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Twelfth Edition

The Handbook of Ocular Disease Management

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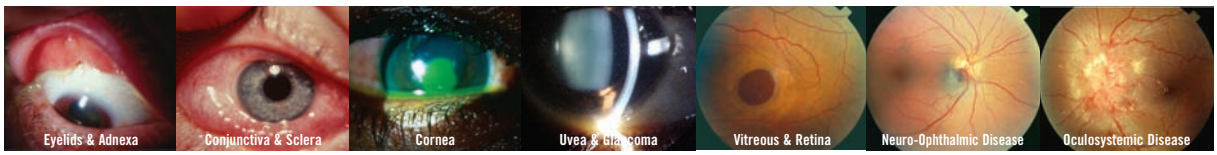

A Peer-Reviewed Supplement

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. Two referees review each manuscript before publication. This supplement was edited by the editors of *Review of Optometry*.

To Our Colleagues:

The publication of the Twelfth edition of *The Handbook of Ocular Disease Management* coincides with many changes within the profession of optometry. Optometry has evolved from what was once a purely visual correction and refractive profession to an integrated member of the healthcare team. There has been increased specialization within optometry to the point that optometrists now utilize *intra-professional* referrals rather than strictly using *inter-professional* referrals. We need to embrace the concept that eye care, patient care, and optometry have become so advanced that it is difficult for any single practitioner to be everything to every patient. Optometric societies have developed to cater to and foster interest in specialized areas of optometry. Sub-specialization has become a real part of optometry. Referral to optometric colleagues for glaucoma and ocular disease management, vision therapy, low vision, and specialty contact lens fittings is now common place.

Common to all of these changes is the need for optometrists to remain current and enhance their knowledge and education. Optometrists must commit to lifelong learning. Reading high quality peer-reviewed publications is necessary. Attending continuing education conferences that are free of commercial bias allows optometrists to keep current and interact, both socially and professionally, with colleagues. We have always felt that the best way to begin this commitment to lifelong learning is through the completion of an accredited residency. Residency training not only provides increased clinical experience, it opens doors and initiates the lifelong learning process. To all optometry students (and practitioners) reading this manuscript, we strongly encourage you to pursue residency training.

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FLOPPY EYELID SYNDROME

Signs and Symptoms

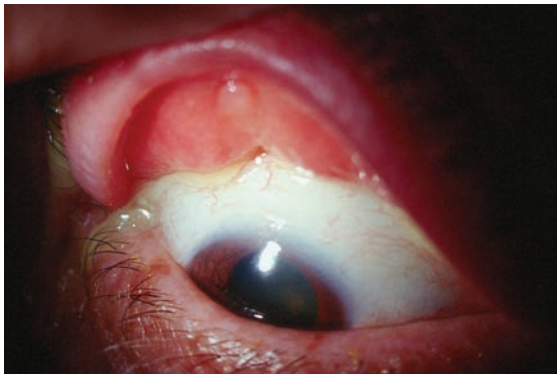
Floppy eyelid syndrome (FES), first described in 1981 by Culbertson and Ostler, is a relatively uncommon ocular condition characterized by flaccid, easily everted upper lids.[1] It is usually seen in overweight, middle-aged males, although it may occasionally be encountered in women, children and non-obese individuals. A fair percentage of patients with FES also suffer from obstructive sleep apnea (OSA), a disorder marked by partial collapse of the pharynx during inspiration while sleeping, resulting in loud snoring and gasping for air.[2-4]

Symptoms generally consist of ocular irritation, itching and stringy mucous discharge, particularly upon awakening.[1-4] The symptoms may appear to be largely unilateral or asymmetric. Patients with OSA characteristically complain of erratic sleep patterns, chronic somnolence, fatigue and morning headaches.

Examination of patients with FES typically reveals chronic papillary conjunctivitis with mild to moderate bulbar hyperemia, often lateralizing to the patient's habitual sleeping side (i.e., if they sleep on their LEFT side, the presentation is more evident OS).[5] Punctate corneal epitheliopathy and mucous strands in the tear film and fornices may also be apparent. The lids themselves routinely display pseudoptosis and an odd "rubbery" consistency.[5] Eversion of the upper lids can be accomplished with minimal manipulation; in fact, it may occur spontaneously during normal ocular examination. Past ocular history may include blepharitis, meibomian gland dysfunction, dermatochalasis, keratoconus and seasonal allergic conjunctivitis.[5]

Pathophysiology

The exact etiology of FES is not thoroughly understood. Research has demonstrated that tarsal elastin is significantly diminished in these patients, such that the tarsal plate of the eyelid no longer displays its customary rigidity.[6] A recent study of patients with FES identified elevated matrix metalloproteinase (MMP) activity in subjects' eyelids; MMPs in these cases have been shown to degrade local elastin fibers and may ultimately lead to eyelid laxity and instability in this disease process.[7] The authors postulated that nocturnal mechanical factors may result in local eyelid ischemia, which upregulates these elastin-degrading enzymes to produce the tissue laxity.[7] Another publication suggested that elevated plasma leptin (a hormone that produces satiety symptoms) in FES patients may play a role in the systemic up-regulation of the MMPs that degrade elastin within the eyelid.[8]



Floppy eyelid syndrome.

Along with the etiopathology, the precise mechanism by which this disorder becomes manifested also remains disputed.[1,6-9] The most widely held theory suggests that, because of the lid laxity and tendency of these patients to lie on their sides or in a "face-down" position, spontaneous lid eversion occurs during sleep.[1] This results in mechanical abrasion of the ocular surface. Others have suggested that the underlying mechanism is simply poor apposition of the upper eyelid to the globe, instigating an inadequate tear distribution and subsequent desiccation of the ocular surface tissues.[9]

Management

In the majority of cases, diagnosis is made by the classic appearance and effortless or spontaneous eversion of the eyelids. There are few ancillary tests to consider beyond the normal ocular evaluation, though vital dye staining (e.g., sodium fluorescein, rose bengal and/or lissamine green) may help to assess the severity of any associated keratopathy.

Treatment for FES consists primarily of lubricating the ocular surface and safeguarding the eye from nocturnal damage. Artificial tears, used liberally throughout the day, help to eliminate mucous debris and promote corneal healing. In cases of moderate or profound epitheliopathy, consider more enduring lubricants such as Systane Ultra (Alcon Laboratories) or Blink Tears (Abbott Medical Optics) on a q.i.d. basis. At bedtime, the patient should instill either a bland ophthalmic ointment (e.g., Systane Nighttime, from Alcon Laboratories or Refresh PM from Allergan) or mild antibiotic ointment and apply a protective eye shield, or simply tape the lids in a closed position. Another option involves the use of removable eyelid weights (e.g., Blinkeze External Lid Weights, by MedDev Corporation) at bedtime.[10] Severe, recalcitrant cases that do not respond to primary therapy may require surgical intervention. Most commonly, this involves an eyelid tightening procedure at the lateral canthus, or a horizontal lid shortening procedure by full-thickness resection of the lateral one-third of the lid mar-

gin.[11] Lateral tarsorrhaphy has been suggested for noncompliant patients with severe disease.[12]

As important as managing the ocular sequela of FES is addressing the associated problem of obstructive sleep apnea. OSA is a potentially fatal condition that has been linked to pulmonary hypertension, congestive heart failure and cardiac arrhythmia. Weight loss and consultation with a sleep physician for appropriate studies are highly recommended, considering the significant comorbidities of both obesity and OSA. At least one study has demonstrated notable improvement of FES when OSA is properly addressed.[13]

Clinical Pearls

• Many patients with FES manifest attendant blepharitis, particularly meibomian gland dysfunction. Rosacea has also been found in association with both FES and OSA. In the course of treating these patients, strongly consider a trial of oral doxycycline 50mg to 100mg b.i.d. for six to 12 weeks.

• In the course of interviewing patients with FES, always remember to inquire about prominent snoring or gasping episodes during sleep. In this regard, realize that a spouse or family member may actually prove to be a more reliable resource than the patient! Any such findings consistent with OSA warrant consultation with a sleep physician, otolaryngologist, or pulmonologist.

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HERPES ZOSTER OPHTHALMICUS

Signs and Symptoms

Herpes zoster ophthalmicus (HZO) typically begins with nondescript facial pain, fever, and general malaise.[1-3] About four days after onset of symptoms indicative of an outbreak, a skin rash appears along the distribution of the fifth cranial nerve (trigeminal). Patients then develop a painful unilateral dermatomal rash in the distribution of one or more branches of the trigeminal nerve (the ophthalmic division, V1, or the maxillary division, V2) with each being able to support lesions amongst its branches. Frequently V1 with its supraorbital, lacrimal, and nasociliary nerves is affected.[1] A characteristic respect for the midline, consistent with the distribution of the affected nerves will be evident.[1,2] The skin manifestations begin as an erythematous macular rash, which progresses over several days into papules, vesicles, and then pustules. The vesicles emanate a fluid discharge and begin to form scabs after about one to three weeks in immunocompetent individuals.[1,2] During this inflammatory stage, the pain is extremely severe, and patients are tremendously symptomatic, even when the rash is minimal.[1-3] A number of patients will continue to experience pain known as post-herpetic neuralgia long after resolution of the acute outbreak.[3]

Ocular involvement in herpes zoster occurs in 20–50% of cases and is by no means invariable.[4,5] However, in patients with vesicular eruptions at the tip of the nose indicating nasociliary nerve involvement (Hutchinson's sign), the patient has a nearly 100% likelihood of ocular involvement.[1,4-6] Severe vesicular eruptions are also predictive of ocular involvement, uveitis, reduced visual outcome and incidence of post-herpetic neuralgia.[5] In addition to nasociliary nerve involvement, lacrimal nerve involvement is also highly predictive of ocular manifestations.[5]

Ocular involvement is highly varied and may involve anterior structures, retina and choroid, as well as the cranial nerves (optic, oculomotor, trochlear, abducens).[5-17] The common presentations include subconjunctival hemorrhage, follicular conjunctivitis, epithelial and/or interstitial keratitis, nummular keratitis, keratouveitis with secondary inflammatory glaucoma, scleritis or episcleritis, chorioretinitis, acute retinal necrosis, optic neuritis, and ophthalmoplegia with cranial nerve III, IV, and VI palsy.[5-17]

Corneal involvement may appear as a non-descript epitheliopathy or pseudodendritic keratopathy. Occasionally, superficial epithelial deposits representing necrotic epithelial cells will manifest.

Patients experiencing HZO are typically elderly, with most cases occurring in patients over age 50 due to natural weakening of the immune system. However, the condition does occur in children as well.[18-20] In adults under the age of 50, HIV co-infection should always be considered.[21]

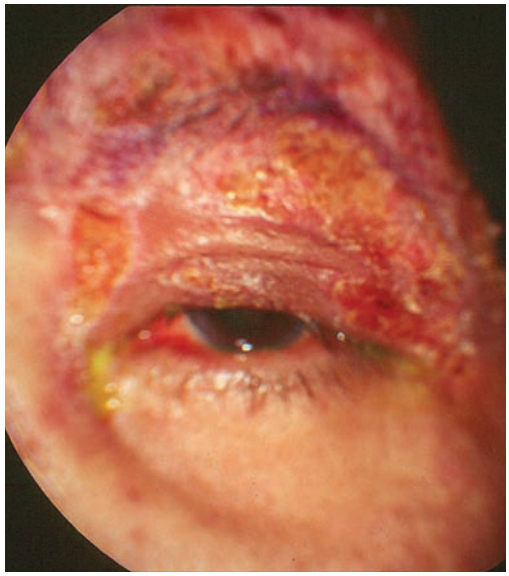
In a rare subset of patients, there

will be unilateral neuropathic pain with other characteristics of HZO, but without the attendant rash. This has been termed zoster sine herpete.[15]

Pathophysiology

Herpes zoster is the second manifestation of the Varicella zoster virus (VZV), which typically causes chickenpox.[2,4] This virus typically enters the human system through the conjunctiva and/or nasal or oral mucosa, and then occupies sensory ganglia throughout the body. 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 fail from natural aging, or other triggers such as chemotherapy or severe systemic disease occur, the virus actively replicates along the route of the ganglia. Due to the widespread exposure to the virus, nearly 100% of the population develops antibodies to the disease by age 60.[4] Cell-mediated immunity keeps the VZV suppressed and periodic re-exposure helps prevent the VZV from activating as herpes zoster. Declining VZV-specific cell-mediated immune response account for the increased frequency of herpes zoster seen in older adults. Periodic subclinical reactivation of VZV serves as immune boosters increasing the cell-mediated immunity and reducing the likelihood of the patient experiencing a full herpes zoster outbreak.[5]

HZO results when the trigeminal ganglion is invaded by the herpes zoster virus. Neuronal spread of the virus occurs along the ophthalmic (1st) and less frequently the maxillary (2nd) division of cranial nerve five. Vesicular eruptions occur at the terminal points of sensory innervation, causing extreme pain. Nasociliary nerve involvement will most likely entail ocular inflammation, typically affecting the tissues of the anterior segment. Contiguous 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).[13,14,16,17] The numerous manifestations in HZO are likely due to the varied pathophysiologic processes initiated by the VZV. There are features of viral infection, vascular and neural inflammation, immune and general inflammatory reactions. These numerous reactions partially explain the success and failure of anti-viral medication in cases of HZO.[4]



Characteristic dermatological manifestations in a patient with herpes zoster and inflammatory glaucoma.

Management

The systemic component of this disorder as well as the myriad of conditions occurring in HZO 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 ten days is standard. Alternately, famciclovir (500mg p.o. t.i.d.) and valacyclovir (1000mg b.i.d. to t.i.d.) for a 10-day course are acceptable.[3,10,22,23] Timing is crucial, and if these agents are started within 72 hours of the onset of the acute rash, they will significantly shorten the period of pain, viral shedding, rash, and anterior segment complications.[23] Valacyclovir and famciclovir may better reduce the incidence and severity of post-herpetic neuralgia compared with acyclovir. However, oral antiviral agents cannot totally prevent post-herpetic neuralgia.[23]

Oral corticosteroids may be utilized as adjuvant therapy to alleviate pain and associated facial edema; 40mg to 60mg of prednisone daily, tapered slowly over ten days is recommended. Topical care of the skin lesions may be afforded by applying an antibiotic or antibiotic-steroid ointment to the affected areas twice daily. Ocular management is dependent upon the severity and tissues concerned. In most cases involving uveitis or keratitis, cycloplegia (homatropine 5% t.i.d.-q.i.d. or scopolamine ¼% b.i.d. to q.i.d.) is warranted. Topical steroids (prednisolone acetate 1% q2h to q3h) may be utilized in addition to oral antiviral agents. Prophylaxis with a broad-spectrum antibiotic is also usually advisable for any compromised cornea. Finally, palliative treatment 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.[23] Cimetidine (H2-histamine receptor blocker) 400mg p.o. b.i.d. may afford some additional relief from the neuralgia, though the mechanism by which this occurs is not entirely understood.[24]

It may well be that the best treatment for HZO is prevention through vaccination.[25-27] The Shingles Prevention Study Group demonstrated that a vaccine against VZV boosted VZV cell-

mediated immunity and significantly reduced the morbidity due to HZ and post-herpetic neuralgia in older adults without causing or inducing an actual herpes zoster outbreak.[25] Overall, VZV vaccine reduced the incidence of post-herpetic neuralgia by 66.5% and the incidence of HZ outbreak was also reduced by 51.3%.[25]

Clinical Pearls

• This disorder has a great propensity for those over the age of seventy. Also, those who are immunocompromised due to lymphoma, HIV and AIDS, are at significantly increased risk of developing HZO.

• Ocular involvement is extremely variable and often confusing in the early stages. Extreme care must be taken in differentiating this condition from herpes simplex virus (HSV), particularly when there is corneal involvement—one key consideration is that the dendriform keratitis which occurs in HZO is infiltrative, while the HSV dendrites are ulcerative.

• In pseudo-dendritic keratitis in HZO, there are no terminal end-bulbs on the lesion whereas true dendritic keratitis in HSV will have terminal end-bulbs.

• The practitioner must also recognize the possibility of more involved and complex ocular sequelae (chorioretinitis, optic neuropathy, cranial nerve palsies, uveitic glaucoma) and apply appropriate management strategies in these cases.

• Herpetic keratouveitis is a common manifestation of HZO where the patient demonstrates elevated intraocular pressure in the face of mild anterior segment inflammation. This is best managed according to standard treatments for anterior uveitis with the addition of oral antiviral medication. In diagnosing this entity, look also for iris stromal atrophy and mild hyphema.

• Malaise and neuralgic prodrome are key diagnostic findings in patients with unusual corneal presentations, other peculiar ocular involvement or headaches without other signs.

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CANALICULITIS

Signs and Symptoms

Canaliculitis is a relatively rare disorder that typically affects older adults. In one recent series, patients ranged from 43 to 90 years of age.[1] An older study suggests that canaliculitis is more common in postmenopausal women.[2] Most cases are unilateral, though bilateral phenomena have been documented.[3] Complaints tend to center around a chronic, recalcitrant red eye and focal swelling of the medial canthus. Epiphora, or 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.

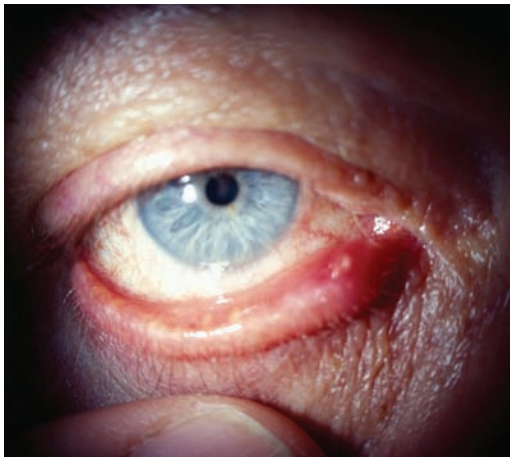
The classic biomicroscopic sign associated with canaliculitis is a "pouting punctum," although it may not be seen in all cases.[1,4,5] This terminology refers to the fact that the punctal orifice is red, swollen and turned outward, resembling a pair of pouting lips. The involved area is often tender to the touch. Discharge and/or concretions may be expressed with digital manipulation of the punctum and/

or canaliculi. Other important signs include erythema and swelling of the lid and adnexal tissue, and a conjunctivitis that is more pronounced inferiorly and nasally. Diagnostic signs can also be encountered with lacrimal probing, although this should never be attempted by a novice. The clinician will encounter a "soft stop" while probing the canaliculus. This blockage indicates the presence of concretions within the drainage system. 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.[6]

Pathophysiology

Canaliculitis represents a primary infection and inflammation of the lacrimal outflow system, at the level of the canaliculus. Multiple pathogens have been associated with the condition, including bacteria, fungi and some viruses.[7] Canaliculitis has been most closely associated with *Actinomyces israelii*, a cast-forming, Gram-positive anaerobe that is difficult to isolate and identify.[8] Actinomyces species are prone to causing infections of the hollow spaces via the formation of canaliculiths.[8] Other bacteria that have been associated with canaliculitis include *Arcanobacterium haemolyticum*, *Mycobacterium chelonae*, *Arachnia propionica*, *Nocardia asteroides*, *Fusobacterium*, *Lactococcus lactis cremoris*, *Eikenella corrodens* and *Staphylococcus aureus*.[4,7,9-12] Fungal pathogens include Candida and Aspergillus species.[13] Herpetic etiologies should be suspected when canaliculitis is encountered in a younger patient (i.e., under 40 years of age).[14]

Canaliculitis is associated with the formation of dacryoliths, which are small stones or concretions that further impede lacrimal drainage. These concretions help to form pockets in which the infection flourishes. In these "pockets" the organisms are not subject to the antimicrobial properties of the precorneal tear film.[4] Foreign objects that reside within the canaliculus, such as intracanalicular punctal plugs, can produce a similar presentation. Indeed, a significant number of published cases have been associated with the SmartPLUG (Medennium, Irvine, CA), a thermoacrylic polymer designed for lacrimal occlusion therapy in patients with dry eye.[3,15-17]



Canaliculitis presents with canalicular inflammation and punctal dacryoliths.

Management

Many cases of canaliculitis are diagnosed only after a seemingly benign case of blepharoconjunctivitis fails to resolve following topical antibiotic therapy. Cases often persist in a recurrent fashion for long periods of time with clinicians failing to observe the hallmark sign of dacryoliths. In one series, an average duration of 36 months was noted before the correct diagnosis was made.[1] Topical antibiotics are generally ineffective alone because many of the offending organisms are not bacterial; in addition, the bacteria *Actinomyces* demonstrates limited susceptibility to some of the more common ophthalmic drugs (e.g., tobramycin or ciprofloxacin).[18] Moreover, canalicular concretions and thick stagnant secretions impede the penetrance of topical eye drops to the site of the infection.

Definitive management of canaliculitis involves surgical excavation of the canaliculus, or canaliculotomy, with plating of extruded material for the purpose of determining the correct pharmacologic course.[4,7,19] 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).[1] Next, a small chalazion curette is used to remove any concretions or dacryoliths. Post-operatively, broad spectrum topical and systemic antibiotics are indicated. The preferred agent for Actinomyces is penicillin, and penicillin G solution may be used for canalicular irrigation. Systemic antibiosis with oral penicillin or ampicillin should be continued for several weeks following surgical recovery.[1] Canaliculitis secondary to herpetic or fungal etiologies should be addressed with the appropriate agents (e.g., trifluridine 1% solution five times daily for two to three weeks, and nystatin 1:20,000 ophthalmic solution t.i.d., respectively). In extreme cases, patients may have such severely scarred nasolacrimal systems that they must undergo intubation via dacryocystorhinostomy to successfully reestablish lacrimal outflow.

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

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.

• Should treatment fail to eradicate the problem or if canalicular patency cannot be restored with a simple canaliculotomy, dacryocystorhinostomy may be required.

• Smears and cultures are usually obtained from the extruded canalicular material. However, in the typical scenario of an older, otherwise healthy individual with canuliculitis, culture and pathology of the specimen may not be necessary. Empirical canaliculotomy is extremely effective in both *Actinomyces* and non-*Actinomyces* infections.[19] Furthermore, since *Actinomyces* is difficult to identify, many studies fail to yield definitive results.

• 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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DACRYOCYSTITIS

Signs and Symptoms

An inflammation of the nasolacrimal sac, dacryocystitis typically presents with focal pain, redness and swelling over the nasal aspect of the lower eyelid. In some cases, the pain may extend to the nose, cheek, or teeth on the involved side. Epiphora and/or ocular discharge is also frequently reported. Examination reveals erythematous swelling over the lacrimal sac, and mucopurulent discharge may be expressed from the inferior punctum when pressure is applied. The condition may be recurrent, and in severe cases associated with fever. While vision may be subjectively blurred due to discharge, acuity is not acutely impacted in most instances.[1-6]

Dacryocystitis demonstrates a bimodal distribution, with the majority of cases seen in infants and those over 40 years of age.[1] Postmenopausal women represent approximately 75% of cases.[1] Untreated, dacryocystitis frequently progresses to preseptal cellulitis.[1,2] Orbital cellulitis is far less common, but has been documented in the literature.[1,2]

Pathophysiology

The nasolacrimal apparatus drains the tears and tear constituents from the eyes into the nose. The system consists of inferior and superior puncta, their respective 10mm canaliculi, the 7mm to 10mm lacrimal sac, and a common 17mm interosseous/intermembraneous nasolacrimal duct that drains into the nose through the valve of Hasner beneath the inferior turbinate.[3] The primary etiology of dacryocystitis is nasolacrimal apparatus obstruction, prompting secondary infection.[4] Most cases of nasolacrimal duct obstruction are found in the older population, resulting from chronic mucosal degeneration, ductile stenosis, stagnation of tears and bacterial overgrowth.[5] The most frequently isolated pathogens are Gram-positive bacteria, particularly *Staphylococcus aureus* and *Streptococcus*; common Gram-negative organisms include *Pseudomonas aeruginosa*, *Fusobacterium* and *Haemophilus influenza*.[6]

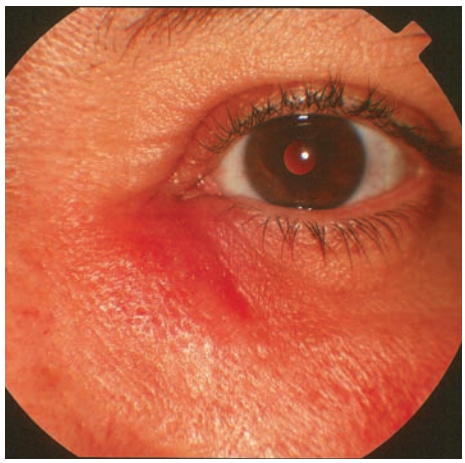
Infantile or congenital dacryocystitis is less common than the adult form, and results primarily from incomplete canalization of the nasolacrimal duct, specifically at the valve of Hasner.[3] Neonatal infection may be a contributory element.[3]

Management

Because dacryocystitis represents a deep tissue infection, systemic antibiotics are indicated. Options for children include oral amoxicillin/clavulanate or cefaclor 20mgs/kg/day to 40mgs/kg/day in three divided doses, along with topical antibiotic drops (e.g., 0.5%

moxifloxacin or 1% azithromycin). Amoxicillin and cephalosporins (e.g., cephalexin 500mg p.o. q.i.d.) are also popular choices for adult therapy.[7,8] Supportive treatment includes the use of warm compresses several times a day, and oral analgesics (e.g., acetaminophen, aspirin or ibuprofen) as needed for pain and inflammation. Management of the febrile patient must be handled with extreme caution. In these instances hospitalization should be considered along with IV antibiotics such as cefazolin q8h.[5] In cases that are atypical or suspect, neuroimaging (CT or MRI) should be considered to rule out potential malignancies and other invasive disorders.

Surgical management of dacryocystitis serves to reduce recurrence rates as well as symptomatic epiphora, and likely helps to normalize the conjunctival flora.[9] The treatment of choice is dacryocystorhinostomy (DCR), a procedure that creates a direct communication between the lacrimal drainage system and the nasal cavity, bypassing the nasolacrimal sac. Historically, DCR was performed as an external surgical procedure, approaching through the skin overlying the nose. More recently, however, surgeons have begun using an endonasal technique, which can be performed by the use of a long-handled scalpel or laser.[4,10,11] The technique begins with the creation of a mucosal flap over the anterior portion of the middle turbinate, exposing the lacrimal fossa at the juncture of the maxillary and lacrimal bones. This bony area is drilled out to expose the nasoacrimal sac, which is then incised. A neo-ostium is created so that tears can drain from the canaliculus directly into the nose through the middle turbinate. This ostium is kept open with a silicone tube placed through the puncta into the sac and out the nose. The tubes are kept in place for anywhere from six weeks to six months.[12]



Dacryocystitis, with characteristic inflammation of the nasolacrimal sac.

Alternatives to DCR include balloon dacryoplasty and recanalizaton using a high frequency lacrimal probe.[13,14] Balloon dacroplasty employs an inflatable probe, inserted through the punctum, to essentially stretch the lacrimal duct and canaliculus; this technique has been shown to work well for incomplete, non-acute nasolacrimal duct obstruction.[13] The recanalization technique described by Chen and associates involves a probe that can discharge a power current (50 to 150 watts) at 150 kHz frequency to cauterize blocked tissue in the nasolacrimal duct, which ultimately dissipates the blockage and allows for enhanced lacrimal drainage.[14]

Clinical Pearls

• Obstruction of the tear drainage system can occur at any age, but is most common in young children and older adults.

• Dacryocystitis must always be differentiated from canalicultis, as the treatment modalities differ significantly. Canaliculitis tends to run a more chronic and indolent course, with less significant pain and swelling near the punctal orifice. Canaliculitis typically requires surgical intervention to remove the concretions with which it is associated from the canaliculi.

• Prompt, decisive and aggressive management is essential in cases of dacryocystitis. Hospitalization with intravenous antibiotics should be considered in severe, febrile or recalcitrant presentations.

• Punctal dilation and nasolacrimal irrigation is ABSOLUTELY CONTRAINDICATED in the acute stages of dacryocystitis, as iatrogenic trauma can facilitate the spread of infection beyond the confines of the nasolacrimal system, potentially resulting in life-threatening consequences.

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ACUTE ALLERGIC CONJUNCTIVITIS

Signs and Symptoms

Allergic conjunctivitis is the most common manifestation of ocular allergy, affecting between 20% and 40% of the U.S. population.[1-10] Acute allergic conjunctivitis describes the abrupt and immediate response seen in sensitized individuals after exposure to a particular allergen or sensitizing agent. Two forms are recognized: seasonal allergic conjunctivitis (SAC), which coincides with pollen blooms such as ragweed, and perennial (or persistent) allergic conjunctivitis (PAC), in which exposure may occur at any time throughout the year (e.g., allergies to animal dander or dust mite feces).[4,5] In the majority of cases, allergic conjunctivitis is a bilateral phenomenon, although the presentation may be asymmetric.

The allergic response classically involves several signs and symptoms, all of which may vary in intensity. Ocular itching remains the hallmark symptom; tearing is also an exceedingly common complaint, particularly after rubbing the eyes in response to itching.[1-7] More severe reactions may prompt symptoms of ocular burning, foreign body sensation, or photophobia, though these are relatively rare.[1] Clinical evaluation reveals variable conjunctival hyperemia and chemosis. Ocular discharge is watery, though mucus may accumulate in the fornices or collect on the lash margin in the form of "crusts," especially during sleep. Eversion of the eyelids may reveal a fine papillary response, particularly along the upper tarsal plate. Externally, the eyelids may be red, swollen and edematous, with a pseudoptosis in pronounced cases. A palpable preauricular lymph node is noticeably absent. If questioned, the patient will often reveal a personal or family history of allergies. Concurrent symptoms of allergic rhinitis, post-nasal drip, or sinus congestion may be present, especially in SAC.[3]

Pathophysiology

The allergic response is classically considered to be an over-reaction of the body's immune system to substances perceived as foreign (allergens), despite the fact that said substances are not inherently pathogenic.[4] This response can be innate or acquired. The key component of the ocular allergic response is the mast cell; mast cells are widely distributed, especially in connective tissue and mucosal surfaces, particularly the conjunctiva.[1] Immunoglobulin (IgE and IgG) receptors, which are sensitized to specific allergens, are expressed on mast cell surfaces. When allergens are encountered at the cellular level, an antigen-antibody response ensues, in turn triggering mast cell degranulation; this process releases pre-formed pro-inflammatory mediators, and spurs the secretion of chemokines and cytokines.[4,8] The primary chemical mediator released during degranulation is histamine, which is responsible for increased vascular permeability, vasodilation, bronchial contraction and increased secretion of mucus.[9] Heparin, chymase and tryptase are also released from mast cells, as well as several chemotactic factors. Degranulation also stimulates the production of newly formed mediators through the activation of phospholipase-A2 on membrane phospholipids, releasing arachidonic acid and platelet-activating factor. Arachidonic acid is further degraded via the cyclooxygenase pathway to form, among other chemicals, prostaglandins and thromboxanes, and via the lipoxygenase pathway into leukotrienes.[8,10] These newly formed mediators drive the inflammatory reaction and incite recruitment and activation of additional inflammatory cells, leading to what has come to be known as the "late phase" of the allergic response.

The late phase reaction typically commences between four and six hours following sustained mast cell degranulation.[8,11] T-lymphocyte activation and infiltration of the conjunctival mucosa by eosinophils, neutrophils, monocytes and basophils are the hallmark of the late phase.[9,12] Leukocytic infiltration is not necessarily inherent to all cases of acute allergic conjunctivitis; in fact, the late phase response is much more characteristic of chronic allergic disorders like atopic and vernal keratoconjunctivitis, which constitute less than 2% of cases seen in clinical practice.[1,5]

Management

The management of ocular allergic reactions is primarily aimed at reducing symptomology and quelling any significant inflammation while attempting to discover, remove and avoid the offending agent, although this may not always be possible or practical. Artificial tear solutions provide a barrier function, serving to flush or dilute the antigens from the ocular surface while soothing and lubricating the irritated ocular surface; these may be used on an as-needed basis. Cold compresses and topical decongestants help to produce vasoconstriction, reducing hyperemia, chemosis and other symptoms by retarding the release of the inflammatory cells into the tissues from the vasculature. Numerous decongestant solutions (containing one of the following: naphazoline, antazoline, tetrahydrozaline, phenylephrine) are available as over-the-counter preparations, either alone or in combination with a mild topical antihistamine (e.g., pheniramine maleate or antazoline phosphate). These agents tend to be the preferred treatment modality for

those patients who self-medicate their allergies. Unfortunately, such OTC preparations have been associated with significant tachyphylaxis as well as chronic follicular conjunctivitis and eczematoid blepharoconjunctivitis when used chronically.[13,14]

The pharmacologic options for managing ocular allergy are extremely diverse. In fact, there are more commercially available topical medications for allergic conjunctivitis today than there are for glaucoma. Overall, five distinct classes or categories of topical drugs are recognized; these include:

1. Antihistamines, e.g., Emadine (0.05% emedastine difumarate, Alcon Laboratories);

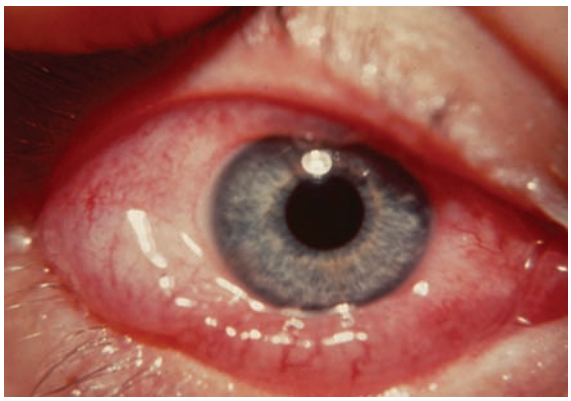
2. Mast cell stabilizers, e.g., Crolom (4% cromolyn sodium, Bausch & Lomb), Alomide (0.1% lodoxamide tromethamine, Alcon Laboratories), Alocril (2% nedocromil sodium, Allergan), and Alamast (0.1% pemirolast postassium, Vistakon Pharmaceuticals);

3. Antihistamine/mast cell stabilizer combinations, e.g., Patanol and Pataday (0.1% and 0.2% olopatadine hydrochloride, respectively, Alcon Laboratories), Optivar (0.05% azelastine hydrochloride, Meda Pharmaceuticals), Zaditor (0.025% ketotifen fumarate, Novartis Pharmaceuticals), Elestat (0.05% epinastine hydrochloride, Inspire Pharmaceuticals) and Bepreve (1.5% bepotastine besilate, ISTA Pharmaceuticals);

4. Corticosteroids, e.g., Alrex (0.2% loteprednol etabonate, Bausch + Lomb);

5. Non-steroidal anti-inflammatory agents (NSAIDs), e.g., Acular (0.5% ketorolac tromethamine, Allergan).

These medications are available only by prescription in the United States, with the exception of Zaditor, which was granted over-the-counter status in October 2006. In the wake of that approval, ketotifen has been released commercially under a variety of other trade names, including Alaway (Bausch + Lomb), Refresh Eye Itch Relief (Allergan), Claritin Eye (Schering-Plough) and Zyrtec Itchy Eye Drops (McNeil Consumer Healthcare).



Profound conjunctival chemosis in a patient with allergic conjunctivitis.

In general, all of these medications are beneficial to a degree by themselves and in combinations. Topical antihistamines provide prompt symptomatic relief, but their effects can be short-lived—on the order of just four to six hours. Mast cell stabilizers prevent degranulation and hence eliminate the allergic response, but they lack the capacity to alleviate itching rapidly. In addition, mast cell stabilizers may take several days to a week in order to achieve full efficacy, and require preloading to be effective when the exposure takes place. Antihistamine/mast cell stabilizer combinations provide the benefits of both of these categories and are by far the most common choice among eye care practitioners; these drugs also have the advantage of b.i.d. dosing, except for Pataday which is the only topical allergy medication currently approved for once-daily dosing.[15]

Topical corticosteroids may serve to quell inflammation and offer relief to those patients with more severe cases of acute allergic conjunctivitis. While there are well-known risks associated with long-term corticosteroid use (e.g., cataractogenesis, ocular hypertension), short-term therapy with steroids can be extremely effective. Also, studies have shown Alrex to have an excellent safety profile in the treatment of ocular allergy, even with therapy of up to four years' duration.[16] Topical NSAIDs are likely the least effective option for ocular allergy. While they may provide mild symptomatic relief, they do not directly address mast cell degranulation or the histamine response, and inhibit only a portion of the inflammatory cascade.

In the last few years, there has been a good deal of discussion regarding the use of nasal allergy preparations and their potential for alleviating ocular allergy symptoms. The literature does demonstrate that nasal corticosteroid sprays can have a direct and beneficial impact on ocular allergy.[18-23] Studies have consistently shown that medications like Flonase (0.05mg fluticasone propionate, GlaxoSmithKline), Veramyst (0.0275 mg fluticasone furoate, GlaxoSmithKline) and Nasonex (0.05mg mometasone furoate, Schering-Plough) help to ameliorate concurrent ocular symptoms when used to treat nasal rhinitis.[18-23] However, it is important to understand that topical agents still offer faster, safer and more complete relief of ocular symptoms than any other form of therapy, as demonstrated in head-to-head studies for ocular itching, redness, chemosis and eyelid swelling associated with allergic conjunctivitis.[24-26]

Oral antihistamines are rarely required for the treatment of acute allergic conjunctivitis, unless there is associated rhinitis, sinusitis, urticaria

or other manifestations of systemic allergy. Some of the older, over-the-counter antihistamines, such diphenhydramine hydrochloride and chlorpheniramine maleate, are effective but can induce drowsiness and functional impairment.[27,28] Loratadine, desloratadine, fexofenadine, cetirizine and levocetirizine are second generation antihistamines; the sedative effect of these drugs is greatly diminished, though it is not entirely eliminated. In addition, all of these oral medications have the capacity for anticholinergic effects, causing dryness of the mucosal membranes of the mouth, nose and eyes.[29]

Clinical Pearls

• When evaluating patients with presumed allergic conjunctivitis, pay special attention to the inferior fornix and medial canthus. In many cases, the caruncle and plica semiluminaris may demonstrate marked hyperemia or inflammation. This is presumably because of the accumulation of histamine-laden tears in the area of the lacrimal puncta. Also, eyelid eversion is recommended to assess the status of the superior tarsus.

• In differentiating allergic conjunctivitis from other forms of ocular surface disease, an extremely helpful question may be, "What happens when you rub your eyes?" Most itchy surface disorders such as dry eye and blepharitis generally improve with digital manipulation because it stimulates the flow of additional tears. However, rubbing in allergy can cause further degranulation of mast cells, releasing more histamine and other chemokines into the ocular tissues and resulting in greater symptomology.[30,31] Hence, patients with true allergies almost always say that their symptoms worsen when they rub their eyes.

• Remember that seasonal allergic conjunctivitis usually occurs around the same time each year, and may last for only a month or two. Therefore, patients who present for their annual examination during other times of the year may go undiagnosed. It is important to ask not only whether the patient is experiencing symptoms at the time of the exam, but also if they EVER suffer from red, itchy, watery eyes. The safety and efficacy of today's medications allows for proactive prescribing, even months before symptoms arise.

• Livostin (0.05% levocabastine hydrochloride), a topical antihistamine introduced by Novartis in 1993, was discontinued in the U.S. and U.K. several years ago. It is still available, however, in Canada, several European countries and Australia/New Zealand.

• Despite marketing efforts to the contrary, most allergy experts agree that topical ophthalmic medications are the best means to manage the symptoms of ocular allery; nasal sprays are best for nasal symptoms, and oral antihistamines should be used as an adjunct to these therapies when necessary.

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PTERYGIUM

Signs and Symptoms

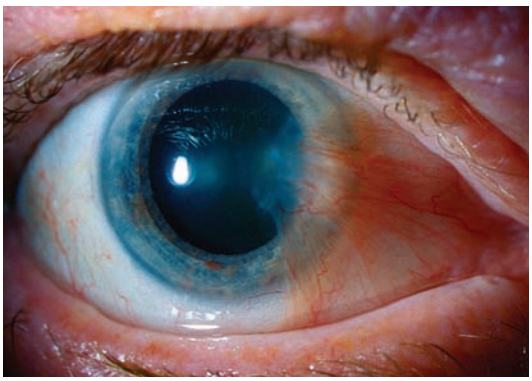
In most cases, pterygia are discovered upon routine ocular evaluation in asymptomatic individuals, or in patients who present with a cosmetic concern about a tissue "growing over the eye." In some instances, the vascularized pterygium may become red and inflamed, motivating the patient to seek immediate care. In other cases, the irregular ocular surface can interfere with the stability of the precorneal tear film, creating a symptomatic dry eye syndrome. Occasionally, the pterygium may induce irregular corneal warpage and astigmatism, or even obscure the visual axis of the eye, resulting in diminished acuity.[1-4]

Clinical inspection of pterygia reveals a raised, whitish, triangular-shaped wedge of fibrovascular tissue, whose base lies within the interpalpebral conjunctiva and whose apex encroaches on the cornea. The leading edge of this tissue often displays a fine, reddish-brown iron deposition line (Stocker's line). More than 90% of pterygia occur nasally.[1] These lesions are more commonly encountered in warm, dry climates, or in patients who are otherwise chronically exposed to outdoor elements or smoky/dusty environments. There is a strikingly significant association between outdoor work, sunlight exposure and pterygium formation.[2-4] The use of UV-blocking sunglasses has been seen to reduce the incidence of pterygia.[4] One study showed that pterygia occurred three times more frequently in patients of African descent than in whites.[4] Men are affected somewhat more frequently than women.[4]

Pathophysiology

Ultraviolet light exposure (both UV-A and, especially, UV-B) appears to be the most significant contributory factor in the development of pterygia.[5] This may explain why the incidence is vastly greater in populations near the equator and in persons who spend a great deal of time outdoors.[6] Other agents that may contribute to the formation of pterygia include allergens, noxious chemicals, and irritants (e.g., wind, dirt, dust, air pollution). Heredity may also be a factor.[5] While the etiology is varied, pterygia represent a degeneration of the conjunctival stroma with replacement by thickened, tortuous elastotic fibers. Activated fibroblasts in the leading edge of the pterygium invade and fragment Bowman's layer as well as a variable amount of the superficial corneal stroma. It has been suggested that multipotential stem and progenitor cells may be involved in the pathogenesis of pterygium through their differentiation into fibroblasts and vascular endothelial cells.[7] The detection of T-lymphocyte infiltration in pterygium epithelium strongly supports the suggestion that cellular immunity plays an important role in pterygium formation.[8] Epidermal growth factors have been localized in pterygium tissue, and are significantly induced by UV-B in pterygium-derived epithelial cells. This may be the means by which UV irradiation causes the pathogenesis of pterygium.[9]

Histologically, pterygium development resembles actinic degeneration of the skin. Surface cells in pterygium exhibit squamous metaplasia with increased goblet cell density. These changes are most pronounced directly over the pterygium surface.[10] Stocker's line represents corneal linear iron deposition, derived from tear film lactoferrin and presumably due to abnormal iron metabolism. The presence of Stocker's line along the advancing head of the pterygium may signify a lack of growth potential.[11] Pterygia often persist after surgical removal; these lesions appear as a fibrovascular scar arising from the excision site. These "recurrent pterygia" probably have no relationship to ultraviolet radiation, but rather may be likened to keloid development in the skin.



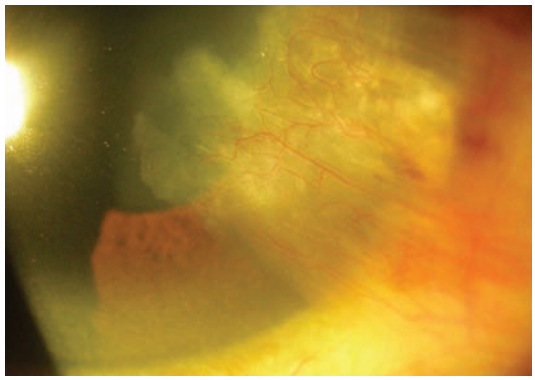
Nasal pterygium encroaching on the visual axis.

Management

Before initiating management, the clinician must be certain that the diagnosis is correct. A clear distinction needs to be made between the potentially progressive pterygium and the less threatening pinguecula. When large, pingueculae may be very difficult to differentiate from pterygia. Pingueculae are more yellow in color and lie within the interpalpebral space, but generally do not encroach beyond the limbus.[12] Pingueculae also lack the wing-

shaped appearance of pterygia, the former being more oval or amoeboid in appearance.

Because pterygium development and proliferation appears to be linked to environmental exposure, management for asymptomatic or mildly irritative pterygia involves UV-blocking spectacles and liberal ocular lubrication. Patients should be advised to avoid smoky or dusty areas as much as possible. More inflamed or irritated pterygia may be treated with topical corticosteroids (e.g., 1% prednisolone acetate or 0.5% loteprednol etabonate q.i.d. for several days).



Close-up view of pterygium; note the pronounced vascularity.

Surgical excision of pterygia is indicated for unacceptable cosmesis, significant induced astigmatism, threats to peripheral corneal hydration and stability and/or significant threat by ingrowth to the visual axis. Surgical excision involves dissection and removal of the fibrous tissue down to the level of Tenon's capsule. Conjunctival autograft—a technique that involves excision of the pterygium and covering of the resulting bare sclera with a free conjunctival graft harvested from an uninvolved site of the ocular surface—is typically used to prevent recurrence.[6,13,14] The use of fibrin glue has advanced the use of conjunctival autografts by eliminating the need for suturing, hence reducing both operating time and postoperative pain and inflammation.[15] An alternative to conjunctival autograft involves use of an amniotic membrane transplantation.[16-18] Amniotic transplants typically are reserved for patients with recurrence following conjunctival autograft and those with insufficient viable conjunctival tissue, or those with glaucoma who may need the superior conjunctiva preserved for future trabeculectomy. Unfortunately, amniotic membrane transplantation is associated with a high rate of recurrence.[16] Medical adjuncts in the form of the antimetabolites mitomycin C and 5-Fluorouracil may be used in order to reduce pterygia recurrence.[19-22] However, these antimetabolites can have attendant complications and are frequently used in cases of previous surgical failure. Beyond medical adjuncts, single-dose beta-irradiation remains the simplest procedure following bare sclera surgery. It is an effective and safe treatment that reduces the risk of primary pterygium recurrence.[23] Removal of large pterygia can greatly reduce the amount of induced corneal astigmatism and preserve limbal health.[24]

Clinical Pearls

• Pterygia represent a benign clinical entity in most cases.

• Another clinical entity that must be ruled out in the diagnosis of pterygia is conjunctival intraepithelial neoplasia (CIN). CIN is a precursor of conjunctival squamous cell carcinoma. This lesion is generally unilateral, elevated and gelatinous, with deep irregular vascularization and an amoeboid shape. CIN is an invasive ocular cancer with the capacity to inflict significant morbidity. Biopsy should be obtained if CIN is suspected.

• Pterygia do have the capacity to affect vision if left unchecked. The corneal degradative effects of a pterygium extend approximately three millimeters beyond the leading edge, or head, of the lesion. This means that the pterygium need not cover the visual axis to inflict significant visual compromise. Clinicians have discovered that seemingly benign pterygia at least two millimeters off the visual axis have induced in excess of 10 diopters of irregular corneal astigmatism and resulted in a best corrected acuity of 20/80.

• It is not wise to wait until a pterygium impacts the visual axis or vision before recommending surgical excision. Since healthy corneal tissue beyond the leading edge of the pterygium must be resected during excision, waiting until the visual axis is affected virtually guarantees permanent visual reduction.

• Follow-up on medium to large sized pterygia should be performed at least once or twice yearly. It should include a manifest refraction, corneal topography, slit lamp evaluation with measurement of the pterygium and photodocumentation if possible.

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SUBCONJUNCTIVAL HEMORRHAGE

Signs and Symptoms

Subconjunctival hemorrhage (SCH) is a common presenting clinical problem for eye care practitioners.[1–11] The condition is marked by a well defined, well circumscribed area of coalesced blood between the bulbar conjunctiva and the sclera. The hemorrhage may be flat or slightly elevated depending on the volume trapped. While they are impressive to observe and often a source of worry or panic for patients, they rarely produce symptoms or disabilities of any kind.[1-10] Although SCH is usually benign, it can be caused by a variety of entities, each with their own important sequelae.[3-11] When the condition is induced by traumatic vectors, no additional work-up is required. SCH has an established relationship with loose, free moving conjunctival tissue.[10] Here, conjunctivochalasis permits the conjunctival surfaces that are redundant to be in frictional contact with one another, resulting in small vessel injury and rupture.[10] This also explains why the phenomenon is observed more frequently in persons of older age and in persons who wear contact lenses.[11,12]

In the event a subconjunctival bleed cannot be explained by mechanical means or redundant tissue sources, a comprehensive history and ancillary testing is indicated to rule out infection or adverse effects from systemic medications or systemic disease.[3,13]

Epidemiologic studies prospectively examined 8,726 and 161 patients, respectively, in outpatient eye clinics.[6,14] In one study, a total of 225 patients (2.9%) presented with a subconjunctival hemorrhage.[6] No sexual or age predilection was found in either cohort.[6,14] The most common causes for SCH found in both studies were minor local trauma, systemic hypertension and acute hemorrhagic conjunctivitis.[6,14] There were some interesting cohorts identified. In both reports, SCH resulting from local trauma were most frequently diagnosed in the summer months, those induced by contact lenses were in younger populations, and those associated with systemic hypertension were noted most often in older patients.[6,10-12,14]

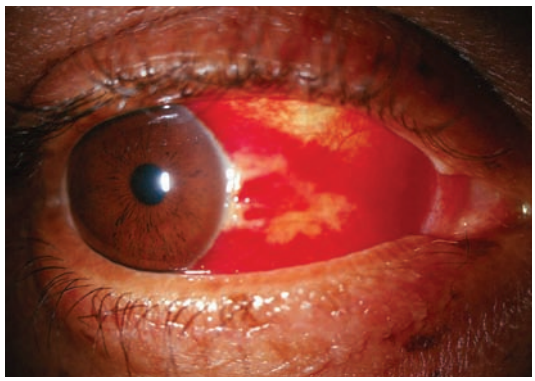
Pathophysiology

The etiopathology of SCH is vascular compromise of capillaries under the conjunctiva.[1-10] This may result from exposure to mechanical forces such as excessive increase in blood or plasma volume, shearing forces, rapid acceleration/deceleration exposure or from hemo-perfusive abnormalities such as blood flow stasis or impaired blood tissue composition.[1-15]

The largest subset of SCH patients suffer from acute trauma.[3-7] Here, something as complicated as rapid acceleration, deceleration and exposure to blunt forces or as simple as a sneeze or Valsalva's maneuver can result in threshold vascular stresses sufficient to overcome vessel cellular barriers. Jarring physical contact, the act of vomiting, coughing, singing, playing an air-driven musical instrument, raising of the voice, lifting heavy weights and attempting to overcome constipation are all reported sources of SCH.[1-11] Hypertension, diabetes, various anemias (such as polycythemia, for example), bleeding disorders (Von Willebrand's disease, hemophilia, those caused by medication side effects or anticoagulation therapy), Behcet's disease and malignancies (tumors of the conjunctiva and blood–leukemia) are all capable of adding to the blood volume, increasing blood viscosity, creating an inability to clot, raising blood pressure, producing abnormal perfusion, altering blood flow and creating vascular stasis and/or leakage—all processes capable of contributing to the processes that generate SCH.[13,16]

Evidence suggests that anatomi-

cal and system-wide abnormalities may induce SCH to occur in lesion specific locations.[1] Researchers examining location of SCH and underlying pathologic causes found that traumatic SCH were smaller in their extent compared with SCH related to hypertension, diabetes, hyperlipidemia or those that were idiopathic.[1] Further, SCH in all groups was significantly more common in the inferior aspect as compared to superior.[1] In patients with SCH secondary to trauma or diabetes, there was a tendency to find temporal areas affected more often than the nasal areas.[1]



A subconjunctival hemmorrhage. This resulted from ocular trauma.

Management

The management for subconjunctival hemorrhage begins with appropriate patient education. Frightened individuals can be reassured and comforted regarding the source and benign nature (in most cases) of the bleeding. Counseling regarding resolution and expected course also can add layers of assurance. Cold compress, hot compress, artificial tears and possibly bed rest are other palliative strategies. While the hemorrhage itself does not require direct medication to promote its resolution, an underlying cause, if it exists, may. If the etiology is trauma, cycloplegia and topical anti-inflammatory therapy may be indicated for any concurrent uveitis. If the cornea or conjunctiva are abraded or infected, a topical antibiotic is required.

Management of any discomfort must be accomplished through means that do not promote anti-platelet activity. This means aspirin and ibuprofen derivatives must be used with caution if they are used at all. In highly recurrent cases, testing for blood-tissue abnormalities, clotting disorders, hypertension, diabetes and malignancies should be done. This includes, but is not limited to, a complete blood count with differential and platelets, prothrombin time, activated partial thromboplastin time, fasting blood sugar, blood pressure evaluation, echocardiogram, lipid profile, homocysteine levels, antiphospholipid antibodies, protein s, protein c, antithrombin III, factor V Leiden, beta-glycoprotein, sickle cell preparation and human immunodeficiency virus titres.[15,16]

In most cases, SCH episodes are not so severe that they warrant cessation of a patient's necessary systemic medications. However, in cases where the occurrence is substantial, communication and discussion with the internist is advised. As a rule SCH is rarely evacuated.[1-11]

Clinical Pearls

• Given the common nature of this entity, so long as there are obvious mechanical vectors and the injury is not recurrent, no further work up is required.

• Since the space between the sclera and conjunctiva is infinitely thin, the smallest amount of blood can produce a striking lesion.

• Arresting patient fear is often more significant than the actual post incident care.

• Blood pressures should be examined in patients with subconjunctival hemorrhages, particularly in older patients.

• Any 360˚ subconjunctival hemorrhage following trauma should invoke a suspicion and investigation to rule out ruptured globe.

• Recurrent events may suggest a situation of abuse, tumor or excessive anticoagulation therapy (Requiring an International Normalized Ratio [INR] evaluation to determine the patient's sensitivity to clotting).

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CORNEAL ABRASION and RECURRENT CORNEAL EROSION

Signs and Symptoms

Corneal abrasion is one of the common urgent clinical entities that present in practice.[1] Patients usually present with some or all of the following: acute pain, photophobia, pain upon blinking and extraocular muscle movement, lacrimation, blepharospasm, foreign body sensation, blurry vision and a history of contact lens wear or being struck in the eye.[2-10] Biomicroscopy of the injured area often reveals diffuse corneal edema and epithelial disruption. In severe cases, when edema is excessive, folds in Descemet's membrane may be visible. Cobalt blue light inspection, with the instillation of sodium fluorescein dye, will illuminate the damaged segment. The newly created wound appears as a bright green area compared to the rest of the cornea because the dye accumulates in the divot, adding density.[4,6] In severe cases, a mild anterior chamber reaction may be present.

Pathophysiology

The cornea has five distinct layers. Below the tear film lays the corneal epithelium. The corneal epithelium is actually composed of three tissues: the stratified surface epithelium, the wing cell layer (containing the corneal nerves) and the mitotically active basement membrane. Next is the Bowman's membrane (a whirling structure designed to prevent penetrating injuries), the organized lamellar sheets of stroma, the Descemet's membrane and finally the endothelium.[11]

There are two categories of corneal abrasion: superficial, (not involving Bowman's membrane) and deep (penetrating Bowman's membrane, but not rupturing Descemet's membrane). Abrasions may result from foreign bodies, contact lenses, chemicals, fingernails, hair brushes, tree branches, dust and numerous other etiologies.[1-11]

The cornea has remarkable healing properties. The epithelium adjacent to any insult expands in size to fill in the defect, usually within 24 to 48 hours.[11] Lesions that are purely epithelial often heal quickly and completely without intervention or subsequent scarring. Lesions that extend below Bowman's membrane possess an increased risk for leaving a permanent scar.[11]

Management

Treatment for corneal abrasion begins with history. The time, place and activity surrounding the injury should be recorded for both medical and legal purposes. Visual acuity (VA) should be recorded before any procedures or drops are given. If the blepharospasm is sufficiently intense to preclude an acuity measurement, one drop of topical anesthetic can be administered with the VA measured immediately thereafter (pinhole, if necessary). The eye examination should proceed in a logical fashion from external adnexa to funduscopic examination. The eyelids should be everted and fornices scrutinized to rule out the presence of foreign material. Fluorescein dye (without anesthetic) should be instilled to identify the corneal defects. The Seidel test (painting of the wound with fluorescein dye observing for aqueous leakage) is used when full-thickness injuries are suspected. The abrasion should be documented for size, shape, location and depth. It should be cleaned and scrutinized for foreign matter. The anterior chamber should be observed for any evidence of inflammation. A dilated examination should be completed to rule out any posterior effects from the trauma.

Ophthalmic treatment is initiated by using adequate cycloplegia (determined on a case by case basis; atropine 1% q.d. - t.i.d., for the worst and scopolamine, cyclogel or homatropine in the office only for the mildest) and topical broad spectrum antibiotics.[12,13] Bed rest, inactivity, cold compresses, artificial tear drops and over-the-counter analgesics can be used to relieve acute pain. In cases where pain is severe, topical nonsteroidal anti-inflammatory medications or a thin, low-water-content bandage contact lens can be prescribed.[2-7,10] Pressure patching is not contraindicated (except perhaps for contact len wearing patients); however, it is no longer considered standard-of-care.[1,3,5,7,8,14,15] Patients should be reevaluated every 24 hours until the abrasion is reepithelialized.[2–8]

Riboflavin-ultraviolet A (UVA) treatment is a new procedure that induces collagen cross-linking to stiffen the corneal stroma.[16] Inducing a reduction in stromal swelling and an increased resistance to microbial and enzymatic degradation, the procedure shows promise for corneal injuries of all types that demonstrate increased healing times.[16]

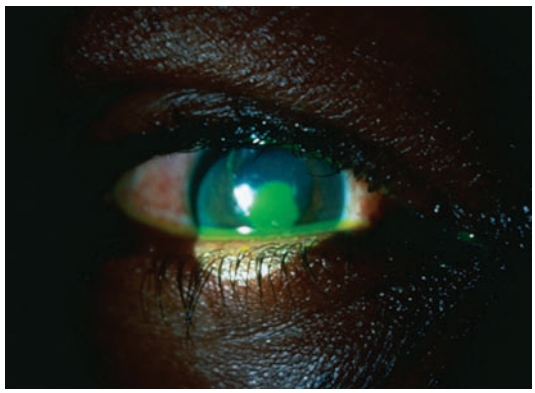
Reports have recognized the oral antibiotic class of the tetracyclines for their ability to protect the cornea against proteolytic degradation after moderate to severe ocular chemical injury.[17,18] Here, oral preparations inhibit matrix metalloproteinases (MMP) via mechanics that are independent of the agent's antimicrobial properties. These compounds, primarily through restriction of gene expression of neutrophil collagenase and epithelial gelatinase suppression of alpha1-antitrypsin degradation and scavenging of reactive oxygen species, are able to limit production of the inflammatory mediator MMP.[17,18]

Oral tetracyclines can be used along with other therapeutic agents to inhibit collagenolytic degradation of the cornea. Topical steroids can also be employed following early stage repair of superficial ocular injuries to increase the efficiency of corneal wound healing by suppressing inflammatory enzymes.[17,18] Using 50mg of doxycycline b.i.d. orally and topical fluorometholone 0.1% t.i.d. for at least four weeks has demonstrated efficacy in patients with recurrent corneal erosion syndrome who have failed other forms of treatment.[18] This non-invasive treatment modality can be effective in concordance with conservative ocular lubricant management.[18]

Patients with a history of corneal abrasions are more prone to recurrent corneal erosions secondary to altered formation of the hemidesmosomes of the epithelial basal cell layer.[9-21] When the hemidesmosomal anchoring fibers are not established properly, a "peeling" off of the epithelium can result. This most frequently occurs upon awakening.[9-16,19-21] Patients who have no history of a corneal abrasion but who suffer from corneal dystrophies (Cogan's microcystic dystrophy, map-dot-fingerprint dystrophy, Meesmann's corneal dystrophy, Reis–Bucklers dystrophy, honeycomb dystrophy, granular and lattice dystrophies) are also more susceptible to recurrent corneal erosions.[9,22] In cases such as these, palliative treatment should include hyperosmotic solutions and lubricants. When recurrent erosion does occur, patching and bandage lenses may be employed.[2,4,5,10,21,23]

When these modalities fail to promote adequate corneal healing, superficial phototherapeutic laser keratectomy (PTK) may prove to be of benefit.[24] PTK attempts to remove poorly adherent superficial layers of the cornea by ablating the corneal surface with an excimer laser. Complications of this procedure include excessive pain, perforation and exposure to infection.[23]

Anterior stromal puncture is another option.[25] Anterior stromal puncture involves repeatedly puncturing the Bowman's layer, penetrating into the anterior 1/3 of the corneal stroma either with a 27 1/2 gauge needle on a tuberculin syringe or via a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser.[25] When applied to loosened epithelium or the recurrent epithelial defect area, both options serve to produce purposeful scarring, which strengthens the adherence of the overlying superficial epithelium to the Bowman's layer.[25] While the complications of the needle-based procedure include pain, infection, reduced acuity secondary to excessive scarring and accidental penetration, a new laser-based practice has been evaluated in small studies to reduce the frequency of attacks while only producing mild post procedural discomfort.[25] Epithelial debridement and diamond burr polishing of Bowman's membrane is also an option.



Epithelial debridement and NaFl staining in a corneal abrasion.

Tarsorrhaphy is the management option that is used primarily for recalcitrant epithelial defects.[26] Here, the eyelids are temporarily sutured together, providing a complete form of patching.[26] Tarsorrhaphy provides complete immobilization of the eyelid, which yields more efficient healing.[26] Often, the sutures are left tied but not knotted and then taped to the forehead, so they can be tightened and loosened for the purpose of opening the lids to instill medications. Partial tarsorrhaphy can be accomplished when complete closure is not required. While a tarsorrhaphy is simple, safe and effective, it can be somewhat unsightly and create cosmetic concern for the patient. This is typically only done in extreme cases, such as neurotrophic keratitis.

Amniotic membrane transplantation (AMT) is a surgical modality used to create a temporary "tissue" patch for non-healing corneal lesions. The membrane can serve as a reconstructive graft for both the cornea and conjunctiva.[27] AMT is primarily used to treat conditions where the normal corneal reparative process is either faulty or cannot gain momentum.[27] In a new procedure, AMT is accomplished using fibrin glue instead of sutures. The procedure was reported as a safe and effective method for restoring the corneal epithelium. It also had the added benefit of not requiring a transplantation of limbal epithelial stem cells.[27]

New and on the horizon is a dendritic polymer known as a dendrimer. This molecule seems to have applications as a nano-adhesive to improve corneal wound repair.[28] The agent is composed entirely of the biocompatible products, glycerol and succinic acid.[28] The adhesive has advantages over sutures in the repair of corneal lacerations, securing unstable LASIK flaps and closing leaky cataract surgical incisions.[28-30] Other applications

for potential usage of the adhesive include ocular emergencies involving perforation of tissues due to trauma or infection. The substance may also be applied to strengthen or build up weak tissues that have been compromised by the destructive processes associated with inflammation.[28-30]

Clinical Pearls

• To promote healing, prevent recurrent erosion and reduce corneal edema, a hypertonic solution or ointment may be prescribed along with the other medications or after re-epithelialization has occurred. The minimum period of recommended application for this type of therapy is one month; however, unusual cases may require months or even permanent use.

• In cases where excess epithelium impairs regrowth, a cotton-tipped applicator saturated with anesthetic may be used to debride the loose or excessive tissue.[5]

• When a significant inflammation is present or if subepithelial infiltration occurs during the reparative process, topical steroids may be required. They must be used judiciously as they can retard corneal healing and raise intraocular pressure.

• Worsening subepithelial infiltration, increased pain and increased injection in the setting of an epithelial break may be a sign of ulceration secondary to infection. Lesions such as these should be considered vision threatening, warranting immediate treatment with a fourth-generation fluoroquinolone antibiotic drops (if one is not already employed) and consideration for culture to determine the presence of an underlying microbial organism.

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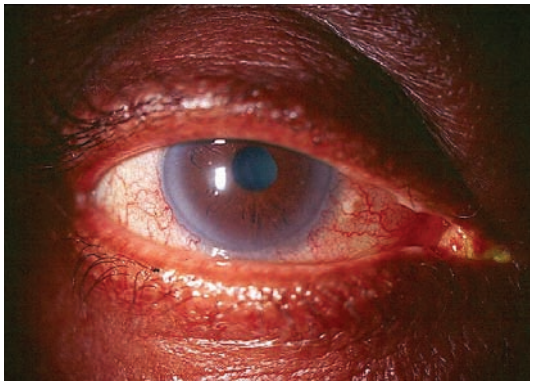
DRY EYE SYNDROME

Signs and Symptoms

Dry eye syndrome may occur in a wide range of individuals, although it is more frequently seen in women and older adults (i.e., those 50 years of age and above).[1-7] A higher incidence has also been noted in those with connective tissue disorders (e.g., rheumatoid arthritis, Sjögren's syndrome), diabetes mellitus, HIV infection and numerous other systemic conditions.[1,8,9] Patients with dry eye commonly present with complaints of ocular irritation or discomfort. As the name implies, dryness is the most frequently cited problem; patients may further report itching, burning, or a "sandy/gritty" foreign body sensation. Symptoms may be exacerbated by poor air quality, low humidity or extreme heat and tend to be more prominent later in the

day.[10] Occasionally, patients will report excess lacrimation, or epiphora, in association with the discomfort, a condition known as paradoxical tearing.

Upon gross inspection, the majority of dry eye patients demonstrate a relatively white and quiet eye. However, key slit lamp findings may include a meager tear meniscus at the lower lid, as well as a reduced tear film break-up time (TFBUT) of 10 seconds or less. Sodium fluorescein staining may be evident as punctate epithelial keratopathy from the interpalpebral region to the lower third of the cornea. In more severe cases, rose bengal or lissamine green staining of the cornea and/or conjunctiva may be seen in the same area. Filaments, which are tags composed of mucus, epithelial cells and tear debris, may also stain with these vital dyes.



Severe dry eye syndrome.

Additional clinical tests for dry eye syndrome are quite numerous. Tear volume assessment is used quite commonly, and may be ascertained by use of Schirmer tear test strips (5mm x 35mm strips of Whatman #41 or other unbonded, porous paper) or the Zone-Quick test (70mm strands of yellow cotton thread impregnated with phenolsulfonphthalein or "phenol red" dye, a pH indicator). Diminished wetting of these test media over a set period of time (five minutes for the Schirmer and 15 seconds for the Zone-Quick test) is indicative of tear volume deficiency and dry eye syndrome. Additional diagnostic methodologies for dry eye include tear film osmolarity, lysozyme analysis, lactoferrin assay, lipocalin assay, impression cytology and tear ferning; however, these tests have seen their greatest utilization within the research community, being too complex, expensive or time consuming for practical clinical use.[11]

Dry eye also commonly occurs secondary to meibomian gland dysfunction (MGD), so another vital aspect of examination includes assessment of the lid margin and meibomian glands. In these cases, the clinician may notice lid erythema, madarosis (loss of lashes), trichiasis (inward turning of the lashes), and meibomian gland inspissation (plugging). Foamy, frothy tears are one of the earliest signs of meibomian gland dysfunction, representing saponification of tear film lipids. Digital expression of the meibomian glands may demonstrate thickened, turbid and/or diminished oil secretion.

Pathophysiology

Dry eye syndrome has traditionally been viewed as a quantitative or qualitative reduction of the tear film, with a multitude of etiologies and contributory factors. The condition tends to be categorized as either "aqueous deficient" or "evaporative," based upon a comprehensive classification scheme that was developed in 1995, and later reiterated in 2007.[1,12] Those conditions that contribute to diminished tear production, such as Sjögren's syndrome or acquired lacrimal gland disease, constitute the aqueous deficient variety. Conditions involving meibomian oil deficiency, poor lid congruity and altered blink dynamics or other surface disorders (e.g., ocular allergy) comprise the evaporative category. Additional contributory factors may include contact lenses, low environmental humidity and a number of medications.[12]

Over the last 15 years, a great deal of research has been conducted in the area of dry eye and ocular surface disease, yielding new information and concepts regarding the pathophysiology of this disease process. Much of this research was summarized in the recent report of the International Dry Eye Workshop (DEWS).[1,10,11,15-17] DEWS represents the most current and complete consensus regarding dry eye. According to the DEWS report, "Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface."[10] The report further suggests that dry eye, while having numerous contributory and etiologic factors, is ultimately the result of "core mechanisms," which can initiate, amplify and potentially change the character of dry eye over time. These are tear hyperosmolarity and tear film instability.[10]

Osmolarity refers to the concentration of particles in the tear film; it is akin to the concept of salinity when referring to the concentration of salt in a sample of seawater. In a dry eye state, the tear film becomes hyperosmotic as a result of diminished aqueous tear flow, excessive evaporation, or a combination of these events. Hyperosmolarity (more particles per sample) stimulates a cascade of inflammatory events, resulting in the production of inflammatory cytokines (e.g., interleukin-1a,

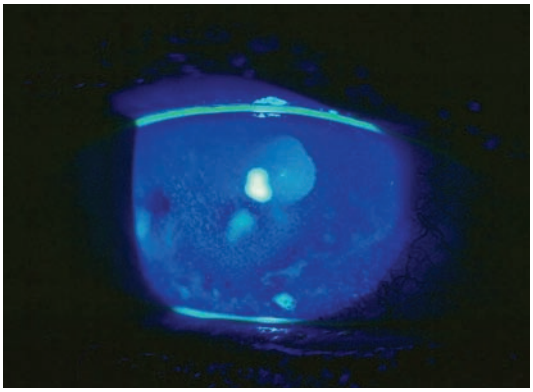
interleukin-1b, tumor necrosis factor alpha) and matrix metalloproteinases, which in turn activate inflammatory cells at the ocular surface.[14,18,19] These inflammatory events lead to apoptotic death of surface epithelial cells and goblet cells.[20] Other factors, such as autoimmune targeting of the ocular surface and noxious environmental stimuli, can amplify these initiating inflammatory events.

Tear film instability may also initiate a dry eye state in the absence of or preceding tear hyperosmolarity. Tear instability results from local deficiencies which causes the tear film to break up too rapidly, thereby minimizing the protective effect to the ocular surface; usually this is described as a TFBUT that is less than the blink interval.[21] This phenomenon induces local drying of the exposed surface, which can result in surface epithelial damage and disturbance of the glycocalyx and goblet cell mucins.[10] Like osmolarity, tear instability can be spurred by a host of factors, including allergic eye disease, chronic use of preserved topical medications (particularly those with benzalkonium chloride) and contact lens wear.[22-24]

Management

Historically, management of dry eye syndrome has been aimed at replenishing the eyes' moisture and/or delaying evaporation of the patient's natural tears. The first line of defense typically involves the use of ophthalmic lubricants or "artificial tears." The purpose of these agents is to alleviate symptoms and, in some cases, to promote healing of the ocular surface and corneal epithelium. A great deal of diversity exists within this market, and practitioners should familiarize themselves with the various options as well as their respective active and inactive ingredients.

In theory, artificial tears may be used as often as necessary. When beginning therapy however, lubricants should be dosed more frequently and regularly; later, this therapy can be tapered based upon patient response and compliance. Highly symptomatic patients may benefit from products that demonstrate enhanced ocular surface residence time, such as Systane Ultra (Alcon Laboratories), which provide relief with less frequent instillation. Solutions have a distinct advantage over ointments, as they tend to induce less visual impairment. In addition, experts recommend that patients with more advanced diseases employ non-preserved artificial tear products, to avoid any potential for toxicity.[16,25]



Sodium fluorescein in dry eye: note areas of negative staining, mucus filaments and diffuse epitheliopathy.

Patients who do not respond to tear rehabilitative/lubrication therapy alone may require treatment with topical immunomodulatory agents, such as Restasis (0.05% cyclosporine A ophthalmic emulsion, Allergan) or topical steroids. Cyclosporine works by suppressing T-cells and inhibiting their activation, while downregulating T-cell mediated cytokine production.[26] In clinical trials, Restasis was shown to ameliorate symptoms in up to 44% of patients and improve basal tear production (as demonstrated by Schirmer testing) in up to 59% of patients after six months of therapy.[27] The use of topical corticosteroids (e.g., 0.5% loteprednol etabonate q.i.d. for two to four weeks) in conjunction with Restasis therapy may hasten recovery and further diminish symptoms associated with dry eye.[16,25,28] Long-term use of topical steroids is not recommended however, due to the potential for cataractogenesis and ocular hypertension.

Oral medications and nutritional supplements are another potential therapy for patients with dry eye syndrome secondary to meibomian gland disease. The use of oral tetracycline therapy (e.g., doxycycline 50mg -100mg daily for six to 12 weeks) may be beneficial in patients who fail to improve with lubricating drops and lid hygiene. Tetracyclines demonstrate a host of anti-inflammatory effects, which have proven beneficial in those with various forms of blepharitis.[29,30] Omega-3 fatty acid supplements may provide similar benefits in restoring meibomian gland function and tear stability, though the body of evidence for such therapy is still emerging.[31]

Oral secretagogues are sometimes used to manage advanced cases of aqueous deficient dry eye, such as those encountered in Sjögren's syndrome. Salagen (pilocarpine HCl 5mg, MGI Pharma) and Evoxac (cevimeline HCl 30mg, SnowBrand Pharmaceuticals) are muscarinic agonists, which stimulate non-selective secretion from exocrine glands via autonomic pathways, resulting in enhanced tear production.[32,33] It should be noted that these agents are specifically indicated for xerostomia (dry mouth) associated with Sjögren's syndrome or certain

forms of cancer, and their use in dry eye is considered off-label. Also, because of the potential for a multitude of systemic side-effects, it is recommended that these agents only be employed after consultation with an experienced rheumatologist.

Occlusion of nasolacrimal outflow with punctal or intracanalicular plugs offers a different management strategy for dry eye: preventing drainage of the tear film and maximizing contact duration with the ocular surface. While the theory is sound, a significant percentage of plugs may be spontaneously expelled, and it has been observed that many patients notice a subjective decrease in improvement of symptoms with plugs over time.[34-36] Some individuals have actually cautioned against occlusion therapy in many cases, citing the potential inflammatory aspects of dry eye; they suggest that the use of punctal plugs may create a "cesspool" of cytokines and promote, rather than alleviate, damage to the ocular surface.[25] This is why experts highly recommend that any inflammatory aspects related to dry eye be addressed prior to the insertion of punctal plugs.[10,25]

The most severe forms of dry eye may require more radical forms of therapy; some options include topical acetylcysteine, punctal cautery, systemic anti-inflammatory therapies, bandage contact lenses, oral cyclosporine, moisture goggles, or surgery.[25] Patients at this level of severity are probably best referred to an experienced, board-certified corneal specialist.

Clinical Pearls

• The symptoms of dry eye syndrome tend to be quite variable. Often, patients seem to be more symptomatic than their clinical signs would indicate. Astute clinicians realize that the diagnosis of dry eye is more often based on subjective complaints than on ocular inspection.

• Many common systemic drugs can transiently decrease lacrimal secretions, creating or exacerbating a dry eye state. These may include antihistamines, oral contraceptives, beta-blockers, diuretics, phenothiazine antianxiety preparations and atropine derivatives. As part of the management for dry eye patients, a thorough medication history–including both prescriptive and over-the-counter agents–is mandatory.

• Likewise, numerous systemic conditions can be associated with dry eye. Beyond directed ocular treatment, it is essential that clinicians obtain a detailed medical history on patients with dry eye to determine if there is any underlying or undiagnosed disease. Conditions to consider include connective tissue disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome), diabetes mellitus, HIV infection, sarcoidosis, thyroid disease and hepatitis C.[1]

• Before initiating any form of therapy, practitioner and patient alike must understand one basic tenet of dry eye management: namely, that this is a CHRONIC disease, marked by exacerbations and remissions. The only way for patients to achieve control of their symptoms and discomfort is through active participation in the prescribed treatment regimen and periodic reevaluation. There is no "magic bullet" cure, and appropriate care requires patience, perseverance and a willingness to try new (and sometimes unconventional) options. Strong consideration must be made for the improvement of lid hygiene through scrubs or other methods to reduce the impact of poor meibomian secretions in the development of dry eye.

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THYGESON'S SUPERFICIAL PUNCTATE KERATOPATHY

Signs and Symptoms

Thygeson's superficial punctate keratopathy (TSPK) is a bilateral, epithelial keratitis of unknown etiology, first described by Phillips Thygeson in 1950.[1] It is characterized by an insidious onset of corneal inflammation with a long duration of exacerbations and remissions. The clinical presentation is characterized by recurrent episodes of photophobia, tearing, ocular burning and foreign body sensation, typically in both eyes.[1,2] Physical examination reveals whitish fine granular "asterisk-shaped" or "dendriform" intraepithelial opacities, sometimes creating an elevation of the overlying corneal epithelium. Characteristically, no conjunctival inflammation is associated with the keratitis, and the eye is otherwise white and quiet.

Most lesions are central; however, peripheral lesions do occur and may be associated with delicate, peripheral vascularization in chronic cases. Fine filaments also may be associated with the keratitis.[1-3] The disease may persist from one month to decades, with an average episodic duration of eight years or longer.[4] Visual acuity may be decreased by the subepithelial opacities, but generally it returns to normal following resolution of the keratitis.[3] Corneal sensation is usually normal, but the physiologic climate for mild hypoesthesia exists.[5]

The onset of TSPK is most common in the second and third decades with an age range of 2.5 to 70 years.[5] No clear sexual predilection exists, although a female preponderance has been suggested.[1-5] Recurrence has been associated with corneal surgical procedures.[7,8]

Pathophysiology

Classically, there are five characteristic features of TSPK: chronic, bilateral punctate inflammation; long duration with remissions and exacerbations; healing without significant scarring; absent clinical response to topical antibiotics and striking symptomatic response to topical corticosteroids.[3]

No established cause for the disease is known; however, allergic, viral and toxic mechanisms that interrupt the keratinization process (tissue drying) have been proposed.[6,9] The clinical manifestations of TSPK resemble a combination of findings that meld the signs of viral keratitis with the reaction that is observed following an exposure to a noxious agent. [2,3,6,10] The TSPK lesions seem to possess the ability to gain access to the deeper corneal epithelial layers.[2,3,6,10] An altered immune response to an unknown exogenous or endogenous antigen may explain the characteristic exacerbations and remissions of the disease.[8,10,11] In some patients, an increase in HLA-Dw3 and HLA-DR3 expression, both of which are HLA loci associated with immune response genes, has been detected.[11,12]

Recently, researchers were able to determine that the number of Langerhans cells (antigen-presenting cells) in the cornea, normally located in the peripheral cornea and to a lesser extent, the central regions of the healthy cornea, were greatly increased within the basal cell layer of the corneal epithelium and within Bowman's layer of affected eyes.[12] Most of the corneal abnormalities in the eyes affected by TSPK are confined to the basal cell layer of the corneal epithelium, the subepithelial nerve plexus, Bowman's membrane and the anterior stroma.[13] The middle and deep regions of the stroma, Descemet's membrane and endothelial cells are spared from pathological changes.[13]

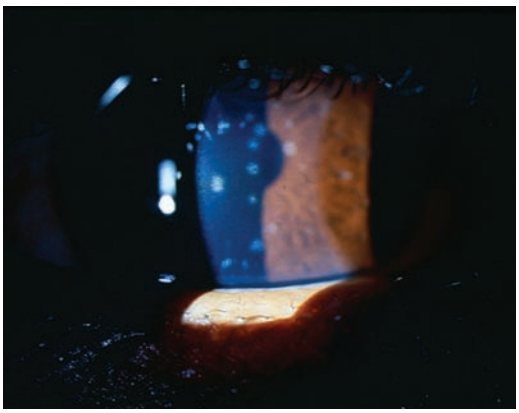
Corneal scrapings of the lesions demonstrate nonspecific findings, which include atypical and degenerated epithelial cells and a mild mononuclear and polymorphonuclear cell infiltrate.[13] Focal cell destruction without the cell-to-cell pattern, typical of herpes simplex keratitis, has been reported. However, the presence of

specific viral particles has not been documented.[13]

Management

The diagnosis of TSPK is generally made from the clinical history and biomicroscopic examination. It is confirmed by the unusually rapid and successful response to topical corticosteroids.[1-3,6,11] Topical corticosteroids decrease the signs and symptoms of TSPK and are most effective during acute exacerbations.[3,11] A rapid taper of the dose to maintain control of the symptoms is recommended.[3] Some evidence suggests that the course of the disease may be prolonged with the chronic use of corticosteroids. Such use should be avoided, especially given the well-documented complications of long-term topical corticosteroid therapy. A recent report outlining the efficacy of topical 2% cyclosporine in the treatment of TSPK may provide direction toward an equally effective treatment associated with fewer side effects.[3,15]

Published evidence suggests that topical 2% cyclosporine A (CsA) placed into in an olive oil vehicle may be an effective and safe topical treatment for Thygeson's superficial punctate keratitis when topical steroids fail or when topical steroidal therapy has the potential to induce high risk complications secondary to long-term use.[14] It is not clear if the commercially available concentrations of cyclosporine (0.05%) is effective in this condition, but an off-label trial would not be unwarranted in cases where steroids are ill-advised. Considering the chronicity of Thygeson's superficial punctate keratitis, CsA alone or in combination with other topical treatments, may offer an advantage and synergy for cases requiring chronic long-term intervention.[15] In a classic paper published in 1984, researchers experimented with the topical antiviral compound trifluridine in unresponsive cases of TSPK.[16] In five of the six trifluridine-treated-eyes, a favorable response was elicited. Symptoms and signs of the disease disappeared, but more slowly than in cases treated with topical corticosteroids.[16] One patient with an 11-year history of topical corticosteroid dependence for clearing TSPK was treated successfully with trifluridine, with his eyes remaining clear for over one year without any therapy once the course was finished.[16] Mild irritation and transient limbal follicle formation are recognized side effects.[16]



Stellate lesions in Thygeson's SPK.

Therapeutic bandage contact lenses, extended wear contact lenses and patching have been used to improve visual acuity, as well as to reduce the irritative symptoms in suffering patients.[3,11,17] Scraping of the lesions is not effective and may stimulate scarring or recurrence.[7,8]

Most patients who have TSPK recover completely with no loss of visual acuity, although some patients may be left with faint subepithelial opacities.[3]

Clinical Pearls

• The granular epithelial findings of TSPK occasionally may be confused with other causes of epithelial keratitis. However, conjunctival inflammation is absent in TSPK.

• No specific systemic associations have been reported for this disease.

• Proper counseling regarding the exacerbations and remissions that occur with this disease can help patients understand what will be required with this sometimes frustrating and often bothersome clinical entity.

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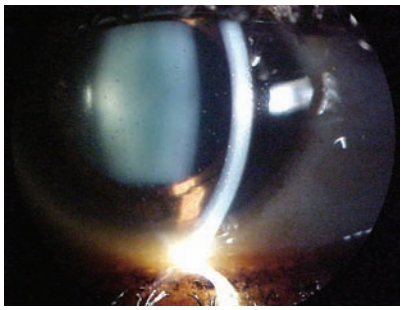
ANTERIOR UVEITIS

Signs and Symptoms

Uveitis is most commonly encountered in persons between 20 and 59 years of age.[1] Children and the elderly are rarely affected, except in cases of blunt ocular trauma. Anterior uveitis does not tend to favor either gender, nor is there any particular racial predilection. Patients with anterior uveitis typically present with a triad of pain, photophobia and hyperlacrimation. The pain is characteristically described as a deep, dull ache, which may extend to the surrounding orbit. Associated sensitivity to lights may be severe; often, these patients present wearing dark sunglasses. Excessive tearing results secondary to increased neural stimulation of the lacrimal gland, and is not associated with a foreign body sensation. In terms of visual acuity, there is variable impact. In the earliest stages of anterior uveitis, visual acuity is minimally compromised; however, as the condition persists over days to weeks, accumulation of cellular debris in the anterior chamber and along the corneal and lenticular surfaces may result in subjectively blurred vision. Accommodative tasks may be difficult or painful due to ciliary spasm. The patient with anterior uveitis may display a sluggish, fixed, and/or irregular pupil on the involved side. Ocular motility is generally intact. Gross observation may reveal a pseudoptosis, secondary to photophobia; there is not typically any notable lid edema.

Clinical inspection of patients with uveitis typically reveals a deep perilimbal injection of the conjunctiva and episclera, although the palpebral conjunctiva remains unaffected. The cornea displays mild stomal edema upon biomicroscopy, and in more severe or protracted reactions keratic precipitates may be noted on the endothelium. In non-granulomatous cases, these small, irregular gray to brown deposits with a predilection for the central or inferior cornea can be observed without large depositions ("mutton fat" keratic precipitate). The hallmark signs of non-granulomatous anterior uveitis are "cells and flare." Cells represent leukocytes (white blood cells) liberated from the iris vasculature in response to inflammation, observable and freely floating in the convection currents of the aqueous. Flare is the term used to describe liberated proteins from the inflamed iris or ciliary body. When present, flare gives the aqueous a particulate, or smoky, appearance. Iris findings may include adhesions to the lens capsule (posterior synechia) or, less commonly, to the peripheral cornea (peripheral anterior synechia—PAS). Synechiae are the cause of irregular and/or fixed pupils in cases of uveitis. Additionally, granulomatous nodules are sometimes seen at the pupillary border (Koeppe nodules) and within the iris stroma (Bussaca nodules) in cases of uveitis associated with systemic disease.[2,3]



Cells and flare—the classic anterior chamber signs of uveitis.

Intraocular pressure is often impacted in anterior uveitis, though it may be depressed, normal or elevated depending on the stage at which it is measured and the duration of the disease process. In early stages, IOP is characteristically reduced due to secretory hypotony of the inflamed ciliary body. However, as the reaction persists, inflammatory by-products may accumulate in the trabeculum, which can cause first, normalization, and later elevation of intraocular pressure. In severe cases, sustained IOP elevation signals the presence of uveitic glaucoma with increased potential for PAS.

Pathophysiology

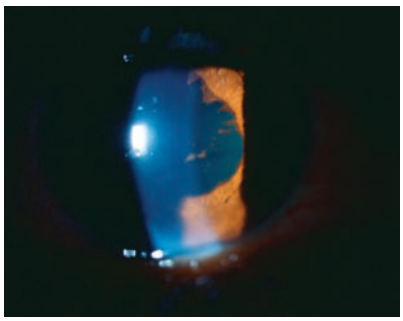
Uveitis should be thought of not as a singular ocular disorder, but rather as a diverse collection of pathological conditions with similar, clinically observable signs. A vast multitude of etiologies may induce uveitis, ranging from blunt trauma to widespread systemic infection (e.g., tuberculosis) to generalized ischemic disorders (e.g., giant cell arteritis).[4-6] Some other well-known systemic etiologies include ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, sarcoidosis, inflammatory bowel disease, multiple sclerosis, syphilis, Lyme disease, and histoplasmosis.[4-6] Of course, not all forms of uveitis are associated with systemic illness. Localized inflammations may occur as well, either by iatrogenic or idiopathic means. Some primary uveitic syndromes include Fuch's heterochromic iridocyclitis and Posner-Schlossman syndrome.

While the precise pathophysiology of anterior uveitis has not been entirely elucidated, we do have a basic understanding of the cascade of events involved during this inflammatory state. In the normal human eye, the anterior chamber remains free of cells and plasma proteins by virtue of the blood-aqueous barrier. The blood-aqueous barrier is comprised of tight junctions between the endothelial cells of the iris vasculature, and between the apico-lateral surfaces of the nonpigmented epithelium of the ciliary body.[7] In an inflammatory ocular state, cytokines mediate numerous tissue changes, among them vasodilation and increased vasopermeability.[8,9] When the uveal vessels dilate, exudation of plasma, white blood cells and proteins into the extravascular spaces (e.g., the anterior chamber) becomes possible. Small molecular weight proteins may cloud the ocular media, but have little impact otherwise; however, as larger molecular weight proteins like fibrinogen accumulate in the aqueous and/or vitreous, pathological sequelae follow. Fibrinogen is ultimately converted into fibrin, an insoluble protein involved in the blood clotting process. In the anterior chamber, fibrin acts as a glue, binding with cellular debris to form keratic precipitates; more importantly, fibrin facilitates the adhesion of adjacent ocular structures, forming synechiae. With synechiae come the risk of secondary glaucomas, particular angle closure with or without pupillary block. Additionally, chronic uveal inflamma-

tion results in an increased concentration of vasoproliferative mediators, promoting angiogenesis or neovascularization.[8,9] Neovascular changes in the iris and angle can further predispose an individual to secondary glaucoma.

Management

The primary goals in managing anterior uveitis are threefold: first, immobilize the iris and ciliary body to decrease the pain and prevent exacerbation of the condition; second, quell the inflammatory response to avert detrimental sequelae; and third, identify the underlying cause. Cycloplegia is a crucial step in achieving the first goal. This may be accomplished using a variety of topical medications. Depending upon the severity of the reaction, physicians may employ 5% homatropine t.i.d. to q.i.d., 0.25% scopolamine b.i.d. to q.i.d, or 1% atropine q.d. to t.i.d. Cyclopentolate is typically not potent enough to achieve adequate cycloplegia in the inflamed eye. Topical corticosteroids are used to address the inflammatory response. The "gold standard" for uveitis management has historically been 1% prednisolone acetate, though newer options such as 0.5% loteprednol etabonate (Lotemax, Bausch + Lomb) and difluprednate 0.05% (Durezol, Sirion) have shown equivalent utility.[10-12] Steroids should be administered in a commensurate fashion with the severity of the inflammatory response. In pronounced cases, dosing every 15 minutes may be appropriate; at minimum however, steroids should be instilled every three to four hours initially. When in doubt, it is usually better to overtreat than to undertreat. If posterior synechia is present, attempts should be made to break the adhesions using 1% atropine in conjunction with 10% phenylephrine, in office. Secondary elevations in IOP that are significant (i.e., >26mm Hg) may be addressed by using standard anti-glaucoma agents, such as 0.5% timolol b.i.d. or 0.1% brimonidine t.i.d. Pilocarpine should be avoided in uveitic glaucoma, as it will only serve to worsen the inflammatory response by mobilizing the uveal tissues and disrupting the blood-aqueous barrier. Likewise, most physicians tend to avoid topical prostaglandin analogs, after early reports that these IOP-lowering agents showed limited efficacy in the face of inflammation, and perhaps even exacerbated the uveitic response.[13] More recent studies suggest, however, that prostaglandin analogs are indeed both safe and effective in cases of uveitic glaucoma, with their principle disadvantage being length of time to adequate pharmacologic effect.[14,15]



Posterior synechiae in acute anterior uveitis.

After treatment is initiated, patients should be reevaluated every one to seven days, depending on the severity of the reaction. As resolution becomes evident, cycloplegics may be discontinued and topical steroids may be tapered to q.i.d. or t.i.d.. Generally, it is better to taper slowly rather than abruptly, and patients may need to remain on steroid drops daily or every other day for several weeks to ensure treatment success. Recalcitrant cases of anterior uveitis that are unresponsive to conventional therapy may necessitate the use of injectible periocular or intraocular depot steroids, oral corticosteroids (e.g., prednisone 0.5 to 1.0 mg/kg), oral nonsteroidal anti-inflammatory preparations or systemic immunosuppressants, such as cyclophosphamide, methotrexate, azathioprine, cyclosporine, tacrolimus, interferon or infliximab.[16-18] These systemic drugs should only be prescribed when the etiology is recognized by clinicians who are well-trained in their use and able to manage their side effects.

Medical testing is indicated in cases of bilateral uveitis (unrelated to trauma), granulomatous uveitis, or recurrent unilateral or bilateral uveitis—defined as three or more unexplained incidents. A medical workup is particularly relevant when the history or associated symptoms are suggestive of a particular etiology. Laboratory testing is not always productive, though the results may be helpful when considered in terms of the complete clinical picture. Some of the more common and important tests to consider include: complete blood count (CBC) with differential and platelets; erythrocyte sedimentation rate (ESR); antinuclear antibody (ANA); human leukocyte testing (HLA-B27); rheumatoid factor (RF); angiotensin-converting enzyme (ACE); purified protein derivative (PPD) with anergy panel; fluorescent treponemal antibody absorption (FTA-ABS) and rapid plasma reagin (RPR); and Lyme immunoassay (ELISA).[19] Imaging studies are also part of the medical workup, particularly when the clinical picture is suggestive of ankylosing spondylitis, tuberculosis or sarcoidosis. X-rays of the sacroiliac joint are useful in the diagnosis of ankylosing spondylitis, while a chest radiograph helps to identify tuberculosis and/or sarcoidosis infiltration into the pulmonary system.[19]

Clinical Pearls

- Most cases of acute anterior uveitis in the optometric setting are the result of blunt ocular trauma. These cases generally resolve without incident and do not recur when properly managed.
- A comprehensive, dilated fundus evaluation is mandatory in all cases of uveitis, and is particularly important when visual acuity is markedly diminished. Many cases of suspected anterior uveitis actually constitute collateral damage from intermediate or posterior uveitis. Such is the case with toxoplasmosis, for example, where the cells observed in the anterior chamber actually represent "spillover" from posterior segment inflammation.
- In cases of endogenous uveitis (i.e., those cases secondary to infectious or autoimmune disease), management may be difficult and lengthy. Indeed, patients with endogenous uveitis often require months of therapy, and some individuals may need to use topical corticosteroids

indefinitely to control the inflammation. Physicians who are uncomfortable with such long-term management are advised to refer patients to a specialist with experience in treating uveitis.

• While most eye care practitioners are capable of ordering laboratory tests for uveitis directly, it is often more productive to communicate with the patient's primary care physician before proceeding, such that all aspects of the systemic history may be taken into account. Should the patient be diagnosed with a contributory systemic disease, comanagement with the primary care physician becomes paramount.

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IRIDOCORNEAL ENDOTHELIAL SYNDROMES (ICE)

Signs and Symptoms

The patient with ICE syndrome is typically a younger female. It is most common in whites, with typically no family history of the disease. It is most commonly a unilateral phenomenon, but bilateral cases have been documented.[1,2] It tends to manifest in early to middle adulthood.[3] However, it has also been reported to develop in children.[4] Common findings include a beaten bronze appearance to the corneal endothelium with concurrent corneal edema, iris atrophy and iris hole formation, corectopia, prominent iris nevus, peripheral anterior synechia with progressive angle closure and secondary closed angle glaucoma. Vision may be unaffected or may be reduced due to endotheliopathy with or without resultant corneal edema or glaucoma. The patient may occasionally complain of monocular diplopia secondary to an exposed area of full thickness iris atrophy creating another entrance for light to enter the eye (polycoria).

Pathophysiology

The ICE syndromes represent a continuum of disease involving three distinct entities: essential iris atrophy, Chandler syndrome, and Cogan-Reese (iris nevus) syndrome. Essential iris atrophy is characterized by progressive iris atrophy and iris hole formation, corectopia, and marked peripheral anterior synechia. The iris and pupil are pulled in the direction of the peripheral anterior synechia. Chandler syndrome, the most common of the three, manifests greater corneal changes and edema, but fewer iris abnormalities. Cogan-Reese syndrome presents with iris atrophy, corneal endotheliopathy, corneal edema and prominent iris nevi. Patients with Chandler's syndrome typically have worse corneal edema than the other two entities, while its secondary glaucoma is more severe.[5]

All of the ICE syndromes share a common underlying pathophysiology and can all be considered to be primary proliferative endothelial degenerations.[6] Recent reports have additionally noted striking similarities between the ICE syndromes and posterior polymorphous dystrophy, suggesting that the conditions may be variants of the same disease process.[7,8] The corneal endothelium has a fine beaten-silver appearance. This, along with ensuing corneal edema, is a cause of vision reduction in these patients. The endothelium is most affected in essential iris atrophy. Some endothelial changes such as migration and reparative processes are identifiable, as is the presence of cell necrosis and chronic inflammation.[9] It appears that the endothelial cells undergo a metaplastic transformation into "epithelial-like" cells that migrate as a membrane over the anterior chamber angle to the iris.[9,10] Confocal biomicroscopy indicates that ICE syndromes are characterized by pleomorphic epithelioid-like endothelial cells with hyper-reflective nuclei.[11]

The migration of the abnormal corneal endothelial cell membrane across the anterior chamber angle and on to the anterior surface of the iris is responsible for corneal edema (due to subsequent dysfunction of the endothelial sodium-potassium pump responsible for corneal dehydration), secondary glaucoma, nevi, atrophy of the iris, and pupillary distortion. The contraction of the migrated membrane-like ICE tissue produces holes in the iris. Subsequent contraction of the membrane pulls the iris toward the cornea inducing a chronic progressive synechial closure of the angle. This results in secondary angle closure without pupil block. The cellular membrane may also cause aqueous outflow blockage in the absence of peripheral anterior synechia.[12,13]

Management

Management of ICE syndromes is case specific and should be dictated by the degree of corneal edema and severity of the secondary glaucoma. Topical aqueous suppressants are the medical mainstay for management of glaucoma secondary to ICE syndromes. Medications that increase aqueous outflow are typically less effective and are not the drugs of choice. Also, laser trabeculoplasty is not seen as

effective. In severe cases, trabeculectomy may be necessary, though there is a risk of closure of the sclerotomy site by the abnormal membranes with subsequent surgeries required.[14,15] Trabeculectomy with adjunctive antimetabolite or glaucoma surgical implant devices may be necessary for this reason.[16] Despite adequate IOP control, corneal edema may persist due to the endotheliopathy. In these cases, penetrating keratoplasty may be necessary to restore vision, though this procedure will not affect abnormalities in the iris or anterior chamber angle.[17] Favorable visual outcomes can be achieved through keratoplasty procedures for patients with ICE syndrome; however, multiple corneal and glaucoma procedures may be necessary.[18]

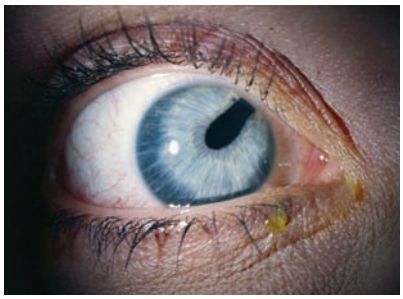
More recently, the trend has moved away from full thickness procedures, such as penetrating keratoplasty, toward selective removal and replacement only of the defective layers of the cornea. Deep lamellar endothelial keratoplasty (DLEK) has been seen as an efficacious surgical procedure in phakic eyes with ICE syndromes.[19] More commonly, Descemet's stripping with endothelial keratoplasty (DSEK) is being used to treat corneal edema associated with ICE syndrome.[20,21] Selective replacement of dysfunctional endothelium with DSEK has been seen to successfully treat corneal edema and associated visual loss caused by ICE syndrome. Visual recovery is much more rapid and rejection rates minimized compared with replacement of the full corneal thickness with traditional penetrating keratoplasty. However, separate procedures or medical therapy may still be required if patients suffer from glaucoma because these procedures do not address peripheral anterior synechiae formation and angle closure.

Clinical Pearls

• Essential iris atrophy, Chandler's syndrome and Cogan-Reese syndrome are all within the same clinical disease spectrum termed the ICE syndromes.

• Progression is unpredictable and many patients have a good outcome. Due to unilaterality, few patients become totally visually handicapped.

• The iris is dragged in the direction of the prominent peripheral anterior synechiae.



Correctopia and iris atrophy in essential iris atrophy.

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PHACOLYTIC GLAUCOMA

Signs and Symptoms

The patient with phacolytic glaucoma is typically elderly with a history of progressively worsening vision from preexisting cataracts. There appears to be no gender predilection with varying reports supporting contradictory findings in this regard.[1,2] Vision typically is reduced to light perception, but the patient may have no light perception either due to the presence of a hypermature cataract or an advanced, related glaucomatous process.[1] The patient will often be experiencing ocular pain. During the acute process, there will be anterior segment inflammation with an anterior chamber reaction. A hypermature lens is invariably present. The intumescence of the lens prevents observation of the fundus ophthalmoscopically. Intraocular pressure (IOP) may be quite elevated, often exceeding 50mm Hg to 70mm Hg.[1,2] The resultant glaucoma is typically unilateral or asymmetric, depending upon the degree of cataractogenesis. Synechiae, either anterior or posterior, is uncommon.

Pathophysiology

Upon cataract hypermaturation, the lens cortex undergoes spontaneous lysis and absorption with secondary lens nucleus shrinkage and capsule wrinkling.[3,4] This allows internal lens proteins to leak out through an intact though permeable lens capsule.[1] While the internal lens proteins are the host's own body tissue, they have never been exposed to the anterior chamber due to their envelopment by the lens capsule. Thus, when the body detects these internal lens proteins, it interprets them as foreign and antigenic. Subsequently, a lens-induced

inflammatory reaction ensues.[3] The chemotactic activity produced by the internal lens proteins contributes to the invasion of the anterior chamber by inflammatory cells in an antigen-antibody immune response.[4] There is a pronounced macrophage response occurring in the anterior chamber.[5] Numerous macrophages containing phagocytized degenerated lens material (phacolytic cells) can be found in the anterior chamber.

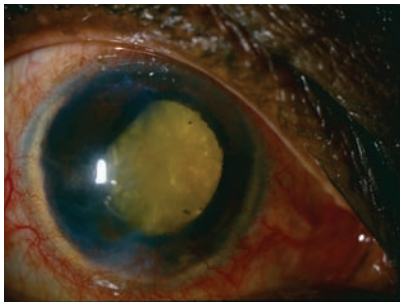
White patches consisting of aggregated macrophages may be seen on the lens surface and often indicate the site of lens protein leakage.[6,7] Other constituents of the anterior chamber in phacolysis have been demonstrated to include free floating degenerated lens material, erythrocytes, and ghost erythrocytes.[6] Lipofuscin granules and phagocytic vacuoles containing lens proteins have also been found.[5]

Additionally, extremely high levels of high molecular weight (HMW) soluble proteins of sufficient size to block trabecular aqueous outflow have been found in patients with phacolytic glaucoma. It has been demonstrated that HMW soluble proteins can directly obstruct aqueous outflow.[8,9] It may be that macrophages are scavenger cells that attempt to remove lens material and re-establish normal aqueous outflow.[8] Further, during the uveitic process, breakdown of the blood-ocular barrier occurs with subsequent influx of proteins as well as inflammatory cells. These constituents are considered to have a major impact on IOP elevation as well. Obstruction of the trabecular meshwork by inflammatory cells and proteins, as well as trabeculitis (inflammation of the trabecular meshwork), likely contribute to the secondary glaucoma.[10]

Management

The first step in the management of phacolytic glaucoma involves quieting the acute inflammatory reaction and ameliorating the elevated IOP.[11,12] Topical corticosteroids are indicated just as they would be for any anterior uveitis. Cycloplegics are also indicated. The choice should be dictated by the severity of the uveitic response and the patient's degree of discomfort. Typically, homatropine and scopolamine are adequate choices.[11,12] In many cases of phacolytic glaucoma, there may be loss of zonular support to the lens, often manifesting as phacodonesis. In cases where there is poor zonular support, cycloplegia with attendant pupil dilation may result in anterior dislocation of the lens, possibly into the anterior chamber. If poor zonular support to the lens is suspected, cycloplegia should be avoided.

The secondary glaucoma accompanying phacolysis is often improved by the reduction in inflammation with topical steroid therapy. However, if additional pressure reduction is necessary, aqueous suppressants are advocated, pending no systemic contraindications. Miotics should be avoided due to their propensity to aggravate the disease.[11,12]



Phacolytic lens.

In most cases, it is necessary to remove the antigenic lens in order to fully manage phacolytic glaucoma. Commonly, extracapsular and even intracapsular cataract extraction is used to remove the antigenic lens. Either anterior or posterior chamber intraocular lens implantation can be an option.[13] Manual small incision cataract surgery with trypan blue staining of the anterior capsule is a safe and effective method of cataract extraction for patients with phacolytic glaucoma.[14] In cases of long duration prior to surgery, trabeculectomy may additionally be needed in order to control IOP.[15] Removal of the antigenic lens and control of the glaucoma should be done quickly. One study found that patients over 60 years and in whom the glaucoma was present for more than five days had a significantly higher risk of poor visual outcome postoperatively.[16] The addition of trabeculectomy to cataract extraction is typically unnecessary in the control of IOP in patients with phacolytic glaucoma who are operated on within two to three weeks of the onset of symptoms. Light perception without projection is not a contraindication for cataract surgery in phacolytic glaucoma as postoperative visual recovery to some degree is possible.[17]

Phacolysis can be considered an innate evolutionary response to cataractogenesis. Prior to the advent of surgical lens removal, many individuals would become blind from cataract formation. The subsequent lytic process and inflammatory degradation would effectively remove the visual obstruction. Unfortunately, the eye would be left aphakic and often irreparably damaged from glaucoma. Spontaneous absorption of cataracts through the phacolytic process have been reported, which supports this evolutionary role of phacolysis.[18,19] It should be emphasized that while the cataract maturation process is typically quite slow, once a lens has become hypermature, the phacolytic process can develop quite rapidly.[7]

Clinical Pearls

- Phacolytic glaucoma develops only in eyes with hypermature cataracts. Vision typically ranges from counting fingers to light perception. If vision is better than 20/400, consider another cause for the glaucoma.
- Be careful to assess lens zonular integrity before employing a cycloplegic in the management of phacolytic glaucoma.
- The benefits of inflammation control in phacolytic glaucoma greatly outweigh the potential risks of steroid-induced pressure complications.
- Ultimately, phacolytic glaucoma is a surgically managed condition, though medical therapy may be initially employed to reduce inflammation and IOP.
- In eyes with phacolytic glaucoma that have no visual recovery potential, and pain and inflammation can be managed with topical corticosteroids, aqueous suppressants and cycloplegics, then lensectomy can potentially be deferred.

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PRIMARY CHRONIC ANGLE CLOSURE GLAUCOMA

Signs and Symptomst

The patient with primary chronic angle closure glaucoma (PCACG) typically is older and asymptomatic.[1] Women are more commonly affected than men. Hyperopia is commonly encountered. Patients of Asian descent are the most predisposed to PCACG, with Eskimos being the most represented group with this condition. White patients are affected to a lesser extent, and patients of African descent are affected even less.

Biomicroscopically, there will be a shallow anterior chamber and narrow angles by Van Herick estimation method. However, the chamber depth is typically deeper in PCACG than primary acute angle closure glaucoma. There will be characteristic glaucomatous damage to the optic disc and visual field. The distinguishing characteristic is the absence of visible anterior chamber angle structures upon the performance of gonioscopy. The angle may be appositionally closed and opened upon manual pressure on the four-miror goniolens or the angle may be synechially closed with broad areas of peripheral anterior synechia (PAS). The superior and temporal quadrants of the anterior angle may be the earliest sites of the synechial angle closure, gradual extension on the nasal quadrant, until the angle may close at the inferior quadrant.[2] Other features of PCACG include a smaller corneal diameter, shorter axial length, shallower anterior chamber, thicker lens, more relative anterior location of lens, swelling of ciliary process and anterior rotation of ciliary body.[3]

Pathophysiology

Anatomical features act in concert to cause shallowing of the anterior chamber. As a patient ages, thickening of the crystalline lens leads to a relative pupil block that exacerbates the condition. This acts to put the iris into apposition with the trabecular meshwork or cornea. In the absence of secondary causes, this is considered to be a primary angle closure. Due to the fact that the closure is slow, there is an absence of symptoms that would typify an acute angle closure. Thus, patients are unaware of the process.[4] Chronic angle closure denotes an angle with areas that are closed permanently with PAS. In angles that have closure without the formation of PAS, the term chronic appositional closure is often used. However, appositional closure often will lead to PAS if untreated. In chronic angle closure, the intraocular pressure (IOP) may be initially low and elevates asymptomatically as more of the angle becomes compromised. Peripheral anterior synechia may occur after acute or subacute attacks of angle closure.

While in most cases, there is asymmetric closure involving, first, the superior angle, there can also be an even circumferential process that slowly progresses to symmetrical closure. This has been termed creeping angle closure and appears as an angle that becomes progressively more shallow over time.[5]

Management

All cases of primary angle closure resulting from pupil block need to undergo laser peripheral iridotomy (LPI) as soon as possible after diagnosis. This allows a communication for aqueous to flow from the posterior chamber to the anterior chamber bypassing any pupil block that may be present. This can allow for the backward relaxation of the iris and a deepening of the chamber and opening of the angle. This is a safe method to open the angle following chronic closure.[6,7] However, while LPI can alter the anatomic status of the angle, a significant number of these patients manifest residual angle closure after LPI.[6] Additionally, there often will be elevated IOP despite a laser-induced open anterior chamber angle.[8] This is most likely due to damage to the trabecular meshwork from appositional and synechial closure. In PCACG eyes, the trabecular architecture has lost its regular arrangement, with fewer and narrower trabecular spaces and fusion of the trabecular beams in areas. In addition, there is evidence of loss of endothelial cells and reactive repair processes.[9] Despite the presence of a patent LPI, most eyes with PCACG present with elevated IOP, optic disc and visual field damage, indicating they require further treatment to control IOP, including trabeculectomy and medical therapy.[10]

Medical therapy that has been seen to be successful in ameliorating the IOP in eyes with PCACG include beta blockers, miotics, alpha-2 adrenergic agonists, and prostaglandins.[11,12] However, in recent years, it has come to light that prostaglandin analogs seem to work especially well in eyes with PCACG that need IOP

reduction both before and after LPI.[13-16] These medications are thought to lower IOP by increasing matrix metalloproteinase activity, which subsequently reduces the amount of extracellular matrix material surrounding the ciliary muscle fiber bundles.[17] Once-daily dosing of any of the commercially available prostaglandin analogs (travoprost, bimatoprost, latanoprost) reduces IOP in eyes with PCACG that have residually elevated IOP following LPI. The degree of pressure lowering seems to be similar to that seen in primary open angle glaucoma.

While the method of IOP reduction from prostaglandin analogs is enhanced uveoscleral outflow, it seems contradictory that these medications would have an effect in eyes where the uveoscleral meshwork is physically blocked by the iris. However, Aung and associates noted that the IOP-reducing efficacy of latanoprost was not affected by the degree of angle narrowing or extent of synechial angle closure.[18] More interestingly, in a study of 14 eyes with PCACG and ultrasound-biomicroscopically-proven-total-occlusion of the angle by 360 degrees secondary to PAS with no visible ciliary body face, once-daily dosing with latanoprost achieved a significant reduction in IOP.[18] Clearly, the mechanism of action of prostaglandin analogs in eyes with complete angle closure is not completely understood. Possibly, uveoscleral tissues other than the ciliary muscle are targeted or these agents reach the uveoscleral meshwork by way of the peripheral iris.[19]

Argon laser iridoplasty has been seen as another option for the management of PCACG as it can affect the shape of the peripheral iris and prevent this condition from deteriorating.[20,21]

In that the crystalline lens can contribute to the development of PCACG, lensectomy remains a viable option for some eyes. Phacoemulsification and intraocular lens implantation can lower IOP, reduce or remove the critical anatomical characteristics that produce pupillary block, and subsequently increase angle width.[22] It has been demonstrated in eyes with PCACG and co-existing cataract that phacoemulsification cataract extraction alone can significantly reduce both IOP and the requirement for topical therapy.[23,24] It has been suggested that phacoemulsification may be a primary treatment for eyes with PCACG. In PCACG medically controlled with coexistent cataract, there appears to be no difference in IOP control with cataract extraction by phacoemulsification alone versus the combined procedure phacotrabeculectomy.[25] However, in eyes where preoperative IOP control with medications is not acceptable, then a combined procedure with phacotrabeculectomy is superior in restoring vision and postoperatively controlling IOP than phacoemulsification alone.[26] In another study, it was recommended that for an angle closed 180 degrees continually or more, that phacotrabeculectomy be employed while phacoemulsification alone was sufficient for angles closed less than 180 degrees.[27]

Clinical Pearls

• After the anterior chamber angle has been successfully opened by LPI, the IOP may still be elevated. Many will erroneously think that the patient has now developed primary open angle glaucoma. In actuality, the trabecular meshwork has been damaged by the chronic appositional closure. This situation is like the trabecular dysfunction seen in angle recession glaucoma.

• Gonioscopy must be done on all open angle glaucoma patients at least annually to ascertain that the patient is not developing a concurrent angle closure mechanism.

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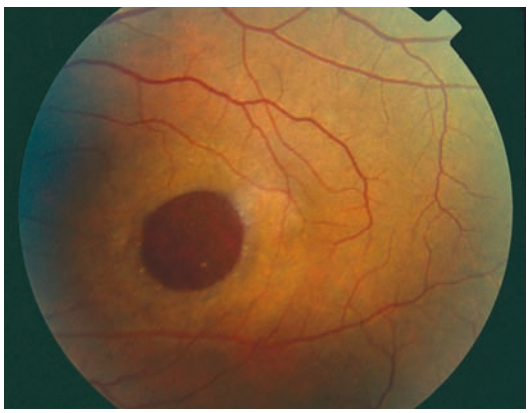
MACULAR HOLE

Signs and Symptoms

Macular holes may range from the incipient stages where the chief presenting sign is a macular cyst with serous foveal detachment, resulting in only minor visual disturbances, to full thickness lesions with catastrophic endpoints.[1-6] While the epidemiology of macular holes may vary depending on the diversity of the population, as a rule, some characteristics are universally accepted: macular holes occur more frequently in women over the age of 65, occur more frequently in women than men at all ages and are typically unilateral with an incidence of bilaterality in less than 29% of cases.[1,7-17] Visual symptoms vary depending upon the hole's staging and severity, ranging from normal vision function (20/20) without symptoms to mild metamorphopsia to visual loss correlating to the size, location and injury to the macular tissue (20/400).[1-28]



Fibrotic traction causing full thickness macular hole.

The prevalence of macular holes is 3.3 per 1,000 persons.[5,12,16] Other associated causes of macular hole include trauma, solar retinopathy, degenerative/pathologic myopia, and intravitreal triamcinolone used in the management of other vitreoretinal events.[10,11,29,30] The majority of macular holes are idiopathic in nature, and this is especially true in older patients (6th-7th decade of life).[1,9,13-18]

Macular microholes are small lamellar defects in the outer retina or retinal pigment epithelium that occur through mechanisms which include spontaneous vitreoretinal interface changes, trauma, phototoxicity as well as through mechanisms that are not well defined or understood.[31] They rarely induce symptoms and are recognized as a condition that is non-progressive, occurring in patients of all ages, with a stable and good visual prognosis.[31] A classic, full-thickness macular hole appears as a symmetric, round, red lesion with a definable border secondary to the lifted and displaced foveal retinal tissue. The increased red coloration is derived from the unobstructed visualization of the rich choroidal blood supply of the choriocapillaris without interference from the retinal structures.

Pathophysiology

Macular holes may be induced secondary to idiopathic factors, partial macular tissue avulsion secondary to posterior vitreous detachment or tractional forces produced by epiretinal membrane formation.[1-8] Chronic cystoid macular edema, choroidal vascular insufficiency and anteroposterior vitreoretinal traction (which is different than tangential traction) have all been implicated as provoking elements in macular hole formation.[1,2,10,13,15,31]

New ultrastructural evidence from flat-mounted, post-mortem preparations have revealed that some macular holes are caused, at least in part, by forces delivered through the insertion of the cortical vitreous into the foveal internal limiting membrane.[32] It appears that vitreous collagen fibers exert traction on the vitreofoveal region, resulting in decompensation of the tissue leading to foveal tearing.[32,33] This is the characteristically reported tangential traction.[2,9,10,11,14,32,33] Vitreo-papillary adhesion increases the risk of full-thickness macular hole formation. When present in the form of macular pucker (sometimes called cellophane maculopathy, epiretinal membrane or vitreoretinal interface maculopathy), vitreo-papapillary adhesion is associated with intraretinal cysts that have the ability to exert vectors of force at the vitreo-retinal interface, inducing both full thickness macular holes and macular cysts.[33]

In his classic publications, Gass devised the standard for classifying and characterizing macular holes, which has essentially been proven correct recently through optical coherence tomography.[2,9,10,14,34,35] He separated the progression of macular holes into four stages:

Stage 1 (macular cyst) is defined by a serous detachment of the fovea. In early stage 1 holes (stage 1-A) the concavity of the fovea is lost and a yellow spot representing increased visibility of the xanthophyll pigment appears in the center of the macular area. Later (stage 1-B), the pigment is displaced outward, towards the circumference of the impending hole causing it to appear ring-shaped.[2,9,10,13,14] This change in pigment appearance, from a spot to a ring is uniquely peculiar to macular hole development. In 50% of cases the process spontaneously aborts.[2]

Stage 2 (early macular hole) is defined by full-thickness retinal dehiscence. Biomicroscopically, it appears as an oval, crescent, or horseshoe shaped retinal defect on the inside edge of the xanthophyll ring. It can emerge as a central, round retinal defect surrounded by a rim of elevated retina with or without an overlying pre-foveal opacity. Secondary to centrifugal movement of retinal receptors, these macular holes may enlarge.[18] Up to 70% of stage 2 holes progress to stage 3.[10]

Stage 3 full thickness macular hole (FTMH) is defined by its size (400µm-600µm diameter hole), and is usually surrounded by a rim of elevated retina. The vitreous becomes separated from the fovea and a pre-foveal opacity, representing this separation, may or may not be visible. Posterior vitreous detach-

ment (PVD) is not present.[2,9]

Stage 4 macular holes are FTMH that demonstrate a detachment of the posterior vitreous.[2] A pseudo-operculum, if present, is usually found near the temporal border of Weis's ring (the free floating oval ring representing the previous site of attachment at the optic disc known as the area of Martigiani).[2]

Patients with stage 1 and 2 macular holes present with symptoms of decreased visual acuity/metamorphopsia.[10-12] Stage 3 usually finds visual acuity significantly more depressed. Acuities for eyes with FTMH range from 20/40 to 5/200 with an average of 20/200.[9] Central scotomas corresponding to the macular hole can be demonstrated using scanning laser ophthalmoscope microperimetry.[8,9]

Fluorescein angiography is usually normal with impending macular holes, stage 1a. Early hyperfluorescence has occasionally been reported in cases of late stage 1b lesions.[9,15] This phenomenon is thought to be secondary to absence of xanthophyll pigment.[9] Fluorescein angiography of stage 2-4 macular holes reveals an area of distinct early hyperfluorescence.[2,9,10,15]

Macular holes may coexist with other retinal pathologies.[21] The presence of a macular hole with any subclinical retinal detachment increases the risk of hypotony and choroidal detachment especially when accompanied by other ocular pathologies, such as high myopia, aphakia, pseudophakia or rhegmatogenous retinal detachment in the presence of advancing age.[21] In this light, management of the macular hole may be required as a first step toward complete repair.[21]

Management

The prognosis for recent onset macular holes not complicated by additional concurrent macular or ocular pathologies or caused by trauma is good.[36,37] Fifty percent of stage 1 macular holes progress to stages 2 and 3.[8-10] Seventy percent of holes reaching stage 2 progress to stage 3.[10] If a patient develops a macular hole of any stage in one eye, there is up to 29% risk of macular hole developing in the fellow eye.[5] Risk factors for developing macular hole in the fellow eye include pigment epithelial defects and macular retinal thinning.[10] However, the presence of a PVD in the unaffected fellow eye lowers the risk to almost 0%.[10,22-24]

The current standard of treatment for early full-thickness macular holes is early intervention rather than observation.[1-3,36-38] Surgical procedures have been shown to decrease the incidence of hole enlargement and can result in improvement of visual acuity.[1-3]

Stage 1 holes should be observed for progression. Stage 2 holes should be treated promptly by a retinologist experienced in vitreomacular procedures. Current modalities include pars plana vitrectomy with gas tamponade using SF_6 (sulfahexafluoride) or C_3F8 (perfluoropropane) with subsequent 80%-90% face-down positioning.[36,37] Because the face-down positioning represents the most unpalatable portion of the reparative process to a significant portion of eligible candidates, new research has examined the benefits of vitrectomy with internal limiting membrane peeling along with expansive gas tamponade using minimal-to-no face-down positioning.[36,37] Data have demonstrated promise in selected cases for minimal face-down posturing with favorable anatomical and functional results.[36,37] Some researchers have experimented with optical coherence tomography (OCT) as a method for visualizing postoperative macular hole closure.[38] Consistent with new thinking, surgeons have been reevaluating the necessity of extensive face-down positioning, trying to establish guidelines for using the technology, as soon as the day after surgery, to determine when to stop this posturing for patients.[38]

The application of vital dyes to facilitate delicate removal of intraocular membranes during vitreoretinal surgery is another evolving practice.[39] Controversy still remains regarding toxicity and safety.[39] The dyes include Evans blue and light green for staining the internal limiting membrane with options for fast green and indigo carmine.[39] Bromophenol blue and Brilliant blue are newer agents with purported increased safety profiles.[39] The dyes currently in use for the procedure known as chromovitrectomy include triamcinolone acetonide for vitreous identification, indocyanine green, infracyanine green and Brilliant blue for internal limiting membrane identification and Trypan blue for epiretinal membrane identification.[39] These adjuncts enhance visualization of fragile microscopic structures, but they also increase the risk of toxicity.[39] As an alternative, autologous heparinized whole blood can be used to coat the internal limiting membrane to facilitate visibility during peeling.[40] Recent work in this area has demonstrated promise as a cost-effective and useful tool for assisting macular hole surgery with less risk of toxicity.[40]

The most recent development in macular surgery is the intraoperative use of a handheld spectral domain optical coherence tomographer (SD-OCT).[41] Here, imaging of macular tissues provides an efficient method for visualizing the macular pathology and related surrounding anatomy. The technology permits surgeons to confirm the existence of lesions, identify additional pathologies and probe the region for the boundaries and limits of macular diseases all while being in the setting of the action of repair.[41] It is recognized that some macular holes hold a poor prognosis for visual recovery.[42] Old macular holes (generally of greater than 1.5 years duration), large holes (greater than 400μm) and holes whose genesis is secondary to another retinal pathology are regarded as those which are least likely to have repairable function.[42]

Classic complications following macular hole surgery include cataract formation, RPE alterations, raised intraocular pressure, additional retinal breaks/detachment, macular hole enlargement, hole reopening, vascular occlusion,

chronic CME, choroidal neovascularization, visual field loss and endophthalmitis.[4,27,28]

Clinical Pearls

• Pars plana vitrectomy with gas tamponade followed by one or more weeks of face-down positioning almost always achieves anatomical hole closure. Functional improvement may not be complete even in the face of hole closure.

• Acuity improvement of two or more lines is almost always realized.

• Pars plana vitrectomy performed within two months of the onset of symptoms indicating hole formation allows for the best outcome.

• In general, surgical solutions are optimally investigated within two years of the discovery.

• Larger holes and those associated with concurrent retinal pathology indicate a poorer prognosis.

• In patients with older holes that would not be optimal for surgical revision, patient education and low vision rehabilitation offer potential assistance.

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BRANCH RETINAL VEIN OCCLUSION

Signs and Symptoms

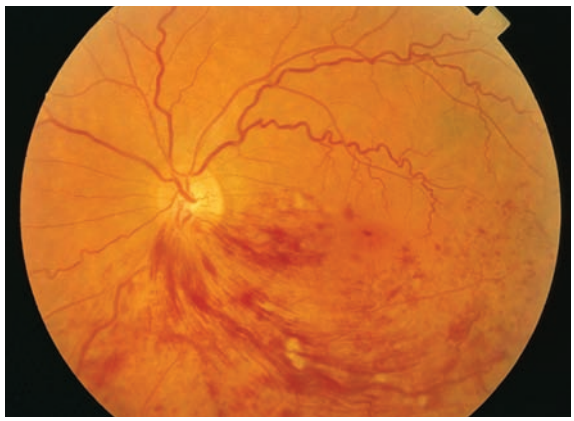
Branch retinal vein occlusion (BRVO) is a commonly encountered intraretinal vascular event.[1-3] Reports on retinal vasculopathy recognize its prevalence second only to diabetic retinopathy.[2,3] Patients who are symptomatic typically present with a chief complaint of painless blurry vision in one eye, although vein occlusion can occur bilaterally.[1-4] In some cases, BRVO may present asymptomatically and be found at a routine examination. Because the disease itself is often the result of the systemic and local genetic factors that induced the event, there is no gender predilection, there is no racial preference and there are no concrete epidemiologic data as that information is subcategorized to the specific diseases that increase its risk.[5]

Branch retinal vein occlusions are categorized as those that permit vascular perfusion (non-ischemic, or perfused) and those that produce vascular stasis, limiting blood circulation (ischemic, or non-perfused). Patients who present

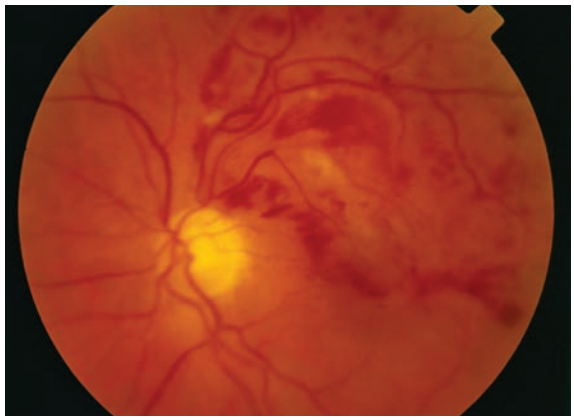
with large, ischemic BRVO may present with an afferent pupillary defect. Patients with ischemic branch retinal vein occlusions where the macula is infarcted have significantly reduced visual acuity with a poorer prognosis then their non-ischemic counterparts.[6] In contradistinction, patients presenting with non-ischemic branch retinal vein occlusions may have minimal to no functional interruptions. In general, non-ischemic BRVO has a good prognosis.[1-6]

The retinal observations seen in BRVO include dilated, tortuous retinal veins, sectoral, flame-shaped intraretinal hemorrhages, variable local patches of retinal ischemia (cotton wool infarcts), intraretinal exudates, and variable retinal and macular edema.[3,6] The site of the occlusion can typically be observed at or just adjacent to the site of an arteriovenous crossing where retinal arteries and veins share a common adventitial sheath.[1] Here, an increased (broadened) retinal arteriolar reflex can be seen connoting ongoing general vascular arteriolar decompensation along with venous nicking, representing the mechanical forces applied by the overlying vessel.[3,7] Complications which can be observed following a branch retinal vein occlusion include variable retinal edema, macular edema, and, in the face of significant ischemia, capillary non-perfusion, retinal neovascularization, vitreous hemorrhage and tractional retinal detachment.[7]

Upwards of 50%-60% of eyes recover a final visual acuity of 20/40 or better without treatment.[8] The entity rarely occurs idiopathically; rather it is frequently associated with systemic coagulopathy, hyperviscosity, infection, inflammation, hypertension, diabetes mellitus, dyslipidemia, antiphospholipid antibody syndromes, cardiac and carotid etiologies.[1-9] Since most branch retinal vein occlusions resolve without sequelae, requiring no treatment, the most important initial step in formulating a management plan is to commit to discovering an underlying cause.[1-9]



Ischemic BRVO.



Non-ischemic BRVO.

Pathophysiology

The provoking mechanism of branch retinal vein occlusion is classically related to disorders of the blood tissue (blood dyscrasias) which incite platelet aggregation through coagulopathy syndromes and/or hyperviscosity syndromes, or by mechanical mechanisms (venous compression secondary to an overlying artery's expansion and hardening via atheromatous formation) which impedes venous drainage.[3,7] This causes the venous wall to be overcome by the forces of an abnormal volume within its lumen. As the walls of the vessel decompensate, deoxygenated venous blood gains access to the retina via the nerve fiber layer, where the large caliber retinal veins reside.[3,7] This produces an inflammatory and immunological reaction in the affected tissue.[1,6] The discontinuation of venous blood flow also interrupts the arterial blood flow; blocked venous egress leaves no direct pathway for the venous blood or arterial blood to proceed.[3-7] The overall flow in both systems becomes sluggish as the blood is forced through other anastomoses around the formed thrombus.[1-11] The deoxygenated blood introduced into retinal tissues—along with other chemokines, cytokines and cellular players—initiates tissue damage in preparation for repair.[1,5,6,-9] These active substances as well as the setting of an ischemic environment can provoke the release of vasoproliferative messengers known as vascular endothelial growth factors (VEGF).[12,13] This category of substances stimulates new vessel growth by inducing neovascular "budding" off of existing arterial tissues. These new vessels lack normal architecture, become "scaffolded" to the vitreous body and have the potential to cause pre-retinal or vitreous hemorrhage and tractional retinal detachment.[14] Additionally, VEGF is associated with breakdown of the blood-retinal barrier, which results in increased vascular permeability and fluid leakage and the resultant retinal and macular edema.

Because the pathophysiology of the event itself is painless, the symptomatology in these cases is typically visual. In the initial stages, this is the direct effect of the light being blocked from reaching the photoreceptors. In cases where chronic, inner-retinal ischemia develops, capillary occlusion can result secondary to failed vascular "push." Here increased hydrostatic (back) pressure in the vessels becomes transmitted to the capillary bed causing affected areas of the retina to become malnourished and hypoxic.

This creates an environment conducive to retinal cellular death and persistent edema, both deleterious to function.[7]

Management

All vein occlusion patients should be assessed both ocularly and systemically. While intraretinal neovascular formation is uncommon in cases involving non-ischemic BRVO, ischemic conversion over time is plausible, requiring the patient to be observed through complete resolution.[1] Systemic laboratory testing may include depending upon patient profile: blood pressure evaluation, complete blood count (CBC), fluorescent treponemal antibody absorption (FTA-Abs), rapid plasma reagin (RPR), lipid profile, antiphospholipid antibody titres, fasting blood sugar (FBS), homocysteine levels, protein S and protein C, lupus anticoagulant, electrocardiogram and carotid imaging.[11] Infectious and inflammatory diseases have also been reported as sources for branch vein occlusion. Testing for sarcoidosis, tuberculosis, rheumatoid arthritis and Lyme infection should be considered when vascular risks are absent and initial evaluation fails to elicit a cause.[15-17]

While rare with BRVO, clinicians should monitor intraocular pressure and iris and angle for neovascularization.[18] The retinal treatment for all forms of vein occlusion is aimed at minimizing the loss of acuity from macular edema and preventing neovascularization.[19-23] Clinical management for BRVO is guided by the classic works of The National Institutes of Health, National Eye Institute. These include the Branch Retinal Vein Occlusion Study (BRVOS) and The Standard Care versus Corticosteroid for Retinal Vein Occlusion (SCORE) studies.[21-23]

Results from the eight-year BRVOS demonstrated that prophylactic scatter argon laser photocoagulation would not prevent the development of neovascularization or vitreous hemorrhage in cases of BRVO, and that macular argon laser photocoagulation (grid or focal photocoagulation) could improve visual acuity in eyes with persistent macular edema following branch retinal vein occlusion where vision was 20/40 or worse following the resolution of the event.[21,22] Importantly, pan retinal laser photocoagulation was found to be of benefit once neovascularization was observed, significantly reducing the likelihood of vitreous hemorrhage by 30 %.[21] This modality of treatment remains the standard of care.

The SCORE study was designed to compare the effectiveness and safety between the standard care of BRVO (grid and focal laser photocoagulation) and intravitreal injection of triamcinolone (two different concentrations) for treating macular edema associated with both branch and central retinal vein occlusion (CRVO).[23] The results of this trial found that there was equal final outcome for improving visual acuity for the steroid groups compared to the standard care group in cases of BRVO.[22] However, rates of adverse events (particularly elevated intraocular pressure and cataract) were increased in the steroid group.[22] This study concluded that grid or focal photocoagulation should remain the standard of care for the treatment of macular edema secondary to BRVO.[23]

New treatment possibilities are being explored with anti-VEGF medications. A recently published report investigated 12-month follow-up results of intravitreal bevacizumab therapy for macular edema secondary to branch retinal vein occlusion.[24] With a mean number of injections at two, ranging from one to four, the study demonstrated a benefit for all patients, with younger patients having the best visual acuity improvement during and after the 12-month follow-up period.[24] Better pretreatment visual acuity was associated with better visual acuity at 12 months but with less overall improvement of the visual acuity.[24] This has opened the door for considering intravitreal bevacizumab alone or in combination with other accepted treatments as a long-term effective treatment for macular edema secondary to branch retinal vein occlusion.[24]

Clinical Pearls

- Optical coherence tomography (OCT) is an excellent adjunct to observation for diagnosing intraretinal edema and to monitor for resolution.
- While neovascularization of the iris, angle, and retina are rare, non-ischemic BRVO should be monitored every four to six weeks for the first four months to rule out late complications.
- While elevated intraocular pressure (IOP), especially in patients with undiagnosed or poorly controlled glaucoma, has been reported as a risk factor for developing central and hemiretinal venous occlusion, it seems to be less of a risk factor in the development BRVO.
- Variations of branch retinal vein occlusion include occlusion of smaller venous tributaries (twig vein occlusion), an occlusion of one side of a bifurcated central retinal vein (hemiretinal vein occlusion) and occlusion of the entire central retinal vein (central vein occlusion).
- The main condition to be evaluated in patients with BRVO is hypertension.

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CENTRAL RETINAL VEIN OCCLUSION

Signs and Symptoms

Patients experiencing central retinal vein occlusion (CRVO) are typically over the age of 50 having concurrent systemic diseases such as atherosclerosis, hyperlipidemia, diabetes and hypertension.[1-5] In regards to these commonly associated systemic conditions, diabetes has the least impact as a risk factor for CRVO.[2] However, those patients with concurrent diabetes tend to have more ischemic CRVO than non-diabetic patients.[6] Younger patients (under age 50, or 40 depending upon reports) tend to less often have the above-mentioned systemic associations. In younger patients with CRVO, there is a greater likelihood of encountering thrombophilic conditions and hypercoagulopathies from blood dyscrasias such as antiphospholipid antibody syndrome, hyperhomocysteinemia and low plasma folate.[7-15] Typically, CRVO is a unilateral phenomenon. Occasionally, patients will experience bilateral CRVO. This should be considered very suspect for underlying systemic disease, such as Waldenström's macroglobulinemia and chronic myeloid leukemia.[16-18]

Patients often will complain of a sudden painless loss of vision and/or visual field in the involved eye(s). The patient may also complain of a sudden onset of floating spots or flashing lights. Visual acuity may range from 20/20 to finger counting in ischemic cases. If vision loss is severe (a sign of an ischemic event), there often will be a relative afferent pupillary defect.[19-23]

Ophthalmoscopically, there will be retinal edema, superficial flame-shaped and deep blot hemorrhages, disc edema, cotton wool spots, and tortuous and dilated retinal veins encompassing all four retinal quadrants. The hemorrhaging in any case may be so severe that all features of the underlying retina are obscured. The presence of multiple cotton wool spots, poor visual acuity and relative afferent pupillary defect is highly indicative of retinal ischemia and capillary non-perfusion.[19-23] In ischemic cases, anterior and posterior segment neovascularization may occur later in the course of the disease. Neovascularization occurs more commonly on the iris and angle with attendant neovascular glaucoma (NVG) than it does on the retina and optic disc with subsequent tractional retinal detachement.[24]

Pathophysiology

The etiology of CRVO is a thrombotic obstruction of the central retinal vein as it constricts through the lamina cribrosa. This may involve abnormal blood flow or blood constituents, atherosclerosis, vessel anomalies, or a combination of these factors. Essentially, properties of blood and the vein itself act in concert to cause thrombus formation with subsequent impedance of venous blood flow from the retina.[1-4,14,25]

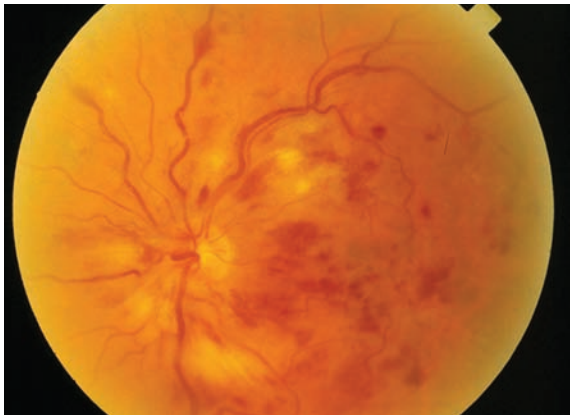
There are numerous ways that a thrombus forms within the central retinal vein. Blood flow combined with vessel wall abnormalities can stimulate vein thrombosis. Additionally, changes in blood constituents, such as hypercoagulability states, elevated viscosity and systemic states of decreased thrombolysis, promote thrombus formation. In that the central retinal artery and vein share a common adventitial sheath, compression of the vein by a sclerotic artery can cause turbulent blood flow causing thrombus formation at the lamina cribrosa, where the intraluminal pressure of the vein is lowest, rendering it susceptible to collapse. External factors, such as papilledema (causing increased pressure in the optic nerve sheath), may cause further compression and contribute to occlusion. Other entities that can induce compression of the vessel include: orbital tumor and abscesses, cavernous sinus thrombosis, and retrobulbar intranerve sheath injection, and optic disc drusen. Further, systemic diseases influence thrombus formation through external compression, primary thrombus formation through stasis, and degenerative or inflammatory disorders of the vein itself.[1-4,14,25]

Thrombotic occlusion of the central retinal vein impedes venous blood flow from the retina. This backup will result in leakage from the retinal capillary beds, accounting for the blood, retinal edema and disc congestion seen in this condition. The capillary beds may be irreversibly damaged by this process, resulting in perpetual non-perfusion of the retinal tissue. If a significant area of capillary non-perfusion is present, then the occlusion is considered ischemic.

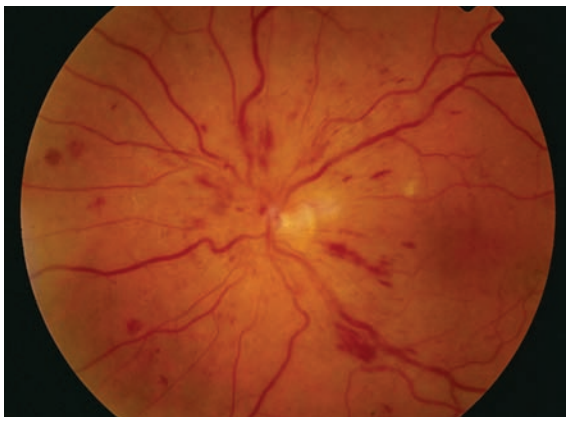
Loss of retinal capillary beds with subsequent retinal non-perfusion will lead to retinal hypoxia and the subse-

quent release of vascular endothelial growth factors (VEGF), which will then stimulate the proliferation of neovascularization from nearby viable capillary beds. In CRVO, the closest viable capillary network from which neovascularization will form is the posterior iris. This can lead to rubeosis irides, and neovascular glaucoma as the vessels move across the posterior and anterior iris into the angle.[24] Additionally, VEGF increases vascular permeability leading to increased retinal edema.[26]

In all cases of venous occlusion, the main cause of vision decrease is macular edema. However, if retinal capillary non-perfusion involves the perifoveal region, then vision is dramatically and irreversibly lost. The other main cause of severe, irreversible vision loss in CRVO is neovascular glaucoma.[24]



Ischemic CRVO.



Non-ischemic CRVO.

Management

When managing patients experiencing CRVO, it is important to consider the natural history of the disease as well as related systemic implications. Non-ischemic CRVO has a much better visual prognosis than does ischemic CRVO.[19,27] Typically, patients with good presenting visual acuity (>20/40) have the best visual prognosis and those eyes with initial acuity worse than 20/200 have the greatest likelihood of poor final acuity. The initial level of vision often correlates well with retinal non-perfusion and is a discriminator of ischemia. It must be noted that eyes with intermediate level acuity are often classified as "indeterminate" in regards to ischemia and have a guarded prognosis for final acuity. Indeed, many of these eyes (as well as eyes that are initially considered non-ischemic or perfused) convert to non-perfused, ischemic eyes with a subsequent propensity to develop NVG.[19,27]

Fluorescein angiography can provide information about retinal capillary perfusion and whether the occlusion is ischemic, and thus more likely to develop neovascular complications.[1,21] However, early in the course of the occlusion when the retina is extremely hemorrhagic, fluorescein details may be blocked.

It has been well documented that argon laser grid photocoagulation for macular edema in CRVO has no beneficial visual effect. Thus, this procedure is not indicated in management.[28] However, intravitreal injections of anti-VEGF drugs such as ranibizumab (Lucentis, Genentech) and bevacizumab (Avastin, Genentech) have proven effective in reducing macular edema and improving visual acuity in eyes with CRVO and vision loss occurring mainly from macular edema.[29,30] Indeed, these are popular treatments today, though there are few controlled studies guiding their usage.

Recently, the SCORE study compared the outcome of standard therapy for vision loss from macular edema in CRVO (in this case, observation without therapeutic intervention) to intravitreal injection of two doses (1mg and 4mg) of intravitreal injected triamcinolone. The conclusion of this study was that intravitreal triamcinolone was superior to observation for treating vision loss associated with macular edema secondary to CRVO and that the 1mg dose safety profile was superior to that of the 4mg dose.[31] Studies comparing intravitreal injected triamcinolone with intravitreal injections of bevacizumab have seen similar improvements with each treatment, though bevacizumab did not have the complicating factors of cataract and intraocular pressure (IOP) elevation as seen in the steroid group.[32,33] However, it should be noted that in the SCORE study, there was equal incidence of IOP elevation and cataractogenesis in both the 1mg triamcinolone group and the untreated observation group.[31]

It is well demonstrated that patients with ischemic CRVO developing anterior segment neovascularization and NVG benefit from pan-retinal photocoagulation to stimulate vessel regression. Eyes with ischemic CRVO do not benefit from prophylactic pan-retinal photocoagulation prior to the development of neovascularization.[34] This procedure should be withheld until the patient develops frank neovascularization of the iris, disc, or retina.[34] Recently, it has been shown that intravitreal injected bevacizumab dramatically regressed anterior segment neovascularization and assisted in the management of NVG associated with CRVO.[35,36] This treatment has become very popular in the management of NVG, both alone and in conjunction with pan-retinal photocoagulation.

In that CRVO is a perfusion imbal-

ance with significant congestion, this condition has been considered a compartment syndrome. Thus attempts have been made to reduce congestion and increase perfusion with an optic nerve decompression procedure known as radial optic neurotomy (RON). In this procedure, the nasal aspect of the optic disc in eyes with CRVO is surgically cut to reduce congestive pressure. There have been numerous reports demonstrating an improvement in visual function and a reduction in macular edema, but there have also been contradictory reports.[37-40] Due to the invasiveness and the advent of other successful intravitreal drugs, it is unclear if RON has any place in the contemporary management of CRVO.

The patient with CRVO should be monitored with serial ophthalmoscopy, fundus photography, and gonioscopy on a monthly basis until resolution is evident. The patient should be closely monitored for neovascularization of the disc, retina, iris and angle. If neovascularization develops, then pan-retinal photocoagulation is indicated. If the patient has unremitting macular edema, then referral for intravitreal injective therapy is indicated. Patients with poor initial acuity should be monitored more closely and will most likely need specialty consultation and tertiary treatment. Patients with good initial acuity should not be recommended for intravitreal injections without a period of observation as there is a chance for spontaneous improvement.

Due to the association of systemic disease with vein occlusions, the patient should be comanaged with an internist. There seems to be a relationship between CRVO, mortality and increased cardiovascular risk factors, such as smoking, diabetes and macrovascular disease. There is the possibility of an association between CRVO and stroke.[41] Older patients should be examined for ischemic vascular diseases, such as hypertension, diabetes, hyperlipidemia, and atherosclerosis while younger patients should be examined for thrombophilic and coagulation disorders, such as antiphospholipid antibody syndrome and hyperhomocysteinemia. There is not strong evidence to support an extensive work-up for thrombophilic and coagulation diseases for the vast majority of patients with CRVO. However, when tests for common cardiovascular risk factors for CRVO are negative, evaluation for potential coagulation disorders may be indicated. This is especially important for young patients, those with bilateral or recurrent CRVO, and those with a history of previous thromboses in other systems or a family history of thrombosis.[25]

Clinical Pearls

• The management of CRVO involves monitoring for resolution or late complications, laser intervention if neovascular complications develop, intravitreal therapy for non-remitting macular edema, and systemic comanagement with an internist.

• Ischemic CRVOs typically present with acuity worse than 20/200. Those eyes with initial acuity better than 20/200 are at low risk of developing severe vision loss, and are likely to spontaneously improve.

• Ischemic CRVOs are likely to present with a relative afferent pupillary defect.

• CRVO is a dynamic phenomenon. There exists the possibility that non-ischemic CRVO with good acuity and perfusion can progress to an ischemic situation with subsequently poor perfusion and bad outcome. Eyes with CRVO with intermediate levels of vision loss (between 20/50 and 20/200) and are neither ischemic nor non-ischemic and are hence considered to be "indeterminate" are more likely to progress on to fully ischemic occlusions.

• When diabetes is present in patients with CRVO, closer observation is necessary as this seems to be a risk factor dictating late onset ischemia.

• Undilated iris evaluation and gonioscopy is necessary at each progress evaluation for eyes with CRVO in order to properly detect the onset of anterior segment neovascularization. The absence of iris neovascularization does not preclude the possibility of angle neovascularization. Gonioscopy must still be performed even in the face of a pristine iris.

• Dilated and tortuous retinal veins are a sign of outflow obstruction and possibly an impending CRVO.

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□□□) HRY S - □(Z[HT 5 □6 aT LY[, □9HVWRKFT VWV] LT LU[VM retinal and iris neovascularization after a single intravitreal bevacizumab injection in a patient with central retinal vein occlusion and neovascular glaucoma. Int Ophthalmol. 2008;28(1):59-61.
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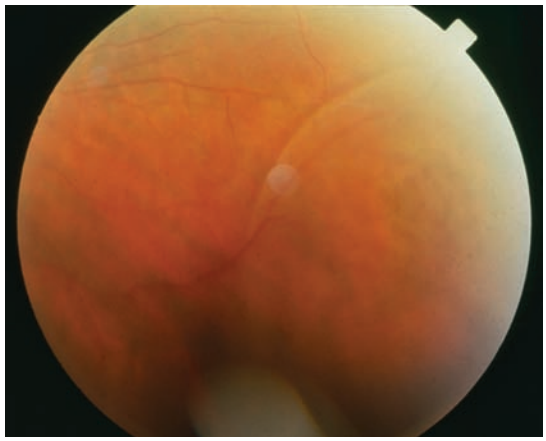
ACQUIRED RETINOSCHISIS

Signs and Symptoms

Acquired retinoschisis is historically known as senile retinoschisis and, as the name implies, is typically found in the eyes of elderly patients.[1] In one large population based study, the mean age of patients with acquired retinoschisis was 69 years.[1] In this study, the prevalence of acquired retinoschisis was 3.9% for persons aged 60 to 80 years. There appears to be no gender predilection.[1] There also do not appear to be any associated conditions, though one report of three cases noted acquired retinoschisis in nanophthalmic eyes.[2] Most commonly, acquired retinoschisis is bilateral, though unilaterality has been noted.[1]



Bullous acquired retinoschisis.

Patients with acquired retinoschisis are nearly always asymptomatic. Typically, symptoms, in the form of vision or visual field loss, occur if fluid from the retinoschisis cavity accesses an outer layer retinal hole to induce a rhegmatogenous retinal detachment. Only rarely will patients report a sharp visual field defect corresponding to the area of the retinoschisis.[1]

Ophthalmoscopy will reveal a smooth, stationary, bullous elevation of either the inferior-temporal or superior-temporal retina.[1-5] The greatest prevalence appears to be the inferior temporal retina. Nasal involvement is very rare.[1] The elevation may extend beyond the equator, and may rarely invade the posterior pole. However, the posterior border of the majority of these lesions remains preequatorial. The dome of the elevation is smooth and translucent. Blood vessels will traverse the dome and cast shadows on the underlying structures. In many cases, the smooth dome of the lesion demonstrates inner and outer layer holes. In some cases, these lesions permit liquid vitreous fluid to leak under the photoreceptors separating the neurosensory retina from the retinal pigment epithelium (RPE) creating a rhegmatogenous retinal detachment.[6-8] A pigmentation line inferring some coexistent irritation to the RPE connotes the presence subretinal fluid from a concurrent or old chronic rhegmatogenous process.[9,10] There will be no RPE hyperplasia in the form of a pigment demarcation line from an acquired retinoschisis lesion alone.

Pathophysiology

Every aging eye manifests peripheral cystic changes in the inner nuclear and outer plexiform layers of the retina. These spaces coalesce to form interlacing tunnels. If enough cystic spaces coalesce, the retina will form a retinoschisis, splitting into an inner and outer layer cavity. The superficial retinal layers comprise the inner layer, while the deeper layers of the retina and RPE represent the

outer layer of the acquired retinoschisis cavity. The split typically occurs in the outer plexiform layer, or less often, in the inner nuclear layer.[2,3] These lesions, with their intraretinal separations, can be clearly demonstrated with optical coherence tomography.[11]

There are technically two types of acquired retinoschisis. There is the typical degenerative retinoschisis, which presents as a shallow elevation of the inner retinal layers. There is also reticular degenerative retinoschisis, which presents in the traditional appearance of a bullous elevation. In all types of acquired retinoschisis, there is the potential for either the inner layer or the outer layer, or both layers, to develop holes.[6-8]

Progression of acquired retinoschisis, either by continued separation of the two layers or the concurrent development of rhegmatogenous retinal detachment, is uncommon.[1,9,12,13] The risk of acquired retinoschisis progression to concurrent rhegmatogenous retinal detachment ranges from 0.07% – 2.2%.[1,9] Those cases that have been noted to progress to rhegmatogenous retinal detachment often have additional complicating factors, such as cataract surgery or a family history of retinal detachment. Cases of acquired retinoschisis most at risk for progression to retinal detachment are those that have outer layer breaks closest to the retinal pigment epithelium.[1,4,5-8]

Should holes develop within the inner layers of the retina (inner layer holes), the patient with acquired retinoschisis may have liquid vitreous potentially egress into the retinal tissue cavity. This will have no prognostic significance. However, if there are also outer layer holes, liquid vitreous will have the potential to gain access to the subretinal space, causing a rhegmatogenous retinal detachment. To this end, acquired retinoschisis with both inner and outer layer holes simultaneously (double layer holes) have greater potential to progress to rhegmatogenous retinal detachment.[4,12,13]

Beyond increased size of the acquired retinoschisis cavity and progression to rhegmatogenous retinal detachment, there are other changes that can occur. The development of acquired retinoschisis in the fellow eye of unilateral cases will occasionally occur during long-term follow up. Additionally, acquired retinoschisis has been noted to spontaneously disappear in up to 2.3%-8.8% of cases over time.[1,5,9] This may possibly occur in cases where the retinal pigment epithelium pumps fluid out of the retinoschisis cavity. However, this mechanism is merely speculative.

Management

The risk of acquired retinoschisis progressing to involve central vision or developing a rhegmatogenous retinal detachment (even with double layer holes) is low. There is no treatment for stable cases beyond routine monitoring every six to 12 months.[8,12,13] In fact, in one long-term population-based study, there was more disappearance of lesions than progression to retinal detachment.[1] This, combined with the fact that prophylactic treatment complications exceed the risk of visual loss from progressive retinal detachment from acquired retinoschisis clearly indicate that these lesion should be observed rather than treated. If possible, the acquired retinoschisis should be photodocumented to increase the ability to detect progression or regression. Because acquired retinoschisis results in a sharply demarcated visual field defect, the stability can be monitored with a threshold visual field as well. Acquired retinoschisis lesions that manifest outer layer holes should be monitored more closely.

Should any retinal detachment or high risk retinal breaks develop from acquired retinoschisis, standard therapies such as barrier laser photocoagulation, gas bubble tamponade and scleral buckling procedures are appropriate.[4,6,9,10]

Clinical Pearls

• While acquired retinoschisis has the potential to enlarge and extend posteriorly and threaten the macula, its progression is extremely slow and may take months to years to threaten vision.

• Because the RPE is not disrupted by acquired retinoschisis, the RPE does not become hyperplastic and a pigment demarcation line will not form. If a pigment demarcation line is present in a retinoschisis, it should be taken as a sign that there is or was a concomitant retinal detachment.

• The acquired retinoschisis is firm and will show no movement or undulation upon eye movement or scleral indentation, whereas a retinal detachment will. Furthermore, scleral indentation will show preservation of the schisis cavity, as opposed to retinal detachment.

• Should a visual field defect be detectable by standard threshold perimetry, it will have a steep and sharply demarcated border. In contrast, the defect will not be as sharp with a retinal detachment.

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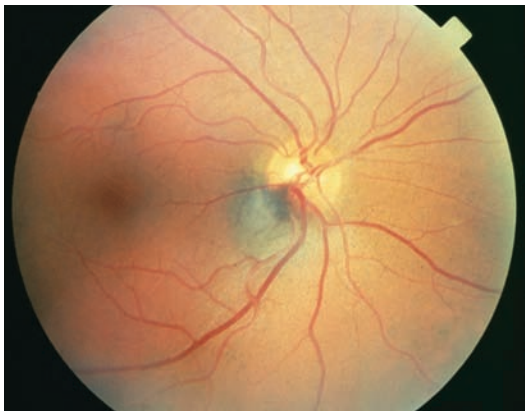
MELANOCYTOMA OF THE OPTIC DISC

Signs and Symptoms

Melanocytomas of the optic nerve head (magnocellular nevus, melanocytic nevus) are slightly elevated, benign, darkly pigmented tumors that classically occur in or about the optic disk, 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 in size.[2,6] They have the potential to obscure the optic disc. The tumor rarely extends more than 2mm into pre-retinal space.[2] In most cases, less than half of the disc is typically obscured.[1]



Melanocytoma of the optic disc and adjacent RPE.

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.[2] Asian, Hispanic, Indian and Arabic races are significantly less affected than the Caucasian or African races.[2] While many regard optic disc melanocytomas as congenital lesions which 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%-15% of cases.[1,8-11] Adjacent portions of the tumor have the capability of damaging nerve fiber bundles and major vessels with resultant variable visual complications (sight loss, field loss, relative afferent pupil defect, choroidal neovascularization) via a variety of mechanisms.[1,8-11] Visual symptoms can be anticipated in up to 24% of patients.[2]

Potential associated ocular findings include invasion into the choroid from the retina, optic disc edema, retinal edema, localized subretinal fluid, retinal exudation, retinal hemorrhage and retinal vein obstruction.[1,2,10,12]

Associated ocular vascular abnormalities may include arterial attenuation, perivascular sheathing, superficial hemorrhages and vascular occlusions.[1,12] 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 necrosis of the optic disc. Circumpapillary subretinal fluid is not uncommon and often produces 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 this lesion.[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]

Bilateral optic disk melanocytoma is uncommon and associated with optic disc hypoplasia and central nervous system abnormalities, such as meningioma and hypopituitarism.[11]

Pathophysiology

Melanocytoma is one of five disorders of cells originating from the neural crest (choroidal nevi, choroidal melanoma, melanocytoma, ocular melanosis and oculodermal melanosis).[17] Melanocytoma 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, which 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 transformation.[1-20] Melanocytomas may transform into malignant melanomas, but this is rare.[6] Other unusual features may include quickened growth pattern, infiltration of the macular region, and

the presence of retinal hemorrhages and exudates.[1,2,6]

Management

Specific diagnostic tests are useful in the identification and clinical management of melanocytoma.[24-26] When a lesion is first detected, careful fundus photodocumentation is necessary to give later inspection a valid comparison database.[1-22] Baseline automated threshold perimetry can permit accurate 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 findings. Optical coherence tomography (OCT) has been shown to be of excellent value in these cases.[22] On OCT imaging, melanocytomas display a gradual sloping transition from normal retina into the mass, with hyper-reflectivity at the anterior tumor surface with posterior shadowing.[22] Thicker tumors display thinner anterior hyper-reflective borders with denser shadowing.[22] Given the catastrophic consequences of misdiagnosis, all questionable lesions should be referred for evaluation by a retinal specialist or ocular oncologist.

Melanocytoma that do not show enlargement over a 24-month observational period are considered benign by circumstantial evidence.[1-10] 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.[21,25] 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 deliver the height of the lesion (typically less than 2.0mm).[6]

Fluorescein and indocyanine green angiography demonstrate persistent hypo fluorescence of the lesion.[2] In most instances there is no leakage.[2]

Computerized tomography (CT scanning) and magnetic resonance imaging (MRI) may aid in the localization and classification of the tumor.[26] The P32 test may be positive if a malignancy exists. The P32 test is a phosphorus uptake test designed to seed tumors of this type.[26]

Today, management of melanocytoma is conservative, with long term observation and meticulous documentation.[1-26] Treatment for vision threatening non-rhegmatogenous lesions, extending toward the macula is variable.[1,2,27] 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.[27]

The management for melanocytomas converting to malignant melanoma is limited typically to enucleation.[1,2,20] Photodynamic therapy can be used effectively for treating choroidal neovascularization secondary to melanocytoma involving the peripapillary area and papillomacular bundle.[28] Submacular surgery may be considered for large choroidal neovascular membranes associated with a melanocytoma of the optic disc.[9]

Clinical Pearls

- Malignant melanoma appears grey-brown (versus the typical brown or black appearance of an optic nerve head melanocytoma).
- Melanomas rarely infiltrate the NFL, so they are generally not feathery.
- Hamartomas of the RPE may extend into the optic nerve head and peripapillary retina and clinically resemble melanocytoma. Hamartomas frequently occur in children, whereas melanocytoma are rare before puberty.
- Reactive hyperplasia of the RPE can also masquerade as a melanocytoma. These often stem from past eye injuries or disease and can be differentiated by their diffuse, rather than localized appearance.
- Melanocytoma must also be differentiated from choroidal nevi. These flat, grey-brown lesions with definite borders have a small malignant potential.
- 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 and photodocumentation are reasonable data to gather.

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DEMYELINATING OPTIC NEUROPATHY (Optic Neuritis, Retrobulbar Optic Neuritis)

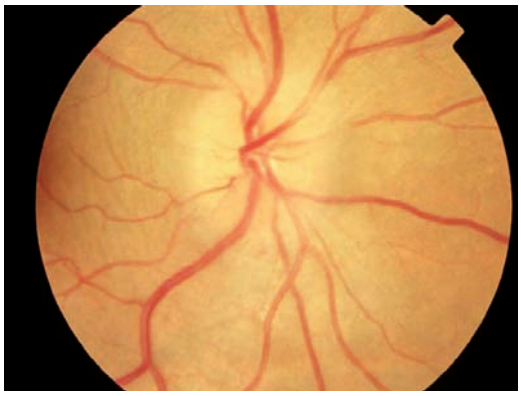
Signs and Symptoms

Optic neuritis (ON) is a broadly-used term that technically implies acute inflammation of the optic nerve. While numerous etiologies include infection (syphilis, mumps, measles), infiltrative/inflammatory disease (sarcoidosis, lupus) and ischemic vascular disease (diabetes, hypertension), the most common etiology is the demyelinating disease multiple sclerosis (MS). While it is acknowledged that ON is commonly used to connote an acute unilateral optic neuropathy from any etiology, the discussion here will be limited to demyelinating neuropathy associated with multiple sclerosis.

Optic neuritis is often the initial presentation of MS.[1-3] After five years, clinically definite multiple sclerosis (CDMS) develops in 30% of patients who present with ON, though the degree of neurological impairment is generally mild.[4] Brain magnetic resonance imaging (MRI) performed at study entry into the Optic Neuritis Treatment Trial (ONTT) was a strong predictor of CDMS, with the five-year risk of CDMS, ranging from 16% in patients with no MRI lesions to 51% in patients with three or more MRI lesions.[4]

However, even a normal brain MRI does not preclude the development of CDMS.[4] Most patients who develop clinically definite MS following an initial episode of optic neuritis will have a relatively benign course for at least 10 years.[5] Patients with rapid succession of severe ON events are more likely to develop a generalized demyelinating disease.[3]

The 10-year risk of MS following an initial episode of acute optic neuritis is significantly higher if there is a single brain MRI lesion; higher numbers of lesions do not appreciably increase that risk. However, even when brain lesions are seen on MRI, more than 40% of the patients will not develop clinical multiple sclerosis after 10 years.[6] Patients with an acute attack of optic neuritis will typically, at 10 years, have good vision with 74% retaining 20/20 acuity.[7] Recently it has been reported at the final follow up for the Optic Neuritis Treatment Trial (ONTT) that the presence of brain MRI abnormalities at the time of an optic neuritis attack is a strong predictor of the 15-year risk of MS.[6] The overall risk of developing MS by 15 years after onset of optic neuritis was 50% and strongly related to the presence of brain MRI lesions. Only 25% of patients with no lesions on baseline brain MRI have developed MS during 15 year study follow-up compared with 72% of patients with one or more lesions.[8] The typical patient with demyelinating optic neuritis is a young female, often between the ages of 20 and 40 years. In the ONTT, 72% of the patients were female and the median age of onset was 32 years.[9] In 92% of cases, the vision loss is painful with increased pain upon eye movement.[9] A retrobulbar neuropathy with a normal appearing optic disc occurs in 65% of cases with a papillitis manifesting in the remainder.[9] There will be associated dyschromatopsia, decreased brightness sense and a relative afferent pupil defect.[1,9] Without treatment, vision typically begins to recover by approximately one month and the recovery is often rapid, progressing over the course of a year's time. Severe vision loss at time of onset seems to be associated with a poorer final outcome, though even patients with poor initial vision recover quite well.[10]



Papillitis in a patient with multiple sclerosis.

Visual field defects are varied, but seem to affect central vision more than far peripheral vision. Central and cecocentral scotomas are common, as are generalized depressions and altitudinal defects.[11-14] Chiasmal and retrochiasmal lesions also may occur.[11] Over the first year of follow-up, the majority of patients with visual field defects from acute optic neuritis returned to normal.[11,13] Systemic signs and symptoms indicative of MS may include headache, nausea, Uhtoff's

sign (decreased vision with or without limb weakness following exposure to increased temperatures i.e., bath or exercise), Romberg's sign (patient falls when they close their eyes), Pulfrich's stereo phenomenon (beer barrel appearance to the environment), L'Hermitte's sign (tingling of the extremities upon chin down posture) and fever.

Pathophysiology

Multiple sclerosis is defined as an acquired, multifactorial, inflammatory demyelinating disease, which affects the white matter located in the central nervous system. Myelin is responsible for insulating the nerves of the peripheral and central nervous system, permitting transmission of electrical impulses along nervous tissues. Loss of myelin greatly slows nervous conduction and leads to the neurological deficits seen in MS. It has long been believed that demyelination in ON damages the fibers in both the visual and pupillary pathways. This damage interrupts nerve impulses within the pathways, producing decreased vision, a corresponding afferent pupillary defect and sluggish pupilomotor activity.

Although the exact cause of MS is presently unknown, many theories regarding its etiology exist. The most common theories involve the immune system. Evidence suggests that the cellular immune response contributes to the degradation of myelin. This patchy demyelination is thought to be caused by a deposition of mononuclear cells, such as macrophages and B-cells in perivascular regions.[2]

Changes in the brain on magnetic resonance images are common in patients with optic neuritis, even when there is no other clinical evidence of multiple sclerosis.[15] The brain lesions of multiple sclerosis are commonly seen as T2 ovoid high-signal white matter lesions on MRI scans of the brain, located in perivenular regions perpendicular to ventricles with variable enhancement.[1]

There have been recent advancements in the understanding of the pathophysiologic process of optic neuritis, and it seems that there may be changes beyond demyelination that account for the visual features and disabilities that patients experience. Advancements in understanding have come from automated diagnostic imaging using optical coherence tomography (OCT) and scanning laser polarimetry (SLP), and have illuminated axonal loss in both optic neuritis and MS.[16-22] In one study using both OCT and SLP, the average peripapillary retinal nerve fiber layer (RNFL) thickness was reduced in patients with MS compared with controls. Both modalities were in agreement and the results support RNFL thickness as a marker for axonal degeneration and use of these techniques in clinical diagnosis and clinical trials.[16]

Another study examining the relationship between visual function and RNFL thickness, as measured by OCT, found that low-contrast letter acuity and contrast sensitivity correlated well with RNFL thickness. It was seen that eyes with a history of acute optic neuritis demonstrated greater reductions in RNFL thickness, but patients with MS, without a history of ON, also had less RNFL thickness than controls. This implied that the occurrence of chronic retinal axonal loss occurred as separate events and not just from acute attacks in MS patients.[17] In a major literature review, it was seen in all studies that there is a significant reduction in RNFL in eyes affected by ON compared with fellow eyes and eyes of healthy controls. This further supports the contention that OCT may be used as a promising new tool for evaluating retinal axonal atrophy in patients with ON and MS. Jeanjean and associates also demonstrated that retinal axonal loss following optic neuritis can be detected with OCT. They noted that the RNFL of MS patients without optic neuritis was also thinner than disease-free controls recognizing that chronic, on-going optic nerve axonal loss is a feature of multiple sclerosis.[21] Numerous studies seem to indicate there is axonal loss as opposed to demyelination alone underlying the visual disability seen in MS.[22]

An expert panel consensus examining the role of RNFL analysis with OCT determined that OCT is valid and reproducible and yields important information regarding patients with ON and MS, but more studies are required to correlate OCT results with other measures of MS disease activity. However, it was also felt that OCT may evolve into an important primary or secondary outcome metric for MS clinical trials and patient care.[20]

Management

In the past, controversy existed as to whether or not patients with ON should be treated with corticosteroids and in which form. The ONTT supports the administration of intravenous methylprednisolone sodium succinate (Solu-medrol) 250mg every six hours for three days followed by oral prednisone (1mg/kg, per day) for 11 days for the purposes of accelerating visual recovery.[23-25] This therapy did not improve visual outcome after one year but was found to increase the rate at which patients recover. The ONTT also determined that the use of oral prednisone (1mg/kg, per day) alone for 14 days is contraindicated.[23] Patients receiving this therapy had a higher rate of new attacks of ON in both the initially affected and fellow eyes than did the intravenous/oral group and placebo group, and overall the intervention contributed to a poorer outcome systemically.[23] As recorded in the three-year follow-up of patients in the ONTT, treatment with intravenous methylprednisolone followed by oral corticosteroid regimens reduced the two-year rate of development of clinical MS, particularly in patients with signal abnormalities consistent with demyelination on MRI of the brain at the time of study entry.[26] Serious side effects of glucocorticoid therapy

are infrequent. Therefore, outpatient administration of high-dose intravenous glucocorticoids may be recommended. Patients should be counseled as to the benefits and disadvantage of this treatment.[24,27]

Patients with typical acute monosymptomatic demyelinating optic neuritis should receive gadolinium-enhanced magnetic resonance imaging (MRI) of the brain and orbits to determine if they are at high risk for the subsequent development of CDMS. A subset of patients with monosymptomatic optic neuritis manifested neither clinical signs nor MRI evidence of demyelination after more than 10 years of follow-up. In other cases followed for this length of time, the MRI signal abnormalities could be shown to accumulate; however, no new clinical manifestations of multiple sclerosis developed.[28] It is important to ascertain the risk of progressing to CDMS in patients with ON, as there are systemic immunomodulatory therapies available. Patients with an initial clinical episode of optic neuritis and at least two characteristic demyelinating lesions within the brain who are treated with interferon beta-1a (Avonex, Biogen Idec) after initial treatment with intravenous corticosteroids showed a 50% less risk of progression to CDMS.[29-32] The Controlled High Risk Avonex Multiple Sclerosis Study (CHAMPS) supports the efficacy of Avonex therapy in significantly reducing the three-year likelihood of future neurological events and worsening of the brain MRI in patients with a first episode of optic neuritis.[29]

Currently, the most commonly employed immunomodulatory therapies for patients with MS include: Avonex (interferon beta-1a, Biogen Idec); Rebif (interferon beta-1a, EMD Serono, Inc.); Betaseron (interferon beta-1b, Bayer Healthcare Pharmaceuticals); and Copaxone (glatiramer acetate, Teva Pharmaceuticals)..[36,37]

Clinical Pearls

- Optic neuritis associated with MS should be considered an ocular finding from a systemic disease. It is imperative to identify patients with ON who are at risk for development of CDMS so that they may receive appropriate immunomodulatory therapy.
- In cases of optic neuropathy presumably secondary to demyelinating disease, MRI can assist in systemic diagnosis by identifying both old and acute demyelinating plaques within periventricular white matter.
- Significant pain with eye movement is present in nearly every case of demyelinating optic neuropathy. Eye pain may precede visual dysfunction.
- The course of ON is predictable with nearly full recovery. However, the course and development of CDMS is less certain. Some patients will experience a rapid decline while others, even with MRI abnormalities, will not. This must all be considered when counseling patients regarding prognosis.

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TRAUMATIC OPTIC NEUROPATHY

Signs and Symptoms

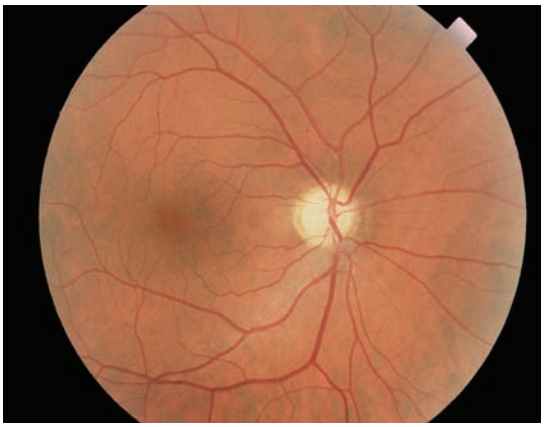
Patients with traumatic optic neuropathy have experienced sudden, severe, vision loss following blunt injury to the head or face.[1-3] The condition may manifest immediately or within hours or days following the trauma.[4] The vision loss may be insidious, with some cases the patient being unaware of any visual deficit until it is detected by routine examination. The epidemiology of traumatic optic neuropathy is non specific; however, it can be extrapolated world-wide, as following trends consistent with those individuals most likely to sustain both eye injuries and general blunt ocular trauma.[5-10] The patient demographic that is most prone to ocular trauma includes young males (average ratio of 4:1 over females), in their teens or twenties, participating in outdoor or work-related activities during seasonal warm weather.[5-10] Women who sustain serious ocular injury tend to be involved in activities around the home.[7] The history often includes a blow to the head severe enough to induce loss of consciousness or high speed penetration of the globe by foreign material.[1-10]

Examination of these patients reveals variably reduced acuity and/or visual field defects, which may be central, paracentral, arcuate or altitudinal in nature.[1-10] An afferent pupillary defect is characteristic and tell-tale for severity with varying degrees of dyschromatopsia noted.[1-11] Ophthalmoscopic evaluation will vary greatly depending on the nature and severity of the injury. Initially, practitioners may note a completely normal fundus without any signs of disc edema, ischemia, or other abnormalities.[12,13] In other cases, a grossly edematous optic nerve head, vitreous hemorrhage, venous congestion or retinal edema may be seen.[1-12] In the vast majority of cases, optic disc pallor ensues within several weeks to months after the injury.[1-4,12-14]

Pathophysiology

Traumatic optic neuropathy results from injury sustained during trauma to the globe, orbital rim or frontal area.[12-15] In adults, the etiology is typically a bicycle or motor vehicle accident, but may also include physical assault, falls, sports-related injuries or (rarely) orbital surgery.[1-11] There are a variety of ways in which the optic nerve can be damaged. In some cases, the pathophysiology may be multifactorial. Mechanisms include transection or avulsion of the nerve, hematoma of the nerve sheath, optic nerve compression secondary to bony fracture of the orbital apex or penetrating orbital foreign body.[1-12] Most commonly, however, concussive shock waves are implicated; transmission of these forces to the bones and meninges of the orbit results in contusion of the intracanalicular optic nerve.[5-15] Subsequently, the axons and microvasculature are compromised by ischemia secondary to reactive edema, as well as the generalized compressive forces.[14] In rare instances, the neuropathy may develop months after the initial trauma, a consequence of scarring within the optic canal that leads to secondary nerve compression.[13,15]

Trauma that precipitates an optic nerve injury almost always results in retinal ganglion cell axon damage.[14] Neurotrophin deprivation secondary to direct shear, edema, bleeding or other neurochemotactic factors induce death of the retinal ganglion cells (RGCs).[14] These cells give rise to the axons that compose the optic nerve. Externally released agents that block mitochondrial electron transport have been used in the laboratory to show that superoxide radicals generated in the mitochondrial electron transport chain also induce cell death after axonal injury.[14]



Optic disc pallor in a patient who suffered traumatic optic neuropathy.

Management

High resolution imaging of the head is critical in any case of blunt trauma to ensure that no life-threatening intracranial damage has been sustained.[15] Particular attention should be given to the orbital apex, optic canal and cavernous sinus if vision is compromised. A complete neurological assessment is also indicated in these cases, especially if there was loss of consciousness, as the optic neuropathy is just one among other injuries resulting from the trauma. In many cases, patients with traumatic optic neuropathy enter the medical system through the emergency department

prior to optometric or ophthalmologic consultation. In this instance, it is likely imaging studies have already been ordered and interpreted by the ER physician.[1-11] However, it may be necessary to later order more appropriate imaging studies in some cases.

Ocular treatment presents three options: 1) observation, 2) systemic corticosteroid therapy, or 3) optic nerve decompression surgery. While a fair number of patients with traumatic optic neuropathy experience some spontaneous improvement of vision, there is great variability in the outcome.[16-18] Negative prognostic factors include blood in the posterior ethmoid cells, loss of consciousness, older age (i.e., > 40) and complete loss of vision at the initial presentation.[1,2] In the 1990's, researchers quoting the Second National Acute Spinal Cord Injury Study recommended megadose systemic intravenous corticosteroid therapy on all patients with traumatic optic neuropathy within eight hours of injury.[12,16] While this approach is controversial (due to insufficient clinical research demonstrating conclusive effectiveness) the therapy is considered worth attempting given the potential for vision preservation.[16-19] Those patients remaining unresponsive to the therapy after several days, or those with poorer visual acuity (i.e., finger counting or worse) at initial presentation are considered candidates for traditional or endoscopic transnasal optic canal decompression surgery.[12,16,19] The endoscopic transnasal approach is well suited for decompression of both the orbit and optic canal.[19] A high-resolution technique, requiring substantial familiarity and skill, the nasal endoscope provides excellent visualization for bone removal along the orbital apex and skull base.[19] The technique is not without risk and may cause complications, which include severe nasal bleeding, cerebrospinal fluid rhinorrhea, nasal polyps, chronic sinusitis and nasal synechia.[20]

Experimental paradigms to promote survival of RGC and optic nerve regeneration through stimulation via neurotrophic factors (NTF) either directly or indirectly through retinal astrocyte/Müller cell intermediary activation are underway.[21] NTF induce disinhibition of axon growth through regulated intramembranous proteolysis.[21] The concomitant release of metalloproteinases (MMP) and plasminogen activators from RGC axons as well as tissue inhibitors of metalloproteinases from optic nerve glia, suppress scarring.[19] MMP also degrade myelin-derived inhibitory messengers along regenerating axon trajectories, encouraging growth. The combination of blocking axon-growth inhibition while stimulating axon growth promoters may be the therapeutic formula for sustained axon regeneration.[21]

For now, medical and/or surgical intervention remains of questionable value.[22] It has been suggested that patients without negative prognostic indicators be effectively managed with careful monitoring.[1,17,22] Research has shown that there is no significant difference in final visual acuity relating to dose of corticosteroid therapy, and that there is no significant difference in outcome between patients treated with steroids or surgical decompression of the optic canal. For patients presenting more than eight hours after the initial injury, steroids are contraindicated as there are no proven data indicating effectiveness in this time frame while the preparations remain capable of producing other collateral unwanted side effects.[17,18,22,23] Patients with traumatic optic neuropathy should, therefore, be managed via the above outlined options on an individual basis, following proper assessment and consultation.[17,18,22]

Clinical Pearls

• There is no classic presentation to traumatic optic neuropathy. The involved optic nerve may be edematous, hemorrhagic, or pale at the time of examination. Visual acuity and fields may likewise be minimally affected or severely compromised. The key to diagnosis lies in a thorough history and meticulous ocular evaluation.

• In evaluating for possible bony fractures of the orbit or skull, computed tomography (CT) is the vastly preferable technique. In addition to being far less expensive than MRI, CT offers much better resolution of bone, and also can demonstrate orbital hemorrhage in the early stages following trauma.

• In those cases that involve penetrating orbital injury or fracture of the sinus walls, systemic antibiotic therapy is mandatory to prevent secondary cellulitis.

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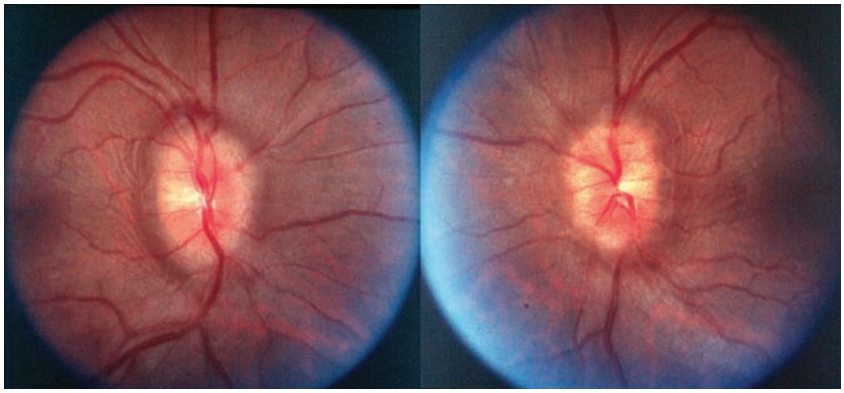
PSEUDOTUMOR CEREBRI

Signs and Symptoms

Pseudotumor cerebri (PTC), also known as idiopathic intracranial hypertension, is encountered most frequently in young, overweight women between the ages of twenty and forty-five years of age.[1-3] Headache is the most common presenting complaint, occurring in more than 90% of cases seen.[4,5] Dizziness, nausea and vomiting may also be encountered, but typically there are no alterations of consciousness or higher cognitive function. Tinnitus, or a "rushing" sound in the ears, is another frequent complaint. Visual symptoms are present in up to 70% of all patients with PTC, and include transient visual obscurations, general blurriness, and intermittent horizontal diplopia.[6] These symptoms tend to worsen in association with Valsalva maneuvers and changes in posture.

Funduscopic evaluation demonstrates bilaterally swollen, edematous optic nerves consistent with true papilledema. Ophthalmoscopy may reveal striations within the nerve fiber layer, blurring of the superior and inferior margins of the neural rim, disc hyperemia, and capillary dilatation. More severe presentations involve engorged and tortuous retinal venules, peripapillary hemorrhages and/or cotton wool spots, and circumferential retinal microfolds (Paton's lines). Chronic papilledema may result in atrophy of the nerve head, with associated pallor and gliosis. Most cases of true, acute papilledema will not present with significant visual loss or a relative afferent pupillary defect; however, visual field deficits may be present. The most common visual field defect associated with PTC is an enlarged blind spot, followed a nasal visual field defect, typically affecting the inferior quadrants. Other field losses seen in PTC include arcuate defects, generalized constriction, and least commonly, cecocentral scotoma.[7] Cranial nerve (CN) VI palsy, secondary to compression of the nerve within the subarachnoid space as it leaves the brainstem is possible; it is typically unilateral and intermittent.[6]



Papilledema in PTC; note the pronounced disc edema, splinter hemorrhages, and Paton's folds.

Pathophysiology

Pseudotumor cerebri is a syndromic disorder that involves elevated intracranial pressure in the absence of mass lesion, hydrocephalus, hemorrhage, or other identifiable intracranial pathology. The modified Dandy Criteria (originally penned by Walter E. Dandy in 1937) delineates the diagnostic paradigm for PTC.[8] Historically, J. Lawton Smith and Michael Wall were among the first to modify the original Dandy listing; most recently, Friedman and Jacobson published their diagnostic criteria, which includes the following:[8]

1. If symptoms present, they may only reflect those of generalized intracranial hypertension or papilledema.

2. If signs present, they may only reflect those of generalized intracranial hypertension or papilledema.

3. Documented elevated intracranial pressure measured in the lateral decubitus position.

4. Normal cerebrospinal fluid (CSF) composition.

5. No evidence of hydrocephalus, mass, structural, or vascular lesion on magnetic resonance imaging (MRI) or contrast-enhanced computed tomography (CT) for typical patients, and MRI and MR venography for all others.

6. No other cause of intracranial hypertension identified.

The precise mechanism of PTC is not fully understood. Cerebrospinal fluid is manufactured by the choroid plexus and small blood vessels of the brain. It is a necessary protective and cushioning agent which protects neural tissue. Many consider PTC to be a result of poor CSF absorption by the arachnoid villi of the meninges surrounding the brain and spinal cord.[1] Many conditions and factors have been proposed as causative or contributory agents, including exogenous drugs (e.g., naladixic acid, tetracycline, minocycline, corticosteroids, vitamin A), anemias, blood dyscrasias, and chronic respiratory insufficiency, including obstructive

sleep apnea.[9] Also, it seems quite probable that the metabolic and endocrine consequences of obesity play an important role in the pathogenesis of PTC.[10] Adipose tissue is now recognized as an active endocrine organ, and its products—leptin and gherlin—may contribute to PTC development.[11] Though current theories are not without merit, there is still little consensus on the exact etiology.

Whatever the cause, the subsequent result is elevation of intracranial pressure. However, because the process is typically slow and insidious, there is ample time for the ventricular system to compensate. This is the reason that there is no dilation of the cerebral ventricles in PTC. Increased intracranial pressure induces stress on the peripheral aspects of the brain, including the cranial nerves. Stagnation of axoplasmic flow in the optic nerve (CN II) results in papilledema and transient visual obscurations; when the abducens nerve (CN VI) is involved, the result is intermittent lateral rectus palsy with resultant diplopia.

Management

All patients presenting with suspected papilledema or other manifestations of intracranial hypertension warrant prompt medical evaluation and neuroimaging. PTC is a diagnosis of exclusion. Current protocol dictates that patients presumptively suspected of having true papilledema undergo magnetic resonance imaging within 24 hours. The purpose of this test is to rule out any space occupying mass lesions, thus intravenous contrast media should be utilized unless medically contraindicated. MRI is the preferred technique for visualizing soft tissue, with intravenous gadolinium providing further image enhancement. Plain CT is generally not adequate in these instances; however, if MRI is not possible because of patient obesity or claustrophobia, a CT scan with contrast is a better study than none at all.[12]

In cases of PTC, neuroimaging typically displays small to normal-sized cerebral ventricles with otherwise normal brain structure. Patients with unremarkable radiographic studies should be subsequently referred for neurosurgical consultation and lumbar puncture. Additional medical testing may include serologic and hematological studies, depending upon the disposition of the attending physician.

Weight loss is an important aspect of treatment for all patients with PTC. Recent studies indicate that even small changes in body mass index—on the order of 5% to 10%—can have a crucial impact on symptom severity.[13,14] Initial medical therapy usually involves a carbonic anhydrase inhibitor, such as oral acetazolamide (Diamox, Lederle Laboratories), which serves to reduce CSF production at the level of the choroid plexus.[1] For those who cannot tolerate carbonic anhydrase inhibitors, the diuretic furosemide (Lasix, Aventis Pharmaceuticals) has been used successfully. Topiramate is yet another option for patients with PTC. This drug, which is a partial carbonic anhydrase inhibitor, has recently been shown to be as effective as acetazolamide in ameliorating headache symptoms, with the added advantageous side-effect of concurrent weight loss.[15] The use of systemic corticosteroids is not a viable long-term option for PTC, and should be avoided.[15]

For patients in whom conventional medical therapy fails to alleviate the symptoms and prevent pathologic decline, surgical intervention is the only definitive treatment. Optic nerve sheath fenestration is recommended for those patients with chronic disc edema and severe or progressive vision loss. Although this technique fails to directly address the issue of elevated intracranial pressure, it has been shown to stabilize or improve visual function in over 90% of patients, and may even help alleviate headaches.[16,17] Patients with more severe complications or recalcitrant PTC may be treated with a cerebrospinal fluid shunting procedure; unfortunately however, high overall failure rates and the risk of infection limits the utility and widespread use of such surgical intervention. Bariatric surgery (i.e., gastric bypass) has been used for some patients with PTC, and has shown anecdotal success, but is not considered a first-line treatment.[18,19]

Ophthalmic management of patients diagnosed with PTC should include careful and frequent evaluation with threshold visual field assessment, acuity measurement, contrast sensitivity testing, and indirect ophthalmoscopy. Photodocumentation of the nerve heads should also be performed. Symptomatic relief of diplopia can be provided via alternate eye patching.

Clinical Pearls

- Past literature refers to PTC as benign idiopathic intracranial hypertension; however, it should be stressed that this condition is far from benign. Patients may suffer intractable headache, severe nausea, intermittent diplopia and permanent vision loss via optic atrophy if not properly managed.
- While PTC is most commonly encountered in obese women of childbearing age, it may be encountered in patients of both sexes and various ages. Numerous cases involving men and children have been documented.[20,21]
- It is possible to encounter patients with PTC that do not manifest papilledema.

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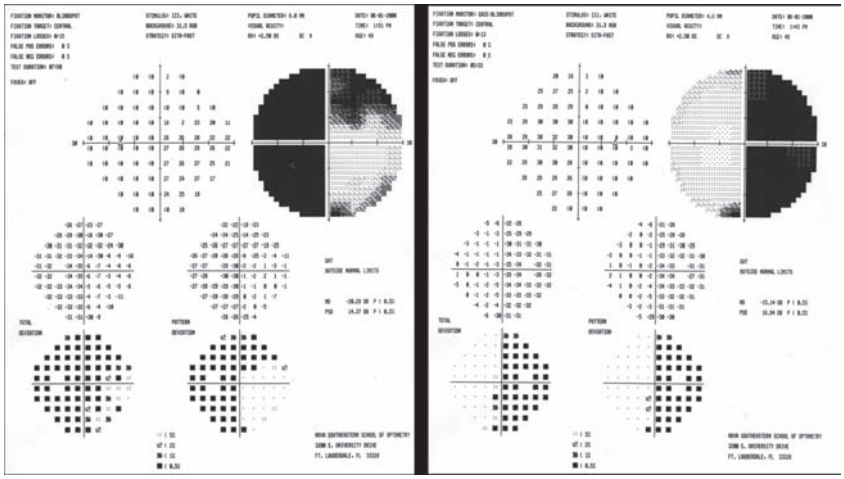
CRANIOPHARYNGIOMA

Signs and Symptoms

Craniopharyngioma represents an uncommon intracranial tumor.[1,2] The incidence of newly diagnosed craniopharyngiomas is between 0.13 and two cases per 100,000 persons per year in the United States.[1] Craniopharygiomas demonstrate a bimodal age distribution, with peak incidence rates in children from five-14 years of age and in adults between 50-74 years of age.[2] There appear to be no significant differences in gender or racial distribution.[2]

Craniopharygiomas are similar to pituitary adenomas in the way they present clinically; visual symptoms result from mass effects on the chiasm and posterior optic nerves. Clinically, this may present in the form of blurred vision in one or both eyes, color desaturation, diplopia and visual field loss. Classically, patients with craniopharygioma experience a bitemporal hemianopic field defect; however, in contradistinction to pituitary adenoma, craniopharyngioma tends to produce a defect that progresses in density from inferior to superior.[3] Less commonly, patients may demonstrate a homonymous hemianopic defect or generalized constriction.[3]



Craniopharyngioma can present with a bitemporal hemianopia.

Funduscopic findings vary—patients with long-standing compression may present with optic atrophy and associated disc pallor.[4] Papilledema is possible, though an uncommon manifestation associated with craniopharyngioma.[5]

Non-ocular signs and symptoms are quite varied. The most frequently described manifestations include headaches, nausea/vomiting, growth failure (in children) and hypogonadism (in adults).[6] Due to compressive forces and expansion of the lesion, pituitary function may also be compromised, leading to potential hormonal dysfunctions, further blurring the diagnostic line between craniopharyngioma and pituitary adenoma.

Pathophysiology

Embryonically, the pituitary gland develops from two sources. The anterior lobe (adenohypophysis) is derived from ectoderm, which ultimately forms the roof of the mouth, while the posterior lobe (neurohypophysis) forms from the neuroectoderm of the diencephalon. Rathke's pouch is the name given to the evagination of tissue that grows upwards to form the adenohypophysis; the downgrowth from the diencephalon is referred to as the infundibulum. Both of these diverticula migrate along a pathway known as the craniopharyngeal canal. As the pituitary gland develops, Rathke's pouch closes on itself, but the cells that line it migrate along the anterior aspect of the infundibulum forming the pars tuberallis. These cells are also retained between the lobes of the pituitary as the pars intermedia.[6] Craniopharyngiomas represent defective development and proliferation of Rathke's pouch and/or remnants of the craniopharyngeal canal. The proposed pathogenic mechanisms include: 1. neoplastic transformation of embryonic squamous cell nests of the involuted craniopharyngeal duct, and; 2. metaplasia of adenohypophyseal cells in the pituitary stalk or gland.[7]

Craniopharyngiomas extend horizontally in various directions as they grow. They can progress anteriorly into the prechiasmatic cistern and subfrontal spaces, or posteriorly into the prepontine and interpeduncular cisterns, cerebellopontine angle, third ventricle,

posterior fossa, and foramen magnum. They can also extend laterally toward the subtemporal spaces. Rarely, they can extend extracranially into the nasopharyngeal area or down the cervical spine.[7] Craniopharyngiomas that progress anteriorly can impinge on the posterior notch of the chiasm, subsequently damaging the superior nasal fibers which decussate in that area. The resultant field defect is a bitemporal hemianopsia with increased density inferiorly; because tumor growth is not always symmetrical, the field loss can likewise be asymmetrical between the two eyes.

Craniopharyngiomas demonstrate benign histology, but paradoxically can display malignant behaviors; they have a tendency to invade surrounding structures and recur after what was thought to be total resection. There are two main varieties of craniopharyngioma, based upon histologic analysis: the adamantinomatous and papillary subtypes. Adamantinomatous tumors may be diagnosed at any age, but predominantly affect young subjects during their first two decades of life.[8] The major distinguishing characteristic is the presence of calcification, most notably in the form of bone or teeth within the mass. Papillary craniopharyngiomas occur almost exclusively in adults.[8] Calcification is rarely seen in this type and infiltration of adjacent brain tissue is also less common in the papillary variety as compared to adamantinomatous type.[7,8]

Management

Patients who present with signs or symptoms indicative of chiasmal pathology, such as craniopharyngioma, warrant prompt neuroimaging and medical consultation. Both computed tomography (CT) and magnetic resonance imaging (MRI) may be used; each has its advantages. CT is preferable for identifying calcification associated with adamaninomatous tumors, but MRI with gadolinium remains superior for delineating the extent of the mass and, in particular, its involvement with the hypothalamus.[3] In addition, magnetic resonance angiography (MRA) is useful in delineating the vascular supply to the craniopharyngioma and also in helping to differentiate it from possible vascular malformations.[9] A medical referral is warranted to assess the hypothalamic-pituitary axis hormones and cortisol levels, as these may often be disturbed.

The decision to intervene therapeutically is typically based upon the overall clinical picture and the radiologic findings; confirmatory diagnosis is based upon histological examination. The preferred form of therapy in all cases of craniopharyngioma is surgical, though approaches differ depending on the size of the tumor and the degree to which it has impacted adjacent structures, particularly the hypothalamus. Radiotherapy is not considered a stand-alone treatment for craniopharyngioma, but it is often used adjunctively with surgical intervention, particularly when a planned, limited technique is employed. External beam irradiation and stereotactic radiosurgery (i.e., gamma knife) are also commonly employed for any residual tumor following surgical excision, as revealed by post-operative MRI.[10] While systemic chemotherapy seems to be of little value in craniopharyngioma, direct injections of bleomycin or interferon alpha into the tumor mass may be of benefit in purely cystic lesions.[11,12]

Clinical Pearls

• Based upon the tell-tale symptoms and visual dysfunction, clinicians must carefully inspect the optic discs to assess for papilledema or pallor, perform visual field testing and appropriately refer suspicious patients for medical evaluation. Electrodiagnostic testing in the form of visually evoked potential may be helpful.[13] Following cessation of therapy, visual function and fields should be reassessed to mark improvements and track stability.[14]

• Despite the potential for visual recovery, endocrine disturbances often persist and may even be exacerbated by surgery.[15] Obesity is present in 50% of patients. Eighty percent of patients require two or more anterior pituitary hormone replacement therapies. Permanent diabetes insipidus occurs in up to 75% of adults and 90% of children.[16] Craniopharyngioma patients require lifelong follow-up with an endocrinologist.

• In general, the 10-year survival rate for craniopharyngiomas is 90% and the 20-year survival rate for pediatric craniopharyngiomas is approximately 60%.[17]

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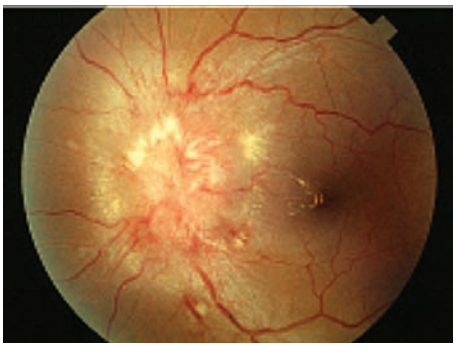
CAT SCRATCH DISEASE

Signs and Symptoms

Patients with cat scratch disease (CSD) are typically younger. Often, there is a history of being scratched by a cat, though this history is not invariably present.[1-5] However, there will usually be a history of exposure to cats, though there have been reports where patients could not recall any feline exposure.[6] The incidence of case presentations tends to be higher during breeding seasons of cats, which is in the fall and winter.



Florid disc edema and macular star in cat-scratch neuroretinitis.

The patient will manifest a regional lymphadenitis with the appearance of a small cutaneous lesion at the site of the inoculation following an incubation period ranging from several days to weeks after initial exposure.[7,8] The patient will develop fever and flu-like symptoms, which typically resolve over three to six weeks. Vision varies widely, from normal to finger counting, depending upon the severity and types of ocular manifestations. While patients may be visually asymptomatic, as the disease affects ocular tissues, relative afferent pupil defects, dyschromatopsia and field loss will be variably present when the eye becomes involved.[7,8]

Systemic signs may include hepatosplenic infection, encephalopathy, osteomyelitis and endocarditis. One of the main ocular syndromes occurring from CSD is Parinaud's oculoglandular syndrome, manifesting as conjunctivitis, retrotarsal conjunctival granulations, regional preauricular and cervical lymphadenitis and fever.[9] Beyond Parinaud's oculoglandular syndrome, the ocular manifestation most associated with CSD is neuroretinitis, a combination of disc edema with a stellate macular star of exudates.[1,10-13] Anterior uveitis is also a common finding.[1,14,15] Peripheral ulcerative keratitis has also been reported.[16] Other fundus findings include choroiditis with maculopathy, peripapillary serous macular detachment, discrete foci of retinitis manifested as white retinal or choroidal lesions, vitritis, posterior uveitis, vascular occlusions, optic neuritis, and submacular exudates.[17-20]

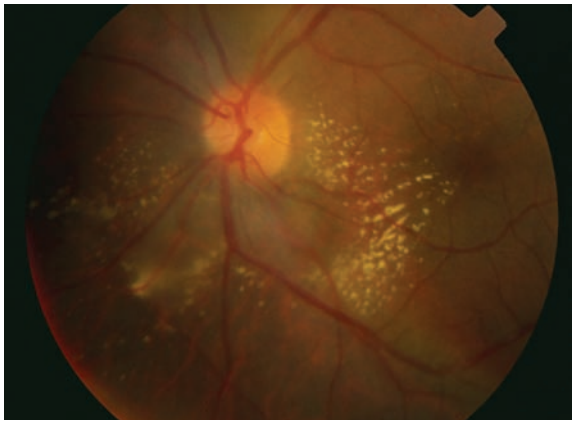
Pathophysiology

Cat scratch disease is caused by the gram-negative bacillus, Bartonella henselae and, to a lesser extent, Bartonella quintana.[1-6] The organism is transmitted through the bite or scratch of an infected cat or kitten. Transmission through flea bites is not reported in humans, though it likely occurs in cats. Following inoculation, there is an incubation period followed by a period of self-limiting febrile illness with lymphadenopathy. The organism spreads to numerous systems via blood and lymph.[1-6,21] Curiously, it may be that there are unrecognized healthy asymptomatic carriers of B. henselae.[15]

Management

Proper diagnosis begins with clinical suspicion based upon ocular findings in association with an antecedent febrile illness. Testing for CSD involves obtaining ELISA Bartonella henselae titres. Additionally, titres for Bartonella quintana are appropriate as well in order to avoid a false negative result. An alternate diagnostic modality is a polymerase chain reaction analysis of lymphadenopathy aspirate. This should be considered in the clinical situation where CSD is strongly suspected and ELISA titers are negative, borderline, or otherwise inconclusive.[8]

In immunocompetent individuals, the course of CSD is self-limiting with a good prognosis.[21] As such, medical treatment is generally unnecessary. However, cases with ocular involvement are generally recommended for treatment. The causative organism is susceptible to a number of antibiotics including penicillins, cephalosporins, aminoglycosides, tetracyclines, macrolides, fluoroquinolones and rifamicin. Doxycycline 100mg p.o. b.i.d. for four weeks is a recommended therapy. This may be used alone or in combination with Rifampin 300mg b.i.d.[5,9-14] Azithromycin is an acceptable substitute.[17,21] In cases with vision loss,



Macula star and retinal edema with minimal disc swelling in cat-scratch neuroretinitis.

typically from neuroretinitis, oral prednisone is often employed with antimicrobial therapy.[17] Any anterior uveitis can be treated in the traditional fashion employing appropriate cycloplegia and topical anti-inflammatory preparations.

Clinical Pearls

• CSD should be considered first when encountering neuroretinitis.

• When the diagnosis is correct and the cause of the neuroretinitis is confirmed secondary to Bartonella infection, the retinal condition, while appearing intimidating, almost always resolves without inducing persistent retinal edema, choroidal neovascularization, chorioretinal scar formation or other deleterious retinal consequences.

• CSD is a benign, self-limiting disease and the value of treatment in immunocompetent individuals appears to be in shortening the duration of the disease.

• Always question for an antecedent history of febrile illness and lymphadenopathy when encountering patients with painless vision loss with disc edema, as well as retinochoroidal exudates, vascular occlusions, serous detachments, occult maculopathy, and anterior uveitis.

• Neuroretinitis occurring from cat scratch disease tends to look much worse than it really is in terms of visual prognosis, which is typically good.

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SJÖGREN'S SYNDROME

Signs and Symptoms

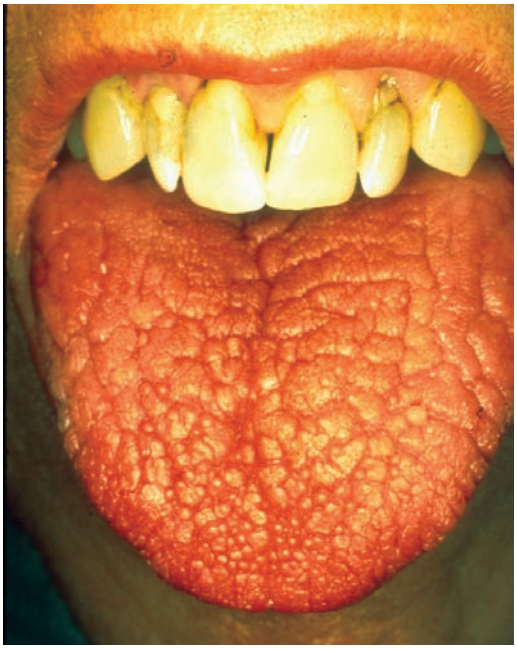
Sjögren's syndrome has a distinct predilection for women, with most sources citing a 9:1 female-to-male ratio.[1-3] All racial and ethnic groups may be affected. Sjögren's also displays a greater incidence with increasing age; the majority of patients fall between the ages of 46 and 75 years, though some patients may begin manifesting the disorder much earlier.[1,3-5] It is not uncommon to encounter systemic diseases in association with Sjögren's syndrome, particularly autoimmune and collagen vascular disorders. Between 25% and 50% of these patients suffer from rheumatoid arthritis; other disorders may include systemic lupus erythematosus (SLE), polymyositis, thyroiditis, scleroderma, hypergammaglobulinemia, and anemia.[1-3,6] Fibromyalgia may also be associated with Sjögren's syndrome in some patients.[3]

The most common symptoms encountered with Sjögren's syndrome involve dry eye and dry mouth complaints. Severe dry eye in the form of keratoconjunctivitis sicca (KCS) is typical and is often the first clinical manifestation.[5] Patients with KCS present with mild to severe ocular burning and discomfort; a sandy or gritty feeling is often reported. Examination may reveal a diminished tear meniscus, epithelial corneal stippling, reduced fluorescein tear break up time (FTBUT), and rose bengal or lissamine green staining in a band-appearing region of the conjunctiva and/or cornea. Tear volume assessment via Schirmer test or Zone Quick (phenol red thread test) will show significant reduction, as aqueous deficiency is a hallmark sign.[5,7,8] Mucus filaments are often present within the tear film; when these become large and adhere to the corneal epithelium, filamentary keratitis may result. Other associated ocular findings may include staphylococcal blepharitis, ropy mucus strand accumulation, meibomian gland dysfunction, and corneal pannus in extreme cases.[7,8]

Dry mouth, or xerostomia, results in complaints of dysphagia, loss of taste and painful lesions of the lips and tongue.[1-3,5,6] Patients may report difficulty in chewing, swallowing, or speak-

ing. They may report the need to drink copious amounts of fluid to simply finish a meal. Signs of dry mouth include fissures at the corners of the mouth, generalized hyperemia of the oral tissues, thick and/or diminished saliva, and a smooth or grooved appearance of the tongue's surface.[9,10] Xerostomia also enhances the likelihood of tooth decay, with many affected patients reporting increased incidence of dental misfortune. If the dry mouth extends to the oropharynx, hoarseness and a dry cough result.[3,9] In addition, parotid gland enlargement may be seen to occur in as many as two-thirds of Sjögren's syndrome patients, leading to a "chipmunk" appearance of the face in later stages.[6]

Sjögren's syndrome may affect organ systems beyond the eye and mouth. Impairment of the neurologic, pulmonary, rheumatologic, dermatologic, renal and genitourinary systems is commonly encountered.[1-3,5-7,10] Symptoms that may be described include dry skin or skin rashes, pain or weakness in joints or muscles, numbness or tingling in the extremities, labored breathing, vaginal dryness, difficulties with memory and mentation, and fatigue. There is a wide range of severity seen with these symptoms; they may be encountered as mild peripheral complaints or may be a source of debilitation.



Oral signs of Sjögren's syndrome: advanced tooth decay, cheilitis and dessication of the tongue.

Pathophysiology

Sjögren's syndrome is a chronic disorder characterized by lymphocytic infiltration of the exocrine glands. It is classified as an autoimmune rheumatic disease, and is the second most common disease in this category after rheumatoid arthritis.[1] The prevalence of this condition varies based upon the population, ranging in studies from 0.6% to 1.5% in the general population, though it may be as high as 3.4% in older individuals.[4,5,11] Although the exact etiology of Sjögren's syndrome has not been identified, researchers speculate that the condition results from a combination of genetic and environmental factors. Several different genes may be implicated in different racial and ethnic groups, and a "trigger" factor such as a viral or bacterial infection may serve to activate the specific gene.[12] Here, the immune reaction that is initiated in response to an infection is somehow altered and is redirected toward the exocrine glands. The accumulation of lymphocytes (white blood cells) and plasma cells in these glands results in inflammation and disruption of normal glandular activity.[3] Ultimately, the glands are rendered dysfunctional.

Two forms of Sjögren's syndrome are recognized clinically: primary Sjögren's syndrome and secondary Sjögren's syndrome. Primary Sjögren's syndrome is generally diagnosed in the absence of other autoimmune conditions. Most of these individuals possess circulating antibodies specific to Sjögren's syndrome, known as SS-A (or Ro) and SS-B (or La).[13] Secondary Sjögren's syndrome is typically associated with pre-existing systemic disorders such as rheumatoid arthritis or SLE. Patients with secondary Sjögren's syndrome are less likely to display antibodies, but are more likely to display severe symptoms and debilitation as a result of the disease.[13] Actually, the distinction between primary and secondary Sjögren's syndrome can be far more difficult than implied above. Often there are confounding factors, such as non-rheumatoid arthropathies and arthralgias that prevent physicians from clearly defining the condition.

Management

While there is no cure for Sjögren's syndrome at the present time, early diagnosis is important for several reasons. First and foremost, a number of therapies have been introduced in recent years that may significantly reduce the potentially debilitating symptoms of Sjögren's syndrome. Secondly, studies have demonstrated that up to 10% of patients with Sjögren's syndrome develop malignant lymphoma as a late complication of the disease.[14,15] While lymphoma is very responsive to chemotherapy, it is still a lethal disease in untreated cases.

Diagnosis begins with clinical suspicion. Particular consideration should be given to older females with dry eye and any of the concurrent symptoms delineated above. Patients should be directed to undergo a full rheumatologic examination; a referral to a dentist or oral surgeon skilled in managing Sjögren's syndrome is also important. Laboratory testing may be ordered by any of the attending physicians. The

major tests to consider include:

• Antinuclear antibody (ANA)—high sensitivity, low specificity.

• Sjögren's specific antibodies (SS-A and SS-B)—medium sensitivity, high specificity.

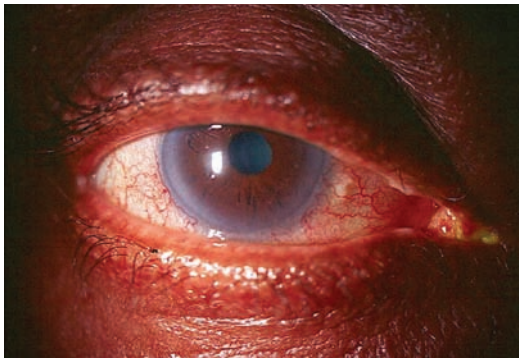
• Rheumatoid factor (RF)—high sensitivity, low specificity.

• Erythrocyte sedimentation rate (ESR)—high sensitivity, low specificity.

In addition, serologic testing may reveal comorbidities such as hypergammaglobulinemia, cryoglobulinemia and thyroid autoantibodies in a fair percentage of patients.[1] Biopsies of the lacrimal or salivary glands are very helpful in identifying lymphocytic infiltration. The easiest location to obtain a biopsy is the mucosal surface of the lower lip, which contains minor or accessory salivary glands. This procedure may be performed by the patient's rheumatologist, or an experienced oral surgeon.

Treatment is aimed at reducing symptoms such that the patient is able to carry on normal day-to-day activities. In the case of dry eye, tear replacement therapy is the initial management strategy. Non-preserved preparations should be used with frequency, on the order of four to six times daily depending on the severity of symptoms. Products with enhanced ocular surface residence time (e.g., Systane Ultra Preservative-Free from Alcon, Blink Tears from Abbott Medical Optics, and Refresh Liquigel or Celluvisc from Allergan) may help provide relief with less frequent instillation. More symptomatic patients or those with evidence of ocular surface damage due to inflammation may require a short course of topical corticosteroids (e.g., 0.5% loteprednol etabonate q.i.d. for two to four weeks), followed by twice-daily administration of topical cyclosporin A (Restasis, Allergan) indefinitely.[16,17] Advanced ocular surface disease may necessitate the use of punctal occlusion therapy, moisture-retaining goggles, or surgical intervention.[18]

Two medications that may offer relief for both dry mouth and dry eye are oral pilocarpine (Salagen, MGI Pharma) and cevimeline (Evoxac, SnowBrand Pharmaceuticals). These agents act on autonomic receptors within the exocrine glands, such that saliva and tear production is stimulated.[1] While these agents are only currently FDA approved for managing xerostomia, many rheumatologists and ophthalmologists have reported a concurrent decrease in symptoms of KCS for patients utilizing these medications.[18-20] Some rheumatologists also feel that hydroxychloroquine sulfate (Plaquenil, Sanofi Winthrop) may delay the progression of Sjögren's syndrome and may lessen the severity of many associated symptoms.[21]



Keratoconjunctivitis sicca associated with Sjögren's syndrome.

Patients with rheumatoid arthritis or other systemic complications typically require anti-inflammatory therapies, including both NSAIDs and corticosteroids in some cases. This is best addressed by participating in comanagement with the patient's rheumatologist.

Clinical Pearls

• Because of the high association with rheumatoid arthritis, it is often helpful to examine the hands of patients with suspected Sjögren's syndrome. Simply inspecting the digits may reveal enlargement of the knuckles and/or a "gnarled" appearance of the fingers, characteristic of arthritis.

• To help with dry mouth, advise patients to sip fluids (preferably water) throughout the day. Also, lozenges can help to stimulate saliva production. Caution patients with Sjögren's syndrome to avoid sugared beverages and candy, as they are prone to rapid tooth decay.

• A small tabletop humidifier may be a way of improving symptoms in some Sjögren's patients. Increasing environmental humidity may help those with mild complaints of dry eye, dry skin, or even dry mouth.

• Sjögren's syndrome is a multisystem disorder that must be comanaged by a variety of medical specialists. Always stress regular dental and rheumatological care to these patients. Be sure that the primary care physician is familiar with possible oculosystemic associations. Correspond as a member of the health care team to review systemic status and conduct systemic screening on a regular basis.

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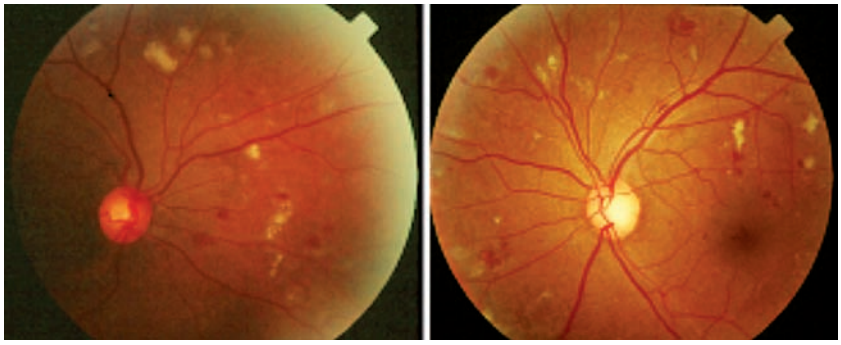


Typical retinal findings associated with hypertension: arteriolar attenuation, superficial hemorrhages and cotton-wool spots.

HYPERTENSION

Signs and Symptoms

Hypertension is a world-wide disease of predominately the middle-aged and older with a trend that demonstrates increasing prevalence with age.[1-9] Black adults have a higher incidence of hypertension than Caucasian adults and typically a more severe form of the disease.[10] Risk factors for the development of hypertension include a positive family history of hypertension or cardiovascular disease, diabetes, hypercholesterolemia, obesity, sedentary lifestyle, high sodium intake, high dietary fat intake, alcohol use, smoking, and a stressful lifestyle.[1,2,9,10,11]

The National Heart, Lung, and Blood Institute (NHLBI) is an organization under the guiding arm of The United States Department of Health and Human Services.[4] Its mission is to provide global leadership for research, training and education for promoting the prevention and treatment of heart, lung and blood diseases.[3] The Joint National Committee (JNC) was created as an NHLBI working group and assigned the ongoing task of developing clinical practice guidelines for topic areas falling under its mission statement.[4] These published guidelines are systematically developed to assist both practitioners and patients through the process of decision making regarding appropriate health care for specific clinical circumstances.[4] The guidelines define the role of specific diagnostic and treatment modalities and offer management paradigms.[4,5] The recommendations in the document are based on evidence from rigorous reviews of the published medical literature.[3,4]

The JNC definition of "normal blood pressure (BP)" is <120mm Hg systolic and <80mm Hg diastolic, with "pre-hypertension" classified as 120mm Hg to 139mm Hg systolic and/or 80mm Hg to 89mm Hg diastolic.[4,5] Conversion to hypertension is any reading above that threshold.[4,5] Longitudinal data obtained from the Framingham Heart Study have indicated that BP values between 130-139mm Hg/85-89mm Hg are associated with a more than a two-fold increase in relative risk for cardiovascular disease (CVD) as compared with those with BP levels below 120mm Hg/80mmHg.[6] In multivariable analyses, age, sex, systolic and diastolic blood pressure, body mass index, parental hypertension, inactivity, and cigarette smoking were not only risk factors but significant predictors of hypertension.[6] Additional risk can be assessed via predictors such as lipoprotein analysis, measurement of lipoprotein-associated phospholipase A(2), C-reactive protein, assessment of hyperglycemia, increased glomerular filtration rate and liver function.[4,7] While the majority of cases may be attributed "essential" etiology (renal dysfunction), systemic hypertension may also result secondary to other disease processes, such as Cushing's syndrome, thyroid and parathyroid disease, medication or substance related side effects, vitamin D deficiency or pheochromocytoma.[4,12]

Hypertension is insidious, causing biomedical alterations to the heart, blood vasculature, blood tissue and end organs, virtually asymptomatically.[4,13] However, the process itself, by way of

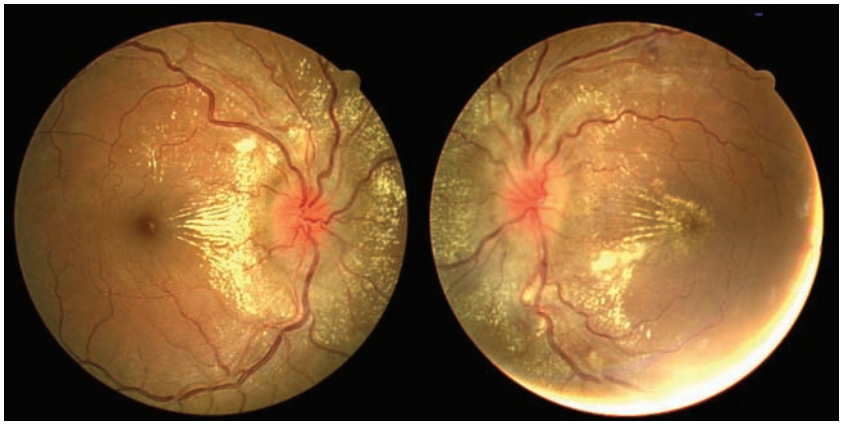
coronary-pressure-overload leads to left ventricular hypertrophy (LVH), myocardial fibrosis and impaired diastolic filling without systolic dysfunction.[12] Systemic symptoms from this process include headache, fatigue, dyspnea (shortness of breath), reduced exercise tolerance and peripheral extremity edema.[13] While chronic, recurrent headache is listed as a potential symptom of hypertension and certainly mandates blood pressure measurement as one of the studies for uncovering diagnosis, it is typically only present in cases where blood pressure peaks from stress or is due to moderate or worse untreated disease.

Hypertension is manifested within the eye as both hypertensive retinopathy and hypertensive ocular complications.[14-19] Hypertensive ocular complications include retinal vessel occlusion, ocular ischemic syndrome, non-arteritic anterior ischemic optic neuropathy, glaucomatous alterations, increased risk of embolic events, internuclear ophthalmoplegia, cranial nerve palsy, amaurosis fugax and transient ischemic attack.[14-19]

Pathophysiology

Essential hypertension develops from renal system dysfunction.[20,21] The kidney is a filtering organ that retains vital blood components and excretes excess fluid. If too much fluid is retained, BP rises. If too little fluid is retained, BP decreases. Arterial pressure within the renal artery triggers a feedback loop.[21,22] The kidneys excrete sodium, which osmotically draws fluid into the excretory system in a process called pressure diuresis. This causes a decrease in both blood fluid volume and arterial pressure. As pressure within the renal artery decreases, the kidneys reflexively secrete an enzyme called renin.[21] This enzyme causes the formation of a protein called angiotensin I.[21] This protein directly stimulates the kidneys to retain sodium and fluid.[21] Angiotensin I is converted in the lungs, via the enzyme angiotensin converting enzyme (ACE) to angiotensin II.[21] Angiotensin II is a potent vasoconstrictor, which increases total peripheral vascular resistance and hence elevates BP.[21,22] As BP elevates, the looped system begins again with pressure diuresis. In healthy individuals, this feedback loop maintains a constant blood pressure with only minor fluctuations. In patients with essential hypertension, this feedback loop fails for any number of reasons. The result is a higher than normal level of pressure within the renal artery, which causes the natural mechanisms of regulation to become unstable and faulty.[21]

Endothelial dysfunction secondary to the processes of systemic hypertension reduces vascular availability of endothelium-derived nitric oxide.[23] This substance has the potential to mediate the adverse vascular effects of hypertension. Increased oxidant stress is thought to represent a major mechanism leading to reduced vascular availability of endothelium-derived nitric oxide.[23] Complicated reactive oxygen species are also players in the pathology.[23] Endothelial dysfunction has been implicated in the macrovascular complications of hypertension, such as stroke or myocardial infarction, coronary microvascular dysfunction and increased arterial stiffness.[23] As such, hypertension plays a significant role in the development of arteriosclerosis and atherosclerosis.[20] Hypertension reduces the elasticity of vessels allowing lipids to deposit in the form of atheromas, which in turn leads to thrombus formation and possible emboli formation. This will impede blood flow and lead to ischemic disease. Coronary heart disease is the leading cause of death in hypertensive patients. Ventricular hypertrophy occurs as a result of increased cardiac output in the face of systemic vascular resistance. Eventually, the heart is unable to maintain this constant output and the hypertrophied muscle outstrips its oxygen supply.[4,13,14] Hypertension induced arteriosclerosis can worsen or hasten atrophy of the renal glomeruli and tubules.[22] Over time, this induces additional renal distress and other potentially mortal complications.[22] Cerebrovascular disease is also a serious complication of hypertension.[22] Hypertension is among the leading causes of stroke.[22]



Stage IV retinopathy associated with severe hypertension.

Management

Reducing morbidity and mortality is the main goal in hypertension manage-

ment.[8-10] Any measurement fitting the definition of stage II disease (>160mm HG systolic and/or >100mm Hg diastolic) requires either re-evaluation within one week to one month or immediate treatment, depending upon the coexistence of other associated complications.[4,5]

Antihypertensive therapy has been associated with reductions in stroke incidence and myocardial infarction. It is estimated that in patients with stage 1 hypertension (SBP 140-159mm Hg and/or DBP 90-99mm Hg) and additional cardiovascular risk factors, achieving a sustained 12mm Hg reduction in SBP over 10 years will prevent one death for every 11 patients treated. In the added presence of CVD or target organ damage, only nine patients would require such BP reduction to prevent one death.

Blood pressure reduction is done in a stepwise approach, often beginning with non-pharmacologic methods, such as weight loss and dietary and lifestyle modifications. This includes the regulation of fatty foods to decrease fat and cholesterol ingestion, a modification for the intake of salt, restriction of over all caloric intake and an increase in exercise and activity.[4,5]

Should non-pharmacological methods prove unsuccessful, there are four families of drugs from which physicians traditionally choose: Diuretics (reduce blood volume by inhibiting sodium and water retention), beta blockers (decrease cardiac output), calcium antagonists (induce vasodilation), and ACE inhibitors (decrease peripheral vascular resistance).[9,11,24] Along with exercise and improved diet, medications from each family can be combined to achieve the desired pressure reduction.[9,11] While the product of one's lifestyle is clearly a modifiable risk factor, recent work in this area suggests that diet and weight loss are only contributors to a complex problem.[2] Proper diet, exercise and weight loss form a solid base for blood pressure protection but, in certain cases of hypertension, they alone may not be able to maintain healthy levels.[2]

Clinical Pearls

• Hypertensive complications are mediated through arteriosclerosis and atherosclerosis.

• Weight reduction is the most potent non-pharmacological method of hypertension management.

• Internists and family practitioners are the most appropriate physicians to manage patients with hypertension.

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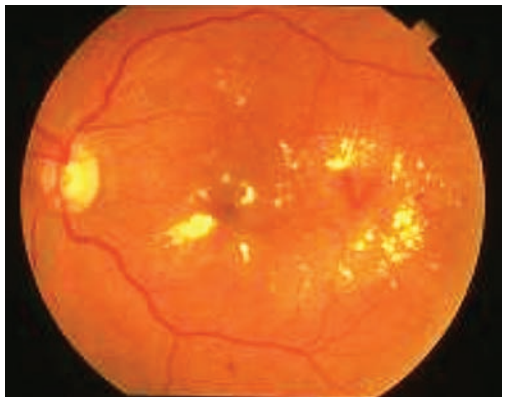
DIABETES MELLITUS

Signs and Symptoms

Diabetes mellitus (DM) is the most common endocrine disorder. It is characterized by a defective or deficient insulin secretory process and or glucose underutilization creating hyperglycemia.[1-23] Possible systemic signs and symptoms include polyuria (increased frequency of urination), polydipsia (increased thirst), polyphagia (increased appetite), glycosuria, weakness, fatigability, weight loss and nephropathy.[1-18] Ophthalmic signs and symptoms may include chronic conjunctival injection, changes in corneal curvature, large fluctuations in refraction, premature cataractogenesis, nonproliferative and proliferative retinopathy and cranial nerve III, IV or VI palsy.[1-24]

Type 1 diabetes, formerly known as insulin-dependent diabetes mellitus (IDDM), juvenile-onset or ketose prone DM, usually begins by age 20 and is defined by an absolute lack of insulin caused by a reduction in the beta-cell mass of the pancreas.[1-23] This may be the result of autoimmune

processes and may involve genetic susceptibility.[17,18] Type 2 diabetes, formerly known as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset DM, usually begins after age 40 and is a multifactorial disease that may involve improper insulin secretion, malfunctioning insulin and/or insulin resistance in peripheral tissues.[17,18] Approximately 10% of diabetic cases are Type 1 and approximately 90% are Type 2.[2,3]



Non-proliferative retinal changes associated with diabetes: dot & blot hemorrhages and hard exudates. This patient also has macular edema.

Pathophysiology

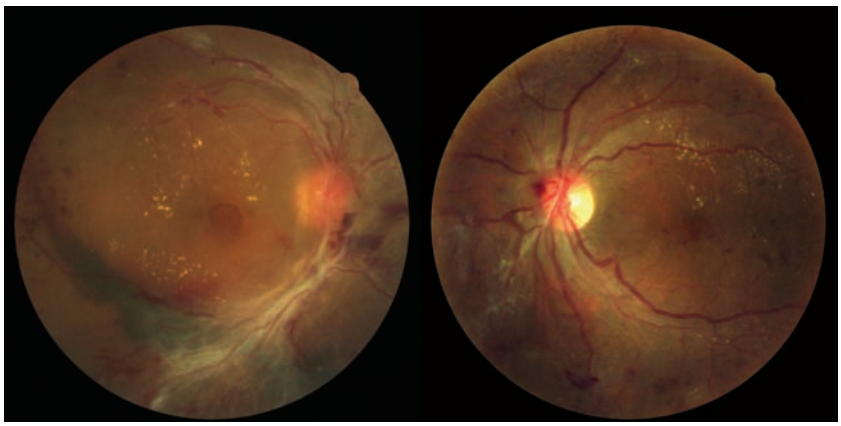
The pancreas plays a primary role in the metabolism of glucose by secreting the hormones insulin and glucagon.[2] The Islets of Langerhans secrete insulin and glucagon directly into the blood. Insulin is a protein that is essential for proper metabolism of glucose and for maintenance of proper blood glucose levels. Inadequate secretion of insulin, or inadequate structure or function of insulin or its receptors results in impaired metabolism of glucose, other carbohydrates, proteins and fats.[1-23] This is characterized by hyperglycemia and glycosuria.[1] Hyperglycemia is the most frequently observed sign of diabetes and is considered the etiologic source of diabetic complications both in the body and in the eye.[2]

Glucagon is a hormone that opposes the action of insulin. It is secreted when blood glucose levels fall. Glucagon increases blood glucose concentration partly by breaking down glycogen in the liver.[1] Following a meal, glucose is absorbed into the blood. In response to increased blood glucose levels, insulin is secreted causing rapid uptake, storage or use of glucose by the tissues of the body. Unused glucose is stored as glycogen in the liver. Between meals, when blood glucose is at minimal levels, tissues continue to require an energy source to function properly. Stored glycogen, via glucagon, is converted into glucose by a pathway known as glycogenolysis.[1] Gluconeogenesis is the production of glucose in the liver from noncarbohydrate precursors such as glycogenic amino acids.

Elevated glucose levels (sustained hyperglycemia) result in the formation of excessive sorbitol (a sugar alcohol) via the aldose reductase/polyol pathway.[2] Since sorbitol cannot readily diffuse through cell membranes, tissue edema with resultant changes in function ensue.[2] Further, sorbitol poisons the supportive pericytes in capillary vessels. With respect to the eye, this mechanism contributes to the evolution of premature cataractogenesis (nuclear sclerotic, senile and snowflake, and posterior subcapsular) and sight threatening diabetic retinopathy (via changes that compromise the supportive pericytes that line capillary walls in the neurosensory retina).[5,6,9,22,23]

Another complication of hyperglycemia is non-enzymatic glycosylation. Non-enzymatic glycosylation is the binding of excess glucose to the amino group of proteins in the tissues.[10] As a result, at the level of the capillary membranes, altered cell function eventually leads to the development of microaneurysms, vascular loops, and vessel dilation, creating the characteristic blood, serum and lipid leakage.[2,7,8,10] Platelet aggregation secondary to these changes initiates tissue hypoxia. These changes result in a system-wide accumulation of edema and release of other chemoattractants and cytokines (glyceraldehydes, endothelin, matrix metalloprotinases, histamines, renin, interleukin-6 and vascular endothelial growth factors), each with the potential to induce vascular constriction, hypoxia and resulting retinal sequelae.[2,7,8,10,22,23]

Evidence in a number of reports has suggested that the renin-angiotensin system (RAS) plays an important role in the pathogenesis of DM and its associated cardiovascular risks.[25,26] The



Proliferative diabetic retinopathy is a sign of advanced, uncontrolled diabetes.

potential role of RAS blockers has also recently been studied for their ability to delay or prevent the onset and progression of diabetes mellitus and cardiovascular disease.[25,26] Data from recently analyzed clinical trials suggest that RAS blockade not only reduces cardiovascular risk in patients with DM but also prevents or delays diabetes in subjects-at-risk.[26] The Diabetes Reduction Approaches With Ramipril And Rosiglitazone Medications (DREAM) trial evaluated ramipril and its capacity to significantly increase the system's regression toward normoglycemia. The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial evaluated whether creating a reduced risk for DM could be associated with a reduction in cardiovascular disease events.[26] The outcomes from both trials have solidified the roles of these suspected pathways.[25,26]

Management

Glycemic control over the course of the disease has been shown to reduce the risk of developing debilitating organ disease and retinopathy.[11,13,14,21,27] Blood glucose levels are of even greater importance in diabetic pregnant women, as hyperglycemia during pregnancy may initiate swift and severe progression of diabetic retinopathy.[4,15,27] Other concurrent systemic variables that may potentiate the onset of diabetic retinopathy include hypertension, nephropathy, cardiac disease, autonomic neuropathy and ocular findings such as elevated intraocular pressure and myopia.[11,13,14]

The easiest method of treating Type 2 diabetes is with diet control.[17] Dietary regulation is set by basing the caloric intake on the patient's ideal body weight, selecting adequate sources of protein and carbohydrate, while maintaining a reasonable distribution of foods (proteins, fats, and carbohydrates).[17] When hyperglycemia persists despite dietary changes, oral hypoglycemic agents become necessary. These agents can be prescribed in small doses, adjusting the dosage to larger levels to achieve tighter control, as necessary.[17]

Insulin is always required for Type 1 DM and is an option for recalcitrant cases of Type 2 diabetes.[17] Conventional therapy involves the administration of an intermediate-acting insulin (NPH or lente), once or twice-a-day, with or without small amounts of regular insulin.[17]

Several studies have shown the benefits of antihypertensive treatment and glucose-lowering therapy on the prevention of macrovascular and microvascular disease.[24-32] The Action in Diabetes and Vascular disease: PreterAx and DiamicroN modified release Controlled Evaluation (ADVANCE) study was designed to provide answers regarding blood-pressure-lowering therapy and intensive glucose control therapy in Type 2 diabetics at high risk for cardiovascular disease.[25-29] Study data demonstrated that patients with Type 2 diabetes mellitus exhibit a marked increase in cardiovascular and renal risk.[25,29] A sub-study of the ADVANCE report evaluated a comparison of blood pressure lowering with perindopril-indapamide vs placebo and an open comparison of standard vs intensive glucose control (targeting an HbA1c of less than or equal to 6.5%).[25] The study noted a trend of lower significant risks for microaneurysms, hard exudates and macular edema in the group with the intensive glucose control, with fewer patients on the blood pressure-lowering treatment experiencing significant progression of retinopathy compared to the patients on the placebo.[25] The study concluded that, while the effects of the comanagement were not clinically significant, there was a trend demonstrating that the effects of the two treatments were independent and additive.[25]

Other interventional trials have shown that diabetic patients benefit greatly from aggressive blood pressure control, especially when the drug regimen includes an inhibitor of the renin-angiotensin system.[29] In a study that examined the effects of overall health improvement, Harder and coworkers tested the effects of a low calorie diet (LCD) on body weight, lipid profile and glycemic control, finding that it was also an effective method for improving glycemic control and blood lipids in overweight type 2 DM patients.[30]

While early work focused on improving glycemic control, new studies such as the European Diabetes Controlled Trial of Lisinopril in Insulin-Dependent Diabetes (EUCLID) and new arms of older studies such as the United Kingdom Prospective Diabetes Study (UKPDS) shifted the focus to observing the control of blood pressure and specifically the RAS as a means of arresting diabetic sequelae.[30-33] There is a body of evidence suggesting that a local RAS, within the eye itself, may be activated upon conversion to clinically definite diabetes.[33] This appears to be directly responsible, as well as indirectly responsible through the production of other mediators, for increasing the concentration of vascular endothelial growth factor (VEGF), a selective angiogenic/vasopermeability factor already well implicated in the pathogenesis of diabetic retinopathy.[33] Inhibition of angiotensin-converting enzyme appears to reduce concentrations of VEGF, with a concurrent anti-proliferative effect independent of systemic VEGF levels or blood pressure.[31,32]

Angiotensin II (Ang II) receptor blockade has been shown to reduce retinal neovascularization independent of VEGF levels in animal models.[30-32] This may be due to antagonism of activation of mitogen-activated protein

kinase. This molecule is a potent cellular proliferation stimulator set into motion by Ang II. The ramifications of this research may yield new medications whose indirect mechanisms slow or arrest the pathogenesis responsible for retinopathy and other pathologic changes, not only in the eye but also throughout the body.[30-32]

Currently, there are a number of large-scale trials evaluating the effects of lipid-lowering therapies in patients with diabetes.[30] The Lipids in Diabetes Study will hopefully provide insight for determining whether lipid lowering with a statin or fibrate medication can substantially reduce cardiovascular morbidity and mortality in patients with Type 2 diabetes. The Atorvastatin Study for the Prevention of Coronary Heart Disease Endpoints (ASPEN) is designed to compare double-blind treatment with atorvastatin against placebo in over 2,500 U.S. diabetic patients without coronary heart disease. A sister trial in the U.K., the Collaborative Atorvastatin Diabetes Study (CARDS), is enrolling 1,820 diabetic patients for completion of a British arm.[33] The results from these trials may provide information that will help determine the future management of dyslipidemia in diabetics and indirectly affect all systemic disease in diabetics.

Clinical Pearls

• Large changes in refraction may be the first sign of diabetic disease. Often, myopic or hyperopic shifts are created as the lens swells, secondary to sorbitol effects, resulting in large refractive changes, in what were otherwise noted as "stable eyes." Clinicians should avoid prescribing refractive correction during this time period, instead educating patients as to why this may have occurred and ordering appropriate tests such as fasting blood glucose.

• Cataracts (senile posterior subcapsular and snowflake posterior subcapsular) may form as well due to sorbitol effects. The cataracts may mature quickly but have been documented to regress once the sugar levels are stabilized.

• The test of choice for monitoring diabetic control is the glycosylated hemoglobin test (HgbA1C), which is a readily available, in-office disposable test.

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