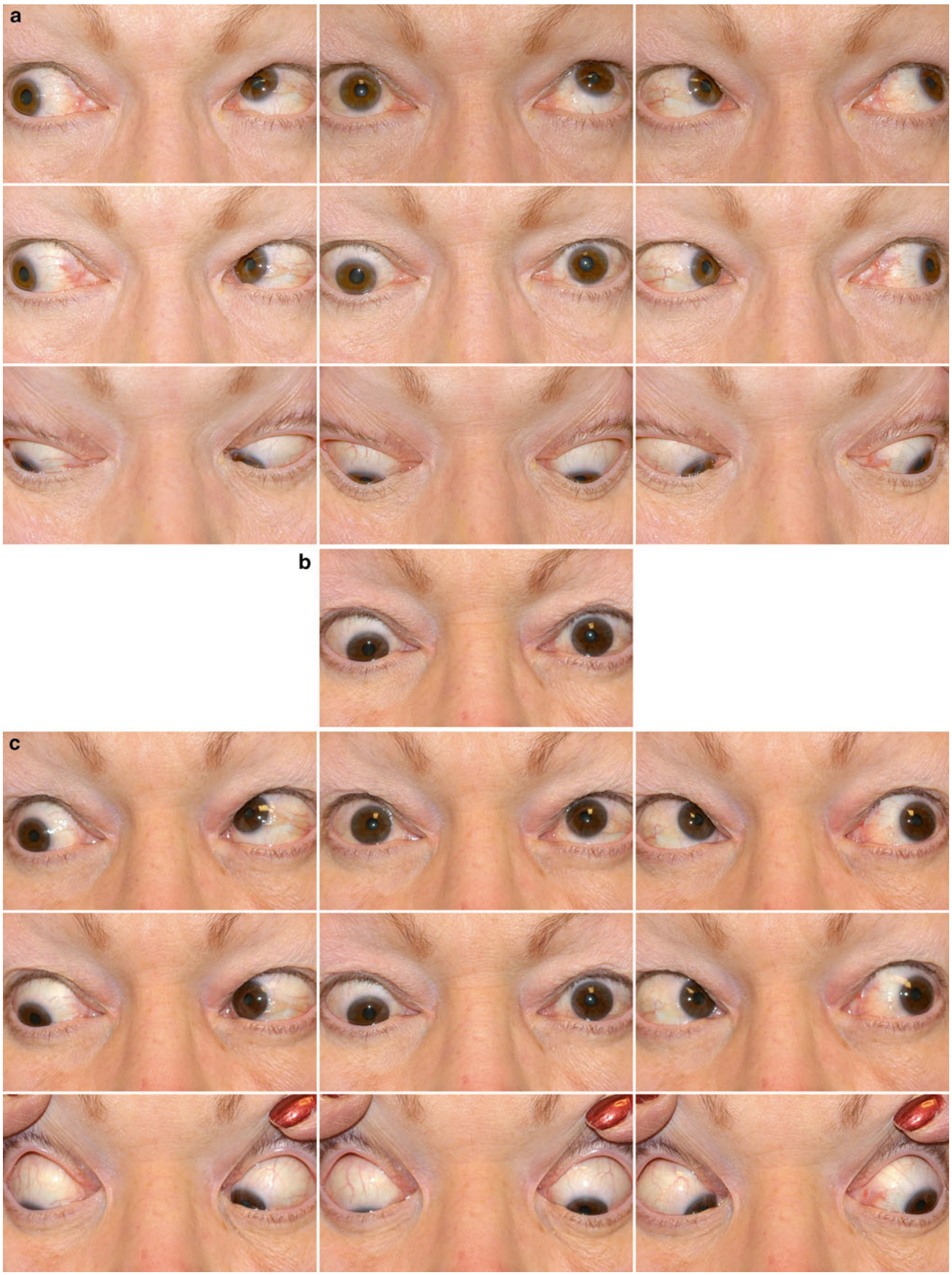

Fig. 53.3 (**a**) Patient with right hypotropia and limited elevation of the right globe, but otherwise relatively unrestricted motility. (**b**) Increased right hypotropia immediately following decompression (note ecchymoses bilaterally). (**c**) Motility following bilateral decompression. Upgaze and lateral gaze of both eyes are now restricted

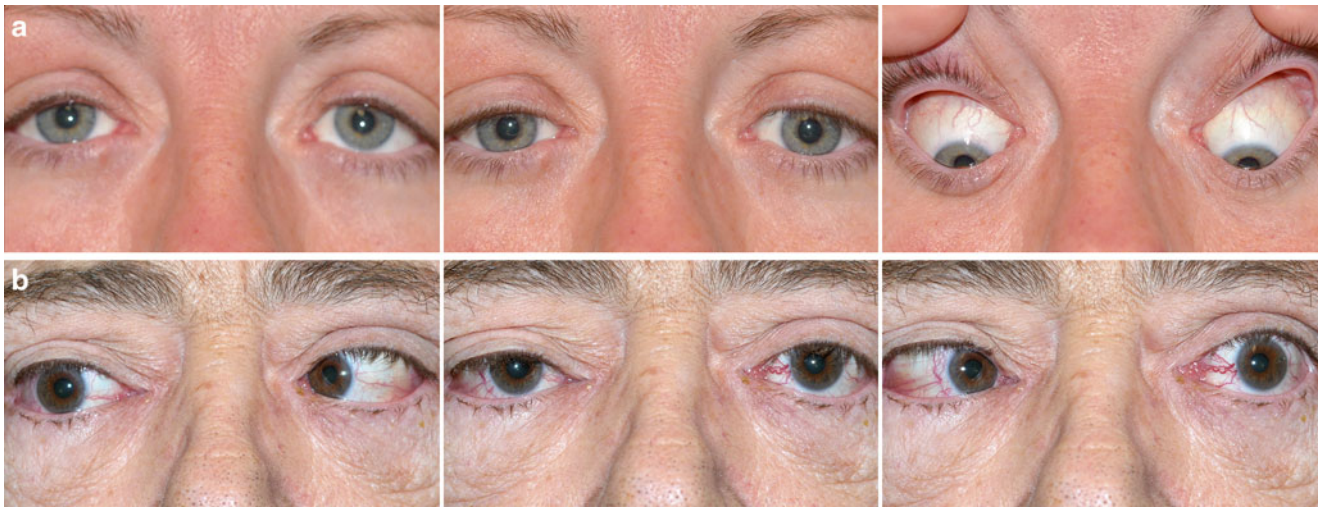

Fig. 53.4 (**a**) Bilateral upgaze limitations. −3.5 elevation deficit OD and −3.0 deficit OS. (**b**) Bilateral abduction deficits with right esotropia in primary gaze. −2 deficit OD and −3 deficit OS

either by estimating it in degrees (Fig. 53.1) or on a scale of −4 to +4, indicating severe limitation to significant overaction at the ends of the scale. Photographs may be useful for documenting and grading the limitation of movements seen in Graves for purposes of surgical intervention (Fig. 53.4a, b). Care must be taken in interpreting ductions and versions in patients with bilateral asymmetric TED as symmetrical vertical restriction can be masked in the setting of asymmetric horizontal muscle restriction [55].

Whether prism and alternate cover testing is performed in all cardinal positions of gaze, or a Hess Screen is utilized, the surgeon should utilize the quantitative measurements of ocular deviations to plan recession of the muscle(s) that cause the patient's diplopia. Although certain techniques discussed in this chapter do not utilize quantitative measurements of the ocular deviation in primary gaze to determine the amount of surgery to perform, it is still helpful to determine stability of measurements before surgery and to mark one's progress postoperatively.

If the patient is unable to perform a prism and alternate cover test in primary gaze because one or both eyes cannot move to primary gaze due to severe restriction of motility, a red filter and prisms can be used to demonstrate fusion after neutralization of the head position and, thus, quantify the deviation in primary gaze [56]. Quantifying the field of single binocular vision using a Goldmann perimeter can be useful to determine the stability of the strabismus preoperatively and to quantify improvement after surgery, particularly for cases in which significant restriction precludes prism and alternate cover testing (or even Hess screen testing) in multiple fields of gaze and/or primary gaze.

Measuring deviations in cardinal gazes also facilitates the discovery of any preexisting A pattern, which may be particularly common following surgical decompression of the orbit [55, 57]. This is an important clinical finding in surgical planning because exotropia in downgaze may preclude binocularity while reading and/or create symptoms of a convergence insufficiency, particularly once esotropia in primary gaze due to medial rectus restriction has been addressed with medial rectus recession(s), and if the inferior recti (tertiary adductors) are also being recessed. Also, reduced proptosis following decompression may encourage increased superior oblique action, further contributing to an A pattern [57].

Armed with the understanding that TED causes restrictive strabismus, it may not be necessary for the examiner to use forced ductions preoperatively to determine if the incomitant strabismus is due to a tight muscle. If forced ductions are performed in clinic, care must be taken to avoid tearing conjunctiva and creating large subconjunctival hemorrhages in these patients with friable conjunctivae and engorged conjunctival vessels (from a crowded orbit). If the examiner does find it necessary to check for a restrictive component, using intraocular pressure measurements in different fields of gaze can help determine if a particular muscle is restricted. In fields of gaze away from a restricted muscle, the IOP will increase (often >10 mmHg) [58–60].

Measurement of torsion prior to surgery (double Maddox rod testing) can give information about tight vertical muscles and the possibility of superior oblique restriction [61]. Restriction of the inferior recti [55] and/or compensatory increases in contraction of the inferior oblique [62] in an attempt to elevate the eye may result in excyclotorsion. When restriction of the inferior recti is not associated with excyclotorsion, the superior obliques may also be restricted, and incyclotorsion may be unmasked after recession of the tight inferior recti [61, 63].

General Approach to Management of Strabismus

Although large and significant strabismic deviations in TED usually require surgical intervention [8], one has to perform serial examinations to determine stability of the strabismus and quiescence of the inflammatory disease process before proceeding with strabismus surgery. Conservative measures to manage diplopia are often useful in patients awaiting strabismus surgery and can sometimes provide a long-term solution to the control of diplopia.

Prisms

Prisms are useful in several situations. For the patient who has not yet met the criteria for strabismus surgery (i.e., there still is active orbital inflammation or unstable motility measurements), prisms can alleviate diplopia and anomalous head postures. Tight inferior rectus muscles can create a chin-up position, and prisms can be used in front of one or both eyes to alleviate the torticollis. They can also be used in patients with diplopia from esotropia and/or a vertical deviation in primary gaze to allow fusion in primary gaze.

Patients may need to use separate glasses for distance and for near viewing. Press-on prisms (3M; Fresnel Prism and Lens Company, Eden Prairie, MN) are practical for patients with active disease and changing ocular alignment; they can be placed obliquely over the nondominant eye when a combination of vertical and horizontal deviations is present. Also, for patients in whom different powers are needed for distance and near viewing and who wish to use bifocals, Fresnel prisms of different power can be cut for the bifocal segment and for the distance segment of the spectacles.

Finally, for patients with mild limitation of eye movements and a more comitant small-angle ocular misalignment with diplopia, prisms may provide long-term effective treatment. Such patients may or may not have undergone strabismus surgery. Ground-in prisms provide clearer viewing but are more expensive than Fresnel prisms and are probably best utilized in patients with stable ocular alignment. When the distance and near prism requirements are different, and the patient desires a ground-in bifocal correction, fused segments can be utilized to provide a different amount of prism for distance and near viewing.

Occlusion

Patches may be applied directly to the skin to occlude one eye and eliminate diplopia. The advantage they provide over prisms is that diplopia will be alleviated in all fields of gaze—something that can only rarely be achieved with prism correction in Graves' disease. However, a patch eliminates all stereopsis and limits peripheral vision, and many patients find them unsightly. Furthermore, in the presence of proptosis, patches can touch the cornea and create abrasions. An occluder placed on a spectacle lens or a frosted lens in glasses provides an alternative form of occlusion and may be better tolerated [64]. The MIN lens (http://www.fresnel-prism.com/products/min-occlusion-lens/) is applied to the back of glasses like a Fresnel prism and provides blur with an acceptable cosmetic appearance.

A black-centered contact lens may also be used to relieve diplopia. It is more cosmetically acceptable than a patch, but may not be tolerated in the patient with exposure and lower lid retraction.

Botulinum Toxin

Botulinum toxin A has been used for the treatment of eyelid retraction in Graves' disease [65]. The agent is injected subconjunctivally and results in eyelid drooping that lasts up to 3 weeks or more. Some patients experience transient diplopia. In one study, 24 patients with upper eyelid retraction from TED received unilateral transcutaneous injection of 5 units (0.1 mL) of Botox. Twelve patients had congestive or active TED, and the other 12 had fibrotic-stage TED. Most patients experienced marked improvement in eyelid retraction, with a mean reduction in palpebral fissure width of 3–4 mm. The treatment lasted significantly longer in patients with fibrotic than congestive TED [66].

With respect to the use of botulinum toxin for strabismus in TED, better results are reported for relatively mild, acute dysthyroid strabismus than for long-standing, large-angle restrictive strabismus. Gair and co-workers reported on 65 patients with strabismus in TED who were treated with botulinum toxin A at Moorfields Eye Hospital between 1984 and 1996. They concluded that patients with a short duration of relatively mild dysthyroid strabismus had the best chance of long-term benefit of treatment with botulinum toxin A and that there is little use for botulinum toxin A in cases of severe dysthyroid disease [67].

While Scott [68] and Dunn et al. [69] found that a larger dose of toxin was required in patients with TED compared to those without it, possibly because of the increased size of the muscles and a longer period of paralysis required to allow the antagonist muscle to contract, Gair et al. used a standard dose for all patients [67].

Surgical Management of Strabismus in TED

Surgical Indications

A surgical intervention for the correction of strabismus is indicated in patients with diplopia or with significant torticollis (generally a chin-up position) that cannot be alleviated with a relatively small prism (<10 PD). Table 53.5 is a checklist that can be used in the planning of surgery in patients with TED and diplopia. As mentioned earlier in the chapter, it is most important to operate in the absence of active inflammation and in patients with stable ocular misalignment and controlled thyroid hormone status.

Introduction and History

In the 1940s, limitation of upgaze was incorrectly ascribed to paresis of the superior rectus and inferior oblique muscles [70–73]. In 1953, Braly noted elevation of intraocular pressure in upgaze and concluded that the inferior rectus was tight and pressed on the globe as the patient looked up [74]. In the early 1960s, Miller used a recession of the inferior rectus to relieve hypotropia in TED [75, 76]. By the mid-1970s, an approach to surgical correction of strabismus in Graves had been developed that forms the basis for current practice: orbital decompression before and eyelid surgery after strabismus surgery [77, 78]. Articles followed that focused on the difficulties in selecting the appropriate amount of recession to achieve the desired results and, hence, the use of adjustable suture techniques by many and of fixed suture techniques with intraoperative adjustment by others (*vide infra*).

Table 53.5 Check list for planning strabismus surgery in TED

☐ Patient's medical condition is stable
☐ Orbitopathy is stable
☐ Patient has had decompression surgery if needed >2–3 months prior to strabismus surgery
☐ Ocular misalignment, limitations of eye movements are significant and stable in magnitude over a period of 3–6 months
☐ Diplopia is constant and significant
☐ Anomalous head position (if present) is significant
☐ Deviation is large (>10 PD) and not amenable to prismatic correction
☐ Orbital imaging has been obtained and reviewed
☐ Consent has been obtained and outcome expectations discussed with patient

Anesthetic Considerations

Many surgeons prefer the use of general anesthesia for strabismus surgery in patients with TED. This stems from the need for bilateral surgery and the difficulty achieving patient comfort with local or regional anesthesia due to the restricted nature of the operative muscles. As patients should be in a quiescent, euthyroid state of Graves' disease to be considered for strabismus surgery, general anesthesia is usually well tolerated. Vagolytic medication is especially necessary to prevent the oculocardiac reflex while pulling on tight muscles without a regional block. However, if the patient's general health is poor (e.g., in the presence of pulmonary or cardiac disease from cigarette smoking) and they are at high risk for an adverse event from general anesthesia, regional anesthesia with sub-Tenon's local anesthetic, a lid block (for exposure), and appropriate IV pain management may be well tolerated with appropriate patient selection. If bilateral surgery and local anesthesia are necessary, the surgeries may be staged, which does offer the advantage of seeing the outcome from the surgery on one eye before approaching the other eye. However, use of intraoperative forced duction testing and surgery based on positioning of the eye during the surgery (such as will be discussed later in this chapter) cannot be performed under local anesthesia.

Surgical Considerations

Strabismus surgery is generally performed before the eyelids are operated on for chronic upper lid retraction or lower lid retraction secondary to recession of the inferior rectus muscle. The patient would have completed any necessary orbital decompression. Tables 53.6 and 53.7 list important surgical considerations and recommendations.

Table 53.6 Considerations in the management of strabismus in the patient with TED

Questions	Choices
What examinations to perform?	Measurement of deviations and ocular ductions; measurement of field of single binocular vision
What technique to use?	Prisms for small deviations
	Fixed vs. adjustable suture muscle recession vs. intraoperative relaxed muscle technique
	All techniques have about the same outcomes
How many muscles to operate on?	Single inferior rectus, both inferior recti, medial rectus, both medial recti, medial recti and inferior recti, others
What incision type to use?	Fornix vs. limbal
Can we resect muscles in TED?	Consideration only if tight antagonist recti have been maximally recessed

Table 53.7 Surgical considerations in strabismus surgery for TED

– The conjunctiva is friable due to chronic inflammation or prior orbital radiation
– The muscles are very tight
– The muscles are diseased and, hence, can tear easily leading to the "pulled-in-two syndrome" (see Chap. 60 on Surgical Complications)
– The inferior rectus should be carefully separated from lower eyelid retractors before it is recessed

Success rates of strabismus surgery in TED patients vary between 38 % [79] and 80 % [80] with fixed suture techniques and between 64 % [79] and 82 % [56] with adjustable sutures. Early reports of surgical outcomes include those of Dyer in 116 patients using fixed sutures with a 45 % reoperation rate [77] and of Ellis in 30 patients using adjustable sutures with a 17 % reoperation rate [78].

Some series have reported relatively good results using surgical nomograms published for pediatric strabismus patients, but results from other series have varied. The success rates for deviation-based or nomogram-based strabismus repairs in TED patients vary between 38 % [79] and 82 % [56], and reoperation rates range from 5 to 45 % [77, 79]. Prendiville and colleagues suggested that the restriction in ductions (particularly of the contralateral vertical rectus muscle) best predicted the amount of surgery necessary [53].

Given the wide variability in technique and outcomes between series, direct comparison of results is currently not possible or meaningful, but it appears that generally similar outcomes are obtained irrespective of the surgical approach.

Adjustable Suture Technique

Adjustable sutures are commonly used in strabismus surgery for the treatment of diplopia in Graves' disease. In 1984, Skov and Mazow [81] advocated the use of adjustable sutures. However, concerns about undercorrection led them to recommend a fixed suture for the fibrotic muscle that remains near its insertion after release. In 1992, Lueder and associates [8] reported 47 patients treated with adjustable sutures, noting a reoperation rate of just 15 % and alleviation of diplopia in primary and/or reading position in 91 % of the patients. The need to adjust the suture postoperatively is much higher in patients with Graves' disease than with other adult patients with diplopia (66 % in Lueder's study), underscoring the difficulty in predicting which patients require more or less recession in muscles that are more or less contractile.

The adjustable suture technique has been widely described. Briefly, a limbal peritomy is performed with radial relaxing incisions in the conjunctiva over the muscle to be operated. Minimal dissection is necessary. Some surgeons utilize a fornix incision, but the author (NCK) prefers a limbal incision. The muscle is isolated on a muscle hook, and a suture is placed through the tendon in the usual fashion near the insertion. This step of the surgery can be very difficult in patients with Graves, as the muscle can be extremely tight, causing limited exposure and space in which to safely and adequately pass the suture. The author uses a two-hook approach and employs an assistant, passing two hooks under the insertion and using the second hook to elevate the tendon off the globe while the suture is passed through the tendon [64]. Care must be taken to avoid too much tension on the muscle, which could result in a pulled-in-two syndrome (PITS). Another option is to use a specially designed grooved hook that allows passage of the suture on top of the hook, such as the Wright hook®. The hang-back sutures are passed obliquely through the original insertion, and additional scleral passes are taken anterior to the chosen primary insertion site for added strength and exposure during the adjustable procedure. The position of the suture is adjusted within 24 h of surgery ("two-stage adjustable suture" technique) under topical anesthesia, although some surgeons delay adjustment even longer [82]. If a local anesthetic is used, adequate time must elapse for the effects of the anesthetic to wear off before the adjustment is performed. A bow tie is preferable for nonabsorbable sutures (too thick for a noose) and a noose for absorbable sutures. Both types of sutures are permanently tied using a square knot at the conclusion of the adjustment. The choice of suture material varies with the muscle operated and the tightness of the muscle. A 5-0 Mersilene for inferior recti helps prevent overcorrections due to non-adherence and slippage, and a 5-0 Vicryl for medial rectus recessions is adequate. A 6-0 Vicryl is also acceptable if the medial rectus muscle is not too tight, but it can be difficult to advance a tight muscle at the time of adjustment without breaking the smaller caliber 6-0 suture. Pre-placed 6-0 plain gut sutures can be used at the end of the case to close the conjunctiva and the ends of the adjustable sutures tucked under the conjunctiva for comfort.

The use of adjustable sutures in patients with Graves' disease has yielded excellent results in 47–81 % of patients and acceptable results in 73–91 % of patients [8, 56, 57, 79]. Adjustable suture techniques have reported reoperation rates that vary from 8 to 27 % [8, 56, 57, 79].

Duction-Based Surgery for TED

Several studies over the last decade have investigated duction-based surgery for strabismus in TED [51, 83, 84]. This approach involves the assessment of limitation of eye

movements using intraoperative forced duction testing as well as preoperative measurements of ductions. The surgery consists of recession of the most restricted muscles and matching the restriction of the less restricted muscles, rather than devising a treatment strategy based primarily on the angle of strabismus. Nguyen and colleagues reported a 74 % success rate with this approach [83], compared to 44 % using traditional surgical nomograms, while Thomas and Cruz reported a 66 % success rate [84]. The results in Nguyen et al. series are perhaps overestimated as the authors have excluded patients who had repeat surgeries in the first 30 postoperative days and by the lack of assessment for diplopia in reading position [83]. Thomas and Cruz also did not comment on diplopia in reading position [84].

Intraoperative Relaxed Muscle Positioning

One of the authors (EIT) described the intraoperative relaxed muscle technique (IRMT) in 2006 (discussed in detail below) [51]. This approach differs from that of Nguyen et al. [83] and Thomas and Cruz [84] in that one is not trying to match the tightness of the less tight muscle by recessing the tighter rectus muscle [51]. In the IRMT the goal is to fully relieve the restriction resulting from each recessed muscle while the eye is in primary position of gaze, rather than trying to match the restriction in the contralateral eye. The surgery is performed via a fornix incision, and the tendon is re-sutured to the globe with the eye relaxed in primary position, rather than attempting to match the intraoperative eccentric position of the contralateral eye. Using the IRMT, the success rate after one surgical intervention in the series by Nicholson et al. was 74 % with a reoperation rate of 8 % [50], compared to 27 % for Nguyen and colleagues and 18 % for Thomas and Cruz.

The reader is directed to view a video of the technique of intraoperative relaxed muscle positioning online at http://vimeo.com/2713202. Surgery is performed under general anesthesia with muscle relaxation. Intraoperative forced ductions are gently performed to confirm which muscles require recession. A fornix-based incision is used to expose the muscle insertions. A single inferonasal incision is used if both media and inferior recti are operated at the same setting. The muscle is hooked and intermuscular attachments and check ligaments are severed using Westcott scissors. Care is taken to lyse the capsulo-palpebral ligaments during inferior rectus recession. The distal rectus tendon is isolated between two muscle hooks and secured with a double-armed 6-0 polyglactin 910 suture on S29 needles in a double-locking fashion. The tendon is disinserted from the globe using the Westcott scissors, and forced ductions are repeated to confirm free ocular movement. The point of reattachment is selected by allowing the muscle to rest freely on the globe with the globe positioned such that the anteroposterior axis is perpendicular to the frontal plane (Fig. 53.5a). The location at which the edge of the tendon meets the globe is marked, and the distance between the mark and the original muscle insertion is measured with calipers or a flexible ruler (preferred) (Fig. 53.5b). The tendon is then sutured at the mark using a cross-swords technique. It is important in the case of the inferior rectus to measure the distance for the needle entry

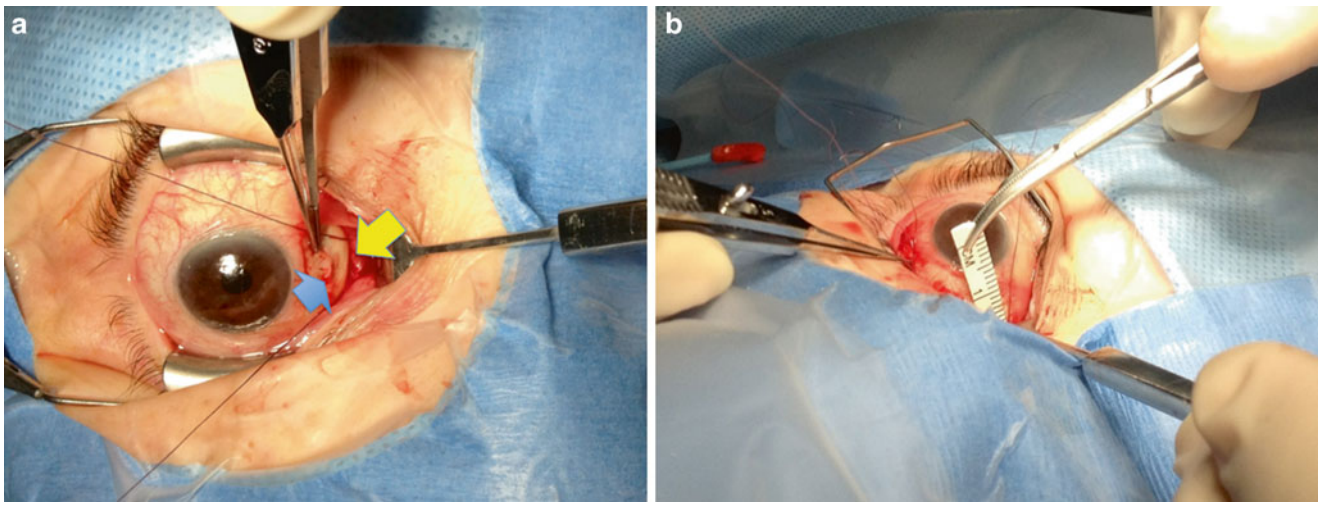

Fig. 53.5 (**a**) Intraoperative relaxed muscle technique. The muscle has been detached and approximates the globe at *yellow arrow*. The globe is held in primary position without sinking it or pulling it out excessively at the original insertion (*blue arrow*). The flat retractor is placed above the muscle and under Tenon's capsule. (**b**) Intraoperative relaxed muscle technique. While the globe is held in primary position and the muscle approximates the sclera, the distance from the original insertion to the edge of the detached muscle is measured using this graduated strip fashioned from a flexible plastic ruler in the operating room

Table 53.8 Comparison between different techniques of eye muscle surgery in TED

Technique	Pros	Cons
Adjustable suture	Allows postoperative adjustment of tendon position	Requires experience and one additional intervention outside of the operating room
	Traditionally considered to have better outcomes than fixed sutures	Discomfort to patient
		Uncertainty about where muscle actually attaches to the globe
		Risk of late overcorrection in inferior rectus recessions if muscle hung back very far and an absorbable suture is utilized
Fixed suture	Easier to perform	Traditionally less predictable than adjustable suture
	Less likely to have muscle slip	
	Know where the muscle is attached	
Relaxed intraoperative positioning	Easy to perform	Requires experience
	Less likely to have muscle slip	As predictable as adjustable suture
	Know where muscle is attached	

point from the edge of the insertion. The insertion is often oblique and it is important to match the obliquity to avoid undue torsion and possibly pattern deviations. The conjunctiva is approximated with interrupted 6-0 polyglactin 910 sutures. No more than two ipsilateral muscle recessions are performed simultaneously.

This technique is especially helpful in cases of bilateral and sometimes asymmetric inferior rectus restriction with or without preoperative diplopia. Inferior rectus recession is important in such patients to improve patient function while viewing in primary gaze and in upgaze and to eliminate a chin-up torticollis. While relatively large (more than 6 mm) bilateral inferior rectus recessions were commonly used in the series by Dal Canto et al. [51] and Nicholson et al. [50], they were not found to limit infraduction significantly, but patients sometimes required additional surgery to address secondary lower eyelid retraction. In the study by Dal Canto et al., 21/24 patients (87.5 %) had excellent final outcomes (diplopia-free in primary and reading positions without prisms) [51]. All 24 patients had clinically acceptable (excellent or good) final outcomes (diplopia-free in primary and reading position even with the use of small prisms). The average number of surgeries was 1.08. Post decompression patients were more likely to have excellent results (100 %) than patients who had diplopia independent of orbital decompression. There was no correlation between the degree of strabismus and the amount of recession required for eliminating diplopia. In the follow-up study of 63 consecutive patients from the same institution, Nicholson et al. reported that bilateral IR and MR recessions were performed simultaneously in 24 % of cases [50]. Regression analysis revealed no correlation between the amount of recession (in mm) and the amount of preoperative strabismus (in PD) when strabismus surgery was performed on *horizontal muscles* ($R^2 = 0.495$) or on *vertical muscles* ($R^2 = 0.312$). They found that patients with horizontal misalignment and large deviations as well as those with diplopia before decompression were more likely to require additional surgeries. Approximately one in five patients required a second surgery. Overall, more than 90 % of patients achieved single binocular vision with or without modest prismatic correction, and the great majority had significant improvement in ocular motility.

Table 53.8 provides a comparison of the three techniques for the correction of strabismus in TED.

Contralateral Surgery

In very large hypotropias (>20 PD in primary gaze), usually due to asymmetric restriction of the ipsilateral inferior rectus, a single inferior rectus recession is not likely to alleviate diplopia in primary gaze. Additionally, attempts at correcting the large hypotropia in primary gaze by recessing the ipsilateral inferior rectus a very large amount (10 mm or more) may induce downgaze limitations, leaving the patient with the potential for a hypotropia in primary gaze and hypertropia in downgaze. The contralateral superior rectus may be recessed at the same time as the recession of the ipsilateral inferior rectus, improving the chances for single binocular vision in primary gaze as well as reducing the chance that diplopia will be worse in downgaze (Fig. 53.6a, b). Additionally, the superior rectus muscle may be placed on the adjustable suture, alleviating the need to adjust the tight inferior rectus and allowing the inferior rectus muscle to be placed on a fixed suture.

Bilateral Inferior Rectus Surgery

While some surgeons would operate on the tighter inferior rectus and try to match the tightness of the contralateral infe-

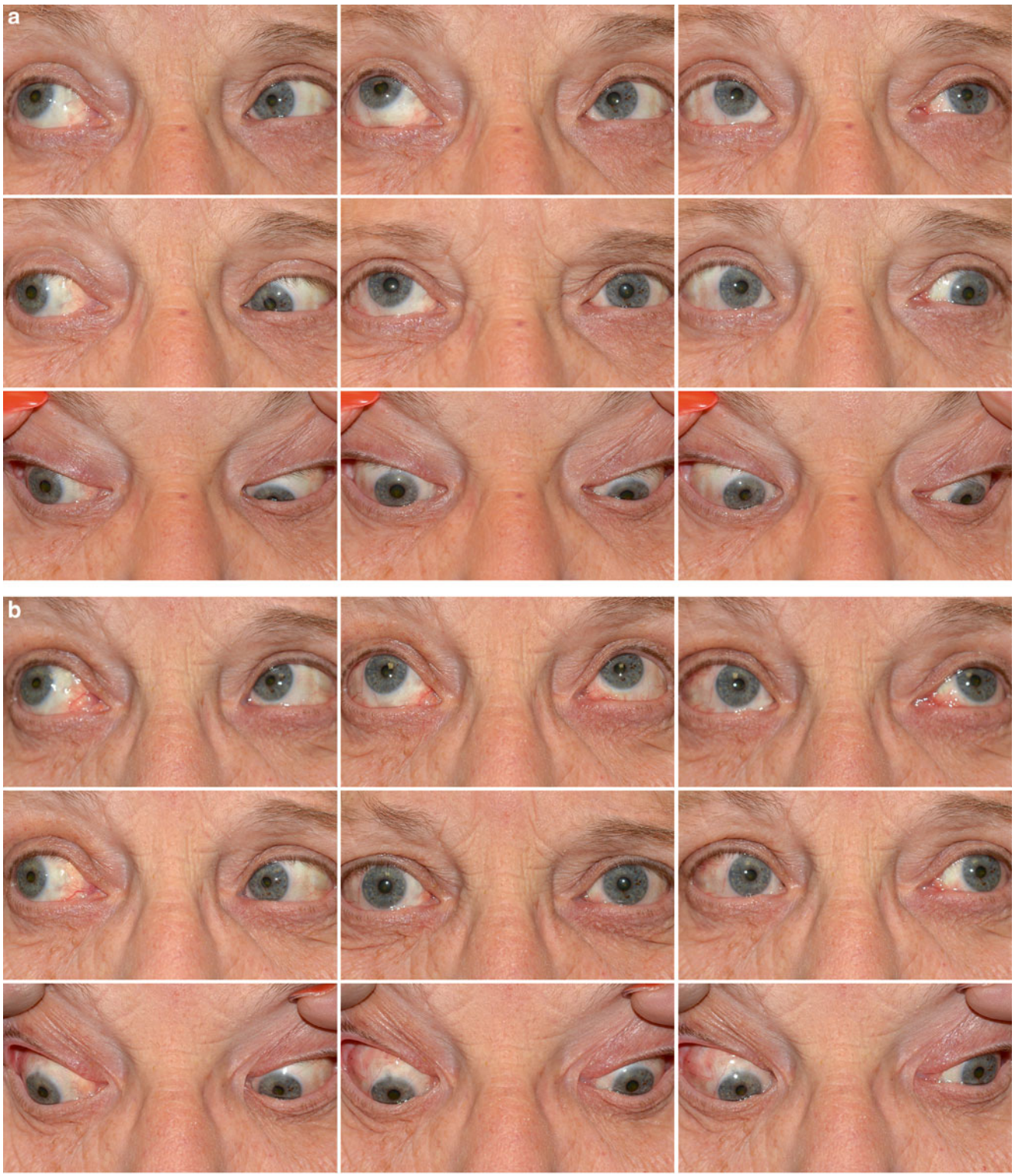

Fig. 53.6 (**a**) Left inferior rectus restriction causing large right hypertropia in primary gaze, worsened on upgaze. (**b**) Same patient in (**a**) following left inferior rectus recession and right superior rectus recession on adjustable suture with excellent result

rior rectus in an effort to relieve or improve the chin-up posture without compromising downgaze, others would operate on both inferior recti. The advantage of performing bilateral recessions if both muscles are tight is that the vertical excursions of both eyes would be moved upward, facilitating elevation of both eyes, with some and, in most cases, minor limitation of downgaze.

Cruz and Davitt reported on 8 patients with hypotropia and bilateral inferior rectus involvement [85]. Bilateral asymmetric inferior rectus muscle recession was performed on all patients using an adjustable suture technique. Seven patients were successfully aligned, while 1 patient remained undercorrected using the success criteria set by the authors.

In another study of 43 patients operated on by five surgeons using a customized approach that depended on the limitation of elevation above midline in each eye, elevation above midline increased from 12° ± 6.9° preoperatively to 19° ± 6.7° postoperatively, while depression decreased from 54° ± 6.2° preoperatively to 48° ± 9.2° postoperatively [86]. Total duction range was unchanged. Excyclodeviation changed from 6.4° ± 6.0° to 0.4° ± 6.0° in primary position. Four patients developed a significant incyclodeviation of >5°.

Both of the authors routinely recess both inferior recti in patients with limitation of elevation of both eyes of less than 15°–20° above midline with the head in primary position.

Four-Muscle Surgery

The combination of tight medial rectus muscles and tight inferior muscles is common in patients with TED. One approach to treatment that has worked well for both of the authors is to recess all four muscles at the same setting, albeit with different techniques. When utilizing adjustable sutures, the medial and inferior recti on the more severely affected eye may be recessed with fixed sutures, while the medial and inferior recti on the less affected eye are placed on adjustable sutures. When using the IRMT, the medial and inferior rectus muscles are approached through a single inferonasal incision; they are isolated and detached; the eye is placed in primary position of gaze; then using the intraoperative adjustment technique, the muscles are placed again on the eye, and the insertion points are marked, following which the muscles are sutured at their respective insertion marks (Fig. 53.7a, b). Thirteen of 58 patients in the series of Nicholson et al. had bilateral medial rectus and bilateral inferior rectus recession at the same setting [50].

Oblique Muscle Surgery

All extraocular muscles are affected by the inflammatory process in Graves' disease, although the muscles of clinical significance are usually the inferior and medial recti. However, affected superior obliques have been demonstrated to cause diplopia. Specifically, they contribute to A patterns, incyclotorsion, and hypotropia/limited elevation on adduction. Clinically significant tight superior obliques may present without any prior surgery [87] or may present after orbital surgery [87] or inferior rectus recession [61]. In one recently reported series, only 2/52 patients had incyclotorsion and A pattern strabismus attributable to superior oblique restriction following inferior rectus recession for vertical diplopia in TED [63]. Recession of the superior obliques alleviates the torsion and other problems. However, A pattern strabismus may also be attributable to inferior and medial rectus recessions, and incyclotorsion can be induced by nasalward transposition of the inferior recti, especially tight inferior recti placed on a fixed suture [88]. Forced ductions at the time of surgery, especially when the inferior recti have already been recessed, may help confirm the role of a tight superior oblique in creating incyclotorsion. One may also suspect tight superior obliques when tight inferior recti do not produce excyclotorsion, masking the incyclotorsion from the superior obliques.

Inferior obliques may be disinserted after orbital decompression, adding to the complexity of repairing the strabismus found in Graves' disease [89]. Though the effect of a tight inferior oblique on the clinical picture of strabismus in Graves is rarely mentioned [90], recession of the inferior oblique on the less involved (hypertropic) eye to improve comitance, in combination with an ipsilateral superior rectus recession or contralateral inferior rectus recession, has been reported [91].

Reoperations

Despite the use of adjustable sutures, 8–27 % of patients may require two or more surgeries to eliminate diplopia, even with the use of prisms [8, 56, 57, 79]. Given the significant percentage of patients who require more than one strabismus surgery for TED-related strabismus, the ability to predict which patients will need more than one surgery would allow for better preoperative counseling and might help clinicians improve management strategies. Nicholson and co-workers examined preoperative characteristics of patients who required reoperation and attempted to identify particular

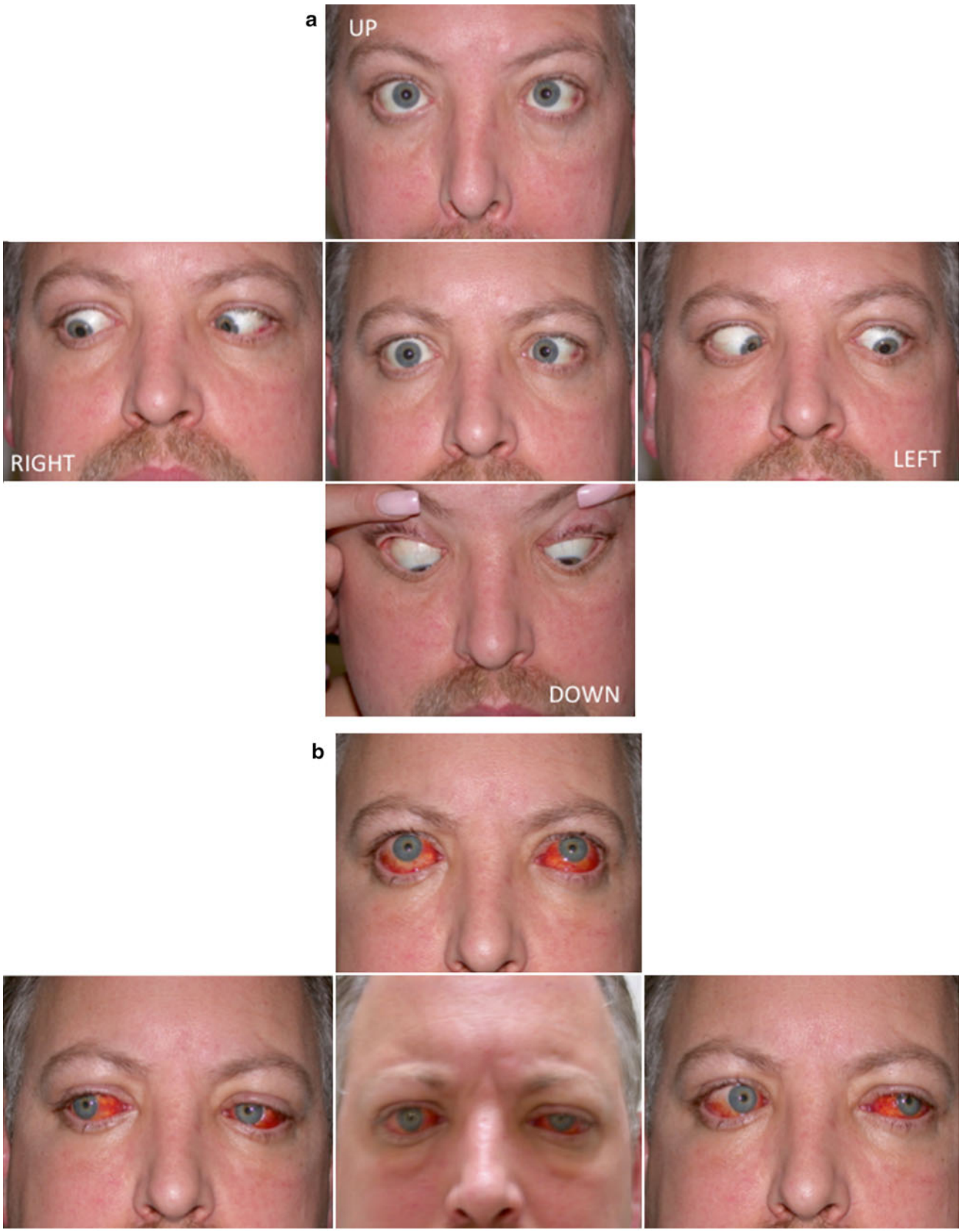

Fig. 53.7 (**a**) Patient with bilateral limitation of elevation and abduction. (**b**) Patient in (**a**) 1 day following bilateral simultaneous recession of inferior rectus and medial rectus muscles. Abduction and elevation are significantly improved. The patient did not require any additional procedures or prismatic correction. He remains diplopia-free

clinical characteristics that predicted reoperations [50]. Ninety percent of patients in their series eventually had a successful outcome. Among those who required a second surgery, the rate of successful outcomes was also relatively high at 85 %. These authors identified two special circumstances that led to more than one reoperation: (1) The treatment of a large-angle esotropia may unmask a smaller-angle vertical deviation and necessitate more surgery; (2) patients with three restricted muscles in one eye may require multiple surgeries to prevent anterior segment ischemia. They also found that patients with more severe disease were more likely to require reoperations. In the same series, patients who had diplopia prior to decompression tended to have a higher reoperation rate [50].

Resection

Resections of eye muscles in TED have been largely discouraged and avoided [92]. However, in select circumstances, they may be of use. The most commonly reported use of resections in Graves is lateral rectus resections for residual esotropia at distance following recession of the medial recti [93, 94]. They have also been reported as an adjunct for medial rectus recession when only one eye is being operated and the deviation is too large to be corrected with a single medial rectus recession [93]. Once ductions have been freed up with rectus recessions, residual strabismus may be addressed with resections, with care in the surgical planning to prevent worsening of ductions and incomitant strabismus. I have found superior rectus resection helpful in a few cases when considerations about inducing anterior segment ischemia limited other options and the ipsilateral inferior rectus had already been maximally recessed in the setting of a residual hypotropia.

Stability of Surgical Results in TED

Dal Canto et al. found that the 2-month visit was a good predictor for long-term results in 13 of 24 patients [51]. Other investigators have also found that intermediate-term measurements typically remain stable [79, 95].

Strabismus that reoccurs 2 months or more after a successful outcome is usually due to long-term changes in the orbit(s), such as recurrent/active disease (Fig. 53.8a–c), and increases in antagonist or yoke muscle contracture [42]. The variability of vertical strabismus in TED, even without surgery, may also play a role in the unpredictable outcomes of vertical strabismus surgery in TED. Most strabismus surgeons wait to operate at least 6 months after changes in thyroid status, orbital surgery, or changes in motility in an effort to avoid late recurrences of diplopia, but reactivation has been seen in my practice as late as 10 years after successful surgical treatment.

Progressive overcorrection has been noted in the first weeks or months after inferior rectus recession in Graves' disease and is one of the most common sources of recurrent postoperative diplopia in TED (Fig. 53.9a–c), with a reported incidence as high as 50 % [96]. Overcorrection in the weeks or months following inferior rectus recession is particularly bothersome, as it cannot, by virtue of the time of its occurrence, be prevented with adjustable sutures. The use of a nonabsorbable suture has been shown to alleviate most progressive overcorrection following inferior rectus recession on an adjustable suture [97]. Use of fixed sutures also reduces the risk of progressive overcorrection of a hypotropia in the first weeks and month following inferior rectus recession in Graves [98].

Pitfalls and Complications in Strabismus Surgery for TED

Unsuspected outcomes and complications can certainly occur in patients with TED who undergo strabismus surgery. As mentioned earlier, a complete and careful preoperative examination is paramount. Special attention should be paid to the activity of orbital inflammation and stability of the ocular misalignment. Assessment of ductions and review of orbital imaging helps to identify all enlarged and tight muscles. Overcorrection after inferior rectus recession is often the result of an overlooked tight ipsilateral superior rectus muscle. Less commonly, an ipsilateral tight lateral rectus muscle can lead to the overcorrection of an esotropia using a medial rectus recession.

In patients with severe proptosis and very tight muscles, perforation of the globe is a definite danger as one detaches the muscle using the scissors. This should be done using very short snips that can be radial or circumferential. Undue traction on the sutures and the insertion can tent the thin sclera and make scleral perforation more likely. Also the muscles in TED are probably more likely to snap at the point of transition between the tendon and the muscle, hence the need to avoid excessive pulling on the muscles after they are hooked.

Patients with severe orbitopathy and larger-angle esotropia are less likely to respond to the usual amounts and even larger amounts of recession [50]. The globe is frequently "frozen," and such patients are less likely than others to achieve a good outcome after multiple strabismus surgical interventions.

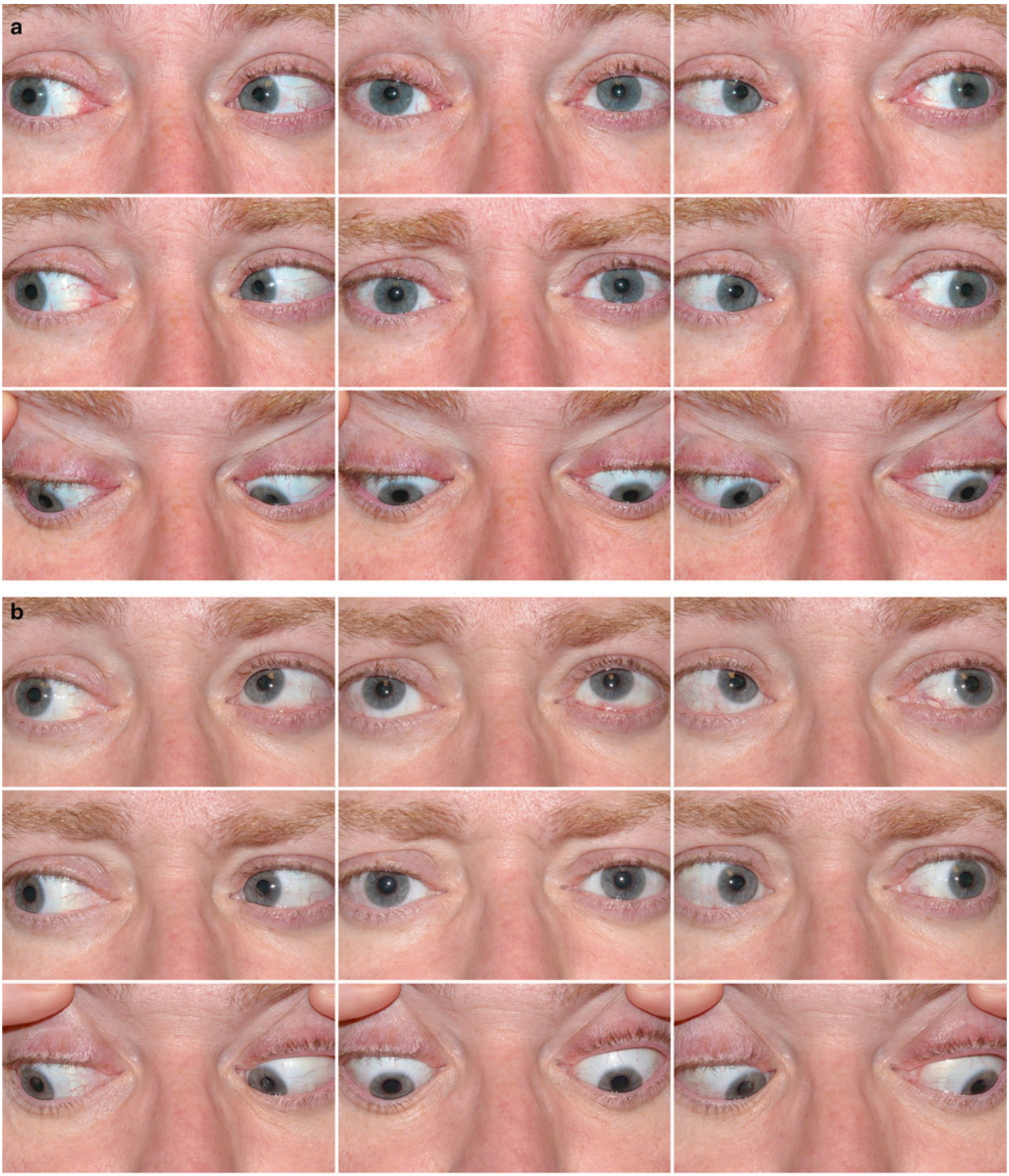

Fig. 53.8 (**a**) Bilateral upgaze restrictions with left hypertropia of 8 PD in primary gaze. (**b**) Excellent result 2 months s/p bilateral inferior rectus recessions (10 mm OD on fixed suture and 8 mm OS on adjustable with no adjustment). Measurement in primary gaze is 4 PD left hypertropia. (**c**) One year later after recurrence of hyperthyroidism. The patient had been managed medically with no thyroid ablation prior to surgery. Note left superior rectus restriction and right inferior rectus restriction causing 25 PD left hypertropia

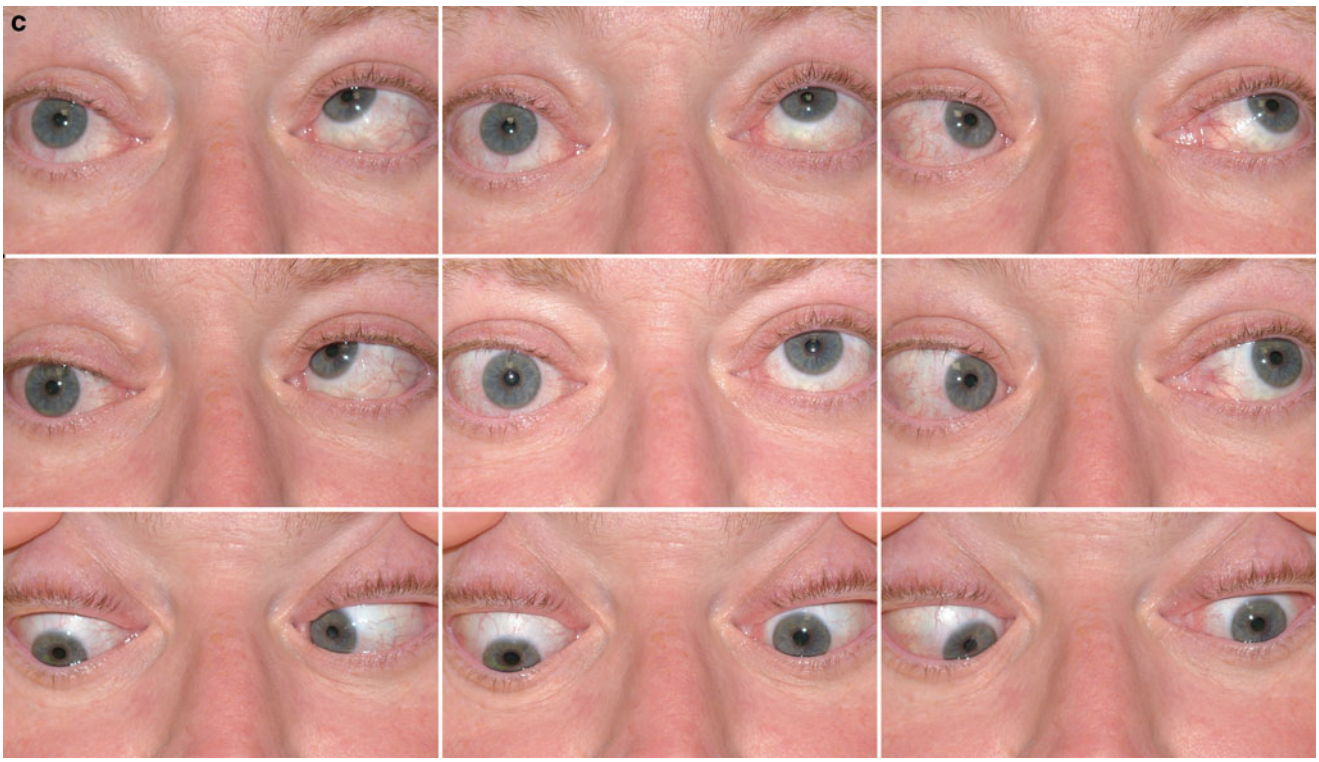

Fig. 53.8 (continued)

The most common and serious pitfall encountered with adjustable sutures is need for reoperation. Even with the "second look" at the effect of surgery afforded by adjustable sutures, progressive overcorrection following inferior rectus recession can mandate reoperation. One of the lowest rates of reoperation was reported by Lueder in 1992 and was 15 % [8]. Careful attention to preoperative planning as has been discussed extensively in this chapter (waiting for stability of disease, choosing the right sutures and muscles on which to operate, etc.) can help reduce the rate of reoperation.

Discomfort in the immediate postoperative period and at the time of adjustment can be an issue with adjustable sutures and is one disadvantage not encountered with fixed sutures. Adequate patient screening must take place prior to offering a patient an adjustable suture, as an anxious and apprehensive patient may not be able to tolerate the procedure. Additionally, patients with heart disease should probably have IV access left in place for adjustment in case of severe bradycardia or asystole induced by the oculocardiac reflex during adjustment requiring emergent IV atropine and circulatory support. The adjustable sutures may become exposed before dissolving or, in the case of nonabsorbable sutures, require removal at the slit lamp if they become irritating (Fig. 53.10).

Impact of Strabismus Surgery on QOL of Patients with TED

Several studies have addressed the significant improvement of quality of life of patients with TED after strabismus surgery [32, 99, 100]. Factors contributing to this improvement include the resolution of diplopia, the widening of the field of binocular vision, and the improvement in appearance. Quality of life questionnaires taken by patients with TED before and after strabismus surgery reveal significant changes in scores related to function and to appearance [32]. The authors attest to the fact that their patients with TED are some of the most grateful and gratified patients.

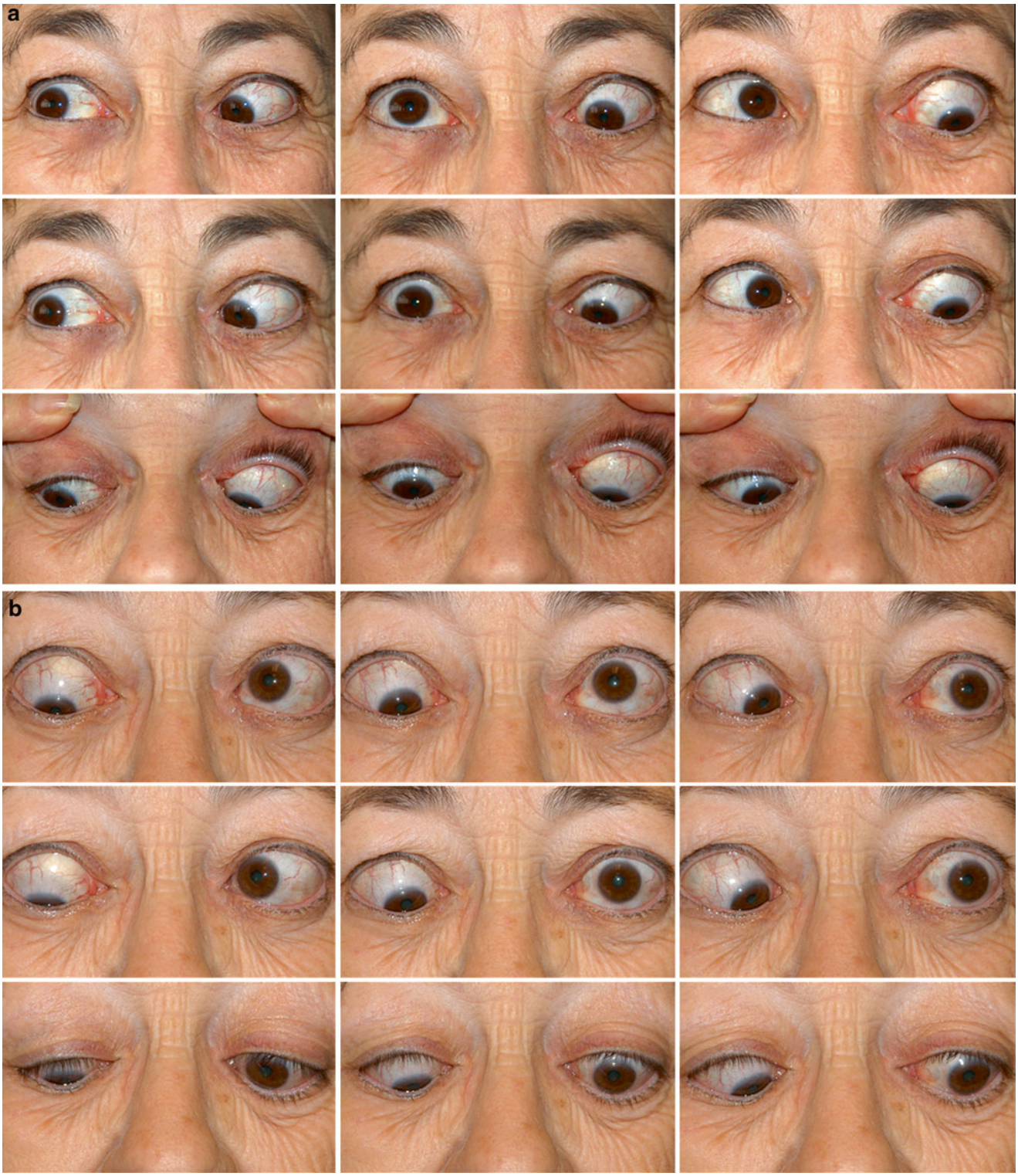

Fig. 53.9 (**a**) Large left hypotropia with restriction of left inferior rectus more than right. (**b**) Large right hypotropia that occurred within 2 months of a 10 mm left inferior rectus recession on an adjustable absorbable suture. (**c**) Following right inferior rectus recession of 10 mm on adjustable absorbable suture, the patient was orthotropic in primary and downgaze, with continued limitation of upgaze bilaterally

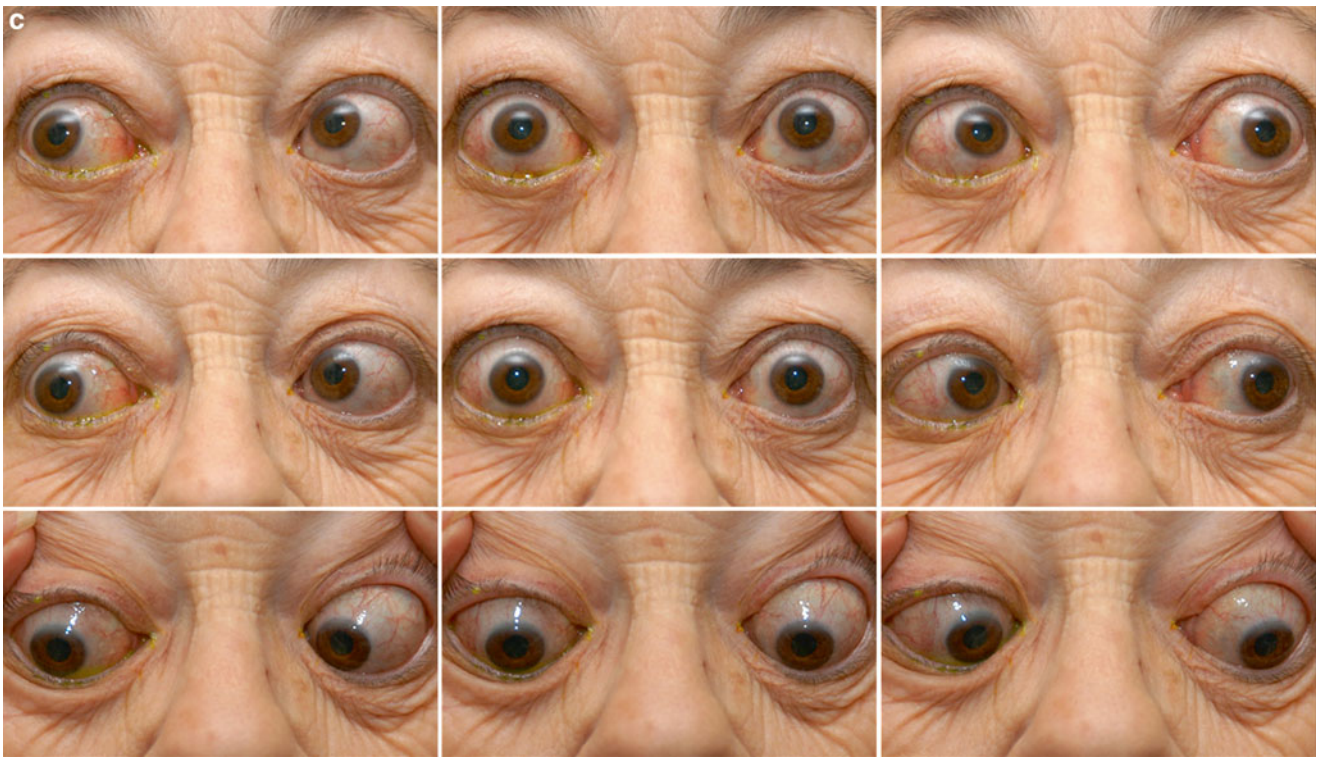

Fig. 53.9 (continued)

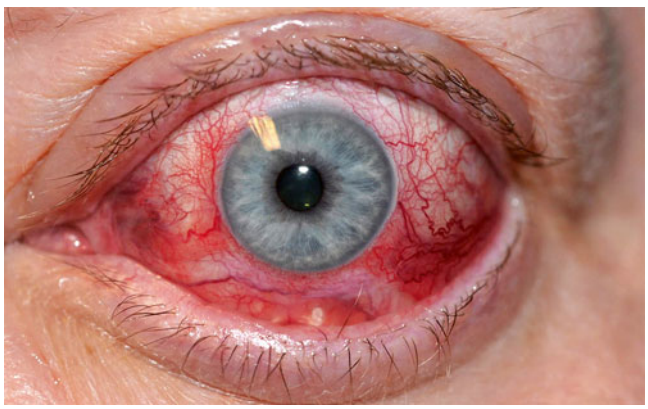

Fig. 53.10 Exposed nonabsorbable suture creating irritation and chemosis inferiorly after successful strabismus surgery involving a single inferior rectus recession on adjustable suture

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A- and V-Pattern Strabismus

54

Steffany M. Straight and Reecha S. Bahl

Abstract

Twenty to 50 % of patients with horizontal strabismus have ocular deviations that measure significantly more or less in upgaze than in downgaze and have been designated as having A- or V-pattern strabismus. An A-pattern strabismus exists when the magnitude of deviation is more convergent or less divergent in upgaze. Conversely, a V-pattern strabismus exists when the magnitude of deviation is less convergent or more divergent in upgaze. Causes of A- and V-pattern strabismus have been attributed to superior or inferior oblique muscle overaction, horizontal rectus muscle overaction or underaction, increases or decreases in vertical rectus muscle adduction, or anatomic abnormalities in the orbit or of the tendon pulley system of the eye muscles. If an A- or V-pattern is clinically significant (greater than 10 prism diopters for A-pattern deviation between upgaze and downgaze measurements or greater than 15 prism diopters for V-pattern deviation), surgical treatment directed at alleviating the pattern is undertaken in combination with treatment of the horizontal deviation. The most common treatment options include weakening of the oblique muscles when overactive, and vertical displacement, or transposition, of the horizontal rectus muscles.

Keywords

A-pattern strabismus • V-pattern strabismus • Oblique overaction • Horizontal muscle displacement/transposition

Background

There is a small subset of patients with horizontal strabismus in whom the magnitude of horizontal misalignment differs significantly between upgaze and downgaze leading to A- and V-pattern strabismus. An A-pattern strabismus describes a deviation that is more convergent or less divergent in upgaze. Conversely, a V-pattern strabismus exists when the magnitude of deviation is less convergent or more divergent in upgaze. To diagnose A- or V-pattern strabismus, measurements using prism and cover and alternate cover testing are taken in all fields of gaze, with specific attention to those in primary gaze, upgaze and downgaze. The patient is instructed to fixate on a distant target while wearing proper refractive correction. An A-pattern is defined as one in which the difference between upgaze and downgaze measurements is 10 prism diopters or greater. In a V-pattern, there must be a difference of 15 prism diopters or more between up- and downgaze. The eyes naturally adopt an esotropia in downgaze; therefore, a larger V-pattern measurement is required for a V-pattern to be clinically significant.

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Twenty to 50 % of patients with horizontal strabismus have deviations with an A or V-pattern [1–4].

Etiology of A- and V-Pattern Strabismus

Oblique Muscle Overaction

Based on the premise that the tertiary action of the oblique muscles is one of abduction, Knapp's theory implies that overaction of the superior oblique muscle results in increased abduction in downgaze, hence an A-pattern occurs in such cases, while overaction of the inferior oblique results in increased abduction in upgaze, thereby leading to a V-pattern. Although A- and V-patterns were previously thought to be due to overaction of the superior and inferior oblique muscles [5], new evidence suggests the dysfunction may also result from abnormalities of connective tissue sleeves that function as a pulley system for the extraocular muscles (EOM) [6]. Demer and colleagues have shown using high-resolution magnetic resonance imaging of the orbits, that heterotopic paths of the EOM pulleys may exist in patients previously diagnosed with superior oblique overaction with an associated incomitant strabismus [6].

Horizontal Rectus Muscle Dysfunction

An abandoned theory attributes A- and V-pattern strabismus to an increase or decrease in the action of the upper half of the lateral rectus muscle or the lower half of the medial rectus muscle [1]. An increase in the pull by the upper half of the lateral rectus or lower half of medial rectus muscle action would result in a V-pattern deviation, whereas a decrease in the upper half of the lateral rectus muscles or lower half of the medial rectus muscle actions would result in an A-pattern deviation. There is no compelling evidence to support this theory.

Vertical Rectus Muscle Dysfunction

The tertiary action of the superior and inferior rectus muscles is adduction. An increase or decrease in adducting power of vertical rectus muscles can contribute to an A- or V-pattern strabismus. Specifically, increased adducting action of the inferior rectus muscle will lead to a V-pattern, whereas increased adduction action of the superior rectus muscle will lead to an A-pattern.

Craniosynostosis Syndromes

While patients with craniosynostosis are at increased risk for a variety of strabismus types, a significant V-pattern strabismus is most common [7]. V-pattern strabismus in craniosynostosis patients is associated with apparent overaction (more accurately, pseudo-overaction) of the inferior oblique muscles. This commonly occurs in Crouzon syndrome and Apert syndrome when one or both coronal sutures are fused. Inferior oblique overaction develops on the side of coronal suture fusion presumably due to one of several reasons [8, 9]. First, an offset of the medial rectus muscle superiorly due to orbit and secondary globe excyclorotation can convert the medial rectus to an elevator on adduction. Secondly, posterior displacement of the superior orbital rim with subsequent posterior displacement of the superior oblique trochlea may induce superior oblique underaction with secondary inferior oblique overaction. Thirdly, patients with craniosynostosis may have anomalous insertion or agenesis of EOM, e.g., the superior oblique muscle. Lastly, strabismus may develop due to changes and abnormalities in the anatomy of the pulley systems [7]. New evidence suggests that excyclodisplacement of the rectus muscle pulleys may be the primary factor in development of V-pattern strabismus in Crouzon syndrome [8].

Treatment of A- and V-Pattern Strabismus

If there is an A- or V-pattern strabismus (greater than 10 prism diopters between upgaze and downgaze measurements for an A-pattern and greater than 15 prism diopters for V-pattern), surgical management of the pattern is undertaken in combination with treatment of the horizontal strabismus. The most common options involve weakening of the oblique muscles or vertical transposition of the horizontal rectus muscles.

Oblique Muscle Surgery

The most common procedure used to correct V-pattern strabismus is weakening of the inferior oblique muscles, which can correct approximately 15–20 prism diopters of difference between up- and downgaze. This is particularly useful when significant inferior oblique overaction is observed on version testing. When correcting V-pattern strabismus, concomitant correction of the horizontal strabismus is performed for the amount measured in primary gaze position, because inferior oblique weakening procedures have little effect on the strabismus in primary position [10]. Weakening the inferior oblique muscle can be achieved using inferior oblique recession, myectomy, or myotomy. Inferior oblique recession involves disinsertion of the inferior oblique, with reattachment of the muscle closer to the origin, thereby inducing muscle slack and reducing muscle tension (Figs. 54.1, 54.2, 54.3, 54.4, 54.5, 54.6, and 54.7). Inferior oblique myectomy involves disinsertion of the inferior oblique from the globe, with removal of the distal portion of the muscle to minimize

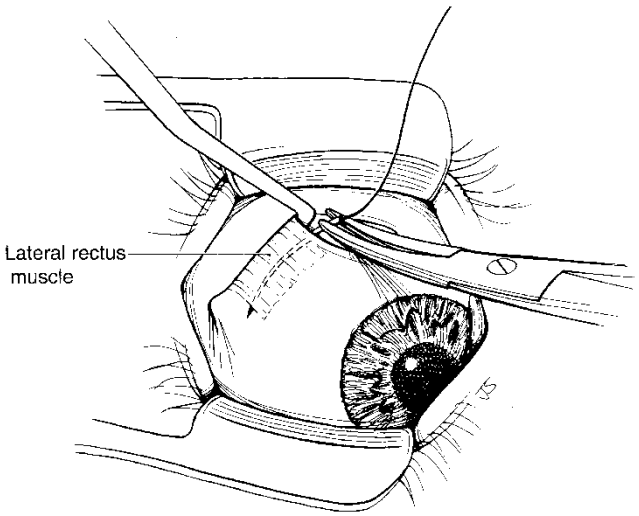

Fig. 54.1 After creation of an inferotemporal fornix incision, the lateral rectus muscle is isolated first with a muscle hook. With the hook lifted away from the sclera to create a space between the lateral rectus and the sclera, a 4-0 silk suture was passed beneath the entire lateral rectus muscle and out through the conjunctiva superiorly. This 4-0 silk suture is then pulled tightly across the bridge of the nose and clamped to the head drape with a hemostat to maintain the eye in a position of maximum adduction and elevation. Photo credit: Atlas of Pediatric Ophthalmology and Strabismus (Ed. MA Del Monte and SM Archer)

its risk of reattachment to the globe. No difference between the effectiveness of inferior oblique recession and myectomy has been demonstrated, and the type of procedure chosen is usually based on the surgeon's preference [11]. Anteriorization, or anterior transposition, of the inferior oblique is another surgical option that involves reinsertion of the inferior oblique muscle adjacent to lateral edge of the ipsilateral inferior rectus muscle insertion. This technique is most often utilized when inferior oblique overaction and dissociated vertical deviation (DVD) are present simultaneously in patients with infantile strabismus; this is less commonly performed for A- and V-pattern strabismus without DVD [12]. This procedure has been associated with postoperative hypotropia and limitation of elevation [13]; however, there is recent evidence that the use of a graded inferior oblique transposition in cases with inferior oblique overaction does not result in limited elevation of the eye in abduction [14].

Superior oblique weakening procedures are used to treat A-pattern strabismus, correcting up to 35–40 prism diopters of difference between up- and downgaze strabismus [15]. Unlike V-pattern surgery where weakening of the inferior oblique has little effect on alignment in primary position, the effect of superior oblique weakening on primary position deviation remains controversial. While some surgeons sug-

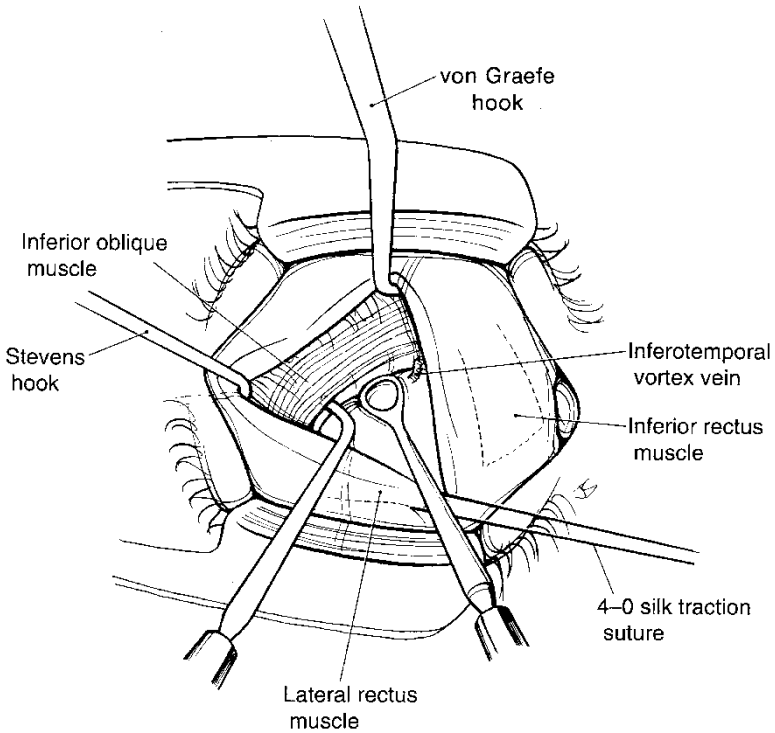

Fig. 54.2 The anterior and posterior borders of the inferior oblique muscle are then exposed by placing one muscle hook into the fornix wound laterally along the inferior border of the lateral rectus muscle and another hook inferiorly, just temporal to the inferior rectus. The exposure is enhanced by using a lens loop to indent the sclera at the posterior border of the inferior oblique muscle, allowing for clear visualization of the "pink/white" junction between the posterior border of the inferior oblique muscle and Tenon's capsule. At this point, the inferotemporal vortex vein is also identified, and inferior oblique muscle is then engaged using a Stevens hook and elevated into the wound anteriorly, along with the adjacent Tenon's capsule and intermuscular septum. Photo credit: Atlas of Pediatric Ophthalmology and Strabismus (Ed. MA Del Monte and SM Archer)

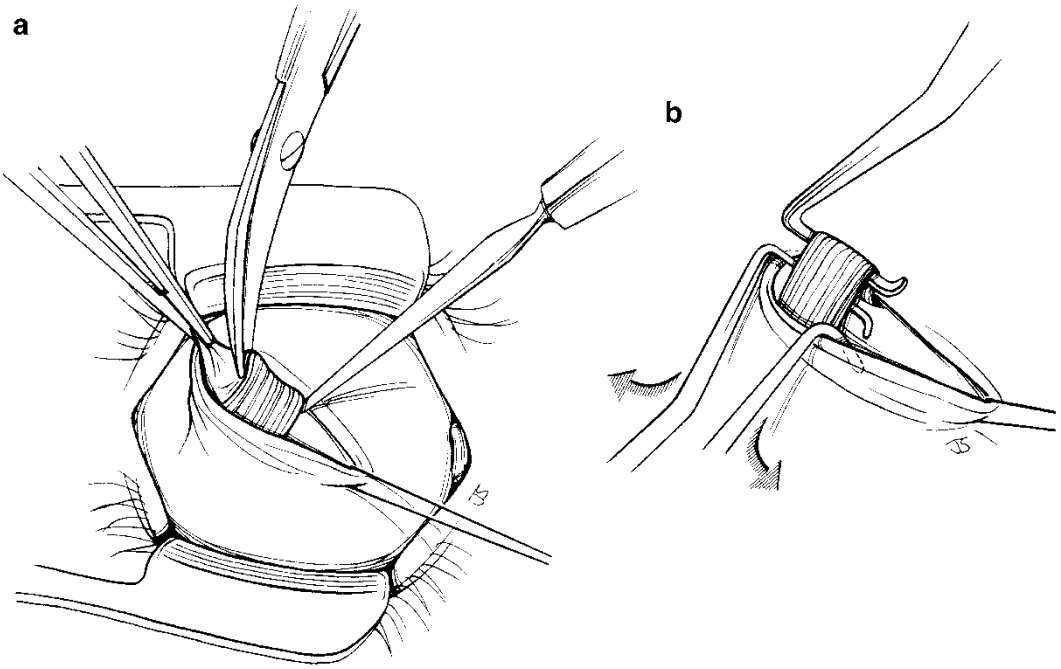

Fig. 54.3 (**a**) The intermuscular septum is incised at the posterior border of the muscle. (**b**) Two muscle hooks are then used to spread and isolate the inferior oblique muscle. Photo credit: Atlas of Pediatric Ophthalmology and Strabismus (Ed. MA Del Monte and SM Archer)

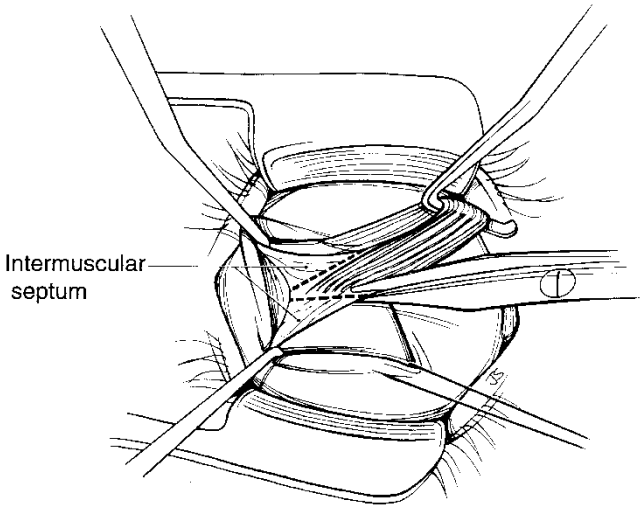

Fig. 54.4 The intermuscular septum is incised at the posterior border of the muscle. Two muscle hooks are then used to spread and isolate the inferior oblique muscle. Photo credit: Atlas of Pediatric Ophthalmology and Strabismus (Ed. MA Del Monte and SM Archer)

gest that weakening of the superior oblique muscle causes a shift of up to 30 prism diopters toward convergence [16–18], others report little to no esoshift in primary gaze [9]. Proponents of this effect on primary gaze deviation recommend modification of the amount of horizontal surgery to compensate for the anticipated change.

Superior oblique muscle weakening procedures include superior oblique tenotomy, tenectomy, recession, Z-lengthening, and spacer placement. Superior oblique muscle weakening can affect vertical alignment and weaken incyclotorsion. After bilateral weakening of the superior oblique muscles, an esotropic shift of up to 30–40 diopters can occur in downgaze with no change in upgaze and variable change in primary position [15].

Rectus Muscle Surgery

Vertical displacement of the insertion of the horizontal recti muscles can be used as an alternative treatment to prevent oblique muscle surgery, especially when there is an absence of oblique muscle overaction (Figs. 54.8 and 54.9) [19, 20]. In such vertical transpositions, the medial rectus insertion is moved toward the gaze of increased convergence, or the apex of the named strabismus (upward in an A-pattern strabismus and downward in a V-pattern strabismus). The lateral rectus muscle insertions are moved toward the gaze of increased divergence, or the open end of the named strabismus (downward in an A-pattern strabismus and upward in a V-pattern strabismus). The goal of this surgery is to reduce the effective pull of horizontal rectus muscle in the position of gaze in which they appear to be overacting. For example, in V-pattern strabismus, the lateral rectus may be considered

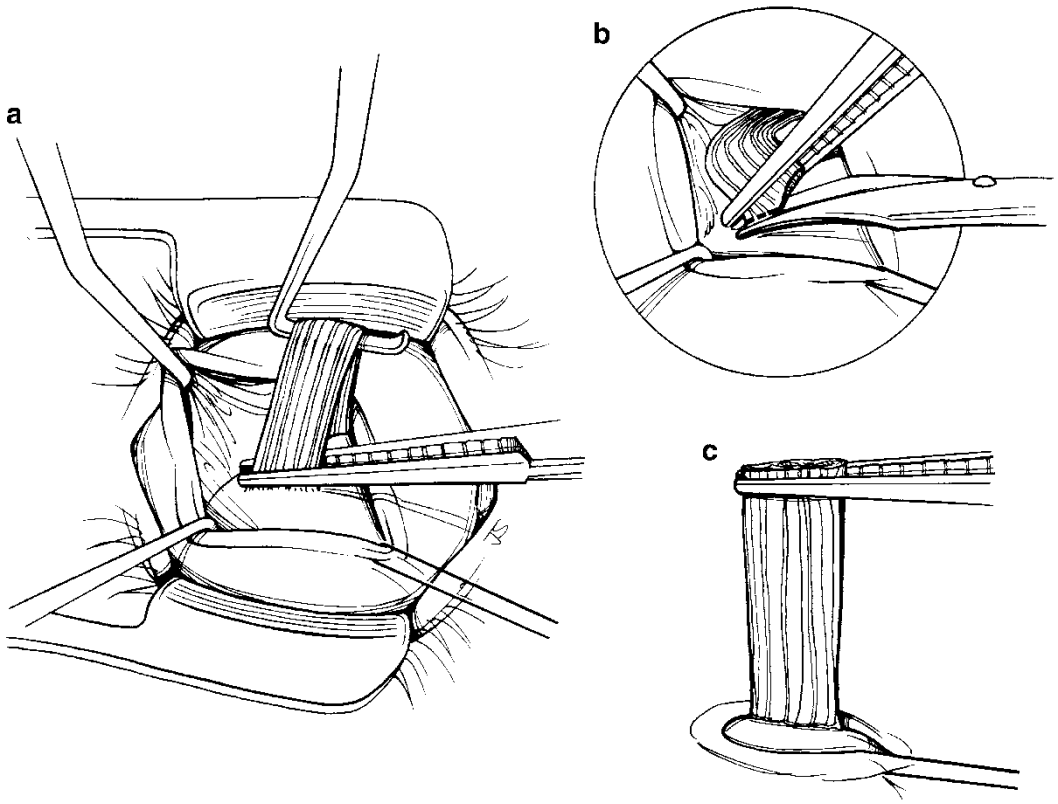

Fig. 54.5 (**a**) The inferior oblique muscle is cross-clamped with a straight hemostat adjacent to its insertion. (**b**) The muscle is then detached from the globe at its insertion and (**c**) secured with a double-armed 6-0 vicryl suture. Photo credit: Atlas of Pediatric Ophthalmology and Strabismus (Ed. MA Del Monte and SM Archer)

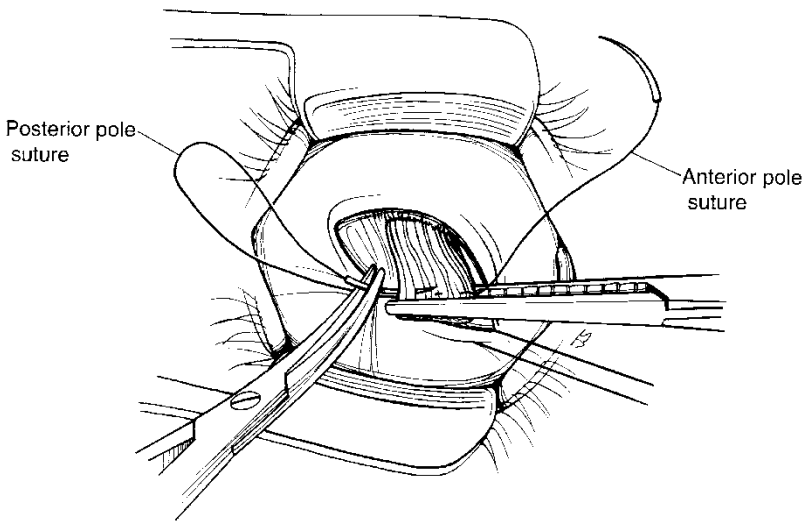

Fig. 54.6 The inferior oblique muscle is cross-clamped with a straight hemostat adjacent to its insertion. The muscle is then detached from the globe at its insertion and secured with a double-armed 6-0 vicryl suture. Photo credit: Atlas of Pediatric Ophthalmology and Strabismus (Ed. MA Del Monte and SM Archer)

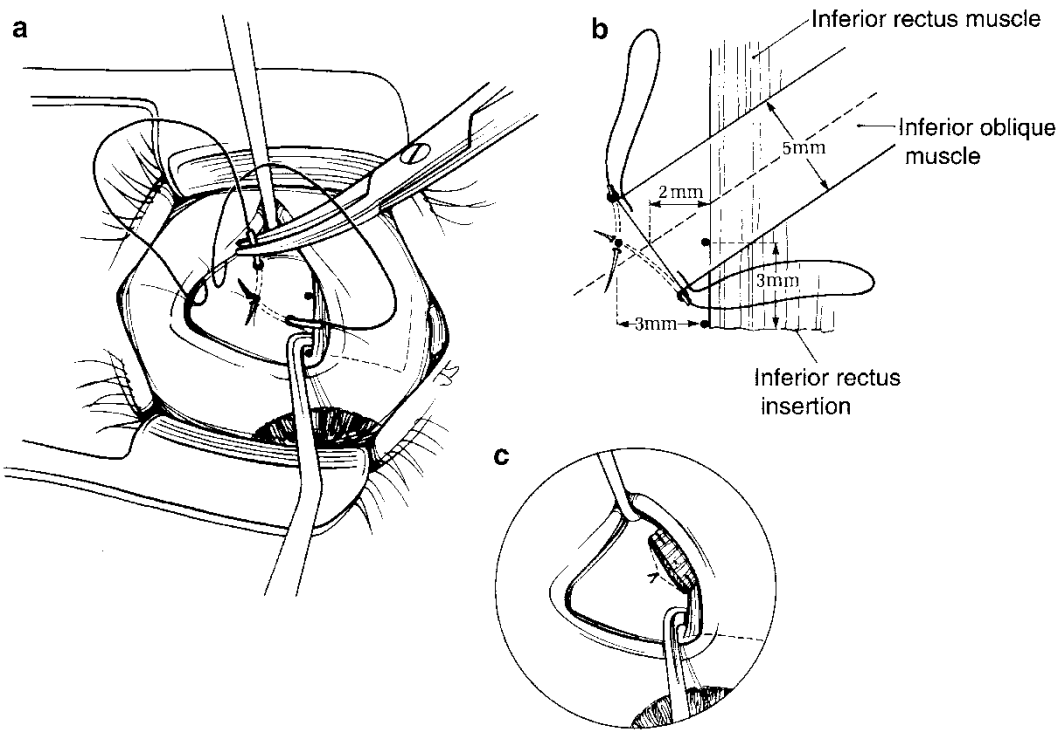

Fig. 54.7 (**a**) The inferior rectus muscle is then isolated on a muscle hook. (**b**) The inferior oblique is reattached to the sclera such that the center of the new insertion is located 3 mm posterior and 2 mm lateral to the temporal border of the inferior rectus insertion in a crossed swords fashion (for a 10 mm recession). (**c**) The sutures are tied in a *square knot* and the muscle is inspected to make sure that it was spread equally. Photo credit: Atlas of Pediatric Ophthalmology and Strabismus (Ed. MA Del Monte and SM Archer)

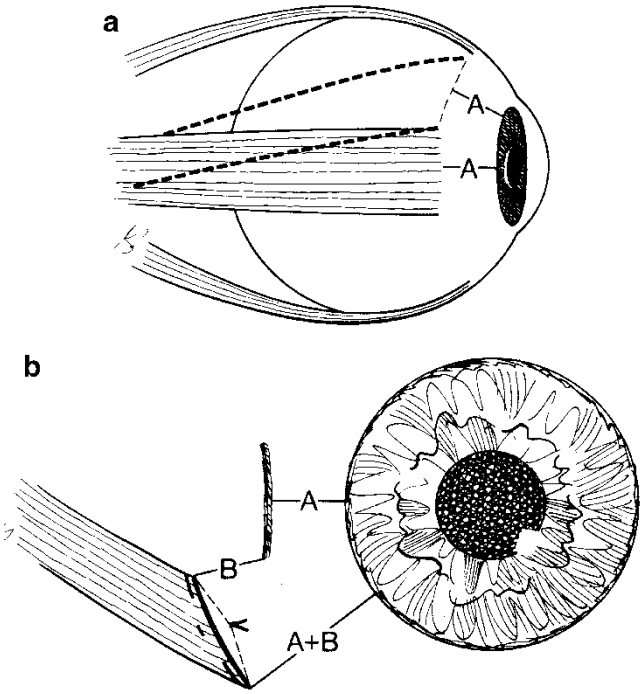

Fig. 54.8 Transposition of a rectus muscle. (**a**) This diagram depicts circumferential displacement of the insertion. The measurement technique in (**b**) can be used to perform a recession and transposition. Placement of the new insertion pole nearest to the original insertion is measured radially as the amount of the planned recession (**b**) from the original insertion site. Placement of the second muscle pole is determined by measuring radially from the limbus a distance of $A+B$. Photo credit: Atlas of Pediatric Ophthalmology and Strabismus (Ed. MA Del Monte and SM Archer)

overactive in upgaze. Displacement of the muscle insertion in a superior direction usually one-half to one the tendon width induces a slack of the muscle and weakens it when the eyes are in upgaze.

Slanted reinsertion of the horizontal muscles has also been described as a treatment modality for A- and V-pattern strabismus [21]. In this procedure, one end of the insertion is placed farther from the limbus than the other. The pole of the muscle to be adjusted and the direction of adjustment are determined by the deviation. For example, in V-pattern esotropia without oblique overaction, the inferior pole of the medial rectus muscle would be recessed a larger amount (2–3 mm depending on the size of the pattern) than the upper pole. This would be considered equivalent to inferior displacement of the medial rectus muscle tendon in V-pattern strabismus. This procedure presumably provides a similar effect to vertical displacement of the insertions and has been advocated as an alternative to vertical transposition [21].

The amount of recession or resection of the horizontal muscles is based on the measurement of strabismus in primary position of gaze. Displacement of the recessed muscle is usually one tendon-width, whereas displacement of the resected muscle is sometimes lessened slightly given the simultaneous strengthening procedure being performed. Displacement of horizontal rectus muscles is also usually only done in the setting of a bilateral symmetric procedure, such as bilateral lateral rectus recession or bilateral medial

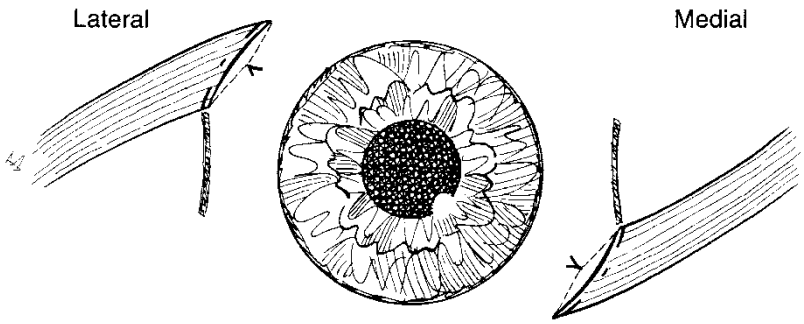

Fig. 54.9 The result of transposition of the horizontal rectus muscles of the right eye to treat a V-pattern strabismus is shown, with the lateral rectus transposed superiorly, and the medial rectus transposed inferiorly. Photo credit: Atlas of Pediatric Ophthalmology and Strabismus (Ed. MA Del Monte and SM Archer)

rectus recession. It is not usually employed in unilateral strabismus surgery, such as a combination recession and resection on the medial rectus and lateral rectus muscles of the same eye, because of the possible consequent unwanted torsional changes.

Horizontal displacement of vertical rectus muscle insertions, although likely effective in treatment of A- and V-pattern strabismus, is rarely employed [22]. The horizontal rectus muscle procedure required to treat the underlying esotropia or exotropia makes surgery on the horizontal rectus muscles the preferred choice. When employing muscle transposition, it is important the surgeon acknowledges the surgery will affect both the A- or V-pattern strabismus and torsion to avoid adverse outcomes. Torsion as a result of transposition for A- and V-pattern strabismus and A- and V-pattern strabismus as a result of transposition for torsion have been reported [23].

Treatment Outcomes

Oblique Muscle Surgery

Surgical weakening of the inferior oblique muscles has been shown to correct 65–75 % of the initial V-pattern deviation [10]. As mentioned above, surgery to correct the deviation in eso- or exo-deviation primary position is needed in addition to inferior oblique weakening. Anterior transposition of the inferior oblique is associated with correction within 10 prism diopters of orthophoria in 80 % of cases [14]. However, anteriorization of the inferior oblique muscle can be complicated by limitation of elevation post-operatively. Several intraoperative factors have been shown to increase postoperative limitation of elevation, including insufficient grading of the transposition, anteriorization of more than 1 mm anterior to the inferior rectus insertion, and lateral spread of the inferior oblique muscle insertion at the time of anteriorization [13, 14].

Superior oblique muscle weakening, commonly used for correction of A-pattern deviations, can be accomplished with many different techniques including tenotomy, tenectomy, recession, and spacer placement. No significant difference in outcome has been shown between the multiple techniques described for superior oblique weakening procedures [23–26]. The magnitude of reduction of A-pattern strabismus has been shown to correlate with the size of the preoperative deviation, not the amount of surgical weakening performed [9, 19–22, 24]. A-pattern deviations have been shown to improve from a difference of 36 diopters (range 15–75) to average 6 diopters (range 0–16) after superior oblique weakening [24]. Superior oblique recession has also been shown to correct 14–40 diopters of A-pattern deviation with, as mentioned above, the amount of pattern corrected correlating to the amount of preoperative deviation.

Rectus Muscle Surgery

A study comparing lateral rectus muscle recession with and without half tendon upward transposition in V-pattern exotropia without inferior oblique overaction demonstrated that 14 % of patients without transposition were within 5° of V-pattern normalization postoperatively, compared to 64 % of patients with transposition [19]. The rate of an outcome within 8 prism diopters of orthophoria in primary position was not statistically different between the two groups [19]. A study of vertical transposition and slanting of the muscle insertion has also shown equivalent results when comparing the two procedures [21].

When utilizing vertical transposition of the horizontal rectus muscles, it is important to consider possible effects of the transposition on the surgical response in primary position. Some studies have shown an increased surgical response with upward displacement of the medial rectus muscle in A-pattern esotropia [20]. No significant response was noted with downward displacement of the medial rectus for correction of V-pattern deviations [20]. It is important to consider this effect when planning surgery for A-pattern esotropia.

Case Examples

Case 1 (Table 54.1)

A 10-month-old female has been noted to have ocular misalignment since birth. Her mother had strabismus surgery at 1 year of age. Strabismus measurements are included in Table 54.1. At age 11 months, she undergoes a bilateral medial rectus recession of 5.5 mm along with a bilateral inferior oblique myectomy to correct for measured inferior oblique overaction. At both her 6 and 12 month postoperative visits, her alignment was measured as 4 prism diopters of esophoria.

Table 54.1 Case 1

Clinical history	10-month-old female with a history of esotropia			
	Past medical history: non-contributory			
	Family history: strabismus in mother			
Key components of exam		**OD**	**OS**	
	Uncorrected visual acuity	Central-steady-maintain	Central-steady-maintain	
	Ductions/versions	Full, with 2+ inferior oblique overaction	Full, with 2+ inferior oblique overaction	
	Distance alignment		30Δ ET	
		40Δ ET	40Δ ET	40Δ ET
		5Δ LHT		5Δ RHT
			50Δ ET	
	Near alignment	40Δ ET′, with continued V-pattern		
	Cycloplegic refraction	+1.50 sphere	+1.50 sphere	
	Dilated fundus exam	Normal	Normal	
Management options	For esotropia:			
	1. Bilateral medial rectus recession			
	2. Bilateral lateral rectus resection			
	3. Unilateral medial rectus recession with lateral rectus resection			
	For V-pattern:			
	1. Bilateral inferior oblique recession or myectomy			
	2. Displacement of the medial rectus tendons downward or of the lateral rectus tendons upward			
Surgery	Bilateral medial rectus muscle recession by 5.5 mm (for 40Δ) with bilateral inferior oblique myectomy			
Interval history (6 months) *Current age: 18 months*	Patient has good alignment, no crossing noted by parents			
Key components of exam		**OD**	**OS**	
	Uncorrected visual acuity	Central-steady-maintain	Central-steady-maintain	
	Ductions/versions	Full, no oblique overaction	Full, no oblique overaction	
	Alignment	4Δ comitant esophoria without an A- or V-pattern (distance and near)		
Management	Monitor/observe			
Interval history (12 months) *Current age: 2.5 years*	Patient has good alignment, no crossing noted by parents			
Key components of exam		**OD**	**OS**	
	Uncorrected visual acuity	Central-steady-maintain	Central-steady-maintain	
	Ductions/versions	Full, no oblique overaction	Full, no oblique overaction	
	Alignment	4Δ comitant esophoria, without an A- or V-pattern (distance and near)		
	Stereopsis	Denies fly	Denies fly	
Management	Continue to monitor/observe			

Case 2 (Table 54.2)

A 3-year-old male presents with a history of outward drifting of the left eye for the past 2 months. An A-pattern exotropia is measured with bilateral superior oblique overaction (Table 54.2). Given the magnitude of the A-pattern (40 prism diopter difference between upgaze and downgaze), the patient undergoes bilateral lateral rectus recession of 5 mm corresponding to the measurement of the exotropia in primary gaze with one tendon-width inferior displacement and bilateral superior oblique tenotomy. Postoperatively, the patient has 2 prism diopters of intermittent esotropia at 6 months and 4 prism diopters of esophoria at 1 year.

Table 54.2 Case 2

Clinical history	3-year-old male with eye misalignment noted for the past 2 months			
	Past medical history: non-contributory			
	Family history: negative for strabismus			
Key components of exam		**OD**	**OS**	
	Uncorrected visual acuity (HOTV)	20/25	20/25	
	Ductions/versions	Full, with 2+ superior oblique overaction	Full, with 2+ superior oblique overaction	
	Stereopsis	Denies fly		
	Distance alignment		10Δ ET	
		20Δ XT	20Δ XT	20Δ XT
			50Δ XT	
	Near alignment	20Δ XT′ with continued A-pattern		
	Cycloplegic refraction	+1.25 sphere	+1.25 sphere	
	Dilated fundus exam	Normal	Normal	
Management options	1. Bilateral lateral rectus recession with 1-tendon width displacement inferiorly			
	2. Bilateral medial rectus muscle resection with ½ tendon width displacement superiorly			
	3. Bilateral superior oblique tenotomy or tendon spacer			
Surgery	1. Bilateral lateral rectus recession of 5 mm (for 20Δ) with 1-tendon width inferior displacement			
	2. Concurrent bilateral superior oblique tenotomy			
Interval history (6 months) *Current age: 3.5 years*	Parents report improved alignment			
Key components of exam		**OD**	**OS**	
	Uncorrected visual acuity (HOTV)	20/20	20/20	
	Stereopsis	+ Fly		
	Ductions/versions	Full	Full	
	Distance alignment	Upgaze: 6Δ esotropia		
		Primary: 2Δ well-controlled E(T), builds to 10Δ E(T)		
		Downgaze: ortho		
	Near alignment	Upgaze: 4Δ esotropia		
		Primary: 6Δ esophoria		
		Downgaze: ortho		
Management	Monitor/observe			
Interval history (12 months) *Current age: 4.5 years*	Parents report improved alignment			
Key components of exam		**OD**	**OS**	
	Uncorrected visual acuity (Snellen)	20/20	20/20	
	Stereopsis	+ Fly, 3/3 animals, 5/9 circles		
	Ductions/versions	Full	Full	
	Alignment	6Δ esophoria (distance and near), no A- or V-pattern observed		
Management	Monitor/observe			

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Congenital Cranial Dysinnervation Disorders

55

Emin Cumhur Sener, Maria Choudhary, and Hande Taylan Şekeroğlu

Abstract

This chapter describes the clinical features, diagnostic evaluation, and management options of patients with congenital fibrosis of the extraocular muscles (CFEOM) as well as those with other types of congenital cranial dysinnervation disorders (CCDD) such as Möbius syndrome, horizontal gaze palsy with progressive scoliosis, and synergistic horizontal deviation. These are rare and challenging strabismus cases to the most experienced pediatric ophthalmologists and strabismologists. The classification and genetics of CCDDs are briefly discussed, and two case presentations are given. Management strategies are discussed and a flowchart for the evaluation and management of CCDD cases is provided.

Keywords

Congenital cranial dysinnervation disorders • Congenital fibrosis extraocular muscle • Möbius syndrome • Horizontal gaze palsy progressive scoliosis • Synergistic divergence • Restrictive strabismus • Paralytic strabismus • Aberrant innervation • Vertical divergence • Strabismus surgery

The Problem

The congenital cranial dysinnervation disorders (CCDD) constitute a group of static congenital neuromuscular disorders characterized by abnormal ocular, eyelid, and/or facial motility that result from innervational abnormalities to the extraocular and facial muscles from brainstem cranial nerve nuclei and their motor nerves [1]. These disorders include a number of rare conditions that affect ocular motility such as Duane syndrome, Möbius syndrome, HOXA1 and HOXB1 spectrum disorders, congenital fibrosis of the extraocular muscles (CFEOM) types 1–3, synergistic horizontal divergence, and horizontal gaze palsy and progressive scoliosis (HGPPS) (Table 55.1).

The phenotypes of CCDDs are expanding and the majority of the causative genes have been identified [1–3]. Intensive genetic research is underway and genetic testing is available for many types of CCDDs [4].

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Evidence for Effective Diagnosis

Clinical Presentation

Congenital Fibrosis of the Extraocular Muscles

CFEOMs comprise a group of genetically determined congenital, non-progressive, paralytic and restrictive strabismus cases with varying degree of aberrant innervation and ptosis. Patients with CFEOMs can have unilateral or bilateral

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Table 55.1 Major clinical, radiological, and genetic features of some of the CCDDs

CCDD	Mode of inheritance	Genetic defect	Clinical presentation	Radiologic finding
Duane retraction syndrome	Sporadic (10 % familial)	Formation or survival of CN VI nucleus (*HOXA1*), abnormal chemotaxis of CN VI neurons to lateral rectus muscle (*CHN1*, *SALL4*)	Depending on clinical type limitation of abduction and/or adduction, with globe retraction and narrowing of the palpebral fissure	Absent or small CN6 nucleus
Congenital fibrosis of extraocular muscles (CFEOM)	Sporadic, AD (CFEOM1 and CFEOM3) and AR (Tukel syndrome and CFEOM2)	Neuronal survival (*PHOX2A*), neuronal development (*KIF21A, TUBB3, TUBB2B*)	See text	Thin extraocular muscles Absent or hypoplastic oculomotor nerves (+/– other cranial nerves)
Möbius syndrome	Sporadic. Some rare chromosomal defects	Unknown	Bilateral or unilateral facial weakness with abduction deficit normal vertical movements	Absence or compromise of CN VI and VII, brainstem hypoplasia
Horizontal gaze palsy and progressive scoliosis	AR	Decussation of neural tracts (*ROBO3*)	Partial or complete absence of horizontal eye movement with intact vertical gaze	Hypoplastic pons and medulla; absence of facial colliculi with normal appearing CN III, VI, and VII nerves
			Debilitating scoliosis	
Monocular elevation deficiency	Sporadic	Not applicable	Unilateral loss of elevation in adduction and abduction	Normal

involvement. Cases can be familial or sporadic, and in some types, such as CFEOM3, the phenotype may be heterogeneous within families in which members carry the same mutation. Although initially considered to have a mechanical etiology, it is now recognized that these disorders have underlying developmental neurogenic abnormalities, and that the fibrosis and the mechanical restriction are secondary to the dysinnervation [5].

CFEOM1

CFEOM1 patients have significant chin-up head posture with bilateral ptosis and restriction of upgaze, with the globes fixed in infraducted position (Case 1 is Möbius syndrome Figs. 55.1 and 55.2). Horizontal gaze is variably restricted and patients have horizontal deviations ranging from orthotropia to large esotropias or exotropias. Very large A-patterns are common. Patients often have synkinesis that manifests as synergistic convergence on attempted upgaze, and divergence on attempted downgaze, as well as Marcus-Gunn jaw-winking phenomenon. Marcus-Gunn jaw-winking phenomenon (trigemino-oculomotor synkinesis) occurs when aberrant innervation (between trigeminal and the oculomotor nerve) causes the ptotic eye to elevate when the jaw moves to the opposite side. In an infant, this can be demonstrated for example by having the child suck on a bottle. CFEOM1 is inherited in an autosomal dominant fashion with full penetrance and a fairly uniform phenotype; however, phenotypic heterogeneity at the CFEOM1 locus has been reported [6, 7]. CFEOM1A results from mutations in *KIF21A*, and CFEOM1B from mutations in *TUBB3* or *TUBB2B*.

CFEOM2

CFEOM2 involves both the oculomotor and trochlear motor neurons and patients present with a typical phenotype with large bilateral exotropia and severely limited horizontal and vertical eye movements, with varying degrees of ptosis. The pupils are small and poorly reactive; this is presumed to be the result of underdevelopment of the noradrenergic innervation to the iris dilator muscles. It is autosomal recessive, and results from mutations in the *PHOX2A* gene [3, 4].

CFEOM3

The phenotype in patients with CFEOM3 can be quite variable, even within the same family, and includes family members that resemble those with CFEOM1 (Figs. 55.1 and 55.2), while others have atypical phenotypes and variable severity of limitation to eye movements. It can be unilateral, and limitation of upgaze can be very mild. It is autosomal dominant with variable expression and incomplete penetrance. CFEOM3 results from mutations in *TUBB3*. No locus has been identified yet for CFEOM3B. CFEOM3C maps to 13q12.1. CFEOM-U maps to chromosome 21qter, and is called Tukel syndrome. It is autosomal recessive with unilateral elevation deficit and restriction in all gaze directions, with ulnar hand anomalies [1].

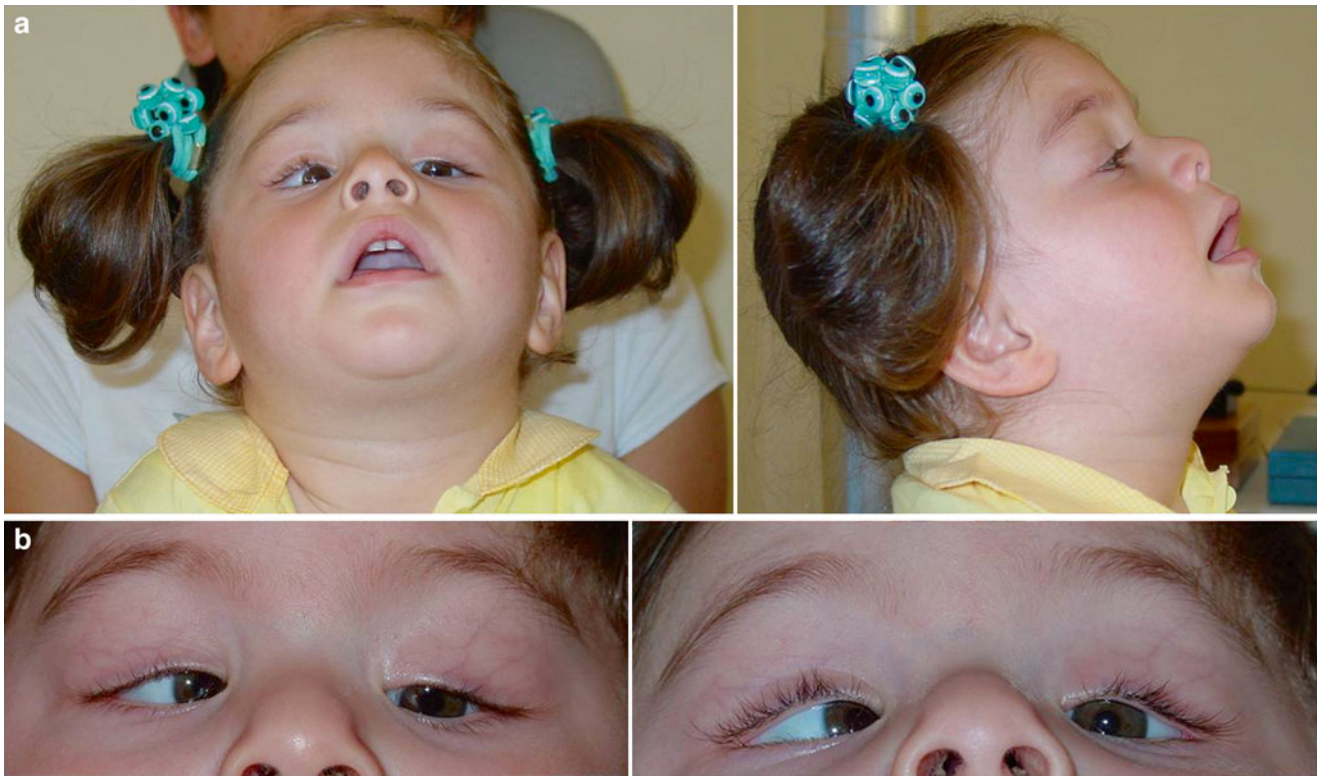

Fig. 55.1 (**a**) Preoperative chin-up head posture in a 1-year-old patient with CFEOM3 (Case #11 in [16]) preoperatively (face and profile shots). (**b**) Preoperative primary position deviation with (*top*) and without (*bottom*) head posture

Mild cases of CFEOM3 may go unnoticed unless a typical severely affected family member is identified and other family members are examined. CFEOM patients can have other associated peripheral and brainstem developmental anomalies that include optic nerve anomalies, especially hypoplasia, olfactory abnormalities (Kallmann syndrome), facial weakness, deafness, progressive peripheral neuropathy, ulnar hand anomaly, developmental delay, as well as intellectual and social disabilities [2, 8, 9].

The *KIF21A* and *TUBB3* genes are important in lower motor neuron axonal development whereas *PHOX2A* is significant in the development of the brainstem and predominantly the lower motor neurons.

Stilling–Türk–Duane's Syndrome (Please Refer to Chap. 52)

Möbius Syndrome

Patients with Möbius syndrome typically present with congenital sixth and seventh nerve paralysis (Case 1 and Figs. 55.3 and 55.4). The condition is usually bilateral although asymmetric involvement is common. Esotropia can be moderate to very large with variable ability to converge. In some cases, mild vertical deviations and vertical gaze patterns may further complicate the clinical picture. Möbius syndrome is frequently associated with pharyngeal dysfunction, speech problems, and limb malformations in the form of reduction anomalies of the digits [3, 4].

Synergistic Horizontal Divergence

Synergistic divergence is synonymous with synergistic horizontal divergence and considered to be a distinct and rare type of CCDD [10]. The eyes in patients with synergistic horizontal divergence are in an exotropic position and paradoxically abduct in attempted contralateral gaze. The condition can be unilateral or bilateral. Occasionally, associated vertical misalignment can further complicate the clinical picture. The adduction capacity of the involved eye can vary from mild to complete impairment. Bilateral cases can also be quite asymmetric in terms of the magnitude of divergent abducting saccades and adduction capacity. Magnetic Resonance Imaging (MRI) of the orbit can reveal a small medial rectus on the involved side, but no other neurologic structural abnormalities. Case reports of missing abducens nerve or atrophic oculomotor nerves have been reported [10, 11]. No genetic locus has been identified yet.

Synergistic horizontal deviation is different from Duane syndrome because it involves the medial rectus and there is no co-contraction of muscles that lead to globe retraction. Both conditions can rarely occur in the same patient. Synergistic horizontal deviation is most likely the result of aberrant innervation of the lateral rectus with the medial rec-

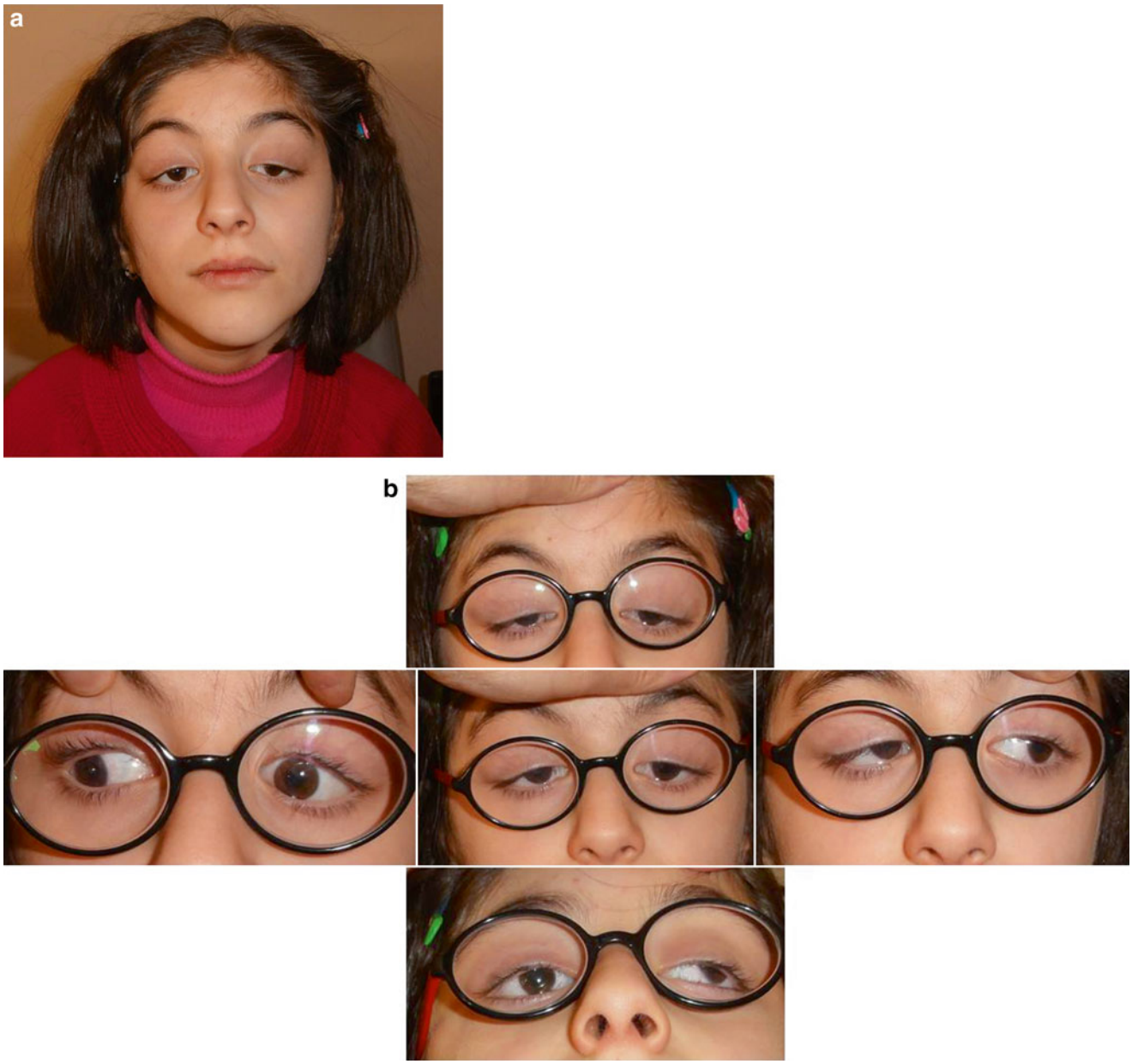

Fig. 55.2 Same patient at age 10 years. Head posture has significantly improved following several strabismus surgeries including left and right inferior rectus recessions by 10 mm from the insertion, transposition and recessions or resections of the horizontal muscles as well as tenectomy of the superior obliques. The superior rectus was not operated on to preserve its ciliary vessels

tus branch of the oculomotor nerve. Aberrant innervation is quite common in CFEOM and can cause synergistic convergence or vertical divergence rather than horizontal divergence. Synergistic convergence usually manifests on attempted upgaze, and when trying to hold fixation in primary position in patients with significant chin-up head postures. The synergistic vertical divergence in CFEOM cases manifests itself as an upshoot of the contralateral eye on downgaze. This condition is especially exaggerated in cases after contralateral large inferior rectus recessions.

Horizontal Gaze Palsy and Progressive Scoliosis

Patients with HGPPS are born with restricted horizontal lateral gaze causing compensatory head turns in some. The eyes are usually well aligned in primary position of gaze, although mild esotropia that responds to bilateral medial rectus recession can be observed [3, 4]. Patients develop progressive scoliosis very early in the first decade of life. HGPPS is caused by the absence of midline decussation of axons in the pons, medulla, and corticospinal tract. It is autosomal recessive and *ROBO3* has been identified as the responsible gene [12].

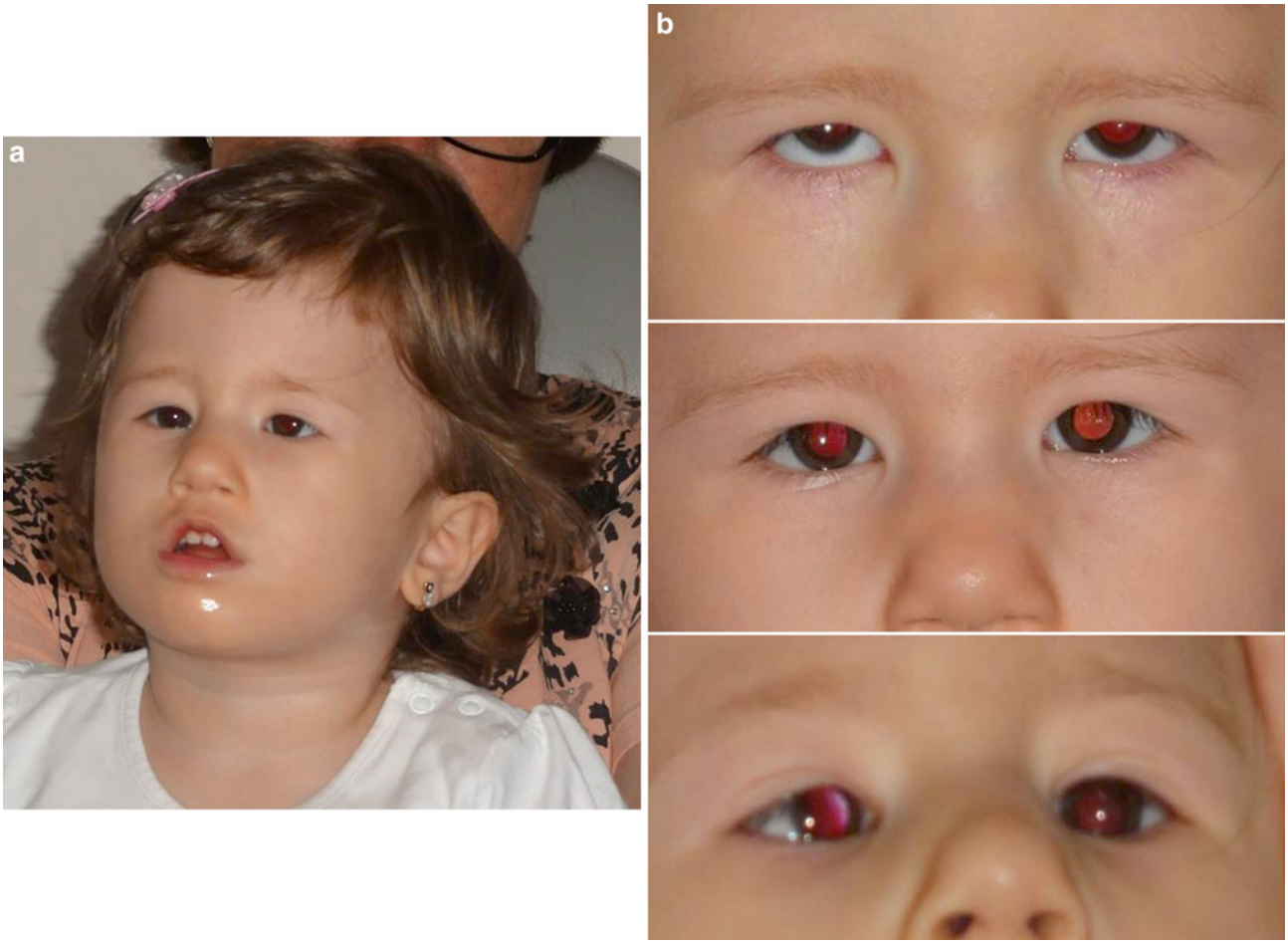

Fig. 55.3 Case 1—Bilateral Möbius syndrome preoperatively. (**a**) With alternating head turn and chin-up posture. (**b**) V-pattern esotropia is evident. She has no lateral motility and her left supraduction is also limited (−2)

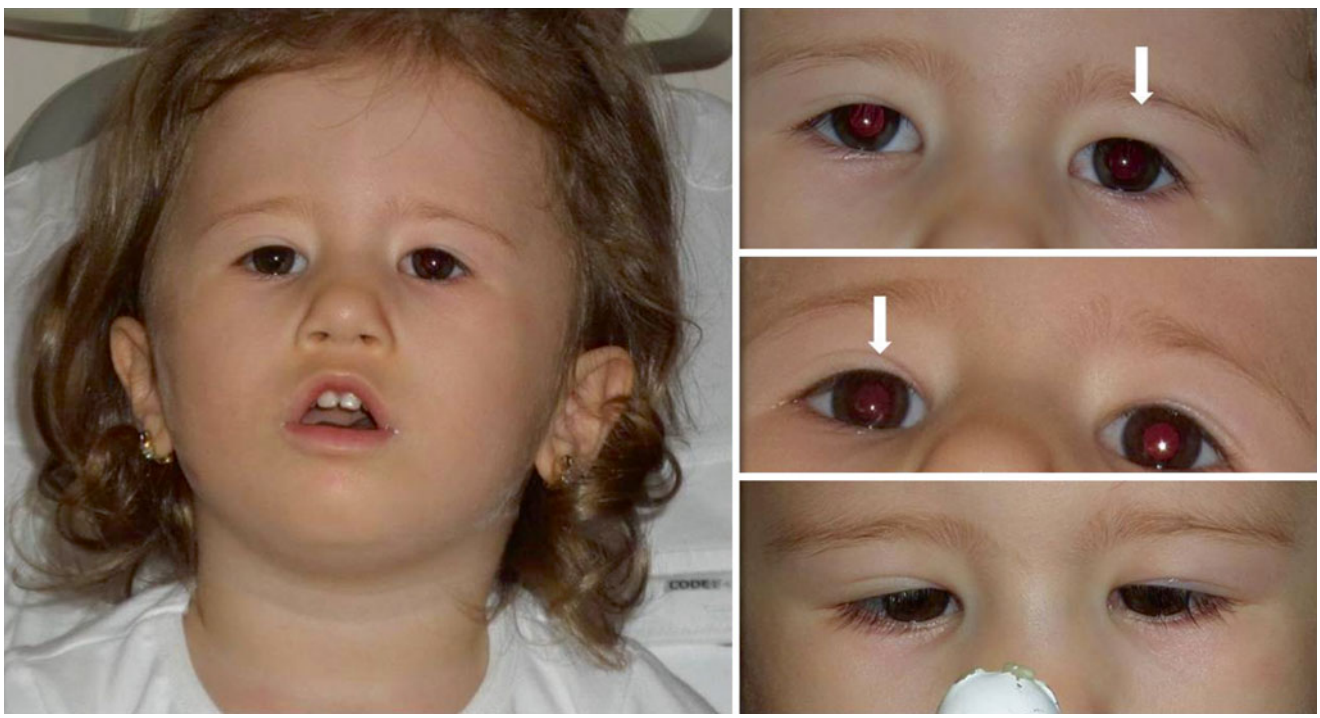

Fig. 55.4 Case 1—Bilateral Möbius syndrome postoperatively. Her head turn has resolved completely. Her chin-up position has decreased. She alternates fixation in primary position of gaze and there is small dissociated vertical deviation of both eyes as evident by Brückner reflex (*arrows* indicate the fixating eye). The modified hang loose technique has preserved the convergence albeit large medial rectus recession

Evidence for Effective Management of CFEOM and Other CCDD

Regardless of the etiology or classification of the CCDDs, the management of individual cases should be tailored to the specific needs of the particular patient. Some patients have significant associated systemic problems, and should be managed by a team of specialists.

Amblyopia

Most patients with CFEOM have decreased vision resulting from either organic etiologies including optic nerve and visual pathway abnormalities and/or from strabismic, anisometropic, or deprivational amblyopia that results from ptosis. Cycloplegic refraction should be performed carefully in patients with CCDD, and amblyopia should be promptly treated. High astigmatic errors are not uncommon and may change dramatically in magnitude following the recession of tight muscles [13].

Ptosis

The surgical management of ptosis should be delayed until the eyes are satisfactorily aligned unless the lids are obstructing the visual axis. The correction of vertical strabismus can sometimes lead to an improvement in the position of the upper lid with respect to the pupillary axis. Bell's phenomenon is absent in most cases of CFEOM with ptosis, and therefore correction of the ptosis should be cautiously exercised because of the risk of exposure keratopathy. In severely affected patients, frontalis suspension procedures are usually necessary and the goal should be limited to a few millimeters of elevation of the lid margin and an attempt at creation of an upper lid crease [14, 15].

Strabismus and Abnormal Head Posture

General Considerations

The correction of strabismus and hence the abnormal head posture in patients with CFEOM depends on the severity of the clinical picture. Cases can be complicated by coexisting abnormal horizontal and/or vertical divergence [16]. The patient and his/her family should be informed of the limitations of surgical outcome based on the severity and complexity of the problem. The surgical goal can be limited to improvement of the anomalous head position and the achievement of an acceptable appearance in primary position in severe cases. Very good alignment and motility may be attainable in milder cases. Patients with HGPPS are usually orthotropic and do not need any surgical interventions, although they develop compensatory head movements to overcome horizontal gaze limitations. Table 55.2 summarizes the steps in the examination and management of the patient with CCDD.

Table 55.2 Essential diagnostic steps for the management of CFEOM

1.	Perform standard motility and cover test examinations in nine cardinal positions of gaze with and without the abnormal head posture. Conventional prism cover test may not be possible in most cases, be prepared to document the case more qualitatively than quantitatively
2.	Measure the head posture, and determine which muscle(s) causes the head posture
3.	Check for the pattern deviation and try to interpret the aberrant innervation patterns
4.	Passive and active traction tests should be performed whenever possible
5.	Look for the reasons and elaborate the extent of restriction and paresis that causes any deficient duction. The speed of the saccade can give important clue of paresis instead of full paralysis at a muscle with restriction
6.	Estimate the diplopia-free visual field
7.	Objectively or subjectively document torsion when possible
8.	Videographic documentation is essential in putting together all of the above mentioned difficult to explain suddenly changing motility characteristics
9.	Correct for the refractive error and manage the amblyopia which are common
10.	Wait for the correction of ptosis until after the strabismus procedures are completed if at all possible

Examination of the ocular motility should include careful evaluation of ductions, versions and convergence, looking for evidence of aberrant innervation; recording the presence of any nystagmus; evaluating the quality and briskness of saccades; and documenting any pattern deviations.

Prism and cover testing should be performed in each cardinal position of gaze with and without the abnormal head posture. Because of the complexity of the motility patterns and the rapid changes in the angle of strabismus, videographic documentation may be very helpful in assessing the effect of the individual surgical procedure in better detail, and for the planning of additional strabismus procedures if needed. Sufficient information should be collected to identify the paralytic muscle(s), the magnitude of the paresis, and the existence of aberrant innervation with particular attention to synergistic vertical and horizontal divergence. The extent of restricted eye movements as a result of fibrosis, together with forced duction testing; the assessment of diplopia-free visual fields is important in evaluating the success of surgical interventions; the patients' grade of binocularity and stereopsis should be recorded as well as the objective and subjective assessment of torsion.

The forced duction test is very important for the diagnosis and surgical planning in patients with CCDDs. As with clini-

cal findings, results of the forced duction test vary among patients with CFEOM. In sporadic cases without an obvious positive forced duction test, it may be prudent not to classify the case as CFEOM, but rather as double elevator palsy or elevation deficiency, unless there is molecular confirmation of CFEOM using genetic testing. In severe cases, the orbital soft tissue and the extraocular muscles can be so stiff that the globes may feel like they are frozen. In such cases, the surgeon can observe the globe to remain in its position even after disinsertion of the fibrotic muscle(s).

Severely affected patients with CFEOM present a challenge to even the most experienced strabismus surgeon, and multiple surgical interventions may be required to achieve the desirable effect. In cases with significant restriction and paralysis, especially those with accompanying aberrant innervation, the classic surgical tables for ordinary strabismus cases do not apply because precise measurement of the deviation is extremely difficult, equal innervation laws are violated, and the surgical anatomy is altered. It is important to be aware of the fact that heterotopic insertions of extraocular muscles are not uncommon in CFEOM.

Strabismus Surgery Planning

CFEOM

The pattern of strabismus in CFEOM1 and CFEOM3 can vary considerably from unilateral to bilateral and asymmetric involvement; large hypotropia to—very rarely—hypertropia; no horizontal deviation to large exotropia or esotropia; and finally a mixture of horizontal and vertical deviations. Large A-patterns are common, and ocular alignment can sometimes be maintained in a certain gaze with the use of a particular anomalous head posture. Some patients have surprisingly good stereopsis [13]. It is not possible to develop a simplified general surgical algorithm for this complex and variable group of disorders. CFEOM2 cases, on the other hand, consistently present with a very large exotropia with accompanying variable amount of vertical deviation in some cases.

The literature on strabismus surgery for CFEOM generally concentrates on the classical CFEOM1 patient who is relatively easily differentiated from the rest of the CCDDs. Patients have characteristic findings of bilateral significant hypotropia with a variable A-pattern horizontal deviation, large chin-up head posture, and ptosis [14–17]. The strabismic deviation that needs to be treated in such classical cases is the hypotropia that leads to the chin-up head posture. For that reason, most surgeons would perform very large recessions of both inferior rectus muscles, or even leave the muscles unattached to the globe following disinsertion. Simultaneous superior rectus resection or plication and/or superior oblique weakening and/or transposition next to the nasal [14] or temporal [15] side of the superior rectus insertion have been used when more supraduction is needed. The correction of residual horizontal deviations is commonly deferred for consequent surgical interventions.

These general guidelines are less than satisfactory for atypical cases of CFEOM that are different from the classic CFEOM1 phenotype. It has been shown that free disinsertion or very large inferior rectus recession causes unsightly lower lid retraction [15, 16] and amplifies the existing synergistic vertical deviation. Recessions alone without accompanying nasal transposition of the inferior rectus may worsen the A-pattern [16]. Hangback sutures are best avoided because the recessed rectus tends to move back toward its original insertion and some of the effects of surgery may be lost [15]. This particular disadvantage also applies to instances in which adjustable suture techniques are used. It has also been observed that residual positive forced duction test following a recession is best managed by increasing the power of the antagonist, or placing a stay suture at the limbus pulling the eye up, to keep the eye in the desired position instead of increasing the recession of the inferior rectus. A temporary stay suture presumably not only stretches the fibrotic soft tissue toward a desired position but also prevents the recessed muscle from sliding back toward its original insertion if it has not been resutured to the globe [18]. Stay sutures have been left in place from 1 day to several weeks without a consensus regarding an effective duration [16, 19]. A permanent stay suture between the medial rectus insertion and the posterior lacrimal crest, on the other hand, has been successful in exotropic fibrosis cases when very large recessions and resections have failed [16]. Its disadvantage in restricting the lateral visual field is outweighed by the improved appearance in CFEOM2 patients. In exotropic fibrosis cases, suturing the lateral rectus to the lateral orbital wall instead of free disinsertion or large recession of the lateral rectus is preferred and appears to achieve a more lasting effect.

A-pattern strabismus is common in patients with CFEOM; this has been attributed to abnormal supranuclear innervation to the extraocular muscles that creates more esotropia on attempted upgaze in CFEOM [20]; another possible mechanism relates to a tethered inferior rectus, which causes adduction of the globe on attempted upgaze [16]. The A-pattern increases following inferior rectus recession in CFEOM, presumably not only because of an amplification of the above mentioned mechanism, but also due to more prominence of the effects of the superior oblique as the only remaining infraductor, which exaggerates the exotropia in downgaze [15, 16, 20, 21]. So the observation of an increased hypotropia in adduction is a typical finding in cases in which the contralateral inferior rectus has been recessed. Superior oblique weakening is indicated, especially when it is tight, to address both the residual A-pattern and the hypotropia [16].

It has been well documented that recession of a tight inferior rectus in a patient with CFEOM causes a significant lateral shift of the eye in primary position [15, 16, 20, 21]. This should be taken into account in planning surgery for the horizontal alignment. It is probably better to leave the correction of the horizontal deviation to a later surgical intervention after that on vertical rectus and oblique muscles.

Vertical overcorrections in CFEOM have not been reported except from near-complete resolution of elevation in adduction in a few patients who underwent inferior rectus and superior oblique weakening operations [16]. However, horizontal overcorrection can occur in cases in which an augmented surgical dose is used for the horizontal recti for only mild limitation of gaze, or if the significant exotropic drift following inferior rectus recession has not been factored into the surgical plan [16].

Although the strabismus in CFEOM is basically paralytic in origin, the resection of an apparently paralytic and fibrotic muscle can surprisingly result in a gain of the motility range in some cases [8, 14–17]. This finding may suggest that not all muscle fibers are necessarily paralyzed or fibrotic in CFEOM. Plication can be used instead of resection in an attempt to preserve ciliary vessels, because vessel-sparing procedures can be technically more difficult in fibrotic muscles.

Transpositions of the extraocular muscles can be successfully utilized in CFEOM; however, there is unfortunately not enough data other than the occasional case report [16] to analyze the effect of these procedures on alignment and torsion.

We have already mentioned the use of nasal transposition of the inferior rectus in relieving the A-pattern. Superior offsetting of the medial rectus insertion and inferior offsetting of the lateral rectus insertions can also help to address the A-pattern. Superior offsetting of the non-paralytic horizontal muscles can also help the hypotropia; however, medial transposition of paralyzed vertical muscles for an exotropia is not effective. In unilateral cases, horizontal rectus transposition causes less incomitance in downgaze compared to large inferior rectus recession although both procedures may be equally effective in the correction of the hypotropia. For patients who have combined horizontal and vertical deviations without significant A-pattern, horizontal rectus recession and resection with superior transposition can replace or decrease the amount needed for inferior rectus recession in select cases [16].

In patients who achieve a good outcome with regard to head posture and ocular deviation in primary position of gaze, aberrant innervation can remain as the most difficult residual disfiguring motility problem. The aberrant innervation in CFEOM that manifests itself as synergistic vertical divergence is particularly exemplified in excessively recessed inferior rectus cases. Limiting the amount of inferior rectus recession and inferior offsetting of the lateral rectus are recommended for decreasing the impact on motility. There is a suggestion that transposing the resected proximal portion of the superior oblique to the nasal aspect of the superior rectus can potentiate the existing vertical divergence if it is present [16].

Synergistic Horizontal Divergence

Synergistic horizontal divergence is a less common and distinct ocular motility pattern of aberrant innervation in CCDD [10, 11]. In synergistic horizontal divergence, large recessions of the lateral rectus muscles, or their fixation to the orbital wall, may be sufficient in patients with good adduction, whereas resection of the medial rectus muscles or medial transposition of the vertical recti may be needed in those with limited adduction [16]. It has been reported that weakening of the oblique muscles enhances the outcome of horizontal rectus surgery in synergistic horizontal divergence [22].

Möbius Syndrome

Patients with Möbius syndrome typically present with esotropia. There is commonly an associated alphabetical pattern, and occasional vertical deviations. Surgery aims at the correction of the head posture and ocular alignment in primary position of gaze. Attempts at gaining some abduction capacity can be marginally beneficial and carry the risk of overcorrection as well as convergence insufficiency. The medial rectus is usually found to be tight at the time of surgery. Various techniques of weakening the tight medial rectus can be utilized. Among these are basic recession, augmented recession with modifications of hang loose recession, botulinum toxin injection, and appropriate offsetting for associated pattern deviation. Because of similarities to Duane syndrome, Möbius syndrome cases can be managed with single vertical rectus transposition toward the lateral rectus insertion and simultaneous medial rectus recession. The author (ECS) has tried all of these techniques with comparable levels of success; however, the surgical dose must be tailored to the existing amount of deviation. Horizontal overcorrection is possible. Recess-resect procedures can be utilized in patients with residual lateral rectus function. Classic transposition of the vertical muscles to the lateral rectus can also be effective.

Summary

Strabismus surgery is successful in many patients with CCDD in correcting abnormal head positions, and achieving a satisfactory ocular alignment in primary gaze position. Careful evaluation of the motility pattern of the individual patient and customization of surgical interventions are critical for the achievement of the most optimal results (Fig. 55.5).

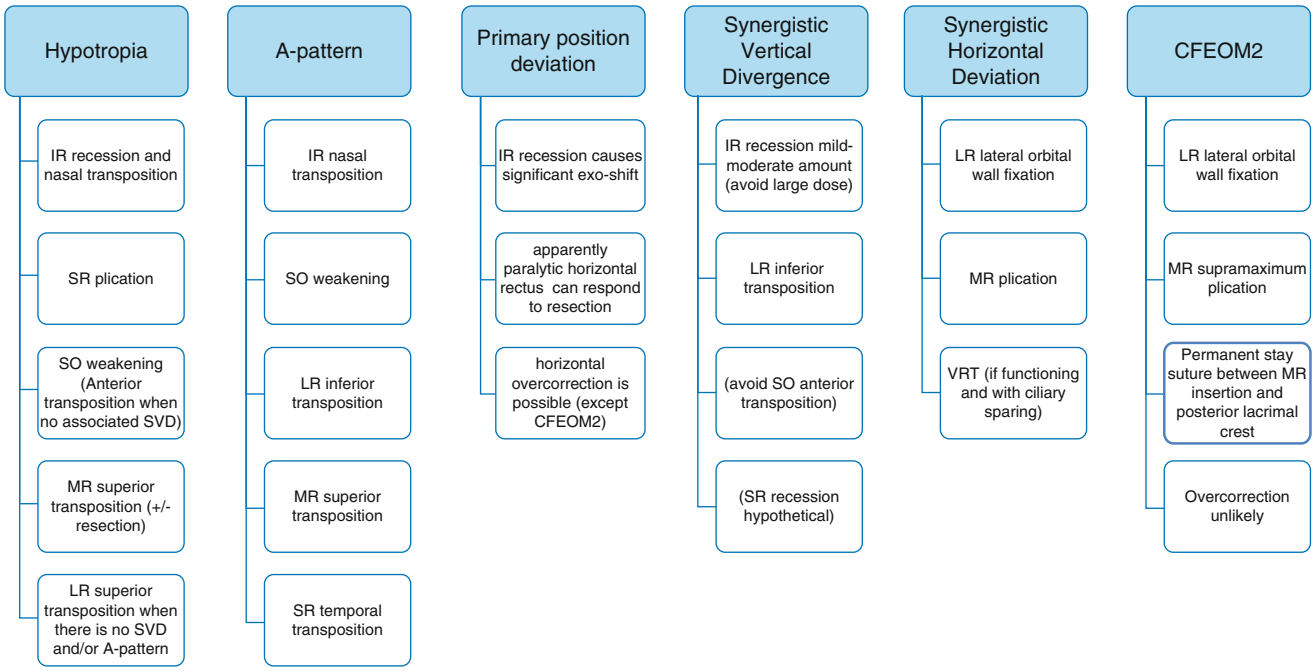

Fig. 55.5 Algorithm for the Evaluation and Management of patients with CFEOMs. This is a simplified algorithm for surgical management for CFEOM cases. Observation of the ductions, versions, the fullness of the saccades, and forced duction test are the mainstay for surgical planning. Stay sutures can be helpful in cases where an antagonist force vector is needed. Refraction and appropriate amblyopia management should be applied for each patient. Ptosis surgery is better postponed until the end of the strabismus surgical sessions unless the eyelids are occluding the visual axis (*IR* inferior rectus, *SR* superior rectus, *SO* superior oblique, *SVD* synergistic vertical divergence, *LR* lateral rectus, *MR* medial rectus, *VRT* vertical rectus transposition)

Case 1

Clinical History

This is a 2-year-old girl with alternating large face turn and chin-up head posture with esotropia and facial paralysis since birth (Fig. 55.3). Developmental history was unremarkable. Peri/prenatal and family history were non-contributory.

On exam uncorrected visual acuity was CSM OU with no fixation preference (CRx: Plano +2.50 × 180° OD and +1.00 + 1.50 × 180°). She had an alternating face turn to right or left 25°. There was 40 PD of esotropia that decreased to 10–15 PD in upgaze and increased to 80 PD in downgaze (V-pattern) along with right DVD or upshoot of 15 PD. On evaluation of extraocular muscles she had a complete abduction deficit on both sides along with a moderate supraduction deficit (−2) on the left.

Impression

This is a case of bilateral Möbius syndrome. Possible management options include:

1. Bilateral medial rectus recessions with inferior offset for V-pattern
2. Bilateral lateral rectus plication or resection for residual esotropia and superior offset for residual V-pattern
3. Single or dual vertical rectus transposition toward the lateral rectus with augmentation suture with or without botulinum injection of the medial rectus of each eye

Management

Examination under anesthesia: Intraoperative forced duction test was +4 for right medial rectus and +3 for left medial rectus, and +2 for both superior recti. Medial recti were recessed with 5.0 nonabsorbable suture. Double needle were passed in the sclera first from 7 mm and then 5 mm for the right eye, and first 8 mm then 4 mm for the left eye from the medial rectus insertions and tied in the middle. Both inferior recti were transposed to the lower insertion of the lateral rectus along the spiral of Tillaux with ciliary vessel sparing.

Rationale

The medial recti were very tight therefore botulinum injection would have been inadequate and the muscles were instead recessed. Large medial rectus recession in these cases causes adduction and convergence insufficiency. Use of the above mentioned modified hangback recession technique with a nonabsorbable suture may

(continued)

overcome this limitation. The large V-pattern could have been addressed with full tendon inferior offsetting of the medial recti simultaneously. Medial rectus recession alone also does not increase the abduction. However, there have been successful reports about the use of superior rectus transposition with medial rectus recession in Duane syndrome. We chose to modify this procedure by transposing the inferior rectus instead of superior rectus toward the lateral rectus insertion in order to gain more abduction capacity and decreasing the V-pattern. Ciliary vessel sparing under microscope was utilized to preserve anterior segment circulation for possible future surgical interventions.

Follow-Up Examination: Two Months After Surgery

Uncorrected visual acuity was CSM OU with no fixation preference. She had a chin-up head posture of 5°–10°. There was bilateral DVD in primary position (right > left) with a very small exotropia (Fig. 55.4). This increased to 10–12 PD of right exotropia and 10 PD of hypertropia on upgaze and 4–6 PD of esotropia on downgaze. Her left supraduction deficit remained the same; however, abduction deficit decreased to −3 on the right and −2.5 on the left (Fig. 55.6). Dilated fundus exam showed 2+ excyclotorsion OU. Alternate patching was started.

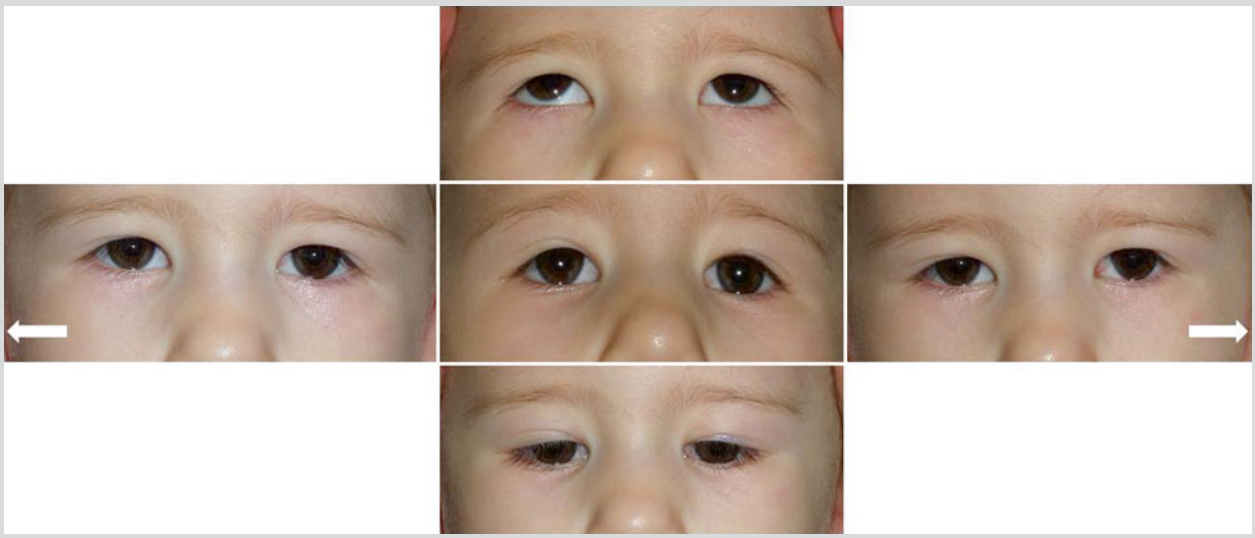

Fig. 55.6 Case 1—Bilateral Möbius syndrome position of gaze postoperatively. Left eye gained small abduction capacity (*arrows* indicate the direction of gaze). V-pattern esotropia improved significantly

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Differential Diagnosis and Management of Hyperdeviations: Non-4th Nerve Palsy—Dissociated Vertical Deviations and Skew Deviations

56

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Abstract

The differential diagnosis and management of dissociated vertical deviation (DVD), inferior oblique overaction (IOOA), and skew deviation are reviewed. As with other types of strabismus, there is no universal consensus on the exact treatment methods of these hyperdeviations. Management is guided by the clinical context and the magnitude and frequency of the deviation. Some patients are observed with optimal refractive correction; others undergo surgical intervention when clinically indicated. Superior rectus recessions are typically performed to treat significant DVD. In cases of DVD with concurrent IOOA, anterior transposition of the inferior oblique insertion may be considered. Primary IOOA, as is commonly seen in association with infantile esotropia, is typically managed with inferior oblique recession or myectomy. In cases of secondary IOOA, correction of the primary problem should be considered in order to control the IOOA. Hyperdeviations that have patterns different from those of a cranial nerve palsy, DVD, or oblique dysfunction are known as skew deviations and are notoriously difficult to manage and may require evaluation with neuroimaging.

Keywords

Dissociated vertical deviation • Inferior oblique overaction • Skew deviation • Hypertropia • Hyperdeviation

Dissociated Vertical Deviation

There is ongoing debate regarding terminology and etiology of dissociated vertical deviation (DVD). In the typical pattern of DVD, the non-fixating eye elevates, excyclotorts, and abducts when the visual axis is occluded and binocular fusion is disrupted. The elevation movement is characteristically the most prominent; however, in certain cases the abduction movement may predominate, historically referred to as dissociated horizontal deviation (DHD), and in other cases the torsional movement may be the dominant one, referred to as dissociated torsional deviation (DTD) [1]. As a result, the term "dissociated strabismus complex" (DSC) has been used to more accurately characterize this entity, realizing that the vertical deviation is only one component of three, yet often the most prominent [1].

DSC is unique in that it does not appear to follow Hering's Law, which states that yoke muscles receive equal innervation [2]. For example, in a true hypertropia, when the vertically deviated eye moves downward to fixate, the fellow, previously fixating eye shifts downward an equal amount into a hypotropic position. When DSC is present, when the vertically deviated eye moves downward to fixate, the previ-

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ously fixating eye does *not* shift downward, thereby appearing to violate Hering's Law.

DSC is observed almost exclusively in patients who lack bi-foveal fusion, such as those with infantile esotropia and is also frequently associated with latent nystagmus. Guyton performed scleral search coil eye movement recordings and showed that latent nystagmus became manifest when either eye was covered and subsequently dampened as the DSC developed [3]. He theorized that DSC is a compensatory mechanism that dampens latent nystagmus, thereby improving visual acuity in the fixating eye [3]. Brodsky, on the other hand, proposed that DSC is a remnant of a primitive light reflex that induces diverging vertical eye movements seen in lower lateral-eyed animals to restore vertical orientation, and may resurface in humans when binocular fusion breaks down [3]. Though many theories exist, the etiology of DSC remains unclear. It appears however, that the tendency to develop DSC is somehow impeded by high-grade fusional mechanisms [1].

As with other forms of strabismus, DSC may be latent or manifest. Recent evidence suggests that patients with infantile esotropia who undergo their first surgery after 24 months of age and have larger angles of esodeviation (>60 prism diopters) are more likely to develop manifest DSC [4]. Regardless, the typical pattern is that the affected eye drifts upwardly on cover testing or during times of visual inattention [5]. DSC is almost always bilateral, although it may be quite asymmetric and can vary in presentation with distance and near fixation [2]. It is particularly difficult to measure as DSC tends to vary in magnitude. Although DSC can be measured with prisms as refixation movements are neutralized, it is frequently recorded on a semi-objective scale from 1+ to 4+ with 1+ being a small angle that only appears with repeated cover testing and 4+ being a large angle, manifest hypertropia [2]. Quantitative measurements have been described based on the use of the simultaneous prism and cover test: grade 1+ = <10 PD; grade 2+ = 11–15 PD, grade 3+ = 16–20 PD, and grade 4+ = >20 PD [6].

The treatment of DSC is guided by the magnitude, frequency (manifest versus latent), and effects of the deviation on the physical appearance of the patient. The concurrent presence of inferior oblique overaction (IOOA) is also considered. Some cases can be managed by optically blurring vision in the preferred fixating eye, forcing the patient to fixate with the eye that has the larger DSC [5]. Some practitioners prefer to treat highly asymmetric DSC by part time occlusion of the eye that deviates less; but this may exacerbate the frequency of DSC in the occluded eye. Other cases are managed surgically (see Fig. 56.1). When the elevation movement predominates, graded superior rectus recession is typically performed as an initial procedure; 4–7 mm superior rectus recession for small DVD and 8–10 mm for large DVD. However, in cases of concurrent IOOA, such as can be observed in association with infantile esotropia, inferior oblique anterior transposition may also be performed. By transposing the inferior oblique insertion anteriorly, its overaction is typically reduced, and its new tethering action on the globe helps decrease the DSC; however, this technique can induce postoperative limitation of upgaze, which becomes most apparent if the surgery is performed unilaterally [1]. For this reason, anterior transposition of the inferior oblique should only be performed bilaterally [1]. This resultant "anti-elevation syndrome" can be minimized, however, by bunching the muscle at its new insertion and

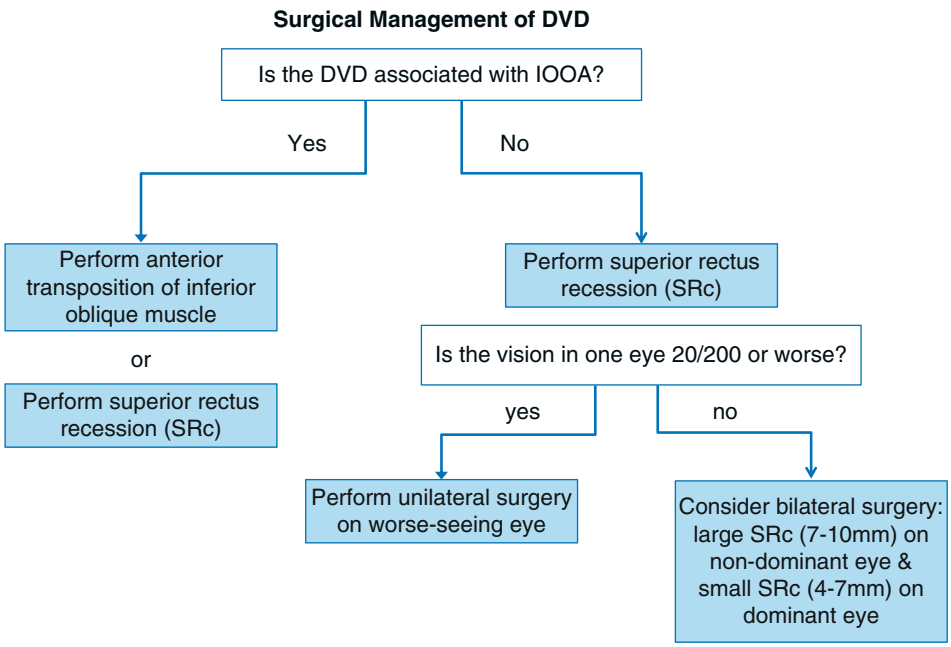

Fig. 56.1 Surgical management of DVD. *DVD* dissociated vertical deviation, *IOOA* inferior oblique overaction, *SRc* superior rectus recession

ensuring that the new insertion site is not anterior to the inferior rectus muscle [7].

It should be kept in mind that unilateral DSC surgery may unmask a DSC in the fellow eye, no matter how asymmetric; therefore, some advocate always doing bilateral surgery whenever treating DSC [1]. However, surgery laterality is debatable. Other surgeons feel that unmasking a DSC in the fellow eye is a rare occurrence, and only operate on the eye with the manifest DSC (even if DSC is detectable on exam in both eyes) with the understanding that they may, on occasion, need to go back and operate on the other eye later on.

Case Example

Case 1 (Table 56.1)

Table 56.1 Case 1

Clinical history	3-year-old male with a history of congenital esotropia status-post bilateral medial rectus recession at age 12 months. Parents do not observe any misalignment.			
Key components of exam	(Linear Allen optotypes)	**OD**	**OS**	
	UCVA	20/40	20/40 (prefers fixation with OS)	
	Ductions/versions	Full	Full	
	Nsc	2+ right DVD with right eye occluded, orthophoria with left eye occluded		
	Dsc	2+ right DVD with right eye occluded, orthophoria with left eye occluded		
			Ortho	
		Ortho	Ortho, 2+ DVD OD	Ortho
			Ortho	
	CRx	+1.25 sph	+1.25 sph	
Management options	• Observation or bilateral superior rectus recession			
Management	Observation			
	Follow-up in 6 months			
Interval history (12 months) *Current age: 4 years*	Parents notice hypertropia of both eyes, especially when tired.			
Key components of exam	**Linear Allen optotypes**	**OD**	**OS**	
	UCVA	20/25	20/25 prefers fixation with OS	
	Ductions/versions	Full OU		
	Alignment Dsc	3+ right DVD with right eye occluded, 2+ left DVD with left eye occluded		
			Ortho	
		Ortho	Ortho, 3+ DVD OD, 2+ DVD OS	Ortho
			Ortho	
	Alignment Nsc	3+ right DVD with right eye occluded, 2+ left DVD with left eye occluded		
Management	• Recommended bilateral superior rectus recession			
Interval history (3 months) *Current age: 4 years*	2 months status-post large 9 mm superior rectus recession on nondominant right eye, and smaller 6 mm superior rectus recession on dominant left eye. Parents report no drifting of eyes. Head position is resolved.			
Key components of exam		OD	OS	
	Ductions/versions	Full	Full	
	Alignment Dsc	Orthophoria		
	Alignment Nsc	Orthophoria		
Management	• Observation			
	• Follow-up in 6 months			

(continued)

Clinical Synopsis

This is a case of DVD without IOOA following bilateral medial rectus recession for infantile esotropia. The patient was initially observed as the deviation was mostly noted upon dissociation during examination. Once the deviation was manifest and noted by the parents (see Fig. 56.2), it was successfully treated with graded bilateral superior rectus recessions.

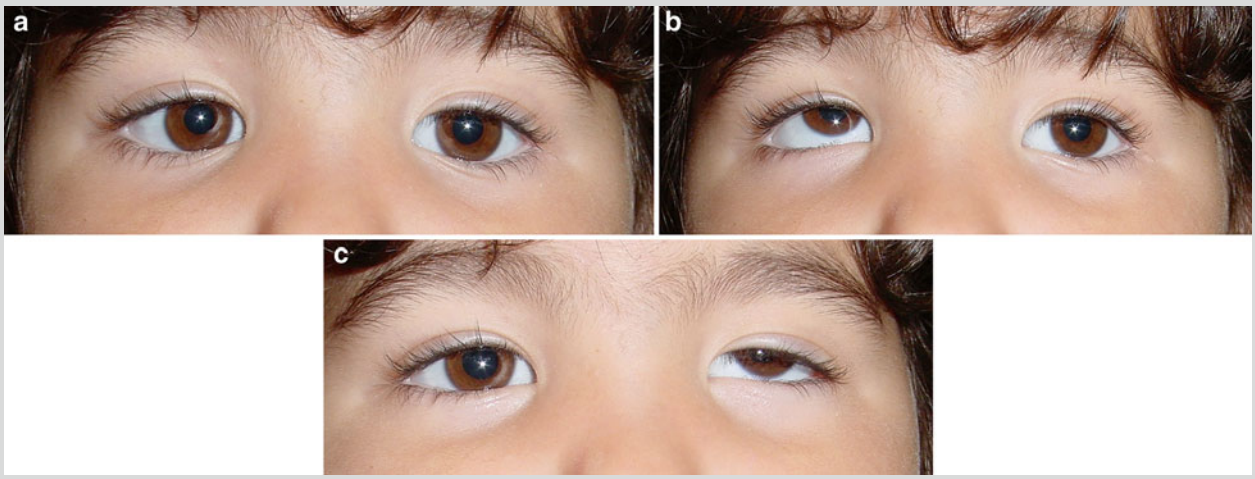

Fig. 56.2 Orthophoria in primary position with both eyes fixating (**a**). Manifest right DVD with left eye fixating (**b**). Manifest left DVD with right eye fixating (**c**)

Inferior Oblique Overaction

Overelevation of the eye in adduction, regardless of etiology, is typically termed IOOA. Its presence is confirmed by observing a hypertropia in adduction on cover testing. IOOA may be primary or secondary. Primary IOOA frequently occurs in association with infantile strabismus and is typically bilateral. IOOA may also occur secondary to paresis of its ipsilateral antagonist, the superior oblique muscle [1]. Alternatively, IOOA may occur secondary to restriction of elevation in the fellow eye, such as can be seen with thyroid eye disease or orbital floor fractures [1]. In cases of secondary IOOA, correction of the primary motility abnormality should correct the IOOA. However, in some cases of secondary IOOA, surgery on the inferior oblique alone will correct the hypertropia, such as in certain cases of superior oblique palsy [8]. Primary IOOA may be treated with inferior oblique recession or myectomy; both procedures have yielded a similar success rate [9]. Anterior transposition of the inferior oblique may be considered in cases with concurrent DVD (*vide retro*).

Case Example

Case 2 (Table 56.2)

Table 56.2 Case 2

Clinical history	6-year-old healthy boy with history of congenital esotropia treated with bilateral medial rectus recession at age 12 months. After surgery, he was orthophoric and was being followed every 12 months. His mother notices that occasionally one eye will "wander," but is not sure which one.			
Key components of exam	Snellen linear	OD	OS	
	UCVA	20/25	20/25	
	Versions	2+ elevation OD with left gaze		
		1+ elevation OS with right gaze		
	Ductions	Full	Full	
	Nsc	Orthophoria (CT/ACT)		
	Dsc	2+ right DVD with right eye occluded, orthophoria with left eye occluded		
			Ortho	
		1+ IOOA OS	Ortho, 2+ DVD OD	2+ IOOA OD
			Ortho	
	CRx	+1.25 sph	+1.25 sph	
Management options	• Observation, strabismus surgery			
Management	Elected to observe with interval follow-up of 6 months. Rationale: although he does have bilateral inferior oblique overaction (IOOA) with a right DVD, there is no compensatory head position or hyperdeviation in primary. Moreover, the parents do not notice any misalignment.			
Interval history (6 months) ***Patient age: 6 ½ years***	Mom states she notices eye drifting upward frequently (mostly the right eye). She feels like kids at school are starting to notice and tease him.			
Key components of exam		OD	OS	
	UCVA	20/25 (Snellen)	20/25 (Snellen)	
	Versions	3+ elevation in adduction OD, 1+ elevation in adduction OS		
	Alignment Nsc/cc	3+ right DVD with right eye occluded, orthophoric with left eye occluded		
	Alignment Dsc/cc	3+ right DVD with right eye occluded, 2+ left DVD with left eye occluded		
			Ortho	
		1+ IOOA OS	Ortho, 3+ DVD OD, 2+ DVD OS	3+ IOOA OD
			Ortho	
Management options	• Observation			
	• Inferior oblique recession			
	• Inferior oblique anterior transposition			
	• Superior rectus recession			
Management	Parents elected for surgery. Bilateral inferior oblique anterior transposition was selected to simultaneously treat the IOOA and DVD.			
Interval history (6 months) ***Age 7 years***	4 months status-post surgery. Mom no longer notes eyes drifting. Incisions are well healed.			
Key components of exam		OD	OS	
	UCVA	20/25	20/25	
	Ductions	Full	Full	
	Versions	Full OU		
Management	Observation with follow-up every 6 months			

(continued)

Clinical Synopsis

This is a patient with IOOA and concurrent DVD. This patient previously underwent bilateral medial rectus recessions at 12 months of age for infantile esotropia. The parents noted progressive hyperdeviation of the eyes, first when in lateral gaze, but later progressing to include primary gaze. This patient had a satisfactory outcome after bilateral inferior oblique anterior transposition. Despite the asymmetry of measurements, bilateral surgery was performed for two reasons: (1) to avoid limitation of upgaze and (2) to avoid uncovering of DSC in the originally less affected side, both of which may occur with unilateral surgery [1].

Skew Deviation

A skew deviation is a form of vertical strabismus caused by supranuclear lesions that often lead to hypertropia, ocular torsion and abnormal head posturing [10]. Importantly, skew deviations may be the initial manifestation of brainstem, cerebellar, or peripheral vestibular disease such as strokes, tumors, or demyelinating disease [10]. Diagnosing skew deviation can be a challenge. Strictly speaking, a skew deviation is an acquired vertical deviation, the pattern of which is inconsistent with DSC, inferior oblique dysfunction or palsy of one or more cyclovertical muscles, without any evidence of mechanical restrictive cause by clinical exam or history. To add to the complexity of diagnosis, a skew deviation can sometimes mimic isolated cranial nerve palsy such as a trochlear nerve palsy; however, there is paradoxical incyclotorsion of the hypertropic eye on head tilt toward the hyperdeviated side [10]. In these cases, the "upright-supine test" can be used to distinguish the two. It is performed by measuring vertical alignment using prism and alternate cover testing, and then measuring torsion using double Maddox rods first with the patient upright, then repeating it with the patient supine [10]. If the vertical deviation decreases by ≥50 % from the upright to supine position, then skew deviation is diagnosed [10]. Skew deviation also frequently presents with other associated neurological signs such as gaze palsy, dysarthria, ataxia, and hemiplegia, which is not typical of isolated trochlear nerve palsy [10].

Once skew deviation is diagnosed, work-up should include MRI of the brain with contrast to evaluate for lesions in the brainstem, cerebellum, or diencephalon [10]. Managing diplopia in these patients can be a challenge, and binocularity in primary gaze is difficult to achieve. Depending on the size of the vertical deviation, prism therapy may be offered vs. surgical correction. Since the presentation of skew deviation is so variable, there is no "cookbook" surgical plan for these patients, and it remains unique to each individual.

Case Example

Case 3 (Table 56.3)

This is an example of a typical presentation of a patient with a skew deviation. Many of these patients will present to their eye care professional with a small new onset diplopia, but will fail prism therapy. The Parks 3-step test may indicate a palsy of the right superior oblique muscle (See Fig. 10.1, Chap. 10). However, fundus exam shows incyclotorsion of the hypertropic eye, which is the opposite of what we would expect with paresis of the right superior oblique. Given these findings, a brain MRI was ordered and showed a small thalamic stroke. The options of observation or right superior rectus recession with a half-tendon width nasal transposition to address the torsional component were discussed with the patient. He was cautioned that he may still have diplopia after the surgery. The patient elected for surgical correction and there was a good outcome.

(continued)

Table 56.3 Case 3

Clinical history	76-year-old male with a history of hypertension presents with vertical diplopia for the last 6 weeks. He was initially treated with prisms by his optometrist, but is still having diplopia. His wife has noticed that he has been tilting his head to the left while watching TV recently.			
Key components of exam		**OD**	**OS**	
	BCVA	20/25	20/25	
	Ductions/versions	Full	Full	
	Nsc	Right hypertropia		
	Dsc	Right hypertropia that worsens with left gaze and right head tilt		
			5 RHT	
		4 RHT	6 RHT	12 RHT
			6 RHT	
		R tilt: 10 RHT		
		L tilt: 4 RHT		
	Fundus	Incyclotorsion of right eye		
Further history	After performing a thorough review of systems, the patient reflects that several weeks ago he felt a little off-balance and "clumsy" on his feet. This lasted for a few hours and then resolved. The diplopia, he thinks, started shortly afterwards.			
Work-up	• Upright-supine test shows a decrease in vertical deviation by ≥50 % from the upright to supine position			
	• MRI with gadolinium shows a small thalamic stroke			
Management options	• Observation for 6 months or eye muscle surgery			
Management	1.5 mm right superior rectus recession with half-tendon width nasal transposition after no improvement for 6 months			
Interval history (1 month post surgery)	Over all, patient's diplopia is much improved and his head tilt has resolved			

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Approaches to Strabismus Reoperation

57

Marina A. Eisenberg and Monte A. Del Monte

Abstract

Patients with strabismus who have undergone previous eye muscle or other extraocular or orbital surgery often present a challenge to strabismus surgeons. The general guidelines used in routine strabismus cases cannot always be applied to these patients and need to be strategically modified to assist in the preparation of an optimal surgical plan. A thorough knowledge of several key surgical principles or pearls can help guide the surgical decision-making process in these often complex and unpredictable situations.

Keywords

Strabismus reoperation • Forced ductions • Scar tissue dissection • Slipped muscles

The Problem

Patients with strabismus after eye muscle or other ocular surgery often present without operative records. The treating physician is left to deduce the nature of the original deviation, what surgery was completed on which eye(s) or muscles, as well as the current location of the insertion of previously operated extraocular muscles. Moreover, the surgeon must also anticipate and deal with restrictive scar tissue or hardware that has been applied to the outside of the eye. All this requires a thorough understanding of the pathogenesis of the strabismus and flexibility in surgical approaches. The flowchart in Fig. 57.1 summarizes the evaluation and management of strabismus in patients with prior surgery.

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Evaluation and Diagnosis

Obtaining a history in patients with previous strabismus surgery can be difficult as some were too young to recall the type of deviation or surgery and others may simply not remember the nature of the original deviation or which eye underwent surgery. It is often surprising how little patients and even their parents remember about the diagnosis and type of strabismus surgery performed in early childhood. The surgeon must consider the recalled history as possibly being inaccurate. Ideally, the physician would need to determine from medical records the cause and type of original deviation, nature and results of previous surgery, history of onset of the current deviation, and any past or current medical problems. Unfortunately, medical and surgical records are often not available. Examination of the conjunctiva surrounding extraocular muscles and their insertion sites at the slit lamp or with a handheld light can also provide clues to the locations of previous surgeries.

The physical exam should begin with measurement of best-corrected visual acuity in each eye, current refractive correction and prism power (if any is ground into the glasses),

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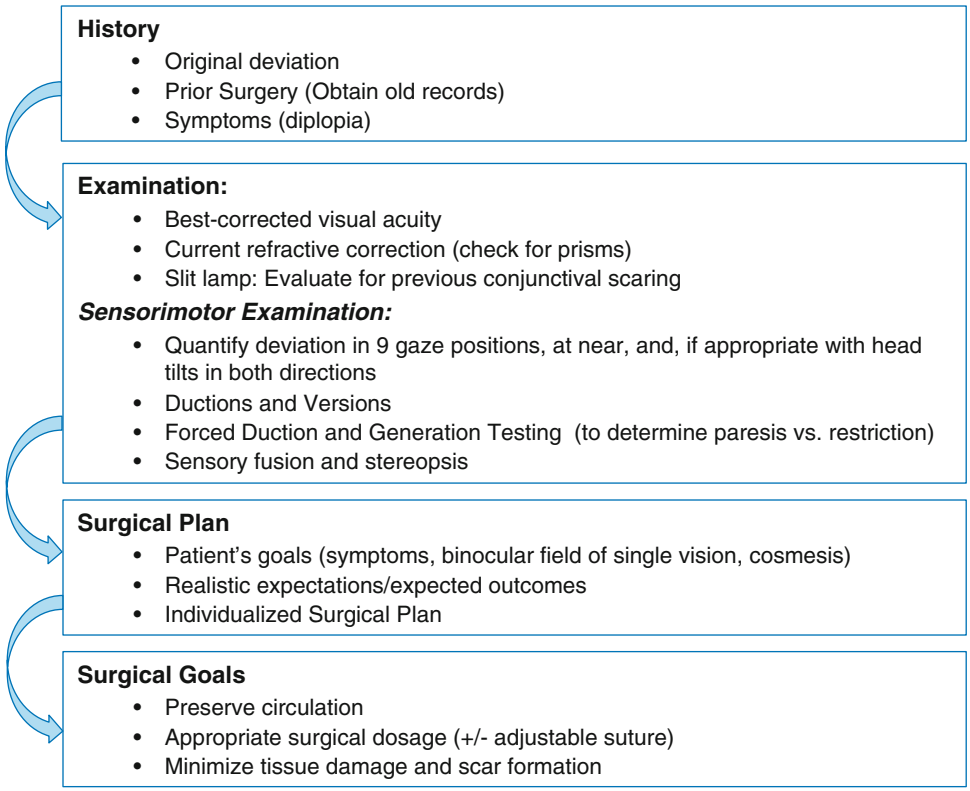

Fig. 57.1 Algorithm of the general approach to a patient with incomitant strabismus and a history of prior eye muscle or periocular surgery or trauma

pupillary reaction, and slit lamp examination as described previously to identify signs of previous surgery. Motor function is evaluated beginning with careful observation for any abnormal head positioning or obvious misalignment of the eyes. Ductions and versions are tested to detect motility limitations as deviations in far peripheral gazes may be missed with simple standard measurements. Documentation of detailed horizontal and vertical ocular misalignment, measured with prism cover test and alternate cover test is preferred in all nine diagnostic gaze positions, right and left head tilts and at near with the patient wearing the appropriate refractive correction. In cases of incomitant strabismus, the clinician must pay careful attention to the fixating eye and primary versus secondary deviations (see Chap. 1). In addition, if a cyclovertical deviation is noted, the presence and nature of any ocular torsion must be assessed by fundus evaluation or double Maddox rod testing (see Chap. 1).

Patients suspected to have restrictive or paralytic strabismus can be further evaluated with passive forced duction and active force generation tests in the office with local anesthesia or in the operating room under general anesthesia.

Forced Duction Testing

In this procedure, the eye to be tested is grasped gently with a single 0.5 mm Castroviejo forceps on the opposite side of the cornea in the clinic or on both sides of the cornea 90° away from the gaze position to be tested in the operating room [1]. Exaggerated forced ductions are also useful in some situations to help determine the degree and nature of restriction. These place the eye in a position where the muscle being tested is on maximum stretch, therefore exaggerating any restriction. For superior, medial, inferior, and lateral rectus muscles, this is accomplished by grasping the globe with 0.5 mm forceps at the limbus 180° away from the muscle to be tested and gently lifting the globe up prior to rotating it in the direction of interest. For the oblique muscles, David Guyton has described an exaggerated forced duction technique referred to as the *Guyton Exaggerated Forced Duction* test [2]. In this test: (1) the eye is extorted for the superior oblique and intorted for the inferior oblique; (2) the eye is then depressed or pushed maximally into the orbit to stretch the oblique muscles; and (3) to test the superior oblique, the globe is then gently rocked from the inferonasal toward the superotemporal aspect allowing the surgeon to assess the degree of tendon tightening, a sort of "flipping" or "seesaw" sensation, as the superior oblique tendon slides over the globe in its most stretched position (Fig. 57.2) [2, 3].

Force Generation Testing

A similar technique can be used to test for active force generation, in which case a patient is asked to move his or her eye while the assistant grasps the limbus with a 0.5 mm forceps (Fig. 57.3) [3]. To maximize patient comfort during this test, a Suction Duction Device (Fig. 57.4) can be used to test

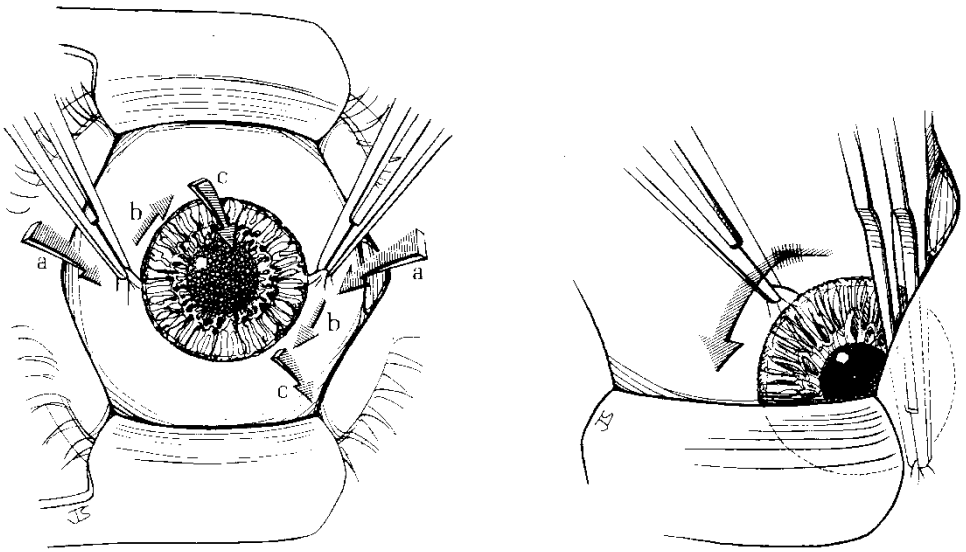

Fig. 57.2 Proper technique for performing exaggerated forced ductions for left superior oblique muscle as described by Guyton. The eye is grasped at limbus 180° apart (*a*) and intorted 45° (*b*) and then the superonasal forcep is depressed posteriorly into the orbit to maximally stretch the superior oblique tendon (*c*). Finally, the Inferotemporal forcep is rocked from infero nasal to superotemporal resulting in feeling a seesaw tightening and loosing of the temporal forceps as the superior oblique tendon "flips" over the surface of the globe (Reprinted with permission from Del Monte M. Superior Oblique Muscle Surgery, Atlas of Pediatric Ophthalmology and Strabismus Surgery, page 95, figures 8-1 and 8-2) [3]

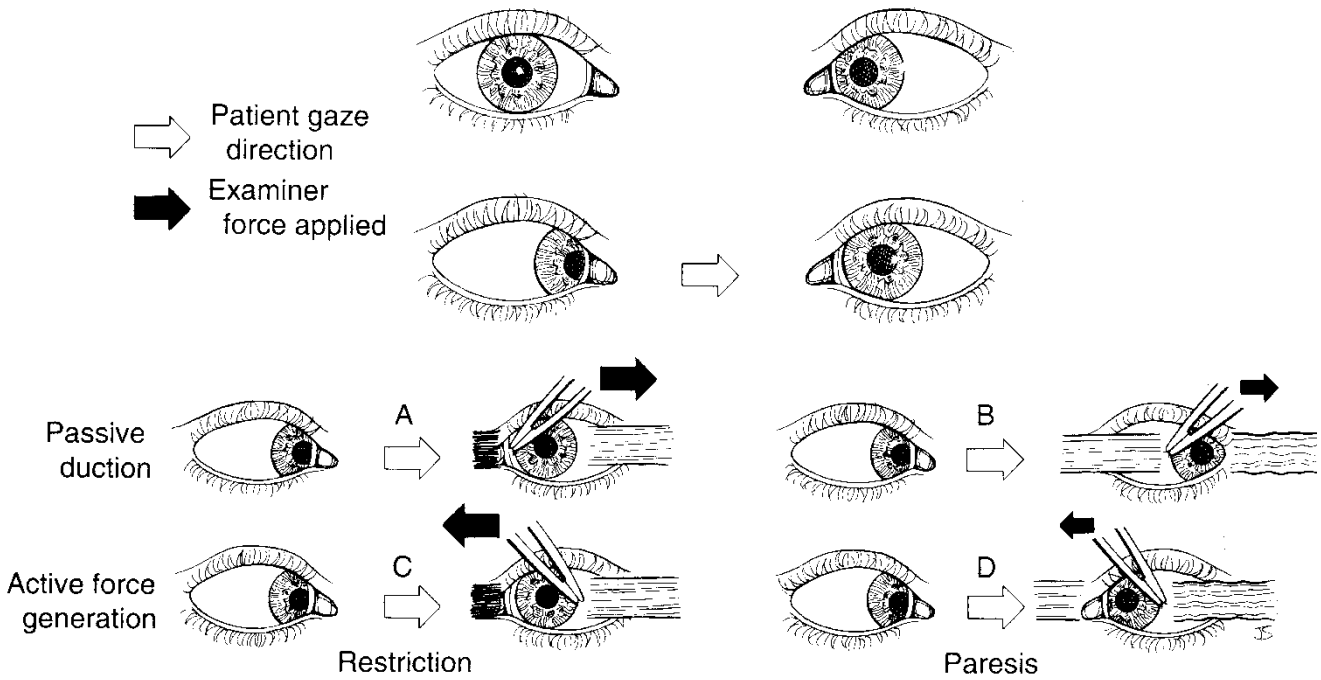

Fig. 57.3 Schematic method of passive forced ductions and active force generation testing in patients with paretic and restrictive strabismus. Part I: Demonstrates a patient with left esotropia and inability to abduction left eye past midline. Part II: Passive Ductions: With topical anesthetic applied in the eye, the examiner grasps the limbus 180° away from the intended direction of gaze (*A*) and gently moved into the abducted position until resistance is appreciated (*B*). In this example, passive forced ductions appear to be grossly full. Active Force Generation: With topical anesthetic applied in the eye, the examiner grasps near the limbus on the side of the intended direction of gaze (*C*). The patient is asked to look to the left while the examiner gently resists eye movement in that direction and subjectively grades the amount of force generated by the muscle (*D*). In this example, the patient is unable to generate a force to look left demonstrating paresis of the lateral rectus muscle (Reprinted with permission from Del Monte M. Strabismus Surgery Planning, Atlas of Pediatric Ophthalmology and Strabismus, page 3, figure 1-1) [3]

Fig. 57.4 Illustration of the use of the Suction Duction Device in the evaluation of passive forced ductions or active force generation. Photograph of the suction device demonstrating the gentle suction cup and attached bulb (**a**). The bulb is compressed as the device is placed onto an anesthetized cornea (**b**) and then released to create suction to the surface. At this point, the device is stable on the surface of the eye such that the examiner does not have to hold onto the handle. Passive forced ductions can be checked by manually moving the suction cut in the various positions of gaze (**c**). Active forced ductions can be tested as well by providing resistance as the patient moves the eyes in various positions of gaze (not pictured)

passive forced ductions and active force generation in the office. To perform ***suction duction testing***: (1) topical anesthetic drops are instilled and a Suction Duction Device is applied directly to the eye while the bulb is squeezed; (2) as the bulb is released the device gently adheres to the scleral/limbal area of the globe as a vacuum is created; (3) the examiner then asks the patient to look in the direction of interest and subjectively estimates the force required to move the globe into the field of action of the tested muscle. The examiner can test active force generation by asking the patient to look in various directions while applying gentle resistance to the movement of the eye by holding the device and assessing the force generated against the examiner's resistance to pull. Testing both forced ductions and active force generation in this manner allows the examiner to differentiate a paralytic muscle from a restricted muscle with normal force generation. Since forceps are not required, this test is much better tolerated by the patient, and avoids tearing the conjunctiva and causing a subconjunctival hemorrhage [3–5].

Surgical Planning

After completing a physical exam in the office, it is important to reevaluate all the measurements. The clinician must take into account the patient's expectations for symptom relief, range of binocular visual field and cosmesis, and discuss risks and benefits of potential surgical options and realistic outcomes to develop an individualized surgical plan.

One of the most common limitations of surgery in patients with incomitant strabismus is the inability to achieve binocular single vision in all fields of gaze. The most important goal for the majority of patients is fusion with single binocular vision in primary gaze and in reading positions of gaze. It is important to consider specific professional or leisure activities that may require or benefit from alignment correction in other fields of gaze. Designing a surgical plan that addresses specific patient needs will aid in creating a trusting relationship between physician and patient, alleviate patient anxiety and achieve best patient satisfaction. It is critical to discuss realistic goals and potential adverse outcomes with each patient so he/she fully understands the risks, benefits, and limitations of any planned surgical treatment.

When planning surgery on patients with prior strabismus surgery, it is often tempting to operate on fresh or previously un-operated muscles because that approach is believed to produce the most predictable results. However, each strabismus case should be evaluated objectively and individually. In patients with consecutive deviations, the observation of lag/limitation of action in a previously recessed muscle or restriction in a previously resected muscle can help guide the surgeon to operate on the muscle or quadrant causing the problem to prevent the deviation from recurring. On the other hand, in cases of recurrent deviations, previously untouched contralateral muscles can often be targeted, assuming no significant motility limitations or incomitance. During the preoperative evaluation, the muscles that had been previously operated should be carefully evaluated for restriction using ductions, versions, as well as forced duction testing. If evidence of previous surgery on a muscle(s) is noted, some strabismus surgeons have suggested that operating on the muscle whose action is most compromised yields the best results, even if that means moving a previously operated muscle [3]. Examples where this would apply include operating on the medial rectus muscles if an esotropia is greater at near or lateral rectus muscles if an exotropia is greater at distance. Finally, it is important to remember that exploring a muscle to remove surrounding restrictive scarring and the measurement of the current location of its insertion relative to the limbus, with or without changing its position on the globe, can also aid in surgical planning intraoperatively.

The amount of surgery varies by muscle, procedure, alignment, fusion potential, and prior operation. The effect of surgery on previously operated muscles can be difficult to predict. Although the surgical dosing tables published by Marshall Parks [6] and modified by others [3] can be helpful as a guide, significant modifications may be required in cases involving reoperations [3]. Resection amounts listed in Parks' table tend to produce a somewhat larger effect than predicted in eyes, where the antagonist muscle has been recessed significantly. Re-recessions also tend to produce slightly larger effects than predicted by the table. Advancement of previously recessed muscles produce a smaller effect than predicted by the table making resection followed by advancement of a previously recessed muscle very powerful in strengthening previously recessed muscles. On the other hand, recessing previously resected muscles produces a larger effect than expected and the table numbers should be adjusted accordingly.

Determining the best location for muscle placement can also be accomplished intraoperatively if preoperative history and examination are ambiguous. In cases of reoperations on previously resected muscles, one approach to further resection involves gently stretching the muscle to the point, where its resistance increases sharply [3]. The length of muscle where this loss of elasticity occurs corresponds to just over the maximum amount of safe resection.

Another approach recommended by some strabismus surgeons has been to disinsert restricted, scarred, or contracted extraocular muscles from misaligned eyes, return the globe to primary position, and then intraoperatively reattach the released muscles on the globe in a relaxed/unstretched muscle position, even if the other eye is not in primary gaze while under anesthesia. This technique has been recommended in patients with thyroid eye disease [7] and in patients with consecutive exotropia [8].

Surgical Approach

In addition to the need for individualizing a surgical plan based on the physical exam and patient goals, reoperations present other challenges not typically encountered in routine strabismus surgery. A detailed knowledge of orbital anatomy and physical principles guiding extraocular movements allows the strabismus surgeon the best opportunity to achieve desired results.

The first challenge of reoperations lies in dealing with the conjunctiva and its contribution to anterior segment blood supply. Older people (above approximately age 50–60 years) tend to have thinner, more friable conjunctiva that is easy to inadvertently tear during routine manipulation. Patients with prior eye surgery may have scarring in unusual places making it difficult to handle the conjunctiva without creating a "buttonhole." For example, prior strabismus surgeries using a limbal conjunctival approach tend to have scarring anterior to the previously operated muscle and sometimes have scarring all the way to the limbus. Prior glaucoma drainage device or filtering procedures and retinal detachment surgery with scleral buckles may also produce significant scar tissue near the limbal area or around the muscle and scleral buckle/drainage device. Blebs from prior glaucoma surgeries must be carefully avoided during strabismus operations to prevent leakage and softening of the globe or postoperative scarring and loss of the bleb. Conjunctival shortening or loss from prior procedures can also limit surgical approaches. In some cases, free conjunctival grafts from the fornix area and around the canthi of the operative or fellow eye can aid in difficult conjunctival closure of surgical sites.

There are two recommended surgical conjunctival incision sites that can be considered for a reoperation. A properly performed two-plane self-closing fornix incision is technically the more difficult of the two approaches and usually requires a skilled assistant. The fornix incision is placed in the relatively avascular areas in between the extraocular muscles, approximately 8 mm posterior to the limbus and parallel to the eyelid margins. This consists of a two-plane incision, the first through the conjunctiva and the second perpendicular to the first through Tenon's capsule. The utility of this approach in reoperations is that it is relatively simple to find and hook operative muscles from the side without getting into scarred areas located around and anterior to the muscle insertion. Placing the muscle on stretch with a hook allows for a controlled dissection of scar tissue without the risk of inadvertent transection of the muscle. As a general rule, it is best to avoid blunt or sharp dissection toward a muscle without having it securely located on a hook. The fornix approach also allows for relatively easy closure and, compared to a limbal incision, promotes less scar formation, less adhesion of conjunctiva to muscle, and less compromise of limbal anterior segment circulation. When sutures are required, the lid covers the area well, limiting patient discomfort. Furthermore, each fornix incision can be used to access two or three muscles and each muscle can be accessed via at least two different incisions, helping minimize conjunctival trauma and preserve periocular vasculature in surgeries with multiple muscle involvement.

Limbal incision approaches provide better exposure of the surgical field and place less strain on the conjunctiva in cases with friable tissue or significant conjunctival scarring. The incision consists of a 4-clock hour limbal conjunctival incision, flush with the limbus and one or two relaxing incisions at each side carried radially posteriorly into the areas between the muscles. Although the limbal incision is technically easier to perform, it always requires suture closure at the limbus, sometimes creating patient discomfort. However, unlike the fornix-based incision, the limbus-based incision

allows for conjunctival recession if scarred conjunctival restriction is noted during the surgery. In some cases, prior surgery, especially with conjunctival recession, leaves bare sclera due to lack of overlying conjunctival tissue. If encountered, it is acceptable to approach the muscle through the defect instead of creating a new incision, if it minimizes strain on the conjunctiva.

Once the conjunctiva is opened, the muscle should be isolated prior to dissecting scar tissue. This is usually accomplished with a combination of a Stevens and Jameson hooks. With the operative muscle secured on a Jameson hook, direction of the muscle tension is documented to be appropriate for the muscle in question, and the tissue is carefully inspected for signs of imbedded muscle fibers so that overlying scar tissue can be gently cleared anterior to the muscle. In cases of prior recessions, a band of scar tissue often forms between the original insertion and Tenon's capsule/conjunctiva overlying the area. It is easy to assume that this adhesion at the original insertion (pseudotendon) is the actual muscle. To avoid this mistake, the surgeon should carefully explore posteriorly with a Stevens hook, as the true insertion is generally the most posterior adhesion to the sclera. The area between the pseudotendon and the actual tendon may contain looser adhesions which need to be cleared with combination of blunt and sharp dissection with Wescott scissors to create space for cutting the pseudotendon. Once the area behind the pseudoinsertion is cleared Wescott scissors are opened and inserted under the conjunctiva such that the pseudotendon band lies between the blades, which are then pressed firmly against the sclera and closed to shave the pseudotendon flush with the sclera. In cases of prior resections, there is usually some scar tissue anterior to the muscle insertion; however, the insertion area may be adherent to the conjunctiva/Tenon's complex, requiring gentle dissection of the overlying tissues. In recessions and resections, the muscle insertion frequently appears widened in the anterior/ posterior direction. Generally, tissue at the anterior aspect is mostly scar tissue whereas the actual muscle insertion tends to lie most posteriorly. Once cleared of overlying scar tissue down to white tendon or pink muscle fibers, the muscle can be further isolated from the surrounding scar. Importantly, the tissue attached to the sclera may not be true muscle but instead stretched scar or empty muscle capsule if a slipped muscle is present and each requires specific measures to correct (see Chap. 60).

Separation of the muscle from scar tissue and Tenon's capsule located posterior to the insertion can also be a challenge in reoperations. The most vital part of this step is to keep the muscle tightly stretched on the hook and gently lift away any loosely adherent scar tissue surrounding the muscle while dissecting as close as possible to the surface of the muscle. Occasionally adjacent muscles may be somewhat entangled in the scar tissue (inferior oblique and lateral rectus or superior oblique tendon and superior rectus), so care must be taken to completely separate them while avoiding transection during this process. Again, the direction and orientation of the muscle fibers or tendons is very helpful in identifying and correcting this problem.

Placing a suture to secure the muscle can also be difficult in patients with prior strabismus surgery. The muscle may have a pseudotendon or stretched scar surrounding its insertion. Care should be taken to identify and incorporate solid pink striated muscle tissue or dense white tendon into ample suture lock bites to help avoid muscle slippage. The size of the lock bites at either end of the suture should be adequate to firmly hold muscle tissue or tendon.

To reattach the muscle to sclera, adequate depth of scleral passes should be accomplished. To help achieve this, it is important to carefully clear the sclera in all possible adherent scarring and fibrous tissue over any potential reattachment site (for adjustable sutures along the entire muscle path) to prevent the muscle from reattaching to this tissue, which is prone to stretch rather than to true sclera.

Proper conjunctival closure over the surgical area is important for patient comfort, cosmesis, and the prevention of new restrictive scarring and adhesions. In cases where limbal incisions are used, the conjunctiva should be sutured with fast absorbing gut with buried knots in interrupted or running locking fashion for maximum wound closure and patient comfort. A properly placed two-plane fornix incision can be self-closing and sutures may only be necessary if there is wound gape from conjunctival shortening. In such situations, extra tissue may be freed posteriorly and brought anteriorly to cover any defects that cannot be repaired with simple closure. If there is significant conjunctival scaring, inappropriate tissue forces should be redirected in a circumferential rather than radial direction to help prevent conjunctival contracture from causing mechanical restriction. Any extra Tenon's capsule protruding through the wound should be trimmed to avoid creation of postoperative Tenon cysts. As a general rule, secure suture closure of all conjunctival incisions is indicated if any hardware is present around the eye, such as scleral buckles or glaucoma drainage devices.

Another method to reduce uncertainty of outcomes and improve success rates is to utilize adjustable sutures for challenging and unpredictable cases. The utility of adjustable sutures in strabismus surgery, whether involving reoperation or fresh muscles continues to be controversial, without a clear consensus or randomized control trials [9]. However, most current studies have demonstrated at least some benefit of the use of adjustable sutures. In a non-randomized comparison study between adjustable and nonadjustable strabismus sutures, Tripathi et al. showed that adjustable sutures produce better postoperative outcomes and higher patient satisfaction [10]. Success of adjustable sutures requires experience and accurate prediction of likely postoperative

Table 57.1 Guidelines for optimal immediate postoperative alignment in patients with different preoperative conditions, types of surgery especially valuable when using adjustable sutures in these patients

Diagnosis	Fusional potential	Operation	Adjustment goal
Accommodative esotropia	Yes	Bilateral medial rectus recession	0–5$^{\Delta}$ XT
Nonaccommodative esotropia	Yes	Recess/resect	4–6$^{\Delta}$ XT
Nonaccommodative esotropia	No	Recess/resect	5–7$^{\Delta}$ ET
Thyroid myopathy	Yes	Medial rectus recession	4–6$^{\Delta}$ XT
Intermittent exotropia	Yes	Bilateral lateral rectus recession	8–10$^{\Delta}$ ET
Basic exotropia	Yes	Recess/resect	4–6$^{\Delta}$ ET
Basic exotropia	No	Recess/resect	5–10$^{\Delta}$ ET
Thyroid myopathy vertical deviation	Yes	Inferior rectus recession	6–10$^{\Delta}$ undercorrection
Nonmyopathic vertical deviation	Yes	Vertical recession	0–5$^{\Delta}$ undercorrection
Nonmyopathic vertical deviation	Yes	Vertical resection	0–5$^{\Delta}$ overcorrection
Palsy, trauma, mechanical	Yes	Depends on diagnosis	Maximize central binocular field
Sensory esotropia	No	Recess/resect	5–10$^{\Delta}$ ET
Sensory exotropia	No	Recess/resect	6–8$^{\Delta}$ ET

Reprinted with permission from [3]

XT exotropia, *ET* esotropia

alignment drift so adjustment goals can be individualized. Many times orthophoria is not the short-term goal of adjustable sutures immediately after surgery because it is natural for patients to experience some alignment drift during the healing process. Although the exact amount or direction of drift may be unpredictable in some cases, factors such as type and size of deviation, etiology, fusion potential, and type of surgery can help surgeons anticipate how initial postoperative results may change during the healing process. Table 57.1 [3] has been used by the authors and provides some general guidelines on adjustment goals for various procedures.

Special Surgical Considerations

Two special situations involving reoperation in strabismus surgery deserve mention:

Slipped and Lost Muscles

Occasionally, patients present with significant under or overcorrection after strabismus surgery caused by a slipped or "lost" muscle [11]. During surgery, muscles can be "lost" acutely by traumatic or iatrogenic inadvertent transection. In the case of a slipped muscle, initial alignment immediately after surgery is often good but changes in the first several days or weeks after surgery with rapidly increasing under or overcorrection associated with markedly decreased duction and widening of the palpebral fissure on attempted movement of the eye into the field of action of the affected muscle. In either case, the best motility results are obtained by recovering the slipped or lost muscle and reattaching it to the sclera rather than by transposition of other muscles to replace the lost forces. It is important to remember that a muscle is never truly "lost." In a "slipped muscle," which occurs because the original surgical suture bites were too superficial and locked into muscle capsule instead of into muscle tissue, an avascular translucent capsule is attached to the intended insertion site. The surgeon can follow it posteriorly and the true muscle tissue which is usually identified as a thickening of the empty capsule with pink muscle tissue. Once true muscle fibers are identified, they should be carefully secured with sutures to reattach to the sclera. If no pseudotendon is attached at the globe, as in cases of a "lost" or transected muscles, the distal muscle can be located by following the anatomy of the muscle path; the transected muscle stump can be located attached to the muscle pulley (found as a thickened slit in the global surface of Tenon's capsule) by the insertion of the orbital layer of the muscle into the pulley as demonstrated by Demer et al. [12]. By following the global surface of Tenon's capsule rather than the globe, posteriorly, the pulley can be found as a thickened slit through Tenon's capsule 12–15 mm posterior to the muscle insertion site with pink muscle tissue of obvious parallel fibers attached to the pulley. The oculocardiac reflex and contraction of the fibers with bipolar cautery can be used to confirm that the identified tissue is indeed muscle. The muscle should be carefully freed, the anterior end identified, carefully and securely sutured and reattached to the sclera. The optimal site for reattachment can be difficult to determine at the time of surgery so it is important to warn the patient that reoperation may be required if the resulting realignment is not optimal. Adjustable sutures can also be valuable in these cases.

Fat Adherence Syndrome

Prior surgery can occasionally lead to violation of Tenon's capsule and allow prolapse of the orbital fat pad into sub-Tenon's space. The displaced fat generally adheres to all tissues including muscle, Tenon's capsule, and conjunctiva with secondary metaplasia into dense hard restrictive scarring that greatly limits rotation of the globe. Surgical planes can be difficult to identify and unplanned dissection through the sclera into the globe is possible. To date, there is no satisfactory treatment for fat adherence syndrome. Some have suggested amniotic membrane transplant [13] sometimes combined with mitomycin C injections [14]. Corticosteroid injections have also been suggested [15] along with careful clearing with closure of the posterior Tenon's defect to prevent additional fat from prolapsing. In reality, it is difficult to prevent recurrence of even more extensive dense scarring with more severe restriction. In many cases, centering the affected eye with little motility is the best result possible.

Clinical Case 1

A 78-year-old man presented with history of longstanding partial sixth nerve palsy in the left eye due to a prior cerebrovascular accident. The patient saw 20/20 out of each eye with corrective lenses (Rx: OD −2.25+ 0.50 × 70, OS −3.00 + 0.50 × 125). He had 6 PD ET in primary gaze that increased to 30 PD in left gaze and could fuse in right gaze with a 15° left face turn.

Dcc measurements by cover test, alternate cover test

Ortho	ET = 6 PD	ET = 30 PD
Ortho	ET = 6 PD	ET = 30 PD
Ortho	ET = 6 PD	ET = 30 PD

Ncc = 4 ET
Right eye fixating (primary deviation)
Ductions: Full OD; −2 Abduction deficit, full in other gazes
Versions: Same as ductions
Anomalous Head position: 15° left face turn (right gaze preference)

The goal of treatment is to improve his ductions and single binocular visual field in left gaze without causing an overcorrection and diplopia in primary or right gaze.

Surgical planning: The observed motility pattern in this patient can be caused by a weak or paretic left lateral rectus muscle and/or by a restricted or contractured left medial rectus. Forced duction and active forced generation testing in the clinic can be very helpful in advanced surgical planning and obtaining proper informed consent. One may assume that a recess/resect procedure on the palsied/ restricted left eye might be the preferred approach if active force generation of the left lateral rectus can be documented. If there is no mechanical restriction to abduction of the left eye on forced duction, and also moderate force generation of the left lateral rectus, then a better plan might be to recess the right medial rectus and potentially place it on an adjustable suture. Recession of the right medial rectus has a greater effect in the problematic left field of gaze, allowing for greater correction in left gaze with less chance of overcorrection in right gaze, and would also have the advantage of preserving the anterior ciliary blood supply of the left medial rectus in the rare event that this partial sixth nerve palsy may progress to a complete sixth nerve palsy, requiring transposition of the left vertical rectus muscles.

Operative findings: Intraoperative forced duction testing did not show restriction of the left medial rectus so a recession of the right medial and resection of the left lateral rectus muscles were performed. Postoperatively, the patient had only a small 4 PD exophoria in primary gaze and right gaze and marked improvement to a small intermittent esotropia of 8 PD in left gaze allowing single binocular vision into 25°–30° of left gaze with much better binocular function for driving and other daily activities.

Clinical Case 2

A 72-year-old man was evaluated for longstanding diplopia after scleral buckle surgery many years ago due to a retinal detachment. Initial evaluation revealed a 30–35 PD left hypertropia and 6° of intorsion. In-office prism adaptation testing revealed fusion with 30 PD BD over the left eye. In the operating room, inspection of the eye revealed significant scar tissue especially in the nasal quadrants. Forced ductions were positive for restriction to infraduction in the area of the scleral buckle in the left eye. Exploration of the area demonstrated that the scleral buckle induced a significant amount of scar tissue adjacent to the buckle that was carefully dissected to explore for the adjacent muscles. The superior rectus muscle was located and recessed on adjustable suture. The inferior rectus muscle proved very difficult to locate as the insertion was scarred to

(continued)

the buckle, Tenon's capsule, and conjunctiva. Furthermore, most muscle fibers appeared to have been separated by the scleral buckle, leaving only a few strands of true muscle tissue attached to the original insertion. The remaining inferior rectus muscle was therefore plicated and advanced to the original insertion. Postoperatively, the patient developed 12 PD of esotropia, likely due to the extensive amount of dissection of scar tissue needed to access the muscles. After careful preoperative and intraoperative assessment, he underwent subsequent left lateral rectus resection as the tissues in that area had less surface scar tissue than medially. Following this second procedure, the patient achieved adequate postoperative alignment in primary position with a small LH (T) of 5, which allowed fusion and a small single binocular visual field.

Summary

Patients, who present with new or recurrent strabismus and/or diplopia after previous eye muscle or other ocular surgery or trauma, present challenges in diagnosis and treatment. As we describe in this chapter, optimal care often requires additional advanced examination and testing to determine appropriate intervention. Information about previous medical and surgical treatment, visual acuity, motility and sensory findings, and consideration of surgical options, risks, benefits and other treatment options, as well as the patient's visual needs and expectations are critical for maximizing treatment success. With proper planning, preparation and execution, acceptable motility, and sensory results are often possible resulting in restoration of useful alignment and relief of symptoms.

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Brown Syndrome

58

Mohamad S. Jaafar

Abstract

Brown syndrome is characterized by an inability to elevate the eye in adduction as a result of either a tight or shortened superior oblique tendon, or a process at the trochlea that limits the movement of the superior oblique tendon in the trochlear opening. While most patients are asymptomatic, some adopt an anomalous head position and others have a very noticeable abnormal eye movement pattern that necessitates the lengthening of the superior oblique tendon, generally with good outcomes. This chapter gives a brief clinical overview of Brown syndrome and, through four case presentations, illustrates some of the general principles of the management of this condition.

Keywords

Brown syndrome • Ocular torticollis • Anomalous head posture • Inferior oblique palsy • Fibrosis of extraocular muscles

Overview

Harold W. Brown first described this syndrome in 1950 [1]. Usually unilateral, sporadic and congenital, Brown syndrome will manifest as an inability of the eye to elevate in aDduction (Fig. 58.1), with or without a hypotropia in primary position and a secondary head turn away from the affected side with or without a chin-up position. The vertical saccade is normal but the eye gets to a sudden stop. Brown syndrome is usually associated with an exotropia in upgaze (Y-pattern) (Fig. 58.2) and widening of the palpebral fissure in aDduction [2, 3]. The inability to passively elevate the eye in aDduction (with a relatively free elevation in aBduction) in the office, together with a positive forced duction test (F.D.T.) in the operating room (Fig. 58.3) solidify the diagnosis [4, 5].

Some cases may be bilateral, albeit asymmetric, and few are hereditary [6]. Acquired cases may be iatrogenic, such as those that follow a superior oblique tuck, or those that may occur after sinus surgery. Cases of intermittent Brown syndrome have been clearly documented; they may be associated with an audible or palpable "snap" and may subside spontaneously [2, 3]. Some acquired cases are associated with systemic inflammatory conditions such as rheumatoid arthritis and juvenile idiopathic arthritis may respond to anti-inflammatory treatment [7, 8].

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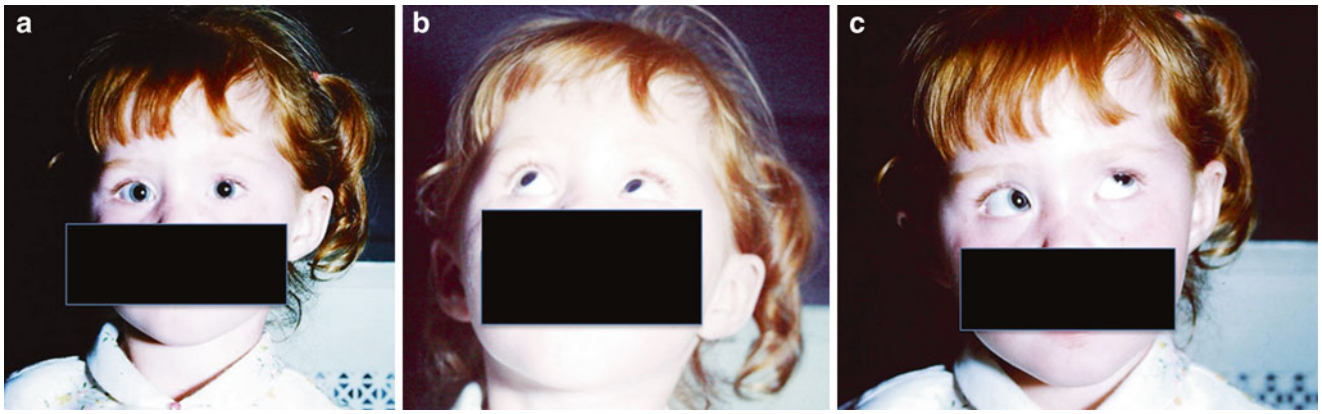

Fig. 58.1 Case 1—Brown syndrome—Right eye. (**a**) Orthophoric in primary position and normal head posture. (**b**) Full elevation of the right eye in aBduction. (**c**) Significant limitation of elevation of the right eye in aDduction and secondary, blemishing over-elevation of the left eye in accordance with Hering's law. Both ductions (not shown) and versions (shown) would demonstrate under-elevation of the right eye in aDduction

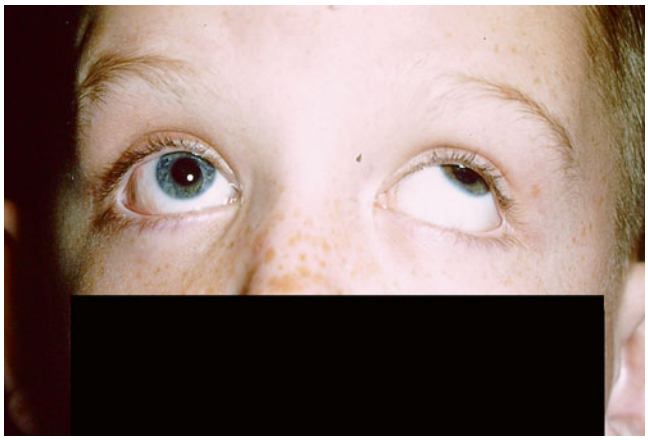

Fig. 58.2 Y-pattern exotropia. Large exotropia (and hypotropia) in upgaze

The differential diagnosis of Brown syndrome includes inferior oblique paresis, monocular elevation deficiency ("double elevator palsy"), orbital fibrosis syndrome, and "simulated Brown syndrome" (e.g., orbital floor fracture, traumatic tenosynovitis, idiopathic orbital inflammation, metastasis to superior oblique muscle, orbital metastasis, frontal sinus osteoma, s/p blepharoplasty, or blunt orbital trauma) [2, 3, 9, 10]. Generalized fibrosis syndrome is the "big mimicker" [11, 12]. It can involve one or both eyes, sometimes in a very asymmetric fashion, and most frequently involves the inferior, medial, superior, and then lateral rectus muscles. It is therefore essential to always properly perform a forced duction test (F.D.T.) on all extraocular muscles (E.O.M.), of both eyes, while the patient is under anesthesia.

Management of Brown syndrome varies widely. Imaging of the orbit with special attention to the region of the trochlea adds significantly to the workup of the patient with acquired Brown syndrome.

Patients who do not have a significant anomalous head position and whose appearance is not disfigured by the abnormal eye movements can be reassured and observed for any decompensation and significant change in head position. Patients with significantly abnormal head positions or who have significant disfigurement benefit from superior oblique weakening/tendon lengthening procedures such as superior oblique tenotomy or tenectomy (with or without inferior oblique weakening), superior oblique recession, Z-tenotomy of the superior oblique tendon, Suture Bridge Technique ("chicken suture"), or silicone expander insertion in the superior oblique tendon [2, 3, 10, 13–21]. It is the understanding of this author that lengthening of the superior oblique using a suture or silicone spacer are the preferred methods at this time.

The following four cases will illustrate clinical situations involving the diagnosis and management of patients with Brown syndrome.

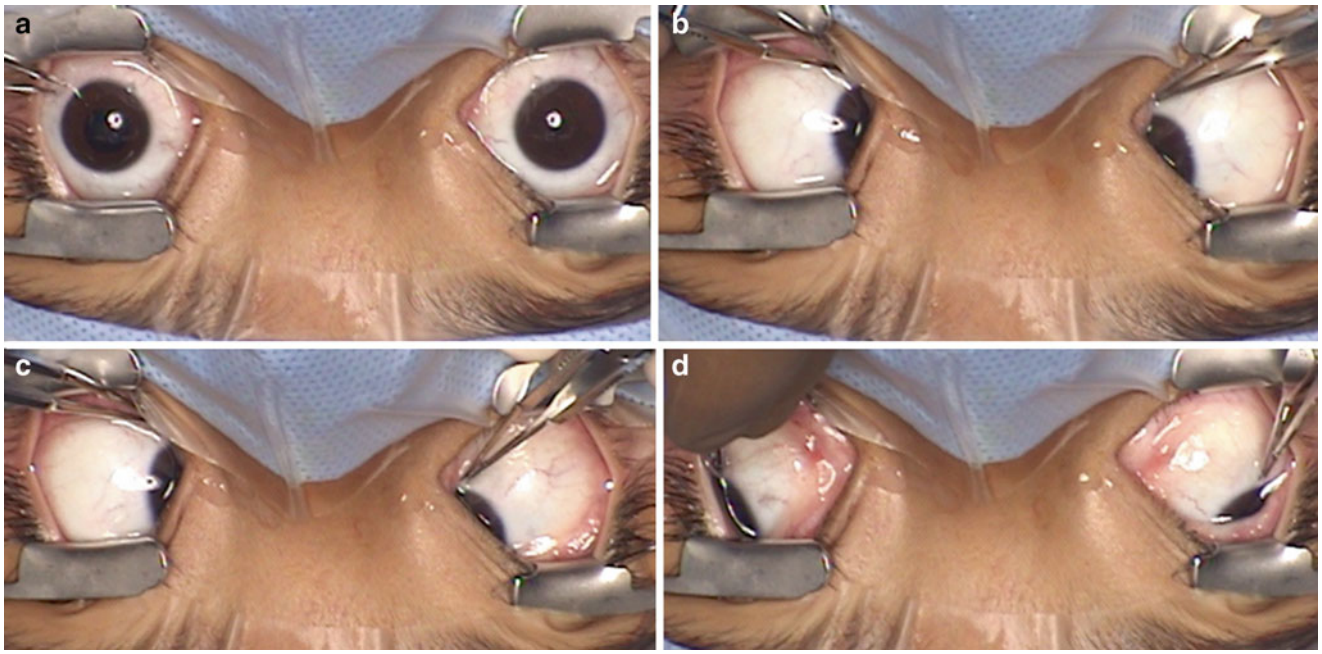

Fig. 58.3 Forced Duction Test under general anesthesia—surgeon's view. (**a**) Eyes in primary position. (**b**) With a firm grip of the eye at the limbus inferotemporally (5 or 7 o'clock) the retropulsed eye is moved into complete aDduction, and then moved up (**c**). (**c**) shows inability to forcibly move the left eye up, whereas the right eye moves up freely. (**d**) Elevation of the left eye is better in aBduction, but is still relatively limited compared to the right eye

Case Examples

Case 1

Clinical Synopsis

A 4-year-old girl presented with sudden abnormal movement of the left eye, noted since early childhood. She was otherwise healthy with no significant ocular or systemic history. On examination, she was found to have 20/25 vision in each eye and a completely normal eye examination except for the ocular motility: She assumed a straight head posture and orthophoria at Distance and Near, in primary position of gaze, but there was marked limitation of elevation of the right eye in aDduction causing a marked left hypertropia in left gaze (Fig. 58.1). Stereopsis was 40″ of arc. She was diagnosed with Brown syndrome of the right eye.

Commentary

No surgical intervention was recommended because of orthophoria in primary position, excellent vision and stereopsis, the absence of an anomalous head posture, and the possibility that the limitation in eye movement may spontaneously improve as she got older. A significant proportion of children with Brown syndrome will have improvement of eye motility as they get older [13, 14]. Dawson, Barry, and Lee retrospectively reviewed 32 patients with Brown syndrome who were followed between 6 months and 9.5 years, and reported that 75 % of patients had some improvement in their ocular movements without any intervention. Of 6 patients with a "click," 5 improved [13]. Also, as the child becomes older and taller, he/she will look at the parents and other adults at eye level and will not need to as frequently look up, inducing the anomalous eye movements. Most adult patients with persistent Brown syndrome, will generally position themselves and/or arrange their desk/office in such a way to avoid looking in the affected position of gaze, where the deviation is manifest (e.g., a patient with right Brown syndrome, will sit in a position in which he/she would look at others straight ahead or in right gaze).

Case 1 was followed for several years with no change in the severity of the eye movement limitations and maintaining a straight head posture.

Case 2

Clinical Synopsis

An 9-year-old girl presented with a history of asynchronous eye movements noted since age 6 months. Her parents reported that a chin-up and head-tilt posture was becoming more noticeable with age. She was otherwise healthy, with no systemic or neurological signs or symptoms. There is a positive ocular family history of a "similar" strabismus condition in her maternal grandfather and uncle, and a documented Brown syndrome in a maternal cousin. She had 20/20 vision in both eyes, and a completely normal eye examination except for the motility assessment below:

Head Posture: 2–5° chin-up and 10–15° Right Head Tilt (Fig. 58.4)

Alternate Cover Test in Forced Primary Position:

At distance:	12 PD R.X.T. + 12 PD R.Ho.T.
At near:	12 PD R.Ho.T.

She had a Y-pattern exotropia (Fig. 58.5)

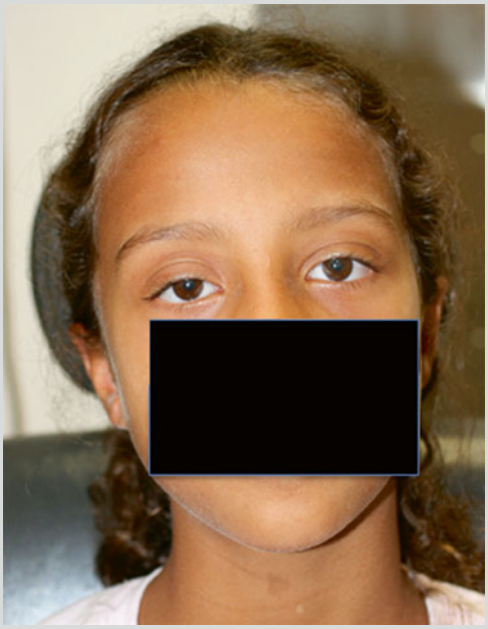

Fig. 58.4 Case 2—a 9-year-old girl with Brown syndrome (Right eye) showing minimal chin up and left head turn and 10–15° Right Head Tilt

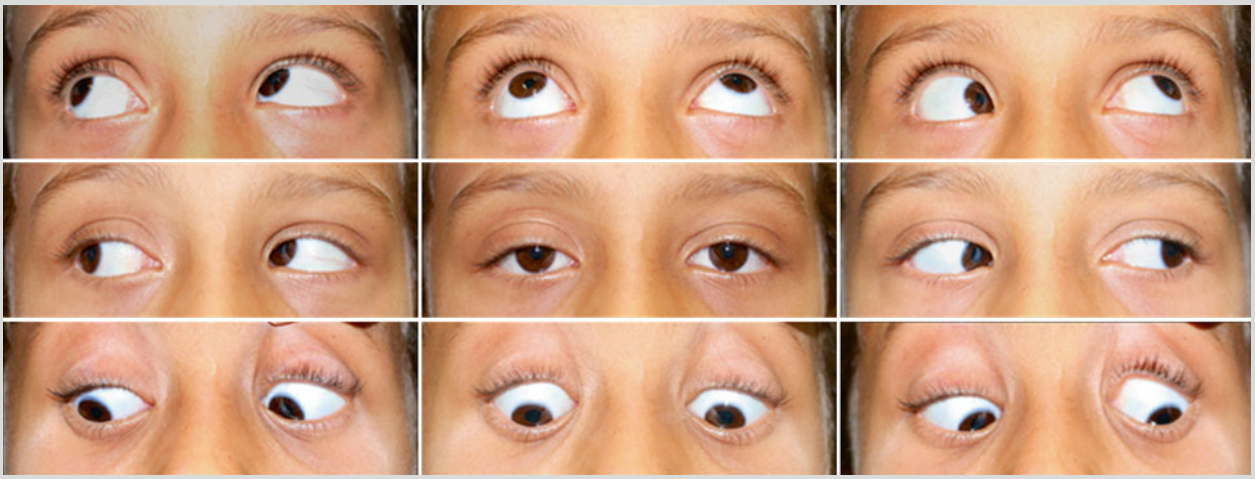

Fig. 58.5 Case 2 showing right hypotropia in primary position, a large exotropia in upgaze (Y-exotropia), limitation of elevation of the right eye in aDduction and excessive depression in aDduction

(continued)

	30 PD X.T.+ 20 PD R.Ho.T.	
10 PD X.T.+ 9 PD R.Ho.T.	12 PD X.(T.)+ 12 PD R.Ho.T.	8 PD X.T.+ 16 PD R.Ho.T.
	4 PD X.T.+ 10 PD R.Ho.T.	

Ductions:	−4 limitation of elevation of right eye in aDduction.
	Very mild limitation of elevation of right eye in aBduction.
	+2 excessive depression of right eye in aDduction.

Bielschowsky Head Tilt test:

Tilt to the Right:	Ortho
Tilt to the Left:	10 PD X.T.+15 PD R.Ho.T.

With 12 PD Base Up prism in front of the right eye, the patient assumed a straight head posture.

Stereopsis at Near: 40″ Arc

Fundus:	Normal; +1–2 Incyclotorsion (Right Eye) (Fig. 58.6)
Diagnosis:	R/O Right Inferior Oblique Palsy
	R/O Brown Syndrome (Right eye)

As the findings were stable, and after a long discussion with the family about the differential diagnosis and the possible surgical intervention to alleviate the anomalous head posture, the patient was taken to the operating room for forced duction testing and possible surgery:

Surgical findings

Forced duction testing, under general anesthesia, showed an inability to elevate the right eye beyond midline in aDduction. The rotations were otherwise full in both eyes. A properly performed exaggerated forced duction test (keeping the eye retropulsed and putting the tendon on stretch) (Fig. 58.3) is key to the diagnosis of Brown syndrome and needs to be performed pre-, intra-, and postoperatively [4, 5]. F.D.T. confirmed the diagnosis of Brown syndrome in the right eye. An uncomplicated superior oblique tenotomy with placement of a 6-mm spacer was performed [19] (*From the Operative Report*: 4 mm nasal to the superior rectus muscle, two double-armed sutures of 7-0 Prolene were placed. The tendon was then severed in between the sutures. Direct exploration revealed that no parts of the superior oblique tendon were left non-severed. The forced-duction test became completely normal with no limitation of elevation. A 6 mm spacer of a #240 silicone retinal band was sutured using the preplaced 6-0 Prolene sutures. Multiple sutures of 7-0 coated Vicryl approximated Tenon capsule and the conjunctiva.)

Follow-Up

On the patient's last examination, 4 years postoperatively, she retained a straight head posture and 40″ of arc of stereopsis. Her Alternate Cover Test in primary position demonstrated a well-controlled intermittent deviation of:

At distance:	8 PD R.X.(T.)+4 PD R.H.(T.)
At near:	6 PD R.X.(T.′)+4 PD R.H.(T.′)

Ductions showed: −1 limitation of elevation and depression of right eye in aDduction.

Commentary

This case describes a patient with familial Brown syndrome who presented with an unusual head tilt, positive Bielschowsky head tilt, and incyclotorsion (signs usually manifested with inferior oblique palsy) [10]. However, a V- or Y-pattern exotropia is not characteristic of an inferior oblique palsy. She responded well to a superior oblique weakening procedure using a silicone band spacer (see discussion about surgery in case 3, below).

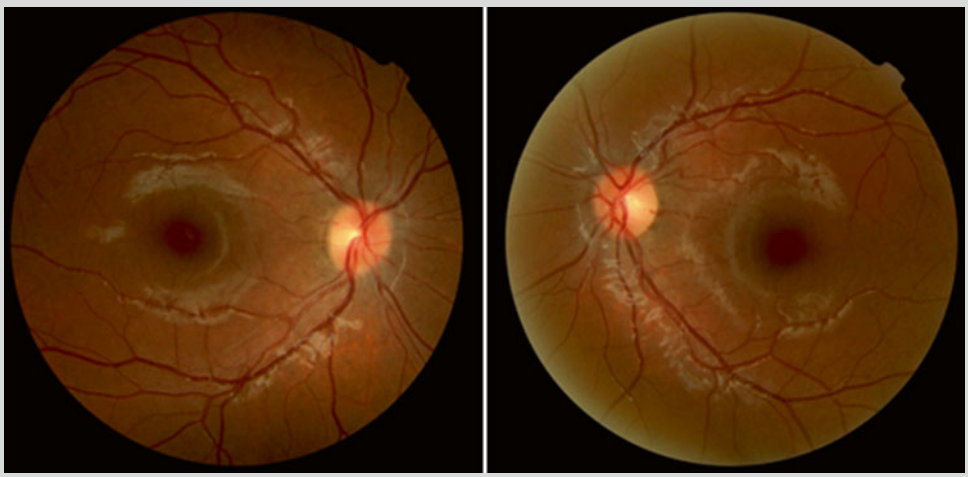

Fig. 58.6 Case 2—Fundus photographs showing 1–2+Incyclotorsion—Right Eye

Case 3

Clinical Synopsis

An 8-year-old girl with Brown syndrome of the right eye was examined for second opinion regarding surgery. She had a completely normal eye examination except for mild myopia and an abnormal ocular motility pattern.

Head Posture:	No head tilt or turn

Alternate Cover Test in Primary Position:

At distance:	Orthophoria
At near:	10 PD Intermittent Exotropia, with good control

Stereopsis at near:	≤200″ Arc

Fundus:	Normal; no cyclotorsion

She had no ocular misalignment except in supraduction in primary and in supraducted left gazes

Ortho	10 PD L.H.T.	30 PD L.H.T.
Ortho	Ortho	Ortho
Ortho	Ortho	Ortho

Ductions:	Marked limitation of elevation of right eye in aDduction

Diagnosis:	Brown Syndrome (Right eye)
Disposition:	Glasses for Myopia
	No surgery was advised as patient was orthophoric and had no anomalous head posture

The patient was brought back 9 months later, 2 weeks after she had undergone a 4 mm weakening of R.S.O. tendon using an adjustable suture elsewhere [21]. The child was complaining of double vision and manifesting a significant left head tilt. She was wearing 8 PD prisms for an R.H.T. to alleviate the double vision.

Examination showed right hypertropia in primary position with −2 limitation of elevation and depression of the right eye in aDduction.

Six weeks postsurgery, she had the following ocular motility profile:

Head posture:	Variable, straight to 5° left head tilt

Alternate Cover Test in Primary Position:

At distance:	14 PD R.H.T.
At near:	8 PD X.T.′ + 8 PD R.H.T.′

Nine cardinal gaze measurements status-post weakening of the R.S.O. tendon 4 mm, using an adjustable 6-0 bridge Mersilene suture, through a superonasal approach.

Fig. 58.7 Case 3—Hung-up syndrome, with limited depression of the right operated eye, in aBduction. Status-post 4 mm weakening of R.S.O. using an adjustable Mersilene suture

16 PD L.H.T.	24 PD L.H.T.	36 PD L.H.T.
16 PD R.H.T.	14 PD R.H.T.	14 PD R.H.T.
26 PD R.H.T.	4 PD E.T. + 18 PD R.H.T.	10 PD R.H.T.

Ductions:	−4 limitation of elevation of right eye in aDduction
	−2 limitation of depression of right eye in aDduction
	−3–4 limitation of depression of right eye in aBduction (Fig. 58.7)
	−1/2 limitation of aBduction of the right eye

Bielschowsky Head Tilt test: Inconclusive

Double Maddox Rod test: Excyclotorsion: 3° in primary position and 6° in downgaze

No cyclotorsion on ophthalmoscopy

Diagnosis: Hung-up syndrome of the right eye [22] following weakening of the R.S.O., 4 mm, using an adjustable 6-0 Mersilene suture, through a superonasal approach and no suturing of Tenon capsule and conjunctiva.

It was decided to take the patient back to the operating room for exploration of the surgical site and additional surgery.

Surgery

Forced Duction Test, under general anesthesia showed:

−4 limited elevation of right eye in aDduction
−3 limited depression of right eye in aBduction

Exploration revealed significant scarring around the insertion of the R.S.R., the R.S.O. tendon and the

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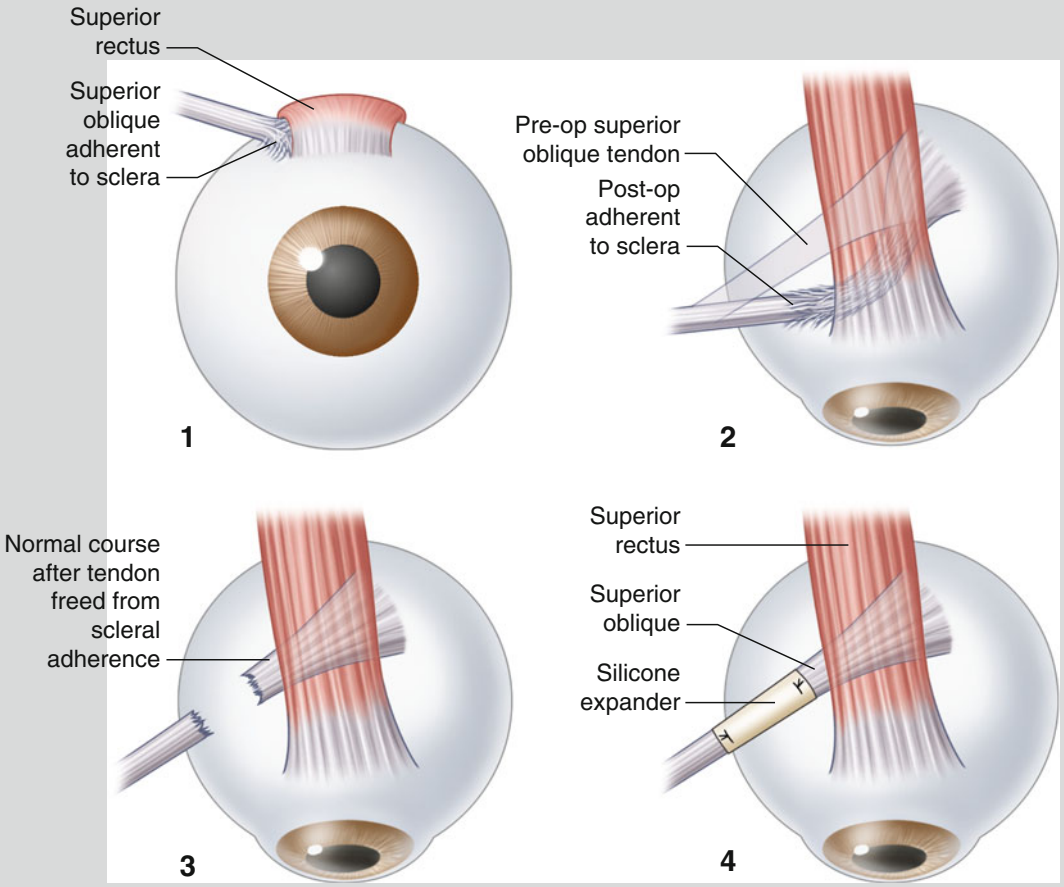

Fig. 58.8 Case 3—Medical artist depiction of surgical findings, release of adhesions and placement of silicone band

Mersilene suture (Fig. 58.8). The proximal end of the R.S.O. tendon was adherent to the sclera nasally and the distal end of R.S.O. tendon was split in half with the anterior 1/2 adherent to sclera 2 mm nasal to R.S.R. and the posterior 1/2 "free." Using meticulous dissection, adhesions were released and scar tissue excised. Double-arm 7-0 Prolene sutures were used to approximate the proximal and distal ends of R.S.O. with an interposed 6 mm segment of #240 silicone retinal band. At the conclusion of surgery, F.D.T. showed −1 limited elevation in aDduction, and −1 limited depression in aBduction.

Seven weeks after the second surgery, she had no diplopia in primary position and the following motility picture:

Head posture:	Straight

Alternate Cover Test in Primary Position:

At distance:	Orthophoria
At near:	Orthophoria

Measurements in 9 gaze positions 7 weeks status-post release of scar tissue around the R.S.R., and insertion of a 6 mm #240 silicone retinal band between the two ends of the R.S.O. tendon.

5 PD L.H.T.	20 PD L.H.T.	35 PD L.H.T.
Ortho	Ortho	10 PD L.H.T.
3PD R.H.T.	3 PD R.H.T.	2 PD X. T′.

Rotations:	Right eye:	−1 limitation of elevation in aBduction and −4 in aDduction
		−1–2 limitation of depression in aBduction and aDduction

Bielschowsky Head Tilt test: Negative

Stereopsis: 50″ of arc

She was diplopia-free up to 30° in upgaze, and 25° in downgaze.

Double Maddox Rod test: No cyclotorsion in primary position or downgaze

No cyclotorsion on ophthalmoscopy.

(continued)

Commentary on the Use of Silicone Expanders

For Brown syndrome patients who meet the criteria for surgery, the author prefers using a silicone expander [19] over a Mersilene suture [21]. The silicone band achieves a rigid separation between the two ends of the severed S.O. tendon. It prevents the loosely connected ends to attach to the sclera, or to the S.R. muscle, and it extends the tendon an effective amount without allowing reattachment of the ends closer to each other, while not inducing an overcorrection or a clinical picture of a fourth nerve palsy like a free tenotomy would. It is important to perform a meticulous dissection around the tendon and to reduce the trauma to the nasal intermuscular septum. It is also advised to properly close Tenon capsule and conjunctiva to minimize scarring in the critical compartment around the S.R. insertion. The tenotomy has to be performed at a minimum 3–4 mm distance nasal to S.R. muscle. The steps described above prevent/minimize the risk of the hung-up syndrome. The use of a #240 silicone retinal band, 6–7 mm in length, has been ideal to effect the proper weakening of the S.O., while minimizing the risk of buckling and extrusion of the band. Double-armed 7-0 Prolene sutures on a BV-1 Needle have worked well for this procedure.

Case 3 illustrates that superior oblique surgery is often non-forgiving and where, more than any other muscle surgery, the benefits of surgery should outweigh its risks. In spite of meticulous and systematic surgery, superior oblique tenotomy with a silicone expander [18, 19], or with a "chicken Mersilene suture" [21], may be associated with the following complications: persistence of Brown syndrome, adhesion to the superior rectus tendon (causing limited depression in aBduction—hung-up syndrome), superior oblique palsy, and/or extrusion of the expander [19, 22]. However, when properly executed, it offers great relief to patients with anomalous head posture or significant disfigurement due to the upshoot of the contralateral eye.

Case 4

A 7-month-old boy presented with a significant chin-up and right head turn noted first at age 4 months. He has remained otherwise healthy, with no neurological symptoms. Family history is negative for strabismus. On examination, he showed excellent, equal vision, and seemed to be fusing with his anomalous head posture. In forced primary position, he had a 15 PD L.Ho.T. −4 limitation of elevation in aDduction, and −1 limitation of elevation in aBduction, with possible lid retraction. A reevaluation at 9 months of age showed stable findings. At 13 months of age, he underwent surgery to alleviate the significant chin-up and right head turn:

Surgery

F.D.T. under general anesthesia showed the following:

OD:	No restriction of any movement
OS:	+3 restriction to elevation in aDduction
	+1 restriction to elevation in aBduction
	Other ductions were free

A diagnosis of Left Brown syndrome was made, and surgery to place a silicone spacer was initiated. However, after performing the L.S.O. tenotomy, F.D.T. became less positive, but there remained some restriction to elevation of the eye in aDduction; no other E.O.M. (including the L.I.R.) were felt to be tight. The surgical field was reexplored to confirm that no portion of the L.S.O. tendon was left uncut. As no other muscle was felt tight and due to the child's strabismus pattern and significant anomalous head posture, the surgeon proceeded with placing a 7 mm silicone band (as per the previously described technique, above [19]). At the end of the procedure, the F.D.T. was less positive than before tenotomy, but still not completely free.

Postoperatively, the chin-up posture disappeared; however, he continued to have a right head turn. As time progressed, the right head turn worsened to 45° and, in addition to the elevation deficiency of −3 in aDduction, he started showing a progressive limitation to aDduction of the left eye (Figs. 58.9 and 58.10).

(continued)

Fig. 58.9 Case 4—Increasing, significant right head turn status-post L.S.O. spacer for chin-up and right head turn

Follow-up

At 28 months of age, the patient underwent, by another pediatric ophthalmologist, exploration of the L.S.O. tendon (no uncut tendon found). The L.L.R. and L.I.R. muscles were found to be tight and were recessed 9 and 4.5 mm, respectively. The strabismus improved little after the procedure, but he continued to have limited elevation and aDduction. He also started having some limitation to depression of the left eye. He underwent extensive evaluation by a third pediatric ophthalmologist and a pediatric neurologist with special interest in strabismus. He had multiple imaging studies of the orbit and brain. No fibrotic bands were found and the brain imaging was normal. The left medial rectus muscle was thinner than its right counterpart and there was, possibly, minimal thinning of the left lateral muscle. He was suspected to have unilateral

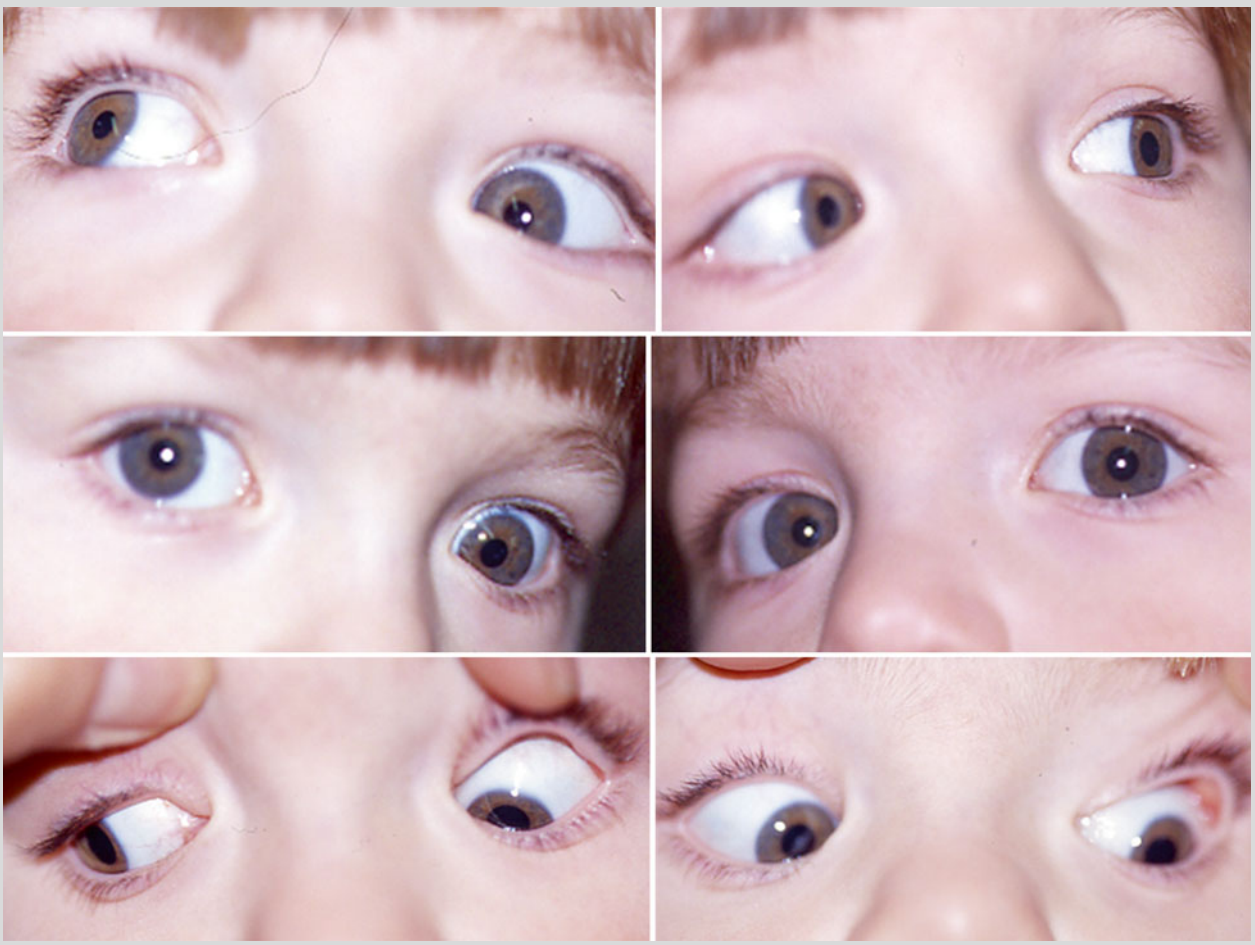

Fig. 58.10 Case 4 at age 2 years. Persistent limitation to elevate the left eye in aDduction and incipient limitation to aDduct the left eye

(continued)

CFEOM3 or partial third nerve palsy (No ptosis and pupil-sparing) (with overexaggerated secondary contraction of the antagonists muscles!). Duane syndrome type II was also entertained (no retraction seen). However, no firm diagnosis was ever reached.

As he continued to show the marked limited aDduction and secondary right head turn that helped him fuse, at age 10.5 years, he underwent his third surgery consisting of disinsertion of the L.L.R. and suturing it to the orbital wall, and a large resection of the L.M.R. He achieved orthophoria in primary position. When last seen, 2.5 years later, he had no ocular misalignment in primary gaze position, a straight head posture (Fig. 58.11), and 40″ of arc of stereopsis, eventhough the left eye had minimal movements in all directions of gaze (Fig. 58.12).

Commentary

The above case describes a patient with pseudo-Brown syndrome who, over time, demonstrated severe, unilateral, progressive fibrosis of the extraocular muscles. This is not characteristic of what we would see in typical cases of CFEOM in which the fibrosis is congenital in nature [12, 23, 24]. A final diagnosis has not been reached.

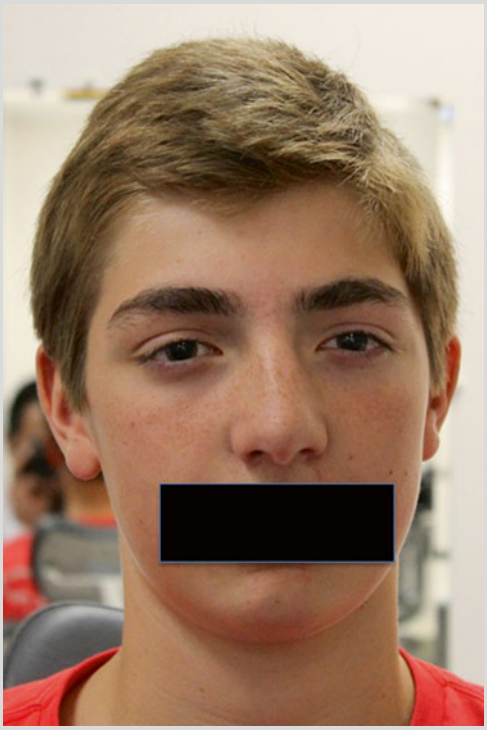

Fig. 58.11 Case 4, 2.5 years status-post third surgery consisting of disinsertion of L.L.R. and suturing it to the orbital wall and large resection of the L.M.R.

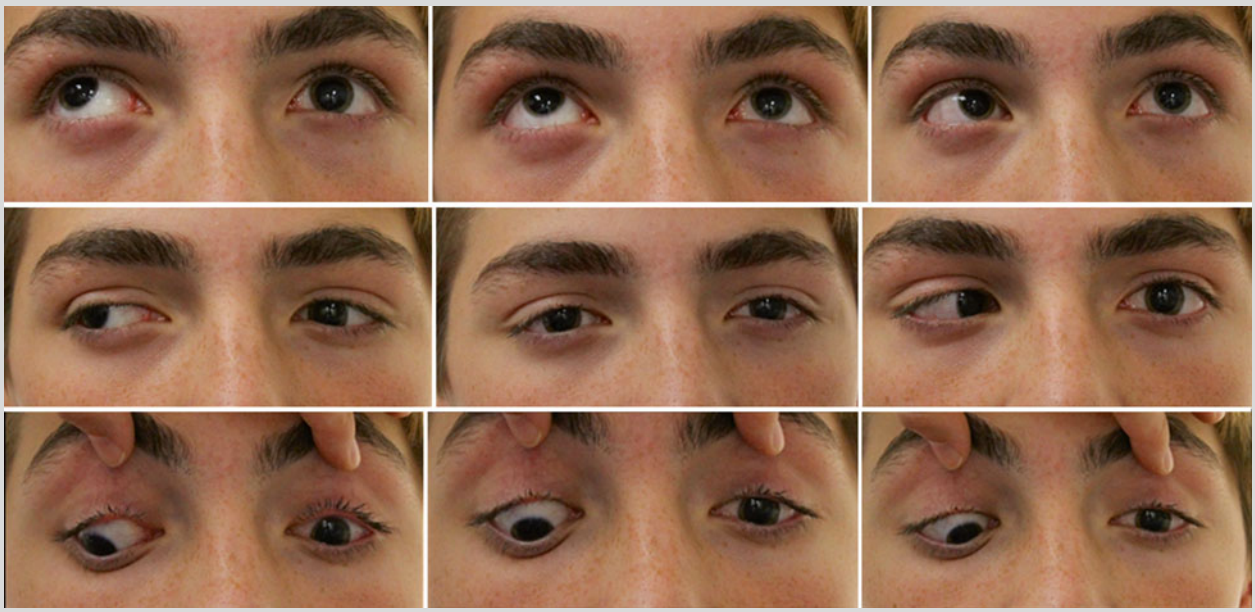

Fig. 58.12 Case 4—Measurements, 2.5 years after last surgery for Pseudo-Brown syndrome, showing orthophoria in primary position. Left eye has restricted movements in all directions of gaze (first surgery at age 13 months: L.S.O. tenotomy with insertion of 7 mm silicone spacer; second surgery at 28 months: Recession of L.L.R. 9 mm and recession of L.I.R. 4.5 mm, for L.X.T. and L.Ho.T.; third surgery: disinsertion of L.L.R. and suturing it to the orbital wall and large resection of the L.M.R.)

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Acute Strabismus

59

Emily Broxterman and Michelle M. Ariss

Abstract

Acute strabismus refers to the acquired onset of ocular misalignment that appears over a period of days to weeks. The history and clinical examination must be carefully differentiated from benign entities such as chronic, decompensated strabismus. Complete ophthalmologic and motility examination should be performed promptly. Findings of incomitance, absence of sensory adaptations to strabismus, variability in the deviation, and other concomitant palsies as well as systemic or neurologic signs and symptoms should prompt further laboratory and/or imaging investigations.

Keywords

Acute strabismus • Incomitant strabismus • Cranial nerve palsy • Myasthenia gravis

Introduction

Acute strabismus refers to the sudden onset of ocular misalignment over a period of days to weeks. While adult patients will typically experience diplopia and seek urgent evaluation, young children are less likely to be symptomatic. Instead, parents may notice that the child closes one eye or assumes an abnormal head posture. In the acute stage, patients typically have an incomitant deviation. With time, however, the deviation may become increasingly comitant, measuring about the same in different directions of gaze. It is critical for the physician to identify patients at high risk for underlying neurologic or systemic abnormalities and initiate the appropriate workup.

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This chapter discusses important clinical features and examination findings of children with acute strabismus and an approach to diagnosis and treatment.

Clinical Features

The patient's presenting signs and symptoms largely determine the need for additional workup of acute strabismus. Additional neurologic evaluation is indicated if the acute ocular misalignment is associated with the following:

- *Clinical History and/or Symptoms*:
  - History of trauma
  - History of previous malignancy or immunocompromised state
  - Headache (especially if associated with supine positioning and/or emesis)
  - Double vision
  - Systemic or neurologic symptoms or deficits
  - Vision-related neurologic complaints
  - Change in behavior or sensorium
- *Clinical Signs*:
  - Ptosis and/or evidence of cranial nerve palsy

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- Abnormal convergence or divergence amplitudes (see Chap. 1)
- Anisocoria
- Nystagmus
- Asymmetric optokinetic nystagmus (OKN)
- Visual field loss
- Optic nerve edema

Etiology

A number of conditions can cause acute or subacute strabismus in children. These range from benign etiologies such as viral respiratory illness to more severe systemic conditions such as myasthenia gravis, traumatic orbital fractures, thyroid disease, meningitis, malignancies, and Gradenigo syndrome (chronic inflammation of petrous bone with ipsilateral sixth nerve palsy and facial pain in children with recurrent otitis media). Table 59.1 identifies specific causes of acute strabismus and associated examination findings. It is critical for ophthalmologists to identify children at risk for systemic disease in order to proceed with additional evaluation. Table 59.2 helps to differentiate patients presenting with acute strabismus from those with congenital/chronic conditions.

Clinical Evaluation

After a thorough history and review of symptoms, the patient should undergo a full comprehensive ophthalmologic examination with attention to the following:

- *Amblyopia and Suppression*: Amblyopia can be associated with long-standing strabismus, but is rarely seen in cases of acute strabismus. Suppression is uncommon in acute strabismus and can be demonstrated by Worth 4 Dot testing at distance and near or other sensory tests (see Chap. 2).
- *Ductions and Versions*: Is the deviation comitant or incomitant? New onset incomitant strabismus is more likely to be acute in nature (Be sure to evaluate for "A" or "V" patterns and oblique dysfunction).
- *Measuring the Deviation*: The examiner must use prisms to objectively neutralize the deviation at near with an accommodative target and at distance fixation (at least 20 ft). At distance fixation, the deviation must be measured

Table 59.1 Causes of acute strabismus and associated examination findings

	Extraocular muscles (EOM) affected	Ocular alignment	Associated historical and examination findings
Head trauma	Most commonly superior oblique muscle (CN IV palsy) due to its long intracranial course	Hypertropia worse in opposite gaze and on head tilt to same side of palsy	Altered mental status, headache
Increased intracranial pressure	Lateral rectus muscle (CN VI palsy)	Incomitant esotropia	Papilledema, headache, transient visual obscurations, pulsatile tinnitus, diplopia, esotropia at distance > near
Post viral illness	Lateral rectus muscle (CN VI palsy)	Incomitant esotropia	Estropia at distance > near
Gradenigo syndrome	Lateral rectus (CN VI palsy)	Incomitant esotropia	Otitis media, facial pain in CN V_1 and V_2 distribution, fever due to inflammation of petrous apex of temporal bone
CNS malignancy	Variable depending on location and size of tumor	Most commonly associated with acute esotropia, but can vary depending on tumor location	May have associated nystagmus or systemic neurologic deficits
Thyroid eye disease/myositis	Most commonly affects inferior > medial > superior > lateral rectus muscles	Variable vertical or horizontal deviations depending on EOM affected	Lid retraction, lid lag on downgaze, inferior scleral show, proptosis, optic neuropathy, exposure keratopathy
Orbital tumors	Variable depending on location of tumor	Variable depending on location of tumor	Proptosis, lid swelling, periocular ecchymosis
Arnold Chiari malformation	Lateral rectus (CN VI palsy)	Comitant esotropia	Vertical nystagmus, headache, dizziness, balance difficulties, divergence palsy
Myasthenia gravis	Variable	Variable	Ptosis, fatigue with prolonged exertion, Cogan lid twitch, speech/swallowing difficulties

CNS central nervous syndrome, *CN* cranial nerve

Table 59.2 Acute versus congenital or chronic etiologies for strabismus

	Congenital/chronic strabismus	Acute strabismus
Diplopia	Rare but may occur suddenly with decompensated strabismus	Always present but may be limited to the paretic field or absent in younger children
Amblyopia	May be present	Absent
Abnormal head posture	May persist on covering paretic eye due to secondary scoliosis and/or contracture of neck muscles	Disappears on covering paretic eye
Facial asymmetry	May be present with long-standing torticollis	Absent
Contracture of antagonist muscles on positive forced duction testing	May be present	Absent
Old photographs	May show anomalous head posture	Negative

in the nine cardinal positions of gaze (see Chap. 1) and on head tilt to the left and right. If a hypertropia is present, the Three-Step Parks-Bielschowsky Test can be applied (see Chap. 49, Fig. 49.1). Importantly, one must distinguish a vertical muscle palsy from a skew deviation. *Skew deviation* is a supranuclear cause of vertical or torsional diplopia and may mimic a hypertropia with a positive Parks-Bielschowsky 3-step test. However, there is a paradoxical incyclotorsion of the hypertropic eye on head tilt. Skew deviation is often caused by brainstem lesions or demyelinating disease, and is usually accompanied by other neurologic symptoms. Evaluation of a skew deviation is discussed in more detail in Chap. 56 on Hyperdeviations.

- *Cranial Nerve Testing and Neurologic Examination*: Patient must have thorough exam to identify systemic neurologic abnormalities and evaluate for associated motor and sensory cranial nerve palsies. Prompt referral to a neurologist may aid in diagnosis and in obtaining and interpreting appropriate imaging studies.
- *Pupillary Abnormalities*: The examiner must look for afferent (APD) and efferent (anisocoria) abnormalities and evaluate for light-near dissociation where the near response exceeds pupillary constriction to light (e.g., infection (Argyll Robertson pupils) or compression of tectum leading to loss of pretectal light input to Edinger-Westphal nucleus: the near reflex is more ventrally located and spared).
- *Cycloplegic Refraction*: A cycloplegic refraction is important to identify patients with high refractive error or anisometropia that are suggestive of chronic strabismus.
- *Fundus Evaluation*: Optic nerve edema or other abnormalities should alert the clinician to pursue further workup.

Management

Not all patients presenting with acute strabismus will require additional evaluation. After completing the comprehensive history and ophthalmologic examination, the physician should use the information above as a guideline to classify the patient as high or low risk for underlying systemic or neurologic conditions. In the case of low risk, it is appropriate to prescribe corrective lenses and closely monitor the patient for any changes. Patients at high risk of associated serious conditions should undergo additional investigations that may include:

- Neuroimaging:
  - Computed Tomography (CT Scan)—most appropriate in setting of acute trauma involving the orbit and/or thyroid disease
  - Magnetic Resonance Imaging (MRI Scan)—evaluate for structural anomalies, malignancies, and demyelinating lesions
  - Magnetic Resonance Venography (MRV Scan) brain—rule out sinus thrombosis (e.g., increased ICP and papilledema)
  - Magnetic Resonance Angiography (MRA Scan) or Computed Tomography Angiography (CTA Scan)—evaluate for compressive aneurysm or vascular malformation
- Laboratory:
  - CBC, metabolic profile, blood cultures
  - Inflammatory markers (ESR, CRP) in conjunction with autoimmune workup (RF/CCP, HLA-B27, ANA)
  - Infectious workup (Lyme titers, VRDL/FTA, ASO titers, Bartonella, EBV)
  - TSH, Free T4 to rule out underlying thyroid disorder
  - Acetylcholine receptor (blocking, binding, and modulating) and muscle-specific kinase (MuSK) antibodies to evaluate for myasthenia gravis (Note: negative testing does not rule out myasthenia gravis, as only 50 % of patients with isolated ocular disease will test positive).
- Lumbar puncture
  - Measure opening pressure to rule out increased intracranial pressure (ICP)
  - Cell count and culture to rule out meningitis

Myasthenia Gravis

One important cause of acute strabismus that may easily be overlooked is myasthenia gravis (MG). Fluctuating fatigability and weakness of the extraocular muscles, levator palpebrae superioris, and orbicularis muscle are seen in both systemic and ocular forms of MG. Common ocular signs of this disease include ptosis, bilateral and asymmetric strabismus, and/or external ophthalmoplegia. Systemic MG can lead to respiratory compromise and death, so it is critical to ask about the presence of speech or swallowing difficulties and shortness of breath in any patient suspicious for MG. On physical examination, the clinician should evaluate for the presence of a Cogan lid twitch (Ask patient to look in downgaze followed by upgaze. As the affected eye supraducts the upper lid overshoots) or worsening ptosis upon manual elevation of the more ptotic eyelid (due to Hering's law of equal innervation). It is important to note that pupils are *never* involved in MG. Diagnosis can be confirmed using the in-office ice pack test, Serum Antibody testing (acetylcholine receptor binding, blocking, and modulating antibodies plus anti-muscle-specific kinase (MUSK) antibodies), and single fiber EMG testing. The patient should then be referred to Neurology for co-management and systemic workup for associated conditions such as thyroid disease and thymoma.

Case 1

An 8-month-old male was admitted to the hospital for respiratory distress. Ophthalmology was consulted for a 2–3 day history of "red eye" OD. On physical examination, Visual Acuity was fixed and follows OU. Pupils were 5 mm, 4+ reactive OU with no APD. Motility examination revealed −4 abduction OD with no evidence of globe retraction on attempted abduction, and was otherwise full OU (Fig. 59.1a–c). Cranial nerve examination revealed decreased sensation on right V1 and V2 distribution with associated weakness of the right orbicularis and right-sided facial droop. The patient had a cycloplegic refraction of +2.75 + 0.50 × 95 OD, +3.25 + 1.00 × 80 OS. Anterior segment and dilated fundus examinations were normal except for the following abnormalities: Adnexa: increased palpebral fissure height with poor lid closure OD, WNL OS. Conjunctiva: one prominent, dilated vessel interpalpebral zone temporally OD, white/quiet OS. Cornea: scattered punctuate epithelial erosions OD, clear OS.

Hospital Course

A consult was placed to the Otorhinolaryngology specialist. Tissue biopsy confirmed a diagnosis of parapharyngeal embryogenic rhabdomyosarcoma with intracranial extension (see Fig. 59.2). A Hematology/Oncology consult was placed for bone marrow biopsy. Results showed dysplasia with no evidence of malignancy. The patient's final diagnosis was a right CN V, VI,

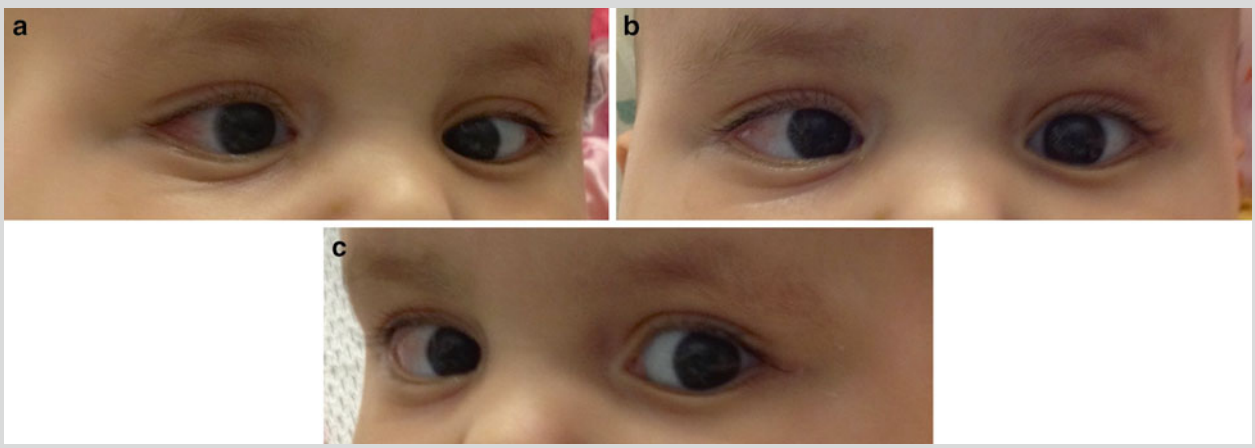

Fig. 59.1 An 8-month-old patient with −4 abduction in the right eye with no associated globe retraction. (**a**) *right* gaze, (**b**) *primary* gaze, (**c**) *left* gaze

(continued)

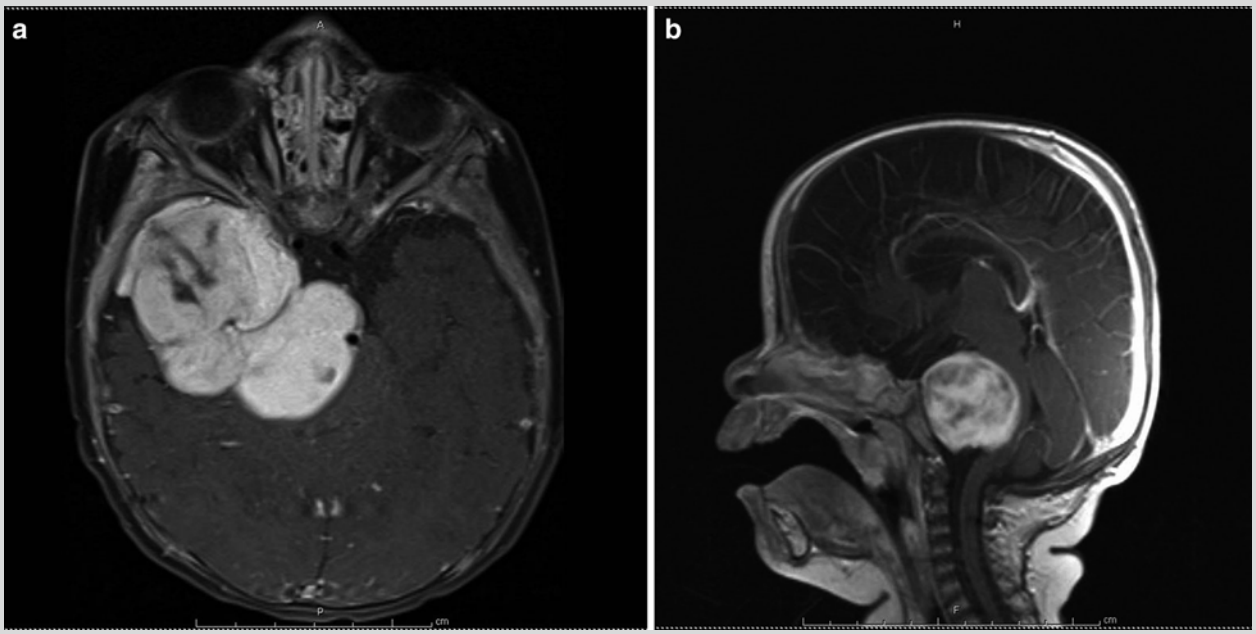

Fig. 59.2 MRI (**a**) axial, (**b**) sagittal: T1-weighted images show a parameningeal right pharyngeal/parameningeal primary lesion with significant intracranial extension including brainstem deviation. No local metastasis

and VII nerve palsy secondary to intracranial spread of embryogenic rhabdomyosarcoma. Treatment was initiated with vincristine and irinotecan chemotherapy plus radiation therapy.

The patient was followed every 2–3 days by the ophthalmologist while inpatient and treated with ointment for the exposure keratopathy. The seventh nerve palsy improved subsequently with systemic treatment of the malignancy. The patient was examined 1 month after treatment to ensure that he did not develop a fixation preference and suppression. The sixth nerve palsy had completely resolved at this time.

Clinical Synopsis: This is an 8-month-old patient presenting with acute incomitant strabismus and multiple cranial nerve palsies prompting urgent neuroimaging. Neuroimaging revealed a paraphayngeal embryogenic rahbdomyosarcoma. The patient was followed closely and treated for keratopathy in the setting of seventh nerve palsy and decreased sensation. The cranial nerve palsies resolved with systemic treatment of the tumor.

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Complications of Strabismus Surgery

60

Oriel Spierer, Kara M. Cavuoto, and Craig A. McKeown

Abstract

Although a generally safe procedure, there are a myriad of complications that can occur during or after strabismus surgery. The complications are varied in their severity, with effects ranging from life-threatening to minor ocular surface irritation. Systematic evaluation of the potential complications and consideration of the timing of the event will aid in successful recognition and management.

Keywords

Strabismus surgery • Eye muscle surgery • Complications of strabismus surgery • Lost muscle • Scleral perforation • Endophthalmitis • Anterior segment ischemia

Introduction

Advances in anesthesia and surgical techniques have improved the outcomes of strabismus surgery, making it a generally safe procedure with a low complication rate. Current estimates suggest that minor complications, such as dellen and pyogenic granulomas, occur with an incidence of 2–4 % [1]. They usually resolve with observation or a short course of conservative treatment such as topical lubrication or steroids without long-term implications. Serious complications, such as a slipped muscle or orbital cellulitis, are rare with an estimated total incidence of less than 1 % [1] and often necessitate medical or surgical management to avoid permanent sequelae. Even with careful surgical planning, meticulous technique and precise execution of the procedure, complications still occur. It is imperative for the strabismus surgeon to be familiar with potential complications in order to reduce the risk of complications, to recognize their occurrence, and to manage them accordingly.

In this chapter, the complications of strabismus surgery will be organized temporally, focusing on ones that occur preoperatively, intraoperatively, and postoperatively.

Preoperative Planning

Careful preoperative preparation is essential to the success of any procedure, especially strabismus surgery. In addition to confirming the stability of the angle of deviation and comitancy of the misalignment, the strabismus surgeon should also consider the method of anesthesia. In general, bilateral surgery and/or pediatric patients necessitate general anesthesia. In children with comorbities, performing the surgery at a children's hospital as opposed to a free-standing outpatient facility should be considered. In cooperative adults scheduled for unilateral surgery, the surgeon can utilize retro- or peribulbar blocks or a sub-Tenon's injection. Sequential blocks or unilateral blocks with a contralateral sub-Tenon's injection are also anesthetic options. Topical anesthesia may be particularly helpful in adult patients with multiple medi-

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cal comorbidities. Even in the case of topical anesthesia, appropriate monitoring by an anesthesiologist is important, not only to ensure adequate pain control but also to enable conversion to general anesthesia if the patient cannot tolerate the procedure.

Intraoperative Complications

Many of the complications that occur during strabismus surgery are preventable with good surgical technique and knowledge of the pertinent anatomy. If identified during the procedure, steps can often be taken intraoperatively to prevent complications. Proper identification and verification of the informed consent in the preoperative holding area as well as marking the operative eye(s) with the patient's/patient's family's confirmation are crucial to prevent mistakes related to wrong site surgery. In a survey among 517 strabismus surgeons, 33.5 % self-reported having operated on the wrong eye or muscle or performed the wrong procedure at least once. The mean error rate was 1 in 2506 surgeries. The risk was higher with inexperienced surgeons, confusion between the type of deviation and the surgical procedure, globe torsion, inattention and distraction, working in more than one operating room, and unmarked surgical sites [2]. Once in the operating room, a surgical "time-out" should be performed to reconfirm the patient's identity, operative eye(s), and procedure to be performed. This routine should theoretically diminish the likelihood of operating on the wrong eye or the wrong muscle.

Systemic Problems

Malignant hyperthermia is a rare event with an incidence of 1:5000 to 1:50,000–100,000 anesthetic events and mortality as high as 80 % [3]. With current treatment strategies and prompt recognition, this rate has decreased to less than 5 % in recent years [3]. The mechanism involves an uncontrolled release of calcium from skeletal muscle resulting in increased intracellular calcium levels and muscle contraction. Almost always, the malignant hyperthermia-susceptible patients have a defective calcium channel in the sarcoplasmic reticulum membrane [3]. There is an established connection between malignant hyperthermia and myopathies, as well as ptosis. Malignant hyperthermia is believed to be more common in children with strabismus, although this association was recently questioned [4]. The surgeon should inquire to determine if there is a personal or family history of malignant hyperthermia prior to scheduling surgery. Early signs include elevated end-tidal carbon dioxide and tachycardia; late signs include temperature elevation and respiratory and metabolic acidoses. Treatment consists of discontinuing anesthetic agents, hyperventilation with 100 % oxygen at high flow rate, intravenous dantrolene, and active cooling of the patient with IV iced saline.

A common occurrence during strabismus surgery is triggering the oculocardiac reflex, a slowing of the heart rate caused by traction on the extraocular muscle(s) or pressure on the globe. It most commonly occurs during surgery on the medial rectus muscle. The induced bradycardia can potentially lead to the point of asystole. Management of the oculocardiac reflex consists of immediate release of traction on the extraocular muscle and/or globe. Administration of intravenous atropine or glycopyrrolate may be indicated.

Major Intraoperative Events

Scleral Perforation

Scleral perforation is an uncommon, but potentially serious problem associated with strabismus surgery. The rate of scleral perforation is estimated to be 0.08 % [5]. However, the true rate may be higher, since affected individuals may be asymptomatic and postoperative retinal examinations are not routinely performed. Recessions, especially on the horizontal muscles, highly myopic eyes, and eyes with previous extraocular muscle surgery, are more commonly associated with scleral perforation [6, 7]. Perforation typically occurs while suturing the muscle to the sclera but may also occur during tenotomy (Fig. 60.1). Perforation can result in vitreous, subretinal, or choroidal hemorrhage, retinal detachment, or endophthalmitis. Cataract and lens dislocation can very rarely occur. Laser retinopexy or trans-scleral cryotherapy may be indicated to create a chorioretinal adhesion around the perforation site. However, in a survey of ophthalmologists, up to

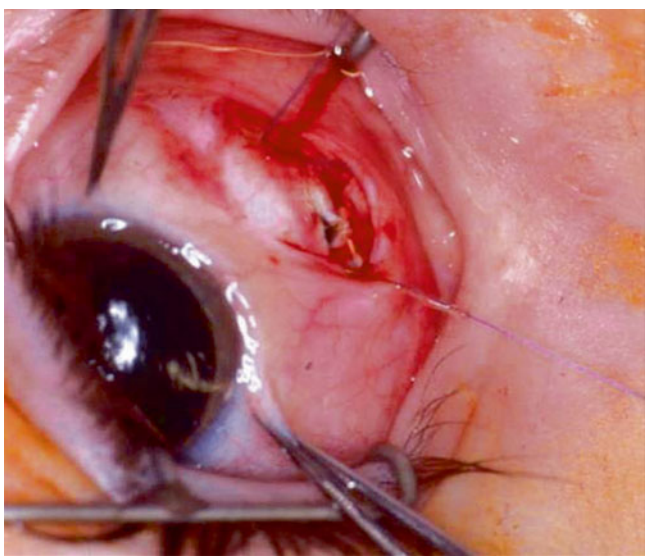

Fig. 60.1 Sclera cut during tenotomy exposing choroidal tissue

Table 60.1 Minor strabismus intraoperative complications, consequences, management, and prevention

Complication	Description and signs	Consequences if not managed properly	Management	Prevention
Severing Tenon's capsule	Orbital fat is exposed	Fat adherence syndrome	Excising and/or cauterizing the prolapsed fat and suturing of Tenon's capsule	Dissection of the intermuscular septum and muscle capsule close to the muscle belly
Split muscle tendon	Hooking partial-thickness tendon	Under correction	Re-hooking the tendon followed by pole test	Good exposure, pole test
Pulled-in-two syndrome (*PITS*)	Tension on the muscle causes rupture at the muscle-tendon junction	Lost muscle	Recovery of the posterior portion of the muscle and reattachment to the anterior portion or the sclera	Caution with reoperations, extraocular muscle palsy, and thyroid eye disease
Ruptured vortex vein	Extensive bleeding	Technical difficulty in performing the surgery	Cauterization	Identifying the vortex vein, especially in inferior oblique procedures

25 % responded that they may choose not to treat the perforation but to observe the patient for development of complications [8]. The reported rate of this complication, with or without intraocular injury, has been in steady decline during the last decades [6]. This is likely due to improvement in surgical technique and the use of spatulated needles and magnification with loupes or microscopes. In the event of a suspected perforation, it is important to perform an intraoperative dilated examination and to consider consultation with a vitreoretinal surgeon. Methods to prevent this potential complication include the use of magnification, good exposure while suturing the muscle to the sclera, and the avoidance of suturing in areas with scleral thinning. If this is not possible, consideration of the "hang-back" technique may be appropriate.

Lost Muscle

The absence of any attachment of the muscle tendon or capsule to the sclera is defined as a "lost muscle." The incidence is unknown [9] but may be as high as 0.02 % [5]. If noticed during surgery, immediate recovery of the muscle is indicated. If unnoticed, or first detected after the procedure, early surgical exploration and repair before contracture of the lost muscle develops is appropriate. The clinical hallmarks of lost muscles are large-angle overcorrection and marked limitation of excursion of the globe into the field of action of the lost muscle [10]. Mild proptosis and widening of the palpebral fissure in attempted gaze toward the lost muscle are additional supportive diagnostic signs. If a lost muscle is suspected, high-resolution magnetic resonance imaging in different gaze positions can be considered to aid with locating the muscle position, although this may not be applicable in young children due to the need for sedation or general anesthesia. Surgery to retrieve lost muscles requires good exposure of the tissue planes without forceful manipulation or undue traction on the tissues overlying the lost muscle, with careful attention to maintaining the integrity of Tenon's capsule to avoid bleeding, disruption of orbital anatomy, and fat adherence syndrome. The search for the lost muscle should generally be focused on the position where the muscle penetrates Tenon's capsule and exploration under magnification along the orbital wall [11]. An anterior orbitotomy approach to the adjacent orbital wall with preoperative orbital imaging may result in successful retrieval of a lost muscle that was irretrievable via a standard transconjunctival approach [12]. If the muscle cannot be found, transposition procedures can be employed. If transpositions fail or the risk of anterior segment ischemia is considered high, tethering the globe in the primary position with permanent sutures or a fixation platform system employing a titanium T plate can be considered [13].

Minor Intraoperative Events

Table 60.1 describes minor intraoperative complications, their management, and their consequences if not managed properly.

Postoperative Complications

Slipped Muscle and Stretched Scar

By definition, a slipped muscle occurs when the tendon retracts within its capsule. The muscle capsule may be attached to the sclera at the intended site, but the muscle itself has retracted posteriorly. The incidence is not clear but has been reported to be as high as 10 % of cases in repeat strabismus surgery [14]. A key for diagnosis is limited ductions in the field of action of the slipped muscle, resulting in an incomitant deviation. Other clues for slipped muscles are:

- Widening of the palpebral fissure on attempted movement into the field of action of the slipped muscle, due to relaxation of the antagonist muscle and the lack of pull of the lost muscle.
- Reduced saccadic velocity in the field of action of the muscle; however this may be a reliable diagnostic sign only in recently slipped muscles but not in long-standing conditions [9, 15].
- Differential intraocular pressure: A change in intraocular pressure may occur in the field of action of the involved muscle as it contracts to rotate the globe. Intraocular pressure has been reported to decrease in the field of action of the slipped muscle [16]; however, false-negative results are possible with this test [15].

The clinical signs of slipped muscles are generally less pronounced than in lost muscles. In the early postoperative period, the eyes may initially appear to be satisfactorily aligned, which may explain why this complication is likely to be underdiagnosed. Later, overcorrection from slipped muscles may become more apparent. A subtype of this complication is caused by scar remodeling with stretching and lengthening of the attachment between the muscle tendon and the sclera. In these patients, misalignment may occur months or years after surgery [17]. The risk of slipped muscles may be reduced by careful dissection of Tenon's capsule as well as removal of the capsule directly over the tendon or muscle in the location where the sutures are to be passed. This allows clear visualization of the tendon or muscle and assists in verifying that the locking sutures are placed in the tendon or muscle, rather than the capsule. Management of slipped muscles should include resection of the empty sheath with secure placement of the sutures in the tendon or muscle and appropriate advancement of the tendon, often to the original insertion site. The mean change in angle of deviation was reported to be ~3 prism diopters for each millimeter of muscle advancement [14]; however, modifications must be made according to operative findings. Due to the somewhat unpredictable outcome of slipped muscle surgery, an adjustable suture can be considered. However, this needs to be weighed against the perceived risk of recurrent slippage.

Infection

As in any ocular surgery, infection is a rare complication, endangering the entire globe. Possible infections include suture abscess, endophthalmitis, preseptal cellulitis, and orbital cellulitis. Signs of endophthalmitis will typically develop within 4 days of surgery [18]. The thought is that the eyelids and conjunctiva act as a reservoir for pathogens, and the surgical site acts as a portal of entry for microorganisms. Possible risk factors for cellulitis are occult sinusitis, eye rubbing, and poor hygiene [19]. Infections may be vision or life threatening if not treated promptly. Figure 60.2 (as flowchart 58.1) summarizes the management of post-strabismus surgery-related infections.

Inflammation

1. Conjunctival pyogenic granuloma (Fig. 60.3): Pyogenic granuloma may occur at the site of the conjunctival incision. The pyogenic granuloma may induce irritation, foreign body sensation, and cosmetic disturbance. Treatment with topical corticosteroids is effective in most patients. If the granuloma fails to respond to conservative measures, surgical excision at the base of the lesion is indicated.
2. Conjunctival inclusion cyst (Fig. 60.4): Transillumination will reveal the clear content of the inclusion cyst. If asymptomatic and cosmetically acceptable, the cyst may be observed. If treatment is indicated, excision by "marsupialization" of part of the cyst wall will cause the cyst to collapse without recurrence. This may be done under the slit lamp in adults, but will necessitate general anesthesia in children.
3. Fat adherence syndrome: Unintended violation of Tenon's capsule during strabismus surgery should generally be followed by meticulous repair. Orbital fat prolapse, particularly when associated with bleeding, may result in excessive scarring involving the fat, muscle, and the sclera. Such patients present with progressive restrictive strabismus weeks to months after surgery; the secondary strabismus is often difficult to treat. Surgical intervention with release of adhesions with or without amniotic membrane transplantation may be considered.
4. Necrotizing scleritis: Necrotizing scleritis is a very rare and potentially blinding complication of strabismus surgery. This complication may occur immediately or up to several years after surgery. Inflammation and ischemia play a role in the pathogenesis, and thyroid eye disease and a history of multiple ocular surgeries are risk factors [20]. Treatment includes nonsteroidal anti-inflammatory agents and systemic steroid therapy. Immunosuppressive agents and tectonic reconstruction may be needed in severe cases. Management should be in collaboration with an ocular inflammation specialist.
5. Poor cosmetic appearance: Possible cosmetic aspects of the surgery should be discussed with the patient and/or parents. These include visible stump at the muscle insertion after recession (Fig. 60.5) and a dark area of choroid visible posterior to the original insertion in recessed muscles (Fig. 60.6).

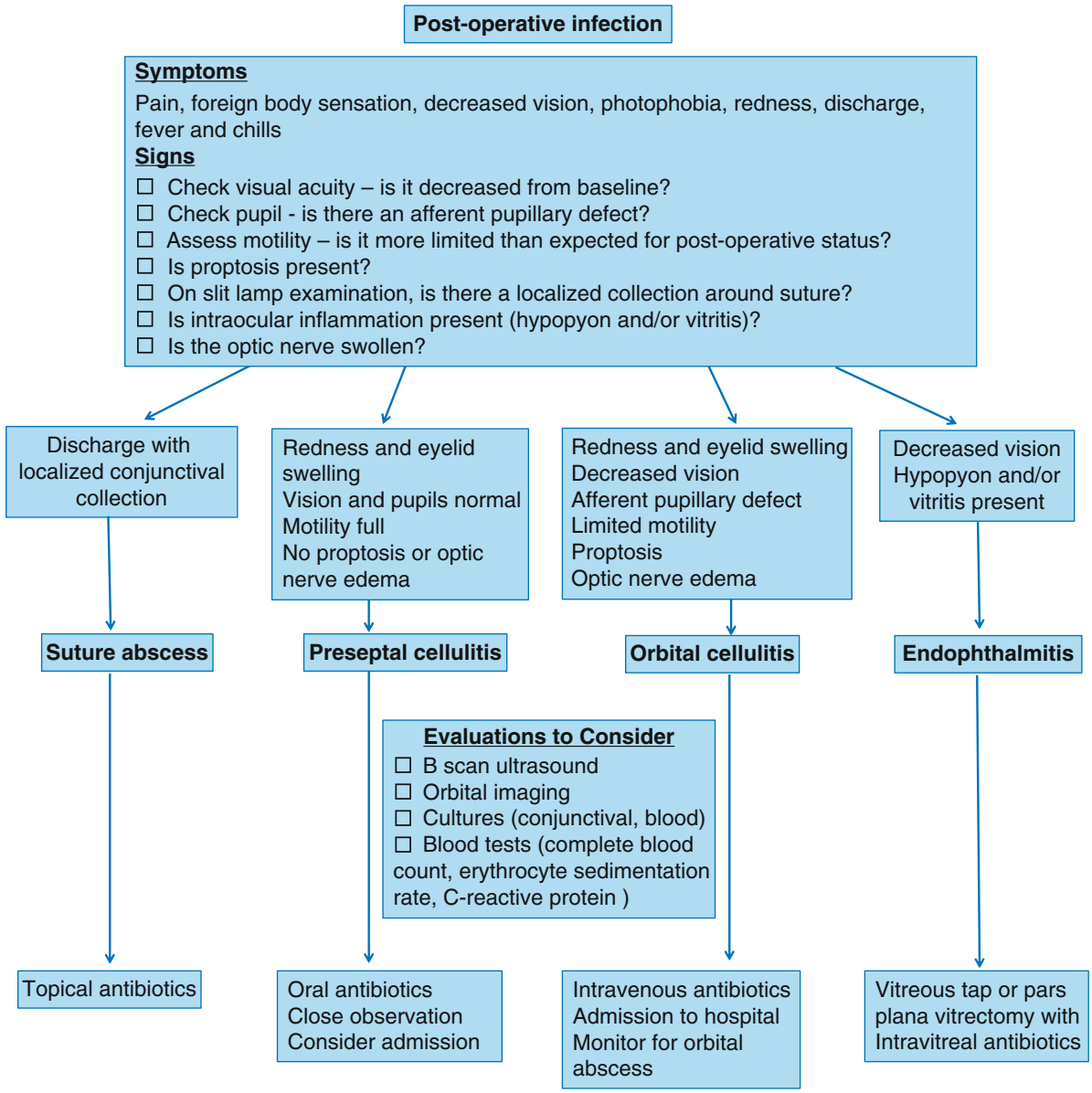

Fig. 60.2 Flowchart showing post-strabismus surgery infections, diagnosis, and treatment

Anterior Segment Ischemia

The four rectus muscles carry in their capsule the anterior ciliary arteries that supply the anterior segment of the eye. Each rectus muscle has two anterior ciliary vessels, except for the lateral rectus, which carries only one. Tenotomy of the muscle from the sclera severs the blood supply to the anterior segment, placing the eye at risk for anterior segment ischemia. The incidence of this potentially serious complication has been estimated at less than 1 in 13,000 surgeries [1] and is more common with vertical muscles. The risk increases with disinsertion of three or more rectus muscles. Systemic risk factors for anterior segment ischemia include older age, atherosclerosis, and hematological disorders. Previous strabismus surgery and thyroid ophthalmopathy are other risk factors. Clinical signs of anterior segment ischemia vary from mild iritis to iris atrophy with pupillary changes, corneal edema, cataract, and phthisis bulbi. Treatment includes topical and systemic corticosteroids.

Several surgical techniques have been described to reduce the risk of this complication, including microvascular dissection to preserve the anterior ciliary vessels [21]. Partial transpositions of the vertical muscles and utilization of fornix incisions instead of limbal incisions are other precautionary approaches. Plication should be considered as an alternative tightening procedure to resection in high-risk patients for

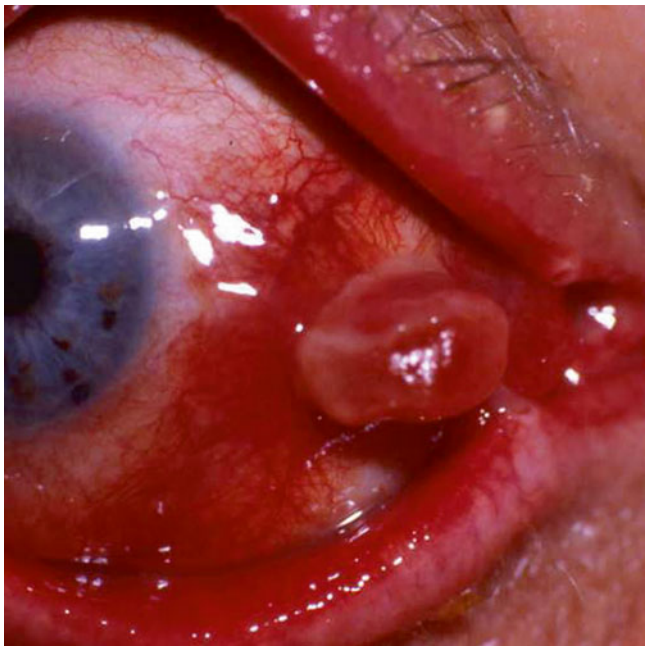

Fig. 60.3 Pyogenic granuloma following right medial rectus recession

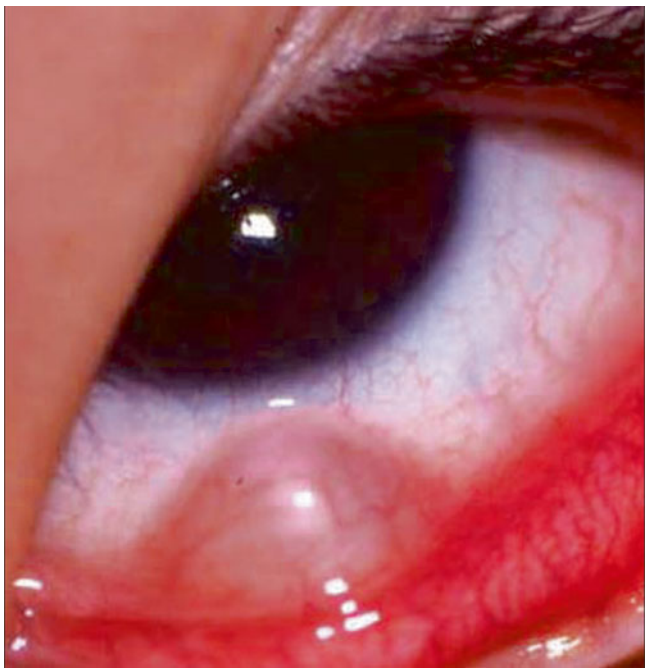

Fig. 60.4 Conjunctival inclusion cyst

anterior segment ischemia as it has the potential to spare the ciliary vessels. A recent study evaluating anterior segment circulation by iris angiography found that rectus muscle plication is associated with significantly less postoperative iris filling defects as compared to tenotomy [22].

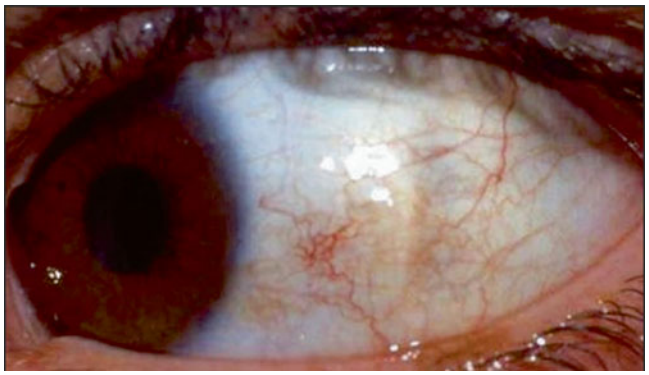

Fig. 60.5 Visible insertion stump of recessed muscle

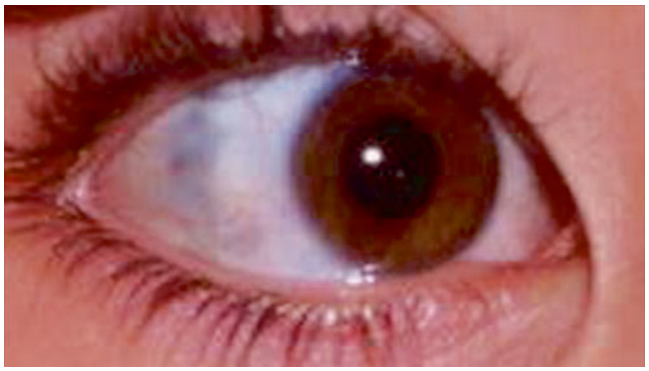

Fig. 60.6 Dark area of choroid visible posterior to the original insertion of recessed muscle

Other

1. Exposed sutures: Exposure of the absorbable 6-0 polyglactin 910 (Vicryl) used to reattach the muscle to the sclera may cause irritation and foreign body sensation. Trimming of the suture may be considered; however, compromising the integrity of the knot may result in a lost muscle if performed during the first postoperative month.
2. Refractive changes: The mechanism for refractive error changes is multifactorial and includes alterations in corneal and scleral curvatures and lenticular changes. In general, the refraction changes are mild and clinically insignificant. These changes are expected to disappear one year after surgery [23].
3. Eyelid position changes: There is a close anatomic relation between the superior rectus muscle and the levator palpebrae superioris and between the inferior rectus muscle and the lower eyelid retractors. Therefore, changes in eyelid position occur in more than 90 % of patients undergoing vertical rectus muscle surgery [24]. There is a correlation between the amount of surgery and the magnitude of lid position change (retraction in cases of recession and advancement in cases of resection) [24]. In general, this rule may be less applicable for superior rectus surgery due

to less direct anatomic connection between the upper eyelid retractors and the superior rectus muscle [24]. One study found that vertical palpebral fissure width also changes after horizontal muscle surgery. In this study, the palpebral fissure significantly increased following recessions of medial or lateral rectus muscles for esotropia or exotropia, respectively [25]. Careful dissection of the tissues surrounding the muscle will aid in minimizing this complication, as it effectively separates the muscle from the eyelid retractors [24]. The recommendation is to avoid a recession larger than 7 mm and a resection larger than 5 mm. The exception to this rule is in patients with thyroid eye disease who frequently require larger inferior rectus recessions.

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Part XII

Eyelid, Orbit and Lacrimal Disorders

Nasolacrimal Duct Obstruction

61

Andreas Marcotty

Abstract

Successful management of the infant with chronic tearing and mucus discharge requires an understanding of the differential diagnosis and natural history of nasolacrimal duct obstruction. Equally important is an understanding of the timing of possible spontaneous resolution as well as medical and surgical treatment modalities that can be employed should spontaneous resolution not occur.

Keywords

Tearing • Nasolacrimal duct obstruction • Tear duct massage • Dacryocystocele • Probe and irrigate • Tear duct stent • Balloon catheter dilation

Statement of Problem and Its Differential Diagnosis

The infant with a blocked tear duct is constantly tearing and has mucus that accumulates and dries on the lashes, often sealing the eyelids closed after sleep. The infant is usually referred after multiple attempts by the pediatrician to treat the process with "massage" and antibiotics (Fig. 61.1). Prior to making the diagnosis of nasolacrimal duct obstruction (NLDO), other causes of tearing must be investigated such as a corneal abrasion (Fig. 61.2), the presence of a foreign body, distichiasis, congenital epiblepharon, and congenital glaucoma (Fig. 61.3) [1].

The ophthalmologist then has to determine the etiology of the epiphora such as nasolacrimal duct obstruction or other malformations of the nasolacrimal apparatus including dacryocystocele or absent lacrimal puncti. The diagnosis of NLDO can be confirmed using the dye disappearance test and the clinical findings of an increased tear meniscus (Fig. 61.4) with mucoid debris in the tear film stained with fluorescein, persisting longer than the normal eye in a unilateral obstruction [2]. There may be regurgitation of mucus from the nasolacrimal duct into the tear film if the lacrimal sac is compressed [2, 3]. Figure 61.5 demonstrates an algorithm for determining the etiology in the infant with tearing.

Lastly, there appears to be a higher rate of anisometropia and subsequent risk of amblyopia in the eyes with congenital NLDO, with a greater rate in unilateral NLDO compared with bilateral NLDO [4–6]. There is no information to suggest that earlier treatment of the obstruction has a beneficial effect on the development of anisometropic amblyopia, or whether the NLD obstruction is associated with some form of orbital abnormality that may be related to the development of amblyopia. Hence, it is critical that a cycloplegic refraction be performed in all infants with NLDO initially and periodically thereafter.

Epidemiology and Natural History

Tearing usually becomes evident by 1 month of age as tear production becomes established, but occasionally the obstruction is evident at birth. NLD obstruction occurs in 6–20 % of newborns [7–9] with the majority of obstructions being

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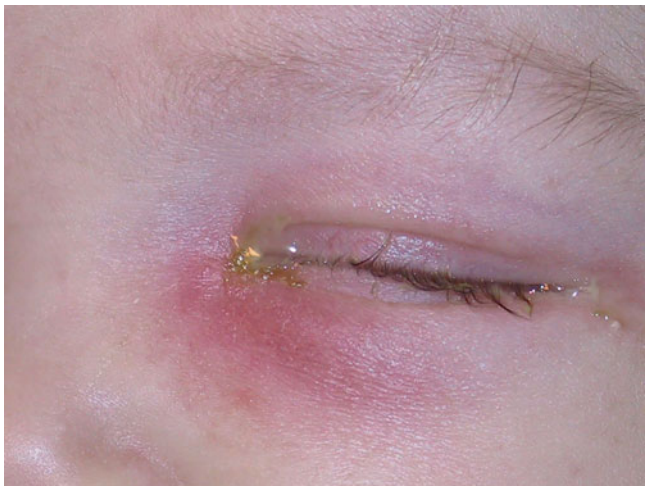

Fig. 61.1 Congenital tear duct obstruction. *Note*: debris, mucous, epiphora and erythema of inner lower lid

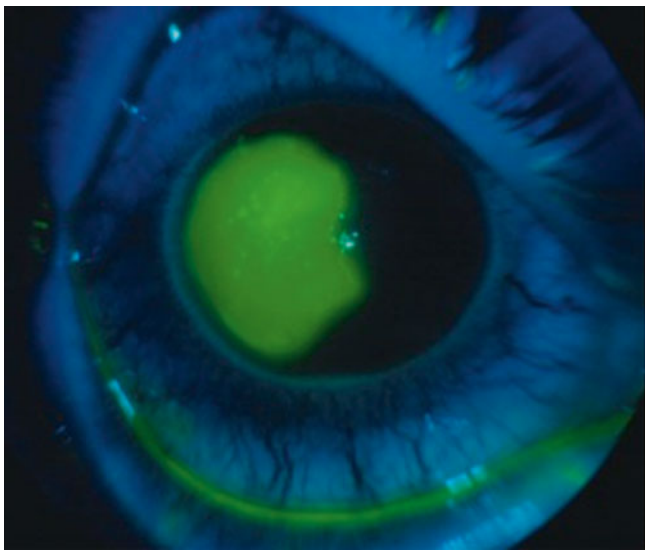

Fig. 61.2 Corneal abrasion. *Note*: fluorescein staining

located at the valve of Hasner [10]. Generally the obstruction resolves spontaneously such that 95 % of patients are asymptomatic by the age of 10 months [8, 11]. The condition persists in only <1 % of cases, and there is less than 5 % chance of spontaneous resolution after 10 months of age [8]. The spontaneous improvement is highly correlated with changes in the length of the NLD and with changes in the maxilla, causing an increase in hydrostatic pressure, occurring most frequently by 6 months of age [12]. A study by the Pediatric Eye Disease Investigator Group [13] found that after 6 months of observation, improvement occurs spontaneously with or without massage in 66 % of cases [14]. This study involved infants referred to pediatric ophthalmologists, while former studies were of infants with NLDO in the general population.

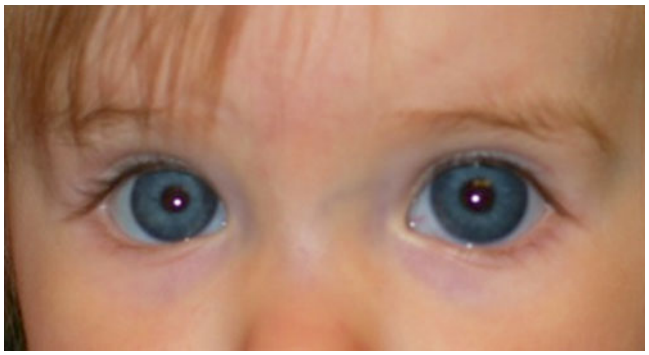

Fig. 61.3 Congenital glaucoma left eye. *Note*: enlarged cornea and increased tear meniscus, left eye

Fig. 61.4 Epiphora. *Note*: increased tear meniscus

Management

In infants with suspected NLD obstruction without dacryocystocele, the ocular adnexa should be examined and the puncti inspected to ensure that they are present. If the adnexa are normal, the [tentative] diagnosis of NLDO is made; however, probing and irrigation is required to definitively diagnose this condition. The initial practice is observation and compression of the tear sac, generally in infants under the age of 6–9 months. While this has generally been described as nasolacrimal sac massage, the actual action is compression that has been described in a medial and then downward direction [9, 15] (Fig 61.6). Qian and Traboulsi recommend infrequent (once or twice a day) medial brisk compression of the sac; when the sac is full, and the hydrostatic pressure inside of it can increase sufficiently, with compression, to burst the membrane at the valve of Hasner [16]. Topical antibiotic drops may be considered if an associated conjunctivitis is present. If there is no improvement, probing and

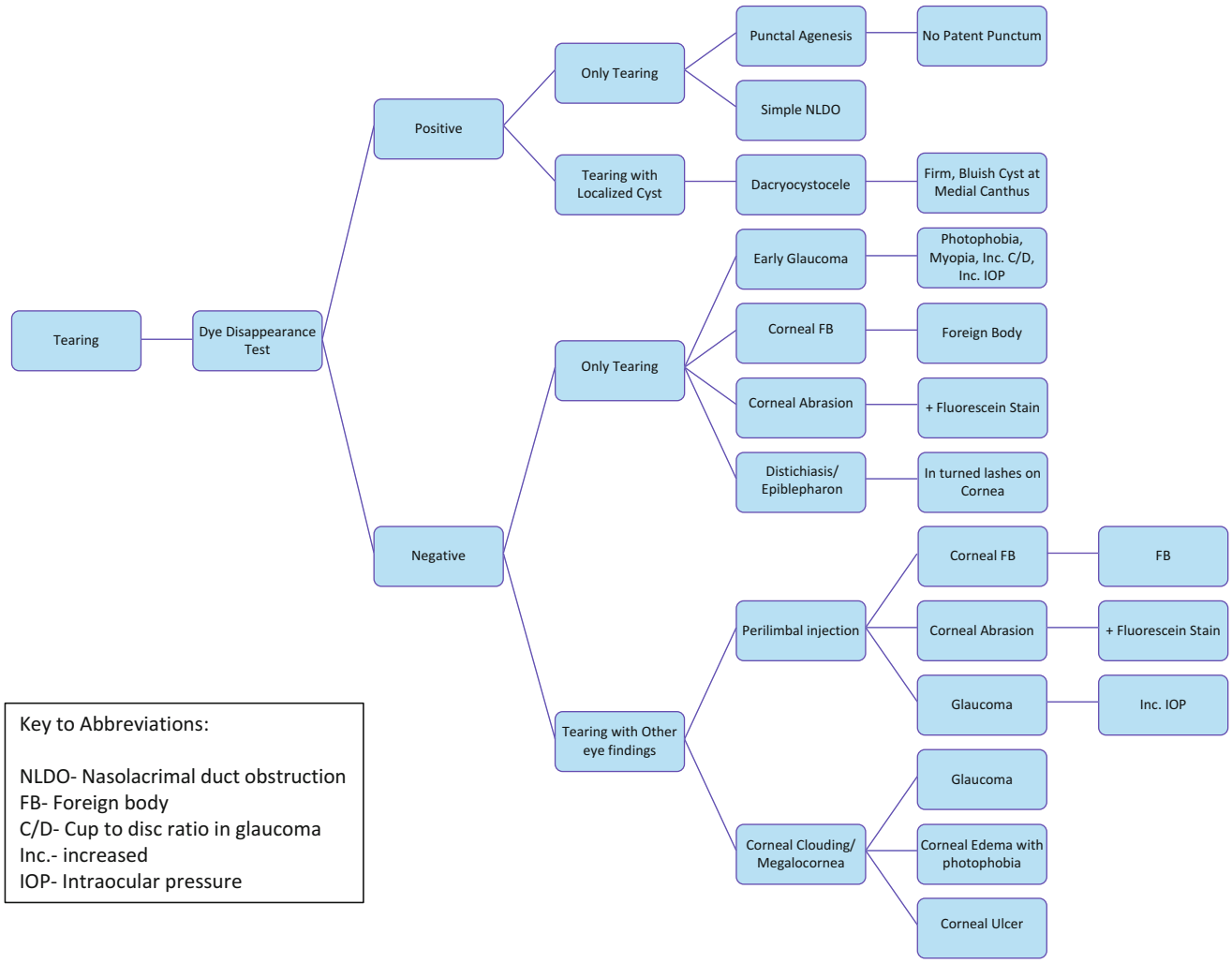

Fig. 61.5 Differential diagnosis and algorithm for epiphora in infants and small children

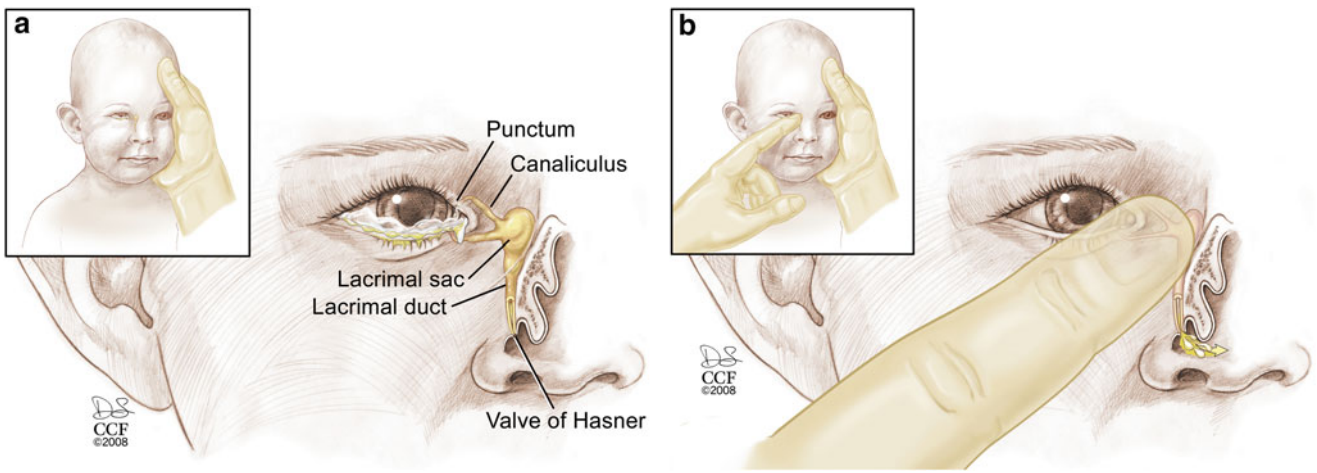

Fig. 61.6 (**a**) NLD compression (Courtesy of Dr. Elias I. Traboulsi. Copyright CCF). (**b**) NLD compression. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2008–2015

irrigation may be considered, with some variation in opinion about the timing of this procedure.

Agenesis of the puncti also results in epiphora; its treatment involves punctoplasty or punctal dilation in addition to probing and irrigation, as there may be additional obstructions further along the NLD system [17, 18]. If the punctum is not visible, it may be possible to reestablish it by identifying its probable location (there may be a small bubble-like spot along the lid margin) and slicing into it using a sharp needle or very fine blade; if the opposite punctum is patent, a small pigtail probe may be carefully used to identify the location of the absent punctum. If there is complete upper and lower punctal agenesis, a dacryocystorhinostomy may be needed to establish drainage.

Congenital Dacryocystocele

A congenital dacryocystocele appears as a bluish tinged cystic mass in the inferior nasal quadrant of the orbit. In some cases, a congenital dacryocystocele can be diagnosed by fetal ultrasound [19]. If a dacryocystocele develops or is present at birth (Fig. 61.7), there is a significant risk for dacryocystitis (Fig. 61.8), a secondary orbital abscess, cellulitis (Fig. 61.9), and associated bacteremia [20]. Early treatment is indicated for a congenital dacryocystocele due to these potential complications. Initial management is often conservative with attempted manual decompression of the cyst; brisk and firm compression may result in opening into the nose. If there is evidence of infection, systemic antibiotics are administered, and in some cases hospital admission may be required; this is generally done if there is fever and/or evidence of cellulitis. If there is insufficient improvement or resolution of the problem, surgical management should occur, with probing and irrigation [21], as well as intranasal examination for a cyst, which is then incised through an endoscope. Such cysts may obstruct the nasal airway. Orbital cellulitis is a significant complication and CT imaging may be necessary in some cases to determine the extent and etiology of the cellulitis. Coordination with the ear, nose, and throat service at the time of surgery allows for intranasal cyst marsupialization and excision of the cyst if the ophthalmologist is not confident in using the endoscope and associated instruments.

Probing in the Office Versus the Operating Room

Recently, there has been renewed interest in earlier treatment with in-office probing as opposed to later intervention under anesthesia. The in-office procedure is performed with topical anesthesia, generally at or before 6 months of age, despite the natural history that a significant number of infants will have spontaneous resolution of the problem with compression, and especially if there are recurrent episodes of conjunctivitis or if the tearing and discharge are very irritating to the infant's eyelids. This early approach avoids the potential risks of general anesthesia and may be more cost-effective than operating room-based probing, although the success rate of the earlier in-office procedure is slightly lower than completion of the procedure in the OR [13, 22–24].

Surgical Outcomes

In patients less than 1 year of age, a simple probing procedure is successful in 78–100 % of cases [1, 25]. If these infants are stratified by the location of the obstruction, the highest success rate is found in those with an obstruction at the valve of Hasner, as compared to more proximal locations in the NLD system [26]. Some reports indicate a decreasing rate of success of simple probing procedures after the age of 1 year [27, 28], while others suggest that the success rate does not decrease until after 2–3 years of age [25, 29]. These observations may indicate that in older infants, persistent NLD obstructions are indicative of a more complex underlying etiology, hence a lower success rate with simple probing and irrigation. However, even in older children, the blockage may be a simple membranous obstruction at the valve of Hasner, and probing without intubation may still be the appropriate initial procedure of choice [26, 30].

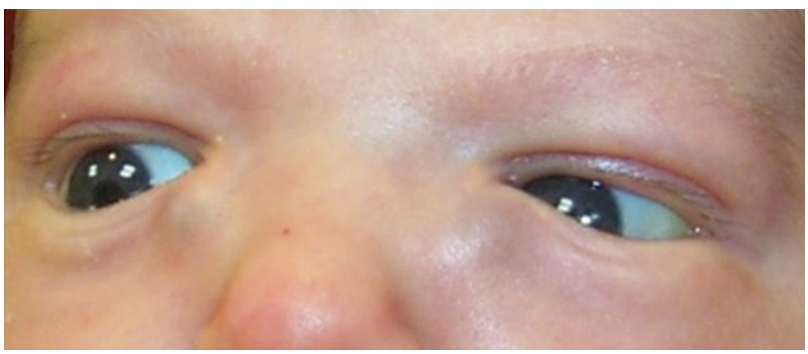

Fig. 61.7 Bilateral congenital dacryocystocele (Courtesy of Dr. Elias I. Traboulsi). *Note*: bluish cystic masses at both inner and lower canthal regions

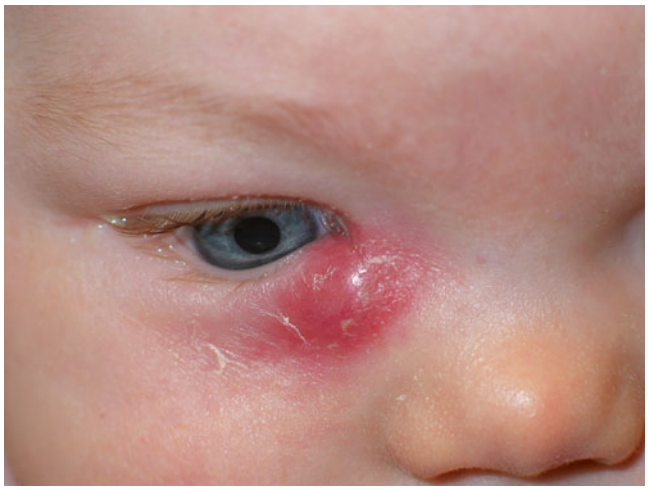

Fig. 61.8 Dacryocystitis. *Note*: cystic mass with erythematous and associated skin changes

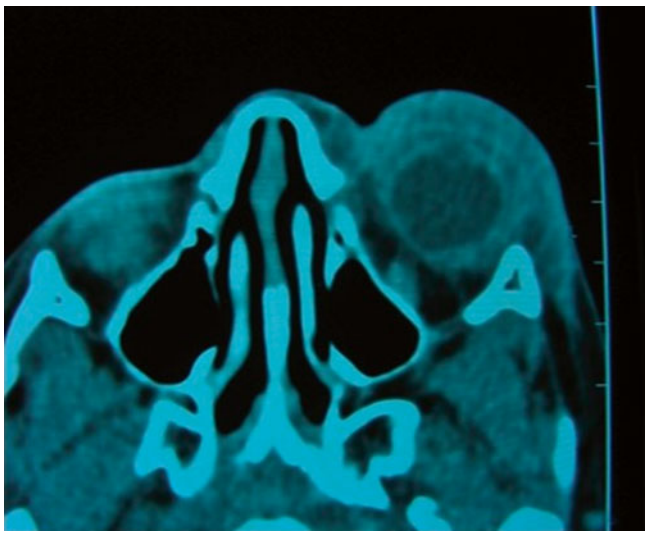

Fig. 61.9 MRI of orbital cellulitis secondary to dacryocystitis. *Note*: significant lid edema, periorbital enhancement, and proptosis

Different procedures may be necessary when the child is older or if the initial simple probing procedure has failed. One can use either a silastic bicanalicular or monocanalicular stent or balloon catheter dilation. These procedures are usually second procedures and require more surgical experience, as well as the use of additional equipments and devices. Studies by the PEDIG group and others [25, 31–35] have attempted to address the issues of timing and choice of procedures, with similar results among different surgical procedures, including stenting with mono- or bicanalicular versus balloon catheter dilation, allowing for a personal choice of procedure and no obvious benefit of one procedure over the other. The only difference in terms of success rates occurred with the duration of stent placement; if the stent was left in place for less than 2 months, a 70 % success rate was achieved, while 90 % were successful if the stent was left in place for more than 2 months [33].

Patients with craniofacial abnormalities and dysmorphic syndromes have NLDO that may be more complex and secondary to underlying anatomic abnormalities [36, 37]. This is most commonly encountered in patients with trisomy 21, in whom there is a higher frequency of unusual causes for the obstruction such as an obstruction proximal to the lacrimal canal as compared to patients without a diagnosed syndrome [38].

Conclusions

The type and timing of interventions for the treatment of NLD obstruction depend on the clinical findings. Initial management should always begin with effective lacrimal compression, and the maneuver should be demonstrated to the parent in the office. The urgent use of surgical procedures should only be considered in infants with recurrent conjunctivitis, cellulitis, or dacryocystocele. The decision to treat earlier than 9–12 months of age involves a careful discussion with the parents including spontaneous resolution with or without massage, the ability to perform a quick and controlled office probing in a struggling infant, and thus perhaps a decreased success rate as compared to performing the procedure under anesthesia versus performing the procedure in the OR with the risks associated with general anesthesia. Generally, the primary surgical treatment should be probing and irrigation, with consideration to add either stent or balloon catheter dilation in older children or those who have failed simple probing. In-office probing should be reserved for surgeons who have achieved a smooth and expeditious technique to prevent complications such as false passage.

Case Presentations

Case 1

See Fig. 61.8

Clinical Synopsis

A 2-day-old infant is referred for evaluation of an enlarging reddish mass at the inner lower lid. There is a cystic quality, and the skin is tense with overlying erythema accompanied by low-grade fever. There is tearing and mucoid debris in the tear film and a normal dilated eye exam, with no foreign body on the corneal

(continued)

or conjunctiva nor epiblepharon or entropion. The eye is soft and quiet. There was no history of a snoring pattern of breathing or difficulty feeding.

The most likely diagnosis is dacryocystitis, which needs to be treated quickly with topical antibiotics and digital massage of the cyst in an attempt to decompress the cyst. Oral or parenteral antibiotics need to be initiated to prevent the infectious spread to the orbit or systemically. CT imaging with contrast should also be considered to evaluate for dacryocystocele or other structural anomalies and/or post-septal extension of infection.

Once the infectious process was controlled (usually 10–14 days of systemic antibiotics), probing and irrigation to open the NLD along with intranasal examination to determine the presence of an airway obstruction was performed due to a complicating infection and the persistence of the tearing and debris, despite the compression.

Case 2

See Fig. 61.3

Clinical Synopsis

A 6-month-old infant has a history of tearing from both eyes and is also noted to have dried tears on cheeks. However, this patient exhibits extreme photophobia. While examination demonstrates an increased tear meniscus, there is a slight haziness to the corneas and enlargement with diameters of 12.5 mm in the right and 12 mm in the left. Cycloplegic retinoscopy demonstrates a refractive error of $-6.00+3.00\times120$ in the right eye and a retinoscopy of $-4.50+2.75\times75$ in the left. The fundus view is hazy and globes were firm to palpation (IOP unable to be obtained with accuracy). The dye retention test is negative.

This clinical appearance is that of congenital glaucoma, which is the major concern in the differential diagnosis of tear duct obstruction. Treatment is an exam under anesthesia (EUA) and possible glaucoma medication or surgical intervention (see Chap. 42 on Childhood Glaucoma). The patient was treated with an exam under anesthesia followed by glaucoma management.

Case 3

See Fig. 61.1

Clinical Synopsis

A 3-month-old infant has a history of recurrent tearing with repeated episodes of conjunctivitis treated by the pediatrician. The examination demonstrates an increased tear film with dried tears around the lower lid and dried and wet mucoid debris throughout the lashes. Ocular examination is unremarkable without evidence of lash abnormality, corneal or conjunctival foreign bodies, corneal abrasion, findings of uveitis, or evidence of glaucoma. The fluorescein dye retention test reveals decreased drainage and persistence of the dye in the tear film suggesting the diagnosis of an NLD obstruction.

The options for management include early NLD probing and irrigation in-office or close observation with NLD massage. The family elects for observation and massage of the obstructed NLD (Fig. 61.1). If the tearing is minimal and there is evidence of improvement, then continued observation for up to 3 years could be considered; however, there was no resolution by 12 months of age, so surgery was planned. The patient undergoes probing and irrigation, with the finding of stenosis and obstruction, proximal to the nasolacrimal sac. One month later, tearing and mucoid debris recur. The family elects for repeat surgery, beginning initially with a probe to determine the site of the obstruction. If the obstruction is at the level of the valve of Hasner ("simple" NLDO), then P&I could be completed. Since the original obstruction was higher, one could consider placement of a stent to maintain patency or balloon catheter dilation. In this case, a Ritleng™ system Monoka™ stent was placed after the finding of multiple membranous obstructions between the lacrimal sac and the valve of Hasner. The silastic monocanalicular stent was left in place for 5 months without evidence of local trauma to the cornea or conjunctiva and was removed in-office, under topical anesthesia. The child remains symptom-free at 5 years.

Case 4

Clinical Synopsis

A 3-year-old child arrives with a history of acquired tearing and debris. The family relates there was a history of spontaneous resolution of an NLD obstruction at 10 months of age with compression. The history is also significant for a number of episodes of conjunctivitis with one episode of sinusitis and URI. The eye exam is normal without findings of foreign body, corneal abnormalities, iritis, or glaucoma. The refraction was normal and there was a normal fundus exam.

The differential diagnoses of acquired epiphora unrelated to tear duct obstruction include distichiasis, corneal or conjunctival foreign body, and photophobia from uveitis or glaucoma. In this case, none of these non-NLD etiologies were present. Initial management began with tear duct compression. However, the symptoms failed to resolve, and a probing and irrigation was completed under anesthesia to determine location of obstruction and to determine the need for possible placement of a stent or for performing balloon catheter dilation. The child was found to have a more complicated probe with higher multiple obstructions. An upper canalicular stent was placed successfully without complications. There was noted postoperatively a mild intermittent tearing without associated infections. After 5 months of observation, the stent was successfully removed in-office with complete resolution of tearing. This might also have managed by using balloon catheter dilation.

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Management of Blepharoptosis in Infancy and Childhood

62

Forrest J. Ellis

Abstract

Ptosis of the eyelid in infancy is most often congenital and is typically due to a developmental abnormality in the subnucleus of the third cranial nerve or its axon, which is responsible for the innervation of the levator palpebrae superioris muscle. The congenitally under-innervated levator muscle fails to develop normal muscle architecture with resultant poor contractility. Congenital ptosis may be unilateral or bilateral and can be inherited. Other etiologies of ptosis in infancy include congenital myasthenia gravis, ptosis associated with congenital cranial dysinnervation disorders or synkinetic dysinnervation disorders (Marcus Gunn jaw-winking ptosis), congenital Horner syndrome, myoneural junction disorders, and congenital third cranial nerve paresis. Ptosis can also occur in association with a variety of genetic syndromes. Acquired ptosis in infancy and childhood can be the result of mechanical factors such as tumors (i.e., capillary hemangioma), trauma, or acquired neurologic disorders. Amblyopia is frequently associated with ptosis of infancy and childhood and can be the result of anisometropia from induced astigmatism in the eye with ptosis or from occlusion in cases of more severe ptosis. The timing of surgical correction and the choice of surgical procedure are determined by the severity and etiology of the ptosis, the threat to vision, and the presence of significant chin-up head posture, as well as by associated ocular or systemic conditions.

Keywords

Congenital • Ptosis • Refractive error • Amblyopia • Strabismus • Dysinnervation

The Problem

Drooping of an upper eyelid(s) is termed blepharoptosis or more simply ptosis. The eyelids are elevated by the levator palpebrae superioris and to a lesser degree by the superior tarsal muscle (Müller's muscle). The nerve supply to the levator muscle is from posterior third cranial nerve (CN-3) nuclear cell bodies. The origin of the levator muscle is just above that of the superior rectus muscle at the orbital apex. The levator muscle merges into a flat layer of tendon, the levator aponeurosis, prior to inserting into the tarsal plate and the skin of the upper lid.

Ptosis may be unilateral or bilateral and can be inherited. It may result from under-innervation of the levator muscle or Müller's muscle, disorders of the myoneural junction, or a developmental defect associated with genetic syndromes [1]. Many cases of congenital ptosis are the result of congenital cranial nerve misinnervation or dysinnervation [2, 3]. If a developing muscle is under-innervated during

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development, the muscle frequently appears fibrotic with poor development of normal muscular tissue. As such the muscle will not only demonstrate poor contractility and result in ptosis but will also demonstrate poor relaxation resulting in varying degrees of lagophthalmos [4].

Isolated Ptosis

Ptosis may be unilateral or bilateral and may be inherited as an autosomal dominant trait [5]. Isolated congenital ptosis has been linked to a defect on chromosome 1 [2]. Ptosis can range from severe, with very limited levator muscle function, to mild with only slight reduction in levator muscle function. A reduced or absent upper eyelid crease is found in children with a greater degree of ptosis.

When viewed microscopically, excised levator muscle and aponeurosis from patients with congenital ptosis generally appear dystrophic. Normal levator muscle fibers are infiltrated or replaced by fat and fibrous tissue [6]. In severe cases, little or no striated muscle can be identified at the time of operation.

Myasthenia Gravis

A defect at the myoneural junction that reduces the contractile response of an affected muscle to acetylcholine characterizes myasthenia gravis [7, 8]. This condition may be transient, congenital, or acquired. Presenting signs and symptoms are frequently ocular and variable ptosis is a common finding of the disorder.

A variety of tests are utilized to establish the diagnosis and include the rest test, the ice test, acetylcholine antibody testing, neostigmine test, edrophonium test (Tensilon), and single fiber electromyography. Imaging for thymic hyperplasia is usually indicated. Responses to acetylcholinesterase inhibitors and immunosuppression further establish the diagnosis. Treatment is tailored to both systemic and localized manifestations.

Craniofacial and Genetic Syndromes

Many developmental disorders are accompanied by ptosis. In fact, the finding of ptosis is so frequent with these disorders that its presence is rarely helpful in identifying a specific disorder. However, the more classic or important entities are discussed.

Blepharophimosis, Ptosis, and Epicanthus Inversus Syndrome (BPES Syndrome)

This autosomal dominant syndrome results from mutations in the *FOXL2* gene. It is characterized by shortened horizontal palpebral fissures and moderate to severe congenital ptosis, epicanthus inversus, and telecanthus. Surgical repair involves correction of the ptosis, typically with frontalis suspension technique, and correction of telecanthus [9]. The management of telecanthus involves a variety of soft tissue techniques such as those described by Mustarde and also Roveda. Transnasal wiring is utilized with more severe cases. While surgical repair of telecanthus and ptosis may be performed simultaneously, many surgeons prefer to perform these procedures at separate settings.

Cranial Nerve III Paresis

Congenital CN-3 palsy is occasionally a cause of ptosis in infancy. A structural lesion is rarely discovered in CN-3 palsy, but central defects involving the CN-3 and other central structures have been reported [10]. Signs of aberrant regeneration or synkinesis are frequently present. The pupil may be paradoxically small and not reactive. Special consideration must be given to the cornea when considering ptosis in cases of CN-3 palsy. If the globe does not elevate, corneal drying may occur if the upper lid is significantly elevated surgically. Surgical results vary and more than one strabismus and/or eyelid surgery is usually required. Usually strabismus surgery is performed prior to ptosis surgery. Amblyopia is common and may be difficult to treat [11, 12].

Double Elevator Palsy

This condition is also known as *monocular elevation deficiency*. It is usually congenital but is occasionally acquired. Congenital ptosis may be accompanied by dysfunction of the ipsilateral superior rectus muscle without other signs of CN-3 palsy. These findings suggest that the abnormality is limited to the superior division of the CN-3. Bell's phenomenon generally is demonstrable in these patients unless an inferior restriction is present. Several variations in clinical presentation have been described [13]. Monocular elevation deficiency may be considered to be secondary to deficient supranuclear innervation, superior rectus weakness, or inferior rectus restriction. Ptosis in such cases may, in fact, be pseudoptosis. Pseudoptosis disappears when the patient fixates with the involved eye.

In some cases of monocular elevation deficiency, ptosis improves after extraocular muscle surgery, especially if an inferior rectus muscle restriction is discovered. In general, ptosis surgical repair is delayed until after strabismus surgery is performed.

Horner Syndrome

Congenital Horner syndrome is characterized by ipsilateral findings of mild ptosis, miosis, and, frequently, anhidrosis of the ipsilateral face. The ipsilateral lower eyelid may be elevated (reverse ptosis). The condition can be present in patients with neuroblastoma [14], but is more often associated with other congenital anomalies or with cardiopulmonary, neck surgery, or brachial plexus injury at the time of birth [15]. Horner syndrome must be included in the differential diagnosis of mild ptosis. Horner syndrome results from sympathetic denervation of Müller's muscle and other structures receiving sympathetic innervation. The iris of the involved eye often has less pigment if the condition is congenital or if it is acquired neonatally.

Neuroblastoma has been reported with both congenital and acquired Horner syndrome. Therefore, children with Horner syndrome without a known surgical etiology require evaluation to rule out a mass lesion. Neuroimaging (MRI with and without contrast) of the brain, neck, and thorax is indicated. In addition, urinary levels of catecholamines should be determined [16].

Synkinetic Syndromes

Marcus Gunn jaw-winking phenomenon is commonly associated with unilateral or bilateral ptosis. In this condition, the motor nerve to the external pterygoid muscle is misdirected to the ipsilateral levator muscle. Lid elevation occurs with mastication or with movement of the jaw to the contralateral side. Treatment is directed toward elimination of lid elevation with mastication, yet retaining adequate lid height. Often, a child will naturally learn to avoid those movements of the jaw that induce a more exaggerated lid elevation. In mild cases, a small external levator advancement may correct the ptosis, but in cases with a more exaggerated "wink," the external levator tendon is disinserted from the tarsus creating a complete ptosis [17, 18]. This ptosis is then corrected with a frontalis muscle suspension procedure. CN-3 palsy may also be associated with aberrant regeneration and synkinesis. Treatment is directed toward correcting the ptosis in primary position after the eye is realigned.

Acquired Ptosis

Head injuries may result in ptosis either from direct injury to the levator muscle tendon complex of the upper eyelid or from damage to CN-3. Aberrant regeneration of the CN-3 also may occur as a result of brain tumors, aneurysms, and neurosurgical procedures.

Kearns–Sayre Syndrome and Chronic Progressive External Ophthalmoplegia

Kearns–Sayre syndrome is a mitochondrial deletion disorder characterized by progressive external ophthalmoplegia, heart block, retinitis pigmentosa, and, occasionally, endocrine and central nervous system manifestations. Patients may present with ptosis and limited eye movements and retinal degeneration are consequently identified. Cardiac evaluation, especially for cardiac conduction block, is paramount. Frontalis suspension procedures are useful for correction of ptosis but limited ocular motility risks corneal exposure.

Myotonic Dystrophy

Myotonic dystrophy is believed to be the most common inherited neuromuscular disease in adults, but may occur congenitally. Additional features include polychromatic cataracts, gonadal atrophy, premature thinning or loss of the hair, and other systemic problems. It is an autosomal dominant disorder characterized by myotonia and progressive muscular weakness. Ptosis is generally mild and bilateral and may be present early in the course of the disease.

Other Etiologies

A lid mass exerts extra weight on the eyelid resulting in mechanical ptosis. This may occur with congenital malformations, congenital or acquired tumors, inflammations, infections and abscess, or imbedded foreign material. Diagnostic evaluation and medical and surgical management are dependent on the etiology and location of the mass.

Diagnostic Evaluation of the Child with Ptosis

A thorough medical history, family history, review of systems, and general physical examination should be done in all cases. A history of ptosis variability may necessitate diagnostic evaluation for myasthenia gravis. However, many

patients with simple congenital ptosis will report increased ptosis when the child is fatigued or ill. Family photographs are useful in determining the onset or variability of ptosis. When a systemic association is suspected, genetic consultation is frequently beneficial.

Visual acuity and refractive error should be determined. A thorough eye examination should be performed with particular attention to ocular alignment and motility, corneal sensitivity, and tear film, as well as retinal function.

Eyelid height should be measured with each eye fixating. Lid position in downgaze should be noted. If ptosis is congenital, the ptotic eyelid appears higher in downgaze. A ptotic eyelid does not appear higher in downgaze when ptosis is acquired. If lid retraction is present, the higher lid remains higher in downgaze. Assessment of Bell's phenomenon with forced eyelid closure should be determined.

Eyelid height, contour, and eyelid crease and eyelash position and contour are determined. Most cases of congenital ptosis will have straighter and more inferiorly directed upper eyelid cilia. Levator muscle function should be measured. Levator muscle function is measured in millimeters as the distance the eyelid margin travels from downgaze to upgaze (without the use of the frontalis muscle). With all this information, the amount of surgical correction desired can be determined and an appropriate procedure selected.

Surgical Management

Surgical correction of ptosis may be considered at virtually any age. Factors such as significant amblyopia, anisometropia, or strabismus may necessitate earlier intervention, whereas milder cases often may be managed with surgery delayed until the child is much older. Correction of ptosis will not alleviate or necessarily prevent amblyopia or refractive error. These conditions should continue to be monitored during the child's development. Surgical correction around age 4–5 years often is preferred when earlier intervention has not been required. By this age, accurate measurements can be obtained preoperatively. In addition studies suggest that negative psychosocial interactions with peers are more likely after 6 years of age for children with a visible abnormality.

Surgical Procedures

External Levator Resection

Resection of the distal levator muscle–tendon aponeurosis complex utilizing a lid-crease incision offers a physiologic and cosmetically pleasing result of ptosis repair for many children. An external levator resection is indicated when lid excursion from downgaze to upgaze exceeds 4 mm. The greater the amount of levator function, the smaller the amount of levator tendon resection (see Table 62.1). The amount of levator resection necessary to achieve adequate results is much greater for the child with congenital ptosis compared to that required in an adult with an acquired ptosis.

Frontalis Suspension Procedure

This procedure is designed to facilitate eyelid elevation utilizing the improvement in lid elevation through brow elevation. This is achieved by attachment of the upper lid to the frontalis muscles with nonabsorbable material. The procedure is indicated when levator function is less than 4 mm such as found in patients with severe congenital ptosis and blepharophimosis syndrome. Frontalis suspension procedures produce lagophthalmos that is particularly noticeable in downgaze. Lagophthalmos effect is more apparent if a unilateral suspension procedure is done, and for this reason, some surgeons perform bilateral frontalis suspension procedures in cases of severe unilateral ptosis. This procedure is relatively contraindicated in

Table 62.1 Choice of procedures for correction of congenital ptosis depending on degree of ptosis

Levator function	4 mm ptosis	3 mm ptosis	2 mm ptosis	1–2 mm ptosis with positive phenylephrine test
<4 mm	Frontalis suspension	–	–	–
5–7 mm	–	External levator resection 17–22 mm	External levator resection 12–15 mm	
8–10 mm		External levator resection 15–17 mm	External levator resection 10–12 mm	
10–13 mm			External levator resection 6–9 mm	
>14 mm				Müller's muscle resection

patients with limited elevation of the eye or when corneal sensation is poor.

Several materials are available for securing the lids to the frontalis muscles. Consensus suggests that the best material in terms of strength, longevity, is autogenous fascia lata, typically obtained from the leg of a child who is at least 3 years old. A variety of alternative materials has been developed and is often preferred over autogenous fascia lata by some surgeons.

Müller's Muscle Resection and Fasanella–Servat Procedures

The upper lid may be elevated by resecting tissue from the conjunctival side of the upper eyelid. This tissue includes a portion of the tarsus, conjunctiva, and Müller's muscle with or without resection of a portion of the tarsus. Indications for this procedure in children with ptosis are typically reserved for those with Horner syndrome.

Case 1

One-year-old otherwise healthy child with 2 mm of ptosis of the left upper eyelid since birth. Ptosis is slightly worse toward evening. Family history is noncontributory. Ocular exam is entirely normal with the exception of 0.50 diopters of hyperopic astigmatism in the right eye. Child was managed with follow-up examinations every 6 months until ptosis surgery was performed at age 4.5 years. Choice of procedure was external levator resection based on amount of levator muscle function (10 mm). Postoperatively the child demonstrates good symmetry to the eyelid height in primary gaze (Fig. 62.1a, b).

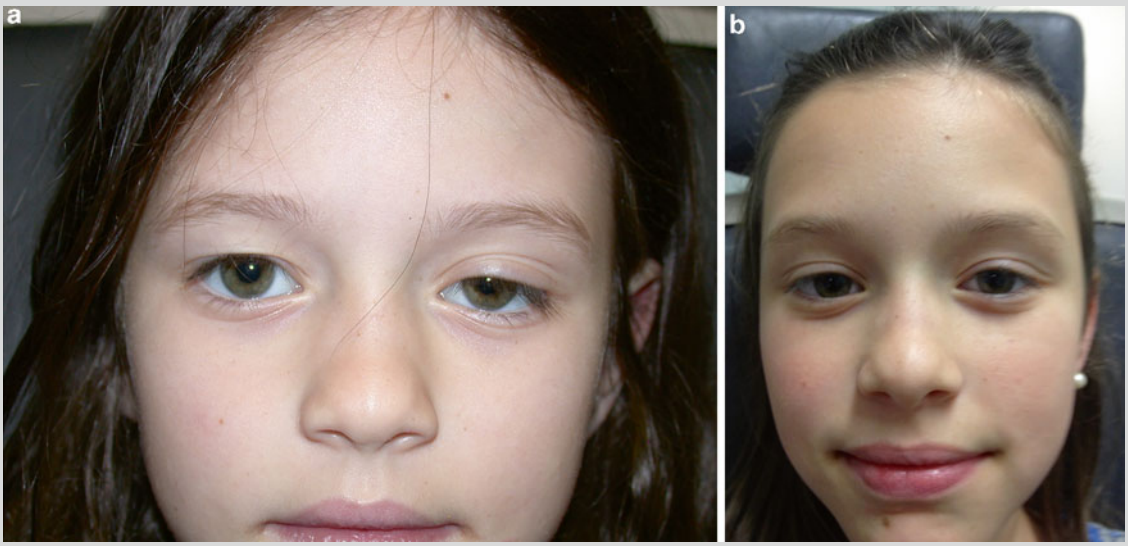

Fig. 62.1 (**a**) Congenital ptosis of left eyelid. Because the levator function was 10 mm, surgical intervention with a levator resection was performed. (**b**) Postoperative image of patient demonstrating resolution of ptosis

Case 2

Five-year-old child with congenital Horner syndrome of the right upper eyelid. Lighter pigmentation of the right iris is noted on exam. Evaluation during infancy was negative for any identifiable etiology. Surgical procedure selected was a Müller's muscle resection [19]. Postoperative results show minimal residual ptosis (Fig. 62.2a, b).

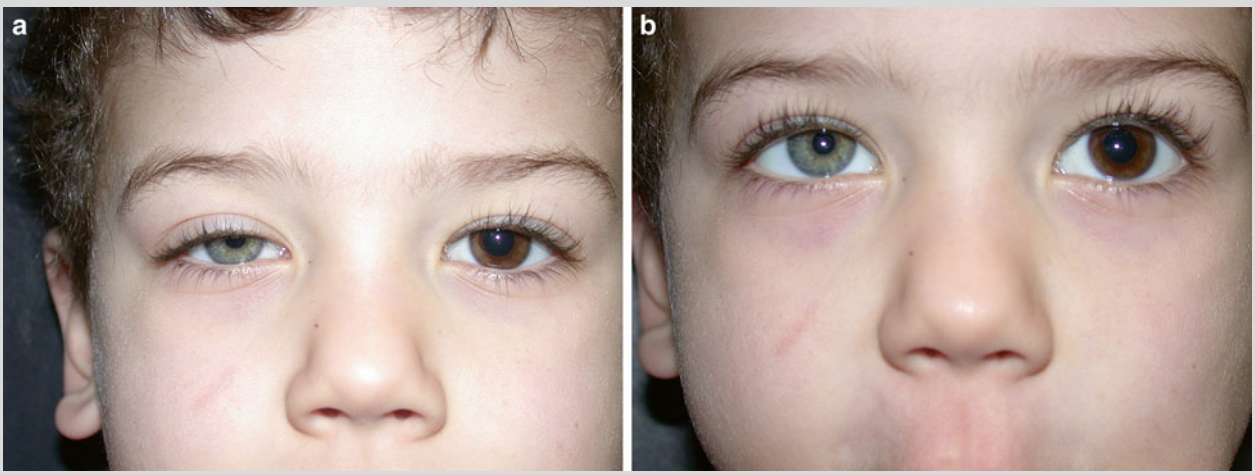

Fig. 62.2 (**a**) Patient with congenital Horner syndrome. In addition to the ptosis, miosis as well as hypopigmentation of the iris is noted in the right eye. (**b**) Resolution of ptosis following Müller's muscle resection

Case 3

Two-year-old Asian child with blepharophimosis syndrome. The father is affected by the same condition. Findings in the child included significant bilateral ptosis, shortened horizontal palpebral fissures (phimosis), telecanthus, and epicanthus inversus. The child manifested a significant chin-up head posture. At 2.5 years of age, the child underwent bilateral frontalis suspension with Ptose-up (expanded polytetrafluoroethylene, FCI Ophthalmics, Marshfield Hills, MA) and simultaneous Roveda procedure to correct the telecanthus. Figure 62.3a shows the child's eyes prior to surgery and Fig. 62.3b is 2 weeks following surgery. Although these procedures are frequently performed separately, the parents elected to have both procedures performed at the same setting to avoid additional anesthesia.

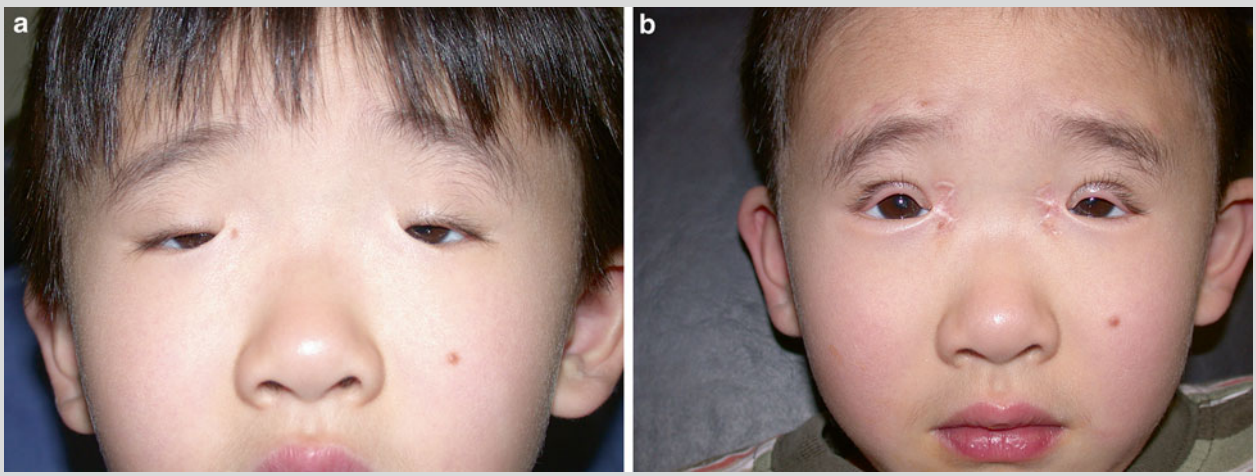

Fig. 62.3 (**a**) Patient with blepharophimosis syndrome with significant bilateral ptosis, shortened palpebral fissures (phimosis), telecanthus, and epicanthus inversus. (**b**) Postoperative images status post bilateral frontalis suspension for the ptosis and Roveda procedure to correct the telecanthus

Complications

Complications from ptosis surgery vary depending on the type of procedure performed. Undercorrections are more common than overcorrections. With large external levator resections and frontalis suspension procedures, exposure keratopathy is of greater concern. This is especially true when upgaze limitation of the affected eye(s) is present. However, lagophthalmos is expected with most procedures. Infection is rare with eyelid surgery, but is more common when non-resorbable material is used, as with frontalis suspension procedures. Contour abnormalities and scarring occur but are minimized with careful attention to surgical technique.

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Preseptal and Orbital Cellulitis

63

Rachel E. Reem

Abstract

It is important to distinguish between preseptal and orbital cellulitis, as both can present with similar signs and symptoms of red, swollen eyelids, with or without discharge, and with or without upper respiratory symptoms. Decreased visual acuity, afferent pupillary defect, motility deficit, and proptosis suggest an orbital process as opposed to a preseptal cellulitis. Orbital cellulitis can threaten vision and, through optic nerve and meningeal involvement, life. Hence, a high index of suspicion of orbital cellulitis and close monitoring of the response to treatment are crucial in preventing the severe complications of orbital infection. Radiographic imaging such as contrast-enhanced CT or MRI can help determine whether a subperiosteal or orbital abscess is present, or if infection has spread beyond the orbit, resulting in cavernous sinus thrombosis or cerebral abscess. Both preseptal and orbital cellulitis must be treated with systemic antibiotic therapy and monitored with serial ophthalmologic examinations. Surgical intervention may be necessary to drain subperiosteal or orbital abscesses.

Keywords

Preseptal cellulitis • Orbital cellulitis • Orbital abscess • Sinusitis • Subperiosteal abscess

The Problem

Periocular infections are often diagnosed as preseptal cellulitis or its more serious and possibly life-threatening counterpart, orbital cellulitis. Differentiation between the two is based on the location of the infection relative to the orbital septum, whether anterior or posterior.

Preseptal cellulitis most commonly arises from eyelid trauma, including insect bites, eyelid lacerations, or infected hordeola, but can also be secondary to sinusitis or conjunctivitis [1–4]. Patients present with erythema and edema of the soft tissues surrounding the eye. They may demonstrate purulent discharge or conjunctival injection on exam, but motility and pupillary reflexes are typically intact. The mean age of patients with preseptal cellulitis tends to be lower than that of patients with orbital cellulitis, even within the pediatric population [5].

Orbital cellulitis, defined as an infection of soft tissue posterior to the orbital septum, is characterized by more ominous signs suggestive of an infectious process in the orbit such as decreased visual acuity, afferent pupillary defect, proptosis, ophthalmoplegia, and pain with eye movements, though an early or subtle orbital process may not display any of these additional signs at first [1, 6, 7]. In orbital cellulitis, patients are more likely to present with leukocytosis, fever, and/or a history of upper respiratory symptoms and generalized malaise [2, 7]. It tends to be more common in males, particularly those of Caucasian race, and occurs at an average age of 6–7 years [5, 8, 9].

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Orbital cellulitis can follow trauma which penetrates the orbital septum, or more commonly in children is secondary to sinusitis, particularly involving the ethmoid and maxillary sinuses [4, 6, 9–15]. Frontal sinus involvement can increase the likelihood of intracranial complications, as can bilateral orbital cellulitis, though rare [16–18]. Studies evaluating the periocular complications of acute sinusitis in children reveal that 50–72 % of sinus-related cellulitis tends to be preseptal, 19–50 % orbital, and 9–15 % associated with subperiosteal abscesses [5, 6, 19].

Due to its underlying sinus infection etiology, orbital cellulitis is often polymicrobial in nature. Commonly involved organisms include *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Haemophilus* species, *Staphylococcus aureus*, Group A streptococcus, and anaerobes of the upper respiratory tract such as *Peptostreptococcus*, *Fusobacterium*, and *Bacteroides* species [2, 15, 20, 21]. *Streptococcus anginosus* and methicillin-resistant *Staphylococcus aureus* (MRSA) are demonstrating a rising presence as well [2, 15, 22, 23]. If fungal agents are suspected, they are most commonly *Mucor* or *Aspergillus* species and rarely occur in settings where host defenses are not already compromised, e.g., by metabolic abnormalities or systemic immunocompromise [24, 25]. Younger patients tend to present with single microbe infections, whereas older children display polymicrobial infections [4, 11, 25].

Evidence for Effective Diagnosis and Treatment

The clinical decision-making process for the diagnosis and management of periocular infections revolves around determining their location relative to the orbital septum. The most commonly referenced classification scheme for periocular infection is one proposed by Chandler in 1970 [26] and further simplified by Jain and Rubin in 2001 [24]. Under the simplified scheme, patients are classified into one of three groups: Group 1, those with preseptal cellulitis; Group 2, those with orbital cellulitis (with or without intracranial complications); and Group 3, those with orbital abscess (with/without intracranial complications). Group 3 is further subdivided into those with subperiosteal abscess and those with intraorbital abscess [24].

Diagnosis

Patients presenting with red, swollen eyelids should be examined carefully for signs of orbital involvement; these include proptosis, vision deficit, afferent pupillary defect, and restriction of or pain with eye movements. Imaging of the orbits should be strongly considered in these patients [1, 9, 27–29]. In pediatric patients, particularly those who are apprehensive, uncooperative, or preverbal, differentiating preseptal from orbital cellulitis can be challenging. Thus, imaging plays a vital role in differentiating pre- from post-septal disease, as well as evaluating for the presence of orbital abscess or intracranial extension. Contrast-enhanced CT scanning is the imaging modality of choice as it can identify soft tissue changes while also providing bony detail [1, 2, 11, 24]. Indeed, there are reports of patients with preseptal cellulitis who display no signs of orbital involvement but have periosteal elevation, enlarged extraocular muscles, or subperiosteal fluid on CT scan [1, 27, 28]. It is crucial to determine whether orbital infection is present, as occasional cases can progress to intracranial involvement such as meningitis, cavernous sinus thrombosis, or cerebral abscess, in addition to permanent loss of vision [6, 18, 24].

A complete blood count (CBC), blood cultures, conjunctival or nasopharyngeal cultures when possible, sedimentation rate, antistreptolysin O titers, and CSF analysis in the context of central nervous system involvement or bilateral disease should be included in the initial workup [11, 24].

On CBC testing, an elevated white blood cell count may occur in either pre- or post-septal disease, but is more common in the latter [11, 24]. The erythrocyte sedimentation rate is often elevated in patients with orbital cellulitis. Antistreptolysin O titers should be considered in cases where alpha-hemolytic *Streptococcus* species are suspected. Blood cultures may be revealing in the setting of septicemia; although more specific, they are less sensitive than conjunctival or nasopharyngeal cultures. Conjunctival cultures are generally low yield, but may provide evidence as to etiology, particularly in settings where discharge or resistant organisms may be present. Likewise, nasopharyngeal aspirates in the setting of sinusitis can be helpful in determining the offending organism. Lumbar puncture with CSF analysis is only recommended in those patients who display meningeal or CNS signs, or bilateral disease with high suspicion of CNS involvement [11, 24, 25].

It is also important to consider masquerade-type conditions that may simulate orbital and periocular infections. Neuroblastoma, rhabdomyosarcoma, fungal infections, orbital myositis, lymphangioma, Graves disease, dermoid cyst rupture or inflammation, trauma, or systemic conditions such as sickle cell disease can all present with signs of orbital inflammation or can simulate such signs [2, 24]. There are also several reports that up to 5 % of retinoblastoma patients can present with inflammatory proptosis that mimics orbital cellulitis [24, 30, 31].

Treatment

The main treatment decisions in patients with preseptal cellulitis revolve around the use of oral vs. intravenous antibiotics and whether the patient's condition should prompt

hospital admission. In a review of 395 papers, Al-Nammari et al. found no evidence to favor the treatment of preseptal cellulitis patients with oral as opposed to IV antibiotics, so this question is yet unanswered in the literature [32]. Brugha et al. suggest there may be some value to outpatient IV antibiotics with daily follow-up in patients with preseptal cellulitis, but acknowledge that patients who were monitored as outpatients in their study tended to have a less severe presentation than those admitted to the hospital [33]. Similarly, Goldman et al. noted that the greater the number of local symptoms (redness, edema, discharge, eyelid swollen shut, conjunctival injection, or pain), the greater the likelihood that a patient was admitted to the hospital [3]. Because pediatric patients have the potential to deteriorate rapidly, admission to the hospital for IV antibiotics should be strongly considered, particularly for those who are younger or display more than one local symptom. If outpatient therapy is elected, daily examinations are necessary, and patients who fail to improve should be admitted to the hospital.

Antibiotics should be broad spectrum, with consideration for increasingly common resistant organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA) in patients with relevant risk factors. These risk factors include previous history of MRSA infection; high community prevalence of MRSA; exposure to long-term care facilities, nursing homes, prisons, homeless shelters, daycare facilities, or neonatal intensive care units; and membership in certain high-risk groups such as athletic teams, military recruits, and health-care workers [2, 19, 20, 22, 34–38]. In fact, the prevalence of community-associated MRSA has been increasing relative to hospital-associated MRSA. Accordingly, the prevalence of MRSA-positive ocular isolates is also increasing [36–39], and resistance of MRSA to bacitracin, erythromycin, ofloxacin, levofloxacin, and ciprofloxacin has been reported in various locations [36, 37, 40]. Rutar et al. [38] caution that community-associated MRSA infections may no longer be unique to high-risk populations and recommend high clinical suspicion for MRSA in patients who fail beta-lactam antibiotic therapy. They also recommend obtaining cultures and sensitivities in patients with severe ophthalmic infections and continued awareness of the prevalence of MRSA in one's locale. Dependent upon regional susceptibility profiles, trimethoprim/sulfamethoxazole, gentamicin, rifampin, clindamycin, and fluoroquinolones seem to be appropriate first-line agents in cases suspicious for resistant organisms [36–38]. Those antibiotics to which organisms are less commonly resistant, such as vancomycin, should be reserved from initial treatment protocols to prevent the development of antibiotic resistance [22, 36]. It is increasingly important for clinicians to be aware of the common flora in their area of practice, as well as resistance profiles, and this should ultimately guide selection of initial antibiotic therapy. For patients admitted to the hospital, the simplest IV antibiotic regimen possible can help to minimize the development of antibiotic resistance as well as facilitate transition to oral antibiotics when appropriate [22, 36].

Patients with subperiosteal abscess present a different controversy: there is no uniformly accepted protocol to determine which of these patients requires surgical intervention. Some patients improve on antibiotics alone, whereas others require surgical drainage. Many of those undergoing surgical drainage turn out to have culture-negative aspirates [13, 24]. The volume of the abscess (>1250 mm^3 per Todman et al.; >3.8 mL per Le et al.) appears to have some bearing on the decision to drain: larger abscesses are more likely to require drainage [9, 16, 19]. Younger patients tend to be more likely to improve without surgical intervention [2], less likely to have positive culture results, and more likely to have only a single pathogen identified [4, 11, 14, 25]. Older age and higher temperature upon hospital admission also tend to be associated with higher incidence of the need for surgical intervention [19]. Finally, patients who worsen or show no clinical improvement after 24–48 h of medical therapy need to have surgical drainage [19, 41]. Garcia and Harris cite the following criteria as indications for surgical intervention: age 9 years or older, presence of frontal sinusitis, non-medial location of subperiosteal abscess, large abscess, suspicion of anaerobic infection (e.g., CT scan evidence of gas in the abscess space), recurrence of abscess after previous drainage, evidence of chronic sinusitis, acute optic nerve or retinal compromise, and infection of dental origin (due to suspicion of anaerobic infection). They assert that patients under 9 years of age who do not meet these criteria can be managed on broad-spectrum IV antibiotics with close observation [18]. These criteria have recently been reevaluated over 35 years of retrospective analysis at a single institution and continue to be effective, particularly in avoiding surgical intervention in younger children who may otherwise improve on their own [15].

Finally, adjunctive treatment of orbital cellulitis patients with systemic corticosteroids is somewhat controversial due to the ability of corticosteroids to mask the progression of an infection. In a prospective, comparative, single-masked interventional clinical study, Pushker and colleagues added oral corticosteroids to the treatment regimen of patients with orbital cellulitis aged 11–59 years old, who had already displayed a response to IV antibiotics [42]. Though used cautiously, corticosteroids did demonstrate a statistically significant reduction in periorbital edema, conjunctival chemosis, and eye pain. Later, residual eyelid ptosis and ocular motility were noted to be more improved in the corticosteroid-treated group as well. Ultimately, the corticosteroid-treated patients had shorter hospital stays and shorter courses of IV antibiotics. Though timing and duration of corticosteroid administration have yet to be studied, particularly in younger children, it may prove to be a beneficial adjunctive treatment in patients with orbital cellulitis.

Case Examples

As stated above, there continues to be a debate as to whether all patients with preseptal cellulitis require admission to the hospital for close observation and whether parenteral or oral antibiotics should be used [3, 32, 33]. Additional controversy exists regarding the need for immediate drainage of orbital abscesses: some patients do well with parenteral antibiotics alone, and others require surgical intervention [13, 24]. The following cases illustrate two specific examples of some of these questions.

Case 1 (Table 63.1)

Table 63.1 Case 1

Clinical history	6-month infant with 2-day history of red swollen eyelid OD		
	No fevers		
	PMH was noncontributory		
Key components of exam		*OD*	*OS*
	UCVA	CSM	CSM
	Ductions/versions	Full	Full
	Pupils	Briskly reactive, no APD	Briskly reactive, no APD
	Eyelids	2+ Upper lid edema, erythema and warmth	Within normal limits
	Anterior segment	No chemosis; 1–2 mm proptosis noted	Unremarkable
	Posterior segment	Unremarkable	Unremarkable
	CRx	Deferred	
CT scan	Opacification of both maxillary sinuses, ethmoid air cells, and infantile sphenoid sinus		
	Periosteal elevation along the right lamina papyracea measuring approximately 2 cm in length and 4.5 mm thick (Fig. 63.1)		
Management options	• Systemic antibiotics		
	• Observation versus immediate abscess drainage		
Management	Patient admitted for IV antibiotic therapy and close observation		
Interval history (2 days)	Slight clinical improvement in eyelid swelling		
Key components of exam		*OD*	*OS*
	UCVA/BCVA	CSM	CSM
	Ductions/versions	Full	Full
	Pupils	Briskly reactive, no APD	Briskly reactive, no APD
	Eyelids	2+ upper lid edema, erythema and warmth	Within normal limits
	Anterior segment	Persistent proptosis	Unremarkable
CT scan	Interval worsening of proptosis as compared to prior scan		
	Soft tissue thickening up to 7 mm (previously 5 mm by second radiologist's read)		
Management	• Endoscopic drainage of abscess per otolaryngology; lid edema improved significantly intraoperatively		
	• Culture results: no growth		
Interval history (3 days)	Patient appearing comfortable, opening both eyes spontaneously		
Key components of exam		*OD*	*OS*
	UCVA/BCVA	CSM	CSM
	Ductions/versions	Full	Full
	Pupils	Briskly reactive, no APD	Briskly reactive, no APD
	Eyelids	Mild upper lid edema, much improved	Within normal limits
	Anterior segment	Unremarkable	Unremarkable

(continued)

Table 63.1 (continued)

Management	• Transitioned to oral antibiotics		
	• Follow-up scheduled as outpatient		
Interval history (5 days)	Patient continuing to improve since his discharge from hospital		
Key components of exam		*OD*	*OS*
	UCVA/BCVA	CSM	CSM
	Ductions/versions	Full	Full
	Pupils	Briskly reactive, no APD	Briskly reactive, no APD
	Eyelids	Small amount residual edema of upper eyelid	Within normal limits
	Anterior segment	Unremarkable	Unremarkable
Management	• Continue full course of oral antibiotics		
	• Follow-up with otolaryngology		
	• One more visit with ophthalmology for full exam with CRx		

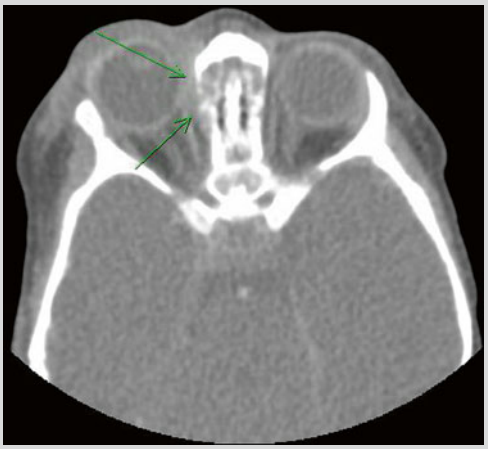

Fig. 63.1 Case 1: Axial CT scan of the orbits with contrast, demonstrating subperiosteal elevation along the right lamina papyracea. Arrows

Clinical Synopsis

This is a 6-month-old infant with clinical signs of preseptal and possible orbital cellulitis who was found to have subperiosteal abscess on CT scan of the sinuses (Fig. 63.1). He was admitted for IV antibiotics, but repeat CT scan and serial ophthalmologic examinations demonstrated worsening proptosis. Thus, the patient was taken to surgery by the otolaryngology team for endoscopic drainage of the abscess. Subsequently, his hospital course improved, and he was transitioned to oral antibiotics and managed successfully as an outpatient.

Case 2 (Table 63.2)

Table 63.2 Case 2

Clinical history	9-month infant with 2-day history of red swollen eyelid OD		
	Fevers up to 101° F		
	PMH was noncontributory (Fig. 63.2)		
Key components of exam		*OD*	*OS*
	UCVA	CSM	CSM
	Ductions/versions	Full	Full
	Pupils	Briskly reactive, no APD	Briskly reactive, no APD
	Eyelids	Within normal limits	2–3+ upper lid edema, erythema and warmth
	Anterior segment	Unremarkable	No chemosis; 1–2 mm proptosis noted
	Posterior segment	Unremarkable	Unremarkable
	CRx	Deferred	
CT scan	Sinus mucosal disease involving ethmoid air cells and maxillary sinuses; left eye proptosis with subtle post-septal inflammatory changes, no abscess		
Management options	• Systemic (IV) antibiotics		
	• Observation		
Management	Patient admitted for IV antibiotic therapy and close observation		
Interval history (1 day)	Clinical improvement in eyelid swelling		
Key components of exam		*OD*	*OS*
	UCVA/BCVA	CSM	CSM
	Ductions/versions	Full	Full
	Pupils	Briskly reactive, no APD	Briskly reactive, no APD
	Eyelids	Within normal limits	2+ upper lid edema, erythema
	Anterior segment	Unremarkable	Persistent proptosis
CT scan			
Management	• Continue IV antibiotics		
	• Continue observation		
Interval history (3 days)	Patient appearing comfortable, able to open left eye much more easily		
Key components of exam		*OD*	*OS*
	UCVA/BCVA	CSM	CSM
	Ductions/versions	Full	Full
	Pupils	Briskly reactive, no APD	Briskly reactive, no APD
	Eyelids	Within normal limits	2+ upper lid edema, able to open eye up to 6 mm
	Anterior segment	Unremarkable	Unremarkable
Management	• Continue systemic antibiotics		
	• Continue observation		
	• Patient discharged to home on oral antibiotics		
Interval history (13 days)	Patient continuing to improve since his discharge from hospital		
Key components of exam		*OD*	*OS*
	UCVA/BCVA	CSM	CSM
	Ductions/versions	Full	Full
	Pupils	Briskly reactive, no APD	Briskly reactive, no APD
	Eyelids	Within normal limits	Small amount residual erythema of upper eyelid, no edema
	Anterior segment	Unremarkable	Unremarkable
Management	• Continue full course of oral antibiotics		
	• Follow-up with otolaryngology		
	• One more visit with ophthalmology for full exam with CRx		

(continued)

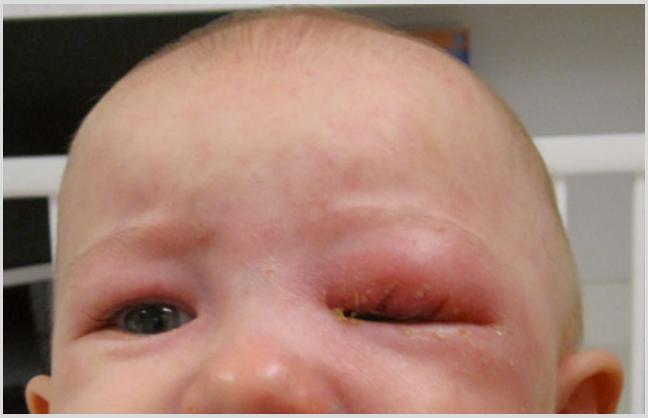

Fig. 63.2 Case 2: 9-month-old patient upon presentation to the ophthalmology clinic with *red* swollen eyelids found to have subtle post-septal inflammatory changes without abscess but no clinical signs of orbital cellulitis, and improved on IV antibiotics

Clinical Synopsis

This is a 9-month-old infant (Fig. 63.2) with clinical signs of preseptal cellulitis whose CT scan demonstrated orbital involvement but no abscess. He was admitted for IV antibiotics and improved clinically. Once improvement was confirmed, he was transitioned to oral antibiotics and managed as an outpatient until complete resolution of the cellulitis.

Overall, patients with periocular infections require close ophthalmologic monitoring and timely, careful clinical decision-making. Choices regarding outpatient versus inpatient monitoring, whether to obtain imaging studies, and whether to intervene surgically or manage conservatively all hinge upon the number of local symptoms with which a patient presents, as well as observed disease progression and appropriate clinical suspicion.

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Current Management of Inferior Orbital Wall Fractures in Children

64

Bryan R. Costin and Julian D. Perry

Abstract

Adult treatment algorithms are often not ideal for the management of orbital fractures in children in major part due to differences in the maturing status of craniofacial structures. A multidisciplinary approach that utilizes imaging studies, an awareness of occult extraocular muscle entrapment, and an emphasis on the findings on physical examination should be used to diagnose and to treat pediatric orbital floor fractures. These injuries can be grouped into two categories based on the status of inferior extraocular muscles: entrapped or "trapdoor" floor fractures and non-entrapped orbital floor fractures. The former requires earlier intervention.

Keywords

Orbital floor fracture • Trauma • Craniofacial trauma • Trapdoor fracture • Extraocular muscle entrapment

Introduction

Trauma represents the leading cause of morbidity and mortality in children, and orbital fractures as well as other craniofacial injuries constitute some of the most common sequelae of trauma [1, 2]. Important differences between the developing pediatric orbit and the adult orbit and craniofacial skeleton explain fracturing patterns unique to children as compared to adults [3]. Therefore, adult treatment algorithms are often not ideal for the treatment of fractures in children. A multidisciplinary approach based on radiographic findings and a high index of suspicion of entrapped orbital tissues based on physical examination clues aid in the diagnosis of pediatric orbital fractures where subtle findings (e.g., the "white-eyed" blowout fracture) and a child's limited cooperation can easily lead to a missed diagnosis. In addition to complete ophthalmic examination, children with suspected orbital fractures should undergo complete trauma and neurological examinations to rule out potential life-threatening coincident injuries [4].

The history and examination offer clues to the presence of an orbital fracture with or without incarceration of the orbital soft tissues. Periorbital ecchymoses, lacerations, edema, and subconjunctival hemorrhage suggest an injury capable of producing a fracture. Palpation may reveal step-off of the orbital rim, crepitus, and hypesthesia in the distribution of the infraorbital nerve (ipsilateral malar surface and upper lip). The patient may report malocclusion or trismus in cases of more extensive fractures. Lateral canthal dystopia and flatness of the malar prominence is suggestive of a trimalar fracture. Exophthalmometry may reveal either proptosis from coexistent orbital edema and/or retrobulbar hemorrhage or enophthalmos from increased orbital volume. Enophthalmos may be initially masked by orbital and periorbital edema. Eye movements may be reduced either from edema and hemorrhage or from entrapped orbital tissues within the fracture. Limitation of upgaze, however, is

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suggestive of entrapment. The practitioner must remember that children may present with little or no signs or symptoms of entrapped or non-entrapped orbital fractures.

Classification

Pediatric inferior orbital wall fractures can be grouped into two categories: entrapped ("trapdoor") floor fractures and non-entrapped ("blowout") orbital floor fractures [5]. Trapdoor fractures are much more common in the pediatric population because of the elastic, cancellous bone of the immature skull. When fractured, the elastic orbital floor rapidly returns to its previous position leaving little time for the inferior rectus muscle and other orbital soft tissues to escape entrapment [6]. This type of fracture, also known as "greenstick fracture," explains the higher rate of entrapment in this age group. Soft tissue, fat, and/or muscle may be entrapped within the greenstick fracture, thereby limiting ocular motility and resulting in a constrictive environment and risk of ischemic injury to involved tissue. Ischemia of the extraocular muscle can result in permanent damage and is therefore treated emergently. Of note, "greenstick" fractures may occur with limitation in ocular motility despite a white and quiet conjunctiva and an absence of external evidence of trauma such as periorbital edema and ecchymoses. Such fractures are known as the white-eyed fractures.

While the term "trapdoor" accurately depicts the bony movement producing incarceration of orbital tissues in entrapped fractures, the term "blowout" is somewhat of a misnomer. While non-entrapped fractures often result in inferior displacement of the inferior wall into the underlying maxillary sinus, the term "blowout" suggests an etiology, and the etiology is still debated. Further, non-entrapped fractures can be associated with bony fragments within the orbit as well. Direct trauma (i.e., trauma impacting the orbital rim) typically produces a "blowout" fracture and is seven times less likely to lead to entrapment than indirect trauma (i.e., not impacting the orbital rim) [3]. Proposed theories underlying blowout fractures include globe retropulsion producing increased orbital pressure ("hydraulic theory") and the rigid orbital rim transmitting force to compress the floor ("buckling theory").

Radiographic evidence can be supportive but is not superior to clinical examination findings and a high index of suspicion for entrapment. Entrapment of orbital contents is often associated with an obscuration of the orbital fat between the inferior rectus muscle and the bone within the fracture. Importantly, computed tomography does not always show muscle tissue within the fracture, and significant limitations in ocular motility may occur through incarceration of fat and/or periosteum around the muscle. Although radiographic findings are critical in fracture management, it has been shown that imaging and intraoperative findings concord poorly with clinical evidence of entrapment, with the latter sometimes not appearing radiographically in the pediatric population [7].

Timing and Indications for Surgical Intervention

Debate exists regarding the need for and the timing of surgical intervention in the management of orbital fractures; however, most authors recommend urgent (within 24–48 h) repair of trapdoor orbital floor fractures with entrapment of extraocular muscle. Sinus bradycardia, heart block, nausea, vomiting, and syncope may occur as vagal responses to entrapment [8]. Findings that constitute indications for early (within 1–2 weeks) repair of non-entrapped floor fractures in adults include enophthalmos greater than 2 mm and larger fractures involving more than 50 % of the orbital floor. Compressive optic neuropathy due to bone fragments is rare, but represents an indication for urgent surgery in a blowout fracture. Positive forced duction testing may also serve to confirm a restricted muscle. Although these indications can be reasonably applied to children, earlier intervention may be required in children given the faster rate of healing and bone remodeling in this age group.

Patients who exhibit reasonably full ocular motility with diplopia outside 30° of fixation, an absence of systemic side effects, and a CT scan that does not show evidence of entrapment may be monitored for improvement without surgical intervention. Patients with a "white-eyed" entrapped fracture require urgent surgical intervention within 24–48 h of the injury.

Evidence for Effective Diagnosis and Treatment

Background: Pediatric Orbital Floor Fracture Long-Term Follow-up

Relatively few studies have looked at treatment outcomes of pediatric orbital floor fractures, but the literature suggests that patients with extraocular muscle entrapment have better outcomes (defined as improved motility) if surgical repair is performed within 2–5 days after injury with an emphasis on the first 24–48 h [9, 10]. Wei and Durairaj performed an extensive literature search and published a meta-analysis of 25 studies pertaining to orbital floor fractures in children [9]. The majority (83 %) of these studies suggested improved outcomes for young patients with entrapment (positive forced ductions, soft tissue entrapment radiographically, and restricted motility) and symptomatic diplopia if surgery is performed. If indications for urgent intervention are absent

but a large fracture (>50 % of the floor) or enophthalmos is diagnosed, it is best to intervene surgically and to restore the orbital anatomy within 2 weeks to avoid soft tissue fibrosis.

Surgical Management of Pediatric Orbital Floor Fractures

Surgical repair of pediatric orbital floor fractures can be achieved through a transconjunctival approach with or without lateral canthotomy/cantholysis, which can be helpful in achieving greater exposure especially in the presence of significant periorbital edema. Once the fracture has been exposed, the choice of implant is made depending on the size and shape of the fracture. Very small greenstick fractures may require only release of orbital tissue from the fault line without implant placement. Larger fractures may be repaired with a variety of alloplastic (porous polyethylene, Supramid, GORE-TEX, Teflon, silicone sheet, or titanium mesh) and autogenous (fascia lata, nasal septum, iliac crest bone) materials (Fig. 64.1) [5, 8, 11].

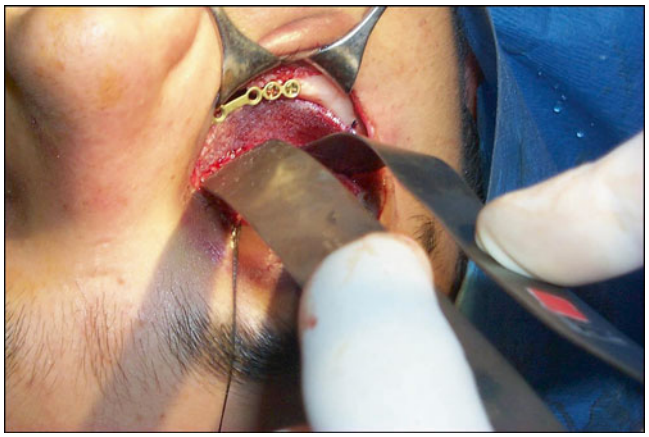

Fig. 64.1 Patient with orbital floor fracture undergoing repair with a porous polyethylene implant with a titanium plate

The following cases will help to illustrate diagnosis and management of orbital floor fractures in the pediatric population.

Case Studies

Case Study 1 (Table 64.1)

Table 64.1 Case 1

Clinical history	A 13-year-old healthy boy presents to the ED 5 days after being struck in the left eye with baseball. CT scan shows a left orbital floor fracture with possible inferior rectus muscle entrapment (Fig. 64.2). Patient denies diplopia but reports left eye pain with extreme upgaze and hypesthesia in the distribution of the infraorbital nerve on the left		
Key components of exam		OD	OS
	BCVA (glasses)	20/20	20/20
	Ductions/versions	Full	Full
	Ncc, Dcc	Orthophoric	
	Exophthalmometry (Hertel)	14, 14 base 90	
Management options	Observation, surgical repair		
Management	Elected to observe with interval follow-up of 2 weeks. Rationale: Although CT scan is suggestive of a trapdoor fracture with tenting of periorbita into the fracture, the muscle itself does not appear entrapped. Most importantly, physical examination shows full ocular motility		
Interval history (2 weeks)	Patient reports resolution of discomfort with upgaze. V2 hypesthesia persists		
Key components of exam		OD	OS
	BCVA (glasses)	20/20	20/20
	Ductions	Full	
	Ncc, Dcc	Orthophoric	
	Hertel	14, 14 base 90	
Management	Resume comprehensive eye exams with eye care provider		

(continued)

Fig. 64.2 CT scan of the orbits showing a left orbital floor trapdoor fracture with tenting of the entrapped periorbita

Clinical Synopsis

This is a case of a trapdoor fracture with entrapment or orbital tissues but not extraocular muscle. It emphasizes the fundamental principle that muscle entrapment is a clinical, not radiographic, diagnosis. The final outcome was satisfactory.

Case Study 2 (Table 64.2)

Table 64.2 Case 2

Clinical history	A 13-year-old healthy boy presents to ED 3 h after being assaulted. CT scan obtained in ED showed possible inferior rectus muscle entrapment (Fig. 64.3). Patient denies diplopia, but examination shows limitation of ocular motility in upgaze and hypesthesia in the distribution of the infraorbital nerve on the left		
Key components of exam		OD	OS
	UCVA	20/20	20/20
	Ductions	Full	Limitation in upgaze
	Nsc, Dsc	Orthophoria	
	Hertel	15, 15 base 93	
Management options	Recommend surgical repair left orbital floor fracture		
Management	Elected to proceed with surgical repair		
	Rationale: This patient has evidence of ocular motility deficit with radiographic suggestion of inferior rectus entrapment. A trapdoor fracture requires early surgical intervention as waiting is likely to result in permanent diplopia		
Interval history (1 week)	Patient complains of persistent pain in upgaze		
Key components of exam		OD	OS
	UCVA	20/20	20/20
	Ductions	Full	Improved upgaze but mild limitation persists
	Alignment Nsc	Orthophoria	
	Alignment Nsc/cc	Orthophoria (CT/ACT)	
	Hertel	15, 15 base 93	

(continued)

Management	Observe		
Interval history (6 months)	Patient doing well. States no pain with upgaze. Hypesthesia persists but improving		
Key components of exam		OD	OS
	UCVA	20/20	20/20
	Alignment	Orthophoria (CT/ACT)	
	Dynamic retinoscopy (cc)	Rapid, complete, and steady OU	
	Hertel	15, 15 base 93	

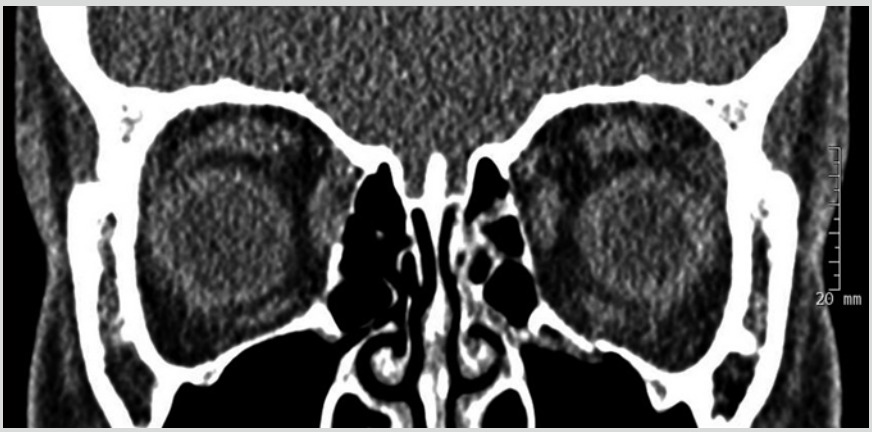

Fig. 64.3 CT scan of the orbits showing a left orbital floor fracture with entrapped inferior rectus muscle. Note the peri-muscular tissue within the fracture and orbital fat and periosteum beneath the fracture. This requires urgent surgical intervention as permanent diplopia will result if not repaired expeditiously

Clinical Synopsis

This is a case of an orbital floor fracture with entrapment of the inferior rectus muscle. The CT scan shows a tented inferior rectus, but note that the fracture is displaced and not a trapdoor. The case illustrates the fact that muscle entrapment, although far more common with trapdoor fractures, occurs with displaced fractures as well. The patient underwent surgical repair and the final outcome was satisfactory.

In conclusion, pediatric orbital floor fractures require a specific approach that involves assessment of imaging studies and physical examination, so that cases of extraocular muscle entrapment are identified. These cases require earlier intervention in an attempt to restore and preserve normal extraocular motility and good ocular alignment.

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Noninfectious Causes of Proptosis in Children

65

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Abstract

Proptosis in the pediatric population is alarming to the patients, their families, and treating physicians alike. Limited history, difficult examination, and the broad differential contribute to a challenging scenario. A thorough understanding of orbital diseases in the pediatric population is essential as proptosis can be associated with significant morbidity and even mortality in some cases. Appropriate medical history, full examination, diagnostic imaging/testing, and sometimes tissue biopsy are essential for determining the correct diagnosis and establishing appropriate management plan. This chapter provides an overview of noninfectious causes of proptosis in children.

Keywords

Orbital tumors • Children • Proptosis

Obtaining the Medical History

Eliciting a detailed pertinent medical history in pediatric patients poses unique challenges as it depends heavily on the patient's age, maturity level, and verbal skills. In most cases, input from immediate family members provides the majority of the necessary information. One must bear in mind that children could potentially forget, exaggerate, or deny certain aspects of the history that could confound objective diagnostic findings.

A thorough medical history should include presenting symptoms and signs, details of onset and progression, birth history, developmental history, previous hospitalizations, and pertinent family history. Certain aspects of the history could narrow the diagnostic considerations and clue the ophthalmologist into certain diagnoses. For instance, pulsating painless proptosis is suggestive of a plexiform neurofibroma with associated absence of the sphenoid wing. Acute progressive proptosis with bilateral eyelid ecchymoses is a feature of metastatic neuroblastoma. Rhabdomyosarcoma typically presents with subacute painless proptosis with discoloration of the overlying skin. Patients with venolymphatic malformations may have fluctuating proptosis with associated viral illnesses. Slowly progressive, painless axial proptosis is suggestive of optic nerve glioma (ONG) while severe progressive proptosis in a newborn child is more suggestive of a teratoma.

Examination of the Orbit

Krohel et al. proposed the practical six Ps approach to orbital examination that guides the ophthalmologist toward the correct diagnosis (Table 65.1) [1]. In addition, external examination of the globe and eyelid positions, ocular motility, and vision, pupillary evaluation, cycloplegic refraction, anterior segment and fundus examination, and quantification of the proptosis using an exophthalmometer are all necessary aspects of a complete examination. Color vision and visual

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field testing may be helpful in older children. Moreover, attention must be taken as eyelid retraction, contralateral ptosis/microphthalmia, shallow orbit, or orbit asymmetry could all be causes of pseudoproptosis.

Diagnostic Testing and Imaging

Ancillary laboratory test provides helpful information to confirm the underlying diagnosis in pediatric proptosis. Blood analyses could uncover a diagnosis of systemic leukemia and lymphoma, while urine homovanillic acid (HVA) and vanillylmandelic acid (VMA) are elevated in neuroblastoma.

Ultrasonography, computed tomography (CT), and magnetic resonance (MR) imaging are very helpful in determining the diagnosis of an orbital disease. CT scan provides the best views of bony detail, while MRI is superior in evaluating soft tissue pathology and blood flow. Orbital ultrasound may play a role in evaluating orbital vascular processes and may also be used as a guide for fine-needle aspiration biopsy (FNAB). Scintigraphy and PET scans are used to detect bony lesions and metastasis, respectively.

Surgical biopsy may be required in certain cases to confirm the diagnosis. Tissue confirmation is especially needed for malignant tumors before starting systemic chemotherapy.

Table 65.1 The six Ps of the orbital examination [1]

The six Ps of the orbital examination:
Proptosis
Pulsation
Periorbital changes
Pain
Progression
Palpation

Differential Diagnosis

The differential diagnosis of proptosis in children is extensive and includes entities that encompass benign conditions to very aggressive tumors. Differential diagnosis based on histopathological origin of the lesion is summarized in Fig. 65.1. Additionally, within the pediatric population, there are trends in the incidence of causative disorders based on age. An algorithm of the distribution of orbital disease by age group in the pediatric population is presented in Fig. 65.2 [2].

Congenital Orbital Cystic Lesions

Some congenital orbital cysts may be present at birth but may not be recognized for years. Congenital cysts include microphthalmia with cyst, dermoid cysts, and teratomas. Other orbital cysts can be acquired from adjacent tissue such as mucoceles and dacryoceles. Vascular neoplasms can often present with cysts and can spontaneously bleed, forming "chocolate" cysts as described in section "Hematologic Tumors."

Microphthalmia with Cyst

Clinical Features

Microphthalmia with colobomatous cyst is a rare severe anomaly of the globe that results from failure of the fetal fissure to close at 4 weeks of development. This results in proliferation of neuroectoderm through the opening and formation of an orbital cyst. The eye is small and can be severely disorganized. The cyst attached to the eye may be

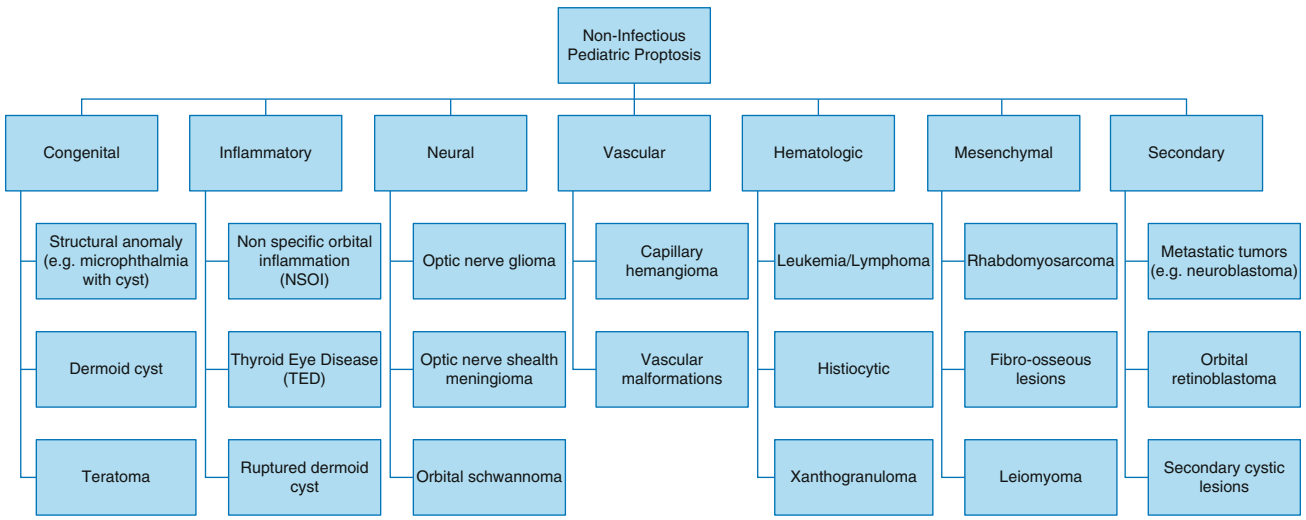

Fig. 65.1 Differential diagnosis of noninfectious pediatric proptosis based on histopathological origin of tumorous process

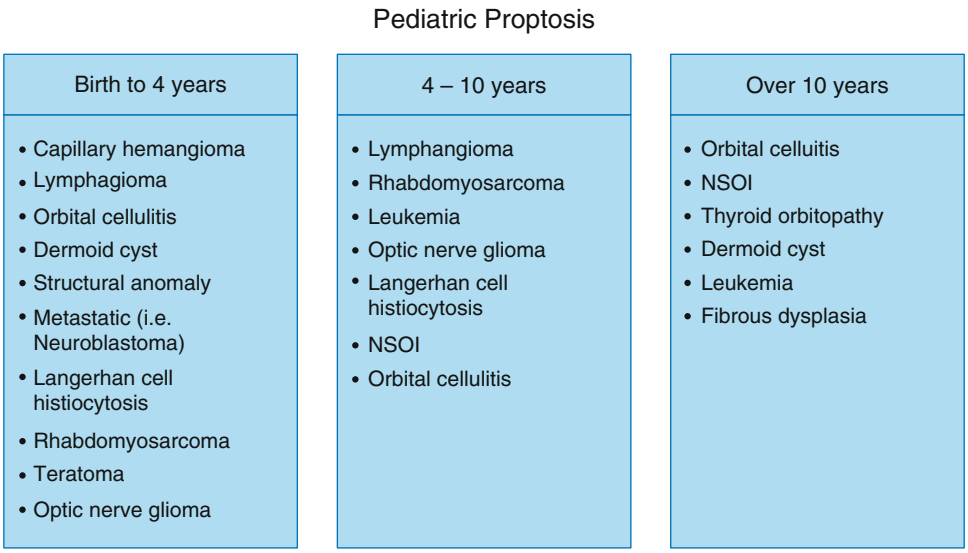

Fig. 65.2 Differential diagnosis of pediatric proptosis based on age

smaller or larger than the eye itself causing variable proptosis [3, 4]. In some cases, the small eye is usually displaced superiorly, and the cyst bulges forward and balloons the inferior lid. The condition sometimes can be confused with dermoid cyst, with arachnoid cyst, or with an encephalocele. Ultrasound, CT, and MRI can help in the diagnosis [5]. This condition can be associated with other systemic abnormalities up to 39 % of cases. Systemic abnormalities are more frequent with bilateral microphthalmos when compared to a unilateral presentation. Systemic conditions can include congenital heart defects, central nervous system abnormalities, cleft lip/palate, pulmonary hypoplasia, and renal agenesis [6].

Imaging Features

B-scan ultrasound of the orbit can show a large orbital echolucent cyst indenting the globe. A-scan shows low internal reflectivity consistent with fluid-filled cysts. MRI will demonstrate a microphthalmic globe with an adjacent cystic structure that protrudes from the posterior aspect of the globe at times or can be inferior to the disorganized globe (Fig. 65.3). MRI helps to rule out other conditions as mentioned previously [6].

Pathologic Features

Histopathologic evaluation usually reveals irregularly shaped cystic lesions with external layers of dense connective tissue with thick internal layers of neuroglial tissue. The cyst interior can contain calcified bodies containing melanin.

Treatment

There is no general consensus or widely accepted strategy regarding treatment for patients with microphthalmos and orbital cysts. If there is functioning vision and the patient is without severe proptosis or systemic abnormalities then observation is advocated [7]. It is rare for individuals with this

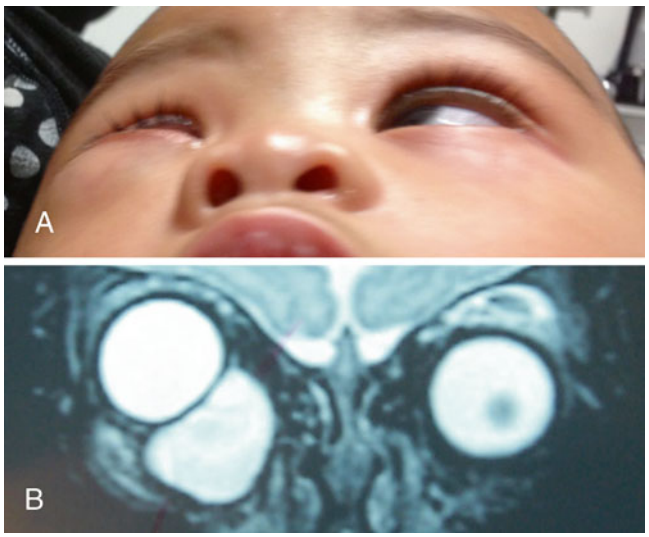

Fig. 65.3 (**a**) Child with microphthalmia with cyst. Note fullness and bluish discoloration of the right lower eyelid. The eye is barely visible when the lids are open. (**b**) MRI brain axial T2 image showing the inferior cyst underneath the right globe (Case courtesy of Elias I. Traboulsi, MD, MEd)

condition to have useful vision. Some surgeons have reported success with aspiration of small cysts [8]. Aspiration may need to be repeated multiple times if fluid reaccumulates. Surgical removal of the cyst together with enucleation is usually performed in severe microphthalmia to improve cosmesis and aid in appropriate orbital growth as the child ages.

Prognosis

Overall prognosis depends on the severity of associated systemic conditions in children with microphthalmia with cyst. Overall, the prognosis is favorable for long-term preservation of the orbit; however, vision generally cannot be preserved if the microphthalmia is moderate to severe.

Dermoid Cysts

Clinical Features

Dermoid cysts are the most common periorbital and orbital tumors in children [9, 10]. They are usually located at the temporal frontozygomatic suture line just above the superior orbital margin in the lateral canthus. The second most common site is the superomedial orbital rim [9]. The cyst may enlarge with age or acutely after trauma (see section "Orbital Schwannoma"). Dermoid cysts of the orbit can be divided into superficial and deep. Superficial or anterior cysts present in younger patients (1–3 years). Given their consistent anatomic location and presentation, they can be accurately diagnosed from examination and history alone.

Anterior cysts will present as smooth and painless swellings near the frontozygomatic suture line. They are generally not attached to the overlying skin, a feature that differentiates them from implantation cysts. They also do not displace the eye on initial presentation. Large anterior dermoid cysts can cause amblyopia from occlusion due to eyelid abnormalities. If the lesion is freely mobile on clinical exam, it is very unlikely to have a deep orbital component, and imaging is not necessary. Posterior dermoid cysts generally present in older children or adults [11]. Rarely dermoid cysts can pass through the bony suture lines and extend intracranially or into the temporal fossa and present as a so-called bilobed dermoid or dumbbell dermoid [12, 13]. If there is concern for posterior extension, a CT or MRI should be considered.

Imaging Features

On CT dermoid cysts have very characteristic features. They are classically well defined with an enhancing wall and non-enhancing lumen. Up to 85 % can have some associated bony changes [12], and up to 14 % can have calcifications [14]. On MRI, dermoids are best visualized with fat suppression and will appear as well-defined and round cystic structures. Most will be hypointense with respect to orbital fat on T1-weighted images. Enhancement is generally minimal due to lack of vasculature in the cyst [15].

Pathologic Features

Dermoid cysts are choristomas and true cysts lined by keratinizing stratified squamous epithelium, which is present in up to 84 % of cases [12]. If the cyst wall contains skin appendages such as hair follicles, sweat glands, or sebaceous glands, then the cyst is considered a true dermoid cyst. If these appendages are absent, the cyst is called an epidermoid cyst [16]. Epidermoid cysts are thought to develop from a rest of epidermis that was entrapped during embryonic development. The entrapped surface epithelium than can develop into a cyst with time [17]. Dermoid cysts can display granulomatous inflammation with a giant cell reaction to hair and keratin up to 38 % of cases [12].

Treatment

Complete surgical excision is the standard of care; however, small dermoid cysts may not require immediate treatment. Anterior dermoid cysts can typically be approached using an eyelid incision overlying the cystic mass. Blunt dissection is essential as any rupture of the cyst may lead to intense postoperative keratin-induced inflammation. A cryoprobe can be used to gently deliver the cyst intact while sealing small ruptures [9]. Deep orbital cysts are more difficult to remove, and imaging should be obtained to guide surgical planning. The surgical goal remains complete excisional removal. A large majority of posterior orbital cysts are located in the upper temporal orbit; therefore, it is common for orbital surgeons to proceed with a posterolateral orbitotomy [18]. Intracranial dermoid cysts will need a multidisciplinary team including orbital surgeons, neurosurgeons, and ENT specialists. All dermoid cysts must be histologically examined as rarely cysts can undergo malignant transformation into squamous cell carcinoma [19].

Prognosis

Surgical removal of intact cysts has been shown to result in excellent visual and cosmetic outcomes [9]. Deep orbital cysts may require additional surgery and multidisciplinary care.

Teratoma

Clinical Features

Teratomas are similar to dermoid cysts in that they are both congenital and choristomas [20]. A true teratoma has tissues derived from all three germinal cell layers: ectoderm, mesoderm, and endoderm. The majority of orbital teratomas present shortly after birth. These tumors are very rare with only single cases reported in the literature. Almost all reported cases are unilateral, and there appears to be a 2:1 female preponderance [20]. The proptosis seen with orbital teratoma can be extensive and disfiguring, resulting in corneal exposure and vision loss [21].

Imaging Features

CT and MRI are essential if an orbital teratoma is suspected as there can be local invasion of the brain [22]. Imaging will reveal a multicystic mass, which can sometimes have varying amounts of calcifications.

Pathologic Features

Teratomas are characterized by a variety of arrangement of a number of tissues. There can be clear cysts lined by either epidermis, gastrointestinal mucosa, or respiratory epithelium [15]. In extreme cases, there can be further differentiation of tissue resulting in a portion of a fetus within the orbit itself [23].

Treatment

Historically, orbital exenteration has been the treatment of choice given the extensive orbital proptosis and obvious loss of vision. Recently, less advanced teratomas have been removed with preservation of the ocular structures [24, 25].

Prognosis

Local invasion of a cranio-orbital teratoma can lead to death; however, this is very rare. Prompt clinical and imaging assessment followed by surgical removal has resulted in overall favorable visual and cosmetic outcomes [25].

Inflammatory Lesions

Inflammatory lesions of the orbit can cause severe vision loss and ocular dysmotility. These lesions can be idiopathic as seen in nonspecific orbital inflammation (NSOI), also known as orbital inflammatory pseudotumor. Specific inflammatory disorders include thyroid eye disease (TED) or ruptured dermoid cysts.

Nonspecific Orbital Inflammation

NSOI and orbital inflammatory pseudotumor can be used interchangeably. NSOI is loosely defined as a benign inflammatory orbital process characterized by a polymorphous lymphoid infiltrate in the setting of no known systemic or local cause. The true incidence and prevalence of NSOI are difficult to assess given the lack of clear clinical guidelines for its diagnosis. Pediatric cases of NSOI can account for up to 6–17 % of all cases [26].

Clinical Features

NSOI can affect specific areas within the orbit. When localized to extraocular muscles, the term orbital myositis can be used, lacrimal gland in dacryoadenitis, and the superior orbital fissure and cavernous may be involved in Tolosa-Hunt syndrome. When diffuse, NSOI may involve the orbital fatty tissues, and differentiation from orbital cellulitis may be difficult. NSOI presents with abrupt onset of pain, proptosis, and other inflammatory signs such as erythema, edema, and tenderness to palpation.

There is a paucity of data about the clinical features of pediatric NSOI; however, few studies have shown important differences between adult NSOI and pediatric NSOI. Pediatric NSOI is more commonly bilateral and can be accompanied by disk edema, anterior uveitis, and the presence of eosinophils in biopsied specimens [27]. Ptosis may occur more frequently in pediatric NSOI compared to adult NSOI [28]. Accordingly, pediatric patients with subacute ptosis of unknown origin should be evaluated for NSOI. Differentiation between NSOI and rhabdomyosarcoma and orbital cellulitis is essential. Patients with orbital cellulitis will commonly have systemic signs such as fever or leukocytosis. With rhabdomyosarcoma imaging may show a space-occupying lesion with bone erosion, as described later in this chapter. Table 65.2 outlines common differential diagnosis for NSOI.

Table 65.2 Differential diagnosis of nonspecific orbital inflammation (NSOI)

Differential diagnosis of NSOI
• Lymphoproliferative
• Metastatic disease
• Orbital cellulitis
• Sarcoidosis
• Thyroid eye disease
• Granulomatosis with polyangiitis
• Arteriovenous fistula

Imaging Features

NSOI can be assessed using a number of imaging modalities including echography, high-resolution contrast-enhanced computed tomography (CT), or contrast-enhanced magnetic resonance imaging (MRI). Lymphoid lesions or orbital cellulitis have different MRI characteristics from NSOI. Lymphoid lesions are brighter than NSOI, and NSOI lesions are brighter than orbital cellulitis [29]. CT is generally the preferred method as it is relatively quick to perform when compared to MRI and demonstrates good inherent contrast of orbital fat, muscle, bony structures, and air in adjacent paranasal sinuses. CT imaging characteristics vary depending on the type of orbital tissues predominantly affected [30]. In dacryoadenitis the lacrimal gland will appear diffusely enlarged but with overall preservation of its shape. Extraocular muscle enlargement may be seen in orbital myositis (Fig. 65.4). The most frequently involved muscle is the medial rectus followed by the superior rectus. The tendon may enlarge contiguously with the muscle belly. This is an important differentiating characteristic and is not typically seen in other condition in which the muscle is enlarged, such as in TED. The sclera, episclera, and Tenon capsule involvement will demonstrate nonspecific thickening and blurring of structures. Diffuse NSOI may be seen as involvement of any orbital structure with additional streaky densities in contiguous orbital fat.

Pathologic Features

There is a spectrum of histopathological presentations ranging from the typical diffuse polymorphous infiltrate to lymphoid, eosinophilic, sclerosing, or vasculitic inflammation [31]. A granulomatous variant has been reported but is rare [30]. Early in the disease course, a polymorphous inflammatory response predominates with later stages predominated

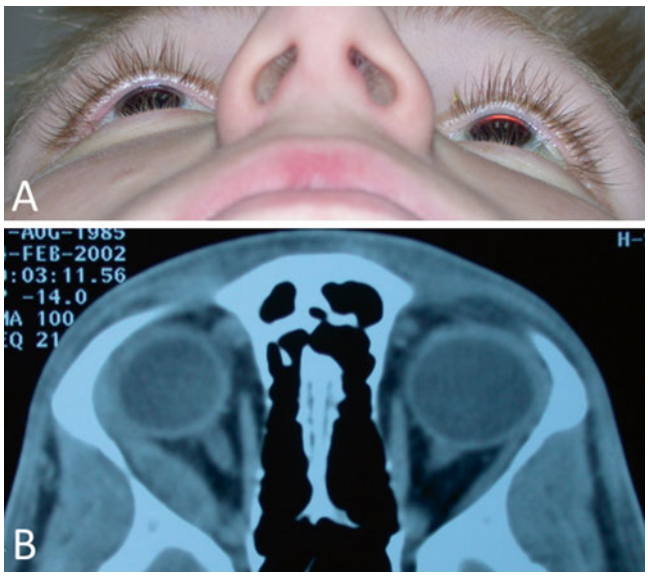

Fig. 65.4 Patient with right orbital myositis. (**a**) Note right-sided proptosis. (**b**) CT scan axial image demonstrates enlargement of the right lateral rectus muscle (Case courtesy of Elias I. Traboulsi, MD, MEd)

by fibrosis. Lymphoid proliferations can replace orbital fat and can even encase extraocular muscles, lacrimal gland, or the optic nerve. Histopathological schemes have been proposed by Blodi and Gass [26], Reese [32], and Farrow [33]. However, no scheme has been universally accepted as there is can be great histopathologic variation.

Treatment

Biopsy for NSOI is not always indicated. If there is diffuse involvement of orbital structures, biopsy may be anatomically difficult. Response to therapy can be confirmatory of the diagnosis [34]. Direct skin incision with orbitotomy is generally required for tissue biopsy. However, ultrasound or CT-guided fine-needle aspiration (FNA) has been shown to be useful in evaluating a patient whom NSOI is suspected [35].

Observation for very mild cases of NSOI can be acceptable [36]. Systemic corticosteroids are considered mainstay therapy in cases of worsening orbital signs, risk of visual compromise, or significant discomfort. The treatment for pediatric NSOI is similar to that of adult NSOI. Typically, response to steroids is very rapid and can be considered diagnostic for NSOI. Treatment doses range from 1.0 to 1.5 mg/kg of oral prednisone for 2 weeks followed by a slow 5–8-week taper [28]. Among adult patients, Mombaerts et al. found that 78 % of patients had a positive initial response to steroids [37]. Intravenous methylprednisolone does not appear to result in a shorter duration of prednisone therapy or difference in symptom-free outcome or recurrence rate [38]. Radiation therapy and steroid-sparing immunosuppressive medication can be used for recalcitrant severe disease. However, caution must be used and secondary biopsy/debulking may be indicated as an alternative disease process should be ruled out.

Prognosis

Pediatric NSOI outcomes vary given the variability in disease presentation and treatment protocols. Cure rates have been reported as high as 30 % with partial resolution in over 90 % of cases [28]. Complete resolution of adult NSOI has been reported as high as 67 %; the difference between adult and pediatric NSOI may be the result of the greater number of therapeutic options that are safe to use in adults. Patients have symptomatic improvement on treatment, and care may need to be coordinated with pediatric rheumatology. In the future, development of a multidisciplinary consortium of clinical and research scientists may lead the standardization of clinical criteria and management of NSOI [39].

Thyroid Eye Disease

TED is an uncommon autoimmune inflammatory orbital disease in children. Its incidence has been reported in between 1.7 and 3.5 cases per 100,000 population per year [40]. Pediatric TED commonly occurs in patients with autoimmune hyperthyroidism and rarely in those with Hashimoto's thyroiditis or in those who are euthyroid [41]. The diagnosis of TED is based on a variety of clinical signs. Given the rarity of presentation within the pediatric population, these clinical signs are less well defined when compared with the adult population.

Clinical Features

The diagnosis of pediatric TED is based on the clinical signs of thyrotoxicosis, laboratory thyroid function testing (thyroid-stimulating hormone, thyroid-stimulating hormone antibodies, thyroid peroxidase antibodies, thyroglobulin antibodies, and thyroxine), and imaging. Most patients with TED will be hyperthyroid; however, euthyroidism does not rule out TED. TED is more common in children with other autoimmune conditions or if there is a family history of autoimmune thyroid disease [42]. Clinical studies suggest that the clinical presentation of TED in children is less severe than in adults [42]. Soft tissue involvement and proptosis are more commonly seen in pediatric TED compared to adult TED. Anterior segment signs of TED include upper and lower eyelid retraction, upper eyelid flare, conjunctival injection near extraocular muscle tendon attachments, increased intraocular pressure, and chemosis. Proptosis and restrictive strabismus can also be seen with diplopia as a presenting symptom. Numerous grading systems (NO SPECS [42], EUGOG [43], CAS [44], and VISA [45]) have been developed for use in the adult population; however, none have

been validated for use in children. There have been no cases of optic neuropathy reported in the literature.

Imaging Features

In children, the orbital component may be more prominent than the enlargement of extraocular muscles that is seen typically in adults [46]. This may explain the lack of strabismus and compressive optic neuropathy in children with TED. CT or MRI imaging findings may show an increase in orbital fat; however, enlarged extraocular muscles may also be seen as in Fig. 65.5b. As opposed to the enlarged muscles as seen in NSOI, muscles affected by TED will have fusiform enlargement as sparing of the tendinous insertions (Fig. 65.5a).

Pathologic Features

In both adults and children with TED, there appears to be an upregulation of an inflammatory autoimmune cascade, resulting in enlargement of orbital contents secondary to fibroblast activation and glycosaminoglycan production/deposition [47]. Histologic studies of extraocular muscles in TED reveal muscles separated by amorphous collections of collagen fibrils and glycosaminoglycans with a hyaluronan predominance [48]. In children and in adults, TED is typically self-limited to 1–2 years of activity where there can be progressive changes. The post-inflammatory course can be variable with remissions and reactivations.

Treatment

The main goal of therapy for TED is to stabilize thyroid function and achieve long-term remission. When serum markers are elevated, stabilization of any thyroid dysfunction with antithyroid medications such as methimazole and propylthiouracil can be very effective [47]. Thyroidectomy and radioiodine treatment can be utilized for severe or recalcitrant disease. Therefore, multispecialty care with pediatric endocrinology is frequently needed and recommended. When there are sight-threatening changes, intervention typically starts with 5–20 mg prednisone daily with a slow taper over the course of 1 month. Prolonged steroid use in children is more problematic than in adults as there have been reports of weight gain, immune dysfunction, and growth failure [49]. Somatostatin analogs, like octreotide, may have therapeutic value. However, a well-controlled trial showed only a modest improvement in TED [50]. It is rare for pediatric TED patients to require orbital decompression surgery and is not recommended within the first decade of life due to incomplete orbital growth [51].

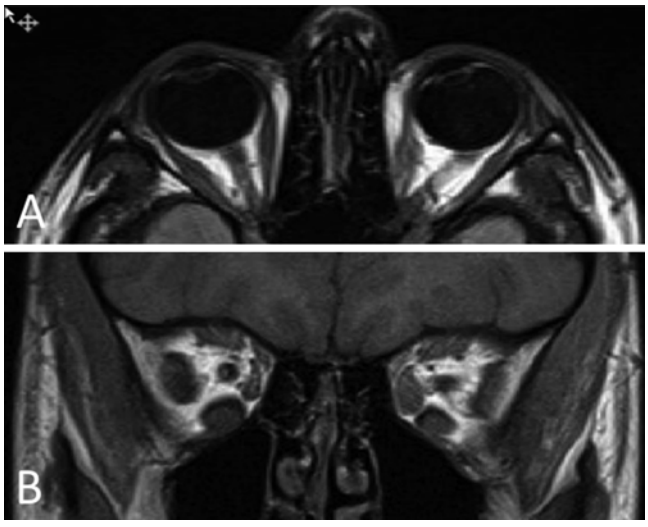

Fig. 65.5 Orbital MRI in a 15-year-old with Graves disease. (**a**) Axial flair view shows fusiform enlargement of the medial and lateral recti with sparing of the tendinous insertion. (**b**) Coronal view demonstrates bilateral enlarged rectus muscles consistent with thyroid eye disease

Prognosis

Interestingly, restoration of euthyroidism does not typically improve ocular signs, especially proptosis as typically seen in adults [52]. This feature of pediatric TED is well known but not well understood. Since TED in children is typically mild, it is rare that specific intervention is needed; therefore, overall prognosis for pediatric TED is favorable. Secondhand smoke and primary smoking should be avoided as these have been shown to exacerbate TED [53].

Ruptured Dermoid Cyst

Clinical Features

Dermoid cysts are discussed in detail in section "Thyroid Eye Disease." After trauma, dermoid cysts can rupture and cause intense inflammation from exposure of cystic keratinaceous material to the surrounding soft tissue. Left untreated, there can be recurrent inflammatory episodes. Patients are frequently treated with antibiotics as preseptal or orbital cellulitis can have a similar presentation.

Imaging Features

CT or MRI may demonstrate a poorly defined enhancing wall with surrounding soft tissue stranding and swelling.

Pathologic Features

The features are identical to dermoid cyst pathology discussed in section "Thyroid Eye Disease."

Treatment

Because ruptured dermoids can masquerade as infectious abscesses, an unaware clinician may drain them. The material expressed will usually be sterile, and inflammation will not improve with antibiotics. This may lead one to consider ruptured dermoids as a potential etiology. Once infection has been ruled out, surgical removal is the treatment of choice.

It is important that the entire cyst be removed, and this may problematic given adjacent tissue inflammation. Many surgeons advocate copious irrigation.

Prognosis

Overall, prognosis is favorable if the entire cyst lining can be removed. Long-standing ruptured dermoids can cause scarring, and second-stage surgery may sometimes be needed to improve function and cosmesis of the eyelid.

Neural Tumors

Neural tumors of orbit primarily arise from the optic nerve and its surrounding sheath. ONG, optic nerve sheath meningioma, neurofibroma, and schwannoma are examples of orbital tumors of neural origins.

Optic Nerve Glioma

Gliomas most commonly involve the optic nerve, but it can affect any part of the optic nerve pathway including the chiasm, hypothalamus, and optic nerve tracts [54].

ONG originates from the substance of the optic nerve and is the most common intraconal tumor in the pediatric population [55, 56]. It is histologically classified as juvenile pilocytic astrocytomas (WHO grade I) [55, 56].

A close relationship exists between ONG and neurofibromatosis type 1 (NF1). Up to 50 % of patients with ONG carry the diagnosis of NF1; on the other hand, only up to 30 % of NF1 patients develop ONG [56]. It has a slight female predominance in the subgroup with NF1 and a mean age of 5 years at time of diagnosis [57, 58].

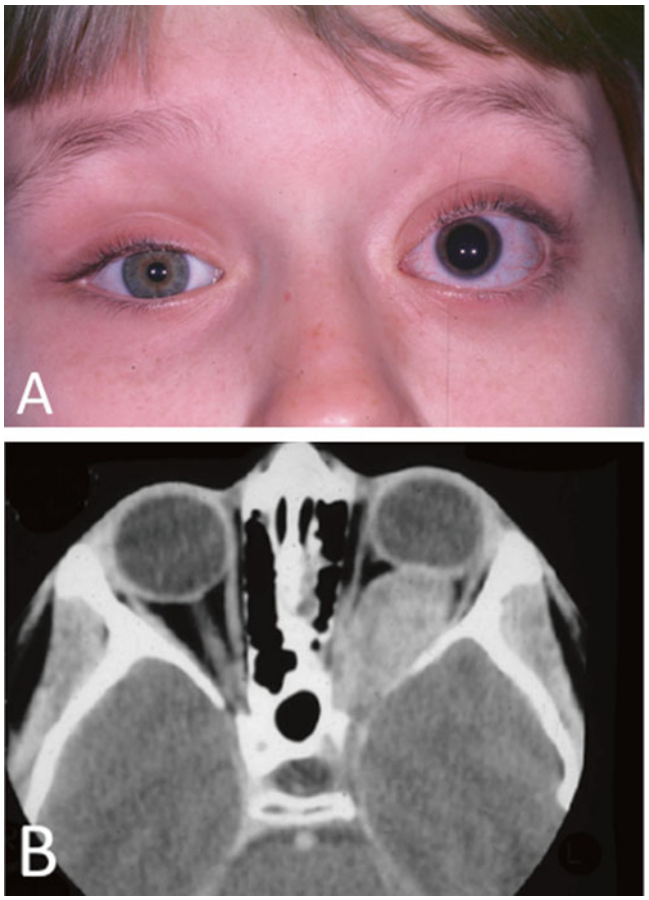

Fig. 65.6 Child with left optic nerve glioma. (**a**) External photograph showing proptosis of the *left* eye with associated inferior scleral show and mild conjunctival injection. (**b**) CT scan axial image demonstrates fusiform enlargement of the optic nerve extending into the orbital apex and optic canal [Reproduced with permission from: Dutton JJ. Optic Nerve Tumors. In : Clinical Ophthalmic Oncology (Orbital Tumors). Eds : JD Perry, AD Singh, Springer, Heidelberg, 2014, Chapter 9, pp 93–104]

Clinical Features

ONG is typically a slow-growing tumor and may remain asymptomatic for many years. When symptomatic, signs include decreased visual acuity, optic disk changes (edema/atrophy depending on the stage of disease), relative afferent pupillary defect, proptosis, strabismus, nystagmus, and visual field defects (Fig. 65.6). Even though visual acuity decline is the most common finding at presentation, it is sometimes difficult to assess vision in young uncooperative children. Locally aggressive disease with significant drop in visual acuity is more likely to be associated with sporadic ONG rather than patients with a history of NF1.

In NF1 patients, ONG can be multifocal or bilateral, and systemic signs of endocrinopathies may arise secondary to astrocytomas of the hypothalamus and optic chiasm.

Imaging Features

MR imaging is superior to CT scans for the diagnosis and delineation of the ONG. It typically reveals a fusiform enlargement of the optic nerve with variable enhancement with gadolinium.

Pathologic Features

ONG is a clinical diagnosis, and biopsy is indicated only in select cases (e.g., undetermined diagnosis or surgical debulking in aggressive disease). On histopathology, ONG will show typical biphasic pattern (loose and dense portions) of astrocytoma. Rosenthal fibers (commonly seen in ONG) are eosinophilic bodies derived from degenerated astrocytes.

Treatment

The natural history of ONG is variable, but most are slow growing that are likely to remain stable and, thus, are managed conservatively. In cases of locally aggressive disease (usually in sporadic cases without NF1), intervention may be necessary. Surgical resection/debulking is indicated in cases of unilateral anterior ONG causing significant proptosis and

compression on the optic nerve. Chemotherapy is a valid option in children younger than 5 years of age but is associated with up to 60 % relapse rate [59]. Radiation is reserved for select patients over 5 years due to high risk of secondary tumor induction, endocrinopathies, and cognitive impairment in this age group [60, 61]. Please see Chap. 39 for further discussion of optic pathway glioma.

Optic Nerve Sheath Meningioma

Optic nerve sheath meningioma is a proliferation of meningothelial cells of the optic nerve sheath. It arises either primarily from the optic nerve sheath (10 % of cases) or is due to extension from an intracranial meningioma (90 % of cases). Primary pediatric optic nerve sheath meningioma (PPONSM) is rare. It behaves more aggressively in children with high incidence of intracranial extension. In a major review published in 2008, Harold Lee et al. were only able to find a total of 53 cases of PPONSM reported in the English literature [62]. It has a slight female predominance and appears to be associated with neurofibromatosis type 2 (NF2) [62, 63].

Clinical Features

PPONSM presents similarly to ONG with decreased visual acuity, visual field defects, proptosis, restriction of ocular motility, and optic disk changes (edema or atrophy). Optociliary shunt vessels may be present in chronic cases.

Imaging Features

Neuroimaging in PPONSM typically reveals a "tam-track" appearance with thickening of the optic nerve sheath surrounding the optic nerve that enhances intensely after injection of contrast material. MRI is superior in showing intracranial spread while CT scan is better in showing calcification and bony changes.

Pathologic Features

Meningiomas are heterogeneous with multiple subtypes. Due to its rarity there is no clear dominant type in PPONSM. In general, meningiomas show whorled meningothelial cells with calcified psammoma bodies.

Treatment

Surgical resection of PPONSM appears to be the standard treatment for this rare and aggressive tumor.

Orbital Schwannoma

Orbital schwannomas are slow-growing tumors that arise from Schwann cells of peripheral sensory orbital nerves. It is rare in the pediatric population. A review published in 2012 by Nagashima et al. reports only five cases of pediatric intraorbital schwannoma published in the English literature.

Clinical Features

In the pediatric reported cases, patients presented with painless exophthalmos with no signs of optic nerve compression.

Imaging Features

Neuroimaging findings of orbital schwannoma are nonspecific and appear as a well-circumscribed mass with homogenous enhancement with contrast.

Pathologic Features

Schwannomas reveal Antoni A and Antoni B tissue types with associated Verocay bodies.

Treatment

Complete resection of the tumor is the treatment of choice.

Vascular Lesions

Pediatric orbital vascular lesions include a very diverse spectrum of tumors and malformations. These lesions can occur anywhere in the body, and when present within the orbit or periorbital tissues, they can cause visual morbidity and treatment may be warranted. The most common vascular lesions are capillary hemangiomas and cavernous hemangiomas.

Capillary Hemangioma

Clinical Features

Capillary hemangioma is also known as infantile hemangioma, strawberry nevus, or strawberry hemangioma. Hemangiomas are the most common benign tumors of childhood and have been reported to be present in up to 10 % of the pediatric population up to 1 year of age [64]. Up to 20 % of affected patients will have multiple lesions [64]. Capillary hemangiomas can be classified as superficial, deep, or mixed. Superficial hemangiomas will typically present as a bright-red, lobulated superficial lesion. Deeper tumors can have a bluish-purple appearance, and those involving the orbit can cause proptosis or strabismus. Diagnosis of capillary hemangioma is predominantly based on clinical presentation and history. Imaging can be helpful but not necessary to make the diagnosis. If there is possible need for surgery or concern for posterior extension ultrasound, CT or MRI may be helpful.

Imaging Features

On ultrasound, patients with hemangiomas present with soft tissue masses with a defined border and low internal echogenicity [65]. The use of color Doppler can help determine

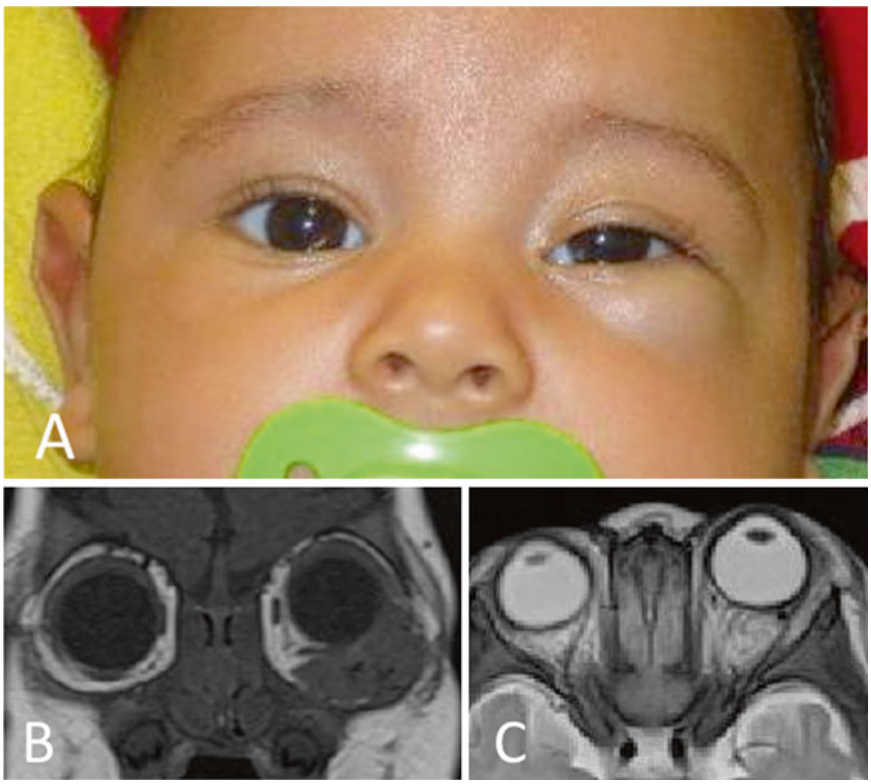

Fig. 65.7 Child with left orbital hemangioma. (**a**) External photograph showing mild superior displacement of the *left* eye with fullness of the lower eyelid. (**b**) MRI orbit coronal T1 image shows inferior and anterior location of hemangioma. (**c**) MRI orbit axial T2 image reveals the mild proptosis and the posterior orbital involvement by the hemangioma (Case courtesy of Elias I. Traboulsi, MD, MEd)

the presence of vascular flow in the tumor [66]. With deeper lesions, ultrasound may not have the penetration required for complete evaluation of the tumor, and MRI or CT will be needed.

MRI is considered the optimal imaging modality for evaluating hemangiomas (Fig. 65.7) [64]. Morphology and architecture of nests of tumors are captured using high-resolution T2-weighted images with fat suppression or T1-weighted images with gadolinium. T2-weighted images can highlight the internal structures of the hemangioma, while T1-weighted images demonstrate signal intensity equal to that of adjacent fat. Gadolinium will display contrast enhancement, and sometimes hemangiomas can mimic highly vascularized rhabdomyosarcoma tumors [64]. CT scanning will show hemangiomas as lobulated enhancing masses with irregular margins; however, internal structures are not well demonstrated with CT as with MRI.

Pathologic Features

Histopathology of hemangiomas will differ in each phase of the tumor. In the proliferative phase tumors will show well-defined, unencapsulated, lobular masses with proliferating endothelial cells. Involution can be seen prior to clinical regression. With time apoptotic bodies increase while mitotic figures decrease. In the end stages of the tumor, all that remains is a fibrofatty background with a few vessels similar to normal capillaries with no remaining endothelial mitotic activity [67].

Treatment

Before treatment is considered or initiated, it is essential to evaluate for syndromes that may be associated with capillary hemangiomas. Kasabach-Merritt syndrome is characterized by consumptive coagulopathy, causing severe thrombocytopenia, and can progress to disseminated intravascular coagulation and even death [68]. Large segmental facial or scalp hemangiomas should alert consideration of other congenital anomalies as seen in the PHACES syndrome. The acronym stands for posterior fossa malformation-hemangiomas-arterial anomalies-cardiac defects-eye abnormalities-sternal cleft and supraumbilical raphe syndrome. Ophthalmologic manifestations include morning glory disk, optic nerve hypoplasia, retinal vascular anomalies, and PHPV. Additional brain imaging, echocardiogram, and formal ophthalmic evaluations may be necessary [69]. Importantly, moyamoya disease and other CNS vascular anomalies may be associated with PHACES, and treatment with beta-blockade may have deleterious consequences if not detected prior to treatment.

Since hemangiomas tend to regress spontaneously, a vast majority can be monitored. However, periocular and orbital hemangiomas can cause amblyopia from occlusion, astigmatism, proptosis, or even compressive optic neuropathy. If there is risk for amblyopia due to a hemangioma, treatment is warranted. Esthetic disfigurement should also be considered and discussed with the guardians prior to initiation of

treatment. Ultimately, each patient should be uniquely evaluated and treatment should be individualized.

Despite recent advancements in hemangioma therapy, no specific guidelines have been established regarding the absolute preferred therapeutic modality. Therapy should be administered in coordination with multiple specialties including pediatricians, cardiologists, and dermatologists. Leute-LaBrese et al. [70] fortuitously discovered the effectiveness of propranolol in the treatment of hemangiomas, and this has truly revolutionized this tumor's management. Propranolol's mechanism of action on capillary hemangiomas is not clearly understood; however, studies have validated its effectiveness. It has relatively few side effects with the most commonly prescribed dose of 2–3 mg/kg/day. The lowest effective dose is continued through the proliferative phase usually until age 1 year. Larger lesions may need to be treated for longer periods of time [71, 72].

A consensus, multidisciplinary set of best practices, published in *The Journal of Pediatrics* [73], states that propranolol can be considered "when there is presence of ulceration, impairment of function, or a risk of permanent disfigurement secondary to an infantile hemangioma." Absolute contraindications to the use of propranolol include cardiogenic shock, sinus bradycardia, hypotension greater than first-degree heart block, heart failure, bronchial asthma, and hypersensitivity to propranolol hydrochloride. Topical 0.5 % timolol maleate drops directly applied to the lesions may also be efficacious; however, further studies are needed to support this therapy [74].

Prior to the advent of systemic propranolol, both systemic and intralesional steroids had been used to treat hemangiomas. Their use may still be considered in those patients in whom propranolol is contraindicated. The 595 nm pulsed dye laser has been shown to be effective for superficial hemangiomas of the eyelids [75]. Surgery is generally reserved for hemangiomas unresponsive to systemic or intralesional therapies. Surgical complications are less when lesions are smaller and noninfiltrating [76]. Complete removal may be difficult secondary to the unencapsulated nature of hemangiomas.

Prognosis

In general, periocular capillary hemangiomas do not need treatment secondary to their natural propensity for spontaneous involution [77]. Up to 33 % are present at birth and often display marked growth during the proliferative phase [64]. However, congenital hemangiomas tend to involute much faster than those that appear weeks to months after birth. A majority of hemangiomas reach 80 % of their final size by the time a child is 5 months of age and most regress nearly completed by 5–6 years of age without any treatment [78].

For larger lesions or in those that impair vision, local or systemic treatments are effective in reducing the size of the lesion. Visual outcomes are generally good when treatment is initiated in early tumor pathogenesis [77]. Lesions that require extended therapy can be monitored using ultrasonography as it is a cost-effective imaging modality [79].

Vascular Malformations

Clinical Features

Vascular malformations are a continually expanding group of vascular entities which can occur at any point during the development of the vascular system [80]. Since vascular malformations of the orbit are frequently derived from vessels of the brain, there can be intracranial components and extension of orbital lesions [81, 82]. Therefore, imaging of not only the orbit but also the brain can be very important in both classification and identification of involvement of more posterior structures [83].

Clinical features suspicious for a vascular lesion include proptosis, especially one that worsens with a Valsalva maneuver, orbital bruit, and hemorrhage. Phenotypical classification of the various congenital vascular malformations has been continually updated as imaging modalities have improved. Table 65.3 outlines classification of orbital vascular malformations expanded upon pathologic features and previous consensus statements on orbital vascular malformations [84–87].

Low-flow malformations (LFMs) are identified when the lesion appears to be relatively hemodynamically isolated. These lesions can be separated into simple and combined vascular malformations. Simple LFM can either be predominantly of venous or lymphatic origin. Those that are purely venous can be divided into nondistensible or distensible LFM. Purely venous malformations are thought to originate from congenital weaknesses in one or more orbital veins. Bilateral involvement is very rare [88].

The most common nondistensible LFM is cavernous LFM, also known as cavernous hemangioma, and is the most

Table 65.3 Orbital vascular malformations

Orbital vascular malformations:
Low flow
• Simple
◦ Venous
■ Nondistensible (cavernous hemangioma)
■ Distensible (orbital varix)
◦ Lymphatic malformation
• Combined
◦ Lymphaticovenous malformation
High flow
• Arteriovenous malformation
• Arteriovenous fistula

common primary orbital tumor in adults. Distensible lesions have more significant connections to the main circulation and can expand with Valsalva maneuvers. These lesions are more commonly known as orbital varices [89]. In older children with distensible VFM, there may be clinical enophthalmos presumably due to fat atrophy [90].

Combined low-flow vascular lesions result in hybrid forms of malformations consisting of both lymphatic and vascular elements [91]. Given their hybrid nature many clinicians describe combined lesions as being lymphaticovenous malformations (LVMs) [92]. Sixty percent of (LVM) occur in the first decade in life and up to 92 % by the end of the third decade [93]. LVM of the orbit can also be associated anterior components which can present with multi-lobulated bluish conjunctival cysts [94].

Valsalva maneuver and changes in head position do not typically change LVM lesion size. There will also be no pulsations or bruit. A typical history may include recent unilateral proptosis during a recent upper respiratory illness. Possible etiology for expansion of the LVM during illness includes lymphoid hyperplasia in response to the infections [95]. Trauma can result in acute proptosis, pain, and periorbital ecchymosis which is thought to occur from the rupture of fine blood vessels surrounding these lymphatic channels [91].

High-flow malformations almost universally involve arterial supply. These include arteriovenous malformations (AVMs) and arteriovenous fistula (AVF). True AVMs of the orbit are rare and orbital manifestations are generally due to cerebral AVM [96]. Although AVMs are thought to be congenital lesions, they are generally not symptomatic in the first 20 years of life. Patients will typically present with a pulsating proptosis and signs of episcleral venous congestion [97]. Hemorrhage from orbital AVM is rare [98]. Orbital AVM can be associated with neurocutaneous syndromes. Orbital and cerebral AVM with racemose hemangiomatosis has been described in Wyburn-Mason syndrome, and orbital AVM can also be associated with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome).

AVF is an acquired direct communication between a trunk of the internal carotid artery and the cavernous sinus. They most often occur after major head trauma but can occur in patients with history of fibromuscular dysplasia and connective tissue disorders such as Ehlers-Danlos type IV [99, 100]. AVF is usually seen in adults, although rare cases have been reported in children [101]. Other clinical signs of AVF include tortuous episcleral vessels, sixth nerve paresis, increased intraocular pressure, and chemosis [102].

Imaging Features

Vascular malformation treatment is dictated by its classification and the risk for permanent vision loss. Assessment of flow is essential in determining malformation classification. The major ways to assess flow include clinical Valsalva, Doppler ultrasound, CT angiography (CTA) or standard MRI with contrast, direct injection of contrast into the malformation, or retrograde access through the venous system [92].

When using CTA, LFMs, which are nondistensible, will show focal filling in the early phase of contrast injection and progressive filling in the venous phase. This suggests modest to minimal communication with inflow and outflow channels. Distensible LFM will have significant communication with the venous system. Clinically, as described previously, they may expand with the Valsalva maneuver.

With CTA imaging, distensible LFM can demonstrate progressive filling and may not be detectable until a Valsalva maneuver is performed. Dynamic CTRA with venous phase Valsalva maneuver may be useful, as the arterial non-Valsalva phase will show an initial small area of filling followed with progressive filling during the venous phase. Phleboliths, local calcifications within a vein, may reflect previous resolution of thrombosis [92].

Imaging of lymphatic malformations can vary given the degree of venous involvement. Purely lymphatic malformations are rare in the orbit and are generally mixed, having a variable venous component [92].

LVMs are typically located in the mid and posterior orbit. There can be two types, those with a significant venous component and those with more of a lymphatic component. Venous dominant LVMs (VD-LVMs) typically have an earlier presentation (mean age, 6 years) while those with lymphatic dominant LVMs (LD-LVMs) present later (mean age, 13 years) [92]. Most VD-LVMs are distensible and have similar imaging characteristics as distensible LFMs. LD-LVMs are composed mostly of lymphatic elements with less prominent venous elements that do change on Valsalva maneuvers. CTA will show irregular patchy contrast filling of the LD-LVM often clustered with cysts. MRI may be better showing the blood and proteinaceous fluid-filled cysts and generally will show a mixture of solid and cystic components (Fig. 65.8). The cysts may show late phase irregular contrast enhancement [92, 103, 104].

Arterial malformations are characterized by high-flow circulation. On CT there may be diffuse enhancement as during contrast studies, the late phase is usually captured. MRI may have flow voids while MRA can demonstrate enhancement of the nidus. Doppler ultrasound will show rapid flow with pulsation and on selective angiography contrast will quickly flow away through an efferent venous system [92].

Pathologic Features

The histopathology of pure lymphangiomas reveals nonencapsulated networks of thin-walled, dysplastic, serous-containing vessels [105]. The absence of lymphocyte aggregates does not exclude the diagnosis. Smooth muscle cells and pericytes may be identified within the septae, suggesting that some of the channels are vascular in nature [92].

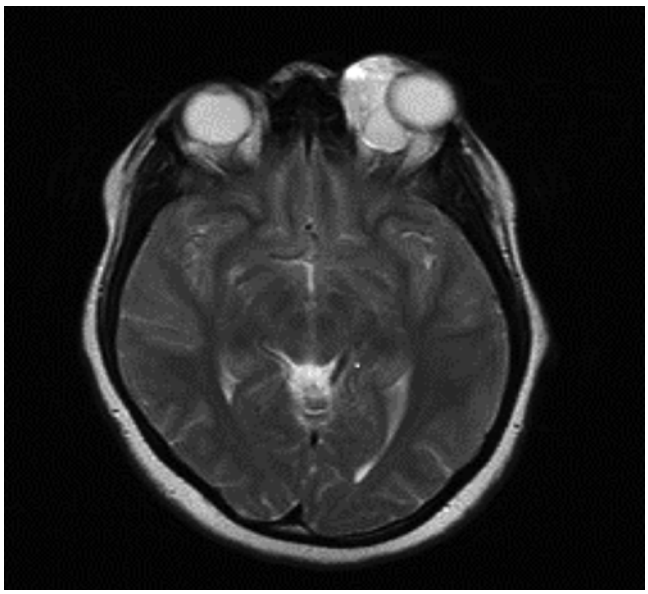

Fig. 65.8 MRI brain axial T2 image demonstrates vascular malformation with multiple cyst walls and fluid levels consistent for low-flow vascular malformation

Nondistensible LFM (cavernous hemangioma) lesions will consist of intertwining plexuses of endothelium-lined channels that appear as adjacent blood-filled spaces [106]. Distensible LFM (orbital varix) will be seen as one or more dilated veins commonly with thrombosis and hyalinization. There can be intravascular hyalinization when varices are thrombosed [107].

Combined lymphatic and venous malformations can be histologically difficult to ascertain whether the endothelium-lined space with lymphocytic infiltration of the adjacent tissue is a lymph vessel or a small vein. Dysmorphic venous and lymphatic channels are present with varying amounts of new and old blood [105].

The mass of an arterial vascular malformation is composed of mature, hypertrophied arteries and veins with many microvascular connections between them [105]. Secondary capillary angiomatosis may occur, presumably in response to chronically elevated capillary pressure [108].

Treatment

Treatment is dictated not only by current clinical symptoms but also must be weighed against the risk of vision loss from surgery and also potentially from amblyopia in younger children. Indications for the removal or debulking of tumors include progressive proptosis, compression of the optic nerve, or even persistent pain. Generally small lesions that do not have functional negative effects can be observed. Identification of the type and position of a lesion through imaging and clinical exam will allow a physician to counsel patients more reliably. Prior to the advent of intralesional sclerotherapy, it was advisable for observation whenever possible as poor final visual acuity appeared to be associated with multiple surgical procedures [91, 92, 109].

Nondistensible LFMs are generally well isolated from the systemic circulation and are encapsulated. If they are located in the anterior orbit, removal is relatively simple and can be performed without marginotomy. Some surgeons utilize simple puncture and then removal or use of a cryoprobe to rotate the tumor during dissection [110].

Distensible LFMs are most often observed; however, indications for treatment may include persistent pain, acute thrombosis, or severe enophthalmos. Because distensible LFMs are generally thin-walled and can be more extensive than initially appreciated, surgery can be complicated by excessive intraoperative bleeding. Direct operative mapping and glue embolization followed by surgical excision is preferred by many. Sclerotherapy when used intraorbitally can cause complications and elevated orbital pressures. However, the use of more gentle sclerosants such as bleomycin A5 and doxycycline may allow for percutaneous treatment [111].

VD-LVMs are usually best observed unless there are indications for treatment. These indications are identical to those described for nondistensible and distensible LVM. Several surgical options can be considered including clipping of an outflow vessel or excision of the lymphatic component with mapping and gluing of the venous component. Sclerotherapy can be used to reduce the size of lesions [112]. Surgical excision with or without the aid of glue can be utilized. Compared with VD-LVM, it appears that sclerotherapy of predominantly macrocystic LD-LVM has had higher efficacy than those primarily composed of microcysts [112, 113]. The use of gentler sclerosing agents may decrease postinjection inflammation [114].

There must be careful planning when treatment is indicated for high-flow vascular malformations as the risk of bleeding can be great. The best method is generally a combined approach with the use of preoperative selective angiography with embolization followed by resection of the nidus. Failure of resection of the nidus appears to result in recurrence. Adjunctive therapy may include alcohol sclerotherapy. At times elimination of the nidus may not be possible without significant morbidity [115].

With AVF, selective cerebral angiography is performed to delineate the lesion, and then the fistula is closed using a variety of thrombogenic materials including minicoils or cyanoacrylic glue. Detachable balloons have also been utilized [116, 117]. If access to the inferior petrosal sinus is not possible, then a direct transvenous approach to the cavernous sinus through a dilated superior ophthalmic vein can be performed [117].

Prognosis

It is important to educate parents regarding the nature of vascular malformations as most cannot be completely removed surgically, the exception at times being nondistensible LFM.

The risk of surgery must be carefully assessed as posterior orbital lesions may be technically challenging to debulk or remove. Careful analysis of imaging studies can help determine the type of vascular malformation a patient may have, and this will dictate the most appropriate treatment plan. Observation should be considered whenever possible as there appears to be poor visual acuity associated with multiple surgical procedures for deeper orbital lesions [109]. Nondistensible LFMs located within the anterior orbit are easier to remove and associated with fewer complications [92]. There has been increasing use of sclerotherapy, and this has been shown to significantly reduce the size of lesions and associated with few complications [118]. Reports indicate that sclerotherapy can be over 80 % effective in reducing the size of a variety of LVM malformations, with fever and diarrhea being the most experienced side effects [119]. A number of studies have shown that sclerotherapy is effective for predominantly cystic LD-LVM. However, more data is needed to determine the overall long-term risk-benefit ratio of such therapy [92, 119, 120].

Hematologic Tumors

Leukemia and Lymphoma

Leukemia is the most common malignancy in children. Leukemic infiltration of the orbit is probably underdiagnosed because of subclinical disease without frank orbital symptoms. In cases of acute myelogenous leukemia (AML), a solid orbital mass termed granulocytic sarcoma (chloroma) may develop.

Granulocytic sarcoma most commonly presents in the first decade of life and is more common in African, Asian, Latin American, and Middle Eastern populations. It can occur before, after (heralding a relapse), or during the active phase of AML [121].

Orbital infiltration in cases of lymphoma is more common in adults than in children. Cases of pediatric orbital lymphoma are typically secondary to Burkitt's lymphoma in the African population. They present with acute proptosis, external ophthalmoplegia, ptosis, and eyelid edema [122].

Clinical Features

Granulocytic sarcoma presents with unilateral or bilateral proptosis typically located in the subperiosteum of the lateral walls of the orbit.

Imaging Features

On both CT and MR imaging, it reveals a nonspecific homogenous mass that uniformly enhances with contrast media. The mass encases the surrounding tissue and does not result in frank bone invasion [123].

Pathologic Features

In a patient with history of AML and a uniformly enhancing orbital mass, it is reasonable to assume the diagnosis of granulocytic sarcoma. If the lesion fails to respond to chemotherapy, a biopsy may be indicated to confirm the diagnosis and rule out secondary malignancy. On pathological sections, granulocytic sarcomas display immature myelocytic cells in a bed of fibrovascular tissue.

Treatment

In cases of granulocytic sarcoma associated with active systemic leukemia, induction of chemotherapy is indicated. Some authors even advocate restarting chemotherapy upon diagnosis of granulocytic sarcoma in cases of systemic remission [124].

Histiocytic

Langerhans cell histiocytosis (LCH) is a rare disease of proliferating histiocytes that are derived from immature dendritic cells of the bone marrow. The pathogenesis remains unknown. It encompasses a wide spectrum of manifestations (focal to systemic involvement) previously divided into three separate clinical syndromes:

- Eosinophilic granuloma: isolated indolent mass
- Hand-Schüller-Christian: triad of diabetes insipidus, osteolytic calvarial defects, and exophthalmos
- Letterer-Siwe disease: diffuse systemic involvement with high rate of mortality

Currently, LCH is classified as a unisystem or a multisystem disease. Unisystem disease can be further classified into unifocal or multifocal disease [125]. In ophthalmology, LCH mainly manifests as an isolated lesion of the orbit in children and young adults with a peak age between 1 and 4 years [126, 127].

Clinical Features

LCH typically presents as unilateral or bilateral proptosis with associated periocular erythema and ptosis [128]. A full workup is indicated when diagnosis of orbital LCH is established to evaluate for systemic involvement [129].

Imaging Features

CT scan of orbital LCH shows isolated "punched-out" lytic lesions with associated orbital soft tissue involvement which typically present superotemporally. MRI reveals a mass with associated destruction of the surrounding boney structures

Pathologic Features

LCH is composed of a histiocytic vascular infiltrate with an admixture of necrotic tissue and acute and chronic

inflammatory cells [125]. Immunohistochemical stains for neural markers (S100 and CD1a) are positive in LCH and help in confirming the diagnosis. On transmission electron microscopy, LCH reveal pathognomonic tennis-racket bodies (Birbeck granules) within the cytoplasm [130].

Treatment

Treatment of LCH depends on the severity of the disease process. After the incisional biopsy, observation or oral steroids are valid options since some unifocal lesions heal spontaneously. Radiation, chemotherapy, and bone marrow transplantation are reserved for recurrences, multisystem disease, and uncontrolled disease, respectively [131].

Xanthogranuloma

Xanthogranulomatous diseases are a heterogeneous group of diseases that may involve the orbit. They are subclassified into: Erdheim-Chester disease, adult periocular xanthogranuloma, juvenile xanthogranuloma (JXG), and necrobiotic xanthogranuloma.

JXG is a non-Langerhans cell histiocytic process that primarily affects the skin, eyes, and less commonly visceral organs. It presents in infants and young children [132]. Orbital involvement is rare and can be locally aggressive with intracranial spread [133].

Clinical Features

JXG typically presents with raised red/yellow lesions of the skin and yellow iris nodules. The iris nodules may spontaneously bleed, resulting in hyphema and secondary glaucoma with possible corneal opacification. Intraocular and adnexal involvements have been previously reported with rare orbital disease.

Pathologic Features

JXG is composed of foamy histiocytes and Touton giant cells.

Treatment

Treatment of orbital JXG involves surgical debulking with adjuvant steroid or radiotherapy to control the disease.

Mesenchymal Tumors

Mesenchymal tumors arise from mesodermal components such as extraocular muscles, fibroblasts, cartilage, and smooth muscles. Rhabdomyosarcoma, fibrous dysplasia, mesenchymal chondrosarcoma, and leiomyoma are examples of orbital tumors of mesenchymal origins.

Orbital Rhabdomyosarcoma

Orbital rhabdomyosarcoma is the most common orbital malignancy in the pediatric population. It is a sporadic tumor with no racial predilection and is slightly more common in males (male/female, 5:3) [134]. It most often presents in the first decade of life with a mean age of 6–8 years [135]. In rare occasions, it is associated with a systemic syndrome including: Li-Fraumeni syndrome, neurofibromatosis type 1, Noonan syndrome, hereditary retinoblastoma syndrome, and Rubinstein-Taybi syndrome, among others [136]. It was once believed to arise from extraocular muscles, but now, it is widely accepted that rhabdomyosarcoma originates from pluripotential mesenchymal cells [137].

Clinical Features

Orbital rhabdomyosarcoma is an aggressive rapidly progressive tumor. Often, a history of periorbital trauma serves as a red herring that could potentially delay the diagnosis. Clinical presentation depends on the location of the tumor within the orbit. Most tumors are extraconal and located in the superonasal quadrant of the orbit, thus, presenting with inferior and temporal displacement of the globe (Fig. 65.9). The signs and symptoms are summarized in Table 65.4.

Imaging Features

CT, MR and to a lesser extent ultrasonography play an important role in establishing the diagnosis of rhabdomyosarcoma. On ultrasound imaging rhabdomyosarcoma appears as a well-circumscribed, heterogeneous mass of low to medium echogenicity. CT and MR imaging features are more reliable (Table 65.5) [138].

Pathologic Features

The diagnosis of rhabdomyosarcoma is based on clinical presentation, imaging features but ultimately is confirmed by tissue biopsy before initiation of therapy. Rhabdomyosarcoma is classified according to four different histological types (Table 65.6). Incisional biopsy is the preferred method of tissue diagnosis, but if the tumor is amenable for excisional biopsy without jeopardizing essential orbital structures like extraocular muscles or the optic nerve, complete tumor resection could be attempted. The role of FNAB is limited and is generally not utilized [139]. The pathologic features of rhabdomyosarcoma are summarized in Table 65.7 [135, 140].

Staging of Rhabdomyosarcoma

The Intergroup Rhabdomyosarcoma Study (IRSG) classified rhabdomyosarcoma of all locations into four groups (Table 65.8) [141, 142]. This classification is also applicable to orbital rhabdomyosarcoma in selecting the treatment and establishing the prognosis.

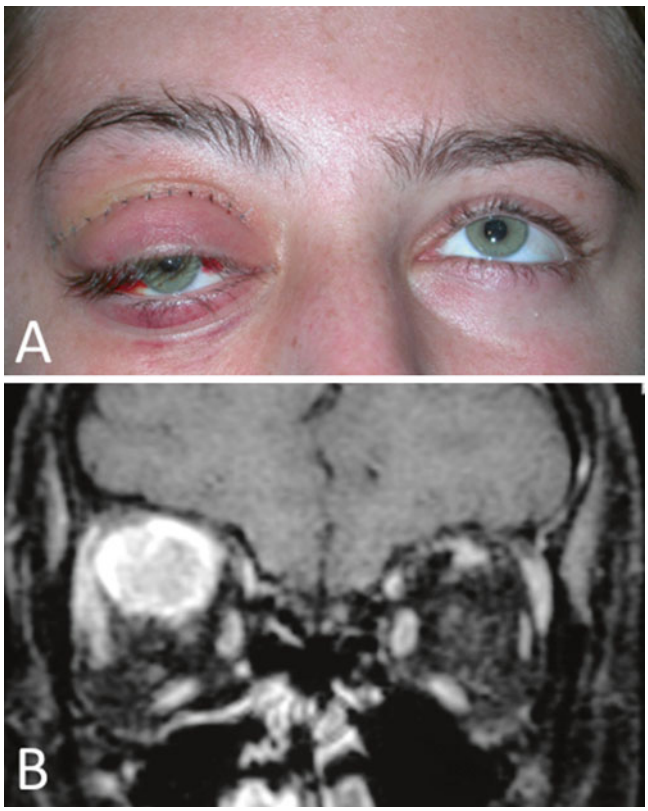

Fig. 65.9 Rhabdomyosarcoma. (**a**) External photograph showing surgical wound along the superior *right upper lid* crease with downward and lateral displacement of the right globe with associated periorbital ecchymosis and subconjunctival hemorrhage. (**b**) MRI coronal image post contrast showing well-circumscribed superior orbital lesion with associated inflammation [Reproduced with permission from: Sakolsatayadorn N, Perry JD. Orbital Rhabdomyosarcoma. In : Clinical Ophthalmic Oncology (Orbital Tumors). Eds : JD Perry, AD Singh, Springer, Heidelberg, 2014, Chapter 14, pp 155–164]

Table 65.4 Signs and symptoms of rhabdomyosarcoma

Symptoms	
Proptosis	80–100 %
Globe displacement	80 %
Eyelid and conjunctival swelling	60 %
Blepharoptosis	30–50 %
Palpable mass	25 %
Pain	10 %
Signs	
Proptosis/hypoglobus	
Palpable mass	
Lid edema or erythema	
Chemosis or exposure keratopathy	
Choroidal folds	
Optic neuropathy or disk edema	

Table 65.5 CT and MR imaging features of rhabdomyosarcoma

CT scan features	MRI features
Well circumscribed	Well circumscribed
Extraconal (most commonly)	Extraconal (most commonly)
Homogeneous	Isointensity relative to the muscle and brain on T1
Isodensity relative to extraocular muscle	Hyperintensity relative to the muscle and brain on T2
Enhancement with dye	Enhancement with dye
Bony destruction could be visualized	Paranasal sinus invasion could be visualized

Table 65.6 Histological types of rhabdomyosarcoma

Histological type	Comments
Embryonal	Most common type, better prognosis, most common location is superonasal quadrant
Alveolar	Worst prognosis, affects older children, most common location is inferior orbit
Anaplastic (formerly called pleomorphic)	Most well differentiated, occurs mostly in adults
Botryoid	Gross appearance resembling a grape bunch, occurs in the orbit by extension from paranasal sinuses

Table 65.7 Pathological features of rhabdomyosarcoma

Pathologic features	Comments
Gross examination	Light-gray to pink color and usually well circumscribed with a surrounding pseudocapsule
Light microscopy	Embryonal type: small round or spindle-shaped cells with abundant eosinophilic cytoplasm and various degrees of myogenic differentiation
	Alveolar type: small round cells with scant cytoplasm with thin fibrovascular septae
Immunohistochemistry	Rhabdomyosarcoma is composed predominantly of small primitive cells with broad pathologic differential immunohistochemical markers that are used in diagnosing rhabdomyosarcoma that include desmin, myoglobin, myogenin, MyoD1, vimentin, muscle-specific actin
Molecular analysis	Cytogenetic studies of alveolar rhabdomyosarcoma often reveal a unique chromosome translocation between chromosomes 1 and 13 1t(1;13)(p36;q14)
	On the other hand, embryonal type often displays aneuploidy (allelic loss at chromosome 11 or gain of chromosome 8)

Table 65.8 Grouping of orbital rhabdomyosarcoma according to the Intergroup Rhabdomyosarcoma Study classification [141, 142]

Group	Comments
Group I	Localized disease
Group II	Residual microscopic disease post biopsy
Group III	Residual gross disease
Group IV	Distant metastasis at time of diagnosis

Treatment

Current management of orbital rhabdomyosarcoma consists of a multimodal therapeutic approach that includes surgery, chemotherapy, and radiation therapy.

Surgery: The status of the surgical margin determines the grouping classification of the tumor and influences the chemotherapeutic and radiotherapeutic regimen. Surgical options include incisional biopsy, surgical debulking, or complete gross excision. The decision is made based on the size and location of the tumor and proximity to vital orbital structures. Preservation of the orbital periosteum is preferred as it acts as a barrier to local spread.

Chemotherapy: Currently all patients receive some form of chemotherapy. The standard regimen is vincristine, actinomycin D, and cyclophosphamide (VAC). High-risk patients may receive additional topotecan or irinotecan. Low-risk patients receive vincristine and actinomycin D only [134].

Radiotherapy: Radiation therapy is necessary for all patients except for those in group I in whom the tumor was completely excised. The dose depends on the amount of residual disease after surgical resection. Low-dose radiation (40 Gy) is usually given to group II, and high-dose radiation (50 Gy) is given to group III patients. Modern techniques that include intensity-modulated radiotherapy, fractionated stereotactic radiotherapy, and proton radiotherapy deliver targeted radiation and potentially decrease radiation-related side effects.

Prognosis

The prognosis of orbital rhabdomyosarcoma has improved greatly over the past 50 years from a dismal 25 % 3-year life expectancy in the 1960s to a >90 % overall survival rate at present [143, 144]. Prognosis typically depends on the tumor size, location, presence of nodal or distal metastasis, and histological type. Isolated orbital involvement, embryonal subtype, and ages from 1 to 10 years carry a more favorable diagnosis. Patients with distant metastasis on diagnosis, alveolar subtypes, or infants and young adults carry a less favorable prognosis. Radiation side effects are relatively common (>70 % of patients) and most commonly include cataracts and facial hypoplasia [145].

Fibro-osseous Lesions

Fibrous dysplasia and juvenile ossifying fibromas are variants of fibro-osseous tumors that affect the pediatric population. They are both benign tumors that involve the craniofacial bones including the orbits. Differentiation between them is important because fibrous dysplasia is slow growing and surgical intervention is rarely needed, while juvenile ossifying fibromas behave more aggressively and complete surgical resection is necessary.

Clinical Features

Fibrous dysplasia is a slowly progressive disease that results from failure of osteoblast maturation and replacement of the bone marrow with immature fibro-osseous tissue. The orbit is affected in up to 40 % of cases with craniofacial involvement [121]. Fibrous dysplasia can be monostotic (only one bone is involved) in 70–80 % of cases and polyostotic (more than one bone involved) in 20–30 % of cases [146–148]. Of note, McCune-Albright syndrome is a rare syndrome characterized by a triad of polyostotic fibrous dysplasia, precocious puberty in girls, and cutaneous pigmentation. Fibrous dysplasia roughly has equal sex distribution and most commonly affects the frontal bone followed by the ethmoid and sphenoid bones [149]. It presents with facial asymmetry, hypertelorism, and proptosis. Diplopia and visual impairment may occur secondary to extraocular muscle palsies and optic nerve compression, respectively.

Juvenile (psammomatoid) ossifying fibroma is a non-metastasizing tumor that affects the facial bones in up to 85 % of cases [150]. It primarily affects children and adolescents and has no gender predilection [151, 152]. When involving the orbit, it most commonly affects the ethmoid and frontal bones [151]. It is a slow-growing tumor but has the potential to be locally aggressive and invade the surrounding structures. Clinically, it resembles fibrous dysplasia and differentiation is based on imaging and pathologic features.

Imaging Features

CT scans of fibrous dysplasia reveal "ground-glass" appearance within the medullary space. MRI has variable characteristics but mostly shows central enhancement of the lesion after injection of contrast material [153]. Bone scintigraphy reveals intense radionuclide uptake in the areas of involvement [121].

CT scans of juvenile ossifying fibroma show a well-demarcated lesion with multiple foci of calcifications with areas of cystic changes. MRI may show fluid-filled cystic spaces and calcification areas that enhance with gadolinium [154].

Pathologic Features

Fibrous dysplasia consists of an admixture of fibrous and osseous components. The osseous portion is irregular and often described as "Chinese characters." The fibrous portion is low cellularity and forms the stroma that surrounds the osseous trabeculae [147].

Juvenile ossifying fibroma is formed of small, uniform "psammoma-like" ossicles within a densely cellular fibrous stroma. Focal cystic changes may be present [155].

Treatment

Fibrous dysplasia is usually observed unless compression of the optic nerve occurs where a local orbital decompression is indicated [156].

Juvenile ossifying fibroma is mainly treated with complete excision because of high chance of recurrence in cases of incomplete resection [157].

Leiomyoma

Leiomyoma is a benign tumor that typically affects the uterus and gastrointestinal tract, but in rare cases it presents within the orbit [158]. It is believed to arise from the smooth muscle of the blood vessels, pericytes, or from Muller's muscle [159]. Orbital leiomyoma has a slight male predominance.

Clinical Features

Orbital leiomyoma typically presents with a slow progressive proptosis over the span of several months to years. It can be located anywhere in the orbit (intraconal or extraconal) and in some cases extends to the orbital apex with possible intracranial involvement [160].

Imaging Features

CT imaging reveals a well-circumscribed orbital tumor, but like most other soft tissue tumors MRI provides a better resolution and delineation of the tumor. Orbital leiomyoma moderately enhances with gadolinium.

Pathologic Features

On histopathology leiomyoma is composed of spindle cells with blunt-ended oval nuclei. The cells are present within a fibrovascular stroma. Immunohistochemistry aids in the diagnosis of leiomyoma and differentiation from other spindle cell tumors that affect the orbit (e.g., schwannoma, neurofibroma, and fibrous histiocytoma). It stains positive with desmin, vimentin, and smooth muscle actin (SMA) [161].

Treatment

Leiomyoma is not radiosensitive and complete excision is the treatment of choice. Recurrence has been observed with residual tumors after incomplete resection [162]. Malignant transformation of orbital leiomyoma has not been reported to date.

Secondary Tumors

Metastatic Tumors

As opposed to adults, where the choroid is the most common site of ocular metastasis, in the pediatric population the orbit is more commonly involved and is the most common culprit.

Neuroblastoma is the most common extracranial solid tumor in children. It originates from any part of the sympathetic nervous system chain, generally from the adrenal glands. Neuroblastoma has no sexual predilection and most cases present in the first decade of life [163]. Ophthalmic involvement is present in up to 20 % of systemic neuroblastoma [164]. Diagnostic orbital biopsy might be indicated in some cases, as other tumors are more internalized and less amenable to tissue diagnosis.

Clinical Features

Metastatic neuroblastoma to the orbit most commonly presents with proptosis and periorbital ecchymosis (raccoon eyes). Other ophthalmic manifestations include opsoclonus/myoclonus (dancing eyes/dancing feet), Horner's syndrome, nystagmus, heterochromia, fixed dilated pupils, optic nerve atrophy, and subconjunctival hemorrhage (secondary to pancytopenia) [165].

Systemic symptoms depend on the location of the tumor and include bone pain (secondary to bone metastasis) and pancytopenia. Increased levels of catecholamine metabolites (HVA and VMA) may be detected on urinalysis.

Imaging Features

On CT imaging, neuroblastoma typically reveals extraconal mass that arises most commonly from the lateral orbital wall or the orbital roof with adjacent bony destruction. MRI typically reveals a heterogeneous extraconal mass that enhances variably secondary to intralesional hemorrhage and necrosis. PET scans and scintigraphy are also helpful in detecting systemic neuroblastoma and its metastasis [121, 165].

Pathologic Features

Metastatic neuroblastoma is similar to primary neuroblastoma and is composed of neuroblasts (small round blue cells) and Schwann cells supported by matrix of fibrovascular tissue [121].

Treatment

Orbital involvement in neuroblastoma places the patient in a stage 4, high-risk category as per the International Neuroblastoma Staging System [166]. Therefore, aggressive treatment is necessary that includes high-dose chemotherapy along with myeloablative therapy and autologous bone marrow transplantation [167]. In some cases, radiation therapy of the

orbital tumor may be indicated. Close follow-up and supportive care is needed to ensure response to systemic treatment [168].

Orbital Retinoblastoma

Retinoblastoma (Rb) is the most common intraocular tumor in the pediatric population. Although extraocular and orbital Rb is rare in the developed world, it is much more common in the developing world secondary to delay in diagnosis. In a study from Nepal, orbital involvement in Rb was as high as 40 % with proptosis being the most common presenting sign [169].

Clinical Features

In addition to the proptosis, advanced signs and symptoms of Rb may be present such as leukocoria, secondary glaucoma, pseudohypopyon, and hyphema. Intracranial extension and systemic metastasis are common in Rb with orbital involvement [169].

Imaging Features

Ultrasonography is the imaging modality of choice in detecting intraocular Rb, but it is less sensitive in detecting orbital involvement. CT imaging can identify calcifications but orbital MRI with fat suppression is superior at delineating orbital infiltration.

Pathologic Features

Retinoblastoma is a small blue-cell tumor derived from primitive neuroepithelial cells. Due to high rate of mitosis, Rb typically outgrows its blood supply, leading to areas of necrosis with viable tumor cells concentrated around blood vessels. Rb cells have the potential for neuronal differentiation and, therefore, can form Homer-Wright rosettes, Flexner-Wintersteiner rosettes, and fleurettes.

Treatment

Management of orbital Rb is challenging and generally requires a combination of initial high-dose chemotherapy followed by appropriate surgical intervention, orbital radiotherapy, and extended course of standard-dose chemotherapy [170] (see Chap. 37 on Retinoblastoma).

Secondary Cystic Lesions

Secondary orbital cysts either originate from surrounding structures and extend into the orbit (i.e., mucocele) or occur secondary to an inflammatory reaction toward an infectious parasitic agent in endemic areas.

Mucoceles are mucous-filled cysts and rarely occur in the pediatric population. When present in childhood, they are associated with cystic fibrosis [171].

Larvae of tapeworms commonly cause inflammatory cysts with *Taenia echinococcus* forming hydatid cyst and *Taenia solium* causing orbital cysticercosis [15].

Clinical Features

Mucoceles present with a slowly progressive proptosis, globe displacement, diplopia, and ophthalmoplegia.

Imaging Features

CT imaging is highly sensitive and specific for mucocele. It typically reveals opacification of the paranasal sinuses with surrounding bony erosion and herniation of the cystic lesion into the orbit [172].

Pathologic Features

Mucoceles are mucous-filled cystic lesions lined by pseudostratified respiratory columnar epithelium.

Treatment

Management of mucocele includes removal of the cystic lining and establishing of a drainage system commonly through marsupialization or exenteration of the involved sinuses [15].

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Craniosynostosis and Congenital Craniofacial Disorders

66

Daniel Straka, Sandy Zhang-Nunes, Cameron Nabavi, and Jill Foster

Abstract

Craniosynostosis refers to the premature fusion of cranial sutures and is often associated with ophthalmologic comorbidities. These associations include, but are not limited to, significant refractive errors, strabismus, ocular adnexal and orbital malformations, and structural abnormalities of the globe. Diagnosis and treatment of the various craniosynostoses and related syndromes can be difficult and is often managed by utilizing a team of physicians who specialize in craniofacial disorders. The role of the ophthalmologist in monitoring the visual development of these patients is extremely important. He or she must be knowledgeable of the common and potentially sight-threatening ocular findings in craniosynostosis.

Assessment begins with a thorough patient and family history based on an understanding of the features of craniosynostosis or craniofacial syndromes, followed by a detailed ophthalmologic examination to rule out causes of amblyopia or other ocular disease. Based on the structural and anatomic variations that may be present, management of the ophthalmic problems is often technically more challenging compared to the general population and requires diligent study and sometimes unique interventions.

Keywords

Craniosynostosis • Craniofacial anomalies • Crouzon • Apert • Strabismus • Amblyopia

Introduction

The craniosynostoses represent a group of conditions characterized by the premature fusion of one or more cranial sutures. Craniofacial deformities may occur as a result leading to several important ophthalmologic sequelae. Craniosynostosis can be an isolated anomaly or associated with a number of syndromes, which will be discussed later in this chapter. The incidence of isolated craniosynostosis ranges from about 0.4 to 1 case per 1000 live births [1, 2], whereas the syndromic cases tend to be much less common, representing about 15 % of all affected patients [3]. The ophthalmic sequelae in children with syndromic craniosynostosis are more severe and require additional interventions.

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Anatomy and Embryology

An overview of craniofacial embryogenesis and anatomy is central to predicting, categorizing, and managing the potential ophthalmic complications associated with each disorder. Perhaps overstating the obvious, the embryology of the periocular area is one of the most complicated in the body. Head, face, and neck development are predominantly governed by the branchial arches. The process begins in the third to fourth week of gestation with the formation of five main facial prominences (two paired, one unpaired) (Fig. 66.1). The first branchial arch contributes to the paired maxillary and mandibular prominences, giving rise to the primitive mouth and surrounding structures. The central frontonasal prominence forms as a proliferation of mesenchyme ventral to the forebrain and fuses with the first branchial arch centrally. Although it is not part of the branchial apparatus, the frontonasal prominence is vital to facial development as it accounts for the forehead, nasal dorsum, and medial and lateral nasal prominences. The mandibular prominences fuse at the facial midline to give rise to the lower jaw, lower lip, lower cheek, and chin by the end of the sixth week of gestation. As the maxillary prominences continue to migrate medially, they fuse with the medial and lateral nasal prominences to form the nose, upper lip, and palate. A deep recess called the nasolacrimal groove forms between the maxillary and the lateral nasal prominences. As the maxillary prominence continues to migrate centrally, the majority of this groove is obliterated, but the remaining portion persists as the nasolacrimal duct. Clefting anomalies can result when the facial prominences fail to fuse. Initially, the developing eyes are located on the lateral forebrain. During the seventh week, they have migrated to a more medial location as frontonasal growth slows and lateral head growth persists. Disruption of this process may

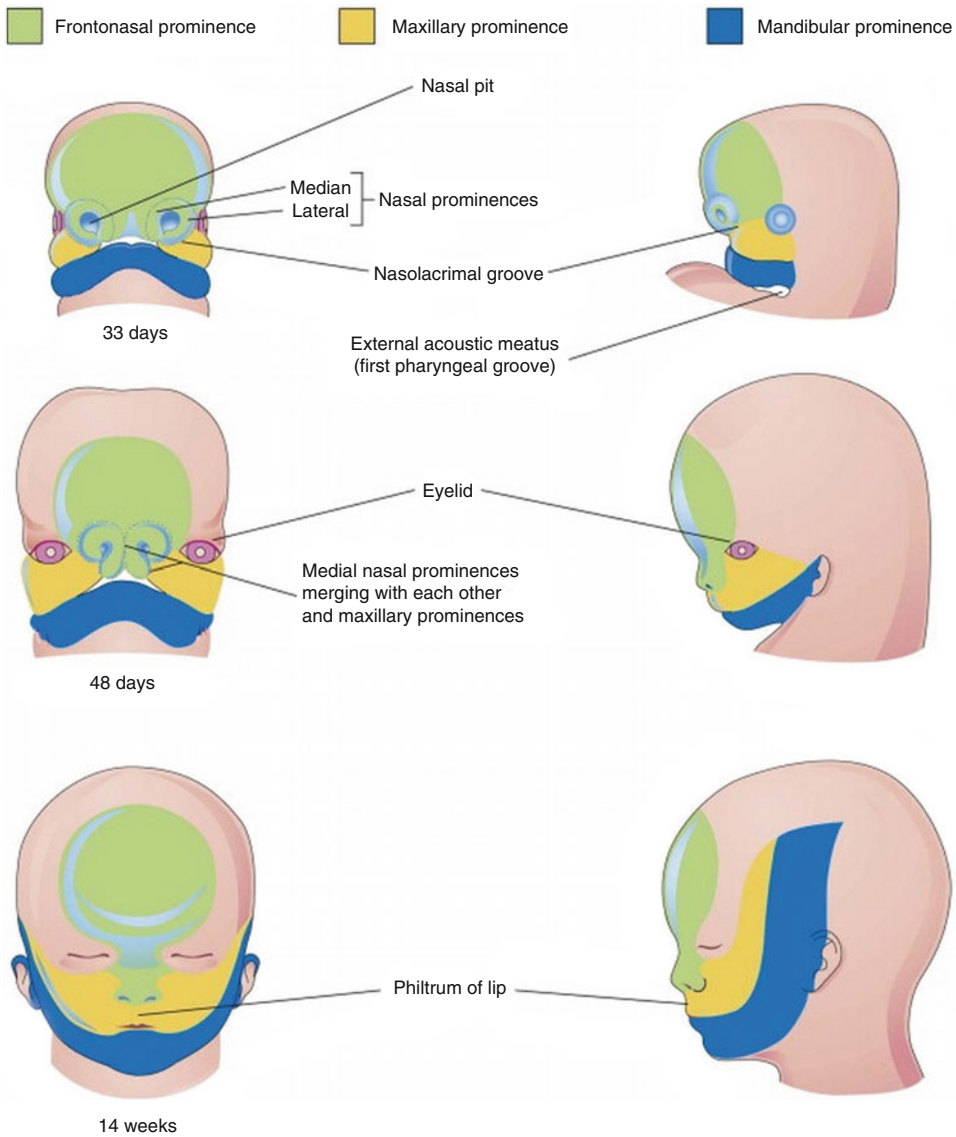

Fig. 66.1 Fetal development of the facial prominences, two paired and one unpaired. Figure courtesy of Moore, Keith L., M.Sc., Ph.D., F.I.A.C., F.R.S.M., F.A.A.A.—Before we are Born: Essentials of Embryology and Birth Defects, 99-125 © 2013 Copyright © 2013 by Saunders, an imprint of Elsevier Inc

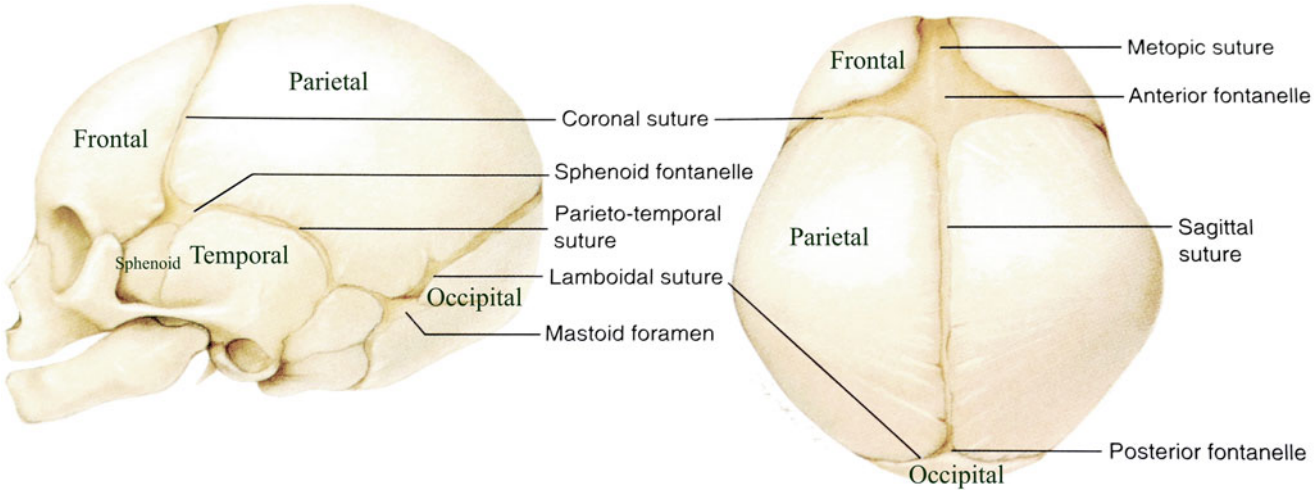

Fig. 66.2 Anatomic features of the pediatric skull and cranial sutures. Reproduced with permission of Jockin YM, et al. "Congenital Craniofacial Deformities: Ophthalmologic Considerations," in *Pediatric Oculoplastic Surgery*. Springer Science+Business Media, Inc., 2002 [3]

result in hypertelorism. By the eighth week, facial development is mostly complete and by 10 weeks the developing embryo has a clear human facial appearance [3, 4] (Fig. 66.1).

The developing skull, or neurocranium, can be embryologically separated into two major parts, the cartilaginous portion (skull base) and the membranous portion (calvarium or cranial vault). The skull base forms from a collection of cartilaginous structures surrounding the notochord. This mesoderm-derived cartilage undergoes endochondral ossification to give rise to the ethmoid and sphenoid bones, zygoma, petrous portion of the temporal bone, and the occipital base. The membranous bones of the calvarium (paired parietal and frontal bones and a portion of the occipital bone) begin as plate-like aggregations of bony spicules that have been stimulated to grow by the underlying developing brain and dura. These bones undergo intramembranous ossification and eventually form the flat bones of the calvarium [5].

The neonatal calvarium is composed of paired frontal, parietal, and temporal bones, as well as a small portion of the sphenoid bones and a single occipital bone (Fig. 66.2). At the intersection of two of these bones, known as the calvarial sutures, active bone deposition occurs via local growth factors on undifferentiated mesenchyme to accommodate the expanding brain and cerebral spinal fluid (CSF) [6]. Similarly to bone growth, patency of the sutures is highly regulated by local signaling and from the underlying dura mater [7]. The primary sutures separating these bones are the metopic (frontal bones), coronal (frontal and parietal bones), squamosal or parieto-temporal (parietal and temporal bones), lambdoidal (parietal and occipital bones), and finally the sagittal (parietal bones) (Fig. 66.2). Fusion of the sutures does not occur until the postnatal period as head malleability permits passage through the birth canal and continued separation of the bones as the brain grows. Roughly 80–85 % of brain growth occurs in the first 30 months of life [8], while sutures do not fully close until around the age of 9 months to 2 years for the metopic suture, and about 16–22 years for the sagittal suture [8, 9].

The pathophysiology of craniosynostosis has yet to be fully elucidated; however, recent developments have pointed to various genetic mutations as major contributors [10–17]. Premature closure of the sutures results in inhibition of growth perpendicular to the axis of the suture line, with continued or increased growth parallel to the suture to accommodate the growing brain, a phenomenon known as Virchow's law [18]. Research during the 1990s using transgenic animal models identified several signaling pathways and genes that play an important role in many of the syndromic craniosynostoses and probably nonsyndromic cases as well. Specifically, mutations in a family of genes known as fibroblast growth factor receptors (FGFR) have, among others, been implicated in Pfeiffer, Apert, and Crouzon syndromes [10–15]. Patients with Saethre-Chotzen syndrome carry mutations in the *TWIST* gene, and the autosomal dominant Boston-type nonsyndromic craniosynostosis has been associated with a mutation in *MSX2* [16, 17].

Nonsyndromic Craniosynostosis

The affected suture predicts the typical skull deformities encountered in isolated craniosynostosis, and a specific term has been given for each condition. Sagittal suture synostosis, known as *scaphocephaly* from the Greek "skaphe" meaning light boat or skiff, leads to an elongated, narrow skull. The term *brachycephaly* describes a shortened calvarium in the anterior-posterior direction due to bilateral coronal suture synostosis. Patients will have exaggerated upward growth due to the patent sagittal suture. *Acrobrachycephaly* also describes bilateral coronal suture synostosis but with a patent anterior fontanelle resulting in a pointed top of the skull.

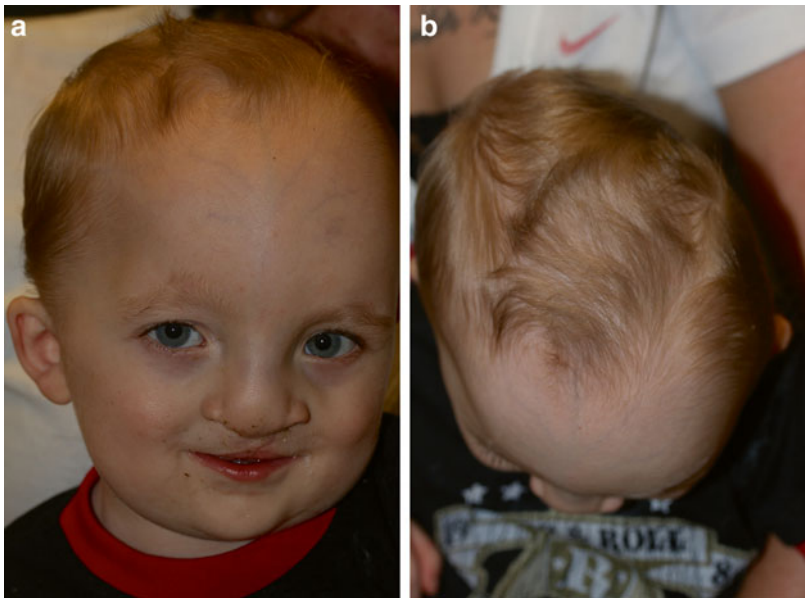

Fig. 66.3 (**a**) Positional plagiocephaly in a child with a history of cleft palate. (**b**) Note the posterior flattening and concurrent anterior bulging of the *left side* of the calvarium which would not be seen in synostosis of the sutures. When the sutures close too early, the anterior and posterior flattening is ipsilateral to the closed suture

Unilateral closure of the coronal suture ventrally or the lambdoid suture dorsally can lead to a similar reduction in anterior-posterior growth, but only on one side, with increased growth on the contralateral side leading to an asymmetric skull. This is known generally as *plagiocephaly*; frontal plagiocephaly if it involves the coronal suture, occipital plagiocephaly if it involves the lambdoid suture. Plagiocephaly can be highly variable depending on the extent and location of suture fusion [3]. Unilateral coronal synostosis may result in a constellation of changes in the ipsilateral orbit called a "harlequin orbital deformity." This name comes from the elevation of the lateral wall and lateral roof of the orbit resulting in a deformity imitating the shape of a harlequin mask. It should be noted that the term "positional" plagiocephaly has also been used to describe deformities of the skull due to infant head positioning while sleeping. Positional plagiocephaly is mechanical, not syndromic (Fig. 66.3). Occipital flattening or asymmetry can develop mimicking isolated lambdoid synostosis. However, the sutures are still patent in these cases [19]. Premature fusion of the metopic suture prevents expansion of the frontal bones and leads to the condition known as *trigonocephaly*. Patients with this deformity will have a narrow frontal and fronto-orbital region with a triangular shape. When multiple sutures are involved the term *oxycephaly* is used, particularly if this includes the coronal and sagittal sutures. The term *turricephaly* is sometimes used instead and refers to a vertically elongated, or "tower skull" as the cranium moves upward [3]. It is important to remember that fusion of multiple sutures can limit the expansion of the underlying cortex with a subsequent increase in intracranial pressure, mental retardation, and papilledema (Table 66.1, Fig. 66.4).

Table 66.1 Nonsyndromic craniosynostoses

Term	Suture involved	Clinical findings
Scaphocephaly	Sagittal	Anterior-posterior elongation of the skull
Brachycephaly	Bicoronal	Anterior-posterior shortening of the skull
Achrobrachycephaly	Bicoronal, patent anterior fontanelle	Brachycephaly with pointed apex of skull
Plagiocephaly with synostosis	Unilateral lambdoid or coronal	Asymmetric skull with variable appearance depending on involved suture
Trigonocephaly	Metopic	Narrowed anterior cranial fossa with triangular shape
Oxycephaly	Multiple sutures, at least bicoronal and sagittal	Vertical elongation of the skull, also called Turricephaly

The most common type of non-syndromic synostosis is sagittal, followed by unilateral coronal, bilateral coronal, metopic, and lastly, lambdoid suture closure. A sex predilection has been determined with sagittal synostosis being 4 times more common in boys and unilateral coronal synostosis being 1.5 times more common in girls [8].

Syndromic Craniosynostosis and Ophthalmic Considerations

As discussed previously, craniosynostosis can be associated with a number of specific syndromes. The following section will discuss some of the more common syndromes encountered in the ophthalmologist's office.

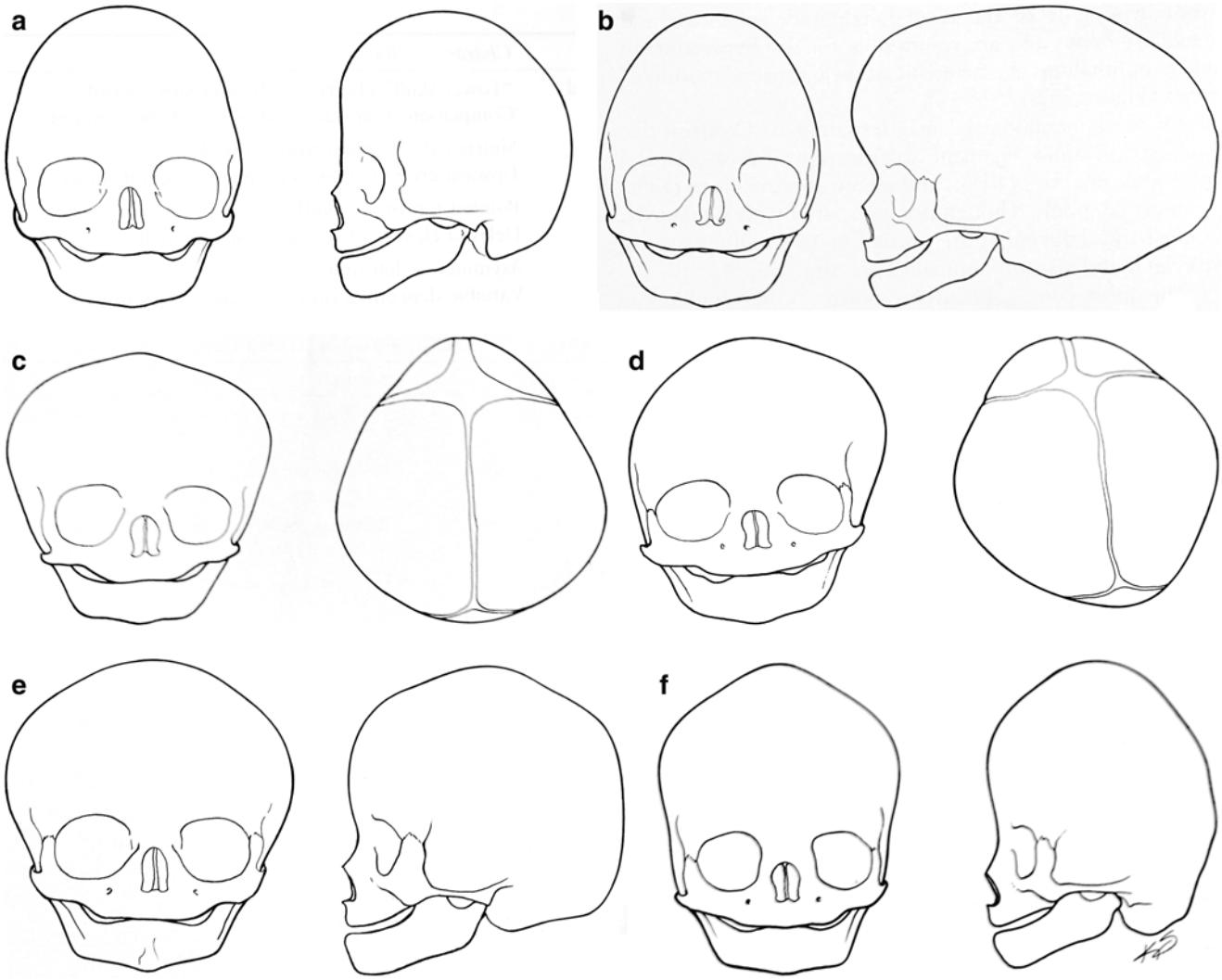

Fig. 66.4 Common nonsyndromic craniosynostoses: (**a**) oxycephaly, (**b**) scaphocephaly, (**c**) trigonocephaly, (**d**) nonpositional plagiocephaly, (**e**) brachycephaly, (**f**) acrocephaly. Reproduced with permission of Jockin YM, et al. "Congenital Craniofacial Deformities: Ophthalmologic Considerations," in *Pediatric Oculoplastic Surgery*. Springer Science + Business Media, Inc., 2002 [3]

Crouzon Syndrome

Crouzon syndrome is an autosomal dominant, phenotypically variable condition caused by a genetic mutation in the *FGFR-2* gene. It is the most common of the craniofacial syndromes accounting for approximately 4.8 % of all craniosynostoses with a prevalence of about 1 in 25,000 in the general population [3, 20]. Although suture involvement can be variable, the classic findings of Crouzon syndrome include bilateral coronal synostosis with or without sagittal synostosis leading to a shortened calvarium, steep forehead, and flattened occiput. Other characteristic findings include shallow orbits with moderate to severe exorbitism, midface retrusion with hypertelorism, and a beak-like nose (Fig. 66.5).

There are many ocular and ocular adnexal complications one considers in patients with Crouzon syndrome. These have the potential to lead to amblyopia and permanent vision loss from optic nerve compression, making ophthalmologic assessment an important component of the patient's care. The prominent exorbitism can lead to severe corneal exposure, ulceration, and opacification. Less common corneal findings reported in Crouzon syndrome include megalocornea, microcornea, and keratoconus [21].

Strabismus is an extremely common finding in Crouzon syndrome. Studies have documented its presence anywhere from 39 to 92 % of Crouzon patients [3, 22]. Many patterns of strabismus have also been reported. Exotropia as well as A- or V-pattern heterotropias are the most common followed by esotropia, and vertical strabismus [22]. Several reports have documented absent or anomalous extraocular muscles and insertion sites as the cause in many cases of craniofacial syndromes. Snir et al. described a patient with agenesis of the superior and

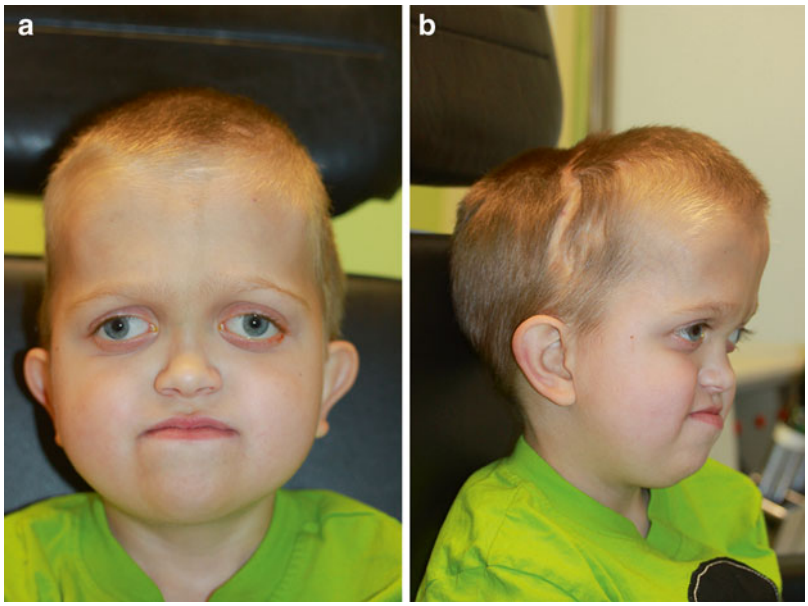

Fig. 66.5 (**a**) This child demonstrates many features of Crouzon syndrome including hypertelorism, midface retrusion, mild proptosis, and a steep forehead. Note the exotropia and (**b**) coronal scar from previous cranial vault surgery

inferior rectus and superior and inferior oblique muscles of both eyes [23]. Although abnormalities in each extraocular muscle have been reported, the superior muscles seem to be more commonly affected. Some experts recommend computed tomography (CT) scans of the extraocular muscles in these patients at the same time as their head CT [22].

Optic nerve disease, either from primary atrophy or secondarily from prolonged papilledema, can be present in patients with Crouzon syndrome. The etiology of the isolated optic atrophy remains unknown, as imaging studies have confirmed a near normal optic canal [24]. A patient with Crouzon syndrome who presents with headaches should be suspected of having increased intracranial pressure, particularly in the presence of optic disc swelling.

Finally, refractive errors are an important cause of amblyopia in Crouzon syndrome patients. In a study by Hertle et al., 20 of 25 patients with Crouzon syndrome had significant refractive errors, the most frequent being astigmatism, and nearly 50 % (12/25) had visually significant anisometropia [25] (see section "Case Study 1").

Apert Syndrome

Apert syndrome is a rare condition characterized by craniosynostosis (bicoronal synostosis, turricephaly), exorbitism, midface hypoplasia, and complex syndactyly of the digits and toes. Although it can be inherited in an autosomal dominant fashion, sporadic mutations account for the majority of cases. The syndrome may result from a mutation in the *FGFR-2* gene. It is estimated to comprise 4.5 % of all craniosynostoses with an overall prevalence of 13.7 to 15.5/1,000,000 live births [3]. Other typical features of Apert syndrome include a flattened occiput, prominent "parrot-beak" nose, low set ears, hypertelorism, bifid uvula, and true megalocephaly often with subnormal intelligence.

The ophthalmic findings in Apert syndrome are similar to those of Crouzon syndrome. Severe proptosis and corneal exposure tend to be less severe in patients with Apert syndrome; however, strabismus may be more prevalent [3, 25]. Fifteen out of 15 patients studied by Hertle et al. with Apert syndrome had a manifest heterotropia, the most common of which was a V-pattern esotropia or exotropia (11/15) [25]. As in Crouzon syndrome and other craniosynostoses, vision loss in Apert syndrome is most often due to a combination of factors, including ametropia, strabismus, ptosis, and/or anisometropia. Other rare ophthalmic conditions that have been reported with Apert syndrome include keratoconus, ectopia lentis, congenital glaucoma, and oculocutaneous albinism [26, 27] (Fig. 66.6).

Saethre-Chotzen Syndrome

Saethre-Chotzen syndrome, like many of the other craniosynostoses, can be phenotypically variable and have significant overlap with other syndromes. The characteristic findings include uni- or bicoronal craniosynostosis (although plagiocephaly, scaphocephaly, brachycephaly, and oxycephaly have all been reported), low-set hairline, ptosis, brachydactyly, frontal bossing with a high forehead, and other abnormalities of the hands and toes (Fig. 66.7). In contrast to Crouzon and Apert syndromes, Saethre-Chotzen typically lacks the midface retrusion. It is inherited in an autosomal dominant pattern due to a mutation in the *TWIST* gene on chromosome 7p21 [28].

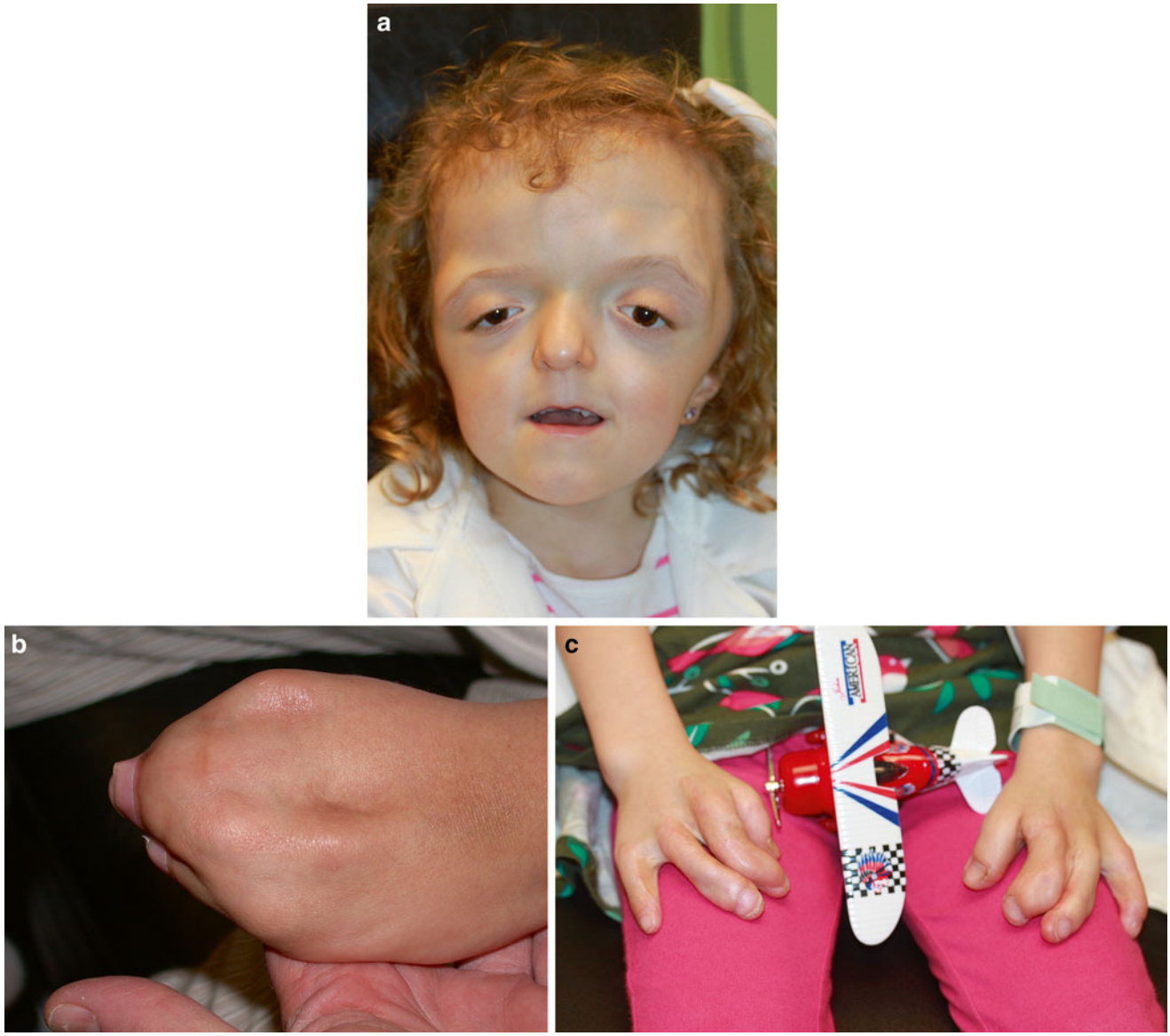

Fig. 66.6 Child with Apert Syndrome (**a**) demonstrating hypertelorism, a "parrot beaked" nose, high arched palate, and syndactyly. (**b**) Syndactyly of the right hand preoperatively and (**c**) both hands after surgery

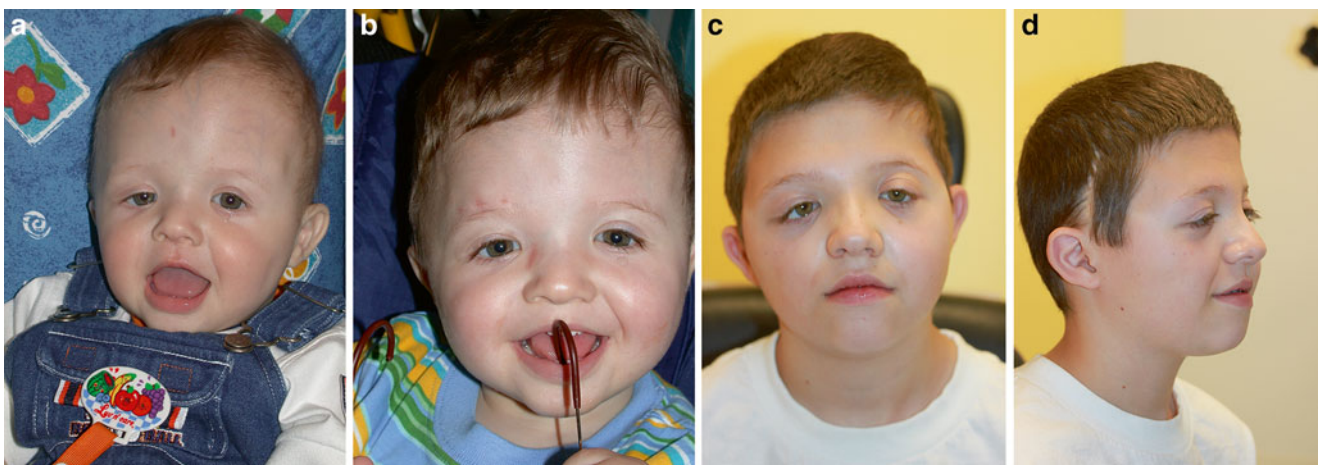

Fig. 66.7 Saethre-Chotzen Syndrome. (**a**) The child has right-sided ptosis, an elevated tear lake in both eyes with epiphora on the *left*, and a *flattened* and *shortened right* forehead indicative of unilateral coronal synostosis (plagiocephaly). (**b**) Improvement in ptosis and tearing after frontalis sling and dacryocystorhinostomy. (**c**) Years later with some residual ptosis and (**d**) coronal scar from previous cranial vault reconstruction

The ophthalmic manifestations of Saethre-Chotzen syndrome have many similarities to other craniosynostosis syndromes; however, there are a few differences worth noting. First, ptosis is much more common. In a study of ten children with Saethre-Chotzen syndrome by Jadico et al. ptosis was present in 90 % of the cases [28]. In addition, nasolacrimal duct obstruction (NLDO) may be more common occurring in 50–60 % of cases [28].

Pfeiffer Syndrome

Pfeiffer syndrome has a similar clinical appearance to Apert syndrome with the unique feature of broad, prominent thumbs and great toes, and less frequent syndactyly. It is inherited in an autosomal dominant fashion but may also develop sporadically. Mutations in the *FGFR-1* and *FGFR-2* genes are responsible for this condition. The similar clinical features make the ophthalmic complications analogous to those seen in Crouzon and Apert syndromes.

Clefting Syndromes

Facial clefts can be an isolated finding or associated with a specific syndrome. The cause of facial clefts remains poorly understood although several theories have been proposed. In general, it occurs either due to failed fusion of the facial prominences or faulty mesodermal migration between the facial prominences. Neural crest cell migration may also be inhibited [3, 29].

In 1976, Tessier developed what is the most recognizable and accepted topographic classification system for describing facial clefts. It divides the face along the sagittal midline and assigns numbers to the location of clefts in relation to this midline and the orbit from 0 (inferior midline) to 14 (superior midline) moving counterclockwise around the orbit on the left, and clockwise on the right [30] (Fig. 66.8).

Treacher-Collins syndrome, or mandibulofacial dysostosis, is a variably expressed syndrome of Tessier clefts 6, 7, and 8. It is inherited as an autosomal dominant trait; however, sporadic cases occur and a family history is often negative. Variable phenotypic expression of the syndrome accounts for the incomplete and complete forms. Complete Treacher-Collins syndrome contains all of the typical clinical characteristics including lateral canthal dystopia with an antimongoloid appearance, coloboma of the lateral lower eyelid, hypoplasia of the facial bones including the zygoma and mandible, flattening of the nasofrontal angle, macrostomia, malformations of the external and inner ear with hearing loss, and the absence of lashes in the nasal aspect of the lower lid [31]. The incomplete form tends to be less severe.

Great care must be taken to monitor the significant ocular, lid, and adnexal abnormalities present in these patients. In addition to the lateral canthal dystopia, patients with Treacher-Collins syndrome will often have lacrimal outflow

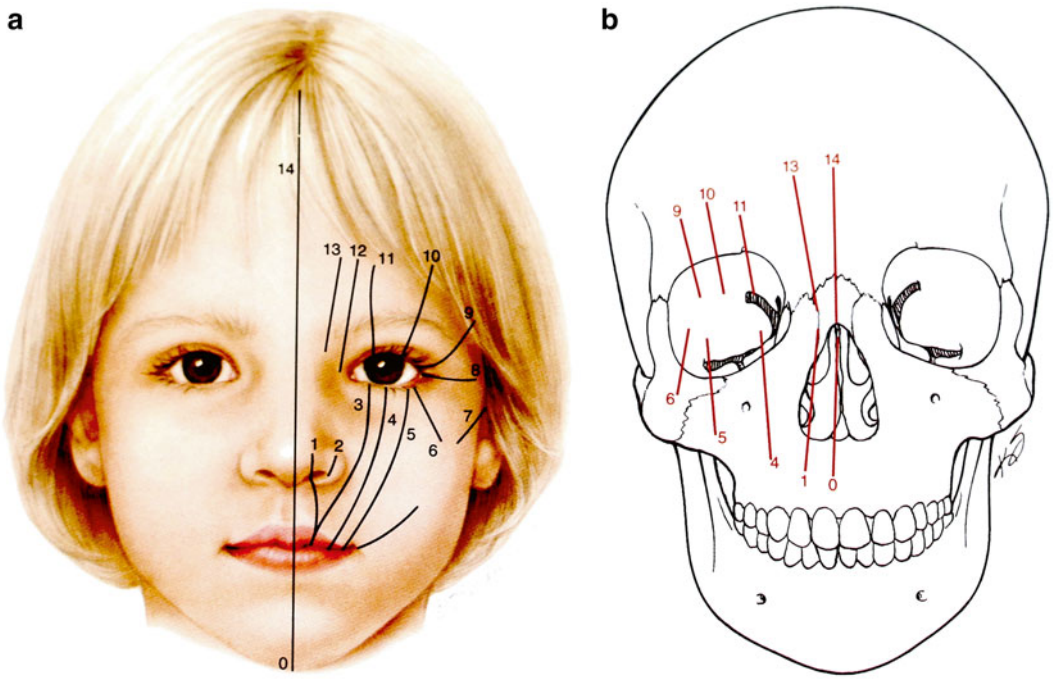

Fig. 66.8 Tessier's clockface system for describing facial clefts. (**a**) Soft tissue clefts and (**b**) bony clefts. Reproduced with permission of Jockin YM, et al. "Congenital Craniofacial Deformities: Ophthalmologic Considerations," in *Pediatric Oculoplastic Surgery*. Springer Science + Business Media, Inc., 2002 [3]

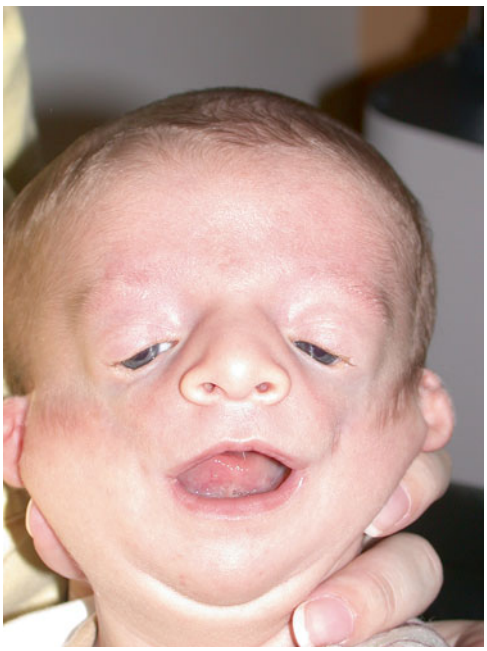

Fig. 66.9 Treacher-Collins syndrome with lateral canthal dystopia, hypoplasia of the zygoma and mandible, and external ear deformities

disease including absence of the puncta or canalicular atresia. Significant refractive errors including astigmatism and anisometropia frequently occur as well as various forms of strabismus and must be monitored in every patient (Fig. 66.9).

Hemifacial microsomia is one of the more common craniofacial syndromes occurring in about 1 in 4000 live births [32]. It is typically sporadic, although familial cases have been reported [33]. The clinical characteristics are quite variable and involve unilateral defects in the first and second branchial arches and Tessier cleft 7. In its fullest expression, patients will have unilateral underdevelopment of the external and middle ear, hypoplasia of the mandible, zygoma, maxilla, and temporal bone, as well as the associated facial soft tissues including muscles of mastication, facial muscles, parotid gland, palate, and tongue. Minimally affected patients may only display isolated microtia and an asymmetric mandible. In 6–10 % of cases, findings can be bilateral [34].

Depending on the severity of the presentation patients can have anywhere from normal ocular and adnexal structures, to severe orbital and lid dystopia with microphthalmos or anophthalmos. Lid colobomas, limbal dermoids, and strabismus are also common, particularly Duane retraction syndrome [3] (see section "Case Study 2").

Goldenhar syndrome (oculoauriculovertebral dysplasia) shares many similarities with hemifacial microsomia, but patents must have a specific constellation of findings to be classified as Goldenhar syndrome. These findings include vertebral anomalies not usually considered a feature of hemifacial microsomia including spina bifida, scoliosis, hemivertebrea, and hypoplastic or fused ribs. The other typical features that define Goldenhar syndrome include the presence of corneoscleral or epibulbar dermoids and preauricular skin tags [35, 36].

Management of Ophthalmic Abnormalities

The complex array of abnormalities involving multiple aspects of head and neck development in patients with craniofacial disorders necessitates a team of physicians who specialize in their care. These typically include a craniofacial surgeon, neurosurgeon, oculoplastic surgeon, pediatric ophthalmologist, geneticist, otolaryngologist, dentist/orthodontist, and numerous therapists and social workers to coordinate care.

As previously outlined, anomalies in visual development can occur for many reasons. The ophthalmologist must assume the responsibility in monitoring for the occurrence of amblyopia or other anomalies that may compromise vision. Subnormal vision in craniosynostoses is less commonly due to structural abnormalities of the globe than it is from refractive or strabismic amblyopia. However, there are occasions when growth and development of the eye can be affected and the ophthalmologist monitors for this possibility. Figure 66.10 outlines the general approach to a patient with a craniofacial deformity.

A baseline exam is obtained on every new patient with craniosynostosis or a clefting syndrome. As early as possible, the infant's ability to fix and follow with each eye should be recorded. A dilated fundus examination must be performed to check for optic atrophy or papilledema and to obtain an accurate cycloplegic refraction to rule out amblyogenic ametropia or anisometropia. With every examination the ocular alignment is assessed for orthotropia, nystagmus, and a child's ability to maintain fixation with either eye independently without a significant preference should also be measured at the appropriate age. This may be challenging in patients who have coexisting cognitive deficits.

The management of amblyopia and strabismus are discussed in Chap. 67.

Measurement of the lids and ocular adnexa is performed annually in children with craniosynostosis assuming they have not had recent surgery. The purpose of the measurements is to document appropriate, symmetric development of the face and orbits. Some common measurements include the vertical and horizontal palpebral fissures, horizontal brow distance, intercanthal distance, and interpupillary distance. A good reference for normal orbital and facial measurements can be found in the textbook *Anthropometry of the Head and Face* by Leslie G. Farkas, M.D. [37]. In addition, the standard measurements when evaluating ptosis including the margin reflex distances, levator function, and location of the lid crease should be recorded (see Chap. 1 on Pediatric Ophthalmology Examination). The position of the medial

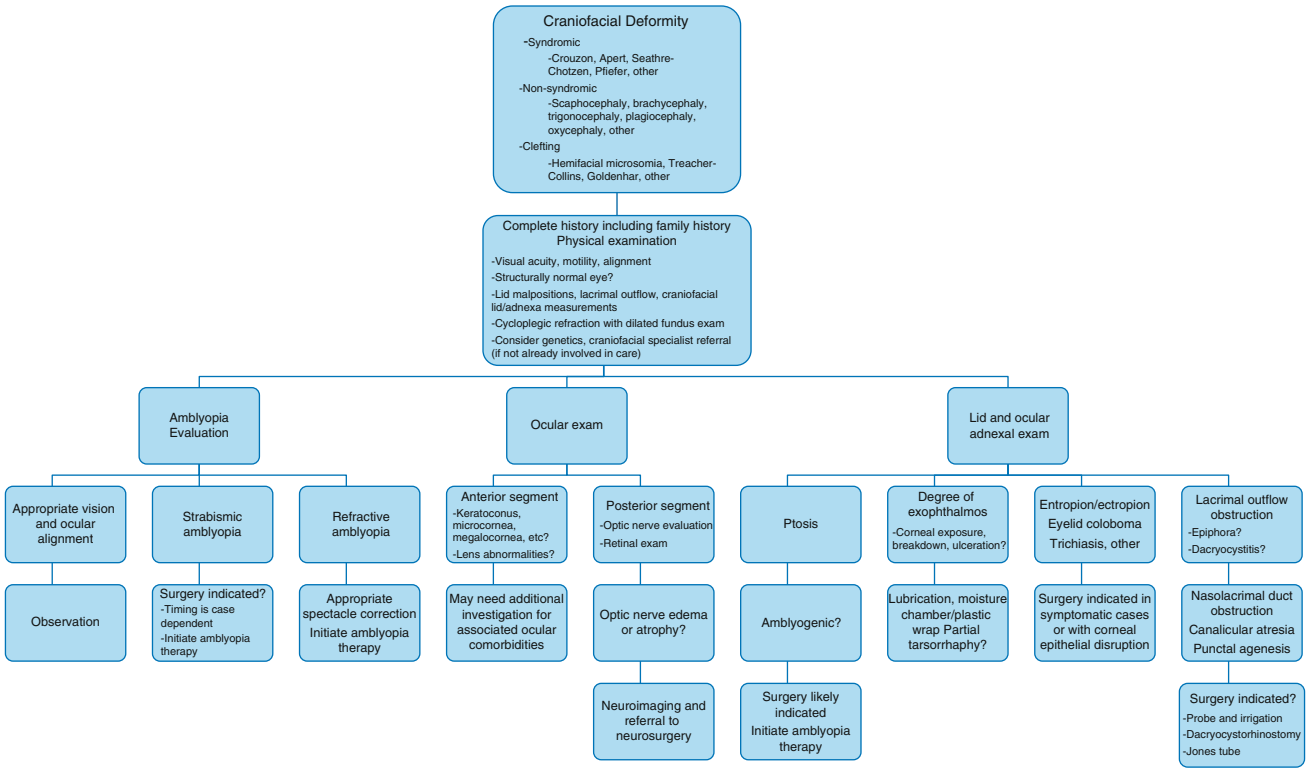

Fig. 66.10 Algorithm for evaluation and management of patient with craniosynostosis

and lateral canthi should be noted, as well as the degree of exophthalmos, presence of colobomas, trichiasis, lagophthalmos, entropion, and other lid malpositions. Assessing the cornea for epithelial disruption with slit lamp examination and fluorescein staining is important in the presence of eyelid abnormalities or exophthalmos. Exophthalmometry can be difficult in young, uncooperative children and may be alternatively performed with the Luedde exophthalmometer rather than Hertel-type devices. The Luedde measures the position of the cornea relative to the lateral orbital rim by looking through a clear measuring device at the lateral canthal angle. Chronic corneal exposure with scarring can be an indication for reconstructive eyelid surgery or temporary or partial tarsorrhaphy for severe corneal exposure. Usually, exposure in the newborn can be managed with frequent lubrication and moisture chambers or plastic wrap. However, in severe cases of Crouzon, Pfeiffer, or Apert syndromes, orbital advancement may be indicated if lubrication and/or eyelid repositioning are not adequate. Finally, ptosis is a known cause of amblyopia both via occlusion of the visual axis and from induced astigmatism and should be continuously evaluated.

Due to the frequency of NLDO and canalicular abnormalities in patients with craniosynostosis or clefting anomalies, the lacrimal outflow systems are evaluated. The physician inquires about the presence of epiphora and any

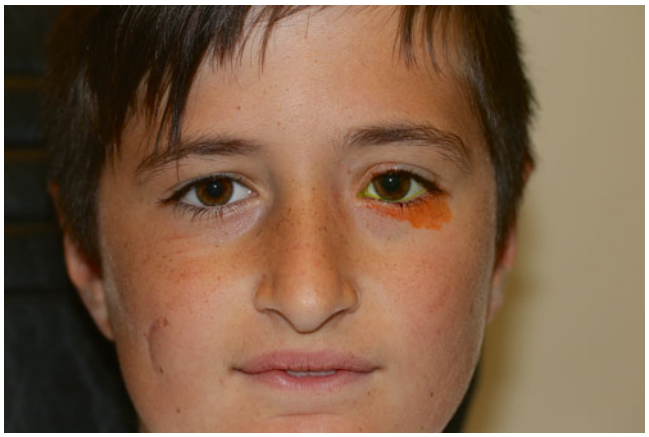

Fig. 66.11 Dye disappearance test showing an elevated tear lake and dye retention on the left with a history of epiphora of the left eye

episodes of dacryocystitis. While patency of the system is often the primary concern, lid anomalies, or lid malposition can also affect the functional status of the outflow system, or cause corneal irritation and should be examined. A dye disappearance test is the easiest way to assess the system in young children (Fig. 66.11). Older children may be able to tolerate more invasive testing measures including Jones tests or irrigation. The specific management of nasolacrimal duct stenosis in patients with craniosynostosis is done on a case-

by-case basis. An approach similar to that of a child with normal anatomy is taken when deciding when to perform probing and intubation; however, the surgeon must be prepared to encounter anatomical variations not typically seen in the general population. The angle of the lacrimal outflow system may be altered, and midface retrusion makes intranasal retrieval of the stenting material more challenging.

Caring for the complex array of ophthalmic and oculoplastic abnormalities in patients with craniosynostosis can be quite challenging. It requires a team approach with the appropriate coordination of care with other health care professionals. The patient will see many physicians and often require multiple operations. In addition to the many medical and surgical issues affecting these children, the genetic implications of a new diagnosis of craniosynostosis can be confusing for families. An appropriate referral to a geneticist and genetic counselor should be considered in these cases. One should also remember that craniofacial surgeries can exacerbate underlying ophthalmic conditions, particularly corneal exposure. In all circumstances, the preservation of vision remains an important concern for the ophthalmologist.

Cases

Case Study 1: Hemifacial Microsomia

This is a case of 2-year-old male born with hemifacial microsomia with failure of development of the left orbit, eyelid, and eye (Fig. 66.12a). The main concerns in this patient involve orbital expansion to permit proper orbital symmetry and development of his eyelids.

Surgical intervention involved serial conformers secured by glue and tarsorraphy (Fig. 66.12b). Hydroxyapatite implantation and mucous membrane grafting were performed once adequate orbital volume was present. Subsequently, craniofacial reconstruction

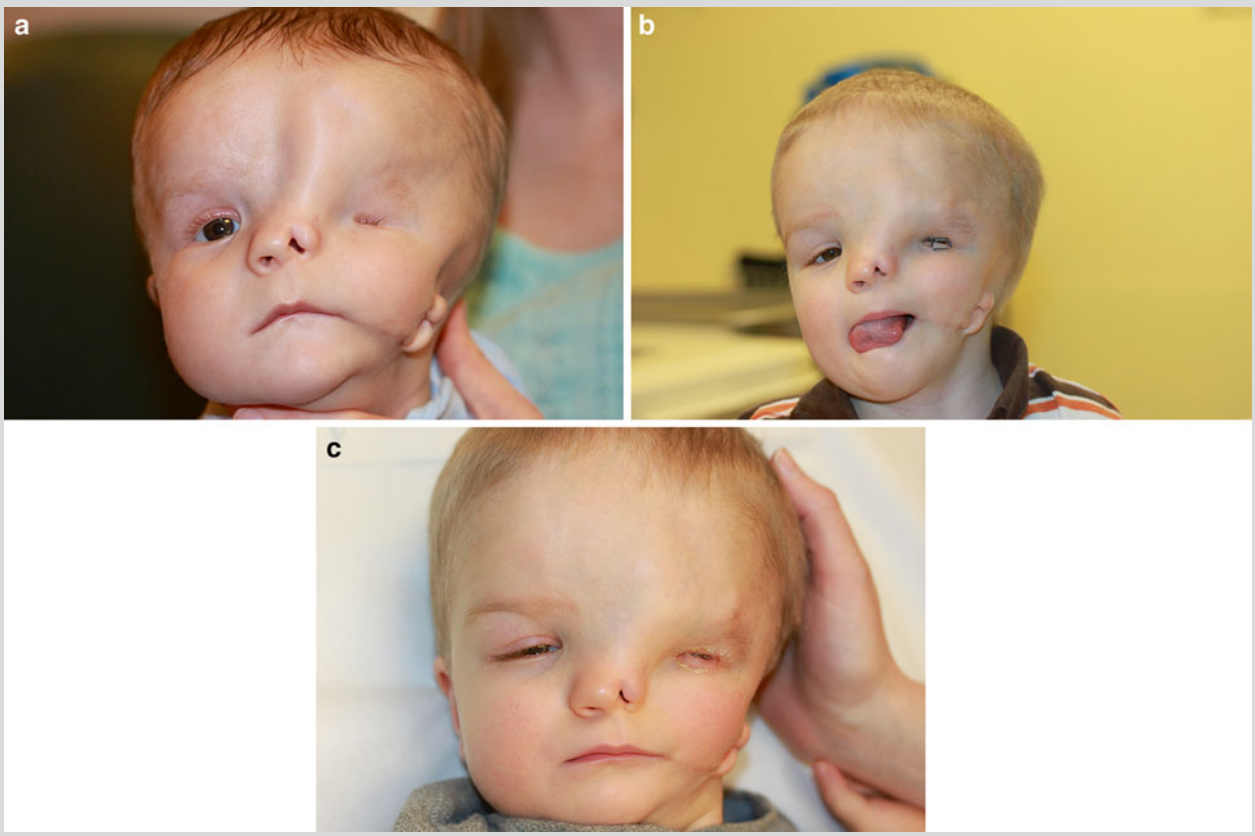

Fig. 66.12 (**a**) Preoperative photo showing severe hemifacial microsomia with anophthalmos and hypoplastic lids. (**b**, **c**) The patient has undergone cranial vault reconstruction as well as placement of serial orbital implants and conformers to stimulate growth of the orbit and eyelids

(continued)

was performed to allow for further orbital expansion. This permitted the placement of a larger conformer and a 0.4 mm hydrogel orbital implant as well as a small dermis fat graft. The 0.4 mm hydrogel implant was exchanged with a larger 0.9 mm hydrogel implant. We continue to monitor the growth and development of his eyelids and orbit (Fig. 66.12c).

Hydrogel implants have a role in hypoplastic orbits since a minimal incision is required and water infiltrates the implant allowing for expansion in the orbit with time. Patients with anophthalmos and orbital hypoplasia require serial examinations, serial conformers, serial orbital implants, and mucous membrane grafting to allow for proper orbital expansion.

Case Study 2: Crouzon Syndrome

This is a 2-year-old male who presented at birth with proptosis and dysmorphic facial features, including a wide anterior fontanelle, overlapping lambdoidal and coronal sutures, midface hypoplasia, and a thin upper lip (Fig. 66.13). Extremities were normal. Midface hypoplasia, shallow orbits with proptosis, and the presence of normal extremities were suggestive of a diagnosis of Crouzon syndrome.

This patient had early issues related to his airway requiring intubation in the NICU in addition to severe exposure keratopathy and globe entrapment, requiring early aggressive lubrication and a permanent lateral tarsorraphy on the right eye. This was completed at 2 months of age. The tarsorrhaphy was removed 2 months later after his exposure improved to allow for visual development. Complete eye examination in time revealed high anisometropia and V-pattern exotropia, but with fusion in primary gaze. The patient had improvement with refractive correction and patching. At 1 year of age, the patient developed hydrocephalus requiring ventriculostomy. At age 3, cranial expansion and distraction are planned.

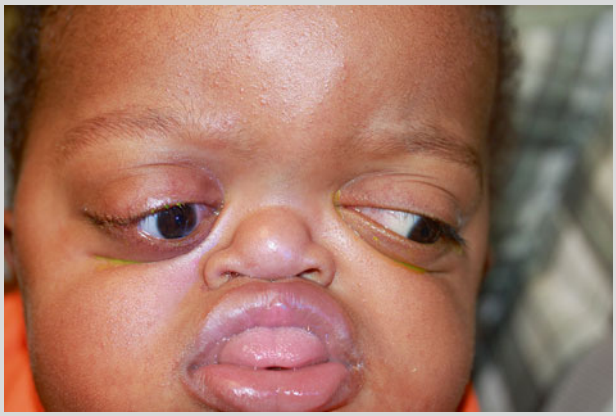

Fig. 66.13 Crouzon syndrome with proptosis and midface hypoplasia. Note the permanent tarsorrhaphy on the right eye

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Supplement: Special Considerations in the Management of Amblyopia and Strabismus in Craniofacial Disorders

67

Rachel E. Reem and Mary Lou McGregor

Abstract

As many as 60–70 % of children with craniosynostosis have strabismus (Coats, J AAPOS. 4:338–42, 2000). The most common ocular motility issue in these patients is V-pattern strabismus, with apparent overaction of the inferior oblique muscles, and/or underaction of the superior oblique muscles (Coats, J AAPOS. 4:338–42, 2000; Nischal, Am Orthopt J. 64:24–31, 2014; Clement and Nischal, Strabismus. 11:239–42, 2003). For many reasons, strabismus surgery in such patients should be considered with care.

Keywords

Craniosynostosis • Strabismus • Amblyopia • Craniofacial disorders

As many as 60–70 % of children with craniosynostosis have strabismus [1]. The most common ocular motility issue in these patients is V-pattern strabismus, with apparent overaction of the inferior oblique muscles, and/or underaction of the superior oblique muscles [1–3]. For many reasons, strabismus surgery in such patients should be considered with care.

Of foremost consideration in craniosynostosis patients is monitoring visual acuity and correcting errors of refraction to prevent amblyopia. Patients are at greater risk for amblyopia due to a higher prevalence of anisometropia, astigmatism, and strabismus than the general population. Amblyopia has been reported as the most common etiology of vision loss in patients with craniosynostoses [4]. Special considerations for the treatment of amblyopia in this patient population include ensuring proper glasses fit, which may be difficult because of abnormalities in facial structure from the craniosynostosis. In addition, organic etiologies of vision loss including ocular surface disease related to corneal exposure, ptosis, and monitoring for visual pathway dysfunction such as optic neuropathy from compression must be evaluated on a periodic basis. Cycloplegic refraction can change quickly in craniosynostosis patients, so examination every 6 months is warranted [2, 5].

Once amblyopia is addressed, consideration of strabismus surgery can begin. Sensory fusion is rare in craniosynostosis patients with constant deviations; therefore, these children usually have large suppression scotomas. Diplopia rarely occurs following surgery, unless a large overcorrection occurs. There are a number of theories for the etiology of strabismus in these patients, including the absence or aplasia of extraocular muscles, particularly the superior oblique; anomalous origins/insertions of the extraocular muscles; morphological abnormalities of the posterior orbit; and excyclorotation of the orbits [1, 3, 6, 7]. In all likelihood, the cause is multifactorial. It is important to note that patients with craniosynostosis typically undergo a number of cranial and/or orbital reconstructive surgeries over the course of their young lives. Since these have the potential to cause or change strabismus patterns, the timing of strabismus surgery relative to other procedures should be determined carefully, especially in patients with fusional potential. It is often reasonable to wait to perform strabismus surgery until after craniofacial

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reconstruction has been completed; however, if intervention is indicated to maintain a patient's binocular vision, strabismus surgery may be performed earlier with careful multidisciplinary planning of future procedures. Interestingly, several studies have indicated minimal changes in postoperative alignment following craniofacial reconstruction. Diamond and Whitaker [8] and Diamond et al. [9] found that only 10 out of 140 patients undergoing craniofacial surgery had changes in their ocular alignment. They concluded that strabismus surgery prior to craniofacial reconstruction was advisable in order to restore binocularity as early as possible. However, a study by Morax of 11 craniosynostosis patients undergoing sagittal expansion of the orbit found more changes in alignment after surgery and therefore recommended waiting at least 6 months after cranial surgery [10]. The difference between these two studies could be related to the prevalence of fusional potential in the respective patient populations, or the variability in surgical interventions. Additional studies are needed to clarify risk of potential alignment change following craniofacial intervention. Caution must be exercised and communication of ocular alignment concerns with the craniofacial surgical team is paramount.

Furthermore, horizontal rectus muscle surgery in these patients is unpredictable; there may be little improvement, and it is rare to have overcorrections following routine horizontal strabismus surgery [1]. When strabismus surgery is warranted, it is recommended to consider either routine exploration of the insertions of all six extraocular muscles in the operative eye(s), or imaging of the orbits to evaluate for absent or anomalous muscles [11]. Larger than standard amounts of recession/resection should be considered for horizontal strabismus in patients without good fusion. Although surgery on the oblique muscles tends to produce less change than anticipated in V patterns, which are quite common in patients with craniosynostosis (Fig. 67.1), it is preferred over vertical transposition of the horizontal rectus muscles due to the risk of worsening or producing an elevation in adduction with the latter procedure [12]. In cases of torsion, transposition of the rectus muscles should be considered, especially if absent or anomalous oblique muscles are discovered on exploration. If a vertical rectus muscle is absent or abnormal, transposition of the horizontal rectus muscles could be considered as well [13].

Another consideration in patients with craniosynostosis is ocular torticollis (Fig. 67.2). One way to determine if an

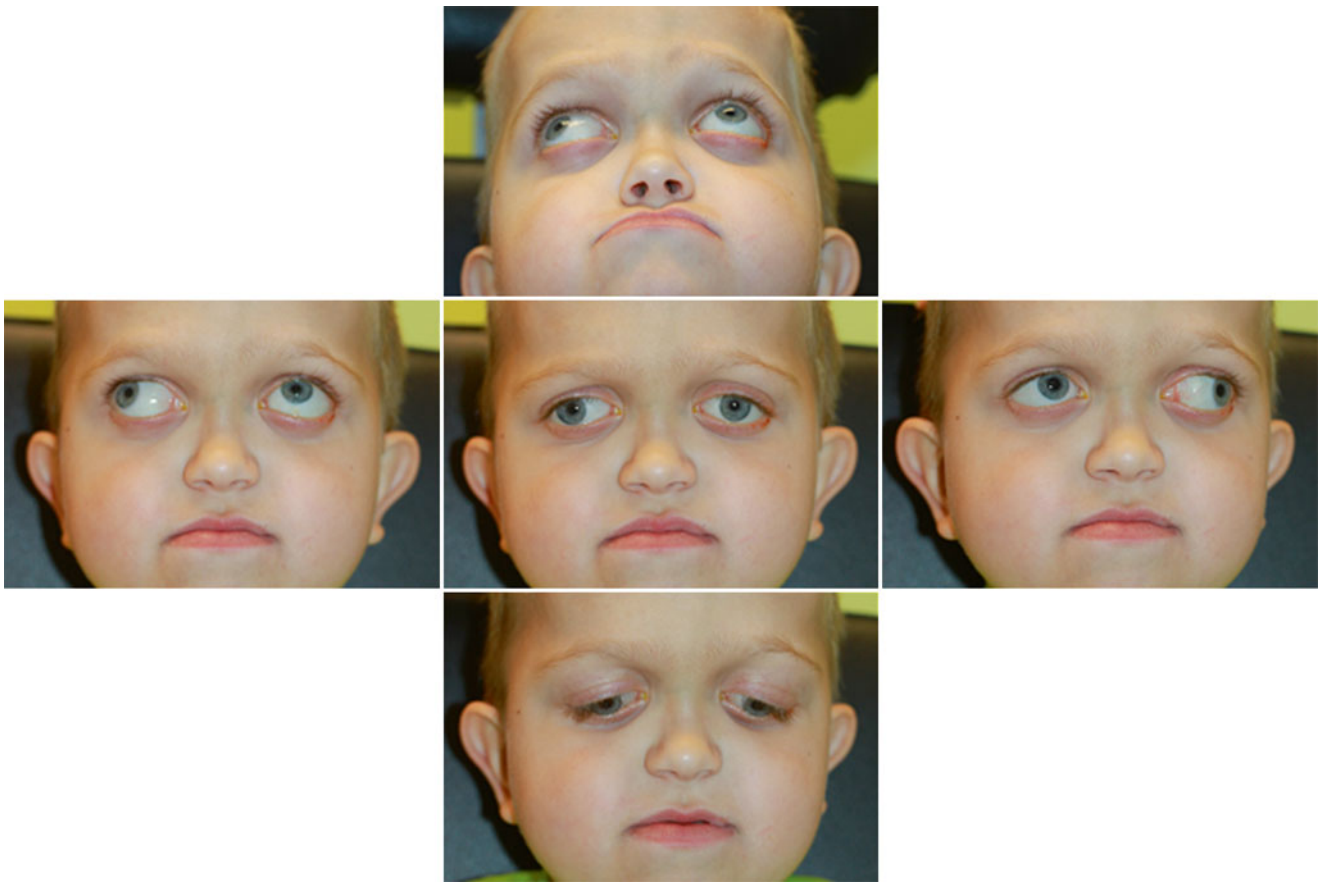

Fig. 67.1 This is a 3-year-old boy with Crouzon syndrome and concurrent strabismus. In primary position, the child has 40 prism diopters of exotropia, fixating with the left eye in this picture. Note the V-pattern with apparent inferior oblique overaction of both eyes. Fixation with the abducting eye in horizontal gaze gives the appearance of decreased adduction in the nonfixating eye. Only by covering the abducting eye and forcing the fellow eye to fully adduct can an apparent motility deficit be properly evaluated. This demonstrates the importance of checking ductions and not just versions

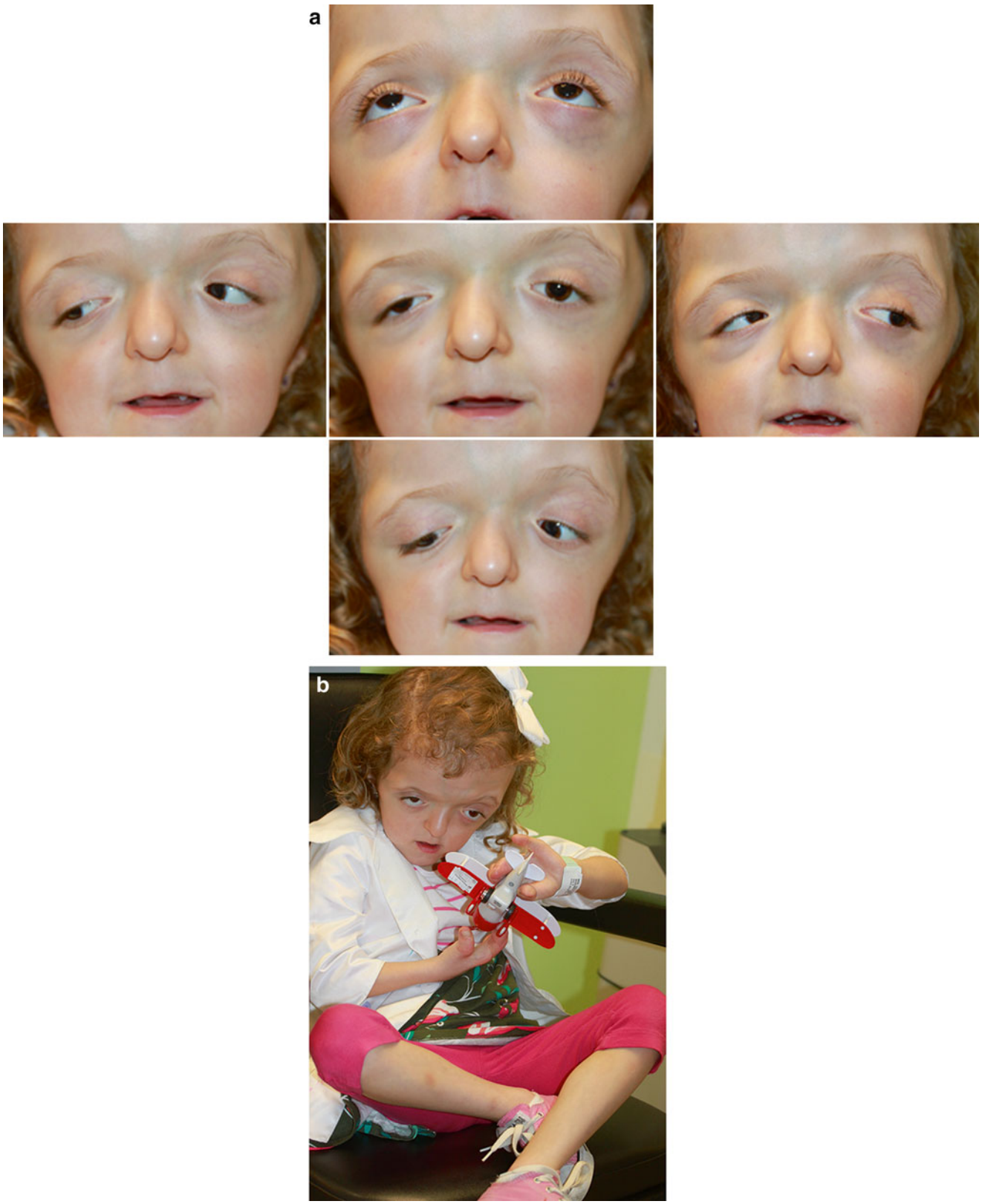

Fig. 67.2 This is a 4-year-old girl with Apert syndrome and accompanying V-pattern strabismus (**a**). Note the large esotropia in downgaze, which becomes a small exotropia in extreme upgaze. On lateral gaze, marked underaction of the superior oblique muscle of both eyes is apparent. On presentation to the eye clinic, a chin-down posture was noted (**b**). With the patient's accompanying ptosis, the only explanation for this head posture is for fusion. Her vision in each eye at the time of the visit was maintained at 20/30 without patching. The equal vision also supports the theory that her head posture helps her to fuse. In this patient, surgery to weaken the inferior obliques could be considered to correct the V-pattern, but evaluation of the superior oblique anatomy, whether by direct exploration or by MRI, should be done prior. As long as her vision remains stable during her amblyogenic period, surgery for strabismus could be safely deferred until further craniofacial surgery is performed

abnormal head posture is in fact ocular torticollis is to patch each eye independently and observe whether the head posture changes. If the head posture changes with patching of either eye, one can assume the abnormal head posture is the result of the ocular misalignment. Head postures can include face turns, chin-up or chin-down posture, head tilts, or any combination of the above. Close examination for nystagmus should be pursued, as this would be a confounding factor in determining the etiology of ocular torticollis. Complex testing procedures such as double Maddox rod testing can be quite difficult in these patients, especially younger ones. Funduscopic exam with attention to torsion can be a useful alternative with which to evaluate.

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Part XIII

Patients with Special Needs

Management of Vision Impairment in Children

68

Kelly Lusk and Terry L. Schwartz

Abstract

Although it is common for pediatric ophthalmologists to provide medical and surgical eye care for children with visual impairment, a treatment algorithm that addresses vision rehabilitation concerns is needed. Distance and near access to the visual environment is critical for children to acquire literacy skills. Defining all aspects of the child's comprehensive visual function combined with referral for appropriate educational placement and programming provides the child with the best opportunity to function independently in the classroom and at home. Knowledge of basic magnification devices is a useful adjunct to any pediatric ophthalmology practice.

Keywords

Low vision • Vision rehabilitation • Albinism • Optic nerve atrophy

The Problem

Eighty-five to 90 % of individuals with vision impairment are reported to have functional, or usable vision, and therefore are not totally or functionally blind [1, 2]. A person is considered to have low vision if vision is measurable, but the individual has difficulty or inability to accomplish visually directed tasks even with the best refractive correction. Vision is a critical determinant of learning, as it assists in unifying input from other senses. In order to access the visual environment at home and at school, children with uncorrectable, permanent, and irreversible visual impairment need tools and other strategies.

Clinical low vision evaluations are adjuncts to primary eye care examinations. Low vision evaluations help determine if a person with poor vision can enhance his/her functional use of existing vision with the assistance of optical or non-optical devices, assistive technologies, or other techniques and strategies. Components of the low vision evaluation that may or may not be included in a typical primary eye care exam include testing of color identification and discrimination, contrast sensitivity, and extent of peripheral visual field. In addition, visual acuity is assessed binocularly at distance and at near. The near measurement is performed at a standard distance of 40 cm. as well as at the child's preferred reading distance. In some children, acuity is assessed both with and without spectacle correction (Table 68.1) [3]. Low vision evaluations also consider lighting needs or problems with glare. Optical devices include ones for near-vision magnification (e.g., handheld or

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spectacle-mounted magnifiers) others for distance vision magnification (e.g., handheld monocular telescopes or binoculars), and light absorptive lenses (including therapeutic contact lenses). Assistive technology devices include electronic and computer magnification systems such as desktop and handheld video magnifiers, as well as computer settings or programs that can enlarge and modify the color and/or contrast of text (Figs. 68.1 and 68.2) [4].

Literacy, the ability to read and write, is critical for success in school and future employment. Optimally, the low vision evaluation includes assessment of measures of literacy (e.g., reading speed, reading fluency, reading comprehension, reading stamina).

Two children with vision impairments from albinism and optic nerve atrophy are presented to demonstrate the low vision assessment algorithm.

Table 68.1 Visual function assessment tools

	Younger children	Older children
Visual acuity	Distance:	Distance:
	Lea symbol low vision flip chart	Low vision flip chart
	Near:	Near:
	Lea symbol near card	Standard near charts
	Lea symbol playing cards	
	Teller acuity cards	
Contrast sensitivity	Hiding Heidi faces	Peli-Robson chart
	Lea symbol flip chart	Lea number flip book
Color vision	D-16 chips (matching game)	D-16 chips
	HRR color plates	HRR plates
Peripheral visual field	2-Person confrontation	Goldmann visual field
	Kinetic arc perimetry	
Dark adaptation	Cone adaptation test	Dark adaptometry

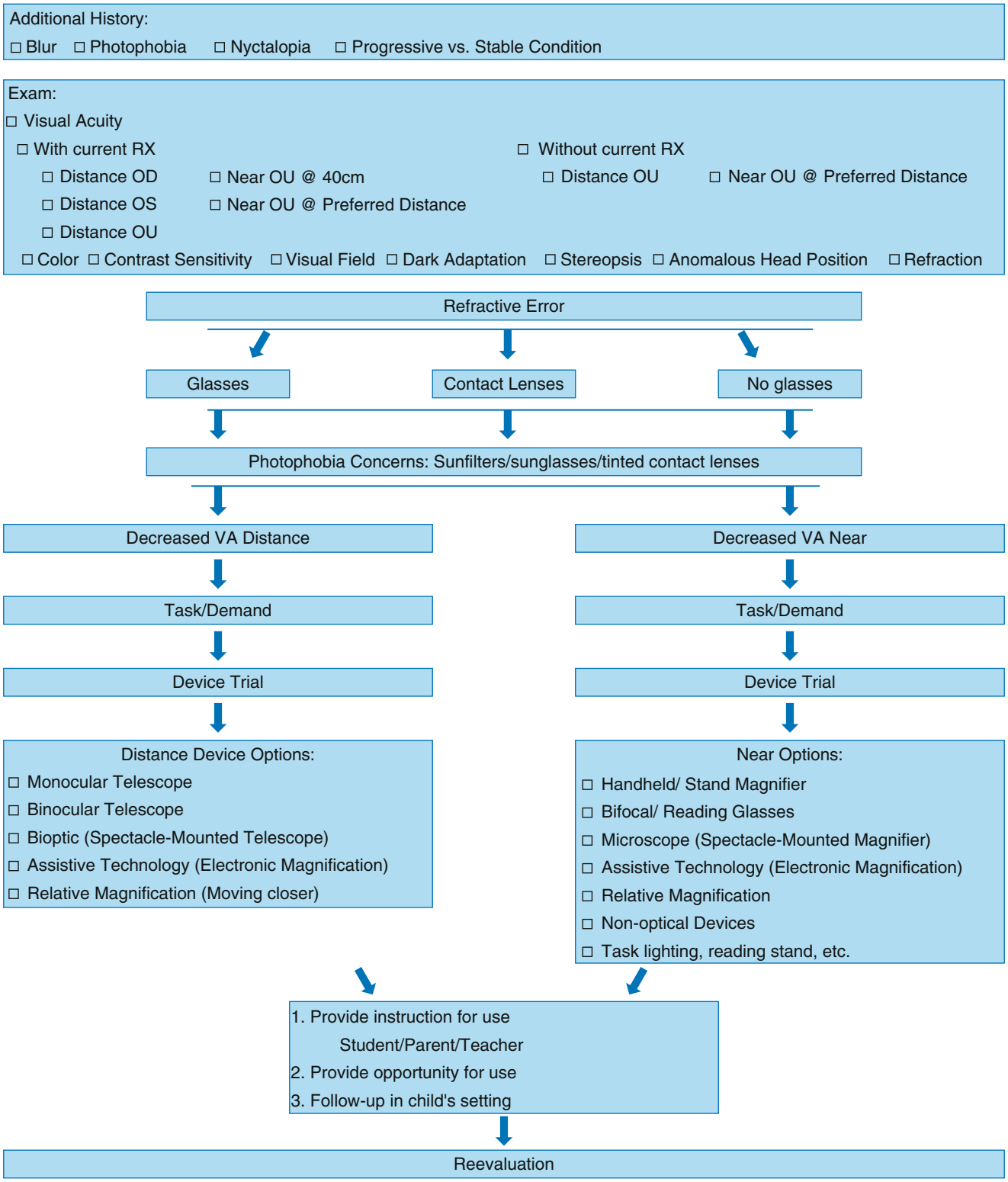

Fig. 68.1 Algorithm for evaluation and management of low vision

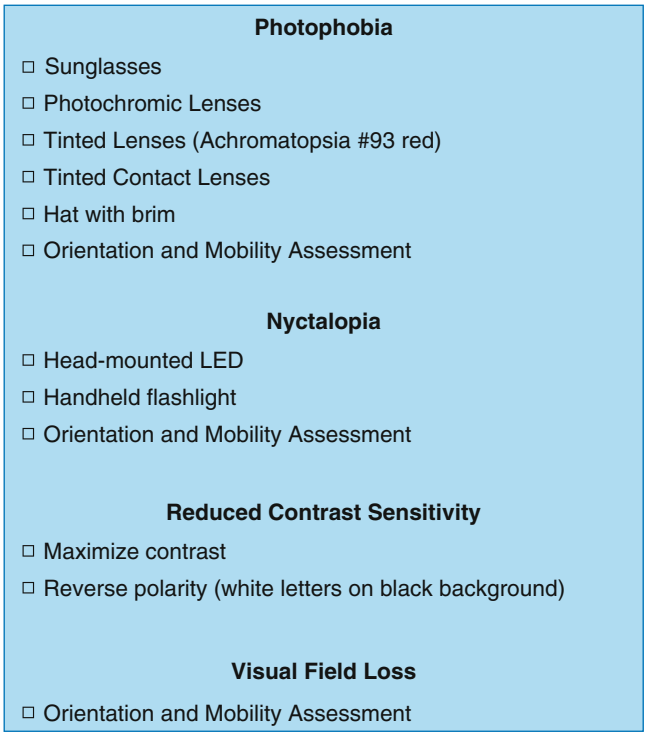

Fig. 68.2 Flowchart for management of visual symptoms

Case Examples

Case 1 (Table 68.2)

Table 68.2 Case 1

Clinical history	5 Years old with oculocutaneous albinism and nystagmus. Visual acuity is reduced, depth perception is absent, and she is very photophobic		
Key components of exam		*OD*	*OS*
	UCVA	20/300	20/300
	Stereopsis	Absent	
	CRx	−1.50 + 2.00 × 100	−1.75 + 2.50 × 85
Management options	• CRx with glasses or contact lenses		
	• Manage ambient lighting		
	• Magnification at near/distance		
	• Refer for special education eligibility determination		
	• Orientation and Mobility evaluation		
Visual tasks/demands	• Accessing wall cards/board in classroom		
	• Access to near print (e.g., books, worksheets)		
	• Safe and efficient travel		
	• Visual comfort		
Management	• CRx in glasses with transition lenses		
	• Snug fitting prescription sunglasses		
	• Low power (2.8×) handheld telescope (monocular)		
	• Stand dome magnifier (for near)		
	• Referred for special education eligibility determination		
	• Orientation and mobility referral for evaluation		
	• Seating with back to the window at appropriate distance for viewing instruction		

(continued)

Table 68.2 (continued)

Interval history (3 years) *Current age*: *8 years*	Poor compliance with glasses. Using dome and monocular in classroom and at home. Photophobia in all environments. Receiving special education services (teacher of students with visual impairments/orientation and mobility specialist)		
Key components of exam		*OD*	*OS*
	UCVA/BCVA	20/300	20/300
	CRx	−3.75 + 4.00 × 100	−4.50 + 5.00 × 80
Visual tasks/demands	• Accessing board in classroom		
	• Access to near print for sustained reading		
	• Safe and efficient travel		
	• Visual comfort		
Management	• CRx in tinted contact lenses		
	• Snug fitting sunglasses		
	• Increased power (4×) handheld monocular telescope		
	• Stand dome magnifier (for near spotting)		
	• Electronic magnification for distance/near		
	• Seating with back to the window at appropriate distance for viewing instruction		
Interval history (6 months) *Current age*: *8.5 years*	Increased comfort and acuity in all environments with tinted contacts (CRx), increased reading speed, comprehension, and stamina with electronic magnification		
Key components of exam		OD	OS
	BCVA (CL)	20/200	20/200
Management	• Follow-up 2 years		

Clinical Synopsis

The patient is a 5-year-old with oculocutaneous albinism, nystagmus, and esotropia. She had difficulty with sustained near-vision tasks from decreased acuity, safe travel due to absent depth perception, and extreme photophobia despite transition lenses. With the prescription of tinted contact lenses and snug-fitting sunglasses, increased comfort and visual function was noted in all environments. The use of both simple and electronic magnification provided access to distance and near instruction, including increased stamina during reading tasks. Orientation and mobility instruction allowed her to incorporate the use of magnification to identify distance information effectively and efficiently.

Case 2 (Table 68.3)

Table 68.3 Case 2

Clinical history	10 years old with optic atrophy from craniopharyngioma resected 6 months earlier. She has reduced visual acuity, visual field loss, and left sensory exotropia		
Key components of exam		*OD*	*OS*
	UCVA distance	20/400	20/2000
	UCVA near	20/80 @ 10 cm (binocular)	
	Motility	Left sensory exotropia, absent stereopsis	
	Contrast sensitivity	10 % (Elevated threshold)	
	Visual field	Bitemporal hemianopsia	
	Color perception	Reduced discrimination—red/green axis	
	CRx	+1.00	+1.25 + 0.75 × 90

(continued)

Table 68.3 (continued)

Management options	• Magnification at near/distance		
	• Increased contrast for print		
	• Refer for special education eligibility determination		
	• Orientation and Mobility evaluation		
Visual tasks/demands	• Accessing board in classroom		
	• Access to near print for sustained reading		
	• Safe and efficient travel		
Management	• Hand held telescope (monocular) 4×		
	• Stand dome magnifier (for near spotting)		
	• Electronic magnification distance/near		
	Option for reverse polarity (white letters on black)		
	High contrast		
	• Refer for special education eligibility determination		
	• Orientation and mobility evaluation		
Interval history (3 months) *Current age*: *10.3 years*	Unable to use monocular (visual field limitation). Receiving special education services (Teacher of students with visual impairments/orientation and mobility specialist), cane instruction		
Key components of exam		*OD*	*OS*
	UCVA	20/400	20/2000
Visual tasks/demands	• No change		
Management	• Discontinue monocular handheld telescope		
Interval history (1 year) *Current age*: *11 years*	Completed chemotherapy. Improved visual function by history. No longer using cane for travel		
Key components of exam		*OD*	*OS*
	UCVA distance	20/100	20/440
	UCVA near	20/32 @ 20 cm (binocular)	
	Motility	Left sensory exotropia, absent stereopsis	
	Contrast sensitivity	1.25 % (within normal limits)	
	Visual field	Bitemporal hemianopsia (increased field)	
	Color perception	Reduced discrimination—red/green axis	
Management options	• Magnification at near/distance		
Visual tasks/demands	• Accessing board in classroom		
	• Access to near print for sustained reading		
	• Safe and efficient travel		
Management	• Hand held telescope (monocular) 4×		
	• Electronic magnification for distance		
	• Follow-up 2 years		

Clinical Synopsis

The patient is a 10-year-old with optic atrophy from craniopharyngioma resected 6 months earlier. She developed optic atrophy with reduced visual acuity, visual field loss, and a sensory left exotropia. She could no longer view distance instruction, read standard sized print, or travel safely and efficiently through the school. Peripheral field restriction limited the usefulness of a handheld telescope for distance spotting. Electronic magnification, using reverse polarity (i.e., white letters on a black background), provided access to print. Orientation and mobility intervention provided cane training for independent travel. Reevaluation at 1-year demonstrated improved visual function after systemic treatment. She was then able to use a telescope for distance. Improved acuity, peripheral field, and contrast sensitivity eliminated the need for near magnification and cane-assisted travel.

Evidence for the Effectiveness of Low-Vision Evaluation and Treatment

Background: Low-Vision Assessment and Providing Access to the Visual Environment

Measurement of only visual acuity provides an incomplete description of a child's visual function. Interdisciplinary assessment including medical, educational, and therapeutic professionals is important to address all aspects of visual demands in an educational environment. The inability to discriminate color or the presence of a scotoma can also have a significant impact on the ability to access visual information in the classroom. Visual acuity assessment in clinic is usually only a monocular distance measurement. The measurement of binocular distance visual acuity, with and without refractive correction, allows the examiner to decide if glasses are needed. Binocular near acuity measurement taken at the child's preferred reading distance demonstrates smallest resolvable print, as well as information about accommodative demand and posture. For example, a preferred reading distance of 5 cm in a 15-year-old with 12 diopters accommodative amplitude cannot be sustained for long periods and can cause musculoskeletal fatigue from chronic neck flexion. Identifying difficulty with color discrimination will help anticipate difficulty with maps and other color-coded activities. Assessment of contrast sensitivity function is a component of the low vision evaluation and is important as a predictor of functional vision. It can be measured with a variety of materials adapted for use with children and provides both functional and clinical information, unlike Snellen acuity which defines the smallest optotype resolvable at the highest contrast. Elevated contrast sensitivity threshold will indicate a need for high contrast print and in some cases, the need for reversed background and print color (i.e., white letters on a black background). Identifying visual field limitations will help determine the functional benefits of magnifying pictures and print.

Consideration for Vision Enhancing Devices and Magnification

A low vision evaluation provides a more detailed examination of visual function and can include recommendations for magnifying devices, environmental adaptations, and assistive technology. Young children typically use handheld telescopes (monoculars) for spotting distant items and stand magnifiers (domes) to access detail at near. Increasing magnification power of the devices and more sophisticated optical and electronic magnification can be implemented as visual demands increase in the classroom and the child gains proficiency manipulating the device.

In a child with impaired visual function, it is important to anticipate that reading speed, stamina, and comprehension might be affected. The use of magnification should be introduced after assessment. Researchers who studied the impact of optical devices within the interdisciplinary model showed increased accessibility to standard print, as well as improvements in functional measures. In a program that included systematic instruction in the use of the devices, the use of optical devices and their impact on reading speeds of school-age students with low vision was investigated [5, 6]. Reading speeds are an especially important indicator of future success, with a reading speed of at least 150 words per minute (wpm) needed to remain academically competitive with peers in an adult work environment [7]. These studies concluded that the use of optical devices increased access to environmental visual material and overall visual performance. These results were replicated in a subsequent study [8].

It must be stressed that prescribing magnification is a highly individualized endeavor. A child's maturity level, cognitive ability, and visual demands must be considered in the selection of devices. However, there are general principles that can be followed as a function of age. In general, the youngest age at which devices are considered is around 2–3 years. With younger children, the field of view must be maximized and the magnification power low (e.g., 2.8× handheld monocular telescope for distance, large light gathering dome magnifier for near). The child who is in late elementary to early middle school can manage higher power telescopes and electronic magnification (e.g., 4–6× handheld monocular telescope for distance, spectacle-mounted microscope for near, video magnifier for distance and near, and accessibility software). The preteen and teenager may become very self-conscious with regard to device use. At this time, one may need to find less conspicuous options (e.g., pocket magnifier) or enhancements for a socially acceptable tablet (e.g., apps, tablet-mounted telescopes or macro lenses). Teenagers may become motivated to use magnification in order to obtain a driver's license and be willing to consider the use of a spectacle-mounted telescope.

Eligibility for Special Education Services Related to Visual Impairment

Many states require that both medical and educational eligibility criteria are met for a child to receive special education services. Medical eligibility varies by state, but generally requires a specific level of visual acuity, a specific measure of decreased visual field, the diagnosis of a condition that is progressive, or a diagnosis of cortical, or neurological, visual impairment. For example, a best corrected visual acuity in the better eye of 20/50 or worse meets the medical criteria for special education eligibility in several states, whereas in others it is 20/70.

Once medical eligibility is determined, proof of educational eligibility is also required in many states. This level of eligibility requires the school system to show that the child needs additional instruction, accommodations, and supports to properly function in the classroom. At a minimum, a functional vision assessment determines how the visual impairment impacts the child's education using information from the child's eye report, as well as direct observation and assessment in a variety of educational settings.

Once medical and educational eligibility are considered, if the child is eligible for special education services, a team meeting including parents, teachers (both general and special educators), administrators/other school personnel, and the student (if appropriate) will occur. At this meeting, the child's Individualized Education Program (IEP) will be developed for implementation via special education services.

Additional Assessments

Children with visual impairments often require additional services related to educational programming that are not a part of their medical care or treatment. To determine if these educational services are needed by a child, the following assessments or evaluations may need to be requested:

1. *Learning media assessment*—A learning media assessment helps determine the most effective medium or media through which a child learns. In terms of literacy medium for children with visual impairments, there are three main choices: braille, print (with or without magnification), and dual media (both print and braille). A learning media assessment investigates how a child learns and how the child is likely to learn in the future based on medical prognosis and a review of educational records and medical charts. Direct assessment is also used to gauge the child's levels of literacy acquisition and predict the best medium or media for the child to use.
2. *Assistive technology*—Technologies such as electronic magnification devices (for both near and distance viewing), screen enlargement and screen reading software for computers, and braille production devices may be beneficial to a child with a visual impairment. A partial assistive technology evaluation may be part of a pediatric clinical low vision evaluation, but the child's school system may also need to be involved to investigate additional options or facilitate acquisition of recommended technologies.
3. *Orientation and mobility* (*O&M*)—As a related service in a special education setting, instruction in orientation and mobility is often necessary for a child with a visual impairment to ensure safe, independent (age appropriate), effective, and efficient travel. School systems can provide orientation and mobility assessments to determine if a child is in need of O&M instruction.

As a condition progresses, the visual function can change. Specific knowledge of new difficulties will aid the school in modifying services. A teacher of students with visual impairment (TVI), who is included as a member of the vision rehabilitation team, can alert the eye doctor to changes in the child's visual function in the classroom setting.

Informing the teacher about visual symptoms typical for specific conditions is crucial. For example, if the school anticipates photophobia in a child with albinism, the child's proximity to the window can be modified to reduce glare and direct sunlight. Knowing that vision is likely to deteriorate in some retinal dystrophies suggests the need for the implementation of alternative reading methods such as braille.

Print, Braille, or Dual Media

Some pediatric patients who have low vision may require a dual-media approach to literacy instruction, including learning and/or using both print and braille. Print choices consist of standard print, standard print with the use of optical or electronic magnification devices, large print, or a combination of print approaches. Factors that may suggest a need for dual media include: severe reduction in visual acuity, inability to maintain visual stamina during reading or other near and/or distance tasks, or a progressive etiology that is likely to lead to severe low vision (further loss of visual acuity or stamina). Children who are dual-media learners generally have a primary literacy medium of print or braille, and will supplement with the other medium as needed, e.g., some children who are dual-media readers will read print during the day at school, but supplement with braille for extended reading during the evening for homework and for pleasure reading due to decreased visual stamina. The decision for a dual-media approach should always be individualized for each child, and guided by medical and educational data, including a clinical low vision evaluation by a clinical low vision specialist (MD or OD) and a learning media assessment by a certified teacher of students with visual impairments (TVI). Many children with low vision will also supplement learning to some extent with auditory materials, although this should not take the place of the primary literacy medium or media, as concepts such as spelling, capitalization, and punctuation are absent in auditory-only learning.

Management of Vision Impairment in Children and Adolescents

Websites and Other Resources

American Academy of Ophthalmology
http://one.aao.org/preferred-practice-pattern/vision-rehabilitation-ppp--2013

http://one.aao.org/smart-sight-low-vision

American Foundation for the Blind
www.afb.org

American Printing House for the Blind
www.aph.org

National Organization for Albinism and Hypopigmentation (NOAH)
www.albinism.org

Foundations of Low Vision [9]

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Down Syndrome

69

W. Walker Motley III

Abstract

Down syndrome (DS) is a common genetic disorder that may affect any ocular structure. Many individuals with DS develop one or more treatable ocular sequelae, and therefore, periodic eye examinations are indicated starting from birth. The ocular disorders associated with DS include strabismus, congenital and acquired cataract, nystagmus, ocular torticollis, keratoconus, refractive errors, chronic blepharitis, nasolacrimal duct obstruction, and accommodation insufficiency. Refractive errors are the most common ocular manifestations and may be associated with accommodation insufficiency in childhood. Extraocular muscle surgery for strabismus is as successful as in the general population. Congenital and acquired cataracts in DS have different morphologic appearances. Some acquired cataracts in Down syndrome are caused by lenticular accumulation of amyloid-β peptide which is the same protein found in the brain tissue of patients with Alzheimer's disease (Moncaster et al., PLoS One 5(5):e10659, 2010). Surgery is appropriate for visually significant or amblyogenic cataracts, but the risk of complications is higher in the DS population. Keratoconus may progress more rapidly in individuals with DS, but cross-linking may improve prognosis if treatment is available (Koppen et al., J Refract Surg 26:623–624, 2010).

Keywords

Down syndrome • Trisomy 21 • Cataract • Strabismus • Nystagmus • Esotropia • Pediatric • Myopia

Introduction

In 1866, John Langdon Down described features of some children with cognitive disabilities as having "eyes obliquely placed, and internal canthi more than normally distant from one another. The palpebral fissure is very narrow" [1]. Now, almost 150 years later, we understand a great deal more about Down syndrome (DS) and the array of ocular manifestations, including refractive errors, strabismus, cataract formation, nystagmus, accommodation insufficiency, chronic blepharitis, nasolacrimal system dysfunction, and Brushfield spots (Fig. 69.1) [2–9].

Down syndrome occurs in 1/733 live births, making it the most common genetic cause of intellectual disability [3].

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Common systemic abnormalities associated with Down syndrome are hypotonia, congenital cardiac defects, atlantoaxial instability, hyperextensible joints, hypothyroidism, brachycephaly, maxillary hypoplasia, short stature, Hirschsprung's disease, hearing loss, and Alzheimer's disease [2].

Genetics

The phenotype of DS may be caused by one of three genetic abnormalities. More than 95 % of cases are due to complete trisomy of chromosome 21 [10]. In such cases, nondisjunction typically occurs during maternal meiosis and results in a gamete with one extra copy of chromosome 21 [2, 10]. Therefore, upon fertilization, the embryo possesses trisomy of chromosome 21 in all cells. The second most common genetic abnormality making up 2–3 % of DS cases is translocation of the long arm of chromosome 21 to another chromosome such as chromosome 14 (unbalanced Robertsonian translocation) [10]. Finally, trisomy 21 mosaicism makes up the remainder of DS cases and is often referred to as mosaic Down syndrome (MDS). An individual with MDS possesses two genetically distinct cell lines: one euploid cell line and one trisomy 21 cell line. Two mechanisms have been proposed to explain the etiology of MDS: (1) one cell of a euploid embryo undergoes nondisjunction of chromosome 21 early in fetal development, resulting in one trisomy 21 cell that proliferates a trisomy 21 cell line in parallel with the normal cell line and (2) nondisjunction of chromosome 21 occurring in a trisomy 21 embryo resulting in one euploid cell that proliferates a euploid cell line in parallel with the proliferating trisomy 21 cell line [10]. In either situation, genetic mosaicism results from proliferation of two cell lines in the same developing embryo. In contrast to complete trisomy 21 DS, patients with MDS have a more variable spectrum of cognitive and physical stigmata and often have nearly normal cognition and physical phenotype [11, 12].

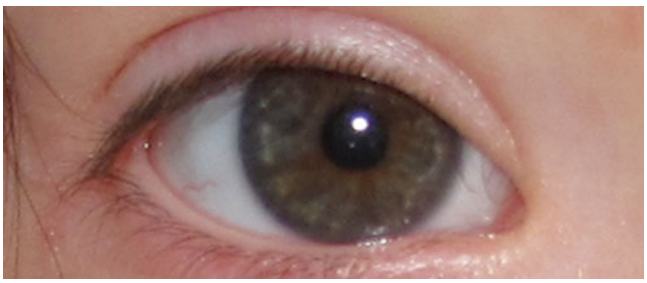

Fig. 69.1 Brushfield spots

Strabismus

Often acquired after 6 months of age, esotropia occurs in 19–70 % of individuals with DS and may be accommodative, non-accommodative, or partially accommodative with a normal or increased accommodative convergence to accommodation ratio [13–18]. If there is significant hyperopia with or without accommodation insufficiency, then optical correction with single-vision lenses or bifocals helps restore ocular alignment. If spectacle correction is not sufficient, then extraocular muscle surgery is appropriate. Bilateral medial rectus recession for esotropia is successful in 66–90 % of cases [13–16]. The dose effect of bilateral medial rectus recession surgery is similar to that of individuals without DS [13, 14]. Therefore no modification of typical surgical dosages is required.

Head tilt-dependent esotropia is a rare type of esotropia found in patients with Down syndrome (Fig. 69.2). In such cases, there is manifest esotropia in primary gaze that resolves with a compensatory right or left head tilt (Fig. 69.2a) [19]. Consequently, the patient typically presents with torticollis, and the esotropia is identified when the

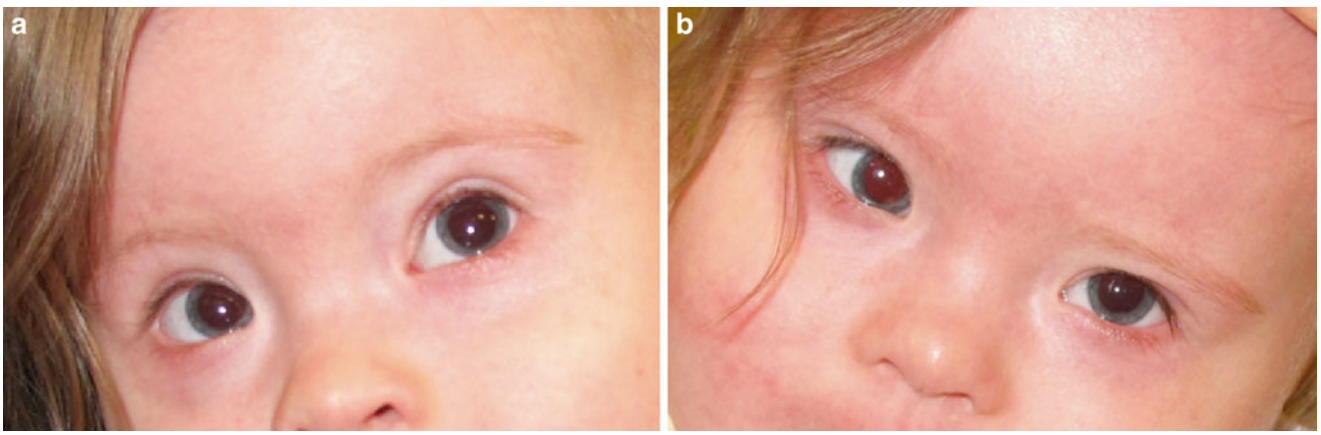

Fig. 69.2 Head-tilt esotropia in Down syndrome. (**a**) Eyes have normal alignment when head is tilted right (compensatory head-tilt). (**b**) Esotropia is revealed in the left head tilt position

examiner tilts the patient's head in the direction opposite to the resting torticollis (Fig. 69.2b). In this type of esotropia, torticollis will typically resolve when either eye is patched or when appropriate base-out correcting prisms are given. Horizontal extraocular muscle surgery can correct the esotropia and improve the torticollis in some patients. Exotropia and hypertropia occur in 0–6 % and 0–3 % of patients with DS, respectively [11–18]. Less is known about surgical outcomes for exotropia and hypertropia due to the lower incidence of these deviations in patients with DS.

Cataract

Cataracts are present in 11–50 % of children and adolescents with DS [4–9]. Although most cases are acquired, 2–6 % of children with DS are born with cataracts [20]. The congenital cataract in DS is typically nuclear with varying degrees of density (Fig. 69.3). Acquired cataracts in adolescents and adults with DS are typically of diffuse cerulean blue-dot perinuclear opacities, with later development of a dense peripheral circumferential ring of perinuclear opacities (Fig. 69.4) [21]. The pattern of peripheral circumferential perinuclear opacification is similar in appearance to cataracts of non-Down syndrome adults with advanced Alzheimer's disease, morphologically distinct from cataracts found in the normal adult population.

The circumferential perinuclear opacities are caused by abnormal deposition of amyloid-β peptide (Aβ) in the perinuclear cortex of the crystalline lens in patients with DS (Fig. 69.4) and in patients with Alzheimer's disease [21]. Aβ is formed by cleavage of amyloid precursor protein (APP) which is encoded on chromosome 21 (21q21). In Alzheimer's disease, Aβ is known to accumulate in the brain tissue and form diffuse plaques. The presence of an additional chromosome 21 in patients with DS leads to increased expression of APP and increased production of Aβ, resulting in the development of perinuclear cortical cataracts (Fig. 69.5).

The decision to proceed with cataract surgery in patients with DS depends on the extent of the opacities and their measured or estimated effects on vision. In children, cataract surgery is indicated if the cataract is judged to be amblyogenic. In adults, surgery is performed when best-corrected visual acuity is not sufficient for the patient's needs as determined through discussions with the patient, ophthalmologist, primary caregivers, and/or family members. The risks of postoperative glaucoma and retinal detachment may be increased in children with Down syndrome [22]. Although contact lens (Fig. 69.6) and spectacle correction of aphakia may be successful in patients with DS, some patients have a great deal of difficulty tolerating either, thereby making intraocular lens implantation the preferred option for optical correction after cataract extraction, unless there are very specific contraindications or concerns.

Nystagmus

Nystagmus is present in 5–30 % of patients with DS and is often noted shortly after birth [4–9, 23, 24]. The pattern of nystagmus may be similar to infantile nystagmus syndrome (pendular or jerk) or fusion maldevelopment nystagmus syndrome (previously called latent/manifest latent nystagmus) [24–26]. Nystagmus in patients with DS commonly becomes less noticeable over the first few years of life.

Esotropia commonly occurs in association with nystagmus but does not meet the criteria for nystagmus blockage syndrome [24]. Null point nystagmus is a common cause for torticollis, yet no studies have been published regarding

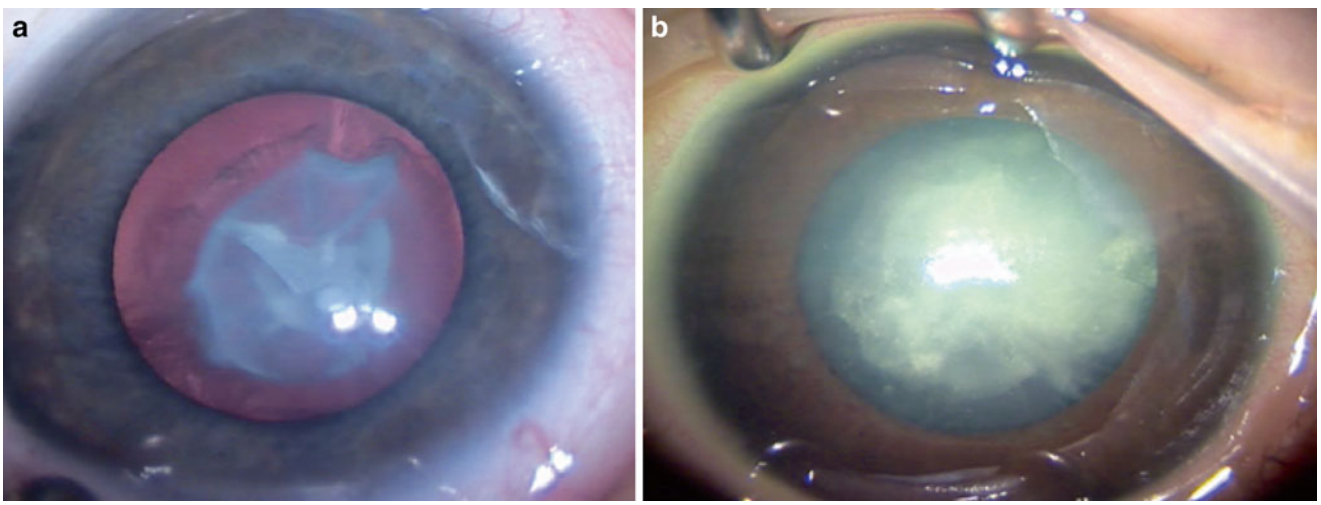

Fig. 69.3 Congenital cataracts in Down syndrome are typically nuclear cataracts but may differ in size and density. The cataract in (**a**) is much less dense than that in (**b**), although both are visually significant secondary to size and location

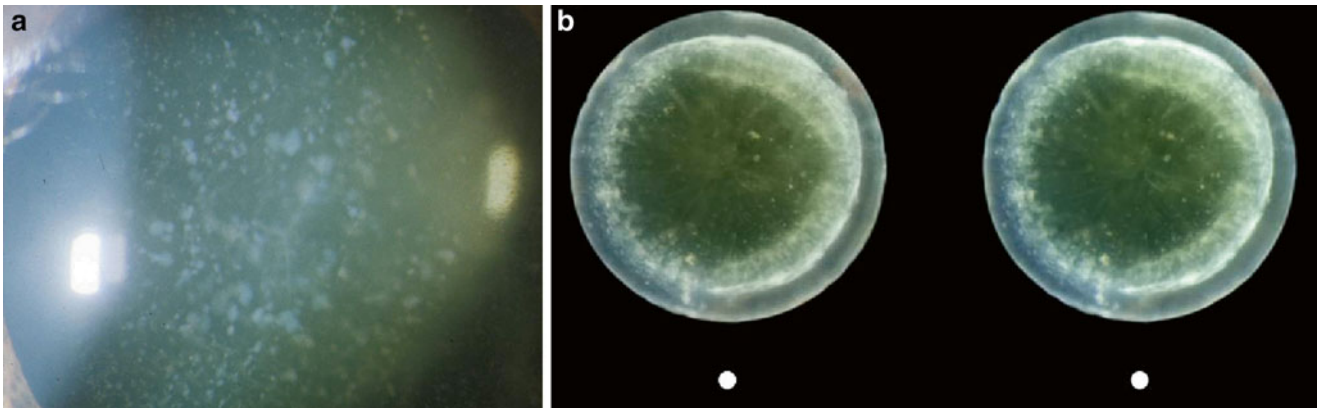

Fig. 69.4 (**a**) Acquired cataracts in Down syndrome in adolescents and adults with DS are typically initially cerulean "*blue dot*" perinuclear opacities. (**b**) Later in adulthood there may be development of a dense peripheral circumferential ring of supranuclear opacities (stereo image). Used with permission Moncaster et al. [18]

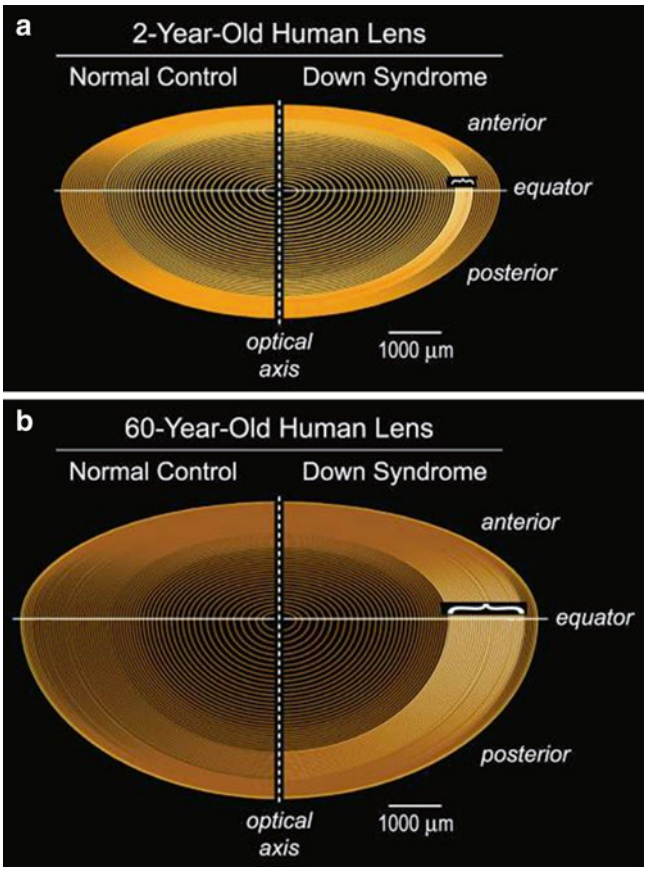

Fig. 69.5 The bracket indicates the location of age-dependent Aβ deposition and acquired perinuclear cataract formation in (**a**) 2-year-old and (**b**) 60-year-old individuals with DS. Used with permission from Moncaster et al. [18]

efficacy of extraocular muscle surgery for nystagmus in patients with DS. Torticollis secondary to nystagmus may improve spontaneously during childhood, and therefore, a conservative approach is reasonable [27].

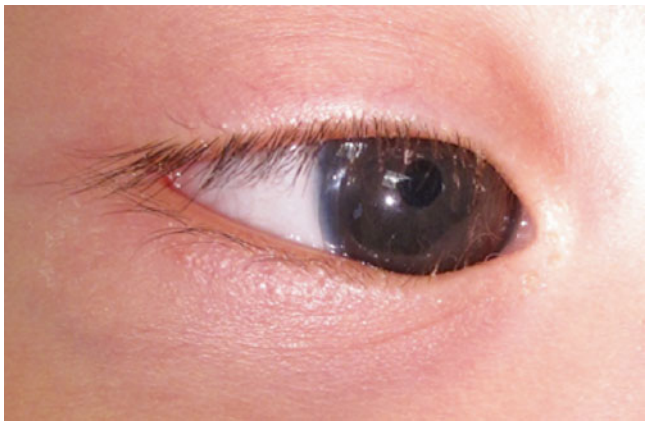

Fig. 69.6 A well-fitting rigid gas permeable contact lens in an aphakic toddler with DS following lensectomy for congenital cataract

Keratoconus

Keratoconus affects up to 18 % of individuals with DS [4–9, 28]. Hydrops may be the presenting sign of keratoconus in a patient with DS, occurring most commonly in early adolescence [28]. While individuals with DS generally have thinner corneas than the general population, the pathophysiology of keratoconus in DS is unclear [29, 30]. Thin corneas and eye rubbing are thought to contribute to the increased risk of keratoconus in patients with DS [29]. Astigmatism of greater than one diopter is also common in patients (67 %) without keratoconus and, therefore, may be difficult to differentiate from true keratoconus early in the course of disease [30]. Anterior segment imaging using a Scheimpflug imaging system to analyze the posterior corneal curvature can be utilized in selected patients with DS.

Treatment of keratoconus involves prevention of eye rubbing and, if possible, spectacles or contact lenses to correct

the associated refractive error. The introduction and fitting of contact lenses in adolescents with DS is challenging. Cross-linking of collagen fibrils in the corneal stroma has been recently introduced to prevent progression of keratoconus [31]. The procedure involves instillation of topical anesthetic, application of riboflavin eye drops, and exposure of the cornea to UVA light. At present, corneal cross-linking has not been approved by the US Food and Drug Administration; however, it has been performed on individuals with DS in Europe [31]. In the USA, patients may enroll in clinical trials but must be able to tolerate the procedure with only topical anesthesia. Since many young patients with DS would require general anesthesia to complete the cross-linking procedure, access to this treatment option is very limited at this time. Cross-linking holds promise for patients with DS if treated before severe thinning or hydrops happens. Penetrating keratoplasty may be performed in selected patients with corneal scarring or severe irregular astigmatism. The 5-year graft survival is 67–75 % in patients with DS [32–34].

Glaucoma

Glaucoma occurs in 0–5.3 % of individuals with DS in various case series. Multiple cases of primary congenital glaucoma have been reported, but an association has yet to be established [35, 36].

Nasolacrimal System Obstruction

Symptomatic nasolacrimal system anomalies, most of which are bilateral, occur in 22 % of children with DS [4–7, 37, 38]. A number of lacrimal system abnormalities can be present in addition to a distal obstruction at the level of the valve of Hasner. In order of frequency, these anomalies include (1) canalicular stenosis, (2) nasolacrimal duct stenosis, (3) anteriorly displaced inferior turbinate, (4) canalicular atresia, and (5) accessory punctum [37]. Consequently, simple probing of the nasolacrimal system is less successful than in children without DS. Balloon dacryoplasty and/or nasolacrimal stenting are more successful than simple probing [37, 38]. Monocanalicular stents may abrade the ocular surface due to malposition of the punctal plug caused by epicanthal folds and flat nasal bridge [37]. Therefore, stent selection (monocanalicular vs. bicanalicular) should be guided by periorbital anatomy and proximity of the puncta to the cornea to avoid this complication.

Lid and Orbit

Patients with DS have a number of eyelid and orbital anatomical abnormalities. When Langdon Down wrote that the eyes are "obliquely placed," we recognize that he was describing the upward slant of the palpebral fissures. His description "the inner canthi are more than normally distant from one another" refers to epicanthal folds that may obscure the true medial canthi. Although he wrote "the palpebral fissure is very narrow," the palpebral fissure height is the same in DS as in the general population [9]. The almond-shaped palpebral fissure creates the illusion of narrowing. In addition, the horizontal length of the palpebral fissure is shorter and the interpupillary distance is reduced. Midfacial hypoplasia is common and results in a recessed maxilla with relative protrusion of the tongue and mandible. Midfacial hypoplasia may account for the lower position of the medial canthi relative to the lateral canthi as well as the reduced interpupillary distance. Individuals with DS commonly have floppy eyelids, thereby causing difficulty with instillation of topical ocular medications and the insertion/removal of contact lenses.

Blepharitis is associated or found in up to 16 % of children and adolescents with DS [4, 39]. Treatment with lid hygiene and warm compresses is appropriate. Systemic tetracyclines may be considered in adolescents. Permanent teeth commonly appear later in children with DS than in typical children, and therefore, caution is advised when considering tetracyclines.

Torticollis

Torticollis has been found in almost 25 % of children with DS [27]. Ophthalmic causes such as strabismus, nystagmus, uncorrected refractive errors, and ptosis account for up to half of cases of torticollis in DS [27]. Non-ocular causes for torticollis include unilateral hearing loss, as well as neck or spine musculoskeletal abnormalities [27, 40]. Atlantoaxial instability (AAI) deserves further discussion aside from its possible link to torticollis in that manipulation of the cervical spine while positioning for surgery or instilling eye drops has been reported to cause spinal cord injury in patients with DS [41]. AAI is present in 10–20 % of individuals with DS. Cervical radiographs and magnetic resonance imaging each have limitations in detecting AAI. Therefore, it is imperative to avoid hyperextending the neck in any patient with DS while positioning for surgery, instilling ocular medications, or performing examinations, even if previous imaging studies have revealed no signs of AAI.

Refractive Errors

Refractive errors are common among individuals with DS [4–9, 39, 42–46]. Although high myopia, in particular, has been associated with DS, the mean refractive error of children and adolescents with DS is very similar to age-matched controls. The pattern of refractive error development in the DS population has been attributed to a failure to achieve emmetropia since the

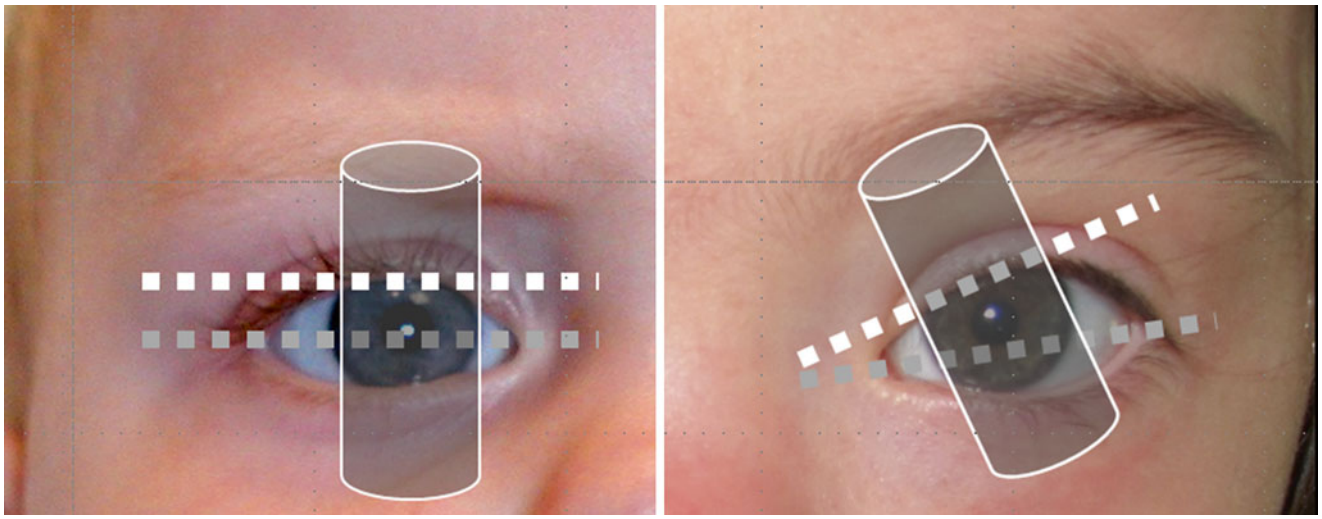

Fig. 69.7 (**a**) Typical palpebral fissure with horizontal fissure axis (*gray line*) and upper lid margin tangential to the limbus at 12 o'clock (*white line*). Astigmatism axis is at 90° perpendicular to the lid margin at 12 o'clock. (**b**) Down syndrome palpebral fissure axis demonstrates upward slant (*gray line*) with lid margin tangential to the limbus at 10:30 o'clock. Resulting astigmatism axis is at 135° which is perpendicular to the lid margin at 10:30 o'clock

distribution of refractive errors becomes increasingly wide over time [42, 43]. In children with DS, accommodation insufficiency is associated with progressive hyperopia and may be a component of the underlying pathophysiology of failure of emmetropization [42–45]. Up to 60 % of children and adolescents with DS have high myopia, hyperopia, and/or astigmatism for which optical correction is indicated [4, 5]. Astigmatism in patients with DS is usually oblique and demonstrates intorsion of the cylindrical axis with right and left eye specificity. The axis of astigmatism is often nearly perpendicular to the upward slanting palpebral fissure (Fig. 69.7) [44, 46].

Accommodation Insufficiency

Accommodation insufficiency, the degree of accommodative lag at all distances of fixation, affects up to 80 % of children and adolescents with DS [47]. This is in contrast to presbyopia in which the refractive error and blur increases as fixation distance decreases. The pathophysiology of accommodation insufficiency remains uncertain, but is thought to result from an abnormality in afferent processing or an efferent neuromuscular deficit involving the ciliary muscle [47]. Optimal treatment consists of prescribing bifocals with the full cycloplegic refraction for distance and a +3.00 diopter add segment for near [48, 49]. It has been suggested that children with DS comply better with wearing glasses when prescribed bifocals instead of single-vision lenses [50]. The use of bifocals may also induce an improvement in accommodation such that the bifocal power may be tapered over time [48, 49]. The efficacy of bifocals to improve accommodation is under further investigation.

The presence of and magnitude of accommodation may be objectively measured using dynamic retinoscopy [50, 51]. Dynamic retinoscopy is performed before instilling cycloplegic eye drops. The patient is placed in full distance corrective lenses either with glasses or trial frames. The patient fixates on a distant target. Using a retinoscope, the examiner will observe "with" movement of the light reflex in all axes. The clinician then prompts the patient to fixate on a near target in the plane of the retinoscope, and the examiner should see complete or near-complete neutralization of the "with" movement of the light reflex. The amount of accommodative lag may be measured using an additional convex trial lens over one eye while the patient fixates with the fellow eye on the near target. Accommodative lag of greater than +0.75 diopters is abnormal in children. In situations of significant accommodative lag, it is appropriate to prescribe bifocals. If the patient's distance refractive error is unknown, then one may obtain an approximation in the undilated eye by using the technique of Mohindra near retinoscopy [52]. Mohindra retinoscopy involves neutralizing the retinoscope reflex with trial lenses in an exam room that is otherwise completely darkened so that the patient has no visual reference points to judge distance or to stimulate accommodation. The patient fixates on the retinoscope light, while trial lenses are used to neutralize the light reflex. The working distance should be subtracted from the dioptric power obtained; then +0.75 diopters is added to the sphere component to account for latent resting accommodative tone. The light-emitting filament of the retinoscope typically does not stimulate accommodation in patients with Down syndrome, and therefore an approximation of the true cycloplegic refraction may be obtained [53].

Case Studies

Case Study 1

A 4-year-old boy with Down syndrome had been seen by another eye care provider and presents for a second opinion regarding glasses. The parent indicates that the child was prescribed with glasses but will not wear them. The glasses have been lost and were not replaced, and records from the prior provider are not available.

Visual acuity without correction		20/80 OD
		20/80 OS
Muscle balance	6 m	Orthophoria
	1/3 m	Orthophoria
Nystagmus		None

How Would You Further Assess the Patient's Refractive State?

Although cycloplegic retinoscopy would be helpful, it would be best to assess the patient's ability to accommodate before cycloplegia. The child's refractive error is unknown. Mohindra retinoscopy performed from a working distance of 2/3 m on the right eye yields that a spherical lens of +4.50 diopters neutralizes the light reflex in the 120° axis which is the axis with the least "with" movement. An additional +1.00 diopters is required to neutralize the "with" movement in the 70° axis. Thus the refractive correction for the right eye estimated by Mohindra retinoscopy is $+3.75 + 1.00 \times 70^{\circ}$. Using the same technique the refractive correction for the left eye is estimated to be $+4.25 + 1.25 \times 110^{\circ}$. The refractive correction is place on the patient using trial frames, and dynamic retinoscopy is performed to assess the child's accommodation. The child fixates on a distant target and "with" movement is seen in all axes in each eye. The child's attention is directed to a small target in the plane of the retinoscope. Some pupillary constriction is observed indicating that the child is fixating on the near target but "with" movement of at least +1.00 diopter is still present in each eye suggesting accommodation insufficiency. Cycloplegic retinoscopy yields refractive correction of $+4.00 + 0.75 \times 70^{\circ}$ OD and $+4.25 + 1.50 \times 110^{\circ}$ OS.

The parent is advised that bifocals are appropriate for distance and near correction and may improve compliance with spectacle wear. The following prescription is prescribed assuming that the child has a near working distance of 1/3 m:

Eye	Sphere	Cylinder	Axis	Add
OD	+4.00	+0.75	070°	+3.00
OS	+4.25	+1.50	110°	+3.00

Compliance with Spectacles

Compliance with spectacles may be challenging for children with DS due to behavioral or tactile sensory issues. Recommending a good optician to fit glasses properly is a good first step. In order to compensate for a flat nasal bridge and shorter distance between the plane of the spectacle lens and back of the ear, as seen in patients with DS, selected frames have been designed with nose pads that are inferiorly displaced and a temple which is shorter in length. Other frames may be modified to compensate for the facial differences of patients with DS. A strap can be helpful in patients to prevent the glasses from slipping down the nose, but in some patients with tactile hypersensitivity using a strap often worsens compliance. If the patient is hyperopic, then temporary use of a cycloplegic agent at home may facilitate compliance.

Management of compliance with eyeglasses wear in children with DS is multidisciplinary, involving physical, occupational, and speech therapists. Families often find that children wear glasses well during these therapy sessions. Gentle, consistent, and firm reinforcement of spectacle wear increases the likelihood of success. Documenting the appropriate use of glasses for a child's individualized education plan helps ensure that teachers and school staff will reinforce compliance with glasses in the classroom.

Patients who refuse to wear glasses or contact lenses in the presence of extreme refractive errors have, in some cases, undergone refractive surgical procedures with success. Excimer laser keratorefractive procedures have generally been avoided due to the typically thin cornea and increased risk of keratoconus in patients with DS. Phakic intraocular lens implantation and clear lens exchange are potential alternatives; however the risks of intraocular surgery must be carefully considered in these situations.

Screening

Based on the high prevalence of ocular abnormalities and visual deficits in children and adolescents with DS, the American Association of Pediatrics has published ocular and other health supervision guidelines for such patients [54]. A red reflex test should be performed by the primary care physician by 4 weeks of age. An infant with DS should be referred to a pediatric

(continued)

ophthalmologist or general ophthalmologist with experience in examining children with DS by 6 months of age. A child with DS should undergo a complete eye examination by an ophthalmologist at least once per year until age 5, followed by at least once every 2 years until age 13, after which an examination every 3 years is deemed sufficient.

Person-First Language

The use of person-first language is a form of speech that aims to avoid derogatory or dehumanizing sentiment toward individuals with disabilities and/or diseases [55]. In its simplest form, one simply refers to the person before the disability or disease such as "a child with Down syndrome" rather than "a Down's child." "Children with Down syndrome" is preferred over "Down's kids." "A child with special needs" is preferred over "a special needs child." Many parents of children with disabilities are accustomed to person-first language. Therefore, a provider who does not use person-first language may appear to the parent as lacking experience in caring patients with disabilities. The use of person-first language may initially feel unnatural or inefficient, but with time, it becomes second nature and helps to reinforce a provider's compassion and expertise.

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Part XIV

Nystagmus

Nystagmus in Pediatric Age Group: Clinical Features and Management

70

Fatema F. Ghasia

Abstract

The purpose of this chapter is to review the clinical features of commonly encountered ocular oscillations in the pediatric age group. The three most common forms of nystagmus in childhood present in the first year of life and include fusion maldevelopment nystagmus syndrome, infantile nystagmus syndrome, and spasmus nutans syndrome. Neurologic signs and symptoms usually accompany nystagmus related to central nervous system abnormalities. Eye movement recordings in the clinical setting can be very helpful in the diagnosis and management of ocular oscillations. A variety of medical and surgical treatment options are available to improve the ocular oscillation of nystagmus and associated abnormalities such as anomalous head positions.

Keywords

Nystagmus • Saccadic oscillations • Spasmus nutans

Introduction

Nystagmus is a commonly encountered problem in pediatric ophthalmology practice that poses diagnostic and therapeutic challenges. The challenge is in characterization of the eye movement as well as deciphering any associated systemic and/or central nervous system abnormalities. Nystagmus is comprised of repetitive slow drift of the eye away from the target of interest followed by a corrective or abnormal eye movement [1]. Thus, it is an involuntary rhythmic oscillation of the eye. These oscillations may cause a decline of visual acuity due to excessive motion of the images on the retina, sometimes with an illusion of motion of the seen world (oscillopsia) [2]. Children with nystagmus usually do not develop oscillopsia unless the nystagmus is acquired in the later childhood years [3].

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Nystagmus is further characterized on the basis of the direction of the fast phase (horizontal, vertical, or torsional), whether it is predominantly pendular or jerk and whether it is conjugate (the amplitude and direction of nystagmus are same in both eyes) or disconjugate (the direction or amplitude of nystagmus varies between the two eyes). Nystagmus and other ocular motor oscillations have been organized and classified by a team of interdisciplinary experts in the National Eye Institute-sponsored workshop, Classification of Eye Movement Abnormalities and Strabismus as physiologic fixational eye movements, physiologic nystagmus, pathologic nystagmus, and saccadic oscillations (Table 70.1) [4]. It is important to identify nystagmus where the pathology is a slow phase with corrective fast phase from saccadic intrusions in which the primary abnormality is an inappropriate initial saccade taking the line of sight away from the target of interest [1] (Fig. 70.1). It can be difficult to differentiate the saccadic intrusions from nystagmus on clinical examination alone. Recent advances in noninvasive eye movement recording techniques have made it feasible to better identify different types of ocular motor oscillations in children.

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Table 70.1 Classification of Eye Movement Abnormalities and Strabismus (CEMAS), National Eye Institute Sponsored Workshop [4]

A. Physiologic fixational movements
Microtremor
Slow drifts
Microsaccades
B. Physiologic nystagmus
Vestibular nystagmus
Optokinetic nystagmus
Eccentric gaze nystagmus
C. Pathologic nystagmus
Infantile nystagmus syndrome
Fusion maldevelopment nystagmus
Spasmus nutans nystagmus
Vestibular nystagmus—central or peripheral imbalance, central instability
Gaze-holding deficiency nystagmus—endgaze, rebound, gaze instability nystagmus
Vision loss—prechiasmal, chiasmal, postchiasmal
Other pendular nystagmus and nystagmus associated with disease of central myelin-multiple sclerosis, pendular nystagmus associated with tremor of palate, pendular vergence nystagmus associated with Whipple's disease
Ocular bobbing
Lid nystagmus
D. Saccadic intrusions and oscillations
Square wave jerk and oscillations
Square wave pulses
Saccadic pulses
Induced convergence retraction
Dissociated ocular oscillations
Hypermetric saccades
Macrosaccadic oscillations
Ocular flutter
Flutter dysmetria
Opsoclonus
Psychogenic flutter
Superior oblique myokymia

It is important to distinguish a benign, congenital cause of nystagmus from an acquired one, as the latter is frequently associated with neurologic disorders (Fig. 70.2). The most common forms of early-onset nystagmus include infantile nystagmus syndrome (INS) and fusion maldevelopment nystagmus syndrome (FMNS). These patients typically have an onset of nystagmus in early infancy (usually 8–12 weeks). If the nystagmus develops later, then deterioration of vision should be suspected as in disorders of the retina and optic pathway. Thus, a detailed history including onset, pre- and perinatal complications, family history, growth and developmental milestones, as well as a thorough ocular examination are essential to accurately identify the etiology of nystagmus. Retinal electrophysiologic testing may be necessary in cases of suspected early retinal disorders such as Leber congenital amaurosis, achromatopsia, or congenital stationary night blindness (see Chap. 28 on Retinal Dystrophies). Neuroimaging is warranted if diagnosis of INS is uncertain or there are coexistent optic nerve abnormalities like optic nerve hypoplasia (to look for coexistent de Morsier syndrome or septo-optic dysplasia for pituitary gland abnormalities) or optic nerve atrophy (tumors or hydrocephalus or periventricular leukomalacia).

We will review the salient features of the most common types of nystagmus and eye movement abnormalities in children.

Latent Nystagmus

Latent nystagmus or FMNS is defined as a jerk nystagmus that is absent when both eyes are viewing, but appears when one eye is covered. When latent nystagmus is present with both eyes viewing, it is referred to as manifest latent nystagmus. One eye is typically preferred for fixation, while the other eye is being suppressed or amblyopic [5, 6]. Latent nystagmus occurs in individuals with disruption of binocularity within the first 6 months of life and with onset in infancy. A majority of these patients are esotropic but can have other types of strabismus [7]. As many as 50 % of patients with infantile strabismus have latent nystagmus [8]. True latent nystagmus that is observed only on monocular occlusion is rare [9]. In most patients, nystagmus (which can be of low amplitude) is present when both eyes are uncovered and is termed manifest latent nystagmus. Children with monocular visual loss (e.g., congenital cataract or optic disc anomaly) frequently have pronounced manifest latent nystagmus with worse nystagmus in the eye with poor vision.

FMNS is characterized by a nasally directed slow phase followed by a temporally directed fast phase (Fig. 70.2 top panel). Eye movements frequently have a cyclovertical component with a superimposed dissociated vertical deviation of the covered eye (Fig. 70.2 bottom panel) [10]. Latent nystagmus follows Alexander's law (the slow phase velocity of the nystagmus increases in the direction of the fast phase, i.e., increases in nystagmus intensity temporally and decreases in intensity nasally under conditions of monocular viewing) [1]. The slow phases show a linear or decreasing velocity waveform.

Clinical Pearls

1. It is important to identify FMNS accurately to avoid workup for other neurologic/ocular causes of nystagmus. FMNS is more pronounced in monocular viewing condition with reversal of direction of nystagmus depending on the viewing eye i.e., right-beating nystagmus when right eye is viewing whereas left-beating nystagmus when left eye is viewing.

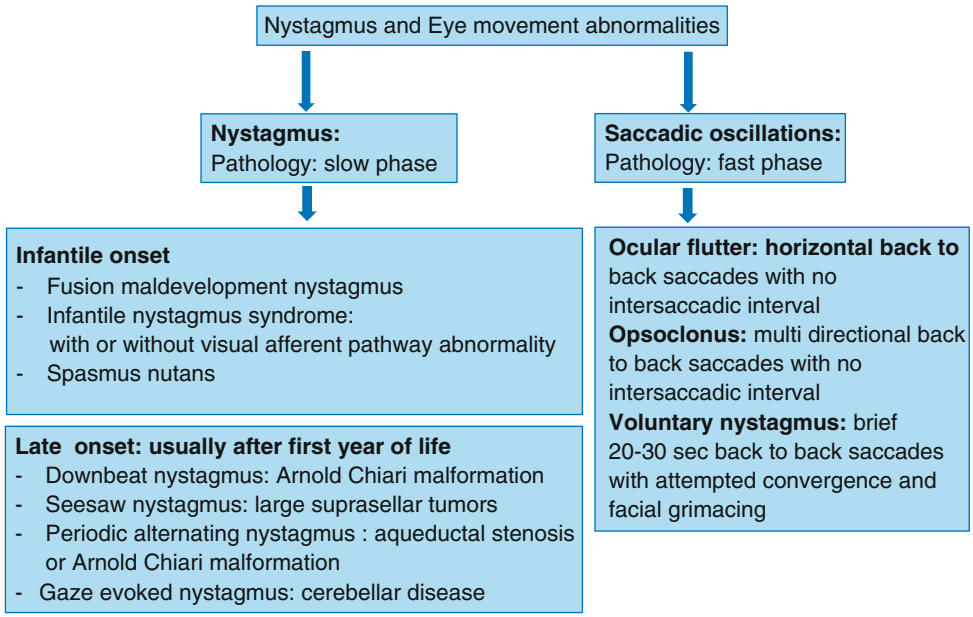

Fig. 70.1 Flowchart of nystagmus and eye movement abnormalities

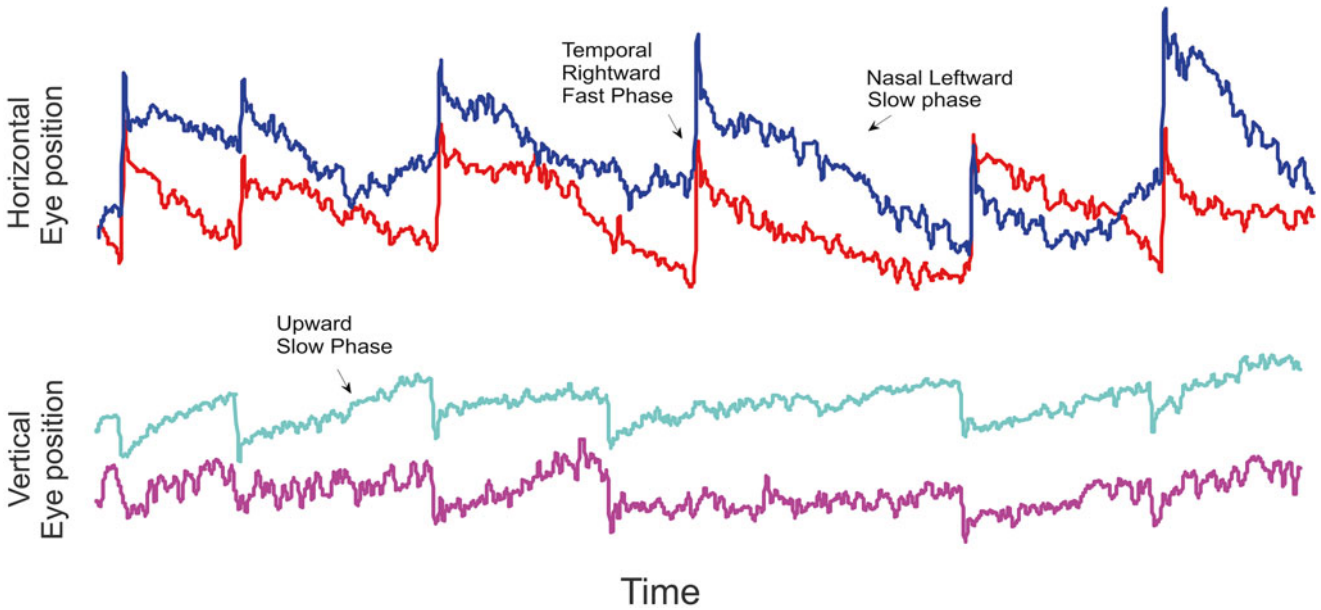

Fig. 70.2 *Top* panel plots horizontal eye position of *right* eye (*red trace*) and *left* eye (*blue trace*) when the *right* eye is viewing. Note the eyes are drifting to the *left* (*nasally*) followed by a *right* (*temporal*) fast phase. *Bottom* panel plots vertical eye positions of *right* (*magenta*) and *left* (*cyan*) eye. Note the small upward drift of both eyes

2. Fogging technique for measurement of visual acuity: If complete occlusion is employed for visual acuity testing, it may result in an underestimation of the acuity due to the appearance of latent nystagmus under monocular viewing conditions. The fogging technique should be employed where a +5.00 D lens is placed over the fellow eye to test monocular visual acuity.
3. Nystagmus blockage syndrome: Patients with manifest latent nystagmus may adopt a head turn such that the viewing eye is in adducting position thus decreasing the nystagmus intensity.

Infantile Nystagmus Syndrome

INS is defined as a conjugate, horizontal-torsional pendular, or jerk nystagmus with or without ocular and afferent visual system deficits (e.g., albinism, retinal dystrophies, cataract, aniridia, etc.) [11, 12]. A positive family history may be present. The waveforms evolve in INS over the first year of life. Initially, they appear triangular, changing to pendular, and finally jerk as the patient reaches 1 year of age [13, 14]. The nystagmus increases on attempted visual fixation [15],

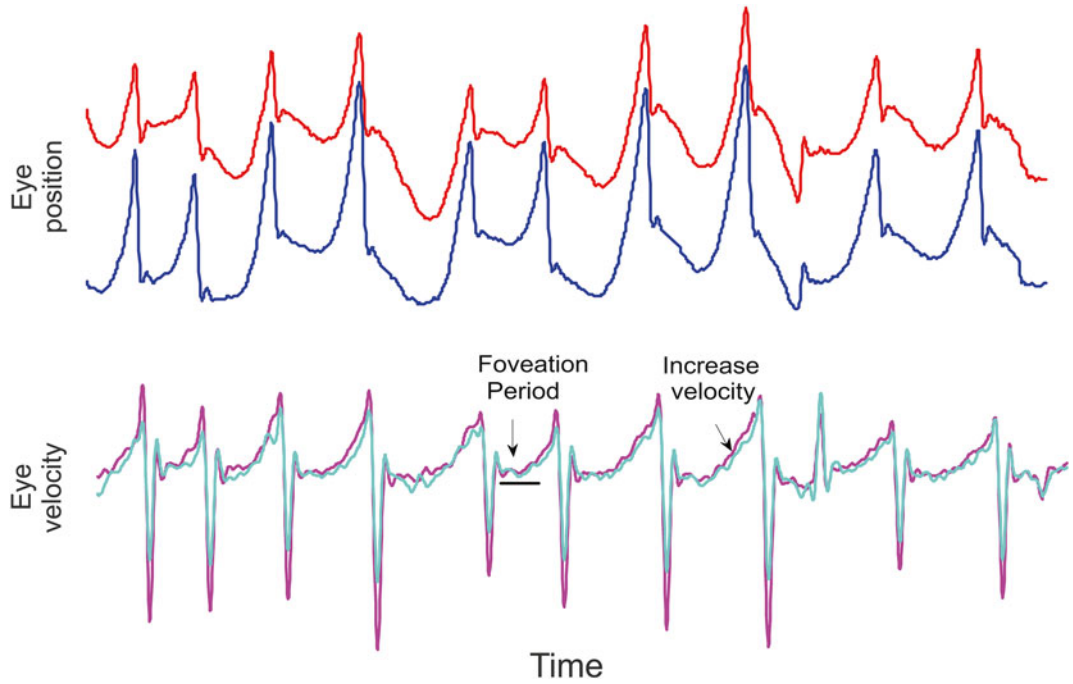

Fig. 70.3 *Top* panel plots the horizontal eye position of *right* eye (*red trace*) and *left* eye (*blue trace*). Note the nystagmus is conjugate with rightward slow phase followed by a leftward fast phase. *Bottom* panel plots the horizontal eye velocity of *right* eye (*magenta trace*) and *left* eye (*cyan trace*). Note the exponentially increasing velocity waveform with a brief foveation period (*solid line*) in between each cycle of nystagmus

whereas it tends to decrease with convergence [16] or eyelid closure [17]. These patients may present with a face turn to maintain the eyes in the null position (the position of gaze where the nystagmus dampens). An anomalous head position can usually be observed before the age of 4 years. They may also exhibit the nystagmus blockage syndrome where they place the viewing eye in adduction to minimize the nystagmus. Head oscillations may be present in patients with INS [18]. These are not compensatory and tend to increase with attempted fixation [19].

Figure 70.3 demonstrates the eye position (top panel) and eye velocity trace (bottom panel) in a patient with INS. The nystagmus waveforms have an increasing velocity (accelerating) slow phase distinguishing this entity from FMNS. There are superimposed foveation periods when the eyes are relatively still (usually <4°/s) and are pointed toward the target of interest, thus accounting for a relatively good visual acuity in INS [20, 21] In contrast, absence of foveation periods is frequently seen in patients with INS and associated afferent system anomalies accounting for the poorer vision encountered. Recently, optical coherence tomography (OCT) and handheld OCT have been used to diagnose INS based on the foveal morphology. The foveal morphology is classified into four types: (a) typical foveal hypoplasia (albinism, *PAX6* mutations), (b) atypical foveal hypoplasia (achromatopsia), (c) other foveal changes (corresponding to retinal dystrophies), and normal fovea (idiopathic INS) [22]. Mutations in the *FRMD*7 gene have been demonstrated to cause X-linked idiopathic INS [23]. These patients (males much more than females) have a pendular nystagmus waveform, lower intensity of nystagmus in the primary position, and fewer occurrences of abnormal head posture as compared to patients with non-*FRMD7* gene mutation [23].

If a significant and consistent face turn is present, the patient may benefit from eye muscle surgery to bring the null position to primary gaze, thus eliminating the anomalous head position [24]. This is most commonly achieved by a Kestenbaum procedure [25] in which recess-resect procedures that move both eyes toward the direction of the head turn and away from the null zone or preferred position of gaze, thus broadening the null position to correct the abnormal head position. Kestenbaum had initially proposed to perform identical amounts of recess-resect procedure on one eye first, with surgery on second eye after a stabilization period [25]. Parks proposed a modification of the Kestenbaum procedure in which he recommended performing maximal surgery on each muscle that would not reduce its full duction [26]. The modification is referred to as Classic (5, 6, 7, 8 rule) (Table 70.2).

Calhoun and Harley reported an undercorrection with the Parks modification (Classic) of the Kestenbaum procedure [27]. They recommended no surgical treatment for face turn of 15° or less, Classic +40 % augmentation for a 30° face turn, and Classic +60 % augmentation for a 45° face turn

Table 70.2 Kestenbaum procedure for nystagmus

Head turn to the right–left gaze preference				
	Right eye—esotropic		Left eye—exotropic	
Procedure	Lateral rectus resection	Medial rectus recession	Medial rectus resection	Lateral rectus recession
Classic (Parks) (5+8=6+7)	8	5	6	7
+40 % augmentation (30° face turn)	11	7	8.5	10
+60 % augmentation (60° face turn)	13	8	9.5	11
Head turn to the left–right gaze preference				
	Right eye—exotropic		Left eye—esotropic	
Procedure	Lateral rectus recession	Medial rectus resection	Medial rectus recession	Lateral rectus resection
Classic (Parks) (5+8=6+7)	7	6	5	8
+40 % augmentation (30° face turn)	10	8.5	7	11
+60 % augmentation (60° face turn)	11	9.5	8	13

(Table 70.2). Other procedures that have been advocated include performing a tenotomy and reattachment of the four rectus muscles or tenotomy on two rectus muscles with large recessions of the other two rectus muscles for face turns less than 20° [28]. For patients with vertical null zone—recess-resect procedure of four vertical rectus muscles have been proposed [29]. Recent studies have shown benefit on nystagmus intensity in INS with children treated medically with gabapentin, memantine, and diamox [30–32]. These medications have shown to be well tolerated in the pediatric patient population.

Clinical Pearls

1. Careful evaluation to rule out structural eye abnormalities is warranted due to the frequent association (up to 25 %) of INS with afferent visual pathway abnormalities.
2. Optical coherence tomography may be useful in the workup of these patients to identify foveal hypoplasia.
3. Genetic mutations in *FRMD7* gene have been described in patients with X-linked INS.

Spasmus Nutans

Spasmus nutans represents a triad of nystagmus, head nodding, and torticollis. The age of onset is generally between 6 and 12 months of age. One may appreciate the classic clinical findings while the baby is feeding. It is a disconjugate, asymmetric high frequency fine rapid nystagmus which may be horizontal, vertical, or torsional [33]. The nystagmus may increase in frequency with convergence. The head nodding in spasmus nutans is an adaptive strategy mechanism and is thought to improve the visual acuity by suppressing the nystagmus [34, 35]. This is in contrast to head nodding seen in patients with INS where the head oscillations are thought to be a pathologic tremor with no effects on visual acuity [36]. There is a frequent association of amblyopia (particularly when the nystagmus is asymmetric) and strabismus in patients with spasmus nutans. Suprasellar tumors (optic pathway gliomas) may cause a clinical picture similar to spasmus nutans, thus neuroimaging and careful monitoring for visual, neurologic, and endocrine function is recommended. Spasmus nutans with no associated CNS abnormalities usually resolves on clinical observation by 2 years of age. However, the nystagmus is usually still evident on eye movement recordings [37].

Clinical Pearls

1. Spasmus nutans is suspected in infants between 6 and 12 months of age who present with high frequency asymmetric nystagmus and head bobbing.
2. Neuroimaging is warranted in these patients due to the association of similar eye movement abnormalities in patients with suprasellar tumors.
3. Isolated spasmus nutans resolves by 2 years of age. Retinal dystrophies should be suspected in patients in whom the nystagmus does not resolve and who have no CNS abnormalities.

Vertical Nystagmus in Infancy

Upbeating nystagmus in infancy is usually associated with anterior visual pathway disease [38]. A full ophthalmologic examination is needed to evaluate for structural abnormalities including optic nerve pathology. If the ocular examination is unremarkable, an ERG to evaluate for retinal dystrophies should be considered. Rarely, vertical nystagmus is familial in which case visual acuity is good with a positive family history.

Congenital downbeating nystagmus is rare in infancy. Usually there is a positive family history with resolution of the nystagmus by 2 years of age [39]. Acquired forms of downbeat nystagmus in older children warrant neuroimaging to evaluate for abnormalities in the craniocervical junction such as Arnold–Chiari malformations [40] (Fig. 70.4). There can be coexisting horizontal nystagmus and thus the nystagmus may have an oblique slow phase in Arnold–Chiari malformation. The downbeat nystagmus results from compression

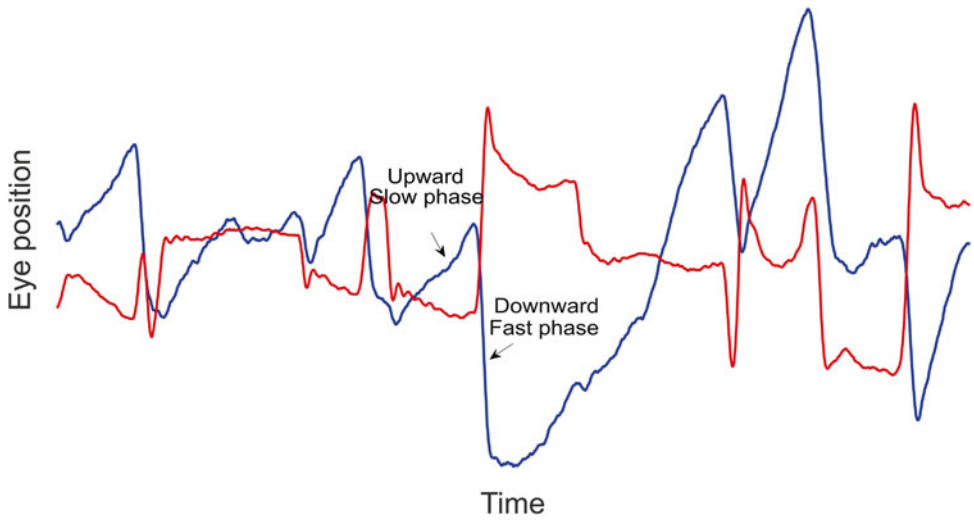

Fig. 70.4 Plots horizontal eye position (*red trace*) and vertical eye position (*blue trace*). Note the upward slow drift followed by a downward fast phase (Aasef Shaikh is acknowledged for providing eye movement recording data for this figure)

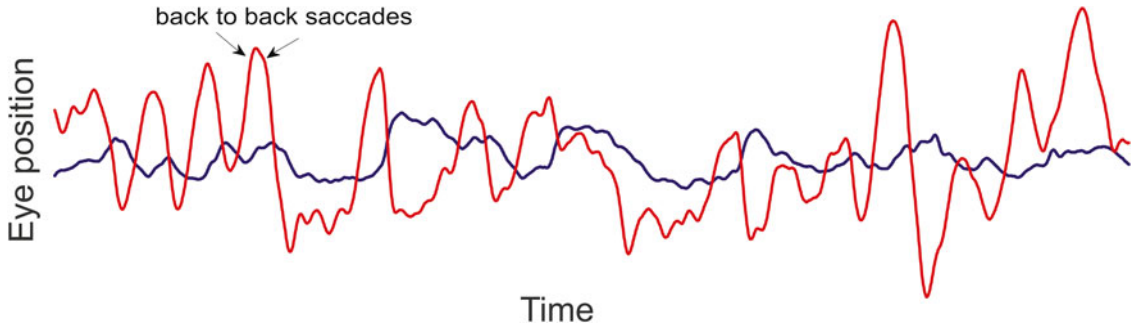

Fig. 70.5 Plots horizontal eye position *red trace*) and vertical eye position (*blue trace*). Note the back to back saccades with no inter-saccade interval (Aasef Shaikh is acknowledged for providing eye movement recording data for this figure)

of the herniated cerebellum against the caudal brainstem with clinical improvement following surgical decompression. Other eye movement abnormalities in patients with Arnold–Chiari malformations include esotropia secondary to divergence insufficiency [41], seesaw nystagmus [42], skew deviation [43], periodic alternating nystagmus [44], and shifted null position of the horizontal gaze-evoked nystagmus [45]. The definitions of all these entities are beyond the scope of this chapter—please refer to a more comprehensive text (Leigh and Zee: The neurology of eye movement) [1].

Opsoclonus and Ocular Flutter

Ocular flutter is defined as intermittent bursts of conjugate horizontal saccades without an intersaccadic interval (Fig. 70.5). Opsoclonus is a combined multidirectional horizontal, vertical, and saccadic oscillation without an intersaccadic interval [1]. Transient opsoclonus has been reported in healthy term and preterm neonates. As many as 50 % of children with opsoclonus have tumors of neural crest origin such as neuroblastoma [46]. An opsoclonus myoclonus ataxia syndrome affects 2–3 % of patients with neuroblastoma [46]. The neurologic symptoms include gross motor delay with decreased muscle tone and speech and sleep problems. Interestingly, patients with opsoclonus myoclonus syndrome have excellent survival (100 %) compared to patients with Horner syndrome (76 %) and orbital metastasis (11 %) [47]. It has been hypothesized that the syndrome is caused by immunological cross-reactivity between the tumor and normal cerebellar neurons [48]. The antineuronal antibodies associated with opsoclonus include anti-Ri, anti-Hu, and anti-Yo antibodies. These antibodies may be negative, and thus testing is not implemented routinely. Whole body imaging is recommended to identify the tumor. Management options include treatment with corticosteroids or intravenous immunoglobulins. Recent studies have suggested that adrenocorticotropin hormone (ACTH) may be superior to corticosteroids in the treatment of opsoclonus. Despite successful treatment, children often have long-term neurologic sequelae.

Voluntary Nystagmus

Voluntary nystagmus appears similarly to ocular flutter with inability to sustain the movement longer than 20–30 s. It can be initiated during convergence and may be associated with mild widening of the palpebral fissures with facial grimacing. It can also be familial. The key feature that differentiates it from pathologic forms of flutter is the inability to sustain it for long periods of time.

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Part XV

Non-organic Vision Loss

Nonorganic Vision Loss in Children

71

Lileth Mondok and Elias I. Traboulsi

Abstract

Some children, usually between the ages of 6 and 10, present with vision loss that cannot be explained on the basis of the physical findings. Studies exploring the possibilities of retinal, optic nerve, or cortical abnormalities yield normal results, yet the child has a variable combination of visual acuity loss, color vision defects, stereo acuity loss, and visual field deficits. While malingering adults who fake vision loss are generally after monetary compensation or other tangible gains, children with nonorganic vision loss generally fall into one of two groups: (1) Those who want their parents to buy them glasses, many times because their friends have them and they do not, and (2) those who utilize, most of the time in a subconscious fashion, the vision loss to gain the attention of their family members and the eye doctor because of an underlying anxiety-producing situation such as stress at home or in school or sometimes abuse or psychiatric illness.

Keywords

Vision loss • Children • Nonorganic • Malingering • Amblyopia school girl syndrome

The Problem

Some children, usually between the ages of 6 and 10, present with vision loss that cannot be explained on the basis of the physical findings. Studies exploring the possibilities of retinal, optic nerve, or cortical abnormalities yield normal results, yet the child has a variable combination of visual acuity loss, color vision defects, stereo acuity loss, and visual field deficits. While malingering adults who fake vision loss are generally after monetary compensation or other tangible gains, children with nonorganic vision loss generally fall into one of two groups: (1) Those who want their parents to buy them glasses, many times because their friends have them and they do not, and (2) those who utilize, most of the time in a subconscious fashion, the vision loss to gain the attention of their family members and the eye doctor because of an underlying anxiety-producing situation such as stress at home or in school or sometimes abuse or psychiatric illness.

While one may immediately suspect the possibility of non-organic visual loss (NOVL), confident elimination of real underlying physical abnormalities of the visual system is paramount. Once the diagnosis of NOVL is made, the ophthalmologist will determine whether it is a benign situation such as wanting glasses or a more serious one that requires counseling and referral to the appropriate specialists such as the patient's pediatrician or a psychologist or social worker, depending on the nature of the problem.

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Case 1

A 7-year-old girl fails the vision examination at school and is brought for an evaluation. She can only read the largest target on the visual acuity testing chart; she cannot recognize any of the 3-D targets on the stereo acuity test or any of the numbers, including the leader on the Ishihara color vision test. The objective components of the eye examination including pupillary reactions, refraction, slit lamp, and retinal examinations are within normal limits. The ophthalmologist suspects NOVL and through cajoling and playing with the child is able to have her read the 20/20 targets with a plano prescription in trial frames. The parents and the child are reassured that she has healthy eyes and after she expresses disappointment for not having been prescribed glasses admits that she wanted them because several of her classmates had recently been prescribed glasses.

Case 2

A 9-year-old boy complains of eye pain and not seeing well and is brought for an eye examination that reveals completely normal physical findings and a visual acuity of 20/100 OU. The child is blinking frequently and appears nervous. NOVL is suspected and in questioning about possible anxiety-inducing factors, his mother tells the ophthalmologist that his father now has to travel to another nearby city for work and is absent most of the time. Father and son are very close and the child misses play and interactions with his dad. NOVL was presumed to be the result of separation anxiety. Counseling was obtained and the child's symptoms and vision improved.

Clinical Findings

Nonorganic visual loss (NOVL) is characterized by disturbances of vision that cannot be accounted for by ocular or neurologic pathology. It is a clinical diagnosis ultimately confirmed by demonstrating that the patient has visual acuity better than reported by conducting a thorough ophthalmologic examination and occasionally using well-described clinical tests that rely on subterfuge. This entity has been called by a number of different terms including: functional visual loss [1], visual conversion disorder [2], psychogenic amblyopia [3], and hysterical amblyopia [4]. It is not uncommon in the pediatric population with a study by Mantyjarvi [5] revealing 1.75 % of school children or 1.4 cases/1000 children per year diagnosed with NOVL. It accounts for around 1 % of new referrals [6] to pediatric ophthalmology tertiary centers coming from optometrists, general practitioners, pediatricians, failed school vision screens, and fellow ophthalmologists. There is an inherent hesitation to diagnose patients with NOVL because of the fear of missing organic pathology that is treatable. It is therefore necessary for the ophthalmologist to accurately diagnose this condition to prevent unnecessary workup and treatment.

Several pediatric studies [5–9] have described that NOVL is diagnosed mostly in prepubertal children aged 8–11 years. In a joint clinic in which adults and children are examined, incidence was highest among teenagers around 16–17 years of age, and this discrepancy was explained by the tendency for teenagers to be seen by general ophthalmologists and not necessarily by pediatric ophthalmologists [10]. There is a greater female predominance across several age groups with a ratio of 2F:1M [9, 11]. Visual disturbance is usually reported as vision loss or decreased vision and can be accompanied by visual field deficits in up to 46 [10]–71 % [11] of patients. Isolated visual field complaints are rare in children, but they can demonstrate spiraling or tubular fields on visual field testing similar to those of adults. Binocular vision loss is more common than monocular (60 %:40 %) [9, 10]. The reported visual acuity is usually moderately to severely reduced, ranging from 20/40 to HM (hand movement), with 50 % of patients testing at 20/100 or better. A number of other additional complaints usually accompany the visual disturbance. Children can also complain of diplopia, eye pain, photophobia, and poor color vision or other systemic complaints most often headache, followed by abdominal pain or limb pain [11].

Functional overlay occurs in around 21 [10] to 25 % [2] of patients who have primary ocular disease. In children, these coexistent diseases are usually amblyopia, retinopathy of prematurity, and refractive errors. The primary ocular disease alone does not explain the degree of visual disturbance the patients are reporting. NOVL can last <24 h (with some patients even reporting resolution within the same clinic visit) or as long as 48 months. The mean time from onset to diagnosis is usually around 3 months and from diagnosis to resolution around 7 months [11].

Evidence for Effective Diagnosis and Treatment

Establishing a diagnosis of NOVL can be easily accomplished in the clinic. The different clinical tools used to determine whether a patient can see better than he or she claims depend on binocular or monocular involvement (Table 71.1).

Table 71.1 Clinical tests for binocular and monocular nonorganic visual loss

Binocular vision loss	Monocular vision loss
Observation	Fogging test
Signature test	Prism shift test
Proprioceptive test	Polarized glasses
Mirror test	Stereoscopic tests
Optokinetic reflex	
Menace reflex	
Tearing reflex	

For binocular vision loss, simple observation of the patient during consultation can clue in to the diagnosis [12]. Truly blind patients will maneuver themselves cautiously in the room and may bump into objects naturally. Those with NOVL have a tendency to exaggerate bumping into objects. While distracted, the examiner can pretend to drop something, and patients may unconsciously reach out or help with picking up said item [13]. In adults or teenagers, asking them to write their name or do proprioceptive tasks (touch fingertips together) can identify deliberate malingerers [14]. Blind patients do not have a problem with performing these tasks. Another tool is the "mirror" test wherein the examiner suddenly produces a mirror in front of a patient. This act involuntary induces the patient to look at self in the mirror with accompanying convergence, accommodation, and miosis [12]. The use of a rotating optokinetic drum to induce the optokinetic reflex, which relies on higher cortical function of smooth visual pursuit with corrective saccades, can aid in establishing binocular vision and corresponds to a visual acuity of at least 20/400. Other tests that may be especially useful in children include the "menace reflex" where visual threats are produced suddenly and patients are observed for flinching or blinking, "tearing reflex" where the use of strong illumination produces tearing, or something as simple as a goofy face or funny cartoon that can induce reaction in a child.

For monocular blindness, the goal is to demonstrate that the "abnormal" eye can see better than reported often by inducing ocular confusion. The fogging test blurs or "fogs" the "normal" eye without patient awareness through the use of high-diopter lens that is initially canceled out. The patient is repeatedly asked to read through the eye chart while the high-diopter lens over the "normal" eye is uncovered usually by rotating the cylinder to 90°. The "abnormal" eye is then tricked into reading the eye chart. Prism shift test employs the use of a 10-diopter prism placed base out in front of the "abnormal eye." Both eyes are expected to move in towards the apex if patient has normal binocular vision. Other methods include the use of polarized red/green glasses that allow patients only to read certain parts of the eye chart [12].

In children, usually repeated encouragement or cajoling is enough to demonstrate better than reported visual acuity [9]. Testing stereoacuity with Titmus stereo test also works well to establish binocular vision in patients who claim significantly reduced monocular vision [11]. Using a plano lens in children desiring glasses sufficiently improves their vision during the office visit [9].

Visual field testing in cooperative children with NOVL shows similar pattern to adults with spiraling visual fields, crossing diopters on Goldmann perimetry, unilateral defect under binocular vision, and non-expanding tunnel visual field at 1- and 2-m distance [10]. The presence of a central scotoma, however, usually warrants an investigation for organic pathology even if the rest of the examination is suggestive of NOVL. A study by Scott [15] in 2003 identified 133 patients labeled as having NOVL. Thirteen patients had a central scotoma and were subsequently diagnosed with retinal or optic nerve pathology on multifocal electroretinography.

Inconsistent performance on various tests is the hallmark of NOVL. Children more often than not are "suggestible innocents" rather than "deliberate malingerers" [16] which is why repeated encouragement and suggestions that they can see better satisfactorily improve their visual acuity to cinch the diagnosis. Bain et al. [6] report normal visual activity in 70 % of patients with NOVL during the first clinic appointment. Similarly, Taich et al. [9] describe visual acuity of 20/30 or better after initial visit.

Diagnostic testing is generally unnecessary if the examination is consistent with NOVL, and Thompson [16] stated that the use of ancillary ophthalmologic or neuroimaging tests may reinforce abnormal behavior. A study by Toldo et al. [11] in 2010 looked into the use of some ancillary studies—visually evoked potentials were obtained in 44/58 patients, all but one were abnormal due to preexisting amblyopia. In the same way, neuroimaging was performed in 22/58 patients, and all were normal except for one with temporal low-grade astrocytoma excised prior to onset of NOVL.

Several authors over the years have described prevalence of psychologic or psychiatric disorder among patients with NOVL [3, 5, 9, 10]. In children, NOVL is less associated with organic disease or psychiatric disease when compared to adults. Incidence of true malingering is higher in the older population and usually occurs after eye trauma [10]. More frequently than a psychiatric diagnosis, 60–70 % of children have social disturbances in the home or school setting [6, 7, 11]. Toldo et al. [11] describes commonly encountered family stressors which include parental disease, death in family, parental separation or divorce, sibling birth or jealousy, strict parents, and adoption. School stressors included bullying, upcoming tests, difficulty with peer socialization, and new school. Preexisting medical illness is also a prevalent stressor especially in patients with chronic headaches or migraines with visual auras [10]. Although most authors believe that psychiatric evaluation is unnecessary in these patients [1, 6, 7, 14], a certain subset may require evaluation by mental health specialists. Taich et al. [9] describe 26.7 % of patients

in their study having concomitant anxiety, depression, and ADHD. Furthermore, these authors identified that patients complaining of monocular vision loss with eye pain had underlying either psychiatric disturbance, with 2 out of 4 suffering sexual abuse. Likewise, Lim et al. [10] report 17.9 % of children with psychiatric disorders in their series, with 3.6 % suffering sexual abuse. Clinicians should maintain a certain level of suspicion in cases with overt psychiatric manifestations and inquire appropriately as to possibly contributing psychosocial factors and when appropriate possible physical or sexual abuse.

Management

The cornerstone of management for NOVL is reassurance. Once diagnosis is established, the ophthalmologist should inform the child and the family that vision is good and there is nothing to suggest that patient's vision should get worse over time. Reassurance alone is better than adding other placebo treatment like non-medicinal drops or weak glasses [1]. Follow-up is essential and strengthens the initial diagnosis as there is usually improvement on subsequent visits. Normalization of one "abnormal" parameter during follow-up occurs in up to 85 % of NOVL patients especially in children [10]. Prognosis is excellent with the resolution of NOVL in 85 [11]–93 % [10] within the first year. Referral to a counselor or child psychologist is imperative if any spychological, psychiatric or cosial issues are suspected. When normal vision is not demonstrated on repeated follow-up, additional workup for organic disease should be considered. Rate of misdiagnosis in NOVL is low (2.2 % [10]). Nevertheless, if normal visual function is not proven and exam is not completely normal, consideration for early-onset macular dystrophy, hereditary optic neuropathy, or retinopathy is warranted. Common diagnoses that were initially diagnosed as NOVL include Stargardt disease, cone dystrophy, and Leber's hereditary optic neuropathy (LHON) [9, 10].

Pearls

1. Consider a diagnosis of NOVL in children whose eye examination findings do not match the low level of vision they exhibit.
2. Do not miss cases of retinal (Stargardt disease). Spectral domain optical coherence tomography and/or fundus autofluorescence can aid in the diagnosis as retinal findings may not be readily visible on fundus exam early in the disease.
3. Evaluate pupils carefully in terms of size, reactivity, and the presence or absence of an afferent pupillary defect. Pupils are objective, whereas visual acuity and other testing are subjective.
4. Do not assume that the child with NOVL just wants glasses. Judiciously ask questions that may uncover underlying stressors or social or psychiatric disturbances.
5. Make sure you document an improvement of vision at some point to seal the diagnosis.
6. Consult the appropriate psychologist or counselor in cases where anxiety or other similar factors are at play.

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Part XVI

Retinoscopic Techniques

Basic Retinoscopy

72

Gonzalo Vike Vicente

This chapter highlights the major principles and technique for obtaining an objective refraction by retinoscopy.

Introduction to Retinoscopy

- Retinoscopic refraction allows the examiner to objectively determine a patient's refractive error and to prescribe proper glasses.
- This technique is very useful in nonverbal or preverbal patients and those with inconsistent responses to a subjective refraction.
- The results may be affected by the patient's accommodation, and therefore, the patient should be fully cyclopleged (or be cooperative enough to consistently focus on a distant target).

Cycloplegia

- In addition to control of accommodation, a larger, dilated pupil will make it easier for the examiner to see a larger red reflex.
- Cycloplegia may be obtained by the following age-based regimens (variations exist among practices):
  - ≤6 months of age: 1 drop OU of cyclopentolate 0.5 %/phenylephrine 2.5 %.
  - 6 months to 12 years: 1 % cyclopentolate.
  - ≥13 years: 1 % tropicamide and 2.5 % phenylephrine for 13 years and older.
  - Patients with dark eyes may require two sets of drops 5 min apart.
- It is important to avoid overdosing young patients as they will be more susceptible to anticholinergic effects such as gastroparesis, psychosis, flushing, etc.

Loose Lenses Versus Phoropter

- For young patients who cannot sit at the phoropter, trial lenses may be used.
- One advantage of loose trial lenses is that they can be superimposed, simulating the phoropter. Make sure to hold them close to the child's eye, especially in higher powers.
- A phoropter can be used in older children. It is useful if the phoropter has an "R" setting. This places a +1.50 sph lens over the eye and allows the examiner sitting 66 cm to measure the refraction without having to subtract the working distance.

The Retinoscope: Sleeve Position

- Retinoscopes are made by different manufacturers and may have different sleeve positions. They will have a sleeve up or sleeve down position (Fig. 72.1a).
- It is important to use the sleeve position that produces a divergent light (Fig. 72.1b).
- If the sleeve is in the proper position, the streak of light will be divergent and cannot be focused on a wall at any distance (Fig. 72.1b–d).
- For animated simulation, please see online version of this chapter (Ch72_online animation).

Electronic supplementary material: The online version of this chapter (doi:10.1007/978-1-4939-2745-6_72) contains supplementary material, which is available to authorized users.

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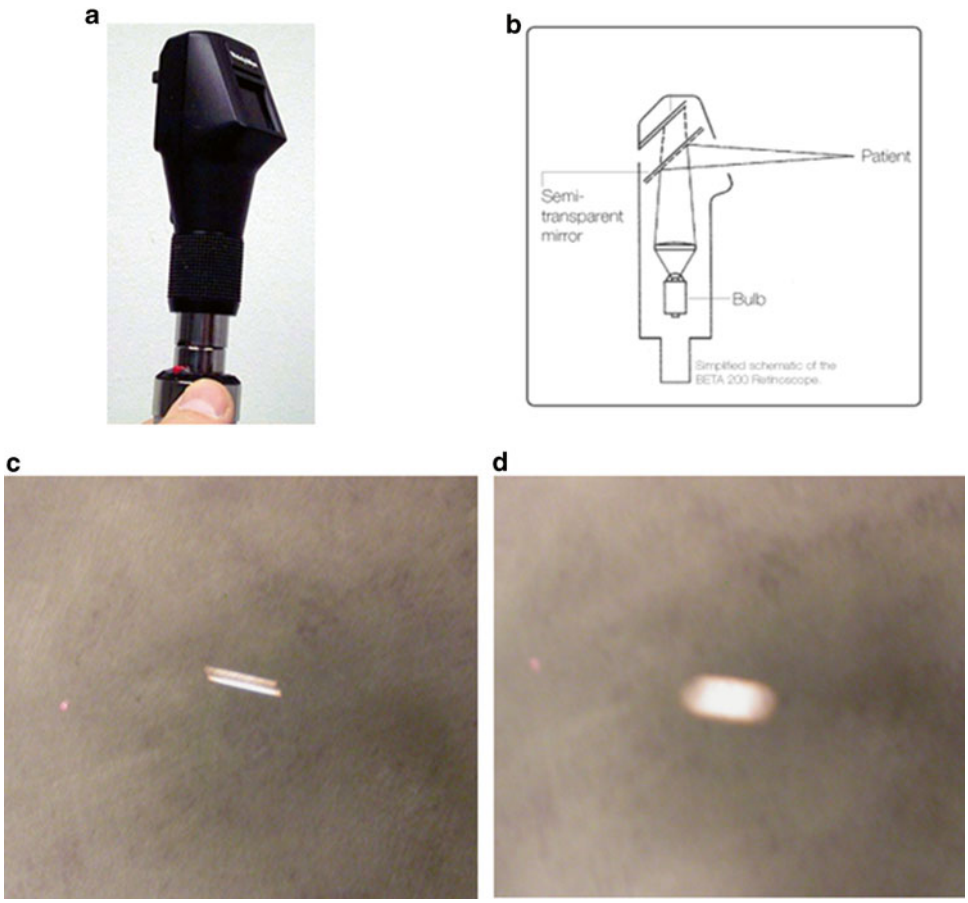

Fig. 72.1 (**a**) Example of a retinoscope. (**b**) Streak retinoscope bulb has linear filament, and sleeve position varies among instruments. The sleeve should be moved up or down to produce divergent light. (**c**) Sleeve position is not correct because light is focused on the wall. This position may be used to refine astigmatic axis. (**d**) Sleeve position is correct because light is divergent and cannot be focused on the wall

Examiner Positioning and Technique

- The examiner and retinoscope should be 66 cm away from the patient. The reciprocal of this working distance, 1.50 D should be subtracted from the final prescription to place the far point of the patient at infinity.
- If retinoscopy is performed on a patient's right eye, the examiner should use his or her right eye and hold the retinoscope in their right hand. This will allow the patient to look past the examiner's right shoulder at a distant target.
  - *If the examiner is too far to the right or left of the patient, a false plus cylinder error will be induced at 180°.*
- As the rectangular light intercept is swept across the pupil, it will create a red reflex that moves or fills the pupil (end point of refraction). The rectangle's long axis should be parallel with the direction in which it is being swept. The light rectangle should be vertical if it is being swept left to right across the 90° axis (Fig. 72.2).
- If the patient's far point is behind the examiner (hyperopia), the red reflex will move in the same direction as at the light intercept; this is called "with motion." Plus lenses should be added to converge the red reflex light and bring the far point onto the examiner until the "with motion" is neutralized and the pupil fills in (Fig. 72.3).
- If the patient's far point is between the patient and the examiner (myopia), the red reflex will move in the opposition direction as the light intercept "against motion." Minus lenses should be placed until the motion is neutralized and the light is diverged away from the patient, onto the retinoscope (Fig. 72.4).
- If the patient has astigmatism, a different red reflex motion will be observed in different axes. If you are working in the plus cylinder form, neutralize the most minus or against motion first, and then add sphere or cylinder power at the axis 90° away.
- If you use trail lenses, you can determine the axis of astigmatism by aligning the with reflex against a neutralized minus axis with the streak movement; then you would neutralize the with movement in that axis by superimposing plus cylinder lenses on top of the minus lens that neutralized the more myopic axis.

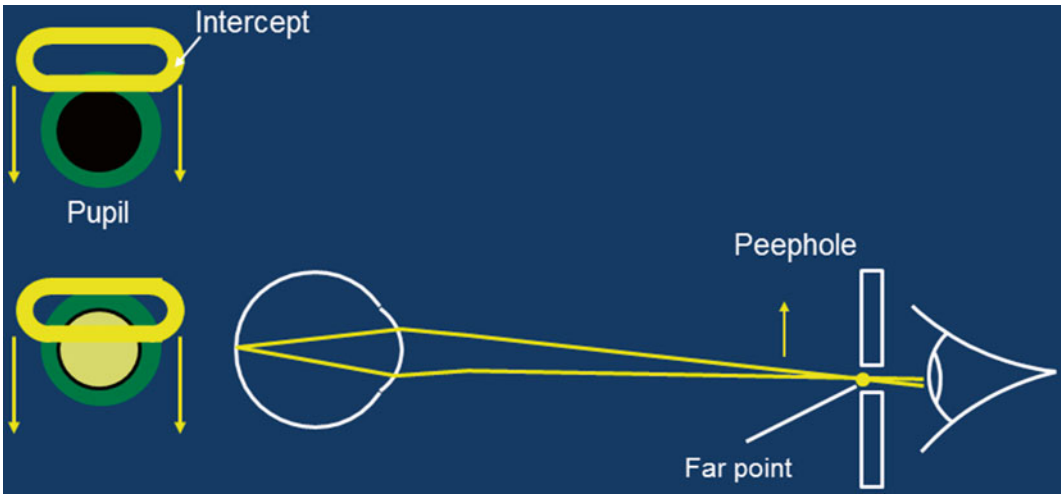

Fig. 72.2 Neutralization occurs when the far point is at the peephole of the retinoscope. This is the end point of refraction

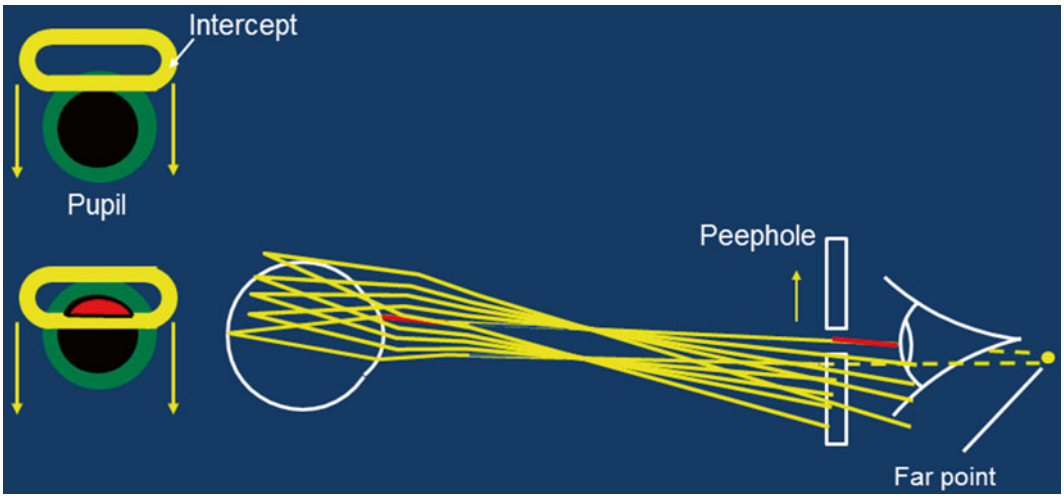

Fig. 72.3 Example of "with movement." The far point is behind the examiner. Plus lenses are needed to neutralize the refractive error

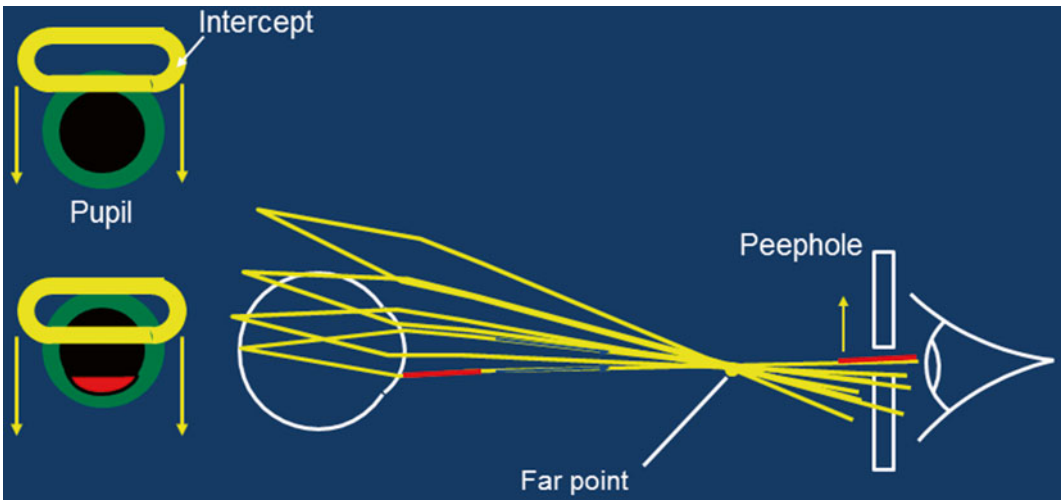

Fig. 72.4 Example of "against movement." The far point is in front of the patient. Minus lenses are needed to neutralize the refractive error

Dynamic Retinoscopy

73

Gonzalo Vike Vicente

This chapter highlights the principles and technique for performing dynamic retinoscopy.

Introduction to Dynamic Retinoscopy

- Technique used to evaluate a patient's ability to accommodate
- Indications:
  - Patients with esotropia
  - Patients with asymptomatic high hypermetropia
  - Subjective complaints of blurred near vision, headaches, or eye strain
  - Patients with Down syndrome or developmental delay
  - Other conditions where inability to accommodate is suspected
- If accommodative deficiency is present, the patient may benefit from reading glasses or a bifocal.

Technique

- Perform prior to dilation or the use of cycloplegic drops and with the patient's refractive correction in place.
- The examiner should be standing at a near working distance from the patient, i.e., 33 cm (Fig. 73.1).
- In one hand the examiner should hold a near accommodative target such as small print on a popsicle stick/tongue depressor. For younger patients, a sticker with fine detail may work better.
- The retinoscope is held in the other hand at the same distance as the target.
- Ask the subject to fixate on distant target and assess retinoscopic reflex ("with motion" should be observed).
  - Check in several meridians in case astigmatism is present.
- The patient tries to read or focus on the near target while the light intercept is swept across the pupil.
- If the patient can accommodate, the "with" motion should quickly change to neutralization (the pupil "fills in"), or "against" movement is observed (see Chap. 73_online animation).
- Normal accommodative effort can be described as brisk and sustained.
- Examples of abnormal responses indicating hypoaccommodative ability include:
  - Reflex still shows "with motion" as the patient is attempting to accommodate on the near target; this shows accommodative deficiency (see Chap. 73_online animation).
  - Accommodative lag: If the accommodative effort at near is equivocal, the accommodative target should be advanced toward the patient while maintaining the retinoscope at the same distance until neutralization, or unequivocal against movement is observed. The target is then moved back toward the retinoscope until with motion is observed (to ensure that the child was not initially inattentive). If the accommodative target has to be moved >1–2 cm in front of the retinoscope to achieve neutralization, the patient likely has accommodative lag. They are able to accommodate, but not fully and accurately. (Please see references for more detailed instructions.)

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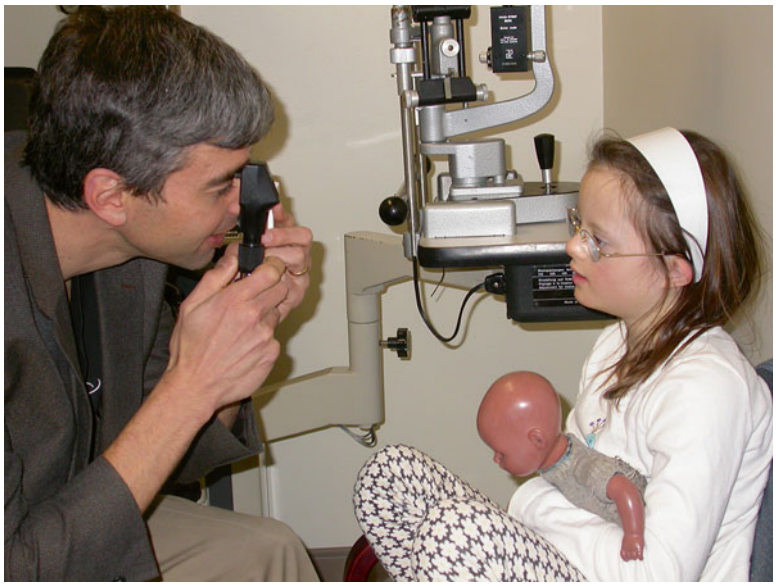

Fig. 73.1 Examiner position when performing dynamic retinoscopy. The examiner holds the near target close to the peephole of the retinoscope. In this case a fixation cube is utilized

  - Other abnormal responses include incomplete accommodation, a brisk accommodative response that is not sustained, and asymmetric accommodation.
- In older, cooperative children, the clinician can quantify the accommodative effort by neutralizing the reflex when the patient is focusing at the distance and at near target respectively.

Suggested Reading

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Appendix 1: Prescribing Practices for Refractive Errors in Pediatric Patients

Virginia Miraldi Utz

This appendix serves as a guideline for prescribing glasses in isoametropic patients (based on specialist experience, Table A1.1), anisometropic patients (Table A1.2), and automated screening guidelines (Table A1.3). Table A1.4 lists the refractive risk factors for amblyopia.

Prescribing practices are based on specialist experience with the following considerations:

1. Assessing visual needs according to the child's age:
   - Children have high accommodation amplitudes, and therefore, mild to moderate hypermetropia does not require correction in the absence of signs such as esotropia or asthenopic or visual symptoms (see Chap. 3 on Hypermetropia).
   - Infants and very young children are most interested in objects at an arm's length up to 2 m from them, and therefore, low levels of myopia are easily tolerated. In contrast, school-age children may benefit from correction of low levels of myopia to meet visual demands of school activities' viewing (see Chap. 4 on Myopia).
2. The prescription must be based on cycloplegic refraction. There are several eye drop regimens utilized depending on age and iris pigmentation:
   - ≤6 months of age: one drop OU of cyclopentolate 0.5 % and phenylephrine 2.5 %.
   - 6 months to 12 years: 1 % cyclopentolate.
   - ≥13 years: 1 % tropicamide and 2.5 % phenylephrine.
   - Patients with dark eyes may require two sets of drops 5 min apart.
3. Whenever possible, the cycloplegic refraction should be subjectively manifested to ensure that vision improves. For example, a small change in axis in a patient with high astigmatism may greatly improve the visual acuity and hence the quality of vision for the patient.

Table A1.1 Practice patterns generated by consensus for prescribing refractive correction

	<1 year	1–2 years	2–4 years	4–7 years
Miller and Harvey [1][a]				
Myopia	−4.50[a]		−3.00[a]	−2.00[a]
Hypermetropia	+5.50[a]		+5.00[a]	+4.50[a]
Astigmatism	+3.00[a]		+2.50[a]	+2.00[a]
AAO PPP [2]				
Myopia	≥−5.00	≥−4.00	≥−3.00	No specific numbers, prescribe based on symptoms
Hypermetropia	≥+6.00	≥+5.00	≥+4.50	
Hypermetropia/ET	≥+2.50	≥+2.00	≥+1.50	
Astigmatism	≥+3.00	≥+2.50	≥+2.00	

[a]Numbers based on 75 % (majority) of American Association for Pediatric Ophthalmology and Strabismus (AAPOS) members would prescribe glasses.
AAO American Academy of Ophthalmology, *PPP* Preferred Practice Patterns

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Table A1.2 American Academy of Ophthalmology Preferred Practice Patterns for treating patients with anisometropia without strabismus [2]

	<1 year	1–2 years	2–3 years
Myopia	≥−4.00	−3.00	−3.00
Hypermetropia	+2.50	+2.00	+1.50
Astigmatism	2.50	2.00	2.00

Table A1.3 American Association for Pediatric Ophthalmology and Strabismus Vision Screening Committee Guidelines for automated preschool screening of refractive error [3]

	12–30 months	31–48 months	≥49 months
Hypermetropia	≥+4.50	≥+4.00	≥+3.50
Astigmatism	≥+2.00	≥+2.00	≥+1.50
Anisometropia	≥+2.50	≥+2.00	≥+1.50

Table A1.4 Refractive amblyogenic risk factors [4]

Anisometropia (spherical or cylindrical): >1.5 D
Hyperopia > 3.5 D in any meridian
Myopia > 3.00 D in any meridian
Astigmatism > 1.5 D at 90 or 180
Oblique astigmatism > 1.0 (>10° eccentric to 90° or 180°)

Appendix 2: Strategies for the Child Who Would Not Wear Glasses

Sarah L. Lopper

In this appendix, we explore possible causes of intolerance to glasses. We will look for possible errors related to the prescription, the manufacturing of the lenses, or the fit of the frame. We will also consider issues related to behavior or intolerance to foreign objects on the child's face. Finally we will explore errors related to the initial examination and original prescription.

I. The Prescription Is Not Accurate or There Is an Optical Problem with the Lenses

1. Step 1: Examine the optics of the glasses.
   - Verify that the lenses were made as prescribed: Optical labs grind lenses in minus cylinder format, and it is possible that the glasses prescription was transposed incorrectly if it was written in plus cylinder format.
   - Use a lensometer to measure the glasses prescription and confirm it was made as prescribed.

Clinical Skill: Nonautomated Lensometry

- Step 1. Place the lens on the lensometer. Secure after finding the intersection of both sets of lines, and place this in the center of the lensometer eyepiece view.
- Step 2. Turn the power wheel back and forth to focus each set of lines. If both sets of lines are in focus at the same time (the single thicker lines and the set of three striped lines), then there is no cylinder present and the lens is spherical power only.
- Step 3. If each set of lines is best focused at a different position on the power wheel, then there is cylinder present to correct for astigmatism. Focus each set separately, and adjust/determine the axis so the lines are exactly straight.
- Step 4. Note power of best focus; the least plus/most-minus set of lines is the sphere and the difference in power strength until the next set of lines is in focus is the amount of cylinder (astigmatism) in the lens if you are documenting in plus-cylinder format.

Clinical Skill: Lens Transposition from Plus to Minus Cylinder

- Step 1. Add the sphere and cylinder together to get the new spherical power.
- Step 2. Change the sign of the cylinder (+ becomes − and − becomes +); do not change the amount of the cylinder.
- Step 3. Change the axis by 90°.
- Example 1: $+3.25 + 2.50 \times 135$ in plus cylinder format becomes $+5.75 - 2.50 \times 045$ in minus cylinder format.
- Example 2: $+3.25 - 2.50 \times 135$ in minus cylinder format becomes $+0.75 + 2.50 \times 045$ in plus cylinder format.

2. Step 2: Verify that the lens is well centered in front of the child's visual axis.
   - The optical center of the lens is the point on the principle axis of the lens through which light passes undeviated, and this should be aligned with the patient's visual axis.
   - The optical center of the lens can be measured and marked with a lensometer. Find the intersection of the two sets of lines in the center of the lensometer eyepiece view, and use the self-recoiling lens marker to make a dot on the lens center.
   - Place the glasses on the patient and determine if the mark matches the center of their pupils. If there is significant horizontal or vertical displacement, the child may not be seeing well because of an induced prismatic effect, especially in higher prescriptions.
     - Prentice's law applies to the amount of induced prism:
       $P = dF$ where P is the prism power in Δ, d is displacement in centimeters, and F is the refracting power of the lens

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3. Step 3: Consider distortions related to polycarbonate material:
   - The Abbe value (range 20–60) describes the amount of chromatic aberration of lens materials and is intrinsic to the specific refractive index of the lens material [5]. Lower Abbe values have more aberrations (spherical aberration, coma, marginal astigmatism, curvature of field, and distortion) and are most pronounced with increasing distances from the center of the lens. Aberrations are more significant in higher plus or minus lenses.
     – Polycarbonate has an Abbe value of 30.
     – CR-39 and Crown glass have Abbe values of 58.

4. Step 4: Consider a defect in or an inappropriate base curve of the lens.
   - Measure base curve of the lenses with a lens clock. They should be no steeper than 7 diopters or flatter than 4 diopters in two primary meridians 90° apart.
   - Lower number = flatter base curve and higher number = steeper base curve.
   - Patients may prefer their "old" glasses with a different base curve than the "new" glasses. Matching previous base curve can help.

5. Step 5: Consider aniseikonia in patients with significant anisometropia.
   - This can be corrected with base curve adjustments or contact lenses.

II. The Glasses Are Not Manufactured Well or Are Not Fitting Well

- When glasses are fitted, several measurements are taken to ensure a proper fit. If there are deviations from these initial fitting measurements, the effective power of the lenses may change and affect visual acuity, or the child may complain of asthenopia.
  – *Vertex distance*: The posterior surface of lenses should generally be 12–15 mm from the corneal plane. This becomes especially significant when lens power is above 5–6 diopters.

Increasing vertex distance	Makes a "plus" lens more "plus"	Makes a "minus" lens less "minus"
Decreasing vertex distance	Makes a "plus" lens less "plus"	Makes a "minus" lens more "minus"

  – *Pantoscopic tilt:* The angle of tilt of the lower rim of the glasses frame toward the cheek. A normal amount of pantoscopic tilt is approximately 10° (±5°). This is taken into account when the frame is fitted. For every 2° of pantoscopic tilt, the optical center is lowered 1 mm [6]. Companies make tools to measure pantoscopic tilt, or you can simply use a protractor. Place the vertical straight edge of the protractor parallel to the floor. The pantoscopic tilt is the angle that is made between the lens and the temple when the 90° mark is aligned with the temple.
  – *Face form*: the wrap of the frame around the face. If there is too much face form or unequal face form for the right and left lenses, the patient will not be looking through the optical center of the lens and the vertex distance is affected.
- Poorly fitting frames:
  – Frames that are too tight on a child's cheeks or those that pinch behind their ears will not be comfortable.
  – Nose pads that are not adjusted appropriately or missing will be uncomfortable.

III. Behavioral Issues

- Behavioral problems of the child may limit success with glasses.
- Sometimes children just do not like the color or style of their frames anymore or they do not want to wear them anymore due to peer pressure from classmates.
- In addition, some patients with Down syndrome or pediatric patients with sensory integration disorders such as autism spectrum disorder may have difficulty adjusting to glasses.
- Discuss with a co-managing occupational therapist to see if the glasses can be integrated into their therapy session or look for additional strategies that might increase compliance.

IV. There Is a Change in the Child's Refraction, a Binocular Vision Disorder, or a New or Previously Undetected Eye Problem

- Repeat the cycloplegic refraction and subjectively manifest if the patient is able.
- Consider cycloplegic eye drops to help the child adjust/accept the hyperopic correction.
- Rule out a binocular vision disorder or accommodative dysfunction.
- Perform a dilated eye exam to rule out ocular health changes.

Appendix 3: Prescribing Prisms for Pediatric Patients

Sarah L. Lopper

Goals of Prismatic Correction

- Restore binocularity and/or fusion
- Relieve or eliminate diplopia
- Alleviate abnormal head position
- Relieve asthenopic symptoms

Steps for Determining and Prescribing Prismatic Correction (Table A3.2)

(1) Always correct refractive error first. Perform a cycloplegic refraction with subjective manifest whenever possible.
(2) Prismatic correction is best tolerated with smaller angle and comitant strabismus.
(3) Perform a prism adaptation trial for 20–30 min.
(4) Demonstrate effectiveness first with Fresnel prism prior to grinding into the lens.
(5) If there is both a vertical and a horizontal deviation, determine first if the vertical deviation is the primary or secondary deviation. If it is the primary deviation, address the vertical deviation first.
(6) Larger amounts of prism add to lens thickness and weight, cause image distortions, and give the lens a poor appearance. Smaller lens, eye size, high index lens material, antireflective coating, and lens edge treatments can all improve prism lens appearance [8]. As a general guideline, 1Δ adds 1 mm of lens thickness [9].
(7) Fresnel prism is available up to 40Δ, but prisms larger than 8–10Δ start having a poorer optical quality and will cause increased reflections and a decrease in visual acuity and contrast sensitivity. Use on the non-dominant eye, Fresnel lenses change color over time.
(8) Sector Fresnel prism can be applied to just a portion of the lens (e.g., "A" or "V" pattern deviations, noncomitant strabismus, hemianopic visual field loss).
(9) Consider prism in the following cases (Table A3.1):
    - Blow out fracture (Fresnel)
    - Nystagmus (place null point in primary position)
    - After retinal surgery (if small-angle strabismus and/or anisometropia with diplopia)
    - Sixth nerve palsy (adjusting Fresnel prism as angle changes)
    - Thyroid disease [10] (Table A3.2)

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Table A3.1 Indications for prismatic correction in pediatric patients

Short-term indications	• To prevent symptoms and/or maintain binocularity while awaiting surgical intervention • Nystagmus with head turn (e.g., to rotate null position to primary)
Long-term indications	• Surgical intervention is not a viable option (patient is medically unstable) • Awaiting resolution of a cranial nerve palsy • Evolving deviation (e.g., thyroid disease) • Incomitant strabismus to move area of single vision straight ahead • Homonymous hemianopia • Surgical correction unpredictable (e.g., phorias, divergence insufficiency, small vertical deviations)
Contraindications, prism is not helpful/ less helpful	• Large stable comitant strabismus • Significant incomitant strabismus • Dragged foveal diplopia syndrome

Table A3.2 Approach to prismatic correction for horizontal and vertical deviations

Type of deviation	Prescribed prism	
Horizontal deviation	EXO: BI prism ESO: BO prism	• Options: Ground-in prism, Fresnel prism • BI in front of either eye for EXO deviation • BO in front of either eye for ESO deviation • Split the prism if above 3Δ • Ground prism best if ≤10Δ per lens • Trial of prismatic correction and confirmation of fusion may be utilized in older children
Vertical deviation	Left hyperdeviation: BU OD, BD OS Right hyperdeviation: BU OS, BD OD	• Options: Ground-in prism, Fresnel prism, slab-off prism (if vertical disparity distance/near), lens decentration (helpful in moderate- to high-powered lenses only, use Prentice's rule[a]), contact lenses (small amounts, only vertical prism) • BD in front of hyper-eye • Split the prism between the eyes if above 3Δ • Ground prism best if ≤10Δ per lens • Superior oblique palsy, DVD, Brown syndrome, inferior oblique paresis

BI base in, *BO* base out, *BU* base up, *BD* base down
[a]Prentice's rule: $P = dF$ where P is the prism power in Δ, d is displacement in centimeters, and F is the refracting power of the lens

Appendix 4: Pathogens and Medications for Infectious Conjunctivitis in Children

Alison E. Smith

As discussed in Chap. 9, Pediatric Conjunctivitis, bacterial and viral infections cause most infectious causes of conjunctivitis. Patients who present within the first month of life with conjunctivitis, termed ophthalmia neonatorum, have specific pathogens associated (Table A4.1) and require urgent ophthalmologic and systemic evaluation and treatment (Tables A4.2 and A4.3). Although the medications presented in these tables serve as a general guide, cases of ophthalmia neonatorum should be co-managed with a pediatric infectious disease specialist. For other forms of pediatric conjunctivitis, the most common etiologic agents are listed in Table A4.1. Depending on pathogen, pharmacologic treatment can be catered accordingly to etiologic agent (Table A4.2). In most cases of suspected bacterial etiology, empiric treatment is started with broad-spectrum coverage (Table A4.2). Unlike bacterial etiologies, viral etiologies usually require supportive care as discussed in Chap. 9 (Pediatric Conjunctivitis).

Table A4.1 Common bacterial and viral pathogens associated with conjunctivitis in children

Bacterial conjunctivitis	*Staphylococcus aureus* *Streptococcus pneumonia* *Haemophilus influenzae* *Moraxella catarrhalis*
Ophthalmia neonatorum (neonatal conjunctivitis)	*Neisseria gonorrhoeae* *Chlamydia trachomatis* Herpes simplex
Viral conjunctivitis	Adenovirus Herpes simplex (usually keratoconjunctivitis) Enterovirus (usually hemorrhagic) Coxsackievirus (usually hemorrhagic) Varicella zoster Picornavirus

Table A4.2 Medications, dosages, and classification of topical and systemic therapy for bacterial conjunctivitis

Generic name	Trade name	Dosing	Class of antibiotics
Erythromycin		4–6 times daily	Macrolide
Trimethoprim and polymyxin B	Polytrim	4–6 times daily	
Tobramycin drops or ointment	Tobrex	4–6 times daily	Macrolide
Zymaxid	Zymar	4–6 times daily	Fluoroquinolone
Erythromycin	Romycin	4–6 times daily	Macrolide
Gentamicin drops or ointment	Gentak	4–6 times daily	Macrolide
Azithromycin (oral)[a]	Azasite	Day 1 two doses then once daily for 5 days	Macrolide
Levofloxacin		4 times daily	Fluoroquinolone
Besifloxacin	Besivance	4 times daily	
Ciprofloxacin	Ciloxan	4 times daily	Fluoroquinolone
Gatifloxacin		4 times daily	
Ofloxacin	Ocuflox	4 times daily	Fluoroquinolone
Moxifloxacin	Vigamox/ Moxeza	4 times daily	Fluoroquinolone

[a]Oral medication dosages should be adjusted for age, and if in doubt, consult a pediatric infectious disease specialist.

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Table A4.3 Medications and dosages utilized in ophthalmic neonatorum (neonatal conjunctivitis)

Generic name	Dosing	Mechanism of action
Ceftriaxone	IM or IV 25–50 mg/kg once	Cephalosporin (3rd generation)
Cefotaxime	IV 1 g q 8 h for at least 7 days	Cephalosporin (3rd generation)
Erythromycin	PO 50 mg/kg/day q 6 h/14 days	Macrolide
Azithromycin	PO, IV 20 mg/kg qd for 3 days	Macrolide

Appendix 5: Medications Commonly Used in Allergic Conjunctivitis Treatment

Alison E. Smith

The following medications are utilized in cases of allergic conjunctivitis (Table A5.1). Most patients should be treated with an H_1-antagonist ± mast cell stabilizer, and families should be educated that medications are for symptom prophylaxis and take 1–2 weeks to be fully effective. In cases of severe allergic conjunctivitis, topical steroids may be utilized adjunctively while awaiting the efficacy of the H_1 antagonist/mast cell stabilizer or for breakthrough symptoms while on these medications. Cyclosporine may be utilized as well for steroid-sparing therapy in severe cases.

Table A5.1 Medications and dosages of medications utilized to treat allergic conjunctivitis

Generic name	Trade name	Dosing	Mechanism of action
Olopatadine Ketotifen Azelastine hydrochloride 0.05 %	Pataday/Pazeo Patanol Zaditor Alaway Optivar	Once daily Twice daily Twice daily Twice daily Twice daily	H_1 antagonist/mast cell stabilizer
Prednisolone 1 %	Pred Forte Omnipred	4–6 times daily	Corticosteroid
Fluorometholone 0.1 %	FML Forte Flarex FML Liquifilm	4–6 times daily	Corticosteroid
Loteprednol 0.2 %	Lotemax Alrex	4–6 times daily	Corticosteroid
Rimexolone 1 %	Vexol	4–6 times daily	Corticosteroid
Restasis	Cyclosporine	2 times daily	Calcineurin inhibitor

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Appendix 6: IOL Power Selection for Children

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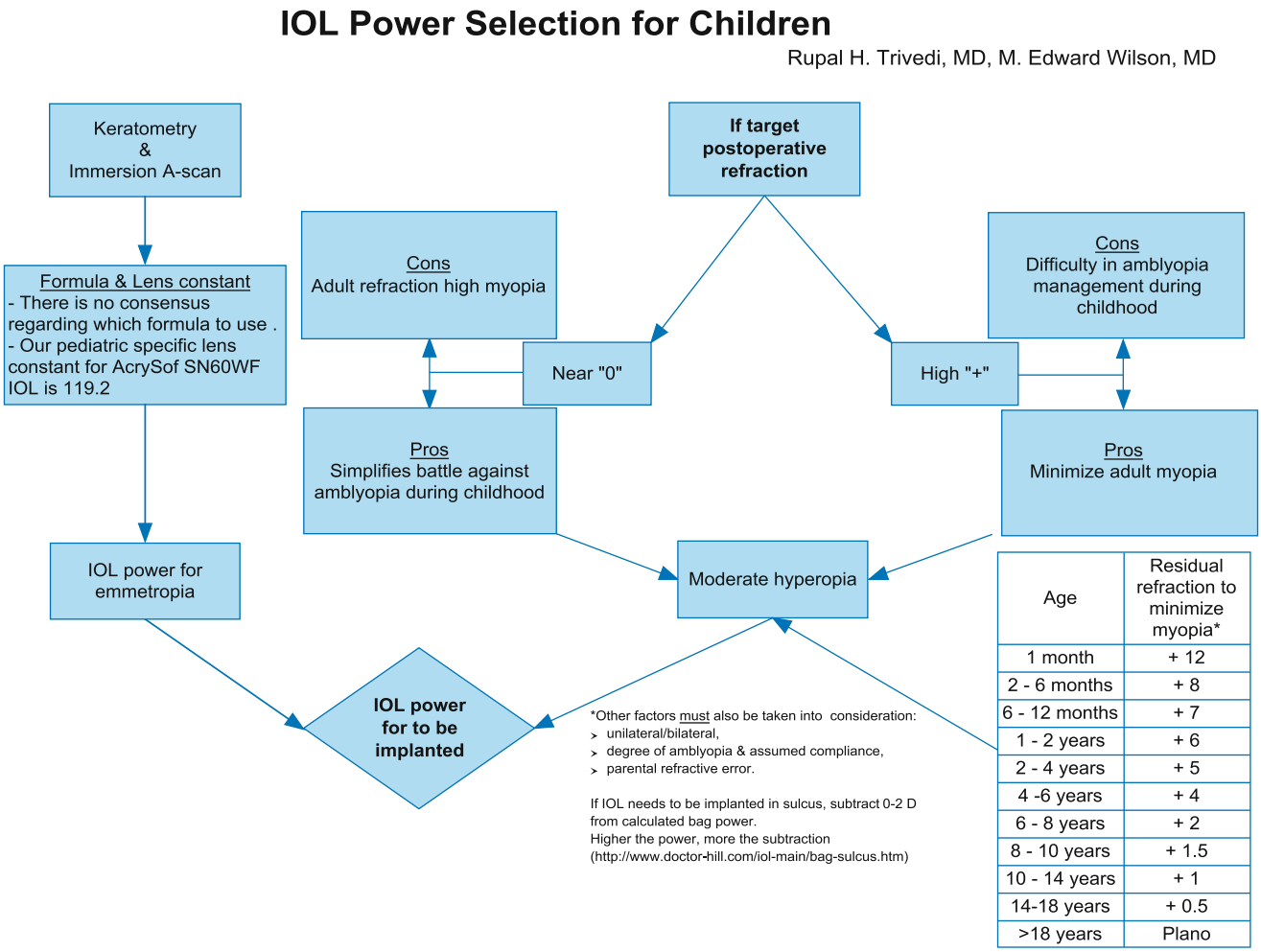

Fig. A6.1 This algorithm (Fig. A6.1) is utilized by the authors to determine intraocular lens power to be implanted based on age at the time of surgery. Factors such as status of the contralateral eye, presence or absence of amblyopia, and familial refractive error need to be considered. Figure A6.1 has been modified and refined based on surgical results of the authors [Table modified from: Trivedi, RH, Wilson, ME, Ophthalmic Pearls: Selecting Intraocular Lens Power in Children. EyeNet Magazine, January 2006]

Appendix 7: Measuring Axial Eye Length in Children

Fadia AlKhawaldeh

In order to determine the correct power for an intraocular lens implant, it is necessary to obtain axial eye length (AEL) and keratometric measurements on the patient. The technique for obtaining these measurements varies depending on the age of the child and his or her physical ability to cooperate during testing.

For most children under the age of 6 or 7 years, a sedated immersion technique performed in the operating room prior to surgery or during a sedated eye exam is best. For children over the age of 7, the ultrasonographer is able to use his/her best judgment to assess the child's ability to cooperate and to follow instructions. If the child is cooperative and able to follow directions, the instrument of choice is the IOL Master® for accurate AEL and keratometric readings. If the child is uncooperative, combative, or unable to comprehend or follow verbal instructions, a sedated immersion technique is preferred.

Using IOL Master® for Axial Eye Length Measurements

When attempting to measure AEL on a child, it's important to ensure that the child understands fully what is about to take place. This will help alleviate any anxiety they may be experiencing due to the impending test, in addition to ensuring their best cooperation and efforts are put forth. To begin with, the ultrasonographer should explain to the patient and his or her parent/guardian what they are about to do in simple terms so the child understands. Then instruct the patient to place his or her chin in the chin rest and focus on the central light. Playing games such as "statue" and staring contests help the child focus and make the test less intimidating. This not only ensures a more a more accurate measurement but the full cooperation of the child as well.

Sedated Immersion A-Scan

For infants, children under 7 years of age, and those who are combative or unable to follow directions, a sedated immersion A-scan is necessary in order to obtain the axial eye length and keratometric measurements required for IOL calculations. This procedure is typically performed under full anesthesia in an operating room environment.

Once the child has been fully inducted and sedated, the ultrasonographer begins by using a handheld keratometer to obtain corneal keratometric measurements for each eye. In order to ensure consistency and accuracy, three separate readings should be taken. Once the keratometric readings are obtained, a plastic scleral shell measuring between 16 and 20 mm is placed directly on the eye and filled with sterile saline solution. The saline solution acts as a medium for the A-scan sound waves to travel through. Next, the ultrasonographer engages the machine using the foot pedal and obtains the requisite axial eye length measurements. Again, a minimum of three should be obtained to ensure accuracy. The procedure is repeated for the fellow eye, thus ensuring all measurements and calculations are complete for future surgical procedures when necessary. Additionally, this allows the ultrasonographer and surgeon to assess for any anatomical differences between the eyes and adjust the calculations and treatments accordingly.

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At this point, the axial eye length measurements are complete, and the physician is able to determine the necessary lens power needed for the IOL implant (see Appendix 6).

If the surgeon's view of the retina is obstructed due to the density of the cataract, he or she may request a B-scan to be performed at the same time. If a B-scan is required, the ultrasonographer will then switch from the A-scan probe to the larger B-scan probe. A gel is used as a coupling agent on the eye to allow for better sound wave penetration, and the ultrasonographer will conduct a full sweep of the eye in all four quadrants and at the cardinal positions of 12, 3, 6, and 9 o'clock. If any abnormal findings are observed, they are reported and their location is documented and addressed by the surgeon accordingly.

Appendix 8: Surgical Instrumentation in Strabismus Surgery

Elias I. Traboulsi

Each surgeon has his/her preference for instruments to use for strabismus surgery. The accompanying photograph (Fig. A8.1) shows a tray with commonly utilized instruments that are sufficient for the performance of most strabismus procedures. A number of modified hooks and other types of needle holders, speculums, and forceps can be selected by the individual surgeon.

Proper cleaning and storage of instruments is critical. Tips of instruments need to be protected to maintain their shape and sharpness. Cross-action scissors and needle holders need to be released before storage in carrying trays to maintain their straightness and rebound flexibility. Fine-needle holders should not be used with large needles. For example, the fine/very fine-needle holder shown in the illustration should not be used to hold needles large than 6-0 gauge. This allows the jaws to hold smaller needles firmly, facilitating suture passage in tissues without wobbling.

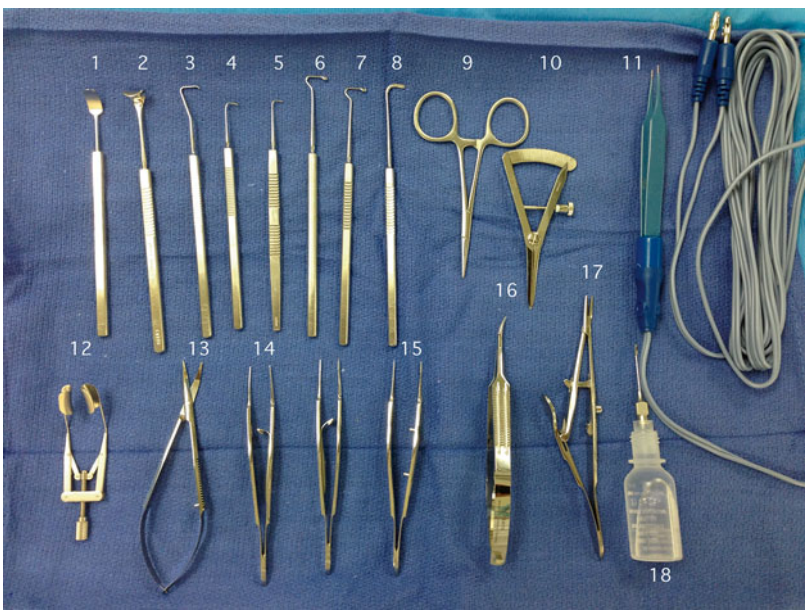

Fig. A8.1 Basic set of strabismus instruments. (1) Barbie retractor, (2) Desmarres retractor, (3) Green muscle hook, (4) curved Stevens small muscle hook, (5) straight Stevens small muscle hook, (6) Jameson muscle hook, (7) Jameson muscle hook, (8) Graefe muscle hook, (9) small straight clamp used for muscle resections, (10) calipers, (11) bipolar cautery, (12) large Helveston lid speculum, (13) Blunt Westcott scissors, (14) pair of locking 0.5 Castroviejo forceps, (15) 0.3 Castroviejo forceps, (16) fine/very fine locking needle holder with flat handles. The flat handle facilitates the passage of long scleral passes by allowing a pushing rather than the rotating motion imparted by needle holders with a round handle. (17) Heavy locking needle holder for 4-0 silk traction sutures and (18) balanced salt solution with cannula

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Appendix 9: Surgical Planning and Numbers

Virginia Miraldi Utz and Elias I. Traboulsi

The following tables are based on the numbers recommended by Marshall M. Parks, M.D., and modified by many [11, 12]. While they have been used to plan pediatric and adult cases, it is unclear if they have been derived from cases performed in either or both groups. We do not address the issue of operating on three horizontal muscles to treat large-angle deviations. We prefer operating on two muscles and addressing the residual deviation, if any, afterward using the two unoperated horizontal muscles. We do not address the topic of adjustable suture use in this appendix.

Horizontal Strabismus Surgery

Esotropia

1. Binocular Surgery

Medial rectus recession	Lateral rectus resection[a]
15 PD = 3.0 mm	15 PD = 3.5 mm
20 PD = 3.5 mm	20 PD = 4.5 mm
25 PD = 4.0 mm	25 PD = 5.5 mm
30 PD = 4.5 mm	30 PD = 6.0 mm
35 PD = 5.0 mm	35 PD = 6.5 mm
40 PD = 5.5 mm	40 PD = 7.0 mm
50 PD = 6.0 mm	50 PD = 8.0 mm
60 PD = 6.5 mm	
70 PD = 7.0 mm	

[a]If a large medial rectus recession has been performed (>6.0 mm) and bilateral lateral rectus resection is planned for residual esotropia, the numbers for the resection of the lateral recti need to be reduced

2. Monocular Surgery

	Medial rectus recession	Lateral rectus resection
15 PD =	3.0 mm	3.5 mm
20 PD =	3.5 mm	4.0 mm
25 PD =	4.0 mm	5.0 mm
30 PD =	4.5 mm	5.5 mm
35 PD =	5.0 mm	6.0 mm
40 PD =	5.5 mm	6.5 mm
50 PD =	6.0 mm	7.0 mm
60 PD =	6.5 mm	7.5 mm
70 PD =	7.0 mm	8.0 mm

Exotropia

1. Binocular Surgery

Lateral rectus recession	Medial rectus resection[a]
15 PD = 4.0 mm	15 PD = 3.0 mm
20 PD = 5.0 mm	20 PD = 4.0 mm
25 PD = 6.0 mm	25 PD = 5.0 mm
30 PD = 7.0 mm	30 PD = 5.5 mm
35 PD = 7.5 mm	35 PD = 6.0 mm
40 PD = 8.0 mm[b]	40 PD = 6.5 mm
50 PD = 9.0 mm[b]	

[a]If a large lateral rectus recession has been performed (≥9.0 mm) and bilateral medial rectus resection is planned for residual exotropia, the amount of resection may need to be reduced.

[b]Recessions greater than 9.0 mm may result in an abduction deficit. In these cases, the surgeon might consider a staged approach (bilateral lateral rectus recession followed by bilateral medial resection if residual exotropia is still present).

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2. Monocular Surgery

	Lateral rectus recession	Medial rectus resection
15 PD =	4.0 mm	3.0 mm
20 PD =	5.0 mm	4.0 mm
25 PD =	6.0 mm	4.5 mm
30 PD =	6.5 mm	5.0 mm
35 PD =	7.0 mm	5.5 mm
40 PD =	7.5 mm	6.0 mm
50 PD =	8.5 mm	6.5 mm

Vertical Rectus Muscle Surgery

Recess up to 1 mm for each 3 PD of desired correction. *Note: If performing larger recessions of the inferior rectus (>5 mm), surgeon should consider disinsertion of lower eyelid retractors to prevent eyelid fissure changes.*

For DVD, please see Chap. 56 on vertical deviations.

Nystagmus Surgery for Face Turn

Face Turn to the RIGHT (Left Gaze Preference)

1. Goal: Move eyes to the RIGHT

Degrees of face turn	<20°	30°	45°
Left eye: recess LR	7 mm	9 mm	10 mm
Left eye: resect MR	6 mm	8 mm	8.5 mm
Right eye: recess MR	5 mm	6.5 mm	7.0 mm
Right eye: resect LR	8 mm	10 mm	11 mm

Face Turn to the LEFT (Right Gaze Preference)

1. Goal: To move eyes to the LEFT

Degrees of face turn	<20°	30°	45°
Right eye: recess LR	7 mm	9 mm	10 mm
Right eye: resect MR	6 mm	8 mm	8.5 mm
Left eye: recess MR	5 mm	6.5 mm	7.0 mm
Left eye: resect LR	8 mm	10 mm	11 mm

[a]If in doubt, draw it out (Fig. A9.1).

Tips for Fellow and Resident Preparation for Surgery

To learn the most from each case, review the medical chart and prepare a surgical plan. Here is a list of what information should be collected from the medical record prior to the case.

1. Patient age.
2. Prior surgery: If prior surgery, record preoperative and postoperative measurements and the surgical intervention performed.
3. Visual acuity: (Is amblyopia present?)
   OD:
   OS:
4. Cycloplegic refraction
   OD:
   OS:
5. Versions and ductions:
6. Gaze measurements at distance and near (review several notes to determine stability of measurements); record with and without correction.

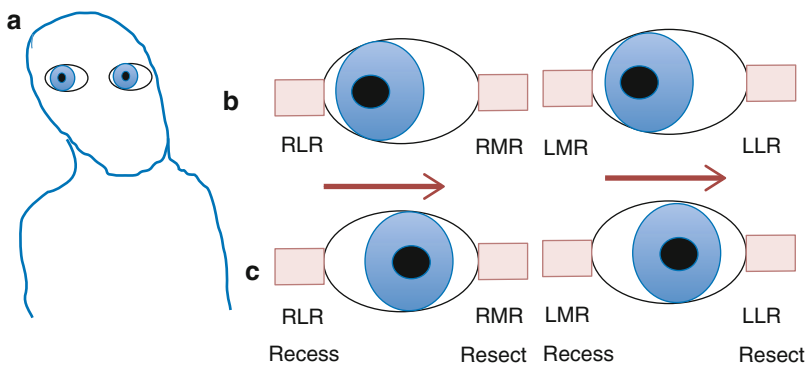

Fig. A9.1 (**a**) This patient has a LEFT face turn (right gaze preference). (**b**) Draw the present position of the eyes. (**c**) Draw the end position of the eyes (in this case move eyes LEFT) and make sure the surgical plan coincides with this goal. *Note: The editor labels the muscles and planned surgical intervention above each muscle of the patient in cases of nystagmus surgery*

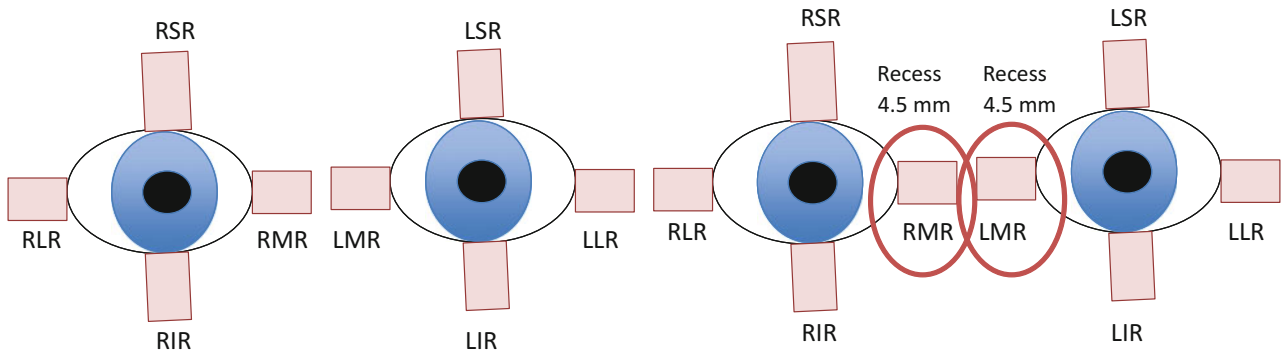

Fig. A9.2 Trainee can mark the surgical muscles and numbers of recession/resection (a) Example of marking muscles as above

7. Stereopsis:
8. Worth-4-Dot Results
9. Resident/fellow proposed surgical plan (Fig. A9.2)
10. Attending surgical plan
11. Intraoperative notes

Example Fellow and Resident Preparation for Surgery

1. Patient age: 3.5-year-old with partially accommodative esotropia
2. Prior surgery: No prior surgery
3. Visual acuity (cc):
   OD: 20/30 [CSM]
   OS: 20/30 [CSuM]
4. Cycloplegic refraction
   OD: +3.00 + 0.50 × 090
   OS: +3.50 + 0.50 × 090
5. Versions and ductions: Full OU
6. Gaze measurements at distance and near (review several notes to determine stability of measurements); record with and without correction.
   8/20/2014 (slightly increased near deviation from visit 7/20)
   ETsc = 45 ET′sc = 70Δ
   ETcc = below ET′cc = 30Δ

20Δ	20Δ	20Δ
20Δ	20Δ	20Δ
20Δ	20Δ	20Δ

9/20/2014 (Pre-op visit)
ETsc = 50 ETsc′ = 75Δ
ETcc = below ET′cc = 30Δ

20Δ	20Δ	20Δ
20Δ	20Δ	20Δ
20Δ	20Δ	20Δ

Stereo: none
W4D: Suppression OS

7. Resident/fellow proposed surgical plan (Fig. A9.3):
   (1) Bilateral medial rectus recession for 30 PD, 4.5 mm (near deviation with correction or distance deviation with correction and add 1 mm to each MR recession) *OR left medial rectus recession (4.5 mm) and left lateral rectus resection (5.5 mm) for 30 PD (as left eye is non-dominant, although no amblyopia present)*
8. Attending surgical plan: Bilateral medial rectus recession

$$= \frac{30+50}{2} = 40 \text{ PD (5.5 mm)}$$

9. Intraoperative notes: Fornix incision, crossing swords technique for muscle reinsertion

Appendix 10: ROP Examination and Treatment Pearls

Michael B. Yang

Order of Examination One recommended sequence of examination outlined below (pupil, optic nerve, then temporal, nasal, superior/inferior retina) is based on the likelihood of detecting examination findings that impact the decision for treatment or follow-up should an abbreviated examination become necessary due to physiologic instability in the infant [1]. (1) Check the pupil for iris neovascularization. (2) Check the optic nerve and posterior pole vessels to evaluate for the presence of plus disease. The diagnosis of plus disease may be subjective. Thus, recalibration of one's mental image of plus disease periodically by comparison with standard photographs from ICROP is recommended [2]. (3) Check the temporal 4 clock hours of retina to determine if the ROP is in zone I or close to the macula, as disease severity is usually greatest in the temporal retina followed by the nasal retina and then the superior/inferior retina. (4) Check the nasal 4 clock hours of retina to determine whether the nasal retina is vascularized to the ora serrata for 2 clock hours. If so, then by definition retinal vascularization has proceeded into zone III temporally. (5) Check the superior and inferior retina last as these areas are unlikely to have a higher stage of ROP than the temporal or nasal retina.

Examination Equipment An Alfonso lid speculum (Storz E4112) effectively retracts the eyelids. The sclera can be indented by using a calcium alginate swab with a thin aluminum shaft or by using a Flynn scleral depressor (Storz E5107). The latter can create a line of white with pressure that mimics the appearance of stage 1 or 2 ROP or that hides potential ROP on the downslope of the indented retina away from the examiner's view. A 28-diopter condensing lens is useful for determining the location of disease because if the nasal border of the optic nerve is placed at one edge of the afforded view during binocular indirect ophthalmoscopy, the other edge of the view marks the temporal boundary of zone I [2]. A 20-diopter lens allows the visualization of the details of plus disease and stage 3 ROP.

Laser Photocoagulation Surgery may be performed under general anesthesia in the operating room or sedation in the nursery. Typical initial settings for a portable diode laser used in ROP treatment (Oculight XLS, Iridex, Mountain View, CA) are 100 mW power, 300 ms duration, and 300 ms repeat interval. The power is gradually increased until a gray-white burn is achieved with the spots set about one-half burn width apart. Applying a row of laser spots to the avascular retina just peripheral to the vascular-avascular junction 360° serves to mark off the posterior extent of the planned treatment. If the view becomes blurry during treatment, one can more safely complete the laser procedure by ablating the avascular retina peripheral to the first row of laser.

Bevacizumab Injection A different drug lot can be used for each eye if bilateral therapy is planned. Slightly more than the standard dose of 0.625 mg of bevacizumab in 0.025 ml should be drawn by the pharmacist directly from the manufacturer supplied vial in a 1-ml tuberculin syringe which is then fitted with a 30-gauge needle without a safety guard that can impede injection. The treating physician can waste the excess just before injection. Povidone-iodine 5 % solution for endophthalmitis prophylaxis is instilled in the eye for a few minutes before injection. Then cotton applicators soaked with topical anesthetic are applied to the injection site. Pretreatment with systemic pain medication

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should be considered. The treating physician's finger should not touch the plunger until the needle has been inserted through the sclera as the minutest pressure will cause a small amount of drug to escape at the needle tip. The injection site should be measured at 0.5–1.0 mm from the corneal limbus since the pars plana is narrow in the premature infant [3]. The eye should be immobilized with forceps or a cotton tip applicator, while the sclera is penetrated with the needle aimed toward the optic nerve to avoid injuring the lens. As the needle is withdrawn, the injection site is blotted with a cotton tip applicator.

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Appendix 11: ROP Follow-Up Schedule

Michael B. Yang

The policy statement of the pediatric and ophthalmology specialty organizations in the United States recommends an *initial ROP examination* at 31 weeks postmenstrual age (PMA) or 4 weeks chronological age, whichever is later, for premature infants ≤1500 g birth weight or ≤30 weeks estimated gestational age at birth.

The ***recommended intervals for follow-up examinations*** based on retinal findings using the revised International Classification of ROP [14] (Table 29.2) are as follows: ***1 week or less*** for immature vascularization in zone I or in the posterior aspect of zone II near the zone I border, stage 1 or 2 ROP in zone I, stage 3 ROP in zone II, or the presence or suspected presence of aggressive posterior ROP; ***1 to 2 week(s)*** for immature vascularization in posterior zone II, stage 2 ROP in zone II, or unequivocally regressing ROP in zone I; ***2 weeks*** for stage 1 ROP in zone II, immature vascularization in zone II, or unequivocally regressing ROP in zone II; and ***2 to 3 weeks*** for stage 1 or 2 ROP in zone III or regressing ROP in zone III.

The suggested ***criteria for termination of screening examinations*** include (1) full retinal vascularization (mature), (2) retinal vascularization into zone III without previous ROP in zone I or II and in an infant ≥35 weeks PMA, (3) the attainment of 50-week PMA in an infant without the presence of prethreshold ROP or worse disease, or (4) absence of vascular tissue that can reactivate after previous regression of ROP in zone II or III.

The responsibilities for educating the family of premature infants at risk for ROP and ensuring timely follow-up examinations (whether inpatient or after hospital discharge) should be carefully delineated between the neonatal intensive care unit (NICU) staff and the examining ophthalmologist [16]. It may be prudent for the ophthalmologist to also independently keep track of the infants who warrant follow-up examinations rather than rely solely upon the NICU to schedule them correctly.[1]

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[1]Many of these recommendations are based on evidence from multicenter studies, but they do not account for center-specific differences or infant characteristics that may modify the risk of individual infants. Ophthalmologists who wish to deviate from the recommended ROP screening guidelines may benefit from developing institutional consensus after a careful review of center-specific evidence. However, some insurance companies may not provide liability coverage, if examiners deviate from the guidelines.

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Appendix 12: Pseudotumor Cerebri Diagnostic Criteria

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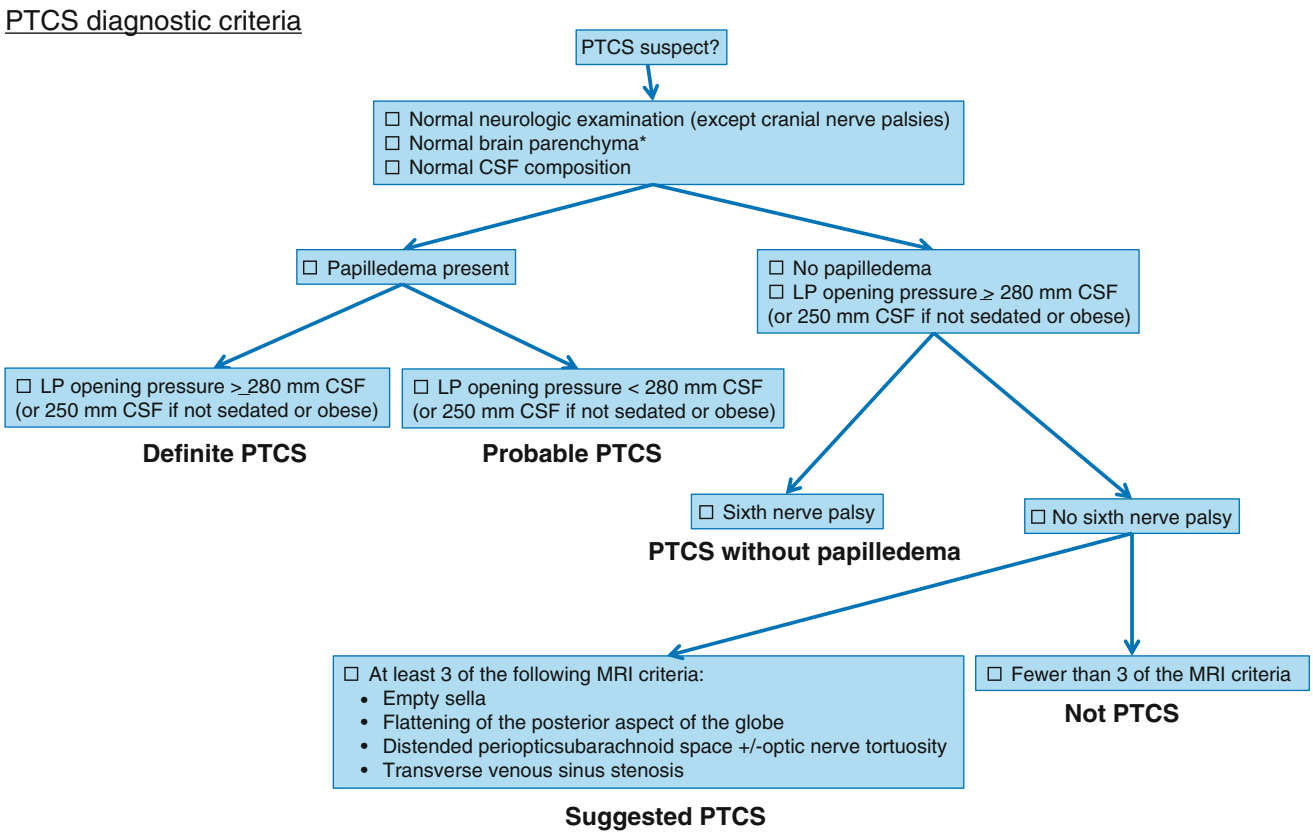

*As seen on contrast-enhanced MRI neuro-imaging for typical patients (female and obese), plus MR-venography for atypical patients (male or non-obese female);or contrast-enhanced CT if MRI is not obtainable.

Fig. A12.1 PTCS diagnostic criteria flow chart

Appendix 13: Anisocoria

Greg Kosmorsky

Figure A13.1

1. The diagnosis of **physiologic anisocoria** is based on a brisk reaction with no dilation lag (e.g., the anisocoria is equal in both dim and light conditions). Physiologic anisocoria is usually ≤1 mm.
2. If there is **brisk reaction to light**, but dilation lag (e.g., anisocoria is greater under dim conditions), the differential diagnosis includes **Horner syndrome** as well as mechanical or pharmacologic miosis. Both apraclonidine and cocaine testing can be used to determine if a Horner syndrome is present, but do not distinguish between preganglionic and postganglionic lesions. Hydroxyamphetamine is used to distinguish between preganglionic and postganglionic involvement.
   - Apraclonidine 1 % testing:
     - Mechanism: Apraclonidine inhibits the alpha-2 receptor on the presynaptic nerve terminal inhibiting norepinephrine release.
     - Testing: Normal eye constricts. **Abnormal (smaller) pupil dilates** because there is adrenergic supersensitivity (increased alpha-1 receptors) on the iris dilator muscle. Apraclonidine has weak alpha-1 activity leading to the dilation observed.

     Use caution in young children as it may cause sedation because of CNS affects
   - Cocaine: Blocks reuptake of norepinephrine (NE) at presynaptic nerve terminal
     - Testing: Normal pupil will dilate. **Abnormal (smaller) pupil will not dilate** because little or no NE is released into the synapse.
   - Hydroxyamphetamine (instill 24 h after cocaine):
     - Mechanism: Releases NE from presynaptic nerve terminal
     - Testing:

       Postganglionic: **Abnormal (smaller) pupil** does not respond and remains **miotic** with testing (nerve terminal has degenerated).

       Preganglionic: **Abnormal (smaller) pupil dilates** as much (if not more) than the normal pupil (postganglionic neuron is intact).
     - **Acquired Horner syndrome requires further diagnostic workup in the pediatric population as the differential includes trauma, malignancy, and neuroblastoma of the sympathetic chain. Diagnostic workup should include imaging of the brain, neck, and chest. Urine catecholamines could also be considered.**
3. If there is a **poor reaction to light** (anisocoria greater in dim illumination), the following etiologies must be carefully distinguished:
   - Mechanical etiology: Evaluate at slit lamp for transillumination defects, sphincter tears, synechiae, or postsurgical abnormalities of the pupil
   - Adie's tonic pupil: An Adie's pupil is caused by postganglionic parasympathetic denervation and is usually unilateral. A tonic pupil is usually poorly reactive, and occasionally sectoral segments of sphincter paralysis can be observed at the slit lamp. Diagnostic testing can be performed with dilute 0.1 % pilocarpine:
     - Mechanism: Pilocarpine is a direct-acting cholinergic agonist.
     - Testing:

       0.1 % Pilocarpine: The denervated iris sphincter is supersensitive to dilute 0.1 % pilocarpine and will constrict. The normal pupil will have minimal reaction at this dilute concentration.

       ****Note: An early Adie's pupil may not be supersensitized and yield a false-negative test. It is prob-*

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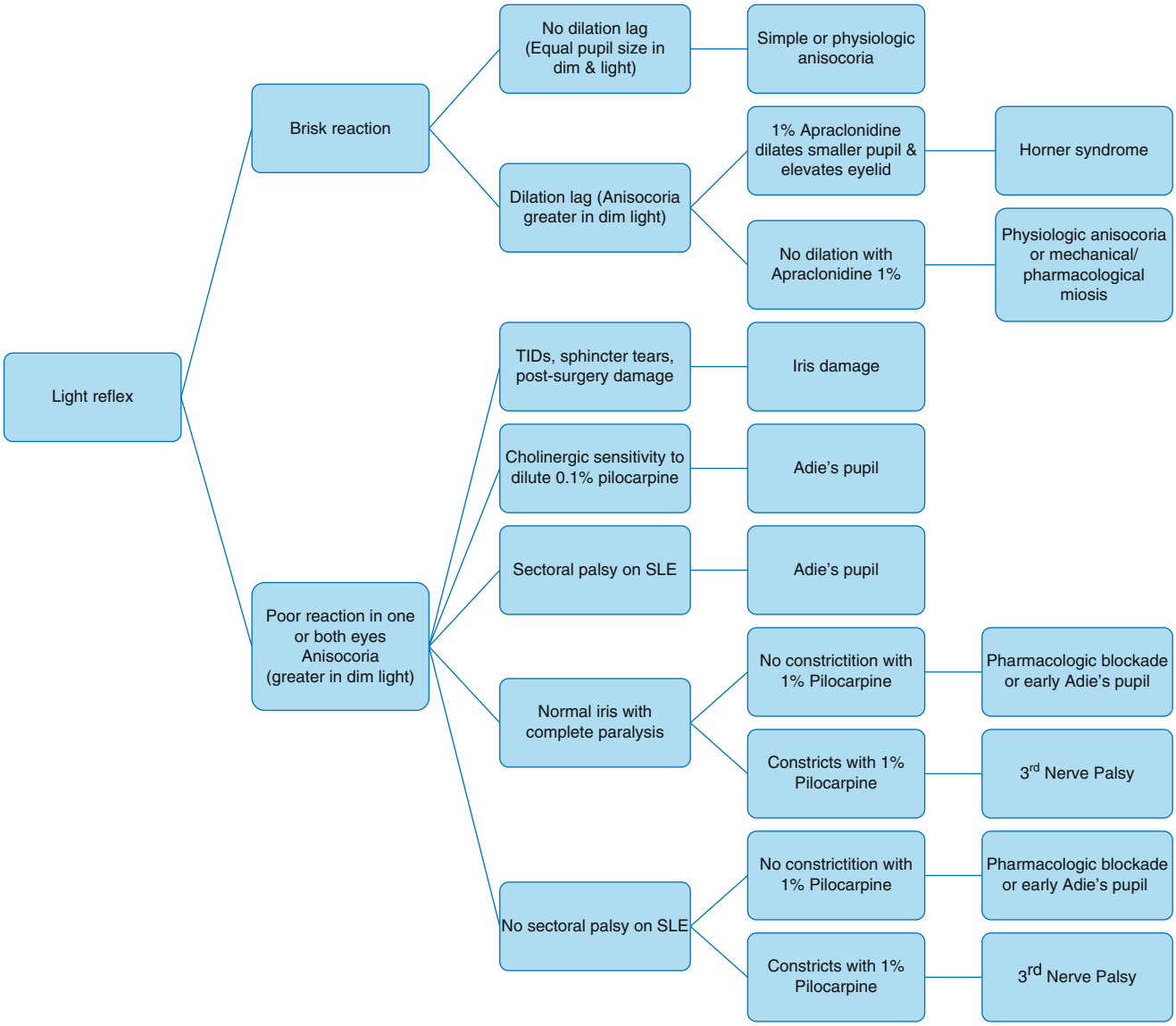

Fig. A13.1 Diagnostic algorithm for the patient with anisocoria. The light reflex is a test of the efferent system beginning at the Edinger-Westphal nucleus. Key: TIDs = transillumination defects

*ably better to assume a possible pupil-involving third nerve palsy and image accordingly for aneurysm. ****

1 % Pilocarpine: Both normal and abnormal pupils should constrict. If the **abnormal (dilated) pupil** fails to constrict to 1 % pilocarpine, then it is likely **pharmacologically dilated**. If the **abnormal pupil (dilated) pupil constricts appropriately**, a **third nerve palsy** must be evaluated by neuroimaging for vascular malformation, aneurysm, and malignancy compressing the pupillary fibers. Other clinical signs of a partial or full third nerve palsy may be present (ptosis, adduction, supraduction, or infraduction deficit).

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