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The Handbook of Ocular Disease Management

THIRTEENTH EDITION

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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*.

FROM THE AUTHORS

To Our Colleagues:

We practice in an ever changing profession. New medications come out every year and the changes in diagnostic technology are amazing, posing a challenge just to keep up.

Lifelong learning is way of life for every optometrist. The committed practitioner is always looking to improve skill, experience and knowledge. This is done in many ways: keeping current with the latest literature, attending conferences and continuing education meetings and participating in collegial discussions where all have the opportunity to share ideas. Talk with colleagues about both of your experiences and gain from them.

Among the most special of the learning experiences we have encountered is residency training. We have each completed residencies and have been intimately involved in residency education over the tenure of our careers. The value of gaining insights and experience under the thoughtful guidance of a mentor is priceless. We have always felt that the additional post-graduate year was not the end of our learning, but the beginning of the process of learning to learn. We urge everyone with the opportunity to pursue residency training to do so. You won't regret your decision.

We hope that you enjoy the thirteenth edition of *The Handbook of Ocular Disease Management*.

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MOLLUSCUM CONTAGIOSUM

Signs and Symptoms

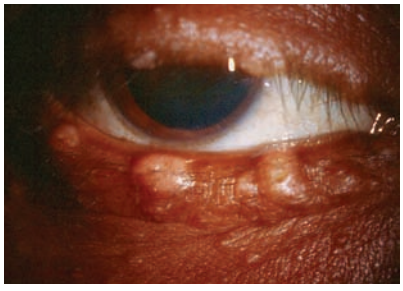
Molluscum contagiosum (MC) refers to a relatively common skin condition, most often encountered in children.[1] The disorder occurs worldwide, but is believed to be more prevalent in tropical regions.[2] The clinical picture of MC consists of one or more firm, smooth, dome-shaped papules with an umbilicated center. Typically, the lesions appear pink and translucent and are between three and five millimeters in diameter.[3,4] They are generally painless, although some patients may report mild itching or irritation. MC most commonly occurs on the arms, legs, trunk and facial regions in those aged ten and under.[4] Adults may also present with MC; however in this population the condition carries a significant association with sexually transmitted disease and/or immunocompromise (HIV infection).[5] In adults, multiple site involvement is the norm, with lesions typically affecting the lower abdomen and genitalia.[4,5]

MC has been noted to affect the eye and ocular adnexa, both in children and in adults. The eyelid is the most common site to be affected, although conjunctival lesions have also been reported.[6-8] MC can also induce a secondary follicular conjunctivitis or keratoconjunctivitis.[6,8] Molluscum lesions associated with immunocompromise tend to be bilateral, as well as larger and more numerous than those occurring in immunocompetent patients.[5]

Pathophysiology

MC is caused by a large DNA pox virus of the same name (i.e., the *molluscum contagiosum virus* [MCV], family *Poxviridae*).[2] There are four recognized strains which affect only humans; in children, MCV-1 is the usual culprit, whereas in adults with HIV, MCV-2 causes about 60% of infections.[9] Transmission of the virus is usually via direct person-to-person contact, although the disease may be spread by contact with exposed surfaces (e.g. bath sponges or towels).[2,4]

A key histopathological finding in MC is the presence of "molluscum bodies" (also called Henderson-Patterson bodies). These are large, round or oval cytoplasmic inclusions containing the molluscum virions as well as eosinophilic and basophilic structures.[10] These cellular inclusions produce an invasive acanthosis (diffuse hyperplasia and thickening of the dermis) that causes the surface of the epidermis to slough and form a central cavity, resulting in the characteristic molluscum lesion.[11]



Molluscum contagiosum.

Management

Like numerous other viral dermatopathies, MC is a self-limited disorder in children, typically resolving spontaneously over the course of six–18 months.[12] However, despite its benign nature, most experts recommend therapy in the majority of cases. The rationale for treatment is multifaceted—the condition is potentially contagious, cosmetically unappealing and has the capacity to spread via autoinoculation.[4,12] In addition, about 10% of individuals will eventually develop a pruritic, eczematous dermatitis around the MC papules. Pruritic, eczematous dermatitis can precipitate bleeding, secondary infection and potential scarring, particularly in children who may be unable to resist the urge to scratch and pick at the lesions.[12] In immunocompromised patients, spontaneous resolution is not typical and hence therapeutic measures are even more critical in this group.

The most common intervention in MC is curettage.[12] Other popular treatment options for solitary, uncomplicated MC include electrodessication, cryotherapy with liquid nitrogen and chemocautery with trichloroacetic acid.[4,12,13] For multiple lesions over a larger area, topical keratolytic agents such as potassium hydroxide (KOH), lactic acid, glycolic acid, salicylic acids, and the vesicant cantharidin may be employed.[12,14] Topical immunomodulatory agents have also gained popularity in recent years, particularly in those patients with immune-deficient conditions.[15] Aldara (imiquimod topical, Graceway Pharmaceuticals) has gained clinical popularity in recent years because of its efficacy, minimal side effects and ease of application. However, it must be noted that imiquimod is presently indicated only for treatment of actinic keratosis, superficial basal cell carcinoma and external genital warts. The use of imiquimod in MC constitutes an off-label use.[15]

Clinical Pearls

• The differential diagnosis for MC must include such conditions as verucca, squamous cell papilloma and basal cell carcinoma. Atypical lesions may resemble comedones, syringomas, keratoacanthomas and cutaneous horns.[5]

• Immunocompromised patients tend to present with larger, numerous, multicentric MC as compared to immunocompetent adults or children.[5,16] Surprisingly while presenting cosmetic concerns, the more extreme cases produce the least subjective symptoms.

• Proximity of MC lesions to the lid margin and ocular surface may limit the utility of several therapeutic interventions, particularly those employing chemical agents. Questionable cases should be referred to an oculoplastics specialist for evaluation and treatment.

• Unlike herpes viruses, MC does not remain dormant in the body after the

dermatologic eruptions have dissipated. Once removed they will not reappear without an additional exposure and contraction.[17] Since there is no permanent immunity it is possible for an individual to become infected with each reexposure.

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HERPES SIMPLEX BLEPHARITIS

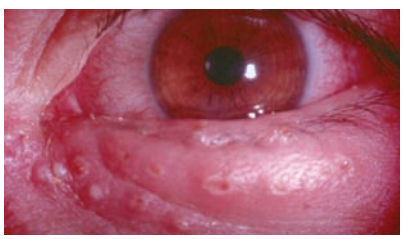
Signs and Symptoms

Herpes simplex virus 1 (HSV-1) blepharitis is encountered primarily in children, although adults may also manifest this disorder as a presenting manifestation of this viral infection.[1-7] Presenting symptoms include variable pain and tenderness upon palpation, papillomacular rash, as well as increased lacrimation in severe cases. If the conjunctiva is involved, tarsal follicles may be observed along with bulbar injection and chemosis. A swollen pre-auricular node on the involved side is common.

HSV infections involving the lid may present in one of two forms. The classic appearance involves an accumulation of small vesicles or pustules along the lid margin and/or periocular skin. These lesions typically have an inflamed, erythematous base. Within the first week of infection, the vesicles may ulcerate or harden into crusts, although they will ultimately resolve without scarring. A second "erosive-ulcerative" form of HSV blepharitis has also been described.[8,9] This presentation is characterized by erosions of the lid at the Gray line or ulcers along the lid margin, or a combination of both. The lid typically displays generalized swelling and redness associated with these lesions. The lesions usually number no more than three and, like the classic variety, they generally resolve without scar formation. Meibomianitis has also been associated with HSV-1, but this manifestation is much less common than the above described blepharitis.[10]

Pathophysiology

Herpes simplex is the most common virus found in humans. A member of the *Herpetoviridae* family, HSV is a double-stranded DNA virus that replicates within cell nuclei. Systemic transmission is via secreted fluid and close contact with mucosal tissues. Ocular transmission occurs either directly or indirectly as infected fluid makes contact with the eye or there is neuronal spread from a non-ocular site, creating ocular manifestations.[11]



Herpes simplex blepharitis (pustular form).

The ocular manifestations of primary infection with HSV-1 include blepharitis, conjunctivitis, or corneal epithelial keratitis. After initial ocular infection, the virus establishes a latent infection within the trigeminal ganglia for the host's lifetime. During this latent period the viral genome is retained in the neuron without producing viral proteins.[11] Several trigger factors, including fever, trauma, emotional stress, menstruation, exogenous immunosuppressive agents, and overexposure to UV radiation have long been associated with viral reactivation, though these features have been called into question.[12]

Primary ocular infections occur most often in children between the ages of six months and five years, and almost invariably present as blepharitis or blepharoconjunctivitis.[11] In recurrent attacks, the virus usually reappears with the classic presentation of dendritic keratitis. Several reports of recurrent HSV blepharitis have been reported in the literature, however.[2,3,9,13]

Management

There is no specific treatment for HSV blepharitis, and most often the course of the disease is self-limiting within two to three weeks.[14] The use of warm saline compresses with a topical drying agent (e.g. 70% alcohol or aluminum sulfate—Domeboro [acetic acid/aluminum acetate, Bayer]—solution) is usually sufficient to palliate the patient. If the lesions are extensive, concomitant use of topical antibiotic ointment is considered prudent to prevent a secondary bacterial infection. The use of topical or oral antiviral agents has not been proven to enhance

the recovery of patients with HSV-1 blepharitis, although the use of oral antiviral medications is still advocated by some practitioners for more severe cases. Viroptic (trifluridine 1%, Monach Pharmaceuticals) or Zirgan (ganciclovir ophthalmic gel 0.15%, Bausch + Lomb) is absolutely indicated in cases presenting with corneal or conjunctival involvement. The use of topical steroids on HSV lid lesions may be unwise, particularly if there is any sign of conjunctival or corneal involvement. Although corticosteroids may be used without fear in cases of herpes zoster (HZO) blepharitis and iritis, their use in cases of HSV infection may predispose the patient to the eruption or worsening of a dendritic keratitis.

While the acute management of HSV blepharitis does not seem to require or benefit greatly from oral antiviral agents, the Herpetic Eye Disease Study II showed that the recurrence of herpes simplex virus eye disease is clearly decreased when long-term acyclovir (extrapolated to other oral antiviral agents) is used.[15,16] Thus, patients who experience two or more recurrences of HSV blepharitis should be offered the option of prophylactic therapy consisting of oral acyclovir 400mg b.i.d. or alternative oral antiviral coverage.[15,16]

Clinical Pearls

• The differential diagnosis of HSV blepharitis should always include HZO. Keep in mind, however, that HZO typically affects elderly patients over the age of 70. Younger patients who present with HZO are often immunocompromised secondary to disorders such as AIDS or lymphoma. HSV blepharitis is usually encountered in children, but can occur at any age.

• Although herpes simplex is known as a sexually transmitted disease, the vast majority of ocular herpes infections are not contracted via sexual contact. This is very important to recognize when considering pediatric cases of HSV blepharitis.

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BLEPHARITIS

Signs and Symptoms

Blepharitis is an overarching term that describes a state of inflammation of the eyelids. It is sometimes associated with infectious microbial pathogens. Involved tissues can include the skin of the eyelids, the eyelid margins, the eyelashes and associated pilosebaceous glands, and the modified sebaceous glands deep within the tarsus, also known as the meibomian glands. Personal hygiene and associated dermatological conditions may have an impact on the development or severity of blepharitis.[1]

Blepharitis is typically bilateral, with variable symptoms including itching, burning, grittiness, foreign body sensation, heaviness, and perhaps tearing. As noted in one study there is notable overlap of these symptoms with dry eye syndrome, often confounding the diagnosis.[1] Crusty or scaly debris in and around the eyelashes, particularly upon awakening, is one of the hallmark signs. Other visible ocular signs include lid erythema, collarettes (ringlike formations around the lash shaft), madarosis (loss of lashes), trichiasis (inward turning of the lashes), meibomian gland inspissation (plugging), conjunctival injection and superficial punctate keratitis on the lower third of the cornea.[1-4] In severe or untreated cases, ulcerative blepharitis may ensue; this is marked by focal, hemorrhagic erosions of the lid margin and associated corneal epitheliopathies. Other complications of chronic blepharitis may include hordeola, chalazia, preseptal cellulitis and marginal keratitis.[1-4]

Pathophysiology

Historically, researchers have described six distinct categories of blepharitis.[2,3] These include: (1) infectious or *Staphylococcal* blepharitis; (2) seborrheic blepharitis; (3) mixed *Staphylococcal* / seborrheic blepharitis; (4) seborrheic blepharitis with meibomian gland seborrhea; (5) seborrheic blepharitis with secondary meibomianitis; and (6) primary meibomianitis.[2,3] Today, the current strategy is to subdivide blepharitis into two broad anatomical classes: ***anterior*** and ***posterior***.[4] Anterior blepharitis denotes those manifestations primarily affecting the lashes and their associated piloseba-

ceous glands; this category may be further divided into ***bacterial*** and ***seborrheic*** categories.[4] Posterior blepharitis deals with disorders of the meibomian glands (modified sebaceous glands) designed to produce the complex lipid tear component. Subsequently, posterior blepharitis is often referred to as *meibomitis* or *meibomian gland dysfunction* (MGD).[4]

Bacterial-associated anterior blepharitis results from bacterial overgrowth. The most common associated organisms are *Staphylococcus epidermidis* and *Staph. aureus*. Both of these bacteria are indigenous to the eyelid margins and lashes. Toxic bacterial products released into the tear film stimulate the production and release of pro-inflammatory cytokines and leads to recruitment of inflammatory cells, triggering host-induced as well as organism-induced inflammation.[5] Bacterial blepharitis may be recognized by its inflamed, erythematous lid margins and dry, crusty debris in the lashes and at the base of the cilia (*collarettes*).

Seborrheic blepharitis results from a dysfunction of the pilosebaceous glands and may be related to *Malassezia furfur* (previously referred to as *Pityrosporum ovale*), a pathogenic yeast fungus that resides on or near hair follicles.[6,7] In seborrhea, the glands produce excessive sebum, resulting in the accumulation of large, greasy scales along the hair shaft and surrounding skin. Common sites include the eyebrows, glabella and anterior scalp; in seborrheic blepharitis, these "dandruff-like" flakes are evident along the lashes and lid margins.

MGD is a condition marked by chronic obstruction and inflammation of the meibomian glands.[8,9] This can be seen clinically as inspissated gland orifices at the gray line and cloudy, viscous or sometimes toothpaste-like meibum upon digital expression of the glands. Clinical and histopathic observations reveal an abundance of ductal occlusion due to hyperkeratinization of the ductal epithelium, as well as a potential loss of glands in advanced disease.[8,9] The meibomian lipid secretions in these individuals are more saturated and contain less-branched chain hydrocarbons and more protein.[10] This change results in more ordered, more viscous lipid secretions, which retards the affected gland's flow and impedes the delivery of meibum to the lid margin. Stagnated meibum means that fewer lipids are available to form the tear film, resulting in increased tear evaporation.[11] In addition, MGD is exacerbated by the presence of bacterial lid flora such as *Propionibacterium acnes* and *Staph. epidermidis*, which thrive in this environment.[5] These bacteria secrete lipases, which act directly on the meibum, initiating conversion of the lipids into free fatty acids and soaps. These unwanted elements in turn cause ocular surface irritation and further disrupt the tear film.[11] Recalcitrant forms of MGD may be associated with rosacea, a generalized dermatologic condition affecting the sebaceous glands of the face, particularly the nose, cheeks, forehead, and periorbital regions.[11]

Management

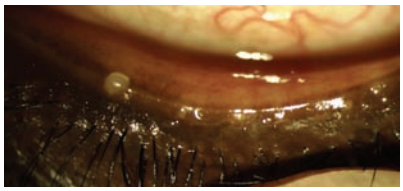
Management for any form of blepharitis must be multifaceted, as a single therapy will rarely serve to eliminate all of the signs and symptoms on a permanent basis. A variety of modalities, including lid hygiene, topical medications, and even oral medications may be utilized.

Lid hygiene is considered by many practitioners to be the mainstay of blepharitis management; in most cases, it consists of two elements: *lid hyperthermia*, a.k.a. warm compresses, and *lid scrubs*, which involve direct cleansing of the lid margins with a mild detergent. Lid hyperthermia can be helpful in both anterior and posterior blepharitis. The direct application of heat (approximately 105–110°F) to the lid margins helps to improve circulation in the lids and lower the viscosity of meibomian secretions, allowing them to flow more freely.[12,13] In addition, heat helps to control bacterial overgrowth and dissolve crusty lid debris in anterior blepharitis, making it easier to remove. Lid scrubs are beneficial for patients with anterior blepharitis, as they serve to remove the excess sebum and debris while further reducing excess bacterial colonization of the lid margins. However, lid cleansing with baby shampoo or another detergent-based product, while effective in controlling bacterial overgrowth in cases of bacterial blepharitis, can actually be counterproductive in MGD. Here, the agents function in a similar fashion as bacterial lipases, breaking down residual, healthy meibum into free fatty acids and soaps, further compromising the lipid tear elements and increasing symptoms.[13] In cases that are not well delineated or are the result of mixed mechanisms, lid hygiene—with or without lid scrubs—should be recommended twice daily for the first two days, and then once daily in the evening for an additional 28 days thereafter.[13]

Historically, the use of topical antibiotics like bacitracin, sulfacetamide and erythromycin ointment was common for chronic or severe cases of anterior blepharitis. For patients with substantial inflammation and symptomology, the use of a combination agent with a concurrent steroid—e.g. tobramycin and dexamethasone (TobraDex, Alcon)—resulted in faster and greater degrees of improvement.[14] Unfortunately, the long-term effects of corticosteroids must always be weighed against the benefit of any chronic disease. Most experts today recommend corticosteroids for short-term use only—usually two weeks or less—in an effort to "jump start" therapy for moderate-to-severe anterior blepharitis or blepharoconjunctivitis. One of the more recent additions to the blepharitis treatment algorithm is topical azithromycin (AzaSite, Inspire

Pharmaceuticals). The medication has demonstrated promise in this area despite the fact that this drug is not specifically FDA-approved for this purpose. A series of published studies have demonstrated a distinct improvement in the signs and symptoms of both anterior and posterior blepharitis when treated with AzaSite.[15-18] The typical regimen is one drop of AzaSite twice daily for two days, then one drop at bedtime for an additional two to four weeks. Patients are advised to instill the drop into the lower cul-de-sac, close their eyes gently, and then spread the residual medication along the lid margins with a clean finger.

More chronic or severe cases of blepharitis—especially MGD—may warrant the use of oral tetracycline derivatives such as doxycycline or minocycline.[19] It is believed that these drugs hinder the production of bacterial lipases, which serve to alter the consistency of the meibomian oils.[19] Additionally, tetracyclines are recognized to be potent anti-inflammatory agents, inhibiting the expression of matrix metalloproteinases and other cytokines which incite the local inflammatory response.[20,21] A regimen of oral doxycycline 100mg b.i.d. p.o. X 4 weeks, then q.d. p.o. for another four-eight weeks, has been shown to be highly effective.[22] Therapeutic effects may be seen with as little as 40 mg of doxycycline hyclate, p.o. daily, though there is typically a delayed response, often taking up to six weeks for patients to appreciate symptomatic improvement.[23] Essential fatty acid (EFA) supplements may also be beneficial in MGD. These agents purportedly have the capacity to improve meibomian gland secretions by stimulating tear-specific anti-inflammatory prostaglandins.[21] Typical dosing consists of two-four grams p.o. daily. There are many varieties of these dietary supplements and patients should be advised to read all packaging directions and precautions



MGD—note plugging, capping and meibomian orifice dropout, along with hyperemia of the palpebral conjunctiva.

as well as have a discussion with their primary care physician before starting these supplements to insure there are no contraindications or potential negative medicinal interactions. EFA supplements must be used with caution in those patients taking systemic anticoagulant or anti-platelet therapy, i.e., "blood thinners" such as aspirin, warfarin sodium (Coumadin, Bristol-Myers Squibb), clopidogre (Plavix, Bristol Myers-Squibb) or ticlopidine hydrochloride (Ticlid, Roche Holding AG) because of a potential dose-related effect on bleeding time.[24,25] Also, patients should be advised that increased urinary and/or bowel frequency can occur following the use of these supplements, particularly at high doses or when first initiating therapy.

Clinical Pearls

• Clinical manifestations of MGD include poor stability of the tear film, which can be marked by a rapid tear break up time and/or the presence of "foamy" or "frothy" tears (representing saponification of the lipids).

• Commercially available eyelid cleansing pads (OCuSOFT Lid Scrubs, Cynacon/OCuSOFT) are available for lid scrub therapy. Such products may provide a more convenient and sterile alternative to the "washcloth & baby shampoo" method.

Anterior blepharitis—note the key diagnostic signs: crusting at the base of the lashes, mild erythema, tylosis and focal loss of lashes.

• Patients with seborrheic blepharitis are likely to have associated dermatitis, which may be evident in the eyebrows, glabella and anterior scalp. If detected, these patients should be referred for additional dermatological care, as numerous treatments are available for this disorder. Antibiotics (topical and oral) are of little value in seborrheic blepharitis.

• Recalcitrant cases of MGD may be indicative of ocular rosacea. Signs include telltale skin thickening and erythema of the forehead, cheeks, nose, and chin. While rosacea is often responsive to a simple course of oral doxocycline, a dermatology consultation is nonetheless warranted in these patients.

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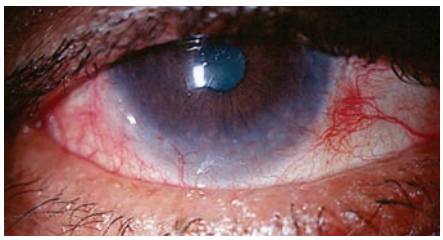
NEW DRUG UPDATE, 2011: TOBRADEX ST

Combination medications have a unique place in eye care. By combining a corticosteroid with an antibiotic, this group of drugs imparts both anti-inflammatory and anti-infective properties, making it the ideal choice for patients with inflammatory ocular disorders that may also involve (or be at risk for) a bacterial component. Clinically, we tend to use these combination agents for specific conditions, including such entities as acute blepharoconjunctivitis, contact lens-associated acute red eye, marginal keratitis, corneal abrasions and possibly uncommon conditions such as shield ulcers (associated with vernal or atopic keratoconjunctivitis). Many practitioners employ these agents for the "idiopathic" red eye presentations that do not fit neatly into any specific diagnosis. Here, the assumption is that the condition has both inflammatory and infectious components and would benefit from both anti-inflammatory and antimicrobial agents. The convenience of having both medications delivered in one drop provides the promise that the condition will be empirically arrested. Hence, combination medications are often impulsively considered first in severe or bewildering cases. When the medications are used to combat conditions which are inflammatory and/or infectious they successfully provide rapid relief of symptoms in a short period of time.



Combination agents like TobraDex ST are indicated for the treatment of inflammatory ocular conditions where superficial bacterial ocular infection or a risk of bacterial infection exists.

There are a number of combination agents available in the United States. Most of these are generic agents, combining corticosteroids such as prednisolone acetate, prednisolone sodium phosphate or dexamethasone alcohol with aminoglycoside (e.g. neomycin, tobramycin) or sulfonamide antibiotics. Over the last 20 years, the three most commonly prescribed agents in this class of topical medications have been TobraDex (dexamethasone 0.1% /tobramycin 0.3%, Alcon), Maxitrol (dexamethasone 0.1% /neomycin 3.5mg/mL/polymyxin B 10,000 units/mL, Alcon) and Zylet (loteprednol etabonate 0.5%/tobramycin 0.3%, Bausch + Lomb). Recently, a new combination agent was introduced—TobraDex ST.

TobraDex ST (dexamethasone 0.05%/tobramycin 0.3%, Alcon) received FDA approval on February 13, 2009, but was not launched in the U.S. until the third quarter of 2010. It utilizes the same pharmacologic components as its predecessor, TobraDex; however, the concentration of dexamethasone in TobraDex ST is actually half of what is found in TobraDex.[1,2] While it may seem that such a reduction would diminish the therapeutic effect of TobraDex ST, this is not the case. TobraDex ST utilizes a xanthan gum delivery platform to enhance the drugs' residence time on the ocular surface and improve tissue concentration.[3] While no human studies have been published at this time, an experimental animal model investigating conjunctival drug concentrations demonstrated a 12.5-fold and 1.4-fold difference in tobramycin and dexamethasone concentrations, respectively, favoring TobraDex ST over original TobraDex.[3] Likewise, corneal concentrations with TobraDex ST were 2.6 times higher for tobramycin and 1.9 times higher for dexamethasone.[3] Head-to-head studies also show distinctly steeper kill curves for the tobramycin concentrations achieved with TobraDex ST as compared to original TobraDex.[3] Another important feature that the xanthan gum vehicle imparts to TobraDex ST is that it permits it the ability to remain more stable in suspension. A study comparing side-by-side samples of TobraDex ST and TobraDex over a 24-hour period showed settling of only 3% for TobraDex ST, as compared to 61% for TobraDex.[3] Clinically, this means that patients may not have to shake the product as vigorously before instillation, or if they neglect to shake it at all, the concentration of the administered drugs should be minimally altered.

Some clinicians are reluctant to use corticosteroid/antibiotic combinations extensively, due to long-term issues related to steroid therapy such as elevation of intraocular pressure, cataractogenesis and impaired wound healing. Since the combination class of topical medications is designed for short-term use only, the risks of secondary glaucoma and cataract formation are exceedingly small when the preparations are used within the traditionally appointed one-to-two week window. With the exception of a very small percentage of the population, adverse responses to topical steroids are only typically encountered with dosing regimens of four or more times-a-day over the course of four weeks or longer.[4-6]

TobraDex ST is a welcome addition to the combination agent arsenal. It offers a potent alternative that is equivalent to TobraDex in terms of both efficacy and safety, with less settling, better tissue penetration and half the dexamethasone concentration.

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CONJUNCTIVOCHALASIS

Signs and Symptoms

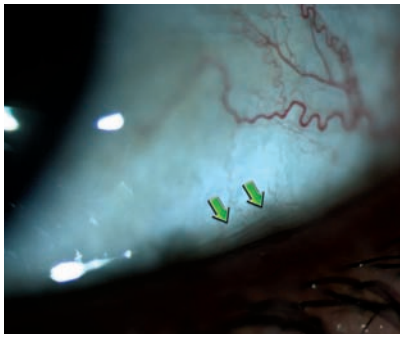
Conjunctivochalasis (CCh) refers to a laxity and redundancy of the bulbar conjunctiva. It is manifested by easy displacement of the conjunctiva from the underlying episclera.[1-3] CCh is more commonly seen in elderly patients and may be associated with a variety of symptoms including itching, irritation or foreign body sensation, intermittent tearing, epiphora and contact lens intolerance.[1,2] Biomicroscopy of these patients reveals pleated folds in the conjunctival tissue, which are especially visible inferiorly just above the lower lid margin. The condition tends to be bilateral, and it may be more obvious with digital pressure on the lower lid or when the patient directs his gaze downward.[2] CCh may less commonly affect the upper bulbar conjunctiva as well, where it has been associated with superior limbic keratoconjunctivitis of Theodore.[4] Subconjunctival hemorrhage is another sign that may be frequently noted in patients with CCh.[1,3,5] In severe cases, the conjunctival folds may prevent normal lid closure during sleep, leading to nocturnal lagophthalmos and subsequent discomfort upon awakening.

The most significant association noted with CCh is dry eye syndrome. "Lip-like" folds in the conjunctiva disrupt the formation of the tear meniscus, inducing delayed tear clearance through the puncta and altering normal tear flow dynamics.[1,3,6] Patients with CCh may present with classic symptoms of irritation, burning and dryness, but may have normal tear volume (as measured by Schirmer testing). Vital dye staining with sodium fluorescein, lissamine green or rose bengal reflects associated pathologies and hence may vary widely; however, accumulation of the dye in the redundant conjunctival folds may help to highlight CCh in mild cases.[1] It has also been suggested that as many as 50% of patients with CCh have concurrent swelling of one or more puncta, reflecting an inflammatory ocular surface state.[3]

Pathophysiology

Numerous mechanisms have been proposed to explain the development of CCh, but unfortunately there is still no absolute consensus on its etiology. Some of the factors that have been implicated include age-related changes, abnormal eye movements or eye rubbing, obstruction of lymphatic flow, mechanical inflammation and loss of elastic fibers. Histopathologic studies of conjunctivae taken from patients with CCh reveal normal cytology in the majority of cases, although lymphangiectasia and inflammatory infiltrate has been observed in a small percentage of subjects.[6,7] The conclusion of most experts is that CCh is likely a multifactorial disorder, resulting from a combination of senescent, traumatic and immunologic effects at the level of the ocular surface.[1,7]

Several authors have described a classification scheme for CCh.[4,8-10] The most elaborate of these was proposed by Meller and Tseng in 1998.[9] This system utilizes five features, including: (1) ***location***—whether temporal, middle, or nasal region of the inferior bulbar conjunctiva are involved; (2) ***height***—whether above, equal to or below the tear meniscus; (3) ***punctal occlusion***—whether or not the folds obscure the punctum; (4) ***changes in downgaze***—whether the folds increase, remain constant or decrease, and; (5) ***changes from pressing on the lower lid***—whether the folds increase, remain constant or decrease.[9]



Conjunctivochalasis—the green arrows indicate the subtle, characteristic conjunctival folds at the lower lid-globe interface.

Management

Patients with asymptomatic CCh generally do not require any particular treatment. Those with mild irritation can often be managed successfully with ophthalmic lubricants and short-term treatment directed at associated pathologies (e.g. topical antihistamine drops for allergic conjunctivitis). The use of long-term medical therapy for CCh is generally not successful, perhaps because delayed tear clearance prolongs retention of the drugs and preservatives on the ocular surface, thereby aggravating the problem.[1] For patients with nocturnal lagophthalmos-associated-CCh, overnight patching or taping of the lids may help prevent exposure.

Severe, symptomatic CCh may require surgical intervention. A number of techniques have been pioneered, but the overarching goal is to reduce the laxity of the conjunctiva and restore normal lid/tear dynamics. The most commonly employed surgical procedure today involves a crescent-shaped resection of the inferior bulbar conjunctiva, closed by absorbable sutures.[9,11] Modifications on this technique include the use of amniotic membrane grafts over the resected area and the employment of fibrin glue in place of sutures.[11-13] Other, less commonly employed procedures include superficial conjunctival cauterization, high-frequency radio-wave electrosurgery, conjunctival-scleral fixation surgery and lateral canthal tendon repair.[14-17]

Clinical Pearls

• One of the key differentials of CCh is conjunctival chemosis associated with allergic conjunctivitis. CCh results in characteristic folds of the conjunctiva which disappear when the lower lid is depressed or withdrawn. The "boggy" edema associated with allergy tends to be constant and often produces a "watchglass" effect around the limbus.

• In assessing CCh, it may be helpful to first ask the patient to blink vigorously several times, and then press the lower lid firmly against the globe while pushing upward. Wrinkling of the conjunctiva along the lid margin nasally and/or temporally is a positive sign.

• Whether contributory or consequential, CCh certainly appears to have a high correlation with dry eye syndrome. In the clinical setting, the presence of these characteristic conjunctival folds is pathognomonic for dry eye, and should warrant a complete ocular surface evaluation.

• A modified form of conjunctivochalasis surgery has been marketed in various parts of the United States as a cosmetic procedure, referred to as "eye whitening". It is important to distinguish between this elective surgery and reparative CCh surgery when discussing this option with patients.

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CONJUNCTIVITIS WITH PSEUDOMEMBRANE

Signs and Symptoms

Conjunctivitis can be generically described as swelling of the bulbar, fornix or palpebral conjuctival tissues. Isolated infection (bacterial or viral), toxic exposure to ultraviolet light, toxic exposure to solid, liquid or gaseous substances, auto inflammatory disease, ischemic processes or combinations of these etiologies have all been implicated as causative.[1-6] The tissue's clinical appearance along with the symptoms will be variably dependant upon the cause but generically may include itchy, irritated, scratchy discomfort in the setting of watery, stringy or mucopurulent discharge, hyperemia, follicles and papillae along with a mild inferiorly-based keratitis with or without subepithelial inflitraton.[1-14]

Pseudomembrane or membrane formation in association with conjunctivitis can occur anytime there is significant damage to the conjunctival surface (toxic/chemical exposure, Steven's Johnson syndrome, ocular pemphigoid, frictional exposure to foreign matter), however, it classically associated with four principle etiopathologies: adenovirus conjunctivitis or epidemic keratoconjunctivitis (EKC), bacterial or acute infectious conjunctivitis, ligneous conjunctivitis and graft versus host disease (GVHD).[1-15] The pseudo or true membrane that forms does not typically alter the symptoms experienced by the patient unless it impacts the ability of the eyelids to perform their function. If the conjunctival fornicies are shortened and symblepharon develops, ocular surface sequelae including ocular dryness, discomfort and variable visual disturbances will follow. If the pseudomembrane or membrane disturbs the integrity of the cornea, mechanical ulceration may occur.[2]

Epidemic keratoconjunctivitis may present as a unilateral or bilateral, inferior palpebral, follicular conjunctivitis with epithelial and subepithelial keratitis and normal corneal sensation.[11,12] When subepithelial infiltrates (SEI) are seen they are typically concentrated in the central cornea, uniquely sparing the periphery.[11,12] Conjunctival injection, tearing, watery discharge, red edematous eyelids, pinpoint subconjunctival hemorrhages, pseudomembrane (with occasional true membrane) formation and palpable preauricular, submandibular, or submental lymph nodes are fundamental clinical signs of the entity.[10-12] In severe cases, conjunctival desiccation can result in scarring of the palpebral and fornix conjunctiva.[11] The condition is known for its contagiousness.[10-12]

Gonococcal conjunctivitis (or gonococcal keratoconjunctivitis when the cornea is also involved), is sometimes referred to as hyperacute conjunctivi-

tis.[9] While most cases are the result of sexually transmitted vectors, infected individuals have been detected without evidence of genital signs or symptoms.[16] The medical literature has recorded communal baths, towels or fabrics, rectal thermometers and poorly sanitized caregivers hands as an alternate means of transmission.[17] The contagious ocular disease typically presents as an acute, red eye with severe muco-purulent discharge of less than four weeks duration.[9] Conjunctival papillae, superficial punctate keratitis and marked chemosis are almost always present.[9,10,16-19] Subconjunctival hemorrhage (hemorrhagic conjunctivitis), pseudo or true membrane formation and preauricular adenopathy are usually present.[9,10,15-19] In chronic, recalcitrant or severe cases, peripheral subepithelial corneal infiltration may occur leading to corneal ulceration with anterior iritis.[10]

Ligneous conjunctivitis is a rare form of chronic conjunctivitis characterized by the development of firm fibrin-rich, wood-like pseudomembraneous lesions on the tarsal conjunctiva of one or both eyes.[3] Less frequently, similar lesions may occur on other mucous membranes of the body indicating that these manifestations are part of a systemic disease.[3] Plasminogen deficiency (hypoplasminoginaemia), congenital occlusive hydrocephalus and juvenile colloid milium are other systemically associated disorders.[3] An autosomal recessive inheritance pattern is reported in the literature.[20,21] Here, the developing intrusive matter organizes and attaches to the underlying tissues mechanically inducing trauma to the ocular surfaces where it has exposure. Foreign body sensation, keratopathy and corneal ulceration are all plausible.[3,5] Ligneous conjunctivitis has also been induced by oral antifibrinolytic treatment with tranexamic acid.[3]

Hematopoietic stem cell transplantation (HSCT) is a treatment for multiple medical conditions that result in bone marrow failure.[22] Graft versus host disease (GVHD) is a complication of allogeneic (taken from different individuals of the same species) hematopoietic stem cell transplantation. GVHD can be considered an exaggerated, undesirable manifestation of the normal inflammatory mechanism where donor lymphocytes encounter foreign antigens in a milieu that fosters inflammation.[23,24] The fundamental interaction of the GVHD response is the interaction of donor T cells with host antigen presenting cells (APC).[24] Cytokines, chemokines and immune cell subsets also play a role.[24] In the eye the lacrimal gland and conjunctival surfaces can be affected inducing dry eye, conjunctival scarring and in severe cases, pseudomembrane induction.[14,15,21-23]

Pathophysiology

While the etiopathology of the conjunctivitis might vary, the base histochemical error that permits conjunctival pseudomembranes and membranes to form is the same.[3-6,15] Pseudomembranes and "true" membranes are composed of the same materials (fibrinogen, granulation tissue, and inflammatory cells) and are only differentiated by the amount of organized exudate that is coagulated and its interdigitation with the underlying tissue.[15,25] A "true" membrane is composed of a greater amount of fibrin. By way of the inflammatory response and time, the constituents comingle with both the necrotic epithelium and the substantia propria of the affected tissue. This makes "true" membranes more difficult to remove, increasing both the likelihood and volume of bleeding upon their extraction.[15] This is a documented clinical diagnostic feature.[15]

Affected humans who become plasminogen-deficient through congenital disease or an acquired process undergo aberrant wound healing, mainly within injured mucosal tissue.[3] Here, impaired plasmin-mediated extracellular fibrinolysis (the disassembly and demolition of unneeded fibrin) results in the deposition of "wood-like" plaque material onto the affected tissues. Pseudomembraneous lesions of the eyes and other mucosal tissues mainly contain clotted fibrinogen.[3]

Plasminogen deficiency has emerged as a well-recognized disorder in which reduced levels of plasminogen lead to the development of pseudo membranes on mucosal surfaces.[4] Two types of plasminogen deficiency have been described in the literature. Type I represents a quantitative deficiency and type II a qualitative deficiency.[4]

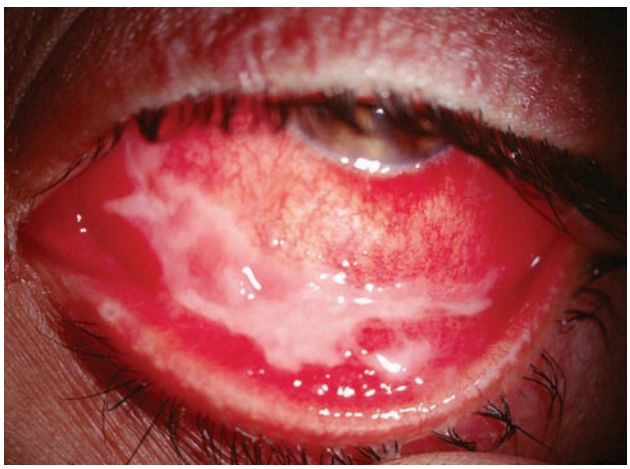
In cases of pseudomembrane or membrane formation secondary to forms of conjunctivitis where there is no plasminiogen deficiency, the exudates and inflammatory response produced by the conjunctivitis itself creates volumes of the substances that form the scaffolding of the process.[5] Pseudomembranes or membranes are comprised of fibrin, chemical mediators of inflammation such as matrix metalloprotinases (MMP) and other inflammatory cells, however, both direct and indirect evidence implicates some mechanism of hypofibrinolysis as the primary defect.[5]

Management

The appropriate method of resolving conjunctivitis with pseudomembrane or "true" membrane has two components: 1) Appropriately diagnose and treat the underlying cause of the conjunctivitis and 2) Remove the pseudo or "true" membranes from the conjunctival surfaces.

Viral conjunctivitis is contagious but self limiting. The primary function of management is to increase patient awareness and comfort by providing education and decreasing symptoms.[26]

Patients should be kept home from work or school until contagious discharge is eliminated.[26] Patients should be warned not to use common utensils, glasses, linens or wash cloths. Medical management may range from supportive cold compress and tears, as needed, to topical vasoconstrictors, topical nonsteroidal anti-inflammatory medications and steroids b.i.d. to q.i.d. If pseudo or true membranes are present they should be peeled using a moistened cotton tipped applicator soaked in a combination of antibiotic and anesthetic solution. Forceps can be used as well for pseudo or "true" membranes that will not separate from the conjunctival tissue with a cotton-tipped applicator alone. Topical antibiotic/steroidal combination therapy q.i.d. or separate drops in the same respective classes can be employed following the removal of the tissue.[11]



Conjunctivitis with pseudomembrane.

In cases of hyperacute or sexually transmitted conjunctivitis, options include oral tetracycline 250-500mgs q.i.d. for three weeks or its alternatives (doxycycline, minocycline, azithromycin) along with a topical antibiotic, such as a fourth generation fluoroquinolone, q.i.d.-q2h, topical steroidals q.i.d. to q2h and cycloplegics as necessary. Since tetracycline requires considerations such as administration one hour before or after meals to avoid gastrointestinal side effects, interference of dairy products with its effectiveness and ability to deform bones and teeth in the young (less than 10 years old), its alternatives may present a better option. Amoxicillin and erythromycin, 250-500mgs, q.i.d. for three weeks or doxycycline, 100mgs, b.i.d., for one week are acceptable alternatives.[16,27-30] Ceftriaxone, cefixime, spectinomycin and azithromycin (1gm) are all acceptable alternatives which may be required should suspicion of resistant strains of gonorrhea or chlamydia be suspected.[31,32] Medical management of gonococcal conjunctivitis begins with an intramuscular loading dose of ceftriaxone, 1gm.[31-33] Ideally, therapy should continue with hospital admission and intravenous administration of ceftriaxone 1gm q 12-24 hours.[33] The oral antibiotics are added subsequently following discharge.[31-33]

Mechanical removal of all discharge and debris is a critical element to both the success of infection resolution and improving patient functioning. The eye lids should be everted to rule out the presence of pseudomembranes; they should be removed if discovered via the method described previously. Over-the-counter oral analgesics can be used to increase patient comfort along with palliative measures such as cold compresses and ocular lubricants.

For ligneous conjunctivitis, a plasminogen concentrate formulated into an ophthalmologic preparation has been found to be an effective local therapy. Unfortunately, no plasminogen concentrate is currently available commercially for either systemic or local therapy.[4]

GVHD produces ocular sequelae consistent with tear dysfunction syndrome.[34] Artificial tear solutions, ointments, punctal plugs, oral medications increase tear and goblet cell function are all reasonable. A report in the literature suggests that 0.05% topical cyclosporine may be an effective treatment.[34] Pseudo or "true" membranes should be removed via the method described previously.

Clinical Pearls

- Pseudomembranes and membranes are the result of an underlying conjunctival infection or inflammation.
- Patients with hyperacute conjunctivitis should be examined every day until consistent improvement is noted and educated that they are contagious until they are symptom free for three days.
- If a sexually transmitted disease is confirmed, The Centers of Disease Control should be contacted for instructions and recommendations.
- Hyperacute conjunctivitis may require conjunctival scrapings for the purpose of culture and sensitivity.
- In young patients diagnosed with ligneous conjunctivitis it is not unreasonable to run appropriate laboratory studies for hypoplasminogenaemia.

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ACUTE BACTERIAL CONJUNCTIVITIS

Signs and Symptoms

Patients with acute bacterial conjunctivitis present with injection of the bulbar conjunctival and episcleral vessels. In some cases the palpebral conjunctiva is also affected. Infection typically begins in one eye and subsequently spreads to the fellow eye within 24-48 hours.[1] There may be mild photophobia and discomfort, but pain is not typical unless there is concurrent corneal epitheliopathy. There will be mucopurulent discharge, and the patient usually reports that the eyelids and eyelashes are matted shut upon waking.[1,2] In fact, a history of the eyelids being "glued shut" in the morning is highly predictive of bacterial infection.[2] There frequently is spillover of the discharge onto the patients' cheeks due to active, rapid, bacterial reproduction with a concomitant, mucopurulent response from the host. While patients of any age can be afflicted with acute bacterial conjunctivitis, it is especially common in children.[3-8] Wearing soft contact lenses presents an additional risk factor.[9]

Visual function typically is normal. However, in that the discharge is corneotoxic, a coarse punctate epitheliopathy may be present. When this occurs, the condition is better termed,acute bacterial keratoconjunctivitis. Significant epitheliopathy may cause vision reduction and discomfort in some cases. Drainage of the infection through the nasolacrimal system minimizes lymph node involvement. A conjunctival papillary or pseudomembraneous response may also be present.[2]

Pathophysiology

The eye has a series of defense mechanisms to prevent bacterial invasion. These include bacteriostatic factors within the tears, a relatively nutrient poor environment unsupportive of bacterial growth, the shearing force of the blink, an intact immune system, and a population of normal colonizing nonpathogenic bacteria which competitively prevent invasion by abnormal organisms. When these defenses break down or they are overwhelmed by a pathogen not sensitive to these defense mechanisms, an infection can occur.

Invading bacteria, along with secreted exotoxins, represent foreign antigens which induce an antigen-antibody immune reaction and subsequent inflammation. In a normal, healthy eye, invading pathogenic bacteria will eventually be eradicated as the eye strives to return to homeostasis.[5,10-13] However, the external load of organisms can potentially induce conjunctival or corneal infection with or without involvement of other adnexal structures.

The most commonly encountered organisms are *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*.[3,4,6,8,9] Several studies have identified *H. influenzae* and *S. pneumoniae* as the most prevalent infective bacteria, ranging from 29%-45% and 20%-31% of isolates repectively.[4,6] *S. viridans*, *Moraxella catarrhalis*, *Enterobacteriaceae*, and *Neisseria meningitides* are also encountered.[6,14] Occasionally, there will be more than one organism in an acute bacterial conjunctivitis.[6] Also, otitis media may present concurrently with acute bacterial conjunctivitis, especially in children. This syndrome is highly indicative of *H. influenzae* infection.[4]

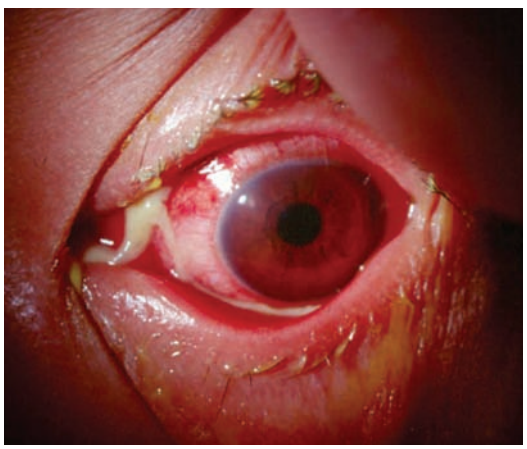
Management

In the vast majority of cases, acute bacterial conjunctivitis is a self-limiting disease. However, most reports indicate, despite the benign, self-resolving nature, bacterial conjunctivitis should be treated with topical antimicrobial therapy in order to shorten the disease course and improve the rate of clinical and microbiologic remission.[5,10,11,13,15,16] This is especially true early in the clinical course. However, if the patient presents having had the infection for several days, then topical antimicrobial treatment likely will provide only marginal benefits if any at all.[11]

As in any bacterial infection, a microbiologic study with culturing and sensitivity testing is the optimum means to reach a conclusive diagnosis and treatment plan. However, due to the expense of microbiologic studies and relatively benign, self-limiting nature of the condition, most clinicians advocate the use of broad-spectrum, empirical topical antibacterial therapy, reserving culturing for hyperacute conditions or those that fail to respond to initial therapy.

There are many options for empirical therapy. Excellent initial broad-spectrum topical antibiotics include Ciloxan (ciprofloxacin hydrochloride 0.3% , Alcon), Ocuflox (ofloxacin 0.3%, Allergan), Quixin (levofloxacin 0.5%, Santen), Polytrim (polymixin B sulfate and trimethoprim, Allergan), gentamicin and tobramycin.[6-8,10,13-17] These agents provide good coverage against gram-positive and gram-negative organisms. A newly tested formulation of tobramycin-enhanced-viscosity ophthalmic solution has shown excellent cure rates, even against tobramycin-resistant pathogens.[17] Polyantimicrobial therapy may be necessary to cover all possible organisms in the worst presentations.

Newer-generation topical fluoroquinolones—Vigamox (moxifloxacin hydrochloride 0.5%, Alcon) and Zymar (gatifloxacin 0.3% , Allergan)—have gram-negative coverage similar to the existing fluoroquinolones but with enhanced coverage of gram-positive species.[18] These antibiotics also have a lower incidence of bacterial resistance.[18] They have been seen to be well tolerated ocularly, with little induced damage to the cornea.[19-23] There is some evidence suggesting that moxifloxacin may have a lesser corneatoxic effect due to the lack of the preservative benzalkonium chloride.[19] They are also more effective than previous fluoroquinolones in resistant bacterial infections.[18,24] Moxifloxacin has been shown to be effective at eradicating superficial bacterial infections with excellent tolerability.[25] Both moxifloxacin and gatifloxacin have been shown to be clinically equivalent to the fortified cefazolin-tobramycin combination in bacterial keratitis.[26] For these reasons, newer generation fluoroquinolones are considered the standard-of-care in managing ocular bacterial infection and surgical prophylaxis.[16]



Bacterial conjunctivitis.

Newly developed medications have been shown to be effective in managing patients with acute bacterial conjunctivitis. Besivance (besifloxacin ophthalmic suspension, 0.6%, Bausch + Lomb) has been demonstrated to be effective against susceptible bacterial with an efficacy and tolerability similar to that seen in topical moxifloxacin.[27-30] Additionally, AzaSite (topical azithromycin 1%, Inspire Pharmaceuticals) in DuraSite has been seen as effective in managing patients with bacterial conjunctivitis.[31] One study showed that topical azithromycin was not as well tolerated as topical moxifloxacin.[32]

Resistance has become an issue with many antibiotics, even including the newer-generation fluoroquinolones.[3,4,7,18,24] Resistance has been noted with all major classes of topical antibiotics including aminoglycosides, polymyxin B combination therapies, macrolides, and fluoroquinolones.[33] However, topical dosing is not the principle reason for resistance. The problem is attributed to antibiotics placed into livestock feed (where individuals consume low levels of the drugs when they consume products from these animals), as well as general medical and surgical overuse of oral formulations.[18]

Although topical antibiotics help to eradicate the antigenic bacteria, they do nothing to suppress the concurrent inflammation. If there is no significant corneal disruption, then corticosteroids such as Pred Forte (prednisolone acetate 1%, Allergan), Durezol (difluprednate 0.05% emulsion, Alcon) or Lotemax (loteprednol etabonate 0.5%, Bausch + Lomb) can be used concomitantly with the antibiotics to speed resolution of the inflammation. Steroid-antibiotic combinations such as Maxitrol (neomycin, polymixin B and dexamethasone, Alcon), Zylet (tobramycin and loteprednol, Bausch + Lomb), and both TobraDex (tobramycin and dexamethasone, Alcon) and TobraDex ST (tobramycin and dexa-

methasone suspension, Alcon) are also possible choices for therapy when the cornea is intact.[34]

In cases where inflammation is problematic, topical steroids may be used, even in the face of a compromised cornea, so long as a topical antibiotic has been adequately loaded and it is clear that the therapy is working. This strategy can allow for a more precise direction of both agents: continuing the antibiotic at a minimum of q.i.d. until the treatment period is finished and then tapering the topical steroid over a longer period if necessary.

Clinical Pearls

• Proper diagnosis is the hallmark of management of acute bacterial conjunctivitis. Patients with viral and allergic conjunctivitis will have crusting of the lashes due to drying tears and serous secretions; those with bacterial conjunctivitis will manifest the wet, sticky, mucopurulent matting of the lashes. Too often, clinicians consider the dry crusting of the lashes to be the same as the mucopurulent matting and misdiagnose the condition.

• Patients with bacterial conjunctivitis are likely to manifest a mild papillary response, whereas an allergic conjunctivitis will have a more pronounced papillary response. Further, allergic conjunctivitis manifests with itching, which is not characteristic of bacterial conjunctivitis.

• Patients with viral conjunctivitis will more likely present with an ipsilateral swollen, tender preauricular node as compared to patients with bacterial conjunctivitis. Patients manifesting viral conjunctivitis commonly have a history of viral illness.

• Due to the excellent defense systems of the external eye, acute bacterial conjunctivitis is an uncommon condition.

• Topical antibiotics should not be tapered below the individual recommended dosing. Once a condition resolves, and the therapy period is completed, the antibiotic therapy should be abruptly discontinued.

• Mucopurulent discharge is corneotoxic. This discharge almost always produces concurrent epitheliopathy. That is why patients often present with bacterial keratoconjunctivitis and not just conjunctivitis. Patients should be instructed to remove the discharge with warm saline lavage frequently.

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CONJUNCTIVAL CONCRETIONS OCULAR LITHIASIS

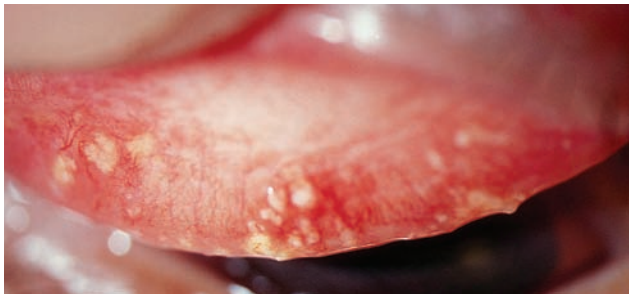
Signs and Symptoms

Conjunctival concretions, or lithiasis, are seen as small, white to yellow nodules superficially buried within and beneath the palpebral conjunctiva. They may occur in either the upper or lower lid. When inferior, they often appear adjacent to or underlying fluid-filled conjunctival cysts. In the majority of cases concretions seem to occur idiopathically or as a normal senescent change.

The patient with lithiasis may report a foreign body sensation that is especially prominent upon blinking, although most patients are asymptomatic. The concretions typically remain buried, benign and unnoticed by patients until they enlarge, at which time they may protrude through the palpebral tissues. Contact with the cornea leads to irritation, as well as epithelial disruption and a potential reduction in acuity if the visual axis is involved.[1,2]

Pathophysiology

These small, round calculi appear to be a side effect of an aging palpebral conjunctiva, or a sequelae of recurrent episodes of chronic conjunctivitis. Reports have shown an association between conjunctival concretions and chronic atopic keratoconjunctivitis, as well as Herbert's pits following post-trachomatous degeneration.[1,2] A potential correlation with dry eye disease and meibomian gland dysfunction has also been suggested.[3,4] Conjunctival concretions have been described as inclusion cysts filled with keratin (a protein constituent of epidermis and hair) and epithelial debris within the inferior and superior palpebral conjunctiva.[5] However, research has confirmed that there is a granular, membranous nature to the masses, which are composed mainly of mucinous secretions of transformed conjunctival glands admixed with degenerated epithelial cells.[6] Histochemically, concretions have been found to stain strongly for phospholipid and elastin, weakly for polysaccharides and negatively for amyloid, iron, and glycogen.[2] Ironically, there is very little calcium integrated within the accumulated material, as previously thought.[2]



Conjunctival concretions.

Management

Concretions do not generally require interventional management as long as the patient remains asymptomatic and the cornea is undamaged. All patients should be appropriately educated as to the etiology and prognosis of this disorder. Those who are mildly symptomatic may be palliated by the use of artificial tear solutions and/or ointments. In more severe cases—those in which palpebral tissues are at risk for damage, corneal erosion has occurred or symptoms have developed, persisted or worsened—excision is the modality of choice. This may be accomplished in-office by applying an anesthetic-soaked cotton tipped applicator over the area and using a small gauge (e.g. 25g - 27g) needle to excavate and extract the small calculi. Jewelers' forceps may be useful in gripping the concretions once the conjunctiva has been breached. In exceedingly superficial cases, simple manipulation with a cotton-tipped swab may be sufficient to loosen the nodule. After removal, the subsequent use of an antibiotic-steroid drop (e.g., TobraDex ST, Alcon) q.i.d. for 24-48 hours will help to minimize iatrogenic inflammation and prevent secondary infection.

Clinical Pearls

- Conjunctival concretions are avascular, granular, yellow-white masses that resemble crystals, and are visible upon lid eversion. Differential diagnoses include amyloid deposits, internal hordeola, adenochrome deposits, debris and foreign matter or tumor.
- Concretions typically respond favorably to excision and normally do not recur after removal. However, since recurrence is a possibility, patients should be appropriately educated.
- As a conservative estimate, perhaps only one patient in 50 with concretions ever requires surgical removal.[7]

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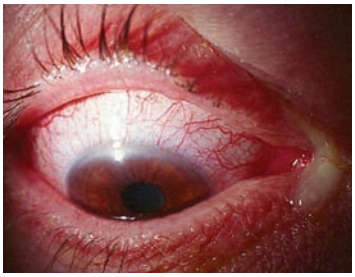
NEW DRUG UPDATE, 2011: BESIVANCE / ZYMAXID / MOXEZA

During the past year and a half, the eye care market has witnessed the introduction of a number of new topical antibiotic solutions. All of the "early generation" fluoroquinolones, including ciprofloxacin, ofloxacin and levofloxacin, have gone generic. The so-called fourth generation fluoroquinolones, Zymar (0.3%, gatifloxacin, Allergan) and Vigamox (0.5% moxifloxacin, Alcon), continue to hold their ground as the most commonly prescribed ophthalmic antimicrobial agents in the United States. Yet even these drugs, both of which are less than seven years since their FDA approval, are beginning to show signs of increasing bacterial resistance.[1] Hence, the pharmaceutical companies have once again decided that the time is right to launch yet a new cadre of topical antibiotic agents

• Besivance (0.6% besifloxacin, Bausch + Lomb) received FDA approval on May 28, 2009, but was not widely released until mid-way through 2010. The active drug, besifloxacin, represents the first new ophthalmic fluoroquinolone agent approved in the United States since 2003. In addition, it is the only topical fluoroquinolone to have never been formulated for systemic use, a fact that proponents claim substantially reduces its potential for acquired resistance.[1,2] Besivance is also unique in that it utilizes a proprietary polymeric mucoadhesive (DuraSite) as its vehicle, which helps to enhance its residence time on the ocular surface, thereby improving tissue concentration and penetrance. Besivance is approved for the treatment of bacterial conjunctivitis in patients aged one year or older, a similar indication as its predecessors, Zymar and Vigamox. Its dosing for conjunctivitis is three times daily for a period of seven days, and it is supplied in a 5 mL bottle containing 2.5 mL of solution. Besivance is preserved with 0.01% benzalkonium chloride (BAK), which is comparatively high; it is twice the concentration found in Zymar, and more than three times that of AzaSite (1% azithromycin, Inspire).



Besivance, Zymaxid and Moxeza are all approved for the treatment of bacterial conjuncivitis, as seen here.

Much of the "buzz" surrounding Besivance is that it is reportedly more effective against resistant strains of bacterial pathogens, particularly methicillin-resistant *Staph aureus* (MRSA) and methicillin-resistant *Staph epidermidis* (MRSE).[1,2,4] There is also a widely-held belief that the addition of BAK helps to contribute to clinical resolution and bacterial eradication of antibiotic formulations[5], although this concept remains debated.[6] What is known for certain is that Besivance has a broad range of antimicrobial coverage, particularly against gram positive pathogens. According to the package insert, it has demonstrated in vivo efficacy against a total of 13 known organisms.[3]

• Zymaxid (0.5% gatifloxacin, Allergan) received FDA approval on May 18, 2010. Unlike Besivance which incorporates a novel fluoroquinolone, Zymaxid is actually a reformulation of gatifloxacin at a higher concentration than its predecessor, Zymar (0.5% vs. 0.3%). Like Zymar, Zymaxid is specifically indicated for the treatment of bacterial conjunctivitis in patients aged one year or older, and is preserved with 0.005% BAK. Its dosage is somewhat different than Zymar, although it still requires a loading dose of q2h while awake on the first day of therapy; thereafter, it is instilled two to four times a day for a total of seven days.[7] Zymaxid is supplied in a 5mL bottle containing 2.5mL of solution; by comparison, this is half the amount supplied in Zymar. Another distinct difference between the two solutions is pH; Zymar maintains a pH of approximately 6.0,[8] while Zymaxid is notably more acidic, ranging between 5.1 and 5.7.[7] Greater acidity has the potential to cause more irritation upon instillation, and also to cause the drug to precipitate out of solution on the ocular surface. This was a problem that was previously encountered with Ciloxan (0.3% ciprofloxacin, Alcon).[9,10]

With regard to its clinical spectrum, Zymaxid covers precisely the same number of in vivo pathogens as its predecessor: five gram positive organisms and one gram negative organism (*Haemophilus influenzae*). It is anticipated that increasing the concentration of active drug in the solution will allow for greater concentrations in the ocular tissue, and hence a greater therapeutic effect. However, at the time of this writing there have been no published studies demonstrating the clinical advantage of Zymaxid over other topical fluoroquinolones.

• Moxeza (0.5% moxifloxacin, Alcon) is the newest topical antibiotic to be introduced to the U.S. market. It received FDA approval on November 19, 2010. Moxeza contains 0.5% moxifloxacin, which is precisely the same concentration as its predecessor, Vigamox. The primary difference between these medications lies in the vehicle. Moxeza utilizes a xanthan gum base, which – like DuraSite - helps to enhance the drug's residence time on the ocular surface and potentiate increased tissue concentration. A recent publication[11] confirms this claim; in a randomized, double-masked study involving 130 patients, subjects dosed with a single drop of Moxeza demonstrated subsequent conjunctival concentrations (Cmax) nearly twice that of subjects dosed with Vigamox.[11] Moxeza is similar to Vigamox in pH (6.8), unit size (4mL bottle containing 3mL of solution) and the fact that it is "self-preserved", containing no BAK.[12,13] It is indicated for the treatment of bacterial conjunctivitis, but unlike the other drugs in this class, Moxeza is the first topical fluoroquinolone to be approved down to 4 months of age (rather than one year).[12] Also, Moxeza enjoys a dosing schedule of b.i.d. for seven days, which represents the fewest drops per course of therapy for any of the fluoroquinolones.[12] According to the package insert, Moxeza demonstrates in vivo activity against an unprecedented 20 organisms: 15 gram-positive and 4 gram-negative species, as well as *Chlamydia trachomatis*.[12]

It seems that we will continue to see the introduction of new topical antibiotics as long as bacteria continue to find ways to mutate and acquire resistance to our best agents. Fortunately, the pharmaceutical companies have found ways to enhance these products beyond just increased spectrum of activity, improving the dosing regimens and safety as well. Hopefully, this latest "generation" of topical antibiotics will serve our clinical needs for many years to come.

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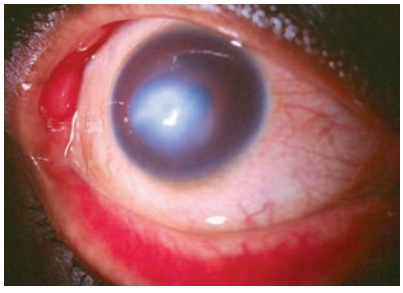
KERATOCONUS AND CORNEAL HYDROPS

Signs and Symptoms

Keratoconus is a progressive, irreversible corneal degeneration that usually begins to manifest during puberty. Patients typically report blurring and distortion of vision that worsens gradually over time. Other common symptoms may include glare and photophobia, monocular diplopia ocular discomfort, and sometimes significant pain. The rate of progression and severity varies from patient to patient. Keratoconus is bilateral in the majority of cases, but asymmetry is common.[1-3] The condition affects all races, although some studies have found a higher predilection in those of Asian descent.[4,5] The impact of gender is unclear, as studies have reported conflicting results; most authorities however, maintain that men and women are affected equally.[2,3,6-8]

In keratoconus, the cornea loses its normal configuration due to progressive steepening and thinning, and slowly assumes a conical shape. This results in a number of characteristic signs. The most recognized clinical finding is *Munson's sign*, a focal protrusion of the lid margin (corresponding to the corneal cone), which is seen in downgaze. Biomicroscopic examination often reveals an annular ring of hemosiderin (iron) pigment at the cone's base, referred to as the *Fleischer's ring*. Another classic finding in keratoconus is *Vogt's striae*, vertical striae in the posterior stroma that vanish with the application of digital pressure. Another common finding involves an abnormal red reflex (*Charleux oil drop*) in which a dark annular shadow surrounds the bright reflex of the cone. Other possible biomicroscopic signs include enlarged corneal nerves, clear spaces in the anterior stroma and fine subepithelial fibrillary lines.[1] Keratometric mires are characteristically distorted and topography shows severe steepening in the inferior region of the cornea.[9]

Corneal hydrops represents an acute state of stromal edema that results from ruptures in Descemet's membrane.[10] It is typically encountered as a severe, late-stage complication of keratoconus. The classic presentation includes limbal injection with pronounced central corneal haze, reduced acuity, pain, photophobia and profuse tearing. Although hydrops is self-limiting, it often results in corneal scarring.[1,2,10] Studies suggest that young males between six and 35 years of age are more prone to corneal hydrops and that there may also be an association with vernal keratoconjunctivitis.[11-13]



Acute corneal hydrops in keratoconus.

Pathophysiology

Keratoconus represents a disease state of chronic, progressive corneal ectasia. The disorder is decidedly non-inflammatory in nature, although the exact etiology and pathogenic mechanism remain unclear. Prevailing biochemical theories for keratoconus development suggest that corneal thinning occurs as a result of structural component failure due to proteolytic enzyme activity.[14-18] It has been proposed that these rampant enzymes result in degradation of the underlying stromal tissue, ultimately leading to the degenerative changes that are noted in this disease. Corneal hydrops represents an extreme sequela of keratoconus-related pathology, in which progressive corneal ectasia and/or trauma or rubbing induces an acute rupture of Descemet's membrane thereby allowing aqueous humor to permeate and accumulate within the corneal stroma.[2,10,11,13]

A variety of systemic conditions and concurrent factors have been observed to have an association with keratoconus. Connective tissue disorders linked to this corneal malady include Ehlers-Danlos syndrome, osteogenesis imperfecta and Marfan's syndrome.[19-21] Genetic disorders such as Apert's syndrome, Crouzon's syndrome, Turner's syndrome and most notably Down's syndrome (trisomy 21) have also been documented with keratoconus.[22-25] A recent publication draws a strong association between keratoconus and certain immune disorders, among them rheumatoid arthritis, ulcerative colitis, autoimmune chronic active hepatitis and irritable bowel syndrome.[26] Atopic disease and eye rubbing may also play a role in keratoconus. A significant incidence of atopy, especially hay fever and asthma, has been noted in those with keratoconus.[26,27] Theory holds that the mechanical trauma of chronic eye rubbing, aimed at relieving the itch associated with elevated histamine levels, may induce or enhance the degeneration and ectasia associated with keratoconus.[27-29] Likewise, corneal hydrops is closely associated with allergic disease and eye rubbing.[10,12,25]

Management

Management for keratoconus begins with early detection. The earliest indications of keratoconus may best be demonstrated by computerized corneal topography, although distorted, irregular mires observed during keratometry or a distorted reflex on retinoscopy should prompt the clinician to investigate further. Once diagnosed, the patient should be thoroughly educated

as to the progressive nature of this disorder. While the prognosis for keratoconus is guarded, the patient should recognize that there are numerous options for maintaining and maximizing functional vision.

In early stages, spectacle correction may be adequate for some patients. Unfortunately, lenses at the spectacle plane are incapable of addressing the irregular astigmatism usually associated with keratoconus. Gas permeable contact lenses are indicated when spectacles no longer provide acceptable visual acuity. It has been suggested that as many as 75% of patients can be maintained safely in therapeutically prescribed contact lenses for their condition.[7] Because of the irregular shape, conventional lens designs may not be sufficient; specialized lenses attempt to create midperipheral bearing for stabilization with vaulting over the paracentral region, creating a design which provides tangential clearance over the cone apex (the first definite apical clearance or FADACL approach endorsed by the Collaborative Longitudinal Evaluation of Keratoconus study [CLEK]). Some well-known lens designs include the Soper, McGuire, NiCone, Rose K, SynergEyes, Clearkone, DynaZcone and miniscleral designs.[7,30] The Softperm lens and "piggyback" systems may help to provide centration and improved comfort for more advanced cases of keratoconus.[31]

Unfortunately, contact lenses do not arrest the corneal ectasia associated with keratoconus, and ultimately a fair percentage of patients may progress to the point where surgical intervention becomes necessary. Surgery is recommended when scarring reduces visual acuity beyond a functional level, or when a stable contact lens fit can no longer be attained. Penetrating keratoplasty (PK) has historically been the treatment of choice, although deep anterior lamellar keratoplasty (DALK) has actually replaced PK as the preferred surgical technique among most corneal specialists today.[32] Newer therapies include intrastromal corneal ring segment implantation (Intacs), conductive keratoplasty, and corneal collagen cross-linking (CXL).[33-37] CXL is a unique and promising new procedure that utilizes topical riboflavin (vitamin B2) in combination with ultraviolet A (UVA 365nm) to form reactive oxygen species and additional covalent bonds between collagen molecules; the end result is a biomechanical stiffening of the cornea that may diminish the rate and extent of corneal ectasia, with a resultant improvement in refractive correction and visual acuity.[37]

Treatment for corneal hydrops is directed at alleviating patient discomfort, typically employing strong cycloplegia and a therapeutic bandage contact lens.[10] Hyperosmotic agents such as 5% sodium chloride ointment are commonly utilized, however it should be noted that these have their primary effect in the epithelium and do little to reduce stromal edema. It is common practice to also employ a prophylactic, broad-spectrum topical antibiotic to prevent against the possibility of superinfection.[10-12] Topical NSAIDs (e.g., nepafenac or ketorolac) or corticosteroids (difluprednate or prednisolone acetate) may be used for severe discomfort, although this is rarely necessary. Usually, hydrops will resolve within weeks to several months; patients should be seen every one-two weeks until resolution is complete. Subsequent corneal scarring from hydrops may prompt the need for keratoplasty if vision cannot be appreciably enhanced with contact lenses.

Clinical Pearls

• Occasionally, keratoconus is discovered in relatively asymptomatic patients in their twenties and thirties. These patients often demonstrate reduced acuity, but because of adaptation and high blur tolerance do not seek vision care.

• Another well-documented sign of keratoconus is a "scissors-type" reflex upon retinoscopy. Historically, this phenomenon offered great prognostic value to the clinician. However, with today's reliance on automated refraction, retinoscopy may be performed rather infrequently. In lieu of retinoscopic signs, look for irregular, high myopic astigmatism and the classic slit lamp findings.

• Keratoconus has been linked to numerous other ocular conditions. These include tapetoretinal degenerations (especially Leber's congenital amaurosis), floppy eyelid syndrome, Axenfeld-Rieger syndrome, Fuch's dystrophy, posterior polymorphous dystrophy, and granular and lattice dystrophies.[38-42]

• Unfortunately, keratoconus may recur even after penetrating keratoplasty.

• Topography should be considered in all patients where unexplained loss of vision is discovered. Here, clinicians without an etiology often attribute the lost visual acuity incorrectly to amblyopia. When topography is completed in these cases cones have been discovered with some frequency (keratometry only measures the central 3 mm of the cornea).

• If a topographer is not available, the clinician can attempt to fit the closest GP contact lens they have in stock, creating a semi-regular corneal surface. If this increases the vision, keratoconus should be suspected.

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PHLYCTENULAR KERATOCONJUNCTIVITIS

Signs and Symptoms

Phlyctenular keratoconjunctivitis is a nodular inflammation of the perilimbal tissues which is typically instigated by an allergic hypersensitivity response within the cornea and or conjunctiva.[1-5] The word phlyctenule takes its origin from the Greek word "phlyctena", meaning "blister."[6] Patients typically present with symptoms of tearing, ocular irritation, mild to severe photophobia and a history of similar episodes.[1-6] Typically the underlying cause is eyelid *Staphylococcus*, however, mycobacteria, parasites such as intestinal worms (*Hymenolepsis nana*), fungi and exposure to topical pharmaceuticals have also been documented.[1-9] The disease has a well documented association with the epidermal manifestations of tuberculosis which include lichen scrofuloderma and lupus vulgaris.[3,7,8] The disease has a worldwide distribution and is seen with greater frequency in countries with crowded living quarters and high endemic risk of tuberculosis.[6,10] The disease seems to affect the young females more than males and has a warm weather seasonal predilection.[6,9]

There are two distinct types of phlyctenular lesions: corneal and conjunctival.[1,2,6] Biomicroscopic evaluation of a conjunctival (vascularized) phlyctenule reveals a 1-3mm, hard, triangular, slightly elevated, yellowish-white nodule, surrounded by a hyperemic response, typically first appearing in the vicinity of the inferior limbus.[1,2,5,6] The lesions may be unilateral but tend to be bilateral.[1,6] Corneal phlyctenules produce more severe symptoms.[6] They usually begin adjacent to the limbus as a white mound, with a radial pattern of vascularized conjunctival vessels.[6] The lesion may migrate toward the center of the cornea, progressing as gray-white, superficial ulcers surrounded by infiltrate in the areas where the lesion has been.[1-6] Several reports recognize that multiple lesions may form and the condition itself may either trigger

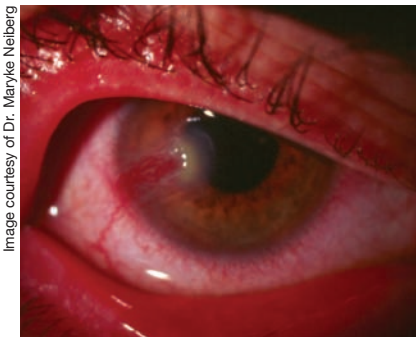


Image courtesy of Dr. Maryke Neiberg

Corneal phlyctenule.

or morph into Salzmann's nodular degeneration.[6]

Pathophysiology

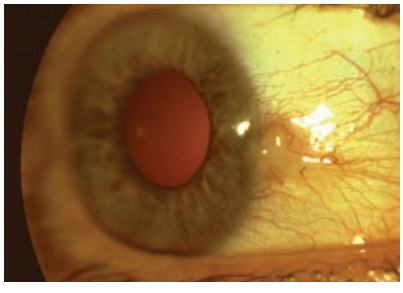
Phlyctenular lesions are the result of a delayed type IV hypersensitivity reaction to tuberculin protein, *Staphyloccocus aureus*, *Coccidioides immitis*, *Chlamydia*, rosacea, some varieties of interstitial parasites, *Candida albicans* and or exposure to a foreign substance.[1] Histologically, phlyectenules are composed of lymphocytes, mononuclear cells (T-lymphocytes, monocytes, macrophages and dendritic cells) and plasma cells.[6] Polymorphonuclear leukocytes are found in necrotic lesions.[2]

Scrapings from phlyctenules and the conjunctiva of 12 patients with phlyctenular keratoconjunctivitis were studied using immunochemical methods including HLA-DR monoclonal antibodies.[11] T-lymphocytes were present in all conjunctival and phlyctenular scrapings.[11] Other cells such as OKT4-Leu3a positive cells, OKT8 positive cells, B1, BA1 positive cells and S-100 cells were found in varying numbers in conjunctival and phlyctenular scrapings depending upon the sample location.[11] Most of the cells in both conjunctival and phlyctenular scrapings were human leukocyte antigen-HLA-DR positive. These findings support the hypothesis that cell mediated immunity is responsible for the pathogenesis of phlyctenular eye disease.[11]

Early classic reports identified significant levels of blood histaminase in patients with phlyctenulosis.[12] Here, it was hypothesized that levels rose secondary to increased release of histamine in the early phase of disease.[12]

Today, the availability to assay monoclonal antibodies can aid in the determination of T-lymphocytic subsets such as T-helper cells and T-suppressor/cytotoxic cells, natural killer cells and monocytes-histiocytes. This has provided a powerful technology for the delineation of the distinctive immune composition in disturbances of T-cell immunoregulation.[13] The B-lymphocytes produce immunoglobulins, which may be misdirected as autoantibodies in local or systemic autoimmune diseases.[13] These conditions include vasculitis, progressive cicatricial ocular pemphigoid, Mooren's corneal ulcer, scleritis, hay fever and vernal conjunctivitis.[13]

T-cells do not produce immunoglobins; instead they either secrete lymphokines or interact directly with receptors, determinants on viruses or target tissues.[13] T-cell diseases include phlyctenulosis graft rejections, graft versus host disease, sympathetic ophthalmia and temporal arteritis.[13] Natural killer cells are involved in many of the same diseases as cytotoxic T-cells, except that the former require no period of sensitization (natural immunity), whereas cytotoxic T-cells must undergo an antigen-specific transformation (acquired immunity of the delayed hypersensitivity type).[13]



Conjunctival phlyctenule.

Management

Ocular management of phlyctenular keratoconjuntivitis begins with patient education to improve eyelid hygiene. Lid scrubs, two-three times a day, along with artificial tears and ointments may soothe and reverse mild cases. Moderate to severe cases require topical steroidal or steroidal/antibiotic combination medicines. Cyloplegia is rarely necessary. In most cases, Pred Forte (prednisolone acetate, Allergan), one drop, q2h-q.i.d. is sufficient, provided there are no corneal contraindications. If the suspected etiology is staph or rosacea, doxycycline, 100 mg t.i.d., q.i.d., p.o., or 250mg q.i.d. of oral erythromycin along with topical antibiotic ointments, such as bacitracin or erythromycin, q.h.s., should be added.[1-3] Also, Metrogel (metronidazole topical, Galderma), applied to the skin, t.i.d. is also effective. Treatment should continue for two-four weeks. In suspicious cases, a chest X-ray and an anergy panel with PPD should be obtained.[1-3]

Clinical Pearls

- Maintenance doses of oral and topical medications may continue to relieve patients' signs and symptoms.
- Once significant improvement is noted, the topical steroid may be tapered. The antibiotic coverage should continue, prophylactically, until the steroid is removed.
- The eyelid hygiene should be maintained indefinitely.
- Other potential differential diagnoses include infiltrates secondary to chronic blepharitis, inflamed pinguecula, herpes simplex and infectious or marginal corneal ulcer.

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SUPERFICIAL CORNEAL INJURY

Signs and Symptoms

Corneal abrasion, toxic keratopathy, corneal foreign body and corneal thermal insult are the predominant mechanisms of superficial injury.[1-4] Most of the time they present as acute injuries making them common urgent clinical entities that present in practice.[1-4] Patients usually present with some or all of the following: acute pain, photophobia, pain upon extraocular muscle movement, lacrimation, blepharospasm, foreign body sensation, blurry vision and a history of contact lens wear or being struck in the eye.[2-16] Light 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]

Ocular or thermal burns account for 7.7%-18% of ocular trauma.[4] The majority of victims are young, typically under age 20. The burns occur secondary to accidents at work or in the home, or through physical attack with chemicals.[4] Chemical burns via strong acids or bases are responsible for the most serious injuries.[4]

Hair care products are consumer goods associated with ocular injury.[7] Up to 78% of these superficial ocular injuries involve a curling iron.[7] Seventy percent of these injuries occur to females who are often younger than 10-years-old, reflecting inexperience.[7]

While welding seems to occupy the highest risk among work-related thermal or photochemical events, household cleaners and adhesives represent the greatest hazards with respect to chemical offenders.[6] Basketball ranked high among sports-related ocular injuries owing to its increasing numbers to the sport's popularity and lack of protective eye wear.[6] Workshop equipment, tools, the activity of construction, toys and lawn equipment all were notable sources of ocular injury among males.[6] Female eye injuries were most often attributable to chemicals, house wares, storage and organization paraphernalia and bed and bath items.[6]

Pathophysiology

The cornea has five distinct layers. Below the tear film lies the corneal epithelium, Bowman's membrane (a whirling structure designed to prevent penetrating injuries) next followed by the organized 250 (approximate) lamellar sheets of the stroma, Descemet's membrane and finally the endothelium.[17] There are two categories of corneal injury; 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 similar materials.[8-17]

The cornea has remarkable healing properties. The epithelium adjacent to any insult expands in size to fill in the defect, usually within 24-48 hours.[17] Lesions that are purely epithelial often heal quickly and completely without scarring. Lesions that extend below Bowman's membrane possess an increased risk for leaving a permanent scar.[17]

If there is any destruction of limbal stem cells, superficial corneal injuries may develop into recurrent epithelial ulcerations, chronic stromal ulcers, develop deep stromal vascularization or develop conjunctival overlap.[10] Corneal avascularity is an active process involving the production of anti-angiogenic factors.[11] These factors counterbalance pro-angiogenic/lymphangiogenic factors that are constantly available and which become upregulated during wound healing.[11] Angiogenic proteins (vascular endothelial growth factor-VEGF and basic fibroblast growth factor-bFGF) and angiogenesis regulatory proteins along with matrix metalloproteinases and lymphangiogenic regulatory proteins all play vital roles during corneal wound healing.[11]

In cases involving chemical trauma, conjunctival and adnexal vasodilation produces chemosis and edema through biochemical pathways.[18,19] Conjunctival follicles form as a result of hyperplasia of lymphoid tissue within the eyelid stroma and papillae form secondary to hyperplastic palpebral conjunctival epithelium infiltrated by lymphocytes and plasma cells.[20,22]

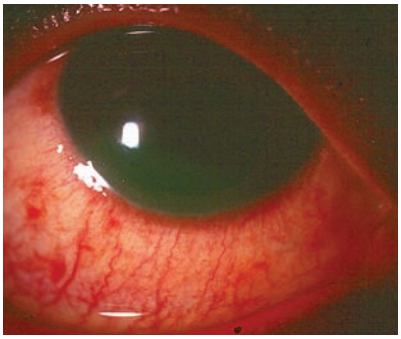
In cases involving exposure to

light (photochemical keratitis) the incident corneal reaction is secondary to provoked cytokine expression.[21] Absorption of excessive amounts of ultraviolet light (UVA, UVB) can overwhelm the corneal endothelial pumps inducing corneal edema.[21]

All corneal injuries induce an inflammatory reaction which exerts trophic influences in the corneal epithelium, damaging sensory nerves.[24] Alterations in normal healing disrupts the integrity and function of the tissue with undesirable consequences, ranging from inability to wet with resultant loss of transparency to infectious ulceration and perforation.[24] Lipids play important roles in this complex process. Lipid mediators such as platelet activating factor (PAF) and cyclooxygenease-2 metabolites contribute to tissue damage and neovascularization while other mediators act as messengers for epidermal growth factor to promote proliferation and repair.[24]

Management

Treatment for superficial corneal injury 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, if possible, before any procedures or drops are given. If the blepharospasm is sufficiently intense precluding acuity measurement, one drop of topical anesthetic from a previously unopened bottle can be administered with the VA measured immediately thereafter. The eye examination should proceed in a logical fashion from external adenexa to funduscopic examination. The eyelids should be everted and fornicies scrutinized to rule out the presence of foreign material. Fluorescein dye (preferably without anesthetic) should be instilled to assist in identifying corneal defects. The Seidel test (painting of the wound with fluorescein dye observing for aqueous leakage) should be performed if a full thickness globe perforation is suspected. Any injury should be documented for size, shape, location and depth. Corneal abrasions or lacerations should be cleaned and scrutinized for foreign matter. The anterior chamber should be observed for any evidence of uveitis. A dilated examination should be completed (either at time of initial evaluation or at follow-up) to rule out any posterior effects from the trauma.



Superficial cornea trauma (acid burn).

In the event of a chemical injury, the first step is to identify the substance. This is important as some substances react with water, making lavage dangerous and potentially destructive. Before attempting lavage it should be confirmed that the recommended antidote for the exposure is irrigation. This information should be on the product label or material safety data sheet (MSDS) kept on the work premises. The MSDS identifies all of the properties of that given substance and provides the recommended solution for accidental exposure or ingestion. When it is confirmed as the correct procedure, lavage should be completed with single and double lid eversion to remove debris and flush away any foreign substances or chemicals.[23,24]

If patients call with the complaint of accidental chemical exposure, they should be advised to insure that lavage is appropriate, using the MSDS or product label and then complete it immediately rather than attempt transport to the office. Patients who require over-the-phone first aid should be advised to brush off all powdered chemicals. The procedure for self-lavage is to run water from a tap or nozzle into cupped hands, placing the eye into the water in the hands. Copious blinking enables the rinse.[23,24] Do not instruct patients to look up under a falling stream of water. Impurities from the source may fall into the eye creating additional injury and the flushed chemical will run down onto the face and neck becoming entrapped in the clothing. In-office irrigation can augment the first aid. It can be done manually by using sterile ophthalmic saline applied forcefully and directly to all surfaces or by flushing the eye with a sterile intravenous saline solution run through a Morgan lens.[23,24]

Treatment for superficial corneal injuries is virtually universal. Pain can be mitigated using adequate cycloplegia (determined on a case by case basis; atropine 1 % q.d.-t.i.d., for the worst and homatropine 5 %, in the office, for the mildest) and infection can be prevented using topical broad spectrum antibiotics.[20,22,25,26] 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.[8-10,15,17] Pressure patching is not contraindicated, however, it is no longer considered standard-of-care.[1,9,12,14,15,27-29] Patients should be reevaluated every 24 hours until the injury demonstrates a restored epithelium.[8-10,12-14]

Riboflavin-ultraviolet A (UVA) treatment is a new procedure that induces collagen cross-linking to stiffen the corneal stroma.[30,31] The procedure demonstrates promise for non-healing

corneal injuries of all types.[30,31]

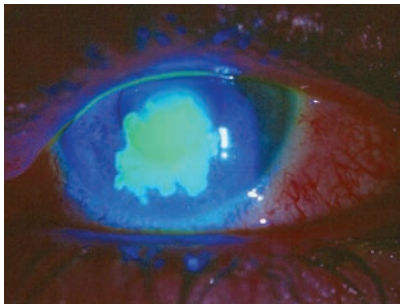
Reports have recognized the oral tetracyclines for their ability to protect the cornea against proteolytic degradation after moderate to severe ocular chemical injury.[32,33] While chemical injuries damage the corneal epithelium through toxic mechanisms rather than a mechanical mechanism, a corneal epithelial injury is the result nonetheless. Here, oral tetracyclines inhibit matrix metalloproteinases (MMP) via mechanics that are independent of antimicrobial properties. These compounds, primarily through restriction of gene expression of neutrophil collagenase and epithelial gelatinase suppression are able to limit production of the inflammatory mediator MMP.[32,33] This inhibits collagenolytic degradation of the cornea.[32,33] 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.[32,33] Using 50mg of oral doxycycline b.i.d. and topical fluoromethalone 0.1% three times daily for at least 4 weeks has demonstrated efficacy in patients with recurrent corneal erosion syndrome who have failed other forms of treatment.[33] This non-invasive treatment modality can be effective in concordance with conservative ocular lubricant management.[33]

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.[27-36]

When the hemidesmosomal anchoring fibers are not established properly a "peeling" off of the epithelium can result. This most frequently occurs upon awakening.[27-29,34-36] 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.[39] In cases such as these, palliative treatment should include hyperosmotics and lubricants. When recurrent erosion does occur, patching and bandage lenses may be employed.[8,10,12,17,36,38] When these modalities fail to promote adequate corneal healing, superficial phototherapeutic laser keratectomy (PTK) may be of benefit.[39] PTK attempts to remove poorly adherent superficial layers of the cornea by ablating the corneal surface with an excimer laser.

Anterior stromal puncture is another surgical option for recurrent corneal erosion.[40] Anterior stromal puncture can be accomplished by using a 27.5 gauge needle on a tuberculin syringe to repeatedly puncture the Bowman's layer, penetrating into the anterior 1/3 of the corneal stroma or via a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser.[40] 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.[40]

Tarsorrhaphy is used primarily for recalcitrant epithelial defects.[41] Here the eyelids are temporarily sutured together, providing a complete form of patching.[41] Tarsorrhaphy provides complete immobilization of the eyelid which yields more efficient healing.[41] 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.



Superficial corneal trauma (corneal abrasion).

Amniotic membrane transplantation (AMT) is primarily used to treat conditions where the normal corneal reparative process is either faulty or cannot gain momentum.[42] The procedure was reported as a safe and effective method for restoring the corneal epithelium.

New and on the horizon is a dendritic polymer known as a dendrimer.[43-47] This molecule seems to have applications as a nano-adhesive to improve corneal wound repair.[43-47] The agent is composed entirely of the biocompatible products, glycerol and succinic acid.[43] The adhesive has advantages over sutures in the repair of corneal lacerations, securing unstable LASIK flaps and closing leaky cataract surgical incisions.[33-35,44,47] Other applications for potential usage of the adhesive includes ocular emergencies involving perforation of tissues due to trauma or infections. The substance may also be applied to strengthen or build up weak tissues that have been compromised by the destructive processes associated with inflammation.[43-49]

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.
- In cases where excess epithelium impairs regrowth, a cotton-tipped applicator saturated with anesthetic may be used to debride the loose or excessive tissue.
- When a significant uveitis is present, 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 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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NEUROTROPHIC KERATITIS

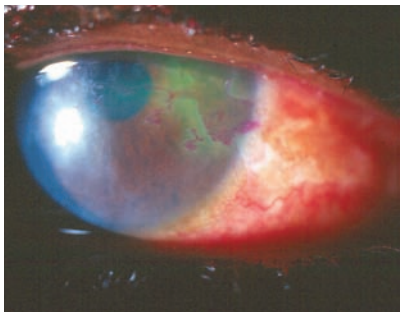
Signs and Symptoms

Neurotrophic keratitis (NK) is a degenerative disease of the cornea caused by reduced corneal innervation.[1-11] Trauma, tumors, inflammatory lesions, corneal infection (Herpes virus simplex and zoster), chronic corneal exposure, amyloidosis and corneal surgical procedures have all been implicated as entities capable of initiating the cascade. Abuse of topical ophthalmic anesthetics is also

a strong cause as well as exposure to smoke from crack cocaine. Here, damage to the nasociliary branch of the ophthalmic division of the trigeminal nerve (V1) triggers a series of events that disables the proper chemistry of corneal healing.[1-13] Damage to the trigeminal nerve anywhere between its origin in the midbrain and the branches within cornea can cause NK.[1-6] Neurotrophic keratopathy may be precipitated by exposure related to blepharoptosis repair.[4] Since the process involves a provoking injury or disease, the symptoms which occur in concordance with the corneal signs and symptoms are variable. The predominant corneal findings include epithelial breakdown, corneal edema, corneal infiltration (indolent corneal ulcer formation), mild to moderate ocular hyperemia, variable uveitis, along with its symptoms and corneal scar formation in the absence of frank corneal discomfort.[1-8] The dominant symptom is visual disability which increases over time as the corneal manifestations worsen.[1-8]

The clinical course of NK varies considerably. The corneal epithelium may demonstrate breakdown even in the absence of desiccation, active microbial infection or direct traumatic insult.[5] A systemic disease known to induce NK is Hereditary Sensory and Autonomic Neuropathy type IV (HSAN IV) previously known as Congenital Insensitivity to Pain with Anhidrosis (CIPA).[7-9] Here there is congenital, profound sensory loss affecting the perception of pain and temperature. The syndrome also includes the absence of sweating.[7-9]

There is no gender predilection. Since NK is a secondary result from other injurious, infectious or congenital sources its risk and course depend on the identification and treatment of the underlying cause along with anti-infective, anti-inflammatory and immunologic support for the cornea itself.[1-13]



Neurotrophic keratitis from herpes simplex.

Pathophysiology

The cornea epithelium responds to injury by synthesizing several cytokines, growth factors and tissue remodeling molecules.[14] Proinflammatory cytokines have been implicated in the inflammation that follows corneal epithelial injury and cytokine-mediated processes play a significant role in corneal epithelial wound healing.[14] Any poorly regulated corneal reactions that occur after insult can retard healing.[14] In turn, persistent corneal epithelial defects and inflammation may lead to ocular morbidity and permanent visual loss.[14]

The cornea is derived from neuroectoderm.[3] To maintain its principle property of clarity, it is devoid of blood vessels. This architecture creates limitations in its inherent capacity to effect repairs to its tissues. As a primary method of protection, the structure alerts the nervous system to the slightest insult through an extensive array of nerves.[3] The exterior corneal surface maintains its homeostasis through metabolic interactions which are facilitated through tear fluid, which serves both as a lubricant and as a conduit for regulatory molecules.[3] The cornea interacts with its surrounding tissues directly and indirectly through both tear fluid and aqueous humor, with such interactions playing an important role in the regulation and maintenance of its design and functions.[3] The resident cells of the cornea which include epithelial cells, fibroblasts (keratocytes) and endothelial cells all engage in mutual interactions through a complicated network of systems.[3] These interactions, as well as those with cells that infiltrate it from the limbal plexus, are regulated by dedicated resident nerves.[1-6]

Impaired corneal innervation leads to a reduced tear film production and reduced supply of available neurotransmitters and trophic factors.[1] This directly reduces the corneal epithelial healing capacity by interrupting both mitosis and cell migration.[1] The combined tear film deficiency and impaired epithelial healing capacity predispose the tissue to persistent epithelial defects, the formation of corneal ulcers and an increased risk of developing perforation.[1] Whenever corneal epithelial wound healing is delayed, the disruption of intercellular junctions between epithelial cells, abnormalities of the corneal basement membrane, altered concentrations of various cytokines in the tear fluid contribute to decreased corneal sensation.[1-9] Loss of corneal epithelial barrier function further permits inflammatory cytokines present in the tear fluid, together with infiltrated cells, to activate keratocytes and elicit excessive degradation of collagen in the stroma, thereby giving rise to chronic, non-remitting corneal degradation and scar formation.[3]

Management

Early recognition of the process, diagnosis and appropriate treatment has the potential to limit the effects of NK, possibly even preventing the inevitable evolution of a catastrophic chain of events. The basic management includes appropriate topical cycloplegia (scopolamine, homatropine, atropine) q.d.-t.i.d., depending upon the severity of the resultant accompanying

inflammation, a topical fourth generation fluoroquinolone antibiotic q.i.d.-q2h, depending upon the extent of the corneal damage and topical steroidal anti-inflammatory preparations, b.i.d.-q.i.d. Effort must be made to uncover and address the underlying cause. Evaluation of corneal sensitivity and tear film function are important diagnostic data.[2] NK that is not treated aggressively with ocular lubricants, tarsorrhaphy or bandage soft contact lenses can progress through stromal lysis to perforation.[5]

Evidence is mounting supporting the idea that topical thymosin beta-4 (Tbeta-4) promotes corneal cell migration and wound healing.[14] The formulation has been shown to possess anti-inflammatory properties and suppresses apoptosis.[14] Tbeta-4 suppresses the activation of the transcription factor, nuclear factor-kappa b (NF-kappaB) in TNF-alpha-stimulated cells.[14] TNF-alpha initiates cell-signaling pathways that are known mediators of the inflammatory process.[14] These clinical implications have caused the community to consider developing a potential role for Tbeta-4 as a corneal anti-inflammatory and wound-healing agent.[14]

Topical eye drops using a combination of a substance P-derived peptide (FGLM-amide) and an insulin-like growth factor-1 (IGF-1)-derived peptide (SSSR) have shown promise to stimulate corneal epithelial migration in both rabbit and human models, assisting corneal epithelial wound closure.[15] The clinical efficacy of eyedrops containing FGLM-amide and SSSR for the treatment of persistent corneal epithelial defects in individuals with neurotrophic keratopathy was examined in a prospective open study.[15] Complete resurfacing of epithelial defects was apparent in 18 of 22 (82%) subjects. No adverse effects of treatment were observed in any subject.[15] Researchers concluded that topical preparations containing FGLM-amide and SSSR induced rapid resurfacing of corneas having persistent epithelial defects in stem cell-positive individuals with neurotrophic keratopathy.[15]

Another novel approach to the pathophysiologic issues presented in patients with NK is direct neurotization of the cornea using the contralateral supraorbital and supratrochlear branches of the ophthalmic division of the patient's own trigeminal nerve to restore corneal sensation.[16,17] Researchers have attempted the procedure in patients with unilateral facial palsy with a hypoesthetic cornea.[16,17] The technique offers the advantage of preserving ocular anatomy and cosmesis while restoring function through improvement of corneal homeostasis.[16,17] The procedure permits donor nerve branches to be inserted at the contralateral anesthetic corneal limbus reestablishing the normal, natural neurologic connection.[16,17]

Advanced cases of NK can also be treated by amniotic membrane transplantation.[18] Lamellar or perforating corneal transplantations are used to treat stromal scarring or perforated ulcerations that develop secondary to persistent epithelial defects.[18] Limbal stem cell transplantation can correct limbal stem cell deficiency states associated with or caused by diseases leading to severe forms of dry eye (e.g. chemical burns leading to destruction of conjunctival mucus-producing cells).[18] Autologous serum treatment, which harbors neurotrophic factors, may provide neural healers to the compromised ocular surface. This treatment seems promising for the restoration of the ocular surface epithelial integrity in patients with NK.[19]

If a perforation develops, depending on its size and location, procedures like the application of cyanoacrylate glue, penetrating keratoplasty or conjunctival flap may be attepted.[5] Aggressive lubrication, punctal occlusion, bandage contact lenses, extended patching, and ultimately tarsorrhaphy are all consistent with traditional neurotrophic keratopathy therapy.[4]

The clinician should also consider the effect of iatrogenic disease on persistent epithelial defects. That is, sometimes the corneal epithelium cannot heal when exposed to multiple medications and their preservatives in high doses. Corneal specialists often consider stopping all topical medications in favor of high viscosity non-preserved artificial tears to initially observe what happens to the cornea. Additionally, corneal non-healing may be due to exposure to anesthetics, either indirectly from exposure to smoked crack cocaine or topical proparacaine obtained illicitly.

Clinical Pearls

- Neurotrophic keratitis (NK) is a degenerative disease of the cornea caused by reduced corneal innervation.
- The course depends on the identification and treatment of the underlying cause along with anti-infective, anti-inflammatory and immunologic support for the cornea itself.
- Neurotrophic keratitis is the result of a dangerous set of evolving pathophysiologic issues. If therapy does not yield stabilizing or improving outcomes, prompt referral to a corneal specialist is indicated.
- Patients in distress from corneal induced pain will illicitly remove topical proparacaine from the exam room more often than most clinicians realize.

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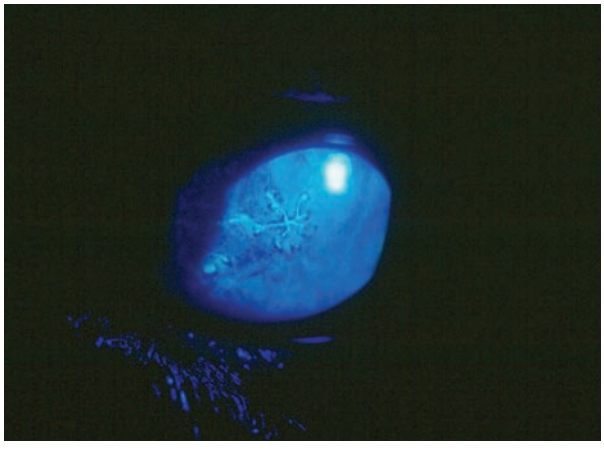
NEW DRUG UPDATE 2011: ZIRGAN

Ganciclovir 0.15% gel is a new medication that has recently been approved for the management of herpetic keratitis. Zirgan (ganciclovir ophthalmic gel, Bausch + Lomb), is now available as the newest topical antiviral agent for the treatment of acute herpetic dendritic keratitis.[1] Zirgan, which has been marketed previously in Europe since 1996, represents an advancement in viral ocular infection management for American physicians.[2-4]

Ganciclovir, a medication used previously for the management of cytomegalovirus retinitis, is a guanosine derivative. Ganciclovir is a potent inhibitor of members of the herpes virus family. However, its hematologic toxicity secondary to systemic administration led to its limited use in herpetic infections.[3] This drug inhibits DNA replication in a number of viruses. Its antiviral mechanism involves transformation of the molecule by viral thymidine kinases (vTK) to ganciclovir triphosphate, which has a dual action on the target virus. It competitively inhibits the action of viral DNA-polymerase, slowing DNA synthesis; and it incorporates directly into the viral primer strand DNA, resulting in DNA chain termination, effectively preventing viral replication.[5] Because ganciclovir is activated only by vTK, its effect is rendered solely in virus-infected cells.[5] This is in contrast to trifluridine (Viroptic), whose mechanism of action involves phosphorylation by both viral and cellular thymidine kinases, which results in DNA synthesis inhibition not only in viruses but also in normal cells. This likely contributes to the high degree of toxicity seen in Viroptic which is not seen in Zirgan. In clinical trials, transient blurred vision was encountered in 60% of subjects, while ocular irritation was noted in 20%; punctate keratitis and conjunctival hyperemia were also seen in a small percentage of patients. These effects were considered very mild.[1]



Herpes simplex dendritic keratitis, ideally treated with Zirgan.

As a therapy for herpes simplex keratitis, ganciclovir gel is administered five times daily (approximately every three hours while awake) until the corneal ulcer heals, and then three times per day for an additional seven days.[1] The reduced dosing is a function of both the drug's improved efficacy as well as the vehicle, a viscous gel that enhances contact time on the ocular surface and facilitates greater drug concentration in corneal tissues

Topical ganciclovir ophthalmic gel is well tolerated, has minimal adverse effects on the ocular surface, and does not cause hematologic abnormalities.[3] Studies comparing the efficacy and tolerability of 0.15% ganciclovir gel to 3% acyclovir ophthalmic ointment in patients with herpetic keratitis demonstrated that ganciclovir gel was as effective as topical acyclovir ointment in healing herpetic corneal ulcers, but with fewer instances of blurring, stinging and ocular irritation.[6,7]

Zirgan is safe and effective in the treatment and prophylaxis of herpetic epithelial disease. Long-term use of Zirgan in patients with penetrating keratoplasty following herpetic keratitis has prevented recurrences of the disease.[3]

In addition to herpetic keratitis, there has been some research into possible applications of Zirgan for patients with adenoviral conjunctivitis (epidemic keratoconjunctivitis-EKC).[8] A study examining the effects of Zirgan with the instillation of preservative-free artificial tears in 18 patients with adenoviral keratoconjunctivitis found that Zirgan was safe and effective for the treatment of adenoviral keratoconjunctivitis.[8]

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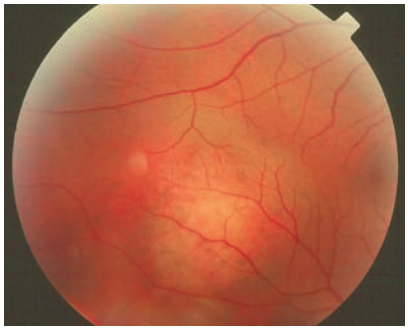
CHOROIDAL NEVUS & CHOROIDAL MELANOMA

Signs and Symptoms

Both choroidal nevi and choroidal melanomas represent space-occupying masses of the uveal tract. Choroidal nevi appear as round or oval, flat or slightly elevated (1mm or less) lesions within the posterior fundus whose margins are typically detectable but indistinct.[1] Nevi may present in a variety of hues, but most commonly they appear slate-blue or greenish-gray in coloration.[1] There may be overlying areas of drusen noted as well.[1,2] The vast majority of choroidal nevi remain under two disc diameters (DD) or 3mm in size.[1] Larger nevi, particularly those in excess of 4DD/6mm carry increased suspicion of malignancy.[3,4] Generally, patients with choroidal nevi are asymptomatic, with the lesion detected upon ophthalmoscopy.

Choroidal melanomas, in contrast to nevi, appear as mottled, often dome-shaped lesions of the ocular fundus. Coloration varies widely, ranging from complete amelanosis (i.e., white) to jet-black.[4,5] Most commonly, lesions are a non-uniform greenish-gray.[4,5] There may be significant elevation in some cases. As they grow, melanomas may break through Bruch's membrane, taking on a "mushroom-shaped" appearance. Subretinal fluid and serous retinal detachments are commonly associated with this presentation.[4-6] Overlying orange pigmentation known as *lipofuscin* may also be seen. Lipofuscin infiltration is considered by many to be a pathognomonic sign of malignancy.[7]

Many patients with choroidal melanomas are entirely asymptomatic; in most cases, lesions are detected via dilated, indirect ophthalmoscopy on routine ophthalmic examination. However, larger lesions or those in close proximity to the macula may induce visual symptoms that prompt the patient to seek attention. These symptoms may include photopsia, visual field deficits, metamorphopsia, or decreased acuity secondary to subretinal fluid accumulation and/or hyperopic refractive shift.[4]



Amelanotic choroidal melanoma.

The vast majority of patients with choroidal melanoma are over the age of 50 years, though the tumor may rarely occur in childhood.[8,9] Race also plays a significant role in the distribution of choroidal melanoma. Caucasians are three times more likely than Asians to manifest choroidal melanoma[10] and at least eight times more likely than those of African descent.[11,12] Not surprisingly, patients with light-colored irides (e.g., blue or grey) also seem to be at greater risk for developing uveal melanomas.[13] The presence of numerous cutaneous nevi—particularly dysplastic nevi—is yet another risk factor.[13,14]

Pathophysiology

Choroidal nevi and melanomas are both derived from uveal melanocytes. In the mid-1960's, Naumann and associates identified the four atypical cell types inherent in choroidal nevi; in order of prevalence, these include: plump polyhedral cells, slender spindle cells, intermediate cells and balloon cells.[15] In contrast, melanomas are comprised of malignant melanocytes. The Callender classification system for choroidal melanomas suggests that there are also four types of cells in these lesions: spindle A, spindle B, fascicular, and epithelioid.[16,17] In general, the presence of epithelioid cells within a melanoma heralds a poorer prognosis.[18]

There is some controversy regarding the precise pathogenesis of melanomas. It is believed that nevi may convert to malignancy in a small percentage of individuals; a recent study suggests a rate of one in 8,845.[19] Risk factors for malignant transformation of nevi include increased diameter (>5mm), increased thickness (>2mm), the presence of subretinal fluid, the presence of lipofuscin, ultrasonographic hollowness and lack of an amelanotic halo.[1,20]

Ultraviolet (UV) radiation has also been associated with the development of ocular and non-ocular melanoma.[4] Some studies have suggested a causal relationship between UV exposure and the development of choroidal melanoma, while others are less conclusive.[21-24] It seems that the specifics of this variable are presently uncertain, but the prevailing opinion is that UV radiation is not a significant factor in the pathogenesis of choroidal melanoma. More than likely, the greatest prognostic indicator for choroidal melanoma development and malignant progression is a genomic variation in chromosomes 3, 6 or 8.[4,25]

Management

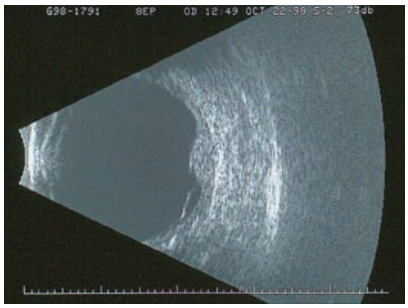
While some choroidal nevi possess the capacity for malignant growth, most are completely benign and require only periodic monitoring. Of course, differentiating between a large, atypical nevus and a small choroidal melanoma requires experience and expertise. Ancillary procedures that may facilitate an accurate diagnosis include stereo photography, standardized ultrasonography, fluorescein angiography, and optical coherence tomography (OCT).[26] More invasive

procedures, including transvitreal fine needle aspiration biopsy can be used to differentiate suspicious lesions.[27]

Those patients who are diagnosed with or suspected of having choroidal melanoma should be referred for prompt medical evaluation by an internist and an expert in ophthalmic oncology. Specifically, this is done to corroborate the diagnosis through expert consultation and ascertain whether there are any additional primary or metastatic malignancies present. The systemic work-up should include a thorough medical and family history as well as a physical examination and directed laboratory evaluation. Choroidal melanomas have been known to spread to numerous organ systems including the lungs, skin, gastrointestinal tract and the liver, which is the primary site of metastasis for uveal melanoma.[4] Depending upon the physical findings, specific ancillary tests may consist of a chest x-ray or computed tomography (CT scan), cellular hematology and liver enzyme studies. The most sensitive tests of hepatic function include serum alkaline phosphatase, glutamic-oxaloacetic transaminase, lactic dehydrogenase and gamma-glutamyl transpeptidase.[28]

Therapy for choroidal melanoma has changed radically in the last 35 years. Until the late 1970's, enucleation was considered the only definitive treatment and the best option for survival among those with melanoma. In 1978 however, a pivotal paper by Zimmerman and associates challenged conventional thinking, suggesting that enucleation might actually contribute to systemic metastasis.[29] This article and another subsequent publication provided the impetus to develop alternative therapies for choroidal melanoma, most notably radiotherapy and tumor resection.[30]

Today, therapy for choroidal melanoma is dictated primarily by the



B-scan ultrasound of a choroidal melanoma; note the serous retinal detachment inferiorly.

size of the lesion. The Collaborative Ocular Melanoma Study (COMS) defined tumors as small (5-16mm in basal diameter and 1.0-2.5mm in height), medium (<16mm diameter and 2.5-10.0mm in height), or large (>16mm diameter and/or >10mm in height).[31] Small tumors may be treated by simple observation, but therapy is initiated if any sign of growth or visual compromise is encountered. Focal laser photocoagulation, cryotherapy and, more recently, transpupillary thermotherapy (TTT), have been employed successfully for selected small melanomas,although TTT as a stand-alone therapy is probably inadequate.[32-34] For some small melanomas, as well as the majority of medium-sized choroidal melanomas, radiation remains the treatment of first choice.[32]

Brachytherapy—in which a plaque with embedded radioactive material is temporarily sutured to the episclera overlying the tumor is the most common method utilized today.[35] Another method employing charged particle irradiation (a.k.a., external beam irradiation) may also be employed for certain tumors. Overall, the success rates and complications (including radiation retinopathy and cataract formation) for plaque therapy and external beam therapy are similar. However, since external beam irradiation does not require surgery, it may be preferred in some cases. Another treatment option for small and medium-sized tumors is block excision, which involves a local resection of the tumor using a partial lamellar sclerouvectomy technique.[34] This procedure may offer advantages over radiation therapy with regard to collateral tissue damage, but it is also quite involved and carries significant risk for surgical complications, including retinal detachment. Local resection of choroidal melanoma is preferred for smaller, more anteriorly located tumors.[34]

While there is still controversy in the field, enucleation is still utilized by many for the treatment of some large uveal melanomas. It has been suggested that enucleation is indicated in the following settings: (1) in a patient who, after being informed of the diagnosis, requests this operation; (2) in a patient with a tumor involving over 40% of ocular volume; (3) after treatment with an alternative modality that has failed; and (4) in patients with significant ocular neovascularization before any therapy.[4] As a matter of protocol, when enucleation is performed on an eye with melanoma, care is taken not to clamp the optic nerve or aggressively handle the eye, in an effort to reduce potential tumor seeding and metastasis.[32] For those advanced tumors that demonstrate massive extrascleral extension into the orbit, and in which the eye is blind and painful, eyelid-sparing orbital exenteration is justified.[36]

Clinical Pearls

• While the majority of choroidal melanomas occur in older, white individuals, younger patients and those of African or Asian descent are not immune. The literature recognizes that melanomas can affect a wide range of demographics. A delayed diagnosis can cause the prognosis to be worse.

• Small melanomas may be misdiagnosed as choroidal nevi, congenital

RPE hypertrophy, or other benign fundus conditions. A mnemonic to recall the most significant risk factors for choroidal melanoma is "*To find small ocular melanomas, use helpful hints*." The first letter of each word in the phrase represents *thickness*, *fluid*, *symptoms*, *orange* pigment, *margins*, *ultrasonographic hollowness*, and *halo* absence.[20]

• The Collaborative Ocular Melanoma Study demonstrated that pre-enucleation radiotherapy for large tumors did not appear to significantly alter the rate of survival as compared to those who underwent enucleation alone.[37,38] These results have forced experts to ponder the issues raised by Zimmerman in 1978—namely, whether enucleation, as a treatment option for choroidal melanoma, is a better or worse option in the long run.

• In recent years, intravitreal anti-VEGF agents, such as bevacizumab, have been widely utilized for a variety of choroidal and retinal disorders, including wet age-related macular degeneration, clinically significant macular edema and some proliferative vitreoretinopathies. In the case of choroidal melanoma, despite speculation and positive results from experimental animal models, these agents appear to be of little clinical value. In a recent report, three patients who were inadvertently treated with bevacizumab due to misdiagnosis experienced not only tumor progression, but also complications in the form of gliotic/fibrotic membrane formation.[39]

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IRIDOCORNEAL ENDOTHELIAL SYNDROMES (ICE)

Signs and Symptoms

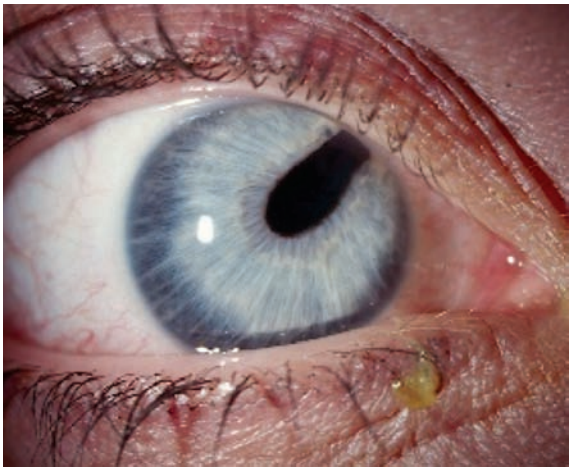
The patient with iridocorneal endothelial syndrome (ICE) syndrome is typically a young adult female.[1-6] Males have been reported to develop ICE syndromes, though uncommonly.[7,8] It is most common in Caucasians, and there typically is no family history of this disease. It is most commonly a unilateral phenomenon, but bilat-

eral cases have been documented.[1,9] It tends to manifest in early to middle adulthood.[2] In some cases, ICE syndromes may develop in children or teenagers.[9-11] Common findings include a beaten bronze appearance to the corneal endothelium, variable degrees of corneal edema, iris atrophy and iris hole formation, corectopia, prominent iris nevus, and peripheral anterior synechia with progressive angle closure and secondary closed angle glaucoma. Vision may be unaffected or may be reduced due to endotheliopathy, corneal edema or visual sequelae from the 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 rest of the group while secondary glaucoma is more severe in the other syndromes.[3,6]

All of the ICE syndromes share a common underlying pathophysiology and can all be considered to be primary proliferative endothelial degenerations.[4] The corneal endothelium develops 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.[12] It appears that the endothelial cells undergo a metaplastic transformation into "epithelial-like" cells that migrate in a membrane form over the anterior chamber angle to the iris.[7,13] These abnormal "epithelial-like" endothelial cells are characterized by marked hyper-reflective nuclei and loss of regularity in cellular size and shape.[14-16]



Iridocorneal endothelial (ICE) syndrome (essential iris atrophy).

Progression occurs at a variable rate.[17] Subsequent contraction of the membrane pulls the iris towards the cornea creating a chronic progressive synechial closure of the angle. This can result in secondary angle closure without pupil block.[18-21] The cellular membrane may also cause aqueous outflow blockage in the absence of peripheral anterior synechia. It is the contraction of the membrane that causes the classic atrophic iris appearance.[6]

The etiology of the ICE syndromes is unclear. There appears to be no hereditary component.[18] There are historic implications with infections involving the herpes and Epstein-Barr viruses, though there appears to be proven causality.[22-24]

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, though overall medical therapy has the reputation of being minimally effective. Medications whose mechanism is to increase aqueous outflow are typically ineffective and should not be used. 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.[18,25,26] Trabeculectomy with an antimetabolite adjunct and glaucoma surgical implant devices may be necessary for this reason.[27-29] Despite adequate IOP control, corneal edema may persist due to the endotheliopathy. In these cases, penetrating keratoplasty (PK) may be necessary to restore vision, though this procedure will not affect abnormalities in the iris or anterior chamber angle.[30] Clear corneas can be obtained after PK, though like glaucoma surgery, multiple procedures may be necessary. Combined glaucoma surgical procedures have also been used with variable success to control all aspects of the dis-

ease.[31] One report noted that all cases of PK for ICE syndromes failed within two years.[32]

Another surgical option is deep lamellar endothelial keratoplasty, which has been seen to afford patients with ICE syndromes rapid visual rehabilitation and low incidence of postoperative complications.[33] Additionally, replacement of the dysfunctional endothelium through Descemet Stripping with Endothelial Keratoplasty (DSEK) can successfully treat corneal edema and associated visual loss caused by ICE syndromes. Visual recovery is more rapid with minimal refractive changes compared with replacement of the full corneal thickness with PK.[34,35]

Clinical Pearls

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

• Progression is unpredictable, but many patients have a good outcome. Due to the unilaterality, patients rarely become completely visually disabled.

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

• ICE syndrome should be suspected in any case of unilateral glaucoma.

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NEOVASCULAR GLAUCOMA

Signs and Symptoms

Patients with neovascular glaucoma (NVG) typically present with a chronically red, painful eye, which often has significant vision loss. The majority of patients will have presenting acuity of less than 20/200.[1-3] Further, there will be significant concurrent vascular disease such as diabetes, hypertension, carotid artery disease, or giant cell arteritis (GCA).[3-8] There frequently is an antecedent history of a retinal vessel occlusion, carotid artery disease, chronic retinal detachment, or advanced diabetic retinopathy.[5,8] In that patients typically have precipitating ischemic vascular disease, NVG is often found in older patients. Diabetes is the most common precipitating cause of NVG.[3]

There will be visible neovascularization of the iris (NVI) and angle (NVA). Only rarely will NVA develop without NVI. The patient will typically have significant corneal edema, anterior segment inflammation, anterior chamber cell and flare reaction, and elevated

intraocular pressure, often exceeding 60mm Hg.[1,9,10] Gonioscopically, there will be total or near-total angle closure with massive areas of peripheral anterior synechiae (PAS) and neovascularization of the angle. In early cases, microhyphema may be seen gonioscopically. Funduscopically, there will often be evidence of retinal vessel occlusion (either artery or vein), diabetic retinopathy, ocular ischemic syndrome, or another condition stimulating retinal ischemia.

Pathophysiology

Ischemia to ocular tissues is theorized to be the genesis of NVG. The most common causes of NVG include ischemic central retinal vein occlusion (CRVO), diabetic retinopathy, carotid artery disease and ocular ischemic syndrome (OIS).[1-4,7,8] Less common causes of NVG include hemi- and branch retinal vein occlusion, retinal artery occlusion, and GCA. In terms of RVOs, NVG typically develops later than from artery occlusions, often within three to four months of the occlusion. In terms of artery occlusions, NVG typically develops within a range of two to 16 weeks with an average of 8.5 weeks following the occlusion.[11]

In ischemic retinal disease, hypoxia induces vascular endothelial growth factor (VEGF), an angiogenic peptide, which acts upon the healthy endothelial cells of viable capillaries to stimulate the formation of vascular buds which develop into new, fragile plexi of vessels (neovascularization).[12-17] In cases of extreme retinal hypoxia, there are essentially very few viable retinal capillaries available. Such is the case with ischemic central retinal vein occlusions. In that instance, VEGF is theorized to diffuse forward to the nearest area of viable capillaries, namely the posterior iris. Neovascularization buds which typically sprout from the capillaries of the posterior iris grow along posterior surface, through the pupil, along the anterior surface of the iris, and then into the angle. Initially, invasion of the anterior chamber angle by a fibrovascular membranes obstruct aqueous outflow in an open-angle fashion.[9] Once in the angle, the neovascularization, along with attendant fibrovascular supporting membranes, act to both physically block the angle as well as bridge the angle and physically pull the iris and cornea into apposition, thus blocking the trabecular meshwork. Peripheral anterior synechiae with permanent angle closure may develop quickly. The result is a secondary angle closure without pupil block. Due to the extremely elevated intraocular pressure, there will be a modest amount of anterior segment inflammation.

Management

Neovascular glaucoma frequently results in a blind, painful eye. For this reason, prompt and aggressive therapy is mandated.[18] This involves understanding and addressing any underlying systemic cause, controlling the intraocular pressure, managing the resultant ocular inflammation, reducing pain and managing any retinal ischemia.

Upon first presentation, a topical cycloplegic such as atropine 1% b.i.d. as well as a topical steroid such as Pred Forte (prednisolone acetate 1%, Allergan) or Durezol (difluprednate 0.05%, Alcon), q.i.d. should be prescribed.[10] This will greatly add to patient comfort. Topical aqueous suppressants may be used in order to temporarily reduce IOP.[10] However; chronic medical therapy is not indicated for neovascular glaucoma. Aqueous suppressants only temporize IOP. They do not arrest the neovascular process which will continue toward further angle closure.[19]

Management of anterior segment neovascularization and NVG involves eradication of the vessels. This is best accomplished with pan-retinal photocoagulation (PRP) to destroy ischemic retina, minimize oxygen demand of the eye, and reduce the amount of VEGF being released.[20-23] PRP tends to be effective in causing regression and involution of anterior segment neovascularization in approximately 60% of cases.[18] This may also reduce intraocular pressure by inducing vessel regression. Endoscopic laser photocoagulation is an excellent tool for photocoagulating the peripheral retina and ciliary processes.[23]

While PRP is the most definitive treatment for the neovascularization causing NVG, the advent and use of antiangiogenic drugs has proven to be a valuable adjunct. Avastin (intravitreal bevacizumab, Genentech) has been demonstrated through numerous reports, both controlled studies and case series, to cause prompt and thorough regression of anterior segment neovascularization in NVG.[24-32] Regression can be significant and occur within a period as short as one day following injection. Also, further formation of PAS can be halted. However, while superficial vessel formation can be halted, deep stromal neovascularization may be less affected.[28] Additionally, neovascularization can recur following antiangiogenic injection if the causative factor is unaddressed.[33] For that reason, antiangiogenic therapy should only be considered a valuable adjunct along with laser photocoagulation in the management of NVG.[34-37]

While PRP and intravitreal bevacizumab can result in IOP lowering, these therapies are rarely sufficient to manage the glaucoma aspect of neovascular disease. Further measures are typically mandated to manage the glaucoma. Continued medical therapy following PRP is common, though frequently insufficient to manage the glaucoma. Often, IOP lowering sur-

gical methods are needed to manage NVG. Trabeculectomy with antimetabolite adjuncts have been seen as an effective method to manage the elevated IOP in NVG.[5] Often, the use of drainage devices are necessary to optimize surgical outcomes.[38-41] Additionally trans-scleral diode laser cyclophotocoagulation reduces aqueous production through the laser-induced ablation of the ciliary processes.[34]

It has been shown that intravitreal bevacizumab is not only beneficial as an adjunct with PRP, but also with glaucoma surgical shunting procedures as well.[42-44] The use of intravitreal bevacizumab reduces the incidence of hyphema as well as provides for superior IOP control following glaucoma surgical shunting procedures.

Clinical Pearls

• The pressure rise in NVG is from secondary angle closure without pupil block.

• Initial management of NVG involves pain and inflammation control in the form of topical atropine and steroids. Even though the angle is closed in NVG, a cycloplegic agent such as atropine is mandatory. The mydriatic effect of atropine will not worsen any angle closure aspect of this disease.

• In cases of NVG in elderly patients, even in the presence of a provoking retinal etiology, systemic laboratory testing should insure that OIS (carotid artery disease) and GCA are ruled out.

• Treatment of the causative ischemic stimulus is necessary in every stage of NVG.

• The pupil border in the early phase of NVI manifests not as blatant vessels, but as a fine reddish hue around the pupil margin.

• Neovascularization can occur on the iris surface and even in the anterior chamber angle without being present at the pupil margin.

Angle micro-hyphema from bleeding iris neovascularization in neovascular glaucoma.

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NEW DRUG UPDATE 2011: DUREZOL

Durezol (difluprednate ophthalmic emulsion 0.05%, Alcon) is a difluorinated derivative of prednisolone with potent anti-inflammatory activity. The addition of two fluorine atoms to the original prednisolone molecule, as well as some other modifications, serves to increase not only the penetrance across the cornea, but also glucocorticoid receptor affinity. This engineering enhances its anti-inflammatory ability.[1] Difluprednate contains sorbic acid as its preservative.

In 2008, the U.S. Food and Drug Administration approved Durezol for the treatment of postoperative inflammation and pain associated with ocular surgery. In fact, an indication for post-operative pain management makes this steroid unique. The recommended dosing regimen is one drop, two to four times daily beginning 24 hours after surgery and continuing throughout the first two weeks of the postoperative period, followed by two times daily for a week with tapering thereafter based upon clinical response.[2]

Another unique feature is the emulsion vehicle which contains the active steroid. The lipid emulsion has a smaller particle size, which increases bioavailability, provides uniform medication concentration in each drop, and eliminates the need for shaking before use. In a study comparing dose drop uniformity of concentration of Durezol with both the branded and generic versions of prednisolone acetate 1%, virtually every drop of Durezol was within 10% of the label claim regardless if the bottle was stored inverted or upright or shaken before testing. The concentrations of prednisolone acetate were varied by both bottle storage and shaking.[3]

Durezol has been shown to be clinically comparable to the very potent betamethasone for postoperative inflammation with an equal likelihood of a steroid response (increased intraocular pressure following administration of a steroid medication).[4,5] Due to its enhanced bioavailability and clinical potency, Durezol tends to need less frequent dosing than other topical steroids.

Currently, there are no label indications for anything other than post-operative inflammation, but clinicians are utilizing Durezol for other steroid responsive conditions such as uveitis and scleritis. There is evidence of the supporting the drug's effectiveness, particularly in recalcitrant ocular diseases.[6]

In one large anterior uveitis trial of 136 patients, topical difluprednate q.i.d. was found to be similar to topical betamethasone q.i.d., and was significantly better at resolving inflammation in more severe cases.[7] Another study reported topical difluprednate administered q.i.d. was at least as effective as topical prednisolone administered 8x/day in resolving the inflammation and pain associated with endogenous anterior uveitis.[8] Notable in this study was that no patients being treated with Durezol q.i.d. had to be withdrawn for lack of efficacy and given rescue therapy (topical prednisolone acetate 16x/day), whereas 12.5% of the patients being treated with topical prednisolone 8x/day had to be withdrawn due to lack of efficacy and given the double dosing rescue therapy.[8]

Difluprednate provides effective treatment for anterior uveitis and requires less frequent dosing than prednisolone acetate. The incidence of steroid-related elevation of intraocular pressure (IOP) is approximately 3%, which is similar to other topical steroids.[2] The IOP elevation may occur earlier than expected and be of a larger magnitude when compared with other topical steroids and patients should be monitored while on Durezol.[6] Due to enhanced anti-inflammatory activity, Durezol can likely be dosed less frequently than other steroids. With conditions such as anterior uveitis, it is recommended to start with q.i.d. dosing and increase it only as the clinical picture dictates, rather than starting at the higher dose frequency typically employed with prednisolone acetate.

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COAT'S DISEASE AND LEBER'S MILIARY ANEURYSMS

Signs and Symptoms

The patient with Coat's disease and Leber's miliary aneurysms typically is male and young, with most diagnoses occurring between the ages of 18 months and 18 years.[1-4] Occasionally, infants, older patients and females may be affected.[5-7] The patient frequently is asymptomatic; however, vision in advanced Coat's disease cases will be greatly reduced. Patients with Leber's miliary aneurysms are more likely to be asymptomatic than patients with Coat's disease and have a better visual prognosis. Both Coat's disease and Leber's miliary aneurysms are typically unilateral conditions and are considered primary retinal telangiectasias.[8] Bilateral cases have been reported.[9] Both conditions tend to occur in the temporal peripheral fundus.

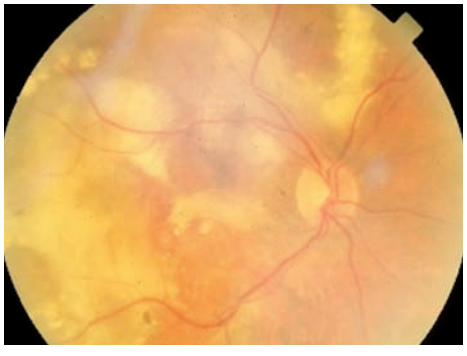
Leber's miliary aneurysms presents as a localized cluster of dilated capillaries, aneurysms, and telangiectasias, typically in the superior temporal quadrants of the retina. However, hemorrhage and exudation are minimal to absent in Leber's miliary aneurysms.[1-5] It is this absence of leakage which separates Leber's miliary aneurysms from Coat's disease. In fact, the Leber's condition is possibly a mild variant of Coat's disease. There have been some uncommon associations between Leber's miliary aneurysms and other conditions such as multiple sclerosis and vitreomacular traction syndrome, though it is not clear, based upon the isolated reports, if these associations are correlated or coincidental.[10,11]

Coat's disease has a much more dramatic appearance, ranging from mild exudation to massive aneurysmal exudation and serous-exudative retinal detachment. There will be retinal edema, intra- and sub-retinal mounds of exudate, retinal detachment, vitreous hemorrhage, and possible neovascularization, both of the posterior and anterior segments.[12-14]

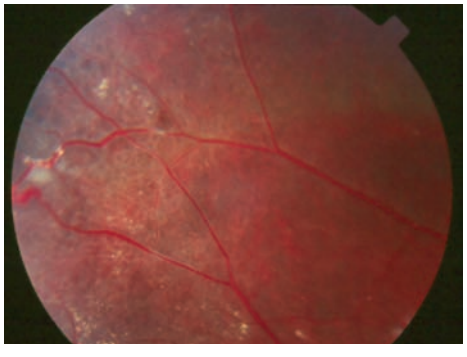
Pathophysiology

The formation of retinal telangiectasia and breakdown of the inner blood-retinal barrier are the fundamental causes of all changes found in Leber's miliary aneurysm and Coat's disease. In Leber's miliary aneurysms, fine telangectatic vessels are found and associated with mild to moderate intraretinal fluid accumulation, exudates and hemorrhages. Thickening of the vascular endothelial basement membrane results in impairment of blood flow and mild leakage.[1-4]

Due to capillary closure at the site of the telangiectasia, retinal neovascularization with subsequent vitreous hemorrhage and tractional retinal detachment can also occur in Coat's disease. There appears to be a macrophage-related deposition of lipid into the deep retina and sub-retinal areas, giving Coat's disease its characteristic exudative appearance. Untreated, there will be gradual progression to total exudative retinal detachment.[12-15]



Coat's Disease.



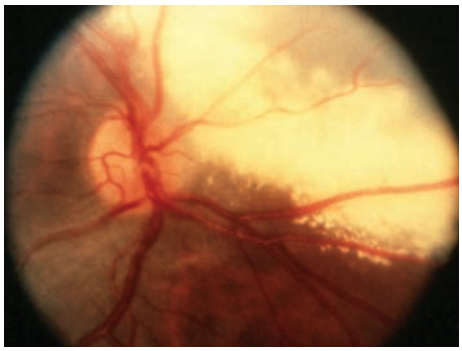
Leber's miliary aneurysms.

Management

The prognosis for patients with Leber's miliary aneurysms is generally good. Progression of Leber's miliary aneurysms is typically slow.[2] Patients should be followed periodically to determine if increased leakage and exudation have occurred. If leakage is moderate and vision is compromised, cryoretinopexy or argon laser photocoagulation of the affected area is recommended.[1,2] Retinal consultation should be obtained when there is suspicion for Leber's miliary aneurysms. Thermal obliteration of the abnormal vessels may be considered by the retinologist before significant leakage and exudation occurs.

The prognosis for Coat's disease is guarded. Treatment includes laser photocoagulation or cryoretinopexy for thermal necrosis of the abnormal vessels. In cases of vitreous hemorrhage and retinal detachment, vitrectomy and scleral buckle procedures are employed.[16-20] Complications following treatment include phthisis bulbi, neovascular glaucoma, epiretinal membrane and rubeosis iridis. In extreme cases where blindness ensues, pain relief may be indicated. Enucleation may be necessary in many cases.[21]

Due to the complications of exudation, macular edema, and neovascularization, chemical vascular stabilization and anti-VEGF therapy have been employed to treat eyes with Coat's disease. It has been recently seen that combination intravitreal therapy with triamcinolone acetonide



Coat's Disease.

(Kenalog, Bristol-Myers Squibb) and bevacizumab improves vision by reducing macular edema and likely should be considered valuable adjunctive therapies for eyes with Coat's disease.[22-28]

Clinical Pearls

• Many cases of Leber's miliary aneurysms and Coat's disease are discovered in asymptomatic patients during routine examination.

• Coat's disease is a prime reason that clinicians should routinely dilate asymptomatic young patients.

• Coat's disease and Leber's miliary aneurysms are possibly different ends of the spectrum of the same disease. Coat's disease is extremely exudative, while Leber's miliary aneurysms is not.

• Whenever massive intraretinal or subretinal exudation occurs, even when the etiology is due to another disease, it is termed a Coat's response.

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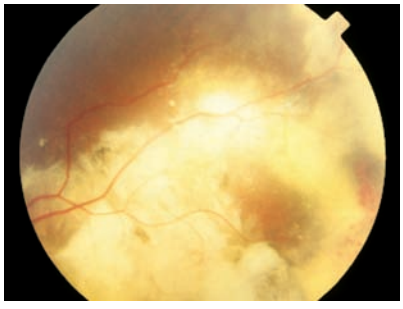
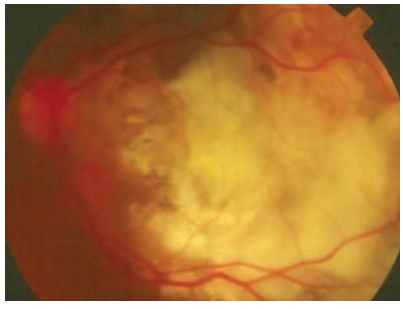


Coat's Disease.



Coat's Disease.

EPIRETINAL MEMBRANE

Signs and Symptoms

Epiretinal membrane has been known by many names in clinical and educational circles. This disorder may be referred to as preretinal membrane, idiopathic preretinal macular gliosis, cellophane maculopathy, macular pucker, or surface wrinkling retinopathy. Most commonly, epiretinal membranes are distinguished according to appearance as either cellophane macular reflex (CMR) or preretinal macular fibrosis (PMF).[1-6]

The ophthalmoscopic picture of this disorder ranges from a fine, glinting, glistening, shifting light reflex overlying the macula (CMR) to a thickened, opaque, whitish retinal folding with traction lines that obscures the underlying vasculature.[1-6] As the epiretinal membrane progresses, trac-

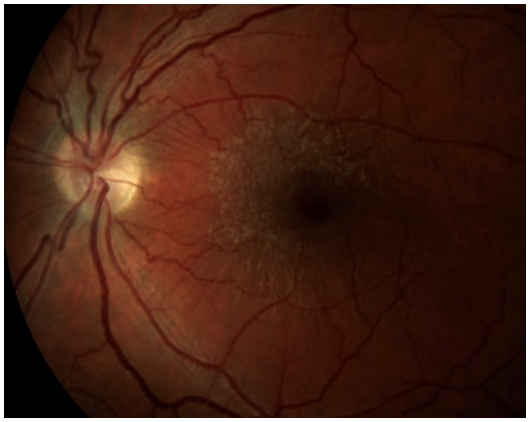


Image courtesy of Brad Sutton, O.D.

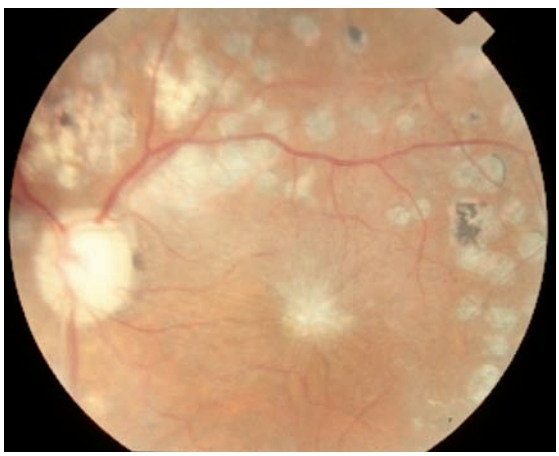
Epiretinal membrane.

tion at the level of the internal limiting membrane (ILM) creates a puckering effect—retinal folds may be observed radiating outward from the macula. Adjacent retinal vessels which course under the ILM often assume a "corkscrew" pattern, which is quite dramatic with fluorescein angiography.

In early stages, epiretinal membranes may induce no symptoms, or may create only a mild reduction in acuity. Patients exhibiting CMR are more likely than those with PMF to be asymptomatic or minimally symptomatic.[4,6] Patients with PMF are often visually symptomatic. CMR is approximately seven-fold more prevalent than PMF and twice as likely to be bilateral.[3] Though initial visual acuity may be good in eyes with epiretinal membrane, progression may cause subjective metamorphopsia and lead to severe visual impairment.[7,8] In very severe cases, macular edema, abnormalities in foveal architecture, disruption of inner-and-outer retinal segments, and even macular hole development has been know to occur.[9-14]

Epiretinal membranes may be either unilateral or bilateral. Various population studies have been examined for epiretinal membranes. The prevalence in these studies have ranged from 2.2% (in Chinese) to 18.5% in Latinos.[1,15] Epiretinal membranes are rare in children and usually form in association with trauma or uveitis.[16] Epiretinal membranes are uncommon in young adults and when they occur tend to be thicker and more adherent to the retina.[6,17] Epiretinal membranes are more common in the elderly with increasing prevalence with age.[1-4] A reported five-year cumulative incidence for PMF and CMR was 1.5% and 3.8% respectively. Progression from CMR to PMF is estimated to occur in approximately 10% of cases.[1] Mostly, epiretinal membranes are considered to be only slowly progressive.

Often there is a causative factor that is readily identifiable. Cataract surgery, retinal vein occlusion, retinal detachment, diabetic retinopathy, blunt ocular trauma, uveitis, retinal photocoagulation have all been implicated in the development of epiretinal mebranes.[3-5,18] In these cases, the epiretinal membrane is considered to be secondary. Primary or idiopathic epiretinal membranes are diagnosed in the absence of any precipitating condition. However, posterior vitreous detachment (PVD) has been strongly associated with idiopathic epiretinal membranes.[1-5,18-20]



Epiretinal membrane (preretinal macular fibrosis) from excessive panretinal photocoagulation.

Pathophysiology

The exact etiology of epiretinal membranes is uncertain. Current theory proposes that epiretinal membrane formation occurs as a result of retinal glial cell proliferation and migration along the surface of the internal limiting membrane (ILM). Small, focal defects in the ILM allow these cells to "break through" to the retinal-vitreous interface and reproduce, creating a thin veil of tissue. The proliferative activity of these glial cells results in the characteristic epiretinal membrane. Other cell types such as fibrocytes, myofibroblasts macrophages, and hyalocytes have also been identified and implicated. In fact, hyalocytes might be one of the critical components of epiretinal membrane contraction through the effect of TGF-beta2 in the vitreous fluid.[21]

Beyond simply forming a membrane that coats the ILM surface, epiretinal membranes disturb deeper retinal layers. The photoreceptor inner/outer segment (IS/OS) junction is often disrupted in eyes with epiretinal membrane.[10-13] Retinal thickening, particularly in the inner and outer layers, also seems to contribute to the visual disturbance created by epiretinal membranes.[22,23]

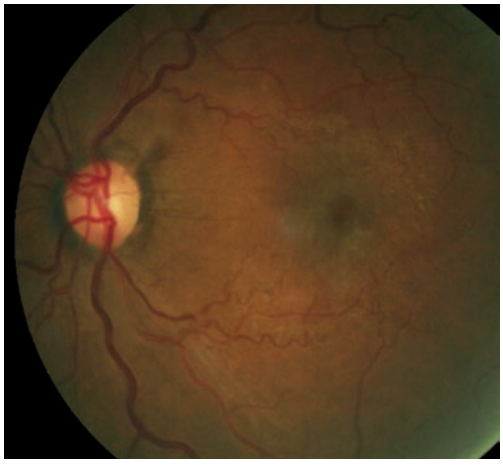
Management

Most patients, fortunately, suffer only a minimal reduction of acuity or slight metamorphopsia. These individuals should be reassured as to the nature of the disorder and fol-

lowed periodically, utilizing an Amsler grid for home monitoring of progression. They can be reassured that the condition is slowly progressive and that vision is not likely to get significantly worse than that seen at time of initial diagnosis. In most cases, there will be no discernible progression over five years. Few cases will develop incident visual impairment. Rarely, there can be spontaneous peeling and resolution.[24] Older patients are less likely to need or undergo surgery for epiretinal membrane.

Younger patients (under age 50) are more likely to have visual impairment and require surgical correction, perhaps due to inherent differences in the membranes themselves, which tend to be thicker and more adherent to the retina and vitreous. Typically, surgery is only considered when acuity drops below the arbitrary level of 20/60. Eyes with idiopathic macular epiretinal membranes and a presenting visual acuity of 20/50 or better have a favorable visual outcome with observation. Eyes with an initial vision of 20/60 or worse, or those who have a subsequent visual decrease to this level often realize significantly improved visual acuity after vitrectomy.[17]

Vitrectomy and surgical peeling of the membrane has been utilized successfully where there is significant visual compromise. This procedure, as one might imagine, is very intricate, and should be reserved for those patients with no acceptable alternatives. Peeling of the ILM is also performed to both enhance visual outcome as well as reduce recurrence rate of membranes.[25-27] The extent of the improvement following surgical repair will not be fully understood until several months post-surgery. Foveal thickness and visual acuity can improve over the several month post operative period but the final visual acuity prognosis is indicated by a combination of preoperative visual acuity, pre-operative foveal thickness, and post-operative foveal thickness.[28] Additionally, eyes with disruption of the photoreceptor inner segments/outer segments (IS/OS) as measured by spectral domain optical coherence tomography (SD-OCT) have a poorer prognosis. It is notable that there is a possibility of membrane recurrence following surgery and patients should be counseled to this effect in advance.[17]



Epiretinal membrane (cellophane macular reflex) causing vascular tortuosity.

Clinical Pearls

• Epiretinal membrane should be suspected in older patients where decreased visual acuity or visual distortion cannot be accounted for by lenticular changes, macular degeneration, or optic atrophy. Early identification of epiretinal membranes requires careful inspection with a slit-lamp fundus lens (78D, Hruby or Goldmann contact lens).

• If there is confusion as to whether the diagnosis is ERM or another etiology such as macular edema, a fluorescein angiogram or OCT can be ordered. Typical fluorescein patterns in epiretinal membrane show "corkscrew" distortion and dragging of the retinal vessels at the posterior pole, with a characteristic diminishing of the foveal avascular zone. Epi-macular traction shows up nicely using these scans.

• Optical coherence tomography is important in the diagnosis and management of eyes with epiretinal membranes. OCT can identify a suspected membrane rather easily and can also delineate the integrity of the photoreceptor IS/OS junction. OCT can also quantify reduction in macular thickness following surgery.

• Epiretinal membranes are often described to patients in a manner suggesting a natural history similar to that of progressing cataract, which is misleading. As opposed to cataracts, which regularly progress throughout the life of the patient, epiretinal membranes form and progress quickly initially and then tend to remain stable with little further reduction of acuity past what is seen on diagnosis.

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PATHOLOGICAL MYOPIA AND POSTERIOR STAPHYLOMA

Signs and Symptoms

Myopia can be defined as an optical aberration brought about by either increased axial length (axial myopia) or, less commonly, by increased ocular power in the cornea and lens (refractive myopia).[1] When the refractive error measures less than –6.00D, it is considered to be a normal physiologic variation. Pathological myopia, also described in the literature as degenerative, malignant or progressive myopia, is a condition defined by refractive error in excess of –6.00D with an axial length greater than 26mm.[2] The disease is characterized by "degenerative and progressive" changes involving a physical stretching of the sclera, choroid and retina. Progressive myopia is encountered with great variability throughout different geographical regions of the world.[2,3] In the United States, the prevalence is roughly 2%; in other countries, the disorder ranges from 1.7% to 3.3%.[2,3] However, certain populations can display greatly increased prevalence, with the highest (24%) noted to be in urban university students in Southeast Asia.[4,5] There are variable gender preferences for pathologic myopia between differing populations.[3]

Pathological myopes typically present with high myopic refractive error. In some instances there may be decreased visual acuity because of retinal pathology or refractive amblyopia. A high percentage of these patients also manifest strabismus.[6] Key ophthalmoscopic findings consist of a myopic crescent, patchy choroidal atrophy and flat, obliquely inserted discs. Posterior staphyloma is considered to be the hallmark lesion of pathological myopia. This finding represents a protrusion of the posterior sclera, due to increased elasticity.[7] Extensive vitreous syneresis and posterior vitreous detachment are typical. Peripheral retinal degenerations—lattice or snail-track, pavingstone and white without pressure—are also common. Additional findings occur with some variability and may include lacquer cracks (breaks in Bruch's membrane), subretinal neovascular membrane, Fuch's spot (RPE hyperplasia secondary to subretinal hemorrhage produced presumably from subretinal neovascularization), retinal breaks and retinal detachments.[8,9] Associated ocular disorders can include open angle glaucoma, premature lenticular opacification (especially posterior subcapsular cataract), neurosensory retinal degeneration, angioid streaks (when associated with systemic diseases that induce them) and choroidal neovascularization.[2,8] From a systemic point of view, progressive myopia often accompanies such disorders as albinism, Marfan's syndrome, Ehler's-Danlos syndrome, Weill-Marchesani syndrome, Knobloch's syndrome and Stickler's syndrome.[10]

Pathophysiology

In virtually all cases, progressive myopia has a genetic predisposition, with elongation of the globe beginning in early childhood.[10] A number of genes at various loci have been implicated, including 4q22-q28, 8q22.2, 10q22, 11q23, 13q22, 14q32 and many genes located on the X chromosome.[10] The precise etiopathogenesis of this disease is still unclear, despite many years of speculation. Papers published in the 1930s and 1940s implicated such things as squinting secondary to under-corrected refrac-

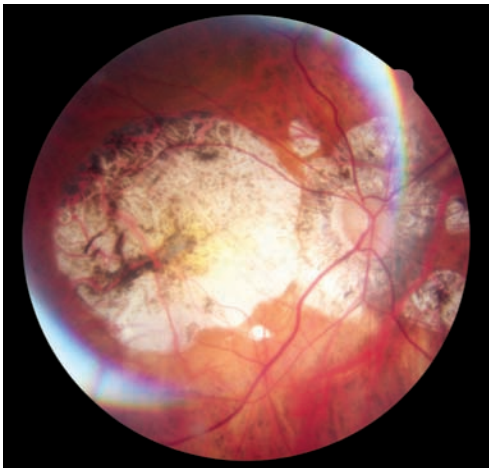
tive error as well as systemic calcium deficiency.[11,12] More recent theories suggest that neurochemical processes trigger a signal cascade based on a visual feedback mechanism, which in turn induces choroidal and scleral remodeling.[13,14] Changes in the sclera's extracellular matrix result in decreased durability, with excessive susceptibility to stretching. This may reflect systemic disorders of connective tissue metabolism.[13,15]

Posterior staphyloma is encountered in roughly 90% of patients with pathological myopia and is the result of progressive elongation of the globe with focal ectasia of the posterior pole.[7] Characteristic fundus changes include retinal thinning and increased visibility of the underlying choroid.[16] The majority of changes associated with staphyloma occur through puberty and adulthood, with a tendency for these lesions to expand and deepen with age.[7] The finding of posterior staphyloma increases the likelihood of visual disturbances and other myopic pathology, including chorioretinal atrophy, subretinal neovascularization, macular retinoschisis and macular holes.[17]

Management

When detected at an early age, most experts recommend full refractive correction (either via spectacles or contact lenses). Under-correction has been implicated in the development of greater amounts and rates of myopic progression and amblyopia.[18,19] Medical therapy is not commonplace for pathological myopia. In clinical studies evaluating medical treatment, the systemically administered adenosine receptor antagonist 7-methylxanthine was shown to help normalize the growth of myopic eyes in children, reducing axial elongation by as much as 22%, compared to placebo.[20]

Clinical findings such as subretinal hemorrhage, angioid streaks, lacquer cracks or Fuch's spot should prompt the clinician to refer the patient to retinology for the purpose of ruling out the need for intravenous fluorescein angiography. Angiography or optical coherence tomography (OCT) may assist in identifying areas of subretinal neovascularization potentially requiring surgical intervention. Patients with neovascular membranes may be treated with laser photocoagulation, photodynamic therapy, or intravitreal injection of vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab.[21] Those without such changes should be screened carefully and regularly (once or twice a year) for peripheral retinal degenerations, retinal breaks and retinal detachments.



Pathological myopia with posterior staphyloma.

While not commonly performed in the United States or Canada, surgical intervention for pathological myopia is often recommended in areas of Eastern Europe and Asia. The procedure known as scleroplasty, sometimes called "scleral strengthening", "scleral reinforcement" or "posterior pole buckling", is designed to help reduce scleral extension and myopic elongation of the globe. This highly controversial procedure was the subject of several recent retrospective studies, all reporting an arrest of myopic progression in the majority of subjects, as well as stabilization of refractive error and improvement in visual acuity.[22-24] Refractive surgeries such as LASIK do not present a viable solution for pathological myopia, due to the unstable nature of the refractive condition and the limitations of central corneal thickness. Phakic intraocular lenses, however, may provide a stable and reliable refractive outcome with a high level of safety.[25]

Patients with pathological myopia must also be counseled regarding the nature of their disorder and associated risks. Since there is diminished structural integrity of the globe, patients should avoid any unnecessary jarring contact to the eyes or head, as well as any activities that jolt the head or body excessively. These include contact sports such as football or boxing, bungee-jumping or high-thrill amusement park rides, as these behaviors can potentiate the risk for sight-threatening retinal damage.

Clinical Pearls

• The clinician should not rely on refractive error alone to make the diagnosis of degenerative myopia. Many patients with myopia exceeding 10 diopters never show signs of myopic progression or pathologically related tissue alteration. Fundus evaluation and ultrasonic measurements are key to the diagnosis.

• Lacquer cracks are more commonly encountered in young males, and may be one of the earliest findings in pathological myopia.[26]

• Differential diagnoses include histoplasmosis, congenital staphyloma, coloboma, gyrate atrophy, age related choroidal atrophy and age related macular degeneration, angioid

streaks and tilted discs.

• B-scan ultrasonography is a quick and easy way of confirming the presence of posterior staphyloma.

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SERPIGINOUS CHOROIDITIS

Signs and Symptoms

Serpiginous choroiditis is a rare, typically bilateral, progressive, recurrent inflammation of the choroid, retinal pigment epithelium (RPE) and choriocapillaris.[1-11] Its etiology is poorly understood.[1-3] There is no racial or sexual predilection.[2]

The choroidal lesions appear grayish-yellow and can be localized to levels of the inner choroid and overlying retinal pigment epithelium with a distinctive retinal distribution.[2,5] The disease presents around the optic disc with peripapillary lesions and finger-like projections extending outward.[2] Macular involvement is not the norm but is possible.[2] Once present, active lesions last from weeks to months often with a seemingly spontaneous resolution manifesting distinct areas of retinal pigment epithelial loss (atrophy) or clumping along with concomitant retinochoroidal atrophy.[1-5] Patients frequently have recurrences at intervals varying from weeks to years.[2] Each recurrence results in an extension further into the periphery.[2] About one third of patients present with an inflammatory reaction in both the posterior and the anterior segment.[2]

Regardless of the presenting form the clinical course includes progressive choroidal inflammation with the potential for multiple recurrences and significant visual loss.[1] The amount and quality of the visual disability corresponds to the extent of the involvement of the para-foveal and foveal regions.[1-5] Here, tissue destruction may be the direct result of the inflammatory lesions or may come secondary to induced choroidal neovascularization (CNV).[1-5] In one study CNV occured in approximately 50% of cases.[3] CNV may evolve at the time of active choroiditis or between episodes.[2,3]

Additional manifestations include retinal vasculitis, papillitis, vitritis, branch retinal vein occlusion, serous neurosensory retinal detachment, RPE detachment, and optic disc neovascularization.[2,3]

Pathophysiology

The histological findings of the lesions seen in serpiginous choroidopathy are cellular atrophy of the choriocapillaris, retinal pigment epithelium and photoreceptor cells with moderate diffuse lymphocytic infiltrates throughout the choroid.[1,4,11] Larger aggregates of lymphocytes were present at the margin of the serpiginous lesions.[4] The margins of most lesions had variable degrees of hyperplastic retinal pigment epithelium and some had defects in Bruch's membrane, through which fibroglial scar tissue extended into the choroid.[4]

Multiple etiologies including autoimmunity, infection via one of the variants of the herpes virus or mycobacteria (tuberculosis), general systemic vasculopathy and idiopathic degeneration of the retinal pigment epithelium with subsequent photoreceptor degeneration have been

proposed but none are proven.[1,11,12] Macular edema and CNV can complicate the course of disease.[2] One report makes the suggestion that serpiginous choroidopathy and multifocal choroiditis have a strong association and may be different presentations on the continuum of the same process.[13]

Management

Serpiginous choroidopathy seems to be a generic inflammatory retinochoroidal condition with a unique set of characteristics that set it aside from the other diseases in its class.[1-11] As such, the ultimate treatment course will depend on the hypothesis of the underlying cause.[8-15] One thing is clear, due to disease's insidious and progressive clinical course, reassessment is required over a lifetime.[1-15] Currently, treatment with immunosuppressive and alkylating agents have shown possible efficacy in a small case series.[1,16,17] In one study evaluating the combination of chlorambucil or cyclophosphamide with a generic alkylating agent, no patients had recurrences while on therapy.[17] In fact, no further visual loss was encountered after starting the therapy.[17] Success has also been demonstrated using a combination of immunosuppressive agents including azathioprine, cyclosporine,and cyclophosphamide.[16] All patients were able to taper oral steroids and five patients were able to discontinue all immunosuppressive medications. Ten eyes had improved visual acuities, while vision remained impaired in two due to macular scars.[16] Recurrence was noted in two patients when an attempt was made to decrease the dose of immunosuppressive medication.[16] Two patients experienced side effects which were reversed by decreasing the dose of the medications.[16]

Intravitreal steroids such as triamcinolone acetonide and fluocinolone acetonide have also been used with success in a limited population of subjects.[18-20] Intravitreal triamcinolone has been evaluated in unilateral serpiginous choroiditis with macular involvement as a rescue medication with success.[20] The principle benefit of local therapy is the ability to avoid the debilitating side effects sometimes caused by systemic immunosuppressive agents.[20] Recently, researchers have reported that anti-vascular endothelial growth factor (anti-VEGF) treatments with both CNV or macular edema in serpiginous choroiditis have demonstrated positive results.[2]

Clinical Pearls

- Long-term immunosuppressive treatment appears to prolong remission and preserve vision in patients with generic serpiginous choroiditis.
- Intravitreal steroid preparations, such as triamcinolone acetonide and fluocinolone acetonide, offer promise for local control of the disease without the projected systemic side effects.
- Other clinical entities which should be considered in the differential are categorized in the "white dot syndromes." These include multifocal choroiditis, multiple evanescent white dot syndrome, birdshot chorioretinopathy, acute multifocal posterior placoid pigment epitheliopathy, punctuate inner choroidopathy and diffuse unilateral subacute neuroretinitis.
- Serpiginous means healing over in one portion while continuing to advance in another. The condition has been named due to its movement and superficial appearance to a snake.
- Posterior placoid maculopathy is a relatively new entity which must be included in the differential diagnosis. These lesions are well-delineated white plaque-like lesions involving the macula and sparing the peripapillary areas of both eyes. In contrast to serpiginous choroiditis, visual acuity remains good despite involvement of the fovea.

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CAROTID-CAVERNOUS SINUS FISTULA

Signs and Symptoms

There are two types of carotid cavernous sinus fistula (CCSF), each with a distinct manner of presentation and etiology. The first is known as a direct CCSF. These usually occur abruptly following significant head trauma, such as that resulting from an automobile accident.[1-6] This type of fistula bridges age, race and sex profiles though is more often seen in young males. About 20% of CCSF occur spontaneously.[1] Patients who develop a direct CCSF traumatically have pronounced symptoms and signs. There will be marked congestion of the eyelids, conjunctiva and orbit. There is typically proptosis (which is often pulsatile) and limitation of ocular movement. The patient will experience vision loss from a host of possible causes, including secondary glaucoma, exposure keratopathy, and retinal and optic nerve ischemia.[1-6] Bleeding from the mouth, nose, and ears as well as intracranial hemorrhage may also occur, any of which may be fatal.[7,8]

The second type of CCSF is considered indirect and tends to develop spontaneously. This patient is typically a post-menopausal female, often with concurrent hypertension. Other associated factors include atherosclerosis, diabetes, sinus thrombosis, collagen vascular disease, and physical exertion by females during peripartum period.[1,9-13]

The signs and symptoms of spontaneous indirect CCSF—also known as a low-flow fistula or dural sinus fistula—is similar to the trauma-induced disorder, albeit much less pronounced and occurring gradually. The patient may experience diplopia and ophthalmoplegia (often from CN III or VI palsy), tinnitus or orbital bruit, and a red, congested eye. The ocular injection is often focused on by the practitioner without regard to the complete clinical picture leading to mistreatment as an ocular infection or inflammation. In CCSF the conjunctival and episcleral vessels are said to be arterialized. That is, the vessels are dilated and tortuous and have a corkscrew-like appearance. This comes from having high-pressure arterial blood coursing through these low pressure vessels. Intraocular pressure is often elevated in the involved eye secondary to increased resistance to aqueous egress caused by increased episcleral venous pressure.[9-13] Subconjunctival hemorrhage has also been reported to occur and initially mask the findings of a CCSF.[14]

Pathophysiology

The cavernous sinus is a trabeculated venous cavern on each side of the sphenoid sinus. It receives blood from the eye and adnexa via the superior and inferior ophthalmic veins, and drains into the jugular vein via the inferior and superior petrosal venous sinuses. Coursing through the cavernous sinus are the internal carotid artery (and its dural branches—the meningohypophyseal artery, inferior cavernous artery and McConnell's capsular artery), cranial nerves III, IV, V and VI, and the oculosympathetic plexus.[1] Carotid cavernous sinus fistulas are abnormal arteriovenous communications between the internal carotid artery (ICA) or its dural branches and the venous cavernous sinus.

A CCSF occurs when there is a rupture within the cavernous sinus of either the ICA or one of its smaller dural branches, resulting in the mixing of high-pressure arterial blood into the low-pressure venous system.

Carotid cavernous sinus fistulas are classified in several ways: etiologically as either traumatic or spontaneous in occurrence; high or low flow rate; and angiographically with either direct connection between a ruptured ICA or indirect connection through leakage of one of the intracavernous dural branches of the ICA or external carotid artery.[1]

Rupture of the ICA itself is typically due to trauma, and the signs and symptoms are pronounced. Occasionally a pre-existing ICA aneurysm may rupture giving the same clinical picture. In such cases, though spontaneous, the condition would be considered direct and high flow if the main trunk of the ICA is involved.

Rupture of one of the smaller dural branches is typically spontaneous, with milder signs and symptoms. Congenital weakness and aneurysms of the smaller dural branches most likely account for the vascular ruptures seen in spontaneous CCSF. Another theory postulates that these lesions develop in response to spontaneous venous thrombosis in the cavernous sinus and represent an attempt to provide a pathway for collateral venous outflow.[15] This mixing of high-pressure blood in a low-pressure venous system results in the ocular congestion and conjunctival arterialization as blood flows retrograde to the eye and adnexa. While typically unilateral, the presence of an intercavernous sinus allows for possible bilateral involvement.

The mixing of arterial blood in the venous system can allow the patient to hear his or her own heartbeat. This orbital bruit may be heard by placing a stethoscope over the patient's eye. This further manifests as a pulsatile proptosis. Diplopia and ophthalmoplegia occur due to congestion by blood of the muscles within the orbit or compression of the cranial nerves within the cavernous sinus. Multiple cranial neuropathies may coexist, though typically the patient with CCSF will manifest a single neuropathy.

With high pressured oxygenated arterial blood mixing in the low pressure deoxygenated venous system, drainage increases from the cavernous sinus. Blood can either follow the traditional drainage route posteriorly through the inferior petrosal venous sinus, basilar venous plexus, along the superior petrosal venous sinus or both or flow anterograde through the valveless superior and

inferior ophthalmic veins to the episcleral venous plexus. Most fistulas initially drain posteriorly. It is theorized that when this normal pathway for drainage thromboses, the fistula begins to drain anteriorly, producing visual symptoms and signs. Such patients initially may experience an acute, isolated, CN VI palsy with a posteriorly draining fistula.[13,16] Shortly thereafter, these patients develop typical signs of an anteriorly draining fistula. Anteriorly draining fistulas often have CN III palsy (typically pupil involved) which cause diplopia and ophthalmoplegia.[5]

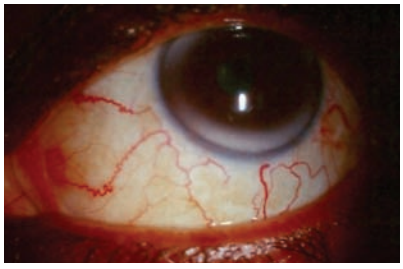
Secondary glaucoma develops frequently. As high-pressure, arterial blood fills the venous system, there is a subsequent rise in episcleral venous pressure. This, in turn, elevates intraocular pressure.[17] In most cases, the glaucoma that develops is secondary open angle due to elevated episcleral venous pressure.[12,13,18] Occasionally, congestion of the cilary body and expansion of the choroid can induce secondary angle closure glaucoma.[19]

In some cases, anomalous blood flow can reroute retrograde to the cortical venous system. These patients may seem to have undergone clinical resolution, but now have blood flowing retrograde not to the eye but to the brain. They will develop neurologic deficits, such as headache which is associated with an increased intracranial pressure. This creates a high-risk situation, as the patient can now possibly develop a fatal intradural hemorrhage.

Management

Suspicion of CCSF is crucial for diagnosis. Many patients with indirect, low-flow, dural sinus CCSF are misdiagnosed and treated erroneously for infections and inflammations, often for months to years.

Diagnosis is accomplished through neuroimaging and angiography. Contrast-enhanced CT scan and MRI will demonstrate a dilated superior ophthalmic vein and cavernous sinus. Additionally, proptosis and extraocular muscle enlargement can be seen. Ultrasonography may also demonstrate superior ophthalmic vein engorgement. Magnetic resonance angiography (MRA) is also very useful in identifying fistulas as well as specific vessel involvement.[21] Digital subtraction angiography will also confirm the diagnosis as well as classify the fistula and delineate the venous drainage pathway.[1,20] Conventional angiography is still the gold standard in identifying CCSF. However, due to the risk of morbidity and mortality associated with this procedure, it is often reserved for suspected potential surgical cases (direct rupture of the ICA in high-flow CCSF or high-risk dural CCSF). Nevertheless, it is often performed as part of the evaluation of low-flow CCSF and this diagnostic procedure has been known to cause closure of the fistula.[13,15]



Arteriolization of conjunctival and episcleral vessels in low flow carotid cavernous sinus fistula.

The goal in treatment of CCSF is to occlude the abnormal communication without sacrificing the vessel.[21-30] The most definitive treatment for CCSF is endovascular embolization using detachable balloons, coils, stents, or liquid embolic agents such as ethylene-vinyl alcohol.[1,21-30] Current microcatheter techniques permit access to the cavernous sinus via several routes, either transarterial or transvenous, for embolization. Trans-venous endovascular therapy is a low-risk treatment that is successful in 90% of all CCSF cases.[21,22]

High-flow direct CCSF resulting from intracavernous rupture of the ICA requires endovascular repair. Only in rare instances have these lesions spontaneously thrombosed.[31] In contrast, low flow, indirect dural CCSF are not at significant risk for ocular morbidity or mortality from intracranial hemorrhage and as such, conservative therapy is advocated. Low-flow dural sinus CCSF that occurs spontaneously is very likely to resolve spontaneously as well. Many will resolve spontaneously within months of symptomatic presentation.[1,2] In these cases, periodic observation is the best therapy because the relatively low risk of morbidity does not merit the risks associated with neurosurgical repair. Medical management of exposure keratopathy and secondary glaucoma as well as patching for diplopia are viable options.

In low flow, indirect CCSF, manual self-administered jugular-carotid compression may be advocated to cause flow obstruction with resultant stasis and thrombosis.[1,32] The patient is instructed to compress the jugular-carotid complex on the affected side with the contralateral hand for 30 seconds many times per day for four to six weeks. The contralateral hand is used so that if hemispheric ischemia develops, the hand will weaken and blood flow will re-establish.[1] This is typically only recommended after the appropriate evaluation has been performed and the diagnosis is certain and is adjunctive to observation waiting for the fistula to spontaneously close.

For low flow, indirect CCSF, neurosurgical repair is only considered in cases in which there is strong risk of vision loss (from glaucoma, corneal exposure or posterior segment ischemia), intolerable visual symptoms or appearance, or the development of headache indicating high-risk cortical drainage. The patient should be monitored for clinical deterioration, headache, and epistaxis that indicate that a high-risk cortical venous drainage has developed.

Transvenous endovascular therapy is indicated as well for low-flow dural CCSFs that merit repair. Radiosurgery is also an option in these cases (but not in cases of direct high flow CCSF). The vascular area is irradiated with 30-40 Gy to promote vascular thrombosis. However, this thrombosis may take up to two years to occur and many indirect low flow CCSF are likely to spontaneously thrombose in this time frame; hence this procedure is often seen as a fall-back strategy when traditional endovascular therapies fail.[1]

The main ocular concern in CCSF is the development of secondary glaucoma. This may be difficult to treat because most glaucoma medications only reduce the gap between intraocular pressure and episcleral venous pressure. As the episcleral venous pressure elevates in CCSF, it is very difficult to reduce IOP medically.[13,33] Prostaglandin-like medications can reduce IOP without involving the episcleral venous system, so these are probably most appropriate to manage this type of glaucoma.

Clinical Pearls

- CCSF present with characteristic corkscrew episcleral and conjunctival vessels. Because initial findings may be subtle, the condition may be misdiagnosed.
- Low flow indirect CCSF is typically not a life-threatening condition.
- The management of low-flow, spontaneously occurring CCSF is conservative observation.
- Consider CCSF in patients with proptosis and "conjunctivitis" and "inflammation" that does not respond to conventional therapy.
- The characteristic arterialization seen in CCSF has been descriptively called "caput medusae" after Medusa's head of snakes.
- Consider CCSF in the differential diagnosis of patients with unilateral red eye and elevated IOP.
- While low-flow CCSF tends to have low risk of morbidity, the drainage can change from the eye to the cortical venous system. This is indicated by headache and other signs associated with increased intracranial pressure. These patients must undergo neurosurgical repair.

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COMPRESSIVE OPTIC NEUROPATHY

Signs and Symptoms

Patients presenting with compressive optic neuropathy are variably symptomatic, depending upon the duration, severity and etiology of the underlying condition. Visual acuity decrease and visual field loss are the most common complaints. In some cases, this loss

may be rapidly progressive.[1-6] In these cases, diplopia and proptosis may also occur, especially if the cause is dysthyroid ophthalmopathy.[7-9] Patients may report feelings of "pressure" or "eye ache," consistent with expansive orbital compression (mass effect). Severe pain is atypical except in acute situations such as orbital cellulitis, mucocele or inflammatory orbital pseudotumor (although this disorder may also be painless).[10] In many cases, the condition is slow and insidious and the visual dysfunction associated with compressive optic neuropathy is painless. Another symptom may be decreased color perception. Occasionally, the patient may be asymptomatic and carry an erroneous diagnosis of amblyopia or glaucoma.[11,12]

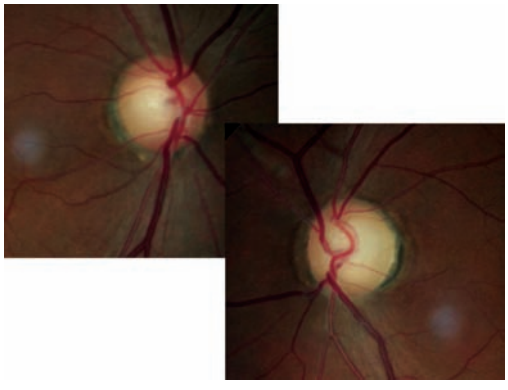
The funduscopic appearance of compressive optic neuropathy is variable. Early in the course, some degree of disc edema is possible, signs of which include hyperemia of the neuroretinal rim, blurring of the disc margins, peripapillary retinal edema, distention and tortuosity of the retinal vasculature, and occasionally hemorrhages on or adjacent to the disc.[5] Rarely, circumpapillary retinal folds known as Paton's lines, may be present, though this finding is more associated with true papilledema.

Prolonged compression results in optic atrophy, which may present as pallor and/or cupping of the nerve head. Optociliary collateral vessels may be noted at the disc margin.[5,13] There will frequently be increased progressive cupping of the optic nerve head somewhat similar to that seen in glaucoma.[14-16] The main differentiating factor from glaucomatous optic atrophy is the pallor of the remaining neuroretinal rim in compressive neuropathy. Additionally, there is more significant neuroretinal rim compromise in the form of notching that occurs in glaucoma that is not characteristic in compressive lesions where cup increase is more symmetrical with pallor. Associated field defects include central scotomas, arcuate or altitudinal defects, paracentral scotomas, field constriction, and defects respecting the vertical hemianopic line.

Other clinical signs consistent with orbital disease may be noted in these patients as well, including proptosis, lid retraction, restriction of ocular motility, and venous congestion of the eye and adnexa. Direct retrobulbar compression of the globe, hyperopic refractive shift, chorioretinal striae (choroidal folds), and elevation of intraocular pressure are all possible sequelae.

Pathophysiology

Direct impingement of cranial nerve II is the mechanism of compromise in compressive optic neuropathy. Most often this stems from a space-occupying mass within the orbit or suprasellar cistern. Conditions that are associated with compressive optic neuropathy include: a dolichoectatic carotid artery, mucocele, thyroid ophthalmopathy, neoplasms including optic nerve gliomas, nerve sheath meningiomas, dermoid cysts, neurilemmomas (schwanommas) and orbital metastases; vascular anomalies such as cavernous hemangioma, lymphangioma, simple venous varix, arteriovenous malformation, carotid aneurysm and carotid cavernous fistula; inflammations including orbital cellulitis and orbital pseudotumor, Wegener granulomatosis and subperiosteal or intraorbital hemorrhage.[7-9,17-23] Additionally, intracranial parasellar lesions, such as pituitary adenoma and craniopharyngioma, can produce the same effect. In these cases, the patient will likely have vertically oriented bilateral visual field loss respecting the vertical hemianopic line.[2,24,25]



Optic disc pallor OS (compared to OD) in a patient with a compressive optic nerve lesion.

The pathogenesis of this condition is mechanical compression of the nerve inducing stagnation of flow within the individual neurons, in both the slow and fast phases of axoplasmic transport. This axoplasmic stasis causes subsequent swelling of the axons as well as leakage of intracellular fluids, lipids and proteins into the extracellular space of the prelaminar optic disc. Vascular changes occur secondarily, as venous drainage via the central retinal vein is impeded by continued mechanical stress. As this process persists, hypoxia and disorganization of the normal neural matrix follows. If left untreated, optic atrophy will ultimately ensue. The atrophy may be total or sectoral.

Management

The biggest obstacle in managing patients with compressive optic neuropathy is proper recognition of the condition. Frequently, patients with compressive optic neuropathy are misdiagnosed with glaucoma due to the disc changes that can occur. Conversely, there are patients with glaucoma which may be unilateral, markedly asymmetric or progressive which are then considered to harbor a compressive lesion. It is a clinical conundrum to separate those eyes with glaucoma from those with a compressive lesion.

Separating patients with glaucoma from those with compressive lesions is accomplished through clinical examination. In a seminal paper on the topic, Greenfield and associates noted the following in eyes harboring compressive lesions: visual acu-

ity less than 20/40, vertically aligned visual field defects, optic nerve pallor in excess of cupping, and age younger than 50 years.[26] Additionally, in the glaucoma case-controls, those findings associated with glaucoma were older age, better visual acuity, greater vertical loss of neuroretinal rim tissue, frequent optic disc hemorrhages, less neuroretinal rim pallor, and more nerve fiber bundle visual field defects aligned at the horizontal midline.[26] Commonly, eyes with compressive lesions demonstrate clinical findings such as disc pallor, unexplained visual reduction, dyschromatopsia, rapid progression, and characteristic non-glaucomatous field defects which differentiate it from glaucoma.[27-29]

Patients with compressive optic neuropathy warrant a complete history and systemic evaluation, particularly if there is no knowledge of concurrent medical illness. The underlying etiology must be identified to appropriately manage the condition. A directed laboratory analysis is usually prudent, particularly if thyroid disease is suspected. Serology is often obtained to rule out infection, infiltrative and inflammatory causes of the neuropathy. Imaging studies of the orbits and chiasm utilizing contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) is often critical in the diagnosis.[21-30] Ultrasonography of the eye and orbit may also be helpful, but is limited in the shallow depth of imaging. However, B scan ultrasonography can identify a lesion impinging directly on the globe.

Since compressive optic neuropathy is merely a sign of a more significant disease, treatment must be specific to the underlying condition, and varies greatly. It is exceedingly important to comanage these patients with the appropriate medical subspecialist. Whenever possible, the offending lesion should be removed. Should the neuropathy fail to respond to this directed therapy, orbital decompression surgery or stereotactic radiotherapy may be necessary to alleviate external pressure on the optic nerve.[31-36] In many cases, surgical treatment can significantly improve visual function, even in cases where there was poor initial visual acuity at discovery.[8,33,36]

Clinical Pearls

• Compressive optic neuropathy is most often encountered as a unilateral condition when the lesion is intraorbital. If the lesion is in the suprasellar cistern, bilaterality ensues.

• In Graves' disease, the neuropathy occurs due to infiltration and expansion of the extraocular muscles, as well as tissue congestion within the orbit. This induces compression of the optic nerve at the bony orbital apex. Usually, this is a late development and other signs such as proptosis, motility restriction, and conjunctival edema and hyperemia (especially at the areas of muscle insertion) are noted earlier.

• Associated clinical signs are specific to the root cause of the disease. For example, restriction of ocular motility is often seen in Graves' disease, orbital cellulitis and orbital pseudotumor, but almost never encountered in neoplasms such as gliomas or meningiomas. Carotid-cavernous fistulas result in a corkscrew-like arterialization of conjunctival veins, while Graves' disease may show only modest conjunctival hyperemia, and orbital cellulitis presents with pain, possibly fever and lids that are firm and literally swollen shut. These factors are crucially important in differentiating one disease from another.

• Compressive optic nerve lesions that present with cupping are frequently misdiagnosed as normal tension glaucoma. In differentiating compressive neuropathy from glaucoma, typically glaucoma is bilateral and has progressive cupping with a pink neuroretinal rim, good acuity and color vision, arcuate visual field defects, and an absence of relative afferent pupillary defect (RAPD). In contradistinction, compressive optic neuropathy harbors pale cupping, diminished acuity and color perception, central and paracentral scotomas, and because the compressive source affects one nerve more extensively than the other or effects one nerve exclusively, an RAPD will more commonly be present.

• Patients being treated for glaucoma who demonstrate neuroretinal rim pallor, unexplained acuity loss, dyschromatopsia, non-glaucomatous field loss or a rapid progression—despite seemingly adequate intraocular pressure (IOP) control—should undergo imaging of the orbits and chiasm. Conversely, patients with glaucoma, despite asymmetry or unilaterality, who don't manifest disc pallor but rather have notched neuroretinal rims and an appearance that is consistent with the severity of glaucomatous field loss observed likely do not need neuroimaging. If the disc appearance does not match the visual field, or if the visual field defect is more vertically oriented, even in the absence of disc pallor, then neuroimaging is warranted.

• There are two rules for differentiating compressive optic neuropathy from glaucoma: 1. Pallor in excess of cupping is not likely glaucoma (alone); 2. Nothing notches a neuroretinal rim like glaucoma.

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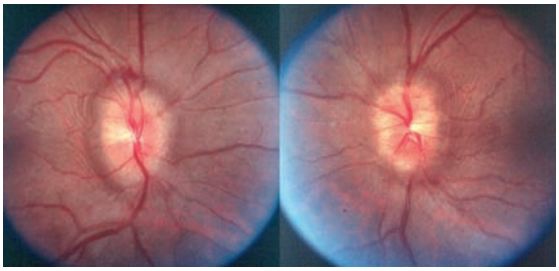
OPTIC DISC EDEMA & PAPILLEDEMA

Signs and Symptoms

Optic disc edema describes a clinical finding in which the optic nerve head appears swollen upon funduscopic evaluation. The condition may be unilateral or bilateral, depending upon the underlying etiology. Optic disc edema may be observed in a variety of optic neuropathies, including those due to inflammatory disorders, infection, infiltration, ischemia and demyelination. In malignant hypertension (defined as a systolic blood pressure >220mm Hg or diastolic blood pressure >120mm Hg, with end-organ damage at the level of the eye), patients present with bilateral optic disc edema and extensive hypertensive retinal changes, including arteriolar attenuation, venular dilation, scattered superficial hemorrhages, macular edema and exudates in a classic "star" pattern.[1,2] The term papilledema refers to a very specific form of optic disc edema that by definition must include the finding of elevated intracranial pressure (ICP).[3] Papilledema is associated with conditions that induce a mass effect within the intracranial space, such as tumors and hemorrhages, thrombosis, abscess, meningitis, hydrocephalus and pseudotumor cerebri (idiopathic intracranial hypertension).

Most patients with unilateral optic disc edema present with reduced visual acuity, diminished contrast sensitivity, dyschromatopsia (i.e., a reduction in color perception, particularly to red/green stimuli) and a relative afferent pupillary defect (RAPD) in the involved eye. These clinical findings can be mild or marked, depending upon the underlying etiology, duration and severity of the neuropathy. Visual field defects vary widely as well. In general, an enlarged physiologic blind spot may be seen in any form of disc edema which displaces the peripapillary photoreceptors.[3,4] Arcuate scotomas are also common when the inferior and superior poles of the disc are compromised.[5] Altitudinal defects may be seen in ischemic and demyelinating neuropathies; central and cecocentral scotomas are common in primary optic nerve inflammations and infections.[5,6] Associated ocular and systemic symptoms will also present with variability. Papilledema, is a bilateral event except in instances where the optic nerve has been infarcted and is incapable of swelling.[7] Visual symptoms include minimal acuity deficits and transient visual obscurations associated with postural changes.[3] Patients with papilledema also commonly manifest other classic symptoms associated with elevated ICP, including headache, intermittent diplopia, vomiting and/or nausea, and pulsatile tinnitus.[8] A relative afferent pupil defect is characteristically absent in papilledema, since both optic nerves are equally involved in most instances.

Ophthalmoscopically, the earliest signs of papilledema include striations within the nerve fiber layer in conjunction with blurring of the superior and inferior margins of the neural rim



Papilledema.

tissue. In time, the disc itself will protrude compared to the rest of the posterior intraocular surface and may, in cases of inflammation or papilledema, display hyperemia and capillary dilatation. In developed cases of arteritic ischemic optic neuropathy, the disc is swollen and elevated, but characteristically pale.[9] In more severe presentations of optic disc edema, the retinal venules become engorged and tortuous, hemorrhages and/or cotton wool spots form in the peripapillary area. In true papilledema, circumferential retinal microfolds (Paton's lines) become evident in the region surrounding the disc.[3] Chronic disc edema may result in atrophy of the nerve head, with associated pallor and gliosis of the rim tissue.[3,5] Interestingly, as the disc becomes infarcted, its capacity to swell is reduced until it is completely extinguished.

Pathophysiology

As the name implies, optic disc edema represents fluid accumulation at the level of the optic nerve head. Edema can result from a number of etiologic factors, including mechanical compression, infiltration, infection, inflammatory disease, demyelinating disease, or compromised vascular perfusion to the nerve. Optic disc edema is caused and/or accompanied by axoplasmic stasis, a phenomenon which describes diminished cellular conduction along the nerve. When this occurs, intracellular fluids and metabolic by-products accumulate and are eventually regurgitated at the level of the nerve head, giving the clinical appearance of optic disc swelling.[10,11] The disc edema in ischemic optic neuropathy has been described as "a 'cotton wool spot' of the optic nerve."[10]

Papilledema is not a primary neural inflammation, but rather a direct sequela of elevated ICP. In this disorder, cerebral edema is effectively transmitted along the common meningeal sheaths of the brain and optic nerve. Distention of the nerve sheath gives rise to axoplasmic stasis and disc swelling, but local edema can cause compression of the central retinal vein. Resultant venous obstruction can result in retinal hemorrhages at and around the disc as well as nerve fiber layer edema and exudates over time.[3] Prolonged swelling and axonal compression within the optic nerve can lead to hypoxia and gliosis, which can ultimately result in optic atrophy and corresponding vision loss.[3]

Management

Appropriate management of optic disc edema begins with accurate diagnosis of the underlying condition. The clinician must effectively distinguish between papilledema, pseudopapilledema (i.e., tilted discs, hypoplastic discs, medullated nerve fibers, optic nerve head drusen or congenitally crowded discs), and a multitude of other neuropathies. Common etiologies of disc edema include ischemic optic neuropathy, demyelinating disease and infectious, inflammatory/infiltrative and compressive optic neuropathies.[11] In order to arrive at the appropriate diagnosis, the clinician must carefully consider the patient's demographics, contributory history and examination findings, such as visual acuity, visual fields, ophthalmoscopic appearance, and especially the laterality of presentation. When available, B-scan ultrasonography is an efficient office-based technique for differentiating true edema of the nerve from incarcerated optic disc drusen.[12] An A/B-scan ultrasound with 30° test can determine if there is increased sub-arachnoid fluid indicative of papilledema.

In cases where the optic disc edema represents a local manifestation of systemic disease, management is aimed at treating the underlying disorder. Examples of such conditions include: malignant hypertension; optic neuritis, secondary to multiple sclerosis; arteritic anterior ischemic optic neuropathy (AAION), secondary to giant cell arteritis; non-arteritic anterior ischemic optic neuropathy (NAAION), secondary to hypertension or diabetes; neuroretinitis, secondary to cat scratch disease, Lyme disease or brucellosis; and compressive optic neuropathy, secondary to thyroid disease.[11] Referral to the proper medical subspecialist ensures that appropriate therapy is initiated promptly. Urgent attention should be given in cases of suspected AAION. Immediate evaluation including erythrocyte sedimentation rate, C-reactive protein, complete blood count and (likely) temporal artery biopsy needs to be performed to diagnose AAION as quickly as possible since aggressive, high-dose corticosteroid therapy is necessary to avert dramatic vision loss in the affected and fellow eye as well as other devastating systemic consequences.[13]

In cases of suspected papilledema, the most crucial ancillary test to perform is neuroimaging. Contrast-enhanced computed axial tomography (CT) or preferably magnetic resonance imaging (MRI) of the cranial cavity should be obtained as soon as possible, ideally within twenty-four hours of the initial diagnosis.[14] Additionally, magnetic resonance venography (MRV) must also be performed in all cases to examine for venous sinus thrombosis. Neuroimaging serves to identify potential causes of elevated ICP; scans may reveal intracranial mass lesions (e.g., tumor, hemorrhage, thrombosis or abscess) or disten-

tion of the cerebral ventricles indicative of hydrocephalus. In the absence of positive radiographic studies, lumbar puncture may yield information suggestive of meningitis, encephalitis, or spinal cord tumors. Pseudotumor cerebri, also known as idiopathic intracranial hypertension (IIH), is defined by the clinical findings of papilledema, normal radiographic studies, normal cerebrospinal fluid profile and ICP above established norms in an alert and oriented patient with no other neurologic deficits other than possibly a CN VI palsy.[15,16]

Papilledema is typically addressed by treating the root cause of intracranial hypertension. Therapy may be medical or surgical, depending upon the nature of the disorder. For example, intracranial neoplasms typically require neurosurgical excision and removal, while hydrocephalus may be treated with hyperosmotic and diuretic medications as well as ventricular shunting procedures.[8] Patients with IIH who are over their ideal body weight should be counseled regarding the need for weight loss. In most instances, we anticipate that papilledema will resolve as the underlying disorder responds to therapy; however, direct surgical intervention of the optic nerve may be advocated for persistent disc edema that threatens to progress to optic atrophy. The technique that has been described for this scenario is referred to as optic nerve sheath decompression (ONSD).[17] ONSD seeks to alleviate fluid retention within the surrounding meninges by creating multiple small fenestrations at a site within the intraorbital portion of the nerve.[17-19] While several large series have shown this procedure to be effective and safe,[18-20] there are also numerous reports of complications and treatment failure.[21-23] Patients should be evaluated on a case-by-case basis by an experienced neurosurgeon when considering ONSD. This procedure is reserved only for cases in which there is significant vision loss not responding to other treatments.

Clinical Pearls

• As a mentor of ours once taught, "Not all swollen discs are optic disc edema, and not all cases of optic disc edema are papilledema." The successful clinician must distinguish true papilledema from pseudopapilledema (e.g., buried drusen, congenitally full discs and even malinserted discs) as well as the multitude of other, primary optic neuropathies previously mentioned. The differences in subsequent testing and management can be quite costly, both to the patient and practitioner.

• The initial visual acuity is typically good in patients with acute papilledema, on the order of 20/30 or better. In those rare instances where vision is reduced, it is most commonly due to associated retinal pathology such as macular edema, exudates, and/or hemorrhage. The same phenomenon is seen in bilateral disc edema associated with malignant hypertension.

• True papilledema represents a critical sign of intracranial hypertension, and constitutes a potentially life-threatening situation. Prompt referral for evaluation is obligatory; confirmed cases warrant neurological consultation and co-management.

• Neuroimaging always precedes lumbar puncture for any case of suspected papilledema or disc edema. This is done to exclude intracranial mass lesions, which if present can shift the pressure gradient upon lumbar puncture so dramatically as to cause brainstem herniation, a life-threatening situation of its own accord.[24,25]

• Paton's lines should highly raise your index of suspicion for true papilledema.

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CROHN'S DISEASE

Signs and Symptoms

Inflammatory bowel disease (IBD) is a difficult to diagnose and debilitating condition.[1-4] Although the exact cause and mechanisms of IBD have yet to be completely understood, it is widely accepted that both are the result of an inappropriate immune response that occurs in genetically susceptible individuals as the result of a complex interaction among environmental factors, microbial factors and the intestinal immune system.[5] The two major subclassifications of IBD include ulcerative colitis (UC) and Crohn's disease.[1-8] Overlapping symptoms of UC and Crohn's disease often delay diagnosis, despite availability of endoscopic and radiologic inspective procedures along with histological samplings.[1]

The Vienna Classification, which arose from the 1998 World Congress of Gastroenterology Working Party, has been used to prospectively design a simple and objective Crohn's disease phenotypic classification. The model includes the components of age at onset, anatomic location and disease behavior.[6] Today, many refer to a revised Crohn's disease classification that combines genotype with phenotype.[5] Severe endoscopic lesions in Crohn's disease are defined by deep and extensive ulcerations on at least one part of the colon.[9]

Pediatric-onset IBD, consisting of Crohn's disease and ulcerative colitis, has significant medical morbidity and in many young persons is also associated with psychological and psychosocial challenges.[2] Depression and anxiety are particularly prevalent, adding to the multifaceted complications of the disease. Unique biochemical cytokines from the disease itself as well as the emotional stressors produce system-wide pathologies as do the vast array of medications which are used to treat it.[2]

Crohn's ileitis may cause an initial proliferation of adipocytes resulting in fat hyperplasia. This leads to an inflammatory process potentially causing mesenteric and retroperitoneal fibrosis.[10]

One-third of the patients with Crohn's disease will develop inflammatory ileitis, colitis or ileocolitis by the time of diagnosis.[3] While the diseased location remains generally stable over time, up to one-third of the patients develop a stricturing (stenosis or narrowing) anomaly or a penetrating intestinal complication.[3,7] Half of all patients experience an intestinal complication within 20 years after diagnosis.[3,7] The annual incidence of hospitalizations is 20%.[3] Half of all patients require surgery within 10 years after diagnosis.[3] The risk of postoperative recurrence ranges between 44%-55% over 10 years.[3,7]

Ocular symptoms can result from the disease itself or may result from toxicities to the immunosuppressant medications used to treat the diseases symptoms and processes.[11] Local signs and symptoms are consistent with uveitis and include pain upon eye movement, conjunctival hyperemia, photophobia and lacrimation. Anti-tumor necrosis factor alpha (TNF alpha) agents are increasingly being used to treat patients with Crohn's disease among other inflammatory systemic diseases and persistent uveitis.[11] One report describes a 68-year-old man with Crohn's esophagitis who developed a bilateral toxic anterior optic neuropathy during infliximab infusion.[11] Three additional cases of possible infliximab-associated anterior optic neuropathy have been reported in the literature.[11] Cataractogenesis may also be stimulated by systemic anti-inflammatory medications. Common ocular findings include acute anterior uveitis, conjunctivitis, peripheral corneal infiltrates, and retinal periphlebitis

Pathophysiology

The current models of Crohn's disease relate disturbances of the epithelial interface between the gut mucosa and intestinal microbiota.[3] This paradigm suggests that mucosal damage by luminal bacteria is an early, initiating factor in the pathogenesis of disease.[4,12] A number of susceptibility genes have been detected by large genome wide screening-approaches.[12] The incidence and development of Crohn's disease in the individual is largely dependent upon genetic and microbial factors as well as childhood hygiene, socioeconomic status and factors determined by living conditions and environment.[12]

Some features of Crohn's disease argue against a primary mucosal process.[4] Phenotypic studies point to a macrophage defect while genetic studies suggest an impaired innate immunity to intracellular bacteria.[3] Intracellular pathogens, such as *Listeria*, *Salmonella*, and *Mycobacteria*, invade via the gastrointestinal tract with minimal or no acute mucosal pathology.[4] These organisms then infect and persist in lymphatic tissues before inducing pathology, in the gut or elsewhere, as a secondary process.[4] Crohn's disease results from impaired macrophage responses to intracellular pathogens causing digestive system mucosal damage.[4] Subepithelial pathology precedes ulceration.[4]

Abnormal immune responses found in IBD have led to the use of serum biomarkers such as anti-*Saccharomyces cerevisiae* antibody [ASCA], perinuclear antineutrophil cytoplasmic antibody [pANCA] and antibodies to flagellin [anti-CBir1]) to improve diagnostic confidence regarding positive IBD identification.[1] These bio-

markers are used to stratify patients with UC and CD according to disease phenotype and risk of complications.[1] Further, the IBD biomarkers can be used to identify the relative risk of progression for early disease states to complicated disease behaviors, permitting the development of long-term strategy regarding therapeutic decisions.[1]

Management

Present therapeutic guidelines for IBD and Crohn's disease follow a sequential approach that focuses on treating the acute disease and inducing clinical remission.[13] Subsequent aims are to maintain an effective clinical response. In general, pharmacologic approaches are geared toward promoting mucosal healing.[13] Early use of biologic therapy, in combination with immunomodulators, seem to produce the best results with the least complications and lowest risks for relapse. This method decreases the need for treatment with corticosteroids while protecting against stricturing complications, hospitalizations and surgeries.[13]

Crohn's disease induces physical signs and symptoms which are primarily secondary to delays which take place in completing the appropriate diagnostic testing.[1] This leads to an extended period where appropriate treatment is omitted.[1] The disease process is chronic and incurable, requiring life-long therapeutic approaches to initiate and maintain symptom control, improve quality of life, avoid hospitalizations, avoid surgery, minimize short and long-term toxicity and minimize complications such as stricturing, fistulae, osteoporosis, associated bony fractures and linear growth failure in pediatric patients.[8,13]

Patients with gastrointestinal symptoms must be evaluated by a gastroenterologist. Endoscopy is used to provide a direct evaluation of the alimentary tube and is capable of uncovering the mucosal lesions that are pathognomonic of the disease. Endoscopic examination permits detailed description of lesions, their surface extent and severity.[10] Endoscopic reassessment can be used to reevaluate tissues, evaluate the success of treatment and serve as a predictor for the risk of clinical relapse and need for surgery.[10] Achievement of mucosal healing, which can be obtained by administration of several types of drugs, is associated with a better outcome, less surgery and hospitalization.[10-13]

Magnetic resonance enterography is a clinically useful technique for the evaluation of both intraluminal and extraluminal small bowel disease. It is particularly useful in younger patients with Crohn's disease.[14] MR enterography offers the advantages of multiplanar capability and lack of ionizing radiation.[14] It allows evaluation of bowel wall with contrast enhancement with the ability to distinguish wall thickening and edema (Crohn's disease activity).[14] It can also depict other pathologic findings such as lymphadenopathy, fistula and sinus formation, abscesses and abnormal fold patterns.[14]

The most important pharmacologic progress with respect to management for Crohn's disease has been in the class of TNF blockers.[12] These agents have been shown to be effective for controlling complicated disease courses.[12] Despite the fact that anti-TNF alpha antibodies are well-tolerated and highly effective in Crohn's disease, 25% to 40% of patients who initially benefit from treatment develop intolerable adverse events (lymphoma, infection) or lose their responsiveness during maintenance therapy.[15,16]

Probiotics (live microorganisms ingested by the host in appropriate quantities for benefit) have become a popular supportive and alternative treatment for conditions of the GI tract, including chronic disorders such as IBD and Crohn's disease.[17] Unfortunately, the evidence suggests there is only minimal benefit by any probiotic for Crohn's disease, though they have been found effective as an adjunctive therapy in inducing and maintaining remission for UC.[17]

The hygiene hypothesis has led researchers to the administration of helminths (deliberate infestation with the ova of a helminth: parasitic worms such as hookworms and whipworms) for the purpose of regaining more efficient modulation of the intestinal immune system.[12] Another new approach has been to improve the system-wide mucosal barrier function known to be impaired in Crohn's disease patients.[12]

Treatments produce variable responses with only approximately 10% of the patients having the benefit of prolonged clinical remission.[3,8] Systemic steroid dependency has been recorded in up to one-third of the patients, with surgery being required in up to one-third of patients following the initiation of steroid therapy.[3]

Management of uveitic and associated oculo-inflammatory complications is accomplished with topical cycloplegia and steroids with dosing dictated by severity. An appropriate topical steroid taper is recommended for cases requiring longer courses of treatment. Complications induced by systemic medicinal toxicity will require adjustments by the systemic medical team. Frequent ophthalmic follow up is recommended for the purposes of reassessment. Communication between the ocular team and systemic medical team will ensure that the systemic strategy is effective and not resulting in additional co-morbidities.

Clinical Pearls

• Crohn's disease is a disabling condition over time. The impact of changing treatment paradigms with increased use of immunosuppressants and biological agents on its natural history remains poorly understood.

• A coordinated approach between the systemic care team and the eye care team is critical. Written or telephone correspondence charting progress and future strategy should be made by all health care providers.

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HOMOCYSTINURIA

Signs and Symptoms

It was the further analysis of a case of homocystinuria from 1933 that led to the discovery that homocysteine causes vascular disease by having a direct effect on arterial cells and tissues.[1] The significance of homocysteine in human disease remained unclear until 1962, when cases of homocystinuria were associated with advancing vascular disease.[1-6] The broader biomedical significance of homocysteine was discovered when children with mental retardation, accelerated growth, dislocated ocular lenses and frequent vascular thrombosis (systemic and ocular) were found to excrete homocysteine in the urine (homocystinuria).[2,3] Methylmalonic aciduria and homocystinuria are the most frequent inherited errors of vitamin B_{12} metabolism, caused by an inability of the cell to convert the vitamin to both of its active forms.[5] Although considered a disease of infancy, some patients develop symptoms in childhood, adolescence, or adulthood.[5] There are four subtypes of homocystinuria with type I manifesting metal retardation.[7] In homocystinurias type II, III and IV, there is accumulation of homocysteine but a decrease of methionine, thus, there is no mental retardation.[7] In the cases involving the eye, in most instances the subtypes are II, III and IV.[7]

Homocysteine contributes to the genesis of arteriosclerosis which is one of the underlying causes of vascular disease.[1-7] This occurs when blood homocysteine concentrations become elevated as a result of dietary, genetic, metabolic, hormonal or toxic factors.[1,2] Numerous clinical and epidemiologic studies have established elevated blood homocysteine as a potent independent risk factor for vascular disease in the general population.[1]

Bone disease and cardiovascular disease is often detected in patients with homocystinuria.[3,6] The major ocular complication of homocystinuria is ectopia lentis, where zonular disease induces alterations of these fibers.[3,8] Changes in zonular chemistry weakens the connection of the supportive fibers to the lens leading to progressive lens dislocation.[3,8] Ectopia lentis occurs in up to 70% of patients with homocystinuria by age eight and in up to 95% of individuals with the disorder by age 40.[3] Ectopia lentis is also associated with other systemic diseases which alter collagen structure and function such as Marfan syndrome and Weill-Marchesani syndrome.[7] Untreated patients develop mental retardation, skeletal disorders and thromboembolic episodes which can lead to death by 20 years of age.[3] Hyperhomocysteinemia has been suggested and documented as a specific risk factor for retinal vein occlusion.[6]

Pathophysiology

Homocysteine is an amino acid in the blood formed by the removal of the terminal methyl group from methionine.[2,3,9] Homocysteine is a compound which is "corrosive" to long-living collagen (elastin), lifelong proteins (fibrillin) and proteoglycans.[9] Homocysteine can be recycled into methionine or converted into cysteine which is necessary for protein synthesis, via the B-vitamins [(pyridoxine (B_6), or cyanocobalamin (B_{12})].[8] This "sulfur metabolic pathway" plays a central role in cell metabolism and includes the sulfur amino acids methionine and cysteine. These

amino acids are essential for protein synthesis and homocysteine formation. Homocysteine is an intermediary molecule that aides in the degradation and demolition of old collagen. The amino acids also play a role in S-adenosylmethionine formation, the universal methyl donor in the cell as well as glutathione (GSH), which performs many functions including protection against oxidative stress.[2,3,9] At the intracellular level these metabolites are closely connected with other cellular metabolic pathways which impact cell physiology and health.[9]

Homocystinuria begins when homocysteine, a sulfur amino acid that is biosynthesized from ingested methionine becomes increased secondary to vitamin B deficiency, chronic renal failure or disorders of metabolism.[3,5,7] Cystathionine-b-synthetase and pyridoxine (vitamin B_6) convert homocysteine into cysteine.[5,7,9] When cystathionine-b-synthetase is dysfunctional or missing, the conversion cannot take place and alterations in body chemistry, structure and function occur.[1-13] Here, homocysteine is left unconverted and in high levels in the blood (homocysteinemia).[7] Plasma homocysteine becomes increased in the form of disulphide homocysteine and spills into the urine creating homocysteinuria.[5] Plasma methionine becomes pathologically increased in type I homocytinuria.[5,7] In homocystinurias type II, III and IV methionine is decreased, protecting against methionine-induced mental retardation.[7]

There are two forms of cystathionine-b-synthetase deficiency.[5] Both forms of the disorder result from an autosomal recessive message for inappropriate methionine metabolism.[5] Both produce the same amino acid abnormalities and clinical features.[5] The first form responds to pharmacological doses of pyridoxine (vitamin B_6). The second, more common, severe form is pyridoxine-unresponsive and requires a low-methionine diet supplemented with cysteine.[5]

Cysteine is an integral component of the chemistry of the zonules.[3] In homocystinuria, the resultant deficiency of cysteine affects normal zonular development predisposing affected individuals' eyes to myopia and lens dislocation.[3] Homocysteine inhibits cross-linkage in collagen and elastic tissue further predisposing the zonules to degeneration and ultimately lens dislocation.[3] In homocystinuria lens luxation is typically bilateral and inferior.[3]

Dietary deficiency of vitamin B_6 and folic acid and absorptive deficiency of vitamin B_{12} (cobolamin), which can result from abnormal traditional food processing or abnormal absorption of B vitamins, are also important factors in causing elevations in blood homocysteine.[1]

Homocysteine is important in the pathogenesis of arteriosclerosis in any person with hereditary, dietary, environmental, hormonal, metabolic or other factors which predisposes them to hyperhomocysteinemia.[2] Hyperhomocysteinemia is a potent independent risk factor for systemic vascular disease in general and ocular vaso-occlusive events.[1-6] The gene responsible for this metabolic alteration has been recently identified as MMACHC.[5]

Management

The diagnosis of homocystinuria may be difficult, as the age of onset, severity, and pattern of clinical manifestations vary widely among affected patients.[3,12] Any time myopia is rapidly progressive in a young patient or a refractive myopic shift is noticed in conjunction with lens luxation, homocystinuria should be considered and ruled out via appropriate laboratory testing.[12] Since the normal ranges for homocysteine levels vary in the general population, tests based on methionine loading can be used to confirm a diagnosis in suspected cases which might have been missed on routine screening.[3]

Dietary improvement, providing abundant vitamin B_6, folic acid, and cobalamin, may prevent vascular disease by lowering blood homocysteine.[1,2] The dramatic decline in cardiovascular mortality in the United States since 1950 may possibly be attributable in part to voluntary fortification of the food supply with vitamin B_6 and folic acid. Fortification of the US food supply with folic acid in 1998, as mandated by the US Food and Drug Administration, was associated with a further decline in mortality from vascular disease, presumably because of increased blood folate and decreased blood homocysteine in the population.[1,2] The dramatic decline in cardiovascular mortality since the 1960s in the United States is directly attributed to initiatives for the fortification of the food supply with synthetic pyridoxine and folic acid.[2] Currently, more than 20 prospective, worldwide, interventional trials involving at least 100,000 participants are examining whether lowering plasma homocysteine levels with supplemental B vitamins will prevent mortality and morbidity from arteriosclerotic vascular disease.[2]

Since lenses which are luxated in this disease are unstable secondary to zonular malfunction, cataract extraction or lensectomy procedures require special aspiration techniques, smaller capusularhexis and transcleral implant suturing into the sulcus.[10]

Clinical Pearls

- The genetic form of the disease is the second most common inborn error of amino acid metabolism.

• The position of the dislocation in homocystinuria is typically inferior.

• The position of the dislocation is not diagnostic, as the lens may migrate in any direction.

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MARFAN'S SYNDROME

Signs and Symptoms

Marfan syndrome (MFS) is the most common human connective-tissue disease.[1-15] The disorder affects the elastic fibers of connective tissues and is inherited via an autosomal dominant trait producing mutations in the fibrillin-1 (FBN1) gene on chromosome 15 (15q21.1).[1-4,5,7-9] The condition has an incidence of two to three per 10,000 individuals.[6] Although neonatal and infant forms of the disease exist, the classic syndrome frequently presents in childhood and adolescence.[3] The majority of cases (70%-85%) possess a hereditary background.[3]

The disease is marked by progressive involvement within different organs and systems including the skeletal, cardiovascular, dura, ocular, skin-integument and respiratory systems.[3] Suspicion of Marfan syndrome typically arises when the skeletal characteristics (typically the first signs) are observed upon clinical examination.[3,5] Skeletal system involvement is characterized by bone overgrowth and joint laxity.[3,5] The extremities of affected individuals are disproportionately long for the size of the trunk (dolichostenomelia).[3,5] Overgrowth of the ribs can push the sternum in (pectus excavatum) or out (pectus carinatum).[3,5] Scoliosis is common and can be mild or severe and progressive.[3,5]

The syndrome is potentially fatal, with cardiovascular complications occurring later in the processes' evolution.[1-3] Aortic dilatation and dissection are the major causes of morbidity and mortality.[4] Other cardiovascular complications include mitral valve prolapse with or without associated mitral valve insufficiency and aortic root dilatation.[8] A series of diffuse signs and symptoms can occur in Marfan Syndrome that are common to other disorders or syndromes serving to make the diagnosis of MFS difficult.[2,8] Cardiovascular involvement deserves special consideration, owing to its impact on mortality and prognosis.[1,8]

Myopia is the most common ocular feature occurring secondary to displacement of the lens.[15] Lens luxation is seen in approximately 60% of affected individuals and is a hallmark feature.[10,11] Individuals with MFS are at increased risk for retinal detachment secondary to traction created by an unstable lens and a tendency toward having an increased axial length.[15] Other risks include primary open angle glaucoma secondary to displacement of Schlemm's canal, secondary angle closure glaucoma with or without pupil block secondary to lens dislocation, strabismus secondary to tendon instability along with amblyopia secondary to the pertinent amblyogenic factors (strabismus, meridianal, anisometropic, refractive) and early cataract formation.[10,11,15]

The diagnosis of MFS should be made according to Ghent criteria and requires an extended family history and comprehensive clinical assessment of multiple organ systems.[1-3] Height and arm span are among the physical findings included as skeletal features used for the diagnosis of MFS.[2] Scoliosis, spondylolisthesis, pectus carinatum (sternum protrusion-pigeon chest) or severe pectus excavatum (sternum depression-sunken chest), severe hind foot valgus (medial displacement of the medial malleolus), arm-span-to-height ratio of >1.05 with elbow flexion and positive thumb and wrist signs are diagnostic as well.[2] The thumb sign (Steinberg sign) is considered to be positive when the entire distal phalanx protrudes beyond the ulnar border of the clenched fist and the wrist sign (Walker-Murdoch sign) is considered positive if the thumb can cover the entire nail of the fifth finger when wrapped around the contralateral wrist.[2] Craniofacial features such as slender cranium (dolichocephaly), malar hypoplasia, enophthalmos with downward-slanting palpebral fissures, skin striae, high-arched palate, myopia (as evidenced by corrective eyewear), and recurrent inguinal hernia are included as features as well.[2]

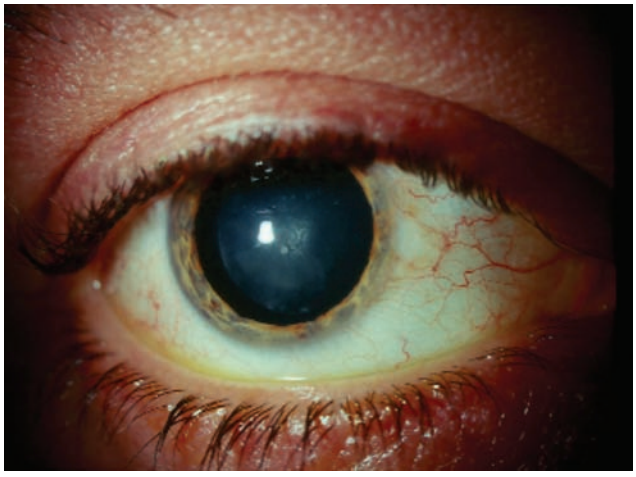
An international expert panel has

recently proposed a revised Ghent nosology, which puts more weight on the cardiovascular manifestations and in which aortic root aneurysm and ectopia lentis are the cardinal clinical features, minimizing the skeletal signs.[12] In the absence of any family history, the presence of these two manifestations is sufficient for the unequivocal diagnosis of MFS.[12] Genetic testing also may be useful in selected cases.[1] If the diagnosis is confirmed, the severity of the organ involvement must be assessed to formulate a preventive and/or therapeutic plan.[3]

Pathophysiology

More than 500 FBN1 mutations have been found in MFS.[9] The FBN1 gene encodes fibrillin-1, a glycoprotein that is the main constituent of the microfibrils of the extracellular matrix.[1] The extracellular matrix is made of collagen, reticular, elastic and oxytalan fibers, amorphous ground substance and adhesive proteins, such as fibronectin, which play a structural role.[13] Basement membrane is a specialized matrix which adheres to non-connective tissues and is continuous with the adjoining tissue remaining matrix by way of reticular fibers, anchoring fibrils, collagen VI filaments and oxytalan fibers.[13] Microfibrils are constituents of elastic and oxytalan fibers that confer mechanical stability and limited elasticity to tissues as well as contribute to growth factor regulation, tissue development and homeostasis.[13] The microfibril core is made of the glycoprotein fibrillin.[13] Microfibril-associated- proteins (MFAPs) and microfibril-associated-glycoproteins (MAGPs) and other peripheral molecules contribute to link microfibrils to elastin, to other extracellular matrix components and to cells.[11] Most of the MFS mutations are unique, affecting affect a single amino acid of the protein.[1] Reduced or abnormal fibrillin-1 leads to tissue weakness, increased transforming growth factor beta signaling, loss of cell-matrix interactions and the different phenotypic manifestations of Marfan syndrome.[1,8-13]

The fibrillinopathies are a series of genetic disorders due to mutations in fibrillin genes (FBN) of which the most frequently seen is MFS.[8-13]



Lens dislocation is seen in Marfan's syndrome.

Numerous patients who meet the Ghent clinical diagnostic criteria for Marfan syndrome do not have identifiable FBN1 mutations.[8] Recently, mutations in transforming growth factor beta receptors 1 and 2, respectively (TGFBR1 and TGFBR2-gene 3p24.1) have been shown to result in Loeys-Dietz syndrome (sometimes referred to as Marfan syndrome type II), a connective tissue disorder with a significant phenotypic overlap with Marfan syndrome.[8-13] Individuals with this Marfanoid disorder lack the ocular findings of Marfan syndrome and often have dysmorphic features such as unusual faces, cleft palate, and contractures.[8,9] Fibrillin-1 and transforming growth factor-beta (TGF-beta) signaling are functionally related in extracellular matrix.[9,13]

Management

Prophylactic medical and surgical intervention is an important method of reducing the cardiovascular risk in Marfan syndrome.[14] Pregnancy increases the cardiovascular risk in MFS women.[14] Signs and resulting symptoms in other organ systems require the input from specialists in those areas.[14,15] High-intensity exercise should be limited in these individuals as it stresses a potentially weak or flawed vascular system.[14] Low intensity dynamic exercise (such as isometrics or recumbent bicycling) may be beneficial.[14]

In the eye, primary open-angle glaucoma must be managed with pharmaceutical and surgical hypotensive therapy. Secondary closed-angle glaucoma, with or without pupil block, as a result of lens dislocation or microspherophakia will require a surgical solution.[15-17] Ectopia lentis may require surgical lensectomy as anterior chamber intraocular lenses (IOL) are contraindicated secondary to the connective tissue disease and the propensity for uveitis, glaucoma and hyphema syndrome (UGH syndrome) as a by-product of haptic erosion.[16,18,19]

Many of these patients are best treated with a careful refraction.[18] For those patients not achieving satisfactory refractive results, who have a partial lens luxation, endocapsular lensectomy using a modified Malyugin-Cionni ring (a device permitting capsule stabilization by

suturing to the sclera) has a history of success and safety.[15,18,19] In cases that result in aphakia, optical correction requires contact lenses or spectacles.[18] Retinal detachment will require surgical intervention for reattachment.[16] Complications from scleral buckle procedure for retinal detachment include scleral erosion of the buckle and sponges.[20]

Systemically, advances toward prophylaxis have been advanced using the mouse model.[21] It seems that many manifestations of Marfan syndrome are less related to a primary structural deficiency than to altered morphogenetic and homeostatic programs induced by altered transforming growth factor-beta signaling.[21] Transforming growth factor-beta antagonism, through transforming growth factor-beta neutralizing antibodies or losartan (an angiotensin II type 1 receptor antagonist), has been shown to prevent and possibly reverse aortic root dilatation, mitral valve prolapse, lung disease and skeletal muscle dysfunction in the mouse model of Marfan syndrome.[21] The COMPARE study (COzaar in Marfan Patients Reduces aortic Enlargement) is an open-label, randomized, controlled trial with blinded end-points designed to provide evidence that losartan treatment in the adult Marfan patient population significantly reduces the occurrence and progression of aortic dilatation.[22] Currently, beta-adrenergic blockers, such as atenolol, are the drugs most commonly used in MFS.[22]

Clinical Pearls

• Patients who exhibit signs of MFS who do not initially fulfill the diagnostic criteria must have yearly evaluations given the potential for the progressive evolution of the disease.

• Any newly confirmed case of MFS requires a search for preexisting, undiscovered disease among relatives.

• Given the catastrophic outcomes of aortic aneurysm and or major vascular dissection, MFS suspicion with subsequent testing and diagnosis could be life saving.

• The diagnosis and management of MFS requires a multidisciplinary team approach.

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SICKLE CELL DISEASE

Signs and Symptoms

Sickle cell disease (SCD) is a widespread inherited hemolytic anemia that results from a point mutation where valine is substituted for glutamic acid in the beta-globin chain.[1] This alteration produces a spectrum of systemic and ocular clinical manifestations along with a hemolysis and anemia.[1] The disease is theorized to have evolved as a protective mechanism against the plasmodium parasites that induce malarial disease.[2] Acute painful crisis is a common sequela that can cause significant morbidity and negatively impact the patient's quality of life.[1] In one study, it was estimated that over 70,000 people live with one form or another of sickle cell disease in the United States alone with many more worldwide.[3] The study estimated that 2000 are born in United States each year.[3] The literature estimates that in African countries such as Nigeria, over 100,000 babies are born with the disease each year.[3] The sickle cell trait occurs in approximately 300 million people worldwide with the highest prevalence estimated at approximately 30% to 40% in sub-Saharan Africa.[4]

The ocular signs of sickle cell anemia include comma-shaped vessels in the bulbar conjunctiva, spontaneous subconjunctival hemorrhage, iris atrophy, iris neovascularization, dull-gray fundus appearance, retinal

venous tortuosity, the potential for retinal hemorrhages in the subretinal, intraretinal or preretinal position, black sun bursts (retinal pigment epithelial hypertrophy secondary to deep retinal vascular occlusions), glistening retractile deposits in the retinal periphery (hemosiderin-laden macrophages), salmon patch hemorrhages (orange-pink-colored intraretinal hemorrhage), angioid streaks (breaks in Bruch's membrane radiating from the optic nerve), "macular depression sign" (a loss of the foveal reflex), venous occlusion, artery occlusion, peripheral neovascularization (sea fan retinopathy) and tractional retinal detachment.[5-7,9-15] Ocular symptoms are uncommon in the early stages of any form of sickle cell disease.[16,17] The incidence of proliferative retinopathy in SCD patients varies from 5%-10% depending on the genotype, with retinopathy being more common in patients with sickle cell hemoglobin C disease than in sickle cell with hemoglobin S or S-thal disease.[18]

Systemic symptoms include recurrent, painful vaso-occlusive crises with abdominal and musculoskelatal discomfort.[8,9] Other systemic manifestations include pulmonary hypertension, jaundice, association with pseudoxanthoma elasticum, cerebrovascular accidents and infections (particularly by encapsulated bacteria).[7,8,19,20] There is associated morbidity with pregnancy.[21]

Pathophysiology

In sickle cell disease, mechanically fragile, poorly deformable red blood cells contribute to impaired blood flow and other associated aspects of the disease.[22] The underlying cause of both the rheology and the hemodynamics is the formation of abnormal hemoglobin S (HbS) and the resultant cell sickling which worsens under deoxygenated conditions.[22,23] The sickling of the red blood cells occurs when partially or totally deoxygenated hemoglobin molecules, induced by the sickle malformation, distort their normal disk shape, producing stiff, sticky, sickle-shaped cells that obstruct small blood vessels and produce vascular occlusion as well as the disruption of oxygen to body tissues.[22-24]

The origin of the sickling gene can be traced to the continent of Africa where data suggests that the mutation of the hemoglobin chain protected individuals from malaria infection.[2,16-19] Inheritance of the sickle cell hemoglobinopathies is autosomal codominant, with each parent providing one gene for the abnormal hemoglobin.[12] Abnormal hemoglobin S results following a single point mutation substituting valine for glutamic acid at the sixth position.[1,9,10] Substituting lysine for glutamic acid at this position results in the formation of hemoglobin C.[9,10] When both parents contribute the S mutation, classic sickle cell anemia or SS disease ensues.[10] When one parent contributes S mutated hemoglobin and the other C mutated hemoglobin, the SC form of the disease is created.[10] Inadequate production of either normal or abnormal globin chains creates the S-thalassemia (S-Thal) variant.[9] Incomplete expression of the disease with some of the genetic mutations produces sickle cell trait (AS).[9] All four variations of sickle cell disease produce systemic and ocular complications secondary to the inherited abnormalities of the beta-globin chain.[3,23]

In the retina, effected erythrocytes, having lost their biconcave shape become rigid, restrict blood flow, produce thromboses and cause tissues to become hypoxic.[1,9-12,16-20,25,26] Fluid leakage, the liberation of angiogenic cytokines and neovascularization, along with all of its complications ensue pending the severity of the condition.[1,9-12,16-19,26,27] The pathogenesis of the resultant retinopathy is ultimately a manifestation of arterial and capillary microcirculation obstructive-vasculopathy.[25]

Salmon patch hemorrhages are preretinal or superficial retinal hemorrhages that often dissect into the vitreous humor.[9,10,15] They are the result of disruptions of the medium-sized arterioles secondary to chronic ischemic-vascular compromise.[10] Although they are initially bright red, their color evolves as they age. Because they have a tendency to push both forward and backward within the retina they may leave a retinoschisis remnant when they finally resolve.[10] Since the movement of this blood can disturb the retinal pigment epithelium, irregularly shaped hyperplasia changes can occur producing the classic pigmentary finding known as black sun bursts.

The treatable ocular hallmark sign of sickle cell disease is the sea fan-shaped frond of retinal neovascularization.[9,10,26] A common trait of the SC and S-Thal variations, sea fan neovascularization represents the body's aggressive attempt to resupply oxygen-deficient retinal tissue.[9,10,12,16-19,26,27] Arteriovenous crossings are the preferential site for sea fan development.[26] Here, preretinal vascular formations develop from a single or multiple feeder vessels at the border of perfused and non-perfused peripheral retina.[9-11,26,27] Since the retinal tissue is not globally ischemic the abnormal vessels arborize along the border of perfused and starved tissue.[10,26,27] Drained by single or multiple venules, the classic kidney-shaped appearance is driven by the retinal environment. Results from the work of Cao and coworkers demonstrate that vascular endothelial growth factors are associated with these formations.[26] The neovascularization in

sickle cell retinopathy can arise from both the arterial and venous sides of the retinal vasculature.[27]

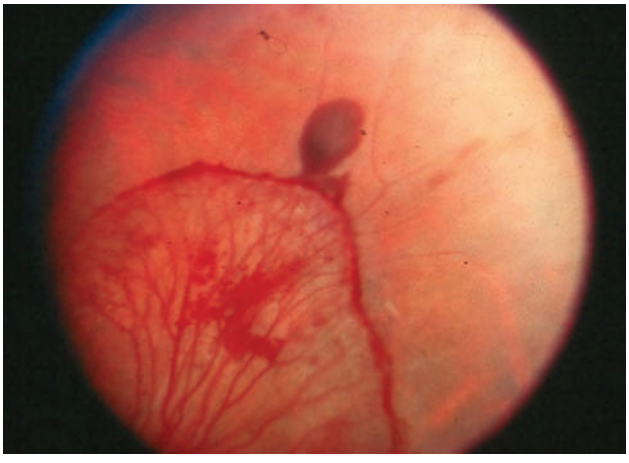
Autoinfarction (complete or partial spontaneous involution) is possible and appears to occur initially at the preretinal capillary level rather than at the level of the feeding arterioles.[27] It is a phenomenon which has been documented to occur in up to 50% of cases.[26] New evidence suggests that proliferative sickle cell retinopathy results when pigment epithelial derived factor (PEDF), secreted by the retinal pigment epithelium, designed to limit and suppress neovascular formation, loses its battle against vascular endothelial growth factor (VEGF), released by hypoxic tissue in non-perfused areas of retina designed to resupply starving neuroglia.[28] PEDF and VEGF have both been found to be significantly elevated in viable sea fan formations in sickle cell disease, however, only PEDF was present in non-viable sea fans.[28] PEDF seems to play an important role in inhibiting angiogenesis and inducing the regression of sea fans.[28] Progression of angiogenesis may be determined by the ratio of PEDF/VEGF.[28]

Proliferative sickle cell retinopathy is classically broken down into five stages. Stage 1 is recognized by peripheral retinal arteriolar occlusions. Stage 2 is marked by the appearance of peripheral arterio-venous anastamoses. Stage 3 is characterized by the growth of neovascular fronds known as seafans. Stage 4 is marked by vitreous hemorrhage as tractional forces and vitreous collapse tear fragile neovascular membranes. Stage 5 is advanced disease, identified by severe vitreous traction and retinal detachment.[9-11, 26,27]

The diagnosis of clearly evident clinical conditions such as leg ulcer, osteonecrosis and retinopathy are considered predictors for developing lethal organ damage and earlier death.[23] Many patients with sickle cell disease who go on to have cerebrovascular accident are known to have a chronic collateral condition.[25,26]

Management

The treatment goal for sickle cell retinopathy is to reduce the risk of, prevent and or eliminate retinal neovascularization.[9,10,16-20] Patients with asymptomatic sickle cell disease, free of ocular signs should be followed biannually with ocular examinations and dilated retinal evaluation.[10,17]



"Sea fan" neovascularization in sickle cell retinopathy.

Optical coherence tomography (OCT) and the multifocal electroretinogram (mfERG) are two relatively new additions to the technologic armamentarium which can be used to evaluate and monitor the health of retinal tissue in sickle cell cases.[29] OCT can image well the macular infarction and retinal depression that occurs in this condition. Likewise, mfERG can identify retinal ischemia and infarction.

Visual loss can result from both non-proliferative (subretinal neovascularization secondary to angioid streaks) and proliferative retinal disease.[9,10,16-20] The treatment for proliferative disease includes panretinal photocoagulation. Cryotherapy can be efficacious but is associated with high complication rates.[5,30] Scleral buckling may be indicated in cases of retinal detachment.[11] Photodynamic therapy and the antiangiogenic compounds, used in the choroidal and retinal neovascularization seen in other entities, have been used but are currently not in vogue as therapies for sickle cell disease.[1-4,31,32]

Conservative estimates find patients beginning to exhibit evidence of proliferative retinopathy from about the age of 10.[18] Eye examinations for children with SC disease should begin around the age of ten.[18] The examination must include dilated binocular indirect ophthalmoscopy. It is recommended evaluation be repeated every two years, switching to annual exams beginning at the age of 20.[18]

Sickle cell anemia instigates tissue damage at multiple foci.[1-10,24] Patients with sickle cell disease are at risk for medical complications that include delayed growth and sexual maturation, acute and chronic pulmonary dysfunction, stroke, aseptic necrosis of the hip, shoulders or both, dermal ulcers and chronic severe pain.[24] The chronicity of the illness combined with frequent hospitalizations for pain and other medical managements contribute significantly to impaired psychosocial functioning with reduced quality of life.[24]

Systemically, genetic risk factors along with other preventative possibilities are also now being explored.[25,29]

Stroke prevention has been made possible through advances in transcranial Doppler ultrasonography permitting both extensive examination and screening.[27] Hydroxyurea is an anticarcinogenic preparation that has significantly reduced the number of deaths and complications from sickle cell disease.[33] It increases fetal hemoglobin levels which seems to prevent red blood cells from sickling.[33,34] The medication has demonstrated an ability to reduce the number of vaso-occlusive crises and acute chest problems; thereby reducing the severity, pain and impact of the disease along with the number of hospitalizations.[33,34] An added benefit is that it also has demonstrated great efficacy and safety in pediatric studies.[25,33,34] Niprisan (Nix-0699) is another naturally occurring anti-sickling agent which has demonstrated promise in experiments with mice. It may offer the promise of an additional preventative solution in the future.[35] Zinc supplementation has been associated with infection protection in this population of patients.[36]

Clinical Pearls

• Other causes of peripheral neovascularization include sarcoidosis, diabetes, retinal venous occlusion, Eales' disease, leukemia and ocular ischemic syndrome.

• The laboratory testing for detecting sickle cell disease in patients with suspicious findings includes the Sickledex, Sickle Prep and plasma hemoglobin electropheresis.

• With respect to the production of systemic symptoms, the sickle cell anemia variation (SS) produces the most symptoms. With respect to the eye, the sickle cell disease mutations SC and S-Thal produces the most effects. Overall, the sickle cell trait expression (AS) produces the fewest complications.

• Sickle cell disease can progress rapidly in pregnant females making scheduled evaluations a requirement.

• Venous occlusion has been associated with strenuous exercise in sickle trait individuals. Counsel should be given to patients with sickle cell disease to participate in highly metabolic activities with caution.

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Pataday™
(olopatadine hydrochloride ophthalmic solution) 0.2%

INDICATIONS AND USAGE
PATADAY™ solution is indicated for the treatment of ocular itching associated with allergic conjunctivitis.

CONTRAINDICATIONS
Hypersensitivity to any components of this product.

WARNINGS
For topical ocular use only. Not for injection or oral use.

PRECAUTIONS
Information for Patients
As with any eye drop, to prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use. Patients should be advised not to wear a contact lens if their eye is red. PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% should not be used to treat contact lens related irritation. The preservative in PATADAY™ solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and **whose eyes are not red**, should be instructed to wait at least ten minutes after instilling PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% before they insert their contact lenses.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 40 L drop size and a 50 kg person, these doses were approximately 150,000 and 50,000 times higher than the maximum recommended ocular human dose (MROHD). No mutagenic potential was observed when olopatadine was tested in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test. Olopatadine administered to male and female rats at oral doses of approximately 100,000 times MROHD level resulted in a slight decrease in the fertility index and reduced implantation rate; no effects on reproductive function were observed at doses of approximately 15,000 times the MROHD level.

Pregnancy:
Teratogenic effects: Pregnancy Category C
Olopatadine was found not to be teratogenic in rats and rabbits. However, rats treated at 600 mg/kg/day, or 150,000 times the MROHD and rabbits treated at 400 mg/kg/day, or approximately 100,000 times the MROHD, during organogenesis showed a decrease in live fetuses. In addition, rats treated with 600 mg/kg/day of olopatadine during organogenesis showed a decrease in fetal weight. Further, rats treated with 600 mg/kg/day of olopatadine during late gestation through the lactation period showed a decrease in neonatal survival and body weight.
There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human responses, this drug should be used in pregnant women only if the potential benefit to the mother justifies the potential risk to the embryo or fetus.

Nursing Mothers:
Olopatadine has been identified in the milk of nursing rats following oral administration. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% is administered to a nursing mother.

Pediatric Use:
Safety and effectiveness in pediatric patients below the age of 3 years have not been established.

Geriatric Use:
No overall differences in safety and effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS
Symptoms similar to cold syndrome and pharyngitis were reported at an incidence of approximately 10%.
The following adverse experiences have been reported in 5% or less of patients:
Ocular: blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus.
Non-ocular: asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sinusitis and taste perversion.
Some of these events were similar to the underlying disease being studied.

DOSAGE AND ADMINISTRATION
The recommended dose is one drop in each affected eye once a day.

HOW SUPPLIED
PATADAY™ (olopatadine hydrochloride ophthalmic solution) 0.2% is supplied in a white, oval, low density polyethylene DROP-TAINER® dispenser with a natural low density polyethylene dispensing plug and a white polypropylene cap. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

NDC 0065-0272-25

2.5 mL fill in 4 mL oval bottle

Storage:
Store at 2°C to 25°C (36°F to 77°F)

U.S. Patents Nos. 5,116,863; 5,641,805; 6,995,186; 7,402,609

Rx Only

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NEW Moxeza™
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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MOXEZA™ Solution safely and effectively. See full prescribing information for MOXEZA™.

MOXEZA™ (moxifloxacin hydrochloride ophthalmic solution) 0.5% as base
Sterile topical ophthalmic solution
Initial U.S. Approval: 1999

INDICATIONS AND USAGE
MOXEZA™ Solution is a topical fluoroquinolone anti-infective indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms: *Aerococcus viridans*, Corynebacterium macginleyi*, Enterococcus faecalis*, Micrococcus luteus*, Staphylococcus arlettae*, Staphylococcus aureus, Staphylococcus capitis, Staphylococcus epidermidis, Staphylococcus haemolyticus, Staphylococcus hominis, Staphylococcus saprophyticus*, Staphylococcus warneri*, Streptococcus mitis*, Streptococcus pneumoniae, Streptococcus parasanguinis*, Escherichia coli*, Haemophilus influenzae, Klebsiella pneumoniae*, Propionibacterium acnes, Chlamydia trachomatis**
*Efficacy for this organism was studied in fewer than 10 infections.

DOSAGE AND ADMINISTRATION
Instill 1 drop in the affected eye(s) 2 times daily for 7 days.

DOSAGE FORMS AND STRENGTHS-
4 mL bottle filled with 3 mL sterile ophthalmic solution of moxifloxacin hydrochloride, 0.5% as base.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
- Topical ophthalmic use only.
- Hypersensitivity and anaphylaxis have been reported with systemic use of moxifloxacin.
- Prolonged use may result in overgrowth of non-susceptible organisms, including fungi.
- Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis.

ADVERSE REACTIONS
The most common adverse reactions reported in 1-2% of patients were eye irritation, pyrexia, and conjunctivitis.

To report SUSPECTED ADVERSE REACTIONS, contact Alcon Laboratories, Inc. or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

References:
1. MOXEZA™ Solution package insert. **2.** Lindstrom R, Lane S, Cottingham A, et al. Conjunctival concentrations of a new ophthalmic solution formulation of moxifloxacin 0.5% in cataract surgery patients. *J Ocul Pharmacol Ther.* 2010;26(6):591-595.

Reference: 1. MOXEZA™ Solution package insert.

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