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Tenth Anniversary Edition

The Handbook of Ocular Disease Management

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Vigamox®

(moxifloxacin hydrochloride ophthalmic solution) 0.5% as base

DESCRIPTION: VIGAMOX® (moxifloxacin HCl ophthalmic solution) 0.5% is a sterile ophthalmic solution. It is an 8-methoxy fluoroquinolone anti-infective for topical ophthalmic use.

CLINICAL PHARMACOLOGY:

Microbiology:

The following *in vitro* data are also available, **but their clinical significance in ophthalmic infections is unknown.** The safety and effectiveness of VIGAMOX® solution in treating ophthalmological infections due to these microorganisms have not been established in adequate and well-controlled trials.

The following organisms are considered susceptible when evaluated using systemic breakpoints. However, a correlation between the *in vitro* systemic breakpoint and ophthalmological efficacy has not been established. The list of organisms is provided as guidance only in assessing the potential treatment of conjunctival infections. Moxifloxacin exhibits *in vitro* minimal inhibitory concentrations (MICs) of 2 µg/ml or less (systemic susceptible breakpoint) against most (≥ 90%) strains of the following ocular pathogens.

Aerobic Gram-positive microorganisms:
Listeria monocytogenes
Staphylococcus saprophyticus
Streptococcus agalactiae
Streptococcus mitis
Streptococcus pyogenes
Streptococcus Group C, G and F

Aerobic Gram-negative microorganisms:
Acinetobacter baumannii
Acinetobacter calcoaceticus
Citrobacter freundii
Citrobacter koseri
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Pseudomonas stutzeri

Anaerobic microorganisms:
Clostridium perfringens
Fusobacterium species
Prevotella species
Propionibacterium acnes

Other microorganisms:
Chlamydia pneumoniae
Legionella pneumophila
Mycobacterium avium
Mycobacterium marinum
Mycoplasma pneumoniae

Clinical Studies:

In two randomized, double-masked, multicenter, controlled clinical trials in which patients were dosed 3 times a day for 4 days, VIGAMOX® solution produced clinical cures on day 5-6 in 66% to 69% of patients treated for bacterial conjunctivitis. Microbiological success rates for the eradication of the baseline pathogens ranged from 84% to 94%. Please note that microbiologic eradication does not always correlate with clinical outcome in anti-infective trials.

INDICATIONS AND USAGE: VIGAMOX® solution is indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of the following organisms:

Aerobic Gram-positive microorganisms:
*Corynebacterium species**
*Micrococcus luteus**
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus haemolyticus
Staphylococcus hominis
*Staphylococcus warneri**
Streptococcus pneumoniae
Streptococcus viridans group

Aerobic Gram-negative microorganisms:
*Acinetobacter lwoffi**
Haemophilus influenzae
*Haemophilus parainfluenzae**

Other microorganisms:
Chlamydia trachomatis

*Efficacy for this organism was studied in fewer than 10 infections.

CONTRAINDICATIONS: VIGAMOX® solution is contraindicated in patients with a history of hypersensitivity to moxifloxacin, to other quinolones, or to any of the components in this medication.

WARNINGS:

NOT FOR INJECTION.

VIGAMOX® solution should not be injected subconjunctivally, nor should it be introduced directly into the anterior chamber of the eye.

In patients receiving systemically administered quinolones, including moxifloxacin, serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported, some following the first dose. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal or facial edema), airway obstruction, dyspnea, urticaria, and itching. If an allergic reaction to moxifloxacin occurs, discontinue use of the drug. Serious acute hypersensitivity reactions may require immediate emergency treatment. Oxygen and airway management should be administered as clinically indicated.

PRECAUTIONS:

General: As with other anti-infectives, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit-lamp biomicroscopy, and, where appropriate, fluorescein staining. Patients should be advised not to wear contact lenses if they have signs and symptoms of bacterial conjunctivitis.

Information for Patients: Avoid contaminating the applicator tip with material from the eye, fingers or other source.

Systemically administered quinolones including moxifloxacin have been associated with hypersensitivity reactions, even following a single dose. Discontinue use immediately and contact your physician at the first sign of a rash or allergic reaction.

Drug Interactions: Drug-drug interaction studies have not been conducted with VIGAMOX® solution. *In vitro* studies indicate that moxifloxacin does not inhibit CYP3A4, CYP2D6, CYP2C9, CYP2C19, or CYP1A2 indicating that moxifloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these cytochrome P450 isozymes.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals to determine the carcinogenic potential of moxifloxacin have not been performed. However, in an accelerated study with initiators and promoters, moxifloxacin was not carcinogenic in rats following up to 38 weeks of oral dosing at 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose for a 50 kg person, on a mg/kg basis).

Moxifloxacin was not mutagenic in four bacterial strains used in the Ames *Salmonella* reversion assay. As with other quinolones, the positive response observed with moxifloxacin in strain TA 102 using the same assay may be due to the inhibition of DNA gyrase. Moxifloxacin was not mutagenic in the CHO/HGPRT mammalian cell gene mutation assay. An equivocal result was obtained in the same assay when v79 cells were used. Moxifloxacin was clastogenic in the v79 chromosome aberration assay, but it did not induce unscheduled DNA synthesis in cultured rat hepatocytes. There was no evidence of genotoxicity *in vivo* in a micronucleus test or a dominant lethal test in mice.

Moxifloxacin had no effect on fertility in male and female rats at oral doses as high as 500 mg/kg/day, approximately 21,700 times the highest recommended total daily human ophthalmic dose. At 500 mg/kg orally there were slight effects on sperm morphology (head-tail separation) in male rats and on the estrous cycle in female rats.

Pregnancy: Teratogenic Effects.

Pregnancy Category C: Moxifloxacin was not teratogenic when administered to pregnant rats during organogenesis at oral doses as high as 500 mg/kg/day (approximately 21,700 times the highest recommended total daily human ophthalmic dose); however, decreased fetal body weights and slightly delayed fetal skeletal development were observed. There was no evidence of teratogenicity when pregnant Cynomolgus monkeys were given oral doses as high as 100 mg/kg/day (approximately 4,300 times the highest recommended total daily human ophthalmic dose). An increased incidence of smaller fetuses was observed at 100 mg/kg/day.

Since there are no adequate and well-controlled studies in pregnant women, VIGAMOX® solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Moxifloxacin has not been measured in human milk, although it can be presumed to be excreted in human milk. Caution should be exercised when VIGAMOX® solution is administered to a nursing mother.

Pediatric Use: The safety and effectiveness of VIGAMOX® solution in infants below 1 year of age have not been established.

There is no evidence that the ophthalmic administration of VIGAMOX® solution has any effect on weight bearing joints, even though oral administration of some quinolones has been shown to cause arthropathy in immature animals.

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

ADVERSE REACTIONS:

The most frequently reported ocular adverse events were conjunctivitis, decreased visual acuity, dry eye, keratitis, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, subconjunctival hemorrhage, and tearing. These events occurred in approximately 1-6% of patients.

Nonocular adverse events reported at a rate of 1-4% were fever, increased cough, infection, otitis media, pharyngitis, rash, and rhinitis.

Rx Only

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4. *Wolters Kluwer Health, Source®* Pharmaceutical Audit Suite, October 2006-September 2007.

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A Peer-Reviewed Supplement

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

To Our Colleagues,

This year sees the publication of the tenth edition of *The Handbook of Ocular Disease Management*. The years that we have been compiling this compendium have been professionally very rewarding to us. We are forever grateful to the management and editorial staff at *Review of Optometry*. They have given us a forum to reach our colleagues annually and allow us to provide this "second opinion" and share our clinical experience.

When we think back upon the years that we have spent writing this supplement, we want to take a moment and reflect back from where we came and those that have influenced us and our professional development. We would not be in the position to share our knowledge and experience with our colleagues had we not been taught and influenced by our mentors. We are forever grateful to the following people for instructing us, guiding us, mentoring us, and providing professional role models: Drs. Larry Gray, Bernie Blaustein, Chris Reinhart, Joel Silbert, George White, Lou Catania, Robert Walker, Irving Gurwood, Lorraine Lombardi, Lester Janoff, Jeffrey Nyman, Neal Nyman, Ed Deglin, Bruce Muchnick, G. Richard Bennett, Vincent Young, Richard Brilliant, and Joseph Toland.

To them we dedicate the tenth edition of *The Handbook of Ocular Disease Management*.

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The authors do not have a financial interest in any of the products mentioned.

ACQUIRED ANOPHTHALMIA

Signs and symptoms

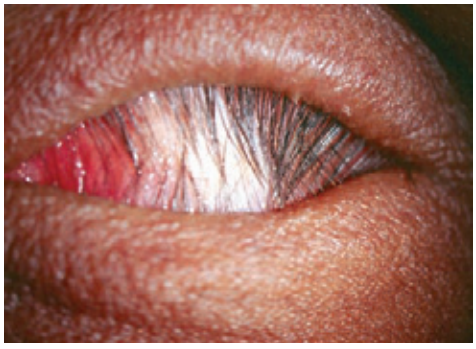
Patients with anophthalmia typically present with an ocular prosthesis; less commonly, they may simply wear a patch to protect the empty socket. While there is no eye, these individuals remain susceptible to a variety of conjunctivitides including allergy, infection and inflammatory disorders. Complaints may include itching, discharge, swelling and erythema or even pain of the lids. Moreover, the anophthalmic patient is predisposed to developing eyelid positioning issues and/or discomfort from a poorly fitted prosthesis.

Visual functioning can also represent a significant challenge to those with acquired anophthalmia. The absence of one eye effectively diminishes a patient's field of vision by 15–20%.[1] Additionally, the anophthalmic patient loses stereopsis, which can compromise the appreciation of depth and parallax, hand-eye coordination and ability to judge distances accurately. Decreased overall acuity is also likely, because monocular patients are unable to benefit from the phenomenon of binocular summation. Finally, there is the potential for impairment in spatial orientation, which results from a lack of kinesthetic cues arising from convergence and accommodation.[2] All of this may compromise the patient's ability to perform visually discriminating tasks such as driving; a study by Keeney, et al. suggests that monocular drivers have, on average, seven times more automobile accidents than the general population of drivers.[3]

Pathophysiology

Anophthalmia refers to the loss or lack of a functioning eye. While congenital anophthalmia is rare, acquired anophthalmia may result from a variety of causes, most notably trauma. Surgically induced anophthalmia (i.e., enucleation) is often indicated in cases of malignant tumor growth (e.g., melanoma, retinoblastoma), intractable glaucoma, chronic inflammation, chronic retinal detachment or endophthalmitis.[4]

The anophthalmic socket consists of a shallow cul-de-sac bounded by conjunctival tissue. The bulk of the orbital space previously occupied by the eye is typically filled with a spherical high-density porous polyethylene or coralline hydroxyapatite implant covered in donor sclera.[5] The extraocular muscles are sutured to this implant, and the remaining palpebral conjunctiva is drawn together to enclose the space. An ocular prosthesis—essentially a convex shell of polymethylmethacrylate, hand-painted to simulate the fellow eye—is subsequently fitted to match the appearance and posture of the remaining eye.



Acquired anophthalmia.

Management

Patients with acquired anophthalmia are prone to many of the disorders of sighted individuals, including infection and allergy, as well as unique problems associated with ocular prostheses and monocular vision. Appropriate management of these individuals must include a thorough history and examination of the anophthalmic socket. Physicians should ascertain the age of the prosthesis, how frequently it is removed and cleaned and whether the patient visits an ocularist regularly. One should also evaluate the cosmesis of the eye to determine whether it appears proptotic or enophthalmic with the prosthesis in place, and whether translation of the prosthesis is good as the patient looks from side to side. Poorly fitted, too-small prostheses often will not move well and can become displaced; a secondary ptosis is also possible in such cases. Similarly, prostheses that are too large can cause pain and incomplete lid closure. Biomicroscopic inspection should reveal pink conjunctiva free of papillae or follicles. Excessive redness, purulent or ropy mucous discharge or significant odors emanating from the socket usually signify infection. The clinician must also ensure that the orbital implant is not visible through the conjunctiva, as any compromise to the socket provides a direct route for potential infectious spread to the orbit. Finally, it is important to inspect the prosthesis itself, ensuring that the surface is smooth and not crazed or cracked, because these imperfections can harbor microbial pathogens.

Lid ptosis, poor translation and lagophthalmos are often the result of a poorly fitted prosthesis. Such cases should be referred to an ocularist for modification or replacement. In some patients, however, problems arise not from the prosthesis but from alterations in the ocular tissues over time. Atrophy of orbital fat, acquired eyelid laxity and dehiscence of the levator muscle can lead to ptosis or involution of the lids, manifesting as entropion. Individuals with these issues are best referred for consultation with an oculoplastics specialist. Surgical intervention, including volume augmentation of the orbit, resection of the levator muscle or lid resection may be employed to rectify these problems.[6,7]

Conjunctival maladies in the anophthalmic patient should be managed intuitively. Bacterial conjunctivitis is appropriately addressed using a broad-spectrum antibiotic such as Vigamox (moxifloxacin 0.5%, Alcon) or Zymar (gatifloxacin 0.3%, Allergan). Allergic conjunctivitis responds well either to antihistamine mast-cell stabilizers (e.g., Pataday; olopatadine 0.2%, Alcon) or a topical corticosteroid (e.g., Alrex; Loteprednol etabonate 0.2%, Bausch & Lomb). Giant papillary conjunctivitis

(GPC) in prosthetic wearers is likewise best managed with topical corticosteroids.

Regarding visual functioning, it appears that patients are most susceptible to the realities of adjustment in the first weeks and months following enucleation.[8] Advise patients to pay special attention to challenging activities such as navigating stairs or curbs, crossing busy streets and especially driving.

Clinical pearls

• Removal of the prosthesis and biomicroscopic evaluation of the anophthalmic socket is crucial, but it is often neglected because of fear or squeamishness. Inexperienced or apprehensive clinicians should consider enlisting the patient's help rather than foregoing this important aspect of the examination.

• Anophthalmic patients must be educated regarding the need for protecting their remaining functional eye. From a clinico-legal standpoint, it is necessary to prescribe protective eyewear with polycarbonate lenses.

• While no treatment can fully restore the peripheral field or binocularity, low-vision rehabilitation can often improve visual function and allow anophthalmic patients to better cope with their environment and day-to-day activities. The use of mirrored systems and visual scanning techniques are some of the available options for these individuals.[2]

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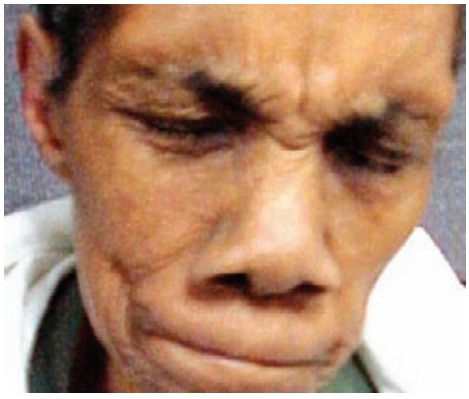
BENIGN ESSENTIAL BLEPHAROSPASM

Signs and symptoms

Benign essential blepharospasm (BEB) refers to the involuntary, tonic spasm of the orbicularis oculi muscle, producing, at the least intermittent closure of the eyelids and at the worst a bilateral syndrome, inducing focal facial dystonia, temporary functional blindness (patients simply can't get their eyes open to see), depression and feelings of social isolation.[1] BEB is often misdiagnosed as a psychiatric condition, which delays correct identification and treatment.[1] True dystonic activity can be uncovered by identifying the presence of muscular weakness.[1] Patients whose BEB involves adjacent focal motor activity of the oral-mandibular region develop interrupted speech, inability to eat and difficulty swallowing and talking. This is known as Meige's syndrome.[1] These individuals may also have pronounced bruxism (clenching of the jaw).[1] If the eyelids are lax, entropion may ensue. Patients with complete eyelid closure who have lost the ability to open them are said to have "apraxia" of lid opening.[1,2] Apraxia of lid opening occupies a separate category because it is often secondary to a supranuclear disorder not demonstrating forceful orbicularis contraction.



Meige's syndrome, a form of benign essential blepharospasm that also involves the oral-mandibular region.

Secondary blepharospasm is a term used to connote a reflexive, involuntary, forceful closure of the eyelids.[1] It occurs after exposure to direct or indirect painful ocular stimuli. Direct exposure can be secondary to chemical injury (solid, liquid, gas, phototoxic), blunt trauma involving the adnexa, thermal injury to the eye or adnexa, dry eye, foreign body introduction and corneal or conjunctival abrasion or laceration, to name a few triggers. Secondary blepharospasm is the result of pain, photophobia and lacrimation produced by the injurious, infective or inflammatory ophthalmic processes. Endogenous sources include but are not limited to anterior uveitis, orbital pseudotumor, dacryocystitis, corneal edema secondary to injury or pupil block glaucoma or other source of acute intraocular pressure rise (neovascular glaucoma, hyphema), vitritis, pars planitis, optic neuritis and retrobulbar hemorrhage. Here, as the pain response to both the injury and the intraocular inflammation build, the patient simply cannot hold the eye open. He or she reflexively winces and squeezes, attempting to find some relief from the intense, throbbing discomfort. Light aggravates the inflammatory response, thus causing photophobia.[1]

Pathophysiology

As the motor division of the seventh cranial nerve (CN VII) is responsible for delivering voluntary motor innervations to the muscles of facial expression (and to the stapedius muscle of the inner ear, which dampens loud sounds), any irritation by adjacent or direct infection, infiltration, inflammation or compression of cranial nerve VII nuclei or its fascicles can produce involuntary contracture of the affected region.[1–18]

Benign essential blepharospasm is poorly understood; in most cases, laboratory testing and neuroimaging do not yield an identifiable underlying cause.[1,2] As such, it is a diagnosis of exclusion.

Abnormal levels of neurotransmitters and/or alterations of the structure, function or architecture of the basal ganglia and/or midbrain have been suspected.[1] New research into benign essential blepharospasm has uncovered a potential neurochemical connection.[19] Altered kynurenine metabolism, a neuroactive metabolite that plays a role in the normal physiology of the human brain, has been identified as a contributor in neurodegenerative disorders such as Parkinson's disease, Huntington's disease and now the pathogenesis of focal dystonia.[19]

Management

The treatment of choice for benign essential blepharospasm is chemodenervation via direct subcutaneous injection.[1,2,20] *Botulinum* toxins in Botox (Allergan, Irvine, CA) are accepted as a first-line treatment for patients suffering from spasms secondary to facial dystonias of all kinds.[4] They work by inhibiting the release of acetylcholine into the synaptic cleft, thereby blocking neuromuscular transmissions.[1,20,22] These treatments are extremely effective and well tolerated.[22] The onset of the effect occurs within one to three days and can last up to three months for cases of essential blepharospasm, slightly longer when used in cases of hemifacial spasm.[1] New agents are being developed to create longer-lasting options to improve the quality of life for patients with facial dystonias who require the paralytic agents to function.[1,20] Treatment failures via antibody production are possible, so treatment more frequent than Q3 months should be avoided.[1] Dopamine-depleting agents, neuroleptics, sedatives, centrally acting cholinergic medications and gamma-aminobutyric acid agonists all have had variable documented success as therapies.[7]

In all cases of blepharospasm, an easy-to-use "Disability Scale" has been developed to quantify the contractures and the changes that occur when treatment is instituted.[21] This allows both patient and treating physician to understand overall inconvenience and functioning and the effectiveness of the mode of intervention.[21]

Secondary blepharospasm will resolve when the root cause has been eliminated. Topical anesthesia is universally helpful in cases where external and superficial anterior segment injury is inducing reflexive closure. Cycloplegia, artificial tears, cold compresses, topical nonsteroidal anti-inflammatory medications and oral analgesics, along with an attack aimed at the root cause of the ocular or adnexal infection, inflammation, intraocular pressure rise or compression will stop the spasm.

Clinical pearls

• Never instill a topical anesthetic until visual acuity has been assessed or at least attempted. In cases where secondary blepharospasm is too severe to determine visual acuity (typically seen in acute corneal injuries) the inability to determine acuity should be documented. Next, instill the anesthetic drop and measure and record the acuity.

• Although it is a radical solution, myectomy—removal of muscle tissue, usually the orbicularis—is listed in the literature as a potential treatment.

• Physical and emotional stress can aggravate symptoms. Even something as simple as participation in a social gathering may cause an exaggeration of the blepharospasm.

• Parkinson's disease and Huntington's chorea (ceaseless jerky movements with mental status changes) are worthy of being placed into the differential diagnosis.[22]

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EYELID MYOKYMIA

Signs and symptoms

The word myokymia is derived from the Greek words *myo*, meaning "muscle" and *kyma*, meaning "wave."[1] It is defined by complex, involuntary, repetitive electrical discharges involving any muscle in the body.[2] With respect to the eye it is known to affect two structures primarily: the eyelid and the superior oblique muscle.[1–5] Patients with superior oblique myokymia (SOM) present with a vertical jerk nystagmus, oscillopsia (the perception that the world is

moving) and transient diplopia.[2–5] Patients with myokymia of the eyelid present with a chief complaint of intermittent "oscillating," "vibrating," "flickering," "quivering" or "twitching" eyelid.[5] Myokymia of the eyelid is the result of repetitive bursts of discharges that stimulate the Muscle of Müller and the ciliary portion of the orbicularis oculi.[3,4] While most patients perceive the unexpected quivering as an annoyance, the seizures are not painful, nor are they so exaggerated that an observer can identify an episode without being within three feet of the person and directly looking at the moving area. Myokymia occurs cyclically and seems to arise at times of increased stress. Patients may be aware or unaware of their body's emotional fluctuations, physical fatigue or illness. The episodes may also be connected to increased sympathetic tone, which can be voluntarily or unknowingly altered by cigarette smoking (nicotine), caffeinated drinks (coffee, tea, sports drinks and energy-boosting supplements or drinks) and some medicines. The episodes are transient, lasting from one to 10 minutes, and can occur one time or multiple times during the day for weeks to months. During normal periods of physical and emotional activity, the episodes cease and the phenomenon moves into hibernation, waiting for the next opportunistic trigger.[3]

Pathophysiology

Traditionally, involuntary, spastic twitching of muscles has been attributed either to tissues recovering from injury, demyelinating disease and neural response to compression or irritation.[2,5–8] In a study that examined acute unilateral facial paralysis, transient long-lasting motor dysfunction featuring disorders of voluntary and involuntary movement was observed.[8] It seems that after an injury (in this instance, the insulted muscles that were studied were around the face) some patients exhibited an increase in their spontaneous blink rate and a sustained, low-level contraction of the muscles of the non-paralyzed side.[7,8] This occasionally lead to full blepharospasm.[8] This was believed to be the result of increased excitability of the facial motor neurons and brainstem interneurons mediating reflexes.[7,8] As one recognized mechanism of occurrence, full-blown "post-paralytic" facial syndrome has been described as levels of muscular synkinesis (muscles responding together), myokymia and unwanted hemifacial contractions accompanying normal facial movements.[7,8] Pathophysiological mechanisms include abnormal axonal branching after injury, with aberrant axonal regeneration and enhanced motor neuronal excitability.[7,8]

Myokymia of the eyelid is often a benign, self-limited disorder, with no relation to injury or paralysis.[3,4] In a study of 15 patients with a diagnosis of isolated eyelid myokymia where the patients in the study had at least 12 months of follow-up, all patients whose symptoms began as unilateral, weekly or biweekly intermittent eyelid spasms with progression to daily spasms over several months demonstrated no manifestation of serious neurologic disease.[3] Thirteen of the 15 patients (86.7%) underwent neuroimaging with no abnormalities found.[2] In this group of 13 patients, the myokymia resolved spontaneously in four participants, with eight of the remaining nine opting to be treated with *botulinum* toxin injection at regular intervals. Most of the patients electing to receive injections reported improvement.[3]

Management

Patients who ask, "Why does my eyelid twitch sometimes?" are most likely experiencing benign eyelid myokymia. The diagnosis can be solidified by confirming the presence of the classic clinical features: it is episodic, limited to the eyelid, painless, has no effect on function, is intermittent throughout the day, seems to come in a cyclic monthly pattern, and recollects other previous symptoms with a repeatable profile, including the possible recognition that the symptoms return when stress levels increase. Patients should be educated that the condition has a name and should be reassured that in almost all instances, it is harmless. They should be counseled regarding signs that may indicate the need for additional work-up. Since increased sympathetic tone, worsened from exogenous sources, can exaggerate or even instigate the problem, patients should be reminded that during stressful situations, they may consciously or unconsciously increase consumption of energy drinks, coffee, sodas, teas or nicotine. Patients should be educated that these coping behaviors may kick-start the aberrant activity. If a patient has recently begun taking a new medication, one should investigate the medication for side effects. Treatments may include modalities as simple as removing the provoking stress, reducing nicotine and/or caffeine consumption, discontinuing a medication, observation, rest, cold compresses and consuming tonic water with quinine (anecdotal), and may progress to medicinal solutions such as topical beta-blockers, anticonvulsants such as carbamazepine 100–200 mg. PO BID-QID as tolerated (minimum medicine to achieve desired effect), gabapentine 100 mg. PO BID building to 300–600 mgs per day or local injections of *botulinum* toxin.[3–8]

Clinical pearls

- Chronic isolated eyelid myokymia is generally considered a benign condition. It tends not to progress to other facial muscles nor elaborate into other facial movements or disorders.
- Excessive benign eyelid myokymia responds well to *botulinum* toxin injection.
- Eyelid myokymia is rarely associated with other neurologic disease. However, eyelid twitching can be a localized manifestation of underlying brainstem disease, making persistent cases of myokymia a diagnosis of exclusion.
- Postparalytic facial dysfunction may occur after idiopathic facial nerve palsy (Bell's palsy), and seems to be the result of increased background muscle

activity and enhanced motor neuron recruitment.

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MADAROSIS AND POLIOSIS

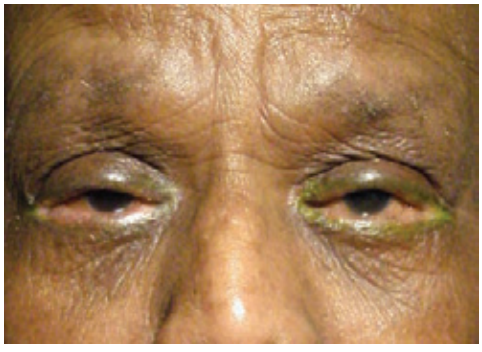
Signs and symptoms

There are few symptoms other than patients' cosmetic complaints directly associated with madarosis, alopecia or poliosis.[1–3] None of these three entities cause frank symptoms by themselves. Madarosis has been well-described in ophthalmic literature as a symptom of blepharitis, *Demodex* infestation, ocular cicatricial pemphigoid, dry eye syndrome, leprosy, exposure to radiation, sarcoidosis, lupus, skin cancer of the eyelids (basal cell carcinoma, squamous cell carcinoma, malignant melanoma), sebaceous cell carcinoma, trauma, thermal burns, contact dermatitis, Steven-Johnson syndrome, eyelid tattooing, miotics, Ehlers-Danlos syndrome, anemia, human immunodeficiency virus (HIV) and some medications.[1–11] Most of the symptoms that occur do so as a result of the root illness; however, in some cases recurrent foreign-body sensation caused by broken lashes, falling hair or lashes trapped in the fornix conjunctiva occur.

In most instances poliosis, a whitening of the lashes, is overlooked or misinterpreted as a sign of aging. Its most infamous associations are with Vogt-Koyanagi-Harada disease (VKH) and vitiligo.[12–15] VKH produces a bilateral granulomatous panuveitis with a tendency toward serous retinal detachment, pleocytosis in the cerebrospinal fluid (a greater than normal amount of cells), alopecia, poliosis and vitligo.[12,13] Vitiligo is a separate entity that causes variable depigmentation of the skin and hair.[14,15]

Pathophysiology

The word "madarosis" is derived from the Greek *madaros*, meaning "bald."[16] It connotes loss of the eyelashes or eyebrow hair. "Alopecia" is derived from the Greek *alopekia*, referring to a disease in which the hair falls out.[2,16] The word "poliosis" is derived from the Greek words *polio*, meaning "gray," and *thrix*, meaning "hair," and describes premature graying of hair or eyelashes.[3,16] Hair follicles possess regenerative potential. They are believed to be crucial for epidermal homeostasis and dermatologic reepithelialization. Unfortunately, hair follicles may be disturbed by systemic and local influences.[17] The pathogenesis of hair, brow and eyelash loss occurs by one of two mechanisms: the scarring form, in which primary inflammatory processes or inflammation, by way of infection, harm the hair follicles, causing hair loss; or the non-scarring form, in which inflammation may be present but the follicles are spared.[1,18] In primary scarring alopecia, the hair follicle is the prime target of destruction. In secondary scarring alopecia, non-follicular processes impinge upon adjacent follicles, ultimately destroying them.[18] Because hair follicles are formed in the second to fifth month of fetal growth, once follicles are lost, hair loss is permanant.[1]



Madarosis results from chronic lid inflammation.

The scarring forms of madarosis are induced by diseases that possess aggressive inflammatory components as part of their pathology, including syphilis, lupus, HIV, leprosy and cancerous tumors.[1,7,9,10,17–21] Non-scarring madarosis is caused by pathological entities in which severe inflammation is not part of the pathogenesis.[1,20] Mechanical rubbing from epidermal irritation, radiation exposure, mild blepharitis or seborrhea create a mild folliculitis without destroying the hair follicle.[1,4,5,20] Chronic irritation of the area may initiate a lymphocytic response, which shrinks the hair bulb and hence the hair itself. In some instances, the hair bulb may convert from an angen (a growing hair) to a telogen (a resting, thin or static hair).[1] This may appear as lost lashes or eyebrow hair when, in fact, the hairs are there but recovering. In some patients, this process occurs secondary to genetic triggers or systemic diseases such as autoimmune disorders, diabetes mellitus or thyroid disease.[1] Androgenetic alopecia (hormonally induced) and telogen effluvium (a disorder of the hair growth cycle) are also primary non-scarring alopecias and sources of reversible madarosis.[20] Androgenetic alopecia is considered the most common form of human alopecia and is believed to affect more than 50% of men by age 50.[16] Alopecia areata (patchy loss of hair in an otherwise healthy individual) affects up to 2% of the U.S. population.[1,20] Telogen effluvium frequently occurs after major life events, such as severe illness, childbirth or high fever, and it may be associated with the use of certain medications or with iron deficiency.[16,22]

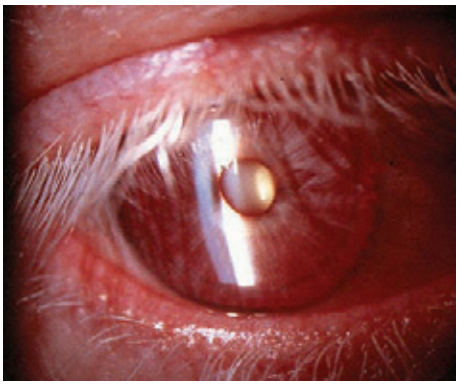
When madarosis accompanies a granulomatous uveitis, VKH should be suspected.[12] VKH is a poorly understood inflammatory process with genetic linkage to people of Asian, Hispanic and Native American heritage. It has a female preponderance and generally emerges in the fourth to fifth decade of life.[12]

Poliosis appearing in isolation has been associated with the use of topical prostaglandin analogs.[8] In one published case series, seven patients treated with different topical prostaglandin medications for primary open angle glaucoma developed bilateral poliosis, either alone or in combination with other predictable side effects.[8] In concert with skin depigmentation, the poorly understood autoimmune disease vitiligo should be suspected.[14]

Management

No management proper exists for the three entities. Rather, in each case the underlying cause must be identified and addressed. Since madarosis is part of a larger clinical picture, keen observational skills are necessary and detailed history must be taken. Carefully inspect the patient's scalp, face, neck and arms for diffuse patterns of hair loss, rashes, inflammations, masses, discolorations or infections. In cases of madarosis secondary to blepharitis, a mixture of baby shampoo and tea tree oil (TTO) has been documented as effective, in addition to any medicinal therapy.[4,5] *Demodex* is resistant to a wide range of antiseptic solutions. Lid scrubs with 50% TTO and 50% shampoo have proven far more effective in eradicating the infection than either of the two substances alone.[4] In cases involving rosacea, oral antibiotics such as doxycycline, tetracycline or minocycline must be added to the regimen.

In cases that involve eyelid or conjunctival inflammation, such as contact dermatitis, medicamentosa and lice infestation, controlling the underlying pathology is the key to reversing the inflammatory process. The optometrist or general practitioner should complete systemic laboratory testing in cases where undiagnosed systemic disease is suspected. Diagnosis is critical, because in cases where follicle destruction is incomplete, the prompt start of systemic immunosuppressive therapy, in combination with topical steroidal and nonsteroidal drops and ointments, may bring about remission or cure.[6]



Poliosis.

In otherwise healthy individuals without evidence of infectious/inflammatory eyelid disease or evidence of loss of the eyebrow or other alopecia, skin cancers, such as basal cell and squamous cell carcinoma, malignant melanoma and sebaceous cell carcinoma, must be suspected in any case of madarosis.[1] Thorough inspection of the eyelids and adnexa is mandatory in these cases, and any finding should be referred to an oculoplastic surgeon capable of completing the excision using the Moh's micrographic technique.[23] In some instances, biopsies may be necessary to achieve a definitive diagnosis.

In the cases of poliosis without suspected systemic disease, the use of newer medications should be considered as a potential source with the possibility of challenge (discontinuing it), to improve cosmesis, as a treatment.[24]

In cases of poliosis associated with vitiligo, conservative therapies include photochemotherapy, phototherapy and systemic steroids.[14] Topical corticosteroids are preferred for localized vitiligo.[14]

Clinical pearls

- Madarosis and poliosis are not diagnoses, but findings. Each requires investigation to determine the underlying cause.
- Trichotillomania is the purposeful self-removal of hair from one's person and should not be confused with madarosis.
- Laboratory work-up should include, but is not limited to, a complete blood count, an erythrocyte sedimentation rate, antinuclear antibody test, a thyroid stimulating hormone test, thyroxine level, triiodothyronine, luteinizing hormone test and fluorescent treponemal antibody absorption test.
- Popular therapeutic options for hair loss secondary to cicatricial etiology include systemic corticosteroids, systemic antimalarials, isotretinoin and antibiotics.

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PROPTOSIS & EXOPHTHALMOS

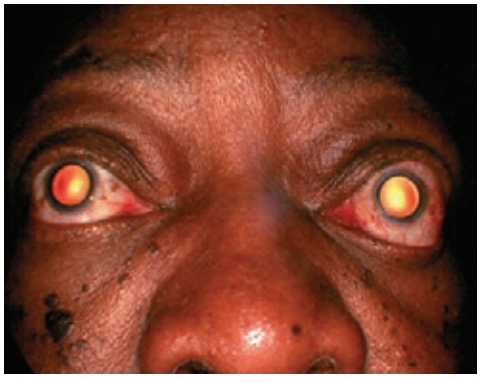
Signs and symptoms

Patients with proptosis and exophthalmos may be symptomatic or asymptomatic, depending upon the severity and duration of the condition. In general, unilateral cases of ocular protrusion are more noticeable and may prompt greater cosmetic concern. The most common symptoms involve ocular discomfort; patients may complain of dryness, burning, grittiness, foreign body sensation or other complaints characteristically associated with exposure. Pain may be reported as well, but this is most often associated with acute events rather than chronic conditions. Redness and swelling of the conjunctiva are also frequent complaints. Visual function may be completely normal or profoundly reduced, depending upon the severity and nature of the underlying etiology. Diplopia is another possible complication of proptosis or exophthalmos and can result from muscle entrapment, infiltration or because of physical displacement of the globe.

Proptosis and exophthalmos are usually associated clinically with increased palpebral fissure width and lid retraction. Extraocular muscle testing may show a restriction of motility, depending on the extent and underlying etiology. Biomicroscopic signs include variable conjunctival hyperemia, chemosis and epithelial keratopathy. Evaluation by exophthalmometry is a helpful diagnostic procedure in these conditions; accepted normal values are between 12 and 21mm (measured from the lateral canthus to the corneal apex), although slightly greater values may be encountered in patients of African descent.[1] A difference of 4–7mm or greater between the eyes is likewise indicative of abnormal ocular protrusion.

Pathophysiology

Proptosis and exophthalmos are both terms that refer to a bulging forward of one or both eyes. A great deal of disagreement exists as to the circumstances in which each of these terms is appropriately used. The medical dictionary suggests that "proptosis" connotes "a forward projection or displacement" of any organ, while "exophthalmos" is specifically defined as "an abnormal protrusion of the eyeball."[2] Other references claim that proptosis refers to unilateral conditions only, while exophthalmos denotes a bilateral condition.[3] A frequently cited textbook insists that the term exophthalmos is reserved for cases that occur secondary to endocrinological dysfunction, while non-endocrine– mediated globe protrusion is appropriately referred to as proptosis.[4] However, the vast majority of published papers seem to use the terms interchangeably.


Bilateral exophthalmos in severe thyroid eye disease.

Proptosis or exophthalmos occurs because of an increase in volume within the bony orbital cavity. Accumulation of extraorbital cellular material or enlargement of any of the orbital contents (e.g., extraocular muscles) may result in forward displacement of the globe. A wide range of etiologies may underlie this phenomenon: infiltrative disorders, infection, inflammatory disease and vascular conditions are the most common causes.

Thyroid eye disease (i.e., Graves' disease, Graves' ophthalmopathy, thyroid ophthalmopathy) is the most frequently encountered etiopathology associated with proptosis/exophthalmos in adults.[5] Infiltration of the extraocular muscles and orbital fat by immune cells (e.g., lymphocytes, macrophages and plasma cells) creates orbital congestion, which in turn causes anterior dislocation of the eye. Since thyroid disease is a systemic condition, bilateral ocular involvement is anticipated; however, some cases may display marked asymmetry, even to the point of unilateral proptosis.[6] Other documented causes of exophthalmos/ proptosis include infection (e.g., orbital cellulitis, phycomycosis), orbital inflammatory disease, lymphoid tumors (e.g., lymphoma, leukemia), vascular disease (e.g., intraorbital and retrobulbar hemorrhage, vasculitis, venous varices, arteriovenous malformations, carotid cavernous fistula), orbital metastasis, lacrimal gland tumors, posterior scleritis, trauma and invasive sinus disease.[7]

Management

Management for any individual presenting with proptosis or exophthalmos begins with a thorough history. Often, additional signs and symptoms can steer the clinician toward the appropriate diagnosis. For example, patients describing intermittent proptosis associated with Valsava maneuvers or postural changes may harbor an orbital venous varix, a low-flow vascular hamartoma that communicates with the normal orbital circulation.[8] Constitutional complaints should also be scrutinized, as these are often

indicative of specific systemic maladies. Occasionally, patients may even volunteer a previously undisclosed medical condition (e.g., thyroid disease, cancer) during pointed questioning.

The most crucial diagnostic test in cases of proptosis/exophthalmos of unknown etiology is orbital imaging. Both computed tomography (CT) and magnetic resonance imaging (MRI) may be used, depending upon the suspected pathology. Imaging of the orbit is especially critical in cases of unilateral involvement, as this technology can identify and differentiate various tumors, vascular malformations and inflammatory lesions. Contrast enhancement can further help to distinguish orbital neoplasms. Orbital ultrasonography can also help in the differential of proptosis or exophthalmos. This in-office technique is rapid, inexpensive, more immediate, and less invasive than either CT or MRI. Unfortunately, ultrasonography can only image the more anterior aspects of the orbit, and it requires a highly skilled and experienced operator to obtain accurate results.

Additional laboratory testing may be indicated if a systemic disorder is presumed. A thyroid function panel—thyroid stimulating hormone (TSH), serum triiodothyronine (T3) and serum thyroxine (T4)—is valuable in patients suspected of having this disorder.[9] In cases where orbital inflammatory disease is suspected as secondary to sarcoidosis, pulmonary function tests, chest X-rays and, in some cases, angiotensin-converting enzyme levels may be diagnostic. A complete blood count is always helpful in identifying potential malignancies such as leukemia and lymphoma. Adjunctive testing for orbital neoplasms may involve fine-needle aspiration biopsy (FNAB) or open conjunctival biopsy if FNAB is inadequate to ensure a definitive diagnosis.

Therapeutic intervention in cases of proptosis/exophthalmos may differ substantially, depending on the underlying etiology. Hyperthyroidism is treated medically in most cases with ongoing therapy with antithyroid drugs (e.g., propylthiouracil, methimazole) or single-dose therapy with radioactive iodine to ablate the thyroid gland. Thyroidectomy is reserved for severe, unresponsive cases or for those in whom medical treatment is contraindicated.[9] Most cases of orbital inflammatory disease are managed with systemic corticosteroids, although additional immunomodulatory agents (e.g., methotrexate, azathioprine, infliximab) may occasionally be required.[5] The preferred treatment for orbital tumors, both vascular and neoplastic, involves surgical resection. Orbital surgery is a possibility, but it can be difficult given the confined space and delicate nature of the surrounding structures. External beam irradiation may be used adjunctively in cases of orbital masses that do not lend themselves to complete surgical excision.

Primary care management of proptosis/exophthalmos entails protection against corneal exposure. Supportive therapy with ophthalmic lubricants can be helpful, as can punctal occlusion. Lid taping at night, in conjunction with lubricating ointment, is additionally beneficial in cases of secondary lagophthalmos. Patients with diplopia may benefit from temporary occlusion of the involved eye or from prismatic correction (e.g., Fresnel prism) until definitive treatment can be offered.

Clinical pearls

• In general, bilateral proptosis/exophthalmos is highly suggestive of thyroid disease, while unilateral proptosis/exophthalmos is indicative of tumor or infection. There are many exceptions to this rule however; cases of unilateral Graves' disease and of bilateral orbital neoplasms have been documented.[10–14]

• In cases in which thyroid dysfunction is suspected, the clinician should inquire about common signs and symptoms of hyperthyroidism, including nervousness, irritability or panic attacks; insomnia; heat sensitivity or increased perspiration; weight loss (despite a normal appetite and diet); tachycardia; hand tremors; muscular weakness in the extremities; thinning of the hair and/or skin; frequent bowel movements; or lighter or less frequent menstrual periods.[15]

• MRI is the preferred orbital imaging technique in most cases of acute proptosis. However, CT may be preferable in conditions that display bony erosion (e.g., sinus abscess); in the evaluation of osseous, cartilaginous and fibro-osseous lesions; and in cases involving recent trauma. Some practitioners also prefer CT for patients with thyroid ophthalmopathy, since it provides excellent detail of both the extraocular muscles and bony architecture of the orbit. CT is also required for those with medical contraindications to MRI, e.g., patients with pacemakers, implanted cardiac defibrillator or aneurysm clips.

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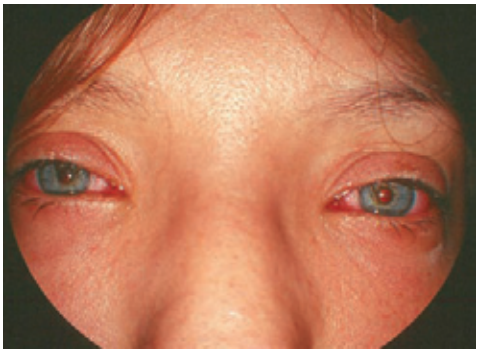
VIRAL CONJUNCTIVITIS (PHARYNGOCONJUNCTIVAL FEVER AND EPIDEMIC KERATOCONJUNCTIVITIS)

Signs and symptoms

The two frequently encountered forms of self limiting viral conjunctivitis are pharyngoconjunctival fever (PCF) and epidemic keratoconjunctivitis (EKC).[1–8] PCF is characterized by a fever, sore throat—or at least a history of recent upper respiratory infection (URI)—and follicular conjunctivitis.[2,5,7,8] It may be unilateral or bilateral with a classic characteristic either of spreading from one eye to the other or becoming apparent in both eyes after realizing infection in one.[1–6] The cornea is rarely affected and infiltrates are uncommon.[3] Although the virus can be eradicated from the conjunctiva in as soon as 14 days, it has the ability to remain in fecal excretions for up to 30 days.[5,6] This may explain why some epidemics are centered around swimming pools in the summer season.[2,5,6] This disorder varies in severity and persists clinically for four days to two weeks.[1–6] The principle symptoms include global conjunctival redness (the "pink" eye) watery discharge, epiphora sometimes leading to a lateral canthal fissure (splitting of the skin at the lateral juncture of the upper and lower eyelids) and variable irritation.[1–8]

Epidemic keratoconjunctivitis, in contrast, may present as a unilateral or bilateral inferior palpebral follicular conjunctivitis, with epithelial and subepithelial keratitis and normal corneal sensation.[9,10] The subepithelial infiltrates (SEI) are typically concentrated in the central cornea, uniquely sparing the periphery.[9–11] These localized gatherings of leukocytes can persist for months, and in one report were documented to remain for more than three years.[11] Since the SEI are pockets of cells underneath the corneal epithelium, they are capable of producing permanent corneal opacities. Conjunctival injection, tearing, watery discharge, red edematous eyelids, pinpoint subconjunctival hemorrhages, pseudomembrane (with occasional true membrane) formation and palpable painful swelling of the preauricular, submandibular or submental lymph nodes are fundamental clinical signs of the entity.[10–12] In severe cases, conjunctival desiccation can result in scarring of the palpebral and fornix conjunctiva.[11]



Viral conjunctivitis (PCF).

Both conditions are contagious.[7–9] As a rule, patients present with a history of contact with a person who had red eyes or had an upper respiratory infection.

Pathophysiology

Viral conjunctivitis can be caused by a number of different viruses.[1–13] Most produce mild, self limiting disease, while others have the potential to produce severe, disabling visual difficulties.[1,2] Most forms of viral/follicular conjunctivitis appear to be the result of a host response to an exogenous substance. Viral conjunctival infections are thought to be caused by airborne respiratory droplets or direct transfer from fingers to the conjunctival surface. After an incubation period of five to 12 days, the disease enters an acute phase, during which inciting particles trigger cytokines and chemoattractants, which initiate a watery discharge, conjunctival hyperemia and follicle formation.[14] Lymphoid follicles are elevated, avascular lesions ranging from 0.2 to 2mm, and they consist of lymphoid germinal centers that have responded to an infectious agent. PCF is commonly caused by adenovirus types 3 and 5, and occasionally by adenoviruses 4 and 7.[8] EKC is commonly caused by adenovirus types 8 and 19.[9] Acute hemorrhagic conjunctivitis (viral/follicular conjunctivitis with subconjunctival hemorrhage) is a variant produced by adenovirus types 19 and 37 and the picornavirus.[12,13] Adenoviruses also have the ability to exert a number of self-limiting effects on the respiratory, genitourinary and gastrointestinal tracts.[1] In fact, adenoviruses account for 5 to 10% of respiratory illnesses in children.[7,8] Adenovirus 7a has the potential to cause community epidemics via transmission through children.[8] There is evidence that adenovirus type 8 can produce a more aggressive response, resulting in extensive keratitis, subepithelial opacities, subconjunctival hemorrhage and pronounced lymphadenopathy.[15]

Subepithelial infiltrates are caused by virus antigens and lymphocytes collecting in the shallow anterior stroma, just beneath the central epithelium.[3,15] Confocal biomicroscopic examination provides evidence of an inflammatory response localized to the basal epithelium and anterior stroma of the central cornea.[8] Some EKC variants include conjunctival membrane formation. Acute and chronic autoreactive mechanisms can cause significant damage to the eye.[17,18] When severe and affecting the corneal epithelium and substantia propria of the palpebral conjunctiva, cicatrization (scarring) may ensue, leading to significant mechanical alterations.[17,18] The end result is fibrosis.[17,18]

Histologically, conjunctival membranes consist of fibrin and leukocytes with fibroblast and collagen deposition. They occur in prolonged cases. Pseudomembranes are differentiated from true membranes by the ease with which they are removed.[11,17,18] As the components accumulate, they interdigitate on a molecular level with the palpebral conjunctiva. As a result, when they are stripped from the con-

junctival surface, they produce trauma to the underlying membrane that often results in bleeding. In cases where the buildup is considered a pseudomembrane, removal is easier and less bleeding occurs. In cases where the buildup is substantial, creating a true, additional membrane, removal is laborious, traumatic, time-consuming and often damaging to the underlying conjunctiva. In these cases, bleeding is often oozing and perfuse.

Diagnostically speaking, one report showed that cultured viral conjunctivitis yielded adenovirus as the most common virus isolated from conjunctiva (66%), herpes simplex virus 1 as the most common virus isolated from the eyelids and cornea (76% and 88%, respectively) and cytomegalovirus as the most common virus isolated from the vitreous (27%).[3] Clinically speaking, a doctor's accurate recognition of the common ocular viral syndromes was measured at 88% for herpes simplex virus 1, 88% for EKC, 70% for acute hemorrhagic conjunctivitis and 100% for varicella zoster virus.[3] However, some misdiagnosed cases did occur. Thirteen percent of conjunctivitis thought to be caused by herpes virus I was determined by laboratory testing to be secondary to adenovirus, 3.2% was determined to have been caused by enterovirus, 3.2% was caused by varicella zoster virus and 3.2% was caused by human cytomegalovirus.[3] Interestingly, 5% of cases with a clinical diagnosis of herpes virus I keratitis were discovered to have been the result of adenovirus.[3] These results indicate the sometimes ubiquitous nature of viral conjunctivitis. Fortunately, because most cases are mild and self limiting with treatments that are similar and supportive, clinical therapies and diagnoses are officially recorded by practitioners as accurate and effective.

Management

In most cases, because viral conjunctivitis is contagious and self-limiting, the primary function of management is to increase patient awareness by providing education and to increase patient comfort by relieving symptoms. Patients should stay home from work or school until contagious discharge is eliminated,[2] and should be warned not to share common utensils, glasses, linens or washcloths. Medical management may range from supportive cold compress and tears to topical vasoconstrictors, topical nonsteroidal anti-inflammatory medications and topical steroids BID to QID. If pseudo- or true membranes are present, they should be removed using a forceps or a moistened cotton-tipped applicator soaked in a combination of antibiotic solution and anesthetic. Topical antibiotic steroidal combination (Tobradex, Maxitrol, Zylet) therapy QID can be employed following the removal of the inflammatory membrane.[11]

Currently, no specific topical antiviral medication is recognized as an effective treatment for viral conjunctivitis.[18] However, cidofovir and ribavirin (nucleoside or nucleotide analogs) have been described as agents that affect adenovirus polymerase.[4] Unfortunately, according to a published report, cidofovir topical ophthalmic solution tested on white rabbits was shown to produce significant narrowing of lacrimal canaliculus, redness of eyelid and conjunctival injection.[18] Until these side effects can be reduced or eliminated, a topical antiviral medication for viral conjunctivitis will not reach the marketplace.

Remarkable anti-adenoviral effects have been observed from adenoviral receptor inhibitors and natural products, along with anti-HIV nucleoside reverse transcriptase inhibitors such as zalcitabin and sanilbudine.[18] Interferon beta and anti-osteopontin peptide are two additional compounds that demonstrate promise.[18]

One of the confounding issues that surround this type of conjunctivitis is that its mode of presentation permits practitioners to speculate on diagnosis rather than react to a positively identified cause.[3] Hence, doctors frequently attempt an empiric, broad-spectrum approach to an observed, nebulous red eye by prescribing topical antibiotics with combinations of topical steroids, nonsteroidal anti-inflammatory medications or mast-cell stabilizer/antihistiminic agents. While one might argue that little harm can come from initiating these modalities separately or together, there is clearly expense, inconvenience and in some cases toxicity. Further, if the patient does indeed have viral conjunctivitis, he or she is contagious and should be advised as soon as possible of the potential to spread the disease to colleagues and coworkers.[7,8]

The Point of Care Diagnostic Services Rapid Pathogen Screening (RPS) Adeno Detector uses technology based on lateral flow immunochromatography to uncover the presence of adenoviral antigens.[19] Foreign substances are captured by the testing tool and presented to antigen-specific monoclonal antibodies inside the apparatus using a sandwich technique (antibody, antigen, antibody). The sample collector is designed to safely gain and transfer an appropriate ocular fluid sample from the lower conjunctiva to the lateral flow immunoassay, located in a plastic cassette. Once the sample has been transferred, a result is available in 10 minutes.[19] The test has a control indicator line; when it appears in the result window, the test is valid. The test is best administered within seven days of the patient's developing a red eye.[19] It requires a reasonable viral antigen load to generate a reading; false-negative readings are possible and a negative reading does not exclude other infectious etiologies.[19] Compared to the polymerase chain reaction test (PCR), the RPS Detector showed a sensitivity of 89%, indicating that it is nearly as sensitive as the gold standard.[19] According to FDA and product literature, the data indicated for the RPS Detector a sensitivity of 88%, specificity of 91%, overall agreement between the two

tests of 90%, a positive predictive value of 76% and a negative predictive value of 96%.[19]

However, three of the apparent false positives found by the RPS Detector were confirmed by the PCR, making the specificity of the RPS 93%.[19]

Clinical pearls

• Office equipment, instruments and areas should be meticulously maintained so they do not become a flashpoint for outbreak.

• Most practitioners reserve topical steroidal therapy for the severely symptomatic (SEI on the visual axis decreasing acuity) or recalcitrant cases.

• EKC infiltrates typically resolve without scarring the cornea. Patients should be told to expect worsening over the first seven to 10 days and improvement over three to six weeks. Steroids should be tapered slowly as the condition remits.

• Pseudoguttata (elevation of the Descemet's membrane) have been reported secondary to superficial corneal injury and keratitis.[20] These unexpected lesions may develop in cases of EKC or PCF, but they are known to dissipate as the inciting disease resolves.[20]

• The adenovirus associated with PCF can be fatal in children if not promptly and properly identified and supported. The URI that preceded the red eye should not be discounted or ignored.

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ATOPIC KERATOCONJUNCTIVITIS

Signs and symptoms

Patients with atopic keratoconjunctivitis (AKC) invariably have a personal or family history of allergic disease. This may include atopic dermatitis (i.e., eczema), asthma, hayfever, food allergies, and/or urticaria.[1,2] Patients are usually male, older than 20 years, with the peak incidence of AKC occurring between ages 30 and 50.[1–3] The condition is marked by exacerbations and remissions, with the most symptomatic periods occurring during colder winter months.[1–4]

Symptoms associated with AKC primarily consist of intense bilateral itching with associated hyperlacrimation. Patients may also complain of a stringy or ropy mucoid discharge. Eyelid swelling may be substantial, with painful burning of the lids and periocular skin. Inspection of the eyelids reveals characteristically scaly, indurated and wrinkled skin, with the possibility of fissure development at the lateral canthus associated with chronic ocular rubbing and epiphora.[2–4] Biomicroscopically there will be pronounced conjunctival hyperemia and edema, as well as tarsal papillae. Gelatinous limbal papillae and Horner-Trantas dots (i.e., collections of degenerated epithelial cells and eosinophils), considered pathognomonic for vernal keratoconjunctivitis, may also be seen in advanced cases.[2–4] Notable corneal involvement may also be encountered, including punctate keratitis, persistent epithelial erosions, "shield ulcers," mucus plaque formation and neovascularization.

The chronic inflammation associated with AKC has the capacity to impart cicatricial changes within the conjunctiva and cornea. Subepithelial conjunctival fibrosis, symblepharon (with subsequent entropion), corneal lipid deposition and pannus are not uncommon.[4,5] Primary corneal ectasias, such as keratoconus and pellucid marginal degeneration, may also occur in association with AKC. These corneal changes often bring associated astigmatic changes and scarring, with subsequent visual impairment. Interestingly, cataract development is pos-

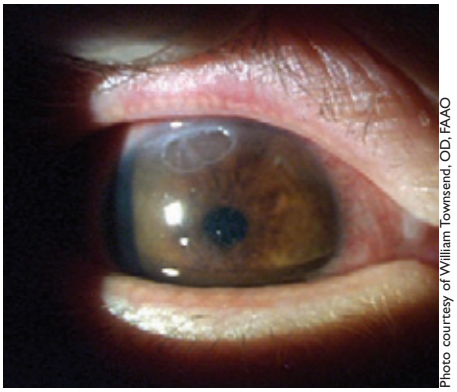


Photo courtesy of William Townsend, OD, FAAO

Shield ulcer in atopic keratoconjunctivitis.

sible in AKC. Anterior subcapsular opacities (sometimes called "shield cataracts") are the predominant variety, and these are thought to result from atopic inflammation.[2,4] Posterior subcapsular cataracts may be encountered to a lesser degree, especially in cases of prolonged topical corticosteroid usage.[2,4]

Pathophysiology

AKC is believed to manifest elements of both Type I and Type IV hypersensitivity reactions.[6] Type I represents an immediate or anaphylactic reaction and involves the sudden degranulation of mast cells mediated by IgE antibodies; this is the response seen in acute allergic conjunctivitis (e.g., seasonal and perennial allergic conjunctivitis). A Type IV reaction, also known as a delayed or cell-mediated hypersensitivity reaction, involves T-lymphocytes and associated lymphokines. Other examples of Type IV reactions include contact dermatitis and phlyctenulosis.

Histopathologic evaluation of conjunctival samples from patients with AKC reveals elevated levels of mast cells, lymphocytes, eosinophils and basophils.[1] Mast cell degranulation—which is seen in acute forms of ocular allergy—initiates the release of histamine, chymase, tryptase and heparin; these mediators are responsible for vasodilation, increased collagenase activity and early fibrinogenesis.[7] In addition, degranulation of eosinophils releases numerous toxic/ inflammatory proteins, such as eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin.[7] Not only do these proteins induce cicatricial changes in the conjunctiva, but they have also been shown to cause cytotoxic disruption in corneal epithelial cells, suggesting a possible mechanism for the extensive corneal pathology seen in AKC.[8]

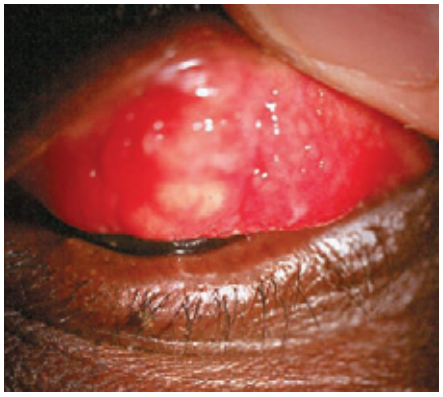
It has been suggested that inherent feedback mechanisms that normally regulate the allergic response may be impaired in atopic disorders, resulting in continuous T-cell activation.[7] Research has identified several specific genes that may be responsible, and this theory is supported by the strong role of family history in atopic diseases such as AKC.[9]

Management

AKC is a chronic and potentially blinding disease. Once it is identified, treatment must be swift and aggressive. The ultimate goals are to alleviate the debilitating symptoms and preserve vision while minimizing the potential side effects of medical therapy. Numerous palliative measures, including cold compresses, ophthalmic lubricants and topical vasoconstrictors, may all be of short-term benefit. In addition, topical antihistamines or antihistamine-mast cell stabilizer combinations (e.g., Pataday QD) address the initial allergic response and can provide longer-lasting relief for many patients. However, since a good portion of the pathology in AKC is associated with leukocyte infiltration/ degranulation, topical corticosteroids are almost invariably required to suppress the inflammatory response. Prednisolone acetate 1% is considered the gold standard of topical ophthalmic steroids, but this agent may also raise intraocular pressure and induce cataract formation with prolonged use. Loteprednol etabonate 0.5% may provide a safer, although possibly less efficacious, alternative in cases of AKC that require long-term corticosteroid therapy.[10] Dosing of steroids varies depending on the individual case; in general, we advocate at least QID instillation, increasing the frequency concurrent with increased levels of inflammation. Steroids should be continued for at least one to two weeks before attempting a slow taper. In the case of corneal shield ulcers, topical cycloplegia (e.g., 0.25% scopolamine BID) and broad-spectrum antibiotic prophylaxis (e.g., 0.3% tobramycin or 0.3% ciprofloxacin BID) may be warranted. Some prefer the convenience of a combination antibiotic/corticosteroid such as TobraDex (Alcon) or Zylet (Bausch & Lomb) in these situations.

Patients with AKC who are inadequately controlled with topical corticosteroids or those who experience negative sequelae warranting discontinuation of steroids may require alternative immunomodulatory therapy. Topical cyclosporine may be an effective alternative in this situation; it has been shown to specifically inhibit T-lymphocyte proliferation while imparting direct inhibitory effects on eosinophil and mast-cell activation.[11] Early research using 2% cyclosporine in maize oil demonstrated a distinct benefit[12]; however, clinical studies involving 0.05% cyclosporine emulsion (Restasis, Allergan) have shown mixed results.[13,14]

For significant atopic dermatitis involving the lids, additional topical therapy may be necessary. Corticosteroid creams or ointments may be highly beneficial in this capacity; some options include 1% hydrocortisone, 0.1% triamcinolone acetonide or 0.05% clobetasone butyrate. In lieu of steroids, topical 0.1% tacrolimus ointment (Protopic, Astellas Pharma) has demonstrated equivalent safety and efficacy in a head-to-head clinical study.[15]



Pronounced tarsal papillae with cicatricial scarring in AKC.

Clinical pearls

• It is important to distinguish between AKC and vernal keratocon-

junctivitis (VKC). VKC is another form of chronic inflammatory ocular allergy; however, unlike AKC, it tends to be seen in younger male patients (ages 3 to 25 years). VKC also has a tendency to become exacerbated during warmer months and in warmer climates, compared with AKC, which worsens in colder climates. Clinically, VKC presents with classic "cobblestone" papillae on the upper tarsus, while the papillae in AKC have a propensity for the lower cul-de-sac.[1]

• AKC must also be differentiated from more acute conditions such as contact eyelid dermatitis and preseptal cellulitis. Contact dermatitis typically involves a history of exposure to some agent or object and presents with edema, erythema and pronounced itching. Corneal involvement is exceedingly rare. Preseptal cellulitis involves a focal infection within the eyelid, presenting with acute unilateral pain and swelling.

• "Shield ulcers," which are not actually ulcers but epithelial erosions, typically occur with VKC, but they may occur with AKC as well. These corneal defects are caused by a combination of corrosive inflammatory cytokines and the mechanical rubbing of the tarsus over the cornea.

• While some have advocated the use of topical nonsteroidal anti-inflammatory drugs (NSAIDs) in the management of AKC, our experience suggests that these agents provide little benefit. In addition, there is a potential risk of corneal melts when these agents are used inappropriately. Likewise, some sources recommend oral antihistamines as adjunctive therapy for AKC. Unfortunately, the histamine response is such a minor element of AKC and the amount of drug delivered to the ocular tissues with oral formulations (vs. topical agents) is so minimal that there is likely to be little clinical benefit.

• Despite the number of therapeutic options, AKC can be exceedingly difficult to treat, particularly in later stages after multiple exacerbations. Consultation and co-management with an allergist, dermatologist and corneal surgeon should be considered for such patients.

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OCULAR MELANOSIS

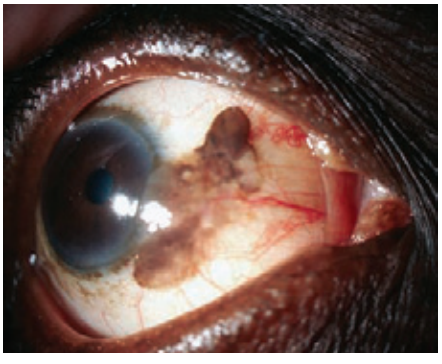
Signs and symptoms

Ocular melanosis represents a pigmented discoloration of the superficial ocular tissues. Patients are not usually symptomatic with regard to discomfort or visual disturbance, but they often present with cosmetic concerns, particularly when the condition is newly acquired. In some cases, patients will report that their eyes are chronically red, mistakenly interpreting the ocular pigmentation as hyperemia. Biomicroscopically, ocular melanosis appears as a brown-to-dark-brown discoloration of the epibulbar conjunctiva. Depending upon the etiology, it may be unilateral or bilateral and flat to slightly elevated, and it may take the form of irregular patches, streaks or circumlimbal darkening.

Racial melanosis is a congenitally acquired condition that is exceedingly common in patients of African descent. It occurs on the order of 92% according to some sources.[1,2] This condition tends to be bilateral and symmetric, is most prominent circumlimbally and remains relatively consistent throughout a patient's life.

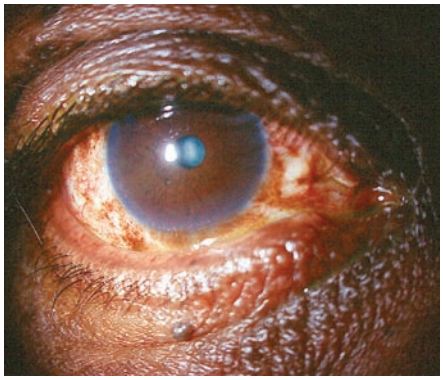
Conjunctival nevi are the most common type of conjunctival melanosis. They present as discrete, well-demarcated congenital lesions, located most often on the interpalpebral bulbar conjunctiva but occasionally affecting the caruncle, plica or lid margin.[3] They may be flat to slightly elevated with occasional cystic formations, and may vary significantly in pigment density. Caucasians are most likely to develop conjunctival nevi as compared to other races accounting for 89% of cases according to one clinical series.[4]

Primary acquired melanosis (PAM) is less common than racial melanosis and conjunctival nevi, and it tends to occur much more frequently in Caucasians than in those of African



Primary acquired melanosis is typically unilateral and irregular.

descent.[3] It may be differentiated from racial melanosis in that it is typically unilateral and irregularly shaped, demonstrating increased growth over time and involving widespread areas of the conjunctiva, including the fornices.


Pronounced racial melanosis.

Malignant conjunctival melanoma is a rare tumor of the ocular surface. It is typically encountered in middle-aged or elderly white patients, although a small number of cases involving patients of African descent have been documented.[1,2,5–7] Clinically, conjunctival melanomas are densely pigmented elevated or nodular lesions with intrinsic vascularization (sometimes called "feeder vessels") arising from the fornices. They are generally unilateral but often multicentric, and may involve areas of the bulbar and/or tarsal conjunctiva.

Pathophysiology

The word *melanosis* is a generic term referring to excessive darkening of a tissue due to a disturbance in melanin production or deposition. In cases where the eye is involved, the condition is sometimes called *melanosis oculi* or *melanosis bulbi*. In racial melanosis, there is an accumulation of benign melanocytes and melanin granules within the basilar layer of the conjunctival epithelium, typically limited to the perilimbal tissues.[8,9] Conjunctival nevi also represent benign proliferations of melanocytes within the basal layer of the epithelium. As a patient ages however, these nevus cells can migrate deeper into the underlying stroma.[3]

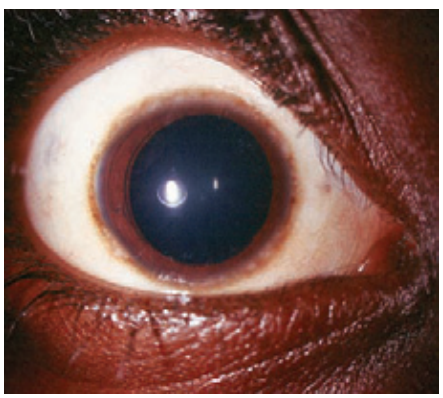
In contradistinction to racial melanosis and conjunctival nevi, PAM is characterized by the presence of abnormal melanocytes within or near the basal layer of the epithelium. Four types of cells—small polyhedral, epithelioid, spindle and dendritic—may be identified in these lesions.[3,10,11] Additionally, PAM may display five distinct growth patterns: basilar hyperplasia, basilar nests, intraepithelial nests, pagetoid growth (i.e., cell invasion into the epithelium) and melanoma-in-situ (i.e., the replacement of normal epithelial cells with melanocytes).[3,10,11] PAM is classified histopathologically, based on the type of atypical cells and the extent of intraepithelial growth. Lesions that show a propensity toward large, atypical (e.g., epithelioid) cells and epithelial invasion constitute PAM with atypia; those that are comprised primarily of small polyhedral cells and remain confined to the basal epithelial layer are referred to as PAM without atypia.[3] These distinctions are important, because atypia has been shown to correlate to a lesion's potential for malignant transformation.[3,8–13]

Conjunctival melanoma may reflect malignant transformation of pre-existing nevi or PAM; less commonly, they arise *de novo*.[1-6,9–13] These lesions often show prominent nesting of atypical melanocytes in the junctional region (i.e., between the epithelial and subepithelial tissues), as well as pagetoid extension of tumor cells into the overlying epithelium.[3] The definitive diagnostic criterion for invasive melanoma is extension of atypical melanocytes into the underlying conjunctival stroma (substantia propria).[12] Melanoma is a highly malignant tumor and has significant capacity for distant metastasis; its spread to the ipsilateral facial lymph nodes, brain, lung and liver are most common.[14,15]

Management

Management strategies for ocular melanosis are dependent upon the nature of the condition. Racial melanosis is considered benign and warrants no intervention other than education and reassurance for patients with cosmetic concerns. Only in cases that are unilateral or seemingly progressive should the practitioner consider additional testing. Conjunctival nevi may require greater scrutiny. Physicians should inquire regarding any recent changes in lesional size, elevation, color or irritation, and also consider unusual features such as increased vascularization or unusual location. Suspicious lesions should be referred for excisional biopsy to rule out malignancy, but in most cases, simple periodic observation constitutes adequate management for conjunctival nevi.[4]

PAM typically warrants greater concern and investigation. Since PAM may have a propensity for malignant transformation and is potentially life-threatening,[11] practitioners should routinely arrange for excisional biopsy on these patients. Those cases that do not display atypia or display only mild atypia on histological evaluation may be followed using the same guidelines as with a conjunctival nevus, as the risk of malignant conversion in these lesions is quite low.[3,12] However, if PAM with moderate or


Mild racial melanosis.

severe atypia is noted, then prompt removal of the lesion is indicated. Management options may include surgical excision with or without cryotherapy, radiotherapy, exenteration or extirpation and topical chemotherapy; the individual treatment for any given case depends on the lesion's size, disposition and location.[3]

Cases of suspected conjunctival melanoma should be referred promptly to an ocular oncologist or oculoplastics specialist for evaluation and excisional biopsy. The management of these lesions can be difficult and varies based upon the extent and severity of the presentation, although surgical removal is typically the treatment of first choice. Excision with wide margins and adjunctive cryotherapy to ensure destruction of the malignant tissue is used for isolated melanomas, while lesions that extend into the globe or orbit may warrant enucleation or orbital exenteration, respectively.[9] Despite treatment, the risk of morbidity is high. One long-term study found the following results: The risk of local tumor recurrence is 26% at five years, 51% at 10 years, and 65% at 15 years; metastasis was present in 16% of patients at five years, 26% of patients at 10 years, and 32% of patients at 15 years; and tumor-related death occurred in 7% of patients at five years and 13% at eight years.[14]

Clinical pearls

• Racial melanosis is exceedingly prevalent in dark-skinned individuals, but pigmented lesions of the conjunctiva are otherwise relatively uncommon. In general, lesions that are unilateral, elevated, or more prominent in the fornices or palpebral conjunctiva have a greater tendency toward malignancy and warrant close scrutiny.

• The transformation of conjunctival nevi to malignant melanoma occurs only in rare instances, about 4% of the time or less.[4,14] Still, practitioners should consider any changes in size, elevation, color or vascularization to be suspicious and an indication for additional consultation or testing.

• PAM and malignant melanoma may sometimes be overlooked or dismissed in dark-skinned patients because the conditions are similar in appearance to racial melanosis. Practitioners must remain diligent and obtain appropriate testing in all cases of atypical conjunctival melanosis, regardless of the patient's race.

• Both conjunctival nevi and melanomas may occasionally present as amelanotic lesions; i.e., devoid of melanin pigment. In such cases, they usually appear as pink, variably elevated fleshy plaques or nodules. The prognosis for these lesions is the same as for the pigmented variety; however, definitive diagnosis is often delayed because of the atypical appearance.[16]

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PYOGENIC GRANULOMA

Signs and symptoms

Considered overgrowths of vascular tissue, pyogenic granulomas are unsightly, sometimes pedunculated, dome-shaped lesions that arise on the face, eyes, lips, hands or mucosal membranes after episodes of chronic irritation or minor trauma.[1–7] They are also known to arise during pregnancy.[5] Pyogenic granulomas have also been reported to arise within congenital capillary malformations such as port-wine stains.[6] However, in these cases they usually present following cosmetic laser treatments.[6] The lesions possess the unusual characteristic of bleeding easily.[8]

The eye, the adnexa, the eyelids, the conjunctiva and rarely the cornea may be affected.[1–5] When the lesions are seen on the cornea they are located anterior to Bowman's layer, leaving the corneal stroma unaffected.[6] Patients may complain of tearing or interrupted eyelid closure, depending upon the location of the growth. The lesions rarely induce pain or discomfort of any kind. Visual acuity is only affected if the lesion interrupts the visual axis or induces a keratopathy secondary to incomplete tear film spreading. In most instances, the patient presents with a concern over a steadily growing, unattractive mass, with fear that it is a cancerous tumor.[6] There is no gender or racial predilection; nor is there a common decade of evolution.[7] Evidence supports unexplained, spontaneous development of pyogenic granulomas.[9] In one study, clinicians reported an anomalous occurrence of multiple, eruptive pyogenic granulomas in a previously healthy 17-year-old girl, who developed more than 200 spontaneous

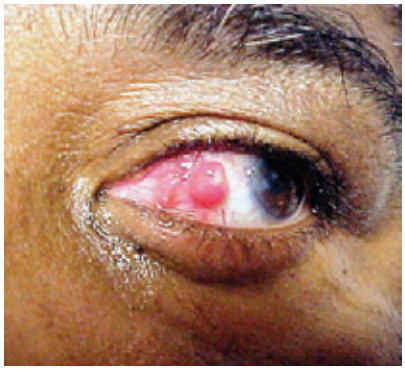
lesions over eight months.[9]

Pathophysiology

Pyogenic granulomas are neither pyogenic (pus-producing) nor granulomatous (being a collection of fibroblasts and macrophages surrounded by lymphocytes produced secondary to inflammation or infection).[1–7] Pyogenic granulomas (lobular capillary hemangioma) are polypoidal vascular proliferations, often accompanied by inflammatory infiltrates, that may affect the skin and mucosal linings of the body.[1–5] Pyogenic granulomas are considered to be among the most common acquired vascular growths of the eyelids.[5] They typically arise following an episode that incites a local vasoproliferative inflammatory response, such as trauma, chronic irritation (the friction created by an exposed suture, punctal plug or prosthesis post, toxic substances and infection) or a surgical procedure such as cataract extraction or a chalazion removal, proximal to the area.[1–13] The inflammatory infiltrate seen in cases involving the cornea is composed mainly of mononuclear cells, with no multinucleated giant cells. The lesions are not malignant.[5,13,14]

Management

Treatment begins with differential diagnosis. Chalazia, internal hordeola, squamous cell carcinoma and sebaceous cell carcinoma are all differential diagnoses. Once the definitive diagnosis is made, one can make a conservative effort to regress tissue proliferation by removing the inciting factor and prescribing topical ophthalmic steroidal creams, ointments and drops BID–QID.[7,11] Should less invasive therapy fail, excision and biopsy (removing the lesion at its base) is common practice.[2,7] When the lesions are properly excised with direct closure, recurrences are uncommon.[7] Uncomplicated pyogenic granulomas (away from the lid margin and free from intimate involvement with adjacent tissues) can be removed using single-shave excision and electrocautery.[8] A pulsed dye laser has been employed to treat pyogenic granulomas due to its ability to induce selective destruction of superficial cutaneous capillaries, thus minimizing trauma and scarring.[15] The procedure seems particularly applicable in apprehensive patients and in children.[15] Another set of investigators reported success using a combined continuous-wave/pulsed carbon dioxide (CO^2) laser.[16] Promising results have been recorded, with few adverse effects and low recurrence rates with excellent tolerability.[16] It has been suggested recently that continuous-wave/pulsed CO_2 laser should be considered as the treatment of first choice.[16] Cryotherapy has also been used to treat these lesions.[17] Due to imperceptible scarring in the majority of cases, cryotherapy should be welcomed into the armamentarium of management options.[17] Silver nitrate cauterization has also been used by dermatologists.[18] In one published investigation, successful cauterization of skin-based masses using silver nitrate applicators following blunt removal resulted in complete resolution in 85% of patients, after an average of 1.6 treatments (range: one to three treatments).[18]



A pyogenic granuloma of the bulbar conjunctiva.

Clinical pearls

• Pyogenic granulomas induced by punctal plugs can spontaneously produce punctal plug extrusion (the movement and/or dislodgement of the plug).

• Larger punctal plug sizes and sharp plug edges (relating to either punctal plug design or deformity) are also associated with pyogenic granuloma formation.

• When corneal mass lesions are discovered, pyogenic granuloma should be considered and ruled out to avoid unnecessarily aggressive intervention.

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HERPES SIMPLEX VIRUS EPITHELIAL KERATITIS

Signs and symptoms

Patients with herpes simplex virus (HSV) epithelial keratitis tend to be young, though more patients in older age groups are acquiring HSV for the first time.[1,2] HSV epithelial keratitis also occurs in children, who may have bilateral involvement.[3,4] There is no gender or racial predilection.[1]

Epithelial keratitis is the most common presentation of ocular infection by HSV-1.[2] Epithelial keratitis caused by HSV typically presents as a unilateral red eye with a variable degree of pain or ocular irritation. Bilateral HSV epithelial keratitis, while uncommon, does occur in 1–2% of cases and is often complicated by immunosuppression, occult malignancy, or atopic disease.[5] Photophobia and epiphora are common. Vision may or may not be affected, depending upon the location and extent of the corneal lesion. A vesicular skin rash and follicular conjunctivitis may be seen with the initial primary infection, but are less common with recurrent HSV.[1] Secondary uveitis is often encountered with the keratitis.

The hallmark sign of HSV infection involves a dendritic ulceration of the corneal epithelium, accompanied by a stromal keratitis in more severe presentations.[1,2] Endothelial inflammation with edema and underlying keratic precipitates, known as endotheliitis, can also be present.[1,2] These lesions may begin as nondescript punctate keratopathies that quickly coalesce to form the familiar branching patterns that stain brightly with sodium fluorescein dye. Early corneal epithelial changes in primary HSV infections often show clear epithelial vesicles and rounded limbal epithelial foci, which eventually form the stereotypical HSV dendrites.[6] Because the virus invades and compromises the epithelial cells surrounding the ulcer, the leading edges (the so-called terminal end-bulbs) exhibit staining with rose bengal dye and lissamine green dye. However, various factors, including duration since onset, medication use, atopic disease and history of corneal transplantation, can give HSV epithelial keratitis lesions an atypical appearance that may be misdiagnosed.[7]

HSV epithelial keratitis commonly recurs.[8,9] The disease itself often recurs in the same clinical pattern as the first episode, with a recurrence rate of 0.6 episodes per year.[9] Precipitating trigger factors include fever, hormonal changes, ultraviolet sun exposure, psychological stress, ocular trauma, trigeminal nerve manipulation, steroid use, ocular surgery, exposure to ultraviolet radiation, immunosuppressive agents and glaucoma treatment with prostaglandin analogs.[1,10–14]

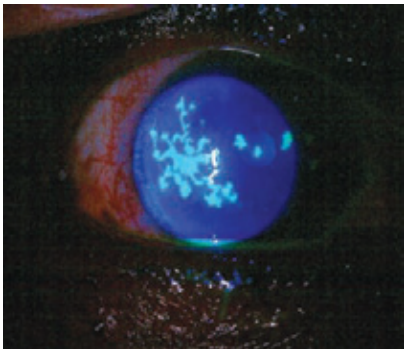
Pathophysiology

HSV is the most common virus in humans and can be found in the trigeminal ganglion in almost 100% of those older than 60 years.[1] HSV-1 affects predominantly the upper half of the body; HSV-2 is associated mainly with the lower half of the body.[15] HSV is transmitted via bodily fluids—usually saliva—and may affect the skin and mucous membranes of the host.[1] Primary herpetic infections occur most often in children ages 6 months to 5 years. The manifestation of this infection is generally a vesicular rash, sometimes affecting the skin of the eyelids (which may go unnoticed) but more commonly resulting in a "fever blister" or "cold sore" in or around the mouth.[1] After resolution, the virus remains dormant in the body. Reactivation of the virus may be triggered by an array of known factors.[1]

While many ocular manifestations of HSV are immune and inflammatory in nature (stromal and disciform keratitis, iridocyclitis), epithelial dendritic keratitis represents infection by the live virus.[1,15,16] Viral replication is usually confined to the corneal epithelium, with stromal invasion impeded by an early onset of non-specific defense mechanisms. These are rapidly complemented by the specific, mainly cellular, immune response.[15] As the epithelial cells die, a dendritic ulcerative keratitis results. After several recurrences, the corneal stroma may become involved.[15] Disciform stromal scarring, conjunctivitis and uveitis are natural sequelae to corneal inflammation.

Management

Corneal epithelial disease secondary to HSV infection must be managed aggressively and quickly to prevent deeper corneal penetration. The treatment of choice consists of topical trifluridine (Viroptic) 1% given at two-hour intervals nine times daily.[2,17,18] As regression of the dendrites becomes evident, the dosage may be tapered to Q3-4H until complete resolution (usually seven to 10 days). At this point, the patient should be observed closely for another week to ensure adequate suppression of the virus. Debridement of the ulcer bed to remove active virus cells has been advocated as an adjunctive therapy to topical antiviral therapy and appears to enhance the speed of resolution.[17] Cycloplegia (homatropine 2% TID-QID or scopolamine 0.25% BID-QID) may be initiated, depending upon the severity of the uveitic response and the patient's subjective discomfort.



The characteristic dendritic epitheliopathy associated with HSV keratitis.

In cases where significant toxicity or other adverse response to the topical antiviral therapy exist, oral antiviral medications can effectively treat HSV epithelial dendritic keratitis.[4,19,20] Valacyclovir 100 mg/kg BID or acyclovir 50 mg/kg 5 times/day for 5 days are suggested dosings.[19] Beyond therapeutic treatment of HSV epithelial keratitis, oral antiviral medications may serve in a

preventative role by reducing the number of clinical infective outbreaks through the course of one year. Most practitioners however, extend prophylais beyond that time frame.[21,22] Acyclovir 400 mg BID PO is the standard suppressing dosage.[21,22]

Studies have shown that HSV replicates more rapidly when corticosteroids are present and worsen the course of the disease.[23] Topical steroids are generally contraindicated in the presence of HSV epithelial keratitis and have been implicated in prolonging the course of herpetic eye disease.[24] However, judicious topical steroid therapy can be beneficial when used with antiviral coverage following several days of initial protective treatment. Topical steroids are also an invaluable addition to therapy should stromal inflammation develop.[24]

Clinical pearls

• A unilateral red eye in an adult patient that is inconsistent with the symptoms (i.e., the patient seems to be in far less discomfort than the appearance of the eye would indicate) should raise suspicions of HSV keratitis, particularly if the individual has a previous history of similar infections.

• Each recurrence induces greater damage to the corneal nerves, leading to hypoesthesia. The cotton-wisp test used for measuring corneal sensitivity is positive in cases of HSV keratitis, and should be utilized whenever HSV is suspected.

• Consider a history of prolonged sun exposure or extreme psychological stress to be significant in diagnosing HSV epithelial keratitis.

• Most adverse steroid-related outcomes in HSV epithelial keratitis have arisen from improper diagnosis, in which steroid use was initiated without antiviral coverage. Judicious use of a topical steroid concurrent with and following several days of antiviral treatment can help reduce scarring should the stroma become inflamed. However, if the infection remains solely epithelial with no stromal involvement, then the benefit of adding a topical steroid is outweighed by the risks of perpetuating infection.

• Anecdotal reports have associated some HSV dendritic outbreaks with the use of prostaglandin analogs. Many practitioners discontinue the use of these agents upon dendrite development. We do not discontinue prostaglandin use because of HSV epithelial keratitis for two reasons: First, no compelling evidence exists that prostaglandin analogs cause HSV epithelial outbreak. Second, HSV epithelial keratitis can be easily treated with antiviral medications, while blindness from glaucoma cannot.

• Beware of toxicity related to topical antiviral medications. Some chronic cases may seem resistant to therapy, when in reality the virus has been killed and the medication is perpetuating a non-healing pseudodendrite.

• Not every case of HSV epithelial keratitis manifests in a classic dendritic appearance, especially early in the disease course. Consider a trial of antiviral medications in atypical or unusual epitheliopathy.

• Upon first HSV epithelial keratitis outbreak, we educate patients about the role of long-term suppressive therapy with low-dose oral acyclovir, and we give the patient this option. At the second outbreak, we recommend suppressive therapy more strongly.

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ACANTHAMOEBA KERATITIS

Signs and Symptoms

Patients with *Acanthamoeba* ocular infection typically present insidiously with a unilateral red eye. Pain may be variable; some individuals manifest only a mild foreign body sensation, while others report severe pain disproportionate to the clinical appearance.[1,2] The initial epitheliopathy associated with *Acanthamoeba* may be non-descript, demonstrating coarse opaque streaks or fine curvilinear opacities, amorphous stippling, microcystic edema or dendritiform keratitis. The finding of radial perineuritis (i.e., irregularly thickened corneal nerves in the anterior to mid-stroma, with shaggy borders) is noted in one-third of cases.[3] Other common signs associated with *Acanthamoeba* keratitis include anterior uveitis with hypopyon and diffuse anterior scleritis. Ultimately, a large disciform corneal ulcer may be seen. Most texts describe these ulcers as being classically associated with a stro-

mal ring infiltrate, though retrospective studies indicate that only 6% of early cases and 16% of late cases actually present with this clinical finding.[4,5]

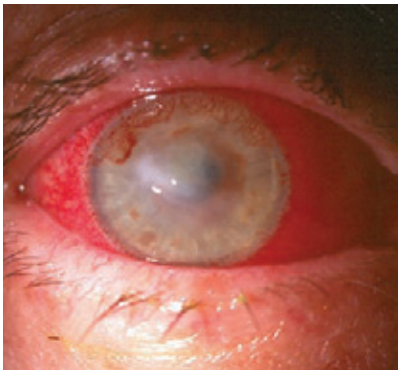
Pathophysiology

Acanthamoeba keratitis is historically associated with contact lens wear and poor hygiene, usually involving exposure to non-sterile water. However, numerous other risk factors have been identified: These include bacterial keratitis, herpes simplex keratitis, anterior basement membrane dystrophy, bullous keratopathy, neurotrophic keratopathy, radial keratotomy and corneal foreign bodies. While there are many species of *Acanthamoeba*, only a few are known to cause keratitis in humans. The most common of these include *A. castellani*, *A. polyphaga* and *A. culbertsoni*.[3] These microbes are ubiquitous and can be isolated from numerous environments. Water is a common medium, and *Acanthamoeba* inhabit virtually all water sources, including lakes, rivers, seas, oceans, chlorinated swimming pools, hot tubs and domestic tap water. In addition, *Acanthamoeba* can be encountered in soil, dust and sewage. These organisms are impervious to cold, surviving at temperatures as low as –20ºC (–4ºF); however, they are typically susceptible to heat above 42ºC (107ºF).[3] *Acanthamoeba* normally exist in a motile, trophozoite phase, but they can survive adverse elements and conditions by encysting.

Acanthamoeba adhere to corneal epithelial cells by virtue of their acanthopodia—small, foot-like projections from the organism's cell membrane—which are more numerous and specialized than in non-pathogenic species of amoebae.[6] Once bound to the ocular surface, they secrete proteases, which have a toxic effect on corneal epithelial cells and help degrade the corneal stroma, facilitating invasion into deeper tissue.[7] *Acanthamoeba* derive nutrition from normal bacterial flora such as *Staphylococcus epidermidis* and *S. aureus*, and hence they can persist indefinitely in an a microbe-rich ocular environment. For this reason, bacterial corneal ulcers are always susceptible to amoebic superinfection in at-risk patients.

Management

Acanthamoeba keratitis can be exceedingly difficult to identify clinically. Often, it requires corneal scrapings and/or cultures using non-nutrient agar overlaid with *Escherichia coli* or *Enterobacter* to achieve a definitive diagnosis. Note that cultures for *Acanthamoeba* may take up to 10 days to yield definitive results, and even then the sensitivity and specificity is typically only 60% at best.[3,4] Encysting of the organisms is the most common reason for delayed or false-negative results. Other beneficial diagnostic techniques include staining of scrapings with Calcofluor white (which can demonstrate *Acanthamoeba* cysts as well as trophozoites), confocal microscopy and polymerase chain reaction of biopsy specimens. Regrettably, such techniques are often expensive and not widely available.



Acanthamoeba keratitis may present with disciform stromal inflammation and perineuritis.

Treatment of *Acanthamoeba* ulcers may involve a variety of therapeutic options, because no single agent is 100% effective. Recognized treatments include amoebicidal drugs such as propamidine isethionate (i.e., Brolene) and hexamidine; surfactant detergent agents such as polyhexamethylene biguanide (PHMB) and chlorhexidine digluconate; antifungal agents such as metronidazole, ketaconazole and clortrimazole; neomycin and other antibiotics (e.g. ofloxacin).[3,8] Most often, two or more agents are employed in concert (e.g., PHMB) plus Brolene or neomycin plus Brolene plus ketaconazole. Mainstay therapy is with a biocide (chlorhexidene or PHMB and an aromatic diamidine (Brolene). The use of topical corticosteroids in active phases of *Acanthamoeba* keratitis is extremely controversial. Some maintain that these agents help limit corneal melting and scarring and prolong graft survival.[9] Experts agree, however, that steroids should only be used with concurrent antiamoebic therapy.[3,8-10]

Corneal healing and visual outcome with topical therapy varies, although most patients with *Acanthamoeba* keratitis actually fare rather well. One published report noted an overall success rate of 79% using a regimen of PHMB and Brolene, with "success" defined as final visual acuity of 20/50 or better.[10] Of those individuals who were successfully diagnosed within 28 days of presentation, 91% had a successful outcome.[10] Hence, the value of therapeutic intervention depends greatly upon the duration of the infection prior to treatment. Penetrating keratoplasty may be considered in patients who have sustained significant visual loss following *Acanthamoeba* keratitis infection; however, this procedure is only performed after the infection is considered fully resolved. Otherwise, the likelihood of recurrent infection and graft failure is nearly certain.[9]

Clinical Pearls

- *Acanthamoeba* keratitis may have a variable appearance and can often coexist with bacterial and/or herpetic ulcers; hence, it is rarely identified in the early stages of infection.
- *Acanthamoeba* keratitis is partially amenable to non-protozoan treatments, e.g., topical antibiotic or antiviral agents. These formulations, as well as the preservatives that they contain, create a hostile environment for the microbe, rather than actually killing the organism. In response, *Acanthamoeba* will encyst and become dormant. While the symptoms and signs may improve temporarily, the keratitis waxes and wanes until

definitive anti-amoebic therapy is prescribed. However, antibiotic and antifungal drugs should not be considered true therapeutic agents for *Acanthamoeba* keratitis and should never replace the amoebicidal drugs. Their main activity is combating co-infections.

• While ring infiltration has historically been associated with *Acanthamoeba* keratitis, it is a relatively rare finding and typically occurs late in the disease process. Non-specific epitheliopathy in the setting of acutely red eye is the more common presenting feature.

• *Acanthamoeba* keratitis can present initially as a dendritic keratitis similar to HSV keratitis, with one critical exception: The classic "terminal end–bulbs" that are seen in herpetic keratitis are characteristically absent in *Acanthamoeba* keratitis.

• *Acanthamoeba* play a part in coinfections, sometimes explaining why other corneal infections do not respond to conventional therapy.

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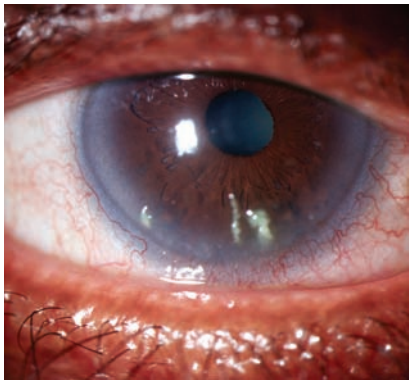
FILAMENTARY KERATITIS

Signs and symptoms

Patients with filamentary keratitis typically present with variable reports of ocular discomfort, ranging from grittiness to mild foreign body sensation to pronounced pain. Tearing, photophobia and even blepharospasm may accompany these symptoms in more severe cases.[1] The condition may be unilateral or bilateral, depending upon the underlying etiology. Signs associated with filamentary keratitis include ocular hyperemia, particularly in the limbal area, as well as a pseudoptosis in some individuals. The hallmark finding is the presence of corneo-mucus filaments; these usually consist of a focal "head" that may firmly adhere to compromised areas of the corneal epithelium, and a strand-like "tail" of varying length that extends across the ocular surface. Filaments can be seen more readily on biomicroscopy with the application of vitals dyes such as rose bengal and, to a lesser degree, lissamine green and sodium fluorescein.[1] Other ocular findings that may accompany filamentary keratitis include a reduced tear break up time (TBUT) and a punctate epithelial keratopathy.



Large mucous plaques may be noted in severe filamentary keratitis.

Experience suggests that filamentary keratitis is more common in elderly patients (particularly women), those with connective tissue disorders and those with immune deficiency.[1] Coincidentally, these same populations tend to demonstrate a greater incidence of keratoconjunctivitis sicca and other ocular surface disorders. The condition also may develop in those with relative atopy, where the pathognomonic changes surface as a side effect of systemic therapy.

Pathophysiology

Filamentary keratitis is seen most commonly in association with advanced dry eye disease, although a variety of other ocular surface disorders can induce this condition.[2] Among the various etiologies are superior limbic keratoconjunctivitis (SLK) of Theodore, prolonged patching following cataract or other ocular surgery, epitheliopathy from aerosol or radiation keratitis, herpetic keratitis, recurrent corneal erosion, neurotrophic keratitis and bullous keratopathy.[1–5] Clinicians must also recognize that some systemic disorders (e.g., Sjögren's syndrome, diabetes) and systemic medications (e.g., oral antihistamines or diuretics) can exacerbate ocular surface inflammation and aqueous deficiency, further contributing to the development of filamentary keratitis.[6]

The precise pathogenesis of filamentary keratitis is unclear. Research suggests that the process involves some degree of corneal epithelial disruption and concurrent tear film corruption.[2,7] According to researchers, subjects with filamentary keratitis suffer progressive dysfunction within the deeper epithelial layers of the cornea, leading to focal detachments at the level of the basement membrane. Under constant shear pressure from the eyelids, these corneal foci become elevated and inflamed, and epithelial desquamation ensues.[7] Filaments arise as a result of these liberated, compromised epithelial cells binding with abnormal, excessive mucins within the tear film. Diminished tear volume (i.e., aqueous-deficient dry eye) is the most common cause of excessive tear mucin, although ocular surface inflammation also contributes heavily to this process.[2] Filamentary keratitis is said to occur when motile filaments within the tear film adhere to compromised areas of the corneal surface. Lid movement across these filaments induces vertical traction and shearing of the corneal epithelium, with each blink resulting in inflammation and stimulation of the pain-sensitive corneal nerves. Thus, a vicious cycle of epithelial damage, inflammation and filament formation ensues.

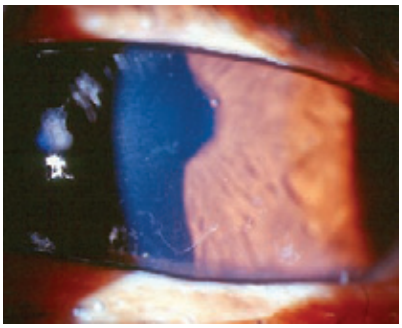
Management

Treatment for filamentary keratitis is targeted toward eliminating the mucus filaments while addressing the underlying cause of the pathology. In most cases, management begins with physical removal of the filaments at the slit lamp, using jeweler's forceps under topical anesthesia. The copious use of ocular lubricants (e.g., Systane Q 1 hour while awake) may be helpful in addressing the ocular discomfort and stabilizing the tear film in mild-to-moderate cases. Alternatively, some have suggested the use of hypertonic saline (e.g., Muro 128 TID-QID) for filamentary keratitis; studies have shown this treatment effective in as many as 95% of subjects.[8,9]

More recalcitrant cases of filamentary keratitis may warrant the use of pharmaceutical agents. Anti-inflammatory drugs, including corticosteroids and non-steroidal agents, have been used with some success.[3,8,10] In theory, these agents have the capacity to diminish filament formation and restore the damaged epithelial regions where filaments may accumulate.[4,11,12] Caution is advised, however, regarding long-term use of corticosteroids, due to the propensity for intraocular pressure elevation and cataract formation. In this capacity, topical cyclosporine (i.e., Restasis BID) may provide a safer alternative for prolonged therapy.[10]

N-acetylcysteine (Mucomyst, Apothecon) is another potential remedy for patients with advanced filamentary keratitis. This mucolytic agent is utilized primarily as an inhalant for patients with bronchial disease (e.g., emphysema, cystic fibrosis), but in topical ophthalmic form (2–10%), acetylcysteine has been shown to effectively dissolve corneal mucus plaques and reduce filament-producing pathogenesis.[13] While not commercially available in the United States, acetylcysteine can be readily obtained from most compounding pharmacists. A 5% acetylcysteine solution is available in the United Kingdom under the trade name Ilube (Alcon Laboratories UK, Ltd).

Cases of filamentary keratitis that do not respond to topical therapy alone may benefit from temporary employment of a soft bandage contact lens.[11] In all cases, practitioners should be prepared to manage this condition for prolonged periods. Filamentary keratitis may take weeks or even months to resolve, depending upon the etiology and the aggressiveness of therapy. Even after the filaments dissipate, the underlying disease or cause must be controlled, or recurrences are likely.



Filamentary keratitis with numerous string-like precipitates.

Clinical pearls

• Filamentary keratitis is not a disease entity itself, but a sign of a severe ocular surface disease. The root cause of this condition must be determined before initiating therapy.

• Patients should be educated that prolonged therapy may be necessary to alleviate this condition, which is often chronic.

• Although practitioners are often tempted to use antibiotic solutions, they are not beneficial as a primary therapy for filamentary keratitis. However, they may be necessary for prophylaxis in cases of severely compromised corneas.

• Topical 5% acetylcysteine BID-QID is often a helpful adjunct in managing filamentary keratitis. Advise patients that this solution may have an unusual color and a peculiar odor. Also, because it is typically formulated without preservatives, it must be discarded after approximately 30 days.

• Soothe XP, a lipid-restorative emollient eyedrop, may be particularly helpful in managing recalcitrant filamentary keratitis. In a small series, patients treated with Soothe four times daily for three to five weeks showed complete resolution of filaments and significant improvement in subjective symptoms.[14] It is theorized that this oil-in-water emulsion, which has been shown to increase lipid layer thickness, improves the wiping action of the eyelid on the ocular surface and hence inhibits epithelial breakdown and filament formation.

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FUCHS' ENDOTHELIAL DYSTROPHY

Signs and symptoms

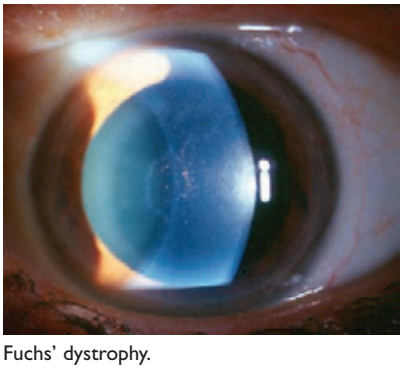
Fuchs' endothelial dystrophy, a bilateral though often asymmetric condition, is relatively common in adults. While it may occasionally be diagnosed earlier based upon biomicroscopic findings, Fuchs' dystrophy is rarely symptomatic before age 50.[1] Patients typically pres-

ent with complaints of diminished vision, foreign body sensation and pain or discomfort, particularly upon awakening. The key clinical finding is central corneal guttae (historically—though incorrectly—referred to as "guttata"), which represent focal thickenings at the level of Descemet's membrane. When viewed in direct illumination, guttae appear as gold-colored, hyper-reflective bodies on the posterior corneal surface; when retroillumination is used, they resemble small bubbles or holes in the endothelium. Fine endothelial pigment dusting is also commonly seen in association with guttae. In later stages, one may observe stromal edema with folds in Descemet's membrane and corneal pannus and bullous keratopathy in severe presentations.

Fuchs' dystrophy is encountered more commonly and with greater severity in women than in men (3:1).[1,2] Hypermetropes and those with shallow anterior chambers may also have a higher incidence.[3] Early reports suggested that patients with Fuchs' dystrophy may have an increased prevalence of open angle glaucoma,[4] though this association has not been corroborated by more recent literature.

Pathophysiology

Fuchs' dystrophy stems from a primary malfunction of the corneal endothelium, which is likely inherited via an autosomal dominant mechanism with incomplete penetrance.[1] This leads to widespread loss of endothelial cells and subsequent disruption of the endothelial pump mechanisms, which are responsible for maintaining normal stromal hydration.[5] The consequence is an excessive influx of aqueous, resulting in corneal stromal edema and a physiologically and optically compromised tissue.



Fuchs' dystrophy.

The clinical and histopathological progression of Fuchs' dystrophy has been well-described.[6,7] A number of stages are recognized, usually spanning a period of 10 to 20 years. Stage 1 is marked by central, irregularly distributed guttae and geographically arranged pigment dusting. Histologically, the endothelial cells show degeneration and deposition of abnormal Descemet's membrane material. Patients with Stage 1 Fuchs' are generally asymptomatic. In Stage 2, patients may begin to experience glare and diminished visual acuity, particularly upon awakening. These symptoms are directly related to an increase in corneal edema, which can be noted in both the stroma (seen as central corneal thickening) and the epithelium (represented by fine microcysts). As stromal edema increases, folds may be observed in Descemet's membrane, and vision diminishes accordingly. Stage 3 of Fuchs' dystrophy is heralded by more profound corneal damage in the form of epithelial and subepithelial bullae. The pressure exerted by these lesions on sensitive corneal nerves can induce pain and photophobia, which can be significantly exacerbated when the bullae rupture.[1] Stromal edema is persistent, as is diminished acuity throughout the day. Permanent corneal scarring occurs in Stage 4, due to the development of subepithelial tissue in the central cornea. Clinically, it appears as an irregular, dense, gray avascular sheet; histologically, this tissue is composed of active fibroblasts and collagen fibrils sandwiched between the superficial stroma and the epithelium.[7] The corneal bullae dissipate at this point, as do the painful episodes. Unfortunately, profound vision loss accompanies the scarring.

Management

Treatment for Fuchs' endothelial dystrophy varies depending upon the severity of the disease. Patients with early

Guttae are a hallmark sign of Fuchs' dystrophy.

stromal and/or epithelial edema may be treated conservatively with 5% sodium chloride solution throughout the day (e.g., Muro 128 every two-six hours) and 5% sodium chloride ointment overnight. These hypertonic agents diminish corneal edema and improve vision. Another non-invasive measure intended to deturgesce the cornea involves the use of a hair dryer, held at arm's length and directed toward the eyes.[8]

As patients become more symptomatic with pain and/or reduced vision, additional treatment options may be employed. Topical nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., Acular LS, Allergan) may be helpful in managing patients with painful bullae; however, the practitioner must understand that these agents merely provide analgesia in cases of Fuchs' dystrophy. In addition, corneal melts have been associated with the use of certain NSAIDs, and hence these drugs should be used judiciously.[9] Ocular hypotensive agents may be therapeutically beneficial also, even for patients in whom intraocular pressure is within normal limits.[2] By reducing the anterior chamber fluid volume, stress on the endothelial pump mechanisms is decreased, and this subsequently helps to diminish corneal edema.

All classes of ocular hypotensives may be used in this capacity, with the possible exception of the carbonic anhydrase inhibitors (i.e., dorzolamide, brinzolamide, acetazolamide), as these may actually disrupt the endothelial Na-K ATPase pump.[10]

Therapeutic (bandage) soft contact lenses may also alleviate patient discom-

fort in advanced cases. A flatly fit, high–water content lens helps mask the irregular astigmatism and diminish pain associated with epithelial bullae.[1,2] Silicone hydrogel lenses also have been used in this capacity, with some success.[11]

Despite medical treatment, most patients with Fuchs' dystrophy will ultimately require keratoplasty.[8,12] If this surgery is performed before involvement of the peripheral cornea occurs, the patient has an 80% likelihood of the graft remaining clear for at least two years.[13] Also, because cataract surgery in eyes with Fuchs' dystrophy often leads to further endothelial failure and greater corneal compromise, it is frequently preferable to perform cataract extraction and penetrating keratoplasty as a combined procedure.[2,5]

Recently, a modified form of corneal transplantation known as Descemet's stripping endothelial keratoplasty (DSEK) has emerged as a preferred technique for those with Fuchs' dystrophy and other forms of corneal endothelial dysfunction.[14] In DSEK, only the endothelial cell layer is removed and replaced with donor tissue. Although this procedure requires much greater skill than other treatments, it has several distinct advantages: It is sutureless, requires significantly less healing time, and typically results in greater visual recovery.[14]

Clinical pearls

• The presence of excessive central guttae in the absence of corneal edema is commonly referred to as *endothelial cell dystrophy*.[5] Endothelial cell dystrophy may remain stable or progress to Fuchs' dystrophy, which by definition includes some degree of stromal and/or epithelial edema.

• Mid-peripheral or peripheral corneal guttae may occasionally be seen in asymptomatic patients over age 40. These are known as *Hassle-Henle bodies* and are of no particular clinical significance.

• In place of hypertonic saline, we have experienced modest success with FreshKote (FOCUS Laboratories) for a variety of corneal disorders. This prescription ophthalmic lubricant uses high colloidal density rather than osmotic pressure from salts to address epithelial edema. In addition, it has the advantage of enhanced lubricity, increased contact time and improved comfort upon instillation.

• While topical NSAIDs may be helpful in ameliorating pain associated with Fuchs' dystrophy, corticosteroids have not been shown to be of significant benefit.[15]

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SALZMANN'S NODULAR DEGENERATION

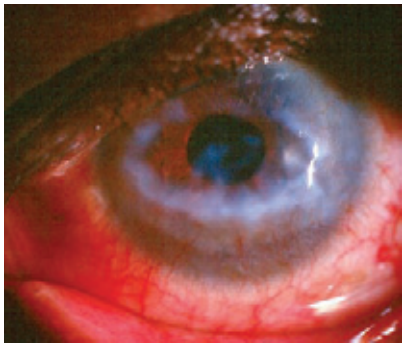
Signs and symptoms

Patients with Salzmann's nodular degeneration are often asymptomatic, particularly in the early stages of the disease. Some may present with diminished visual acuity if the nodules are situated on or near the visual axis.[1,2] Non-specific "dry eye" complaints, e.g., burning, grittiness and foreign body sensation, may also be reported.[3] Eyes with a more advanced form of the disease are prone to intermittent bouts of recurrent corneal erosion. During these episodes, patients may experience pronounced discomfort, photophobia, blepharospasm and excessive tearing.[1]

Clinically, Salzmann's degeneration appears as an accumulation of round-to-oval, bluish-white (and sometimes yellowish-white) subepithelial corneal nodules, often arranged in a circular or semicircular shape.[1] Usually the nodules are situated in the mid-peripheral cornea, but central and peripheral lesions have also been noted.[1] Vascularization of Salzmann's nodules is likewise variable. The condition is non-inflammatory; hence, the involved eye is typically white and quiet, unless there is associated corneal erosion. In that event, there will be limbal injection, corneal edema and an anterior chamber reaction. Conflicting historical reports exist regarding the laterality of Salzmann's degeneration, with the prevalence of bilateral involvement ranging from 20% to 80%;[4,5] however, the largest retrospective series to date noted bilateral disease in approximately 63% of cases.[3] The condition affects individuals of various ages and races, but appears to occur far more frequently in women than in men.[1–3]

Pathophysiology

The underlying etiology of Salzmann's nodular degeneration is not fully understood, but it has been suggested that chronic ocular surface irritation is contributory.[1] The condition is often preceded by some form of ocular inflammation, which may occur many years antecedent.[1,3,5] Some associated disorders include phlyctenular disease, meibomian gland dysfunction (including ocular rosacea), vernal keratoconjunctivitis, trachoma and interstitial keratitis;



Salzmann's degeneration; note the accumulation of bluish-white nodules.

additionally, patients with a history of epithelial basement membrane dystrophy, rigid contact–lens wear, keratoconus, filamentary keratitis, chemical (or thermal) trauma or incisional corneal surgery may be at increased risk.[1–6]

One theory behind the development of Salzmann's degeneration suggests that the inciting corneal trauma creates an irregular surface, allowing for uneven tear film distribution and exposure.[5] The subsequent chronic irritation and inflammation provokes histopathologic and functional changes to the superficial stroma and particularly Bowman's layer.[1,3,5–8] As corneal nodules proliferate, concurrent damage occurs to the basement membrane, often leading to painful epithelial erosions.[3]

At the cellular level, the nodules seen in Salzmann's degeneration represent hyaline plaque formation between the corneal epithelium and Bowman's membrane.[9] Oxytalan fibers, which are present in other degenerative corneal disorders including keratoconus and Fuchs' endothelial dystrophy, have also been identified in Salzmann's nodular degeneration.[8] As the condition progresses, there is subsequent degradation of Bowman's layer in the area overlying the nodules, and this is replaced by accumulation of a basement-membrane-like substance. The corneal epithelium associated with these areas thins accordingly, and in some specimens consists of only a single layer of flattened squamous cells. Descemet's membrane and the corneal endothelium characteristically remain intact.

Management

It has been suggested that asymptomatic patients with Salzmann's degeneration require no therapy;[1,9] however, since chronic low-grade irritation of the ocular surface has been proposed as a driving force for disease progression[5], it seems reasonable and appropriate to employ topical lubrication in these individuals (e.g., Systane, Alcon Laboratories, QID). In one large series of patients with Salzmann's nodular degeneration, 68% of patients responded favorably to conservative medical therapy (i.e., artificial tears, lid hygiene and systemic doxycycline for associated meibomianitis), and did not require surgical intervention.[3]

Corneal surgery is warranted for more severe or symptomatic cases of Salzmann's degeneration; the most common indication for surgical intervention is visual disturbance, followed by subjective discomfort associated with recurrent corneal erosions.[3] Superficial keratectomy is beneficial in cases of subepithelial lesions on or near the visual axis or for mid-peripheral lesions inducing irregular astigmatism.[1] Phototherapeutic keratectomy (PTK) with the excimer laser is another option. Unfortunately, these procedures tend to induce scar formation and/or recurrence in some cases. Recent papers[10,11] suggest that application of the antimetabolite mitomycin-C can improve outcomes and diminish recurrent disease in those undergoing superficial keratectomy or PTK.[10,11] If central or deep stromal scarring is present, or if chronic epithelial breakdown makes the condition otherwise unmanageable, lamellar or penetrating keratoplasty may be the only recourse.

Clinical pearls

• The critical issue in managing Salzmann's degeneration is proper diagnosis. Conditions such as band keratopathy, spheroid degeneration (i.e., climatic droplet keratopathy) and corneal keloids may all present with a similar clinical appearance. Consultation with a corneal specialist is advisable in cases in which diagnosis is questionable.

• It may be tempting to prescribe topical corticosteroids for Salzmann's degeneration, particularly if the patient is symptomatic. However, since this condition is non-inflammatory, steroids are merely palliative and do not alter the progression of the disease. Additionally, their use introduces several unnecessary risks, including intraocular pressure elevation and secondary infection.

• Patients with associated corneal erosions require specific treatment aimed at diminishing pain and promoting reepithelialization. This is best accomplished with cycloplegia (e.g., 0.25% scopolamine BID) and topical nonsteroidal anti-inflammatory agents, as well as prophylactic, broad-spectrum antibiotics and copious lubrication with artificial tears. Some sources also recommend bandage contact lenses in cases of recurrent corneal erosion.[12,13]

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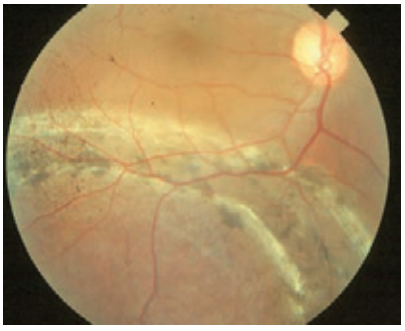
CHOROIDAL RUPTURE

Signs and symptoms

Choroidal rupture is a common occurrence following blunt trauma directly to the eye.[1–7] Patients developing choroidal rupture are often younger men involved in activities, such as ball sports, which expose them to high-speed impact to the eye or adnexa. While it seems that men are more likely to experience blunt ocular trauma, one report of patients experiencing blunt orbital trauma indicated that choroidal rupture occurred more often in women.[7] Common causes of blunt trauma directly to the eye include impact injuries from paintballs, bottle corks, elastic bands, airbags and sports equipment.[8–12]



Choroidal rupture.

Choroidal ruptures may be single or multiple, and may affect any part of the posterior segment.[2,13,14] They are not typically seen acutely secondary to hemorrhages that may be present from the inciting trauma. Hemorrhages from acute choroidal rupture may occur in any layer of the eye, ranging from the choroid to the vitreous.[3,15] However, if the trauma was many years antecedent, there will only be hemorrhage if choroidal neovascularization has developed and is bleeding.[16,17]

Visual acuity and visual field may be unaffected, depending upon the location of the choroidal rupture and degree of collateral damage that occurred at the time of trauma. Unfortunately, choroidal ruptures often herald more significant damage throughout the eye with poor visual results.[7] Many patients will have reduced acuity, sometimes dramatically, if the rupture occurred within the posterior pole, and especially with subfoveal involvement.[10-12,14,15]

Ophthalmoscopically, there may be a curvilinear lesion parallel to the ora serrata or, more commonly, a posteriorly located disruption which may be crescent-shaped. Often, the rupture will have the concave aspect toward the disc. Many ruptures are concentric with the optic nerve and are vertically oriented, consistent with a break in Bruch's membrane.[2] There is usually significant reactive retinal pigment epithelium (RPE) hyperplasia, giving the rupture a pigmented appearance. The sclera may be seen underneath a choroidal rupture depending upon the degree of damage and exposure of the underlying tissue.

Pathophysiology

Direct or indirect injury can precipitate a choroidal rupture. Direct ruptures are usually located anteriorly at the exposed part of the eye and parallel to the ora serrata.[18] More common are indirect ruptures occurring at the posterior pole. These are usually concentric to the optic nerve.[18] As the globe is compressed along an anterior-posterior vector, it expands outward, often resulting in a break in Bruch's membrane. In most cases, the sclera maintains the globe's integrity, limiting the damage to the resultant choroidal rupture and the collateral injuries sustained as a result of the trauma. Unfortunately, in some cases the sclera tears with a resultant ruptured globe.[4,6,7]

Hemorrhage and edema may be present initially, but will resolve. Typically, reactive retinal and choroidal pigment epithelial hyperplasia will give the rupture a heavily pigmented appearance. In some cases, the overlying retina will be undisturbed in choroidal rupture. However, if the RPE is disturbed and becomes hyperplasic, invading the sensory retina, visual dysfunction will ensue.

Due to the subsequent disruption of Bruch's membrane that occurs in choroidal rupture, the possibility exists for the development of choroidal neovascular membranes within the rupture.[13,14,16,17–19] This may be a late development and can occur years after the precipitating trauma.[18,20] Several factors have been shown to be predictive of the development of choroidal neovascular membranes in choroidal rupture; namely, proximity of the rupture to the center of the fovea, length of the rupture, older age and macular choroidal rupture.[13,14] Hence, patients with these factors should be monitored closely.

Management

There is no direct intervention in the acute phase of choroidal rupture, as long as the sclera is intact and no rupture of the globe has occurred. Any acute management is directed toward concomitant traumatic iritis, potential hyphema, retinal detachment or breaks and issues pertaining to intraocular pressure. Patients with choroidal ruptures should be educated about their condition and counseled to consider full-time protective eye-wear (protective frame with polycarbonate lenses). The patient must be monitored funduscopically for the development of choroidal neovascularization within the rupture scar. The use of home monitoring with an Amsler grid is recommended. Any late bleeding should receive a fluorescein angiogram to determine whether a choroidal neovascular membrane has developed.

Various therapeutic modalities have been used to treat choroidal neovascularization occurring from choroidal rupture. Thermal laser photoablation has been a mainstay for treating these membranes.[14,18] Newer modalities, such as photodynamic therapy (PDT), have been used with success.[19–21] PDT often reduces membrane leakage and can completely eliminate the membrane with few adverse effects. Surgical removal of the neovascular membranes has also been reported.[17] At this time, no reports are evident regarding the application of the anti-angiogenic drugs commonly used in exudative macular degeneration for choroidal rupture–induced neovascularization.

While choroidal rupture involving the macula tends to have a poor visual

prognosis, there are reported cases of patients with foveal choroidal ruptures regaining central vision over a protracted recovery period.[22]

Clinical pearls

- Choroidal neovascular membranes resulting from choroidal rupture may spontaneously involute. For this reason, close observation may be a management option if there is no imminent threat to vision.
- Choroidal neovascularization can occur years after the initial trauma.
- Sub-retinal hemorrhage from choroidal neovascularization is the most common cause of late vision loss.
- Because the retina overlying a choroidal rupture may be unaffected, patients may retain excellent visual function and present asymptomatically years after the trauma has occurred.
- Gonioscopy should be performed to rule out angle damage and an increased risk for developing late traumatic glaucoma.

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METASTATIC CHOROIDAL TUMORS

Signs and symptoms

Metastatic tumors to the choroid may present with an assortment of signs and symptoms. Most commonly, patients complain of visual discomfort such as metamorphopsia, decreased vision or blurred vision.[1] Additionally, patients may report visual field defects, floaters, photopsia, red eye and even pain in some cases.[1,2] Less commonly, patients may be entirely asymptomatic.[3] Ophthalmoscopically, choroidal metastases appear as mildly to moderately elevated placoid or oval lesions. They are typically creamy yellow with variable mottling, although the color may vary from white to orange depending upon the tumor's origin.[1,4] These lesions characteristically display irregular brown pigment deposits overlying the mass, which gives them a unique "leopard skin" appearance; the pigment spots have been shown histologically to represent macrophages containing lipofuscin.[5] Choroidal metastases are often multilobular, multifocal and occasionally bilateral,[5] in contradistinction to choroidal melanomas, which are almost invariably isolated and unilateral. Another very common finding with choroidal metastases is the presence of subretinal fluid and serous retinal detachment, which may be present in as many as 91% of cases.[5]

Choroidal metastases may occur at virtually any age, although patients are generally between 50 and 60 years, on average, at the time of diagnosis.[3,6] There is no known racial predilection. Women are more commonly affected than men, with a reported female prevalence of up to 70%.[2] Patients typically have a concurrent history of cancer, although on occasion the diagnosis of ocular metastasis actually precedes the discovery of a systemic malignancy.[3,4,7,8]

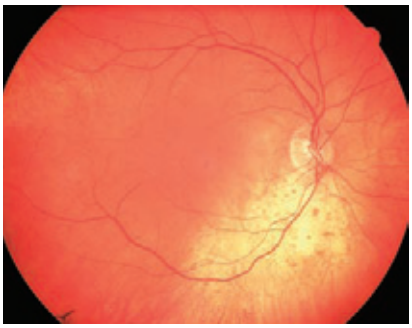
Pathophysiology

Metastasis is the process by which malignant cells disseminate through the body from one organ system to another. It is a complex mechanism that occurs via vascular and lymphatic channels. The choroid, which is particularly well-vascularized, is the most common site of ocular metastasis.[3,9] Embolic tumor cells reach the uvea by traveling through the internal carotid artery, the ophthalmic artery and the posterior ciliary arteries until they arrive at the choriocapillaris. Some theories suggest that the choroid may also produce chemokines. Metastatic lesions appear to have a preference for the posterior pole.[1,3,4]

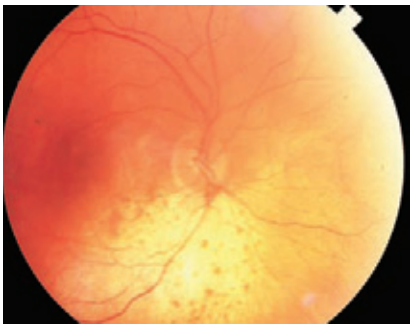
A number of specific tumor types have been associated with metastic choroidal tumor; the most common of these is breast carcinoma, accounting for 39%–49% of all uveal metastases.[1,3,4] The second most common primary tumor site is the lung (21%), followed by the gastrointestinal tract (4%).[4] Metastasis to the eye has been reported for carcinomas of the kidney, skin, prostate, pancreas, thyroid and testes, as well as carcinoid tumors and cutaneous melanoma.[1,2,10] In roughly 18% of intraocular metastases, the primary tumor site remains unknown.[2,4]

Management

Differentiating choroidal metastases from other malignant and non-malignant conditions is the first priority of proper management. Usually this is accomplished by direct clinical inspection, but additional diagnostic testing may be helpful in confirming the diagnosis. Perhaps the most frequently used ancillary techniques are fluorescein angiography and ultrasonography. Angiography of choroidal metastases characteristically demonstrates early hypofluorescence with diffuse late staining; however, this is not entirely diagnostic, as other entities may demonstrate similar features.[1,2] On ultrasound evaluation, choroidal metastases show moderate-to-high reflectivity and an irregular internal structure.[1,2] Ultrasonography can also help demonstrate shallow serous detachments that may not be discernable with ophthalmoscopy alone. Additional diagnostic modalities may include indocyanine green angiography, magnetic resonance imaging, fine needle aspiration biopsy, serum carcinoembryonic antigen levels and radioactive phosphorus uptake.[1] The most common differential diagnoses when considering metastasis include (amelanotic) choroidal melanoma, choroidal hemangioma, disciform macular scarring and rhegmatogenous retinal detachment.



Metastatic choroidal carcinoma in a patient with breast cancer.



The same choroidal tumor following proton beam irradiation.

Treatment for choroidal metastases depends on the degree of tumor activity, the location of the tumor, the extent of the ocular or visual symptoms and the patient's overall health status. For those who are asymptomatic and/or show evidence of clinical improvement with systemic chemotherapy, periodic observation alone may be sufficient.[2] Likewise, for patients who are terminally ill with disseminated metastases and poor constitutional health, surgeons may elect to initiate palliative therapy only.[7] Aside from these scenarios, invasive treatment is indicated if the metastasis is threatening vision or the overall health of the globe, or if the tumor continues to grow despite concomitant systemic therapy.[1,7]

Therapeutic options for choroidal metastases include conventional external beam irradiation, cytotoxic chemotherapy, hormonal therapy, biological therapy, plaque brachytherapy, proton beam irradiation, laser photocoagulation, photodynamic therapy and transpupillary thermotherapy.[1,11] Several sources recommend external beam irradiation or proton beam irradiation as a first-line option for lesions inducing acute visual involvement.[1,2,11] Plaque brachytherapy, transpupillary thermotherapy, laser photocoagulation and photodynamic therapy are viable options for localized, smaller lesions or as second-line treatments in conjunction with external beam irradiation or systemic chemotherapy.[11] Enucleation, which is employed much more readily for a variety of other ocular malignancies, is generally reserved for cases of choroidal metastasis that are associated with severe, intractable pain from secondary glaucoma.[1,2,11]

Despite numerous treatment options, ocular metastasis carries an exceedingly poor systemic prognosis. For these patients, life expectancy is reported to range from 0.2–48 months (median 6–9 months) from the time of diagnosis.[11-15] In general, patients with breast, thyroid and carcinoid tumors seem to have a longer survival rate than those with metastases from the pancreas, kidney, gastrointestinal tract or cutaneous melanoma.[2] Given the bleak outlook, quality of life should be a key consideration when weighing any invasive therapeutic options.

Clinical pearls

- Metastatic lesions are considered the most common type of intraocular tumor in adults.[1] Despite this fact, metastases are not typically encountered in most clinical practices. Since these patients are frequently terminally ill and usually have concurrent metastases to other organ systems, the diagnosis is often made in an alternate setting, e.g., a tertiary care center, a hospital or a nursing home, or even on autopsy studies.
- While the choroid is the most common site of ocular metastasis, numerous other tissues can be involved, including the eyelids, iris, ciliary body, retina, optic nerve and even the vitreous. Anterior segment metastases account for less than 15% of reported cases.[16]
- Perhaps more important than treating the choroidal lesions associated with ocular metastasis is ensuring that the primary neoplasm is properly addressed, especially if the patient presents without a prior diagnosis of cancer. Immediate referral to an oncologist is paramount in these cases.

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PIGMENTARY GLAUCOMA

Signs and symptoms

Pigment dispersion syndrome is an asymptomatic disorder typically discovered upon routine evaluation.[1] Pigmentary glaucoma, a sequela of pigment dispersion syndrome, is also mostly asymptomatic. Rarely though, patients present with complaints related to episodic rises in intraocular pressure secondary to exercise, such as colored haloes around lights, blurred vision or subtle ocular pain.[2,3] Both conditions are typically encountered in young, white men between ages 20 and 40.[4] A myopic refractive error is a commonly associated finding. One population-based study observed pigment dispersion syndrome in 2.45% of white patients undergoing glaucoma screening.[4] Pigment dispersion syndrome and pigmentary glaucoma also occur in black patients, though less commonly than in white ones.[5–7] The majority of patients in this category are older, female, and hyperopic.[5–7]

Patients with pigment dispersion syndrome and pigmentary glaucoma demonstrate liberation of iris pigment within the anterior chamber. Often, this is seen as diffuse accumulation or possibly a granular brown vertical band along the corneal endothelium known as a Krukenberg's spindle.[8–10] Pigment accumulation may also be evident on the lens, the surface of the iris and at the anatomic boundary denoting the termination of Descemet's membrane known as Schwalbe's line. When pigment accumulates here, it is called Sampaolesi's line.[5]

Dense pigmentation may be seen gonioscopically, often covering the trabecular meshwork for 360°; but usually it is most prominent in the inferior quadrant due to gravity.[8,11,12] The angle recess remains unchanged and open. Radial, spoke-like transillumination defects of the mid-peripheral iris are common.[5,7,8]

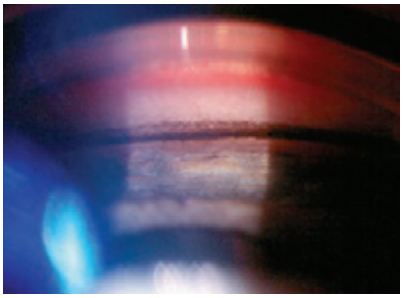
There seem to be some differences in the appearance of pigment dispersion syndrome and pigmentary glaucoma in black patients. In these patients, the degree of corneal endothelial pigmentation is quite mild and Krukenberg's spindles are not usually present. The degree of corneal endothelial pigmentation is not predictive of the amount of trabecular meshwork pigment that may have accumulated. Iris transillumination defects are rarely present, possibly due to a thicker iris stroma.[5,6,9]

Intraocular pressure (IOP) may rise sharply in cases of pigmentary glaucoma. Patients with pigment dispersion syndrome present with a normal optic nerve appearance, while patients with pigmentary glaucoma manifest evidence of glaucomatous optic atrophy, nerve fiber layer damage, and associated field loss.

Pathophysiology

The pathophysiology of pigmentary glaucoma must be considered in two parts: mechanism of pigment release and mechanism of pressure elevation. Pigment dispersion occurs as a result of the proximity between the posterior iris pigment epithelium and the zonular fibers of the lens. The abrasive nature of this physical contact leads to mechanical disruption of the iris surface and release of pigment granules into the posterior chamber, which follows the flow of the aqueous convection current into the anterior chamber angle.[13–15]

Many patients with pigment dispersion syndrome and pigmentary glaucoma demonstrate a concave approach of the iris as it inserts into the anterior chamber angle, giving the iris a "backward bowed" appearance on gonioscopy.[15] This posterior bowing of the iris places the posterior surface of the iris in apposition to the lens zonules. As the iris responds to light, iridozonular friction results in pigment liberation from the posterior iris. Sometimes the degree of pigment loss in the mid-peripheral



Dense trabecular pigment accumulation may be indicative of pigmentary glaucoma.

areas produces visible transillumination defects corresponding to packets of iris zonular fibers.[14] Although the majority of these patients have a concave iris approach, others may have a flat or planar approach.[15]

It has been theorized that in cases with a markedly concave iris insertion the iris functions as a flap valve lying against the anterior lens surface. When a pressure gradient develops that is greater in the anterior chamber, the iris is forced backwards, closing the valve and trapping the aqueous from moving into the anterior chamber. This increased anterior chamber pressure subsequently forces the iris into the aforementioned backward bowed configuration of the iris and has been termed "reverse pupillary block." The blocked flow increases the IOP and over time or in cases of chronic episodes, it produces the expected neural damage.[16,17] This phenomenon has been shown to increase with patient blinking.[14,18,19]

Excessively released pigment accumulating in the trabecular meshwork has two possible consequences. First, pigment may reside benignly in the trabecular meshwork where IOP is unaffected, and the condition remains pigment dispersion syndrome. Alternatively, the pigment causes a rise in IOP and via the mechanisms described previously and the patient may develop pig-

The Ocular Hypertension Treatment Study (OHTS),[1,2] Collaborative Normal Tension Glaucoma Study (CNTGS),[3,4] Advanced Glaucoma Intervention Study (AGIS)[5,6] and Early Manifest Glaucoma Treatment Study (EMGTS)[7] are well-designed, well-executed glaucoma investigations that have greatly advanced our understanding of the disease. While most practitioners are familiar with the initial publications and outcomes, we must not forget that new information from these studies is published on an ongoing basis. These subsequent publications have provided even greater understanding of glaucoma and have greatly assisted clinicians in managing patients with glaucoma.

OHTS

The most notable finding from the original OHTS publication was that lowering IOP in patients with ocular hypertension reduced the risk of their developing primary open-angle glaucoma (POAG) over five years from 9.5% to 4.4%.[1] At the time of the publication of OHTS in 2002, it had merely been noted that there was a trend for treatment being protective in African-American patients. However, this finding did not achieve statistical significance due to short follow-up time for these patients at the time of initial publication. A subsequent publication that allowed for proper follow-up time reported that, among African Americans in the study, 16.1% of the control group developed glaucoma but only 8.4% of the treated group progressed. This confirmed the benefit of pressure reduction in African Americans who had ocular hypertension. Further, African-American patients in the study demonstrated twice the risk of developing POAG as white patients, despite similar baseline and treated IOPs.[8]

An initial OHTS publication identified central corneal thickness as a strong predictive factor for conversion to glaucoma from ocular hypertension.[2] A later ancillary study attempted to determine whether any factors on confocal scanning laser ophthalmoscopy (Heidelberg Retinal Tomograph II —HRT II) could be associated with a positive prediction for progression to POAG from ocular hypertension. Notably, an overall HRT classification of "outside normal limits" had a 14% positive predictive value for POAG development. If the superior temporal sector of the optic disc had a classification of "outside normal limits," there was a 40% positive predictive value for the conversion to glaucoma.[9]

Using OHTS visual field data, it was found that a visual field endpoint for conversion to glaucoma (identifying a decrease in threshold perimetry beyond predetermined criteria) confirmed by three consecutive visual fields appeared to have greater specificity and sensitivity than either one or two consecutive visual field test results. However, some eyes whose visual field POAG endpoint was confirmed by three consecutive reliable test results still managed to have one or more normal tests on follow-up. Clearly, these results mean that before judging change in a visual field, multiple confirmatory tests are required.[10]

A recent report from OHTS compared the rates of detection of optic disc hemorrhages by clinical examination and by review of optic disc photographs. Further, an attempt was made to determine whether optic disc hemorrhages were predictive of the development of POAG.[11] Remarkably, 16% of disc hemorrhages were detected both by clinical examination and review of photographs, and 84% were detected *only by review of photographs* following clinical examination. Thus, review of stereo photographs was more sensitive at detecting optic disc hemorrhage than actual clinical examination.[11] Clearly, the message from this report is that clinicians should photograph patients when possible and critically examine the photographs following the actual examination. The occurrence of an optic disc hemorrhage was associated with an increased risk of developing POAG (as defined by OHTS endpoints), although it must be acknowledged that 86.7% of eyes in the study in which a disc hemorrhage developed have not converted to POAG to date.[11]

CNTGS

The initial result of the CNTGS indicated that IOP is part of the pathogenic process of normal tension glaucoma (NTG).[3,4] Further, it was seen that therapy that reduced IOP and was free of side effects would be expected to be beneficial in patients who are at risk of disease progression.[3,4]

However, the initial results of the CNTGS did not identify which patients were at greatest risk of disease progression. Later analysis of this data indicated that patients who were at risk of disease progression included women, those with history of migraines (many of whom were female) and those with manifesting disc hemorrhages. Factors that were not associated with an increased risk of progression included older age, higher mean IOP, and visual field defects threatening fixation.[12]

The CNTGS attempted to identify which patients with NTG might benefit most from lowering IOP. Factors associated with an improved clinical course from treatment included patients without a baseline disc hemorrhage, women, those with family history of glaucoma, those without family history of stroke, those with no personal history of cardiovascular disease and those with lesser amounts of disc damage (cup-to-disc ratio of 0.7/0.7 or less). Characteristics not associated with treatment benefit included disc hemorrhages and migraine. Curiously, the presence of a disc hemorrhage was strongly predictive of disease progression, but patients with this feature saw no difference in the clinical course of their disease, either with or without treatment.[13]

AGIS

One of the most referenced findings from AGIS was that low IOP is associated with reduced progression of visual field defects.[7] Later, an attempt was made to identify risk factors associated with visual field progression. Fluctuations in IOP was the variable consistently associated with visual field progression.[14] This seems to illustrate the importance not only of lowering IOP, but also of consistently controlling the diurnal pressure curve.

An analysis was conducted to distinguish visual field fluctuations from true deterioration in AGIS patients. A single confirmatory test six months after detection of visual field worsening indicated at least a 72% probability that defect would be persistent when the worsening was defined by at least 2 decibels of Mean Deviation (MD). When the number of confirmatory tests was increased from one to two, the percentage of eyes that showed a persistent defect increased from 72% to 84%.[15] This further demonstrates the need for multiple visual fields to truly judge progression.

Later analysis of the AGIS data investigated the association of pre-intervention and post-intervention patient and eye characteristics with respect to failure of argon laser trabeculoplasty (ALT) and

trabeculectomy. ALT failure was associated with younger age and higher pre-intervention IOP. Trabeculectomy failure was associated with younger age, higher pre-intervention IOP, diabetes and one or more postoperative complications, particularly elevated IOP and marked inflammation.[16]

EMGTS

A landmark study with an untreated control group of patients who had early, newly diagnosed glaucoma found that progression of the disease was less frequent in the treated group (45%) than in the control (untreated) group (62%) and occurred significantly later in treated patients.[7] Interestingly, many of the patients remained stable over time, even those in the untreated control group, while glaucoma progressed in as many as 30% of treated patients after four years, despite the clear effect of treatment. The time it took for glaucoma to progress varied greatly among patients and was sometimes rather brief, even in treated patients. Clearly, it was difficult to predict the initial course of newly diagnosed early glaucoma.[7]

Later analysis using the EMGTS data aimed at identifying factors associated with glaucoma progression, as well as the beneficial effect of pressure reduction. It was later seen that patients treated in the EMGTS had half of the progression risk of control patients.[16] Further, the magnitude of initial IOP reduction was a major factor influencing outcome, with greater initial IOP reductions associated with the greatest degree of disease stabilization. It was noted that glaucoma progression was also increased with higher baseline IOP, exfoliation, bilateral disease, worse mean deviation on visual fields and older age, as well as frequent disc hemorrhages during follow-up.[16] It can be asserted that patients presenting with factors such as exfoliation or recurrent disc hemorrhage may have a worse prognosis and would likely need greater degrees of therapy and closer observation.

Clearly, we must not limit our knowledge to the initial reports from landmark studies. It is important to review the literature constantly, especially for follow-up reports from major studies. Often, clinical data is analyzed long after the initial publications from milestone studies. The subsequent publications are typically very strong as they represent information from very well-designed and well-conducted studies, powered by great numbers of patients.

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mentary glaucoma.[14]

Interestingly, physical blockage of the trabecular meshwork by pigment granules is not the likely cause of the pressure rise.[20] Endothelial cells lining the trabecular beams of the trabecular meshwork quickly phagocytize small amounts of accumulated pigment preserving the normal architecture of the trabecular meshwork.[21–23] However, in chronic cases of pigment dispersion, greater amounts of pigment are more difficult for the cells to phagocytize. When this occurs, the endothelial cells that line the trabecular meshwork beams disintegrate. The resultant degeneration of the trabecular meshwork with the accumulation of debris, collapsed beams and loss of intratrabecular spaces is what produces the rise in IOP.[23] The IOP rise in pigmentary glaucoma mostly occurs due to a breakdown of normal phagocytic activity of the endothelial cells and subsequent loss of normal trabecular architecture and function.[23]

Management

Because pigment dispersion syndrome has no direct ramifications on ocular health or vision other than potential future development of pigmentary glaucoma, patients with this condition should be treated as glaucoma suspects. Patients should be monitored for IOP spikes and optic nerve changes three to four times a year, with threshold visual fields, diagnostic lasers and gonioscopy performed annually. One study noted the conversion rate from pigment dispersion

syndrome to pigmentary glaucoma at 20%, with the vast majority converting within 10 years of a diagnosis of pigment dispersion syndrome.[24] However, patients with pigment dispersion syndrome who were followed for longer than 10 years without developing pigmentary glaucoma had a low risk of developing pigmentary glaucoma subsequently.[24] A more recent study noted that the risk of developing pigmentary glaucoma from pigment dispersion syndrome was 10% at 5 years and 15% at 15 years. Young, myopic men were more likely to convert to pigmentary glaucoma, and an IOP greater than 21 mm Hg at initial examination was associated with an increased risk of conversion.[25]

Medical treatment of pigmentary glaucoma is similar to primary open angle glaucoma.[8] There has been conjecture that prostaglandin medications should be avoided in glaucomas in which pigment liberation is involved in the etiology, because these medications increase the amount of melanin in stromal melanocytes and could potentially further impair drainage. However, this fear is unfounded: The melanocyte size increase occurs within the iris stroma, and these cells are not liberated in the disease. Prostaglandin medications have been proven to successfully lower IOP in eyes with pigment dispersion from pseudoexfoliative glaucoma; thus, they are good therapeutic options for pigmentary glaucoma.[26–28]

Laser peripheral iridotomy (LPI) is a consideration for patients with pigment dispersion syndrome and pigmentary glaucoma in which significant iris concavity is evident.[14–16]

It has been well-reported that the iris can convert from a concave to a planar approach following LPI. In cases in which there is significant iris concavity, LPI should be considered to reduce the amount of pigment being liberated. However, very little information is available regarding the effect of LPI on IOP in pigmentary glaucoma.

In a retrospective analysis, it was shown that LPI had very little effect on IOP in patients with pigmentary glaucoma.[29] Although this study did not provide support for the benefit of LPI regarding IOP control, it also did not disprove value of LPI in this patient population; rather, it identified the need for a large, prospective study.[29]

Patients with pigmentary glaucoma tend to respond well to argon laser trabeculoplasty, presumably due to the improved thermal effects secondary to the increased meshwork pigmentation.[30–34]

Little published data appears to be available regarding the efficacy of selective laser trabeculoplasty in pigmentary glaucoma. In one series involving four patients, it was seen that post-SLT IOP elevations can be a serious adverse event in these patients.[35] Trabeculectomy remains an option for patients with pigmentary glaucoma.[35]

However, because such patients tend to be younger, there may be an increased failure rate compared to that of older patients because of fibrosis. Medical modulators for wound healing, such as mitomycin-C, are generally indicated in this group.[37]

Clinical pearls

• Pigmentary dispersion syndrome is a common cause of glaucoma in younger patients, and this diagnosis should be strongly considered when encountering glaucoma in young patients.

• Pigmentary glaucoma is often underdiagnosed in black patients because of the lack of corneal endothelial pigment and iris transillumination defects. Often, the trabecular hyperpigmentation is incorrectly attributed to overall racial pigmentation.

• Diurnal IOP variations can be quite extreme in pigmentary glaucoma.

• The increased IOP is not from pigment "clogging" the trabecular meshwork, but from degradation of the trabecular meshwork support structure.

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EXFOLIATIVE GLAUCOMA

Signs and symptoms

Exfoliation syndrome and exfoliative glaucoma occur throughout the world but especially in high rates throughout northern Finland, Iceland, Saudi Arabia, Great Britain and Greece, and it is a common phenomenon in patients with these ethnic backgrounds.[1–4] Exfoliation occurs in 5% of older Americans.[5] This condition is considered uncommon in patients of African descent, though it does occur.[6,7] The true overall prevalence of exfoliation syndrome may be underestimated as 15% of cases may be missed clinically.[8]

Exfoliative glaucoma is predominately a disease of the elderly and is rarely found in patients younger than 50 years.[4,9] The lowest age of onset reported thus far occurred in a 17-year-old girl.[10] The highest prevalence rates have been found in patients older than age 70.[11–15]

Patients present with a fine, flaky material on the anterior lens capsule at the pupillary margin. Over time, this coalesces into a characteristic "bulls-eye" pattern typically seen in exfoliation syndrome. This classic pattern is usually only observable when the patient's pupil is dilated. Beyond the anterior lens surface, exfoliative material is most commonly seen accumulating at the pupillary margin. This may be visible in an undilated state. Pigment loss from the pupil margin with subsequent deposition on anterior chamber structures is a hallmark of the condition.[9] This leads to increased transillumination of the iris at the pupillary margin, which is termed peripupillary transillumination defects. There may be pigment granules on the corneal endothelium and iris surface. Within the angle, there may be observable pigment, clear flaky material or both.[16–18]

Initially, intraocular pressure (IOP) is unaffected in exfoliation syndrome; however, over time, elevated intraocular pressure can develop, and characteristic glaucomatous cupping and visual field loss may ensue.

In one report, 16% of patients with clinically apparent exfoliative material required treatment upon presentation, with 44% of these developing a need for therapy over the next 15 years.[13] In another study, roughly a 32% conversion rate from exfoliation syndrome to exfoliative glaucoma occurred over 10 years.[14]

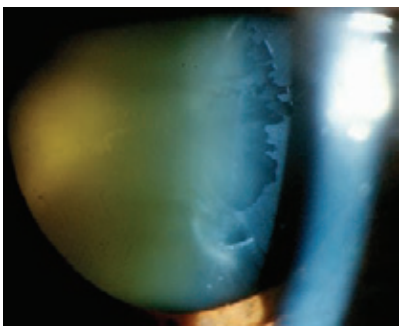
Another report noted a 45% conversion rate from exfoliation syndrome to exfoliative glaucoma over a mean time frame of five years.[19] Clinically, exfoliation is markedly asymmetric, with biomicroscopically unilateral involvement in many cases.[4,5,13,14,20]

Patients with exfoliation are more prone to developing cataracts as well as surgical complications during extraction.[21–25]

Complications include poor pupillary mydriasis, poor zonular integrity and intraoperative zonular dialysis, spontaneous lens dislocations and vitreous loss during surgery. Occasionally, lens displacement with pupil block and angle closure may occur.[26,27]

Pathophysiology

Exfoliation involves the production and accumulation of an abnormal fibrillar extracellular material in the anterior chamber of the eye as well as other various parts of the eye and adnexa.[28,29] The accumulated material consists of a fibrillar component and an amorphous component, though the exact chemical composition remains unclear.[30–34] It appears that the material represents abnormal basement membrane secreted by all structures in the anterior chamber and deposited on the anterior lens capsule, iris surface and trabecular meshwork.[30–34] Because of the accumulation of material at the pupillary margin, there is increased lenticular apposition with the iris, and subsequent erosion of iris pigment as the pupil dilates and constricts. This leads to increased iris transillumination and deposition of pigment granules on the endothelium, iris surface and trabecular meshwork—similar to pigment dispersion syndrome. As this is a condition that involves deposition of material on the anterior lens capsule and not delamination of the lens capsule, lensectomy is not curative.



Exfoliation on the anterior lens surface.

The development of glaucoma typically occurs as a result of a buildup in the trabecular meshwork of pigment granules and exfoliative material. The primary cause of IOP elevation appears to be phagocytosis of accumulated pigment and material by the trabecular cells and Schlemm's canal cells, with subsequent degenerative changes of Schlemm's canal and trabecular meshwork tissues. Thus, this is a secondary open-angle glaucoma mechanism.[26,27] However, due to zonular dehiscence from accumulations of exfoliative material, there can be lens displacement with secondary pupil block and angle closure mechanisms.[26,27]

Patients with exfoliation have demon-

strated aggregates of similar material in the fibrovascular connective tissue septa of the skin as well as in some internal organs (e.g., heart, lungs, liver and kidneys). Some evidence suggests an association with transient ischemic attacks, aortic aneurysm formation and systemic cardiovascular diseases.[27,33] Exfoliation syndrome is therefore considered a generalized systemic disorder rather than solely an ocular condition.[33]

Management

Exfoliation syndrome without IOP rise requires periodic monitoring of IOP, discs, nerve fiber layer and visual fields in case IOP elevation later develops.[13,14,19] Multiple IOP readings to establish a diurnal pressure curve is especially important as patients with exfoliation syndrome and exfoliative glaucoma demonstrate great variations in IOP.[35,36] Patients with exfoliative glaucoma, more than those with primary open-angle glaucoma (POAG), exhibit a diurnal range greater than 15 mmHg. Forty-five percent of exfoliative glaucoma patients demonstrate a peak IOP at times outside normal physician office hours.[37]

Exfoliative glaucoma is medically treated in the same manner as POAG. The clinician may use, if not systemically contraindicated, topical beta-blockers, topical carbonic anhydrase inhibitors, prostaglandin analogs and alpha-adrenergic agonists. However, the IOP level in exfoliative glaucoma is typically higher than with POAG and is more difficult to temporize. Typically a greater amount of medical therapy is needed to control patients with exfoliative glaucoma compared to POAG patients.[38-40] Laser trabeculoplasty and trabeculectomy, both viable treatment options, are often employed earlier in cases of exfoliative glaucoma than for patients with POAG.[39]

Clinical pearls

• Peripupillary iris transillumination defects are a common and important finding in patients with exfoliation. In fact, they may precede the development of clinically observable exfoliative material on the lens surface. This finding mandates a careful inspection of the anterior lens surface following dilation.

• A pigment shower in the anterior chamber can occur following diagnostic dilation.

• Eyes with exfoliation typically do not dilate well due to subclinical posterior synechiae.

• Exfoliative glaucoma can be especially difficult to control. Special care should be given to earlier, aggressive pressure reduction when exfoliation is present.

• While exfoliation can appear to be unilateral, it is actually bilateral and asymmetric.

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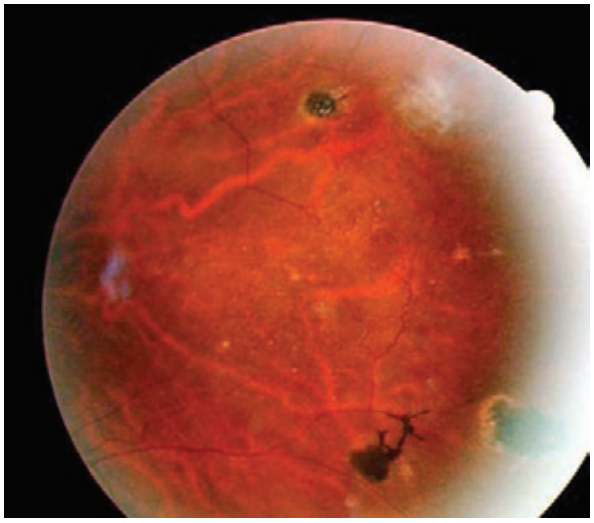
SICKLE CELL RETINOPATHY

Signs and symptoms

The ocular signs of sickle cell anemia variably include comma-shaped vessels in the bulbar conjunctiva, iris atrophy, iris neovascularization, dull gray fundus appearance, retinal venous tortuosity, nonproliferative retinal hemorrhages (which may be subretinal, intraretinal or preretinal), black sunbursts (retinal pigment epithelial hypertrophy secondary to deep retinal vascular occlusions), glistening retractile deposits in the retinal periphery (hemosiderin-laden macrophages), salmon patch hemorrhages (orange-pink-colored intraretinal hemorrhage), angioid streaks (breaks in Bruch's membrane radiating from the optic nerve), "macular depression sign" (a loss of the foveal reflex), venous occlusion, artery occlusion and peripheral neovascularization (in a "sea fan" appearance) with possible attendant vitreous hemorrhage and tractional retinal detachment.[1–5] Ocular symptoms are uncommon in the early stages of any form of sickle cell disease.[6,7]

Pathophysiology

In all four variations of sickle cell disease, systemic and ocular tissues have the potential to become deprived of oxygen secondary to inherited abnormalities of the beta-globin chain.[6,7] The origin of the genetic abnormality can be traced to the continent of Africa where, data suggests, the mutation of the hemoglobin chain protected individuals from malaria infection.[6–8] Inheritance of the sickle cell hemoglobinopathies is autosomal co-dominant, with each parent providing one gene for the abnormal hemoglobin.[5] Abnormal hemoglobin S results following a single point mutation substituting valine for glutamic acid at the sixth position.[2,3] Substituting lysine for glutamic acid at this position results in the formation of hemoglobin C. When both parents contribute the S mutation, classic sickle cell anemia or SS disease ensues.[3] When one parent contributes S-mutated hemoglobin and the other C-mutated hemoglobin, the SC form of the disease occurs. Inadequate production of either normal or abnormal globin chains creates the S-thalassemia (S-Thal) variant.[3] Incomplete expression of the disease with some of the genetic mutations produces sickle cell trait (AS).[3]



Sickle cell retinopathy; note the arteriovenous changes and "black sunbursts," representing peripheral retinal ischemia.

The retina erythrocytes, having lost their biconcave shape, become rigid, restricting blood flow, inducing thromboses and inducing tissues to become hypoxic.[1–11] Vascular leakage and liberation of angiogenic cytokines with subsequent retinal neovascularization (along with all of its attendant complications) dictate the severity of the condition.[1–8,11,12] The pathogenesis of the resultant retinopathy is ultimately a manifestation of arterial and capillary microcirculation obstructive vasculopathy.[10]

Salmon-patch hemorrhages are preretinal or superficial retinal hemorrhages that often dissect into the vitreous humor.[3] They are the result of disruptions of the medium-sized arterioles secondary to chronic ischemic-vascular compromise.[3] Although they are initially bright red, their color evolves as they age. Because they have a tendency to push both forward and backward within the retina, they may leave a retinoschisis remnant when they resolve.[3] Since the movement of this blood can disturb the retinal pigment epithelium, irregularly shaped hyperplastic changes occur, producing the classic pigmentary finding known as black sunbursts.

The hallmark proliferative sign of sickle cell disease is the sea fan–shaped frond of neovascularization.[11] A common trait of the SC and S-Thal variations, sea fan neovascularization represents the body's aggressive attempt to supply oxygen to hypoxic retinal tissue.[3,5–8,11,12] Arteriovenous crossings are the preferential site for sea fan development.[12] Here, preretinal vascular formations develop from a single or multiple feeder vessels at the border of perfused and non-perfused peripheral retina.[11,12] Since the retinal tissue is not globally ischemic, the abnormal vessels arborize along the border of perfused and starved tissue.[3,11,12] Drained by single or multiple venules, the classic kidney-shaped appearance is driven by environment. Vascular endothelial growth factors are associated with these formations.[11] The neovascularization in sickle cell retinopathy can arise both from the arterial and venous sides of the retinal vasculature.[12] Autoinfarction (complete or partial spontaneous involution) appears to occur initially at the preretinal capillary level rather than at the feeding arterioles, and it has been documented to occur in up to 50% of cases.[12]

The abovementioned proliferative

sickle cell retinopathy development is classically broken down into five stages. Stage 1 is recognized by peripheral retinal arteriolar occlusions. Stage 2 is marked by the appearance of peripheral arteriovenous anastamoses. Stage 3 is characterized by the growth of neovascular sea fan fronds. Stage 4 is marked by vitreous hemorrhage, as tractional forces and vitreous collapse tear fragile neovascular membranes. Stage 5 is advanced disease, identified by severe vitreous traction and retinal detachment.[1–4, 11,12]

The diagnosis of clearly evident clinical comorbidities such as leg ulcer, osteonecrosis and retinopathy are considered predictors for lethal organ damage.[10] Fifty-one percent of patients with sickle cell disease who eventually have a cerebrovascular accident report a prior chronic collateral condition.[12]

Management

The treatment goal for sickle cell retinopathy is to reduce or eliminate retinal neovascularization.[6–9] Patients with asymptomatic sickle cell disease with no ocular manifestations should be followed biannually with dilated retinal evaluation.[5–8] Referral to a retinal specialist is indicated when proliferative retinopathy is evident. Treatment for proliferative disease involves panretinal photocoagulation. Cryotherapy has not been proven efficacious and is associated with high complication rates.[5] Scleral buckle procedure may be indicated in cases of retinal detachment.[5] Photodynamic therapy and antiangiogenic compounds, used in choroidal and retinal neovascularization seen in other entities, are not yet documented as therapies for sickle cell retinopathy.[1–4]

Systemically, genetic risk factors and other preventative possibilities are now being explored.[10,13] Stroke prevention has been made possible by advances in transcranial Doppler ultrasonography, which permits extensive examination and screening.[5] Hydroxyurea, an anticarcinogenic preparation, has significantly reduced the number of deaths and complications from sickle cell disease.[14] It increases fetal hemoglobin levels, which seems to prevent red blood cells from sickling.[14] The medication has demonstrated an ability to reduce the number of vaso-occlusive crises and acute chest problems, thereby reducing the number of hospitalizations and reducing the severity and impact of the disease. It also has demonstrated great efficacy and safety in pediatric studies.[10,14] Niprisan (Nix-0699), another naturally occurring anti-sickling agent, has demonstrated promise in experiments with mice. It may offer the promise of an additional preventative solution.[15]

Clinical pearls

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

• The sickle cell anemia variation (SS) produces the greatest number of systemic symptoms. The sickle cell disease mutations SC and S-Thal produce the greatest number of ocular effects. Overall, the sickle cell trait expression (AS) produces the fewest complications.

• The sea fan frond of neovascularization is so characteristic to this disease that, when encountered, it must be the prime consideration in undiagnosed patients.

• Systemic symptoms include recurrent, painful vaso-occlusive crises with abdominal and musculoskelatal discomfort.[6,7] Other systemic manifestations include jaundice, cerebrovascular accidents and infections (particularly by encapsulated bacteria).[8,9]

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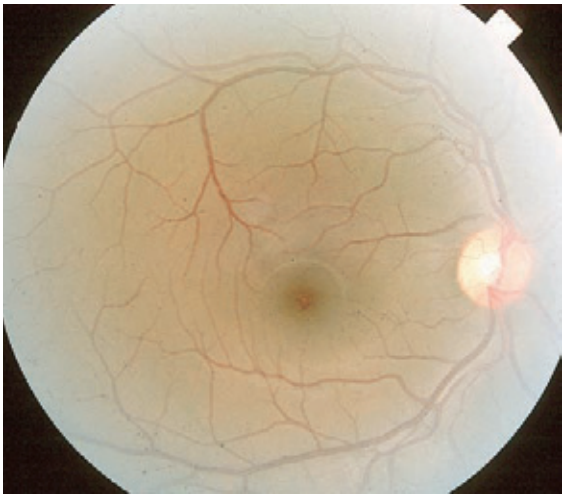
SOLAR RETINOPATHY

Signs and symptoms

Patients will variably present with visual acuity loss, metamorphopsia, positive or negative after-images and central scotomas after intentional or unintentional sungazing. However, this history may not always be forthcoming. In acute cases, the causative factor is often apparent to the experienced clinician. However, in chronic cases, the etiology is often discovered only after careful history guided by the ophthalmoscopic findings. Solar retinopathy occurs as a result of direct-fixation retinal exposure to the sun for a variety of reasons such as watching a solar eclipse, religious rituals, mental



Solar retinopathy.

illness, mental or emotional immaturity, sunbathing, drug use, the false belief that it is therapeutic and alcohol intoxication, to name a few.[1–12]

The characteristic early ophthalmoscopic finding is a small, irregularly shaped lamellar defect, often described as yellowish-white, in the foveal center.[1,2,13–15] There may be a surrounding circular area of hyperpigmentation. After several weeks, the yellowish lesion fades to reveal a sharply defined foveal cyst-like defect with irregular borders, surrounded by a coarse, pigmented halo.[2,13]

Presenting visual acuity is highly variable and contingent upon many factors, including duration of exposure and time of onset. Patients may present many months to years following the sungazing event with normal Snellen acuity but distortions on Amsler grid testing or macular threshold perimetry.[6] Alternately, patients may present acutely or chronically following the incident with markedly reduced acuity in the range of 20/50 to 20/200.[9,13,16]

Solar retinopathy can present unilaterally or bilaterally. Unilateral and asymmetric bilateral cases typically show more effects in the patient's dominant eye. The duration of the sun gazing needn't be extreme; effects have been demonstrated after only 20 seconds of direct viewing.[9]

Pathophysiology

Solar retinopathy likely develops from a combination of photochemical and thermal mechanisms.[16–19] Retinal cells die by apoptosis in response to light-induced injury, and the process of cell death is perpetuated by diverse, damaging mechanisms.[19] Two classes of photochemical damage have been recognized. The first type is characterized by the rhodopsin action spectrum and is thought to be mediated by visual pigments, with the primary lesions located in the photoreceptors. The high-energy wavelengths and low levels of ultraviolet A (UV-A) radiation are absorbed by the outer retinal layers, with subsequent photochemical damage that likely involves oxidative events.[13,19] The second type of damage is generally confined to the retinal pigment epithelium (RPE). The RPE pigmentation absorbs sunlight energy, converting it to heat, with a resultant rise in temperature that results in a burning of the RPE.[14] This RPE damage is often permanent.

Fluorescein angiography does not consistently identify the underlying pathophysiology in solar retinopathy. Occasionally, fluorescein angiography will reveal small window defects or other mild RPE defects.[2,3,13] Often, however, fluorescein angiography reveals no abnormalities.[13,16,17]

In acute onset, optical coherence tomography (OCT) demonstrates increased reflectivity of the inner foveal retina as well as a hyporeflective area of the underlying RPE and an increase in retinal thickness.[1,13,14,20] OCT also has demonstrated abnormal reflectivity at the outer foveal retina, with fragmentation and interruption of the inner high reflective layer corresponding to the junction between the photoreceptor inner and outer segments.[21] Involvement of the entire photoreceptor reflective layer at the fovea has also been observed in patients with poor acuity.[21] In chronic cases, hyporeflective spaces within the RPE have been observed, corresponding to the damaged RPE and photoreceptors.[13,20] Essentially, multiple findings in OCT analyses have been seen with alterations in different levels. These are likely representative of the different types of photochemical and thermal damage occurring within the retina and RPE. Abnormalities in the multifocal electroretinogram have been found, and this may also be a helpful diagnostic modality.[22–24]

Management

Thus far, no successful intervention for vision loss occurring from solar retinopathy has been identified. However, it is important to understand the natural history of this condition so that patients can be counseled regarding their visual prognosis.

Reports of spontaneous visual recovery vary greatly. In perhaps the majority of reported cases, visual acuity returns to normal or near-normal levels, though slight deficits such as central scotomas, after-images and metamorphopsia may persist despite good Snellen acuity.[1,5–8,11,14,15,24] However, in many reported cases patients have had little-to-no visual recovery and, in some cases, had significant visual impairment.[2–4,7,9–11,19,21,25,26] One study with long-term follow-up saw improvement in participants' visual acuity occur mostly during the first two weeks to one month after viewing an eclipse. Further improvement in visual acuity was not observed in any of the eyes after 18 months.[17]

Clinical pearls

• While it is not common to ask patients in a routine history whether they have ever stared at the sun, the presence of small unexplained foveal cysts or visual acuity loss should ini-

tiate this unusual line of questioning. We have encountered patients who didn't readily admit to or associate their vision loss with sungazing and this history didn't become apparent until the patients were pointedly asked.

• Visual recovery is unpredictable. Duration of exposure, degree of intensity, macular pigmentation, lenticular opacification and geographic location of exposure are some of the many variables that work in concert to create retinal damage. It is best to counsel patients that although there may be some visual recovery, there is no guarantee. The chances of late visual recovery are lower than in patients who have recently had exposure.

• Prevention is still the best management approach. In cases of impending eclipse, place warnings in all common patient waiting areas.

• OCT and fluorescein angiography demonstrate no consistent diagnostic pattern for solar retinopathy but may confirm visible retina changes associated with the disorder.

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ACUTE POSTERIOR MULTIFOCAL PLACOID PIGMENT EPITHELIOPATHY

Signs and symptoms

Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) is an idiopathic, typically bilateral inflammatory disorder of the posterior segment seen in otherwise healthy young adults.[1–9] It manifests as patchy inflammatory defects in the choriocapillaris, retinal pigment epithelium (RPE) and outer retina.[1–8] It is characterized by multiple, whitish-yellow, creamy inflammatory lesions in the form of flat, large, irregularly shaped discs located at the level of the choroid, RPE and outer retina.[1–6] Common onset occurs between the second and third decades of life.[5] There seems to be no predilection for men or women.[5]

Often, a systemic viral prodrome precedes the onset of ocular signs and symptoms.[5] Patients may complain of headache, stiff neck and tinnitus before realizing that their vision has changed.[5,10] Patients present with variable visual acuity, which may be markedly asymmetric. They may describe vision reduction yet still measure 20/20; conversely, visual acuity may be as poor as 20/400.[1,2,5] Alterations in vision and in visual recovery seem dependent upon where the choroidal placoid inflammatory patches reside and the level of inflammation and ischemia within the affected regions.[1,2] When the patches reside in or adjacent to the macula relative scotomas can profoundly affect vision and the patient's ability to track and read.[1,2] When the patches lie outside this critical viewing zone, vision and function may be unaffected. In the instances where retinal anoxia is mild, only temporary visual disturbances are reported, with full recovery anticipated.[1,2] However, when lesions present with significant inflammation, the visual disturbances tend to be more profound, leaving permanent visual defects as remnants despite resolution of the condition.[1,2] Other noted signs and symptoms associated with APMPPE include episcleritis, disc hyperemia and neurosensory retinal detachment.[5,9] Indocyanine green and sodium fluorescein angiography demonstrate early hypofluorescence of the placoid lesions with late staining.[1,3,5]

A potential new entity has been proposed, with clinical features similar to APMPPE and serpiginous choroiditis. It has a prolonged progressive clinical course with more widespread distribution of lesions.[11] This condition is noted for being clin-

ically atypical, demonstrating prolonged periods of pathologic activity that result in the appearance of more than 50 and sometimes hundreds of lesions scattered throughout the fundus.[11] The appearance of new lesions may continue for as long as five to 24 months after initial examination.[11] It is unclear whether this is a variant of serpiginous choroiditis, APMPPE or a new entity altogether.[11] It has been named for the characteristics of its behavior: Relentless Placoid Chorioretinitis.[11]

Pathophysiology

In the literature, APMPEE has been recognized and categorized as one of the uveomeningeal syndromes, a group of disorders that share involvement of the uvea, retina and meninges.[8] Inflammatory and autoimmune etiologies are the frequently recognized cause of the uveomeningeal syndromes.[8] Acute posterior multifocal placoid pigment epitheliopathy is caused by vasculitic inflammation of the choriocapillaris.[1,2,11,12] Evidence suggests that the vascular inflammation causes transient occlusion of these vessels, producing mild ischemia.[7–13] While the pathophysiology is not precisely understood, there is debate over whether the disease is a primary RPE disorder or a choroidal vascular disease.[4] Angiography has demonstrated a profound delay in choroidal filling time, along with the discovery of extensive areas of choroidal nonperfusion in its acute stages.[3,4] Recovery of choroidal blood flow following clinical resolution is a hallmark of the entity.[4] These findings demonstrate that APMPPE is a primary choroidal vascular disease.[1–14]

The vasculitis associated with APMPPE may affect the long and short posterior ciliary vessels that supply the optic disk.[13] This may result in neural axoplasmic stasis and compression of the central retinal vein, leading to optic neuropathy and central retinal vein occlusion.[14]

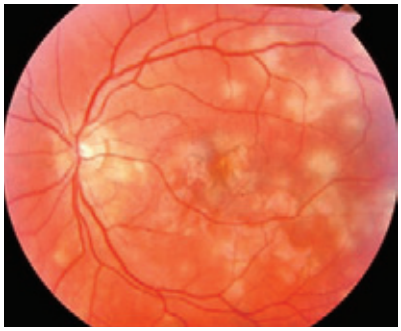

Photo courtesy Jerome Sherman, OD, FAAO.

As seen here, APMPPE is typically bilateral and affects otherwise healthy young adults.

The perinuclear pattern antineutrophilic cytoplasmic antibody (pANCA), myeloperoxidase (MPO-ANCA) is often associated with systemic vasculitis, producing systemic and ocular effects.[12] This particular marker is known to be an identifier in the disease process of APMPPE.[7–13]

The most frequent systemic manifestation associated with APMPPE is glomerulonephritis.[6] However, inflammation in other tissues of the body (along with those detected in ocular structures) is possible.[8] A paraneoplastic disorder has been described in patients who have combined optic neuritis and retinitis.[8] This syndrome is defined serologically by the presence of a paraneoplastic IgG autoantibody CRMP-5-IgG.[8] These patients may present with an inflammatory vitritis similar to those seen with APMPPE.[8] The disease has also been identified as potentially producing neurological sequellae.[10] One study reported that three patients with APMPPE developed neurological disease.[10] All three presented with marked visual disturbances and headaches.[10] One patient developed recurrent strokes involving different vascular territories of the brain, and two patients had cerebrospinal fluid pleocytosis in the setting of persistent headaches.[10]

Management

While APMPPE tends to be self-limiting, there is evidence suggesting that systemic corticosteroids may have a benefit in its management.[9] Unfortunately, other studies demonstrate that oral steroids have no effect on recovery.[5,15] Treatment options should be explained but left in the hands of the treating retinal specialist. These experts, by default of their clinical experiences, will possess a philosophy favoring one choice over the other. Most individuals enjoy a full recovery of function with little residual deficit.[1,2,5,15] However, some researchers have discovered that the long-term visual outcome following an episode may not always be favorable.[15] Older age of onset and initial foveal involvement appear to be associated with worse visual outcomes.[15]

Since an association with the antineutrophilic cytoplasmic antibody (ANCA) marker has been established, testing using both pANCA and cytoplasmic patterns might help establish a systemic diagnosis in patients who present with eye manifestations such as scleritis, retinal vein occlusion, optic neuropathy or APMPPE who are otherwise determined to be in good health.[7–13]

Clinical pearls

- The association of a uveitis with an acute or chronic meningoencephalitis may suggest an infectious etiology or even a specific organism known to possess a relationship with the meningeal syndromes.
- Wegener granulomatosis, sarcoidosis, Behçet's disease and Vogt-Koyanagi-Harada syndrome are other notable uveomeningeal disorders.
- The disease has also been categorized as a "white dot" syndrome because of its classic appearance. Other white dot syndromes requiring consideration include multiple evanescent white dot syndrome (MEWDS), birdshot chorioretinopathy, serpiginous choroiditis, punctate inner choroidopathy (PIC disease) and acute retinal pigment epitheliitis (Krill disease).

• Disruption of Bruch's membrane seems to occur far less frequently in this condition as compared to others such as age-related macular degeneration, making the formation of choroidal neovascularization a rarity.

• One should consider the diagnosis of primary ocular-CNS lymphoma in patients with unilateral or bilateral vitritis and intermediate uveitis with or without neurological findings.

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BIRDSHOT RETINOCHOROIDOPATHY

Signs and symptoms

Birdshot retinochoroidopathy (BRC), sometimes referred to as vitiliginous chorioretinitis, is a rare ocular disorder named and delineated as a separate clinical entity by Ryan and Maumenee in 1980.[1,2] Known to be a bilateral, progressive, retinal-choroidal vascular inflammatory disease with a strong association to middle-aged white individuals of Northern European decent, BRC produces a diffuse posterior choroidopathy with an associated anterior segment reaction, vitritis and retinal vasculitis.[1–9] The typical age of presentation is the fourth to fifth decades of life, with a slight female predominance.[6] As the disease progresses, profuse retinal-vascular leakage ensues, with resultant retinal, macular and disk edema developing.[1–9] The fundus lesions are often described as creamy, small (less than 1 disc diameter) and scattered throughout the entire fundus.[1–8] As the retina and disc swell and cystoid macular edema (CME) advances, visual acuity is affected variably.[1–5] Individuals presenting with a duration longer than 30 months have a higher likelihood of visual acuities reduced to 20/50 or worse than those presenting with shorter durations.[8] Visual loss can progress to levels as poor as 20/200.[10]

The fundus exhibits a characteristic patterned distribution of depigmented spots with an absence of adjacent hyperpigmentation reaction.[2] Traditionally, no pathologic alterations are evident on the optic disc (peripapillary atrophy), even when the optic disc itself succumbs to the effects of the disease process (disc swelling ensues).[4] Early complications of the disease may include the inability to see in the dark, visual field deficits, epiretinal membranes (with the potential for macular hole development),

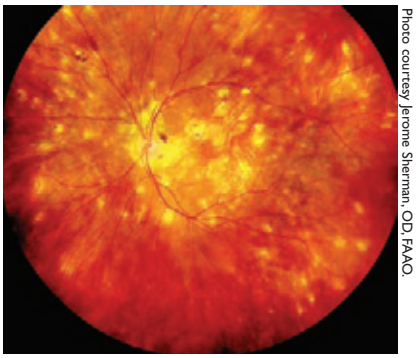

Photo courtesy Jerome Sherman, OD, FAAO.

Birdshot retinochoroidopathy.

venous sheathing, retinal neovascularization with or without recurrent vitreous hemorrhage and subretinal neovascular membranes occurring in the juxtapapillary and perimacular regions. At the end stage is optic atrophy and changes that mimic retinitis pigmentosa, despite the absence of typical findings.

The diagnosis of BRC is made classically upon its appearance and ocular findings.[5] The fluorescein angiography appearance demonstrates mild hyperfluorescent patches that correlate with the areas of hypopigmentation. There is often mild vascular leakage, late optic disc staining and petalloid appearance classic of CME.[5]

Pathophysiology

The specific etiology of BRC remains unknown.[1–15] The majority of patients possess autoimmune human leukocyte antigen disease (HLA), in which the body fails to distinguish self from nonself.[1–5] The HLA-A29 marker is a specific identifier for this condition.[1,4,5] Lymphocyte reactivity to the retinal S antigen also points to an autoimmune etiology.[4] The distribution and appearance of the lesions map them to the major choroidal veins.[4] The preponderance of evidence suggests that this is a single, unique disease rather than a conglomeration of concomitantly occurring disorders, because in each case there is core similarity in the ophthalmologic appearance, clinical course and

association with HLA-A29 marker.[4]

Under the influence of released inflammatory cytokines, retinal vessels (capillaries and retinal arterioles) become more permeable, creating an environment conducive to the formation of CME.[1–5] CME is the predominant cause of lost visual function.[1–14] Defects in the visual field can be correlated to the areas of choroidal depigmentation.[1–16]

Management

Treatment for BRC is not always required. In instances in which there is no threat to macular integrity and no loss of function, careful photodocumentation and monitoring will suffice. When vision is threatened or macular edema evolves, intervention should be considered. Periocular and systemic steroids are the mainstay of treating the disease.[5,9,11,12] Here, the goal is to slow or arrest the inflammatory process, decreasing vascular leakage and preserving function by limiting impingement on macular structures.[5–14]

Azathioprine, a commonly used immunosuppressive agent, is designed to be deployed in cases in which inflammation is unsuccessfully controlled with oral or intravenous steroids.[11] Given the inflammatory vasculopathic nature of BRC, the agent is suitable for augmenting disease control along with steroids. It also provides an option in cases of steroid-related complications.[11] The principal indication for azathioprine with respect to BRC is uncontrolled disease with maximum systemic steroid therapy.[5,11,12] The medication, typically prescribed for one year or longer, demonstrates an ability for decreasing relapse rate and reducing total steroid dosage.[11] Improvement or maintenance of visual acuity is the rule more than the exception.[11] Other medications in the same class with a similar mechanism of action are methotrexate and cyclosporine.[5,11–14] Interestingly, cyclosporine reduction appears possible with adjunctive ketoconazole usage.[12] The regimen appears safe and efficacious.[12] The combination of systemic corticosteroids and immunomodulating agents is sometimes referred to in the literature as corticosteroid-sparing systemic immunomodulatory therapy (IMT).[13] Without question, this particular strategy has gained momentum as the current standard, with prompt induction clearly able to preserve tissue structure, architecture and function.[12–14]

Since some patients may be apprehensive about the effects of an intricate medicinal cocktail, another viable option is intraocular corticosteroid injection.[15] Intravitreal triamcinolone injection has demonstrated reasonable efficacy as a therapy for BRC.[15] Its advantages include a swift, stabilizing effect that also reduces the potential for systemic side effects that are often produced by the intravenous and oral preparations.[13] Of course, the inherent complications of this class of medicine remain and include cataract formation and increased intraocular pressure.[15]

Intravenous polyclonal immunoglobulin (IVIg) has been successfully administered for treating numerous autoimmune conditions.[16] Investigators have used this modality in BRC as an alternative to traditional therapy, with some success.[16]

While laser photocoagulation for the exuding lesions and the uveitic-based CME is not specifically recommended, even in advancing cases, oral acetozolamide therapy can be attempted in an effort to reverse the progression of macular leakage.[17] As a last resort, if all other standard and current modalities have failed to resolve CME, pars plana vitrectomy (PPV) with intravitreal triamcinolone application has recently shown promise as a procedure that at the least may temporarily stabilize the condition.[17] Frequent complications, however, include premature cataract formation and ocular hypertension.[17]

Fluorescein angiography, optical coherence tomography, indocyanine videoangiography and other instruments that measure or image retinal thickness and retinal structures, along with electrodiagnostic testing, can help monitor the disease and its rate of progression.[5,18] Quantified measurements can assess treatment efficacy.[5,18]

Clinical pearls

- The long-term prognosis of BRC is guarded.
- End-stage disease can result in sensory retinal and optic nerve atrophy, with resultant permanent visual consequences.
- The amount of visual loss with BRC is typically proportional to the chronicity and extent of the cystoid macular edema.

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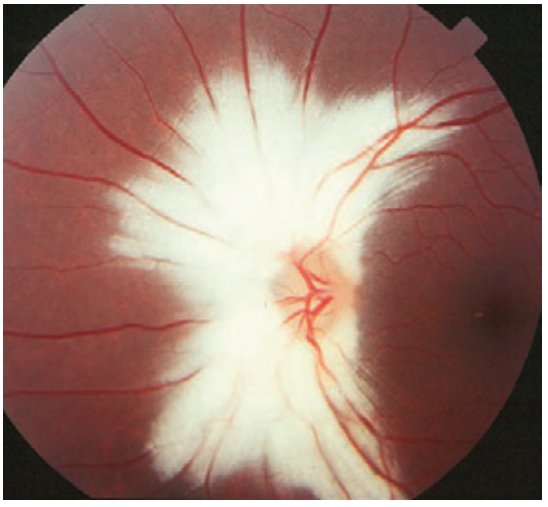
MYELINATED NERVE FIBERS

Signs and symptoms

Occasionally, myelinated nerve fibers will be discovered upon consultation for reduced visual acuity, strabismus or leukocoria, though in the vast majority of cases it is discovered upon routine ophthalmic examination.[1] One report noted a greater incidence among women.[2] Myelinated nerve fibers may be unilateral or bilateral.[1,2] The prevalence of myelinated nerve fibers in the general population approaches 1%.[1] There may be multiple patches within an eye.[1–3]

Funduscopically, myelinated nerve fibers are white to gray patch densities that follow the pattern and architecture of the retinal nerve fiber layer. The concentration is greatest at the origin of the myelinated nerve fibers and "feathers out" at the edges. This classic pattern helps to identify myelinated nerve fibers and differentiate the condition from cotton wool spots. Depending on the density of myelinated fibers, retinal vessels and choroidal detail may be obscured. Lesion size may range from less than one-half disc diameter to several disc diameters. Myelinated nerve fibers may be contiguous with the optic disc or may appear distant in the fundus with normal retina between the lesion and the optic disc.

Visual acuity is typically unaffected. Visual field defects can occur and, due to the fact that myelinated nerve fibers involve the nerve fiber layer, they can produce visual field defects that mimic those seen in glaucoma. However, in most instances, visual field defects tend to be mild and are smaller than would be expected given the extent of the lesion—indicating that light penetrates to the photoreceptor level.[1,4]


Myelinated nerve fibers may be focal or diffuse, as seen here.

While typically a benign finding in itself, multiple associated complicating factors have been reported to occur with myelinated nerve fibers, including cilioretinal artery occlusion, retinal neovascularization, juxtapapillary hemorrhage, branch vein occlusion, vitreous hemorrhage, telangiectasis and branch artery occlusion.[1,5–9] Additionally, myelinated nerve fibers appear to present more frequently in patients with Down's syndrome, neurofibromatosis and craniofacial dysostosis.[4]

It has long been thought that myelinated nerve fibers represented a congenital anomaly, and in the vast majority of cases, that is likely correct. However, it has also been documented that myelination of retinal nerve fibers can be acquired later in life and may actually advance over time, although this seems uncommon.[10–13]

Further, atrophy and regression of myelinated nerve fibers have been documented to occur as a result of glaucoma, optic neuritis and multiple sclerosis, anterior ischemic optic neuropathy, Behçet's related papillitis and following vitrectomy.[14–18]

There appears to be a well-documented but as-of-yet unnamed syndrome consisting of (aniso)myopia and anisometropic amblyopia in association with myelinated nerve fibers.[19–26] This syndrome appears distinct from simple unilateral myopia with amblyopia and from myelinated nerve fibers without myopia or amblyopia.[24] Macular changes, including irregular pigmentation and loss of foveal reflex, are often present in association in these cases, and these may contribute significantly to vision loss beyond amblyopia.[20–24]

Pathophysiology

During normal development, retinal ganglion cell myelination begins in the lateral geniculate nucleus and proceeds anteriorly to the optic nerve, stopping at the lamina cribrosa in most cases. This process is completed shortly after birth.[1,4]

Normally, the retina is not myelinated because oligodendroglia, the cells responsible for myelination in the central nervous system, are absent in the retina. An anomalous distribution of oligodendroglia is thought to be the etiology of myelinated nerve fibers, rather than myelination simply continuing beyond the lamina cribrosa.

While myelinated nerve fibers themselves are typically benign, they may be associated with other causes of vision reduction. Visual deprivation imparted by myelination is insufficient to cause any significant degree of visual loss or deprivational amblyopia. However, in cases in which unilateral myelination occurs in association with high myopia, profound anisometropic amblyopia often occurs. It has been suggested that

myelination may cause myopia development, though the cause is truly unknown.[25] At this time, it is not clear whether high myopia contributes to the development of myelination or vice-versa. Peripapillary myelinated nerve fibers in an eye with myopia may be secondary to an imbalance between the process of myelination and the formation of the lamina cribrosa.[21]

Management

There is no intervention for myelinated nerve fibers. The most important facet of management involves correct identification. In that myelinated nerve fibers can superficially resemble cotton wool spots, careful differentiation must be performed to avoid unnecessary medical testing. Because glaucoma-like visual field defects can arise from myelinated nerve fibers, it is important to examine for these lesions before therapeutic management, especially if the optic disc and other features do not suggest glaucoma. Of note, scanning laser polarimetry measurements of patients with myelinated nerve fibers demonstrate increased retardation.[27] Thus, GDx analysis may assist in the differential diagnosis of these lesions.

Patients with myelinated nerve fibers in association with unilateral high myopia develop what many describe as anisometric amblyopia. However, such vision loss in association with myelinated nerve fibers tends to be refractory to standard amblyopia therapy.[19–26] Although there has been limited success in the amblyopic management of these patients, there appears to be a subset who have associated macular abnormalities that do not respond to standard management strategies. Thus it can be said that many of these patients with extensive myelination, monocular high myopia and amblyopia have vision loss that has developed from more than one source. Anisometropia imparts an amblyogenic factor, while subtle macular abnormalities, which may somehow result from extensive myelination, additionally contribute to vision loss that is unresponsive to amblyopia therapy. Nevertheless, in patients with myelinated nerve fibers, anisometropia and vision loss, aggressive amblyopic therapy must be instituted, with the understanding that the outcome may be poor because of conditions other than the amblyogenic anisometropia.

Clinical pearls

• Myelinated nerve fibers can be confused with cotton wool spots. The edges of myelinated nerve fibers appear feathery and follow the architecture of the nerve fiber layer, however, while cotton wool spots do not. If uncertainty persists, photograph the lesion and reappoint the patient for re-evaluation. Cotton wool spots fade over several weeks, whereas myelinated nerve fibers do not.

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CONGENITAL HYPERTROPHY OF THE RETINAL PIGMENT EPITHELIUM

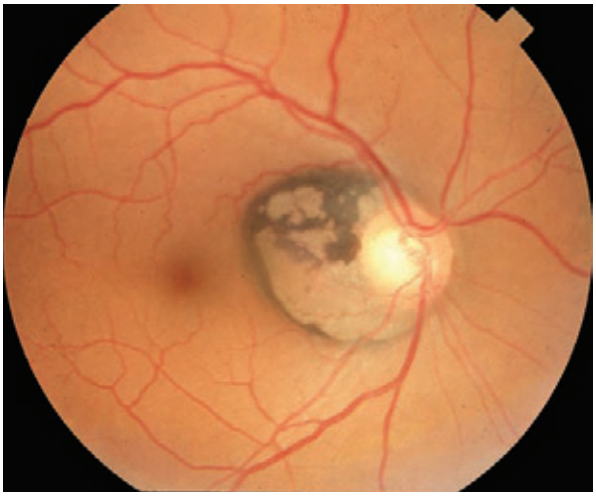
Signs and symptoms

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) is typically an incidental finding discovered during routine dilated fundus examination. Patients are almost invariably asymptomatic, with 3% reporting visual photopsiae (i.e., flashes and floaters), diminished acuity or visual field defects.[1] Clinically, there are three recognized presentations: solitary, grouped, and multiple.[2]

Solitary CHRPEs are classically unilateral and appear as flat, well-demarcated, darkly pigmented lesions of the ocular fundus. They may appear gray, brown or black and are often surrounded by a white ring or halo. Less commonly, CHRPE may be non-pigmented centrally and display a dark border. Solitary CHRPEs are typically round or oval. Approximately 13% assume a more amorphous geographic configuration.[1] These lesions are usually located in the retinal periphery, but may sometimes be found in the macula or peripapillary area.[3,4] Size varies tremendously: Solitary CHRPE may range from 0.2–13 mm in basal diameter.[1] Lacunae, which appear as focal round areas devoid of pigment, are often observed within larger lesions; choroidal vessels may be visible at the lacunar base. Other variations in solitary CHRPE can include overlying vascular sheathing, adjacent areas of white without pressure and, rarely, development of a focal elevated nodule within the lesion.[1]

Grouped CHRPE describes a presentation of sectorially oriented hyperpigmented spots in one or more quadrants of the fundus.[2] These lesions are also flat and well-delineated, but are on average smaller than solitary CHRPE.[2] The ophthalmoscopic appearance often resembles a cluster of animal footprints; hence the condition is colloquially referred to by many clinicians as "bear track retinopathy." Grouped CHRPE is commonly found near or contiguous with the optic nerve, and it also tends to be unilateral in presentation.[2]

Multiple CHRPE is the most significant of the three presentations because it carries an association with familial adenomatous polyposis (FAP), a potentially life-threatening hereditary form of colon cancer. Multiple CHRPE is marked by the presence of numerous scattered lesions averaging six per eye.[5] The hallmark of this condition is bilaterality, which occurs in 86% of patients.[6] Multiple CHRPE seems to have a slight predilection for the retinal periphery, although it may also be found in the posterior pole. The size of the lesions tends to be small, with most being less than one-half of a disc diameter (0.75 mm).[7] There is a fair amount of variability in ophthalmoscopic appearance. As with solitary CHRPE, the lesions may differ in pigmentation (gray to black or amelanotic), shape (round, oval, tear-shaped, bean-shaped or linear) and the presence or absence of a surrounding halo.[5–7] When multiple CHRPEs are discovered with a concurrent diagnosis of FAP, the condition is referred to as Gardner's syndrome.



A circumpapillary CHRPE; such presentations are often mistaken for other forms of pathology.

Pathophysiology

Histologic evaluation of solitary CHRPE lesions reveals cellular hypertrophy of the retinal pigment epithelium (RPE) with associated accumulation of macromelanosomes; in other words, the RPE cells are larger and contain more pigment than usual, but they are not otherwise abnormal. The RPE basement membrane is somewhat thickened locally, and there is evidence of progressive photoreceptor loss in the outer retina, although the underlying choriocapillaris remains unaltered.[4,8] Lacunae, more common in solitary CHRPE than in other varieties, represent focal depigmentation and atrophy of RPE cells with concurrent thickening of Bruch's membrane.[10]

In contrast to solitary CHRPE, the RPE cells in grouped CHPRE appear to be normal-sized, but contain increased amounts of large pigment granules as well as a thickened basement membrane.[11] The multiple CHRPEs of Gardner's syndrome show distinct histological differences from the other two presentations; notably, these lesions are often multilayered and extend throughout the sensory retina, with evidence of associated RPE hyperplasia.[7,11] Multiple CHRPE has been frequently described as a hamartoma of the RPE.[5–7,11]

CHRPEs are often evident in newborns, and they have even been observed in prematurely born infants.[9] They are present throughout life, and until recently they were thought to remain invariably stable. However, evidence now suggests that most solitary CHRPEs show progressive enlargement over time. The mechanisms of RPE growth may involve horizontal expansion, development of additional lacunae and/or broadening of existing lacunae.[1] A small percentage of solitary CHRPEs exhibit intralesional nodules, and these may display enlargement as well.[1] At least three published reports have demonstrated malignant growth associated with solitary CHRPEs.[12–14] Grouped CHRPE and multiple CHRPE are not believed to demonstrate any significant growth in number or size.[7]

Management

Solitary and grouped CHRPE rarely

require any significant intervention. The most important consideration is differentiating these lesions from other, more ominous conditions, particularly choroidal melanoma. Typically, the diagnosis is straightforward and made by ophthalmoscopic examination alone, but ambiguous cases may benefit from additional diagnostic testing. Ultrasonography can be helpful in demonstrating a flat lesion without acoustic hollowing, choroidal excavation or orbital shadowing. Fluorescein angiography of CHRPEs shows a characteristic hypofluorescence within the pigmented area and hyperfluorescence associated with lacunae and halo; there is no evidence of vascular filling or leakage, as is typical with melanoma. Solitary CHRPEs should be carefully documented using detailed drawings, fundus photography or both, and monitored periodically for changes in size or elevation.

Multiple CHRPE, because of its close association with FAP, must be evaluated and managed with great care. One study suggested that the presence of at least four lesions (regardless of size), or at least two lesions, one of which is large, carries high sensitivity and maximal specificity for Gardner's syndrome.[6] All patients who meet this criteria or those who display atypical bilateral CHRPEs should be evaluated for the possibility of polyposis; this is particularly important in those with a positive family history of colon polyps or cancer.[15] Appropriate referral for these individuals is to a gastroenterologist for sigmoidoscopy or colonoscopy. In addition, genetic testing is available to identify the specific mutation in the APC gene that has been associated with FAP.[6] This test can also be used to identify FAP carriers within the immediate family.

Clinical pearls:

• Historically, CHRPE was sometimes called a "halo nevus," referring to the nearly pathognomonic depigmented border associated with these lesions.[16] While descriptive, this term was also quite misleading; nevi are histologically distinct from CHRPE, and are localized to the choroid rather than the retina.

• The red-free (green) filter on the ophthalmoscope or slitlamp can be helpful in differentiating ambiguous CHRPE from choroidal nevi or melanoma. With the filter in place, choroidal pigmentation becomes almost imperceptible, while retinal pigmentation remains visible.

• Generally, when CHRPE is encountered unilaterally and/or fewer than three pigmented lesions are evident, there is little risk of Gardner's syndrome. These patients need only to be followed for associated changes in the size or elevation of the lesions, which are typically minimal and benign.

• A rare variant of grouped CHRPE is the presentation of white variably sized spots in a clustered pattern of the posterior fundus. It has been referred to in the literature as "polar bear tracks."[17] This condition may be unilateral or bilateral. The lesions are relatively stable and considered to be of no functional significance.[18] Visual acuity, fields, color vision and electrophysiologic testing are all normal, and fluorescein angiography reveals hyperfluorescence throughout the various phases.[18]

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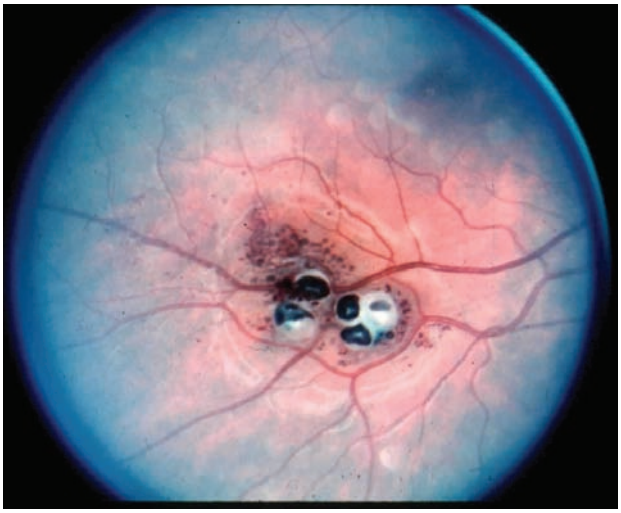
CAVERNOUS HEMANGIOMA OF THE RETINA

Signs and symptoms

Cavernous hemangioma of the retina (CHR) and optic disc are rare lesions. They were noted by Gass in 1971 as deserving their own separate classifications as unique entities.[1–3] They represent asymptomatic congenital malformations of the retinal blood vasculature that are typically non-progressive and usually unilateral, with a propensity for increased frequency in women.[4] CHR appears most commonly as a solitary vascular lesion of limited size (1 or 2 disc diameters) in the midperipheral or peripheral retina, posterior pole or optic nerve head.[4] CHR can be seen in all ethnicities.[3] Since they produce no dysfunction unless they occur in the macula (causing decreased acuity) or hemorrhage (with patients reporting the symptom

of floating spots), they often remain undiscovered until they are observed during a routine dilated fundus examination. However, CHR rarely are a source of intraocular hemorrhage.[1–4] When they do produce spontaneous vitreous bleeding, the episodes are often recurrent and significant.[3] CHR are easily recognized by their characteristic saccular "grape-like" appearance.[1,3,4]



A cavernous hemangioma of the retina with its characteristic saccular "grape-like" appearance.

Most individuals have a single lesion (consisting of multiple saccular components) in one eye with no other ocular or systemic anomalies.[3] However, on occasion the disturbance can be found demonstrating multiple lesions in one retina with abnormal vascular lesions of the skin and central nervous system (CNS).[3] While the tumors are generally considered static and incapable of growth, the literature documents two cases of cavernous hemangioma of the optic nerve which demonstrated an increase in size.[1] The literature has also documented a case in which a cavernous hemangioma interfered with oculomotor nerve function, causing ophthalmoparesis, ptosis and visual impairment via a compressive etiology.[5]

Cavernous hemangioma of the retina, optic nerve or choroid may serve as the ocular component of the neuro-oculocutaneous phacomatosis sometimes referred to as cavernoma multiplex.[6]

Pathophysiology

CHR are considered hamartomas (from the Greek meaning a benign overgrowth of mature cells normally found in the affected area) with an autosomal dominant inheritance pattern.[2,7,8] The lesions themselves consist of clustered, large, thin-walled intraretinal vessels lined with normal, healthy, vascular endothelium that have taken the shape of round saccules.[3] As the tumor evolves, it displaces and replaces the sensory retina in that zone.[3] There is no recognized malignant potential.[1–7]

The fluorescein angiographic features include a normal arterial and venous supply, extraordinarily slowed venous drainage, no arteriovenous shunting, no disturbances of vascular permeability, no secondary retinal exudation and the unique formation of isolated clusters of vascular globules, with plasma/erythrocyte sedimentation surrounding the main body of the malformation.[4]

Management

These lesions rarely require therapeutic intervention over the patient's lifetime.[1–7] They do not necessitate any restriction of activity and they typically remain stable and unchanged over time.[1–5] However, because of their vascular nature and potential to serve as markers for additional lesions in alternate locations, there is always some risk of other lesions developing that may not be as benign.[1–7] Unfortunately, these unusual formations may also exist in the brain.[6] While rare, the possibility of intracranial hemorrhage must be viewed as a life-threatening sequela.[6] For these reasons, individuals with cavernous hemangioma of the retina should be referred for neurological consultation and possibly for neuroimaging.[2–7] Family members should be advised to be properly evaluated for these vascular lesions.[2,7]

Clinical pearls

- CHR are considered stable intraretinal lesions. However, the same tumor occurring on the optic disc has the potential for growth and causing vitreous hemorrhage and therefore should be closely monitored.
- The presence either of CHR or choroidal hemangioma should alert the clinician to search for features suggestive of systemic and familial involvement.
- The principle differential diagnoses include exudative retinal telangiectasias and Coat's disease, the vascular Von Hipple Lindau tumor and the arteriovenous malformation (Racemose hemangioma/Wyburn Mason syndrome).

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NEURORETINITIS

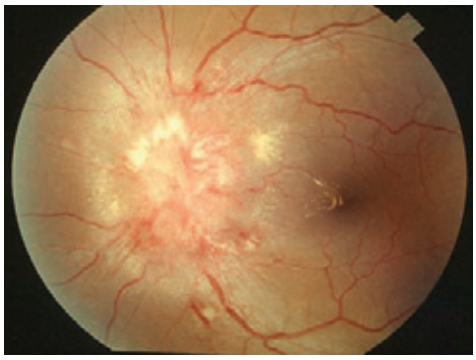
Signs and symptoms

While neuroretinitis can present in any age group due to several potential causative etiologies, patients are typically young. It is common for neuroretinitis to affect children. In fact, the majority of patients are younger than 20 years.[1–13] There is no gender predilection.

Neuroretinitis typically presents as a unilateral, acute, painless loss of vision. Rarely, it presents bilaterally. It can also present without symptoms. Alternatively, vision may be decreased to the finger-counting level.[1–13] The typical visual field loss is a central or cecocentral scotoma.[2,14] A relative afferent pupil defect (RAPD) will be present if the condition is unilateral or markedly asymmetric. Interestingly, the magnitude of the RAPD will be small relative to what one would expect given the profound degree of vision loss. In fact, in many unilateral cases, no detectable RAPD is evident despite profound vision loss in the affected eye.[2,14]

Ophthalmoscopically, there will be a markedly edematous disc. There may also be peripapillary hemorrhages due to venous stagnation. Occasionally a mild vitritis will be evident overlying the disc. Initially, there will be a serous retinal detachment extending from the disc to the macula. The key diagnostic feature in well-developed neuroretinitis is the presence of macular exudates in the form of a florid macular star.[1–13] However, this finding may not occur for up to several weeks after onset, and the diagnosis may not be apparent early in the course of the disease. It is not uncommon to have a serous retinal detachment within the posterior pole occur early on in association with the advent of disc edema. This is highly suspicious for early neuroretinitis, with the macular exudates ensuing later.[2,13]

Numerous conditions have been shown to be associated with neuroretinitis, including toxoplasmosis, toxocariasis, measles, syphilis, Lyme disease, herpes simplex and zoster viruses, mumps, tuberculosis, malignant hypertension, ischemic optic neuropathy and leptospirosis.[15–25] However, the most common cause by far is *Bartonella henselae*, the organism responsible for cat scratch disease.[26–36] Occasionally, cat scratch disease will be caused by *B. quintana*.[37] In cat scratch disease neuroretinitis, the patient may have an antecedent history of fever, malaise and/or lymphadenopathy occurring several weeks preceding the visual loss. There may also be an antecedent history of a cat scratch or flea bite.[26–37]



Neuroretinitis associated with cat scratch disease.

Pathophysiology

Neuroretinitis was initially identified by Leber in 1916 as a retinopathy associated with unilateral vision loss and disc edema. Later, upon the discovery that the foci of dysfunction was the optic nerve rather than the retina, the condition was renamed Leber's idiopathic stellate neuroretinitis.[38] Neuroretinitis, like most optic neuropathies, has many proposed mechanisms, although the exact pathophysiologic pathway has not been identified. In that the majority of cases are the result of infectious etiologies, it is plausible that cell invasion with proinflammatory activation and suppression of apoptosis may occur.[39]

Visual loss results predominately from the retinal edema rather than from optic nerve dysfunction. This is evidenced by the fact that the visual field defects reflect a retinal cause as well as the relative mild degree (or absence) of afferent pupil defect in the face of profound vision loss.[2,14] While the macular exudates are characteristic of this condition, it may not be present upon early presentation and may take several weeks (typically two) before developing.[2,40] After development of disc and retinal edema, there will be spontaneous resolution and fluid resorption. The aqueous phase of the edema resolves most quickly, leaving the accumulated lipid exudates within the outer plexiform layer forming the characteristic macular star.

Management

When encountering neuroretinitis, it is important to medically consider and evaluate patients for all possible causes. A history should be elicited for exposure to cats, flea or tick bites, travel to Lyme-endemic areas, exposure to sexually transmitted disease, lymphadenopathy, skin rashes, malaise, myalgia and fever. Tests that should be ordered (as dictated by the history) include Lyme titer, toxoplasmosis titer, toxocariasis titer, purified protein derivative skin testing and chest X-ray for tuberculosis. However, because the most common cause is infection by *B. henselae* or *B. quintana* from a cat scratch, one must carefully examine for these entities. Cat scratch disease can be identified by immunoassay antibody testing for *B. henselae* and *B. quintana*.[5,14,41]

Prognosis for visual recovery in neuroretinitis is generally excellent, especially if the cause is cat scratch disease. Most patients will return to normal or near-normal vision without treatment.[2,14,30] While neuroretinitis from cat scratch disease is typically a self-limiting condition with an excellent prognosis, antimicrobial therapy may be used to hasten recovery. Successful agents include rifampin, ciprofloxacin, doxycycline, sulfamethoxazole and trimethoprim.[2,3,14,28,29] A commonly used therapy

is doxycycline 100 mg PO BID for one month.[2,3,14,28,29]

In neuroretinitis, the disc edema will resolve in approximately eight weeks. The macular exudates will resolve over several months. However, a residual macular pigmentary atrophy or optic atrophy may remain. Occasionally, this will lead to a poor visual outcome.[2,3,26]

Clinical pearls

• Neuroretinitis should be suspected in cases of disc edema with profuse adjacent retinal edema and painless vision loss with a relatively mild afferent pupil defect. A confirmatory sign is the appearance of a macular star within 10–14 days.

• Very few entities will mimic neuroretinitis with its characteristic macular star. Mimicking entities include malignant hypertension and anterior ischemic optic neuropathy.

• The afferent pupil defect will be remarkably mild (or even absent) despite severe vision loss. This is a prominent diagnostic feature of neuroretinitis.

• The absence of pain on eye movements greatly helps differentiate neuroretinitis from demyelinating optic neuropathy. Patients with neuroretinitis need not have the same concerns for the development of multiple sclerosis.

• Fleas may be the vectors of the *Bartonella* organisms and hence neuroretinitis. However, history of a cat scratch or bite is not always necessary to make this diagnosis.

• While antibiotics are frequently used for cat scratch disease neuroretinitis, there are no controlled clinical trials that indicate a better clinical outcome from this therapy.

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TILTED DISC SYNDROME

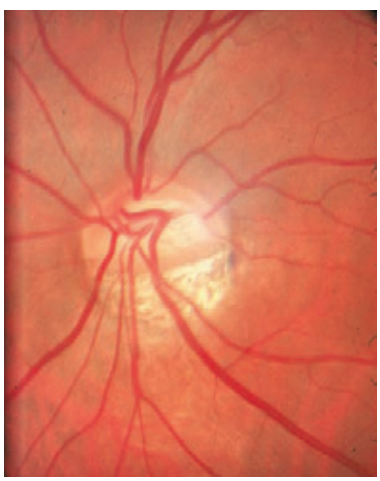
Signs and symptoms

Tilted disc syndrome (TDS) is a unilateral or bilateral congenital optic disc anomaly that can be discovered in patients of any age, with an incidence of 2% in the general population.[1] There is neither gender predilection nor an identifiable hereditary pattern.[1]

The opthalmoscopic appearance is variable.[2] In TDS, the disc appears to be rotated about its axis, with the long axis of the disc approaching the horizontal meridian in extreme cases. Instead of a vertically oriented disc, the nerve fibers appear shifted so that the superior portion of the disc appears to be positioned in the superior nasal quadrant, giving the disc a D-shaped appearance.[3,4] In many cases, the major retinal vessels emerge from the disc, immediately run nasally, then abruptly turn and course temporally in the traditional vascular branching pattern. This vascular anomaly is termed *situs inversus*.[3,5,6]

Despite the varied appearances,

there are some consistent findings. The most consistently encountered finding is a conus in the inferior and inferior nasal aspect of the peripapillary retina contiguous with the optic disc. In some cases, the conus can involve the inferior aspect of the disc with apparent rim thinning or obliteration with a pseudoglaucomatous appearance. This inferiorly located conus is associated with significant ectasia as well as staphylomatous formation within this localized area.[1,3,7,8] The inferiorly located conus has been referred to as Fuchs' coloboma. The colobomatous formation may extend inferiorly outward from the disc and manifest as hypoplasia of the retina, retinal pigment epithelium (RPE), and choroid.[1–5] This appears as a very lightly pigmented fundus. Other findings encountered with TDS include myelinated nerve fibers, lacquer cracks, choroidal folds, foveal retinal detachment and retinoschisis and peripapillary choroidal neovascular membranes with subretinal hemorrhages.[1,9,10–13]



Tilted disc syndrome.

Visual acuity is unaffected in TDS; however, visual field loss is common. The most commonly encountered visual field defect is a superior temporal scotoma.[1,14–18] In cases in which TDS is bilateral, this can appear as superior bitemporal scotomas suggestive of chiasmal compression. However, in TDS the visual field defect is unchanging and does not respect the vertical hemianopic line as it would in a chiasmal compressive mass, thus helping to distinguish the two conditions.[14–18] Other potential visual field defects include arcuate scotoma, nasal contraction and an enlarged blind spot.[16]

The most commonly encountered refractive error in patients with TDS is myopic astigmatism at an oblique axis.[1,6,16] There has been conjecture that the refractive error results from fundus alterations seen in TDS.[5] However, it has been seen more recently that clinically significant lenticular astigmatism is present in TDS patients.[19] Another report showed that in the majority of TDS cases, astigmatism was mainly corneal, and it suggested that morphogenetic factors in the development of the tilted disc might possibly influence the corneal development in such a way as to result in corneal astigmatism.[20] It has also been recently reported that color vision abnormalities consisting of red-green, blue and mixed defects were found in eyes with TDS.[21]

Pathophysiology

Contrary to popular belief, there is no actual tilting or rotation of the disc in TDS, even though the disc may appear to have rotated by as much as 90° about its axis. Actually, TDS represents a congenital coloboma due to incomplete closure of the embryonic fetal fissure at six weeks' gestation.[22] During development, the eye first appears in the form of the optic sulci in the fourth week of gestation. The optic vesicle forms from growth of the optic sulci towards the surface ectoderm. As the optic vesicle reaches the surface ectoderm, it invaginates to form a goblet-shaped optic cup. If there is incomplete closure upon invagination, a coloboma potentially involving the disc, retina and RPE results.[2,22]

The inferior aspect of the disc (and adjacent fundus) therefore has a congenital absence of tissue.[3,4,8,23] Automated perimetry has disclosed reduced mean deviations in this and other areas of the visual field as well, leading to the theory that TDS is a variant of optic nerve hypoplasia.[24] The colobomatous formation affects the shape of the chorioscleral canal due to a deficiency in the choroid, neural retina and RPE. As such, the nerve fibers will be concentrated in the superior and superior temporal aspect of the disc and the inferior and inferior nasal section will be deficient in axons.[3,4,8,23] This gives the nerve a D-shape, with the flat edge along the area of the conus. The congenital absence of tissue in the inferior nasal aspect of the nerve may be significant enough that the patient will have a corresponding superior temporal visual field defect that does not respect the vertical hemianopic line.[14–18]

Theoretically, the staphylomatous and ectatic formations caused by the incomplete fetal-fissure closure producing the conus also stretch the tissues, permitting secondary lacquer crack formation. These breaks in Bruch's membranes form a nidus for the development of choroidal neovascular membranes with subsequent subretinal hemorrhages.[2,7,9]

Management

Because TDS is a congenital anomaly, there is no management for the finding itself. In cases in which choroidal neovascular membranes form as a result of TDS, the visual outcomes tend to be quite good in that the membranes are very responsive to photocoagulation or demonstrate no progression or even involution without treatment.[9]

The most important factor in managing TDS is proper diagnosis. The heaped-up axons in the superior aspect of the nerve in TDS frequently have been misdiagnosed either as disc edema or papilledema. Also, the inferior nasal conus and possibly colobomatous extension into the disc has been frequently misdiagnosed and treated as normal tension glaucoma. Further, the superior temporal defect

in TDS has been confused with chiasmal compressive disease, especially when TDS is bilateral.

Clinical pearls

• TDS has a varied ophthalmoscopic appearance. However, the most diagnostic feature is the inferiorly located conus. This is invariably present in TDS and must be present for the clinician to make this diagnosis.

• The main differentiating factors between the visual field defect in TDS and chiasmal compressive disease is that the field defects in TDS are nonprogressive and do not respect the vertical hemianopic midline.

• TDS is sometimes misdiagnosed as disc edema, papilledema, normal tension glaucoma and pituitary tumor.

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MORNING GLORY SYNDROME

Signs and symptoms

Morning glory syndrome is a rare congenital optic disc anomaly that can be discovered at any age, although most patients are usually made aware of the condition with their first eye examination. The incidence is unknown. It occurs equally in males and females.[1,2] Morning glory syndrome can be either bilateral or unilateral.[2–8] When morning glory syndrome is bilateral, visual acuity is typically quite good.[4,9] However, most patients with unilateral morning glory syndrome have markedly reduced visual acuity, often to the level of hand motion vision.[4,10] While reports are often contradictory regarding the level of visual function, it can safely be stated that morning glory syndrome has a spectrum of severity, with most patients retaining useful vision.[11]

There will be a markedly enlarged anomalous disc and peripapillary retina. The nerve will appear larger than the fellow eye in unilateral cases. The condition gets its name from its resemblance to a tropical flower of the same name. It is characterized by a funnel-shaped excavated and enlarged dysplasic optic disk, with white tissue surrounded by an elevated pigmented peripapillary annulus. White glial tissue is present at the bottom of the cup and represents an important diagnostic criterion. The retinal vessels arise from the periphery of the disc anomaly and run an abnormally straight, radial course over the peripapillary retina. The origin of the vessels is obscured by the central tuft of glial tissue. This can give the morning glory disc a pseudoglaucomatous appearance.[1,6,12–14] There appear to be an excessive number of retinal vessels; however, this is simply because glial tissue obscures the branching of the vessels within the optic cup. In a number of cases, a retinal detachment may be present or may develop during the clinical course.[15–21] Strabismus is frequently encountered in patients with morning glory syndrome.[22]

Many ocular conditions have appeared in association with morning glory syndrome, including microophthalmos, cataracts, myopia, ciliary body cysts, Bergmeister's papilla and hypertelorism.[12,23] Numerous systemic abnormalities have also been identified as being associated with morning glory syndrome, including Goldenhar's syndrome; sphenoidal encephalocele; porencephaly and hydronephrosis; renal failure; cerebral malformation; frontonasal dysplasia; endocrine irregularities; neurofibromatosis Type 2;

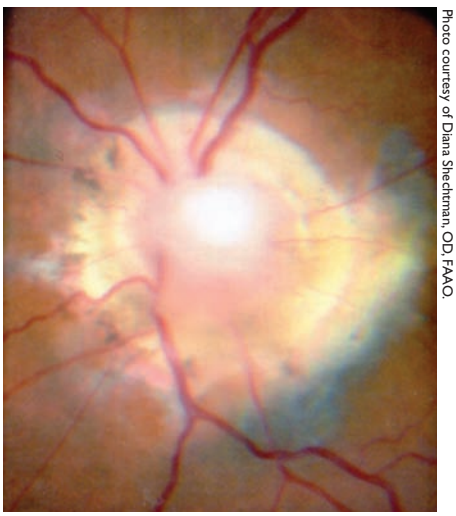

Photo courtesy of Diana Shechtman, OD, FAAO.

Morning glory syndrome.

midline craniofacial defects such as basal encephalocele, cleft lip and palate; and agenesis of the corpus callosum.[3,5,6,10,15,24,25] However, despite numerous reported associations, these comorbidities seem to be mostly anecdotal cases and morning glory syndrome is considered an isolated ocular abnormality. Further, in the absence of consistent systemic associations, perhaps the term "syndrome" truly does not apply to this condition.

Pathophysiology

Morning glory syndrome is a nonprogressive congenital optic nerve anomaly. This condition has been shown to be limited to the eye, with no involvement of the retrobulbar nerve and brain.[2,15,23] It has long been considered a variant of optic nerve coloboma;[23] however, this may not be true. The central glial tissue, vascular anomalies, scleral defects and adipose and smooth muscle tissue within the peripapillary sclera is more consistent with a mesenchymal abnormality.[24,26] An alternate theory suggests that abnormal enlargement of the distal optic stalk during development allows formation of the characteristic excavation seen in morning glory syndrome.[24]

The only potential active pathology that occurs in association with morning glory syndrome is rhegmatogenous retinal detachment. The etiology was unclear until the development of more sophisticated imaging techniques, namely optical coherence tomography (OCT). OCT has demonstrated slit-like retinal breaks within or at the edge of the excavation within morning glory syndrome. These slit-like retinal breaks provide a direct communication between the subretinal space and the vitreous cavity, permitting the fluid movement that leads to the evolution of tissue separation.[16–21]

Management

Management of morning glory syndrome typically does not extend beyond proper diagnosis. While the appearance can be quite dramatic, extensive neurological evaluation must be avoided, as this is a nonprogressive disc anomaly and not acquired disc pathology. While many systemic abnormalities have been associated with the condition, there is not enough consistency to consider these comorbidities anything but coincidental, making extensive evaluation unwarranted. Similarly, glaucoma treatment based solely upon the disc appearance in patients with morning glory syndrome should be avoided. In unilateral cases, protective eyewear should be recommended to protect the better-seeing eye.

The patient must be monitored and educated about the signs and symptoms of retinal detachment. Management of this unique type of rhegmatogenous retinal detachment often includes pars plana vitrectomy with posterior hyaloid removal, fluid-air exchange, endolaser in the area of the retinal break, and long-acting gas bubble injection.[17,18]

Clinical pearls

- The neuroretinal rim of the morning glory disc is recessed and not truly readily visible. This appearance has been mistakenly identified as acquired thinning of the rim, as seen in glaucoma. Morning glory syndrome has frequently been misdiagnosed and mistreated as normal tension glaucoma. Always rule out morning glory syndrome in cases of suspected normal tension glaucoma. Avoid impulsive diagnoses.
- In cases where there is reduced visual acuity, morning glory syndrome has been misdiagnosed as amblyopia.
- While dramatic in appearance, morning glory syndrome has very little future impact and virtually no management options for patients. If clinicians can recognize the accompanying images in this manuscript as morning glory syndrome, then referral and special testing can be obviated.

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FACIAL NERVE PALSY

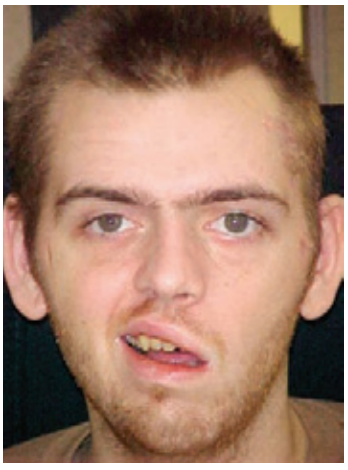
Signs and symptoms

The seventh cranial nerve (CN VII, facial nerve) is responsible for the voluntary motor innervation to the muscles of facial expression and the stapedius muscle of the inner ear, and for sensory innervation to the anterior two thirds of the tongue.[1–7] The orbicularis oculi is responsible for eyelid closure, and is under the control of CN VII.[1–6] Consequently, damage to one of the CN VII nuclei, damage to one of the CN VII fascicles or interruption to its peripheral course will produce characteristic clinical findings that include weakness or paralysis of one side of the face with an inability to voluntarily close the ipsilateral eye. Additional findings on the affected side include flattening of the nasolabial fold, drooping of the corner of the mouth, ectropion, lagophthalmos, decreased tear production, conjunctival injection, corneal compromise, decreased taste sensation and hyperacusis (supersensitivity to sound).[1–5]

Facial nerve palsy shows no gender preference; men and women are affected equally. Risk factors include diabetes, pregnancy and family history.[2,6] Facial nerve palsy can be marked or subtle. In cases of suspected involvement, the clinician must selectively test the involved muscles of the face, looking for asymmetry between the right and left sides. Specifically, patients should be instructed to look up and wrinkle the forehead (moving the frontalis and corrugator muscles), purse the lips and whistle (orbicularis oris muscle), smile and/or puff out the cheeks (buccinators muscle) and squeeze the eyes tightly closed (orbicularis oculi).

Pathophysiology

Supranuclear motor neurons connecting cortical areas 4 and 6 with the facial nuclei descend as fascicles of the corticobulbar (cortex-to-cranial nerve nuclei) tract through the internal capsule to the level of the lower pons by way of the cerebral peduncles.[2,3]



A left facial nerve palsy in a young man, the result of trauma.

The portion of each facial nucleus that controls the muscles of the upper face (frontalis, orbicularis oculi and corrugator) receives corticobulbar stimulation from the right and left (crossed and uncrossed) precentral motor cortices. The supranuclear innervations supporting the muscles of facial expression in the lower face is crossed only.[2,3,5] The muscles that close the eyes and wrinkle the forehead are bilaterally innervated; therefore a lesion in the cortex or supranuclear pathway on one side spares eyelid closure and forehead wrinkling but results in contralateral paralysis of the lower face.[2,3] Since the area of the cortex associated with facial muscle function lies near the motor representation of the hand and tongue, weakness of the thumb, fingers and tongue ipsilateral to the facial palsy is not uncommon.[2–5] Lastly, because supranuclear lesions are upper motor neuron lesions (sometimes referred to as central lesions), they produce spastic rather than flaccid paralysis. This allows the amount of flattening to the nasolabial fold and mouth-corner-droop to often be significantly less than its lower motor neuron counterpart.[2,3]

The facial motor nuclei are located in the lower pontine tegmentum and possess an intimate relationship with the trigeminal nerve (CN V), abducens nuclei (CN VI), cochlear nuclei (CN VIII), medial longitudinal fasciculus (MLF), paramedian pontine reticular formation (PPRF), descending corticospinal fibers and descending sympathetic fibers. The facial nucleus contains four separate cell groups, which innervate specific muscle groups. Motor axons exit the nucleus dorsally, loop around the CN VI nuclei and emerge into the subarachnoid space from the lateral aspect of the pons.[2,3,5] Fibers from the superior salivatory and lacrimal nuclei (parasympathetic preganglionic fibers supplying the sublingual, submandibular and lacrimal glands) join the facial nerve as the nervus intermedius at the cerebellopontine angle. CN VIII is present here as well. Lesions at this level include temporal bone fractures and infections, schwannomas, neuromas (cerebellopontine angle tumors) and vascular compressions, producing deficits in hearing, balance, tear production and salivatory flow.[2,3,5]

The facial and the vestibuloacoustic (CN VIII) nerves enter the internal auditory meatus together.[1–3] The facial nerve then departs from the acoustic nerve to enter the fallopian (facial) canal, which courses 30 mm through the temporal bone and incorporates the geniculate ganglion.[2] Lesions that involve the ganglion include geniculate ganglionitis. Lesions such as acoustic neuroma, which involve cranial nerve VIII, can impair hearing and facial nerve function and produce corneal hypoesthesia. Lesions that begin within the nucleus or along the fascicles are said to involve the final common pathway of neural transmission and are known as lower motor neuron or peripheral lesions.

The first major branch of CN VII, the greater superficial petrosal nerve, traverses the geniculate ganglion, proceeds forward, traverses the dura

mater of the middle cranial fossa and synapses in the sphenopalatine ganglion. The sphenopalatine ganglion gives rise to postganglionic fibers, which join the zygomatic and lacrimal nerves of CN V to innervate the lacrimal gland. Lesions here impair reflex tear secretion. It is important to note that when defective tear production accompanies CN V (muscles of mastication) or CN VI palsy, middle cranial fossa disease is indicated.[2,3,5]

The stapedius branch of CN VII arises from the distal segment of the facial nerve.[2,3] Lesions here disable the ability to dampen sound, producing hyperacusis. As the facial nerve continues downward in the facial canal, the chorda tympani branch arises from it. The chorda tympani contains sensory afferent fibers, which transmit taste sensation from the anterior two-thirds of the tongue. It also contains autonomic (parasympathetic preganglionic) nerve fibers, which innervate the submandibular and sublingual salivary glands.[2,3] Lesions anywhere along this pathway cause an interruption in salivatory flow and the ability to sense taste from the anterior two-thirds of the tongue.[2,3] Lesions of the parotid gland must also be investigated as part of the workup. Sensory afferents from the external auditory meatus and a small area of skin behind the ear transmit pain, temperature and touch information.[2,3]

The most common etiology (53%) of unilateral facial weakness is idiopathic.[2] The term "Bell's palsy" is often used to describe idiopathic CN VII dysfunction, though this remains a diagnosis of exclusion.[1–11] Bell's palsy may be related to idiopathic inflammation or may be secondary to viral infection or vascular compression of CN VII. Other common causes of peripheral CN VII palsy include trauma (21%), cerebellopontine angle tumor (7%), otitis media, herpes zoster oticus (Ramsay-Hunt syndrome), Lyme disease, sarcoidosis, Guillain-Barré syndrome, Epstein-Barr virus, parotid neoplasm, syphilis, diabetes mellitus, herpes simplex infection, pregnancy and HIV.[1–11]

Management

The optometric management of a patient who presents with CN VII palsy begins with a detailed history and a cursory evaluation of the 12 cranial nerves. Close attention should be given to the affected eyelid's posture, corneal wetting (tear break up time), blink posture, tear quality (sodium fluorescein staining) and tear quantity (Schirmer tear testing).

Exposure keratopathy associated with facial nerve palsy can be managed with ocular lubricating drops and ointments. Moisture chamber shields can be attached to spectacle temples to create a moist ocular environment and lessen tear evaporation. Temporary external eyelid weights may also be of benefit as a temporary measure in cases that are likely to resolve or as a stopgap measure prior to surgical intervention.[7]

Since idiopathic facial nerve palsy is a diagnosis of exclusion, laboratory testing (Lyme titer, rheumatoid factor, erythrocyte sedimentation rate, antinuclear antibody, fluorescent treponemal antibody absorption test, HIV titer), echocardiogram, chest X-ray, lumbar puncture (in patients with suspected neoplasm), neuroradiologic studies (computed tomography and magnetic resonance imaging) and appropriate referrals (otolaryngology, neurology, neurosurgery) should be obtained.[1–6]

Treatment for peripheral facial weakness depends upon the etiology and is usually relegated to the specialist.[4] For example, treatment of Ramsay-Hunt syndrome consists of 800 mg acyclovir Q5H, PO for 7–10 days; Lyme disease: 100 mg doxycycline TID PO for 7–10 days; sarcoidosis: 20–80mg prednisone, PO. According to Salinas and colleagues, most of the available evidence from randomized controlled trials demonstrates no significant or clear benefit to treating Bell's palsy with systemic corticosteroids.[9] Allen and Dunn assert the same position for oral antivirals.[10] However, because using these agents rarely creates complications, their use in cases of Bell's palsy remains controversial.

Clinical pearls

- Patients with idiopathic facial nerve paralysis (Bell's Palsy) typically complain of acute (24–48 hours) unilateral facial weakness with a widening of the palpebral fissure and impaired ability to close the eye.
- Chronic, slowly progressive facial nerve palsy suggests a neoplastic etiology.
- Mobius syndrome is a rare, nonprogressive, congenital neuromuscular disorder that presents with multiple dental and medical complications, including congenital, bilateral or unilateral palsies of the sixth, seventh and eighth cranial nerves.[8]
- The number-one concern of the eyecare practitioner is corneal protection via tears, punctal plugs, moisture chambers, internal or external weights or complete or partial tarsorrhaphy.
- Occasionally after injury, some fibers of CN VII regenerate to erroneously innervate adjacent structures. This phenomenon is known as aberrant regeneration. The result is simultaneous movements of muscles or synkinesis (e.g., the corner of the mouth contracts on attempted eyelid closure) or the stimulation of glands supplied by the redistributed branches of CN VII when the nerve is activated (e.g., excessive lacrimation upon eating, known as crocodile tearing or gustolacrimal tearing).[2–5]

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HEMIFACIAL SPASM

Signs and symptoms

While patients with hemifacial spasm (HFS) are aware of facial contracture, it is typically not painful. Half of the patient's face is usually seen in constant, spastic motion.[1,2] The spasms often start in the upper portion of the face and progress downward, increasing in involvement and frequency.[1,2] The spasms are usually brief, only lasting seconds but ongoing and often persistent during sleep. If it prevents eyelid opening, symptoms will include lost functional vision, corresponding losses of visual field and stereopsis. Patients are often predominantly concerned with cosmetic appearance. HFS frequently affects middle-aged individuals ages of 40–60.[1] In one study of 230 patients clinically diagnosed with HFS, 6.5% had young-onset HFS and 21.7% had old-onset HFS; the remaining patients in the study were uncategorized because their acquiring the condition took place during the classically recognized time period. In young-onset HFS, the mean age of onset of symptoms was 26 years, with a range of 6–30 years. Eighty percent of the cases occurred in women. Seventy-five percent of the young-onset cases demonstrated neurovascular compression of the root exit zone of the facial nerve. While the prevalence of hypertension, diabetes mellitus and other associated vascular disorders in the late-onset group was higher than in young-onset group, the clinical features and frequency of compression between the two groups were similar. Genetic, anatomic or other unidentified factors are the most likely contributors to young-onset HFS, and hypertension may be a risk factor involved in late-onset HFS.[1,2]

Pathophysiology

The motor division of the seventh cranial nerve (CN VII) is responsible for delivering the voluntary motor innervations to the muscles of facial expression and to the stapedius muscle of the inner ear (helping to dampen loud sounds).[3–8] Irritation by adjacent or direct infection, infiltration, inflammation or compression of CN VII nuclei or its fascicles can produce involuntary contracture of the affected region.[1,2,9–15] The facial motor nuclei are located in the lower pontine tegmentum and possess an intimate relationship with the trigeminal nerve (CN V), abducens nuclei (CN VI), cochlear nuclei (CN VIII), medial longitudinal fasciculus (MLF), paramedian pontine reticular formation (PPRF), descending corticospinal fibers and descending sympathetic fibers.[4,5] The facial nucleus contains four separate cell groups that innervate specific muscle groups. Motor axons exit the nucleus dorsally, loop around the CN VI nuclei and emerge into the subarachnoid space from the lateral aspect of the pons.[4,5] Fibers from the superior salivatory and lacrimal nuclei (parasympathetic preganglionic fibers supplying the sublingual, submandibular and lacrimal glands) join the facial nerve as the nervus intermedius at the cerebellopontine angle.[4,5] CN VIII is present here as well. Lesions capable of impinging on the nerve at this level include temporal bone fractures and infections, schwannomas, neuromas (cerebellopontine angle tumors) and vascular compressions. These injuries may concomitantly produce deficits in hearing, balance, tear production and salivatory flow.[4,5]

The facial and the vestibuloacoustic (CN VIII) nerves enter the internal auditory meatus together.[3–5] The facial nerve then departs from the acoustic nerve to enter the fallopian (facial) canal, which courses 30 mm through the temporal bone and incorporates the geniculate ganglion.[4] Lesions that may affect the homeostasis here include geniculate ganglionitis (Ramsey-Hunt syndrome or herpes zoster oticus).[3–6] The first major branch of CN VII, the greater superficial petrosal nerve, traverses the geniculate ganglion, proceeds across the dura mater of the middle cranial fossa and synapses in the sphenopalatine ganglion.[4,5] The sphenopalatine ganglion gives rise to postganglionic fibers, which join the zygomatic and lacrimal nerves of CN V to innervate the lacrimal gland. Lesions here, in addition to their effects on the facial nerve, impair reflex tear secretion.[4–6] The portion of the facial nerve containing the motor fibers that innervate the muscles of facial expression exits the stylomastoid foramen and enters the substance of the parotid gland before distribution, making lesions of the parotid gland part of the differential diagnosis.[4,5]

There is considerable evidence that primary hemifacial spasm (HFS) is in almost all cases related to vascular compression of the facial nerve at its root within the exiting region of brainstem (root exit zone).[14] The offending vessels include the vertebral arteries, the posterior inferior cerebellar arteries, the anterior inferior cerebellar arteries and, in some circumstances, an artery of uncertain origin.[14] Clinical and electrophysiological features suggest the presence of mechanical mechanisms at the level of the neural fibers, demyelinating pathology and functional changes in nuclear cells, which cause them to assume a posture of hyperactivity within the facial nucleus.[9,10,14] Measured lateral spread responses

(LSR) elicited by this excessive stimulation of the facial-nerve branches testify to the existence of these electrophysiological disturbances.[9,10] Although vascular compression is accepted as a main producer of HFS, facial nucleus supersensitivity is also deemed to be a cause of emphatic HFS.[14]

Management

Treatment of the contractures of HFS is aimed at treating the underlying cause. Detailed evaluation is mandatory in all patients with newly acquired cases of HFS or with essential blepharospasm, with or without apraxia. Magnetic resonance imaging (MRI) and three-dimensional magnetic resonance angiography (MRA) are proven techniques for identifying causes and predicting the prognosis of HFS.[16,17] When HFS spasm is produced by abnormal vascular compression or tumor, the area should be surgically decompressed by neurosurgical specialists.[2,11–14] Gamma knife radiosurgery, a relatively new modality, has been recently used in a patient with HFS secondary to an intracanalicular vestibular schwannoma.[6] The resolution of the spasm and cessation of the tumor's growth were achieved with a single session of gamma knife radiosurgery.[8]

Microvascular decompression (MVD) constitutes a potentially curative treatment. A sponge or barrier is placed between a compressing vessel and the facial nerve.[9,10] In one study of 33 patients, LSR disappeared with vascular decompression in 23 patients, with no evidence of LSR upon surgical closure.[10] The other 10 patients had evidence of LSR following the surgical conclusion. In the study, the authors considered 20 of the 23 LSR-absent patients clinically cured at the three-month follow-up. Three patients continued to present with mild/moderate spasm. At the 10-month follow-up, two of the remaining LSR-absent patients were free of spasm, with only one having recurrence.[10] In contradistinction, seven of the 10 LSR-present patients exhibited cure at the three-month follow-up, with all 10 meeting the criteria for cure at the 10-month evaluation. This underscores the thinking that HFS not only results from mechanical pulsations of an elongated artery positioned against the CN VII root exit zone, but also that elements of demyelination of the nerve and acquired neural hyperactivity are generated by the neurovascular compression.[9,10]

In extreme cases, facial nerve decompression with exposure of the facial nerve from the brainstem to the parotid gland can be accomplished without injury to the nerve, tympanic membrane, external auditory canal or other structures.[12] The procedure has had good results for patients with facial paralysis from Bell's palsy, herpes zoster oticus, infection, hemifacial spasm, temporal bone fracture and tumors. Access occurs through the mastoid, middle cranial fossa and retrolabyrinthine fossa.[12] For completeness, myectomy, either surgical (removal of muscular tissue) or neurochemical (elimination of axons via injection of neurotoxin:doxorubicin), is mentioned in the literature as a potential remedy.[18]

Acupuncture has shown some benefit in these cases. Appropriate needling can markedly improve the blood supply to the vertebral basilar artery, increase the cerebral blood flow, relax the spasm of the vascular smooth muscles and create the effects of resuscitating and tranquilizing the mind, dredging channels and relieving spasm and pain.[13]

Clinical pearls

- Chronic, slowly progressive HFS with the development of or conversion to facial nerve palsy suggests a space-occupying lesion.
- The presence or a parotid mass suggests tumor of the gland.
- When defective tear production accompanies CN V (muscles of mastication) or CN VI palsy, middle cranial fossa disease should be suspected.
- Tardive dyskinesia (late twitching secondary to exposure to antipsychotic medications) can produce similar symptoms.
- Facial synkinesis, abnormal movements created by aberrant sprouting of axons following injury (similar to the "jaw wink" phenomenon) is a separate entity.

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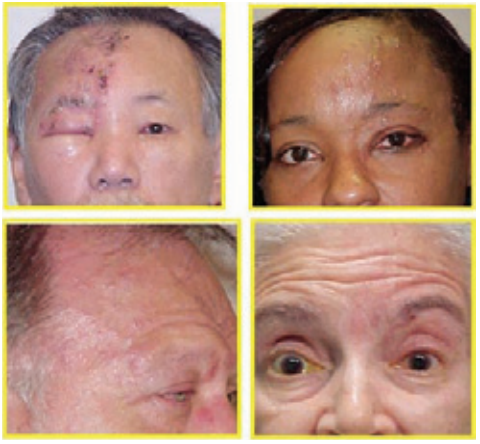
HERPES ZOSTER

Signs and symptoms

Herpes zoster rash can affect any dermatome on the body, but it most commonly resides in the facial and midthoracic-to-upper lumbar dermatomes.[1,2] The rash appears as erythematous macules and papules, which progress into vesicles within 12–24 hours. The rash progresses into pustules at days three and four, with crusting of the pustules at seven to 10 days. This rash is often accompanied by a regional lymphadenopathy.[1–8] Herpes zoster patients frequently present with a prodrome of fever, malaise, headache and dysesthesia over one to four days prior to developing any visible cutaneous involvement.[1] In fact, it may take 48–72 hours after the onset of pain for any sign of rash to emerge. Burning pain classically precedes rash eruption and can persist for several months after the rash resolves.[1–12] The pain preceding the systemic form of the rash is often misdiagnosed as myocardial infarction, ulcerative appendicitis, herniated intervertebral disc or temporal arteritis, to name a few.[2] Following resolution of the crusting pustules, about 9% of all patients suffer from extreme pain known as postherpetic neuralgia.[1–8] Severe and possibly debilitating pain remains, despite the absence of active, visible skin lesions.[1–12]

The presentation of herpes zoster ophthalmicus may vary from dermatologic involvement alone to ocular manifestations such as lid retraction, keratitis, scleritis, uveitis, glaucoma, retinitis (acute retinal necrosis and progressive outer retinal necrosis), optic neuritis and panophthalmitis. When ophthalmic manifestations arise, the condition is termed herpes zoster ophthalmicus (HZO) and occurs in 7% of all zoster patients.[2,4] Anecdotally, cases involving the eye have been observed to produce adnexal pain over months, without iritis, uveitis or vesicular breakout, making the chief complaint a mystery until the skin manifestations appear. The lesions of herpes zoster generally completely resolve within one to three weeks.[6–7] Severe complications include pneumonia, other collateral bacterial infections, seizure activity and encephalopathy.[8,9]



The many faces of herpes zoster ophthalmicus.

Pathophysiology

Varicella zoster virus (VZV) causes chickenpox.[1–12] Herpes zoster represents a separate clinical condition caused by the same virus.[7] Both conditions are characterized by areas of intense dermatomal pain followed by a rash 1 to 3 days later.[1] The varicella zoster virus is a member of the herpes virus family. Varicella is spread by direct contact with active skin lesions or airborne via droplets and is highly contagious.[1–12] The virus has an affinity for the upper respiratory tract and typically enters the human system through the conjunctiva and/or nasal or oral mucosa, producing the characteristic pox appearance.[1–10] When the host's immunity fails, the dormant virus leaves the confines of the dorsal route ganglion where it lies dormant to produce shingles (the zoster presentation) upon recurrence.[1–12]

Chickenpox is usually a mild, self-limiting disease of childhood. It is more severe when it develops in adults.[11] One study reported that for every 100,000 people who contract the malady, four to nine will die from it, and most of the deaths are adults.[11] Chickenpox infection during pregnancy can lead to a severe maternal illness.[11] Further, the disease seems to be more virulent in non-pregnant women.[11] Interestingly, while most women who contract chickenpox during pregnancy give birth to healthy children, some babies are susceptible to in utero infection.[11]

Ninety percent of the population develops serological infection by adolescence, with nearly 100% of the population having some evidence of antibodies to the disease by age 60.[1] Only 20% of patients suffer reactivation after initial infection.[2] Any condition that decreases immune status, such as human immunodeficiency virus infection, chemotherapy, malignancy and long-term oral corticosteroid or other immunosuppressant use, increases the risk of herpes zoster activation. A second reactivation is even more rare and occurs mostly in immunosuppressed patients such as organ transplant recipients or those who suffer from AIDS or neoplasm.[1]

Management

Herpes zoster is managed using orally administered antiviral medications such as acyclovir (800 mg PO 5 times a day), famciclovir (500 mg PO TID) and valacyclovir (1,000 mg PO TID) for one week.[1,10,12,13] The antiviral medications seem most effective when initiated within the first 72 hours of the onset of the rash, especially for reducing the degree of post-herpetic neuralgia.[12] Acyclovir has been documented as effective in preventing disease reactivation; however, the proper dose, duration and circumstances of its use are still controversial.[10]

Orally administered corticosteroids are reputed to reduce pain and potentially the onset of postherpetic neuralgia.[10,12] Since the disease is self-limiting, most care is palliative, including

the use of astringents such as calamine lotion or aluminum acetate solution (Domeboro, Bayer) to minimize weeping and soothe the affected area, and topical antibiotic creams and ointments to prevent secondary infection. Patients with postherpetic neuralgia may require narcotics for pain control.[12] Tricyclic antidepressants and anticonvulsants in low dosages are potential options for unremitting pain.[12] Capsaicin cream (based on the chemical in chili peppers that makes them hot), lidocaine patches and injectable nerve blocks can be used in the worst cases.[12]

Antiviral agents can play role in preventing varicella zoster disease in immunocompetent and immunosuppressed patients.[10] As with herpes zoster, acyclovir has been documented as effective in preventing disease reactivation, but the proper dose, duration and circumstance of its uses are controversial.[10]

Since VZV-specific cell-mediated immunity and cell-mediated immunity in general declines with age, it should be expected that the incidence of herpes zoster increases with age. This may also explain the increased incidence of zoster in immunocompromised individuals or those who are undergoing immunosuppressive therapy.[7,8] Therefore, any patient younger than 50 who presents with signs of an acute zoster infection must be referred to rule out an immunocompromised state.

Clinical pearls

• Once infection with chickenpox occurs, it usually confers lifelong protection against a subsequent attack. Secondary infections have been reported, but they usually only occur when the initial episode was mild.[1–10]

• The zoster virus has a high affinity for the first (ophthalmic) division of the trigeminal nerve. This manifests as Hutchinson's sign, a series of skin lesions along the nose (and ending at the tip of the nose) that respect the vertical midline.[5]

• There is evidence suggesting that varicella can be prevented by vaccination. Vaccine is about 80–85% effective against the disease and highly (more than 95%) effective in preventing severe disease.[10]

• A significant issue is postherpetic neuralgia and decreases the quality of life for patients experiencing this condition.

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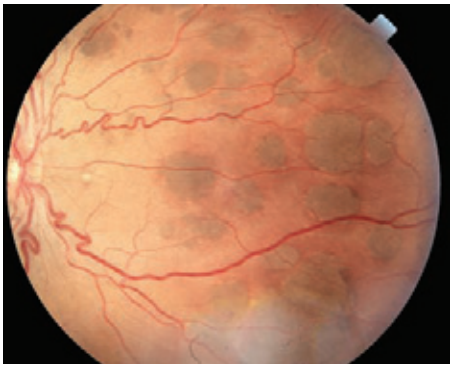
GARDNER'S SYNDROME

Signs and symptoms

Gardner's syndrome, a variation of familial adenomatous polyposis (FAP), is a multisystem disorder characterized by a triad of findings: polyps of the gastrointestinal (GI) tract, multiple osteomas (benign tumors of bony origin) and a variety of soft tissue tumors.[1–4] There may also be a predisposition to thyroid and periampullary cancers.[2] Patients may present at any age, from infancy to late in life, with a variety of symptoms.[1] Gardner's syndrome is of interest to eyecare practitioners due to a high association with congenital hypertrophy of the retinal pigment epithelium (CHRPE). These are typically benign and asymptomatic fundus lesions, normally discovered on routine ophthalmoscopy. CHRPE is present in approximately 70% of patients with FAP and can be the initial diagnostic indication of Gardner's syndrome.[4] The characteristic ocular presentation is bilateral and involves two to 30 pigmented lesions, averaging about six per eye.[5,6] This unique form of CHRPE (referred to as multiple CHRPE or atypical CHRPE) seems to have a slight predilection for the retinal periphery. The lesions tend to be small: most are less than 0.5 disc diameter (0.75 mm).[7] Ophthalmoscopically, there is a fair amount of variability; individual lesions may show differences in pigmentation (gray to black or amelanotic), shape (round, oval, tear-shaped, bean-shaped or linear) and the presence or absence of a surrounding halo.[5–7]

GI-related symptoms of Gardner's syndrome may include episodes of rectal bleeding and/or mucous discharge, diarrhea and abdominal pain.



Multiple CHRPE with wide variation in size and shape should be considered suspicious for Gardner's syndrome, especially if the condition is bilateral.

Weight loss, anemia and intestinal obstruction typically portend the presence of cancer. As many as 25% of patients with the syndrome may have

colorectal cancer at the time of initial diagnosis.[2] Non-GI-related symptoms can be diverse: desmoids (benign but locally aggressive fibroid tumors of connective tissue), which can cause focal swelling, pain or bleeding; dental abnormalities associated with tooth or jaw pain; thyroid carcinoma which presents as a tender neck mass with hoarseness and symptoms of hypo- or hyperthyroidism. Since the soft tissue and bone abnormalities may predate the development of actual colon polyps in Gardner's syndrome by as much as 10 years, patients may report a history of seemingly unrelated nondescript symptoms.[2,3]

Pathophysiology

Gardner's syndrome is considered a rare hereditary disorder, with an approximate incidence of 1 in 14,000 live births.[2] The condition displays an autosomal dominant inheritance pattern with variable penetrance. It is believed that Gardner's syndrome and FAP represent variants of the same disorder, since both conditions display an association with a genetic mutation in the adenomatous polyposis coli (APC) gene.[8] Although most cases show familial clustering, one-third are believed to result from spontaneous mutations.[1] Precisely what determines the extent and variability of the extracolonic manifestations in Gardner's syndrome is unknown; however, some have proposed that environmental factors such as diet, exercise and smoking play a role in the disease pathogenesis.[1,2,9]

Management

Gardner's syndrome represents a potentially life-threatening disease that can cause great morbidity to a variety of organ systems. In cases where this condition is suspected, the physician is obligated to initiate appropriate medical testing. Specific laboratory studies for Gardner's syndrome involve genetic testing to identify the APC gene and its associated mutation.[2,6] Also, these patients must be evaluated by sigmoidoscopy or colonoscopy to rule out the presence of polyps and other associated pathology.[2,10] Additional testing may include: complete blood count with differential and platelets; carcinoembryonic antigen; liver function (to rule out metastasis); thyroid function; abdominal CT or MRI; X-rays of the chest, skull and teeth (for osteomas) and upper gastrointestinal endoscopy.[11]

Treatment options for Gardner's syndrome are limited. Regular administration of oral nonsteroidal anti-inflammatory agents (e.g., sulindac, indomethacin) have demonstrated some success in diminishing the size and number of polyps.[1,12] Recent clinical trials with celecoxib (Celebrex, Pfizer) 400 mg daily have shown that this drug significantly prevents the development and growth of colorectal adenomatous polyps in patients with FAP; unfortunately, celecoxib also carries a substantial risk of adverse cardiovascular events and therefore cannot be routinely recommended for this indication.[13,14] Tamoxifen or toremifene may be helpful in managing unresectable desmoid tumors.[1]

Despite medical therapy, virtually all cases of Gardner's syndrome ultimately require surgery to prevent the development of colon cancer. Treatment options include total proctocolectomy (surgical removal of the rectum and colon) with permanent terminal ileostomy or subtotal colectomy with reconstructive anastomosis surgery.[1] Prophylactic colon resection is recommended even in asymptomatic family members demonstrating signs of the disease, and it is typically performed by the time the patient is 20 years old.[1]

Clinical pearls

• Multiple CHRPE is one of the earliest diagnostic features of Gardner's syndrome and is seen in more than one-half of patients with FAP. Patients who display atypical or bilateral CHRPE should be evaluated for the possibility of polyposis, especially if they report a positive family history of colon polyps or cancer.[10]

• Gardner's syndrome is a multisystem disorder, and as such it requires care by a multidisciplinary healthcare team. In addition to receiving ophthalmic examination, individuals with this condition may warrant consultative evaluation by specialists in the following medical areas: colorectal surgery, dentistry, dermatology, endocrinology, gastroenterology, internal medicine, neurology, oncology, orthopedic surgery and proctology.

• Colon cancer will inevitably develop in all individuals with Gardner's syndrome unless prophylactic surgery is performed. Even after subtotal colectomy, there is a significant possibility of recurrence; hence, these patients need to be monitored for life.

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ANTIPHOSPHOLIPID ANTIBODY SYNDROME

Signs and symptoms

Patients with antiphospholipid antibody syndrome (APAS) are typically female and young.[1–6] Rarely, children are affected.[7] Up to 10% of healthy individuals have circulating antiphospholipid antibodies.[8] Approximately 50% of patients with antiphospholipid antibodies also have systemic lupus erythematosus (SLE) or other autoimmune diseases.[3,8,9] However, in many cases, APAS exists without associated autoimmune disease.[1,3,5,8] The most common conditions that result from APAS that affect the eye and visual system are arterial or venous thrombosis with resultant ischemia. This manifests as central retinal vein or artery occlusion (CRVO or CRAO), papillophlebitis, anterior ischemic optic neuropathy (AION), migraine, ophthalmoparesis and diplopia, amaurosis fugax, isolated retinal hemorrhages and cotton wool spots, and retinal neovascularization.[9–29] While these conditions typically occur in elderly patients, the patient with APAS experiences them at a younger age, typically under 50 years.

In addition to ocular manifestations, thrombi are often present in other systems. Venous thromboses of the arms and legs, pulmonary embolism, sagittal, pelvic, mesenteric, portal, and axillary thromboses have all been encountered in APAS. Transient ischemic attack (TIA) and cerebrovascular accidents are the most common occurrences from thrombosis in the arterial system. Another systemic finding is thrombocytopenia (reduced platelet count).[5,6,8,30–37]

A common and in many cases defining event in APAS is recurrent pregnancy loss that can occur in any trimester. Preeclampsia and intrauterine growth retardation have also been found to be associated with APAS.[5,6,8,33]

Pathophysiology

Antiphospholipid antibodies are a group of circulating antibodies that include anticardiolipin antibody, lupus anticoagulant, and the Biologic False Positive Test for Syphilis (BFP-TS). These antibodies are directed against phospholipid binding proteins, which prolong phospholipid-dependent coagulation assays.[8] In this condition, phospholipids present in cell membranes are erroneously identified by the body as foreign; consequently, the body produces antibodies to them. The antibodies appear to have an affinity for the cell membranes found in platelets, vessel endothelial cells, and clotting factors.[1,5,8,33]

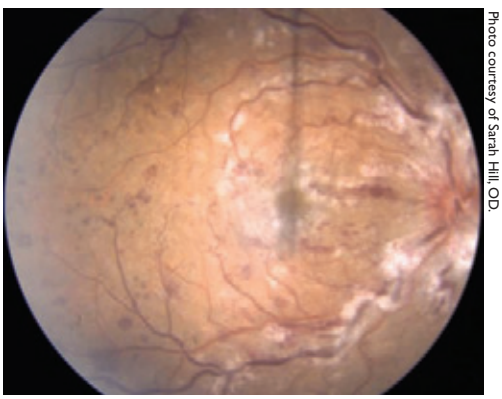

Photo courtesy of Sarah Hill, OD.

Papillophlebitis/CRVO in a patient with high anticardiolipin antibodies.

APAS is an autoimmune disorder with two forms: primary and secondary. Antiphospholipid antibodies (anticardiolipin antibodies and lupus anticoagulant) are known to occur commonly in patients with SLE.[3,8,9,37] When these antibodies occur in the presence of SLE, it is considered a secondary syndrome.

Not until 1985 did Hughes identify these antibodies in seemingly normal patients experiencing thrombotic events and pregnancy loss in the absence of SLE.[39] This primary form exists in the absence of clinically or serologically proven autoimmune disease and has been termed Primary Antiphospholipid Antibody Syndrome and occasionally referred to as Hughes Syndrome.[1,3,33] APAS is diagnosed by arterial and venous thrombosis, pregnancy loss and/or thrombocytopenia in the presence of lupus anticoagulant and anticardiolipin antibodies.[33] The method of promoting thrombosis by the antiphospholipid antibodies is unclear. Thrombosis appears to be the cause of pregnancy loss.[8]

Anticardiolipin antibody is one of the few autoantibodies in which subtypes can be identified. These subtypes are IgM, IgG and IgA.[38–44] Cardiolipin, present in mitochondria, is actually unlikely to be the offending antigen. However, because antiphospholipid antibodies cross-react with other phospholipids, cardiolipin serves as a representative antigen. IgG antibodies are associated with thrombosis and pregnancy loss. IgM antibodies are associated with thrombosis and hemolytic anemia. Most patients with APAS have moderate-to-high levels of IgG anticardiolipin antibody levels.[38–44]

Lupus anticoagulant, an antiphospholipid antibody originally discovered in SLE, is an immunoglobulin (either IgG or IgM) that agglutinates phospholipids present in plasma clotting factors and subsequently prevents their participation in clotting. Lupus anticoagulant inhibits conversion of prothrombin to thrombin, prolonging in vitro clotting time as measured by the prothrombin time (PT), partial thromboplastin time (PTT), Kaolin clotting time and dilute Russell Viper Venom time.[38–44] Curiously, while this antibody prolongs clotting time in vitro, in vivo it appears to promote thrombosis.[43] Lupus anticoagulant appears to be the antibody most asso-

ciated with thrombosis.[33,38,41,42]

The Venereal Disease Research Laboratory (VDRL) test for syphilis was the first test to detect an antiphospholipid antibody. The phospholipid antigen involved here caused erroneous reactivity on this test. Patients with this antigen tested false-positive for syphilis; consequently, this antiphospholipid antibody was named the Biologic False Positive Test for Syphilis. Patients with autoimmune disorders frequently will test false-positive for syphilis on VDRL testing.[8,45] However, those with with BFP-TS do not appear to have a significant risk for thrombosis, so BFP-TS is not strongly associated with APAS.[8,45]

Management

While it appears that rheumatologists and other primary care physicians are aware that patients with APAS can have ocular manifestations, many ophthalmic practitioners often don't associate ocular thrombosis with APAS, and consequently don't test for these antibodies or suggest its inclusion as a diagnostic possibility. APAS must be considered, however, in cases of retinal vascular occlusion and other thrombotic conditions in young patients. It should be especially considered in unusual thrombotic events such as recurrent or bilateral artery or vein occlusion, or with combined artery and vein occlusion (especially if there is no history of vascular disease)—particularly if the patient is young.[9–29] Patients with a history of thrombotic conditions (retinal vein or artery occlusions, TIA, amaurosis fugax), thrombocytopenia, or autoimmune disorders should be investigated for APAS.

Testing includes a complete blood count with differential, prothrombin time (PT), activated partial thromboplastin time (aPTT), antinuclear antibody (ANA), ELISA anticardiolipin antibody assay, Dilute Russell Viper Venom Time (DRVVT), plasma clot time or kaolin clot time for the lupus anticoagulant. The diagnosis of this condition requires positive serology either for the lupus anticoagulant or anticardiolipin antibody (positive anticardiolipin antibody ELISA) on two separate occasions at least eight weeks apart.[42] Beyond the positive serology, there must also be thrombocytopenia, thrombotic disease (such as retinal vein occlusion, for example) or (recurrent) pregnancy loss.[5,8,33]

In patients with ocular manifestations of APAS, standard management is undertaken for each condition. Patients with thrombotic events arising from APAS may potentially experience recurrent thrombosis with resultant morbidity, including cerebrovascular accident and even death. It has been recommended that APAS should also be managed so as to improve outcomes as well as to reduce recurrences. Oral anticoagulants such as heparin or low-dose aspirin therapy (80–100mg/day) are typically employed.[1,5,8,40,46,47] In cases in which antiplatelet therapy is insufficient and thrombotic events recur, high doses of oral corticosteroids and possibly other immunosuppressants such as cyclophosphamide, are used in conjunction with low dose aspirin therapy.[1,5,8]

Clinical pearls

- Primary APAS is a relatively newly discovered condition. It must become part of the differential diagnosis in thrombotic conditions.
- Conditions in which one should consider APAS as a diagnosis include amaurosis fugax, migraine, TIA, retinal hemorrhages and cotton wool spots, central retinal vein and artery occlusion, anterior ischemic optic neuropathy or ophthalmic and cilioretinal artery occlusions.
- Consider APAS in younger patients with central retinal vein and artery occlusion, or in any patient with bilateral or recurrent CRVO.
- When suspecting APAS in female patients, inquire about a history of pregnancy loss.
- APAS can exist independently of known autoimmune disease, in which case it is called Primary APAS. Through serologic testing and appropriate consultation, the optometrist may be the physician who diagnoses this autoimmune condition.

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