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The Handbook of Ocular Disease Management

FOURTEENTH EDITION

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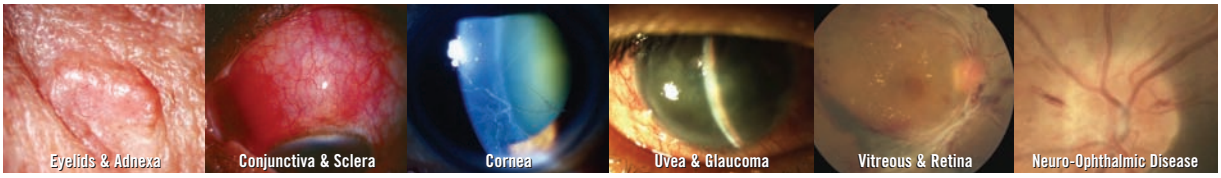

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A Peer-Reviewed Supplement

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 clinical experts review each manuscript before publication. This supplement was edited by the *Review of Optometry* staff.

FROM THE AUTHORS

To our Colleagues:

Optometry has evolved from what was once a purely visual correction and refractive drugless profession to an integrated member of the health care team. Therapeutic management of ocular disease has been a part of optometry for many years, but this has not always been so. It was the forward thinking of one of our mentors, Dr. Lou Catania that pioneered optometry into the therapeutic arena. As students of his, we have endeavored through the publication of *The Handbook of Ocular Disease Management* to continue and advance Dr. Catania's work by providing a concise, peer-reviewed, evidence-based compendium designed to give fellow colleagues a quick reference when practicing therapeutic optometry. We can all thank Dr. Catania for our ability to treat patients therapeutically.

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

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

Joe, Andy and Al

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

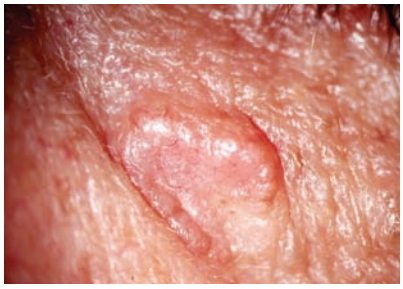
BASAL CELL CARCINOMA

Signs and Symptoms

Basal cell carcinoma (BCC) is the most common cutaneous neoplasm in humans. It is also the most frequently seen periocular malignancy in clinical practice.[1-4] BCC is typically found on the body in regions that are directly exposed to sunlight; thus, these lesions are often observed about the head and neck, especially in the vicinity of the eyelid and nose.[5] This tumor often presents as a cosmetic concern for patients (particularly those with a previous history of skin cancer); however, it may occasionally be discovered upon routine biomicroscopic evaluation. There is usually no associated pain or discomfort in the early stages. BCC is typically encountered in older, fair-skinned individuals, many of whom offer a history of prolonged or excessive exposure to sunlight.[3] The lower lid margin and medial canthus appear to be the most frequently involved sites.[4] Men also appear to be affected more commonly than women.[5]

Clinically, BCCs may be classified into at least four groups: (1) localized (nodular, ulcerative); (2) diffuse (morpheaform, sclerosing); (3) superficial multifocal; and (4) fibroepithelioma of Pinkus.[5,6] Of these, the nodular and ulcerative varieties are most prevalent and recognized as the "classic" presentations.[1-6] The nodular form appears as a small, translucent, raised area with poorly defined edges, which is firm to the touch. Over time, nodular lesions may develop telangiectatic vessels along the surface, and the inner portion may atrophy. This creates a "pearly," indurated (firm) outer margin with an excavated center, giving rise to the classic ulcerative presentation.

The sclerosing or morpheaform variety accounts for only about 6% of all BCCs, and presents as a firm, pale, waxy yellow plaque with indistinct borders.[5,7] The superficial multifocal form of BCC is also uncommon; it appears as well-circumscribed, red scaly patches with pearly borders, interspersed between areas of normal skin.[5] Fibroepithelioma of Pinkus presents as a sessile (broad-based), flesh-colored mass, whose histologic appearance closely resembles BCC. These lesions are almost exclusively found in the lumbosacral area.[5,8]



Basal cell carcinoma. Note the characteristic "pearly" appearance and raised, rolled borders.

Pathophysiology

The etiology and pathogenesis of BCC is not entirely known, but current research supports the likelihood of a genetic mutation that is triggered by certain environmental factors.[9] The most significant of these risk factors appears to be exposure to ultraviolet radiation, followed by increasing age.[7,9] In addition, Caucasians (particularly those with Celtic ancestry, e.g. Irish, Scottish and Welsh) have a significantly greater incidence of developing BCC than other races.[9] Those individuals at greatest risk are labeled as skin type 1 ("always burns, never tans").[9] A positive family history of BCC, immunosuppressive therapy, exposure to certain toxins (e.g. arsenic and coal tar derivatives) and irradiation are additional risk factors.[1,5,7,9]

In the vast majority of cases, the progression of BCC is exceedingly slow; lesions often develop over the course of years, rather than weeks or months. Metastasis is also very infrequent, with a rate documented between 0.0028% and 0.55%.[9] The larger lesions have a greater propensity for metastasis.[1] Despite favorable statistics, clinicians must realize that all BCCs possess the propensity to invade deeper structures and ultimately metastasize if they do not receive definitive treatment in a timely manner.[9]

Management

A wide range of surgical and non-surgical treatment options are available for BCC. Generally, surgical resection is regarded as the treatment of choice for periocular malignancies.[10] To diminish the likelihood of recurrence, control of the surgical margins is crucial. There are two techniques used for microscopic margin control: traditional frozen-section controlled excision and Mohs micrographic surgery.[10-15] Both of these techniques are associated with a low reported recurrence rate.[10-15] Frozen-section controlled excision has historically employed 3mm to 4mm margins, although newer surgical procedures may be able to accomplish similar outcomes with only 1mm to 2mm margins.[10-11] Mohs micrographic surgery involves serial removal of the affected tissue with progressive, real-time histologic evaluation of the margins; it is considered the surgical treatment of first choice for primary facial BCCs.[12,13] Opponents of the Mohs technique for periocular BCC cite the fact that it is costly and time-consuming, and can result in irregular margins that complicate reconstruction.[10]

Non-surgical therapies may be utilized in several instances: (1) as adjunctive therapy to surgery; (2) in those instances where the lesions are

extensive, and surgery is not appropriate; (3) when patients are too physically compromised to withstand surgery; or (4) when patients simply refuse surgery. Options may include laser cautery, external beam irradiation, cryotherapy with liquid nitrogen, photodynamic therapy with δ-aminolevulinic acid, topical Efudex (5% fluorouracil, Valeant Pharmaceuticals) and topical Aldara (5% imiquimod, Graceway Pharmaceuticals).[10,14] Recent studies have shown imiquimod to be an attractive alternative for small, nodular periocular BCC; this agent appears to offer a cure rate similar to surgical excision while preserving cosmesis and avoiding the emotional trauma associated with surgery.[16,17]

Clinical Pearls

• BCC constitutes approximately 75% to 80% of non-melanoma skin cancers. If an eye care practitioner diagnoses any periocular malignancy during his or her career, the odds are favorable that it will be BCC.[5]

• As important as therapeutic intervention is for confirmed BCC, preventive measures are even more crucial for at-risk individuals. At-risk patients (fair-skinned, older age, history of skin cancer in family) should be advised to avoid excessive sun exposure and employ topical sunscreen while wearing appropriate clothing whenever spending time in high UV conditions.

• Both duration and intensity of UV light exposure seem to be important in the development of BCC. Hence, the effect is not necessarily cumulative; an individual with a few instances of excessive UV light exposure may be of equal or greater risk than someone with a lifetime of modest UV light exposure.

• BCC is rarely life threatening because of its non-metastatic, slow-growing nature. However, the tumor does possess the capacity, over time, to cause significant local destruction, and should always be treated appropriately and aggressively.

• Early biopsy is the key to diagnosis in any malignancy. Suspicious lid lesions that demonstrate irregular growth, changes in color or appearance, or discharge of a purulent or bloody nature that do not heal should be biopsied to rule out cancerous etiologies. Confirmed malignancies should be referred promptly for treatment to an oculoplastic specialist or, when possible, an ocular oncologist.

• The ABCDEs apply: Asymmetry of the lesion, Borders which are irregular, Coloration that is abnormally dark or speckled, Diameters of 6mm or more (greater than the diameter of a pencil eraser) and Elevation with any changes over time of any of the aforementioned should be treated with suspicion.

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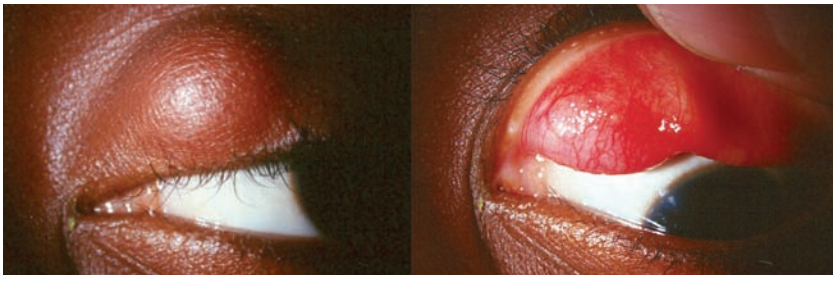
CHALAZION

Signs and Symptoms

Chalazia typically present as one or more focal, firm, painless nodules in the upper or lower eyelid.[1-7] While many patients seek care because of the cosmetic concern, some cases with larger lesions may produce mechanical ptosis resulting in some degree of obstructed vision. Still, in some instances, patients may be unaware of their presence. The lesions do not cause discomfort, though a history of painful lid infection such as a hordeolum or preseptal cellulitis prior to its discovery, is possible.[1] Enlargement of the lesion over time is possible. Often, there is a history of concurrent blepharitis, usually in the form of meibomian gland obstruction/dysfunction.[1-7] In some patients, chalazia may be recurrent and indicative of chronic blepharitis, lid hygiene issues, acne rosacea or, in rare cases, meibomian



Chalazion—external view (left) and everted (right).

gland or sebaceous cell carcinoma.[5] Men appear to be affected somewhat more often than women.[8]

Pathophysiology

Chalazia are the most common inflammatory lesions of the eyelid.[1,4-6] Chalazia are non-infectious and sterile, representing a lipogranulomatous inflammation of the sebaceous meibomian gland(s).[4] The typical etiology is obstruction of meibomian ducts with resultant retention of glandular secretions.[4] This frequently occurs in cases of chronic posterior blepharitis.[2,7,8] Occasionally, chalazia form from the collection of inflammatory cells following eyelid infection such as a hordeolum or preseptal cellulitis; this is referred to as a secondary chalazion.[2]

Histological evaluation of the chalazion reveals an inert collection of corticosteroid-sensitive histiocytes, multinucleated giant cells, plasma cells, polymorphonuclear leukocytes and eosinophils.[7,8] The nodule is encapsulated by connective tissue, often interdigitating with the tarsal plate.

Management

In cases not exhibiting concurrent infection, the use of oral antibiotics is unnecessary. While chalazia do respond to anti-inflammatory therapy, the anatomically deep nature of this condition renders a topical medication strategy virtually ineffective. Nevertheless, warm compresses (to clear the meibomian ducts of stagnant oils), accompanied by gentle digital massage (to rupture and express the nodule), can be attempted on a t.i.d to q.i.d. basis for lesions discovered early in their process (less than three weeks old).[9-12] Unfortunately, this therapy tends to be ineffective, with less than 25% of lesions resolving spontaneously or with hot compresses.[9-12]

Chalazia that do not respond to conservative therapy can be treated with excision or intralesional corticosteroid injection.[10,13-17] Studies document a success rate of approximately 80% to 90% using intralesional injection.[10,13-17] Using a standard 1cc tuberculin syringe and 30-gauge needle, 0.1ml to 0.3ml of triamcinolone acetonide 10mg/ml (Kenalog-10, Bristol Myers Squibb) or 40mg/ml (Kenalog-40) is injected directly into the lesion. The approach should preferably be from the palpebral side, because eyelid skin depigmentation may occur when the injection occurs on the dermal side.[17] This side effect is more common in dark-skinned individuals.[17] The use of a chalazion clamp and topical anesthesia may be helpful, but is not absolutely necessary.[15] One recent report documented adequate anesthesia with topical lidocaine gel only. The end result of the study produced equivocal success compared to procedures with standard injectable anesthesia.[6] Patients usually demonstrate marked improvement within one week of initial treatment, though repeat injections may be necessary for larger chalazia.[12-17] Should intralesional steroid injections prove ineffective or if the patient cannot tolerate the procedure, surgical curettage under local anesthesia is indicated.

Finally, recurrent multiple giant chalazia have been recognized as an ophthalmic feature of Job's syndrome (hyperimmunoglobulin E with connective tissue, skeletal and immunologic abnormalities).[18,19] In addition to meibomian gland/sebaceous cell carcinoma, this unusual syndrome should be suspected in cases where recurrent giant chalazia are documented, regardless of the patient's age.[18] Measurement of serum IgE and eosinophils is essential to establish a proper diagnosis.[18]

Clinical Pearls

• While vision problems are uncommon with chalazia, large lesions may cause a mechanical ptosis and resultant obscuration of the vertical visual field. For this reason, it is important to treat chalazia aggressively in young children. Obscuration of the visual field in the young has been documented to produce a deprivational amblyopia. Also, the induced chronic external pressure produced by larger lesions has the capability of inducing alterations in corneal curvature; several cases of chalazion-induced astigmatism have been documented.[20,21]

• Patients with chalazia should be cautioned against vigorous massage of the involved area. While gentle massage is beneficial, vigorous massage may cause further extravasation of the granulomatous inflammation into the surrounding tissue and exacerbation or complication of the condition.

• Many practitioners consider intralesional steroid injection to be contraindicated in dark-skinned individuals because of the risk of local skin depigmentation. These blemishes can persist for months or may be permanent. While injecting through the palpebral conjunctiva diminishes the risk, the side effect remains a possibility.

• Recurrent chalazia, especially those that recur in the same location within the same lid after surgical excision or lesions associated with madarosis, warrant excisional biopsy.[5] The greatest concern in these cases is sebaceous gland carcinoma.[5] This is an extremely aggressive form of eyelid malignancy, which carries a high mortality rate and great propensity toward metastasis. The majority of misdiagnosed recurrent chalazia represent sebaceous gland carcinomas; however, other significant lesions include BCC and pyogenic granuloma.[6,7]

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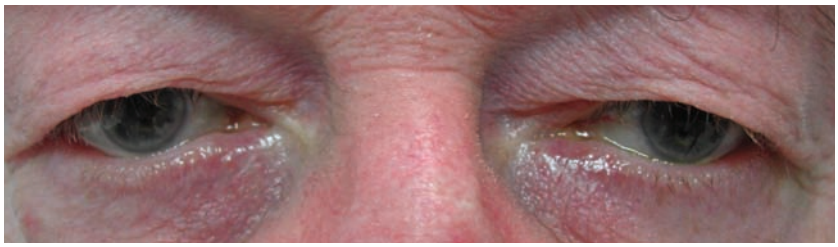

Dermatochalasis.

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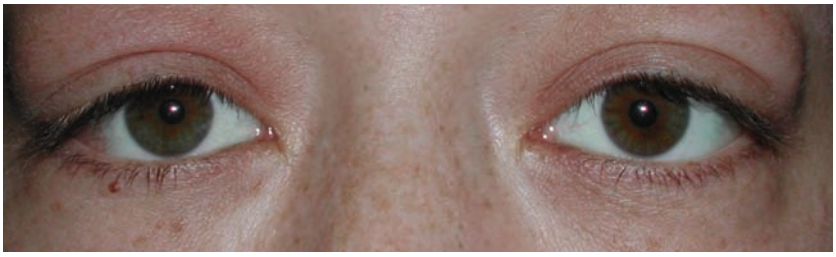
DERMATOCHALASIS & BLEPHAROCHALASIS

Signs and Symptoms

Dermatochalasis describes a common, physiologic condition seen clinically as sagging of the upper eyelids, and to some degree, the lower lids. It is typically bilateral and most often seen in patients ages 50 years or older. The condition is progressive and may be noted to a lesser degree in younger individuals. Inspection of the patient's lids reveals redundant, lax skin with poor adhesion to the underlying muscle and connective tissue. An excess flap or fold of skin in the upper lid is characteristic, and the normal upper lid crease may be lost. When the skin fold drapes over the eyelashes, the term "hooding" is used. Dermatochalasis typically results in a ptosis, though patients may employ the frontalis muscle to pull the lids open; this action eliminates the ptosis but results in furrowing of the forehead, as well as potential fatigue and headaches in the frontal region.[1] Additional clinical signs may include upper eyelid entropion, lower eyelid ectropion, blepharitis or dermatitis.[1]

Most commonly, dermatochalasis presents as a simple cosmetic concern. Patients complain of "droopy eyelids" that make them appear older. However, some patients report true functional difficulties, the most common being obstruction of the superior and/or peripheral aspect of the visual field.[1-3] Less commonly, patients may complain of ocular irritation secondary to misdirected lashes or chronic blepharitis.

Dermatochalasis is sometimes confused with blepharochalasis. Though similar in nomenclature, these two disorders are quite different in presentation and etiology. Blepharochalasis is a rare condition that is characterized by recurrent bouts of painless eyelid



Blepharochalasis.

edema, each instance of which may persist for several days.[4] It typically affects only the upper eyelids, and may be unilateral or bilateral.[5,6] Most commonly, the onset occurs during puberty, with the majority of patients being adolescents and young adults.[4,5] Inspection can reveal a variety of findings, depending upon the stage of the disease. Most sources recognize three stages of blepharochalasis.[7] Stage 1, the *edema stage*, presents with the aforementioned transient, painless lid swelling, often accompanied by mild redness. In Stage 2, the *atonic-ptosis stage*, the skin assumes a reddish-brown coloration, becoming telangiectatic and loose to the point of overhanging the lashes. Stage 3, termed *ptosis adipose*, involves dehiscence of the orbital septum with herniation of orbital fat into the eyelid. Additional complications of blepharochalasis may include conjunctival hyperemia and chemosis, entropion and ectropion.

Pathophysiology

The pathophysiology of dermatochalasis has not been well described. Much of the process appears to involve the normal involutional changes of aging, including the effects of gravity, loss of elastic tissue and degeneration of connective tissue, which results in laxity, redundancy, and thinning of the epidermal skin.[8,9] Both mechanical (the repeated action of facial expression) and photochemical (i.e. chronic exposure to UV radiation) etiologies have been proposed as causative factors.[1,4,9] Less commonly, systemic disorders—such as Ehlers-Danlos syndrome, cutis laxa, thyroid eye disease, renal failure and amyloidosis—may hasten the development of dermatochalasis.[1,4] Some patients may additionally have a genetic predisposition toward developing dermatochalasis at a younger age.[10] One report suggested that dermatochalasis may begin with subclinical inflammation, accelerating the elastolysis process and leading to secondary lymphostasis (obstruction and retention of lymphatic fluid).[4]

Blepharochalasis stems from recurrent episodes of eyelid edema; it is believed that the chronic exacerbating and remitting edema of this condition results in a stretching and subsequent atrophy of the eyelid tissue.[4-6,11] Proposed etiologies include both localized angioedema and inflammatory mechanisms, based upon histological studies and biomarkers that have been identified in patients with the disorder.[4,12,13] Ultimately, damage to the levator aponeurosis may ensue, resulting in ptosis. Blepharochalasis is considered idiopathic in most instances, though cases have been published suggesting a systemic association with conditions such as kidney agenesis, vertebral abnormalities and congenital heart defect.[14]

Management

Patients with asymptomatic dermatochalasis require little treatment. Automated perimetry may be beneficial to document any significant compromise to the visual field; any such field defect may be an indication for surgical intervention.[2,3] Patients should also be evaluated for blepharitis, trichiasis, ectropion, entropion or dry eye and treated accordingly with palliative and/or therapeutic agents, epilation or surgical corrective procedures. If examination reveals any other indications of underlying systemic disorders (e.g. thyroid or renal disease), then appropriate laboratory testing should be performed. Those individuals with symptomatic dermatochalasis should be referred for oculoplastic consultation.

Blepharoplasty is considered the procedure of choice for dermatochalasis. Typically, this involves the removal of a crescent-shaped wedge of skin (and occasionally some of the underlying muscle) from the upper eyelid, with suturing of the viable ends along the lid crease.[15] The technique may be performed in numerous ways incorporating a variety of instrumentation, from "cold steel" (i.e. stainless steel scalpel) to electrocautery to CO_2 laser.[16] More extensive or severe cases may warrant additional surgical measures, including browpexy (brow-lift surgery) and/or lower eyelid blepharoplasty with transconjunctival fat resection.[1,17]

Many clinicians consider the primary treatment of blepharochalasis to be surgical. Medical therapy during the acute stages of the disease remains controversial. The use of systemic corticosteroids has been suggested, and while some have found success with this treatment, others have reported cases recalcitrant to corticosteroid therapy.[18-20] More recently, reports of success using oral diuretics and tetracycline derivatives have been published.[19-21] Because the specific etiology of this disorder

is still unclear, it is difficult to delineate a foolproof medical regimen for all cases. The only certainty is that, ultimately, surgery is necessary to address the cosmesis of patients with blepharochalasis. Blepharoplasty with or without ptosis repair remains the surgical technique of choice.[4]

Clinical Pearls

- Realize that dermatochalasis is a normal, physiologic condition that affects virtually all patients over the age of 50 years, to varying degrees. It is commonly asymptomatic and requires little intervention. In contradistinction, blepharochalasis is an atypical, pathologic syndrome that can result in significant visual impairment of young, active adults.
- A common feature to both dermatochalasis and blepharochalasis is the herniation of orbital fat through the septum orbitale in the upper or lower eyelids. This phenomenon is referred to as steatoblepharon. Like dermatochalasis, steatoblepharon is common with age, and may be quite pronounced in some individuals. It is most often noted in the medial upper eyelid. Treatment of this condition involves transconjunctival blepharoplasty with resection of the excess fatty tissue.
- Dermatochalasis should not be confused with floppy eyelid syndrome, a condition in which the lids become flaccid due to a loss of tarsal elastin. Floppy eyelid syndrome is most commonly seen in obese, middle-aged men with respiratory problems such as obstructive sleep apnea. The poor lid-globe apposition in floppy eyelid syndrome often results in symptomatic papillary conjunctivitis.

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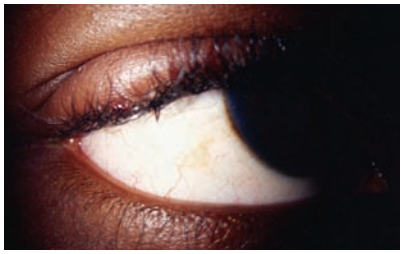
HORDEOLUM

Signs and Symptoms

The prominent symptom of patients presenting with hordeolum



Hordeola (upper lid) are typically acute and painful.

is an acutely painful, focally swollen eyelid exhibiting edema and erythema directly adjacent to or surrounding the affected eyelid margin gland or cilia.[1-8] Visual acuity is typically unaffected by the local infection so long as the swelling of the region does not obstruct the visual field, induce distortion effects by compressing the cornea or indirectly incite keratopathy.[1-7] Associated inflammation of the conjunctiva is possible, as is mucopurulent discharge that may ooze from the infected gland or from the base of the affected cilia.[2,3] The affected area of the eyelid will exhibit pain upon palpation and may hurt upon blinking (often the first sign the entity is evolving). Since the condition results from infection of the glands of the eyelid margin that produce the oil element of the tears, it can occur where the gland opens (external) or within its inner workings (internal hordeolum). There will be an associated lump within the eyelid in cases that are internal. There may be an erythematous volcanic or pimple-like lesion at the affected site of the lid margin in external cases.[1-7] Chronic eyelid disease and various forms of blepharitis are frequently present.[1-10] While there has been no reason to assign a sexual or racial predilection for patients with hordeola, one recent study involving more than 5000 subjects found a prevalence for blepharokeratoconjunctivitis in boys over girls.[2] Hordeola are among the

most commonly acquired lid lesions in children.[6]

Pathophysiology

The sebaceous glands of the eyelids (the meibomian glands, glands of Moll and glands of Zeiss) are the sites of origin for hordeola.[1-10] There are 20 to 30 glands in the upper lid and 10 to 20 in the lower lid, that are all embedded in the tarsal plate. The glands of Zeiss are associated with the eyelash follicles. All of these glands produce the superficial lipid layer of tears.[6,10]

Traditionally, a hordeolum represents bacterial infection of these glands of the eyelid with subsequent abscess formation.[1-10] If the superficial glands of Zeiss or Moll are involved, then the hordeolum is considered to be external and appears focal in nature.[1-10] This will be associated with a tender, inflamed swelling at the lid margin, often pointing anteriorly through the skin. If the deeper meibomian glands are involved or the infection becomes prosperous inside the workings of the gland preceding its opening, the hordeolum is considered to be internal. Internal hordeola create more diffuse swelling of the tarsus and have a greater propensity for creating cellulitis.[1-10] In either case, the lesion may enlarge and discharge either through the conjunctiva or through the skin.[1-10] Multiple recurrent hordeola associated with selective IgM deficiency has been reported.[7] Abnormal triglyceride fatty acid composition has been discovered in association with chronic blepharitis.[9]

The most commonly encountered organisms producing hordeola are *Staphylococcus aureus* and *Staphylococcus epidermis*.[2-6] Acute and chronic inflammation associated with hordeola may result in a hard retention known as a chalazion, especially if it is untreated or improperly treated. Spread of infection to neighboring glands or other lid tissue anterior to the tarsal plate may lead to the formation of preseptal cellulitis.[1-6,10] While uncommon, hordeola can produce ocular surface disruptions as a thickened lid rubs against the cornea and conjunctiva during blinking.[8]

Necrotizing fasciitis is a rare soft tissue infection with the ability to rapidly spread. It is characterized by widespread necrosis of the superficial fascia.[12] While it usually occurs about the limbs and the abdomen, one case of periocular necrotizing fasciitis originating from a hordeolum has been reported in a patient who was immunocompromised.[11] The infection occurs secondary to Group A beta-hemolytic *Streptococcus* and *Staphylococcus aureus*.[11] The eyelid has an excellent blood supply, making it an ideal place for supporting this type of growth.[11]

Management

Hordeola are generally self limiting and will resolve within five to seven days with spontaneous drainage of the abscess.[1-11] Traditionally, the hallmark treatment for hordeola is the use of topical antibiotic solutions and/or ointments coupled with warm/hot compresses.[1-11] Unfortunately, unless the lesion is superficial, this treatment yields poor results, as topical antibiotics may not generate sufficient intratissue concentrations to be therapeutic.[3] Topical antibiotics (solution or ointment) are prudent when there is significant concomitant blepharitis or acne rosacea.[1-11] The advantage of ointments is that they provide increased contact time with the infection. The disadvantage of ointments is cosmesis (appearing greasy) with the potential to blur vision.

Oral antibiotic therapy is necessary when hordeola do not resolve with a conservative topical approach.[10,12] If the hordeolum is external and there is a pimple formed, the lesion can be perforated and drained (anesthetic is usually unnecessary) or nearby lashes can be epilated to enhance drainage. Digital expression of purulent material in the office will expedite healing, but is not absolutely necessary. Oral antibiotic therapy includes cephalexin 500mg p.o. b.i.d., dicloxacillin 250mg p.o. q6h; erythromycin or tetracycline 250mg p.o. q.i.d.; or amoxicillin 500mg p.o. t.i.d. for 10 days. Warm/hot compresses, applied directly to the lesion, should be maintained to enhance pointing and drainage. Reassessment can generally be scheduled weekly until resolution.

Early recognition of failed therapy should prompt reevaluation of both the diagnosis and the etiology.[10-12] Surgical debridement and intensive intravenous antibiotic treatment are necessary for any non-resolving cellulitic expansion or any tissue destructive (necrotizing fasciitis) complications.[11]

Clinical Pearls

- The most common misdiagnosis of a hordeolum is a chalazion. The distinguishing factor is pain on palpation. If the lesion is not painful upon palpation, then it is most likely a chalazion.
- Topical treatment of infectious lid conditions offer a conservative approach. Results will be variable as this mode presents some therapeutic obstacles.
- Occult HIV disease should be entertained in a young person with an atypical hordeolum as Kaposi's sarcoma can mimic this condition.[13]
- Recurrent lesions or lesions associated with madarosis should undergo biopsy to rule out sebaceous cell carcinoma.[14-16]

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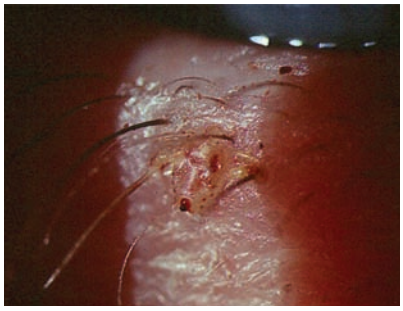
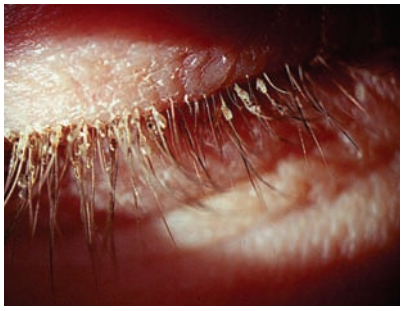


Phthiriasis organism.



Phthiriasis infestation of the eyelids.

PHTHIRIASIS PALPEBRARUM

Signs and Symptoms

Adult patients that manifest this particular form of blepharoconjunctivitis typically are sexually active.[1] There is often concurrent genital involvement.[2] The patient will frequently report eyelid irritation and itching; pruritic lid margins will be grossly apparent. Biomicroscopically, there will be visible organisms and egg sacs (nits), which may be raptured or intact, within the scalp, hair, eyebrows, eyelashes or beard; visible blue skin lesions (louse bites); reddish brown deposits (louse feces); secondary blepharitis with preauricular adenopathy; follicular conjunctivitis; and, in severe cases, marginal keratitis.[3-6] Superinfection of bites may lead to preauricular gland swelling.

Pathophysiology

Pediculosis refers to eyelid infestation by *Pediculus humanus corporis* (body louse) or *capitis* (head louse). These organisms rarely will infect the eyelids, though. Phthiriasis palpebrarum refers to eyelid infestation by *Phthirus pubis* (pubic louse, sometimes referred to as crab louse). Eyelid infestation is almost always by *Phthirus pubis*. However, this organism will occasionally infect the scalp.[7] It appears that outbreaks of *Pediculus capitis* are more frequent in the warmer months, whereas *Phthirus pubis* are more dominant in the cooler months.[8]

Pediculus is an organism 2mm to 4mm long that typically infests the hair of the patient. Infestation of the cilia is rare and only occurs in the worst cases. *Phthirus* is 2mm long with a broad-shaped, crab-like body. Its thick, clawed legs make it less mobile than the *Pediculus* species and lend it to infesting areas where the adjacent hairs are within its grasp (eyelashes, beard, chest, axillary region, pubic region).[5,7] Both organisms suck the blood of the host, and *Pediculus humanus* may serve as a vector of diseases, such as typhus and trench fever.

Pediculus and *Phthirus* interbreed freely. Both types of lice lay eggs on the hair shafts. These eggs remain firmly adherent, resisting both mechanical and chemical removal.[5,9] *Pediculus* possesses good mobility and can pass from person to person by either close contact with an infested individual or by contact with contaminated bedding. Conversely, *Phthirus* are slow-moving organisms that cannot typically pass unless cilia are brought into close proximity with infested cilia, though contaminated bedding is a possible source.[10,11] Both species are associated with crowding or poor personal hygiene.

Management

Management begins with forceps removal of all visible organisms and nits.[2,3,5,6,9,12] The removed organisms and nits should be killed by placing them onto an alcohol wipe (or dipped in alcohol). They can then be discarded. Adjunctive topical therapy may be employed to ensure eradication following physical removal. If physical removal is not possible or practical, topical therapy will suffice. The lice and nits can

be smothered with petroleum jelly or other bland ophthalmic antibiotic ointments t.i.d. for one to two weeks. Even pilocarpine gel has been used successfully. The organisms breathe through their body walls, thus ointments are effective as a tool to smother them. Other topical therapies that act to interfere with their respiratory systems include 1% yellow mercuric oxide, 20% fluorescein (as used in angiography), 2.5% permethrin cream or 3% ammoniated mercuric oxide b.i.d. for one to two weeks.[4,6,13,14] Alternate treatments include cholinesterase inhibitors such as physostigmine.[6,15-17] Typically, the nits will survive a single application of these agents as the egg is totally encased by a proteinaceous sheath, and must hatch before becoming susceptible to topical therapy.[18] For this reason, therapy is always recommended for one to three weeks.

Oral Stromectol (ivermectin, Merck & Co., Inc.), an agent for the treatment of scabies infection as well as onchocerciasis, has had some anecdotal success in the management of phthiriasis palpebrarum.[19]

When phthiriasis palpebrarum is diagnosed, genital involvement must be suspected. Infested patients should be instructed to obtain and use a pediculocidal medicated shampoo. These include, but are not limited to, lindane 1%; permethrin 1% (marketed as Nix cream rinse by Warner Lambert; Elimite cream by Allergan; or Acticin cream by Mylan Bertek); A-200 Pyrinate (pyrethrins, piperonyl butoxide and kerosene, Hogil Pharmaceutical Corp.); and Kwell (lindane, Reed and Carnrick), or RID (pyrethins/piperonyl butoxide, Bayer Healthcare LLC), which are safe, effective, non-prescription pediculicides. However, due to toxicity, these agents cannot be used on the eyelids.

Patients must be instructed to thoroughly wash all clothing and linens that may have been exposed. Clothing, linen and personal items must all be disinfected with heat of 50° C (125° F) for 30 minutes or more.

Medical testing for other sexually transmitted diseases, including HIV infection, should be recommended.[1] When the issue is discovered in children, contraction within the school network and abuse must be considered.[10] Such infestations should be reported to the child's pediatrician.

Clinical Pearls

- Follow-up is required through seven to 10 days, as nits hatch within that period.
- Educate patients about how the organisms are transmitted, and advise that they should refrain from all close and personal/sexual contact with others until the disease is 100% resolved. Finally, counsel patients to educate exposed partners to report for examination and evaluation.
- Mechanical removal at the biomicroscope with a jeweler's forceps is time consuming, but it is the preferred method of treatment. This can be a detailed, painstaking process. In that the egg sacs are termed "nits," the lay public has historically referred to this overall infestation as "nits." This is where the terms, "nitpicker" and "nitpicking" come from.
- Live organisms will cling tightly to the eyelashes and many lashes will be removed during this process. Educate the patient to expect some discomfort associated with inadvertent lash removal.
- Smearing the lids and lashes with an ophthalmic ointment may make removal easier as the organisms cannot grasp as firmly to the greasy lashes. However, this may make visualizing and grasping the organisms with forceps more difficult.
- There is virtually no chance of the doctor or other office staff members contracting the infestation through the examination or removal process.

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EPISCLERITIS

Signs and Symptoms

Episcleritis is an inflammatory condition of the external eye involving the conjunctiva and its underlying connective tissue.[1-11] The signature presentation demonstrates a sectorial injection involving both the episcleral tissues and overlying conjunctiva, usually concentrated in either the nasal or temporal quadrant without discharge.[1-10] It is hard to document epidemiologic data as the inflammation is primarily a response to either a noxious/toxic exposure (solid, liquid, gas) or secondary to an underlying systemic disease.[1-7] Idiopathic cases have been documented and seem to account for 33% of occurrences.[12,13] Acute onset is typical, with patients often reporting that they "woke up with a red eye."[7] Superior injection has the potential to go unnoticed and may be completely masked by the upper eye lid in primary gaze. Most cases of episcleritis are unilateral; however, it may occur bilaterally in cases of exposure or cases precipitated by underlying systemic disease.[7] Occasionally, a translucent white nodule is seen within the inflamed area (nodular episcleritis).[7,11] Nodular episcleritis represents focal concentration of the inflammatory response.[7,11] The nodule is often linked to underlying tissues and can be distinguished from cysts and phlyctenular lesions by its characteristic lack of mobility with the conjunctiva.[7,11] Patients may complain of mild pain or tenderness to the affected region, pain upon manipulation or a stabbing sensation upon moving the eyes (particularly saccadic movement). Visual acuity is unaffected.[1-12] The cornea is also unaffected, although long-standing or recurrent episcleritis may lead to dellen formation.[8] While it is rare that episcleritis provokes anterior iritis/uveitis, like all ocular inflammatory reactions, it is possible anterior chamber cells may be seen in more pronounced cases.[1-12]

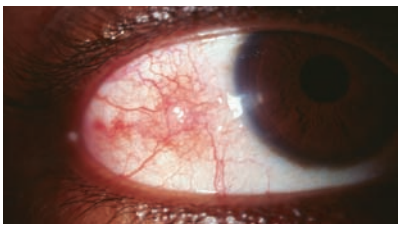
Diagnostically, most cases of episcleritis will blanch with the application of topical 2.5% phenylephrine.[11] In contrast, more significant ocular inflammations such as scleritis and uveitis will not result in blanching. Gently manipulating the inflamed region with a cotton-tipped applicator may also help distinguish the level of inflammation.

Pathophysiology

Episcleritis represents an inflammation of the episclera, the highly vascularized ocular tunic that encircles the globe between the overlying conjunctiva and the underlying sclera.[1,7-12] The inflammatory response in these cases remains localized to the superficial episcleral vascular network with the histopathology showing nongranulomatous inflammation and vascular dilatation with perivascular infiltration.[14] The disorder may be idiopathic or in association with some underlying systemic disease.[1-12,15,16] Among those conditions linked to chronic or recurrent episcleritis are: rheumatoid arthritis, polyarteritis nodosa, systemic lupus erythematosus, inflammatory bowel disease, sarcoidosis, Wegener's granulomatosis, tuberculosis, Lyme disease, gout, herpes zoster and syphilis.[4,6,7,10,11,15,16] The nodular form comprises the minority of cases.[14]

Management

Most cases of episcleritis are self-limiting, resolving spontaneously within two to three weeks even in the absence of treatment.[7,11,12] Patients who are symptomatic or who do not like their cosmetic appearance may benefit from a regimen of cold compresses, lubricants, topical nonsteroidal anti-inflammatory preparations and topical corticosteroids.[1-12] Since the inflammation produced in episcleritis is relatively superficial, virtually all topical steroids are acceptable, including fluorometholone, rimexolone, loteprednol, prednisolone and difluprednate. Dosing on both the topical NSAID and topical steroid typically range from b.i.d. to q4h.[1,7,11,12]



Nodular episcleritis.

Cycloplegia is rarely necessary. Recalcitrant or severe cases associated with systemic disease may require oral nonsteroidal anti-inflammatory drugs. Viable options for these rare instances include ibuprofen (600mg to 800mg b.i.d. to q.i.d.), naproxen sodium (250mg to 500mg t.i.d.), or indomethacin (25mg to 75mg b.i.d.).[1,7,11,12]

The follow up on these cases should be weekly. Patients placed on steroids of any kind are at risk for steroid-induced elevation of IOP.[17] Difluprednate also possesses a similar risk profile for this event.[18] However, the addition of topical aqueous suppressants along with some modulation of the topical steroidal agent almost always mitigates the pressure spike. Because of the association with systemic disorders, patients with extremely severe presentations or recurrences should be referred for a medical evaluation.[4,6,7,10,11,15,16]

Clinical Pearls

- Episcleritis is a condition similar to subconjunctival hemorrhage: it typically looks worse than it is and, in most cases, it is self-limiting.
- Care must be taken to distinguish episcleritis from the more severe scleritis, which has more serious implications for visual compromise and ocular sequelae. Scleritis is typically more painful, more commonly encountered bilaterally and much more likely to demonstrate an attendant uveitis. Unlike episcleritis, 2.5% phenylephrine will not

induce blanching of the vascular injection in cases of true scleritis.

• Not every case of sectorial injection is episcleritis. Trichiasis may mechanically induce a "pseudo-episcleritis." Signs and symptoms should be considered before prescribing any medications.

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SCLERITIS

Signs and Symptoms

Scleritis represents an inflammation of the sclera of the eye.[1-11] As the sclera holds a proximity to the choroid and its abundant innervation, scleritis almost always produces symptoms.[1-10] Patients characteristically report a severe, boring ocular pain that may radiate to involve the adjacent head and facial regions. Photophobia and lacrimation are common. Decreased vision is possible depending upon the involvement of the cornea, the amount of inflammation and the quadrants of the eye that are involved.[6-9] While the disease may be local and idiopathic, many instances of scleritis evolve secondary to advancing systemic disease (typically an immune-mediated inflammatory disease such as arthritis or Wegener's granulomatosis), the side effects of medicine or as a complication of ocular surgery.[6-8,12-17] This makes the epidemiology difficult to calculate.[6-8,12-17] In one recent study, a slight preponderance was found for women over men.[16]

Examination typically reveals significant dilation of the scleral vessels, as well as the overlying vasculature of the episclera and bulbar conjunctiva.[4-6,17] The affected eye may assume a deep red, almost purple hue (violaceous).[4-6] The presentation may be sectorial or diffuse.[4,5] The condition is bilateral in more than 50% of cases, although it is often asymmetric.[6] A concurrent anterior chamber reaction is noted in upwards of 40% of patients with scleritis.[10,11] Corneal involvement is also possible, and may present as an infiltrative stromal keratitis, non-inflammatory corneal thinning or peripheral ulcerative keratitis.[3,10,18] Glaucoma in the form of an angle closure secondary to choroidal effusion and expansion is possible.[19]

Severe cases may present with overlying interpalpebral inflammatory nodules, which develop in the limbal region.[4-6,10] In necrotizing scleritis, the sclera may become transparent due to chronic inflammation, revealing the underlying dark blue hue of the choroid.[4-6,20] The most destructive form of necrotizing scleritis is *scleromalacia perforans*.[5,6,21] It presents insidiously without substantial pain or visible inflammatory signs.[5,6,21] Uveal herniation through the thinned or perforated scleral wall is a classic manifestation that may result in the catastrophic outcome of enucleation.[5,6,21,22]

Finally, scleritis may also affect more posterior structures of the eye, including the choroid and retina.[1,4-6,16,19,23-25] When posterior involvement occurs along with anterior scleritis the diagnosis is straightforward. However, a purely posterior scleritis is uncommon and may be quite variable.[5,9,16] Posterior scleritis presents with pain and loss of vision.[5,9,16,23-25] It less commonly presents with diplopia and/or proptosis.[23,24] Dilated fundus examination may reveal a focal choroidal mass or effusion, choroidal folds, optic disc edema, retinal folds, cystoid macular edema or exudative macular detachment.[23-25] Ocular ultrasonography (B-scan) demonstrates increased thickness of the ocular coats and/or fluid in the episcleral space posteriorly and may be essential to make the diagnosis.[23]

Pathophysiology

Scleritis represents a primary inflammation of the sclera.[1-17] Although the pathogenesis is not entirely understood, research points to a deposition of immune complexes within the sclera, leading to a vasculitis with associated inflammatory cell infiltration and edema.[26] Pathogenic mechanisms point to enzymatic degradation of collagen fibrils by resident cells and infiltrating leukocytes.[17] Several forms of inflammation have been distinguished histologically. Interestingly, although the disease typically presents with engorgement of scleral vessels, vasculitis is not universally

present at the microscopic level.[17] One recent report described a T-helper cell population known as Th-17, and implicated its association with the inflammatory process and scleritis formation.[1]

Once the inflammatory cascade begins, destruction of the scleral collagen matrix can ensue if prompt intervention is not initiated.[27,28] Chronic inflammation of the sclera may instigate capillary closure and subsequent necrosis of focal or diffuse areas of tissue.[11] Capillary closure may be observed under a slit lamp as unusual white patches of tissue. Severe anterior chamber inflammation may lead to subsequent cataract formation, trabecular meshwork outflow stasis, synechial angle closure and secondary glaucoma.[11]

Scleritis can be associated with both infectious and non-infectious vectors. Infectious scleritis can be very difficult to diagnose as it may mimic an immune-mediated disease.[12] Although uncommon, infectious scleritis can occur following subconjunctival corticosteroid injections.[12]

While the etiology remains idiopathic for many cases of scleritis, more than half are associated with systemic disease.[4,6-8,10,12,17,29] Posterior and necrotizing forms of scleritis have an even higher incidence of underlying disease.[29,30] More than 50 distinct disease entities have been associated with scleritis in the literature. The most common related disorders are rheumatoid arthritis, polyarteritis nodosa, systemic lupus erythematosus, inflammatory bowel disease, sarcoidosis, Wegener's granulomatosis, tuberculosis, herpes zoster and syphilis.[1,2,4-6,14,15,17,29,31-34]

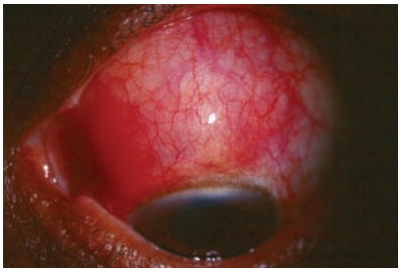
Management

Topical therapy for scleritis is designed to ameliorate the symptoms associated with the anterior segment inflammation.[1,4-7,17,19] The primary focus should be the identification and treatment of the underlying cause.[1,2,4-6,14,15,17,29,31-34] Topical medications are not sufficient to appropriately manage these conditions. Cycloplegia (scopolamine 0.25%, homatropine 5%, atropine 1%, q.d to t.i.d.) and topical steroid therapy (prednisolone acetate 1% q2h to q.i.d., difluprednate q4h to q.i.d.) should be combined with appropriate medications to address the severity of the condition as well as the underlying cause (i.e., infectious, autoimmune). Systemic anti-inflammatory agents are also req uired.[1,2,4-6,14,15,17,29,31-34] With respect to resolving the ocular inflammation, oral non-steroidal anti-inflammatory drugs (NSAIDs) are generally used as first-line treatment for mild to moderate, non-necrotizing, anterior scleritis. Recommended regimens may include ibuprofen (600mg to 800mg q.i.d.), naproxen sodium (250mg to 500mg t.i.d.) or indomethacin (25mg to 75mg q.d. to t.i.d.).[1,2,4-6,14,15,17] If the inflammation is more severe or necrotizing, or if NSAIDs alone fail to suppress the inflammation, systemic corticosteroids are indicated.[1,2,4-6,14,15,17] Oral prednisone 60mg to 80mg p.o. q.d. should be given for two to three days and then slowly tapered to 10mg to 20mg daily. A small maintenance dose may be required to control the condition.[4-6,17] Systemic immunosuppressive agents such as cyclophosphamide, cyclosporine or methotrexate are necessary in the most severe cases.[4-6,35,36] Rituximab is a monoclonal antibody that has been used in the treatment of lymphoma, leukemias, transplant rejection and some autoimmune disorders.[37,38] Rituximab has been documented as an alternative treatment in severe scleritis that is refractive to conventional therapy.[37,38] Given the potential for adverse reactions as well as interactions that may provoke or worsen other systemic conditions, all of these oral or intravenous medicines should be initiated and monitored by the patient's internist or rheumatologist. Scleritis management may range from several weeks to more than a year.

Scleromalacia perforans tends to be poorly responsive to all forms of therapy. Globe perforation can result.[5,6,21,22] The vast majority of these patients suffer from severe autoimmune disease and the five-year survival rate for these individuals is poor.[5,6,10,21]

Clinical Pearls

- Since the onset of scleritis is often slow and insidious, patients in the early stages may be only mildly symptomatic and the condition initially misdiagnosed.
- The differential diagnosis between episcleritis and scleritis may be difficult. Unlike episcleritis, scleritis does not show significant blanching with topical phenylephrine, nor can the vessels be manipulated with a cotton-tipped applicator. Some sources suggest that viewing the eye under regular sunlight helps to reveal its true violaceous color, aiding in the diagnosis.
- Unlike episcleritis, scleritis presents a significant risk of vision loss due to "collateral damage." The choroid, cornea, retina and even optic nerve are subject to damaging inflammation. Additionally, scleral thinning poses the risk of globe rupture.
- In all cases of scleritis, one should assume the etiology to be underlying systemic disease until proven otherwise. Patients should be referred for a comprehensive medical evaluation, including serology and radiology. Specific tests may include: complete blood count (CBC) with differential and platelets, antinuclear antibody (ANA), human leukocyte antigen (HLA) testing, rheumatoid factor (RF), angiotensin-converting enzyme (ACE), rapid plasma reagin (RPR), Lyme titer, chest X-ray, and sacroiliac joint films. A rheumatologist is likely the best referral source.
- Patients placed on steroids of any kind (topical, oral or inhaled) are at risk for steroid-induced elevation of IOP. Difluprednate also possesses a similar risk profile for this event.[39] However,



Scleritis in a patient with rheumatoid arthritis.

the addition of topical aqueous suppressants along with some modulation of the topical steroidal agent almost always mitigates the pressure spike.

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SUPERIOR LIMBIC KERATOCONJUNCTIVITIS

Signs and Symptoms

Superior limbic keratoconjunctivitis (SLK) was first described as a unique clinical disorder by Dr. Frederick Theodore in 1963.[1] Individuals presenting with this condition typically report symptoms of ocular discomfort, including burning, foreign-body sensation or non-descript pain.[1,2] Additionally, complaints of photophobia and excessive tearing may be described. Visual acuity is usually not affected. SLK predominantly affects women between the ages of 30 and 55 years.[3]

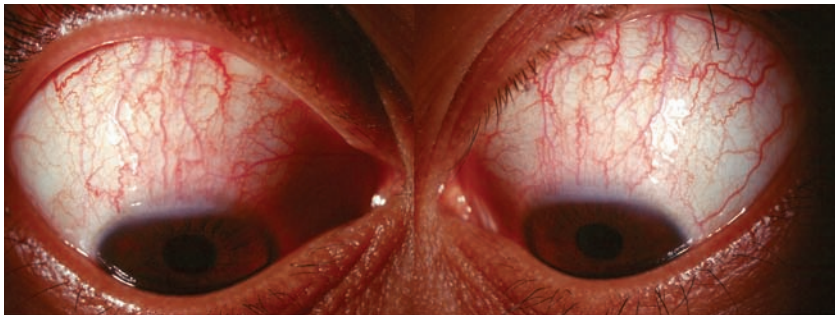
Gross clinical signs often include mild lid swelling and pseudoptosis as well as blepharospasm. Inspection of the ocular surface in SLK reveals a sectoral redundancy of the superior bulbar conjunctiva, with corresponding injection and inflammation. The limbal margin of the cornea may be inflamed as well. Eversion of the upper lid reveals a uniform papillary hypertrophy along the tarsus, which may be mild to marked. Vital dye staining is characteristic in SLK, with patients displaying punctate epithelial disruption of the affected region; this is evident with both sodium fluorescein dye as well as rose bengal or lissamine green solutions.[2] Filament accumulation in the tear film is also common, being encountered in about half of all patients with SLK. The condition is typically bilateral but often asymmetric. In most instances, the diagnosis of SLK is made solely based upon the characteristic presentation. Recently, laser scanning confocal microscopy has been applied to the study of SLK in an effort to more thoroughly clarify the

pathophysiological mechanisms; the correlation of in vivo confocal microscopy with more conventional testing methods is quite high.[4] Such testing may be beneficial in cases that are not clinically evident, have atypical histories or fail to respond to aggressive therapy.[5]

Pathophysiology

The precise etiology and pathogenesis of SLK remains controversial.[4-6] The most widely accepted theory today holds that SLK results from conjunctival redundancy and soft-tissue microtrauma.[7,8] Mechanical irritation occurs in the superior limbal region as loose conjunctival tissue rubs against the limbus during the blinking process. Research has shown that this repeated trauma causes damage, injury and inflammation, as represented by increased levels of expressed matrix metalloproteinases.[9] In biopsy specimens of the superior tarsal conjunctiva, patients with SLK display infiltration of polymorphonuclear leukocytes, lymphocytes and plasma cells.[3] In years past, additional laboratory confirmation has been obtained from scrapings of the affected superior bulbar conjunctivae, demonstrating the presence of keratinized, acanthotic epithelial cells.[6]

Several anatomical factors seem to predominate in SLK, particularly tight lids and prominent globes.[1,2] These findings are consistent with the aforementioned mechanical theory of pathogenesis. Another theory implicates local tear deficiency to the superior keratoconjunctiva. Researchers have proposed that this deficiency results in significantly reduced levels of vital tear-based nutrients to the affected region as well as increased mechanical friction from the superior lid.[8] An autoimmune etiology has been considered, based upon the pattern of the disorder (i.e., exacerbations and remissions) the female predominance of the disorder, and an association with thyroid disease and other autoimmune diseases. In fact, SLK is considered to be a strong prognostic indicator for thyroid eye disease.[10]



Superior limbic keratoconjunctivitis.

Management

A great many treatment modalities have been employed in the management of SLK, though few have been found to be truly and consistently effective. Therapy using a wide variety of topical pharmaceutical agents has been attempted. Antibiotics and corticosteroids have been found to be essentially ineffective in this condition. Other preparations have demonstrated limited success; among these are vitamin A eyedrops, topical mast cell stabilizers (e.g., 4% cromolyn sodium, 0.1% lodoxamide tromethamine, and 0.025% ketotifen fumarate), autologous serum, n-acetylcysteine, and 0.5% cyclosporine A eyedrops.[3,8,11-16] Bandage contact lenses have been used both with and without drug therapy, in an effort to alleviate the mechanical irritation of SLK.[17,18] Occlusion of the superior puncta/canaliculi may also be beneficial in this condition.[2,19] Additionally, injectable agents such as botulinum toxin A (to induce temporary ptosis) and triamcinolone (injected supratarsally to diminish lid inflammation and lid-globe contact) have been used with some success.[18,20]

More invasive therapies seek to eradicate the dysfunctional conjunctiva and replace it with new, healthy tissue. Silver nitrate solution (0.5% to 1.0%) applied topically to the superior bulbar and tarsal conjunctivae was at one time the preferred therapy for this condition, and is still used to some degree today.[21] Silver nitrate serves as a chemical form of cauterization; unfortunately, there is a significant chance of iatrogenic burns with this technique, and even when applied correctly recurrences have been known to occur.[21,22] Chemocautery can also be achieved by freezing the tissue with liquid nitrogen (i.e., cryotherapy).[23] Surgical options for SLK include thermal cauterization, conjunctival recession and resection.[24,25]

Clinical Pearls

- SLK of Theodore must be differentiated from contact lens-induced SLK (CL-SLK), a condition that is occasionally observed in young, otherwise healthy hydrogel lens wearers. Solution hypersensitivity as well as poorly fitted lenses have been implicated as the main contributory factors. The typical presentation of this entity consists of increasing contact lens intolerance, superior tarsal and bulbar injection and significant superior corneal staining with stromal hazing. Corneal involvement may be noted as far inferiorly as the superior pupillary margin. Treatment for CL-SLK consists of temporarily discontinuing contact lens wear, along with the liberal use of preservative-free ocular lubricants. Upon resolution, contact lenses should be refit and a preservative-free care system should be employed.

• Past studies have demonstrated a very high correlation between SLK and systemic thyroid disease, on the order of 65%.[26] Other conditions such as rheumatoid arthritis and Sjögren's syndrome may also have similar associations. All patients presenting with SLK should be referred for a systemic evaluation, including a serologic thyroid panel.

• Some sources consider SLK to be the result of a localized, severe, superior form of conjunctivochalasis. Laxity of the distal conjunctiva (i.e., within the fornix) leads to mechanical irritation and inflammation of the proximal or limbal conjunctiva. Surgical treatment to resect only the lax area of the superior conjunctiva—similar to the procedure used to treat conjunctivochalasis—has shown promise in restoring the limbal tissues to normal health within two weeks.[24,27]

• SLK can be chronic and recalcitrant. In attempting to manage this disorder, the rule of thumb is to employ topical agents such as mast cell stabilizers or cyclosporine A in the earliest stages, followed by noninvasive procedures such as bandage contact lenses or lacrimal occlusion therapy. Injections, chemocautery, thermocautery and surgical intervention should be considered only when these other interventions have failed.

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TOXIC CONJUNCTIVITIS

Signs and Symptoms

Toxic conjunctivitis, sometimes referred to as toxic follicular conjunctivitis, results from ocular exposure to noxious foreign substances.[1-8] The exposure may involve a new topical medication, an old or chronically used medication or contact lens.[3-6] Occasionally, the reaction is seen in those starting or undergoing glaucoma therapy.[1-3] When the toxic conjunctivitis is associated with a prescribed topical medication, it is sometimes called a medicamentosa conjunctivitis. Cosmetics, moisturizers, aerosolized colognes, other personal hygiene products, household or automobile products or nickel can likewise induce a toxic conjunctivitis when the eye is exposed to these agents.[7-10] Toxic conjunctival reactions have also been documented secondary to exposure to bio-waste or toxins of organisms infesting the eye lashes or residing on the eyelid (*pthiriasis* and *molluscum*).[4,11] The process may occur unilaterally or bilaterally, depending upon the exposure.

Clinical features of toxic conjunctivitis include ocular itching, burning, tearing, blepharospasm, as well as marked injection and chemosis of the bulbar conjunctiva.[1-12] The most recognizable feature is a pronounced follicular reaction involving the inferior (and sometimes superior) tarsus with a notable absence of preauricular lymphadenopathy.[2-5] A variable keratopathy is often secondarily present depending upon the amount of direct exposure the cornea endured and the severity of the conjunctival response. In cases that are chronic, pannus formation may result.[13]

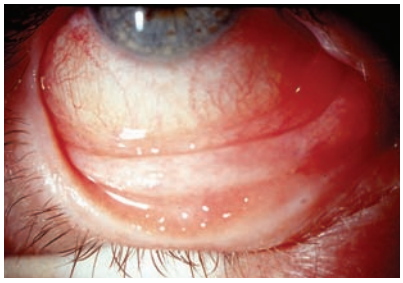
Pathophysiology

The inflammatory response is triggered by chemical messengers that are released in response to an exposure to undesirable foreign substances (antigens, immunogen, allergens).[14-17] The reaction is necessary and protective and works to limit contact with the rest of the anatomic region by creating boundaries. The response is also designed to begin the process of eliminating the antigen by activating the elements of

the immune system.[14-17] Toxic/allergic conjunctivitis occurs when the body's immune system responds to an exposure of a foreign substance around the eye or adnexa.[14-18] This response can be innate or acquired.[18,19] A variation of this response is manifested when the body responds hyperactively to exogenous materials such as medicines, contact lenses, contact lens solutions, dust, dander or viral shedding.[14-18] Over-activity of this type is commonly referred to as a toxic or allergic reaction. With respect to the eye and its adnexa, the result is toxic conjunctivitis.

The key component to the ocular allergic response is the mast cell.[14-18] When a mast cell interacts with a specific allergen, the outer cell membrane is altered, and it releases chemical mediators into the surrounding tissues; this process is referred to as mast cell degranulation.[14-18] The primary chemical mediator is histamine, which is responsible for increased vascular permeability, vasodilation, bronchial constriction and increased secretion of mucus. Other preformed mediators such as tryptase, chymase, bradykinin, interleukin and heparin contribute to the allergic response.[14-18] Sustained allergic responses in some bodily tissues can induce eosinophil-mediated inflammation, which through the release of prostaglandins and leukotrienes, may result in tissue remodeling and damage.[14-18] Antibody and/or T-cell mediated mechanisms are involved.[17] Predominantly allergic responses are characterized by immunoglobulin E (IgE), mast-cell-mediated mechanics.[17] Chronic mast cell activation with a eosinophil/T-lymphocyte-mediated response is the hallmark of giant papillary conjunctivitis, vernal keratoconjunctivitis and atopic keratoconjunctivitis.[17] T-lymphocyte-mediated responses are distinctive in contact ocular allergic processes.[17] There are four recognized types of hypersensitivity reactions.[20,21]

- **Type I** reactions are immediate hypersensitivity reactions or anaphylactic reactions. These reactions occur when immunoglobulin IgE comes into contact with a particular antigen or allergen producing a cascade that results in sudden and massive degranulation of local mast cells.[21,22] Upon activation, through high affinity IgE receptors, mast cells can release up to 100% of their content of preformed mediators stored in cytoplasmic secretory granules via compound exocytosis.[22]



Toxic conjunctivitis.

- **Type II** reactions involve the body's ability to distinguish itself from non-self. Abnormalities in this element of the system give rise to autoimmune disease.[23] The mechanism that leads to autoimmunity is complex and not fully understood.[23] Recently a team of researchers has hypothesized that autoimmune diseases are caused by two age-related processes: (1) senescent cell accumulation in the immune system and target tissue/organ, (2) heterogeneous accumulation of senescent cells in tissues/organs.[22] Separately or combined, these two processes are being examined as the basis for autoimmune diseases.[22]
- **Type III** reactions involve combinations of antigens and antibodies known as immune complexes.[24] Offending triggers may be intrinsic (i.e., a protein molecule) or extrinsic (e.g., a penicillin molecule) and produce a significant tissue response in an attempt to rid the area of the invader. It is this incorrect regulation of the complement system that causes inflammation and targeting of self-tissue.[24] Examples of type III complex disease include systemic lupus erythematosus and rheumatoid arthritis.[24]
- **Type IV** reactions—sometimes referred to as cell-mediated hypersensitivity reactions involve T-lymphocytes and lymphokines.[20,21,25] The reaction is classically delayed until sufficient antigens are present to stimulate the chemical cascade. In the ocular tissues, these chemical exchanges incite conjunctival and adnexal vasodilation, chemosis, edema and lacrimation.[20,21,25] Individuals experience local pain, itching, swelling and irritation. The discharge produced is typically serous and the conjunctival findings may include follicles (hyperplasia of lymphoid tissue within the eyelid stroma) and/or papillae (hyperplastic palpebral conjunctival epithelium infiltrated by lymphocytes and plasma cells).[4]

Management

Management of toxic conjunctivitis is aimed at reducing symptoms and speeding resolution of the inflammation.[4] Of course, the first step is to remove the offending agent if possible. Palliative treatment with cold compresses works by producing natural vasoconstriction, limiting the movement of released cytokines. Artificial tear administration can help to mitigate the event by coating the corneal epithelium, providing uniform cover for underlying nerves exposed by keratopathy and diluting the foreign substance and physically washing it away.[4]

The mast cell/histamine response can pharmacologically be controlled with topical and oral allergy medications.[26-30] A topical combination mast cell stabilizer/antihistamine is the mainstay of therapy. This includes drugs, such as Patanol (olopatadine HCl 0.1%, Alcon), Zaditor (ketotifen fumarate 0.025%, Novartis), Elestat (epinastine HCl 0.05%, Inspire) and Optivar (azelastine HCl 0.05%, MedPointe)—all of which are indicated for b.i.d. dosing. Pataday (olopatadine HCl 0.2%, Alcon) and

Lastacaft (alcaftadine, Allergan) add convenience of administration and are approved for once-a-day usage. Topical non-steroidal anti-inflammatory drugs (NSAIDs) may be added q.d. to q.i.d., depending upon the severity of the occurrence, to provide mild analgesia for patients with corneal compromise, however they do little to address the histamine-mediated response. New agents in this class such as Acuvail (ketorolac tromethamine, Allergan) and Bromday (bromfenac sodium hydrate, ISTA) can be used off label (they are approved for controlling postoperative inflammation following cataract surgery), q.d. to provide increased comfort.[30] Topical corticosteroids (e.g., Pred-Forte, Lotemax or Durezol), which address the effects of inflammation, may be desirable in severe or highly symptomatic reactions, but are generally not necessary. Oral antihistamines can be added if the reaction involves the eyelids or adnexa.

Clinical Pearls

• Toxic conjunctivitis is a diagnosis that can be made based primarily upon the history and clinical course. Typically, vision is unaffected despite the unruly appearance. Even if left untreated, toxic conjunctivitis often begins to resolve within days, providing that the offending agent is identified and removed or discontinued.

• Medicamentosa is a sub-category of toxic conjunctivitis used to connote a toxic reaction to the preservatives in medications. A substantial keratitis is the hallmark of the medicamentosa response.

• While many patients choose to self-treat allergic or toxic conjunctivitis with topical decongestants (e.g., Vasocon or Visine), these agents are not recommended. While decongestants may produce short-term vasoconstriction, hence reducing hyperemia, the effects are short-lived. In addition, these products have been shown to actually induce toxic conjunctivitis in a significant percentage of patients, and they may cause even more severe allergic responses such as contact dermatitis.[26] Advise patients to avoid these over-the-counter remedies, and instead recommend a prescription-strength topical allergy medication.

• The use of oral antihistamines for purely ocular allergic responses, such as toxic conjunctivitis, is less efficient. Studies have shown that topical agents provide more rapid relief than oral antihistamines alone.[27,28] In addition, many oral antihistamines (particularly the older generation drugs such as Benadryl) can induce central nervous system depression (e.g., dizziness, drowsiness, etc.) as well as antimuscarinic effects (e.g., dry mouth and dry eyes, pupil dilation with possible subsequent angle closure).[29]

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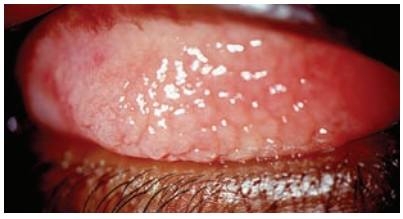
VERNAL KERATOCONJUNCTIVITIS

Signs and Symptoms

Vernal conjunctivitis (VKC) is chronic allergic/inflammatory disorder that affects the superior tarsal and lim-

bal palpebral conjunctiva. It presents classically with severe ocular itching, photophobia, tearing, conjunctival redness and a thick, ropy mucous discharge. The condition is bilateral in 98% of cases, though asymmetry may be observed.[1,2] The hallmark sign of VKC is the presence of extreme papillary hypertrophy on the upper tarsal conjunctiva and/or at the limbal margin. When large "cobblestone" papillae are seen upon lid eversion, the condition is described as the tarsal form of VKC; by contrast, when multiple gelatinous elevations are seen at the superior corneoscleral interface, this constitutes the limbal form of VKC.[1] Horner-Trantas dots (focal, white limbal infiltrates), usually located at the superior corneal margin, are another feature of the limbal form of this disorder. Additional corneal involvement may be manifested as punctate keratitis and, in severe cases, corneal shield ulcers, which are typically encountered in the superior one-third of the cornea.[1] Less commonly, pseudogerontoxon is seen in association with VKC. This rare finding may be seen as a local, grayish-white lipid deposit occurring in the peripheral cornea of patients with the limbal form of VKC.[3,4] Pseudogerontoxon is often confused with arcus senilis, a condition seen in older individuals that is characteristically bilateral and secondary to cholesterol deposition in the cornea as a result of dyslipidemia. Pseudogerontoxon is only noted in young patients, is unrelated to serum lipid levels and may be unilateral as a result of allergic pathophysiology.[4] In patients with VKC, acuity may be mildly to severely affected, depending upon the type and extent of corneal involvement.

VKC tends to be a seasonal disease with a skewed geographic distribution, occurring primarily during the spring and summer months in warm and dry geographic regions; however, in about



Cobblestone papillae in VKC.

25% of VKC patients the disease smolders year-round, without any remission.[2] Males are predominantly affected by a ratio of 3.3:1.[5] The average age of disease onset is seven years, though patients may range from three to 25 years.[5,6] In most cases, a personal or family history of allergic disease (seasonal rhinitis, asthma, atopic eczema) can be elicited; one-third of patients exhibit multiple atopic disorders.[2]

Pathophysiology

Unlike the more common seasonal allergic conjunctivitis, VKC is not simply a Type I, IgE-mediated hypersensitivity disorder.[1] Numerous autoimmune cells—including mast cells, eosinophils and lymphocytes—as well as chemical mediators have been identified in the tears, conjunctiva and the serum of patients with VKC.[7] Bonini and colleagues suggest that VKC is "a Th2-driven mechanism…similar to that of asthma."[2] Mast cells and basophils spur the immediate response via histamine release and by recruiting inflammatory lymphocytes and eosinophils.[7] This results in the release of toxic cell mediators with ensuing ocular surface inflammation and tissue damage.[2]

The etiology of pathologic sequelae in VKC is multifactorial, involving tissue inflammation, infiltration and remodeling. Vernal papillae represent hyperplastic conjunctival epithelium infiltrated by lymphocytes and plasma cells; these may form on the upper tarsal plate or at the limbal margin. Histopathological studies of conjunctival specimens from chronic VKC patients reveals thickening of the conjunctiva with proliferation of collagen, capillaries and other cellular components.[8] Horner-Trantas dots, noted in the peripheral cornea, are actually focal accumulations of degenerated eosinophils and desquamated epithelial cells, liberated by the inflammatory process.[9] Vernal shield ulcers are composed of abnormal mucus, fibrin and serum, deposited within the superficial epithelium as a grayish plaque. By a combination of corrosive inflammatory chemicals (e.g., major basic protein) and the mechanical rubbing of the papillae over the cornea, epithelial erosions may occur; this represents the source of the shield ulcer in VKC.[2,4]

Management

A clinical staging strategy has been proposed for patients with VKC; this allows for proper differentiation and appropriate therapy, based upon the severity of the disease.[10] Features of the condition are graded on a zero-to-five scale, in categories including patient symptoms, conjunctival hyperemia, conjunctival secretion (i.e., discharge), papillary reaction, Horner-Trantas dots and corneal involvement (e.g., punctate keratitis or erosion). It should be noted however that VKC can be extremely variable; hence, the proposed scale is not necessarily a progression, but rather a classification that may be applied at any point in the course of the disease process.

For patients with mild to moderate VKC (Grade 1 and 2), treatment consists primarily of topical anti-allergy drugs, using either a single action (e.g., antihistamine or mast cell stabilizer) or a multiaction mechanism. Though there are many options in this family of medications, newer drugs such as Pataday (olopatadine 0.2%, Alcon) or 0.25% Lastacaft (alcaftadine, Allergan) afford patients the greatest potential for symptomatic relief at a dosing of just

once daily. Other medications in these categories (e.g., azelastine, emadastine, epinastine, ketotifen and lodoxamide) require dosing from two to four times daily for the same level of relief. In severe cases of VKC, the use of topical corticosteroids becomes more critical. Grade 3 (i.e., severe) VKC denotes the use of pulsed steroids, over and above the use of the topical anti-allergy drugs employed daily. At the present time, Alrex (loteprednol etabonate 0.2%, Bausch + Lomb) is the only topical steroid specifically approved by the U.S. Food & Drug Administration for allergic disorders of the eye, but other steroids may be just as effective, including prednisolone acetate, fluorometholone or difluprednate. For chronic, severe VKC, the use of topical cyclosporine A (CsA) may be attempted in lieu of corticosteroids and in conjunction with topical antihistamines. CsA has the capacity to control ocular inflammation by blocking Th2 lymphocyte proliferation and interleukin production; to a lesser degree, it can also inhibit histamine release and the recruitment of eosinophils within the conjunctiva.[10-12] Clinical studies and personal experience have shown a distinct benefit to topical CsA (i.e., Restasis, Allergan) in VKC patients who do not respond to conventional treatment options or who are at risk for complications associated with prolonged steroid therapy.[13] Experimental treatment with immunomodulatory agents, including tacrolimus and omalizumab, have shown promise for recalcitrant VKC.[14,15]

At all levels, the adjunctive use of lubricant ophthalmic drops may help to enhance comfort by increasing the barrier function of the tear film.[10] Selection from among the many available artificial tear products should be guided by the severity of symptoms and the extent of corneal compromise. Gel-forming solutions and higher viscosity agents should be reserved for those with more severe forms of keratitis. Additional therapy for VKC may include topical cycloplegia (e.g., 0.25% scopolamine b.i.d.) and broad-spectrum antibiotic prophylaxis (e.g., tobramycin 0.3% q.i.d. or moxifloxacin 0.5% t.i.d.) for associated shield ulcers. Mucolytics such as 5% n-acetylcysteine t.i.d. to q.i.d. may be helpful in eliminating the ropy, mucous discharge.

Patients using topical medication for VKC should be re-evaluated at one week and closely monitored thereafter. Patients using topical steroids for more than two weeks should have periodic ocular health assessments, including tonometry to ensure that intraocular pressure remains normal. Shield ulcers need to be followed every 24 to 72 hours until re-epithelialization ensues.

Clinical Pearls

- Cobblestone papillae in VKC are substantially larger and less uniform in size and shape than papillae associated with giant papillary conjunctivitis (GPC) or seasonal allergic conjunctivitis. Additionally, cobblestone papillae may be scant in number; these authors have seen patients with VKC who had between one and five papillae, yet were exceedingly symptomatic.
- The term "shield ulcer" is something of a misnomer, in that the name suggests an infectious etiology. The shield ulcers in VKC are sterile in nature, and result from mechanical forces rather than microbial organisms. Also, an "ulcer," by definition, involves a loss of tissue beyond the surface epithelium; those conditions that involve only the epithelium are more appropriately termed "erosions."
- Evidence suggests that VKC often subsides with the onset of puberty. However, some individuals may require therapeutic intervention well into their teens or early twenties to control the course of the disease.
- While oral antihistamines may reduce some of the generalized symptoms associated with ocular allergy, they have little or no effect on VKC.[7] Topical multiaction (i.e., antihistamine and mast cell stabilizer) anti-allergy compounds deliver far greater concentrations of the drugs to the ocular tissues, and have less potential systemic side effects. In contrast, the use of oral non-steroidal, anti-inflammatory agents, particularly aspirin therapy, has been shown to be effective in reducing some of the signs and symptoms of VKC.[16]

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CONTACT LENS-ASSOCIATED ACUTE RED EYE (CLAARE)

Signs and Symptoms

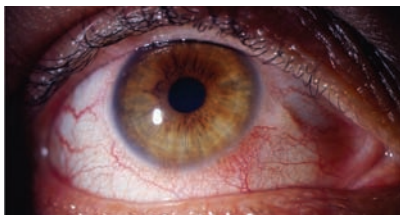
Contact lens-induced or contact lens-associated acute red eye (CLAARE) (sometimes known as contact lens over wear or immobile lens syndrome) is a descriptive term that connotes a characteristic clinical history, clinical presentation and a broad range of specific ocular findings connected with contact lens over exposure. The classic scenario involves a contact lens patient sleeping in their lenses who, upon awakening, experiences unilateral ocular pain (e.g. foreign body sensation), tearing, variably decreased vision and photophobia. Biomicroscopic inspection typically reveals moderate to severe conjunctival and limbal hyperemia with the potential for diffuse or focal subepithelial infiltrates in the midperipheral or peripheral cornea.[1,2] Associated clinical signs may include corneal edema and mild to moderate blepharospasm, while pronounced lid edema, corneal epitheliopathy, and anterior chamber reaction are notably absent.

The history of patients with CLAARE can also be exceedingly variable. While most resources cite cases involving hydrogel lenses, the condition may be encountered with both daily wear and extended wear materials, including silicone hydrogels.[3] Rigid lenses have also been implicated. There is no apparent association with any specific type of care system, nor is poor contact lens fit or hygiene necessarily a factor, although these may be encountered in some patients. Likewise, some individuals may present with an immobile, "stuck-on" lens, but this is not universal.

Pathophysiology

CLAARE is believed to represent an immune reaction of the cornea that is associated with bacterial colonization of the contact lens, contact lens solution, lens case or other accessories.[4] Gram-negative bacteria appear to be the most common culprit, particularly *Pseudomonas, Haemophilus* and *Serratia* species.[4,5] These strains differ from those that typically cause corneal ulcers; they release endotoxins that recruit inflammatory cells via the limbal vasculature into the corneal stroma.[5] Earlier theories regarding the etiology of CLAARE suggested that mechanical factors such as lens-induced hypoxia or corneal microtrauma were implicated in this disorder.[6,7] More recent research confirms specific bacterial strains as the primary causative agent.[1,3,4,8]

Nomenclature and classification of corneal infiltrative events includes CLAARE and other descriptively-named conditions such as contact lens-induced peripheral ulcer (CLPU), contact lens-induced keratitis (CLIK), infiltrative keratitis, sterile corneal ulcer and marginal keratitis.[8] At least one critic believes these classification schemes to be arbitrary with significant overlap and confusion.[8] Corneal surgeons, contact lens specialists and general eye care providers may likely continue to disagree on terminology but in all likelihood these conditions fall on a continuum with multiple etiologic factors and variable degrees of clinical morbidity. The one entity that is distinct from these other conditions is microbial keratitis (MK). MK connotes a focal area of pathogenic invasion and replication rather than an immune response to surface toxins.



Contact lens-associated acute red eye (CLAARE).

Management

Since the contact lens represents the primary antigen in CLAARE, the initial therapeutic measure must involve cessation of lens use. Typically, patients are advised to remain without contact lenses until the infiltrates resolve. This may require several days or even weeks. Concurrent lubrication with topical lubricants helps to provide palliative relief of symptoms, and lid hygiene therapy is beneficial to reduce resident bacterial populations. In mild presentations, these simple measures may be sufficient to enable full resolution of the condition. However, for more severe or symptomatic cases, the use of pharmaceutical agents can help to significantly speed resolution and ameliorate discomfort. Prophylactic antibiotics are helpful in addressing bacterial overgrowth that is at the heart of CLAARE. Broad-spectrum antibiotics with gram-negative coverage are preferable, such as aminoglycosides (gentamicin, tobramycin) or fluoroquinolones (moxifloxacin, gatifloxacin, besifloxacin or levofloxacin). Topical corticosteroids are also beneficial in cases of CLAARE, as they rapidly mitigate symptoms and corneal infiltrates. Since the condition is superficial, virtually any corticosteroid may be used, including prednisolone, dexamethasone, fluorometholone, loteprednol or difluprednate. Perhaps the most effective and easiest therapeutic regimen is to use an antibiotic-corticosteroid combination, such as TobraDex ST (tobramycin, dexamethasone, Alcon) or Zylet (tobramycin, lotoprednol, Bausch + Lomb), on a q.i.d. basis. Cycloplegia is rarely necessary as deep inflammation is highly atypical; however, in such cases, a mild agent such as homatropine 5% b.i.d. may be employed. Reevaluation should be performed every 24 to 48 hours as patients remain on therapy. After resolution, refitting of the contact lenses should be considered.

Clinical Pearls

• Many clinicians use the term "contact lens overwear syndrome" or "tight lens syndrome" interchangeably with CLAARE to describe an acutely inflamed eye associated with excessive or abusive contact lens wear. These designations imply a purely hypoxic stress situation, which typically presents with punctate epitheliopathy and, in some cases, a corneal/conjunctival indentation corresponding to the edge of the entrapped lens. CLAARE, by definition involves an immune response to bacterial pathogens.

• CLAARE must also be carefully differentiated from microbial keratitis. True bacterial corneal ulcers will always show an overlying epithelial defect in association with focal corneal infiltration, usually in a 1-to-1 ratio. If a definitive diagnosis cannot be made, treat the condition as microbial keratitis and prescribe a fluoroquinolone antibiotic frequently for at least 24 hours before considering a topical corticosteroid.

• While CLAARE can occur with virtually any type of contact lens or wearing regimen, it has been shown that extended-wear significantly increases its risk. Further, patients who have endured one episode are more susceptible to repeat occurrences.[10,11] These individuals should ideally be reassigned to a lower-risk regimen, such as daily wear, gas permeable, or ideally, daily disposable lenses.

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DISCIFORM KERATITIS

Signs and Symptoms

Patients with disciform keratitis will present with a moderately painful eye that is both tearing and photophobic. Vision may be modestly reduced, particularly if the visual axis is involved; however, the vision reduction does not have to be dramatic. Often, the patient will have a history of prior ocular or systemic outbreak of either herpes simplex or zoster.[1-8] The patient may have had a recent outbreak of epithelial herpes simplex or may concurrently have a dermatological outbreak of herpes zoster. However, a history of herpes is not mandatory as disciform keratitis is a finding that may also occur secondary to *Acanthamoeba* and other protozoan infection, cat scratch disease, LASIK surgery, Kawasaki disease, smallpox and smallpox immunization, among other numerous etiologies.[9-17]

There will be modest conjunctival injection as well as a mild anterior chamber reaction. While the anterior chamber reaction is typically mild, there may be a disproportionately large rise in intraocular pressure. The key diagnostic sign is a disc-shaped area of focal corneal stromal edema that may be either peripheral or central.[18] There may be a surrounding ring of infiltrate known as a Wesley ring at the junction of the microbial antigen and host immune reaction. There typically is no stromal vascularization and the epithelial integrity remains intact. In some cases, there may be folds in Descemet's membrane.

Pathophysiology

Disciform keratitis is a delayed hypersensitivity reaction involving the corneal stroma. In disciform keratitis, corneal endothelial cells demonstrate significant increases of variation in cell size (polymegathism) and shape (pleomorphism) when compared to the cells in the fellow unaffected eyes.[19] There is a granulomatous reaction within Descemet's membrane, Bowman's membrane and the corneal stroma.[14,20,21]

Disciform keratitis results from an antibody-mediated response to microbial antigens, typically viral, within the corneal stroma.[21-23] It must be stressed that these are inactive antigens and that the edematous response is immunological. Also, there is no active stromal infection. As such, antiviral medications serve no direct therapeutic benefit, but may be beneficial prophylactically in the case of herpetic disease.[4,24,25]

Management

Cycloplegic agents such as homatropine 5% or scopolamine 0.25% b.i.d., along with copious topical lubrication should be used for patients with disciform keratitis. In addition, topical corticosteroids must be employed to resolve the condition. Excellent choices include Pred forte (prednisolone acetate 1%, Allergan), Durezol (difluprednate emulsion, Alcon) and Lotemax (loteprednol etabonate 0.5%, Bausch +Lomb) q.i.d. (or greater, depending upon the severity). The lowest dose of topical steroids that will control the inflammation should be used.

In that there is increased corneal thickness due to corneal edema in disciform keratitis, therapeutic responses can be monitored through patient symptoms, biomicroscopic appearance and

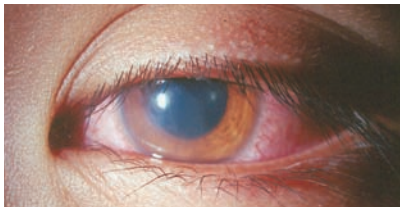
corneal pachymetry.[26,27]

As the main cause of disciform keratitis is typically herpes virus, topical antiviral medications should be used prophylactically if topical steroids are being used to prevent a breakout of epithelial dendritic keratitis. Topical trifluridine dosed q.i.d. is typically sufficient. While there are no studies on prophylactic use, topical Zirgan (ganciclovir gel, Bausch + Lomb) has been shown to be effective in the management of herpes simplex epithelial keratitis.[28-30] It can be speculated that ganciclovir gel at four to five times per day may provide prophylactic coverage when a patient with disciform keratitis secondary to herpetic disease is being treated with topical steroids.

Should the epithelium ulcerate during topical steroid therapy, the steroid should either be reduced or discontinued altogether until the epithelium heals. In cases where topical antiviral therapy is unavailable or not well tolerated, oral antiviral agents such as acyclovir can provide prophylactic protection.[24-34] Steroids should be slowly tapered over several weeks in order to avoid a rebound reaction. Some patients will require topical steroids once daily for prolonged periods and some patients may require steroids indefinitely.

Clinical Pearls

- Disciform keratitis is a finding that occurs secondary to some causative agent and is not truly a diagnosis. The causative agent should be identified, if possible. More often than not, herpes virus is the causative agent.
- If a patient manifests a disc-shaped area of focal stromal edema, it is disciform keratitis.
- Cases of disciform keratitis caused by herpes virus are typically mild and best managed with topical cycloplegia, lubrication and low doses of topical steroids.
- When a case of disciform keratitis in discovered, probe for a history of herpes simplex or zoster. This may involve serologic testing, as there have been cases of disciform keratitis secondary to herpes simplex in patients who had never previously had an epithelial outbreak. Similarly, there have been instances where a patient experienced disciform keratitis secondary to herpes zoster without ever having had a previous dermatological outbreak. This particular entity has been termed "herpes zoster sine herpete."[35]
- As disciform keratitis is immune modulated and there is no active microbial infection present, any use of antibiotic and antiviral medications would be prophylactic not therapeutic. Anti-inflammatory therapy is the mainstay.



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FUNGAL KERATITIS

Signs and Symptoms

Fungal keratitis—also known as keratomycosis—represents a focal infection of the cornea caused by fungal organisms. While there is no distinct racial predilection for this condition, men do appear to be affected at least twice as often as women, and those in the middle decades of life (16-49 years) have the highest incidence with regard to age.[1-3] The most common predisposing factor is corneal trauma, usually from organic vegetative matter such as a tree branch.[1,2,4] Other significant risk factors include prior corneal surgery, prolonged use of topical and oral corticosteroids or other immunosuppressive agents, systemic diseases (such as diabetes) and contact lens wear.[1,3] Fungal infections tend to be more common in agricultural and tropical environments.[3]

Patients typically report moderate to severe unilateral pain with associated vision loss. Clinically, fungal keratitis has a well-known, classic pattern of presentation. The infection begins slowly and insidiously, producing a feathery, branching pattern at the level of the epithelium with a propensity for forming ring infiltrates with satellite lesions.[4,5] The cornea often takes on a dull gray appearance with heaping of the epithelium. The epithelium often acquires a dry, rough texture. In most cases, this characteristic corneal appearance disappears over time and the fungal ulcer begins to resemble advanced bacterial keratitis. Misdiagnosis at this point occurs frequently if the history has not been adequately elucidated. Fungal keratitis is most often accompanied by a severe anterior uveitis exhibiting a plasmoid aqueous with hypopyon.

Pathophysiology

Fungi can be broadly divided into two groups. The first group consists of molds, which are filamentous in nature and grow in elongated, multicellular clusters called hyphae. Branching hyphae intermingle to form fungal colonies. Molds can be further subdivided into septate and non-septate fungi; this distinction refers to the structure of the hyphae. Less well-developed molds contain simple, cylindrical filaments, while higher order molds contain thicker-walled cells with distinct junctions (or septa) between them. These septa allow for a tougher, more durable structure that is substantially resistant to attack, while allowing neighboring cells the capacity to communicate. Septate fungi represent the most common causes of fungal keratitis.[4] The second group of fungi consists of the yeasts. Unlike filamentous molds, yeasts exist as unicellar organisms. By definition, yeasts do not form hyphae, but they can form pseudohyphae, which are essentially chains of cells formed by incomplete budding. Considering all fungal pathogens, the vast majority of keratitis is associated with *Fusarium, Aspergillus* (both septate filamentary fungi) and *Candida* (a yeast).[4,6,7]

In order for fungal keratitis to develop, there must first be a breach in the epithelial integrity. Fungi are opportunistic organisms; they cannot penetrate an intact cornea and they do not enter from limbal blood vessels.[8] Hence, the vast majority of cases can be traced to some form of antecedent corneal trauma, whether overt like a fingernail scratch, or subtle, like a patient might experience from overworn contact lenses. Immunosuppression from disease or topical corticosteroids can further exacerbate the situation. Once within the epithelium, fungal pathogens can gain access to the stroma, where growth is uninhibited in the absence of leukocyte recruitment.[9,10] Here, they proliferate and give rise to hyphae colonies, in the case of filamentous fungi or by simple budding in the case of yeast fungi. Thus begins a cycle of corneal destruction by fungal expansion, inflammatory cell infiltration and degradative cytokine liberation. Over time and without appropriate therapy, some pathogens may even penetrate the corneal endothelium, leading to fungal endophthalmitis.[9]

Management

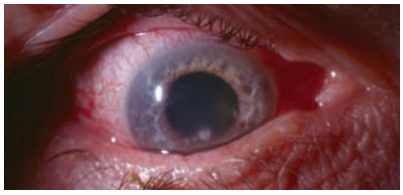
Diagnosis of fungal keratitis begins with clinical suspicion. Physicians should have heightened suspicion in cases that involve wispy or feathery-appearing corneal ulcers, cases with a central lesion and multiple satellite lesions or cases presenting with a ring infiltrate, particularly if the history is positive for corneal trauma or contact lens wear. Also, failure of a presumed bacterial keratitis to respond to seemingly appropriate topical antibiotic therapy after several days should lead the clinician to suspect a possible fungal etiology.

Historically, confirmatory testing for fungal keratitis involved performing corneal scrapings for smears (using Gram, Giemsa, potassium hydroxide and calcofluor white stains) and cultures.[11,12] Sabouraud's media and blood agar are the preferred media for facilitating fungal growth. Unfortunately, the use of stains on corneal scrapings typically has a sensitivity of only about 50% in fungal keratitis. Cultures may produce confirmatory results within 72 hours, however, cultures in up to 25% of cases become positive only after two weeks of incubation.[4,11] Hence, there has been a need to develop more effective diagnostic tests. One method that has demonstrated success on a small scale is polymerase chain reaction (PCR).[12] The advantage of PCR is that it requires only a small sample of corneal tissue

and both viable and nonviable organisms can be detected.[4] The downside of this test is that it has a high tendency toward false positives, is not yet widely available and is quite expensive. In recent years, confocal microscopy has emerged as an efficient and reliable method of identifying fungal keratitis in vivo.[13,14] This technique allows for high resolution visualization of the corneal cellular anatomy and is capable of imaging specific pathogens and inflammatory elements.

Treating fungal keratitis can be quite difficult. Most antifungal medications are merely fungistatic, requiring both an intact immune system and a prolonged therapeutic course in order to be effective. Drug classes used to treat fungal keratitis include the polyene antibiotics (nystatin, amphotericin B and natamycin), pyrimidine analogs (flucytosine), imidazoles (clortrimazole, miconozole, econazole and ketoconazole), triazoles (fluconazole, itraconazole voriconazole and posaconazole), echinocandins, (caspofungin and micafungin) and nonspecific antiseptics, such as chlorhexidine gluconate and silver sulfadiazine. Natamycin is only available as a topical formulation, while the other medications have various routes of administration.[15] Corticosteroids are generally avoided in fungal keratitis as they can exacerbate the disease.

Once diagnosed as fungal keratitis, the treatment of first choice is typically Natacyn (5% natamycin ophthalmic suspension, Alcon), primarily because of its commercial availability.[16,17] Common alternatives for filamentary fungal pathogens such as *Aspergillus* or *Fusarium* include 0.15% amphotericin B, 1% itraconazole, 2% econazole, and more recently 1% voriconazole.[16-19] For yeast infections of the cornea (e.g., *Candida*), 0.15% amphoteracin B is the preferred therapy; alternatives include 0.2% fluconazole and 1% miconazole.[20] All of the aforementioned topical therapies are indicated hourly around the clock. Adjunctive oral therapy with ketoconazole or fluconazole should be considered for patients with deep stromal infection. Antifungal medications are usually maintained for approximately 12 weeks with close monitoring of the patient.



Fungal keratitis secondary to *Fusarium* infection.

For those cases of fungal keratitis that do not respond to aggressive drug therapy, surgical intervention must be considered.[4] In a small 2005 study, adjunctive therapy with phototherapeutic keratectomy (PTK) seemed to show promise, but no large scale studies investigating PTK for fungal keratitis have been published since that time.[21] Collagen cross-linking therapy using riboflavin and UV-A light has also been suggested as an adjunctive treatment for a variety of corneal disorders, including fungal keratitis. While no human studies have been published to date, the results of in vitro and in vivo animal studies are favorable.[22,23] Ultimately, if the keratitis progresses to the point of impending corneal perforation or extracorneal infection despite maximum medical therapy, lamellar or penetrating keratoplasty is indicated. Unfortunately, even after corneal transplant surgery, fungal keratitis may recur. A review of nearly 900 patients undergoing lamellar or penetrating keratoplasty found the recurrence rate to be just over 6%.[24] Risk factors for recurrence included preoperative steroid use and more severe infection prior to surgery.

Clinical Pearls

• While a significant risk factor for fungal keratitis, injury by organic vegetative matter is by no means a guarantee that the patient will develop the disease. Fungal keratitis is quite uncommon, particularly in temperate climates.[4] For this reason, it is not appropriate to use antifungal medications on a prophylactic basis.

• As a rule, fungal keratitis is a slow, insidious process. Acute and severe corneal infections appearing overnight should prompt the clinician to consider a bacterial etiology, such as *Pseudomonas* or *Neisseria*.

• Although topical natamycin is *commercially* available, it is usually not *readily* available. When prescribing, anticipate that the commercial pharmacist will need to order this agent from the manufacturer and advise the patient accordingly. If antifungal medication is required immediately due to the risk of perforation or penetration, the services of a compounding pharmacist will be necessary; or, an immediate referral to a corneal specialty center that may have the resources to have the medications in stock is indicated.

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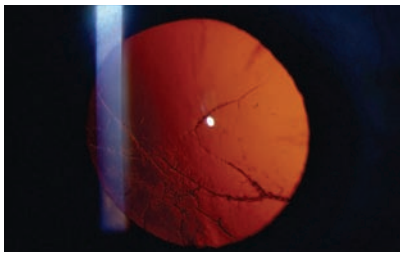
LATTICE CORNEAL DYSTROPHY

Signs and Symptoms

Lattice dystrophy (sometimes referred to as Biber-Haab-Dimmer dystrophy) is typically seen as a bilateral condition that affects the central regions of the cornea while generally sparing the periphery.[1,2] Patients may be diagnosed on routine examination in their teens or twenties, although the condition may not become symptomatic until the third or fourth decade of life.[2,3] Because of its autosomal dominant inheritance pattern, patients with lattice dystrophy characteristically have a parent and/or a sibling with a similar history and findings.[1-3]

Clinically, lattice corneal dystrophy can be viewed as a series of translucent, linear, radially-oriented, branching opacities that somewhat resemble cracked glass. Located in the anterior stroma, the deposits are best viewed with retroillumination on biomicroscopy or direct ophthalmoscopy. In the early stages, vision may be unaffected or only mildly reduced; however, as the lattice lines and other deposits coalesce, a corneal haze develops, and visual acuity may drop off precipitously. It is not unusual to see older patients with this condition manifesting vision of 20/80 or worse. Patients may also report varying degrees of ocular irritation, ranging from a mild foreign body sensation to pronounced pain. This is complicated by the fact that corneal sensitivity may be diminished in lattice dystrophy.[1] The most significant complication, aside from reduced vision, is the propensity toward recurrent epithelial erosions—a consequence that is seen in several of the stromal dystrophies.



Lattice dystrophy as seen with retroillumination of the cornea.

Pathophysiology

Corneal dystrophies are non-infectious, non-inflammatory, hereditary disorders that involve abnormal deposition or retention of material within the cornea. They are usually due to faulty cellular metabolism. The underlying etiology is often related to a specific genetic mutation.[4] Corneal dystrophies are categorized by the layer of the cornea in which they are found, including the superficial anterior layers (epithelium and epithelial basement membrane), Bowman's layer, the corneal stroma, or the endothelium.

In lattice dystrophy (as with granular, Avellino and Reis-Bückler), the mutation appears to be in the Transforming Growth Factor Beta 1 gene (TGFβ-1), also known as the BIGH3 gene.[1,2,5] This mutation leads to production of an abnormal adhesion protein in the cornea (keratoepithelin), which in turn results in accumulation of insoluble proteins. The deposits in lattice dystrophy are composed of amyloid, a protein associated with a number of other degenerative conditions including Alzheimer's disease, Parkinson's disease, rheumatoid arthritis, atherosclerosis and bovine spongiform encephalopathy ("mad-cow disease").[6] Amyloid can be seen on histopathologic evaluation as amorphous pink deposits with hematoxylin and eosin stains; amyloid deposits also stain positively with Congo red dye.[2,7]

In the cornea, the amyloid deposits of lattice dystrophy assume a linear and dendritic pattern, accumulating within and radiating outward from the visual axis at the level of the anterior stroma. This aggregation of material and the resultant disruption of the normal architecture of the stromal collagen fibrils results in diminished transparency, stromal haze, scarring and ultimately visual deterioration. Additionally, amyloid deposits often occur between the epithelium and Bowman's membrane, resulting in irregular epithelial basement membrane complexes.[8] These abnormalities interfere with normal epithelial adhesion, creating a propensity toward recurrent corneal erosion syndrome.

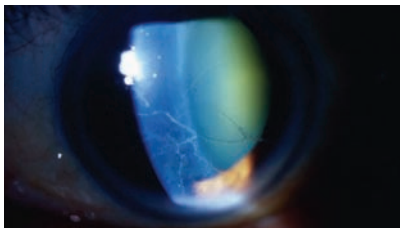
Management

Unfortunately, there is no universally accepted restorative process for individuals with lattice corneal dystrophy. Patients typically endure the situation as long as possible, relying on a variety of lubricants for palliative relief of ocular irritation. The most significant event associated with lattice dystrophy

is recurrent corneal erosion; historically, this has been treated with artificial tears, hyperosmotic agents (e.g., 5% sodium chloride solution or ointment), and bandaging with either a pressure patch or soft contact lens. Prophylaxis with a broad-spectrum topical antibiotic (fourth-generation fluoroquinolone, q.i.d.) is recommended during acute stages, while topical non-steroidal anti-inflammatory drops, q.i.d., may help to ameliorate the discomfort associated with this event. Anterior stromal puncture is not advisable for recurrent erosions secondary to corneal dystrophy, and should be employed only in those cases of erosion associated with prior ocular trauma.

In later stages involving significant visual compromise or recalcitrant corneal erosions, PTK may be employed as a means to restore some degree of functional vision and also diminish the recurrence of erosion.[9] The excimer laser ablates the more superficial opacities, helping to smooth the corneal surface and allow the new epithelial cells to re-adhere more tightly to the underlying Bowman's membrane.[10] In most cases of corneal dystrophy, PTK is effective in achieving symptomatic improvement; however, the greatest success has been noted in granular and macular dystrophies.[10-12] Comparatively, PTK may induce delayed epithelial wound healing in cases of lattice dystrophy.[10] In the most severe cases, a lamellar or full-thickness keratoplasty may be required to restore functionality to the cornea, although lattice dystrophy has been known to recur even after corneal transplant surgery.[1]

Recently, a non-invasive, topical, therapeutic approach to managing lattice dystrophy has been described. In a small, non-randomized study,[13] the application of autologous fibronectic eye drops to a freshly debrided cornea was shown to restore a more regular corneal surface and actually improve



Characteristic refractile corneal deposits in lattice dystrophy.

visual acuity over a two- to four-month period. The authors suggested that this procedure, which unlike PTK does not involve stromal ablation, might provide a viable, repeatable option for less severe cases of lattice corneal dystrophy.[13]

Clinical Pearls

• There are actually three recognized types of lattice corneal dystrophy. Type I, which is the most common form seen clinically, is described above. Type II, also known as Meretoja or Finnish, involves concurrent systemic manifestations such as nerve palsies, skin disorders, and facial abnormalities; decreased corneal sensation and open angle glaucoma are common associations.[1-3,7,8] Type III lattice dystrophy is autosomal recessive with a late adult onset, usually in the sixth decade of life. First described in 1987, it may be unilateral or bilateral, and presents with coarse lattice lines that stretch from limbus to limbus.[14]

• The most common corneal dystrophies encountered in clinical practice include lattice dystrophy, granular dystrophy, epithelial basement membrane dystrophy (EBMD) and Fuch's endothelial dystrophy. These conditions are distinguished based upon: 1) the involved layer of the cornea, and 2) the clinical and histological appearance of the lesions.

• Since the majority of lattice cornea dystrophy is autosomal dominant, it is important to examine family members (especially siblings or children) for similar ocular findings.

• The use of oral doxycycline has been advocated in the management of recalcitrant recurrent corneal erosions.[15] Doxycycline serves to inhibit the production of matrix metalloproteinases, which are important mediators in the process of corneal inflammation. Despite this premise, there is no direct evidence that the use of cycline medications promotes resolution of recurrent erosions in cases of lattice corneal dystrophy.

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THE ABCs OF CORNEAL SURGERY

Over the last 25 years, a multitude of new ophthalmic procedures have been pioneered and perfected. Corneal surgery, once limited to penetrating keratoplasty and reserved for only the most severe and sight-threatening of disorders, has evolved to include a wide variety of specialized procedures for both corrective and cosmetic purposes. With such diversity and rapid change, it can be difficult for non-corneal specialists to recognize the jargon and communicate effectively with surgeons and patients. For this reason, we've included a glossary of the more commonly discussed corneal surgeries.

- **PK** or **PKP** – ***P**enetrating **K**eratoplasty.*
  - o PK refers to full-thickness corneal transplant surgery. It is usually performed in cases of extensive scarring, degeneration or perforation of the cornea. PK has been employed successfully in many cases for nearly a century, but it has numerous shortcomings, the most significant of which include the need for sutures, healing time, visual instability and the potential for graft rejection.[1] The need for prolonged use of corticosteroids post-operatively also puts the patient at risk for secondary glaucoma and cataracts.
- **DLK** – ***D**eep **L**amellar **K**eratoplasty*. Sometimes referred to simply as **LK** – ***L**amellar **K**eratoplasty*.
  - o DLK is a very general term describing the surgical replacement of a portion of the corneal depth by donor tissue, in contrast to PK, which replaces the entire thickness of the cornea. In the literature, the term DLK has been used to refer either to anterior or posterior lamellar keratoplasty.
- **DALK**– ***D**eep **A**nterior **L**amellar **K**eratoplasty*.
  - o DALK is a surgical procedure that serves to transplant the anterior cornea down to the level of Descemet's membrane. The surgeon employs a trephine and scalpel to remove the corneal stroma after dissecting it away from the deeper structures. DALK is most useful for the treatment of corneal disease in the setting of a normally functioning endothelium; it offers an alternative to PK, lessening the risk of graft rejection, irregular astigmatism and corneal opacification. On the other hand, DALK carries the potential danger of decreased visual acuity due to possible opacification at the interface layers.
  - o *Indications*: Common indications for DALK include keratoconus and corneal scarring. Keratoconus patients are typically good candidates for DALK because of their young age and healthy endothelium. Less common indications for DALK include vernal keratoconjunctivitis, corneal dystrophies and ocular surface diseases with limbal stem cell deficiency, including Stevens-Johnson syndrome, ocular cicatricial pemphigoid and chemical or thermal burns.[2]
- **PLK** – ***P**osterior **L**amellar **K**eratoplasty.*
  - o PLK is a surgical procedure that serves to transplant only the most posterior elements of the cornea in an effort to replace a dysfunctional endothelial layer. Earlier surgeries accomplished this by creating an anterior flap of tissue, trephining the damaged endothelium out and suturing the donor tissue in its place. PLK instead preserves the preoperative corneal surface, achieving transplantation of donor tissue via a large diameter scleral tunnel. A button of donor cornea consisting of posterior stroma, Descemet's membrane and endothelium is inserted via the scleral tunnel into the anterior chamber, and positioned into place with the aid of an air bubble. PLK has undergone several iterations since it was first conceived by Dr. Jose Barraquer in the 1960s, and later developed and perfected by Dr. Gerrit Melles in the 1990s.[3]
  - o *Indications*: The main indications for PLK (and its progeny listed below) are diseases of the endothelium, such as Fuch's dystrophy or bullous keratopathy. Other conditions that may warrant this procedure include some of the less common endothelial corneal dystrophies (e.g., posterior polymorphous dystrophy) or the iridocorneal endothelial (ICE) syndromes. In order for these procedures to be successful, there must be an absence of visually significant stromal scarring.
- **DLEK** – ***D**eep **L**amellar **E**ndothelial **K**eratoplasty*.
  - o DLEK was the name given to PLK when it was adopted in the United States by Dr. Mark Terry in the early 2000s. Part of his modification included reducing the surgical incision from 9mm to a more manageable 5mm. The recipient cornea in this procedure is dissected at the level of the posterior lamella and removed; donor cornea is then prepared by cutting it to a depth of 150µm via manual dissection. The button is then inserted into the anterior chamber and positioned with the aid of an air bubble to form a self-adhering interface with the exposed stromal bed of the recipient.[4] In recent years, DLEK has generally given way to DSEK and Descemet's Membrane Endothelial Keratoplasty, which involve the removal of far less corneal tissue from the recipient.
- **DSEK** – ***D**escemet's **S**tripping **E**ndothelial **K**eratoplasty*. Sometimes referred to as **DSAEK** – ***D**escemet's **S**tripping **A**utomated **E**ndothelial **K**eratoplasty*
  - o Descemet's stripping was first proposed in 2003, and reported in 2005.[5] Rather than dissecting the recipient cornea at the midstroma, this procedure peels away only Descemet's membrane and the endothelium (much in the same fashion that a capsulorhexis is performed on the anterior lens capsule during cataract surgery). The donor button of posterior stroma, Descemet's membrane and endothelium is then implanted. DSEK has the advantage of a smaller, potentially self-sealing incision, as well as a smoother recipient interface for the donor tissue. Additionally, DSEK has a more rapid rate of visual recovery, with full recovery typically between one to six months post-operatively.
- **DMEK** – ***D**escemet's **M**embrane **E**ndothelial **K**eratoplasty*. Sometimes referred to as **DMAEK** – ***D**escemet's **M**embrane **A**utomated **E**ndothelial **K**eratoplasty*.
  - o DMEK represents the most recent and least invasive approach to endothelial keratoplasty. Like DSEK, DMEK involves an in vivo stripping of Descemet's membrane through a scleral incision. However, rather than dissecting the donor cornea at the level of the posterior stroma, only Descemet's membrane and the endothelium are removed and transplanted. The DMEK procedure combines the anatomical benefits of DSEK with enhanced visual rehabilitation, typically to 20/40 or better in 90% of cases and 20/25 or better in 60% of cases within the first three months.[6] As one can imagine, DMEK is a painstakingly detailed and challenging procedure, and is not yet widely performed by all surgeons.

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ACUTE ANGLE CLOSURE GLAUCOMA

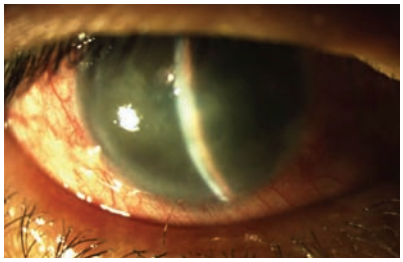
Signs and Symptoms

While any person can experience acute angle-closure glaucoma (AACG), this condition is most common in patients of Asian descent.[1-6] Patients are more likely to be older, hyperopic and female.[2-8] The etiology of angle closure in young individuals differs from the older population and is typically associated with structural and developmental anomalies.[9]

Patients with acute AACG manifest the signs and symptoms of ocular and facial pain, unilateral blurring of vision, photopsia in the form of colored haloes around lights, and occasionally nausea and vomiting. Acuity may be reduced significantly in the involved eye, often to 20/80 or worse.[6,10,11] AACG is frequently unilateral, but may be bilateral and, as a rule, should always be considered to have bilateral potential, though the timing of the fellow eye involvement may be different.[2,3]

The hallmark signs of AACG include significantly elevated intraocular pressure (IOP), virtually no visible anterior chamber angle structures upon gonioscopy, deep conjunctival and episcleral injection in a circumlimbal fashion, and a fixed, mid-dilated pupil. Biomicroscopically, there typically will be an edematous or "steamy" cornea and shallow anterior chamber. There may be a flat anterior chamber, or significant iris bombé, depending upon the mechanism of the angle closure.

Applanation tonometry reveals IOP in the range of 30mm Hg to 60mm Hg, occasionally higher in some cases.[12-14] Gonioscopy, which may prove difficult because of microcystic corneal edema, reveals no visible angle structures without indentation. There may be evidence of previous angle closure episodes in the form of peripheral anterior synechiae (PAS) in the



Steamy corneal edema in acute angle closure glaucoma.

involved or fellow eye.[15,16]

Medication history is important in patients with AACG as the attack may be medically induced. Of particular importance is the use of the sulfa-based anti-epileptic medication Topamax (topiramate, Ortho-McNeil Pharmaceutical). Topiramate has been associated with the development of AACG (unilateral and bilateral) and acquired myopia in patients previously not at risk for angle closure.[6,17-21]

Pathophysiology

Anatomically, patients with AACG have smaller eyes. It has been shown that these patients have axial lengths 5% shorter, lenses that are 7% thicker, anterior chambers that are 24% shallower, and anterior chambers with 37% less volume than other age-matched individuals.[22] It has recently been shown that eyes undergoing acute angle closure have greater iris thickness contributing to a shallower anterior chamber.[23,24] There is a high resistance to forward movement of aqueous through the iris-lens channel due to a tight apposition between the posterior iris and anterior lens capsule. This resistance is known as relative pupil block. It must be understood that pupil block is a normal physiological phenomenon occurring in virtually every phakic person. In some cases, this resistance becomes pathological and results in AACG. In these individuals, there is an increased pressure differential between the anterior and posterior chambers with resultant iris bombé and angle closure. When this occurs, there is a marked bowing forward (convexity) of the iris, termed iris bombé.

Angle closure occurs when the peripheral iris physically opposes the trabecular meshwork or corneal endothelium and impedes aqueous outflow. Several mechanisms are possible. This may be simply due to genetic predisposition and anterior segment anatomy (primary pupil block), or from sources of secondary pupil block such as posterior synechiae, iris neovascularization, aqueous misdirection syndrome, lenticular enlargement or displacement of the lens or IOL.[1,25]

Another mechanism that may induce angle closure involves an abnormal configuration of the iris, the so-called "plateau iris syndrome." Patients with this presentation may boast a deep anterior chamber centrally; however, the iris demonstrates an unusual laxity, coming into close approximation with the angle peripherally. These patients may be prone to "angle crowding" and subsequent closure during physiologic or pharmacologic dilation.[25]

Expansion of the choroid appears to be a significant contributory factor for AACG in some cases.[21,26-28] Ultrasound biomicroscopy has clearly demonstrated choroidal expansion as well as shallow choroidal effusions in patients undergoing angle closure attacks. This is associated with anterior rotation of the ciliary body as well as forward movement of the iris and lens with subsequent shallowing of the anterior chamber and closure of the angle.[6,21,26-29] Due to expansion of the choroid and ciliary body edema (with possible choroidal effusion), there is a relaxation of the lens zonules with increased laxity and thickening of the lens. Along with the angle closure glaucoma, there is refractive error shift with several diopters of acquired myopia. The clinical picture of choroidal

expansion-induced AACG differs from that seen in primary pupil block in that there is a flat anterior chamber without iris bombé.

A number of conditions may lead to choroidal expansion and secondary angle closure in eyes not at anatomical risk for angle closure, including scleritis, Vogt-Koyanagi-Harada syndrome, pan retinal photocoagulation, HIV infection and cavernous sinus fistula.[29] Choroidal expansion-induced angle closure glaucoma has also been reported frequently due to administration of sulfa-based medications, such as sulfonamide, acetazolamide, topiramate and hydrochlorothiazide. Topiramate, which is used to manage chronic headache as well as induce weight loss, among other uses, has been strongly implicated in choroidal expansion-induced bilateral angle closure glaucoma along with induced myopia.[21,28] The theorized mechanism may be an inflammatory sulfa-allergic reaction.[6]

Management

The paramount concern in managing any pupil block angle-closure attack is to alter the physiologic mechanisms that cause the cornea to appose the trabecular meshwork.[1] In primary pupil block, the tight apposition of the posterior iris to the anterior lens surface in the mid-dilated state must be broken. This is done by lowering the IOP so that the iris can function normally and move from this mid-dilated, pupil-blocking state. This must be done quickly, as structural damage to the nerve fiber layer and trabecular meshwork and functional damage to the visual field can occur within 48 hours.[11,12,30]

Choice of primary medication depends upon the pressure at presentation. As most miotics are ineffective at pressures over 40mm Hg due to iris ischemia, aqueous suppressants such as topical beta-blockers, alpha-2 adrenergic agonists and carbonic anhydrase inhibitors should be used initially.[30] Prostaglandin analogs also appear to be an efficacious topical therapy for patients with chronic angle closure glaucoma. Though they will not cause harm it is widely felt that the medications' effects are too slow to be effective in acute situations.[33-37]

Once the IOP is below 40mm Hg, topical pilocarpine 1-2% can be used to miose and reopen the angle. Higher concentrations of pilocarpine should be avoided as this can lead to uveal congestion and actually worsen the condition. Topical steroids, such as prednisolone acetate 1% or difluprednate 0.5% emulsion, can be used for the resultant inflammation. If the patient does not achieve significant reduction in IOP after 60 minutes, an oral carbonic anhydrase inhibitor (acetazolamide 2 x 250mg tablets) can be employed. A hyperosmotic agent, such as three to five ounces of oral glycerin over ice, may also assist in lowering the IOP and breaking the attack. It is safe to discontinue acute medical intervention when the IOP falls below 30mm Hg and the angle structures are again visible with gonioscopy. The patient should be maintained on the following medications until surgical therapy can be employed: pilocarpine 2% and prednisolone acetate 1% q.i.d., as well as a topical beta blocker and an alpha-2 adrenergic agonist b.i.d.

The quintessential treatment for primary pupil block AACG is laser peripheral iridotomy (LPI).[6,8,11,16,37-41] This should be performed as soon as safely possible. LPI will allow the aqueous fluid pressure to equilibrate between the posterior and anterior chamber. This will permit the iris to relax backward with dissipation of iris bombé allowing deepening of the anterior chamber opening of the angle, and aqueous access to trabecular drainage again. LPI should also be performed subsequently on any fellow eyes that are potentially occludable.[42] Adjunctively, laser peripheral iridoplasty—an irido-retraction procedure—can be performed to physically pull the iris taught and away from the trabecular meshwork. In fact, laser peripheral iridoplasty has been shown to be a safe, primary treatment for AACG.[8,38,39] Incisional ocular surgery in the form of trabeculectomy, cataract extraction, cyclodestructive procedures, glaucoma implant and goniosynechialysis remain as options for cases unresponsive to medical and laser therapies.[38,43-45] Trabeculectomy and goniosynechialysis are often combined with cataract extraction.

In cases of AACG that are determined to be precipitated by a systemic medication, therapy is different. Often, discontinuation of the medication will resolve the glaucoma. However, when the choroid contributes to angle closure glaucoma (which is often the mechanism of medicine-induced AACG), the use of a potent cycloplegic agent such as atropine, as well as topical steroids, will allow for ciliary body relaxation and posterior rotation with resolution of the angle closure.[6,17,21,26,27,29] Aqueous suppressants can be used concurrently, but miotics should be avoided in these cases.

Following successful LPI, IOP may still be elevated secondary to damage to the trabecular meshwork caused by the prolonged or repeated iris-meshwork apposition.[31] Persistent trabecular-iris contact or peripheral anterior synechia may block aqueous outflow resulting in a progressive process in which Schlemm's canal sustains endothelial damage with subsequent canal occlusion. Trabecular cell damage may also produce impairment of mitochondrial function and subsequent fusion of the trabecular beams.[46] These changes may be the reason for residual glaucoma after laser iridotomy or cataract surgery.

For this reason, long-term medical therapy may be necessary. Aqueous suppressants are a good choice and it appears that prostaglandin analogs also work especially well.[31-34]

The abrupt IOP elevation in AACG rapidly causes structural alterations. It has been shown with optical coherence tomography that there is an increase in retinal nerve fiber layer (RNFL) thickness immediately after the acute attack, with subsequent atrophy months later.[47-51] This can explain later-onset visual field and RNFL damage. The acute attack has been shown to cause disc pallor, RNFL atrophy and visual field loss, but not necessarily an increase in focal disc damage.[51,52]

Primary phacoemulsification plus intraocular lens implantation is a viable initial option for eyes with AACG, resulting in lowered IOP, reduced the use of antiglaucoma medications and improved vision in patients. This is a safe and effective method of IOP control and can be considered a first treatment option in managing patients with AACG and coexisting cataract.[53,54]

Clinical Pearls

• The most important consideration in handling an acute angle-closure attack is accurate diagnosis and prompt intervention. AACG must be differentiated from other acute open-angle conditions such as uveitic glaucoma, glaucomatocyclitic crisis and phacolytic glaucoma. The mechanism of angle closure, such as primary pupillary block, plateau iris, secondary pupillary block or choroidal expansion, must be delineated. If the etiology is uncertain, or if an inflammatory glaucoma may be present, a miotic should not be used, as this will only exacerbate the condition.

• In unilateral cases of suspected acute angle closure, the cornea may be too edematous to allow for gonioscopic evaluation of the anterior chamber angle. In such a case, gonioscopy should be performed on the uninvolved fellow eye. In the vast majority of cases, by nature of symmetry, the fellow eye will have an occludable angle.[55] If the fellow eye demonstrates a non-occludable angle, it is not likely that the patient has a primary acute angle closure. In the event both corneas are edematous, topical glycerin can be applied with a cotton-tipped applicator to provide appropriate deturgescence.

• The presence of a patent peripheral iridotomy does not necessarily ensure that a patient is safe to dilate. Gonioscopy must still be performed prior to pharmacologic dilation.[56]

• The ultimate goal in the management of AACG attack is not to merely lower the IOP, but to assist in resolving the apposition of the iris to the trabecular meshwork. Reduction of IOP is one means by which clinicians can alter this anatomic relationship.

• Often, following successful LPI for AACG, the angle will be open, but the IOP will be elevated and the patient is said to have "mixed mechanism glaucoma." The use of this term is not accurate. Angle damage following AACG compromises the outflow facility following appositional closure. Thus, there is one mechanism for the residual IOP elevation and the term "mixed mechanism glaucoma" should be avoided.

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PARS PLANITIS

Signs and Symptoms

Pars planitis typically affects younger patients, between five and 40 years of age.[1] Pars planitis seems to have an association with Crohn's disease and multiple sclerosis.[2-8] Patients are frequently asymptomatic, but may present with modestly diminished vision that is slowly progressive. Typically, they will complain of floaters. Visual acuity tends to be worse in children with pars planitis as compared to adults both at time of diagnosis and at follow-up.[9] Further, in children, vitreous hemorrhage appears to be a more common complication than in adults.[10,11] Visual acuity ranges from 20/20 to no perception of light, with a mean range of 20/40-20/50.[12,13] Pars planitis is typically bilateral, with both eyes affected in 85% of the cases according to one report.[12] This disease has a good prognosis with a final mean visual acuity ranging from 20/30 to 20/40 in 90% of cases.[7,12,14]

Vitritis is present in virtually all patients with pars planitis.[12] Vitritis may cause subsequent vitreous degeneration with a resultant posterior vitreous detachment. There frequently will be an accumulation of inflammatory exudates. This accumulation may be small (snowballs) or extensive (snowbanks) and may occur anywhere in the fundus. However, these inflammatory aggregates are typically regulated by gravity to the inferior fundus. There also is likely to be the presence of cataracts (especially posterior subcapsular), secondary glaucoma, retinal neovascularization with vitreous hemorrhage and tractional retinal detachment, exudative retinal detachment, retinal vascular sheathing, papillitis and cystoid macular edema (CME).[7,10-12,14-19] While vitreous snowballs and snowbanks are frequently encountered, they are by no means present in every eye with pars planitis and need not be present to make this diagnosis.[12,18,20] CME and cataract are the most frequently encountered visual complications in patients with pars planitis.[12,17,18]

A detailed family history (or examination) may disclose other family members with pars planitis. The genetic predisposition of pars planitis is unknown; however, the frequent occurrence of this condition in family members suggests that a common hereditary and/or environmental factor contributes to the disease.[21-25]

Pathophysiology

Pars planitis is a posterior/intermediate uveitis. It may be associated with various systemic diseases or may be idiopathic in nature.[1] There are exacerbations and remissions and typically this disorder runs a very long course. Inflammatory mediators will increase

vasopermeability of retinal capillaries resulting in posterior segment inflammatory cells as well as CME.

The chronic inflammation in pars planitis appears to consist of helper T cells, both in the pars plana and the retinal vasculature.[24] Snowbanks consist of posteriorly detached and collapsed vitreous with cellular proliferation from the retina with nonpigmented ciliary epithelium. Electron microscopy has demonstrated the presence of fibrous astrocytes and collagen. Vitreous snowballs consist of granulomatous inflammation.[19,26]

Serologic evaluation of patients suggests an immunogenic predisposition exists to pars planitis. Several studies attempting to identify frequencies of human leukocyte antigen (HLA) class II alleles with pars planitis have shown a strong association with the HLA-DR2 suballeles, -DR15, HLA-DR51 and HLA-DR17.[8,14,24,27] A common immunogenetic link between multiple sclerosis and pars planitis may be associated with the HLA-DR15 allele. This association may represent genetic linkage to the HLA-DR locus or a role for the HLA-DR15 gene product in the pathogenesis of both of these diseases.[14] The strong association of pars planitis with HLA-DR2 and the temporal development of MS in some patients with pars planitis further supports an association between pars planitis and MS.[8]

Management

Pars planitis generally has a favorable outcome.[6,7,12-14,17,28,29] Treatment should be conservative and often involves only periodic monitoring, especially if vision is only minimally disturbed by vitritis and CME.

If treatment is undertaken due to vision loss from CME or vitreous clouding, then steroids form the cornerstone of management.[7,12,17,18,30,31] Periocular, intravitreal, and systemic corticosteroids have all been employed, as well as other immunosuppressive drugs. However, once a commitment to use systemic steroids is made, typically they are used for months. With this treatment comes the possible attendant complications of steroid-induced cataracts and glaucoma.[32] Topical steroids, such as prednisolone and loteprednol, are employed if there is a concomitant anterior uveitis or CME. However, in these cases, the anterior chamber reaction is not a true anterior uveitis, but a spill-over from the posterior uveitis. Topical non-steroidal anti-inflammatory drugs (NSAIDs) for CME remain a consideration.

In severe or unresponsive cases, transscleral cryoretinopexy or thermal laser photocoagulation can be directed against the snowbanks to destroy the inflamed areas along with the infiltrates.[15,32-35] These treatments can reduce intraocular inflammation, increase visual acuity, and decrease dependence upon systemic steroids. Vitrectomy can also be used to clear the vitreous of both cells and hemorrhage.[36,37] In that CME is a significant cause of vision reduction in eyes with pars planitis, intravitreal bevacizumab has been seen as an effective therapy to manage this complication.[38-42]

A recent report examined the successful use of twice-daily topical difluprednate 0.05% emulsion (Durezol, Alcon) in a child with pars planitis. Although not a standard treatment, it was speculated that topical difluprednate therapy could be a useful short-term treatment option while alternative treatments are considered or immunosuppressive agents build to therapeutic levels.[43]

Due to the strong association with pars planitis, MRI testing for multiple sclerosis is indicated as part of management. This is especially true for females between the ages of 20 and 40 years.[6,7]

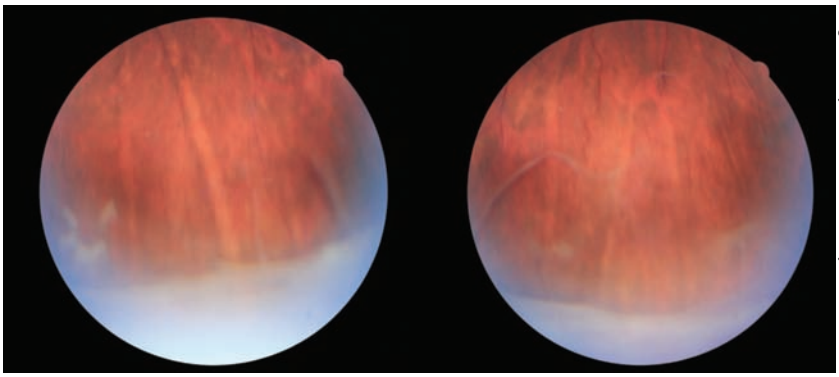

Image courtesy of Dr. Catherine Derewyanko

Inferiorly located snowballs and snowbanks in pars planitis.

Clinical Pearls

- Posterior vitreous detachment is rare in younger patients; however, PVD is quite common in pars planitis. Consider pars planitis when encountering PVD in younger patients.
- Always consider pars planitis in cases of asymptomatic vitreous cells in healthy, younger patients.
- When suspecting pars planitis, carefully examine the inferior retina and vitreous for snowballs and snowbanking.
- Children with pars planitis are more likely than adults to experience vitreous hemorrhage. Pars planitis should be considered in the differential diagnosis of pediatric vitreous hemorrhage.
- Pars planitis is the leading cause of pediatric vitreous hemorrhage.

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STEROID-INDUCED GLAUCOMA

Signs and Symptoms

The patient with steroid-induced glaucoma may be of any age, sex or race. There may be a pre-existing personal or family history of primary open angle glaucoma.[1] Invariably, there will be a history of corticosteroid use. While topical ophthalmic corticosteroids are most likely to precipitate a rise in IOP, other modalities of steroid use including intraocular and periocular injections, topical periocular dermatological creams, inhaled steroids and oral steroid use have been documented to have the potential to cause a rise in IOP.[2-13] Frequently, there will be a history of long-term steroid use on the order of weeks to months. Beyond the condition for which the patient is using steroids, there will be no visual or ocular symptoms of steroid-induced glaucoma, unless the IOP elevation is profound with resulting corneal edema and vision blur. The rise in IOP may be modest or may be dramatic. Topical steroids such as betamethasone, dexamethasone, prednisolone and difluprednate are more likely to cause a rise in IOP than steroids such as loteprednol or fluorometholone.[3,14-17]

Pathophysiology

Steroid-induced glaucoma presents with an open anterior chamber angle and increased IOP. The nature of the raised pressure appears to be due to outflow reduction. Beyond that, nothing more conclusive regarding the pathophysiology of this condition can be stated. One theory postulates that steroids are responsible for the accumulation of glycoaminoglycans in the trabecular meshwork.[18] Once hydrated, glycoaminoglycans cause an aqueous outflow obstruction.[18] Another thought holds that steroids decrease the phagocytic ability of the trabecular meshwork endothelial cells with a resultant increase

in debris and concomitant decrease in aqueous processing ability.

Recently, genetic mapping has led to greater understanding of steroid-induced glaucoma. Steroids are believed to induce the expression of a gene that is located on chromosome 1 and is known as TIGR or GLCIA. The resultant genetic product is a glycoprotein called myocilin.[5] In the eye, myocilin is highly expressed in the trabecular meshwork, sclera, ciliary body and iris. In the trabecular meshwork, myocilin is found within the cytoplasm of the cells and in the juxtacanalicular region in association with fibrillar extracellular matrix components. Recombinant myocilin increases outflow resistance.[19,20] In TM cells, the expression of myocilin can be induced via treatment with dexamethasone at a time course similar to that observed in steroid-induced glaucoma.[18-21]

Management

Intuitively, management of patients with steroid-induced glaucoma involves discontinuation of the precipitating medication, if possible. In cases where the steroid has been injected, surgical removal of the drug depot may be necessary.[22] When steroid treatment has not exceeded 12 months, discontinuation of the steroid will usually result in a return to pre-treatment IOP levels.[5] However, patients undergoing steroid treatment over several continuous years may develop a chronic IOP elevation that is unalterable by steroid cessation.[23]

In patients where ocular steroid cessation is not an option, management may include utilization of topical steroids such as loteprednol, which is known to reduce this complication. If this is not successful or if changing steroids is unacceptable, then the IOP elevation can be treated with topical aqueous suppressants. In that steroid-induced glaucoma appears to be due to increased resistance to aqueous outflow at the trabecular meshwork, therapies designed to increase trabecular outflow, such as laser trabeculoplasty and miotics, are of questionable benefit. One study did, however, note a modest effect of selective laser trabeculoplasty in five of seven eyes with steroid-induced glaucoma and felt that this was a reasonable temporizing procedure for this condition.[24] However, prostaglandin analogs appear to be successful in the management of steroid-induced glaucoma.[25,26] However, their use may be contraindicated by whatever ocular inflammatory process necessitated the need for steroids. Trabeculectomy, stents and tube procedures remain an option in patients who are uncontrolled medically.[27-30]

Clinical Pearls

- Remember the realistic risks of steroid-induced glaucoma. While approximately 2/3 of the population are "steroid responders," only 5% of the population will have a dramatic (>15mm Hg) rise in IOP requiring glaucoma therapy.
- An elevation in IOP resulting from steroid use typically takes four to five weeks. Short-term steroid use is unlikely to result in a significant glaucoma concern.
- Safe steroids that have a reputation of lower propensity to cause IOP elevations must also be monitored carefully as these agents can also cause a significant IOP elevation.[31,32]
- While the incidence of IOP response rate is similar to that of prednisolone acetate, patients using Durezol should be monitored closely as the IOP response may occur sooner (one to two weeks) and may be of a greater magnitude.[33]
- Patients with primary open-angle glaucoma are apt to demonstrate a rise in IOP with steroid use.
- Children and infants are susceptible to steroid-induced pressure elevations and should be monitored carefully.[34]

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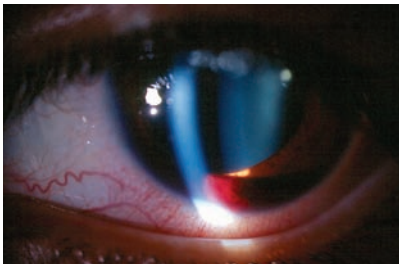

Hyphema.

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HYPHEMA

Signs and Symptoms

Hyphema is defined as blood in the anterior chamber (AC).[1-23] The condition where non-layered red blood cells circulate in the anterior chamber is referred to as microhyphema.[2,15] Hyphema can occur as a result of blunt or lacerating ocular or adnexal trauma; following intraocular surgery; secondary to conditions that induce iris neovascularization, such as diabetes, venous occlusion or iris melanoma; secondary to systemic conditions, such as juvenile xanthogranuloma, myotonic dystrophy, as a complication of keratouveitis (e.g., herpes zoster); as a complication of other blood disorders, such as leukemia, hemophilia, von Willebrand disease; and in association with the use of substances that alter platelet or thrombin function (e.g., ethanol, aspirin, warfarin).[1-3] Complications of traumatic hyphema include increased intraocular pressure, peripheral anterior synechiae, decreased visual acuity and corneal dysfunction secondary to both blood being in the anterior chamber and the complication of corneal blood staining and rebleeding with secondary hemorrhaging.[1-3]

Patients may present with the classic signs of uveitis including conjunctival hyperemia, blurred vision, throbbing eye pain, photophobia, lacrimation, blepharospam and blood in the anterior chamber.[1-3] Any time that IOP is elevated following blunt traumatic ocular injury, hyphema should be suspected whether blood is visible in the anterior chamber or not.

Since the underlying cause of most hyphema is trauma, the epidemiologic data regarding traumatic ocular injury applies (mostly male, with injuries occurring in or around the house, using domestic tools or struck by a projectile).[3-7] The most common concurrent ocular injury associated with traumatic hyphema is corneal injury, however, adenexa echymosis and lacerations of the eyelid are also common.[3,4,6,7]

The risk of secondary hemorrhage seems to be higher in African-Americans than in whites.[1,2,15] Secondary hemorrhage is generally thought to convey a worse visual prognosis, although the outcome seems to depend more on the size of the hyphema and the severity of the associated ocular injuries.[1,8]

Hyphemas are classically graded by the amount of visible blood occupying the anterior chamber (AC). Less than 1/4 of the AC is grade 1; 1/4 to 1/2 is grade 2, 1/2 to 3/4 is grade 3 and complete AC filling is grade 4. The term "8-ball hemorrhage" connotes complete filling of the anterior chamber with blood. It is so named because when the clotted blood fills the AC it makes the anterior chamber appear black like a billiard "8-ball."

Pathophysiology

There are two postulated mechanisms regarding traumatic hyphema formation.[1,2,15-17] Either direct, concussive forces cause mechanical tearing of the fragile vasculature of the iris and/or angle or concussive trauma creates rapidly rising intravascular pressure within these vessels, resulting in their rupture.[1,2,15-17] Blood in the AC is not, by itself, necessarily harmful to the ocular environment. However when quantities are sufficient, macrophages ingest the hemoglobin from the lysed red blood cells. These hemoglobin-laden macrophages obstruct the outflow of aqueous humor by physically blocking access to the drainage area, resulting in glaucoma.[1-14,17] This is known as hemolytic glaucoma.[17] Hemosiderosic glaucoma results when the trabecular meshwork becomes obstructed by iron from degraded red blood cells.[9,17] It is the rarest of the hypema-induced glaucomas.[17] Ghost cell glaucoma results from the trabecular meshwork being obstructed by the denatured skeletons of the disintegrating red blood cells.[9,17] Finally, there is an inferred implication that any external force strong enough to produce internal ocular

bleeding is also sufficiently strong to produce direct damage to the adjacent trabecular meshwork, resulting in sluggish aqueous drainage.[18-21] When IOP begins to rise with all of its potential deleterious sequelae following a blunt injury, the pathology is termed late or chronic traumatic glaucoma.[1,2,9,18-21] Clinically, the presence of increased angle pigmentation, elevated IOP at the time of the injury, hyphema, lens luxation and the gonioscopic finding of angle recession measuring more than 180˚ were all associated with the occurrence of chronic traumatic glaucoma.[19] Researchers using ultrasound biomicroscopy found that a wider angle and the absence of cyclodialysis were significant predictors for the subsequent development of traumatic glaucoma.[19]

Finally, patients with the sickle trait have a greater risk for elevated IOP. Sickled red blood cells are not as malleable as normal red blood cells. Hyphema involving any sickled cells further impedes the flow of aqueous humor, slowing both aqueous and oxygen transfer. The hypoxic environment encourages red blood cells encoded with the sickle trait to undergo the sickle transformation, which further obstructs the trabecular meshwork.[17] This is also dangerous as only slightly elevated IOP (>21mm Hg) can produce similar difficulties with perfusion at the nerve, requiring management consideration.[17]

Management

A thorough ocular and systemic history is critical to managing hyphema. Circumstances surrounding the event and current medicines are important pieces of data. Bleeding in the eye warrants concern for systemic blood disorders, such as antiphospholipid antibody disease (protein S and protein C), hyperhomosysteinemia, dysfunction or the clotting factors, sickle cell anemia, hemophilia and Von Willebrand's disease.[1,2] If the patient is a poor historian or questions arise regarding a patient's systemic status, testing for sickle cell anemia (sickle prep or sickle dex), the status of the commonly involved clotting factors (factor V Leiden, antithrombin III) and testing to rule out other disorders of clotting (prothrombin time [PT] and activated partial thromboplastin time [aPTT]) should be obtained.[1,2]

Ocular examination should include evaluation of the adenexa. Imaging should be ordered when appropriate to rule out fracture or entrapment (X-ray, CT scan). The cornea should be stained to rule out abrasion, laceration or penetrating injury (Seidel sign or evidence of iris prolapse). Signs indicating scleral rupture (ruptured globe) include visual acuity of 5/200 or worse (usually light perception, if any vision is present), subconjunctival hemorrhage of 270˚ or more, IOP < 10mm Hg, shallowing of the anterior chamber or unusual deepening of the anterior chamber, generalized ocular/ adenexa chemosis and inability to ophthalmoscopically visualize structures of the posterior segment.[22,23] The iris should be inspected for iridodialysis. The lens should be inspected for luxation. A dilated fundus exam should be completed to rule out vitreous hemorrhage and retina tears or detachments. If a clear view of the fundus is obstructed by the hyphema or vitreous hemorrhage, B-scan ultrasonography should be completed.[1,2]

Controversy is ongoing whether these individuals should be managed as in- or out-patients.[1-3,15] Most practitioners manage microhyphema and uncomplicated grade I and II hyphema without hospitalization. Cycloplegia is accomplished using atropine 1 %, b.i.d. to t.i.d. Lesser cycloplegics have decreased working times, permitting iris movement, which increases the risk of clot movement and rebleeding.[15] Local inflammation is controlled via topical prednisolone acetate 1 %, q2h to q.i.d. or Durezol b.i.d. to q.i.d.[15,24]

If IOP is above 28mm Hg, becomes increased through steroid response or is judged to be too high for a fragile optic nerve secondary to increased cupping or a systemic disease state that reduces perfusion, it can be controlled through the use of a topical beta blocker b.i.d. (respiratory function permitting) or brimonidine b.i.d. to t.i.d.[1,2,15] When IOP requires acute attention (> 35mm Hg), acetazolamide tablets, 500mg (2 x 250mg), b.i.d. can be prescribed (barring contraindications) along with topical aqueous suppressants, until the pressure is adequately controlled or until the event resolves.

If corneal epithelial defects exist, a topical antibiotic drop should be employed. Patients should be instructed to limit their activity to bathroom privileges and bed rest, laying with the head elevated at an angle of 30˚ to help the hyphema settle and avoid clot movement, which is a stimulus for rebleeding.[15] Some type of eye shield should used for additional protection.[1-3,15] To further reduce the complication of rebleeding only acetaminophen should be used to manage pain.[1]

Immediate referral for surgical evacuation is indicated if there is corneal blood staining, if IOP is > 60mm Hg, if there is 8-ball hemorrhage or if the IOP remains > 35mm Hg for seven or more days.[1-3] Follow-up should be set no later than one week for uncomplicated cases and should be set for consecutive days, as necessary in cases where there are vision-threatening issues.[1,3]

The use of oral antifibrinolytic medications has been advocated by some as the standard of care for cases of hyphema.[15,16] ACA-Amicar (aminocaproic acid, Xanodyne) and TA-Lysteda (tranexamic acid, Ferring) tablets have demonstrated superior properties for stabilizing bleeding and maintaining clot performance, reducing the risk for rebleeding and injury worsening.[15,16]

The surgical intervention of first choice for hyphema with high intractable intraocular pressure with persistent corneal staining is anterior chamber washout.[10,16] Here, free-floating blood and obstructive clots are removed via a single or double paracentesis.[10] Under the influence of a topical anesthetic, a penetrating incision can be made at the limbus through which syringes can be placed for the purpose of both introducing sterile fluid into the AC, permitting forced flow within the chamber and for withdrawing aqueous and free blood.[10] A two-paracentesis procedure has been described where the first is made in the lower temporal quadrant to accommodate a 20-gauge anterior chamber maintainer that is connected to a bottle of balanced salt solution and the second is made in an upper quadrant to serve as the evacuation site for liquefied blood and clots.[10] Proponents of the two site technique approve of the well maintained intraoperative IOP and a stabilized AC depth with a minimized risk of re-bleeding owed to the continuous positive intraoperative maintenance of IOP.[10]

While intraocular pressures following paracentesis typically drop to zero, measurements of IOP improve to normal in as little as two hours after the procedure, frequently remaining at acceptable levels thereafter.[7] The procedure is of particular importance for patients with variations of sickle cell disease as using IOP-lowering agents which induce metabolic acidosis such as acetazolamide, methazolamide or manitol can both induce crisis as well as worsen resultant elevation in IOP and pathologic damage to the optic nerve.[11]

Trebeculectomy with anterior chamber washout has also been examined as a solution for cases involving pathologically elevated IOP secondary to hyphema.[12-14] While the filtering bleb with iridectomy frequently encounters the complication of closing during the course of the hyphema resolution, minimal post surgical events coupled with excellent short-term IOP reduction has made it a reasonable alternative for cases that cannot be managed medically or through less invasive means.[12-14] In one study, average IOP was lowered from 40mm Hg to 15mm Hg.[12]

Clinical Pearls

- A complete medical history is necessary for successfully managing hyphema.
- If the dilated view of the posterior segment is obscured, B-scan ultrasonography is indicated to ensure the absence of vision-threatening retinal pathology.
- Eyes presenting with traumatic hyphema must be evaluated for ruptured globe, orbital fracture, retinal detachment and systemic bleeding disorders which might exacerbate the condition.
- Gonioscopy increases the risk of rebleed and is contraindicated.
- Gonioscopy should be performed following resolution to assess the angle's status and formulate a risk profile for late traumatic glaucoma.
- Oral analgesic medications must be limited to those that do not have anti-platelet effects (no aspirin or NSAIDs).
- Aminocaproic acid or traexamic acid antifibrinolytic therapy remains variably used throughout the community. It can serve as an adjunct in cases experiencing rebleeding.

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DIURNAL CONTROL OF INTRAOCULAR PRESSURE IN OPEN-ANGLE GLAUCOMA

It has been shown through well-performed clinical trials that lowering of intraocular pressure (IOP) prevents or delays progressive glaucomatous damage.[1,2] Ideally, IOP should be lowered consistently at all times in order to affect the best outcome and prognosis for patients. Typically, measurement of IOP occurs during office hours with the patient seated upright in the exam chair. Often, several IOP measurements would be taken on separate days, preferably at different hours in the morning and early and late afternoon in order to understand the diurnal trend of each patient.

It has long been thought that IOP tends to be highest in the early morning and decreases throughout the day in most individuals. It was postulated that IOP was lowest while patients sleep, due to a reduction of aqueous production. However, this information typically came from studies performed in clinical settings during normal office hours.

Newer information has provided a better assessment of what actually happens to IOP during the full diurnal cycle. Nakakura and colleagues examined patients with glaucoma being treated with three IOP-reducing medications (latanoprost, a beta blocker, and a topical carbonic anhydrase inhibitor) and, using Goldmann tonometry with the patients sitting upright, found that the peak IOP occurred during the night outside of typical office hours in 61% of tested eyes.[3]

Liu and colleagues, in an effort to better identify natural diurnal IOP values, used a sleep laboratory where trained observers using night vision goggles and a pneumotonometer, could measure IOP with patients sitting upright in the 16-hour waking cycle and supine during the eight-hour sleep period.[4-6] Measurements of IOP were taken every two hours in the sitting position during the diurnal/wake period (7:00 a.m. to 11:00 p.m.) and in the supine position during the nocturnal/sleep period.[4-6] In contrast to the previous thinking that IOP was lowest during the sleep period, they found that IOP actually peaked during this time.[4-6] This was true for healthy patients as well as for those with glaucoma.[7] The reason for this finding is not clear, but it is postulated that, when patients are supine, there is a gravitational effect increasing episcleral venous pressure. In order for aqueous to flow, there must be a pressure differential with IOP highest in the posterior chamber, reducing in the anterior chamber, reducing further in Schlemm's canal and beyond. As episcleral venous pressure rises, the resistance to aqueous outflow increases. The result is an IOP that rises until it can overcome the backpressure and reestablish forward flow.

If the IOP is highest when patients sleep in the supine position, it is likely a person's highest IOP measurement will remain undiscovered. However, we can speculate that the pressure measured during typical office hours possibly reflects their lower range of the diurnal IOP, reasoning that IOP is likely higher when patients sleep supine. Knowing that IOP is highest while patients sleep supine, it becomes imperative to choose therapies, both primary and adjunctive, which demonstrate effects evenly throughout the 24-hour cycle.

It has been well shown that prostaglandin analogs are excellent in reducing IOP both during waking hours as well as during the supine sleep cycle.[8,9] This could possibly be explained by the fact that prostaglandin analogs increase aqueous outflow through the uveoscleral pathway, which is independent of episcleral venous pressure. Nomura and associates and Sit and colleagues found a sustained IOP-lowering effect of travoprost throughout the 24-hour diurnal cycle.[10,11]

What is less certain are the effects of other therapies in the 24-hour diurnal cycle. Liu and associates observed that although 0.1% brimonidine monotherapy significantly lowered IOP during the diurnal/wake period, it did not significantly lower IOP during the nocturnal/sleep period.[12] Similarly, once-daily gel-forming beta blocker monotherapy failed to provide IOP reduction from the untreated baseline during the sleep cycle though IOP was significantly reduced during the day.[8]

When choosing adjunctive therapy to prostaglandin analogs, considerations for sleep time effects are warranted. It has been shown that, while brinzolamide and timolol added to latanoprost have similar ocular hypotensive effects during the waking cycle, only brinzolamide seems to have an additional adjunctive effect during the sleep cycle while timolol does not.[13-15] Curiously, the opposite effect was seen with laser trabeculoplasty as an adjunct to medical therapy. In a group of medically treated open-angle glaucoma patients, laser trabeculoplasty reduced IOP more consistently during the supine sleep cycle than during the upright diurnal time period.[16]

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DIABETIC RETINOPATHY

Signs and Symptoms

Diabetes mellitus is a disease of broken glucose metabolism.[1-26] A microvascular disease, it primarily effects the capillaries. In the eye, its effects are far reaching, altering the blood vasculature in the conjunctiva, the neurologic homeostasis of the cornea, the blood vasculature of the iris, the fluid dynamics of the lens and the capillary network of the retina and nerve.[1-20] It also has the potential to affect the central nervous system and the cranial nerves—notably II, III, IV, V, VI, and VII.[15-20] In most instances, patients remain asymptomatic. Symptoms manifest ocularly when architectural alterations impact the macular area producing reduced acuity or when vitreous hemorrhage or tractional retinal detachment induce catastrophic vision loss or when ischemic-vascular pathophysiology alters cranial nerves to produce ophthalmoplegia or lagophthalmos.

An early symptom is fluctuating visual acuity.[13] Increased myopia is most common (myopic shift) but hyperopia is possible.[13,14] While previously thought to be a process secondary to unstable blood sugar, recent reports suggest that refractive variation is secondary to overall disease decompensation rather than fluctuating glucose levels alone.[13,14] Swelling within the crystalline lens can also produce large sudden shifts in refractive error as well as premature cataract formation.[15] Changes in visual acuity will depend upon the severity and stage of the disease. Other subtle ocular signs include injected bulbar conjunctivae and neovascularization of the iris (rubeosis irides) with or without ectropion uvea.

In the retina, weakening of the arterioles and capillaries results in the characteristic appearance of intraretinal dot and blot hemorrhages, exudates, intraretinal microvascular abnormalities (IRMA), edema and cotton wool infarcts. Proliferative diabetic retinopathy occurs as a result of severe ischemia and manifests as neovascularization of the disc (NVD), neovascularization elsewhere in the retina (NVE) and neovascularization of the iris (NVI).[1-12,21,23-26]

Systemically, patients may complain of unexplained weight loss despite a larger than normal appetite (polyphasia), abnormal thirst (polydypsia) and abnormally frequent urination (polyuria).[22]

Pathophysiology

Diabetes mellitus is a genetically influenced group of diseases that share glucose intolerance.[1-4] It is characterized as a disorder of metabolic dysregulation as a result of deficient or malfunctioning insulin or deficient or malfunctioning cellular insulin receptors.[1-27] Two forms of retinopathy emerge from the complications of this process that impair retinal autoregulation: nonproliferative diabetic retinopathy and proliferative diabetic retinopathy.[1-12,23-27]

Nonproliferative diabetic retinopathy is characterized by capillary compromise, intravascular microaneurysms, IRMA, intraretinal hemorrhages (dot and blot hemorrhage), intraretinal lipid leakage (exudates), nerve fiber layer infarction with axonal stasis (cotton wool patches) and the leakage of plasma-based fluid (retinal/macular edema).[1-12,23] Sustained hyperglycemia creates elevated levels of biologically active compounds that include diacylglycerol, histamine, advanced end-products of glycation, lipoxygenase and nitric oxide. These chemical mediators trigger the release of protein kinase C and endothelin as well as directly induce oxidative damage to vessels.[23] They also directly destabilize the chemistry of the vitreous humor.[23] The result is vascular vasoconstriction, hypoxia and the concomitant release of interleukin-6 along with the accumulation of pathological acidic proteins in the vitreous.[23] Interleukin-6 and these acidic proteins inspire the release of vascular endothelial growth factors and increase direct vitreoretinal adhesions.[23] As the traction builds and retinal vascular endothelial junctions are overcome by the chemokines, the inner blood retinal barrier becomes compromised and intraretinal leakage ensues.[23] The influx of water across the blood retinal barrier cannot be compensated for by the retinal pigment epithelium and fluid accumulates.[23]

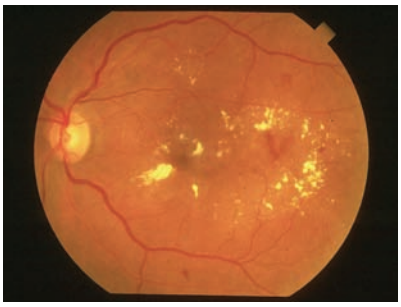
Simultaneously, the polyol pathway enables the formation of sorbitol, a toxic byproduct of glucose metabolism, to form in large quantities. Sorbitol poisons the supportive capillary pericytes, which further induces vascular leakage.[23] When fluid accumulates within the boundaries articulated by the National Eye Institute of National Institutes of Health's Early Treatment of Diabetic Retinopathy Study (ETDRS), the fluid accumulation is considered to meet the criteria of what the study termed *clinically significant macular edema* (CSME).[8-11,23]

Proliferative diabetic retinopathy is the result of chronic, untreated diabetic retinal disease. Here, thickened, glucose-laden blood, prolonged vascular insufficiency, capillary nonperfusion, retinal hypoxia and altered structure induces the formation and release of vasoproliferative factors (vascular endothelial growth factor-A: VEGF-A) that play a role in the genesis of retinal neovascularization.[5,6,23] Pigment epithelial derived factor (PEDF), secreted by adipocytes (adipokine), is a natural antiangiogenesis molecule that also promotes pericyte health.[23-26] PEDF is secreted less as the hyperglycemic condition persists, permitting hypoxia and tumor necrosis factor to rise.[24-26] Other growth factors known to participate in the

pathogenesis of neovascular growth include platelet derived growth factor (PDGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF), transforming growth factor (TGF), placental endothelial cell growth factor (PlGF) and connective tissue growth factor (CTGF).[26] Other associated molecules include integrins, angiopoietins, protein kinase C (PKC), ephrins, interleukins, leptin, angiotensin, monocyte chemotactic protein (MCP), vascular cell adhesion molecule (VCAM), tissue plasminogen activator (TPA) and extracellular matrix metalloproteinases (ECM-MMPs).[26] The result of this complicated cascade is the formation of fragile fibrovascular vessels (neovascularization) that scaffold onto the posterior hyaloid surface of the vitreous, creating traction, increasing the risk of vitreous hemorrhage and tractional retinal detachment.[1,5,6,28-30] Proliferative vitreoretinopathy is associated with severe vision loss.[1,5,6]

Management

When retinal findings consistent with diabetes are found in an undiagnosed individual a Fasting Blood Glucose (FBS), Glycosylated hemoglobin and Oral Glucose Tolerance Test (OGTT) should be ordered from a general medical practitioner.[31] A physical examination should also be recommended to determine general health status as hypertension and dyslipidemia are associated accomplices.[32] Researchers have hypothesized that low levels of erythropoietin (EPO), a glycoprotein hormone that controls erythropoiesis or red blood cell production may place patients at increased risk for retinopathy development.[32] EPO is locally expressed and has been correlated with increased VEGF levels in eyes with diabetic macular edema and work is underway to assess the benefit of EPO injection.[32]



Non-proliferative diabetic retinopathy, displaying extensive exudates, dot/blot hemorrhages and macular edema.

Most of the mild non-vision-threatening ocular sequelae of diabetes resolve spontaneously over the course of weeks to months following medical control. In cases where there are large refractive changes, patients may require a temporary spectacle prescription until the refractive status of the eyes stabilize. The most important element of this management is education so that patients are informed that there may be a need to change the lenses as the condition evolves. Even retinal findings can be minimized and resolved when tight systemic control is maintained.[1,7,12] When retinopathy threatens the macula and subsequently visual acuity, or when new blood vessels proliferate, laser photocoagulation and other retinal surgical modalities are recommended.[1-12]

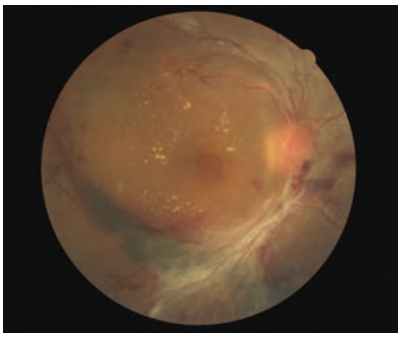
The Diabetic Retinopathy Study (DRS) has conclusively proven that panretinal photocoagulation (PRP) is successful for reducing the risk of severe vision loss in patients with PDR.

The ETDRS has conclusively shown that focal/grid laser photocoagulation reduces the risk of moderate vision loss in patients with CSME.[8-11] The ETDRS defined CSME as: (1) retinal thickening at or within 500 µm (1/3 of a disc diameter) of the center of the foveola, (2) exudate at or within 500 µm of the center of the foveola only if associated with retinal thickening or (3) an area of retinal thickening one disc diameter or greater in size, within one disc diameter of the foveola.[8-11] If any of these criteria are discovered or suspected, regardless of the acuity, a referral to a retinal specialist is warranted.[8-11]

New additions to the standard traditional treatment regimens include treating patients who have significant retinopathy prior to cataract extraction with grid laser and/or anti-VEGF injection. This can be done at the time of cataract extraction with simultaneous injection of steroid and anti-VEGF medication. It is also now recommended to use intravitreal anti-VEGF medications for proliferative retinopathy along with PRP and vitrectomy, as well as of intravitreal anti-VEGF medications or steroids as a pretreatment for focal/grid laser photocoagulation and the use of strategic vitrectomy (viscosurgery) for severe proliferative diabetic vitreoretinopathy.[33-42]

Clinical Pearls

- CSME is a visual acuity independent finding and can exist in the presence of 20/20 vision.
- CSME is traditionally identified through observation, using stereoscopic indirect biomicroscopy (60.00 D, 78.00 D, 90.00 D, Hruby lens or 3 mirror lens); however, optical coherence tomography (OCT) can confirm suspected cases or identify subtle thickening not detectable with observation alone.[43] OCT technology can also be used to track macular edema resolution following treatment.[44]
- Fluorescein angiography is a technique used for treatment. It identifies the areas of leakage that require focal grid laser photocoagulation after CSME has been diagnosed by stereoscopic indirect biomicroscopic observation. Prophylactic laser photocoagulation to prevent proliferative retinopathy has been proven to be contraindicated.[1,5,6]



Proliferative diabetic retinopathy, displaying fibrovascular proliferation, tractional retinal detachment and vitreal hemorrhages.

• It should also be remembered that the development of diabetic retinopathy is time dependent. Even in the face of optimal blood sugar control, patients with long-standing disease can be expected to develop some form of retinopathy eventually.

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CENTRAL SEROUS CHORIORETINOPATHY

Signs and Symptoms

Patients with central serous chorioretinopathy (CSC) usually present with complaints of sudden onset dis-

tortion or blurring of central vision. They may report metamorphopsia, decreased color perception, or even a relative central scotoma. The presentation is typically unilateral, although bilateral cases have been reported, and the likelihood of subsequent involvement of the fellow eye may be as high as 40%.[1-3] There is typically no pain and no history of recent trauma. Patients often have a history of using corticosteroids (topical, injectable, or oral), sympathomimetic agents, or medications for erectile dysfunction.[1-9] Other contributory elements may include antibiotics, uncontrolled hypertension, alcohol, allergic respiratory disease and obstructive sleep apnea.[2,10] However, steroids are considered to be the greatest precipitating factor, at least from an exogenous point of view.[2]

Patients with CSC are typically younger, with most cases occurring between the ages of 25 and 50.[11] According to one report, the mean age at diagnosis is 41 years.[12] Men are afflicted far more frequently than women, with an incidence ratio of about 6:1.[1,2,12,13] There are few, if any, racial predilections. Patients of European and Asian descent appear to be affected equally.[1,2,14] Reports differ regarding those of African descent; some sources suggest that these individuals are diagnosed less frequently with CSC, while others report no differences.[1,15] Perhaps the most well-known association with CSC is the psychological profile known as "Type A" personality. These individuals, who are described as exhibiting the characteristics of time urgency, aggressiveness, hostility and competitiveness, seem to be particularly predisposed to developing CSC.[16-19]

Clinical evaluation of the patient with CSC reveals no external signs of ocular disease or inflammation. Mild hyperopic refractive shift (+1.25 or less) is often noted in the affected eye. Funduscopic examination shows a distinct, round or oval serous elevation of the macula with a loss of the foveal light reflex. An underlying area of RPE detachment may be seen concurrently in about 10% of patients.[20,21] Associated findings can include cystoid macular degeneration, retinal atrophy, and RPE tears (sick RPE or gutter syndrome), especially in chronic cases.[22-24] There exists the possibility of choroidal neovascularization (CNV) as well.[25,26] Cases involving CNV are typically associated with a poor visual outcome. Today, optical coherence tomography (OCT) is often used to confirm the diagnosis of CSC. OCT classically shows a bullous neurosensory retinal detachment from the underlying choroid, separated by an optically empty zone. Fluorescein angiography will typically demonstrate a focal point of fluorescein leakage under the serous detachment that gradually expands to fill the entire lesion; it is sometimes referred to as a "smokestack" or "ink blot" hyperfluorescent pattern.[1]

Pathophysiology

While a great deal of research has been conducted in this area, CSC remains incompletely understood. CSC appears to have a multifactorial etiology, with various systemic associations and a complex pathogenesis. The primary dysfunction appears to be localized ischemia and/or inflammation at the level of the choriocapillaris, which leads to hyperpermeability; this in turn results in decompensation of the retinal pigment epithelium, causing a focal detachment of the overlying neurosensory retina.[19,20] Biochemical changes are likely at the root of this process. In patients with CSC, serum levels of catecholamines and glucocorticoids appear to be elevated, and this is believed to have a direct influence on the integrity of Bruch's membrane.[17-19,27] Based on these observations, it is reasonable to speculate that adrenergic receptors within the choroidal circulation are involved in the pathogenesis of CSC. Stimulation of adrenergic receptors often results in release of secondary messengers, (e.g., cyclic adenosine monophosphate) and this may produce the vascular or RPE changes that result in CSC.[28]

Recently, an association between CSC and *Helicobacter pylori* has been reported.[29-30] *H. pylori* is a gram negative bacterium that resides in the gastrointestinal tract; it has been associated with a number of ocular conditions including dry eye, ocular rosacea, adnexal tumors and several forms of glaucoma.[31] Researchers have proposed that the immune responses generated against *H. pylori* result in the genesis of antibodies and proteins that have the capacity to alter the endothelial vascular wall.[29] Such processes may contribute to the development of CSC in some patients.

Management

Most cases of CSC are self-limiting over a period of three to 12 months.[1,11] The prognosis for visual recovery is excellent, with most regaining their pre-event acuity. Upon diagnosing the condition, any corticosteroid therapy should be immediately discontinued, if possible. A consultation with the patient's primary care physician may be indicated in cases involving steroidal anti-inflammatory agents for systemic conditions and steroidal inhalers for asthma. Fully 90% of CSC cases resolve spontaneously following the cessation of steroids.[32] While the acute phase of CSC is usually self-limiting, the condition may be recurrent in as many as 50% of affected individuals.[33] These patients often demonstrate cystic yellow lesions in the macula known as lemon-drop nodules. Lemon-drop nodules are indicative of mild RPE

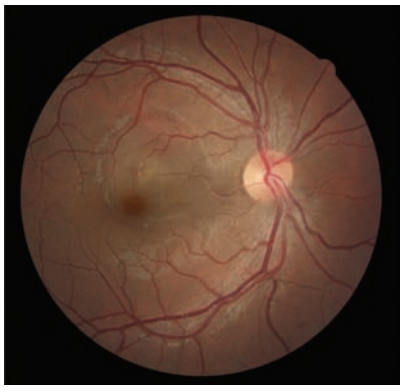
detachment. They may also stimulate RPE hyperplasia.

In non-remitting or recurrent cases, focal laser photocoagulation has been utilized in an attempt to arrest the leakage.[34] Laser debridement of the damaged RPE allows adjacent RPE cells to assume their function at the site of the lesion.[1] However, focal laser therapy does not necessarily ensure improvement in visual acuity; it merely hastens recovery and diminishes the likelihood of recurrence.[1,34] There are risks associated with this treatment, most notably iatrogenic damage to the fovea and subsequent formation of CNV.[1,25,26] For these reasons, most practitioners will employ laser therapy only in cases that fail to respond within a reasonable period of time, recurrent cases, or cases in which the patients are overtly symptomatic and insist on definitive treatment.

Photodynamic therapy (PDT) with verteporfin has also been used successfully in the treatment of CSC; it has been demonstrated to improve visual acuity, reduce leakage on fluorescein angiography, reduce subretinal fluid as demonstrated by OCT and foster choroidal remodeling with decreased choroidal permeability.[34-36] Other experimental treatments for CSC have shown modest success, including anti-VEGF treatment and transpupillary thermotherapy.[37,38] Oral therapy with corticosteroid antagonists, adrenergic receptor antagonists and carbonic anhydrase inhibitors (e.g., acetazolamide) has also been documented, but with limited efficacy.[1]

Clinical Pearls

• An experienced, astute clinician can often diagnose CSC based solely upon the history and chief complaint. A young, anxious, otherwise healthy patient who presents with unilateral metamorphopsia of recent onset represents the classic presentation for CSC.



Bullous macular elevation in central serous chorioretinopathy.

• Patients presenting with CSC for the first time should be reassured, counseled as to the natural course of the condition, and monitored every three to four weeks for three to six months as resolution occurs. A referral to retinology is indicated to rule out the need for fluorescein angiography. If the patient fails to resolve after six months, one should consider more aggressive therapy, i.e., laser photocoagulation, PDT, or anti-VEGF.

• While CSC is classically thought of as a male disorder, it must be noted that both genders may be affected. Women account for between 12% and 28% of the affected population.[39,40] Moreover, pregnancy is a recognized risk factor for CSC, with an identified odds ratio of 7.1 in a case-control study of 312 patients.[2] Hence, it is important to consider this condition in pregnant women who present with sudden onset of visual complaints.

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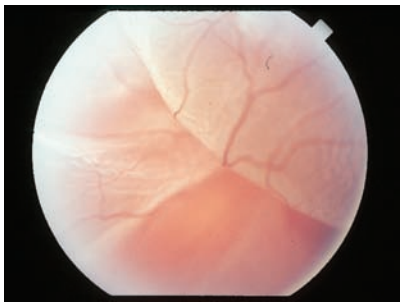
RETINAL DETACHMENT

Signs and Symptoms

Retinal detachments occur in approximately 6.1:100,000 persons in the general phakic population.[1-3] The rates between men and women are similar world wide, with a slight preponderance for female gender with myopia.[2-4] There are three recognized forms of retinal detachment.[1-9] These include: **rhegmatogenous** retinal detachment (RRD-resulting from a retinal break), **exudative** or **serous** retinal detachment (ERD-resulting from fluid accumulation under the sensory retina without a retinal break) and **tractional** retinal detachment (TRD-resulting from the pull of proliferative fibrovascular vitreal strands).[1-10] Any type of retinal detachment may be initially asymptomatic. Rhegmatogenous retinal detachments may remain asymptomatic up to discovery.[11,12] In symptomatic RRD, patients report photopsiae (flashes of light), floating spots, peripheral visual field loss (curtain phenomenon) and depending upon the involvement of the macula, central blurring of vision with or without metamorphopsia.[1,13] There are anecdotal reports of exudative retinal detachments producing photopsiae (flashing purple lights) but the common symptoms experienced by these patients are vision loss and metamorphopsia consistent with the degree of macular involvement, with or without a visual field deficit.[5,14]

Tractional retinal detachments have the capacity to produce the same symptoms as rhegmatogenous and exudative retinal detachments. They may also remain asymptomatic until central vision is threatened.[5,15] Pain is not a feature of any retinal detachment as the tissue has no pain receptors. In fact, the only sensory receptors in the retina are for light; hence the sensation of flashing lights experienced by patients from mechanical vitreoretinal tractional forces.[12] Any pain encountered by a patient experiencing any form of retinal detachment is secondary to an associated cause such as headache, iritis, corneal abrasion, uveitis or raised intraocular pressure and not the detachment itself.[1,5,16,17] Extensive unilateral retinal detachment will produce a relative afferent pupillary defect.[1,16] Intraocular pressure may be notably reduced in eyes with acute retinal detachment.[19-21]



Bullous, rhegmatogenous retinal detachment.

Clinical observation of fresh RRD usually reveals a clumping of pigment cells within the vitreous (Shaffer's sign/tobacco dust) adjacent to the retinal break.[1,22] An area of white or grayish elevated retina may be seen adjacent to the instigating retinal break secondary to influx of subretinal fluid (SRF).[4] If a significant area of the retina is involved it may appear bullous and undulating. A rhegmatogenous detachment is produced by a retinal break that allows liquefied vitreous to separate the sensory retina from the retinal pigment epithelium (RPE) through poorly understood posterior segment fluid mechanics.[21] Osmotic and oncotic pressures help keep the retina in place.[22] As such, RRD do not change positions when body posture is altered.[23] RRD do shift and return to their original orientation with quick eye movements.[1] Associated findings of RRD may include posterior vitreous detachment and preretinal or vitreal hemorrhage.[24-26] Retinal pigment epithelial hyperplasia may be noted in cases of long-standing retinal detachment of any kind (pigment demarcation line). Increased RPE density is a feature of attempted self repair.[1,5,27]

ERD appear as focal, serous elevations of the retina in the absence of retinal breaks.[5,28-34] Because the fluid

is contained underneath an intact neurosensory boundary, the bullous separation possesses the characteristic of following gravity, shifting position with changes in posture and eye movement.[1,5] Ophthalmoscopic observation reveals a smooth, translucent, dome-shaped protrusion of the retina along with variable other signs secondary to the causative etiology (blood, exudate, or serosanguinous fluid).[5] Causes of ERD include Coats' disease, age-related macular degeneration, idiopathic central serous chorioretinopathy (ICSC), fluid exudation from chroidal tumors and Vogt-Koyanagi-Harada syndrome, among numerous others.[5,28-34]

TRD is always associated with fibrovascular vitreal strands and membranes.[1,35-37] The clinical appearance of these detachments is varied with tangential fibrovascular bands anchoring into the vitreous body and extending to the dis-inserted retina.[1,35-37] The tractional membranes may encircle intact retina, resulting in a "pseudo-hole" appearance. TRDs are dense and immobile, as compared with ERD and RRD. Any pathology that can induce posterior segment ischemia and retinal neovascularization can proceed to TRD. The common underlying causes include diabetes, vein occlusion, ocular ischemic syndrome, retinopathy of prematurity and sickle cell disease.[35-39]

Pathophysiology

All retinal detachments involve a dissection of the sensory retina from its underlying RPE layer by SRF.[1-40] In rhegmatogenous detachments this fluid is thought to be composed of liquefied vitreous, which gains access to the subretinal space via a retinal break.[1,22] In exudative detachments, the fluid is derived from the choroid, passing through a breach in Bruch's membrane.[5,28-34] The origin of the subretinal fluid in tractional retinal detachments is similar with slightly varied mechanisms. Generally, altered balance between the passive and active movement of SRF induces RD progression.[1] While all retinal detachments have the potential to produce visual scotomata (depending upon their size and location), it is the involvement of the macular region, where apoptotic mechanisms deteriorate macular photoreceptors, that will determine the extent of acuity loss.[40]

Retinal breaks are the predisposing factor in patients with rhegmatogenous retinal detachment.[1,22-27] These may occur spontaneously from preexisting conditions or as a result of ocular trauma.[1-3] Some of the common entities associated with RRD include lattice degeneration, flap tears, atrophic holes, operculated retinal breaks and acquired retinoschisis with both inner and outer holes.[1,3,4,41] As the retinal tissue loses its connection to the RPE, it becomes edematous and dysfunctional.[22] The detached retina loses its oxygen supply and relies on anaerobic pathways to metabolize glucose.[22] Long-duration retinal detachments feature increased lactic acid and dextrose concentrations.[23] Phospholipids are also increased in the SRF, reflecting retinal organelle degradation.[23] Eventually, photoreceptor death occurs within 48 to 72 hours unless surgical intervention is employed.[23,40]

Exudative retinal detachments occur in association with subretinal disorders which damage the RPE layer.[5,28-34] Transudation of fluid from the choroidal reservoir through Bruch's membrane and a breach in the RPE overcomes the eye's natural mechanisms for deturgescing the plasma solution, causing it to build under the photoreceptors. When the threshold is reached it causes them to disinsert from the RPE.[5,23,28-34] Affected by gravity, as the fluid accumulates, the detachment will shift with eye and head movements. However, since the density of fluid affecting the retina changes with movement, no particular area of the retina is continuously affected.[5] This may explain why patients with ERD have final functional outcomes that are better than those with RRD or TRD.[5,28-34]

Tractional retinal detachments occur in the presence of proliferative vitreoretinopathies.[1,35-39] The etiology of TRD involves fibrotic scaffolding of the vitreous along proliferative vascular networks, which through vitreal shrinkage, induce strong anterior tractional forces.[39,42-44] RPE cell proliferation and migration are believed to play a role in the pathogenesis.[43] Findings suggest that the vitreous contributes modulators that stimulate RPE cells along with macrophages, fibroblasts and glial cells to interact with constituents of the extracellular matrix such as fibronectin, vitronectin, and factor XIII.[43,44] These mechanisms induce the formation of membranes that capture the sensory retina and forcibly separate it from the underlying RPE.[39,42-44] Unlike rhegmatogenous or exudative retinal detachments which tend to occur acutely, TRD often develop slowly. When positioned peripherally TRD may not be noticed by the patient until visual acuity is compromised by the underlying disease process.

Management

Retinal detachments demand repair and treatment of both the retina and the underlying cause.[1-49] Patients presenting with an acute onset RRD involving or threatening the macula warrant an immediate and emergent referral to a retinal surgeon. Fresh RRD should be repaired within 24 to 48 hours; chronic or long-standing RRD or RRD that do not threaten the macula should be addressed within one

week of diagnosis.[50,51] Small peripheral RRD secondary to atrophic holes or RRD secondary to small tears displaying minimal SRF may be managed with barrier laser photocoagulation or cryopexy.[1,45-49] While cryopexy has been reported to provoke a more aggressive postoperative inflammatory response, its outcomes over time compared to laser barrier treatment are similar.[49] An advantage of cryopexy over laser procedures is that it is generally less expensive and does not have to be repeated.[49] Larger RRD require surgical repair using procedures that include vitrectomy, scleral buckling, needle aspiration, laserpexy, cryopexy, pneumatic retinopexy and intraocular silicone oil tamponade.[13,52-55]

Vitrectomy has been investigated as a principle treatment method for RRD.[56-58] Vitrectomy seems to allow improved control of more complicated situations.[57] The Scleral Buckling vs. Primary Vitrectomy in Rhegmatogenous Retinal Detachment Study (SPR study) is a prospective, randomized, multicenter study comparing primary vitrectomy with or without additional scleral buckling to scleral buckling alone.[56,58] In the pseudophakic subgroup, no difference in functional outcome was seen; however, better anatomical results with a lower rate of retina-affecting reoperations was observed in the vitrectomy group.[56-58] Based on this data, primary vitrectomy combined with a scleral buckle is the method of choice in complicated retinal detachment in pseudophakic patients. In contrast, primary vitrectomy does not seem to offer an advantage over scleral buckling in phakic patients.[56,58] The primary drawback of vitrectomy is its significant propensity to create cataract and postpone complete visual recovery.[58]

Scleral buckling is accomplished under general anesthesia where a soft silicone sponge or hard silicone band is used to indent the eye at the location of detachment.[59] The intent of the buckle (explant-on top of the sclera, implant-placed into a scleral dissection) is to eliminate the vitreoretinal traction that induced the retinal tear and to prevent fluid seepage underneath the retinal break.[1,59] This process also encourages RPE pumping to eliminate the SRF. Drainage of SRF via syringe is controversial with some believing it is not necessary and others believing it is crucial.[58] Raised IOP, choroidal detachment, diplopia, macular edema and macular pucker are all potential complications.[59]

Pneumatic retinopexy utilizes an intravitreal gas bubble (usually perfluoropropane, C_3F_8 or sulfahexafluoride) to achieve reattachment of the retina for RRD.[60-62] This technique is performed under local anesthesia and is more common for treating smaller, superiorly located RRD.[60] Careful eye and head positioning are important postoperatively to ensure resolution.[60] In certain instances, silicone oil tamponade may be favorable to either of the aforementioned techniques.[63] The use of polydimethylsiloxane (PDMS) as a silicone oil endotamponade has become a standard in retinal surgery.[63] In cases of complicated inferior and posterior retinal detachment heavy silicone oils are sometimes considered.[63] A randomized prospective clinical trial (HSO study) comparing heavy and standard silicone oil in patients with PVR of the lower retina have failed to demonstrate superiority of a heavy oil tamponade.[64]

Exudative detachments, because of their nature, generally require less intervention than RRD.[5,7] ERDs may resolve spontaneously or following management of the underlying condition.[5,7,23,28-34] This may involve oral antibiotics in cases involving infection, high dose oral or vitreal injectable/implantable corticosteroids in the case of inflammatory disorders, oral acetazolomide in cases of ICSC and radiation therapy and/or local resection in the case of intraocular neoplasms.[65-67] In cases involving choroidal neovascularization laser photocoagulation, photodynamic therapy and vascular endothelial growth factor inhibitor injections may all be used.[65,68]

Tractional retinal detachments are more difficult to manage than either RRD or ERD. Managing the underlying cause is an essential precursor.[39,35-37] Endolaser scatter photocoagulation must be employed directly to the retina to correct the underlying inciting retinal cause for new vessel growth.[39] Surgical repair of TRD involves pars plana vitrectomy to remove the traction and the fibrovascular membranes along with the inciting vitreal cytokines. Gas or oil tamponade is used to promote retinal reattachment.[63,64,69]

Clinical Pearls

- All patients presenting with symptoms of retinal detachment or a predisposing history (peripheral retinal thinning or breaks, blunt ocular trauma, proliferative diabetic vitreoretinopathy, etc.) must undergo a thorough dilated fundus evaluation, with scleral indentation where appropriate.
- Fresh rhegmatogenous detachments should be immediately referred for evaluation of surgical intervention.
- The effect of gravity increases the risk for superior detachments to spread.
- Conservative surgical management may be indicated for partial or sectoral RRD (laser barrier).

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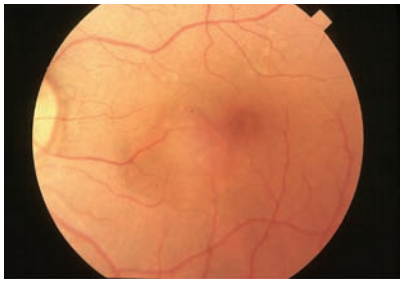
RETINAL PIGMENT EPITHELIAL (RPE) DETACHMENT

Signs and Symptoms

Serous retinal pigment epithelial detachment (PED) occurs when the retinal pigment epithelium (RPE) becomes separated from the Bruch's membrane.[1-6] The process occurs asymptomatically unless the macula is affected. It is often associated with diseases that can produce choroidal neovascularization.[1-6] Concurrent ocular conditions such as age-related macular degeneration (AMD), polypoidal choroidal vasculopathy (PCV), retinal angiomatous proliferation (RAP), idiopathic central serous chorioretinopathy (ICSC), ocular histoplasmosis syndrome (OHS) or vitreomacular traction syndrome (VMTS) are common associations.[7-12] PED is also an associated complication of laser photocoagulation and vascular endothelial growth factor (VEGF) inhibitor injection.[2,13,14] Systemically, tubulointerstitial nephritis and uveitis syndrome (TINU) has been linked to posterior segment features that include bilateral vitritis and RPE detachments.[15] The condition has also been documented to occur idiopathically.[16,17] Patients who experience PED within the macular area will report sudden, painless blurry vision, metamorphopsia, micropsia or positive scotomas.[1-6] Other associated clinical and epidemiologic findings will depend upon the underlying cause. For example, in cases involving ICSC males outnumber females with many patients experiencing hyperopia and delayed retinal recovery time upon photostress test.[18,19]



Focal RPE detachment nasal to the macula.

The ophthalmoscopic appearance of PED will depend upon its etiology.[1-17,20] Each clinical and fluorescein angiographic likeness is unique to the specific cause.[20] A PED caused by subretinal hemorrhage will appear as a small, dark, elevated subretinal nodule and will demonstrate a fluorescein pattern consistent with blockage throughout the angiogram.[20] Serous PED appears as a single, creamy yellow, well-circumscribed round or oval subretinal lesion demonstrating a fluorescein pattern of fast filling hyperfluorescence contained within the boundaries of the attached RPE.[20] Drusenoid PED appear similar to coalesced soft drusen and demonstrate a fluorescein pattern of staining with fading over the course of the angiogram without evidence of leakage or ooze.[20] Fibrovascular PED exhibit mottled and elevated subretinal irregularities with fluorescein patterns that demonstrate a slow stippling hyperfluorescence that increases in size and intensity over the course of the angiogram.[20] There may be pooling of the dye in the recirculation phase with evidence of lacy-leakage in cases that have occurred secondary to choroidal neovascularization (CNV).[20] Overlying RPE defects (clumping or mottling) are commonplace in cases of longstanding PED that have spontaneously resolved. Lesions may vary in size from 1/5 of a disc diameter (DD) to over 5 DD, but most are less than 1 DD.[2,3,5-7,9-14,16,17,20,21] The small size is due to the fact that the RPE is tightly adherent to Bruch's membrane and fluid does not easily extravasate between these two layers. Leakage into the neurosensory retina occurs only in cases of concurrent RPE junction failure with central serous retinal detachment.[1,4,9,19]

Pathophysiology

RPE detachment is a non-specific anatomical alteration that may result from any number of vitreo-choroidal disorders.[1-24] A definitive pathomechanism underlying the development of PED has not yet been completely elucidated.[24] One theory suggests that the PED separates from Bruch's membrane as a result of increased choroidal pressure.[24] A contrasting view, related to AMD, is that CNV forms and contracts producing scarring, which in turn produces a secondary tractional tear.[24] An alternative pathogenetic theory hypothesizes that an underlying disease (or idiopathic condition) sets the stage for reduced hydraulic conductivity of Bruch's membrane.[10,11,22,23] Here, increased deposition of lipids, fibrin, enhanced collagen cross-linking and alteration in the ratio of tissue-dissolving enzymes and their inhibitors contribute to the RPE release.[10,22,23] Serous PED result from idiopathic, AMD-related and ICSC etiologies. In selected cases the mechanics of neovascular vessel formation produces fibrovascular PED.[23,24] In cases where the pathophysiologic

mechanisms are amplified by subretinal neovascular or capillary rupture, hemorrhagic PED ensue. When soft lipofuscin coalesce to create an environment that erodes the RPE barrier junction, drusenoid PED occur.[10,20]

Ischemia and hypoxia have been implicated in the pathophysiology of AMD. These processes share a possible common thread in the pathogenesis of PED.[22] The common pathologic feature of all diseases that produce PED is impaired retinal oxygen metabolism.[22] Confluent drusen, serous or hemorrhagic retinal detachment, retinal edema, vitreoretinal adhesion and other disease processes may all contribute to relative retinal hypoxia by increasing retinal elevation and the retinal distance from the choriocapillaris.[22] This mechanism results in impaired diffusion and convection of oxygen towards the retina.[22] Hypoxia-inducible-factor is known to exist in subretinal neovascularization and hypoxia is the main stimulus for the production of VEGF.[22] Further, thickening of Bruch's membrane and any detachment of the retina or RPE increases the distance between the choriocapillaris and the retina, reducing the oxygen flux from the choroid to the outer retina.[22] Retinal elevation and choroidal ischemia can combine forces to reduce choroidal oxygen delivery to the outer retina and produce retinal hypoxia.[22] Hypoxia leads to production of VEGF leading to neovascularization and tissue edema, creating the potential for RPE breakdown, PED and a cycle that has the potential to result in CNV formation before or after PED.[22]

An interesting association has recently surfaced linking ICSC with the *Helicobacter pylori* (HP) infection.[25] In one case, a recurrence of ICSC was associated with HP-positivity and improvements of both retinal findings and visual acuity were significantly correlated with a successful eradication of the bacterium.[25] In a second case, the prevalence of HP infection was found to be significantly higher in ICSC-affected subjects compared to age- and sex-matched controls from the same country.[25] ICSC seems to be a disease of choroidal microcirculation dysfunction.[25] In fact, several vascular abnormalities, such as localized vasoconstriction and impaired fibrinolysis have been demonstrated in ICSC.[25] Focal occlusion of the choriocapillaries, decreased foveal choroidal blood flow, secondary RPE defects and serous macular detachment are all consequences.[25]

AMD, choroidal neovascular membranes, high myopia, hereditary choroidal degeneration, OHS and tumors of the choroid have all been identified as precipitating conditions in the development of RPE detachment.[7-11,23-26] Uncomplicated idiopathic serous detachments of the RPE often resolve spontaneously.

Management

There is no direct or interventional treatment for PED. Those caused by more complicated processes associated with generalized damage to the choriocapillaris may be complicated by hemorrhage, choroidal neovascular membrane formation and disciform scarring.[2,3,5-7,9-14,16,17,20,21]

Treatment is directed at the underlying cause. If there is an ocular infection or inflammation it must be diagnosed and managed. All PED, especially those secondary to AMD must undergo investigation for CNV (optical coherence tomography-OCT, fluorescein angiography-FA). If CNV is detected, it can be treated with injectable therapy or laser surgery.[6,13,14,23] If there is no CNV, and drusen or choroidal atrophy are present, vitamin therapy can be attempted to arrest high risk drusen and CNV formation.[27,28] Full macular translocation (FMT) with 360° retinotomy has been examined with optimism as a solution for patients with PED where anti-VEGF therapy has been unresponsive or is contraindicated.[29]

The treatment for PED secondary to ICSC begins with treating the underlying cause of the ICSC. Once CNV has been ruled out, monitoring with a home Amsler grid, cessation of any causative medication (i.e., steroids), oral antibiotic therapy for suspected HP infection, aspirin therapy (100mg p.o. q.d. then 100mg p.o. q-other-d every five months), photocoagulation, photodynamic therapy and oral finasteride therapy (inhibitor of dihydrotestosterone synthesis) are all possible options.[25,30-32]

Most patients under the age of 55 who present with small serous PED without evidence of other retinal or choroidal disease typically recover without intervention.[23] Older patients who manifest PED without angiographic evidence of choroidal neovascularization have a higher risk of developing CNV during their lifetime. These cases require careful semiannual dilated funduscopic examination as well as home observation with an Amsler grid.[1,2]

Clinical Pearls

- Approximately 90% of cases of PED have or will manifest concurrent serous neurosensory retinal detachment over the natural history of the disorder.
- The presentation of PED requires the clinician to rule out ICSC, CNV, malignant choroidal tumors, choroidal hemangioma and Best's disease (vitelliform dystrophy). History and angiography are the most helpful factors in making this differential diagnosis.
- PED in patients over 55 years of age should be considered secondary to choroidal neovascular membrane until proven otherwise. Prompt fluorescein angiography is suggested.

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RETINITIS PIGMENTOSA

Signs and Symptoms

Retinitis pigmentosa (RP) is a group of inherited disorders affecting one in 3,000 to 7,000 people.[1,2] It is characterized by abnormalities of the photoreceptors (rods and cones) or the retinal pigment epithelium (RPE) of the retina, which lead to progressive visual loss.[1-14] The predominant symptom is bilateral progressive visual field and acuity loss often proceeding to blindness.[1-13] These diseases are transmitted through genetic pedigrees echoing all known modes of inheritance.[3] To date, 45 causative genes/loci have been identified in non syndromic RP (for the autosomal dominant, autosomal recessive, X-linked, and digenic forms).[3] The most common form of RP is a rod-cone dystrophy.[3]

Syndromic RP is defined as the disease and its variations with associated groupings of signs, symptoms and systemic findings involving one or more organ systems.[3,14] The disease process has many variations with the potential for both early or delayed onset.[15] Most patients with RP are diagnosed in the second or third decade of life.[5-12] Bardet-Biedl syndrome (BBS) and Usher syndrome (US) are the most prevalent syndrome forms involving RP.[1,3,7,11,12,16,17] Together they make up almost a quarter of the patients with RP.[12] Bardet-Biedl syndrome is defined by the association of retinopathy, obesity, hypogonadism, renal dysfunction, postaxial polydactyly and mental retardation.[1,3,11,12] Usher syndrome is characterized by the combination of congenital or early-onset sensorineural deafness, RP and variable degrees of vestibular dysfunction.[11,12,16] Kearns-Sayre syndrome (KS) is a rare disorder consisting of ptosis, limited movement of the eyes and atypical retinal pigmentary changes.[7,17] Occasionally KS manifests other neurological and endocrinological symptoms such as ataxia, dementia, diabetes and hyperaldosteronism.[7] Refsum's syndrome is characterized by defective peroxisomal alpha oxidation of phytanic acid with

clinical features that include retinitis pigmentosa, polyneuropathy, anosmia and hearing loss.[12,13,18] Bassen-Kornzweig disease is an autosomal recessive disorder featuring altered lipoprotein metabolism characterized by fat malabsorption, hypocholesterolemia retinitis pigmentosa, progressive neuropathy and acanthocytosis from early infancy.[19,20]

Patients with RP may present with varying symptoms, which are often gradual and insidious with many patients failing to recognize the advancing manifestations until the disease has progressed significantly.[1-24] When symptoms are reported, they initially include difficulty with night vision (nyctalopia), difficulty with vision in bad weather as well as loss of peripheral vision.[1-8,23] Many patients with RP will also experience visually debilitating photopsia as the disorder progresses.[21,22] This phenomenon is believed to represent aberrant electrical impulses from the degenerating retina.[21] Central visual acuity is generally not affected until very late stages, although variants have been encountered that cause devastating macular compromise early in the disease course (e.g., X-linked recessive RP, RP inversa).[8,23,24] Color vision typically remains intact as long as visual acuity is better than 20/40.[8,23] Most patients experience their greatest reductions in central vision between the ages 50 to 80 years.[5-13]

The ophthalmoscopic appearance of RP involves attenuation of the retinal arterioles, intraneural retinal pigment (bone spicules) in the midperipheral retina and at perivascular locations, thinning and atrophy of the RPE in the mid and far periphery, preservation of macular integrity (except in the condition of RP inversa [macular presentation] and RP sine pigmento [without pigment]), gliotic atrophy of the axons composing the optic nerve (waxy pallor) and choriocapillaris atrophy with increased visibility into the choroid.[5-13,24-28] There is a correlation with acquired optic disc drusen in RP.[9] In the traditional forms of RP, the appearance and function of the macula and optic nerve remain normal in the early stages of the disease's development; however, tissue changes in response to the pathology may provoke preretinal gliosis (cellophane maculopathy), which may lead to macular hole, cystoid macular edema and focal RPE defects.[29,30] Additional ophthalmologic findings within the vast expression of RP include ectopic lentis, microspherophakia (Weill-Marchesani syndrome), atypical cataract formation, pigment cells in the vitreous, posterior vitreous detachment and associated vitreous hemorrhage.[31-34] Most patients with retinitis pigmentosa are myopic although high hyperopia has been reported.[34-36] There is also a correlation with keratoconus.[37]

Pathophysiology

The pathophysiology of retinitis pigmentosa is complex.[38-46] The common theme of the disease, in virtually all forms, stems from genetic and mitochondrial defects that produce disturbances in the RPE leading to destruction of the photoreceptors' outer segment disc membranes.[2,8,45] The resultant accumulation of metabolic by-products creates disruption of the normal retinal function advancing varying combinations of lipofuscin deposition, retinal gliosis, photoreceptor loss, choriocapillaris occlusion, choroidal atrophy and RPE hyperplasia.[2,8,44,45] As the RPE alterations progress, the blood-retina barrier becomes eroded, resulting in intraretinal and subretinal leakage. The clinical manifestation is the loss of visual field, nyctalopia, and eventual formation of cystic macular edema and acuity loss in later stages of the disorder.[24-30] There are many recognized forms of retinitis pigmentosa and while most present with similar findings and outcomes, some presentations are atypical.[44] Classification of RP may be made on the basis of inheritance pattern (autosomal dominant, autosomal recessive, X-linked, simplex-no family members, multiplex-multiple genes), age of onset (congenital, childhood onset, juvenile onset, adult onset), predominant photoreceptor involvement (rod-cone, cone-rod), or location of retinal involvement (central, pericentral, sectoral, peripheral).[5-13,24,44-47]

Electrodiagnostic testing remains the gold standard for diagnosis.[1-3,24,26,38-40] In RP, both the electroretinogram (ERG) and multifocal electroretinogram (mERG) show significantly diminished red, white, blue and 30hz flicker waves.[35,36] The electro-oculogram (EOG) and dark adaptometry remain as staples in diagnosis and monitoring.[5-13,39,40] New testing being evaluated by researchers includes pupillary light reflex evaluation in conjunction with optical coherence tomography as an indicator of photoreceptor dysfunction in patients with advancing typical retinitis pigmentosa.[41-43] Fundus autofluorescence (FAF), which measures the density of lipofuscin granules, has emerged as a potential tool as well.[25,41-43] Genetic testing can determine the risk of expression in offspring and identify specific gene defects in the affected.[1-4,9-25]

Management

There is no known treatment to diminish or reverse the progressive retinal dysfunction encountered in retinitis pigmentosa.[1-53] Management therefore is three pronged: 1) Prompt diagnosis, 2) Rectify the treatable associated ocular and systemic complications (i.e., refractive error, cataract formation, macular edema, vitreous

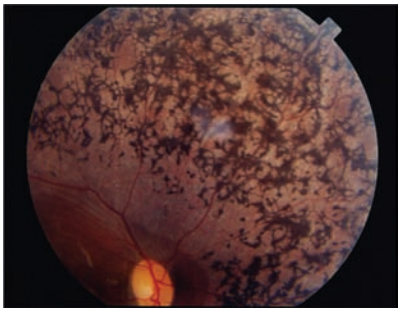
hemorrhage, hearing loss, dyslipidemia.) and 3) Suggest counseling to maintain quality of life.[1-53] While the suspicion of RP is based upon clinical appearance, there are retinopathological conditions that mimic its distinctive retinopathy. These may include rubella retinopathy, syphilitic retinopathy, cytomegalovirus retinopathies, toxoplasmosis, cancer-associated retinopathy, retinal drug toxicity secondary to thioridazine, chlorpromazine or chloroquine, pigmented paravenous retinochoroidal atrophy and traumatic retinopathy.[48-53]

Visual field analysis and electrodiagnostic testing along with dark adaptometry should always be obtained to confirm suspected cases.[1-3,24,26,36-38] FAF can provide information regarding the integrity of the photoreceptor layer, serving as a secondary instrument for both diagnosis and therapeutic monitoring.[41,42]

A pedigree can be done to determine the inheritance pattern and to assess risk to offspring.[1-4,14,15,44,46-48] Low-vision services are indicated as the disorder affects normal visual function.[5,36] Field expansion devices, infrared blocking sun lenses and contrast enhancing filters may all be helpful. Visual field analysis and evaluation for cataract development or macular edema should be performed at least biannually.

The artificial silicon retina (ASR) microchip is a new technology designed to be implanted into the subretinal space to treat vision loss.[5] The ASR microchip is a 2-mm diameter silicon-based device that contains approximately 5,000 microelectrode-tipped microphotodiodes.[5] It is powered by incident light.[5] Visual function improvements have been documented in patients and included unexpected improvements in retinal areas distant from the implant.[5] Subjective improvements included improved perception of brightness, contrast, color, movement, shape, resolution visual field size.[5] No trial patients have shown signs of implant rejection, infection, inflammation, erosion, neovascularization, retinal detachment, or migration.[5]

Animal models have led to the development of therapeutic strategies aimed at identifying and curing specific genetic disorders (gene therapy).[1-4,44-47] Newly developed algorithms are being designed to slow down or even stop the process of photoreceptor degeneration. These include growth factors, calcium blocker applications and vitamin supplements. The use of stem or precursor cells is also being investigated.[5,6,9,54] The newest treatment options include trophic factor therapy, visual cycle inhibitors and cell transplantation.[55] A radically different approach has been given the name neural prosthetics ("artificial vision").[55] Rewiring of inner retinal circuits are known to occur naturally in RP making researchers believe it is possible to create visually useful percepts by stimulating retinal ganglion cells electrically.[55] This has lead to the development of techniques to induce photosensitivity in cells that are not normally light sensitive as well as the development of what is being termed "the bionic retina."[55] The use of molecular engineering and nanotechnology to render cells light-sensitive and to target ion channels in appropriate cell types (e.g., bipolar cell) and/or cell region (e.g., dendritic tree vs. soma) continues and offers promise where there was none before.[55] Findings in some controlled trials indicate that nutritional interventions, including vitamin A palmitate and omega-3-rich fish, slow progression of disease in many patients.[56-58] Patients having retinitis pigmentosa placed on vitamin A therapy with docosahexaenoic acid, 1,200mg/d, demonstrated a slowed the course of disease over the following two-year period.[58] Lutein supplementation of 12mg/d also has shown promise for slowing loss of midperipheral visual field in nonsmoking adults with retinitis pigmentosa taking vitamin A.[57] Supplementation therapy is not free of controversy. As there is no universally agreed upon regimen and the affects of long-term use remain in question. The literature also suggests that while patients may experience some degree of measurable visual preservation they do not seem to benefit functionally and must be closely medically monitored while on these preparations.[44]



Peripheral "bone spicules" are the hallmark sign of retinitis pigmentosa.

Clinical Pearls

- The earliest clinical indicators such as attenuation of the retinal arterioles, midperipheral intraneural retinal pigment (bone spicules), perivascular pigmentary hyperplasia, thinning and atrophy of the RPE in the mid and far periphery are frequently detectable before the emergence of macular signs or subjective symptoms.
- It is often beneficial to recommend psychological or family counseling early in the course of this disease as the process has no cure.[54,59]
- Patients should be educated regarding the need for periodic examination to reassess status as well as manage ongoing refractive and mobility needs.

• The potential for visual enhancement with low-vision devices and vision rehabilitation should be explained and explored.

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ARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY

Signs and Symptoms

The patient with arteritic anterior ischemic optic neuropathy (AAION) will typically be elderly (with an average age of 75 years), more commonly female, Caucasian, and will present with a loss of vision and visual field.[1-3] The visual loss is typically profound.[1-3] Visual acuity may initially, in rare instances, be quite good; however, acuity usually deteriorates quickly into the range of of 20/200 to no light perception.[3] While the vision loss is typically not accompanied by frank eye pain, the patient will frequently complain of scalp pain, headache, and jaw claudication.[1-5] The vision loss is typically unilateral, but may be bilateral or rapidly sequential.[3] The field defect in testable eyes includes central scotomas associated with acuity loss, as well as altitudinal or arcuate patterns.[3] Unless the case is bilateral, an afferent pupil defect will be present. Visual loss may be rapidly progressive over several days.[3,6,7] Patients may recount several occurrences of amaurosis fugax or intermittent diplopia and ophthalmoparesis preceding the onset of the AAION.[8]

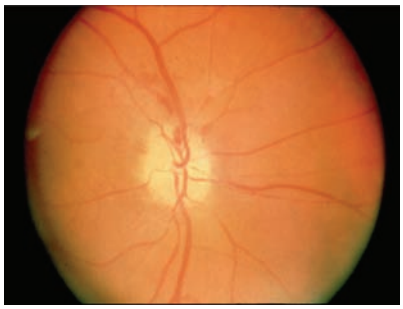
Patients with AAION will usually present with a prodrome of anorexia, weight loss, decreased appetite (all due to discomfort while eating from jaw claudication), fever and malaise.[4,9] There will be a relative afferent papillary defect and dyschromatopsia. Funduscopically, the involved optic disc will be swollen, edematous, pale and atrophic, often with associated splinter hemorrhages.[1,4] The disc edema is often described as "chalky white." After the initial ischemic event, the disc will undergo a glaucoma-like optic disc degeneration with cupping, though there will often be pallor of the remaining neuroretinal rim.[10,11]

Patients experiencing AAION typically have rheumatologic disease, often manifested by polymyalgia rheumatica. Typically, following the event of acute vision loss, the patient will test positively for giant cell arteritis (GCA).[12]

Pathophysiology

Arteritic anterior ischemic optic neuropathy is caused by infarction of the short posterior ciliary arteries supplying the anterior optic nerve. Fluorescein angiography and color Doppler imaging readily demonstrate non-filling of the posterior ciliary arteries and significant delay in choroidal filling times.[13-15] These vessels, as well as the ophthalmic and portions of the central retinal arteries, are compromised by an infiltration of the vessels' walls by inflammatory macrophages, lymphocytes and multinucleate giant cells. As most arteries are affected in GCA, there usually is an attendant constellation of systemic symptoms. Due to the widespread vascular involvement in GCA, there is a propensity for the fellow eye to become similarly involved, often quite rapidly, with severe bilateral vision loss ensuing.[16-19]

Patients with GCA and AAION have been found to have serologic abnormalities that not only may contribute to the development of AAION, but also may prove useful diagnostically. A strong association between IgG anticardiolipin antibodies and AAION secondary to biopsy-proven giant cell arteritis has been identified.[20,21] An elevated level of IgG anticardiolipin antibodies may be a risk factor to thrombotic complications, such as AAION, in patients with GCA.[20,21] Elevated platelet count is often seen in patients with GCA and AAION. Thrombocytosis is considered to be especially predictive of vision loss and the excess platelets may lead to thrombosis.[22-24] Often, plasma viscosity is elevated and may reflect a more specific component of the acute inflammatory response.[25]



Pale disc edema in arteritic anterior ischemic optic neuropathy.

Management

Elderly patients with unilateral sudden vision loss and a pale edematous optic disc should be presumed to have ischemic optic neuropathy. The history should be probed for the concurrent ocular and systemic symptoms to determine if the patient has GCA and AAION. A Westergren erythrocyte sedimentation rate (ESR) should be ordered immediately for these patients. In most AAION cases, this will be grossly elevated. It must be noted that 15% of patients with GCA will have a normal ESR.[26] Thus, a normal ESR does not preclude the diagnosis of AAION, especially in the presence of constitutional symptoms suggestive of GCA. Elevated white blood cell and platelet count, as well as IgG anticardiolipin antibodies, may also be diagnostic.[20-24] C-Reactive protein (CRP) is also elevated in patients with AAION secondary to GCA and is now considered a mandatory test in the diagnosis of patients with GCA-related complications.[22,24-27] In fact, the CRP may be a better diagnostic marker of GCA-related AAION than the ESR. However, like a normal ESR, it is possible to have a normal CRP in a patient suffering from GCA. The finding of an elevated ESR and a normal CRP is consistent with GCA.[28] At a minimum, patients with presumed

AAION must be evaluated with ESR, CRP, and complete blood count with differential on an emergency basis.

Should the diagnostic evaluation (elevated ESR & CRP, thrombocytosis, increased plasma viscosity, etc.) and/or clinical presentation (systemic signs and symptoms of GCA) indicate AAION, then a temporal artery biopsy must be performed to examine for the presence of inflammatory cells in the muscular walls of the artery.[29-31] If the patient is either suspected to have, or diagnosed with, AAION, then systemic steroids must be initiated immediately in order to prevent vision loss progressing to the other eye.[4,27,31-33] Steroid therapy should not be withheld pending the biopsy. The treatment can be initiated in suspicious cases before the biopsy while awaiting the results. The dosage and route of steroid administration cannot been scientifically determined through controlled studies due to the high morbidity of this disease. However, anecdotal evidence suggests that the best known current therapy involves hospital admission with 1g-2g IV methylprednisolone for two to three days, followed by chronic use of oral steroids (60mg to 100mg q.d. of prednisone).[32-40] This aggressive therapy has been shown to have the best outcome in regards to preservation of existing vision and well as rare visual recovery of involved eyes.

While the vision loss associated with AAION is typically devastating and considered irreversible even with prompt treatment, there have been anecdotal reports of visual recovery, often associated with IV steroid use.[32-36] Oral steroids are tapered and maintained for prolonged periods; an increase in systemic symptoms is not a reliable indicator of disease reactivation.[35] In spite of aggressive therapy, GCA-related vision loss has been seen to frequently progress to the fellow eye, giving this disease a guarded prognosis.[16]

There have been attempts to identify non-steroidal therapies for patients with manifestations of GCA. Methotrexate and azathioprine have been used as steroid-sparing agents based on anecdotal evidence. More recently, evidence is emerging that antitumor necrosis factor-alpha may be efficacious.[41] However, success with medications other than steroids is merely anecdotal. A controlled study looking at methotrexate as an adjunctive therapy along with steroids did not demonstrate any benefits.[42] It has been noted that antiplatelet or anticoagulant therapy may reduce the risk of ischemic events in patients with GCA. Low-dose aspirin has been shown in studies to decrease the rate of cranial ischemic complications secondary to giant cell arteritis and decreases the rate of visual loss and cerebrovascular accidents. Low dose aspirin therapy has been recommended as an adjunct to steroids in the management of patients with GCA.[43-49]

Clinical Pearls

- Any patient over the age of 60 years with sudden unilateral vision loss and a pale edematous disc must be considered to have GCA and AAION.
- The pallor in AAION has been described as chalky white.
- **This is a true emergency,** and warrants immediate consultation with a physician (typically a neurologist or neuro-ophthalmologist) specifically skilled in the management of GCA and AAION. Further, any elderly patient presenting with headache, head pain or, especially, amaurosis fugax must be evaluated for GCA.
- Central retinal artery occlusion (CRAO), while usually caused by embolism, occurs due to GCA in 2% to 10% of cases. Any patient in the proper demographic over the age of 65 years presenting with CRAO must be assumed to have GCA until proven otherwise. Single or multiple cotton wool spots in this demographic should also be considered as possible signs of GCA.
- Though visual recovery has occurred in patients with AAION (typically with high dose steroid therapy), do not expect improvement. Instead, direct efforts at preserving the existing level of vision in the involved as well as fellow eye.

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NON-ARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY

Signs and Symptoms

Non-arteritic anterior ischemic optic neuropathy (NAAION) typically presents as a painless, unilateral disturbance of vision. Patients are older but not necessarily elderly, generally in the 55- to 65-year-old age group. The onset of NAAION may occur as early as the late 30s and early 40s.[1] Men and women are affected equally, although there are racial disparities, with the disease being most prevalent in Caucasians.[1,2] Many patients with NAAION have some underlying systemic disease, although they may not be aware of any health problems at the time of presentation. Most often, vascular disorders such as hypertension, diabetes, and/or atherosclerosis are present. It has also been demonstrated

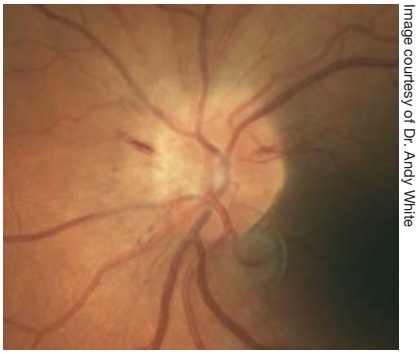

Image courtesy of Dr. Andy White

Hyperemic disc edema in a case of non-arteritic anterior ischemic optic neuropathy.

that elevated plasma homocysteine and lipoprotein(a) levels, as well as low vitamin B6 levels, may increase the risk of developing NAAION.[3]

In contrast to the arteritic variety, vision loss in NAAION tends to occur gradually. While some patients report a rapid decline in acuity over several days, 45% of cases present with a history of vision loss that worsens over two weeks, with another 29% reporting progression of the visual deterioration over 30 days.[4] Visual acuity may be moderate to poor; about half of patients present with 20/60 or better, while roughly a third have entering acuity of less than 20/200.[2] It is exceedingly rare to encounter no light perception (NLP) vision in patients with NAAION. Visual field defects most commonly include inferior altitudinal, inferior arcuate, inferior nasal and cecocentral scotomas.[1]

Examination of these patients reveals a relative afferent pupil defect (RAPD) in the involved eye. There is generally little pain or other associated symptoms, a feature that helps to distinguish this condition from other optic neuropathies. Ophthalmoscopy reveals disc edema, which may be diffuse or segmental.[1,5] Disc hemorrhages are common, occurring in more than two-thirds of patients with NAAION.[1] In addition, the optic disc is characteristically hyperemic, often

displaying dilation of the overlying arterioles (which is sometimes erroneously diagnosed as neovascularization). The retinal veins are typically dilated and tortuous. Significant concurrent retinopathy may be present, depending upon the severity of the patient's underlying systemic condition.

Finally, a key diagnostic characteristic of NAAION involves a small, crowded optic disc with minimal cupping in the contralateral eye. This "disc at risk," as some have called it, is recognized as a significant risk factor for the development of NAAION in predisposed individuals.[1,6,7]

Pathophysiology

NAAION represents an infarction of the anterior portion of the optic nerve, typically involving the paraoptic branches of the short posterior ciliary arteries.[7,8] By definition, this infarction occurs in the absence of inflammation, demyelination or compression.[9] The vasculopathic etiology is usually hypertension or diabetes, both of which are often accompanied by arteriosclerosis. According to one report, diabetes is the most consistently identified vasculopathic risk factor in NAAION.[6] Genetic factors and smoking may also play a role.[10,11]

Hayreh and others have proposed that NAAION results from dysfunctional vascular autoregulatory mechanisms at the level of the optic nerve.[8,12-14] This may occur as a result of transient nocturnal arterial hypotension, overtreatment for systemic hypertension, or simply because of the "crowding" of neurons within the optic disc of these patients and associated poor perfusion. Optic disc drusen have also been identified as a potential causative factor, although this may simply represent coincidental pathology in congenitally small optic discs.[15]

There have been numerous reports of vision loss presumed from NAAION in patients using phosphodiesterase type-5 (PDE-5) inhibitors for the management of erectile dysfunction.[16-20] However, these reports which have suggested a relationship between PDE-5 inhibitor use and NAAION are case reports and small series observations without adequate controls or monitoring of co-variables. Additionally, the small number of cases compared against the widespread use of these medications makes it difficult to conclude a causal relationship. Still, it is recommended that men experiencing any form of vision loss while using these medications stop their use immediately and seek medical attention. Further, it is recommended that patients be made aware of this possible adverse event prior to using the medications. It is felt that men with a history of myocardial infarction or hypertension have a greater risk of experiencing NAAION while using these medications.[17]

Cataract surgery is a known risk for developing NAAION. Furthermore, patients with unilateral NAAION are at a significantly higher risk of developing NAAION in the fellow eye after cataract extraction.[21] This also should be a consideration when planning fellow-eye surgery.

Management

Appropriate management for NAAION begins with making the correct diagnosis. NAAION must be differentiated from demyelinating optic neuropathy, which tends to present abruptly in younger patients, and arteritic anterior ischemic optic neuropathy (AAION), which tends to present apoplectically in older patients. While there are no specific laboratory studies that can confirm a diagnosis of NAAION, an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be ordered for any older patient in whom the diagnosis is uncertain. Taken together, the ESR and CRP have a specificity of 97% for giant cell arteritis, the primary etiology of AAION.[22] Likewise, MRI of the brain, chiasm, and optic nerve should be performed on any younger patients with this differential diagnosis to rule out paraventricular white matter lesions that may be seen in multiple sclerosis.

The prognosis for NAAION is guarded, but better than the prognosis seen in AAION. In general, visual acuity improves by three or more lines in 43% of patients at six months.[3] Involvement of the fellow eye occurs just 18% of the time, and may take three years to occur.[3] Recurrent NAAION in the same eye is rare, occurring in less than 5% of cases.[23,24]

There is no specific, universally accepted treatment for NAAION. NAAION eyes can spontaneously recover some visual function. Optic nerve sheath fenestration was investigated in the early 1990's, but abandoned as a therapy because of poor efficacy and high risk.[25] Likewise, a study published in 2000 suggested that treatment with levodopa may be beneficial for patients with NAAION[26], but numerous articles have since refuted this research and therapy.[27,28] Even daily aspirin therapy has been recommended as prophylactic therapy, but the five-year cumulative benefit was shown to be less than 3%.[29]

Recently, intravitreal injections of ranibizumab and erythropoietin individually have been noted to increase visual function in eyes with NAAION, but again these were very small, uncontrolled cases.[30,31] Intravitreal injection of triamcinolone acetonide (IVTA) likewise has been seen to improve visual function in eyes with NAAION.[32-34] Most of these were case reports with no control group. Larger, controlled studies are needed before intravitreal-injected triamcinolone acetonide can

be considered an effective therapy. One study comparing four eyes of four patients treated with 4mg of intravitreal triamcinolone acetonide against six NAAION eyes receiving no treatment found that IVTA provided relatively improved recovery of visual acuity and relatively rapid resolution of optic disc swelling, but it did not provide visual field improvement.[35] Based upon these results, the researchers felt a larger, controlled clinical trial was warranted before making a conclusion and recommendation.

Effectively, there is no specific treatment available for NAAION.[36,37] The only recommendations are to aggressively manage the predisposing and precipitating factors. This means better control of blood sugar, blood pressure, cholesterol levels, and smoking cessation for all patients with NAAION. Those with severe vision loss may benefit from a low-vision consultation.

Clinical Pearls

- Dr. Larry Gray described the detection of NAAION as "diagnosing in the negative." Essentially, this means that we arrive at a diagnosis of NAAION by eliminating all other possible neuropathies. Rule out AAION and demyelinating disease first, followed by infectious, inflammatory, infiltrative, and compressive etiologies. Most of these other conditions have a specific therapy that may help restore vision or prevent further vision loss. No such therapy exists for NAAION.
- Systemic corticosteroids, while a mainstay of therapy for AAION and other optic neuropathies, are apparently of no benefit in NAAION.
- Current research on neuroprotective agents (e.g., memantine) has shown some benefit in treating animal models of ischemic optic neuropathy.[38] Human trials with agents such as brimonidine unfortunately have not shown efficacy in the treatment of NAAION.[39,40]

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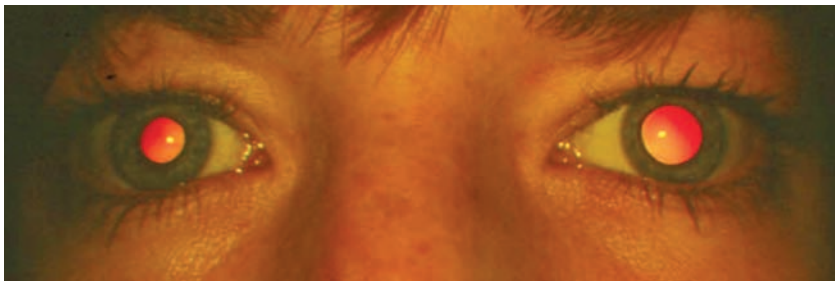
BENIGN EPISODIC PUPILLARY MYDRIASIS

Signs and Symptoms

The patient experiencing benign pupillary mydriasis is typically female, though this has occurred in males as well to a much lesser degree. Also, the patient is younger, with a typical occurrence between the ages of 20 and 40 years.[1-6] There may be a concurrent medical history of migraine headache, but otherwise the patient is systemically well.[7,8] There has been an isolated report of a patient with unilateral mydriasis as well as other focal neurologic abnormalities including loss of smell and associated pleocytosis (cells in the cerebrospinal fluid), all of which resolved within several days.[9]

The condition is defined by unilateral dilation of the pupil. Rarely is the condition bilateral.[10] The anisocoria may be quite marked with several millimeters of size difference between the involved pupil and the pupil in the fellow eye. The anisocoria is often greater in bright illumination. The pupil will react, albeit sluggishly, to light and near stimuli. The dilation is transient, lasting minutes to weeks.[1-6] Often, the patient will be isocoric in the office, but present a history of transient pupil dilation. The event is unilateral and there is a concurrent blurring of vision, especially at near. If tested, there will be a dysfunction of the patient's ipsilateral accommodation during an episode of mydriasis. There will often be an ipsilateral headache, which may be either dull or throbbing, but not debilitating and not typical of migraine. There will be no associated lid or ocular motility disorders.



Transient anisocoria lasting a day in a patient with benign episodic pupil mydriasis.

Pathophysiology

Benign episodic pupillary mydriasis has a characteristic triad of findings: (1) episodic, transient unilateral pupil dilation, usually in young healthy females; (2) peculiar sensations in and about the affected eye with progression to headache or possible associated migraine; and (3) defective accommodation without evidence of lid or ocular motility dysfunction. The underlying etiology of benign episodic pupillary mydriasis is unknown. While the anisocoria is greater in bright room illumination pointing to a painful dysfunction within the parasympathetic pupillary pathway, there is no associated ocular motility disorder suggestive of compressive aneurysmal cranial nerve III palsy.

It has been postulated that brief spasms of segments of the pupil radial muscle leads to this intermittent dilation. However, in those cases, the pupil will often be tadpole-shaped. In true cases of benign episodic pupil mydriasis, the pupil is round. Thus, this is not a plausible explanation. There have been instances where an irritative lesion in Pancoast's tumor compressed sympathetic fibers near the superior cervical ganglion, resulting in a reverse Horner's syndrome that resolved with the removal of the tumor. However, this phenomenon did not have the same characteristics as benign episodic pupillary mydriasis.

It is commonly believed that benign episodic pupillary mydriasis occurs due to an atypical migraine phenomenon. It is not uncommon for ophthalmoplegic migraines to present with anisocoria. However, the anisocoria in migraine tends to last longer, particularly with repeated episodes. Also, in these types of migraines, there is ophthalmoplegia. Benign episodic pupillary mydriasis is unique as an entity because it does not have ophthalmoplegia as a component of its presentation.

A report examining the relationship between migraine and mydriasis strongly suggested a pathogenic link between the pupil dysfunction and migraine, rather than a simultaneous coexistence of two independent disorders.[11] Other theories attempting to explain the presentation included a latent Adie's pupil that could have been triggered by migraine; a ciliary ganglionic dysfunction produced by the migraine process and an episodic ciliary ganglionitis with migraine features.[11] Ciliary ganglioplegic migraine was proposed as a term identifying a possible anatomic source of the migraine-related pupil dysfunction.[11]

Medical examination of patients with benign episodic pupillary mydriasis, including serology, MRI, cerebral angiography and lumbar puncture with CSF analysis has failed to disclose any associated abnormalities.

Management

The most important aspect in management of benign episodic pupillary mydriasis is correct diagnosis. To this end, it must be differentiated from

tonic pupil syndrome, pharmacologically dilated pupil, and pupil involvement from compression-related aneurysmal cranial nerve III palsy. In aneurysm-related CN III palsy, there will be ophthalmoplegia and ptosis, whereas motility and eyelid position is normal in benign episodic pupillary mydriasis. In tonic pupil syndrome, there will be no return to normal size; thus it is not episodic. In a pupil pharmacologically dilated by a parasympatholytic agent, there will be no direct or accommodative pupillary responses. Further, there will be no response to the administration of topical pilocarpine. Once benign episodic pupillary mydriasis is diagnosed, no further testing or management is necessary beyond patient education and reassurance.

Clinical Pearls

• With a sudden dilation of the pupil, most practitioners worry that there is a life threatening aneurysm. While there have been cases reported where an aneurysm compressed CN III without initially involving the pupil, there has never been a reported instance where an aneurysm compressed CN III involving only the pupil and not ocular motility. If the pupil is dilated and there is no ocular motility deficit, you can rest assured that there isn't an aneurysm.

• Sudden unilateral pupil dilation in a young healthy female with concurrent headache and near vision disturbance occurs more commonly than realized and should be considered to be benign episodic pupillary mydriasis until proven other wise.

• Pupillary mydriasis, pupil dysfunction and accommodation anomalies can occur pharmacologically from exposure to parasympatholytic agents such as scopolamine from motion sickness preparations and the handling of certain plants, such as jimson weed. In these cases, the pupil will be totally unreactive to light and near stimuli. The use of pilocarpine 1% solution will also fail to produce miosis.

• Pupillary mydriasis and dysfunction can also occur due to overuse of sympathomimetic agents, such as those found in over the counter topical allergy and whitening/vasoconstriction medications. In these cases, the pupil will be responsive to light and near stimuli.

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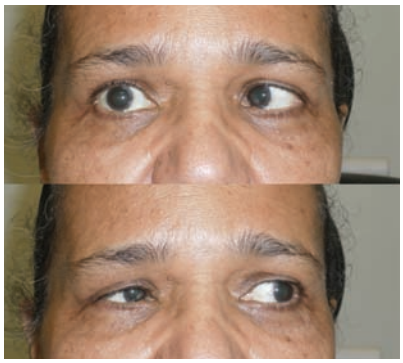
DUANE'S RETRACTION SYNDROME

Signs and Symptoms

Duane's retraction syndrome (DRS) is a congenital, non-progressive disorder of ocular motility that is characterized by limited abduction, limited adduction, or both. The hallmark clinical signs that allow for differentiation from other strabismus syndromes are the classic retraction of the globe and narrowing of the palpebral fissure upon attempted adduction of the involved eye.[1-4] Most cases are unilateral, with a greater preponderance for left-eye involvement.[1-3] Additionally, the majority of cases are isolated, meaning that there are no accompanying congenital anomalies. Most DRS patients present with an orthophoric posture, although some will demonstrate esotropia or exotropia in primary gaze, along with a compensatory head posture that is adopted to maintain single simultaneous binocular vision.[1,2] Unusual associations can include crocodile tearing and Marcus Gunn jaw-winking, both forms of aberrant innervation phenomena.[5,6] Undiagnosed or uncorrected DRS can lead to amblyopic vision loss in about 10% of patients.[1]



Duane's Retraction Syndrome Type I. Right abduction deficit (above) with retraction of the right eye on adduction (below).

Huber described three distinct types of DRS in 1974, and these categorizations are still widely used today.[7]

• **Type I** represents the most common variant, occurring in 75% to 80% of cases.[1] Its characteristic presentation includes *"marked limitation or complete absence of abduction, normal or only slightly defective adduction* [along with] *narrowing of the palpebral fissure and retraction of the affected eyeball on adduction* [and] *widening of the palpebral fissure on attempted abduction."*[7] Women are affected more commonly than men in Type I, with a ratio of 60:40.[3]

• **Type II** is seen less commonly, in approximately 5% to 10% of cases.[1] It may be described clinically as a *"… limitation or complete defect of adduction with exotropia of the affected eye. Abduction appears to be normal or only slightly limited. There is further distinct narrowing of the palpebral fissure and retraction of the globe on attempted adduction."*[7] Type II DRS shows no real gender differences in clinical practice.[1]

• **Type III** accounts for ~10% to 20% of all DRS cases. It is defined as a *"… limitation or absence of both abduction AND adduction of the affected eye. There is further characteristic retraction of the globe and narrowing of the palpebral fissure on attempted adduction."*[1] Clinicians are more likely to observe an upshoot or downshoot of the affected globe on attempted adduction in Type III as opposed to the other two forms of DRS.[1]

Up to 30% of DRS cases demonstrate systemic associations, including such conditions as: limb abnormalities, cardiac abnormalities, neurosensory deafness, Goldenhar syndrome (oculovertebralauricular dysplasia), Klippel-Feil syndrome (shortness of neck secondary to cervical vertebrae absence or fusion), Wildervanck syndrome (Klippel-Feil + labyrinthine deafness) and Marfan syndrome.[8]

Pathophysiology

DRS may be described as a congenital cranial dysinnervation disorder. The condition is characterized by abnormal development of the cells in the abducens nucleolus (CN VI), resulting in restricted or absent abduction and erroneous innervation of the lateral rectus muscle by branches emanating from oculomotor nuclei (CN III). Anatomic and histologic pathology show that, between four and eight weeks of gestation, there is maldevelopment or injury to developing structures of the CN VI nucleus and nerve(s). Branches from the third nerve are then redirected to the lateral rectus, causing a wide spectrum of anomalous innervations.[4] The fact that DRS seems to demonstrate a familial inheritance pattern in at least 10% of cases suggests that the condition is not simply due to a sporadic mutation or to trauma.[9] Although numerous chromosomal abnormalities may be associated with DRS, two important loci have been mapped; these are 8q13 (DRS Type I) and 2q31 (DRS Type II).[10] A number of cases have also been reported in association with chromosomal duplications and rearrangements.[10-13] While autopsy studies are limited, individuals with absent CN VI nerves and/or nuclei have been reported.[14,15] The exact pathophysiology remains elusive, but mechanically, DRS is explained by the poorly understood development of abnormal communication with the lateral rectus via the inferior division of cranial nerve III. This "miswiring" produces the classic, dual, electromyographic firing of the recti upon attempted adduction, resulting in globe retraction and palpebral fissure narrowing.

Management

The initial step in managing patients with DRS is differentiating this essentially benign condition from other disorders of ocular motility. Some of the motility disorders that must be ruled out include: acquired sixth nerve palsy, internuclear ophthalmoplegia, congenital esotropia with significant medial rectus contractures, Graves disease with extraocular muscle involvement and medial orbital wall fracture with incarceration of the medial rectus.[3] Testing of suspected DRS patients should include a thorough family history, cover test in primary gaze and determination of habitual head position, careful evaluation of motility patterns including versions (binocular), ductions (monocular) and possibly even forced duction testing. If systemic complications are suspected, a comprehensive physical examination and neuroimaging may also be warranted.[3]

In most cases, therapeutic intervention is unnecessary for patients with DRS, as they typically develop effective sensory adaptations to overcome their limitations of motility. The major indications for surgical management are an abnormal head position of greater than 15° and/or a significant deviation in primary position of gaze, where the risk of amblyopia appears certain.[16] Options typically include horizontal rectus muscle recession or vertical rectus muscle transposition. "Y-splitting" of the lateral rectus muscle with recession and resuturing of the sections above and below the original axis may be employed for patients with significant up/downshoot, or severe globe retraction.[17] Amblyopia in DRS is treated conventionally by prescribing full correction spectacles, direct patching therapy and intensive, well-monitored vision therapy.

Clinical Pearls

• DRS has a prevalence of 0.1% in the general population and accounts for 1% to 5% of all strabismus cases.[3,4,8,16]

• Since systemic abnormalities are present in a significant number of cases, a complete health examination with blood work, hearing and EKG is recommend for all new diagnoses of DRS.

• The differential diagnosis for DRS should include epicanthal folds, congenital esotropia with and without an accommodative component, convergence excess, accommodative excess, excessive hyperopia with resultant esotropia, Brown's syndrome (limited elevation and adduction secondary to a restriction of the superior oblique via inflammation or scarring in the area of the trochlear tendon), double elevator palsy (congenital limitation of up gaze), Mobius syndrome (congenital unilateral or bilateral limitation of horizontal

eye movements + facial nerve palsy), congenital fibrosis syndrome (congenital ptosis and external ophthalmoplegia with limited horizontal gaze), CN VI palsy, Grave's disease and orbital pseudotumor.

• In general, children with DRS benefit the most from surgical intervention. Adults are usually not candidates for surgery unless the condition is cosmetically unacceptable.

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HORNER'S SYNDROME

Signs and Symptoms

Horner's syndrome is characterized by an interruption of the oculosympathetic nerve supply somewhere between its origin (in the hypothalamus) and the eye.[1-9] The classic clinical findings associated with Horner's syndrome are ptosis, pupillary miosis, facial anhidrosis, apparent enophthalmos, increased amplitude of accommodation, heterochromia of the irides (if congenital or occurring before the age of two years), paradoxical contralateral eyelid retraction, transient decrease in intraocular pressure and changes in tear viscosity.[1-9] Horner's syndrome has no predilection for age, race, gender or geographic location. Horner's syndromes of congenital origin present around the age of two years with heterochromia and absence of a horizontal eyelid fold or crease in the ptotic eye.[1-5,9] Iris pigmentation (which is under sympathetic control during development) is completed by the age of two, making heterochromia an uncommon finding in Horner's syndromes acquired later in life.[1-3] Old photographs can aide the clinician in distinguishing congenital Horner's by documenting heterochromia present at birth.[1-5]

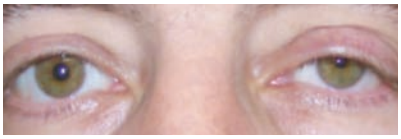
Pathophysiology

Sympathetic innervation to the eye consists of a three-neuron arc.[1-10] The first neuron originates in the dorsolateral hypothalamus. It descends through the reticular formation of the brainstem and travels to the ciliospinal center of Budge, between the levels of the eighth cervical and fourth thoracic vertebrae (C8-T4) of the spinal cord. There, it synapses with second order neurons whose preganglionic cell bodies give rise to axons that exit the white rami communicantes of the spinal cord via the anterior horn. These axons pass over the apex of the lung and enter the sympathetic chain in the neck, synapsing in the superior cervical ganglion.[1-9] Here, cell bodies of third order neurons give rise to postganglionic axons that course to the eye with the internal carotid artery via the cavernous sinus.[1-10] Fibers from these axons form the long and short posterior ciliary nerves of the eye. These sympathetic nerve fibers course anteriorly through the uveal tract and join the fibers of long posterior ciliary nerves, which course with branches of the fifth cranial nerve, to innervate the dilator of the iris. Postganglionic sympathetic fibers also innervate the muscle of Mueller, responsible for the initiation of eyelid retraction during eyelid opening. Postganglionic sympathetic fibers responsible for facial sweating follow the external carotid artery to the sweat glands of the face.[1-10] Interruption at any location along this pathway (preganglionic or postganglionic) will induce an ipsilateral Horner's syndrome.

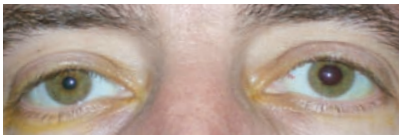
Management

The diagnosis of a suspected Horner's syndrome can be accomplished with pharmacological testing.[5-9] In this dysfunction, there is a lack of the sympathetic neurotransmitter norepinephrine. The iris dilator does not receive sympathetic stimulation in Horner's syndrome, thus accounting for the miosis that increases in dim light conditions and the dilation lag (relative to the normal contralateral pupil) when the lights go down.

Topically applied 10% cocaine works as an indirect-acting sympathomimetic agent, producing pupillary dilation in the normally innervated pupil by inhibiting the reuptake of norepinephrine at the nerve ending.[4-9] A Horner's pupil will dilate poorly



Left ptosis and miosis in a patient with Horner's syndrome.



Reversal of ptosis and miosis 30 minutes after instillation of apraclonidine.

compared to the normal eye because of the absence of norepinephrine at the nerve ending.[4-9] The test should be evaluated thirty minutes after the instillation of the drops to ensure accuracy. The cocaine test is used to confirm or deny the presence of a Horner's syndrome. A positive cocaine test does not localize the lesion.[1-9]

However, topical liquid cocaine is a controlled substance and not readily available, and Paredrine (hydroxyamphetamine, Akorn), historically used to localize the lesion, is no longer available. To that end, it appears that Iopidine (apraclonidine 1% and 0.5%, Alcon) can be used effectively to diagnose Horner's syndrome.[11-16] Apraclonidine is an alpha-2 adrenergic agonist that seems to also stimulate alpha-1 receptors to a negligible degree in the normal state. Pupil dilation in suspected Horner's syndrome is considered diagnostic. The theory is that the Horner's syndrome pupil undergoes denervation hypersensitivity with upregulation of both the number and sensitivity of available receptors. When a very weak alpha-1 adrenergic agonist is applied, the hypersensitive pupil dilates while the normal pupil has no effect. In most cases, there will actually be a reversal of the anisocoria, which is easier to appreciate than the asymmetric dilation induced by cocaine. It appears that the most readily available agent, apraclonidine 0.5%, is at least as sensitive and specific in the diagnosis of Horner's syndrome as is cocaine.[15,16]

There exist concerns with apraclonidine testing. The main concern is the possibility of false-negative responses.[12,14] This can occur if reversal of anisocoria is demanded to make the diagnosis, as reversal may not occur in all patients—though there may be sympathetic effects such as ptosis improvement or some degree of mydriasis in the affected eye.[14] Additionally, false-negative results may occur if apraclonidine is used too early after the onset of Horner's syndrome because it takes time, typically several weeks, before denervation hypersensitivity develops. However, there are reports of positive apraclonidine tests only several hours after the onset of symptoms and Horner's syndrome.[13,17]

The common etiologies of acquired Horner's syndrome include, but are not limited to: trauma, aortic dissection, carotid dissection, tuberculosis, and Pancoast syndrome.[1-9] Aortic dissection is a tear in the intimal region of the ascending aorta near the aortic valve.[1-9] It often occurs along the right lateral wall of the ascending aorta where the hydraulic stress is the greatest.[1-9] Compression of adjacent tissues (e.g., superior cervical ganglia, superior vena cava, bronchus, esophagus) by the expanding dissection, can result in Horner's syndrome, superior vena cava syndrome, vocal cord paralysis, hoarseness, dysapnea, and dysphagia. Patients with long-standing systemic hypertension, Marfan's syndrome and Ehler's Danlos syndrome are at increased risk.[1-9]

In that the oculosympathetic plexus travels with the abducens nerve for a short distance within the cavernous sinus, the combination of a Horner's syndrome and cranial nerve VI paralysis indicates a parasellar lesion within the cavernous sinus. Typically the lesion is an aneurysm of the parasellar internal carotid artery.[18,19]

If the patient reports recent ipsilateral neck trauma, neck and face pain, ipsilateral transient monocular visual loss, or contralateral transient weakness or numbness, acute cervical carotid dissection must be immediately suspected. In this case, there is a substantial risk of hemispheric (middle cerebral artery distribution) stroke within the first two weeks of onset. Cervical carotid dissection is a relatively common cause of acute onset Horner's syndrome.[20-22]

The patient should be questioned for a history of previous accidental or surgical trauma to the neck, upper spine or chest. Trauma, including carotid endarterectomy and epidural anesthesia, is a common cause of Horner's syndrome.[23,24] The patient should also be questioned regarding any history of migraine headache.

As the oculosympathetic plexus courses over the lung apex, various pulmonary diseases can cause a Horner's syndrome. Pancoast syndrome is a malignancy of the superior pulmonary sulcus carcinoma, with subsequent destruction of the thoracic inlet and involvement of the brachial and oculosympathetic plexuses.[25] Most cases involve non-small cell lung carcinoma. The oculosympathetic plexus is prone to compression by a malignant space-occupying lesion as it courses over the superior aspect of the lung. This would cause a second order lesion. The Horner's syndrome is accompanied by shoulder pain radiating to the axilla and scapula. There is also atrophy of the hand and arm with resultant muscle weakness. Bony structures of the chest are often invaded by the malignancy, especially the thoracic vertebrae and ribs. Clinical characteristics of Pancoast syndrome include shoulder pain, loss of limb

function, atrophy of the muscles of the hand, Horner's syndrome and dullness of feeling in the region of the upper chest.[25]

A true Pancoast tumor usually extends through the visceral pleura into the parietal pleura and chest wall. The tumor is considered to be epithelial in its histopathology, but its exact origin remains uncertain. Despite its small size and general lack of metastasis, Pancoast tumor has a rapid and almost universal mortality rate. Approximately 80% to 90% of all lung cancers are linked or associated with smoking.[25] Occasionally a Pancoast syndrome may be from a infectious etiology, such mucormycosis or tuberculosis. If the infectious agent or tuberculosis tubercle occupies a position at the lung apex, it may compress preganglionic sympathetic axons producing a Horner's syndrome.[26]

The unique presentation of unilateral headache, partial Horner's syndrome and V1 sensory disturbance, in the presence of negative neuroimaging studies may identify the rare entity know as Raeder's syndrome.[27] This vasculopathic postganglionic malady produces a painful Horner's syndrome that may be remedied, in most cases, with pharmacologic agents. There has been a report in the literature linking this unusual syndrome to the cluster migraine headache.[27]

Based upon the history and physical findings, patients with Horner's syndrome should undergo a targeted evaluation if the cause is not already clear. In many cases such as recent trauma, the cause may be known or, in the case of associated acute neck and face pain, suspected with a degree of certainty. In these cases, medical evaluation and neuroimaging may be unnecessary or may be targeted to the suspected etiology. If, in the course of examination, no diagnostic clues are identified, a non-targeted evaluation consisting of imaging of the upper chest, neck and brain must be done.[28] It is recommended to order magnetic resonance imaging (MRI) of the chest to include the lung apex and brachial plexus, magnetic resonance angiography (MRA) or CT angiography of the neck and cervical spine, and MRI of the middle cranial fossa. Even with such extensive testing, a cause is rarely uncovered with such untargeted evaluations.[28]

In general, the treatment for Horner's syndrome depends upon the cause. In many cases, there is no treatment that improves or reverses the condition. Treatment in acquired cases is directed toward eradicating the cause. Recognizing the signs and symptoms is tantamount to early diagnosis, as is making expedient referrals to appropriate medical specialists.

Clinical Pearls

- Horner's syndrome can be considered not just a diagnosis, but also a finding that should be investigated for a cause. Diagnosing Horner's syndrome is not the challenge. The challenge is finding the cause.
- In cases where the onset is acute and the exam gives no clues as to the cause, the patient must be imaged from the chest to the brain.

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