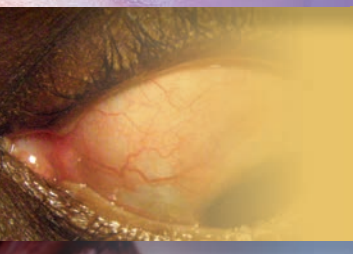
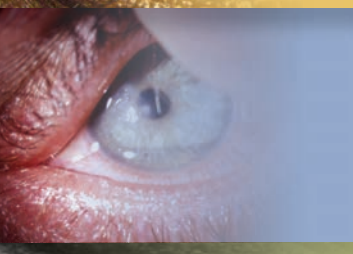
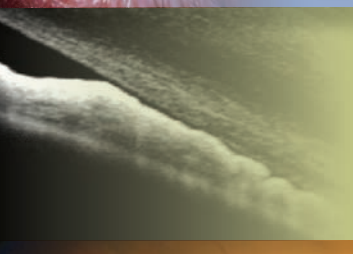
19TH EDITION

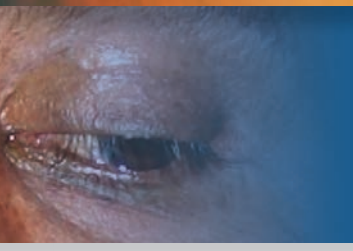
THE HANDBOOK OF OCULAR DISEASE MANAGEMENT

JOSEPH W. SOWKA, OD ANDREW S. GURWOOD, OD ALAN G. KABAT, OD







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SUPPLEMENT TO REVIEW OF OPTOMETRY JUNE 15, 2018

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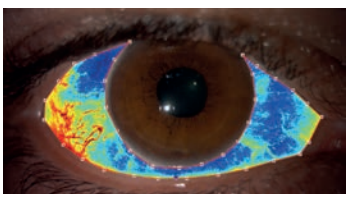
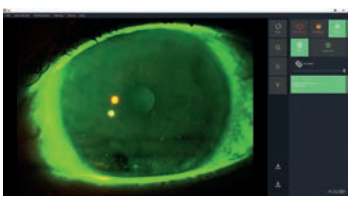


Bulbar redness



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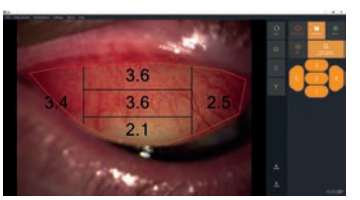

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This publication addresses the management of various conditions with support from the best available peer-reviewed literature. This is done to provide the most up-to-date management of patients with various conditions and to indicate when patient referral is appropriate. In many cases, the management may necessitate treatment from a specialist or subspecialist. This manuscript does not recommend that any doctor practice beyond the scope of licensure or level of personal comfort. It is up to the reader to understand the scope of state licensure and practice only within those guidelines.

A Peer-reviewed Supplement

The articles in this supplement were subjected to *Review of Optometry*'s peer-review process. The magazine employs a double-blind review system for clinical manuscripts in which experts in each subject review the manuscript before publication. This supplement was edited by the *Review of Optometry* staff.

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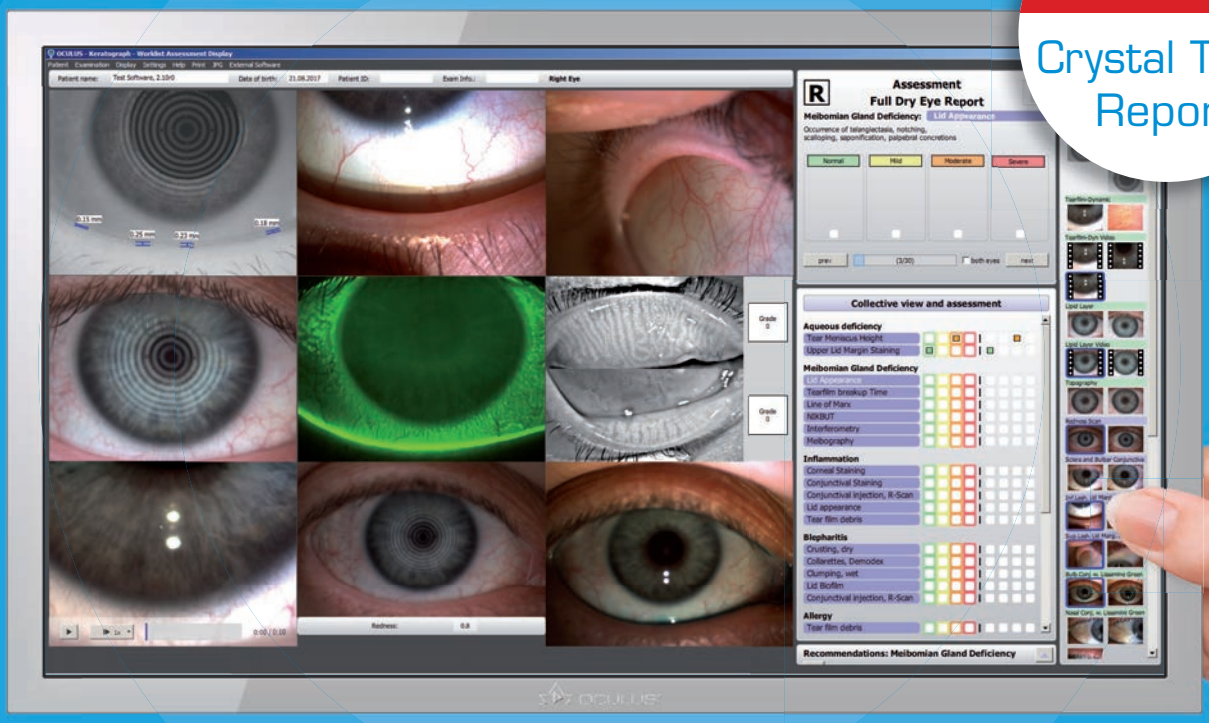

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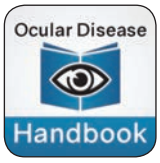
THREE CAREERS' WORTH OF KNOWLEDGE, IN THE PALM OF YOUR HAND

It is our pleasure to present to you another edition of *The Handbook of Ocular Disease Management*. We are fortunate our publishing partners at *Review of Optometry* continue to support this project and we remain enthusiastic about its mission: to bring you concise, evidence-based advice that can be clinically useful for managing all eye diseases, be they commonplace or rare. The *Handbook* has stayed true to that mission for over two decades.

Time marches on and things change. In the era when the *Handbook* launched, we three were early in our careers as educators. We remember creating actual slides using Kodachrome or Ektachrome for printed text with clinical images on the same medium. These had to be loaded into a slide carousel and used with a projector. If you wanted to simultaneously show a picture, you needed two projectors. Once created, there would be no further editing as we do today with PowerPoint and similar programs. Today, we are able to use software to create digital presentations, which easily allow for embedding videos, audio and animations.

We have encountered colleagues who told us that they kept all the old copies of the *Handbook* for reference and wished that they could have everything in one place. In keeping with the technological revolution, this summer we and *Review of Optometry* are launching *The Handbook of Ocular Disease Management* in new digital forms: a downloadable mobile app as well as a stand-alone website. The project will allow us to place more pictures with the text, keep a running archive of all the entities rather than just the 30 we traditionally publish in each printed version, and update the project regularly as new information becomes available. It will be searchable and available on several platforms. Instead of a stack of printed manuals that take up a lot of space, you literally will have everything at your fingertips.



All the content from this year's print issue will appear there, along with a comprehensive archive from the recent past. We expect to launch with approximately 150 ocular diseases covered—five times as much material as the print issue you hold in your hands now. And updates will come to you once per quarter to keep the material fresh and relevant. Look for announcements soon about how you can subscribe.

We see this new digital form of the *Handbook* as the distillation of all we've learned, and taught, during our careers as optometric educators. Creating it is one way we can give back to the profession that has enriched our lives and sustained our careers.

Awards are the product of shared efforts. We thank our teachers who not only shared with us their knowledge but provided inspiration, we thank our mentors for guidance and advice that allowed us to grow and excel, and we thank the *Review of Optometry* staff for promoting and protecting this project.

We hope you find both the print version and the new digital incarnation useful to you during practice. We strive to create a resource that answers questions, solves problems, reviews concepts and makes your clinical life easier. Truly, we consider it an honor to be there for you whenever the need arises. Thank you for the opportunity.

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The authors have no direct financial interest in any product mentioned in this publication.

ACQUIRED BLEPHAROPTOSIS

Signs and Symptoms

The word *ptosis* generally describes a drooping or sagging of the upper eyelid; however, the term is not specific to the lids and can be applied to any body part, including the breasts, stomach (gastroptosis) or kidneys (nephroptosis). When referring to the eyelids, the term *blepharoptosis* is technically more accurate. Blepharoptosis may be congenital or acquired, but those with the acquired form are typically the patients who present symptomatically. Most individuals with congenital blepharoptosis develop adaptations early in life, making their concerns primarily cosmetic.

The most common symptoms associated with acquired blepharoptosis involve an inability to fully open the involved eye, decreased vision and superior loss of field due to lid obstruction.[1-3] Nonspecific symptomology may include eyelid fatigue, blurred vision and epiphora.[1-3] Compensatory efforts by the patient may result in neck soreness (from tilting the head back to see) or headache (from chronic contracture of the frontalis muscle).[2,3] Cosmetic issues are a common complaint, and, in some individuals, this self-image problem combined with functional limitations can have psychological implications, including depression and social withdrawal.[2]

Examination of the patient with acquired blepharoptosis reveals a narrowed palpebral aperture and notable lid droop. The condition may be unilateral or bilateral, with laterality potentially indicative of the underlying etiology. Unilateral blepharoptosis often stems from neurologic or mechanical disease (e.g., levator disinsertion from trauma or lid droop from focal swelling), while bilateral blepharoptosis is typically associated with generalized muscle disorders (e.g., myasthenia gravis) or aging changes (e.g., dermatochalasis).[1]

Associated signs may also help to identify an underlying cause. For example, Horner's syndrome involves a unilateral eyelid ptosis with a miotic pupil on the ipsilateral side. Oculomotor (cranial nerve III) nerve palsy demonstrates lid ptosis with restriction of both upgaze and adduction, and, in some cases, a pupil that is dilated and unresponsive to light. Pain and swelling of the eyelid may point to an inflammatory or neoplastic disorder, such as dacryocystitis or preseptal cellulitis. When blepharoptosis is intermittent, variable or shifts from one eye to the other, myasthenia gravis should be suspected.[1,4]

Pathophysiology

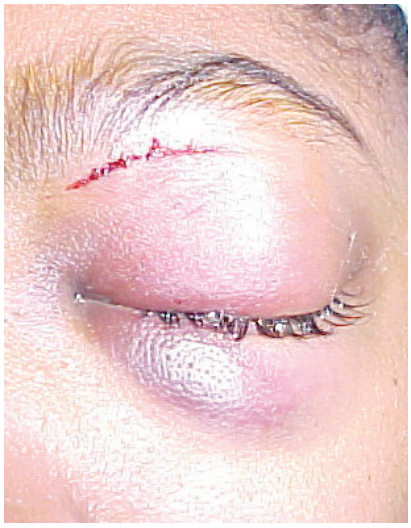
Acquired blepharoptosis may be encountered in a number of clinical scenarios, but all cases can ultimately be ascribed to one of four categories: *aponeurogenic*, *myogenic*, *neurogenic* or *mechanical*.[1-3,5-7]

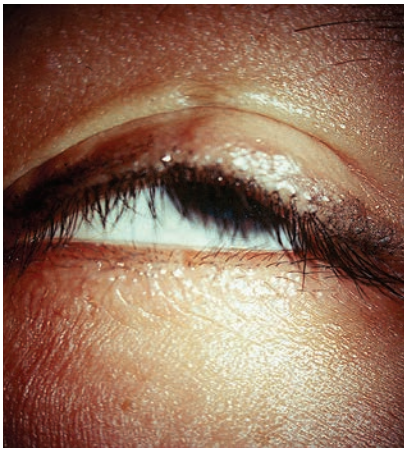
Aponeurogenic (sometimes referred to as aponeurotic or involutional) blepharoptosis involves local dehiscence, stretching and disinsertion of the levator aponeurosis from its attachments to the tarsus and pretarsal orbicularis muscle. This results in progressive drooping of the upper eyelid.[1,2] It is the most commonly encountered form of acquired eyelid ptosis, particularly in older adults.[1-3,6,7] More than 60% of blepharoptosis cases seen clinically can be ascribed to this category.[7] Histologic evaluation of these patients demonstrates atrophy, fatty infiltration and fibrosis of the levator muscle, as well as an attenuated levator aponeurosis.[8] While elderly patients are primarily affected, younger patients can develop this condition as a result of trauma, severe lid swelling, blepharochalasis, prior ocular surgery or long-term contact lens wear.[1,2,9-13]

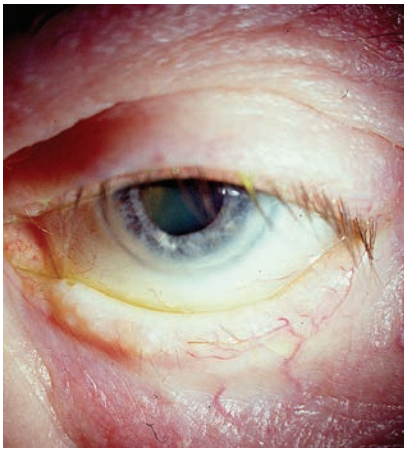
Myogenic blepharoptosis is less commonly encountered, representing only about 4% of cases seen clinically.[8] It is associated with several neuromuscular disorders acting locally at the level of the levator palpebrae superioris muscle. Etiologies include acquired mitochondrial dysfunction (*chronic progressive external ophthalmoplegia*), muscle fibrosis and degeneration (*myotonic dystrophy* and *oculopharyngeal-muscular dystrophy*) and dysfunction of neuromuscular junction signaling due to acetylcholine receptor autoantibodies (*myasthenia gravis*).[1,4,14-17]

Neurogenic etiologies account for roughly 6% of acquired blepharoptosis cases.[8] Disruption of innervation can result from numerous causes, including vascular ischemia, inflammation, infection, demyelination, toxicity, compression and trauma. Most commonly, neurogenic ptosis implicates either the levator muscle via oculomotor palsy (i.e., cranial nerve III palsy) or the muscle of Müller via oculosympathetic dysfunction (i.e., Horner's syndrome). It may also be seen in cases of aberrant regeneration of either cranial nerve III or cranial nerve VII.[8,18,19]

Mechanical blepharoptosis represents about 9% of cases seen clinically. It results







Acquired blepharoptosis can develop in several ways. ***Left and middle:*** Blepharoptosis of traumatic origin. ***Right:*** Involutional ptosis in an elderly patient.

from either a mass effect weighing down on the upper lid or any condition otherwise providing physical resistance to the action of the levator muscle. The most common etiologies include trauma, lid tumors, dermatochalasis and conjunctival scarring (i.e., secondary to ocular cicatricial pemphigoid or Stevens-Johnson syndrome).[1] Floppy eyelid syndrome also falls within this category.[20] Excessive allergic and papillary responses, such as vernal keratoconjunctivitis or giant papillary conjunctivitis, can also result in mechanical eyelid ptosis.[1,21,22]

MEASUREMENT	DEFINITION	NORMAL VALUE
Upper Lid Height	Distance to which the upper lid margin extends inferiorly past the superior limbus	0.5mm to 2mm
Marginal Reflex Distance	Distance from the corneal light reflex to the upper eyelid margin	4mm to 5mm
Palpebral Fissure Height	Distance between the upper and lower lid in vertical alignment with the pupillary center	9mm ± 2mm
Levator Function	Distance upon excursion of the upper lid margin from full downgaze to full upgaze (with the brow held immobile)	≥15mm
Margin-Crease Distance	Distance from the upper lid margin to the eyelid crease, measured centrally with the eye in downgaze	8mm to 10mm

Management

Proper management begins with careful evaluation. To qualify and quantify the blepharoptosis, several measurements are considered essential. These include *upper lid height*, *marginal reflex distance*, *palpebral fissure height*, *levator function* and *margin-crease distance*.[2,3,5,23] The definitions and normal values for these are listed in the accompanying table. It should be noted that age, gender and race may influence these measurements, causing small variations. Blepharoptosis may be graded in severity using the upper lid height and marginal reflex distance as follows:

- *Mild:* ULH > 2, MRD = 2;
- *Moderate:* ULH ≥ 3, MRD = 1;
- *Severe:* ULH > 4, MRD ≤ 0.

The next important step in managing a patient with acquired blepharoptosis is determining the underlying cause. History is crucial in differentiating from among the various potential etiologies; in addition, the clinician must consider laterality, overall motility function and pupillary responses. *Pseudoptosis*—any condition that gives the appearance of a drooping lid but actually involves no lid dysfunction in the involved eye—must be ruled out. Some examples of pseudoptosis include patients with small globes (e.g., microphthalmos or phthisis bulbi), enophthalmos, blowout fracture, contralateral lid retraction and ipsilateral hypotropia.[2]

Blepharoptosis of an aponeurogenic nature is typically bilateral and often asymmetrical such that the patient complains of one eye being affected more than the other. Patients with this condition demonstrate a decreased marginal reflex distance and palpebral fissure height, but an increased margin-crease distance and normal or increased levator function in the involved eye.[1]

Treatment for aponeurogenic ptosis may involve several methods of varying invasiveness. The use of a prosthetic ptosis crutch (also known as *lid crutch*) attached to the spectacle frame can provide relief from some of the major symptoms encountered by these patients.[25,26] The principle advantage of this modality is diminished cost without the risks of surgical intervention.[26] Scleral contact lenses (previously referred to as *haptic* or *prop contact lenses* when used for this purpose) may also be helpful as an alternative or adjunct treatment to surgery.[25,27] Of course, the most complete, consistent and long-term solution for patients with aponeurogenic blepharoptosis remains corrective lid surgery. Procedures such as levator resection and aponeurosis tightening are the principle considerations. The type of surgery depends greatly upon levator function; aponeurosis advancement is usually performed in cases where good levator function still exists.[28] All surgical patients should be followed closely for the development of secondary lagophthalmos and exposure complications.

Blepharoptosis that is myogenic or neurogenic in nature is best managed by a specialist with advanced training in the area of neuro-ophthalmology, since the potential exists for life-threatening etiologies. Diagnostic evaluation is critical in such instances, and, in addition to a comprehensive ocular examination, the workup may involve neuroimaging, diagnostic medications (e.g., intravenous edrophonium or neostigmine for myasthenia gravis, and topical apraclonidine and hydroxyamphetamine for Horner's syndrome), serologic testing for autoantibodies, muscle biopsy or genetic testing.[29,30]

Therapeutic intervention is aimed at treating the underlying disease state, when possible. Surgical management of myogenic or neurogenic blepharoptosis is reserved for those cases that fail to resolve spontaneously or with first-line treatment. In general, surgical technique is dictated by severity of the ptosis. Levator muscle resection is typically employed when the levator function is >5mm, while brow/frontalis suspension procedures are required when levator function is <5mm.[2]

Cases of mechanical blepharoptosis are the easiest to remedy, in principle, as removal of the lesion creating the resistance should render improvement. Tumors and other large or suspicious masses of the eyelids should be referred for oculoplastic consultation and treatment. For patients with dermatochalasis, simple blepharoplasty is often effective. In cases of extensive scarring from long-standing disease, more extensive surgical management by an oculoplastic specialist may be advised.

Clinical Pearls

- Some sources list *traumatic* blepharoptosis as a separate and distinct category, but experience suggests that eyelid trauma typically results in either aponeurogenic or mechanical ptosis.
- If it is not possible to obtain a complete and accurate history, reviewing old photographs may often help to differentiate a congenital or long-standing ptosis from an acquired ptosis.
- Another method of evaluating levator function is to evert the upper lid and then ask the patient to look up toward the ceiling. If the lid does not spontaneously re-evert, then levator function is compromised. This is known clinically as Iliff's sign.

• The sudden onset of blepharoptosis (i.e., over a course of hours or days) should generate a greater sense of urgency on the part of the clinician. This finding is often consistent with a systemic or neurologic etiology and may implicate such conditions as myasthenia gravis, stroke, aneurysm, Horner's syndrome or even temporal arteritis.[32-34] Less commonly, acute-onset blepharoptosis may reflect an infectious or inflammatory condition such as orbital cellulitis or orbital myositis.[32]

• Blepharoptosis is usually the initial and most common complaint in myasthenia gravis.[1,17] In-office confirmatory testing may include several tests. During the *sleep test*, the patient rests with eyes closed for 20 minutes. If the ptosis improves significantly after this, myasthenia should be suspected. As part of the *fatigue test*, the patient is asked to maintain an upward gaze for a period of about one or two minutes. Patients with myasthenia will show a progressively worsening ptosis during the course of this test. During the *ice-pack test*, a bag of crushed ice or a cold pack is placed over the closed eye for two minutes. As with the sleep test, improvement in ptosis following this is suggestive of myasthenia.

• Like myasthenia gravis, aberrant regeneration of cranial nerve III may be noted to have a variable ptosis. This condition presents with characteristic findings including: *horizontal gaze-eyelid synkinesis* (the patient's upper eyelid will lower on abduction and elevate on adduction); *pseudo-Graefe sign* (the eyelid will elevate when the patient looks down); *pseudo-Argyll Robertson pupil* (the pupil will constrict with attempted adduction); limitation of elevation and depression of the eye with retraction of the globe on attempted vertical movements; adduction of the involved eye on attempted elevation or depression; and absent vertical optokinetic response. Pseudo-Graefe's sign is the most common finding.

• Neurogenic blepharoptosis may occasionally result from a lesion to the supranuclear pathway, a condition referred to as *apraxia of eyelid opening*. This bilateral condition is characterized by inability to open closed lids voluntarily; it may be seen in patients with extrapyramidal dysfunction, including progressive supranuclear palsy, Parkinson's disease, Shy-Drager syndrome and Wilson's disease.[31]

• Recall that third nerve palsies are variable in presentation and may or may not show pupillary involvement. Issues with upgaze and adduction are the most common findings. Third nerve palsies will be unilateral except in those rare cases involving the third nerve nucleus. Here, patients present with bilateral ptosis.

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ACQUIRED ENTROPION

Signs and Symptoms

Entropion represents a condition of eyelid malpositioning in which the lid margin rotates inward against the ocular surface.[1-8] This phenomenon may occur unilaterally or bilaterally and may involve the upper or lower eyelid, although the lower lids are affected more frequently.[1,3,6]

Clinical features associated with entropion may be observed both in and out of the slit lamp. The obvious gross finding is a turning-in of the lid margin, with eyelid skin or eyelashes contacting the bulbar conjunctiva and/or cornea. Associated hyperemia of the bulbar conjunctiva may also be noted. Biomicroscopy reveals variable corneal pathology, ranging from superficial punctate epitheliopathy to frank corneal abrasions and even corneal ulceration and pannus formation in extreme cases.[1,4,6,8-10] Patients with entropion typically complain of ocular irritation and/or foreign body sensation, tearing/epiphora and a persistent red eye. Vision may be variably affected, depending upon the location and extent of corneal disruption.

Most commonly, entropion occurs as an involutional change in older patients; however, it can also represent cicatricial damage following blunt, chemical or thermal injury to the lids.[1,3] A careful history should be elicited from all patients presenting with entropion to assess for prior trauma, particularly those who are under 60 years of age. Entropion may also present as a congenital disorder, secondary to a structural defect in the tarsal plate or the eyelid retractors.[11]

Pathophysiology

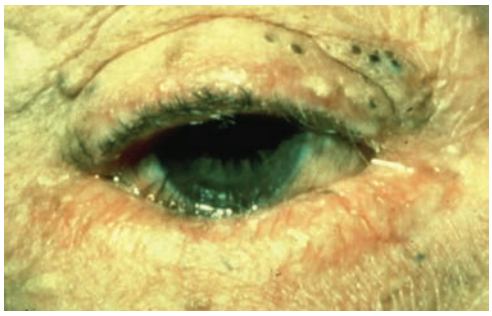
Etiologically, there are three commonly recognized forms of acquired entropion: *involutional*, *cicatricial* and *spastic*.

Involutional (historically referred to as *senile*) entropion is by far the most common form of entropion encountered clinically, occurring in roughly 2% of the elderly population.[1-3,5,6,8,9] By its very nature, involutional entropion almost exclusively affects the lower eyelids.[5,9] A number of structural features and causative factors have been identified, including: loss of horizontal lid support with canthal tendon laxity; loss of vertical lid support with tarsal plate thinning; attenuation, dehiscence or disinsertion of the lower lid retractors; orbicularis muscle dysfunction, with the preseptal portion overriding the pretarsal portion; and enophthalmos secondary to orbital fat atrophy.[1,6-9,12]

At the histological level, involutional entropion appears to involve a significant loss of elastic fibers in the eyelid skin, the pretarsal orbicularis oculi muscle, and the perimeibomian and intermeibomian tarsal stroma.[13] These tissues likewise demonstrate an overexpression of MMP-2, MMP-7 and MMP-9, suggesting that the depletion of elastic fibers may be due to upregulation of elastolytic enzymes.[13]

Cicatricial entropion occurs due to scarring of the ocular tissues, resulting in a vertical shortening of the tarsus. Most commonly, cicatricial tissue changes are associated with trauma (e.g., chemical, thermal, blunt or penetrating injury) or iatrogenic causes (i.e., previous eyelid surgery).[1,3,4] However, cicatricial entropion also may be encountered following inflammatory or infectious eyelid processes, including such conditions as Stevens-Johnson syndrome, ocular cicatricial pemphigoid, trachoma, herpes zoster ophthalmicus, radiation exposure, Sjögren's syndrome or chronic ocular allergy.[3,10] Studies of entropic eyelids in trachoma reveal a wide spectrum of subepithelial cicatricial changes, ranging from fine strands of amorphous tissue to broad bands of connective tissue.[10,14]

Spastic entropion represents a quite different type of disease state compared with the other categories; it occurs when the preseptal orbicularis muscle becomes overactive and hypertrophic secondary to blepharospasm, inflammation, irritation or ophthalmic surgery.[1,15] In addition, there may be some degree of eyelid edema, which adds to the abnormal mechanical forces turning the margin inward. A recent report indicates that children with syndromic facial nerve palsy (FNP) may also suffer from spastic entropion of the lower eyelid.[16] This is unusual since adults with FNP tend to display ectropion as a consequence of this neurogenic disorder.[17] Unlike the other forms of entropion, spastic entropion has the potential to resolve spontaneously when the underlying inflammatory or irritative factors are eliminated.[1] If it persists, an underlying cause must be sought (e.g., acoustic neuroma).



Three forms of acquired entropion exist: involutional (pictured above), cicatricial and spastic.

Management

While treatment for any case of acquired entropion should be guided by its underlying cause, two fundamental philosophies are central to entropion management: protect the potentially compromised cornea, providing adequate lubrication to mitigate irritation; and redirect the lid margin and lashes away from the ocular surface. The liberal use of artificial tear products is recommended for all entropion patients, regardless of the etiology. For more sustained relief of symptoms, gel-forming solutions, gels and ointments may prove more advantageous than drops. Bandage contact lenses may also be helpful in providing a barrier between the ocular surface and entropic lid margin.[18] Also, prophylactic antibiotic coverage may be beneficial in cases with more severe keratitis. Options include bacitracin or erythromicin ointment QID, or topical 1% azithromycin once daily.

A basic and cost-effective method for alleviating contact between the eyelid and ocular surface is to apply surgical tape to the lid in such a way as to rotate it out and away from the globe. Unfortunately, this technique is neither precise nor permanent, and requires cooperation and participation by the patient. It is typically employed as a stopgap measure for individuals awaiting surgical intervention.

Another temporary measure that has been described with some success is the use of cyanoacrylate glue, applied to an induced crease in the lower eyelid for involutional entropion.[8] This technique provides improved cosmesis over lid taping and lasts, on average, about 72 hours.[8] If the entropion is only partial, epilation of the offending lashes is another short-term solution.

Botulinum toxin injection into the preseptal orbicularis muscle has been shown in numerous series to provide temporary relief of spastic as well as involutional entropion.[15,19-22] By effecting a transient paralysis of the eyelid protractor muscles, botulinum toxin may help to alleviate the inward turning of the lid margin for a period of two to four months.[15,20] Specifically in cases of spastic entropion, these injections may serve to break the cycle of spasm and irritation, resulting in permanent resolution.[19]

Unquestionably, surgery provides the most definitive and permanent solution in cases of involutional and cicatricial entropion, and may also be employed for spastic entropion if more conservative measures fail to succeed, or the neurologic cause cannot be remedied. One of the least invasive procedures for all three forms is the application of everting sutures, sometimes referred to as "Quickert sutures," as their use was first described by Quickert and Rathbun in 1971.[23]

In this technique, a 4-0 or 5-0 silk or monofilament suture is placed through the eyelid from the conjunctiva deep within the inferior fornix, exiting through the skin just below the lash line; the other end of the suture is passed in a similar manner 3mm apart, and the arms are then tied together over a small bolster.[1,2,23,24] Typically, three or four equally spaced sutures are placed, avoiding the nasal third of the lower lid to prevent the induction of punctal ectropion. The sutures remain in place for one to four weeks, depending upon the surgeon and the material used. Unfortunately, the use of Quickert sutures alone has been found to be less successful overall than when it is combined with another more invasive surgical technique.[2,6,7,24]

A wide range of surgical interventions for involutional entropion repair have

been described in the literature, including transverse blepharotomy with marginal rotation (Wies procedure), the orbicularis transposition technique, transconjunctival or transcutaneous advancement of the lower lid retractors and the tarsal strip procedure.[1,2,6,25,26] If there is significant horizontal lid laxity, a combination technique involving horizontal shortening of the eyelid and resuspension of the lower eyelid retractors may be performed. In cicatricial cases, surgical repair may include excision of the scar with a tarsal plate graft from preserved sclera, ear cartilage or hard palate (in most severe circumstances), along with conjunctival and mucous membrane grafting using buccal grafts or amniotic membrane tissue.[27-29]

Clinical Pearls

• A thorough history should be completed on all patients with entropion. Attention to previous eye surgery, trauma, chemical injury, chronic infection and changes in eyelid tonus should be given.

• The differential diagnosis of involutional entropion includes eyelash anomalies such as trichiasis (i.e., misdirection of the cilia toward the ocular surface without inward turning of the lid margin) and distichiasis (i.e., multiple rows of eyelashes), blepharospasm, traumatic etiologies, scarring from chemical injuries and lid malposition secondary to previous ocular surgeries.

• While most cases of entropion are chronic and constant, a smaller percentage may be intermittent and, therefore, challenging to definitively diagnose. In symptomatic cases where the patient (or referring physician) suggests having observed ectropion—but it is not evident on presentation—the following physical testing may prove useful:

• *Step 1.* Grasp the lower eyelid skin between the thumb and forefinger between the inferior border of the tarsal plate and the inferior orbital rim.

• *Step 2.* Pull the eyelid anteriorly away from the globe, assessing general eyelid laxity.

• *Step 3.* Direct the patient to forcefully close his or her eyes while releasing the eyelid.

• *Step 4.* Observe for evidence of entropion.

This technique is referred to as the manual provocation test (MPT). In a published study of 12 consecutive patients, the MPT successfully elicited entropion in 100% of cases.[5]

• The easiest way to resolve spastic entropion is to remove the offending irritant. In cases that involve the seventh cranial nerve (e.g., benign essential blepharospasm, orofacial dyskinesia, hemifacial spasm, facial myokymia) a neuro-ophthalmic consult is indicated. In some instances, these conditions can be managed pharmacologically using anti-seizure medications.

• Thermal cautery of the lid was once a popular corrective procedure for the treatment of involutional entropion.[30] However, this technique appears to have fallen out of favor over the last 20 years, particularly with oculoplastic surgeons.[31]

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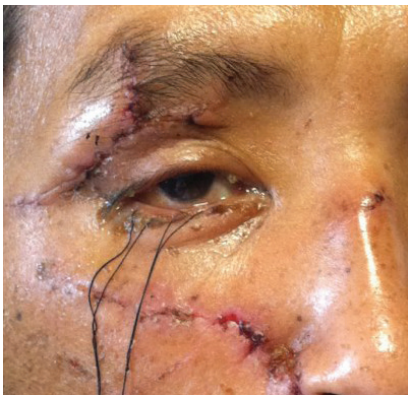
BLOWOUT FRACTURE

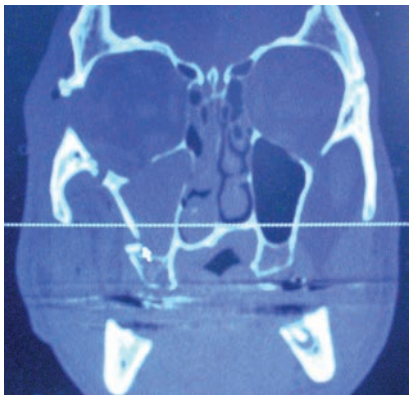
Signs and Symptoms

Blunt trauma to the orbital rim is the typical cause of orbital floor and medial orbital wall fractures.[1-4] While there is no epidemiologic predilection for blowout fractures, clinical trends regarding those most likely to sustain these injuries point to males between the ages of 18 and 30 who are engaged in activities of poor judgment, with most incidents occurring in or near the home.[3,5-8] Traffic accidents are the most common causes of unilateral or bilateral blowout fractures in males between the ages of 30 to 60 years, with violent assault also common.[7,8]

The specific term "blowout fracture" is reserved to connote an isolated orbital floor or medial wall fracture in the setting of an intact orbital rim.[1-4] Patients present with a history of blunt-force trauma, such as being struck with a projectile, like a ball, bat or fist, or being a participant in a collision injury such as those caused by the impact of an air bag or the contact of an object following a fall.[7-9]

Pain, photophobia and lacrimation associated with post-traumatic uveal inflammation (uveitis), variable facial swelling secondary to fluid or air (orbital emphysema), crepitus (a crackling noise when tissue infiltrated with air is palpated), gaze-evoked diplopia and pain upon movement of the eyes are all common.[6-10] Other collateral damage may include subconjunctival hemorrhage, ruptured globe, corneal abrasion, conjunctival laceration, hyphema, iridodialysis, lenticular





Left: **Blowout fracture will characteristically be accompanied by marked physical injury on gross examination.** ***Right:*** **CT scan (in a different patient) demonstrates the extent of involvement of a blowout fracture of the right orbital floor.**

subluxation, retinal detachment, vitreous hemorrhage, choroidal rupture, traumatic optic neuropathy and optic nerve avulsion. If the eye settles inferiorly or medially into the exposed sinus, enophthalmos with restricted ocular motility will be present with or without loss of facial sensation.[1-10]

Pathophysiology

The seven bones of the orbit include the *frontal*, *zygomatic*, *maxillary*, *ethmoid*, *sphenoid*, *lacrimal* and the *pterygopalatine*.[4,11] The orbital roof includes the orbital plate of the frontal bone and the lesser wing of the sphenoid; the lateral wall is composed of the zygomatic bone and the greater wing of the sphenoid; the floor of the orbit is composed of the orbital plate of the maxilla, the zygomatic and orbital process of the pterygopalatine bone; the medial wall of the orbit is composed of the maxilla, the lacrimal, the ethmoid and body of the sphenoid.[4,11]

The other critical anatomical players are the surrounding paranasal air sinuses.[12] Several sinuses surrounding the orbit help to lessen the weight of the skull and aid in the resonance of the voice.[12] Pneumatized ethmoid air cells, which maintain structural stability and resist fractures of the medial orbital wall, act as a safeguard for the globe during trauma.[4] Unfortunately, these structures leave the superior, medial and inferior orbital walls less supported and vulnerable to catastrophic failure (e.g., blowout or trap-door fracture) from blunt-force trauma. The sinuses surrounding the orbit include the *ethmoidal air cells* (anterior, middle and posterior), the *sphenoidal sinuses*, the *maxillary sinuses* and the *frontal sinuses*.[11,12]

There is some debate about the mechanism of blowout fractures. The injury can be classified into three different categories: *greenstick* (partial break), *simple* and *complex*.[13] When a blunt force impacts the face, it may produce a combination of effects: the force may strike the bone, producing a shock wave causing "bone buckling;" the force may be transmitted to the eyeball, causing the globe to strike one of the orbital walls such that it fractures ("eye to wall"); or the force may be transmitted by the globe, via the principle of fluid incompressibility, causing generalized increased orbital content pressure or a "hydraulic" effect resulting in bone fractures.[12-17]

The point of breakage usually occurs along the axis of least support in an area where the tissue is weakest.[13-17] Since the orbital floor is not parallel to the horizontal plane, the vector of the striking force seems to affect the resultant fracture patterns.[12]

While all three mechanisms are mentioned in the literature, the "buckling" mechanism and the hydraulic mechanism seem to have the most support.[14-17] Fractures produced by the buckling mechanism are often limited to the anterior part of the orbital floor.[14] In contrast, hydraulic fractures are often larger, involving both the anterior and posterior parts of the floor as well as the medial wall of the orbit.[16,17]

The orbital floor has a lower threshold for fracture than the medial wall and other orbital bones, and occurs most commonly. When it gives way, the globe and its attached components become unsupported, slipping down into the vacant sinus below, producing visible enophthalmos and gaze-evoked, symptomatic diplopia along with degrees of extraocular muscle dysfunction and infraorbital nerve hypoesthesia.[15-18]

Management

The treatment of blowout fracture centers on ocular first aid. The most challenging aspect of beginning an examination on patients that have encountered facial blunt-force injury is getting the eye open for inspection. Facial and orbital swelling or orbital emphysema can literally force the lids shut. Here, a lid retractor can be placed in between the eyelids and used as a speculum to achieve lifting of the superior lid or lowering of the inferior lid.

Eyes sustaining blunt-force trauma must have imaging to rule out concomitant maxillofacial-orbital fracture or ruptured globe.[17] Facial lacerations can be treated with topical antibiotics unless they require cosmetic or functional closure. Seidel testing is essential to rule out perforating injuries. Topical anti-infective drops can be prescribed for any observed conjunctival/corneal laceration or abrasion and topical and oral anti-inflammatory therapy can be used for resultant ocular inflammation along with the appropriate-strength topical cycloplegic. Topical and oral nonsteroidal medications can assist with inflammation and analgesia.

Since blunt ocular trauma involving the eye or face is the result of being struck by an object at velocity, upon contact a shock wave within the local area is generated. This produces what is known as the "coup" injury, from the French/Scottish derivation meaning *to upset*. Injuries may also be seen directly opposite the impact point, in line with the shock wave; these are known as the "contrecoup" effects (from the French derivation meaning *occurring at a site opposite the area of impact*). For these reasons, dilated fundus evaluation ruling out vitreous hemorrhage, retinal tears and detachment is required.

Computed tomography (CT) scanning is best for assessing orbital fractures.[4,17,19] Newer CT technology (multi-slice CT) has improved the acquisition of coronal images of the orbit without the need for hyperextension of the neck.[4,19]

Treatment of blowout fractures may not be emergent. Compressive threats to the optic nerve via swelling and retrobulbar hemorrhage will require referral for an emergent lateral canthotomy and orbital

decompression. Typically, surgical intervention is postponed until orbital health is consistent with a good surgical environment unless large amounts of soft tissues are incarcerated in the bony rupture.[13,17,20] Management of orbital floor fractures traditionally has been accomplished through transnasal, transcutaneous, transconjunctival, transcaruncular and subciliary incisions.[13,17,19] However, postoperative lid malposition is a complication.[18] Some surgeons have begun to evaluate an endoscopic approach to orbital floor fractures. Endoscopy offers a hidden incision and improved fracture visualization.[21]

When the orbital floor requires replacement (inlay technique) or reconstruction (repositioning technique), numerous materials are available to make the repair.[17,22] Autologous materials include bone, cartilage, fascia lata and periosteum.[17] Natural materials are favored because of their mechanical properties, ability to revascularize and low potential for infection or scarring.[17] Other materials include titanium, porous polyethylene, resorbable materials, gel films, bioglass and silastic sheeting.[17]

In cases that are seen before an orbital fracture is diagnosed and in cases of orbital fracture where surgery is being postponed or not being considered, a course of broad-spectrum oral antibiotics such as Keflex (cephalexin) or amoxicillin, 500mg BID PO, may be indicated to protect against secondary infection while the osseous tissues heal.

Clinical Pearls

• Patients presenting following orbital blunt trauma should be discouraged from nose blowing until orbital fractures can be positively ruled out via imaging (X-ray, CT or magnetic resonance imaging). This helps to avoid the unwanted complication of orbital emphysema.

• While history, signs and symptoms may suggest an orbital fracture, neuroimaging is the only way to make a conclusive diagnosis.

• Air from the external environment may enter the subcutaneous tissue surrounding the orbit or globe via a communication created by a fracture. This is often visible as "soft" or "puffy" swelling and known as orbital emphysema.

• If there is no ocular displacement or muscle entrapment, minor fractures will heal over time, and oral antibiotics can be used to prevent infection of the orbital contents from the sinus.

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CANALICULITIS

Signs and Symptoms

A relatively rare disorder, canaliculitis accounts for less than 2% of all lacrimal disease.[1-4] It is typically encountered in older adults, with a mean age of 59 years.[2] Women are affected approximately five times more often than men.[2,5] Most cases are unilateral, though bilateral instances have been documented.[6,7] Complaints tend to center around a chronic, recalcitrant red eye with focal swelling and tenderness of the medial canthus. Epiphora—excessive tearing to the point of overflow—is often reported. The discharge may range from a simple watery consistency to full-blown mucopurulence. In many cases, the patient will report previous therapy with topical antibiotics, but to no avail. Recurrent episodes are not uncommon.

The classic biomicroscopic sign associated with canaliculitis is a "pouting" punctum, although it may not be seen in all cases.[1-5,8-10] This term describes the red, swollen and outwardly turned punctal orifice, such that it resembles a pair of pouting lips. However, the most commonly encountered sign is the presence of discharge and concretions upon canalicular compression.[11] According to a recent study, 90% of patients demonstrate this feature.[4]

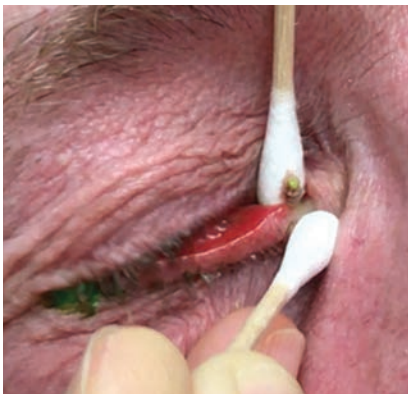
Other important signs include erythema and swelling of the lid and adnexal tissue, and a conjunctivitis that is more pronounced inferiorly and nasally.[8]

Diagnostic signs can also be encountered through lacrimal probing, although this procedure should only be undertaken by experienced clinicians. Characteristic to canaliculitis is a "soft stop" while probing the horizontal canaliculus. This blockage is indicative of concretions within the lacrimal drainage system, a feature indicative of canaliculitis. Concurrent with this finding is the so-called "wrinkle sign"; as the clinician's probe meets resistance, the overlying skin of the medial canthus may be seen to compress and wrinkle.[12] The Jones test for fluorescein dye disappearance is inherently negative, demonstrating a robust lacrimal lake secondary to poor tear drainage with poor or no recovery of dye from the nostril.[2]

Pathophysiology

Canaliculitis may be described as a primary or secondary condition. *Primary canaliculitis* represents an infection and subsequent inflammation of the lacrimal outflow system, at the level of the canaliculus.[2] Multiple pathogens have been associated with this condition, including bacteria, fungi and even the herpes virus.[2] Historically, canaliculitis has been most closely associated with *Actinomyces israelii*, a cast-forming, gram-positive anaerobe that is often difficult to isolate and identify.[2,9]

Photo: Laura M. Perlman, MD



Expressing the canaliculus firmly on either side with cotton-tipped applicators should help "roll" dacryoliths through the punctum, affording medications greater access.

More recent studies, however, show that *Streptococcus* and *Staphylococcus* have now evolved as the new most common causative organisms.[4,5] Additional bacteria that have been associated with canaliculitis include *Proteus vulgaris*, *Klebsiella pneumoniae*, *Corynebacterium*, *Eschericia coli*, *Eikenella corrodens*, *Mycobacterium chelonae*, *Aggregatibacter aphrophilus*, *Nocardia asteroides*, *Lactococcus lactis cremoris* and many others.[2,4,13-17] Fungal pathogens include *Candida* and *Aspergillus* species.[18]

Primary canaliculitis is characteristically associated with the formation of intracanalicular concretions, sometimes referred to as *dacryoliths* (from the Greek *dakryon*, meaning "tear," and *lithos*, meaning "stone"). On histologic analysis, these deposits are composed of basophils and eosinophils associated with a variety of pathogenic bacteria, as previously discussed.[13] Dacryoliths also contain numerous inorganic compounds, such as calcium, magnesium, potassium, sulphur and phosphorus.[19] As the concretions develop, small pockets form between them where the bacteria flourish, unimpacted by the natural antimicrobial properties of the tear film or even the application of topical antibiotics.[2]

The term *secondary canaliculitis* is used when the condition results as a complication of lacrimal occlusion, either from migrated punctal or intracanalicular plugs.[2,3] These "man-made" obstructions can function as artificial dacryoliths, harboring potentially pathogenic bacteria and providing an environment in which they can thrive. In some cases, concretions can form around or adjacent to retained plugs.[20] Secondary canaliculitis has seen its greatest incidence with use of the SmartPlug device (Medennium), a thermoacrylic polymer designed for lacrimal occlusion therapy in patients with dry eye.[6,7,20-22]

Management

Many cases of canaliculitis are diagnosed only after a seemingly benign case of blepharoconjunctivitis fails to resolve with topical antibiotic therapy. Low-grade infections can sometimes persist for long periods of time because the clinician fails to observe the subtle signs of canaliculitis. Studies suggest that the average duration before a correct diagnosis is made may be as long as 36 months.[23,24]

Conservative measures such as warm compresses, digital massage, topical antibiotics and even oral antibiotics are generally insufficient to completely eradicate canaliculitis infections, although they may provide temporary improvement and symptomatic relief.[2,11,25] Slightly more invasive procedures may demonstrate greater success, especially when employed early in the course of canaliculitis.

One study employed manual expression of the obstructive material through the punctum, followed by canalicular irrigation with fortified cefazolin (50mg/ml) and the use of topical antibiotics for several weeks.[25] The success rate in this small (n=7) series was 100%, although most subjects required multiple irrigations.[25]

Another study evaluated the intracanalicular injection of ophthalmic tobramycin 0.3%/dexamethasone 0.1% ointment following dilation and probing of the canaliculus to the lacrimal sac.[10] This technique demonstrated a 72.7% resolution rate for novel patients, as compared with 22.2% for those on conservative therapy only and 100% for those managed surgically.[10]

Historically, the gold standard treatment for canaliculitis has involved *canaliculotomy* (surgical excavation of the canaliculus) with *canalicular curettage* (surgical removal of the dacryoliths and other obstructions of the canaliculus).[1-5,25] Canaliculotomy is performed under local anesthesia; a probe is inserted through the punctum and an incision is made through the adjacent conjunctiva into the dilated canaliculus, effectively dissecting the nasal lid from the punctal orifice down to the level of the common canaliculus (approximately 10mm). Next, a small chalazion curette is used to remove the dacryoliths and other debris, and canalicular irrigation with antibiotic solution (aqueous penicillin G) or povidone-iodine may be subsequently performed at the surgeon's discretion. Performing smears and/or cultures of the retrieved material may be helpful in determining the correct pharmacologic course, as postoperative antimicrobial therapy is generally indicated.[23]

In cases of bacterial canaliculitis, oral penicillin or ampicillin is commonly prescribed for several weeks following surgical recovery, since penicillin is the preferred treatment for *Actinomyces*.[2,23] The use of topical, broad-spectrum antibiotics (e.g., ciprofloxacin 0.3% solution QID or bacitracin zinc/polymyxin B ointment BID) may be employed as an adjunct to systemic therapy.[4] Rare cases of mycotic canaliculitis require post-surgical treatment with antifungal agents (e.g., voriconazole 2% ophthalmic solution every two hours and oral voriconazole 450mg BID for two weeks).[26] Herpetic canaliculitis is likewise managed with antiviral agents after canaliculotomy (e.g., oral acyclovir 400mg five times daily for two to three weeks).

For cases of secondary canaliculitis, removal of the plug is paramount to treatment. In some cases, simple lacrimal irrigation can dislodge the plug and effect patency of the canaliculus. This is the procedure recommended by the SmartPlug manufacturer.[7] However, it should be noted that irrigation also introduces a risk of creating an occlusion more distally in the nasolacrimal system, further complicating the issue.[2] Alternative options may include retrograde plug expression (as one would express dacryoliths from the punctum), or attempting to retrieve the plug with forceps if visible in the canaliculus.[2,7,21] Once the obstruction has been cleared, treatment with topical antibiotics should help to resolve any residual issues. Should these more conservative measures fail however, canaliculotomy and curettage is recommended.[2,7,21]

Clinical Pearls

• Canaliculitis must always be differentiated from dacryocystitis, as the treatment modalities differ significantly. Dacryocystitis typically presents more acutely and with greater pain and swelling in the canthal region; it is treated with systemic antibiotics alone and generally does not require surgical intervention.

• Herpetic canaliculitis often follows herpes simplex blepharoconjunctivitis. This should be considered in cases that manifest persistent epiphora after resolution of the herpes vesicles.

• In extreme cases, canaliculitis (and the surgical interventions used to treat it) can leave the nasolacrimal system scarred and permanently occluded. In such cases, dacryocystorhinostomy may be required to successfully reestablish lacrimal outflow.

• Interestingly, while *Actinomyces* is not susceptible to many commercial topical antibiotics, agents to which it may be sensitive include several older drugs such as chloramphenicol, sulfacetamide and erythromycin.

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HERPES ZOSTER OPHTHALMICUS

Signs and Symptoms

The most frequently affected branch of the trigeminal nerve in herpes zoster ophthalmicus (HZO) is the ophthalmic division (V1) with its supraorbital, lacrimal and nasociliary distribution (lesions on the tip of the nose, the Hutchinson's sign).[1-16] An HZO rash will maintain a characteristic respect for the midline, consistent with the nerve's distribution.[8,12]

The skin manifestations begin as an erythematous macular rash that progresses over several days into papules, vesicles and then pustules. The vesicles discharge fluid and begin to form scabs after about one to three weeks in immunocompetent individuals.[8,11] During this inflammatory stage, the pain is severe, even when the rash is minimal.[1-11] In a rare subset of patients, there will be unilateral neuropathic pain (one-sided headache) but without the attendant rash.[13] This entity is challenging to diagnose; the headache may be prodromal to an eventual rash outbreak, or a rash may never become apparent (*zoster sine herpete*).[13]

In addition to the dermatologic findings, about 50% of cases demonstrate some other form of ocular compromise ranging from nonsuppurative conjunctivitis, superficial and/or stromal keratitis and uveitis, iris atrophy, non-traumatic hyphema to cranial nerve palsies (III, IV, VI), zoster paresis, progressive outer retinal necrosis and acute retinal necrosis.[1-34] Additional sequelae include subconjunctival hemorrhage, follicular conjunctivitis, epithelial and/or interstitial keratitis.[7,13-19]

Corneal involvement may appear as a nondescript epitheliopathy or in the pattern of dendrite (pseudo-dendritic keratopathy).[20] These inflammatory (not infectious) lesions are sometimes termed "meta-herpetic" keratopathy. They may occur with or without keratouveitis and can lead to corneal desensitization.[7,13-18,20]

Chronic corneal inflammation (three to five months) may induce band keratopathy, the production of corneal epithelial mucus plaques and endotheliitis.[7] Patients younger than 60 years of age often present with pseudo-dendriform keratitis and flares of inflammation with or without elevated intraocular pressure (trabeculitis) compared with patients older than 60 who manifest complications related to poor healing and nerve damage (neurotrophic keratopathy).[7,20,24,28]

If the skin lesions surrounding the eye are left unattended, bacterial superinfection is possible, creating the potentially life-threatening complication of orbital cellulitis.[21] Secondary inflammatory glaucoma, scleritis, episcleritis and optic neuritis are all possible.[7-19,24,28] A number of patients continue to experience pain long after resolution of the acute outbreak. This phenomenon is known as *post-herpetic neuralgia.*[14]

The literature estimates that herpes zoster virus (HZV) has the potential to affect 20% to 30% of the unvaccinated population at some point in their lifetime; approximately 10% to 20% of these individuals will manifest HZO.[6] The incidence of HZV in the US population, controlled for the coexistence of cancer, human immunodeficiency virus (HIV) and organ transplantation, is approximately 3.2 per 1,000 persons with about one million new cases reported each year.[11,34] The disease shows a slight preponderance for females over males likely due their increased interactions with the young.[11] The incidence of HZV increases with age, with the highest rates observed among individuals over age 80 (10.9 per 1,000 persons).[8] The literature recognizes little variation by US region.[11]

Pathophysiology

Varicella zoster virus (VZV) is an exclusively human neurotropic herpetic virus.[1-7] Primary infection causes chickenpox; by the age of 60, 90% of the United States population will react seropositive for VZV.[7] Following the initial infection, the virus becomes latent, residing in ganglionic neurons along the entire neuroanatomical axis.[1-3]

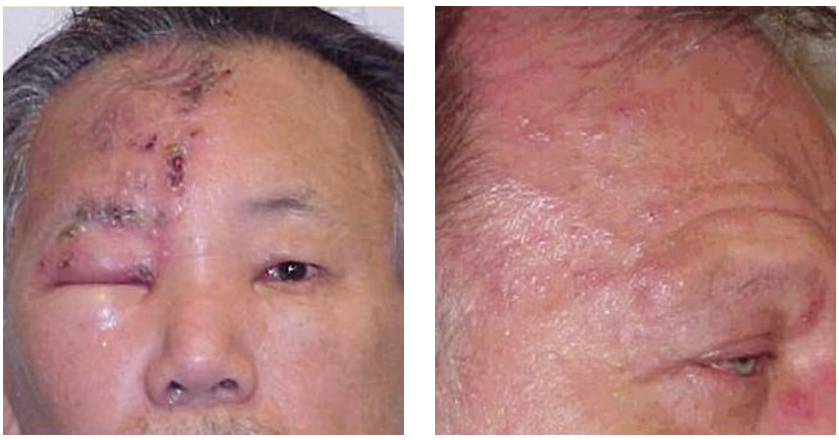
The human immune system is efficient at maintaining balance with the organism allowing only approximately 20% of

non-HIV/transplant patients to convert to active zoster.[7] With advancing age or immunosuppression from normal declining immunity, human immunodeficiency virus, cancer chemotherapy or organ transplantation, cell-mediated immunity to VZV declines, increasing the potential for the virus to reactivate.[1-5] When the immune system fails to maintain virus homeostasis, sectoral, weeping, dermatologic excoriative rash can erupt. The painful dermatomal inflammation is termed "shingles" by laypersons and typically manifests on the back, side and neck. When it involves the eye or lid, within the distribution of the trigeminal nerve on the face, it is termed herpes zoster ophthalmicus.[1-8] Ocular involvement in herpes zoster patients overall occurs in 20% to 50% of cases.[9,10]

HZO is the second manifestation of the varicella zoster virus, after chickenpox.[6,7,31] This virus typically enters the human system through the conjunctiva and/or nasal or oral mucosa, and then occupies sensory ganglia throughout the body.[6,7,31] The herpes zoster rash most commonly resides in the facial and mid-thoracic-to-upper lumbar dermatomes. An active immune system suppresses the virus, which lies dormant in dorsal ganglia. Should the body's immunity become compromised, as described above, the virus actively replicates and travels anterograde along the route of the ganglia.[32]

The pathophysiology of virus suppression is executed via cell-mediated immunity. Natural, environmental periodic re-exposure helps keep this modus active and vital, preventing dormant VZV from activating as herpes zoster.[15] Declining VZV-specific, cell-mediated immune response accounts for the increased frequency of herpes zoster seen in older adults.[6,7,15,20] Periodic subclinical reactivation serves as an immune booster, increasing cell-mediated immunity and reducing the likelihood of a full herpes zoster outbreak.[15]

HZO results when the dormant herpes zoster virus within the trigeminal ganglion is activated. Neuronal spread of the virus occurs along the trigeminal nerve (CN V) primarily in the ophthalmic division (V1), although all divisions are susceptible. When the eye is involved, the nasociliary branch of V1 is affected. Vesicular eruptions on the tip of the nose at the terminal points of this branch is termed *Hutchinson's sign*.[6,7,15,16,31,33] Nasociliary nerve involvement is often coincident with ocular inflammation of the tissues of the anterior segment.[16] Spread of the virus may lead to involvement of other cranial nerves, resulting in optic neuropathy (CN II) or isolated cranial nerve palsies (CN III, IV or VI).[19,21-23,24-27]



Herpes zoster ophthalmicus skin outbreaks respect the midline, consistent with the nerve's distribution.

Recent research has recognized that the virus also traffics through afferent fibers that are in close proximity to the carotid artery and its branches.[32] VZV has been found in temporal arteritis biopsies.[34] Subsequently, VZV-induced inflammation within these vessels has been postulated to increase the risk of arterial occlusion and cerebrovascular accident.[32,34] In one retrospective analysis of people with HZO, a 4.5-fold higher risk of stroke was observed.[32]

The numerous manifestations in HZO are likely due to the varied pathophysiologic processes initiated by the VZV. Features of viral infection, including vascular and neural inflammation, immune and general inflammatory reactions, partially explain the success and failure of anti-viral medication in cases of HZO.[1-35]

Management

The systemic component of this disorder is best treated by initiating oral antiviral therapy as soon as the condition is diagnosed. Oral acyclovir, 600mg to 800mg 5x/day for seven to 10 days is standard. Alternately, famciclovir (500mg PO TID) and valacyclovir (500mg BID to TID) for a seven-day course are acceptable.[7,34-41] Timing is crucial; if these agents are started within 72 hours of the onset of the acute rash, they significantly shorten the rash, the period of pain, viral shedding, anterior segment complications and risk of post-herpetic neuralgia.[7,38] Valacyclovir and famciclovir have a record of reducing the incidence and severity of post-herpetic neuralgia compared with acyclovir.[7] However, oral antiviral agents cannot totally prevent post-herpetic neuralgia.[7,38] Ascertain whether the patient has normal kidney function before prescribing oral antivirals. If in doubt, consult the patient's primary care physician. Topical antiviral medications are unnecessary or, at best, adjunctive treatments.

Oral corticosteroids (prednisone or Medrol methyprednisolone dose pack, Pfizer) may be used as adjuvant therapy to alleviate pain and associated facial edema. Standard prescribing dictates 40mg to 60mg daily, tapered slowly over 10 days.[39] Topical care of the skin lesions may be afforded by applying an antibiotic or antibiotic-steroid ointment to the affected areas twice daily in combination with skin drying agents like calamine preparations or Domeboro (Moberg Pharma) soaks. Ocular management depends upon the tissues involved.

In cases involving uveitis or keratitis, cycloplegia and topical steroids will reduce inflammation and create analgesia. Prophylaxis with a broad-spectrum antibiotic drop or ointment is advisable in the event of a compromised cornea. Finally, palliative therapy may consist simply of cool compresses; however, some patients may require oral analgesics in severely painful cases. Tricyclic antidepressants, antiseizure drugs, opioids and topical analgesics are pain relief options when antivirals do not provide enough relief.[24-42]

The best treatment for HZO is prevention through vaccination.[38-42] The Shingles Prevention Study Group demonstrated that a vaccine against VZV boosted VZV cell-mediated immunity and significantly reduced the morbidity due to herpes zoster and post-herpetic neuralgia in older adults without causing or inducing an actual herpes zoster outbreak.[39] Overall, VZV vaccine reduced the incidence of post-herpetic neuralgia by 66.5%, and the incidence of herpes zoster outbreak was also reduced by 51.3%.[40-42]

Clinical Pearls

- HZO has great propensity for affecting those over the age of 70. Individuals of any age who are immunocompromised due to lymphoma, HIV, acquired immune deficiency syndrome, and individuals with blood dyscrasia, are at increased risk.
- Ocular involvement is extremely variable. The disease is not always obvious in its presentation, especially in the beginning stages. Some patients may present with prodromal headaches of several weeks' duration but display no lesions. Malaise in attendance with an unusual corneal presentation may signal the initial onset.
- Meta-herpetic (pseudodendriform) HZO keratopathy is an inflammatory/infiltrative process, while the dendriform ulcerations seen in herpes simplex virus (HSV) are infectious, resulting from shedding viral particles.
- The pseudo-dendritic lesions seen in HZO have no terminal end-bulbs while true dendritic lesions as seen in HSV do.
- Herpetic keratouveitis is a common manifestation of HZO. Here, intraocular pressure may be elevated in the setting of mild anterior segment inflammation. This is best managed using standard treatments for uveitic inflammation (topical cycloplegia, topical steroid) with the addition of oral antiviral medication and intraocular pressure lowering agents such as beta blockers or alpha-adrenergics BID.
- To reduce risk of outbreak, the Centers for Disease Control (CDC) recommends Shingrix (GlaxoSmithKline), a new shingles vaccine approved in 2017, be given to healthy adults age 50 and older. Shingrix is now preferred over Zostavax (Merck), per the CDC.

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XANTHELASMA

Signs and Symptoms

The term *xanthelasma* is derived from the Greek *xanthos* (meaning "yellow") and *elasma* (meaning "plate"). Xanthelasma are seen clinically as oval or elongated yellowish plaques that arise just beneath the skin of the periorbital region. Most commonly, they are noted near the inner canthus of the upper eyelid (70%), although they may be seen on the lower lid as well.[1] In rare instances, the lesions can involve both upper and lower aspects of the lids and adnexa, encircling the eye in a mask-like fashion.[2] Inspection and palpation may reveal a soft, semisolid or calcified texture.

Individuals with xanthelasma may present because of a cosmetic concern, or the condition may be detected upon routine ocular examination. Symptoms such as pain or tenderness are uncommon. In very rare instances, abnormally large xanthelasma can interfere with lid function causing ptosis or lagophthalmos. There is no tendency toward malignancy, although the lesions may enlarge and/or coalesce over time.

Most patients with xanthelasma are over 50 years of age.[1] Historically, women were believed to be affected more commonly than men; however, more recent prospective data seem to indicate little difference between the sexes.[3] Additionally, there is no recognized racial

predilection. The overall prevalence of xanthelasma is estimated at 4.4%.[3]

Pathophysiology

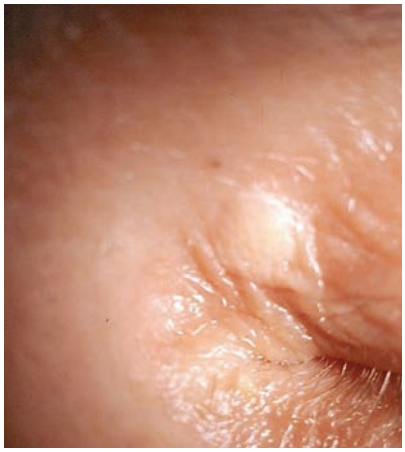
The term *xanthoma* describes a cutaneous deposit of fatty material, appearing as a well-circumscribed lesion in the connective tissue of the skin, tendons or fasciae.[1] Xanthelasma (or more precisely, *xanthelasma palpebrarum*) refers specifically to any xanthoma that affects the periocular area, and these account for >95% of such lesions.[4] Histological evaluation of xanthelasma reveals an aggregation of foamy histiocytes (macrophages), laden with intracellular fat deposits and located primarily within the upper reticular dermis.[5] The main lipid component in xanthelasma is esterified cholesterol.[6] A variety of factors is believed to contribute to the etiopathogenesis of xanthoma formation, including local and systemic lipid abnormalities, hormonal influences, accumulation of macrophages and leakage of plasma lipids into the dermis due to mechanical vascular trauma.[4]

Xanthelasma is associated with increased serum lipid fractions in about half of patients manifesting the disorder.[1] In a recent study, subjects with xanthelasma were found to display elevated mean serum cholesterol, low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) levels in a statistically significant fashion as compared with their age-matched counterparts.[6] A slightly higher incidence of hypertension, ischemic heart disease, familial hypercholesterolemia, familial xanthomatosis and diabetes has also been observed in these patients.[5,6]

Management

In most cases, the diagnosis of xanthelasma is straightforward and can be made based upon the clinical appearance alone. If the presentation is atypical, or if the personal history suggests a possibility of malignancy, incisional biopsy may be indicated. Given the significant potential for dyslipidemia and related comorbidities, laboratory evaluation of total serum cholesterol, high-density lipoprotein (HDL), LDL, VLDL, triglycerides, plasma glucose levels and liver function testing is recommended for all patients who are newly diagnosed with this condition.[3,5-7]

While xanthelasma is considered a benign skin lesion, the cosmetically unappealing nature of the condition often prompts patients to seek treatment. Several techniques can be employed to remove these lesions successfully.



A 45-year-old woman exhibited xanthelasma of the left upper eyelid.

Perhaps the least invasive modality involves the use of chemocautery agents, such as dichloracetic acid. This colorless, mildly pungent liquid agent has both keratolytic and cauterant properties, and may be obtained from a compounding pharmacy or purchased as part of a complete treatment kit (Derma-Cauter-All, Sigma Pharmaceuticals).[8] Use of gentle liquid nitrogen cryotherapy has also been advocated as a potentially effective therapy, but this modality is rarely used due to the risk of associated discomfort and intense post-treatment eyelid swelling.[9] Additionally, cryotherapy carries a risk of depigmentation in individuals with darker skin tones.[10] More invasive therapies include low-voltage radiofrequency ablation, laser photoablation (CO_2, pulsed dye or Nd:YAG) and surgical excision.[11-14]

Clinical Pearls

• Xanthelasma is extremely uncommon in patients under the age of 30. If noted, these individuals should be evaluated thoroughly for dyslipidemia and associated vascular, metabolic or cardiovascular disorders.

• Numerous anecdotal remedies for xanthelasma may be found on various websites and blogs. Some of these include: topical application of crushed garlic, castor oil or lemon rind; a "cleansing diet" consisting of only fresh papaya or pineapple and water for three consecutive days; niacin supplements; and exercise and stress reduction techniques. There are also a variety of cosmetic products (e.g., XanthRemover and Naturalis Xanthelasma Treatment), which claim to be effective and less expensive than surgical treatment. Unfortunately, none of these therapies offer any scientific evidence regarding their efficacy.

• While dietary modifications and the use of statin drugs (e.g., atorvastatin and pravastatin) may be advantageous in managing hypercholesterolemia and other forms of dyslipidemia, little evidence can be found that they have a direct impact on formed xanthelasma lesions. One published case from 2005 illustrated a striking disappearance of eyelid xanthelasma in a patient after starting a course of simvastatin.[15]

• Patients should be aware that, despite effective local treatment for xanthelasma, recurrences can and often do occur. Likewise, patients must understand that all surgical treatment modalities have the potential for complications such as persistent erythema, hypo- or hyperpigmentation, scarring and ectropion.[16,17]

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BLUE SCLERA

Signs and Symptoms

Blue sclera is not a diagnosis but rather a sign of imperfect connective tissue, collagen and collagen-vascular construction and assemblance.[1-10] The etiology of the blue hue comes from the pigmentation of the uveal tunic showing through from beneath an abnormally thin outer scleral coat.[1-10] This is in contradistinction to ocular melanosis, which produces a brown superficial scleral hue. While the blue coloration may be apparent to examiners, in most instances there are no symptoms, unless there is accompanying ocular inflammation or vision loss secondary to an associated retinal vascular occlusion, retinal detachment or choroidal neovascularization (CNV).[6,7]

The ocular signs and symptoms that accompany the findings of blue sclera are consistent with the underlying condition producing it. The systemic diseases frequently associated with blue sclera include nevus of Ota, Ehlers-Danlos syndrome (EDS), Marfan's syndrome, osteogenesis imperfecta and rheumatoid arthritis.[1-10] Recently, the antibiotic minocycline and antiepilectic ezogabine have been recognized as producers of these scleral and retinal pigmentary changes.[11,12]

Pathophysiology

Nevus of Ota, also known as *congenital melanosis bulbi* and *oculodermal melanosis*, is a congenital or acquired benign oculodermal melanocytosis capable of producing patchy blue-gray hyperpigmentation on the face and eyes.[4,8,9,13] In the eye, melanocytes, which are derived from neural crest cells, migrate to the conjunctiva and uvea. When these cells invade the episclera and sclera scaffolding upon branches of trigeminal nerve they can produce, patchy areas of bluish subconjunctival discoloration.[8,9]

Women are nearly five times more likely to be affected than men.[13] The entity is rare among Caucasians.[13] Most cases are unilateral (90%); however, bilaterally does occur.[13] Ocular abnormalities include pigmentation of the sclera, cornea, retina, optic disc, cavernous hemangiomas of the optic disc, ocular melanoma and elevated intraocular pressure (IOP).[13] Secondary open-angle glaucoma is hypothesized to result from aberrant angle pigmentation producing slowed aqueous egress.[4,13] Not every case develops raised IOP.[13,14]

EDS is a heterogeneous group of connective tissue disorders characterized by joint hypermobility, skin hyperelasticity, tissue fragility, easy bruising and poor healing of wounds.[15-17] Abnormal bruising and bleeding with skin extensibility are cardinal features.[16] The vascular complications seen in type IV disease may affect all anatomical areas, with a tendency toward large and medium diameter arteries.[17] In addition to producing a blue sclera via tissue thinning enabling visualization of the underlying uveal pigmentation, conjunctival chalasis is also common.[17]

Orbital pain from dissection of the vertebral or carotid arteries (with accompanying Horner syndrome) may occur.[7,18,19] Patients experiencing such artery dissection (a stretching and tearing of the affected vessel's walls) may present with variable headache along with fleeting visual symptoms such as transient vision loss and transient visual blur.[20]

Patients with EDS may present with blue sclera and dilated and tortuous conjunctival vessels with pulsatile proptosis from affected dilated orbital or adnexal vasculature.[19] EDS has the capability of producing radiating angioid streaks, which are known to have association with acquired choroidal neovascularization (CNV).[21]

Marfan's syndrome is an autosomal-dominant multisystem connective tissue disorder resulting from mutations in the gene for fibrillin, FBN[1.18,22-24] The clinical diagnosis is based on a set of well-defined clinical criteria (long face, cardiac issues, dental issues, ocular issues and lumbosacral dural ectasia).[18,22,24,25] Ocular complications include blue sclera, lens subluxation (typically superiorly—a common diagnostic feature), keratoglobus, keratoconus, vitreous degeneration and angioid streaks (predisposing the potential for CNV).[18,24-27]

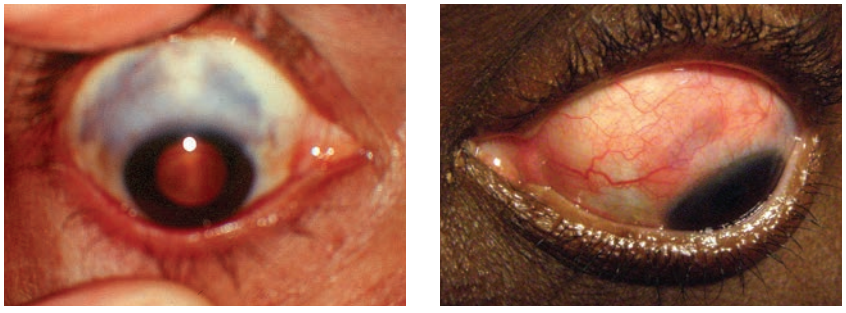
Osteogenesis imperfecta (OI) is a heritable condition characterized by bone fragility and reduced bone mass.[2,5-7,28,29] OI produces systemic complications that include dentinogenesis imperfecta, hearing loss, joint laxity, restrictive pulmonary disease and short stature. Its ocular complications, along with blue sclera, include fragile cornea, decreased ocular rigidity, myopia, glaucoma, keratoconus, corneal opacity, small corneal diameter and congenital Bowman's layer agenesis.[30-32]

Rheumatoid arthritis (RA) is a systemic disease with manifestations in many organ systems.[26] While the articulating surfaces are a focus, extra-articular manifestations occur in almost every organ system with varied incidence.[33-35] Pathogenic mechanisms include pro-oxidative dyslipidemia, insulin resistance, prothrombotic state, hyperhomocysteinemia and immune mechanisms such as T-cell activation. Ophthalmic presentations may include blue sclera, Sjögren's syndrome (autoimmune rheumatic variant characterized by fatigue, dry eyes and dry mouth), episcleritis, scleritis, scleromalacia perforans (inflammation and thinning of the wall of the eyeball), artery and vein occlusion.[33-35]

Management

There is no management course for blue sclera per se. The key to managing patients is recognizing its appearance, and referring for the proper medical workup. Since the management of a discovered systemic disease and its potential complications will rest within the domain of the internist or other specialist, the role of the primary eye care provider is to discover undiagnosed cases and monitor ocular health for the ocular complications.[1-33]

- Cases experiencing refractive consequences secondary to corneal irregularities



In blue sclera, the distinctive hue comes from the pigment of the uveal tunic showing through an abnormally thin outer scleral coat.

can be managed with soft, rigid or scleral contact lenses.[34] Keratoconus or "fragile corneal" complications may receive structural architectural rehabilitation/stabilization using riboflavin/ultraviolet or rose bengal green light procedures.[35]

- Cases producing dry eye or ocular surface abnormalities can be managed with tear drops, ointments, hypertonic solutions and ointments, topical cyclosporine, topical LFA-1 (lymphocyte associated antigen) inhibitors or punctal plugs.
- Cases presenting with ocular inflammation can be managed with topical cycloplegia, topical and oral steroids, topical and oral anti-inflammatory preparations and oral antimetabolite medications such as methotrexate, cyclosporine, azathioprine, mycophenolate or infliximab.
- Cases with raised intraocular pressure should have a complete glaucoma workup, including gonioscopy, photodocumentation of the nerves and pachymetry, as well as structural and functional testing.
- Cases exhibiting signs of the disease can be treated using any topical anti-glaucoma medications, trabeculoplasty or surgery.
- Cases not exhibiting elevated IOP or conversion to treatable disease should be monitored for IOP elevation at regular intervals.

Medical testing is required to determine potential causes for blue sclera.[1-13,36-38] The laboratory testing includes complete blood count with differential and platelets, X-rays of the chest and hands, sacrolumbar/iliac X-ray, Westergren erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), human leukocyte antigen (HLA) testing, rapid plasma reagin (RPR), venereal disease research lab (VDRL) test, fluorescent treponemal antibody absorption test (FTA-Abs), blood urea nitrogen (BUN), total serum protein, homocysteine, skin biopsy and genetic analysis.[32,36-38]

Though primary eye care practitioners may not typically initiate such an evaluation themselves, sharing this information with other medical practitioners who do the workup can be invaluable. Once the underlying disease is diagnosed, ophthalmic comanagement can take place for any evolving comorbidities such as conjunctivitis, corneal irregularities, iritis, dry eye, retinal vasculitis and raised IOP.[1-38]

Clinical Pearls

- Blue sclera may be associated with systemic collagen dysfunction that includes Ehlers-Danlos syndrome, Marfan's syndrome, osteogenesis inperfecta and rheumatoid arthritis.
- Cases occurring secondary to Ehlers-Danlos syndrome or Marfan's syndrome may develop angioid streaks. Any patient with blue sclera should be monitored for angioid streak formation and subsequent CNV formation.
- Corneal thickness has been reported to be reduced in patients with osteogenesis imperfecta and blue sclera. This may be of importance as these patients may have increased risk for glaucoma or exhibit artificially low intraocular pressure measurements.
- Scleritis occurring secondary to rheumatoid arthritis has the potential to cause blinding consequences. Systemic comanagement with a rheumatologic or uveitic specialist is required.

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HERPES SIMPLEX CONJUNCTIVITIS

Signs and Symptoms

The herpes simplex virus (HSV) is a common pathogen and a frequent source of ocular infection.[1-6] Nearly 60% of the American population is seropositive for HSV-1 and another 17% for HSV-2.[1] Initial ocular infection by HSV tends to be seen in younger patients, with an approximate average age of 24 years.[1,2,6] While most cases of HSV conjunctivitis are associated with serotype-1, newborn disease can result from serotype-2.[2,7-9]

Herpes simplex conjunctivitis tends to occur in individuals younger than five years of age.[2,6] Cataract, vitritis, retinitis, retinal detachment and optic nerve

inflammation have all been seen coincident with neonatal HSV conjunctivitis.[2] Secondary HSV infection may occur at any age and in any form (dermatologic, conjunctival or corneal).[1,2,6] The Recurrence Factor Study (RFS) of the Herpetic Eye Disease Study (HEDS) II found no specific trigger factors to be conclusively associated with recurrence.[3] There is no recognized racial or gender predilection in HSV keratitis.[1-10]

The coxsackievirus, enterovirus, human adenovirus, herpes simplex virus and chlamydia have been identified as causes of conjunctivitis in the young, with HSV and chlamydia being most common.[4] HSV conjunctivitis presents similarly to adenoviral disease, demonstrating a non-suppurative, follicular red eye with watery discharge and variable lymphadenopathy.[2] Upon primary infection, the skin around the eyelid may exhibit either epidermal punctate vesicular eruptions or a vesicular papillomacular rash affecting the skin of the lids or lips ("fever blister" or "cold sore") referred to as *herpes labialis*.[2]

The cornea may or may not be involved, exhibiting marginal subepithelial infiltrates—a coarse punctate keratitis, depending upon the severity of the outbreak and exposure to the conjunctival and lid sequellae.[2,10] When the lid alone is involved, the condition is termed *HSV blepharitis*. With concurrent conjunctivitis, the condition is known as *HSV blepharoconjunctivitis*. Dendritic ulcerations with classic terminal end bulbs staining brightly with sodium fluorescein and rose bengal dyes have been reported as part of the syndrome.[1-12] Symptoms include dermatologic irritation, weeping sores, ocular itching, general ocular irritation, epiphora and photophobia with a variable amount of pain.[2-5]

Vision may or may not be affected, depending upon the amount of watery discharge and presence of corneal epitheliopathy. Bilateral HSV conjunctivitis may be encountered in a small number of cases, e.g., those involving children or individuals with immune or atopic diseases.[11,12]

Secondary anterior uveitis is also possible in severe cases.[2,6-12] More severe sequelae—including stromal keratitis, necrotizing stromal keratitis and progressive endotheliitis—can result in corneal complications such as band keratopathy, corneal opacification, neovascularization, thinning and perforation.[11]

Pathophysiology

HSV conjunctivitis can be caused by either type 1 or type 2 herpes simplex.[2,7-9] Infection by HSV-1 predominantly affects the upper half of the body (e.g., eyes and mouth) whereas HSV-2 is mainly associated with diseases of the lower half of the body (e.g., genitalia and perianal region).[13] The virus is transmitted via bodily fluids and affects the skin and mucous membranes of the infected host.[1]

Primary herpetic infections are generally encountered in children and young adults.[1,2,7-9] The herpes simplex virus is a pathogen that establishes what is known as a lytic and latent infection.[14] Reactivation from latency occurs intermittently and chronically, serving as a lifelong source of recurrent infection. HSV has the capability of simultaneously triggering and neutralizing innate immunity.[14] This creates a unique and dynamic equilibrium between the virus and the innate immune system; when the immune system prevails, the signs and symptoms are negligible. When the virus prevails, more substantial signs and symptoms ensue.[14]

In cases where a culture is taken, diagnosis is confirmed by the presence of eosinophilic intranuclear inclusion bodies.[2] After resolution of the initial infection (primary infection), the herpes virus migrates along local nerves to regional ganglia to remain dormant until reactivated by specific stimuli. While the Herpetic Eye Disease Study II failed to positively identify specific risk for recurrence, stimuli postulated by other reports include fever, malaise, stress, exposure to excessive heat, exposure to ultraviolet light and fatigue.[3,15] On average, patients experience recurrences at a rate of 0.6 episodes per year.[16]

While many of the ocular manifestations related to the herpes simplex virus are immune (delayed hypersensitivity reaction) or inflammatory in nature (e.g., stromal and disciform keratitis, iridocyclitis), the epithelial microdendrites seen in cases of HSV conjunctivitis represent infection by live virus.[17,18] More recently, the migration and maturation of dendritic cells within the corneal stroma of patients with HSV keratitis have been recognized as contributors to recurrent disease, suggesting a role for delayed type hypersensitivity in the immunopathogenesis of HSK.[18]

Viral replication in most cases is confined to the corneal epithelium, with stromal invasion impeded by early-responding, non-specific defense mechanisms.[14,18] These are rapidly complemented by the specific, mainly cellular, immune response.[14,18,19] In the case of chronically recurring disease, the corneal stroma may become involved.[17,18] Disciform stromal scarring, conjunctivitis and uveitis are natural sequelae occurring in tandem with the corneal inflammation.[18]

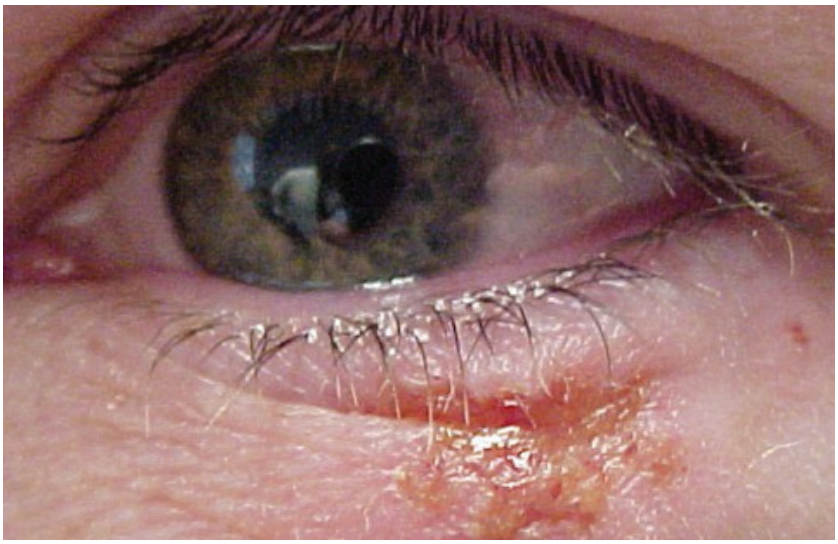
Management

The treatment of neonatal HSV serotype-1 conjunctivitis includes topical trifluridine 1% drops Q2H for seven days along with lid hygiene.[2,6] Ophthalmic antibiotic ointment such as bacitracin or polysporin can be prophylactically applied to any exposed dermatologic excoriations. The mother in such cases should be examined for concurrent gynecological infection.

In cases involving serotype-2, concurrent systemic infection or issues where immunosuppression is suspected, consider concurrent use of oral antiviral therapy with dosage based on age and body weight.[2,6] More recently, ganciclovir 0.15% ophthalmic gel (Zirgan, Bausch + Lomb) has emerged as an alternative to trifluridine. The medication requires less frequent initial dosing (approximately every three hours while awake) and can be tapered as resolution is seen over seven to 10 days. Additionally, ganciclovir demonstrates greatly reduced corneal toxicity, primarily because it is only taken up by virus-infected cells.[17,22,23]

Most cases of HSV conjunctivitis come and go without ever presenting to the practitioner. The disease is generally self-limiting and can be managed with palliative therapies such as artificial tear drops and ointments along with oral over-the-counter analgesics for any additional discomfort. If a papillomacular rash is present, topical prophylactic antibiotic ointments can be prescribed to prevent secondary cellulitis. If the rash is vesicular and "weepy," drying agents such as calamine products or Domeboro (Moberg Pharma, Ceder Knolls) soaks can be employed BID to TID.

Epithelial keratitis concurrently present, with or without subepithelial marginal infiltrates, may be cautiously



Blepharoconjunctivitis from active herpes simplex virus infection is typically self-limiting but palliative therapy can improve patient comfort while healing is underway.

monitored with frequent follow-up appointments for the formation of dendritic microulcerations, frank dendriform ulcers or painful iridocyclitis. A topical antibiotic can be protectively prescribed QID. However, if iritis is present, topical steroid use in the absence of topical antiviral coverage is not advised.[2,20,24,25] Any dendritic ulcer must be managed quickly and aggressively to prevent penetration into deeper corneal tissues with subsequent scarring.

Clinical Pearls

• A unilateral, non-suppurative red eye in a child with watery discharge and lid rash should arouse suspicion for HSV conjunctivitis/blepharoconjunctivitis, particularly if the individual has a previous history of similar episodes.

• The majority of adverse steroid-related outcomes in HSV conjunctivitis have arisen from non-judicious use of a topical steroid (alone or in antibiotic combination). In the setting of corneal involvement, topical steroids should not be used without topical antiviral coverage.

• Not every case of HSV conjunctivitis presents with corneal sequelae. Factors such as severity, recurrence, other topical medications used, atopic disease or a history of immunosuppression can significantly alter the presentation and risk of corneal involvement.

• If corneal involvement is present, recurrent episodes of HSV keratitis induce greater damage to the corneal nerves, leading to hypoesthesia. The cotton-wisp test used for measuring corneal sensitivity is positive in cases of HSV keratitis when one cornea is less sensitive to the touch of the wisp then the other. It should be used whenever HSV is suspected.

• Always consider HSV when unusual epitheliopathies are uncovered.

• Test if HSV dendritic keratopathy is suspected.

• In most cases, HSV conjunctivitis is a self-limiting, nondescript condition that resolves without intervention. Topical prophylactic antibiotic ointment can be dispensed to prevent secondary eyelid infections in cases where a rash is apparent, and drops can be used in cases where keratopathy is significant.

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MEMBRANOUS AND PSEUDOMEMBRANOUS CONJUNCTIVITIS

Signs and Symptoms

Conjunctivitis refers to any generalized inflammation of the conjunctival tissues. Numerous etiologies, including infection, toxicity, allergy and autoimmune disease, may be implicated; nonetheless, signs and symptoms are often the same. Patients typically present with variable edema and hyperemia of the affected tissues of the bulbar and/or tarsal conjunctiva, sometimes with associated pathological manifestations such as follicles or papillae. Discharge is common, and may range from serous to mucopurulent, depending upon the etiology. Individuals of any age, race or gender may be affected by conjunctivitis, although certain pathogens or other causative factors may show a predilection toward a particular cohort.

Associated symptoms may include variable discomfort in the form of itching, burning, scratchiness or other irritation. Pain is less common and tends to be more indicative of concurrent corneal involvement; this is more often the case in certain infectious disorders. Patients may also present due to excessive watering or mucus accumulation in the eyes, or even simply because of cosmetic concern.

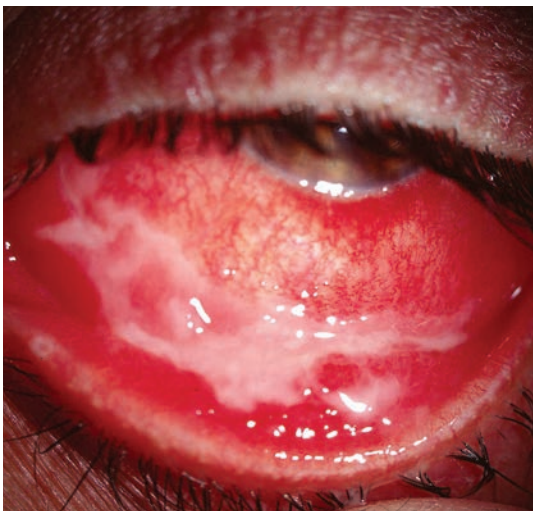
Membranes and pseudomembranes may occur as a complication of any acute or severe conjunctivitis, although classically they have been associated with five principle conditions: adenoviral conjunctivitis, especially epidemic keratoconjunctivitis (EKC); acute bacterial keratoconjunctivitis; ligneous conjunctivitis; toxic/hypersensitivity conjunctivitis, specifically as a manifestation of Stevens-Johnson syndrome; and graft-vs.-host disease (GVHD).[1-9]

Biomicroscopically, membranes and pseudomembranes are seen as a variably thick, yellow-white to porcelain-white film covering the conjunctival surface, most often in the inferior cul-de-sac or along the tarsus. They may likewise affect the upper tarsus, which is why routine lid eversion is important in all cases of conjunctivitis. Membranes and pseudomembranes do not typically impact the symptoms experienced by the patient, unless the condition is so severe as to alter the eyelids' ability to perform their normal functions. For example, if symblepharon develops and the conjunctival fornices become shortened, ocular surface sequelae, including dryness, discomfort and variable visual disturbances, will follow. Likewise, if a membrane or pseudomembrane disturbs the integrity of the cornea, mechanical ulceration may occur.[2]

Differentiation between a pseudomembrane and a true membrane can typically only be made upon attempted removal of the exudate. Pseudomembranes, by definition, lack blood and lymphatic channels, and do not bind tightly with the underlying tissue; hence, upon physical removal there is little to no bleeding. True membranes, on the other hand, penetrate and adhere to the necrotic epithelium and the substantia propria of the affected tissue. This tight adherence causes greater difficulty with removal, and results in an increased likelihood and volume of bleeding upon their extraction.[4]

Pathophysiology

Membranes and pseudomembranes are composed of the same histological materials, primarily consisting of fibrin with some collagen and an assortment of leukocytes, including neutrophils, macrophages, T-cells and activated dendritic cells within an eosinophilic extracellular matrix.[1] These components create a scaffolding over, and superficially within, the underlying mucosal membrane. It has been proposed that the difference between pseudomembranes and true membranes may simply be a matter of degree and intensity of inflammation.[1,10] With a greater or more prolonged inflammatory response, the constituents of the formed membrane invade and commingle with the necrotic epithelium and substantia propria of the conjunctiva, forming more pronounced adhesions.



Pseudomembrane formation in a patient suffering from EKC. As pseudomembranes lack blood and lymphatic channels, they are more easily removed than true membranes, which penetrate and adhere to the affected tissue.

Membranes and pseudomembranes are often associated with severe infections of mucosal tissue. In addition to ocular tissues, such infections can involve the mouth, trachea, colon and skin.[11-13] In the eye, adenoviral serotypes 8 and 19 (e.g., those associated with EKC) and certain bacteria, including *Corynebacterium diphtheriae*, β-hemolytic *Streptococci* and *Neisseria gonorrhoeae* are the most frequently implicated pathogens.[14]

Plasminogen deficiency (both congenital and acquired) has also been associated with the formation of membranes and pseudomembranes on mucosal tissue throughout the body, including the conjunctiva, gingiva, larynx, peritoneum and cervix.[3,15-17] Impaired plasmin-mediated extracellular fibrinolysis (i.e., the disassembly and demolition of superfluous fibrin) results in deposition of ligneous or "wood-like" plaque material onto the affected tissues.

Ligneous conjunctivitis is a rare condition characterized by these conjunctival membranes, associated with an underlying genetic mutation in the plasminogen gene and potentially involving a variety of systemic associations.[18-20]

Membranous conjunctivitis may also be encountered as a complication of inflammatory mucocutaneous disorders, most notably Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[4,8,9] These conditions represent immune-mediated responses, usually to one or more systemic medications, constituting a delayed hypersensitivity reaction.[4,9] SJS and TEN also commonly affect the mouth and throat (in the form of ulcers) as well as the skin, presenting as a series of target lesions or diffuse purpuric macules.[4] When such findings accompany membranous conjunctivitis, immediate medical attention is warranted.

Finally, membranes and pseudomembranes can form as a result of GVHD, a well-recognized complication of allogenic hematopoietic stem cell (i.e., bone marrow) transplantation.[2,21,22] GVHD can be envisioned as an exaggerated, undesirable manifestation of the normal inflammatory mechanism where donor lymphocytes encounter foreign antigens in a milieu that fosters inflammation.[23,24] The fundamental interaction of GVHD is that of donor T-cells with host antigen presenting cells, stimulating the release of cytokines, chemokines and immune cell subsets.[24] In the eye, lacrimal gland and conjunctival tissues can be affected, resulting in dry eye disease, conjunctival scarring and pseudomembrane induction in severe cases.[21-23,25]

Management

Appropriate management of membranous or pseudomembranous conjunctivitis consists of two components: physical removal of the membrane from the conjunctival surface(s) to prevent cicatricial damage to these tissues, and accurate diagnosis and treatment of the underlying etiology.

Removal of membranes and pseudomembranes may be accomplished using a variety of instruments. In less severe cases, a cotton-tipped applicator (CTA) soaked with a combination of anesthetic and antibiotic solution may be adequate. Short,

firm brushing and rolling motions help to loosen the pseudomembrane from the underlying conjunctiva, progressively gathering up fibrinous tissue as one proceeds from nasal to temporal, or vice-versa.

If a CTA alone is inadequate, forceps may be used. It is recommended that the physician first dissect the edge of the membrane or pseudomembrane away from the underlying conjunctiva at either the nasal or temporal aspect of the lid. Then, after obtaining a firm grasp of the inflammatory tissue, it can be peeled away using steady and continuous force. Our preference is to use fine, straight tissue forceps (e.g., Bishop-Harmon style), which have small teeth to maintain one's grip. However, others may prefer smooth (e.g., jeweler type) forceps for this purpose. CTAs may be used concurrently with forceps to help loosen the membranes, while simultaneously absorbing any blood that may be liberated in the removal process. Bleeding can be further addressed using sterile gauze applied firmly to the affected conjunctival surfaces until hemostasis is achieved.[19] Topical astringents such a phenylephrine can be applied prior to removal in order to vasoconstrict superficial vessels and reduce bleeding.

Additional therapy is dictated by the causative disorder. EKC represents a self-limiting, viral infection without any specifically indicated pharmacologic treatment. Nonetheless, intuitive therapeutic intervention often hastens recovery and dramatically improves symptoms. Popular treatment options for EKC include: topical antibiotic-corticosteroid combinations (e.g., tobramycin 0.3%/dexamethasone 0.1% QID); ganciclovir 0.15% gel QID; and povidone-iodine 5% (applied for 30 to 60 seconds in office, followed by thorough rinsing with sterile saline).[7,26-29] Acute bacterial conjunctivitis typically responds to treatment with late-generation fluoroquinolones, such as besifloxacin 0.6% or moxifloxacin 0.5% TID. Topical corticosteroids may be added judiciously to this regimen as improvement in clinical signs is noted. Hyperacute conjunctivitis, if associated with *N. gonorrhoeae*, requires systemic therapy with ceftriaxone (1 gram intramuscularly) along with azithromycin (1 gram orally) for presumptive concurrent *Chlamydia trachomatis* infection.[30]

Ligneous conjunctivitis, while quite rare, requires special consideration due to its genetic implications and potential associations with systemic disorders, including hypoplasminogenemia, Crohn's disease, juvenile colloid milium and congenital occlusive hydrocephalus.[3,18-20] Surgical excision of pseudomembranes in this condition is frequently followed by rapid regrowth and, hence, requires supplemental therapy.[31] A variety of successful treatments have been described, including topical plasminogen, fresh frozen plasma, amniotic membrane transplantation, heparin and topical (or systemic) application of immunosuppressive drugs (e.g., cyclosporine A, azathioprine).[31-35]

SJS and TEN require prompt recognition and therapy to minimize potential scarring and vision loss. Once membranous conjunctivitis has become manifest, inflammation typically leads to corneal epithelial breakdown; treatment is aimed at suppressing this process.[3] Topical corticosteroids (e.g., 0.25% fluorometholone QID) are strongly advocated during the acute conjunctivitis phase, despite the relative dearth of prospective clinical trials to support this practice.[3,36,37] Many practitioners also include a topical antibiotic for prophylaxis, although drugs with a known propensity toward inducing SJS (e.g., sulfonamides and macrolides) should be avoided.[3] Some sources further recommend the concurrent use of topical cyclosporine A twice daily.[37]

Liberal use of artificial tears is also important. Beyond topical therapy, amniotic membrane transplantation (AMT) may help to ameliorate inflammation and prevent scarring associated with fibrosis and angiogenesis.[38] The Prokera device (Bio-Tissue) may be particularly appropriate in cases of SJS, since this system employs an amniotic membrane suspended over a polymethyl methacrylate ring; this ring may in and of itself help to mechanically prevent some degree of symblepharon formation.[38]

Ultimately, nearly 90% of patients who are diagnosed with SJS or TEN will develop chronic ocular complications, and therefore, surgical intervention is often necessary despite primary care efforts.[39] Some of the techniques that may be employed include blepharoplasty and entropion repair, salivary gland transplantation and mucous membrane (typically buccal) grafting.[36]

Pseudomembranous conjunctivitis secondary to GVHD is treated much in the same way as SJS. In addition to mechanical removal of any membranes, most sources now recommend topical treatment with corticosteroids and cyclosporine A during the acute stages.[21,22,40,41] Other topical therapies such as retinoic acid and autologous serum tears have also been used with some success.[42,43] Late-stage complications of persistent ocular GVHD can include superior limbic keratoconjunctivitis, episcleritis, keratoconjunctivitis sicca, corneal epithelial sloughing, corneal neovascularization and even corneal melting with perforation.[22,44] Long-term management for these patients must incorporate lubrication therapy and appropriate use of anti-inflammatory or immunomodulatory agents, possibly including AMT.[44,45] Physicians skilled in the medical and surgical management of advanced ocular surface disease are the most appropriate individuals to care for these patients.

Clinical Pearls

- The finding of a conjunctival membrane or pseudomembrane implies either an underlying ocular infection or an immune-mediated inflammatory disorder. This should be the first differential for the clinician encountering a membranous conjunctivitis.
- In cases of hyperacute conjunctivitis associated with membranes, cultures and scrapings are recommended to help identify the causative pathogen and direct treatment.
- Persistent dry eye disease is a common sequela following membranous and pseudomembranous conjunctivitis, regardless of the etiology. This is true even in cases of EKC, which is considered to be a self-limiting disorder. The etiology is believed to involve a loss of goblet cells, in addition to potential alteration of lid-globe apposition and ocular surface morphology due to scar formation.[46]
- For ligneous conjunctivitis, a plasminogen concentrate formulated into an ophthalmologic preparation may serve as an effective topical therapy. Unfortunately, such a product is not available commercially in the United States; it must be prepared from human plasma by a qualified compounding pharmacist.[32]
- In young patients diagnosed with ligneous conjunctivitis, it is not unreasonable to order laboratory studies for hypoplasminogenemia.

- Patients with disseminated, multifocal manifestations of SJS or TEN likely require medical attention by a team of physicians including burn surgeons, intensive care specialists, anesthetists and other health care personnel specifically trained in the management of such disorders. Systemic immunosuppressive and immunomodulatory therapies are most appropriately provided in such a setting.[36]
- Scleral contact lenses may be of great benefit in managing the resultant ocular surface disease and visual disability that can result following membranous or pseudomembranous conjunctivitis.

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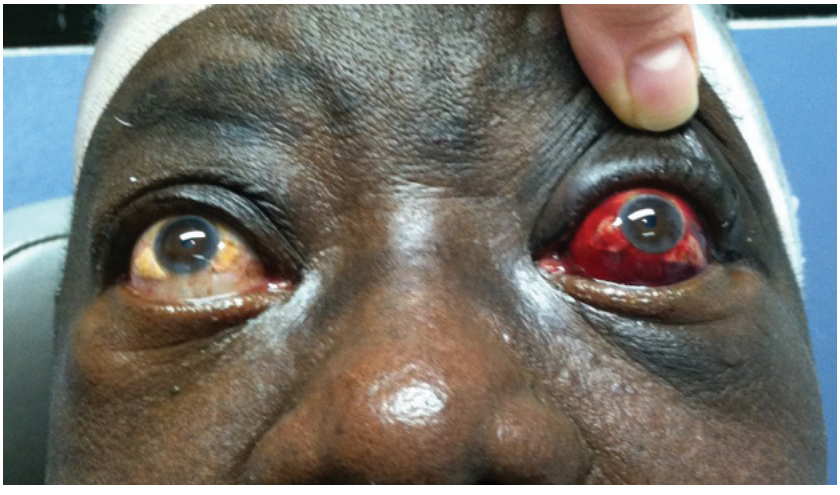
SUBCONJUNCTIVAL HEMORRHAGE

Signs and Symptoms

Subconjunctival hemorrhage (SCH) is a frequently seen ocular condition. Patients typically present acutely, often with great anxiety regarding a "blood-red eye." A history of antecedent trauma is often, but not always, present. Pain and/or photophobia are atypical unless the condition has been associated with blunt injury. Likewise, visual acuity is not impacted unless there is associated ocular compromise due to trauma.

Clinical presentation involves a well-defined, circumscribed area of visible, coalesced blood between the bulbar conjunctiva and episclera.[1-5] The hemorrhage may be flat or elevated depending upon the volume of blood involved. Slit lamp examination can reveal a widely variable clinical picture, with mild cases demonstrating only blotchy, focal areas of hemorrhage, to severe cases covering the full range of the palpebral aperture and completely obscuring the underlying sclera.[1]



This patient's blood-red eye is a typical presentation of subconjunctival hemorrhage.

SCH can be encountered at any age, with individuals of any race and either gender. Traumatic SCH tends to occur more commonly in men and a younger demographic.[4,5] In cases not associated with trauma, patients tend to be older, typically over 60 years of age.[2,4] In such individuals, the systemic history often reveals associated risk factors, the most common of these being hypertension, arteriolosclerosis, diabetes, hematologic disorders and medical therapy with anticoagulant or antiplatelet drugs.[1,2,4-7] The patient may also relay or confirm a history that includes a recent Valsalva maneuver. By definition, the Valsalva maneuver involves either an intentional or involuntary expulsion of air against a closed glottis, causing rapidly and often severely increased pressure in both the chest and head.[1,8,9] Episodes of violent sneezing, coughing, vomiting, forced defecation, weight lifting or other forms of straining may be consistent with this phenomenon and, hence, with SCH.[1,8,9]

SCH may also occur in association with or subsequent to other primary ocular disorders. Numerous studies have suggested that individuals with conjunctivochalasis are predisposed to more frequent and chronic instances of SCH, likely due to the frictional forces of a loosely adherent, redundant conjunctiva.[10-12] Infectious conjunctivitides, most notably epidemic keratoconjunctivitis and acute hemorrhagic conjunctivitis, but also those caused by systemic infection such as typhoid, dengue fever and Ebola may induce SCH as well.[13-17] Ophthalmic procedures, including laser-assisted in situ keratomileusis, cataract extraction and intravitreal injections, can produce SCH as an unintentional sequela.[1,4,18] Injury associated with application or removal of contact lenses is another common source of SCH.[3,4,19]

Pathophysiology

Histologically, SCH is defined as hemorrhage in the subconjunctival space, localized between the conjunctiva and Tenon's capsule, superficial to the episclera and sclera.[1,5] It is associated with rupture or leakage of subconjunctival capillaries, which may result from a variety of factors. External mechanical forces are responsible for a good portion of cases seen clinically. In one study, nearly 78% of patients under the age of 40 had SCH associated with some type of traumatic event.[4]

Potential etiologies in this category include penetrating injury, iatrogenic trauma, blunt trauma, contact lens-related injury or vigorous eye rubbing.[1,4,5] Rapid acceleration or deceleration (as might be encountered in a motor vehicle accident) and barotrauma associated with scuba diving (i.e., "mask squeeze") would also fall into this category.[20]

Internal mechanical forces can also induce SCH. As previously discussed, Valsalva maneuvers result in both increased intrathoracic and intra-abdominal pressure.[9] This pressure is transmitted along the vasculature as well, primarily affecting the non-muscular walls of the venous system. The jugular, orbital and choroidal veins are subject to rapidly expansive forces; smaller tributaries of these blood vessels within the conjunctiva or retina may be susceptible to rupture.[1,8,9,21] Conditions that further increase abdominal pressure, such as elevated body mass index or pregnancy, may enhance this susceptibility.[22]

Most cases of SCH in patients over age 60 are associated with small-vessel disease, primarily hypertension and diabetes.[2,4] Hypertension causes increased pressure on arterial and venous walls, making them more prone to structural damage, while diabetes induces macrovessel dilation and capillary dropout.[23] A hallmark of these diseases is vascular leakage in end-organs, such as the eye.

Finally, hematologic abnormalities can be influential in the development of SCH. Anemias, blood dyscrasias and blood malignancies (e.g., polycythemia, hemochromatosis, hyperlipidemia, acute lymphoblastic leukemia and multiple myeloma) serve to increase blood volume and viscosity while diminishing blood flow. Bleeding disorders (e.g., Von Willibrand's disease, hemophilia and adverse effects of anticoagulation therapy) diminish one's ability to form clots and promote hemorrhagic conditions. All of these conditions may also be associated with SCH.[6,7,24-26]

The etiologic factors underlying SCH may be reflected in its presentation, although individual variations certainly may occur. A prospective study of 151 consecutive patients with SCH reached the following conclusions: Traumatic SCH had a smaller extent compared with SCH related to hypertension, diabetes, hyperlipidemia or those designated as idiopathic; the extent of SCH was greater in older patients (>60 years), especially those who had previously undergone cataract surgery; overall, SCH was significantly more common in the inferior areas than the superior areas, but in patients with SCH secondary to trauma or diabetes, the temporal areas were affected more often than the nasal areas.[3]

Management

For all patients, the management of SCH must begin with appropriate education and reassurance. In most instances—especially those involving spontaneous (i.e., non-traumatic) SCH—the condition is substantially worse in terms of cosmesis than prognosis. It is typically self-limiting, and resolves completely within a week or two in the vast majority of cases.[27,28] As the hemorrhage dissipates, it is normal for the color to change, first from bright to dark red, then fading to yellow and ultimately clearing. To date, no specific therapy has been shown to expedite this process, although many practitioners continue to recommend artificial tears and warm or cool compresses in an effort to palliate the patient.

SCH associated with trauma warrants a comprehensive ophthalmic examination to identify any additional ocular compromise. Blunt injury carries a risk of concurrent uveitis, hyphema, angle recession, lens subluxation and retinal detachment. Lacerations and puncture wounds may penetrate deeper, whereby the SCH may conceal a possible perforation of the globe. Treatment of these comorbidities is case-specific and may necessitate referral for surgical consultation.

In those cases that are seemingly idiopathic—particularly recurrent or persistent cases—a systemic etiology should be considered and investigated. A comprehensive physical examination is prudent if the patient has not undergone one in the past year, as hypertension, diabetes and hyperlipidemia are the most common associations.[1] Additional laboratory testing may be directed toward identifying blood dyscrasias, clotting disorders and other hematological abnormalities. Suggested testing may include (but is not limited to) the following: a complete blood count (CBC) with differential and platelets, prothrombin time (PT), activated partial thromboplastin time (PTT), homocysteine levels, antiphospholipid antibodies, protein S, protein C, antithrombin III,

factor V Leiden, beta-glycoprotein, sickle-cell preparation and human immunodeficiency virus titers. Patients taking warfarin (Coumadin, Bristol-Myers Squibb) or dabigatran (Pradaxa, Boehringer Ingelheim Pharmaceuticals) should obtain international normalized ratio (INR) values to determine if therapy needs to be adjusted.[29-31] However, before any systemic medications are discontinued or modified, communication and discussion with the internist is essential.

Clinical Pearls

- It is not unusual for patients with SCH to present wearing dark sunglasses, presumably to hide the disquieting appearance from the public. We have observed this many times in clinical practice.
- In discussing SCH with patients, we sometimes like to use the "ketchup under plastic wrap" or "blood blister" analogy. Even a small drop of ketchup (blood) can look menacing if it's compressed over a large area by a tight layer of plastic wrap (conjunctiva). This description using common household items nearly always helps to make the patient less anxious about the presentation.
- The word *hyposphagma* is sometimes used synonymously with subconjunctival hemorrhage. This term is considered obsolete by most and is rarely taught in today's educational institutions; still, some authors persist in using this term (particularly in publications originating outside the United States).[32]
- Additional, though rarely encountered, causes of SCH include strangulation injuries and conjunctival tumors. Patients who have survived asphyxiation may present with a triad of SCH, eyelid ecchymosis and petechial hemorrhages of the face.[33] If noted in infants or young children, this may be a potential sign of abuse and should be reported to the proper authorities.[34] Vascular or malignant tumors of the conjunctiva may also be the source of SCH, although these diagnoses are typically evident well before the patient presents with hemorrhage.[35,36]
- Patients with traumatic SCH may report discomfort if associated with blunt injury to the orbit or face. When considering an analgesic medication, it is preferable to avoid aspirin, ibuprofen and any of their derivatives that may promote anti-platelet activity. Acetaminophen, with or without narcotic or non-narcotic agents (e.g., codeine, hydrocodone and tramadol), is likely the best choice for these individuals.
- The medical workup of a patient with SCH should be directed by the history, both of the immediate preceding events and the known health status at the time of presentation. Seemingly idiopathic cases that are recurrent or persistent in nature certainly warrant further investigation. An isolated SCH due to obvious trauma, Valsalva maneuver, contact lens injury or similar singular event likely does not require a comprehensive medical evaluation, assuming the patient is otherwise healthy.
- One simple systemic investigation that can be readily performed on virtually all patients with SCH is blood pressure measurement. This is of particular value in patients over the age of 60, where systemic conditions are usually the causative etiology.
- Although it may be tempting to employ surgical evacuation for a large or extensive SCH, this technique is rarely used. It should only be considered in cases that present with severe pain and significant ophthalmic morbidity to adjacent structures, such as might be seen in a subconjunctival hematoma.[37]
- Any 360-degree subconjunctival hemorrhage following trauma should invoke suspicion and prompt an investigation to rule out a ruptured globe.
- Patients should be educated that topical vasoconstrictor agents will not help and that eye rubbing may increase rebleeding.

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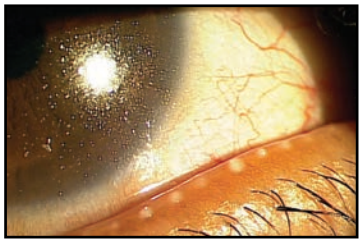

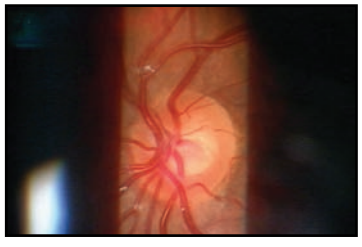

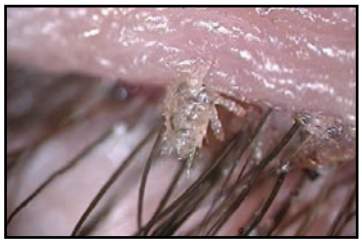

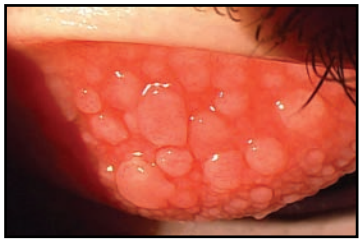

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IMMUNE STROMAL (INTERSTITIAL) KERATITIS

Signs and Symptoms

Immune stromal keratitis (ISK), historically referred to as interstitial keratitis, may be seen as either an active corneal inflammation or as an inactive disorder with characteristic signs of cicatrization (i.e., scarring). The condition may be unilateral or bilateral, depending upon the underlying etiology.[1] There is often a history of past ocular infection or of systemic illness, such as tuberculosis or syphilis.[1,2] In other cases, ISK may be the initial manifestation of an undiagnosed systemic disease. The condition may also be idiopathic.

In the active or acute form of ISK, patients characteristically present with pain, photophobia, lacrimation and blepharospasm of the involved eye. Vision is often reduced, although the severity of visual compromise varies greatly. Biomicroscopy demonstrates single or multiple white patches within the central and/or peripheral cornea. Upon closer inspection, these patches reveal inflammatory cellular infiltrate and associated edema at the level of the stroma.[3] As a general rule, the overlying epithelium typically remains intact. Rapid neovascularization is another hallmark of active ISK, extending from the limbus to the stromal lesions.[4] Concurrent uveitis is common, with patients displaying inflammatory cells in the anterior chamber as well as keratic precipitates along the corneal endothelium.

Cicatricial changes may ensue in chronic cases over months or years, including stromal scarring, corneal thinning, "ghost" vessels (i.e., residual neovascular networks devoid of active blood circulation), the formation of band keratopathy and reduplication of Descemet's membrane.[1,3,5] In severe cases, endothelial decompensation may occur, leading to chronic stromal edema. When patients present with this array of findings in the absence of acute inflammation, the disease is said to be in the inactive stage.[3]

Particular attention must be paid to patients presenting with ISK and hearing loss, heralding the potential for Cogan's syndrome. This is an idiopathic inflammatory disease that primarily affects young adults. Its characteristic presentation involves painful, bilateral ISK, sometimes with concurrent conjunctivitis, uveitis, episcleritis or scleritis.[1] Vestibuloauditory dysfunction in the form of tinnitus, deafness and/or rotatory vertigo is the other classic feature of Cogan's syndrome.[1]

Pathophysiology

ISK has been described as a nonsuppurative, immune-mediated inflammation of the corneal stroma without primary involvement of the epithelium or endothelium.[5] The inflammatory response appears to be directed toward antigens within the cornea which may be microbial or autoimmune in nature.[1,5,6] Numerous conditions have been associated with ISK, most notably herpes simplex and syphilis, but also herpes zoster, mononucleosis (Epstein-Barr virus), measles, rubella, chlamydia, tuberculosis, Lyme disease, leprosy, leishmaniasis, onchocerciasis, trypanosomiasis, *Acanthamoeba*, sarcoidosis and Hodgkin's disease.[1-3,5-9]

According to a widely held, authoritative study on this subject, the most common etiology of ISK is the herpes simplex virus (HSV), accounting for more than 70% of unilateral, active cases and 50% of unilateral inactive cases.[3] Syphilis, once synonymous with the term interstitial keratitis, is believed to be responsible for just over 50% of bilateral inactive cases, but less than 20% of total cases of ISK.[3] It has been estimated that 60% of cases exhibiting bilateral, active ISK are idiopathic in nature, with 10% due to HSV and 5% due to syphilis.[3]

It must be stressed that, despite the potential presence of microbial antigens, ISK involves no active microbial infection at the level of the corneal stroma. Generally, ISK is considered a Type 4 hypersensitivity response to an infectious organism or its antigen.

For example, in ISK secondary to HSV, DNA fragments and immune complexes persist within the cornea long after the live organism has been vanquished. These remaining viral components are highly immunogenic and potentiate the formation of cytokines, chemokines and angiogenic factors via a CD4 T-cell orchestrated response, together with neutrophils, macrophages and other inflammatory cells.[10,11] The release of various interleukins, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, macrophage inflammatory proteins, monocyte chemoattractant proteins, matrix metalloproteinase (MMP)-9 and vascular endothelial growth factor (VEGF) drive the pathogenesis of ISK.[10] Subsequent stromal vascularization and cicatrization will invariably result if the condition remains untreated.

Management

Because a wide range of etiologies are potentially involved, the patient with ISK should undergo a directed diagnostic evaluation; that is, unless the cause is known to be herpetic based upon the history or evidence of physical examination. Laboratory testing is of little value in HSV keratitis, since the virus is exceedingly difficult to culture.

The medical workup for ISK of unknown etiology should include testing for syphilis (fluorescent treponemal antibody absorption [FTA-ABS] or microhemagglutination assay for *Treponema pallidum* [MHA-TP]), tuberculosis (purified protein derivative [PPD] or QuantiFERON-TB Gold [QFT-G] and chest X-ray), Lyme disease (enzyme-linked immunosorbent assay [ELISA] and/or Western blot test) and collagen vascular disorders (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], serum creatinine, rheumatoid factor [RF] and antinuclear antibodies [ANA]).[1] Additional testing may be ordered after consultation with the patient's primary care physician, based upon the history and physical examination.

The principal management of active interstitial keratitis involves the use of medications aimed at the underlying disease process, combined with potent systemic and local immunosuppressant agents to stem the local inflammation within the cornea.[12] The primary therapy will vary depending upon the etiology. In cases of HSV, the use of oral antiviral agents is critical.

According to a recent white paper by the American Academy of Ophthalmology, oral antiviral medications are preferable to topical agents due to potential toxicity associated with trifluridine solution and an inability of both trifluridine and ganciclovir to demonstrate adequate penetration into the corneal stroma.[13] Therapeutic options therefore include acyclovir 400mg twice daily, famciclovir 250mg twice daily or valacyclovir 500mg once daily. While these are considered prophylactic doses, they are

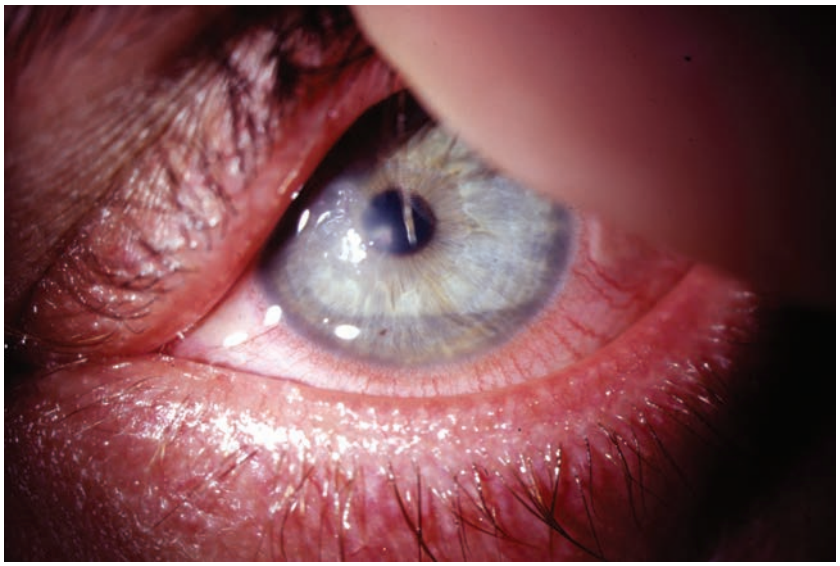
nonetheless crucial in the management of HSV ISK.

Systemic treatment for syphilitic ISK is indicated in cases of active infection, absence of previous treatment or presence of clinical signs of neurosyphilis.[1] The drug of choice remains parenteral penicillin (benzathine penicillin G, 2.4 million units administered intramuscularly).[14] Doxycycline, erythromycin and tetracycline may be acceptable options for patients allergic to penicillin. However, these drugs are not sufficiently effective in cases of neurosyphilis; therefore, those with late-stage disease first require penicillin desensitization.[14] For other infectious or non-infectious etiologies of ISK, systemic treatment is best guided by the primary care physician.

The inflammatory aspect of ISK is typically addressed with the concurrent use of potent topical corticosteroids. In the arm of the Herpetic Eye Disease Study (HEDS) that dealt with stromal keratitis, researchers used 1% prednisolone phosphate, dosed eight times daily at the initiation of therapy, in conjunction with a topical antiviral agent (1% trifluridine QID).[15] Today, most practitioners would likely prescribe 1% prednisolone acetate every two to three hours while awake; 0.5% loteprednol Q2H or 0.05% difluprednate QID are also reasonable options.

Tapering of steroids should be initiated very slowly, consistent with clinical improvement. It is not unusual for low doses of topical corticosteroid to be required for months or years, and some patients may require treatment indefinitely. In the aforementioned HEDS, medications were tapered over a 10-week period, and the authors concluded that even this was insufficient for most patients, recommending a longer period of therapy.[15] In addition to topical corticosteroids, cycloplegia (e.g., 1% atropine QD to BID) is often helpful in ameliorating patient discomfort, particularly for those with concurrent anterior uveitis. Choice and dosing of topical steroids and cycloplegics should match the degree of inflammation.

For those with HSV ISK, a prophylactic dosage of oral antiviral medications should be maintained as long as treatment with topical immunosuppressants is necessary. In fact, based on additional information from the HEDS reports, the ongoing use of these medications appears to significantly reduce the recurrence rates of epithelial and stromal keratitis associated with HSV.[16-18]



Acute ISK in a patient with a history of HSV keratitis. Treatment in this case requires oral antivirals as well as topical corticosteroid therapy.

While topical corticosteroids remain the standard of care for acute ISK, the use of alternative therapies may be beneficial in cases where long-term steroid use places the patient at risk for complications (i.e., ocular hypertension or cataractogenesis) or where steroid therapy alone is insufficient. Topical cyclosporine has been well-documented as an effective steroid-sparing therapy for cases of ISK.[19-22] Topical tacrolimus also has been shown to be effective in cases of ISK refractory to cyclosporine.[12]

As corneal vascularization and scarring are the primary sources of visual morbidity in ISK, it seems reasonable that antiangiogenic medications might provide therapeutic benefit for improving visual outcome.[23-25] A reported case of subconjunctivally injected bevacizumab demonstrated the potential to dramatically regress corneal vessels within one week after the injection.[26] Potentially, bevacizumab (and similar VEGF inhibitors) may be a valid adjunct for patients with corneal neovascularization caused by ISK.

Patients with suspected Cogan's syndrome warrant prompt referral to a rheumatologist, as this condition may be associated with systemic vasculitis as well as aortitis.[27] In addition, there is significant potential for profound hearing loss with recurrent episodes. While the ocular manifestations respond well to topical steroids and are rarely serious, systemic therapy is essential to avert serious hearing impairment and prevent life-threatening complications. Treatment, which typically involves intravenous and oral corticosteroids, methotrexate, cyclophosphamide and/or other immunosuppressant agents should be guided by an experienced physician.[27]

Clinical Pearls

- If a patient develops ISK on the same side as a prior episode of either herpes simplex or herpes zoster infection, and there is no indication of other disease in the patient's history, then no further diagnostic evaluation is necessary. In such cases, it can safely be assumed that the cause of the ISK is herpetic.
- Historically, ISK has been associated with syphilis. Today, syphilis is recognized as the main cause of bilateral, inactive ISK. By far, the main identifiable cause of active cases of ISK is herpes simplex virus.
- In rare instances, HSV ISK may present as a necrotizing stromal keratitis. Necrotizing keratitis is far more severe and aggressive than non-necrotizing ISK, manifesting as a dense, cheesy-yellow-white stromal infiltration often following recurrent ocular herpetic disease. Unlike typical ISK, the necrotizing form has a propensity toward epithelial ulceration, corneal thinning and possible perforation.[13,29] This condition has been associated with various extenuating circumstances, including refractive surgery, inflammatory

bowel disease and acyclovir-resistant HSV.[29-31]

- Stromal inflammatory infiltration in ISK can sometimes be mistaken for microbial keratitis (e.g., bacterial, fungal or *Acanthamoeba* keratitis). It is important to remember that ISK will have a generally intact epithelium, whereas MK presents with frank epithelial ulceration. Moreover, ISK runs a protracted and indolent course, while MK from bacteria is much more acute in presentation and demonstrates a substantially more rapid progression if untreated.
- Suspect Cogan's syndrome in any patient presenting with ocular inflammation who develops hearing loss, vertigo, ataxia, tinnitus, systemic vasculitis or cardiovascular symptoms.
- In patients on long-term oral antiviral suppressant therapy, ensure that the patient gets kidney function studies every six months.

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MICROCORNEA

Signs and Symptoms

A number of corneal anomalies are present at birth. They may be caused by idiopathic genetic alterations, mutations or exposure to a teratogen during gestation.[1] The normal cornea's horizontal diameter at birth measures between 9.5mm and 10.5mm.[1] The vertical dimension is slightly smaller, as the horizontal limbus is wider than the vertical at delivery.[1] As the individual matures, normal corneal growth occurs with final dimensions measuring 10mm and 12.5mm in adulthood.[1] Microcornea is defined as an adult cornea measuring less than 10mm in either the horizontal or vertical meridian in an otherwise normally sized eye.[1-5]

Microcornea is a congenital condition with no gender predilection. It often becomes apparent or detected during childhood.[1-5] In some cases, the cornea may be as small as 4mm.[6] Isolated cases of microcornea often present with normal visual acuity, though more demonstrate ocular and systemic complications such as iris coloboma, cataract, lens microphthalmia syndrome, glaucoma, optic disk pits, Ehlers-Danlos syndrome, Waardenburg's craniofacial syndrome, Norrie's syndrome, Turner's syndrome and Kabuki syndrome.[7-20] There is an association with congenital rubella.[10,21] In the setting of congenital cataract, glaucoma, iris coloboma or retinal/optic disc colobomas, vision can become significantly compromised.[7-20]

Patients with microcornea are at risk for the development of secondary open-angle, primary angle-closure and secondary angle-closure glaucoma.[14,19-20,22] While most cases are of the open-angle variety, related to altered angle architecture and function, pupil block and other complex angle-closure mechanisms occur as well.[14,19-20,22] In a recent report, children born with aphakia and microcornea were found to have thicker central corneal thicknesses (CCT) and higher measured intraocular pressures (IOP) compared to normal eyes.[19]

Pathophysiology

At the fifth week of gestation the lens separates from surface ectoderm.[1] Mesenchymal neural crest cells migrate between the surface ectoderm and optic cup, producing what will become the anterior chamber.[1]

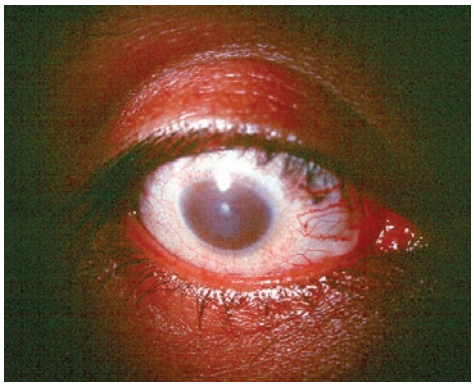
The first wave of mesenchyme becomes the corneal endothelium and trabecular meshwork. The second wave processes stromal keratocytes. The third wave generates iris stroma.[1] Alterations in this developmental process have the potential to alter corneal size, shape and clarity.[1] Microcornea typically occurs following an arrest in corneal development after the fifth month of fetal growth.[1,23]

The condition can be a feature of a multitude of ocular or oculosystemic syndromes, or it may occur as an isolated autosomal dominant defect.[24] Microcornea with cataract has been identified as a unique syndrome, associated with a genetic defect for transcription factor MAF, a proto-oncogene sometimes associated with multiple myeloma.[4,23] More commonly, microcornea occurs in association with conditions such as Peter's anomaly or sclerocornea.[24]

Microcornea must be differentiated from microphthalmos, also referred to as nanophthalmos. Microphthalmos describes a condition in which the entire eye is smaller than normal, rather than

just the cornea. This condition may result from arrested development at a number of stages of fetal developmental.[14,25] It is more significant than microcornea in terms of visual health.[14,25]

In some cases of microphthalmos, there is orbital cyst formation and pronounced hypermetropia.[25] As microphthalmos is accompanied by impaired aqueous outflow secondary to compression of vortex veins and abnormal scleral thickness, the risk of glaucoma is increased.[26] In these cases, any relative increase in lens volume has the potential to induce ciliary block and a malignant (ciliary block) glaucoma.[26] Some cases demonstrate extreme deformation of the eye.[14,25]



Any adult whose cornea measures smaller than 10mm in diameter in an otherwise normal-sized eye is considered to have a microcornea.

Management

Appropriate management for microcornea begins with a comprehensive evaluation of ocular structure and function. In unilateral cases, refractive error may be substantially different between the eyes, making it fusion averse with potential amblyopia development. Refractive correction should be issued as early as possible to decrease the likelihood of amblyopia. Also, polycarbonate lenses should be used if there is any significant difference in visual function between the eyes in order to protect the good eye.

Evaluation of the anterior chamber is critical in patients with microcornea to rule out anterior chamber cleavage syndromes.[24] Increased central corneal thickness may be have the ability to modify applanation intraocular pressure readings, making pachymetry an important measurement in these patients.[19] Tonometry must be performed to rule out the presence of raised IOP. Angle assessment gonioscopy should be completed to understand iridocorneal relationships and angle status. IOP-lowering agents should be initiated in those found to have ocular hypertension.

Congenital glaucomas require surgical intervention and are best managed by a pediatric glaucoma specialist. If microcornea has an impact on a child's cosmesis and self-image, use of opaque soft or scleral contact lenses may provide improvement.[27,28] These are particularly useful in individuals with unilateral microcornea.

Since microcorneas also possess the properties of being flatter or steeper than average corneas, custom lens designs may be required. Patients with unilateral microphthalmos can enjoy improved cosmetics with a scleral shell ocular prosthetic lens. The lens can be fit over the existing eye and worn like a scleral contact lens. They are particularly useful in eyes that have limited or no functional ability. The fit of any contact lens is influenced by the combination of anterior segment features such as lid characteristics, palpebral aperture, corneal dimensions, scleral toricity, corneal asphericity, sagittal depth, tear volume and lens features such as lens design and material, water content, edge profile and thickness.[28]

Successes will be determined by the extremes of the case and the ability to match the correct lens material with a company who is willing to custom design parameters of that lens and then modify them after clinical feedback is presented. The motivation of the patient to try is critical; they must also be able to engage in good contact lens practices. If the eye begins to undergo phthisis, a full prosthesis can be considered.

Clinical Pearls

- Microcornea is a finding rather than a diagnosis. It may be associated with a host of hereditary conditions.
- Upon the discovery of microcornea (or microphthalmos), a referral must be made to an internist suggesting comprehensive medical testing.
- Comprehensive ocular evaluation should be performed, as retinal colobomas may also be present and IOP must be assessed.
- Pedigree analysis and genetic counseling may be indicated given the multiple genetic associations with microcornea.

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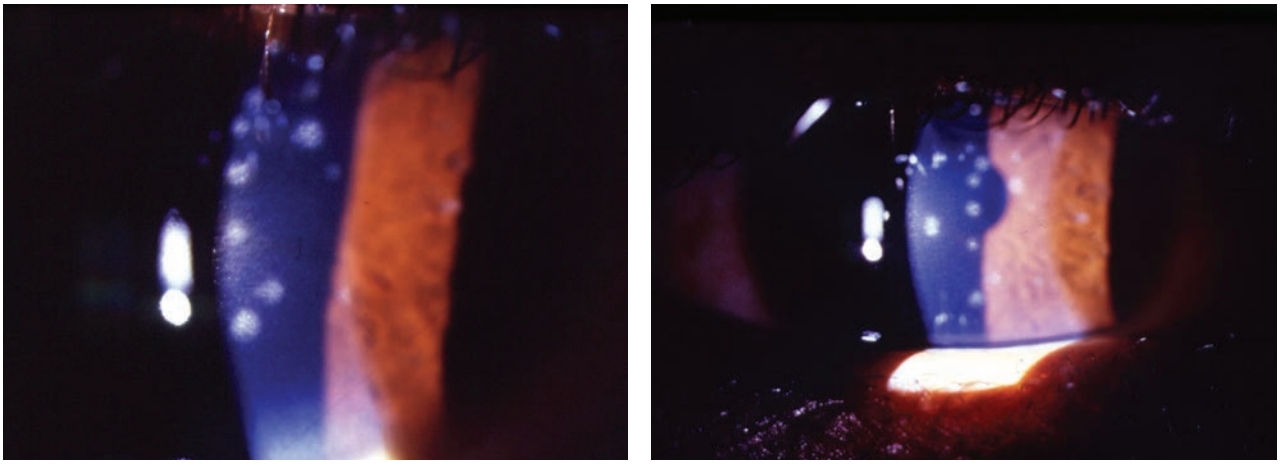

Lesions associated with Thygeson's superficial punctate keratitis appear as whitish-gray, asterisk-shaped intraepithelial corneal opacities, sometimes inducing a slight elevation of the overlying tissue.

THYGESON'S SUPERFICIAL PUNCTATE KERATITIS

Signs and Symptoms

Thygeson's superficial punctate keratitis (TSPK) represents a corneal epitheliopathy of unknown etiology. It was first described in 1950 by Phillips Thygeson as a series of case reports.[1] TSPK is characterized by the insidious onset of superficial corneal inflammation, with a long duration of exacerbations and remissions. TSPK usually presents initially during the second or third decade of life, but has been noted in individuals from 30 months to 70 years of age.[2] While no clear gender predilection exists, a slight female preponderance has been suggested.[1-3] No specific systemic associations have been reported for this disease.

The clinical presentation is marked by recurrent episodes of photophobia, tearing, ocular burning and foreign body sensation.[1-9] Biomicroscopy reveals anywhere from one to 50 fine, granular, whitish-gray, "asterisk-shaped" or "dendriform" intraepithelial corneal opacities, sometimes inducing a slight elevation of the overlying tissue. These lesions may stain minimally with fluorescein, and rarely with rose bengal or lissamine green dyes.[2] Most corneal lesions in TSPK are noted centrally; however, peripheral lesions do occur and may be associated with delicate, peripheral vascularization in chronic cases.

Characteristically, no conjunctival inflammation is associated with the keratitis, and the eye is otherwise white and quiet. The disease may persist from months to decades, with an average episodic duration of roughly 11 years.[3] However, one reported case is noted to have persisted for more than four decades.[10] TSPK most commonly presents as a bilateral disease, although it is often asymmetric and can be unilateral in a small percentage of cases.[3,4]

Despite the corneal opacities, visual function typically remains good. Snellen acuity of 20/30 or better is seen in about 80% of individuals at presentation.[3] Rarely has acuity worse than 20/50 been recorded, and in most cases, vision returns to normal following resolution of the keratitis.[3,11] Recurrence of the disease appears to occur randomly, although it has been associated in some cases with laser photorefractive surgery.[12-14]

Pathophysiology

At present, no established etiology is recognized for TSPK, although viral mechanisms have been suspected and suggested for many years.[2,9,15,16] The clinical manifestations resemble a combination of findings that meld the signs of viral keratitis with the reaction that is observed following exposure to a noxious agent.[3,17] An altered immune response to an unknown exogenous or endogenous antigen may explain the characteristic exacerbations and remissions of the disease.[4,9,17] In some patients, an increase may be noted in HLA-DR3 expression, which is a histocompatibility antigen gene locus associated with the immune response.[4,9,18]

Corneal scrapings of the classic lesions tend to yield nonspecific findings, showing atypical and degenerated epithelial cells and a mild mononuclear and polymorphonuclear cell infiltrate.[19] Focal cell destruction without the cell-to-cell pattern typical of herpes simplex keratitis has been reported; however, the presence of specific viral particles has not been documented.[19]

Laser confocal microscopy studies of patients with TSPK reveal characteristic findings. Most abnormalities are confined to the basal cell layer of the corneal epithelium, the subepithelial nerve plexus, Bowman's membrane and the anterior stroma, while the deeper regions of the stroma, Descemet's membrane and endothelium are spared from pathological changes.[19] The punctate lesions noted on biomicroscopy can be seen as aggregates of highly reflective deposits within a starburst-like appearance, localized to the superficial and basal epithelial cell layers, and Bowman's membrane to a lesser extent.[7,8] Subepithelial haze can also be reported.

Most notable in TSPK is an abnormal accumulation of Langerhans cells in the cornea.[7,8,19] These cells play a major role in the corneal immune response by activating T-cells and participating in the maintenance of corneal homeostasis.[20] Under normal circumstances, Langerhans cells are found only in the epithelium, primarily within the peripheral cornea.[20] In TSPK, the number of Langerhans cells has been found to increase more than 15-fold at the basal epithelial layer, and more than seven-fold at the level of Bowman's membrane.[19] After appropriate therapy, these cell counts have been seen to diminish greatly, although they may not return fully to normal levels.[8,19]

Management

The diagnosis of TSPK is based upon clinical appearance and history; it may be confirmed by its rapid and successful response to topical corticosteroids during acute episodes.[1,3,4] Corticosteroids (e.g., fluorometholone 0.1% or loteprednol 0.2% QID) are known to decrease the symptoms and signs of TSPK, and are considered the mainstay of therapy.[1,4,5] Symptomatic control is typically achieved within one to two weeks, although complete resolution of corneal lesions may require a month or longer of carefully tapered therapy.[3,4] Long-term topical steroid use is not recommended; should patients have persistent symptoms or refractory lesions, alternative options exist.

A number of case reports and small studies have shown topical cyclosporin A 2% (compounded in oil) to be effective as a steroid-sparing therapy for managing symptoms and preventing reactivation.[5,21,22] Likewise, topical tacrolimus 0.03% ointment has been reported to successfully control TSPK over the course of several years, although its effects do not seem to be curative.[6] Non-pharmacologic therapy may include the use of lubricating drops and therapeutic contact lenses to diminish friction and reduce irritation.[3-6] Mechanical scraping or laser photoablation of the lesions is not effective, and may stimulate scarring or recurrence.[12,13]

Most patients with TSPK recover completely with no loss of visual acuity. In one of his earlier publications, Thygeson suggested that a key element of this disorder is its potential to heal without scar formation.[23] However, he later observed that some patients actually developed persistent "ghost" subepithelial opacities directly beneath the intraepithelial lesions, although these did not seem to compromise visual function.[24] In the ensuing years, several publications have demonstrated that scarring is indeed possible in patients with TSPK and can produce a visual deficit.[2,11,18] Some of these cases were associated with (seemingly inappropriate) use of topical antiviral agents, while others involved subsequent development of Salzmann's nodular degeneration, band keratopathy or subepithelial fibrosis.[11]

It has been proposed that, in a small percentage of patients with TSPK, chronic corneal inflammation may persist and involve deeper tissue, to the level of the anterior stroma. This phenomenon sets the stage for disorganization of the collagen fibrils, resulting in opacification as well as irregularities that can spur fibrosis and other secondary scar-forming pathologies. When such patients are identified, the ongoing use of anti-inflammatory therapy is well-warranted.

Clinical Pearls

- In 1966, Thygeson described the five characteristic features of TSPK as follows: bilateral punctate epithelial keratitis; chronic disease with exacerbations and remissions; healing without scar formation; no response to antibiotics; and striking symptomatic response to topical corticosteroids.[23] With the exception of the third feature in rare cases, these elements are still considered to represent the diagnostic criteria for TSPK.
- The granular epithelial findings of TSPK occasionally may be confused with other causes of epithelial keratitis. An important diagnostic feature of TSPK is the absence of concurrent conjunctival inflammation.
- While the physiologic climate for mild hypoesthesia exists in TSPK, corneal sensation is usually normal.[2] This factor is an important consideration in differentiating TSPK from herpetic keratitis, which can present similarly in early stages.
- Patients using topical corticosteroid therapy for TSPK in excess of one month require monitoring with tonometry every one to two weeks. These agents are known to potentially cause elevation of intraocular pressure in susceptible patients.
- A 1984 study examined the use of trifluridine 1% in six patients with refractory TSPK in which the ophthalmic solution was found not to be as effective as corticosteroids.[25] Still, some continue to advocate the use of newer antivirals such as ganciclovir 0.15% gel as a component of therapy.[26] To date, there have been no prospective clinical trials examining antiviral medications as a primary or adjunct therapy for TSPK.
- Although topical cyclosporin A 2% has been used successfully in the management of refractory TSPK, it remains unclear whether the commercially available formulation Restasis (cyclosporine 0.05% ophthalmic emulsion, Allergan) is effective in this condition. No clinical trials were found during the production of this resource.
- Patients with TSPK must be properly counseled from the outset regarding the condition's tendency toward exacerbations and remissions. Understanding the nature of the disease course as well as the need for ongoing treatment in some cases may help patients to improve adherence to therapy and cope psychologically with this sometimes frustrating disorder.

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CHOROIDAL FOLDS

Signs and Symptoms

Choroidal folds can occur in any patient regardless of age, race or sex. Patients may report visual acuity reduction though in many instances choroidal folds themselves are asymptomatic. Hyperopia is frequently present, and a number of patients will manifest an increase in hyperopia coincident with the development of choroidal folds.[1-4] The condition may be unilateral or bilateral. When unilateral, proptosis is often present.[2]

Numerous conditions are associated with the development of choroidal folds, including acquired hyperopia,[1-4] orbital and sellar tumors,[5-9] orbital cysts,[10] papilledema and increased intracranial pressure (with and without papilledema) from intracranial mass lesions and pseudotumor cerebri,[11-14] hypotony (often occurring post-surgically or due to uveitis),[15-19] choroidal neovascularization and macular degeneration,[20] scleritis and other inflammatory conditions,[21] disc drusen and disc congestion,[22] sinusitis,[23] diabetic retinopathy,[24] Grave's disease,[25] cavernous sinus fistula[26] and, commonly, Vogt-Koyanagi-Harada (VKH) disease.[27-29] In some instances, an underlying cause is not apparent and choroidal folds may be considered idiopathic.[30,31]

Ophthalmoscopically, choroidal folds appear as dark and light striations across the posterior pole of the fundus. They can be oriented horizontally or vertically and are usually arranged in parallel. The appearance of this arrangement may be enhanced with a red-free filter, and can be well delineated using either fluorescein or indocyanine green angiography.[32]

Spectral-domain optical coherence tomography (SD-OCT) will demonstrate a wavy appearance of the retinal pigment epithelium and a flat retinal surface. SD-OCT can differentiate epiretinal membranes and chorioretinal folds (undulating retinal as well as retinal pigment epithelial lines of normal thickness) from true choroidal folds.[33-35]

Pathophysiology

Choroidal folds are not a diagnosis, but a finding that must be investigated in every presentation in order to ascertain what precipitating cause(s) may exist. Choroidal folds are likely to develop in association with any intra- or extraocular process that induces sufficient compressive stress within the choroid, Bruch's membrane and retina to force these tissues to buckle.[36]

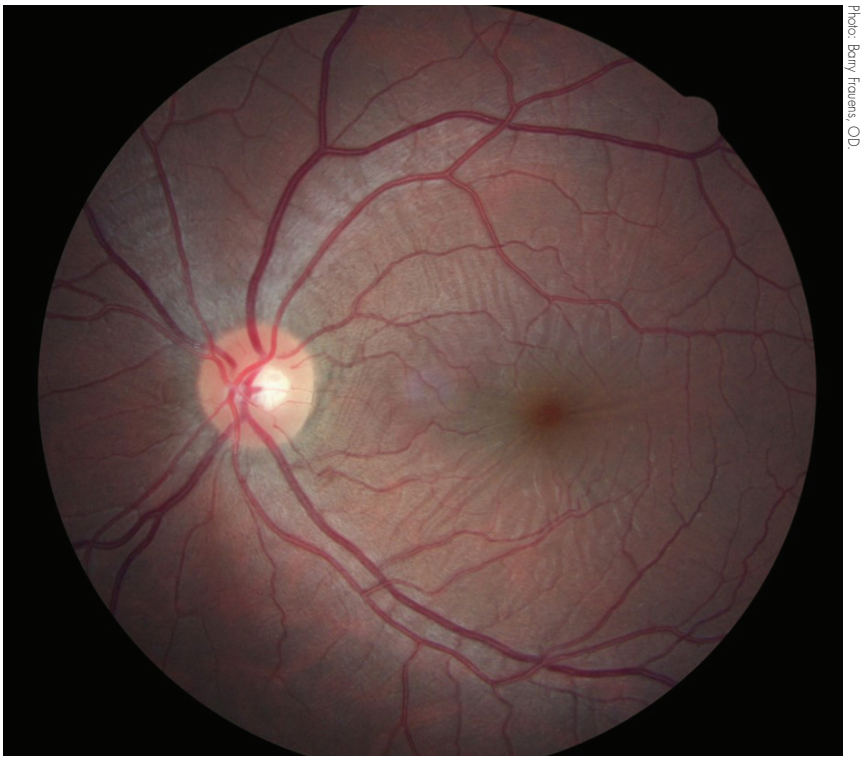

Photo: Barry Frauens, OD.

Choroidal folds—dark and light striations across the posterior pole—are associated with processes that induce compressive stress sufficient to buckle the choroid, Bruch's membrane or the retina.

Virtually any ocular surgery (or trauma) that pierces the globe can cause choroidal folds. Hypotony secondary to an open globe combined with loss of ocular contents (aqueous, vitreous, lens) are thought to be a cause of choroidal folds.[17] Hypotony (as well as extraocular compression) can cause deformation of the sclera, especially when combined with choroidal thickening. Folds in Bruch's membrane can occur due to redundant tissue. Scleral shrinkage from prolonged inflammation can also result in choroidal folds.[17] Overall, congestion of the choroid seems to be a strong precipitating factor towards the development of choroidal folds.[17]

Choroidal vessel dilation and hyperpermeability may be involved in atypical presentations of chorioretinal folds-related maculopathy characterized by sub-/intraretinal fluid accumulation. Dilated and hyperpermeable choroidal vessels may result in focal retinal pigment epithelium alterations that can progress to choroidal neovascularization or chronic central serous chorioretinopathy.[32]

Most cases of high hyperopia do not show choroidal folds. Rather, choroidal folds typically occur in cases where hyperopia is acquired when the globe is foreshortened. There exists a well-known, largely benign syndrome involving acquired hyperopia and choroidal folds, occurring both with and without increased intracranial hypertension. In this syndrome, there is a flattening of the posterior pole (demonstrated with orbital ultrasound or neuroimaging), variable enlargement of the optic nerve, a discernible space between the optic nerve and nerve sheath (as seen on MRI), distension of the perioptic subarachnoid space and scleral shortening with choroidal congestive thickening.[1,3,4,17]

There has been more emphasis on the role of increased intracranial pressure causing choroidal folds. Studies of astronauts following prolonged space travel have identified characteristic changes including globe flattening, hyperopic shift, choroidal fold development and increased intracranial pressure. It is hypothesized that these optic nerve and ocular changes may result from intracranial fluid shifts brought about by prolonged microgravity exposure.[37-39]

Management

The majority of choroidal folds occur idiopathically. However, this is a diagnosis of exclusion. Choroidal folds themselves are generally not treated. The management is identifying and eliminating the underlying cause, thereby causing them to resolve as the source is eliminated.

Complete ocular evaluation to ascertain a possible cause is mandatory. Unilateral choroidal folds are associated with a higher frequency of orbital disease such as retrobulbar mass lesions.[40] Tonometry will identify ocular hypotony. Exophthalmometry will identify proptosis. SD-OCT will identify and differentiate choroidal folds from an epiretinal membrane. Echography or neuroimaging will identify retrobulbar mass lesions, sinus expansion and muscle enlargement in thyroid eye disease.[41] MRI of the brain, orbits, chiasm and sinuses will examine for mass lesions, as well as enlargement of the optic nerve with discernible space between the optic nerve and nerve sheath associated with the syndrome of acquired hyperopia. Lumbar puncture will reveal if intracranial pressure is elevated with a diagnosis of pseudotumor cerebri.

Choroidal folds arising from Vogt-Koyanagi-Harada disease can be managed with systemic steroids.[27-29] Patients who concurrently have idiopathic increased intracranial pressure may be treated with acetazolamide.[13] Additionally optic nerve sheath fenestration has been reported successful.[42] In cases where significant subretinal fluid and choroidal neovascularization were noted, anti-VEGF therapies have shown anecdotal success.[32] In many cases, once the cause is addressed, choroidal folds resolve though there may be instances where they persist.[43]

Clinical Pearls

- Most cases of choroidal folds are idiopathic.
- Idiopathic choroidal folds are a diagnosis of exclusion. A thorough evaluation is required prior to making this diagnosis.
- Unilateral choroidal folds are more likely to be associated with ocular pathology than bilateral cases.
- High hyperopia is much less likely to be a cause of choroidal folds than moderate acquired hyperopia.
- Discovery of choroidal folds with no overt cause should lead to an investigation for increased intracranial pressure. Referral for lumbar puncture is reasonable if neuroimaging is unremarkable for an intracranial mass.

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CRYSTALLINE LENS SUBLUXATION

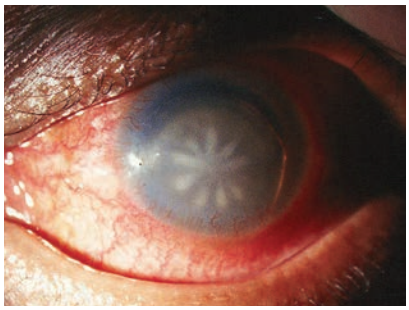
Signs and Symptoms

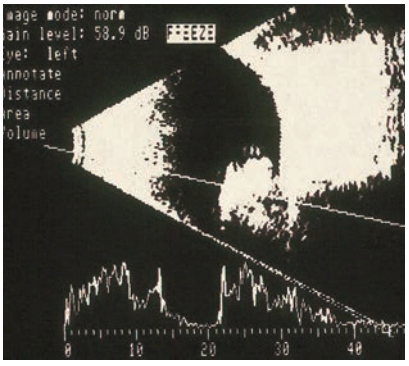
While subluxation of the crystalline lens can occur in any patient, there are primarily three situations in which it is encountered:

The first is a patient who has received significant blunt trauma to the eye, or, in some cases, to the head.[1-5]

The second is in patients with systemic conditions known to be associated with lens subluxation such as Marfan syndrome, homocystinuria, Weill-Marchesani syndrome, Ehlers-Danlos syndrome, hyperlysinemia, sulfite oxidase deficiency disorder and hereditary ectopia lentis.[6-9]

The third is a patient with a hypermature cataract, in whom zonular support has been lost.[10] In rare instances, crystalline lens subluxation can occur idiopathically and spontaneously.[11-13] Other potential causes include ocular surgery, exfoliation syndrome, retinitis pigmentosa, congenital aniridia and vigorous eye rubbing.[14-18]





Above: Slit lamp view of crystalline lens subluxation. ***Right:*** B-scan view of the condition.

Lens subluxation commonly induces visual disturbance, which may range in severity from mild to extreme. Monocular diplopia is a common complaint, particularly when the crystalline lens bisects the pupil.[19] Displacement of the lens can also result in extreme refractive hyperopic or myopic changes, as well as induced astigmatism; in children, such changes can be amblyogenic.[6] Occasionally, vision can be seen to fluctuate dramatically as the patient alternates between phakic and aphakic status.[20]

In most cases, there is no physical sensation unless the lens physically blocks the pupil, leading to pupil block and secondary angle closure.[17,21,22] In this scenario, the patient may manifest the symptoms of acute angle-closure glaucoma including an edematous cornea, blurred vision, headache, pain, photophobia, lacrimation, nausea and vomiting. Open-angle glaucoma is also possible in cases of crystalline lens subluxation, with the primary mechanisms being traumatic damage to the anterior chamber angle (e.g., angle recession) or lens particle-induced inflammation.[23]

Examination demonstrates a displaced crystalline lens upon biomicroscopy. Using direct illumination, this is seen as an intrapupillary dark crescent against the convex edge of the displaced lens; with retroillumination, the dark crescent is replaced by a red reflex crescent that appears brighter than the adjacent lens. Dislocation (not true subluxation) of the lens may be up and out, down and in, down and out, nasal or temporal, or the lens may be completely displaced into the posterior or anterior chamber. The lens may also be "secluded" within the pupil. One may observe phacodonesis (tremulousness of the lens due to loss of zonular support) and/or iridodonesis (tremulousness of the iris) as the patient makes small saccadic eye movements.[11,17]

Pathophysiology

The term *subluxation* implies a partial dislocation of an organ from its normal anatomical location. Hence, crystalline lens subluxation describes a scenario in which the lens is displaced from its typical position within the anterior vitreohyaloid fossa. *Ectopia lentis* is sometimes used as a synonym for lens subluxation; however, this terminology is typically reserved for associated hereditary disorders (e.g., Marfan syndrome) in which the displacement is bilateral and symmetrical.[6] The term *luxation* refers to an organ that is completely dislocated. When a lens is dislodged such that it falls back into the vitreous body or posterior chamber, or forward into the anterior chamber, the condition may be referred to as crystalline lens luxation.

Subluxation associated with trauma appears to be slightly more common than lens displacement associated with underlying systemic disorders.[24,25] It is believed that the physical stretching and/or breaking of the zonules associated with traumatic insult is the mechanism by which subluxation occurs.[25] This occurs as the eye is compressed in an anterior-posterior direction (such as with impact by a fist or other projectile) and the subsequent distention of the globe in the medial-lateral plane ruptures the zonular fibers.

Crystalline lens subluxation associated with congenital disorders varies in pathophysiologic mechanism depending upon the individual condition. The direction of displacement in each case is characteristic, but by no means completely diagnostic. Marfan syndrome is the most commonly encountered underlying condition in patients with crystalline lens subluxation. About 60% of these individuals demonstrate ectopia lentis.[26] The typical direction of lens displacement in Marfan syndrome tends to be superior-temporal, but superior-nasal subluxation has also been documented.[6,27] The underlying mechanism is believed to be abnormally constructed collagen vascular tissue and faulty lens zonules.

Typically, the subluxation associated with Marfan syndrome is non-progressive. Furthermore, since the zonules remain attached to the lens capsule, some degree of accommodation persists. Homocystinuria, a defect in amino acid metabolism, results in degeneration of the zonules—with zonular rupture being the ultimate result.[6] The characteristic displacement is inferior-nasal, but some cases have been noted to luxate into the anterior chamber.[6,9] Unlike Marfan syndrome, accommodation is typically lost in homocystinuria, and the subluxation may be progressive.[9]

Patients with Weill-Marchesani syndrome commonly exhibit microspherophakia, which is defined as a small, spherically shaped crystalline lens. The lens also lacks microfibrils around its equator, resulting in rupture of the zonules and a characteristic downward displacement of the lens.[6,28,29] The microspherophakia combined with forward lens subluxation place the patient with Weill-Marchesani syndrome at increased risk for pupil block and secondary glaucoma.[29,30]

Two rare conditions that bear mentioning are *ectopia lentis simplex* (also known as *simple ectopia lentis*) and *ectopia lentis et pupillae*, both forms of hereditary ectopia lentis.[6] Ectopia lentis simplex is believed to be inherited as an autosomal dominant trait, despite having no other associated systemic abnormalities. In this condition, the crystalline lenses are bilaterally and symmetrically dislocated superior-temporally, while the iris and pupil remain normal and intact. Ectopia lentis et pupillae is likewise an isolated congenital condition, albeit with autosomal recessive heredity.[31] Features of this condition include enlarged corneal diameters, microspherophakia and corectopia. The lenses and pupils are displaced opposite each other in this bilateral condition.[6,31]

A major concern with lens subluxation is the development of secondary angle-closure glaucoma. Displacement of the crystalline lens introduces the possibility of firm apposition between the lens and the posterior aspect of the iris. When the pupil becomes obstructed (i.e., pupil block), iris bombé and secondary angle

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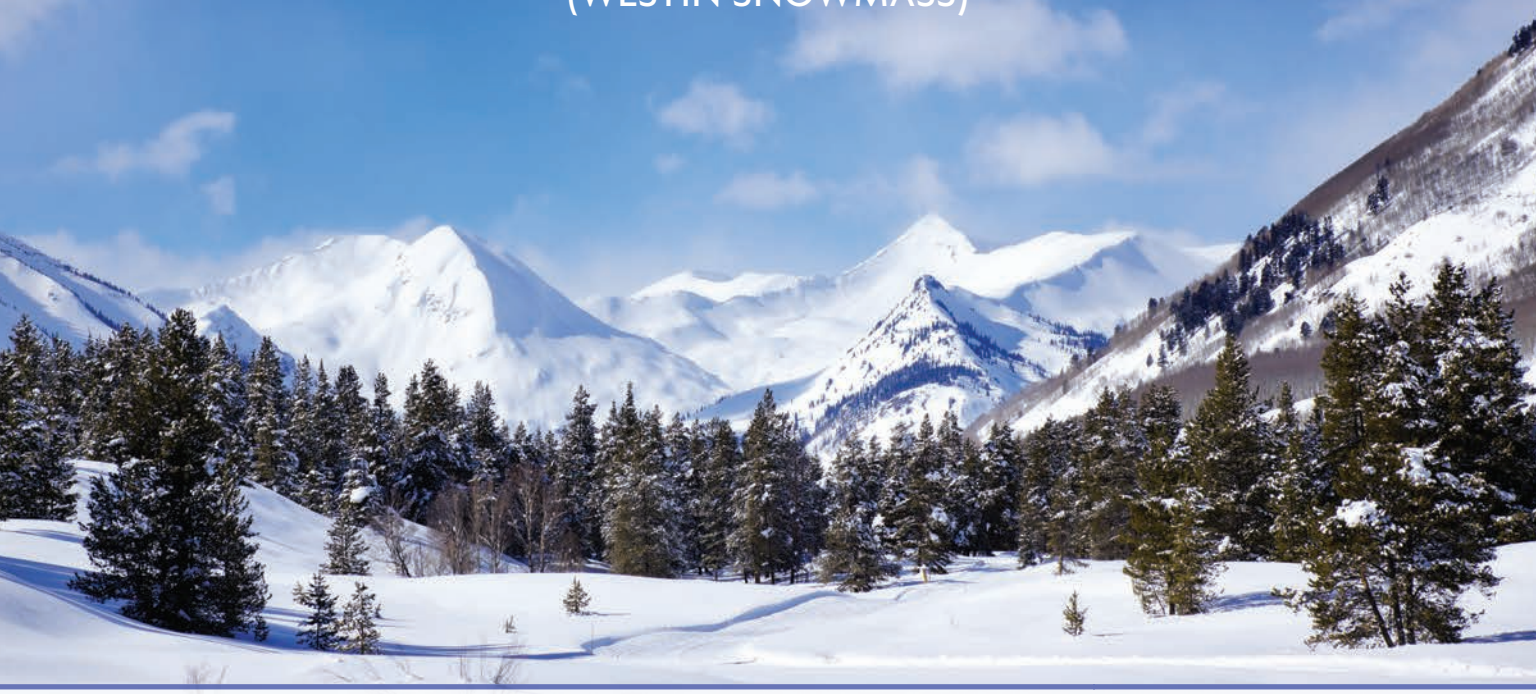

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closure can result.[21,29,32] Should a lens completely dislocate into the anterior chamber and potentially touch the cornea, irreversible damage can occur to the endothelial cells, with subsequent chronic corneal edema and decompensation.[11] Displacement of the lens into the anterior chamber can also result in a reverse pupil block angle-closure glaucoma, where the backward sagging pupil becomes sealed by the anterior hyaloid face of the vitreous.[22]

Management

The management of patients with crystalline lens subluxation depends greatly on the severity of the condition, etiology as well as the degree of visual impairment imparted. The degree of lens dislocation can be broadly classified into three categories: minimal to mild lens subluxation, in which the lens edge uncovers less than 25% of the dilated pupil; moderate lens subluxation, in which the lens edge uncovers 25% to 50% of the dilated pupil; and severe lens subluxation, in which the lens edge uncovers greater than 50% of the pupil.[33]

Management tends to be conservative, especially for categories 1 and 2. The primary goal is optimization of vision through refractive correction.[34] Improvement or elimination of monocular diplopia may be accomplished via the use of opaque contact lenses with small pupillary apertures. While it may be tempting to employ a miotic agent such as pilocarpine, this practice should be discouraged for long-term management. Pilocarpine can induce anterior rotation of the lens and exacerbate preexisting anterior subluxation secondary to zonulopathy, increasing the risk of pupillary block.[12,35]

Surgical intervention should be considered when functional visual acuity becomes difficult to maintain despite best correction, or in cases of anterior dislocation resulting in secondary glaucoma and/or corneal decompensation.[34,36,37] For cases of posterior dislocation into the vitreous, intervention depends upon the status of the lens capsule. If it remains intact and no inflammation is detected, the condition can be monitored indefinitely.[37,38] However, if persistent lens-induced (phacoanaphylactic) inflammation occurs or if the retina is compromised at any point in time, then pars plana vitrectomy and lens extraction are indicated.[2,37]

Pupillary block with angle-closure glaucoma warrants intervention with laser peripheral iridotomy as soon as possible to help temporize the intraocular pressure.[39] Unfortunately, this procedure rarely succeeds in managing the condition fully. Patients frequently require lens extraction with intraocular lens implantation. Phacoemulsification with posterior chamber intraocular lens and capsular tension ring (CTR) implantation has long been recognized as definitive surgical management of crystalline lens subluxation.[40-42] More recently, a modified CTR and capsular tension segment has improved stability and intraocular lens centration via scleral-suture fixation.[42]

Clinical Pearls

- Patients with so-called "congenital" lens subluxation are rarely born with displaced lenses. Rather, the phenomenon typically develops during life due to predisposing systemic conditions, such as Marfan syndrome.
- In cases where there is suspected loss of zonular adherence (often in cases of hypermature cataracts) with subsequent risk of dislocation into the anterior chamber, pharmacological dilation should be avoided until surgical consultation can be obtained.
- In any case of lens dislocation, there exists a strong possibility of pupil block and secondary angle-closure glaucoma.
- The mere fact that a lens is subluxed is not sufficient reason for surgical extraction.
- Patients with crystalline lenses that dislocate into the vitreous are at risk for chronic and severe inflammation. This sequela may occur years after the initial incident.

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MILKY NUCLEAR SCLEROSIS

Signs and Symptoms

Patients typically develop "milky" nuclear sclerotic cataracts at an earlier age than other forms of lens opacification. The onset is often unilateral or asymmetric, usually developing during middle age, often beginning in the 40s and 50s. Males are often more affected than females, and patients are typically moderately to highly myopic.[1,2]

Patients will often complain of declining vision, which is more rapid than with other types of aging cataract. Monocular diplopia occurs, although most patients will describe it as blurred vision. Pinhole testing relieves monocular diplopia and may significantly improve vision, although the patient may not see similar improvement with subsequent refraction. Patients will commonly have a myopic shift that can be relatively dramatic, accounting for up to 1D to 2D per year. As the myopia is refractively corrected, best visual acuity declines to a point where the patient cannot tolerate the spectacle imbalance, visual acuity or both.[1,2]

In contrast to generalized cataractogenesis, a white density will be present within the nuclear core that is best appreciated with a fine biomicroscopic slit beam (optic section) directed off the visual axis. Comparison with the fellow eye in unilateral or asymmetric cases is often helpful in making the diagnosis. Also in contrast to other types of cataracts, patients can present with significantly reduced vision, yet the funduscopic view is minimally altered; that is, practitioners will have a clear view into the eye, yet the patient reports poor visual acuity but no afferent pupil defect. When this occurs, diagnosing cataract is not intuitive, and the patient may go through additional testing and referral needlessly.

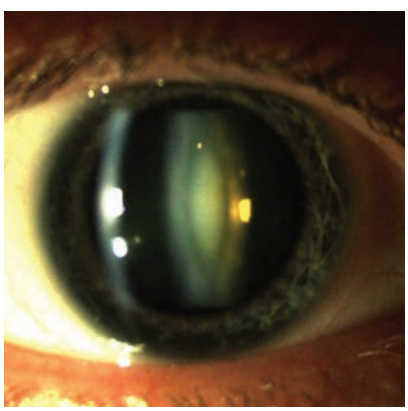

Photo: Lori Vollmer, OD

Milky nuclear sclerosis often goes undetected due to an unobstructed view of the fundus.

Pathophysiology

Numerous types of cataracts are seen in clinical practice. Cataracts are described from generalized nuclear sclerosis, cortical changes, anterior and posterior subcapsular cataracts, and polar cataracts, among others.[3-5] One type is "white" nuclear sclerosis. This form is often referred to as having nuclear opalescence or "milky" nuclear sclerosis. This delineates a unique type of cataract that is not often described in the literature as a distinct clinical entity, and that has specific and unusual properties and behaviors as described above.

Due to an unobstructed view of the fundus, this type of cataract often goes undiagnosed. Despite the clear view of the fundus, differing refractive indices can produce a "bowing" effect of the slit beam when examining the retina with a biomicroscope and non-contact fundus lens.

A known association exists between cataract formation and high myopia.[6,7] Patients with high degrees of myopia prior to refractive surgery are likely those who experience milky nuclear sclerosis, and any association with LASIK or other refractive procedure is likely more coincidental than causal.

Management

While milky nuclear cataracts may be insidious and difficult to diagnose early, they pose no management issues or unusual risks of complications with removal. Standard phacoemulsification with intraocular lens implantation provides excellent visual rehabilitation. Femtosecond laser-assisted cataract surgery is also a viable option for surgical rehabilitation.[8] The Pentacam Scheimpflug system can be used as an objective and repeatable method for assessment of lens density, which could be helpful in longitudinal studies monitoring nuclear cataracts.[9,10]

Clinical Pearls

- One type of cataract is characterized by a dense, milky nuclear opalescence that is out of proportion to the degree of visual disability. The "view-in-equals-the-view-out" philosophy does not apply to milky nuclear sclerosis.
- The key to diagnosis is to look, with a very thin slit beam on the microscope, for the characteristic milky appearance of the nuclear lens core.
- When diagnosing milky nuclear opalescence, remember the "M"s: male, myopic, middle-aged, myopic shift.
- Laser interferometry and glare testing may help with diagnosis. Patients with this type of lens opacity will complain that visual acuity and nighttime driving are affected daily-living activities.

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PHACOANAPHYLAXIS (RETAINED LENS FRAGMENT)

Signs and Symptoms

Phacoanaphylaxis is a term used to describe inflammation caused by the crystalline lens. Depending upon the clinical etiology, sequelae and area of impact, lens-induced inflammation has been synonymously referred to as *phacoanaphylactic uveitis*, *phacoanaphylactic endophthalmitis*,

phacoanaphylactic glaucoma, *phacolytic glaucoma*, *retained lens fragment* and *lens particle glaucoma*.[1-9]

In nearly all cases, patients are elderly with cataracts, although younger patients experiencing penetrating lens trauma or ocular surgery can also experience phacoanaphylaxis. No racial or gender predilection has been identified. In the majority of cases, the patient has undergone cataract extraction, often seemingly without complications. In the immediate (and sometimes late) postoperative period, the eye will demonstrate persistent inflammation unresponsive to topical steroid treatment. If the inflammation is in the anterior chamber or the vitreous, it is known as *phacoanaphylactic uveitis* or *phacoanaphylactic endophthalmitis*, respectively. In addition, intraocular pressure (IOP) may be elevated, and the resulting condition is called phacoanaphylactic glaucoma.[1-9]

In post-surgical cases, the presence of lens cortex or nucleus material (which may not be readily observable) that was not completely removed during the operation is termed *retained lens fragment*. If penetrating lens trauma is the inciting factor, then the term *lens particle glaucoma* is used.[8,10]

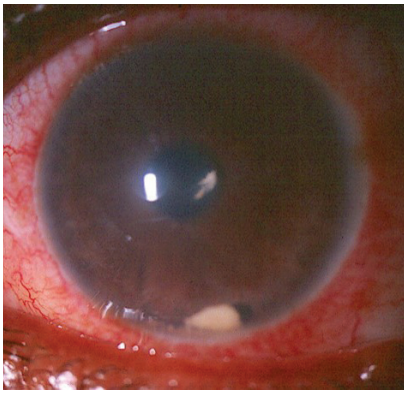
Retained lens fragments may be biomicroscopically visible in the anterior or posterior chamber. However, in many cases, the fragment is elusive, and gonioscopy may be necessary to locate the material.[6,11,12] In myopic eyes, small fragments may hide in the posterior chamber.[13]

In addition to persistent inflammation, another hallmark feature is corneal edema. In many cases, edema is diffuse, but in others, it appears in a wedge shape involving primarily the inferior cornea. The retained lens fragment is often close by, and visual acuity will be variable depending upon the degree of intraocular inflammation and corneal edema.[6,12,13]

Pathophysiology

Phacoanaphylaxis is an autoimmune phenomenon in response to release of sequestered antigens consisting of lens nuclear proteins, not recognized by the body. The antigens are more likely to induce the phacoanaphylactic response—typically consisting of granulomatous uveitis—than are cortical remnants.[2] In comparison, phacolytic glaucoma typically presents with a non-granulomatous macrophage response.[14]

Photo: Lori Vollmer, OD



Phacoanaphylaxis from a retained lens fragment.

With this phenomenon, retained lens fragments are extensively infiltrated by polymorphonuclear leukocytes, histiocytes, eosinophils and giant cells. The iris and ciliary body are also inflamed and infiltrated by lymphocytes and plasma cells.[2,15] Concurrent inflammation of the trabecular meshwork, as well as blockage by inflammatory cells and a poorly flowing proteinaceous aqueous contribute to IOP rise and glaucoma development.

There exists no well-explained pathophysiologic process accounting for the corneal edema frequently seen. Direct endothelial trauma from a nuclear lens fragment resting against the cornea is obvious in some cases. However, in the absence of direct contact with the cornea in this area, it is difficult to account for the wedge-shape or inferior location of the edema.[12,16] In some instances, an immune-related process targeting the endothelial cells could explain this phenomenon.[12,16]

More perplexing is the timing of onset of phacoanaphylaxis. Most cases occur and are discovered soon after surgery. However, reports abound of phacoanaphylaxis from retained lens fragments occurring years after surgery.[11,17,18]

Management

Often, the inclination in managing persistent postoperative inflammation is to continue or increase steroid usage. While this may be done initially to temporarily ameliorate the condition, the approach is rarely effective in providing a cure.

While cases exist in which phacoanaphylaxis from retained cortical fragments have been managed conservatively, this is not appropriate in cases with retained nuclear fragments, as virtually all of the latter cases will fail on topical therapy alone. As such, these situations require surgical removal of the fragments.[12]

Since it is difficult to clinically differentiate cortical from nuclear fragments, it is advocated to expedite removal of all retained fragments if phacoanaphylaxis or phacoanaphylactic glaucoma complications arise. However, if fragments are seen and the eye is quiet, there is no emergent need to proceed to extraction; many cases never convert to the inflammatory disease, while others will years later.

Vitrectomy is successful in removing retained lens fragments within the vitreous.[19] One series noted a better visual outcome when early vitrectomy was performed for retained vitreal nuclear lens fragments, and poorer visual outcomes if the procedure was delayed.[20] Another report advocated immediate vitrectomy and intravitreal phacoemulsification in the management of posteriorly dislocated nuclear lens fragments in order to enhance visual outcome, and minimize the risk of uveitis, secondary glaucoma and cystoid macular edema.[21] Removal of lens fragments from the anterior chamber is best accomplished with surgical irrigation and aspiration, with phacoemulsification if the piece is large. In most cases, the corneal edema and inflammation resolve with postoperative anti-inflammatory, topical medications and surgical removal of the lens fragment. Prolonged duration of lens fragments in the setting of an inflammatory response increases the risk of corneal decompensation. Some eyes will continue to decompensate even after surgical removal, necessitating keratoplasty.[13]

Clinical Pearls

- Along with retained lens fragments, herpes keratouveitis, autoimmune uveitis, trauma and uveitis-glaucoma-hyphema syndrome are possible causes of persistent ocular inflammation and corneal edema after cataract surgery.
- Gonioscopy should be performed on all eyes with persistent postoperative inflammation and corneal edema to look for retained lens fragments.
- Though most cases of phacoanaphylaxis occur soon after surgery, the process can begin many years later.

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PRIMARY OPEN-ANGLE GLAUCOMA

Signs and Symptoms

Patients with primary open-angle glaucoma (POAG) are typically older, with men more likely to be affected than women.[1-3] People of African ancestry are more likely to have POAG than people of European ancestry, and people living in urban areas are more commonly affected than those in rural areas.[2] In 2013, the number of people (ages 40 to 80 years) with glaucoma worldwide was estimated to be 64.3 million, increasing to 76 million in 2020 and 111.8 million in 2040.[2]

Family history of glaucoma is often a factor, with mother or siblings at higher risk.[4,5] A strong association has also been found with vascular and perfusion dysregulation, where both hypertension and hypotension have been implicated in the disease, as well as with axial myopia.[6-8] Additionally, vasospasm, migraine, obstructive sleep apnea syndrome, diabetes, medication usage and Alzheimer's disease have been variably linked to POAG.[9,10]

Patients with early and moderate stage POAG are visually asymptomatic. As the disease progresses to advanced levels, patients may complain of poor peripheral vision and missing things in their visual field, eventually manifesting as a slow, painless progressive loss of visual acuity. Due to the slowly progressive loss of vision, patients remarkably may delay consult, presenting with very poor visual acuity in one or both eyes.

Eyes with POAG typically have elevated intraocular pressure (IOP), rising above the statistical normal value of 21mm Hg, although a large number of patients never manifest an IOP measurement above this level.[11-13] Therefore, it is better said that POAG patients have an IOP in which the pressure value is elevated beyond what that eye can tolerate, as well as observable glaucomatous damage. Some individuals can tolerate IOP levels well above the statistical norm of 21mm Hg, while others cannot. Thus, the tolerability of intraocular pressure is highly variable among individuals; it can be quite high in persons who do not develop glaucomatous damage and quite low in others who progress to normal pressure disease with visual disability. In those who develop glaucoma with IOP within a statistically normal range, it is thought that vascular perfusion issues may also play a role in disease pathogenesis.[6,7]

Biomicroscopically, little evidence will be apparent beyond age-appropriate abnormalities in POAG patients. Findings of pigment dispersion, exfoliation, trauma, inflammation, blood, neovascularization, or lytic or phacomorphic cataract will not be obvious upon observation. Gonioscopically, there will be no anterior chamber abnormalities, and the pigmented trabecular meshwork will be visible throughout. Any other finding is defined by the nomenclature as "secondary" open-angle glaucoma. Open angles gonioscopically, with no abnormalities in the drainage channels, define POAG.

Funduscopically, focal damage to the optic disc is characteristically seen. Damage occurs most commonly superiorly and inferiorly on the optic disc; it may be asymmetric within an eye and is often asymmetric between eyes. Nerve fiber layer hemorrhages ("Drance" hemorrhages) may emanate from the neuroretinal rim of an optic disc, with glaucoma. Parapapillary atrophy is commonly found in association with POAG. Loss of retinal nerve fiber layer (RNFL) axons manifests as wedge defects in the arcuate areas or widespread diffuse atrophy.[14] In early disease, the neuroretinal rim may appear intact, but characteristic RNFL damage may be apparent ophthalmoscopically or detectable with spectral-domain optical coherence tomography (SD-OCT).

SD-OCT will demonstrate abnormalities of the RNFL as well as ganglion cell complex (GCC) in eyes with glaucomatous damage. This technology can be used to quantify existing damage and follow the disease for progression. Threshold automated perimetry will, in many cases, show abnormalities in the visual field corresponding to the structural defects, which may consist of paracentral defects, nasal steps, arcuate defects or variable retinal sensitivities. However, it is not essential for an eye to have visual field abnormalities in order to diagnose POAG. In some instances, thinning within the macular vulnerability zone is missed by standard 24-2 automated perimetry. In such cases, central 10-degree threshold perimetry may disclose early defects.[15] Indeed, many eyes may manifest characteristic optic disc or RNFL damage in the setting of a full visual field; this is termed pre-perimetric glaucoma.[16]

Pathophysiology

Primary open-angle glaucoma, as well as all forms of glaucoma, is characterized by progressive degeneration of retinal ganglion cells (RGC) with resultant optic neuropathy and visual field loss.[17] Intraocular pressure, in concert with other known and unknown risk factors, is related to RGC death. In the biomechanical mechanism, intraocular pressure causes mechanical stress and deformation of the lamina cribrosa, which serves as organizer of axons of the ganglion cells that form the optic nerve. Backward bowing of the entire lamina cribrosa preferentially effects the upper and lower poles more than other

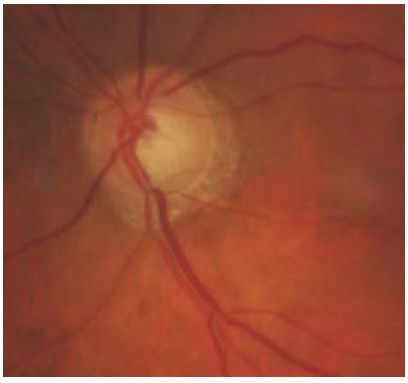
regions of the collagenous structure, leading to loss of neuroretinal optic disc rim in these areas.

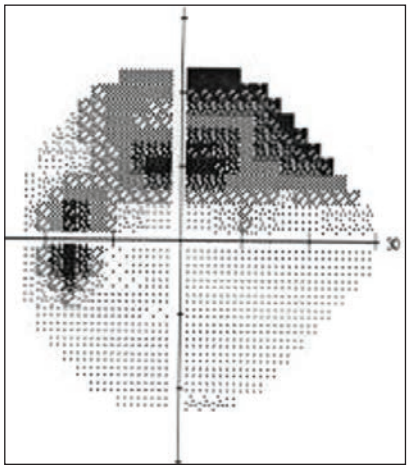
Mechanical compression of the nerve head occurs early enough to be considered a primary pathogenetic event in glaucomatous damage.[18] This results in axonal damage and loss of axonal transport, which then deprives the optic disc of vital neurotrophic factors which are essential to RGC survival. Additionally, IOP levels incompatible with the health of the optic nerve induce chronic ischemia, which also disrupts axonal transport, leading to neurotrophin deprivation to the RGCs from the lateral geniculate nucleus. This initiates the apoptotic process where the RGCs, convinced that they are nonessential elements to the nervous system, begin to disassemble themselves in a genetically pre-programmed cellular 'suicide.'

Apoptosis is triggered by oxidative stress via mitochondrial damage, inflammation, endothelial dysregulation and dysfunction, and hypoxia.[19] It can also be triggered erroneously by genetically programmed messages (genetic mechanism).

Alterations in IOP, blood pressure (BP) and ocular perfusion pressure (OPP) play a significant role in the pathogenesis of POAG (the vascular mechanism). Impaired autoregulatory capacity of ocular blood vessels may render tissues vulnerable to OPP changes and potentially harmful tissue ischemia-reperfusion damage. Vascular risk factors should be considered in patients with POAG when treated hypertension or normal hypotension is present. These risk factors should also be considered in patients with unusually progressive disease despite seemingly adequate IOP reduction, and in those whose IOP consistently falls within a statistically normal range.[20,21] Non-glaucomatous sources of optic disc cupping and axonal loss should also be considered in cases that present with suspect data.

Levels of IOP are related to aqueous humor production by the secretory neuroepithelium of the ciliary body and the compensatory drainage through the trabecular meshwork and uveoscleral outflow pathway. In POAG, there is an imbalance owing to changes in the aqueous outflow pathways due to increased resistance in the juxtacanalicular trabecular meshwork and the inner wall endothelium of Schlemm's canal. The increase in resistance is related to biological changes in the resident cells of the juxtacanalicular meshwork, which acquire the structural and functional characteristics of contractile myofibroblasts. This scenario leads to an overall stiffening of the inner wall region modulated by transforming growth factor-β/connective tissue growth factor signaling. Stiffening of juxtacanalicular trabecular meshwork and Schlemm's canal cells is a critical causative factor for increased trabecular outflow resistance in POAG.[22]





Above: **Inferior neuroretinal rim damage in primary open-angle glaucoma.** ***Right:*** **Corresponding visual field defect.**

As RGCs die, they release glutamate, which at low levels is an excitatory neurotransmitter and at high levels is a neurotoxin. Extracellular accumulation of glutamate acts on N-methyl-D-aspartate receptors on RGCs to open sodium channels, which in turn open calcium channels. This activates the enzyme nitrous oxide synthase, which leads to the formation of nitrous oxide, a destructive free radical that induces oxidative stress and cell death. While this excitotoxicity phenomenon is well-considered to be part of the pathogenesis of glaucoma, it is unclear if it is a direct participant or an epiphenomenon of glaucoma.[23]

Overall, though the exact pathogenesis of POAG is truly unknown and includes several mechanisms happening concurrently rather than sequentially, it can be well-said that glaucomatous damage involves impaired microcirculation, altered immunity to stress, excitotoxicity, oxidative stress, chronic ischemia, structural changes to drainage channels, subsequent neurotrophin deprivation and apoptosis.[17]

Management

The only accepted management for any form of glaucoma is IOP reduction, which has been shown to delay disease progression.[11-13,24] Despite treatment, POAG can progress, and, in some patients, change can be quite rapid. Conversely, there will be patients who may not show progression for a considerable amount of time, even without treatment.[24]

The goal of treatment is to reduce IOP below a level thought to slow progression and, ultimately, reduce risk of visual disability. Once treatment is initiated, a target pressure is often chosen to guide ongoing care. Considerations in choosing a target pressure include patient health and expected lifespan, risk of visual disability and the peak IOP level at which glaucomatous damage occurred. Typically a 20% to 30% IOP reduction from baseline is initially chosen, though a greater reduction may be necessary for more advanced disease.

The initial glaucoma evaluation typically will include multiple IOP readings to establish an untreated baseline, optic disc photography, SD-OCT RNFL and GCC analysis, threshold perimetry and gonioscopy. As thin corneas have been shown to be a risk factor for disease development and progression, pachymetry is also necessary.[25] Diagnosis is based on correlating data with structure and function. Once the initial evaluation has been completed, tests will be repeated periodically to monitor disease stability or progression. The frequency of repeat testing is typically contingent upon disease severity.

IOP reduction is typically accomplished through the use of topical and oral medicines, although laser trabeculoplasty, incisional glaucoma surgery and cataract surgery, with or without stent placement, are also effective. Due to effectiveness and

low risk profile, treatment is usually initiated with topical medications, most often with a prostaglandin analog (PGA) such as travoprost 0.004%, latanoprost 0.005%, bimatoprost 0.01% or tafluprost 0.0015%, once daily. In many instances, IOP can be sufficiently lowered with monotherapy. These medications enhance uveoscleral outflow pathways.

Additionally, topical aqueous suppressants such as a beta blocker (e.g., timolol 0.25% or 0.5%) BID, alpha-2 adrenergic agonist (e.g., brimonidine 2%, 1.5% or 0.1%) TID, carbonic anhydrase inhibitor (e.g., dorzolamide 2% or brinzolamide 1%) TID can be used alternately or adjunctively with a PGA. Fixed combination agents (brimonidine/brinzolamide, timolol/dorzolamide or timolol/brimonidine) offer two agents in one bottle to ease use and enhance compliance. In rare instances, topical miotics (e.g., pilocarpine 2% or 4%) and oral carbonic anhydrase inhibitors (acetazolamide, methazolamide) can be used, but are limited due to often intolerable local and systemic adverse effects.[17,26]

In cases where additional IOP reduction beyond topical therapy is necessary or a patient is unable or intolerant to medications, laser trabeculoplasty can be used. Laser trabeculoplasty will initiate a thermal or biological alteration (depending upon the type of laser and wavelength energy used) in the trabecular meshwork to enhance aqueous outflow. Laser trabeculoplasty can be used in conjunction with topical therapy or may be employed as a first-line alternative to medications.[27]

For patients who need a great degree of IOP reduction or a consistently low IOP, incisional surgery remains a viable option. Trabeculectomy, which creates a fistula for aqueous to escape the anterior chamber and accumulate within the superior conjunctival space where it drains to conjunctival and episcleral vessels, is a common procedure with a long documented history of successfully reducing IOP into the low teens. Often, antimetabolites such as mitomycin-C (MMC) are employed surgically to reduce postoperative healing and scarring, allowing for better aqueous filtration.[28] In cases of trabeculectomy failure, or even as a primary procedure, a tube shunt drainage device may be employed in a modification of the original trabeculectomy procedure.

Trabeculectomy with MMC has higher rates of surgical failure and reoperation for glaucoma compared with tube-shunt surgery. Early complications are more frequent after trabeculectomy with MMC relative to tube-shunt surgery, but the procedures have similar rates of late postoperative complications and serious complications. Improvements in tube shunt surgery support their use beyond refractory glaucomas.[29] Tubes connected to fenestrated resevoirs (setons) can also be employed stand-alone or to increase outflow following other procedures.

Interventions in the treatment of mild to moderate glaucoma have evolved to include a heteronymous group of procedures collectively named *minimally invasive glaucoma surgery* (MIGS). These procedures are less invasive than traditional filtering surgery and tube implants, don't suffer from blebs, are technically easier to perform and offer the benefit of an improved side-effect profile. Such interventions offer lower IOP, decrease reliance on topical medications, do not impact refractive outcomes and can be safely done following failed tube surgery.[30] They are typically performed at the time of cataract surgery and are best-suited for patients with mild to moderate POAG in order to affect a lower IOP or reduction in medications. They are not procedures for patients with advanced disease, high baseline IOP or those needing a very low IOP.

Clinical Pearls

- POAG is typically a disease of months and years, not days and weeks. Unless an undiagnosed patient presents with extremely high IOP (40s or higher) and/or very advanced disease, it is far better to take a measured approach to the evaluation. There is ample time to get several pretreatment IOP measurements, visual fields (with repeat), SD-OCT, pachymetry, disc photographs, gonioscopy and pachymetry. Once all of this information is collected, a rational diagnostic and therapeutic decision can be made. There typically is no rush to make a diagnosis and initiate treatment.
- A patient with POAG can be designated "well-controlled" only in retrospect. Lowering IOP by a significant amount does not necessarily mean that the patient is well-controlled, but merely that therapy is having a desired effect on the pressure. If, after several years the treated patient shows no progression, then the designation can be used.
- Some patients with POAG may progress rapidly, even when undergoing treatment. Conversely, other patients will show very slow progression even if untreated. Unfortunately, there is no way to identify which category a patient falls into.
- Glaucoma is treatable, not curable; even a well-treated patient may show signs of progression after several years. This is not necessarily a sign of treatment failure.
- Once the decision is made to treat a patient with POAG, the goal is not to make the IOP normal, but safe for each individual patient. Consideration must be taken for the patient's health, age and life-expectancy, adverse effects imparted by any therapy and risk of visual disability in the patient's lifetime.
- A segment of patients with POAG will never become visually disabled, even if untreated, and others will become blind regardless of aggressive therapy.

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UVEAL EFFUSION GLAUCOMA

Signs and Symptoms

Uveal effusion glaucoma results in intraocular pressure (IOP) elevation from non-pupil block secondary angle closure. It arises from numerous causes; hence, there is no age, gender or racial proclivity. There is often a precipitating condition or event that may be either inflammatory (scleritis, drug-induced such as with topiramate, traumatic, HIV/AIDS, Vogt-Koyanagi-Harada [VKH] syndrome), hydrostatic (nanophthalmos, malignant infiltration, cavernous sinus fistula, pulmonary hypertension, hypotony), or the disease may be idiopathic (uveal effusion syndrome).[1-4]

In many cases, there will be a recent history of initiation or dose increase of sulfonamide medications for seizures or antidepression.[5,6] Medications used to treat various conditions that have been reported to cause uveal effusion glaucoma include chlorthalidone (hypertension), escitalopram (depression and generalized anxiety disorder), acetazolamide (glaucoma and pseudotumor cerebri), bupropion (smoking cessation aid and antidepressant) and indapamide (hypertension and systemic edema) among others.[7-12] The most widely reported medication inducing uveal effusion glaucoma is the anticonvulsant medication topiramate, often used to manage chronic headaches.[13-16]

Patients will normally complain of a sudden bilateral decrease in vision. Commensurate will be a myopic shift that can easily reach 6D to 8D or more.[13,14] The level of vision decrease is impacted by the degree of myopic shift and concurrent corneal edema arising from the abruptly elevating IOP (which can range from 30mm Hg to 70mm Hg or higher). In many cases where acuity is decreased mostly due to the myopic shift, patients may report improved near vision with poor distance vision. In these cases, pinhole acuity or refraction may yield improved acuity and aid in diagnosis.

There will often be ocular congestion, discomfort, photophobia, lacrimation, headache, corneal edema and elevated IOP. When there is a causative inflammatory condition such as VKH or scleritis, there may be a substantial concurrent anterior or posterior chamber reaction.[1-4] The anterior chamber will be shallow without iris bombé, which is more characteristic of primary pupil block angle closure. Also differentiating uveal effusion secondary angle-closure glaucoma from primary pupil block angle-closure is the fact that most cases (especially when medication-induced) are bilateral whereas primary angle-closure is typically unilateral.[7,10,17,18]

Pathophysiology

Uveal effusion results from a transudation of fluid from the choriocapillaris into the potential subarachnoid space. This fluid accumulation triggers choroidal edema and eventual detachment from the scleral spur, which prompts anterior rotation of the ciliary body and forward displacement of the iris-lens diaphragm with resulting shallowing of the anterior chamber and appositional angle closure.[1]

The ciliary body edema leads to a relaxation of the zonular fibers with lens thickening and forward displacement, the latter of which causes a myopic refractive shift.[13,14]

Ultrasound biomicroscopy (UBM) will show the anatomic relationships between the iris, lens, ciliary body and angle structures.[19] B-scan ultrasonography will reveal choroidal detachment, which typically extends 360 degrees, as well as possible scleral thickening in posterior scleritis.[1] Anterior segment optical coherence tomography can illuminate a shallow anterior chamber and absence of iris bombé.

Topiramate is a sulfamate-substituted monosaccharide that works via blockage of voltage-gated sodium channels, hyperpolarization of potassium currents, enhancement of GABA receptor activity and suppression of AMPA/kainite

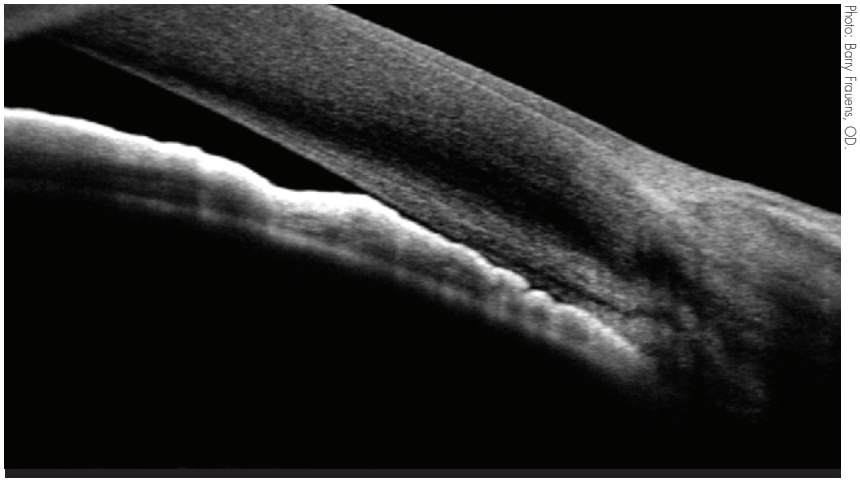

Photo: Barry Frauens, OD

Uveal effusion glaucoma happens when fluid from the choriocapillaris enters the subarachnoid space, causing a secondary angle closure.

receptors.[13] It is an antiepileptic medication that is also used off-label to treat migraine, depression and neuropathic pain, and assist in weight loss, decrease psychological dependency on alcohol and assist in mood stabilization.[20] The ciliochoroidal effusion that occurs in response to topiramate and other sulfonamides is an idiosyncratic response occurring in uveal tissue. Reactive drug metabolites bind to and alter proteins, which are then recognized as foreign antigens that incite immune reactions. Typically, there will be a sensitizing dose, with the response occurring with subsequent doses. In general, there is a 3% risk of having an adverse reaction to sulfonamides.[13]

Uveal effusion glaucoma arising from medication use is a fast-evolving phenomenon. In these cases, there may be no warning or progressive creeping angle-closure occurring. Instead, uveal effusion angle closure develops within two weeks of medication initiation in 85% of cases with a mean onset at seven days. In some instances, the angle closure develops within hours of dosing. Additionally, patients tolerating low doses have developed uveal effusion angle closure upon doubling of the therapeutic dose.[13,17] Patients undergoing this idiosyncratic uveal effusion angle closure do not need to be at risk of primary angle-closure (anatomically narrow angles or moderate degree of hyperopia). This can occur in myopic patients, children and others who would otherwise not be previously suspected to be a risk for angle closure.[21]

Management

Uveal effusion glaucoma occurring from topiramate or another medication will often resolve with cessation of the instigating agent.[22] A potent cycloplegic such as atropine 1% BID to TID will greatly assist in relaxing the ciliary body and allow the iris-lens diaphragm to retreat to its natural position, with subsequent increased forward aqueous flow and opening of the anterior chamber drainage angle. Concurrent use of a potent topical corticosteroid such as prednisolone 1%, loteprednol 0.5% or difluprednate 0.05% TID-QID is highly recommended.

Topical aqueous suppressants such as timolol 0.5% and brimonidine can be used to temporize IOP.[1,13] Oral and IV hyperosmotics, steroids and carbonic anhydrase inhibitors (CAIs) reportedly have been successful in managing the condition.[23] However, extreme measures should be reserved for cases that don't rapidly respond to topiramate cessation and topical therapy. Once topiramate has been discontinued and topical therapy initiated, the angle closure and IOP elevation will typically resolve within 24 to 48 hours, and the myopic shift within one to two weeks.[13]

Precipitating conditions must also be addressed in order to resolve the uveal effusion and subsequently open the anterior chamber drainage angle. Patients with VKH syndrome or posterior scleritis often respond well to systemic steroids or other immunosuppressants such as methotrexate or azathioprine.[1] Patients with thickened scleral (possibly occurring in nanophthalmos) benefit from partial thickness sclerotomy.[1]

Despite temptations, laser peripheral iridotomy (LPI) should not be performed, as there will be no benefit or resolution in this non-pupil block situation.[5,17] Laser peripheral iridoplasty has anecdotally shown adjunctive efficacy, but is typically not needed to manage the condition.[1] There is some controversy as to whether oral or topical CAIs or prostaglandin analogs should be used due to the sulfa and inflammatory potential complications. However, they have all been used to varying degrees with reported success and no instances of poor outcomes directly associated with their use.[13,24]

Topical and oral CAIs and prostaglandin analogs should be considered second-line agents. Miotics, which have the potential to worsen the situation by causing contraction of the ciliary muscle resulting in further anterior rotation of the ciliary body, should be avoided.[1]

Clinical Pearls

- Topiramate-induced uveal effusion glaucoma occurs soon after starting or increasing the dosage of the medication. If the medication is initially tolerated, long-term usage does not increase risk.
- As the angle closure is not pupil block, LPI should not be attempted.
- When differentiating uveal effusion glaucoma from primary acute-angle closure glaucoma, remember that the anterior chamber will be uniformly shallow or flat in uveal effusion glaucoma without iris bombé, which is seen in acute primary open-angle closure.
- Treatment for uveal effusion glaucoma includes atropine, steroids and aqueous suppressants, and discontinuation of topiramate or other causative medications. Miotics and LPI may worsen the condition.
- Sudden decreased visual acuity is often the first complaint.

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CONGENITAL HYPERTROPHY OF THE RETINAL PIGMENT EPITHELIUM

Signs and Symptoms

A congenital hypertrophy of the retinal pigment epithelium (CHRPE) is typically discovered incidentally during routine, dilated fundus examination.[1-7] Patients who have them are unaware of their existence and are asymptomatic. Clinically, there are three recognized presentations: solitary, multiple and grouped.[1-17] The prevalence of CHRPE in the general population is between 1.2% and 4.4%.[13,16]

Solitary CHRPE, the most commonly encountered form, are presumed to be congenital in origin and are not associated with any specific systemic disease.[2-4] They are classically unilateral but may appear bilaterally as flat, well-demarcated, darkly pigmented lesions set in retinal pigment epithelium of the retina.[1-7] In young myopic patients of pigmented ethnicity, the lesions may appear elevated with a "shadow sign" (an area next to the lesion that appears darker than the rest of the fundus) secondary to dark without pressure.[18] This recent finding is postulated to be related to unique alterations of the vitreoretinal interface seen in young myopic pigmented patients.[18] The changes may range in coloration from gray to brown to black, and are often surrounded by a white or dark ring.[1-7]

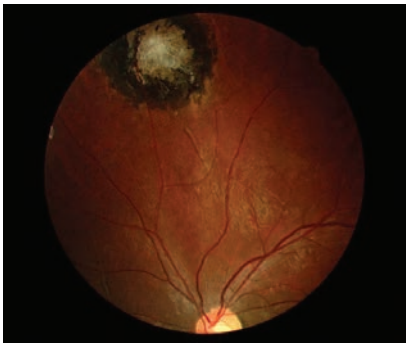
Solitary CHRPE usually have sharply demarcated smooth or slightly scalloped borders. They may show a central depigmented area known as a *lacuna* (cavity, depression and missing portion).[3] Lacunae, which appear as focal round areas devoid of pigment within the region of dark pigmentation are often observed in larger lesions; underlying choroidal vessels may be visible. CHRPE may also be non-pigmented (referred to in the literature as an *albinotic patch* or *polar bear tracks*).[3] These lesions may be devoid of pigment or speckled centrally, and may display a dark surrounding border.[3] Solitary CHRPE are typically round or oval in shape. Approximately 13% assume a more amorphous, geographic configuration.[1-5] These lesions are usually located in the retinal periphery, but sometimes are found in the posterior pole.[4,5] Size is variable, ranging from 0.2mm to 13mm in diameter.[1,2]

Other variations include overlying vascular sheathing, adjacent areas of white without pressure and, rarely, development of a focal elevated nodule within the lesion.[1,2] Overlying retinal vessels appear normal without significant deflection. CHRPE have no gender or racial specific predilection.[1-7] Subtle, flat enlargement may be noted in lesions followed with photography for a time greater than three years. The increasing size is related to the percentage of the CHRPE occupied by one or more lacunae.[1]

CHRPE display hypo-autoflouorescence and hyporeflectivity with hyperreflective lacunae on infrared imaging.[2,18] On enhanced-depth optical coherence tomography (EDI-OCT), CHRPE are flat with thickened, irregular RPE or uniquely absent RPE within lacunae.[2] A prominent OCT feature is outer retinal loss, generally involving the outer nuclear layer and photoreceptors. This finding corroborates the potential for visual field defects despite a lack of symptoms.[2,18]

The hyporeflectivity of the ellipsoid region, as it interdigitates with layers of the adjacent retinal area can create what is now being referred to as *dark without pressure* and the "shadow" sign.[18] The "shadow" appearance may create the illusion of lesion elevation.[18] However, studies that have completed ultrasonography have confirmed that the lesions are flat with no associated subretinal fluid.[18] CHRPE lesions may appear with "white" or "dark" without secondary-to-associated vitreoretinal interface alterations; however, the "shadow sign" results in cases producing dark without pressure.[18] SD-OCT of CHRPE may not show frank simple thickening of that retinal layer; in fact, in most cases it looks normal.

When more than one CHRPE are present, the term *grouped CHRPE* can be used. Grouped lesions are flat, clustered, medium-sized hyperpigmented spots in one or more quadrants of the fundus.[1-7] These lesions are also well-delineated but are on average are slightly smaller than solitary CHRPE.[1-7] The ophthalmoscopic appearance often resembles a cluster of animal footprints; hence, the condition is referred to by many as "bear track retinopathy." Grouped CHRPE are commonly found near or contiguous with the optic nerve and tend to be unilateral in presentation.[1-7] Grouped CHRPE are typically void of lacunae.[3]



Congenital hypertrophy of the RPE, located peripherally, with sharply segmented borders and a lacuna.

The term *pigmented ocular fundus lesions* (POFL-multifocal) refers to multiple, very-small (<0.1 disc diameter), variably dark, pigmented lesions located in the peripheral fundus in the vicinity of the vortex veins. POFL can be oval to tear-shaped and sometimes are surrounded by a hypopigmented halo. They may have a "fish-like" or "comet-like" tail.[3] POFL tend to occur bilaterally, while solitary and grouped CHRPE are more commonly a unilateral finding.[3,4,8] The presence of four or more POFL is a highly specific (>90%) and sensitive (70% to 80%) marker for familial adenomatous polyposis (FAP).[10] POFL are present at birth in approximately 75% of patients with polyposis.[3]

Gardner's syndrome is an autosomal dominant subtype of familial adenomatous polyposis (FAP). FAP is a potentially life-threatening colon cancer associated with adenomatous intestinal polyps, multiple osteomas in the skull, maxillae, mandible, multiple cutaneous and subcutaneous masses (epidermoids and desmoid) and pigmentary changes (soft tissue tumors) of the hard and soft palate and retinal pigment epithelium (RPE).[9-11] Intestinal polyps, if not treated, have 100% chance of becoming malignant by the fourth decade of life.[6-13] There is no gender specific incidence; however, half of the offspring of an affected individual parent is at risk of developing the disease, which has a 100% penetrance when the genotype is present.[13]

FAP is marked by multiple CHRPE, averaging six per eye.[6-12] The hallmark of this condition is bilaterality, which occurs in 86% to 90% of patients.[7,12,13] The lesions tend to be small, with most being less than 0.5 disc diameter (0.75mm) with no intraretinal extension.[1-8,13,14] The

lesions can be seen and followed from early in childhood; up to 80% of CHRPE associated with FAP are present from birth.[13] There is a fair amount of variability regarding ophthalmoscopic appearance. As in the case of solitary CHRPE, the lesions may differ in pigmentation (gray to black or amelanotic), shape (round, oval, tear-shaped, bean-shaped or linear), and the presence or absence of a surrounding halo.[1-14]

A lesser-known association finds CHRPE in combination with retinoblastoma and brain tumor, known as Turcot's syndrome.[13]

Pathophysiology

Histologic evaluation of solitary CHRPE lesions reveals cellular hypertrophy of the retinal pigment epithelium (RPE) with associated accumulation of macromelanosomes; the RPE cells are larger and contain more pigment than usual, but are not otherwise abnormal.[1-3] The RPE basement membrane is somewhat thickened locally, and there is evidence of progressive photoreceptor loss in the outer retina, although the underlying choriocapillaris remains unaltered.[1,2,5,15] Lacunae, more common in solitary CHRPE than other varieties, represent focal depigmentation and atrophy of RPE cells with concurrent thickening of Bruch's membrane.[16]

In contrast to solitary CHRPE, the RPE cells in grouped CHPRE appear to be normal-sized, but contain increased amounts of large pigment granules as well as a thickened basement membrane.[19,20] The multiple CHRPE of Gardner's syndrome show distinct histological differences from the other two presentations; notably, these lesions are often multilayered and extend throughout the sensory retina, with evidence of associated RPE hyperplasia.[8,21] Multiple CHRPE has been frequently described as a hamartoma of the retinal pigment epithelium.[6-8,21]

CHRPE are often evident in newborns, and have even been observed in premature births.[19] They are present throughout life, and, until recently, had been thought to remain invariably stable. However, evidence now suggests that most solitary CHRPE show progressive enlargement over time. The mechanisms of RPE growth may involve horizontal expansion, development of additional lacunae and/or broadening of existing lacunae.[1-7] A small percentage of solitary CHRPE exhibit intralesional nodules, and these may display enlargement as well.[1-7] At least three published reports have demonstrated malignant growth associated with solitary CHRPE.[21-24] Grouped CHRPE and multiple CHRPE are not believed to demonstrate any significant growth in either number or size over time.[8]

Management

Solitary and grouped CHRPE require no intervention; however, they should be monitored for changes in size, shape, color, elevation and the induction of either intra-retinal exudative or sub-retinal processes.[1-24] Initially, the most important consideration is differentiating these lesions from other, more ominous, conditions—particularly choroidal melanoma.[18]

Typically, the diagnosis is straightforward, made by ophthalmoscopic examination alone. Ambiguous cases may benefit from additional diagnostic testing such as infrared imaging, optical coherence tomography and ultrasonography.[2,24]

Ultrasonography should not be underestimated or placed in the shadow of newer technologies as it can demonstrate acoustic hollowing, choroidal excavation, orbital shadowing or the beginnings of an abruptly elevated "derby hat-shaped mass" with medium-to-high internal reflectivity in uveal melanoma.[24] Ultrasonography can identify exudative retinal detachment, intraocular inflammation and vitreous traction.[24,25]

Fluorescein angiography of CHRPE shows a characteristic hypofluorescence within the pigmented area and hyperfluorescence associated with lacunae and halo; there is no evidence of vascular filling or leakage, as is typical with melanoma.[24] Solitary CHRPE should be carefully documented using fundus photography (or widefield imaging, depending upon location) and monitored periodically for changes in size or elevation. They can be drawn, but detection of change is very difficult from renderings.

Multiple CHRPE, because of their close association with FAP and Turcot syndrome (glioma-polyposis) must be evaluated.[1-23] Studies suggest that the presence of four or more lesions (regardless of size), or at least two lesions, one of which was large, carries high sensitivity and specificity for Gardner's syndrome.[1-14] All patients who meet this criteria, or those who display atypical bilateral CHRPE, should be evaluated for the possibility of polyposis; this is particularly important in those with a positive family history of colon polyps or cancer.[26]

Appropriate referral for these individuals is to a gastroenterologist for evaluation. In addition, genetic testing is available to identify the specific mutation in the APC gene, which has been associated with FAP.[7] This test can also be used to identify FAP carriers within the immediate family.

Clinical Pearls

- An older term for CHRPE was *halo nevus*, referring to its nearly pathognomonic depigmented border. While descriptive, this term is misleading; nevi are histologically distinct from CHRPE and localized to the choroid rather than the retina.
- The red-free filter on the ophthalmoscope or slit lamp can be helpful in differentiating ambiguous CHRPE from choroidal nevi or melanoma. With the filter in place, choroidal pigmentation becomes almost imperceptible, while retinal pigmentation remains visible.
- Generally, CHRPE are encountered unilaterally with fewer than three pigmented lesions; when there are more of a smaller size (POFL) or the lesions are bilateral, the risk of Gardner's syndrome must be considered.
- Solitary CHRPE and POFL should be photodocumented and measured in disc areas. They need only be followed for associated changes in the size, shape, color or elevation of the lesions, which are typically minimal over a lifetime. Any changes against baseline requires referral to an ocular oncologist or retinal specialist to rule out ocular melanoma.

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FAMILIAL EXUDATIVE VITREORETINOPATHY

Signs and Symptoms

Familial exudative vitreoretinopathy (FEVR) is a bilateral inherited disorder characterized by peripheral retinal nonperfusion and vitreous degeneration.[1-12] FEVR was described in 1969 by Criswick and Schepens, who analyzed six patients with clinical conditions similar to the ones seen in retinopathy of prematurity (ROP) but without history of prematurity or oxygen supplementation.[13] FEVR is not accompanied by any extraocular malformations or causative systemic disease.[1-9]

Cases can be inherited in an autosomal dominant, autosomal recessive or X-linked manner or can affect individuals with no family history whatsoever.[1,8] The disease, in general, has no gender predilection but has a regional predilection to northern Europe and Asia.[8,12] The disease is known for its highly variable and asymmetric expression, ranging from producing no symptoms to producing severe expressions even in cases seen within the same family.[1,8]

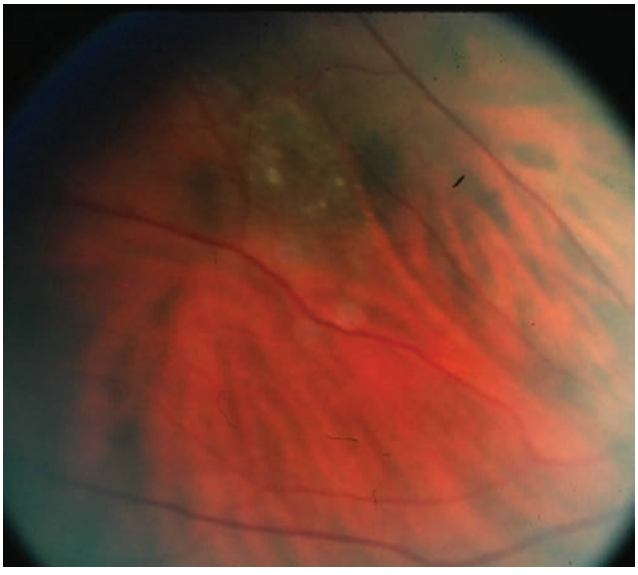
The hallmark of FEVR is temporal, peripheral, "V-shaped" retinal avascularity.[1] When significant retinal ischemia is present, secondary neovascularization can occur, leading to retinal fibrosis, tractional retinal detachment (TRD), retinal folds or retinal dysplasia.[1,5,6,8] The diagnosis of FEVR can be made if there is evidence of peripheral retinal avascularity in one eye of a patient of any age who was born at full term, or in preterm individuals with no evidence of hyper-oxygenation or ROP.[1] In the majority of cases, so long as tractional forces do not impact the fovea, FEVR does not affect vision.[1-10] The prognosis for infants born with FEVR is poor, as they tend to have macular dragging with concurrent strabismus and, in some cases, nystagmus.[7,8]

The long-term prognosis for patients with later-onset FEVR is guarded, depending upon its severity.[1-8] Retinal detachment is a common finding and occurs in 21% to 64% of affected individuals.[1,10] When retinal detachments occur they may be rhegmatogenous, tractional or serous.[1,8,10] Tractional retinal detachments can progress to form radial retinal folds known as "falciform" folds.[1] These folds represent one of the classic features of FEVR.[1] There is a slight preponderance for male gender associated with rhegmatogenous retinal detachment.[10]

Cases with the worst prognosis develop macular dragging, secondary cataract, and neovascular or phacomorphic glaucoma.[1-11] Additionally, less common findings include retinal exudation (in some cases, severe) resembling Coat's disease, peripheral retinoschisis, vitreous hemorrhage, phacolytic uveitis, retinal capillary angioma and retained hyaloid vascular remnants.[1-11] These complications may begin early or late in the disease staging, even emerging spontaneously in eyes whose past examinations appeared stable.[1,7]

Pathophysiology

Genetic research has mapped the locus producing FEVR to the long arm of chromosome 11, but the specific gene remains elusive.[8] FEVR is considered a genetically heterogeneous disease because it can exhibit different hereditary patterns.[8,11] The most frequently described pattern is autosomal dominant.[1-11] The literature also describes cases of autosomal recessive inheritance with sporadic X-linked cases. The primary abnormality in FEVR is the failure of the peripheral blood vessels to progress to the ora serrata, preventing vascularization of the peripheral retina.[1-12] While the course of the disease can be rapid in children and adolescents, most patients do not undergo deterioration before they are 20 years old.[8,11] Fortunately, 50% to 80% of all patients with FEVR remain asymptomatic.[1-13] FEVR was first mapped to chromosome 11q by Criswick and Schepens.[13]



In FEVR, peripheral blood vessels fail to progress to the ora serrata, preventing vascularization of the peripheral retina.

Early works provided a classification system which characterized FEVR into three stages.[12,14,15]

The clinical appearance of FEVR varies greatly between individuals.[1-15] Patients affected severely may present in infancy or in childhood with decreased visual acuity, nystagmus or strabismus.[8] In stage I, affected patients are usually asymptomatic with good visual acuity. A zone of peripheral avascular retina is seen in 100% of patients. This avascular zone remains a permanent feature throughout life. Often there is excessive branching of the retinal blood vessels. The angles of the vessel bifurcations are narrow, and at times the vessels seem to run parallel. Excessive white without pressure, vitreous shrinkage and vitreous band formation may also occur.[11,12,14,15]

Stage II retinopathy is marked by proliferative and exudative changes. In addition to stage 1 findings, affected individuals exhibit neovascularization along with subretinal and intraretinal exudation. The amount of exudation may be substantial. Vitreous adhesion with subsequent traction and maculopathy are the most common causes of visual loss. Peripheral vision loss occurs when tractional retinal detachment or vitreous hemorrhage develops. Fortunately, in many patients, posterior progression is slow or never occurs. The majority of retinal detachments occur in the first decade of life, with little progression thereafter. An ectopic macula can be found in 50% of cases.[8,12,14,15]

Stage III FEVR possesses sight-threatening complications secondary to growing tractional forces from cicatricial lesions in the temporal periphery.[1-15] Tractional retinal detachment is more common in younger patients, with combination rhegmatogenous/tractional detachments in patients who acquire complications beyond the second decade.[8] Falciform retinal folds, fibrotic scaffolding with traction, subretinal exudates, cataracts, rubeosis irides, vitreous detachment and vitreous hemorrhage are all possible sequelae.[1-15] Pendergast and coworkers revised this system into five succinct stages: avascular periphery; retinal neovascularization, without exudate, and with exudate; extra-macular retinal detachment, without exudate, and with exudate; subtotal macula-involving retinal detachment, without exudate and with exudates; and total retinal detachment.[15]

Management

The primary treatment for patients with asymptomatic FEVR is periodic monitoring.[1-16] Amblyopia almost always complicates congenital cases and requires prompt attention. Strabismus secondary to dragged maculae must be identified early and managed aggressively with surgery and amblyopia therapy.

Under normal circumstances, the term amblyopia is not used when there is an organic source for vision loss. However, in these cases the dragged macula induces eccentric viewing and strabismus, which produces strabismic amblyopia. Since the fovea is intact, patching and direct occlusion often supports realignment through the use of a "still-competent" macula.

Prophylactic photocoagulation and cryotherapy can be done depending on the severity of the disease.[17] Timely diagnosis and protective intervention is essential in view of the potential for late exacerbations.[17]

In cases with a high index of suspicion, family screening and early prophylaxis are recommended to prevent blinding complications.[17] The treatment of FEVR in patients with ischemic peripheral retinas that demonstrate evidence of exudative or neovascular disease remains panretinal photocoagulation and cryopexy.[1-12,17,18] Retinal detachments are addressed with scleral buckling and vitrectomy.[19] Results of treatments have been mixed, and only patients at high risk for progression should be considered for drastic intervention. Genetic signaling to normalize the retinal vasculature is currently under investigation to arrest and potentially reverse the process.[20]

Clinical Pearls

- The diagnosis of FEVR is made based upon clinical findings, family history and lack of evidence of ROP or oxygen therapy.
- Screening with fluorescein angiography in suspicious cases may identify nonperfused peripheral retina aiding diagnosis.
- The list of differential diagnoses for FEVR includes retinopathy of prematurity (ROP), X-linked retinoschisis, Norrie's Disease, persistent fetal vasculature retinopathy, Coats' disease and incontinentia pigmenti.

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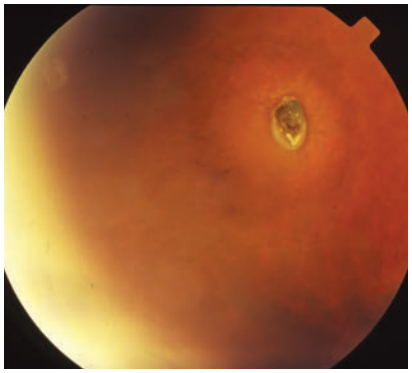
INTRAOCULAR FOREIGN BODY

Signs and Symptoms

Patients with intraocular foreign body (IOFB) may present either as a catastrophic open globe injury following significant trauma or with mild or no symptoms but with some awareness that something may have gotten into their eye.[1-20]

In cases involving an overtly open globe, signs may include reduced visual acuity, gross subconjunctival hemorrhage, corneal or scleral laceration or defect, accounting for the object's portal of entry into the eye, traumatic cataract, iris damage with pupil irregularities (D-shaped



Metallic intraocular foreign body in a patient with sideritic glaucoma.

pupil as seen when there is iridodialysis or peaked pupil as seen when a foreign body penetrates the diaphragm), tonic pupil, hyphema, anterior or posterior segment inflammation, endophthalmitis, retinal detachment and uveal extrusion.[1-20] In cases that are mildly symptomatic the signs and symptoms may be multiple, variable and vague, including visual disturbances, ocular irritation, focal pain, mild tearing and eye redness.[1-4] Generally, symptoms are governed by the severity of the injury, the injury location and the amount of inflammation produced.[19]

Outcomes are most influenced by the size of the IOFB and if it causes retinal detachment.[20] Intraocular foreign bodies can enter the globe through the thin skin of the lids.[19] A visible foreign body may be detectable anywhere from the lids to the cornea and retina, or there may be a visible tissue vector through the cornea, aqueous, lens or vitreous defining the matter's trajectory without the foreign body being visible. It is also conceivable the foreign body is clinically undetectable without additional imaging.[2,3,20] Multiple IOFB are present in up to 25% of injuries.[1]

Intraocular foreign bodies may pass through tissues (penetrating) or create a hole in tissues (perforating), lodging or bouncing off.[1] As a rule, intraocular foreign body injuries follow the general trend seen in ocular trauma; overwhelmingly young men with an average age of 29 to 38 years with the likely place of injury being at work (54% to 72%) followed by home (30%).[1,11,20] The most common intraocular foreign bodies include nail hammering (60% to 80%), usage of power or machine tools (18% to 25%), fireworks mishaps and weapon-related injuries (19%).[1,9-12] Some patients may not recall any specific trauma or injury as the foreign body entered the eye via an accidental or incidental occurrence while biking, cutting grass (often high-speed line trimmer) or hiking without eye protection.[6,10]

Glass is a commonly retained IOFB, occurring mainly from automobile accidents.[7,8] Less common IOFBs are wood, organic material from landscaping mishaps, human hair, plastic and insect parts.[1] Special considerations must be given to metallic intraocular foreign bodies (iron or copper). Copper foreign bodies can induce reversible retinal toxicity and/or a severe anterior and posterior segment inflammatory reaction depending on its purity (chalcosis).[1] Iron intraocular foreign bodies have the potential to cause the sight-threatening condition siderosis bulbi.[1-21]

Pathophysiology

The pathophysiology of IOFB injuries includes: mechanical (size, shape, velocity, perforation vs. depth of penetration); degree of infection and inflammation; and toxicity.[1-24] Despite the potential for subconjunctival hemorrhage, conjunctival laceration, hyphema, iris damage, lens opacification, lens luxation, intraocular infection/inflammation and retinal detachment, the degree of damage produced by intraocular foreign body is not predictable.[1-24] Intralenticular foreign bodies are often associated with phacoanaphylaxis or cataract formation secondary to lens insult, though there are reported cases where cataracts did not form.[14] Ocular morbidity is closely related to IOFB size (the larger the worse), presence of retinal detachment and endophthalmitis.[17, 20,22-24]

Ocular siderosis bulbi is a sight-threatening complication of retained iron-containing metallic foreign body and a significant source of ocular morbidity.[25] In toxic siderosis bulbi, iron released from an iron-containing foreign body becomes deposited as ferritin; it is scattered throughout the cytoplasm and sometimes accumulates as "siderosomes" in cells.[23-26] It generally occurs from 18 days to 12 years following introduction into the eye.[1,2,9,13-15,25]

Early clinical findings include iris heterochromia, pupillary abnormalities, cataract, secondary open-angle glaucoma ascribed to trabecular fibrosclerosis resulting from direct toxic effects of iron ions and retinal pigmentary degeneration secondary to toxic dysfunction of all the layers of the retina (the more severe damage occurring in the inner retina than in the outer retina).[15,25]

Characteristic electroretinogram (ERG) findings can be considered diagnostic of this condition and should prompt immediate referral for removal.[1,25] The most common changes include a markedly reduced or unrecordable scotopic and photopic response with the reduced A-wave and B-wave amplitudes representing the level of retinal degeneration.[2,15,25] In some instances the A-wave can become transiently increased.[25] As siderosis progresses, the B-wave will fall, causing the B-wave/A-wave ratio to diminish (a classic finding).[25] Rod-dominated responses are predominantly affected, as they have a greater susceptibility to iron toxicity.[25]

If left untreated, the tissues will degenerate until no response is obtainable.[25] Retinal degeneration is typically permanent; however, in some instances, the ERG rebounded following extraction of the retained IOFB.[22-25] B-scan ultrasonography has great value in these cases, but it must be performed with care so as not to invite tissue extrusion or wicking effect. Gentle but strategic maneuvering of the probe can often locate intraocular foreign matter in the office, permitting faster decision making and accuracy of referral.

Management

First-aid in cases of penetrating or perforating injury and suspected IOFB includes immediate consultation with a surgeon and covering of the eye with a FOX eye shield. The prognosis for preserving or improving vision is dependent upon the size and number of the penetrating matter and the damage induced.[1-26] Even if the patient has good vision and the wound is sealed, retained IOFB must be removed to avert the potentially blinding complication of siderosis.[23-26]

In cases where no IOFB is detected, a plain X-ray, computed tomography (CT) or gentle ultrasonography can be employed.[1,25-27] In cases of suspected delayed siderosis, supported by history, decreasing vision, decreasing dark adaptation, heterochromia and retinal pigmentary changes, an ERG can be employed.[25] The visual potential in eyes with siderosis

is good if the toxicity is removed so long as the optic nerve and macula have not been injured.[25]

Magnetic resonance imaging is contraindicated in the examination of patients with suspected metallic IOFB, as the magnet can cause displacement of the object with subsequent tissue damage.[29] Helical multiplanar CT scanning has been used as the imaging modality of choice in the assessment of metallic intraocular foreign bodies.[29,30]

The removal technique of a retained IOFB is dependent upon its location, clarity of the media, whether or not the IOFB is embedded in the retina and the best route of accessibility.[25-37] Needles, surgical lassos and magnets have all been used with success to retrieve these objects.[31-37] Removal may be done via an external approach (sclerotomy with large electromagnet) or an internal approach (vitrectomy followed by forceps or internal magnet use).[25-37]

If the foreign body is located in the posterior vitreous or embedded in the retina, a pars plana vitrectomy (PPV) is the preferred surgery.[25] In cases displaying delayed siderosis, PPV with forceps removal may be required, as iron-containing foreign bodies may lose their magnetic properties over time.[25] PPV also has the advantage of providing direct viewing and controlled removal of the IOFB, so some may prefer it as the technique of choice.[14,18,30,36,37] Following the procedure, close follow-up is required to monitor topical cycloplegia, anti-infective and anti-inflammatory therapies, as well as monitor intraocular pressure.

Clinical Pearls

- The visual prognosis in an intraocular foreign body injury will depend on its size, shape, velocity at impact, tissues affected, speed of diagnosis and complications.
- Multiple foreign bodies are found in up to 25% of cases.
- A retinal consultation should be obtained in cases of iron-containing intraocular foreign bodies. The potential for siderosis with late damage from toxicity is strong, and removal should be strongly considered.
- Non-healing eye injuries should be re-examined for foreign matter.
- Secondary open-angle glaucoma can occur from siderosis. Aqueous suppressants are the mainstay of treatment, though prostaglandin analogs are not contraindicated.

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PURTSCHER'S RETINOPATHY

Signs and Symptoms

In 1910, Otmar Purtscher described the occurrence of bilateral patches of retinal whitening with intraretinal hemorrhage within the posterior pole surrounding the optic disk in patients who had suffered head trauma (*angiopathia retinae traumatica*).[1] These classic fundus findings, as a collective syndrome, have since been titled, in his honor, Purtscher's retinopathy.[1-14] Today, Purtscher's retinopathy is associated with head/neck trauma and thoracic compression but can be seen following general body trauma or injury from straining or mechanical acceleration/deceleration events such as shaken baby syndrome, Valsalva maneuver, childbirth and weight lifting.[6,7,14]

When findings consistent with the traumatic form are seen in concert with a variety of non-traumatic systemic diseases including acute pancreatitis, systemic lupus erythematosus, thrombotic thrombocytopenic purpura, autoimmune diseases, chronic renal failure and pre-eclamptic pregnancy, the condition is referred to as Purtscher's-like retinopathy.[1–14] The incidence of Purtscher's and Purtscher's-like retinopathies is estimated to be 0.24 per million per year; however, this statistic is a loose estimate, as patients may be unaware of symptoms or are underdiagnosed.[8]

There is a loose gender bias towards young males consistent with the epidemiology of traumatic injuries.[12] The condition presents bilaterally in up to 60% of cases but can present unilaterally.[6,7,12]

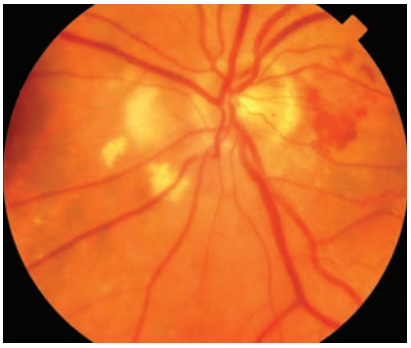
Patients experience acute, painless, sight-threatening loss of central vision that ranges from slight impairment to hand motion.[1-14] The visual disturbances may be delayed by 24 to 48 hours from the onset of the event or start of symptoms from the systemic illness.[6,7,12] Loss of acuity may be accompanied by field loss in the form of central, paracentral or arcuate scotomata.[6,7] Peripheral visual function is typically spared.[6,7] The acute changes in the retina may not be apparent until 24 to 48 hours after the systemic illness.

Ophthalmoscopy reveals "Purtscher flecken" consisting of multiple, discrete areas of intraretinal retinal whitening (retinal infarctions somewhat like cotton wool patches) between the arterioles and venules.[6-8] The "flecken" are variable-sized polygons ranging from a quarter of a disc area to several disc areas.[6-8] A clear zone usually exists between affected retina and adjacent arteriole/venuloes.[6] Flame-shaped and dot intraretinal hemorrhages may be present around the optic nerve head or confined to the posterior pole.[6] Acutely, the optic nerve head and peripheral retina will appear unaffected; the optic discs may eventually exhibit pallor over time.[1-14] A pseudo-cherry red spot may be seen when the patches of retinal whitening surround the fovea.[6,7] The presentation is variable, depending upon the cause; cotton-wool spots and/or hemorrhage without Purtscher flecken have been noted in 4% of patients with long bone fractures.[6]

The acute pathologic findings of Purtscher's retinopathy resolve spontaneously within one to three months and are replaced with mottling of the retinal pigment epithelium, optic disc pallor if concurrent traumatic optic neuropathy has occurred, and attenuation or sheathing of the retinal vessels, commensurate with the overall amount of retinal inflammation that was produced.[6]

Pathophysiology

Purtscher's retinopathy is a sight-threatening, occlusive microvasculopathy associated with trauma (long bone/sternal fractures) and systemic inflammatory/infectious disease.[1-15] Described in 1910 as an occlusive microvasculopathy associated with raised intracranial pressure from head trauma, the first case was observed in a man who fell from a tree and sustained a severe head injury while suffering



Purtscher's retinopathy is characterized by areas of retinal whitening.

temporary loss of vision.[1,2,7,8] Purtscher connected his observations to pathological changes associated with extravasation of lymph from retinal vessels.[6,8]

Today, others have recognized alternative mechanisms involving retinal vasculitis induced by lipase after systemic injury. Researchers have hypothesized that thrombosis and retinal microvascular occlusion is associated with retinal microvascular damage from acute increased vascular pressure detonated by the injury.

Lamina cribrosa precapillary injury is seemingly precipitated by trauma and microvascular occlusions induced by coagulopathy, hyperviscosity or traumatic venous distention.[6,12] While the exact mechanism remains unclear, multifocal lesions restricted to the posterior pole, bilateral involvement and occlusion of the retinal vessels seen on fluorescein angiography all suggest a pathogenesis that involves embolic occlusion of the precapillary arterioles before transition into the venules.[6,8]

Investigators analyzing the clear zone seen between affected portions of the retina and normal retina have concluded that it corresponds to a capillary-free zone extending for 50µm on either side of the microscopic vessels.[6] Proximal occlusion of the retinal arteries by larger emboli would produce a confluent whitening similar to that seen in branch arterial occlusion.[6] In contradistinction, if the emboli simply lodged at the distal region of retinal capillaries the outcome would be cotton-wool spots.[6]

Autopsy results in a patient known to have Purtscher's retinopathy following death from pancreatitis showed retinal edema, cystoid degeneration and loss of inner retinal architecture with abrupt transition to normal retina. Some areas also showed loss of photoreceptors, the outer segments being affected to a greater degree than inner segments. However, both retinal arterioles and choroidal vessels showed occluding material, positive for fibrin, indicating the process was present in both vascular trees. Electron microscopy showed small arterioles with narrowed lumina containing proteinaceous material centrally consistent with recanalized thrombi.[6]

Fat emboli are commonly released from the intramedullary fat into the venous circulation after long bone fracture, surgery and pancreatitis.[1-15] Fat embolism syndrome (FES) is a collection of symptoms and physical signs that occurs 12 to 36 hours after long bone fracture, orthopedic surgery, crush injury, chest compression and acute pancreatitis.[6] Other microembolic phenomenon in FES may be the result of fibrin clots and the intravascular activation of the complement system.[6]

Other potential emboli in the pathogenesis of Purtscher's and Purtcher's-like retinopathy include air, leukocyte aggregates, platelets and fibrin.[1-15] Unilateral Purtscher's retinopathy has been described after retrobulbar anesthesia and orbital injection of suspended steroid particles.[6] Systemic embolism may also occur following arteriovenous pulmonary shunts or via a patent foramen ovale or persistent ductus arteriosus.[6]

Management

Intervention for Purtscher's and Purtscher's-like retinopathy is controversial.[1-16] The intraretinal retinal hemorrhages, whitening and cotton-wool patches self-resolve over weeks or months as the fractures heal or systemic disease is managed.[1-15]

The prognosis for visual recovery is variable and associated with the severity and size of the areas affected. When the recovery is poor, speculation is acuity remains decreased secondary to infarction of either the foveal photoreceptors or optic nerve itself.[1-16] Some reports document cases successfully treated with large doses of IV corticosteroids.[6,12] Visual improvement has been attributed to the ability of corticosteroids to stabilize damaged neuronal membrane and microvascular channels while inhibiting granulocyte aggregation related to complement activation.[12]

Despite the apparent benefits, this has not yet become the standard of care.[6,12]

The use of vascular endothelial growth factor inhibitors is under investigation with promising results in one report.[17] Hyperbaric oxygen therapy is also being examined to increase tissue oxygenation during the early periods of ischemia.[6] Despite the apparent anecdotal benefit of some of the above-mentioned treatments, little evidence supports intervention over observation in Purtscher's retinopathy.[1-15] Best practices do not currently support the use of anti-fibrinolytic agents in the treatment of Purtscher's retinopathy.[1-18] In fact, data suggests that leaving the condition untreated results in resolution as fast and complete as cases that are treated.[12,18]

Clinical Pearls

- Neuroimaging of the face, orbit and brain should be completed during any hospital stay to rule out fractures and intracranial lesions following trauma.
- Purtscher's retinopathy has pathognomonic findings and should not be confused with retinal artery occlusion, hypertensive retinopathy, commotio retinae or retinal detachment, each of which require different management strategies and offer varying prognoses.
- Crush injuries, often involving broken long bones of the body or sternum, are associated with Purtscher's retinopathy.
- Retinal photodocumentation and optical coherence tomography are advisable at the baseline to understand the extent of the damage as well as to document resolution/progress.
- Treatment with spinal cord levels of intravenous corticosteroids may offer the best chance for visual recovery; its use should be gauged carefully against potential complications.

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TERSON'S SYNDROME

Signs and Symptoms

Terson's syndrome was first described by the French ophthalmologist Albert Terson in the early 1900s.[1-4] He did not name the collection of findings he found (vitreous hemorrhage in concert with subarachnoid hemorrhage) after himself; rather, the occurrence was coined by Paunoff in 1962 in honor of Terson's original paper.[2,3,5] The syndrome is defined as intraocular hemorrhage associated with acute intracranial hemorrhage.[1-21] It has since evolved to include the presentation of any type of intraocular hemorrhage after spontaneous or trauma-induced intracranial bleeding.[1-5]

Funduscopically, there may be unilateral or bilateral hemorrhages occupying intraretinal, preretinal (subhyaloid) or intravitreal locations.[1-3,5] The primary causative feature is spontaneous or trauma-induced intracranial bleeding (usually subarachnoid hemorrhage).[1-15] Subarachnoid bleeding from a cerebral aneurysm, in particular an aneurysm of the anterior communicating artery, has been described as the most common underlying cause.[1-14] Benign colloid cysts located in the rostral part of third ventricle and subdural hematoma have also been documented causes.[13,16] There is no specific predilection for gender or age.

Intraocular hemorrhage is seen in approximately 20% of patients with acute intracranial bleeding.[1] The phenomena is bilateral approximately 50% of the time.[16] Significant vitreous hemorrhage occurs in a smaller percentage of these patients.[1,6] Although the intraocular bleeding may consist of subretinal and deep intraretinal hemorrhage, it may also lie superficially, being just under the internal limiting or subhyaloid membrane.[1-15] Significant vitreous hemorrhage will occur only if the blood breaks through the internal limiting membrane or the posterior hyaloid face to move into the vitreous gel.[1,6]

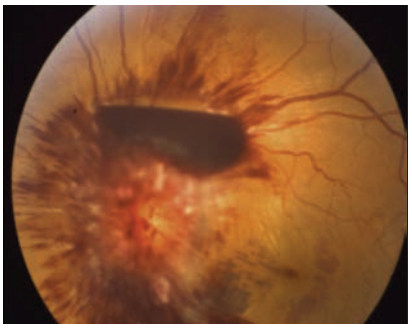
Visual acuity may be significantly diminished, depending upon the amount of blood and its location within the eye. Decreased visual acuity or field in some cases is the first sign of trouble.[1-8] Late complications include epiretinal membrane formation and, rarely, macular hole formation or tractional or rhegmatogenous retinal detachment.[6] It is important to note that some patients suffering from ruptured intracranial aneurysms may exhibit vision loss secondary to the associated vitreous hemorrhage while demonstrating little if any headache, neurological deficits or signs of meningeal irritation.[4] Therefore, vitreous hemorrhage without a retinal cause should be considered suspicious.[4]

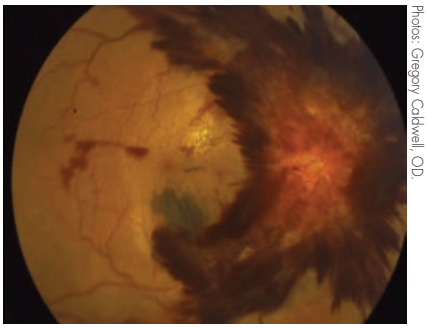
Disturbances in ocular homeostasis can cause premature cataractogenesis and proliferative retinopathy resulting from expressed chemokines, and cytokines can induce proliferative retinopathy.[10-15] Secondary open-angle glaucoma can occur if any of the vitreous blood (intact or degenerated) migrates into the anterior chamber (ghost cell glaucoma).[16-20] Secondary angle closure in the form of ciliary block or ciliochoroidal effusion have been documented as a consequence of subarachnoid hemorrhage independent of, and associated with, Terson's syndrome.[18-21]

Terson's syndrome is an anomaly of adults; the maximal incidence of intraretinal hemorrhage in children not having sustained abuse (intracranial hemorrhage associated with shaken baby syndrome) is 8%.[7] Chronic untreated vitreous hemorrhage in young patients can be detrimental to vision through derivational amblyopia.[1]

Pathophysiology

Terson thought his discovery was peculiar since pathology specimens of patients with intracranial and vitreous hemorrhage demonstrating no hemorrhage in the optic nerve sheaths existed at the time.[2,3,5] Both Terson and Paunoff believed the source





Photos: Gregory Caldwell, OD

Vitreous hemorrhage in Terson's retinopathy is associated with intracranial hemorrhage.

of the vitreous hemorrhage arose from the retinal vasculature.[3,5] Today, it is generally agreed that both the subarachnoid and subdural spaces of the optic nerve "end blindly" without ever directly communicating with any of the intraocular chambers.[5] Although extension of intracranial hemorrhage by this route does not seem possible, the explanation still persists in the modern literature.

The current theory for the pathophysiology of Terson's syndrome is sudden spiking of intracranial pressure at the time of an acute intracranial hemorrhage precipitating intraocular bleeding.[1-10] Frequently, the amount of ocular hemorrhage correlates directly with the rapidity and magnitude of the intracranial pressure elevation.[1] Why this happens remains unclear.[1]

Researchers have postulated that increased orbital venous pressure, which translates directly through the cavernous sinus, or compression of the ophthalmic veins and adjacent retinochoroidal anastamoses secondary to rapid effusion of cerebrospinal fluid or blood into the optic nerve sheath could explain the phenomenon.[1] Either way, it appears that an acute obstruction of the retinal venous circulation is resulting in the rupture of superficial retinal vessels.[1] Subdural and epidural hematomas have both been documented as causing the phenomenon.[9,16]

Management

Patients demonstrating Terson's syndrome have suffered a catastrophic intracranial event and may have already presented to a general or emergency physician with other significant systemic symptoms and signs. When poor vision is discovered, ocular examination will uncover the sequelae.[1–20] In instances where the neurosurgery team prohibits pupillary dilation, B-scan ultrasonography can be performed at the bedside to uncover the associated vitreous hemorrhage.[20]

Some have suggested that the presence of Terson's syndrome may be associated with a higher rate of mortality; however, this remains controversial.[1,11,16] In cases that do not have an established traumatic source for the intracranial hemorrhage, emergency neuroimaging with CT or MRI is indicated, as ruptured intracranial aneurysm is the likely cause.[1-16] Most cases of Terson's syndrome remit following proper attention to the initial cause.[1-20] If poor vision persists after three months, or in cases of bilateral vitreous hemorrhage, epiretinal membrane or proliferative retinopathy, early pars plana vitrectomy with an internal limiting membrane peel can be considered.[9,11,17] Recent studies describe better visual outcome in cases of early vitrectomy performed within 90 days of vitreous haemorrhage.[16]

Clinical Pearls

- Terson's syndrome caries a good visual prognosis; when the blood clears visual acuity typically returns.
- Decreased vision may be secondary to retinal pigment epithelial disturbances, epiretinal membrane formation with vitreomacular adhesion or traction, macular hole formation or the result of sequelae brought about by the development of proliferative disease.
- Persistent visual acuity loss may persist if subretinal hemorrhage is present or if the event precipitates optic nerve damage. In these cases, electrodiagnostic testing may be useful in providing definitive diagnosis.
- Undilated fundus examination is always indicated in cases of acute painful cranial nerve (CN) III palsy; vitreous hemorrhage may ensue due to the high incidence of intracranial aneurysm. When a patient with acute CN III palsy presents, a funduscopic examination must be done through an undilated pupil to ascertain if vitreous hemorrhage is present, indicating an aneurysmal cause. The reason for not dilating the patient is that subsequent treating physicians need to be able to examine the eye and pupil responses free from pharmacologic contamination.
- Unexplained retinal or vitreous hemorrhage in patients with new onset headache should raise suspicion of a ruptured intracranial aneurysm and subarachnoid bleed.
- Terson's syndrome from trauma is an emergency.

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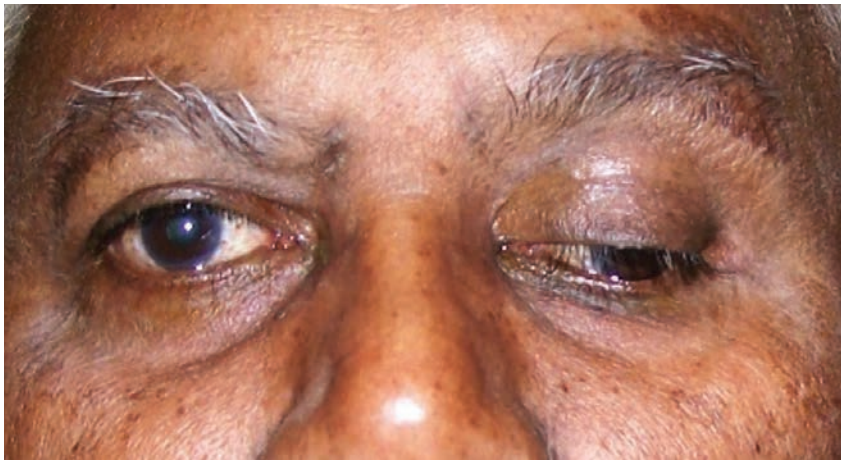
The Handbook of Ocular Disease Management

REVIEW OF OPTOMETRY

ABERRANT REGENERATION OF CRANIAL NERVE III (OCULOMOTOR SYNKINESIS)



Any patient whose upper eyelid lowers on abduction and elevates on adduction should be examined for aberrant regeneration of CN III. This patient's pathology occurred secondary to intracranial aneurysm.

Signs and Symptoms

Aberrant regeneration of cranial nerve (CN) III, also known as oculomotor synkinesis, is a condition with two forms and a variable presentation. The most common form is termed *secondary aberrant regeneration* and occurs following the development of CN III palsy of traumatic or compressive etiology.[1-7] A less common form is *primary aberrant regeneration of CN III*; these patients will not have an antecedent CN III palsy in their history.[8-14]

Patients with either form will have characteristic eyelid positioning and actions (lid gaze dyskinesis and/or pseudo-von Graefe's sign). Secondary aberrant regeneration often demonstrates residual motility dysfunction such as adduction, elevation and depression motility deficits. Some degree of ptosis is usually present as well. The ptosis and motility disturbances are typically less pronounced than what is observed during the acute phase of the CN III palsy.

The variable features of the syndrome include horizontal gaze–eyelid synkinesis. The patient's upper eyelid on the involved side will lower on abduction and elevate on adduction (lid gaze dyskinesis sign). Additionally, the eyelid will elevate when the patient looks down (pseudo-von Graefe sign). There can be limitation of elevation and depression of the eye with retraction of the globe on attempted vertical movements, as well as adduction of the involved eye on attempted elevation or depression, often with resultant diplopic complaints. There may be pupil constriction with attempted adduction or downgaze (pseudo-Argyll Robertson pupil sign), and absent vertical optokinetic response. Pseudo-Graefe sign is the most common finding.[1,2,4-6,15] Not all findings are present or prominent in every case.

Pathophysiology

CN III is the only cranial nerve with a subnuclear complex that arises in the dorsal mesencephalon (midbrain) at the level of the superior colliculus. Fascicles pass through the red nucleus and corticospinal tract of the midbrain as they exit and emerge into the subarachnoid space between the cerebral peduncles.

CN III enters the lateral wall of the cavernous sinus, bifurcating into superior and inferior divisions before exiting. Finally, it enters the superior orbital fissure where it again divides to innervate the muscles. Nerve fibers of CN III innervate the medial rectus, inferior rectus, inferior oblique, superior rectus, levator palpebrae superioris of the eyelid and the iris sphincter.

Aberrant regeneration is largely thought to occur when damage to CN III, anywhere along its route, results in a resprouting and miscommunication of portions of the nerve to the muscles. There is either misdirection of regenerating nerve fibers at the site of the injury or collateral sprouting of uninjured neurons in the nerve nucleus to replace damaged axons. Fibers meant for certain muscles additionally innervate wrong muscles.[9,12,16]

As an example, the inferior rectus and medial rectus both simultaneously communicate with the levator palpebrae superioris. As a result, when the medial rectus receives stimulation to contract and adduct the eye, it also stimulates the levator palpebrae superioris. In this case, upon adduction, there will also be lid elevation and widening of the palpebral fissure. With attempted abduction, the medial rectus and the levator will be inhibited. Here, the lid assumes a ptotic state when the eye abducts.

Under these abnormal circumstances the inferior rectus may also share fibers with the levator palpebrae superioris. Thus, when the patient looks down, the eyelid will retract, increasing the interpalpebral fissure. The medial rectus may also share communication with the iris sphincter. Thus, when the patient adducts, the pupil constricts. An alternate theory for the oculomotor synkinesis is ephaptic transmission where, as a result of injury, the nerve loses its myelin covering, causing cross-talk between different oculomotor nerve fibers.[21] This may explain cases where there is disappearance of these misdirections over a period of time.

Secondary aberrant regeneration occurs after CN III palsy, resulting from direct damage to CN III. Aneurysm, trauma and compression by tumor are typical causes.[1-3,5-7,17,18] Inflammatory causes of CN III palsy rarely result in secondary aberrant regeneration.[18] The condition does not occur after CN III palsy from ischemic infarct.[4,19-22] For aberrant regeneration to occur, the axon endoneurium must be damaged.[16] Microvascular infarct does not disrupt the endoneural integrity.[21]

Primary aberrant regeneration occurs independently of CN III palsy. Likely, subclinical compression of CN III damages the nerve fibers, producing ongoing simultaneous regeneration and aberrant resprouting of fibers to incorrect muscles. The patient may not complain of diplopia or ptosis, or even be aware of the changes occurring. A slow-growing mass, such as a meningioma within the cavernous sinus, typically causes this variant.[11-14] Such lesions have a low potential for causing morbidity or mortality.

However, not all cases of primary aberrant regeneration of CN III occur from

benign causes. Intracranial aneurysms of the posterior communicating artery have also resulted in primary aberrant regeneration of CN III.[8] Additionally, primary aberrant regeneration may also occur from oculomotor neuromyotonia, an episodic involuntary contraction of one or more of the extraocular muscles resulting from spontaneous neural discharge of the oculomotor nerve.[23,24]

Management

Secondary aberrant regeneration following the acute phase of traumatic or compressive CN III palsy requires no management beyond recognition. However, if asymptomatic oculomotor synkinesis is observed or develops following a presumed ischemic vascular palsy, neuroimaging must be undertaken to search for compression by a tumor or aneurysm along the anatomic course of CN III.

Cases of primary aberrant regeneration of CN III mandate investigation for a meningioma or internal carotid artery aneurysm within the ipsilateral cavernous sinus, as well as other more sinister compressive lesions. Neuroradiological imaging—preferably MRI with contrast—of the chiasm, cavernous sinuses and parasellar areas is appropriate. Neurosurgical consultation will be necessary if imaging reveals a mass lesion within the cavernous sinus.

Clinical Pearls:

- Primary aberrant regeneration of CN III typically represents a lesion within the cavernous sinus.
- The most clinically identifiable sign in CN III aberrant regeneration is lid elevation and retraction in downgaze (pseudo-von Graefe sign).
- Secondary aberrant regeneration commonly occurs after compressive or traumatic CN III palsy.

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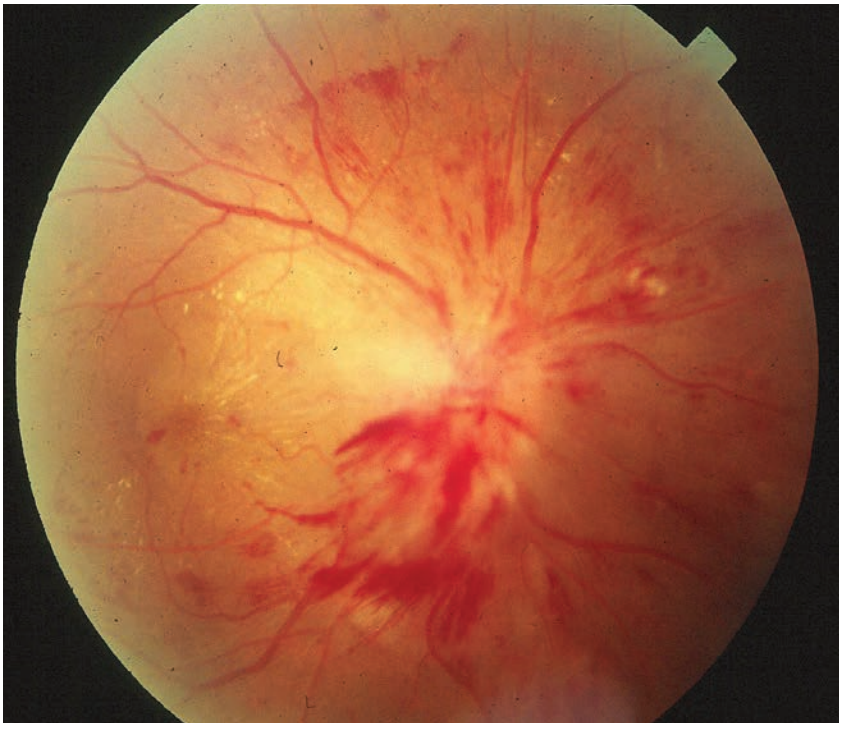
DIABETIC PAPILLOPATHY

Signs and Symptoms

Diabetic papillopathy is a unilateral or bilateral (though often asymmetric) painless optic disc edema occurring in patients with diabetes. It was first described in 1971 and was long thought to occur only in young type 1 diabetics.[1] Since being recognized as a distinct clinical entity, diabetic papillopathy has been reported to also occur in older individuals and in type 2 diabetes.[2,3] It is frequently associated with the presence of both proliferative and nonproliferative diabetic retinopathy.[4]

Visual acuity is typically unaffected or only minimally reduced, though there have been rare cases where vision had been permanently compromised.[5] Unilateral or bilateral disc swelling caused by vascular leakage and axonal edema in and around the optic nerve head will be observed. Occasionally, it may be accompanied by intraretinal hemorrhages and hard exudates as a feature of concurrent diabetic retinopathy.[5] Radially distributed telangiectatic disc capillaries will often be noted on the disc surface, giving the optic nerve a hyperemic appearance.[6] Profound hyperfluorescence of the disc will be seen during fluorescein angiography secondary



Contrary to initial speculation, diabetic papillopathy can occur in both type 1 and type 2 diabetes, and has been reported in both young and old patients.

to the telangiectatic vessels.[7] Visual field defects may be present and consist of an enlarged blind spot, diffuse depressions or defects in the arcuate areas.[8]

In most cases, minimal optic nerve dysfunction occurs; there is typically no relative afferent pupil defect (RAPD), even in unilateral or asymmetric cases, which speaks to the minimal optic nerve dysfunction. In cases where a marked decrease in visual acuity exists, the loss is usually due to concurrent diabetic macular edema and not the diabetic papillopathy. This is supported by the lack of an RAPD in these eyes.

Diabetic papillopathy has been associated with rapid reductions in glycemia.[5,9,10] It also appears that diabetic papillopathy may be a harbinger to rapid progression of nonproliferative diabetic retinopathy to proliferative disease.[11,12]

Pathophysiology

There is no consensus on the pathophysiology of diabetic papillopathy. The current hypotheses are that the condition results from a microangiopathy at the anterior optic nerve or a possible disruption of the parapapillary vasculature.[4] It is possibly ischemic in origin and has been considered by many to be a benign variant of anterior ischemic optic neuropathy (AION).[13] Indeed, some patients with diabetic papillopathy progress to clinically identifiable AION, complete with nerve dysfunction and identifiable RAPD.[8,14]

A rapid resolution following injection of anti-vascular endothelial growth factor (VEGF) medications suggest that VEGF plays a role in pathogenesis, possibly inducing vasogenic disc edema when an optic nerve is ischemic.

Management

The most important aspect of management is to remember that diabetic papillopathy is a diagnosis of exclusion and should not be made until other causes of disc edema, such as sarcoidosis, Lyme disease, infectious neuroretinitis (*Bartonella*), malignant infiltration (leukemia), hypertension, increased intracranial pressure and disc ischemia (ischemic optic neuropathy and giant cell arteritis) are first investigated.

Diabetic papillopathy runs a self-limiting course over several months; typically, there is a good visual outcome, and patients tend to be minimally symptomatic. In these cases, no intervention other than close monitoring for worsening of retinopathy is warranted.[2,11,12] Cases that have poor visual outcomes tend to be those that progress to true AION; however, there is no treatment to prevent this rare occurrence.

Several anecdotal case reports and series exist where intravitreal injections of anti-VEGF drugs such as ranibizumab and bevacizumab have sped resolution of diabetic papillopathy from several months to a few weeks.[6-8,15-18] Additionally, intravitreal and periocular steroids have also been noted to speed resolution.[19,20] In these cases, therapy was being directed at concurrent macular edema or proliferative retinopathy and not to diabetic papillopathy. Due to the fact that there is no clinically proven benefit of these treatments for diabetic papillopathy, they are not advocated, as risk does not appear to outweigh benefit.

Clinical Pearls

- There is minimal visual dysfunction in diabetic papillopathy. If vision is significantly decreased, macular edema is typically the cause. The lack of an RAPD would support this.
- Patients experiencing diabetic papillopathy should be closely monitored for the subsequent development of worsening diabetic retinopathy and possible rapid progression to proliferative retinopathy.
- Diabetic papillopathy needs no treatment and typically has a good outcome, though resolution may take several months.
- Diabetic papillopathy is a diagnosis of exclusion.

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MELANOCYTOMA OF THE OPTIC DISC

Signs and Symptoms

Melanocytomas (magnocellular nevus) of the optic disc are slightly elevated, typically benign, darkly pigmented tumors that classically occur in or about the optic disc, sometimes with contiguous involvement of the adjacent retina or choroid.[1-3] They have been known to occur most commonly in the disc and peripapillary area, but can be found anywhere melanocytes reside (iris, uvea, sclera, episclera, meninges).[4,5] Classically, they appear as unilateral black or dark brown lesions (other variations in color are possible) with non-feathery margins involving the disc and adjacent retina.[1-3]

Variations in size can occur; however, they are usually no more than a few disc diameters.[2,6] They have the potential to obscure the optic disc. The tumor rarely extends more than 2mm into preretinal space.[2] In most cases, less than half of the disc is obscured.[1]

In a study of 115 patients (116 eyes) with melanocytoma of the optic disc, the mean age at diagnosis was 50 years, with a slight preponderance for female predilection.[2] The lesion was unilateral in 99% of patients, with whites affected more commonly than African Americans, though other reports and observations dispute this.[2] Asian, Hispanic, Indian and

Arabic races are significantly less affected than Caucasian or African races.[2] While many regard optic disc melanocytomas as congenital lesions that mature over time, there is published evidence supporting the potential for spontaneous development in adulthood.[7]

While most lesions remain stable throughout life, minor enlargement can occur in 10% to 20% of cases.[1,8-11] Bilateral optic disc melanocytoma is uncommon and associated with optic disc hypoplasia and central nervous system abnormalities, such as meningioma and hypopituitarism.[11]

Adjacent portions of the tumor have erosive/invasive capability, damaging retinal nerve fiber layer bundles and major vessels with resultant variable complications, such as acuity decrease, visual field loss, relative afferent pupil defect and choroidal neovascularization.[1,8-11] Visual symptoms due to neural or vascular compromise, or tumor necrosis can be anticipated in approximately 24% of patients.[2]

Other potential associated ocular findings include invasion into the choroid from the retina, optic disc edema, retinal edema, localized subretinal fluid, retinal exudation, arterial attenuation, perivascular sheathing, superficial hemorrhages and vascular occlusions.[1,2,10,12,13] Nerve fiber layer hemorrhages and vitreous hemorrhage are atypical and may cause confusion in the diagnosis.[14,15] Disruptions in the ocular circulation or direct compression may also cause secondary atrophy of the optic disc. Circumpapillary subretinal fluid may occur, producing retinal striae, optic disc swelling and peripapillary swelling.[14] Subretinal or intraretinal exudates, intraretinal thickening and even serous detachment of the macula have been associated with melanocytoma of the optic disc.[14]

Melanocytoma has also been associated with increased levels of catecholamine in the body.[16] The relationship stems from the common neural crest origin of melanocytes, adrenal medullary cells and chromaffin cells.[16] As a result, systemic hypertension has recently been added to the list of possible concurrent findings.[16]

Pathophysiology

Melanocytomas are hyperpigmented magnocellular nevi of the optic disc. Melanocytoma is one of five cellular disorders originating from the neural crest (choroidal nevi, choroidal melanoma, melanocytoma, ocular melanosis and oculodermal melanosis).[17]

These lesions are derived from uveal dendritic melanocytes, which also form uveal nevi and malignant melanoma.[18,19] The predominant cell in nevi and melanomas are of the spindle cell type.[20] Characteristically, melanocytoma display a static growth pattern; however, enlargement by a very small degree over long periods of time has been documented as normal.[1,8-11,18] Growth of melanocytoma produces locally invasive behaviors.[1-21] Tumors that extend down the optic nerve through the lamina cribrosa become secluded from direct observation but can produce vision losses ranging from 20/50 to hand motion, vascular compression and axonal swelling.[12,19,20]

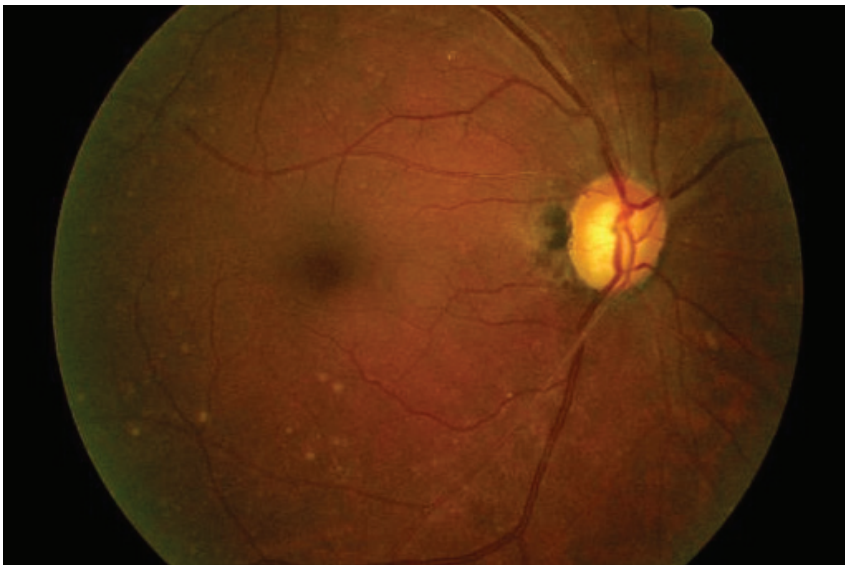
Anterior segment changes associated with melanocytoma are mostly related to the unlikely migration of pigment to structures that include the posterior lens capsule, anterior hyaloid of the vitreous, iris, zonule fibers and anterior chamber angle.[18,21-23] Melanocytomalytic glaucoma is a secondary open-angle pigmentary glaucoma uncommonly encountered with melanocytoma of the optic disc. It typically occurs in selected cases of necrotic iris melanocytoma.[22,23]

In general, these tumors are regarded as benign and stationary, with little preponderance for undergoing malignant melanoma transformation (1% to 2% of cases).[1-20,24,25] Spread to other ocular structures can occur, rarely, due to vitreous seeding similar to retinoblastoma.[26,27]

Management

Though melanocytoma of the optic disc is usually identified clinically, specific diagnostic tests are useful for diagnosis and clinical management.[28-30] When a lesion is first detected, photodocumentation is necessary to give later inspection a valid comparison database.[1-22] Automated threshold perimetry can permit accurate baseline assessment and quantitative tracking over time and is indicated regardless of visual symptoms. Nerve fiber bundle defects, enlarged blind spot, central and paracentral scotomas, or peripheral field constriction are all potential visual field abnormalities. Visual evoked potential reduction has also been noted.[31]

Spectral-domain optical coherence tomography (SD-OCT) has been shown to be of excellent value in these cases.[22] On SD-OCT imaging, melanocytomas display a gradual sloping transition from normal retinas into the mass, with hyperreflectivity at the anterior tumor surface and posterior shadowing.[22] Thicker tumors display thinner anterior hyperreflective borders with denser posterior optical shadowing.[22] The retinal nerve fiber layer is thin adjacent to these lesions and often corresponds to the opposite hemifield visual field defect.[32-35]



Melanocytomas—darkly pigmented lesions—typically reside in or around the optic disc. Clinicians usually fall back on long-term observation and careful documentation as a conservative management approach.

Melanocytomas of the optic disc are largely stable, and those that do not show enlargement over a 24-month observational period are considered benign by circumstantial evidence, though some non-malignant growth can occur.[1-10,36-39] Amsler grid, observing for alterations once or twice monthly, can be used for home monitoring. The patient should be instructed to return should any changes in visual acuity or grid appearance occur.

Ultrasonography, particularly color Doppler imaging, can help to differentiate a melanocytoma from a choroidal melanoma and is indicated if visual symptoms do not correspond with the fundus presentation.[21,29] B-scan ultrasonography will identify a melanocytoma as a smooth-surface solid mass with a high amplitude of internal reflectivity (high spike), without underlying scleral excavation, subretinal fluid or retinal detachment.[21] It can also determine the extent of penetration into the optic nerve.[21] A-scan ultrasonography, though less useful diagnostically, can measure the height of the lesion (typically less than 2mm).[6]

Fluorescein and indocyanine green angiography demonstrate persistent hypofluorescence of the lesion.[2] In most instances, there is no leakage or evidence of specific vascular supply.[2] Computed tomography and magnetic resonance imaging may aid in the localization and classification of the tumor.[30]

Recently, fundus autofluorescence (FAF) has been identified as an effective diagnostic tool separating melanocytoma of the optic disc from malignant lesions and those with malignant potential. FAF is highly correlated to lipofuscin content at the retinal pigment epithelial (RPE) level. Lipofuscin formation is an indirect marker of metabolic activity between the photoreceptor outer segment and RPE phagocytic activity. Accumulation of lipofuscin-laden macrophages over pigmented tumors gives a characteristic orange appearance to a malignant lesion. This pigment may be subtle ophthalmoscopically, but appears as a strong hyperfluorescent signal on FAF. Melanocytomas of the optic disc will show a hypofluorescent pattern, indicating that there is little or no lipofuscin associated with the lesion, implying no malignancy.[40,41]

Today, management of melanocytoma is conservative, with long-term observation and meticulous documentation.[1-28] Repeat analysis should be done twice during the first year of discovery and then annually thereafter. Should growth occur, visual dysfunction progress or any signs of malignant transformation be identified with FAF, then ocular oncologic consultation is recommended. Intravitreal anti-VEGF treatment may be an effective treatment for rare choroidal neovascular membrane formation associated with optic disc melanocytoma.[42]

Clinical Pearls

- Malignant melanoma appears grey-brown (vs. the typical brown or black appearance of an optic nerve head melanocytoma).
- Hamartomas of the RPE may extend into the optic nerve head and peripapillary retina, and clinically resemble melanocytoma.
- Reactive hyperplasia of the RPE resembles melanocytoma. However, these often stem from past eye injuries or disease and can be differentiated by their diffuse, rather than localized, appearance.
- Leber's neuroretinitis, a finding associated with cat-scratch disease has also been associated with melanocytoma of the optic nerve head. It should be included in the differential diagnosis of neuroretinitis.[36]
- Bilateral melanocytomas are a rare phenomenon. Because they have documented associations with central nervous system dysfunctions, systemic evaluation is warranted in such cases.
- Baseline visual fields, SD-OCT, photographs and FAF are reasonable data to gather upon diagnosis.
- Given the catastrophic consequences of misdiagnosis, all questionable lesions should be referred for evaluation by a retinal specialist or ocular oncologist.

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MIGRAINE

Signs and Symptoms

Migraine refers to a group of related chronic episodic conditions chiefly epitomized by headache, but additionally characterized by a specific group of neurological signs and symptoms.

The disorder is more common than previously believed, likely affecting upwards of 15% of the population.[1-3] Migraine commonly begins in the teens or early 20s and may persist until late in life. Women are affected approximately three times as often as men, with a peak prevalence between the ages of 35 and 45.[4,5] Genetics are believed to play a significant role in migraine; about 50% of *migraineurs* have a first-degree relative with the same or a similar condition.[3,6,7]

Migraine episodes are often preceded by a *prodrome*, a premonitory sensory experience that occurs hours or even days before the headache. According to a recent publication, approximately 35% of migraineurs suffer from prodromal events.[8] The most common experiences include increased sensory sensitivity (e.g., blurred vision, sound sensitivity, smell sensitivity), pain or stiffness, fatigue and negative affect (e.g., feelings of anxiety, irritability or anger).[9] Migraine prodrome must be distinguished from migraine *aura*, which describes a complex of transient, focal neurological symptoms that typically occur antecedent to, or along with, the headache. About 36% of migraineurs experience these phenomena.[8]

Auras typically develop over five to 10 minutes and may persist for up to 60 minutes.[5,7,10] They may occur as visual, sensory or motor phenomena, or they may occur in combination. Visual aura is the most common type of aura, and is often described as a "scintillating scotoma" or "fortification spectrum." It begins as a small blurry spot near the point of fixation and gradually expands to the right or left, assuming a laterally convex shape with a shimmering, angulated or "zigzag" edge.[10] The center of the scotoma may be relative or absolute, but the vision loss is transient by definition. Patients who cannot articulate the visual aura may simply report flashing lights and/or distortion of vision. Non-visual auras may include paraesthesias (i.e., progressive numbness or tingling in the extremities or face), generalized motor weakness, speech/language disturbances (e.g., aphasia), hearing disturbances or even olfactory hallucinations.[11]

An artist's interpretation of the scintillating scotoma a migraine sufferer might experience during an episode.

Headache is the overwhelming complaint reported by migraineurs. Migraine headaches are typically described as throbbing or pulsatile in nature, with pain intensity ranging from moderate to severe. Even routine physical acts such as coughing or sudden head movements may exacerbate the pain.[5,7,10] Migraine headaches are often unilateral at onset, and localize to the frontotemporal and ocular area.[10] Over several hours, the intensity builds and the headache expands to involve additional areas of the head. These episodes may persist from four hours to 72 hours in extreme, untreated cases.

Symptoms that characteristically accompany migraine headache may include nausea, vomiting, photophobia and phonophobia (i.e., sensitivity to loud sounds or noise).[10] More than 60% of migraineurs report nausea with or without vomiting during their attacks.[12] Another common symptom is cutaneous allodynia (i.e., the perception of pain in response to normally innocuous stimuli) in the periorbital region. About two-thirds of migraine patients report this particular complication.[7]

Migraine episodes tend to resolve gradually rather than abruptly. Following cessation of the headache, a majority of migraineurs experience persistence and slow resolution of associated symptoms.[8] This phase is known clinically as the *postdrome*, although it is sometimes referred to in lay terms as the "migraine hangover." The most common postdromal symptoms include fatigue, difficulty concentrating, neck stiffness, irritability and residual head or scalp tenderness.[13] The postdrome characteristically lasts less than 24 hours after headache resolution.[13]

Pathophysiology

A number of potential pathophysiological mechanisms for migraine have been proposed throughout history. The vascular theory of migraine, first described in the 1940s, is, perhaps, the most well-known. This theory holds that migraine results from an abrupt vasoconstriction of intracranial blood vessels (resulting in the aura phase), followed by rebound vasodilation, which induces the headache via stimulation of perivascular sensory nerves.[14] It should be noted, however, that this relatively simplistic view of migraine has been all but abandoned by today's headache experts.

Current theory hypothesizes that migraine is actually a complex and exquisitely organized interaction between the peripheral and central nervous systems, the *trigeminovascular* system (i.e., those neurons innervating the cerebral vessels whose cell bodies are located in the trigeminal ganglion) and the cerebral cortex.[3] It occurs in individuals who are genetically hard-wired toward a state of generalized neuronal hyperexcitability.[15] In many migraineurs, a "trigger" initiates the episode; these triggers are varied and may include such stimuli as glaring or flickering lights, strong smells (e.g., perfumes, cigarette smoke), physical exertion, lack of sleep and many food items (e.g., caffeinated drinks, strong cheeses,

International Headache Society Classification of Migraine, 3rd Edition[10]

***1.1* Migraine without aura**

***1.2* Migraine with aura**

1.2.1 Migraine with typical aura
1.2.1.1 Typical aura with headache
1.2.1.2 Typical aura without headache
1.2.2 Migraine with brainstem aura
1.2.3 Hemiplegic migraine
1.2.3.1 Familial hemiplegic migraine
1.2.3.1.1 Familial hemiplegic migraine type 1
1.2.3.1.2 Familial hemiplegic migraine type 2
1.2.3.1.3 Familial hemiplegic migraine type 3
1.2.3.1.4 Familial hemiplegic migraine, other loci
1.2.3.2 Sporadic hemiplegic migraine
1.2.4 Retinal migraine

***1.3* Chronic migraine**

***1.4* Complications of migraine**

1.4.1 Status migrainosus
1.4.2 Persistent aura without infarction
1.4.3 Migrainous infarction
1.4.4 Migraine aura-triggered seizure

***1.5* Probable migraine**

1.5.1 Probable migraine without aura
1.5.2 Probable migraine with aura

***1.6* Episodic syndromes that may be associated with migraine**

1.6.1 Recurrent gastrointestinal disturbance
1.6.1.1 Cyclical vomiting syndrome
1.6.1.2 Abdominal migraine
1.6.2 Benign paroxysmal vertigo
1.6.3 Benign paroxysmal torticollis

chocolate, nuts, smoked meats, red wine). The most common triggers, however, have been identified as hormonal changes (in women), emotional stress, lack of eating and sudden changes in weather.[16]

The cascading events of the prodrome and aura likely begin centrally, involving the hypothalamus, cerebral cortex and/or the limbic system.[17] Trigger mechanisms spur a phenomenon known as *cortical spreading depression* (CSD), in which a slowly propagating wave of depolarization is induced across adjacent cortical neurons, traversing the brain. CSD is considered the neurophysiological correlate of aura; the fact that it often begins in the occipital cortex is consistent with the high prevalence of visual auras in migraineurs.[3,10]

CSD is also believed to be the neurochemical stimulus that activates the trigeminovascular system, either via a shift toward parasympathetic tone in the meninges or by increased activity in the thalamocortical pathway.[1] It is this trigeminovascular pain pathway that is now thought to be responsible for the classic migraine headache. Activation induces sensitization of nociceptors in the meninges and their associated large blood vessels.[18] Through the release of vasoactive neuropeptides including substance P, calcitonin gene-related peptide and neurokinin A, inflammation ensues in the dura and meningeal arteries.[3] This inflammation potentiates and perpetuates the headache and other symptoms associated with acute migraine episodes.

While the pathophysiology of migraine is complex, the understanding of migraine subclasses and variants can be equally confusing. A classification scheme has been developed to categorize migraines based upon their presentation.[10] The International Headache Society currently recognizes the following categories:

• ***Migraine without aura.*** Previously known as *common migraine* or *hemicranias simplex*, this condition involves the typical, pulsatile migraine headache associated with nausea and/or vomiting, photophobia or phonophobia, but no demonstrable sensory or motor aura.

• ***Migraine with aura.*** Previously referred to as *classic* or *classical migraine*; *ophthalmic*, *hemiparaesthetic*, *hemiplegic* or *aphasic migraine*; *migraine accompagnée*; or *complicated migraine*, this variety manifests some form of aura (e.g., visual, somatosensory, motor) in the early phase of the attack. The headache associated with this form of migraine may be somewhat diminished in severity and/or duration than in migraine without aura. In some cases, the headache may not ensue at all, a condition that is subcategorized as *typical aura without headache*, also known as *acephalgic migraine*.

Other subcategories include *migraine with brainstem aura*, *hemiplegic migraine* and *retinal migraine*. While quite uncommon, retinal migraine presents as a recurrent, transient, monocular visual disturbance, including scintillations, scotomata or blindness, associated with migraine headache. In some cases, retinal migraine may be brought on by exertion or postural change.[5,19] Commonly, the visual episodes range from five minutes to 60 minutes. If one is fortunate enough to encounter a retinal migraine attack in progress, funduscopy may reveal a narrowing of the retinal vessels, disc pallor and a "cherry-red" macula (similar to a retinal artery occlusion) in the absence of visible emboli with a history of previous events.[20]

• ***Chronic migraine.*** This describes a clinical scenario in which headache occurs on 15 or more days per month for more than three months, and has features of migraine on at least eight days per month. Aura may or may not be present in these episodes, and patients often suffer from other non-migraine headaches such as sinus or tension-type. Ironically, chronic migraine may result from chronic overuse of migraine-relieving medications.[10]

• ***Complications of migraine.*** Now recognized as a distinct subcategory of the disease, complications include severe and unusual sequelae associated with migraine, such as *status migrainosus* (a severe, incapacitating migraine attack that persists for more than 72 consecutive hours), *persistent aura without infarction*, *migrainous infarction* and *migraine aura-triggered seizure*.

• ***Probable migraine.*** Previously referred to as *migrainous disorder*, this term is reserved for migraine-like attacks that are

devoid of just one key feature normally ascribed to the aforementioned categories, such as headache duration, quality or associated symptoms. In essence, this diagnosis is used when most of the criteria for migraine are met, and the condition cannot be better described by another recognized headache classification.

• ***Episodic syndromes that may be associated with migraine.*** Previously referred to as *childhood periodic syndromes*, this group of disorders occurs in known migraineurs or those with an increased likelihood to develop migraine later in life. It includes the following conditions: *cyclical vomiting syndrome* (recurrent episodic attacks of intense nausea and vomiting with predictable timing of episodes, sometimes associated with pallor and lethargy); *abdominal migraine* (recurrent attacks of moderate to severe midline abdominal pain, associated with vasomotor symptoms, nausea and vomiting, lasting two hours to 72 hours); *benign paroxysmal vertigo* (recurrent brief attacks of vertigo, occurring without warning and resolving spontaneously in otherwise healthy children); and *benign paroxysmal torticollis* (recurrent episodes of spontaneously remitting head tilt to one side, perhaps with slight rotation, noted to occur in infants and small children).

Management

While migraine is typically identified by the clinical presentation alone, more serious conditions (e.g., mass lesions, aneurysms, impending stroke and venous sinus thrombosis) must always be considered in the differential. Ideally, the diagnosis of migraine should be confirmed by an experienced neurologist after a comprehensive evaluation.[21] Ancillary testing such as neuroimaging and serology are necessary, as the condition is a diagnosis of exclusion; headaches that are persistent, worsening, increasing in frequency and accompanied by neurologic signs should never be presumed to be migraine.

Pharmacologic therapy for migraine falls into two broad categories: abortive therapies, which are used to terminate an ensuing migraine episode; and prophylactic medications, which are taken daily to prevent attacks. The choice of medication depends on the severity and frequency of the episodes. Those with minor and sporadic migraine headaches may be adequately controlled with oral analgesics and NSAIDs. Over-the-counter medications including aspirin (up to 1,000mg), ibuprofen (200mg to 800mg), naproxen sodium (500mg to 1,000mg) and acetaminophen/aspirin/caffeine (250mg/250mg/65mg) remain popular options for mild to moderate migraine.[21]

Moderate to severe episodes typically warrant migraine-specific prescription medications such as ergotamine tartrate (e.g., Ergomar, TerSera Therapeutics) or dihydroergotamine mesylate (Migranal nasal spray, Bausch Health). However, these ergot derivatives are contraindicated in uncontrolled hypertension and many vascular disorders; additionally, they have been associated with a high frequency of adverse events, such as nausea and vomiting, cramps, sleepiness and transient lower limb muscle pain.[21] For this reason, the triptans—potent serotonin receptor agonists—are now considered by most to be first-line therapy for severe migraine attacks. Sumatriptan (Imitrex, GlaxoSmithKline) was the first of these compounds to be developed.

Other commonly used drugs in this category may include almotriptan (Axert, Janssen Pharmaceuticals), eletriptan (Relpax, Pfizer), frovatriptan (Frova, Endo Pharmaceuticals) naratriptan (Amerge, GlaxoSmithKline), rizatriptan (Maxalt, Merck) and zolmitriptan (Zomig, Impax Laboratories/AstraZeneca). These medications should be prescribed by the treating neurologist or headache specialist.

Patients who experience more than two acute migraines monthly, or those whose attacks are so severe as to compromise their daily activities are candidates for prophylactic therapy. Numerous medications have been used in this capacity with varying success. Currently, the drugs of first choice in the United States include the beta-blockers propranolol, timolol and metoprolol, as well as the antiepileptic drugs divalproex sodium (Depakote, AbbVie) and topiramate (Topamax, Janssen Pharmaceuticals).[21,22] OnabotulinumtoxinA injection (Botox, Allergan) has also been approved for use in the treatment of chronic migraine.[23]

Beyond pharmacologic therapy, behavior modification to eliminate triggers (e.g., smoking cessation, avoidance of red wine, limiting caffeinated beverages) can go a long way toward diminishing the frequency of episodes and improving quality of life. Additionally, several forms of extracranial neurostimulation have demonstrated success in migraine prevention, in particular transcutaneous supraorbital or supratrochlear nerve stimulation, and vagus nerve stimulation.[24,25] These noninvasive techniques appear to be devoid of serious adverse effects, and can be combined with drug therapies for maximal efficacy. However, at the present time this technology is not widely available and lacks an abundance of prospective, controlled clinical trials.[25]

Clinical Pearls

- Migraine is one of the oldest known medical conditions, with descriptions dating back in history some 5,000 years.
- Headache patients are commonly referred to the eye care practitioner. If the treatment or prescription does not relieve the episodes, a medical referral should be made. Migraine headache should never be diagnosed based upon assumption.
- Many patients do not understand that migraine is a complex syndrome of neurologic signs and symptoms, and, thus, may "self-diagnose" any severe headache—chronic or otherwise—as migraine. These individuals require a careful history and should be counseled that if the episodes continue, a medical and possibly neurologic evaluation is necessary.
- It is important for migraineurs to recognize their specific prodromal symptoms so that abortive therapy can be initiated during this phase to divert the attack.
- Since migraineurs may be susceptible to multiple triggers, these patients should be urged to maintain a detailed diary. In this way, trigger factors can be retrospectively identified and prospectively avoided or minimized.
- The symptoms of photophobia and phonophobia that commonly accompany migraine will typically prompt migraineurs to seek out a dark and quiet place. While not universal, this is a common element of the history for many patients with this disorder.
- The mnemonic POUND may help doctors to remember the major characteristics of migraine: Pulsatile headache, One-day duration (four to 72 hours), Unilateral location, Nausea or vomiting and Disabling intensity.[21]
- Lifestyle modification and the use of medications can significantly improve the quality of life for migraineurs; however, patients must realize that there is no cure for the disorder.

• Migraine in all of its various forms remains a diagnosis of exclusion.

• Practitioners should remain highly suspicious of apparent "migraines" that onset later in life. It is unusual for someone who has not had migraines to suddenly experience them after age 50.[21] Migraineurs more commonly begin to show improvement or lessening of their symptoms with the onset of middle age.

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NYSTAGMUS

Signs and Symptoms

Patients with nystagmus will present with a rhythmic oscillation of the eyes. Nystagmus can be *pendular* (equal oscillatory movements) or *jerk* (a slow phase followed by a fast phase). In jerk nystagmus, the first movement is the initial deviation—a slow drift of the eyes in one direction. This is followed by a compensatory return to fixation of the opposite direction, which may be fast (defining jerk) refixation at the same rate as the drift defines pendular nystagmus.

Jerk nystagmus is more common than the pendular form. It is named for the direction of the fast phase (e.g., slow drift right with a fast correction to the left creating a "beating" left jerk nystagmus.) Nystagmus may "beat" laterally, upwards or downwards. Pendular or "searching" nystagmus is defined by a back-and-forth drift with no corrective saccade. Nystagmus may be present in primary gaze or may occur only in certain gazes.[1,2]

Nystagmus can afflict any age; however, the majority of cases are present at birth or shortly thereafter. It may be physiologic, resulting from visual pathology, associated with strabismus or developmental disorders, or develop from underlying conditions such as demyelinating disease, stroke or drug use. Thus, nystagmus can be classified as either *congenital* or *acquired*.[1,2]

Patients may complain of reduced visual acuity, oscillopsia (the feeling that the world is moving), dizziness, imbalance (disequilibrium), gait disturbance or ataxia. Alternately, many patients with congenital nystagmus remain asymptomatic. Visual symptoms and acuity loss are often related to associated afferent visual system abnormalities such as optic nerve hypoplasia, foveal hypoplasia, cone dystrophy and achromatopsia.[3]

Pathophysiology

Numerous etiologies are associated with the many forms of nystagmus. The most common cause of nystagmus is drug intake. Common drugs include alcohol, phenytoin, barbiturates, lithium, opioids and anticonvulsants.[3,4] Congenital forms of nystagmus are typically identified during infancy, though some cases may not be recognized until later in life.

Infantile nystagmus is a predominately horizontal jerk nystagmus, although there may be a vertical or torsional component. *Fusional maldevelopment nystagmus syndrome* (formerly known as *latent nystagmus*) is a horizontal jerk nystagmus present when the patient is fixating with one eye, with a concomitant strabismus and amblyopia. *Spasmus nutans* is a pendular nystagmus with an associated anomalous head positioning and head bobbing.[3,4]

Congenital nystagmus presents at birth or shortly thereafter. Some systemic associations with congenital nystagmus include prenatal problems, low birth weight and asphyxia. Additionally, intracranial hemorrhage, cortical atrophy, ventricular dilation, brainstem atrophy, cerebellar atrophy and cerebral palsy have some association with congenital nystagmus. The amplitude of congenital nystagmus typically decreases with age. The nystagmus is limited to only one plane (typically horizontal) despite the direction of gaze. There is a null point of gaze where the amplitude dampens and visual acuity can be maximized. The amplitude of nystagmus tends to decrease with convergence or accommodation and voluntary closure of the eyes. Patients never complain of oscillopsia and rarely complain of disequilibrium.

Knowledge of proper anatomical areas helps identify the location and cause of acquired nystagmus. Lesions of the *peripheral vestibular system* (the labyrinth, vestibular nerve and its root entry zone) produce peripheral vestibular nystagmus manifesting as a jerk nystagmus. The slow phases of this nystagmus arise due to an imbalance in the level of tonic neural activity in the right vs. left vestibular nuclei.[3,4]

Nystagmus can also arise from lesions affecting the central pathways and structures responsible for relaying and processing vestibular information. *Central vestibular nystagmus* comes from central pathway lesions. They contribute to downbeat, upbeat and torsional nystagmus and can occasionally cause nystagmus that is horizontal or in the plane of a single semicircular canal.[3,4]

Downbeat nystagmus is a jerk nystagmus that manifests as a slow upward drift followed by a rapid downward correction. Downbeat nystagmus signifies neurodegenerative cerebellar dysfunction affecting the flocculus. Common causes

include acquired and inherited cerebellar dysfunction, stroke, Chiari malformation, multiple sclerosis and drug-induced (from lithium, anticonvulsants and opioids).[3,4]

Upbeat nystagmus manifests as a slow downward drift followed by a rapid upward correction. Lesions in the medulla or midbrain occurring from multiple sclerosis, stroke, tumor or Wernicke's encephalopathy are usually the cause.[3,4]

Torsional nystagmus is a jerk nystagmus with the eyes rotating around the line of sight. Torsional nystagmus is uncommon and can produce debilitating oscillopsia. Causes include demyelinating lesions from multiple sclerosis, ischemic infarct and tumor in the lateral medulla, medial longitudinal fasciculus and rostral midbrain. Identification can be difficult and requires close observation of the conjunctival blood vessels and iris to detect the movements.[3-5]

Gaze-evoked nystagmus is a jerk nystagmus existing only in eccentric fixation and is due to impairment of gaze-holding mechanisms. Causes include drug intoxication (carbamazepine, phenytoin, lithium, alcohol), cerebellar degeneration (inherited or acquired) and demyelinating disease.[3,6]

Seesaw nystagmus is a rhythmic disturbance where one eye elevates and intorts while the fellow depresses and extorts.[3,4] It may be pendular or jerk in nature. The pendular form occurs in patients with dense bitemporal visual field defects, and the jerk form is due to lesions in the rostral midbrain near the interstitial nucleus of Cajal.[3,4,7]

Periodic alternating nystagmus is a horizontal nystagmus that reverses direction every 90 to 120 seconds. This movement results from cerebellar degeneration (inherited or acquired), demyelinating disease, cerebellar tumors and stroke.[3,4,8]

Acquired pendular nystagmus in multiple sclerosis has a variable combination of horizontal, vertical and torsional movement. It is characterized by smooth pendulum-like oscillations of the eyes, without corrective quick phases. This occurs due to instability of the gaze-holding mechanism due to loss of central myelin in MS and Pelizaeus-Merzbacher disease.[3,4,9]

Acquired pendular nystagmus with oculopalatal tremor develops as stroke involving projections between the cerebellar dentate and inferior olivary nuclei. It is characterized by synchronous oscillations of the eyes (typically vertical), palate and brachial muscles.[3,4] Oculopalatal tremor usually develops weeks to months after brainstem or cerebellar stroke, although it may not be recognized until many years later. Occasionally, patients develop the eye oscillations without movements of the palate, or the oscillations develop acutely following the stroke, with the associated palatal movements not appearing until several weeks later.[3,4,10]

Convergence-retraction nystagmus is characterized by fast convergent-retractory movements of the eyes, elicited during attempted upward saccades or by asking the patient to follow the downward-moving stripes of a hand-held optokinetic drum or tape. Slow downward eye movements occur, but the upward quick phase is replaced by rapid movements of the globe retracting into the orbital socket. The condition is classically caused by dorsal midbrain lesions in the region of the posterior commissure. In such cases, other signs of the dorsal midbrain syndrome are usually present, such as vertical gaze palsy, skew deviation, eyelid retraction and light-near dissociation of the pupils. Common causes include hydrocephalus, dorsal midbrain stroke, dorsal midbrain compression by pinealoma and third ventricular tumors.[3,4,11]

Management

Congenital and infantile forms of nystagmus are identified by the age of onset and rarely need intervention, as patients are often asymptomatic. However, if visual disturbances or cosmetic concerns develop, infantile nystagmus can best be managed with correction of refractive error and prisms to induce convergence during distance viewing. Retinal image stabilization using a high plus spectacle lens and minus contact lens may improve visual function. Spasmus nutans is a benign condition that does not require treatment.[3]

Later-onset and acquired forms of nystagmus merit evaluation to identify a precipitating lesion. Neuroimaging of the suspected area is recommended in these cases. A thorough history of drug use should also be elicited. Any treatable lesions or toxic ingestion should be addressed.

Treatment of any underlying causative condition is most effective at reducing acquired nystagmus, but rarely abolishes the movements. If visual disability or cosmetic concerns arise, medications may provide some relief.

Downbeat nystagmus can be suppressed with clonazepam, chlorzoxazone and aminopyridine medications. Upbeat nystagmus may respond to memantine and aminopyridine medications. Torsional nystagmus can be treated with modest success using gabapentin. Gaze-evoked nystagmus can be managed with medication cessation if a toxin is found to be the cause. Otherwise, it doesn't have a specific treatment because it doesn't produce symptoms or intolerable cosmetic concerns. Seesaw nystagmus can be reduced by gabapentin and memantine. Periodic alternating nystagmus can be abolished with baclofen. Acquired pendular nystagmus in multiple sclerosis can be suppressed with gabapentin and memantine. Gabapentin and memantine can also benefit patients with acquired pendular nystagmus in oculopalatal tremor.[3]

Clinical Pearls

- Most cases of acquired nystagmus are drug induced.
- Patients with congenital nystagmus are often asymptomatic, and treatment is not needed.
- When patients present with new onset acquired nystagmus, neuroimaging and medical evaluation are paramount.
- The distinguished neuro-ophthalmologist Hermann Wilbrand once advised, "Never write on nystagmus, it will lead you nowhere." We agree.

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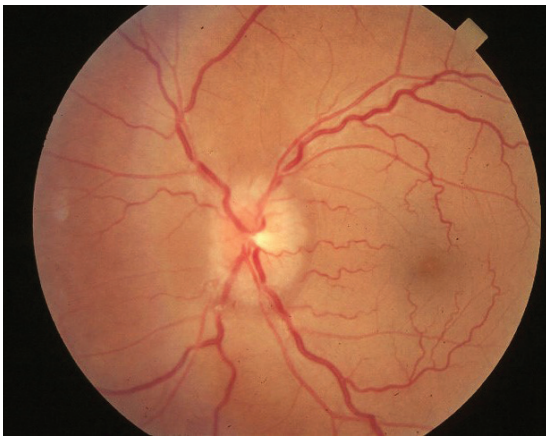

Optic perineuritis, while causing a marked thickening of the optic nerve sheath, includes minimal optic nerve involvement.

OPTIC PERINEURITIS

Signs and Symptoms

Optic perineuritis is an inflammatory pseudo-optic neuropathy that may be either unilateral (typical) or bilateral. Though optic nerve dysfunction will be present, the pathology is focused in the optic nerve sheath, with minimal involvement of the optic nerve.[1] Similarities to optic neuritis include female preponderance and pain upon eye movement. In contrast to optic neuritis in demyelinating disease, optic perineuritis has a more widespread age distribution, often occurring later in life and also affecting children.

Although the disease has the potential to reduce visual acuity and cause significant vision loss, visual acuity often remains quite good with central visual field sparing in most cases. However, peripheral visual field contraction is common.[1-4]

Optic perineuritis typically presents with disc edema, though occasionally the nerve will appear normal. Characteristics include afferent pupillary defect, brightness loss and red desaturation, consistent with the severity of the presentation. Visual field defects include arcuate defects, central and paracentral scotomas, and peripheral constriction with central sparing.[1] Many cases will be associated with underlying systemic disease. Systemic abnormalities commonly associated with optic perineuritis include Crohn's disease, granulomatous polyangiitis, Lyme disease, giant cell arteritis, Behçet's disease and leukemia to name a few.[5-11] Both acute and late-stage syphilis are significantly associated with optic perineuritis.[12-14]

Pathophysiology

Though little is known about the pathophysiology of optic perineuritis, the condition affects mainly the optic nerve sheath, with minimal involvement of the optic nerve itself. A marked thickening of the optic nerve sheath with non-specific fibrosis and lymphocytic infiltration of the tissues can be detected.[2,15] In addition, necrobiotic collagen and granulomatous inflammation have been identified in the optic nerve sheath.[15,16]

Management

Diagnosis of optic perineuritis can be elusive, especially as it is commonly mistaken for demyelinating optic neuritis. Optic perineuritis may fall outside the typical age range for optic neuritis, and central acuity may be spared (though peripheral field contraction may occur), whereas optic neuritis often has a central or cecocentral scotoma.

Clinical examination and neuroimaging are key to diagnosis. Optic nerve sheath inflammation can be seen using gadolinium-enhanced, fat-saturated, T1-weighted MRI. Coronal cuts will demonstrate circumferential thickened optic nerve sheath inflammation with a "donut" appearance. The MRI enhancement is perineural rather than intraneural as seen in optic neuritis. On axial view, the sheath will take on a "tram track" appearance that may be confused with optic nerve sheath meningioma.[1,4]

An underlying cause for optic perineuritis should be sought. Should a patient present without any of the above-mentioned associations, then serology should be performed for anti-neutrophil cytoplasmic antibodies, syphilis and IgG4. Additionally, chest x-ray should be performed to investigate for sarcoidosis. Comanagement with neurology, internal medicine, neuro-ophthalmology and infectious disease specialists is appropriate.

Optic perineuritis responds well to systemic steroids. High dosing in the form of IV methylprednisolone for three days followed by oral prednisone 1.2mg/kg/body weight has been shown to be successful.[1,4,17] A slow taper is necessary, as it is common for patients to relapse upon therapy cessation. The dramatic response to steroids and frequent relapse with cessation are features that further separate optic perineuritis from optic neuritis. Fortunately, therapeutic prognosis for eyes with optic perineuritis is excellent. Cases of poor outcome typically have been due to delayed diagnosis and treatment.

Clinical Pearls

- Optic perineuritis can be mistaken for optic neuritis. Clinically, optic perineuritis has a broader age distribution, with onset age later than that seen in optic neuritis.
- Optic perineuritis does not carry the same risk of developing multiple sclerosis as optic neuritis.
- The optic nerve may be edematous or normal in appearance.
- The key diagnostic finding is optic nerve sheath enhancement on contrast-enhanced MRI.

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