Sixteenth Edition

The Handbook of Ocular Disease Management

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SUPPLEMENT TO

REVIEW® OF OPTOMETRY

June 15, 2014

For the treatment of elevated IOP

UNLOCK TREATMENT POSSIBILITIES

SIMBRINZA™ Suspension provided additional 1-3 mm Hg IOP lowering compared to the individual components[1]

- IOP measured at 8 AM, 10 AM, 3 PM, and 5 PM was reduced by **21-35%** at Month 3[2-4]
- Efficacy proven in two pivotal Phase 3 randomized, multicenter, double-masked, parallel-group, 3-month, 3-arm, contribution-of-elements studies[2,3]
- The most frequently reported adverse reactions (3-7%) in a six month clinical trial were eye irritation, eye allergy, conjunctivitis, blurred vision, dysgeusia (bad taste), conjunctivitis allergic, eye pruritus, and dry mouth[5]
- Only available beta-blocker-free fixed combination[2,3]

INDICATIONS AND USAGE

SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination indicated in the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration

The recommended dose is one drop of SIMBRINZA™ Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA™ Suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

IMPORTANT SAFETY INFORMATION

Contraindications

SIMBRINZA™ Suspension is contraindicated in patients who are hypersensitive to any component of this product and neonates and infants under the age of 2 years.

Warnings and Precautions

Sulfonamide Hypersensitivity Reactions—Brinzolamide is a sulfonamide, and although administered topically, is absorbed systemically. Sulfonamide attributable adverse reactions may occur. Fatalities have occurred due to severe reactions to sulfonamides. Sensitization may recur when a sulfonamide is readministered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation.

Corneal Endothelium—There is an increased potential for developing corneal edema in patients with low endothelial cell counts.

Severe Hepatic or Renal Impairment (CrCl <30 mL/min)—SIMBRINZA™ Suspension has not been specifically studied in these patients and is not recommended.

Adverse Reactions

In two clinical trials of 3 months' duration with SIMBRINZA™ Suspension, the most frequent reactions associated with its use occurring in approximately 3-5% of patients in descending order of incidence included: blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Adverse reaction rates with SIMBRINZA™ Suspension were comparable to those of the individual components. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA™ Suspension patients.

Drug Interactions—Consider the following when prescribing SIMBRINZA™ Suspension:

Concomitant administration with oral carbonic anhydrase inhibitors is not recommended due to the potential additive effect. Use with high-dose salicylate may result in acid-base and electrolyte alterations. Use with CNS depressants may result in an additive or potentiating effect. Use with antihypertensives/cardiac glycosides may result in additive or potentiating effect on lowering blood pressure. Use with tricyclic antidepressants may blunt the hypotensive effect of systemic clonidine and it is unknown if use with this class of drugs interferes with IOP lowering. Use with monoamine oxidase inhibitors may result in increased hypotension.

For additional information about SIMBRINZA™ Suspension, please see Brief Summary of full Prescribing Information on adjacent page.

Learn more at myalcon.com/simbrinza

SIMBRINZA™
(brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%

ONE BOTTLE. MANY POSSIBILITIES.

References: 1. SIMBRINZA™ Suspension Package Insert. **2.** Katz G, DuBiner H, Samples J, et al. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2% [published online ahead of print April 11, 2013]. *JAMA Ophthalmol.* doi:10.1001/jamaophthalmol.2013.188. **3.** Nguyen QH, McMenemy MG, Realini T, et al. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. *J Ocul Pharmacol Ther.* 2013;29(3):
290-297. **4.** Data on file, 2013. **5.** Whitson JT, Realini T, Nguyen QH, McMenemy MG, Goode SM. Six-month results from a Phase III randomized trial of fixed-combination brinzolamide 1% + brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension. *Clin Ophthalmol.* 2013;7:1053-1060.

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For more information go to professional.openingsprogram.com

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References: 1. Cognizant - OPENINGS™ Program Consumer Survey, September 2012.

* Online quantitative survey with patients currently using active ingredient The Test group consisted of 220 patients enrolled in the OPENINGS™ Program while the Control group included 151 patients not enrolled in the OPENINGS™ Program and not using the Alcon Savings Card. Statistical testing was performed at the 95% Confidence Interval.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2% is a fixed combination of a carbonic anhydrase inhibitor and an alpha 2 adrenergic receptor agonist indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSAGE AND ADMINISTRATION

The recommended dose is one drop of SIMBRINZA™ Suspension in the affected eye(s) three times daily. Shake well before use. SIMBRINZA™ Suspension may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

DOSAGE FORMS AND STRENGTHS

Suspension containing 10 mg/mL brinzolamide and 2 mg/mL brimonidine tartrate.

CONTRAINDICATIONS

Hypersensitivity - SIMBRINZA™ Suspension is contraindicated in patients who are hypersensitive to any component of this product.

Neonates and Infants (under the age of 2 years) - SIMBRINZA™ Suspension is contraindicated in neonates and infants (under the age of 2 years*) see Use in Specific Populations*

WARNINGS AND PRECAUTIONS

Sulfonamide Hypersensitivity Reactions - SIMBRINZA™ Suspension contains brinzolamide, a sulfonamide, and although administered topically is absorbed systemically. Therefore, the same types of adverse reactions that are attributable to sulfonamides may occur with topical administration of SIMBRINZA™ Suspension. Fatalities have occurred due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Sensitization may recur when a sulfonamide is re-administered irrespective of the route of administration. If signs of serious reactions or hypersensitivity occur, discontinue the use of this preparation *[see Patient Counseling Information]*

Corneal Endothelium - Carbonic anhydrase activity has been observed in both the cytoplasm and around the plasma membranes of the corneal endothelium. There is an increased potential for developing corneal edema in patients with low endothelial cell counts. Caution should be used when prescribing SIMBRINZA™ Suspension to this group of patients.

Severe Renal Impairment - SIMBRINZA™ Suspension has not been specifically studied in patients with severe renal impairment (CrCl < 30 mL/min). Since brinzolamide and its metabolite are excreted predominantly by the kidney, SIMBRINZA™ Suspension is not recommended in such patients.

Acute Angle-Closure Glaucoma - The management of patients with acute angle-closure glaucoma requires therapeutic interventions in addition to ocular hypotensive agents. SIMBRINZA™ Suspension has not been studied in patients with acute angle-closure glaucoma.

Contact Lens Wear - The preservative in SIMBRINZA™, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA™ Suspension but may be reinserted 15 minutes after instillation *[see Patient Counseling Information]*.

Severe Cardiovascular Disease - Brimonidine tartrate, a component of SIMBRINZA™ Suspension, has a less than 5% mean decrease in blood pressure 2 hours after dosing in clinical studies; caution should be exercised in treating patients with severe cardiovascular disease.

Severe Hepatic Impairment - Because brimonidine tartrate, a component of SIMBRINZA™ Suspension, has not been studied in patients with hepatic impairment, caution should be exercised in such patients.

Potentiation of Vascular Insufficiency - Brimonidine tartrate, a component of SIMBRINZA™ Suspension, may potentiate syndromes associated with vascular insufficiency. SIMBRINZA™ Suspension should be used with caution in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangitis obliterans.

Contamination of Topical Ophthalmic Products After Use - There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface *[see Patient Counseling Information]*.

ADVERSE REACTIONS

Clinical Studies Experience - Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

SIMBRINZA™ Suspension - In two clinical trials of 3 months duration 435 patients were treated with SIMBRINZA™ Suspension, and 915 were treated with the two individual components. The most frequently reported adverse reactions in patients treated with SIMBRINZA™ Suspension occurring in approximately 3 to 5% of patients in descending order of incidence were blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy. Rates of adverse reactions reported with the individual components were comparable. Treatment discontinuation, mainly due to adverse reactions, was reported in 11% of SIMBRINZA™ Suspension patients.

Other adverse reactions that have been reported with the individual components during clinical trials are listed below.

Brinzolamide 1% - In clinical studies of brinzolamide ophthalmic suspension 1%, the most frequently reported adverse reactions reported in 5 to 10% of patients were blurred vision and bitter, sour or unusual taste. Adverse reactions occurring in 1 to 5% of patients were blepharitis, dermatitis, dry eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis.

The following adverse reactions were reported at an incidence below 1%: allergic reactions, alopecia, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

Brimonidine Tartrate 0.2% - In clinical studies of brimonidine tartrate 0.2%, adverse reactions occurring in approximately 10 to 30% of the subjects, in descending order of incidence, included oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions, and ocular pruritus.

Reactions occurring in approximately 3 to 9% of the subjects, in descending order included corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain.

The following adverse reactions were reported in less than 3% of the patients: lid crusting, conjunctival hemorrhage, abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

Postmarketing Experience - The following reactions have been identified during postmarketing use of brimonidine tartrate ophthalmic solutions in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The reactions, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to brimonidine tartrate ophthalmic solutions, or a combination of these factors, include: bradycardia, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation), and tachycardia.

Apnea, bradycardia, coma, hypotension, hypothermia, hypotonia, lethargy, pallor, respiratory depression, and somnolence have been reported in infants receiving brimonidine tartrate ophthalmic solutions *[see Contraindications]*.

DRUG INTERACTIONS

Oral Carbonic Anhydrase Inhibitors - There is a potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and brinzolamide ophthalmic suspension 1%, a component of SIMBRINZA™ Suspension. The concomitant administration of SIMBRINZA™ Suspension and oral carbonic anhydrase inhibitors is not recommended.

High-Dose Salicylate Therapy - Carbonic anhydrase inhibitors may produce acid-base and electrolyte alterations. These alterations were not reported in the clinical trials with brinzolamide ophthalmic suspension 1%. However, in patients treated with oral carbonic anhydrase inhibitors, rare instances of acid-base alterations have occurred with high-dose salicylate therapy. Therefore, the potential for such drug interactions should be considered in patients receiving SIMBRINZA™ Suspension.

CNS Depressants - Although specific drug interaction studies have not been conducted with SIMBRINZA™, the possibility of an additive or potentiating effect with CNS depressants (alcohol, opiates, barbiturates, sedatives, or anesthetics) should be considered.

Antihypertensives/Cardiac Glycosides - Because brimonidine tartrate, a component of SIMBRINZA™ Suspension, may reduce blood pressure, caution in using drugs such as antihypertensives and/or cardiac glycosides with SIMBRINZA™ Suspension is advised.

Tricyclic Antidepressants - Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with SIMBRINZA™ Suspension in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Monoamine Oxidase Inhibitors - Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine tartrate and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

USE IN SPECIFIC POPULATIONS

Pregnancy - *Pregnancy Category C:* Developmental toxicity studies with brinzolamide in rabbits at oral doses of 1, 3, and 6 mg/kg/day (20, 60, and 120 times the recommended human ophthalmic dose) produced maternal toxicity at 6 mg/kg/day and a significant increase in the number of fetal variations, such as accessory skull bones, which was only slightly higher than the historic value at 1 and 6 mg/kg. In rats, statistically decreased body weights of fetuses from dams receiving oral doses of 18 mg/kg/day (180 times the recommended human ophthalmic dose) during gestation were proportional to the reduced maternal weight gain, with no statistically significant effects on organ or tissue development. Increases in unossified sternebrae, reduced ossification of the skull, and unossified hyoid that occurred at 6 and 18 mg/kg were not statistically significant. No treatment-related malformations were seen. Following oral administration of ^{14}C-brinzolamide to pregnant rats, radioactivity was found to cross the placenta and was present in the fetal tissues and blood.

Developmental toxicity studies performed in rats with oral doses of 0.66 mg brimonidine base/kg revealed no evidence of harm to the fetus. Dosing at this level resulted in a plasma drug concentration approximately 100 times higher than that seen in humans at the recommended human ophthalmic dose. In animal studies, brimonidine crossed the placenta and entered into the fetal circulation to a limited extent.

There are no adequate and well-controlled studies in pregnant women. SIMBRINZA™ Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers - In a study of brinzolamide in lactating rats, decreases in body weight gain in offspring at an oral dose of 15 mg/kg/day (150 times the recommended human ophthalmic dose) were observed during lactation. No other effects were observed. However, following oral administration of ^{14}C-brinzolamide to lactating rats, radioactivity was found in milk at concentrations below those in the blood and plasma. In animal studies, brimonidine was excreted in breast milk.

It is not known whether brinzolamide and brimonidine tartrate are excreted in human milk following topical ocular administration. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SIMBRINZA™ (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use - The individual component, brinzolamide, has been studied in pediatric glaucoma patients 4 weeks to 5 years of age. The individual component, brimonidine tartrate, has been studied in pediatric patients 2 to 7 years old. Somnolence (50-83%) and decreased alertness was seen in patients 2 to 6 years old. SIMBRINZA™ Suspension is contraindicated in children under the age of 2 years *[see Contraindications]*.

Geriatric Use - No overall differences in safety or effectiveness have been observed between elderly and adult patients.

OVERDOSAGE

Although no human data are available, electrolyte imbalance, development of an acidotic state, and possible nervous system effects may occur following an oral overdose of brinzolamide. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Very limited information exists on accidental ingestion of brimonidine in adults; the only adverse event reported to date has been hypotension. Symptoms of brimonidine overdose have been reported in neonates, infants, and children receiving brimonidine as part of medical treatment of congenital glaucoma or by accidental oral ingestion. Treatment of an oral overdose includes supportive and symptomatic therapy; a patent airway should be maintained.

PATIENT COUNSELING INFORMATION

Sulfonamide Reactions - Advise patients that if serious or unusual ocular or systemic reactions or signs of hypersensitivity occur, they should discontinue the use of the product and consult their physician.

Temporary Blurred Vision - Vision may be temporarily blurred following dosing with SIMBRINZA™ Suspension. Care should be exercised in operating machinery or driving a motor vehicle.

Effect on Ability to Drive and Use Machinery - As with other drugs in this class, SIMBRINZA™ Suspension may cause fatigue and/or drowsiness in some patients. Caution patients who engage in hazardous activities of the potential for a decrease in mental alertness.

Avoiding Contamination of the Product - Instruct patients that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions *[see Warnings and Precautions]*. Always replace the cap after using. If solution changes color or becomes cloudy, do not use. Do not use the product after the expiration date marked on the bottle.

Intercurrent Ocular Conditions - Advise patients that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container.

Concomitant Topical Ocular Therapy - If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart.

Contact Lens Wear - The preservative in SIMBRINZA™, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA™ Suspension, but may be reinserted 15 minutes after instillation.

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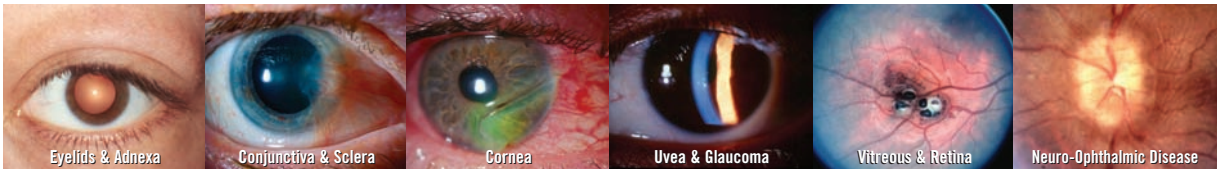

This publication addresses the management of various conditions with support from the best available peer-reviewed literature. This is done to provide the most up-to-date management of patients with various conditions and to indicate when patient referral is appropriate. In many cases, the management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

A Peer-Reviewed Supplement

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

TO OUR COLLEAGUES

Over the years that we have written *The Handbook of Ocular Disease Management*, we have made many dedications. However, we have never discussed how this supplement came to be. If you ask the three of us how *The Handbook* came about, you will get three different versions and perspectives. But the story has a common theme, which is generally entertaining, involves perseverance, being in the right place at the right time, and having people behind the scenes who had a vision regarding the potential of the project and faith in a newly forming team.

The flashpoint for the entire idea came when we saw the first edition of *The Clinical Guide to Ophthalmic Drugs,* by Drs. Ron Melton and Randall Thomas. Seeing this great use of the journal supplement medium, we sought to complement their guide with one of our own that summarized the description and etiology of the most frequently encountered ocular diseases, along with abbreviated management discussions. While we thought that this was a great idea that would be embraced by the profession, publishers were far less excited. Whether it was lack of obvious funding or our "unknown" status, the pitch was received and returned with a polite but less-than-enthusiastic response. *"Don't call us… we'll call you,"* was the common reply. Since standalone monographs were rare in those days and most journals did not have formats that were conducive to the project, we abandoned the idea.

Several years later while wandering the exhibit floor at the SECO International meeting, we fortuitously ran into a then-new and young editor named Jack Persico (now Editor-in-Chief of *Review of Optometry*) who recognized a name on a badge, recalled the earlier pitch, introduced himself and wondered if we were still interested in doing the project. Admittedly, we had to convince ourselves that we indeed wanted to resurrect the idea. After some thought and debate, we decided that we would do one supplement encompassing the most common ocular diseases encountered in clinical practice and call it a day.

So, here we are at edition 16. Hopefully, readers find our material educational. However, few realize what goes into production of this supplement. Nobody sees the way we bicker about material that each of us edits out or material each of us tells the other to add. The way we have to prod one another from hibernation each year to begin another edition. The way that one will be told by the others that his work is all wrong. At one point or another, each of us has called it quits, with a different member of the team stepping up to mend fences. Unquestionably, production has gotten easier over time as we have perfected our system and our expectations of each other. We truly like each other, each respecting the others for the unique expertise and talents they bring to the table. We consider ourselves lucky that we get to do this and we hope it helps. We enjoy the process and thank everybody behind the curtain who takes the project from the rough draft phases to finished supplement that you are holding. We want to give our sincere gratitude to Jack Persico, for without his belief and that chance meeting, this supplement would never have happened. *—Joe, Al & Andy*

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

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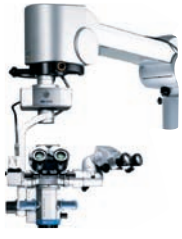

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Haag-Streit is more than the sum of its parts. Our mission is innovation, which leads to the development of important diagnostic devices and equipment. Used by doctors in nearly every country, they're noted for accuracy, durability and engineering. It's what your patients expect, and you demand. Watch for what's coming out of Haag-Streit next. Science. Brilliance. Certainty.

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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. It is defined by complex, involuntary, repetitive electrical discharges involving any muscle within the body.[1] With respect to the eye, it is known to primarily affect two structures: the eyelid and the superior oblique muscle.[1-3] Patients with superior oblique myokymia present with a vertical jerk nystagmus, oscillopsia (the perception that the world is moving) and transient diplopia.[3-6] In contrast, patients with myokymia of the eyelid present with a chief complaint of intermittent "oscillating," "vibrating," "flickering," "quivering" or "twitching" eyelid.[3]

Eyelid myokymia is the result of repetitive bursts of electrical discharge that stimulate the Muscle of Müller and the ciliary portion of the orbicularis oculi.[1,7] While most patients perceive the unexpected quivering as an annoyance, the spasms are not painful, nor are they so exaggerated that an observer could identify an episode without being within a three-foot distance, directly looking at the affected area. In contrast, benign essential blepharospasm is a disorder involving involuntary and sustained contractions of the muscles around the eyes, often with forced closure.

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.[8] The episodes are transient, lasting from one to 10 minutes, and can occur just once or multiple times during the day for weeks to months. During normal physical and emotional periods, the episodes cease and the phenomenon moves into "hibernation," often recurring during or following a trigger.[2]

Pathophysiology

Traditionally, involuntary spastic twitching of muscles has been attributable to either (1) tissues recovering from injury, (2) demyelinating disease and neural response to compression, or (3) irritation.[1,3,6,9] In a study that examined acute unilateral facial paralysis, transient long-lasting motor dysfunction featuring disorders of voluntary and involuntary movement was observed.[10] It seems that, after an injury, some patients exhibit an increase in their spontaneous blink rate as well as a sustained low-level contraction of the muscles of the non-paralyzed side.[9,10] This occasionally leads to full blepharospasm.[10] The finding was hypothesized by the authors to be due to increased excitability of the facial motor neurons and brainstem interneurons mediating reflexes.[9,10]

As one recognized mechanism of occurrence, full-blown "postparalytic facial syndrome" has been described as levels of muscular synkinesis (muscles responding together), myokymia and unwanted hemifacial contractions accompanying normal facial movements.[9,10] Pathophysiological mechanisms include abnormal axonal branching after injury with aberrant axonal regeneration and enhanced motor neuronal excitability.[9,10]

Myokymia of the eyelid is generally considered to be a benign, self-limiting disorder, with no relation to injury or paralysis.[2] In a study of 15 patients with a diagnosis of isolated eyelid myokymia where the patients 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.[2] Thirteen of the 15 patients (86.7%) underwent neuroimaging and no abnormalities were found; in this group of 13 patients, the myokymia resolved spontaneously in four individuals, with eight of the remaining nine opting to be treated with botulinum toxin injection at regular intervals. Most patients who elected to receive injections reported improvement.

Recently, several reports have suggested that eyelid myokymia may, in very rare instances, be a presenting sign of multiple sclerosis.[7,8] The described patients were young and seemingly healthy individuals with no relevant medical history or known drug use. In one case, the eyelid myokymia gave way after several weeks to facial myokymia involving the ipsilateral brow and cheek; in another, the eyelid twitching persisted and became continuous, prompting neuroradiologic investigation. In both instances, periventricular white matter lesions were noted on MRI of the brain.[7,8]

Management

Patients who pose the question in passing, "Why does my eyelid twitch sometimes?" are most likely experiencing benign eyelid myokymia. The diagnosis can be solidified by confirming the presence of these classic clinical features in their history if they are described as: (1) episodic, (2) limited to the eyelid, (3) painless, (4) not affecting visual function, (5) intermittent throughout the day, (6) cyclical and (7) repeatable, in that the symptoms have occurred previously and that recurrences may happen 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 benign. They should be counseled regarding signs that would indicate the

need for additional testing or consultation, such as persistence, worsening or involvement of other facial muscle groups. Since increased sympathetic tone, worsened from exogenous sources, can exaggerate or even instigate the problem, patients should be reminded that during stressful situations they often consciously or unconsciously increase energy drink, coffee, soda pop, tea and nicotine consumption, which can exacerbate the phenomenon. If a new medication has recently been introduced, it should be investigated for side effects.

Treatment for eyelid myokymia typically consists of behavior modification in the form of stress reduction, elimination of nicotine and/or caffeine, and rest. Direct forms of intervention may include discontinuation of provoking medications (where feasible), use of cold compresses or consumption of tonic water with quinine (based on anecdotal reports). In more severe or intolerable cases, pharmacologic intervention may be attempted with topical beta blockers, anticonvulsants such as carbamazepine (100mg to 200mg PO BID-QID) or gabapentin (100mg PO BID building to 300mg to 600mg per day), or local eyelid injections of botulinum toxin.[2,3,6,10]

Clinical Pearls

- Chronic isolated eyelid myokymia is generally considered a benign condition. It tends not to progress to other facial muscles, nor to evolve into other facial movements or disorders. When these complications occur, the practitioner needs to be suspicious for more significant systemic disorders such as multiple sclerosis or neoplastic disease.
- Excessive benign eyelid myokymia responds well to botulinum toxin injection.
- Isolated eyelid myokymia is rarely associated with other neurologic disease. However, eyelid twitching can be a localized manifestation of underlying brainstem disease, making cases of persistent myokymia a diagnosis of exclusion.
- *Postparalytic facial dysfunction* may occur following idiopathic facial nerve palsy (Bell's palsy) and seems to be the result of increased background muscle activity and enhanced motor neuron recruitment.[11]

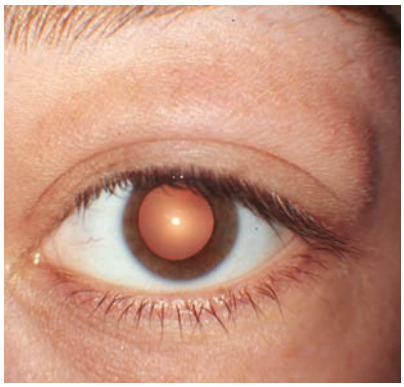
1. Banik R, Miller NR. Chronic myokymia limited to the eyelid is a benign condition. J Neuroophthalmol. 2004;24(4):290-2.
2. Mancias P, Butler IJ. Trigeminal myokymia in a young girl. J Child Neurol. 2003; 18(8):572-4.
3. Straube A. Therapeutic considerations for eye movement disorders. Dev Ophthalmol. 2007;40:175-92.
4. Williams PE, Purvin VA, Kawasaki A. Superior oblique myokymia: efficacy of medical treatment. J AAPOS. 2007;11(3):254-7.
5. Ruttum MS1, Harris GJ. Superior oblique myectomy and trochlear resection for superior oblique myokymia. Am J Ophthalmol. 2009;148(4):563-5.
6. Foroozan R, Buono LM, Sergott RC et al. Jumping Jack Flash. Surv Ophthalmol. 2006;51(1):63-7.
7. Palasí A, Martínez-Sánchez N, Bau L, Campdelacreu J. Unilateral eyelid myokymia as a form of presentation of multiple sclerosis. Neurologia. 2013;28(3):187-9.
8. Barmettler A, Dinkin MJ, Lelli GJ. Eyelid myokymia: not always benign. Orbit. 2011;30(6):289-90.
9. Valls-Solé J, Montero J. Movement disorders in patients with peripheral facial palsy. Mov Disord. 2003;18(12):1424-35.
10. Valls-Sole J, Tolosa ES, Pujol M. Myokymic discharges and enhanced facial nerve reflex responses after recovery from idiopathic facial palsy. Muscle Nerve. 1992;15(1):37-42.
11. Valls-Solé J. Facial nerve palsy and hemifacial spasm. Handb Clin Neurol. 2013;115:367-80.

DACRYOADENITIS

Signs and Symptoms

Patients with dacryoadenitis may be highly symptomatic or only mildly distracted by their cosmetic appearance, depending upon the underlying etiology and clinical course. By definition, dacryoadenitis represents an inflammatory enlargement of the lacrimal gland, either due to infection or infiltration in response to the presence of systemic disease.[1,2]

In acute cases, patients will present with unilateral pain or discomfort in the region of the eye and orbit. Focal swelling and tenderness of the temporal aspect of the upper eyelid is characteristic, as is hyperemia and swelling of the superotemporal bulbar conjunctiva overlying the lacrimal gland. In rare cases, mucopurulent discharge may be seen in the involved eye.[3] Patient history may include recent or concurrent fever, lymphadenopathy, malaise and/or upper respiratory infection.[3,4] In severe instances, the inflamed gland may cause proptotic displacement of the globe, inducing diplopia.[1,5]



Dacryoadenitis—note the characteristic S-shaped swelling of the upper lid.

In cases of chronic dacryoadenitis, patients are typically less symptomatic, reporting only a mild "fullness" of the lid and perhaps slight tenderness to the touch. In general, these patients are more concerned about their apparent lid swelling. Seemingly unrelated in the patient's mind, there may also be secondary dry eye complaints, including burning, scratchiness or a gritty sensation.[6] The history most often conveys a gradual onset of the condition over weeks or months.

Chronic cases tend to be bilateral, with nonerythematous inflammation of the lacrimal gland seen upon inspection. A firm, non-tender enlargement of the lacrimal gland may be noted upon lid eversion and palpation. In rare or untreated cases that linger, local ocular effects such as anterior uveitis are possible, complete with the full complement of circumlimbal flush, along with cells and flare in the anterior chamber.

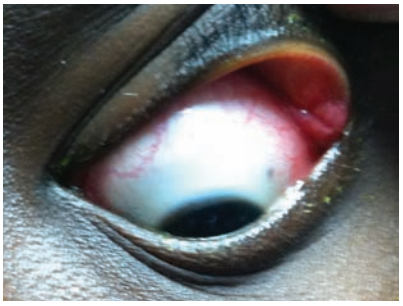
Pathophysiology

The etiology of dacryoadenitis varies widely and depends largely on the presentation. In general, acute cases tend to be infectious in nature, while chronic cases are more indicative of autoimmune disease.[2] Sources of infection may be derived from a broad range of microbes, including viruses, bacteria, fungi and parasitic organisms.[1,2,7]

Viral pathogens appear to be the most common cause of infectious dacryoadenitis; rubulavirus (mumps), Epstein-Barr virus (infectious mononucleosis), herpes simplex, herpes zoster, cytomegalovirus and rarely human immunodeficiency virus have all been implicated as potential causes.[2,6-10] Bacterial etiologies of acute dacryoadenitis include the ubiquitous *Staphylococcus, Streptococcus* and *Haemophilus* species, but can also involve the less common *Neisseria, Moraxella* and *Pseudomonas*.[2,6,7] In some cases, these infections have been known to follow ocular trauma.[2]

Disseminated systemic infection can also manifest as acute dacryoadenitis; these cases are somewhat rare, however, and may be complicated by their potential to present in a bilateral fashion. Implicated organisms include *Chlamydia, Brucella, Mycobacterium* (tuberculosis), *Treponema* (syphilis) and *Borrelia* (Lyme disease).[6,7,10-12]

In cases of chronic dacryoadenitis, the underlying cause is typically an infiltrative autoimmune disease, such as sarcoidosis, granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis), thyroid disease, Sjögren's syndrome, inflammatory bowel disease or Immunoglobulin G4-related disease (IgG4-RD).[1,3,13-17] Accumulation of granulomatous tissue, lymphocytes, plasma cells and edema in the lacrimal glands may be seen in these various disorders, leading to the clinical diagnosis.



Swollen lacrimal gland seen with eyelid retraction in dacryoadenitis.

Management

The initial step in any case of suspected dacryoadenitis is careful consideration of the differential diagnosis, in an attempt to establish an underlying etiology. Dacryoadenitis needs first to be differentiated from other infiltrative disorders of the orbit, such as idiopathic orbital inflammatory disease (also known as orbital inflammatory pseudotumor) and malignant neoplasia of the lacrimal gland or orbital tissue. The preferred technique for such testing involves T1-weighted enhanced magnetic resonance imaging (MRI), both with and without contrast, of the involved orbit.[18] Beyond orbital imaging, surgical biopsy is often helpful in further differentiating these presentations.[19] Fine-needle aspiration cytology is an alternative technique for identifying the underlying cause in chronic inflammation of the ocular adnexa.[20]

In cases of acute infectious dacryoadenitis, treatment will depend upon the specific organism. Culture and staining of any discharge may help to identify bacterial and/or fungal pathogens, while hematology, serology and additional radiographic studies are indicated in suspected cases of systemic infection (e.g., syphilis, tuberculosis, etc.). Specific tests will depend on patient demographics, history and other presenting signs, and may include such investigations as a complete blood count (CBC) with platelets and differential, fluorescent treponemal antibody absorption test (FTA-Abs), rapid plasma reagin (RPR), purified protein derivative (PPD), Lyme titer and chest X-ray.

Viral etiologies such as mumps or Epstein-Barr virus are often self-limiting, and warrant no specific action other than relative isolation, rest and supportive therapy; this may involve cold compresses to the involved area and oral nonsteroidal anti-inflammatory agents to mitigate inflammation and discomfort (e.g., naproxen sodium 250mg to 500mg PO BID). For cases of bacterial infection, a course of broad-spectrum antibiotics is warranted; common choices include cephalexin 500mg QID or amoxicillin 250mg to 500mg PO TID. In cases of systemic infection such as syphilis, chlamydia, tuberculosis or Lyme disease, it is recommended that the patient be comanaged with an infectious disease specialist.

Cases of chronic dacryoadenitis may warrant more extensive testing, particularly in those cases where no established diagnosis exists at the time of presentation. Testing for these patients should include such hematologic and serologic investigations as a CBC with platelets and differential, Westergren erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), angiotensin converting enzyme (ACE), human leukocyte antigen typing (HLA-B27), antinuclear antibody (ANA) and antineutrophil cytoplasmic antibodies (ANCA). A thyroid panel—encompassing thyroid stimulating hormone (TSH), T4, Free T4 and Free T3—may be ordered if additional signs and symptoms suggest such an etiology.

Likewise, testing for Sjögren's syndrome may be performed in cases that are suggestive of that particular disease; historically, this has consisted of non-specific serologic testing for inflammation in addition to specific antinuclear antibodies, most notably anti-Ro and anti-La.[21] Recently, however, a new point-of-care test for Sjögren's became

available in the United States. Called Sjö (Nicox), it uses blood sampled from a simple finger stick rather than venipuncture, which is collected on a paper card; the dried blood is evaluated by a central laboratory for a total of seven biomarkers, including ANA, anti-Ro, anti-La, rheumatoid factor, salivary gland protein-1, carbonic anhydrase-6 and parotid secretory protein.[22]

Treatment for chronic dacryoadenitis typically involves a course of systemic corticosteroids with a slow taper, especially when associated with conditions like sarcoidosis, granulomatosis with polyangiitis or IgG4-RD. Of course, therapy is dependent upon the unique disease and its relative severity.

It is important to remember that chronic dacryoadenitis is merely a sign of a more widespread condition, which is often best managed by a rheumatologist, endocrinologist or infectious disease specialist.

Treatment of associated ocular inflammation such as anterior uveitis is best accomplished through the use of a topical cycloplegic agent and topical corticosteroids, dosed consistently with the level of inflammation.

Clinical Pearls

- The diagnosis of dacryoadenitis is made principally by symptomatology and observation.
- There are myriad conditions (thyroid orbitopathy, myositis, orbital cellulitis and tumors of the orbit) that can induce inflammation and injection of the conjunctiva, produce proptosis and or limit ocular motility. All deserve consideration at the onset.
- Other entities that mimic dacryoadenitis are prolapsed orbital fat (dermolipoma) and dislocation of a healthy lacrimal gland.
- Untreated dacryoadenitis can progress to involve collateral tissue, resulting in preseptal cellulitis, orbital cellulitis and/or orbital mucocele.
- Pleomorphic adenoma represents 25% of all lacrimal gland mass lesions occurring most commonly between the second and fifth decades of life.[1] Adenoid cystic carcinoma is another common lacrimal gland tumor.[1]

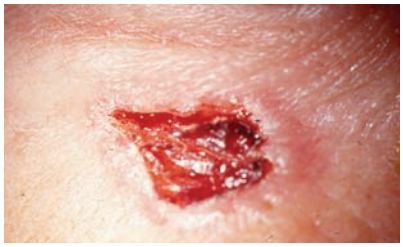
1. Dutton JJ. Orbital diseases. In: Yanoff M, Duker JS, eds. Ophthalmology, 2nd Ed. Philadelphia:Mosby, 2004. 729-43.
2. Rai P, Shah SA, Kirshan H. Acute Dacryoadenitis - analysis of 23 cases. Med Channel. 2009;15(4):71–6.
3. Derr C, Shah A. Bilateral dacryoadenitis. J Emerg Trauma Shock. 2012;5(1):92-4.
4. Hoshino A, Fujii T, Hibino S, et al. Acute infantile dacryoadenitis. J Pediatr. 2014;164(2):425.e1.
5. Goold LA, Madge SN, Au A, et al. Acute suppurative bacterial dacryoadenitis: a case series. Br J Ophthalmol. 2013;97(6):735-8.
6. Witmer M. Unraveling the difficult diagnosis of dacryoadenitis. Review of Ophthalmology. 2009;16(8):43-8.
7. Wald ER. Periorbital and orbital infections. Infect Dis Clin North Am. 2007;21(2):393-408, vi.
8. Foster WJ Jr, Kraus MD, Custer PL. Herpes simplex virus dacryoadenitis in an immunocompromised patient. Arch Ophthalmol. 2003;121(6):911-3.
9. Obata H, Yamagami S, Saito S, et al. A case of acute dacryoadenitis associated with herpes zoster ophthalmicus. Jpn J Ophthalmol 2003;47(1):107-9.
10. Toledano N, Tit-Liviu Stoica B, Genol Saavedra I, et al. Tuberculous dacryoadenitis unveils HIV infection. Can J Ophthalmol. 2013;48(5):e128-30.
11. Bekir NA, Gungor K. Bilateral dacryoadenitis associated with brucellosis. Acta Ophthalmol Scand. 1999;77(3):357-8.
12. Nieto JC, Kim N, Lucarelli MJ. Dacryoadenitis and orbital myositis associated with Lyme disease. Arch Ophthalmol. 2008;126(8):1165-6.
13. Nebrass C, Moslem S, Mghaieth F, et al. [Sarcoidosis revealed by bilateral dacryoadenitis] [Article in French]. Tunis Med. 2013;91(6):419-20.
14. Wiesent F. .Bilateral chronic dacryoadenitis. Z Rheumatol. 2013;72(7):719-22.
15. Kiratli H, Sekeroglu MA, Soylemezoglu F. Unilateral dacryoadenitis as the sole presenting sign of Wegener's granulomatosis. Orbit. 2008;27(3):157-60.
16. Lee FJ, Varikatt W, Kairaitis K, et al. IgG4-related dacryoadenitis. Ophthalmology. 2010;117(2):398.e3-4.
17. Koizumi S, Kamisawa T, Kuruma S, et al. Clinical features of IgG4-related dacryoadenitis. Graefes Arch Clin Exp Ophthalmol. 2014;252(3):491-7.
18. Nayak BK, Desai S, Maheshwari S. Interpretation of magnetic resonance imaging of orbit: Simplified for ophthalmologists (Part I). J Clin Ophthalmol Res. 2013;1(1):29-35.
19. Mahr MA, Salomao DR, Garrity JA. Inflammatory orbital pseudotumor with extension beyond the orbit. Am J Ophthalmol 2004; 138(3):396-400.
20. Dhaliwal U, Arora VK, Singh N et al. Clinical and cytopathologic correlation in chronic inflammations of the orbit and ocular adnexa: a review of 55 cases. Orbit 2004; 23(4):219-25.
21. Busamia B, Gonzales-Moles MA, Mazzeo M, et al. Assessing the determination of salivary electrolytes and anti-Ro and anti-La antibodies for the diagnosis of Sjögren's syndrome (SS). Med Oral Patol Oral Cir Bucal. 2010;15(3):e437-40.
22. Shen L, Suresh L, Lindemann M, et al. Novel autoantibodies in Sjogren's syndrome. Clin Immunol. 2012;145(3):251-5.

SQUAMOUS CELL CARCINOMA

Signs and Symptoms

Squamous cell carcinoma (SCC) is the second most common malignant neoplasm of the eyelid (after basal cell carcinoma), accounting for 5% to 10% of all eyelid neoplasms in the United States.[1-3] SCC is most often encountered in fair-skinned individuals over 60 years of age, particularly those who have a history of chronic or excessive sun exposure.[2-5] Studies have identified a nutritional risk factor for SCC development as well; diets rich in fats (e.g., cream and whole-milk dairy products) are associated with a higher incidence of SCC, whereas high intake of leafy green vegetables appears to be protective for SCC.[6,7]

Although there is no "classic" presentation, patients often demonstrate a roughened, scaly patch of tissue; the area is typically red, elevated and nodular, with crusted and/or bloody margins. Often, patients will describe the lesion as "a scab that will not heal." Other signs that may be associated with SCC include a history of rapid growth, asymmetrical shape, telangiectatic vessels, and focal loss of lashes (madarosis). Periocular carcinomas tend to occur most frequently on the lower lid or lid margin, followed by the medial canthus and upper lid or lateral canthus.[1,4,5]



Squamous cell carcinoma of the face, just below the right eye.

Patients with SCC are rarely symptomatic beyond cosmetic concerns when the lesions present in their earliest stages (local to the epidermis). When the lesions invade tissue or occur in tissues with mucous membranes such as the conjunctiva or caruncle, unlike basal cell carcinoma, they can present as painful masses.[8] As the lesions acquire depth, they have the capability of invading deeply into tissues or transferring into other body cavities by growing along nerves (perineural invasion).[9,10] This often leads to malfunction of the affected nerve, causing pain or numbness along its distribution.[9,10] Acuity is not affected unless the lesion is so large it obscures the visual axis.

Pathophysiology

Squamous cell carcinoma is a potentially invasive tumor derived from surface epithelium. In the early stages, normal epithelial cells are replaced by atypical squamous cells throughout the epidermis, resulting in a loss of normal maturation. This stage is sometimes referred to as *squamous cell carcinoma-in-situ*. Continued growth along with the production of matrix metalloproteinases and other factors can bring about disruption of the basement membrane and subsequent tumor spread into the underlying dermis; when this occurs, the lesion is referred to as *invasive squamous cell carcinoma*.[11]

While no single causative agent for the development of SCC has been identified, it is clear that ultraviolet radiation is a substantial risk factor and demonstrates a distinct association with this disease.[2,11-13] This is supported by the finding that the majority of ocular squamous cell tumors arise on the lower lid margin and medial canthus, the two periocular areas most susceptible to sunlight exposure. Additional risk factors may include exposure to arsenic, hydrocarbons, radiation or immunosuppressive drugs.[2,11]

Like other malignant forms of skin cancer, invasive squamous cell carcinoma possesses the capacity for both local invasion with destruction of normal periocular architecture, as well as lymphatic, hematogenous and neurotropic spread—a process referred to clinically as metastasis.[14]

Management

The preferred management of virtually all malignant periocular lesions involves surgery. While radiation therapy, chemotherapy or cryotherapy may achieve some success, the potential for complications combined with high recurrence rates make these options less desirable. Typically, nonsurgical treatment modalities are employed only when the patient refuses surgical intervention or when a procedure is considered intolerable due to other health concerns.

When SCC excision is performed, wide margin excision is recommended with histological confirmation of the surgical margins.[15] In one study published in 2006, researchers created a 5mm margin beyond the clinically identifiable borders of the lesion; however, the authors acknowledge that "the actual tumor edge may be difficult to determine clinically, and the result is an increased surgical tissue defect."[15]

Mohs micrographic surgery represents an alternative to wide-margin excision.[1] The Mohs technique examines *en-face* frozen-prepared sections of the entire outer surface of excised tissue, rather than just the lateral borders. This procedure carries the lowest reported rate of recurrence for SCC (3.64%) while affording maximal preservation of normal tissue, as compared to all other treatment modalities.[1] However, Mohs surgery is also quite time consuming and expensive. Hence, many oculoplastics specialists still prefer wide-margin excision for small, initial or uncomplicated cases of SCC.

Clinical Pearls

- SCC in its early stages may be easily confused with a multitude of other eyelid lesions, both malignant and benign. Some of these lesions include basal cell carcinoma, sebaceous gland carcinoma, follicular keratosis, actinic keratosis, seborrheic keratosis and keratoacanthoma.
- While SCC is the second most common eyelid malignancy, it is far less common than basal cell carcinoma, which represents about 90% of malignant eyelid neoplasms.[16]
- While squamous cell carcinoma does possess the ability to invade local tissues and metastasize to other organ systems, it is not a particularly aggressive tumor. Its rate of development is quite slow, and metastasis is exceedingly rare. Still, the potential for damage exists in cases where diagnosis and treatment are delayed.
- Early biopsy is the key to diagnosis. Suspicious lid lesions, which demonstrate irregular growth, changes in color or appearance, or discharge of a purulent or bloody nature should be biopsied to rule out cancerous entities.
- Confirmed malignancies should be referred promptly for treatment by an oculoplastic specialist or, where possible, an ocular oncologist.

1. Malhotra R, Huilgol SC, Huynh NT, Selva D. The Australian Mohs database: periocular squamous cell carcinoma. Ophthalmology. 2004;111(4):617-23.

2. Limawararut V, Leibovitch I, Sullivan T, Selva D. Periocular squamous cell carcinoma. Clin Experiment Ophthalmol. 2007;35(2):174-85.

3. Slutsky JB, Jones EC. Periocular cutaneous malignancies: a review of the literature. Dermatol Surg. 2012;38(4):552-69.

4. Faustina M, Diba R, Ahmadi MA, Esmaeli B. Patterns of regional and distant metastasis in patients with eyelid and periocular squamous cell carcinoma. Ophthalmology. 2004;111(10):1930-2.

5. Thosani MK, Schneck G, Jones EC. Periocular squamous cell carcinoma. Dermatol Surg. 2008;34(5):585-99.

6. Hughes MC, Pols JC, Marks GC, et al. Food intake and risk of squamous cell carcinoma of the skin in a community: the Nambour skin cancer cohort study. Int J Cancer. 2006;119(8):1953-60.

7. Ibiebele TI, van der Pols JC, Hughes MC, et al. Dietary pattern in association with squamous cell carcinoma of the skin: a prospective study. Am J Clin Nutr. 2007;85(5):1401-8.

8. Van De Put MA, Haeseker BI, De Wolff-Rouendaal D, De Keizer RJ. Squamous cell carcinoma of the lacrimal caruncle: case reports. Eur J Ophthalmol. 2014;24(3):441-5.

9. Adams CC, Thomas B, Bingham JL. Cutaneous squamous cell carcinoma with perineural invasion: a case report and review of the literature.Cutis. 2014;93(3):141-4.

10. Tyers AG. Orbital exenteration for invasive skin tumours. Eye (Lond). 2006;20(10):1165-70.

11. Sullivan TJ. Squamous cell carcinoma of eyelid, periocular, and periorbital skin. Int Ophthalmol Clin. 2009;49(4):17-24.

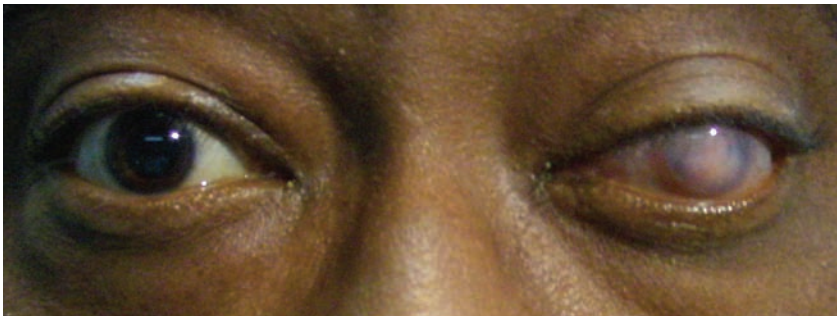
12. Melnikova VO, Ananthaswamy HN. Cellular and molecular events leading to the development of skin cancer. Mutat Res. 2005;571(1-2):91-106.

13. Mehta M, Fay A. Squamous cell carcinoma of the eyelid and conjunctiva. Int Ophthalmol Clin. 2009;49(1):111-21.

14. Kerkelä E, Saarialho-Kere U. Matrix metalloproteinases in tumor progression: focus on basal and squamous cell skin cancer. Exp Dermatol. 2003;12(2):109-25.

15. Nemet AY, Deckel Y, Martin PA, et al. Management of periocular basal and squamous cell carcinoma: a series of 485 cases. Am J Ophthalmol 2006; 142(2):293-7.

16. Prabhakaran VC, Gupta A, Huilgol SC, Selva D. Basal cell carcinoma of the eyelids. Compr Ophthalmol Update. 2007;8(1):1-14.



Stage I phthisis of the left eye.

PHTHISIS BULBI

Signs and Symptoms

Phthisis bulbi is an ocular condition defined by atrophy and disorganization of the intraocular structures that leads to a soft and anatomically disfigured, shrunken globe.[1-3] The term is derived from the Greek word *phthiein*, meaning shrinkage or consuming.[3] Ocular atrophy and phthisis bulbi connote consecutive stages in the degeneration process of a severely damaged eye.[3,4] The process is often set into motion following an event of blunt or penetrating trauma with catastrophic functional and anatomic consequences.[1-9] The condition is known to develop in eyes experiencing a protracted, non-remitting inflammatory course.[1-8] It may also occur from tumor, ischemia, complications from cataract surgery, infection, rampant proliferative vitreoretinopathy, complicated retinal detachment and ocular inflammatory disease.[1-13]

The condition itself has no symptoms per se; the diagnosis is a term given to the end-stage degeneration of the globe and its contents.[1-12] The first classification system of phthisis bulbi was based simply on observed structural changes: (1) ocular atrophy without shrinkage, (2) ocular atrophy with shrinkage and (3) ocular atrophy with shrinkage and ocular tissue disorganization.[4] The classification system has since been modified to include the amount and description of the cosmetic complications:[3]

(Ia) Corneal opacity with no enophthalmos and normal sclera without corneal sensitivity.

(Ib) Corneal opacity with no enophthalmos and normal sclera with corneal sensitivity.

(IIa) Corneal opacity with mild enophthalmos and normal sclera without corneal sensitivity.

(IIb) Corneal opacity with mild enophthalmos and normal sclera with corneal sensitivity.

(III) Moderate enophthalmos with disfigured sclera.

(IV) Severe enophthalmos with disfigured sclera and loss of orbital fat.

The symptoms that are experienced during the chronic process are related to the underlying cause and the inflammation occurring (pain, severe vision loss); the eye is failing after the fact.[1-11] Symptoms also include loss of color perception and loss of acuity. Signs include enophthalmos, variable ossification of ocular structures, variable injection of the conjunctiva, corneal-scleral sequelae such as sclerocornea and the formation of band keratopathy.

Other features that accompany the degeneration include anterior chamber collapse, iris neovascularization, hypoyon uveitis, hyphema, posterior synechiae and peripheral anterior synechiae.[1,2,5-12] In the beginning stages, dense vitritis, vitreous hemorrhage, massive intraretinal exudation, florid proliferative retinopathy, choroidal rupture, subretinal hemorrhage or signs of tumor (choroidal folds) may be seen.[14-16]

Pathophysiology

Phthisis bulbi can follow any situation in which the normal neurology, cytokines and chemo-attractants responsible for routine ocular homeostatic signals are interrupted.[17,18] The condition itself is enigmatic, usually beginning as errant wound healing.[17,18] Here, a runaway cascade of tissue reactions is seen, similar to other aggressive inflammatory wound healing scenarios elsewhere in the body.

What makes the phthisis bulbi reaction unique is that tractional changes are induced by fibroproliferative mechanisms set off by exposure to intraocular bleeding.[17,18] Wound or injury bleeding induces fibro-ingrowth, creating mechanical forces on adjacent structures perpetuating the course.[17,18]

Ocular hypotensive induction is another factor. This provokes an environment of ischemia that is a critical player in the pathology.[17]

Phthisis bulbi reactions reach a plateau within the first three months, but

can go on for years.[17] Cell proliferation and transformation are important features of the process; these eventually culminate in retinal and ciliochoroidal detachment, hypotony and marked shrinkage of the globe.[17] The process has been considered an "intraocular fluoride proliferative reaction."[17] The prominent area of this proliferative reaction centers in the pars plana, the optic disc and the base of the iris.[17]

Management

The management of phthisis bulbi is rooted in maintaining patient comfort and slowing the degenerative process. Cycloplegic medications such as atropine 1% QD-BID, topical steroids and topical nonsteroidal anti-inflammatory drugs QD-QID are all employed. Topical artificial tear drops and ointments can provide lubrication and soothing comfort. Oral analgesics can also be prescribed. While chronic use of oral steroids is rarely undertaken, timely use of injectable steroids (e.g., triamcinolone) can be attempted to quell inflammation and improve or maintain comfort.[19] If the phthisical eye has visual ability in the setting of a failed fellow eye, low vision rehabilitation can be attempted.[19]

Scleral cosmetic contact lenses can be fitted, with or without surgical resection of the conjunctiva, so long as the enophthalmos is not significant.[3,20] Some patients report irritation from the lenses, leading to decreased wear time. The surgical resection is designed to create a protective flap (mucous membrane vs. Gunderson flap), covering sensitive corneas, improving function and comfort.[21,22]

If the enophthalmos is significant, a spacer can be implanted and the scleral contact lens subsequently fitted over top.[3] When the globe is painful, evisceration or enucleation can be performed.[23-26] Since evisceration leaves the scleral shell with extraocular muscle connections intact, a well-designed prosthesis can move naturally, creating an excellent cosmetic result.[23-26] While the thought of evisceration may conjure an association with sympathetic ophthalmia, the risk is actually quite small.[26] Enucleation with placement of a hydroxyapatite spacer or simple acrylic sphere implant to build orbital volume yields few complications.[25]

Clinicians encountering individuals who have undergone these procedures should be familiar with removal and replacement of the prosthesis. This will permit the remaining ocular contents to be examined and maintained. It will also permit examination of the prosthetic, to ensure quality, proper placement and integrity. Orbital implant movement, flap and spacer tissue erosion and chronic mucous formation or conjunctival infection are possible complications.

Retrobulbar alcohol or chlorpromazine injection remains a possibility for patients with blind, painful eyes.[27] However, the procedure is rarely used as it is painful, often ineffective and—when it does work—its effect is often only temporary, making repeat injections necessary. The procedure often shrinks the orbital fat, increasing the enophthalmic posture. Today, it is only recommended for patients in persistent pain who cannot accept the thought of losing their eye (evisceration/enucleation).[27]

Clinical Pearls

- While phthisis bulbi is most common in cases of penetrating trauma, it can occur following any injury, infection, complicated surgery, inflammation or retinal detachment when the healing system fails.
- Treatment is directed at preserving comfort, maintaining the integrity of the socket and preserving the function of the prosthesis to maximize cosmesis.
- Prostheses are fabricated by craftspersons known as ocularists.

1. Naveen HC, Porwal A, Nelogi S. Prosthetic rehabilitation of phthisis bulbi by digital imaging technique--a case report. Cont Lens Anterior Eye. 2010;33(5):231-4.

2. Tan LT, Isa H, Lightman S, Taylor SRJ. Prevalence and causes of phthisis bulbi in a uveitis clinic. Acta Ophthalmologica 2012;90(5):e417-18.

3. Aggarwal H, Singh RD, Kumar P, et al. Prosthetic guidelines for ocular rehabilitation in patients with phthisis bulbi: A treatment-based classification system. J Prosthet Dent. 2014;1(1);pii: S0022-3913(13)00320-X.

4. Hogan MJ, Zimmerman LE. Phthisis bulbi. In Hogan MJ, Zimmerman LE Eds. Ophthalmic pathology. An atlas and textbook, 2nd ed. Philadelphia, PA, WB Saunders, 1962:168-221.

5. Semba RD, Bloem MW. Measles blindness. Surv Ophthalmol. 2004;49(2):243-55.

6. Ostler HB, Thygeson P. The ocular manifestations of herpes zoster, varicella, infectious mononucleosis, and cytomegalovirus disease. Surv Ophthalmol. 1976;21(2):148-59.

7. Kim PS, Choi CW, Yang YS. Outcome and significance of silicone oil tamponade in patients with chronic serous retinal detachment. Korean J Ophthalmol. 2014;28(1):26-31.

affecting the development of phthisis bulbi after pen-
2012;18(4):317-20.

Complicated retinal detachment and its management with pars plana vitrectomy.Br J Ophthalmol. 1977;61(12):754-60.

10. Hadjistilianou T, De Francesco S, Marconcini S et al. Phthisis bulbi and buphthalmos as presenting signs of retinoblastoma: A report of two cases and literature review. European Journal of Ophthalmology 2006;16(3):465-9.

11. Mullaney PB, Karcioglu ZA, Al-Mesfer S, Abboud EB. Presentation of retinoblastoma as phthisis bulbi. Eye.1997;11(1)403–8.

osseous metaplasia. A clinico-pathological study. Indian J Ophthalmol. 2002;50(3):183-8.

13. Limaiem R, Merdassi A, Lahdhiri, et al. Orbital cellulitis and endophthalmitis after cataract surgery. Bull Soc Belge Ophtalmol. 2008;(309-310):27-30.

14. Phillips BN, Chun DW, Colyer M. Closed globe macular injuries after blasts in combat. Retina. 2013;33(2):371-9.

15. Kashyap S, Meel R, Pushker N, et al. Phthisis bulbi in retinoblastoma. Clin Experiment Ophthalmol. 2011;39(2):105-10.

syndrome associated with unusual intracranial vascular malformations and Phthisis bulbi. J Neurol Sci. 2010;15;291(1-2):107-9.

17. Stefani FH. Phthisis bulbi--an intraocular fluoride proliferative reaction. Dev Ophthalmol. 1985;10 (1):78-160.

18. Kreiger AE. Wound complications in pars plana vitrectomy. Retina. 1993;13(4):335-44.

19. Rodriguez ML1, Juarez CP, Luna JD. Intravitreal triamcinolone acetonide injection in blind painful eyes. Intraocular steroids as a treatment for blind painful red eyes. Eur J Ophthalmol. 2003;13(3):292-7.

bilitation in pre phthisis bulbi's patient: case report. Arq Bras Oftalmol. 2009;72(4):540-2.

21. Ding J, Chen T, Hou Z, et al. Cosmetic shell fitting over a sensitive cornea in mild phthisis bulbi using total conjunctival flap. Aesthetic Plast Surg. 2013;37(2):398-401.

22. Ma'luf RN, Awwad ST. Mucous membrane graft versus Gunderson conjunctival flap for fitting a scleral shell over a sensitive cornea. Ophthal Plast Reconstr Surg. 2005;21(5):356-8.

23. Georgescu D, Vagefi MR, Yang CC, et al. Evisceration with equatorial sclerotomy for phthisis bulbi and microphthalmos. Ophthal Plast Reconstr Surg. 2010;26(3):165-7.

24. Aggarwal H, Singh RD, Kumar P, et al. Prosthetic guidelines for ocular rehabilitation in patients with phthisis bulbi: A treatment-based classification system. J Prosthet Dent. 2014; S0022-3913(13)00320.

25. Tanenbaum M. Enucleation, eviseraction and exenteration. In: Yanoff M, Duker JS. Ophthalmology. Mosby-Elsevier, St. Loius, MO 2009:752-760.

26. Zheng C, Wu AY. Enucleation versus evisceration in ocular trauma: a retrospective review and study of current literature. Orbit. 2013;32(6):356-61.

27. al-Faran MF, al-Omar OM. Retrobulbar alcohol injection in blind painful eyes. Ann Ophthalmol. 1990;22(12):460-2.

PROPTOSIS (EXOPHTHALMOS)

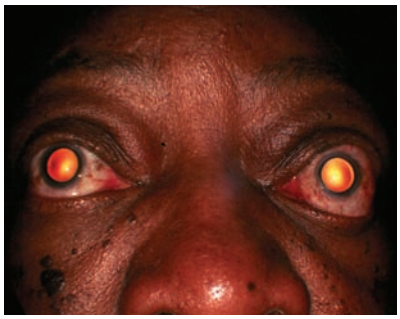
Signs and Symptoms

Proptosis is a non-ocular term generically meaning "to push forward." Ocularly, it is the forward projection or displacement of the eyeball.[1] *Exophthalmos* is a term specific to the eye, connoting an abnormally protruding globe.[2] The ophthalmic community uses the words interchangeably. Normal exophthalmometry measurements increase with age:[4]

Age..... Normal Exophthalmometry
≤4 ..... 13.2mm
5-8 ..... 14.4mm
9-12 ..... 15.2mm
≥13 ..... 16.2mm to 21.0mm

Asymmetry is common, estimated to occur in 14% of the population, with an average difference of 2.5mm between the two eyes.[4,5] Normal values also vary by race, with patients of African origin measuring slightly larger.[6]

Proptosis is not a diagnosis but rather a finding. While the configuration of the orbital margins and position of the eyes relative to the facial plane varies considerably, pathologic proptosis/exophthalmos is generally a condition that evolves to produce symptoms in one or both eyes.[5-8] In general, unilateral cases of ocular protrusion (>6mm) are more noticeable and of greater concern.[9-16]



Bilateral proptosis.

A common initial symptom produced by globe protrusion is ocular discomfort caused by exposure, with ocular dryness due to evaporation and reduced coverage of the lacrimal lake.[9-14] Dryness, burning, grittiness, foreign body sensation and paradoxical tearing with epiphora are all common. Pain may be reported and signify an acute onset rather than a chronic condition. Redness and swelling of the conjunctiva are visible accompanying features.

Visual function may be normal or profoundly reduced, depending upon the severity and nature of the exposure (corneal damage) and underlying etiology.[14] Visual fields may also be compromised if the optic nerve has been affected by the entity producing the forward displacement.[14,15] If the extraocular muscles are involved (entrapment, infiltration, myositis, tendonitis, tumor) diplopia is possible, though not uniformly present.[9-13]

Proptosis and exophthalmos are usually associated clinically with increased palpebral fissure width and lid retraction.[9-15] This is measurable using the marginal reflex distance (MRD), where the distance from the lid margin to the central corneal reflex is increased.[17]

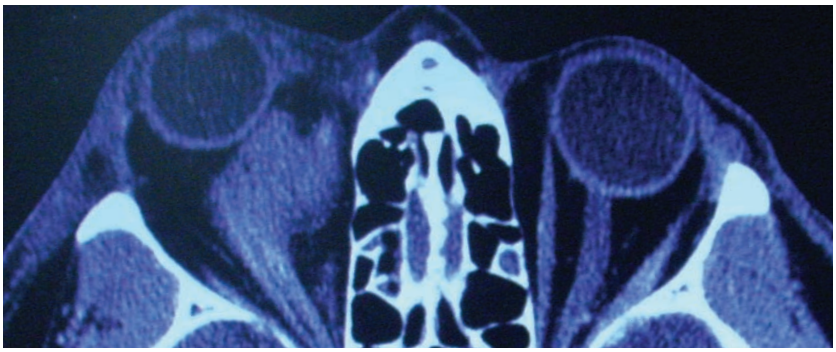
Extraocular muscle motilities may show restrictions and a positive forced duction test depending on the severity of underlying etiology.[8-15] Other biomicroscopic signs include variable conjunctival hyperemia, conjunctival chemosis, epithelial keratopathy and corneal scarring in chronic cases. Exophthalmometry (Hertel or Ludde methods) is the diagnostic procedure of choice to measure the ocular protrusive value.[5,13]

Pathophysiology

Proptosis or exophthalmos is the clinical result of increased volume within the orbital cavity. Accumulation of extraorbital cellular material (blood, vasculature, fluid, new tissue) or enlargement of any of the orbital contents (extraocular muscles, optic nerve, lacrimal gland, displacement of orbital bones) may result in forward displacement of the globe.[18-25] A wide range of etiologies may produce this phenomenon. Infiltrative disorders, infection, inflammatory disease, vascular conditions and neoplasm are the most common causes.[7,8,10,12,13,18-26]

Thyroid eye disease (i.e., Graves' disease, Graves' ophthalmopathy, thyroid ophthalmopathy) is among the most frequently encountered etiopathologies associated with proptosis/exophthalmos in adults.[8,13,26] Infiltration of the extraocular muscles and orbital fat by the cells of a maladapted immune system (e.g., lymphocytes, macrophages and plasma cells) along with thyroglobin-stimulated complexing of glycosaminoglycan with the extraocular muscles (EOM) creates orbital congestion and tendon-sparing EOM thickening that causes anterior dislocation of the eye.[26-30]

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.[26-30] Other documented causes of exophthalmos/proptosis include infection (e.g., orbital cellulitis, phycomycosis), orbital inflammatory disease, lymphoid tumors (e.g., lymphoma), 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. [7,8,10,12,13,18-26]



Unilateral proptosis associated with orbital tumor, as seen on CT-scan.

Axially myopic eyes and eyes with shallow orbits or greater than normal amounts of orbital fat may appear to be exophthalmic. This appearance may be verified by old photographs. When questioned, patients will confirm this appearance existing all their lives with no evidence of symptoms, loss of function or changes.

Management

For individuals presenting with new-onset ocular asymmetry or bilateral exophthalmos, management begins with a thorough history.[6,16] The correlation of signs with symptoms while cross-referencing epidemiologic characteristics like race, age, sex and genetics can help to shorten the list of possibilities.[6-8,10,12,13,18-30] Constitutional complaints should also be scrutinized, as these are often indicative of specific systemic conditions.[6,16]

Initial management for patients with new-onset ocular proptosis concentrates on corneal lubrication and reduction of local inflammation. Therapy includes frequent topical artificial tear drops and ointments as needed. Patients must be educated that thicker tear products (both drops and ointments) will increase contact time but temporarily blur vision. The use of protective topical antibiotic drops and ointments can protect damaged corneas. Topical non-steroidal and steroidal anti-inflammatory drops can improve comfort if inflammation is severe. Cycloplegia is usually not necessary. A moisture chamber by day and lid taping at night may be helpful. Punctal plugs can be considered to enhance natural tear volume in chronic cases. Diplopia, if present, can be eliminated by Fresnel press-on prisms in the best scenarios and by alternate eye patching when that fails.

The secondary concern is the underlying cause. The critical diagnostic test in cases demonstrating proptosis/exophthalmos of unknown etiology is orbital imaging.[31,32] Computed tomography (CT) and magnetic resonance imaging (MRI), with and without contrast, may be used.[31,32] Orbital ultrasonography can also help in the differential of proptosis or exophthalmos.[31,32] The advantage of this technique is that it can be completed in the office and interpreted immediately; the test is rapid and far less expensive than its imaging counterparts. Unfortunately, the principle disadvantage is that it can only image the anterior aspects of the orbit.

Laboratory testing is indicated when a systemic disorder is presumed. A thyroid function panel—including thyroid stimulating hormone (TSH), serum triiodothyronine (T3), serum thyroxine (T4), thyroglobin antibodies, thyrotropin receptor antibodies and thyroid stimulating immunoglobulins—is appropriate.[25-32] In cases where orbital inflammatory disease is suspected secondary to sarcoidosis, pulmonary function tests, chest X-ray and angiotensin-converting enzyme level may be diagnostic.[10] A complete blood count (CBC) is always helpful in identifying general health status, though it is nonspecific. CBC is particularly useful for uncovering malignancies such as leukemia and lymphoma. Adjunctive testing for orbital neoplasms may involve fine-needle aspiration biopsy (FNAB) or open conjunctival biopsy.[10]

Clinical Pearls

- Bilateral evolving proptosis/exophthalmos is highly suggestive of thyroid disease, especially if ophthalmoplegia and diploia are concurrent.
- Slowly progressive or new-onset unilateral proptosis/exophthalmos has a more ominous etiology.
- The common signs and symptoms of hyperthyroidism include eyelid retraction, 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.
- MRI is the preferred orbital imaging technique in most cases of acute proptosis. CT may be preferable in conditions that display bony erosion (e.g., sinus abscess, mucocele); the evaluation of osseous and cartilaginous lesions and in cases involving recent trauma.
- CT is necessary for patients with medical contraindications to MRI, such as patients with pacemakers, implanted cardiac defibrillator, aneurysm clips or claustrophobia.

1. Merriam Webster Online Dictionary. Available at: www.merriam-webster.com/dictionary/proptosis. Accessed 2-18-14.

2. Merriam Webster Online Dictionary. Available at: www.merriam-webster.com/dictionary/exophthalmos. Accessed 2-18-14

3. Dunsky IL. Normative data for hertel exophthalmometry in a normal adult black population. Optom Vis Sci 1992;69(7):562–4.

4. Dijkstal JM, Bothun ED, Harrison AR, Lee MS. Normal exophthalmometry measurements in a United States pediatric population. Ophthal Plast Reconstr Surg. 2012;28(1):54-6.

5. Chan W, Madge SN, Senaratne T, et al. Exophthalmometric values and their biometric correlates: The Kandy Eye Study. Clin Experiment Ophthalmol. 2009;37(5):496-502.

6. Masud MZ, Babar TF, Iqbal A, et al. Proptosis: Etiology and demographic patterns. J Coll Physicians Surg Pak 2006;16(1):38–41.

7. Oyster CW. The orbit. In: Oyster CW. The human eye structure and function. Cinaur Associates Inc., 1999: 111-131.

8. Dutton JJ. Orbital diseases. In: Yanoff M, Duker JS. Ophthalmology. Mosby-Elsevier, St. Loius, MO 2009:1450-64.

9. Limaiem F, Bellil S, Bellil K, et al. Primary orbital hydatid cyst in an elderly patient. Surg Infect (Larchmt). 2010;11(4):393-5.

10. Titlic M, Bradic-Hammoud M, Miric L, Punda A. Clinical manifestations of neurosarcoidosis. Bratisl Lek Listy. 2009;110(9):576-9.

11. Dériot JB, Ledoux-Pilon A, Pilon F, et al. Solitary fibrous tumor of the orbit: an unusual cause of unilateral proptosis. Case report with a review of the literature. J Fr Ophtalmol. 2005;28(9):999-1005.

12. Costa RM, Dumitrascu OM, Gordon LK. Orbital myositis: diagnosis and management. Curr Allergy Asthma Rep. 2009;9(4):316-23.

13. Levy J, Sobel R, Marcus M, Lifshitz T. Thyroid ophthalmopathy. Minerva Endocrinol. 2005;30(4):247-65.

14. Lee AG. Neuroophthalmological management of optic pathway gliomas. Neurosurg Focus. 2007;23(5):E1.

15. Malloy KA, Chigbu DI. Anterior temporal chordoid meningioma causing compressive optic neuropathy. Optom Vis Sci. 2011;88(5):645-51.

16. Kamminga N, Jansonius NM, Pott JW, Links TP. Unilateral proptosis: The role of medical history. Br J Ophthalmol 2003;87(3):370–1.

17. Liao SL1, Wei YH. Correction of lower lid retraction using tarSys bioengineered grafts for graves ophthalmopathy.Am J Ophthalmol. 2013 Aug;156(2):387-392.

18. Soroudi AE, Goldberg RA, McCann JD. Prevalence of asymmetric exophthalmos in Graves orbitopathy. Ophthal Plast Reconstr Surg 2004;20(3):224–5.

19. Islam N, Mireskandari K, Rose GE. Orbital varices and orbital wall defects. Br J Ophthalmol 2004;88(8):1092–3.

20. Kim YJ, Kim YD. Orbital venous anomaly presenting with orbital hemorrhage. Jpn J Ophthalmol. 2009;53(4):408-13.

21. Reid JR, Wheeler SF. Hyperthyroidism: Diagnosis and treatment. Am Fam Physician 2005 15;72(4): 623–30.

22. Adam A, Mishriki YY. The painful, protruding eye. Unilateral euthyroid Graves' ophthalmopathy. Postgrad Med 1999;105(7):81–4.

23. Sivagnanavel V, Riordan-Eva P, Jarosz J, et al. Bilateral orbital metastases from a neuroendocrine tumor. J Neuroophthalmol 2004;24(3):240–2.

24. Buescu A, Teixeira P, Coelho S, et al. Orbital lymphoma misdiagnosed as Graves' ophthalmopathy. Endocr Pract 2001;7(2):110–2.

25. Nayak B, Hodak SP. Hyperthyroidism. Endocrinol Metab Clin North Amer 2007;36(3):617–56.

26. Piantanida E, Tanda ML, Lai A, et al. Prevalence and natural history of Graves' orbitopathy in the XXI century. Endocrinol Invest. 2013;36(6):444-9.

27. Khoo TK, Bahn RS. Pathogenesis of Graves' ophthalmopathy: the role of autoantibodies. Thyroid. 2007; 17(10):1013-8.

28. Garrity JA, Bahn RS. Pathogenesis of graves ophthalmopathy: implications for prediction, prevention, and treatment. Am J Ophthalmol. 2006; 142(1):147-153.

29. Prabhakar BS, Bahn RS, Smith TJ. Current perspective on the pathogenesis of Graves' disease and ophthalmopathy. Endocr Rev. 2003; 24(6):802-35.

30. Karasek M, Lewinski A. Etiopathogenesis of Graves' disease. Neuro Endocrinol Lett. 2003; 24(3-4):161-6.

31. Sipos JA1, Kahaly GJ. Imaging of thyrotoxicosis. Am J Med. 2012;125(9):S1-2.

32. Sergott RC, Glaser JS. Graves' ophthalmopathy. A clinical and immunologic review. Surv Ophthalmol. 1981; 26(1):1-21.

33. Rose GE, Verity DH. Neuro-ophthalmology of orbital disease. Handbook of Clin Neurol. 2011;102:467-91.

ACUTE ALLERGIC CONJUNCTIVITIS

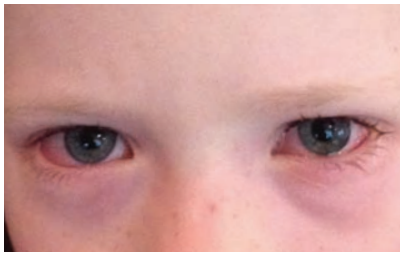
Signs and Symptoms

Allergic conjunctivitis is the most common manifestation of ocular allergy, affecting between 20% and 40% of the US population.[1-11] Acute allergic conjunctivitis describes the abrupt and immediate response seen in sensitized individuals after exposure to a particular allergen or sensitizing agent. Two main forms are recognized: *seasonal* allergic conjunctivitis (SAC), which coincides with pollen blooms such as ragweed, and *perennial* (or persistent) allergic conjunctivitis (PAC), in which exposure may occur at any time throughout the year (e.g., allergies to animal dander or dust mite feces).[4,5] In the majority of cases, allergic conjunctivitis is a bilateral phenomenon, although the presentation may be asymmetric.

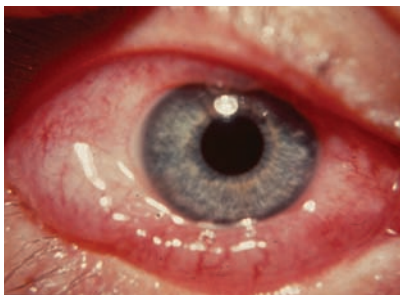
The ocular allergic response involves a constellation of signs and symptoms, all of which may vary in intensity. Itching remains the hallmark symptom; tearing is also an exceedingly common complaint, particularly after rubbing the eyes in response to itching.[1-7] More severe reactions may prompt complaints of ocular burning, foreign body sensation or photophobia, though these are relatively rare in acute disease.[1]

Clinical evaluation reveals variable conjunctival hyperemia and chemosis. Ocular discharge is watery, though mucous may accumulate in the fornices or collect on the lash margin in the form of "crusts," especially during sleep. Eversion of the eyelids may reveal a fine papillary response, particularly along the upper tarsal plate. Externally, the eyelids may be red, swollen and edematous, with a pseudoptosis in pronounced cases. If questioned, the patient will often reveal a personal or family history of allergic disease.

Clinical signs of infection (e.g., fever, pharyngitis, palpable preauricular lymph nodes) are notably absent in allergic conjunctivitis. While patients with seasonal allergy may suffer from concurrent symptoms of rhinitis, post-nasal drip or sinus congestion, these should not be mistaken for evidence of viral or bacterial infection.[3] Likewise, the eyes will display no mucopurulent discharge or follicular response. Microbial cultures or assays for viral proteins (e.g., AdenoPlus, Nicox) will be consistently negative.



Classic eyelid edema, hyperemia and lacrimation seen in allergic conjunctivitis.



Severe allergic conjunctivitis presentation with a chemotic, "watch glass" appearance.

Pathophysiology

The allergic response is classically considered to be an over-reaction of the body's immune system to substances perceived as foreign (allergens), despite the fact that said substances are not inherently pathogenic.[4] This response can be innate or acquired.

The key component of the ocular allergic response is the *mast cell*; these are widely distributed throughout the body, especially in connective tissue and mucosal surfaces, particularly the conjunctiva.[1] Immunoglobulin (IgE and IgG) receptors, which are sensitized to specific allergens, are expressed on mast cell surfaces. When allergens are encountered at the cellular level, an antigen-antibody response ensues, in turn triggering mast cell degranulation; this process releases pre-formed proinflammatory mediators and spurs the secretion of chemokines and cytokines.[4,8]

The primary chemical mediator released during degranulation is histamine, which is responsible for increased vascular permeability, vasodilation, bronchial contraction and increased secretion of mucous.[12] Heparin, chymase and tryptase are likewise released from mast cells, as well as several chemotactic factors.

Degranulation also stimulates the production of newly formed mediators through the activation of phospholipase-A_2 on membrane phospholipids, releasing arachidonic acid and platelet-activating factor. Arachidonic acid is further degraded via the cyclooxygenase pathway to form, among other chemicals, prostaglandins and thromboxanes, and—via the lipoxygenase pathway—leukotrienes.[8,10] These newly formed mediators drive the inflammatory reaction and incite recruitment and activation of additional inflammatory cells, leading to what has come to be known as the "late phase" of the allergic response.

The late-phase reaction typically commences approximately six hours following sustained mast cell degranulation.[8,9] T-lymphocyte activation and infiltration of the conjunctival mucosa by eosinophils, basophils, neutrophils and macrophages are the hallmark of the late phase.[9]

Leukocytic infiltration is not necessarily inherent to all cases of acute allergic conjunctivitis (usually only in the more severe presentations); in fact, the late-phase response is much more characteristic of chronic allergic disorders like atopic and vernal keratoconjuncti-

CATEGORY	NAME	DRUG & CONCENTRATION	MANUFACTURER
Antihistamine	Emadine	emedastine difumarate 0.05%	Alcon
Mast cell stabilizer	Crolom	cromolyn sodium 4%	Bausch + Lomb
	Alomide	lodoxamide tromethamine 0.1%	Alcon
	Alocril	nedocromil sodium 2%	Allergan
	Alamast	pemirolast potassium 0.1%	Santen
Antihistamine + mast cell stabilizer	Patanol Pataday	olopatadine hydrochloride 0.1% olopatadine hydrochloride 0.2%	Alcon
	Optivar	azelastine hydrochloride 0.05%	Meda Pharmaceuticals
	Zaditor	ketotifen fumarate 0.025%	Alcon
	Elestat	epinastine hydrochloride 0.05%	Allergan
	Bepreve	bepotastine besilate 1.5%	Bausch + Lomb
	Lastacaft	alcaftadine 0.25%	Allergan
Corticosteroid	Alrex Lotemax	loteprednol etabonate 0.2% loteprednol etabonate 0.5%	Bausch + Lomb
NSAID	Acular	ketorolac tromethamine 0.5%	Allergan

vitis, which constitute less than 2% of cases seen in clinical practice.[1,5]

Management

The management of ocular allergic reactions is primarily aimed at reducing symptomology and quelling any significant inflammation while attempting to discover, remove and avoid the offending agent, although this may not always be possible or practical. Nonpharmaceutical measures such as artificial tear solutions and cold compresses are often used for mild cases of allergic conjunctivitis, or as adjunctive therapy to more traditional management.[11,13,14] Artificial tear solutions provide a barrier function, serving to flush or dilute antigens from the ocular surface while soothing and lubricating the irritated ocular surface. While these are typically recommended to be used as needed, the clinician must be cognizant of the cumulative effect of preservatives in hypersensitive allergy patients; therefore, preservative-free artificial tears should be used whenever possible.[15]

Cold compresses and topical decongestants help to produce vasoconstriction, reducing hyperemia, chemosis and other symptoms by inhibiting the release of the inflammatory cells into the tissues from the vasculature. Numerous decongestant solutions (containing one of the following: naphazoline, antazoline, tetrahydrozaline, phenylephrine) are available as over-the-counter preparations, either alone or in combination with a mild topical antihistamine (e.g., pheniramine maleate or antazoline phosphate).

These agents tend to be the preferred treatment modality for those patients who self-medicate their allergy symptoms. Unfortunately, such OTC preparations have been associated with significant tachyphylaxis and "rebound hyperemia," as well as chronic follicular conjunctivitis and eczematoid blepharoconjunctivitis when used chronically.[16,17] The consensus of most experts today is that products containing topical decongestants are not recommended, particularly given the array of other available options.[13,15]

The pharmacologic options for managing ocular allergy are exceedingly diverse. In fact, there are nearly as many commercially available topical medications for allergic conjunctivitis today as there are for glaucoma. Overall, five distinct classes or categories of topical drugs are recognized: (1) antihistamines, (2) mast cell stabilizers, (3) antihistamine/mast cell stabilizer combinations, (4) corticosteroids and (5) non-steroidal anti-inflammatory drugs (NSAIDs).

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

In general, all of these medications are beneficial to a degree by themselves and also in combination. Topical antihistamines provide prompt symptomatic relief, but their effects can be short-lived—on the order of just four to six hours. Mast cell stabilizers prevent mast cell degranulation and hence attempt to decapitate the allergic response, but they lack the capacity to alleviate acute itching rapidly. In addition, mast cell stabilizers may take several days to a week to achieve full efficacy, and are best used with a preloading strategy to be effective before the exposure takes place. Antihistamine/mast cell stabilizer combinations provide the benefits of both of these categories and are by far the most common choice among eye care practitioners today; these drugs

also have the advantage of BID dosing, except for Pataday and Lastacaft, the only topical allergy medications currently approved for once-daily dosing.[15]

Topical corticosteroids may serve to quell inflammation and offer relief to those patients with more severe cases of acute allergic conjunctivitis. While there are well-known risks associated with long-term corticosteroid use (e.g., cataractogenesis, glaucoma), short-term therapy with topical steroids can be extremely effective. Studies have shown Alrex to have an excellent safety profile in the treatment of ocular allergy, even with therapy of up to four years' duration.[18] Topical NSAIDs are likely the least effective option for ocular allergy, and should be considered a treatment of last resort.[13] While NSAIDs may provide mild symptomatic relief, they do not directly address mast cell degranulation or the histamine response, and inhibit only a portion of the inflammatory cascade (i.e., that involving the prostaglandin cascade, not leukotriene effects).

In recent years, there has been a good deal of discussion regarding the use of nasal allergy preparations and their potential for alleviating ocular allergy symptoms. The literature does demonstrate that nasal corticosteroid sprays can have a direct and beneficial impact on ocular allergy.[19-24] Studies have consistently shown that medications like Flonase (fluticasone propionate 0.05mg, GlaxoSmithKline), Veramyst (fluticasone furoate 0.0275mg, GlaxoSmithKline) and Nasonex (mometasone furoate 0.05mg, Merck) help to ameliorate concurrent ocular symptoms when used to treat nasal rhinitis.[19-24] However, it is important to understand that topical ocular agents still offer faster, safer and more complete relief of ocular symptoms than any other form of therapy, as demonstrated in head-to-head studies for ocular itching, redness, chemosis and eyelid swelling associated with allergic conjunctivitis.[25-27]

Oral antihistamines are rarely required for the treatment of acute allergic conjunctivitis, unless there is associated rhinitis, sinusitis, urticaria or other manifestations of systemic allergy. Some of the older, over-the-counter antihistamines such diphenhydramine hydrochloride and chlorpheniramine maleate are effective, but can induce drowsiness and functional impairment.[28] Loratadine, desloratadine, fexofenadine, cetirizine and levocetirizine are second-generation antihistamines; the sedative effect of these drugs is greatly diminished, though it is not entirely eliminated.[29] In addition, all of these oral medications have the capacity for anticholinergic effects, causing dryness of the mucosal membranes of the mouth, nose and eyes.[30]

Clinical Pearls

- When evaluating patients with presumed allergic conjunctivitis, pay special attention to the inferior fornix and medial canthus. In many cases, the caruncle and plica semiluminaris may demonstrate marked hyperemia or inflammation. This is presumably because of the accumulation of histamine-laden tears in the area of the lacrimal puncta. Also, eyelid eversion is recommended to evaluate the status of the superior tarsus to diagnostically assess the fine papillary response.
- In differentiating allergic conjunctivitis from other forms of ocular surface disease, an extremely helpful question may be, "What happens when you rub your eyes?" Most itchy surface disorders such as dry eye and blepharitis generally improve with digital manipulation, because it stimulates the flow of additional tears. However, rubbing in allergy can cause further degranulation of mast cells, releasing more histamine and other chemokines into the ocular tissues and resulting in greater symptomology.[31] Hence, patients with true allergies almost always say that their symptoms worsen when they rub their eyes.
- Seasonal allergic conjunctivitis usually occurs around the same time each year, and may last for only a few weeks or months. Therefore, patients who present for their annual examination during other times of the year may go undiagnosed. It is important to ask not only whether the patient is experiencing symptoms at the time of the exam, but also if they *ever* suffer from red, itchy, watery eyes. The safety and efficacy of today's medications allow for proactive prescribing, weeks to months before symptoms arise.
- Despite marketing efforts to the contrary, most allergy experts agree that topical ophthalmic medications are the best means to manage the symptoms of ocular allergy; nasal sprays are best for nasal symptoms, and oral antihistamines should be used as an adjunct to these therapies when necessary.

1. Bielory L, Friedlaender MH. Allergic conjunctivitis. Immunol Allergy Clin North Am. 2008;28(1):43-58, vi.

2. Ono SJ, Abelson MB. Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. J Allergy Clin Immunol. 2005;115(1):118-22.

3. Butrus S, Portela R. Ocular allergy: diagnosis and treatment. Ophthalmol Clin North Am. 2005;18(4):485-92, v.

4. Chigbu DI. The management of allergic eye diseases in primary eye care. Cont Lens Anterior Eye. 2009;32(6):260-72.

5. del Cuvillo A, Sastre J, Montoro J, et al. Allergic conjunctivitis and H1 antihistamines. J Investig Allergol Clin Immunol. 2009;19 Suppl 1:11-8.

6. Bielory L. Ocular allergy overview. Immunol Allergy Clin North Am. 2008;28(1):1-23, v.

7. Uchio E, Kimura R, Migita H, et al. Demographic aspects of allergic ocular diseases and evaluation of new criteria for clinical assessment of ocular allergy. Graefes Arch Clin Exp Ophthalmol. 2008;246(2):291-6.

8. Chigbu DI. The pathophysiology of ocular allergy: a review. Cont Lens Anterior Eye. 2009;32(1):3-15.

9. Saban DR, Calder V, Kuo CH, et al. New twists to an old story: novel concepts in the pathogenesis of allergic eye disease. Curr Eye Res. 2013;38(3):317-30.

10. Leonardi A, Motterle L, Bortolotti M. Allergy and the eye. Clin Exp Immunol. 2008;153 Suppl 1:17-21.

11. Bielory L. Ocular allergy. Mt Sinai J Med. 2011;78(5):740-58.

12. Jones BL, Kearns GL. Histamine: new thoughts about a familiar mediator. Clin Pharmacol Ther. 2011;89(2):189-97.

13. Bielory L, Meltzer EO, Nichols KK, et al. An algorithm for the management of allergic conjunctivitis. Allergy Asthma Proc. 2013;34(5):408-20.

14. Bilkhu PS, Wolffsohn JS, Naroo SA, et al. Effectiveness of nonpharmacologic treatments for acute seasonal allergic conjunctivitis. Ophthalmology. 2014;121(1):72-8.

15. O'Brien TP. Allergic conjunctivitis: an update on diagnosis and management. Curr Opin Allergy Clin Immunol. 2013;13(5):543-9.

16. Adamczyk DT, Jaanus SD. Anti-allergy drugs and decongestants. In: Bartlett JD, Ed. Clinical Ocular Pharmacology, 5th edition. St. Louis: Elsevier, 2008: 245-60.

17. Soparkar CN, Wilhelmus KR, Koch DD, et al. Acute and chronic conjunctivitis due to over-the-counter ophthalmic decongestants. Arch Ophthalmol. 1997;115(1):34-8.

18. Ilyas H, Slonim CB, Braswell GR, et al. Long-term safety of loteprednol etabonate 0.2% in the treatment of seasonal and perennial allergic conjunctivitis. Eye Contact Lens. 2004;30(1):10-3.

19. Bernstein DI, Levy AL, Hampel FC, et al. Treatment with intranasal fluticasone propionate significantly improves ocular symptoms in patients with seasonal allergic rhinitis. Clin Exp Allergy. 2004;34(6):952-7.

20. Kaiser HB, Naclerio RM, Given J, et al. Fluticasone furoate nasal spray: A single treatment option for the symptoms of seasonal allergic rhinitis. J Allergy Clin Immunol. 2007;119(6):1430-7.

21. Fokkens WJ, Jogi R, Reinartz S, et al. Once daily fluticasone furoate nasal spray is effective in seasonal allergic rhinitis caused by grass pollen. Allergy. 2007;62(9):1078-84.

22. Baroody FM, Shenaq D, DeTineo M, et al. Fluticasone furoate nasal spray reduces the nasal-ocular reflex: a mechanism for the efficacy of topical steroids in controlling allergic eye symptoms. J Allergy Clin Immunol. 2009;123(6):1342-8.

23. Anolik R, Nathan RA, Schenkel E, et al. Intranasal mometasone furoate alleviates the ocular symptoms associated with seasonal allergic rhinitis: results of a post hoc analysis. Int Arch Allergy Immunol. 2008;147(4):323-30.

24. Igarashi T, Nakazato Y, Kunishige T, et al. Mometasone furoate nasal spray relieves the ocular symptoms of seasonal allergic rhinoconjunctivitis. J Nippon Med Sch. 2012;79(3):182-9.

25. Rosenwasser LJ, Mahr T, Abelson MB, et al. A comparison of olopatadine 0.2% ophthalmic solution versus fluticasone furoate nasal spray for the treatment of allergic conjunctivitis. Allergy Asthma Proc. 2008;29(6):644-53.

26. Spangler DL, Abelson MB, Ober A, et al. Randomized, double-masked comparison of olopatadine ophthalmic solution, mometasone furoate monohydrate nasal spray, and fexofenadine hydrochloride tablets using the conjunctival and nasal allergen challenge models. Clin Ther. 2003;25(8):2245-67.

27. Horak F, Stuebner P, Zieglmayer R, et al. Efficacy and safety of ketotifen eye drops as adjunctive therapy to mometasone nasal spray in subjects with seasonal allergic rhinoconjunctivitis. Clin Drug Investig. 2003;23(9):597-604.

28. Turner C, Handford AD, Nicholson AN. Sedation and memory: studies with a histamine H-1 receptor antagonist. J Psychopharmacol. 2006;20(4):506-17.

29. Belsito DV. Second-generation antihistamines for the treatment of chronic idiopathic urticaria. J Drugs Dermatol. 2010;9(5):503-12.

30. Ousler GW, Wilcox KA, Gupta G, Abelson MB. An evaluation of the ocular drying effects of 2 systemic antihistamines: loratadine and cetirizine hydrochloride. Ann Allergy Asthma Immunol. 2004;93(5):460-4.

31. Raizman MB, Rothman JS, Maroun F, et al. Effect of eye rubbing on signs and symptoms of allergic conjunctivitis in cat-sensitive individuals. Ophthalmology. 2000;107(12):2158-61.

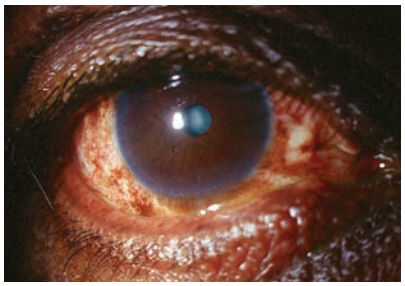
OCULAR MELANOSIS

Signs and Symptoms

Ocular melanosis represents a pigmented discoloration of the superficial ocular tissues. Patients are not symptomatic with regard to discomfort or visual disturbance, but 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, flat to slightly elevated, and may take the form of irregular patches, streaks or circumlimbal darkening.

Racial melanosis—which has also been referred to as *primary conjunctival hypermelanosis* and *complexion-related conjunctival pigmentation*—is a congenitally acquired condition. According to some sources, it is seen in up to 92% of patients of African descent, but may also be encountered in those whose ancestors hail from the Caribbean, South America or southern Asia.[1-4] This condition tends to be bilateral and symmetric, is most prominent circumlimbally, and remains relatively consistent throughout the patient's life.

Aside from racial melanosis, nevi represent 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.[5] Conjunctival nevi may be flat to slightly elevated with occasional cystic formations, and may vary significantly in pigment density. Caucasians



Marked racial melanosis of the conjunctiva.

are most likely to develop conjunctival nevi as compared to other races, accounting for 89% of cases according to one clinical series.[6]

Primary acquired melanosis (PAM) is less common than racial melanosis or conjunctival nevi, and tends to be encountered much more frequently in Caucasians than in those of African descent.[5] It may be differentiated from racial melanosis in that PAM: (1) is typically unilateral and irregular in shape, (2) demonstrates increased growth over time and (3) involves widespread areas of conjunctiva, including the fornices.

Malignant conjunctival melanoma is a rare tumor of the ocular surface. It is typically encountered in middle-aged or elderly white individuals, though a small number of cases involving patients of African descent have been documented.[1-4,7,8] 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 concurrently involve areas of the bulbar and/or tarsal conjunctiva.

Pathophysiology

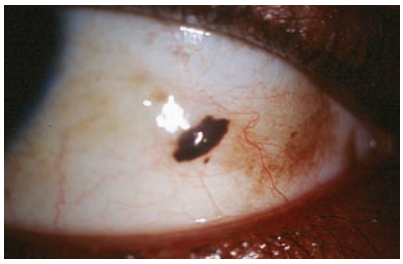
The word *melanosis* is a generic term referring to excessive darkening of a tissue due to a disturbance in melanin production or deposition. In cases where the eye is involved, the condition is sometimes called *melanosis oculi* or *melanosis bulbi*. In racial melanosis, there is

an accumulation of benign melanocytes and melanin granules within the basilar layer of conjunctival epithelium, typically limited to the perilimbal tissues.[1,9] Conjunctival nevi also represent benign proliferations of melanocytes within the basal layer of the epithelium. As the patient ages, however, these nevus cells can migrate deeper into the underlying stroma.[5] Another common characteristic feature of conjunctival nevi is the presence of intralesional cysts.[10]

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.[5] Additionally, PAM may display five distinct growth patterns: (1) basilar hyperplasia, (2) basilar nests, (3) intraepithelial nests, (4) pagetoid growth (i.e., cell invasion into the epithelium) and (5) melanoma-in-situ (i.e., replacement of normal epithelial cells with melanocytes).[5]

PAM is classified histopathologically based on the type of atypical cells and the extent of intraepithelial growth. Those lesions that show a propensity toward large atypical (e.g., epithelioid) cells and epithelial invasion constitute *PAM with atypia*; those lesions that are comprised primarily of small polyhedral cells and remain confined to the basal epithelial layer are referred to as *PAM without atypia*.[5,11,12] These distinctions are important, because atypia has been shown to directly correlate with a lesion's higher potential for malignant transformation.[5,11-13] Because of this phenomenon, some have advocated abandoning the term *primary acquired melanosis with atypia* in favor of the more specific and straightforward *melanoma-in-situ*.[2,3,14]

Conjunctival melanoma may reflect malignant transformation of pre-existing nevi or PAM; less commonly,



Conjunctival melanosis (lighter, larger region) juxtaposed with a conjunctival nevus (darker, smaller lesion).

they arise *de novo*.[4-6,11-13] 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.[5] The definitive diagnostic criterion for invasive melanoma is extension of atypical melanocytes into the underlying conjunctival stroma (substantia propria).[11,12] Melanoma is a highly malignant tumor and has significant capacity for metastasis; spread to the ipsilateral facial lymph nodes, brain, lung and liver are most common.[15-17]

Management

Management strategies for ocular melanosis depend upon the nature of the condition. Racial melanosis is considered benign and warrants no intervention perhaps other than photodocumentation. Education and reassurance should be given for patients with cosmetic concerns. Only in those cases that are unilateral or seemingly progressive should the practitioner consider additional testing such as biopsy. Conjunctival nevi may require somewhat greater scrutiny. Physicians should inquire regarding any recent changes in lesional size, shape, elevation, color, firmness or irritation. Also, unusual features such as increased vascularization or unusual location should be considered. 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.[6]

PAM typically warrants greater concern and investigation. Since PAM may have a propensity for malignant transformation and is potentially life-threatening, practitioners should routinely arrange for excisional biopsy on these patients.[18] Those cases that do not display atypia (or only mild atypia on histological evaluation) may be followed using the same guidelines as one would for a conjunctival nevus, as the risk of malignant conversion in these lesions is quite low.[5,12] However, if PAM with moderate or severe atypia is noted, then prompt removal of the lesion is indicated. Management options depend on the size, disposition and location of the lesion, and may include surgical excision with or without cryotherapy, radiotherapy or topical chemotherapy with antimetabolites such as mitomycin-C.[5,19] In those rare instances that demonstrate local or regional spread of malignant cells, enucleation or even exenteration may be indicated.[5]

Cases of suspected conjunctival melanoma should be referred promptly to an ocular oncologist or oculoplastics specialist for evaluation and excisional biopsy. Because of the high risk of metastasis, all patients with biopsy-proven melanoma need to be referred to a medical oncologist for sentinel node biopsy and full-body staging.[17,20,21]

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 possible adjunctive cryotherapy or chemotherapy to ensure destruction of the malignant tissue is employed for isolated melanomas.[20] Lesions that extend into the globe or orbit may unfortunately demand enucleation or orbital exenteration, respectively.[9]

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Despite treatment, the risk of morbidity is high with conjunctival melanoma. 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.[15]

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—on the order of 4% or less.[6,15] Still, practitioners should consider changes in size, elevation, color or vascularization as suspicious and an indication for additional consultation or testing.
- Primary acquired melanosis, as well as malignant melanoma, may sometimes be overlooked or dismissed in patients of color because of the similarity in appearance to racial melanosis.[4,7,22,23] Eye care practitioners must remain diligent during examination, 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.

1. Azari AA, Agapov J, Rezaei Kanavi M, et al. Racial melanosis: a striking presentation. JAMA Ophthalmol. 2014;132(1):76.

2. Damato B, Coupland SE. Conjunctival melanoma and melanosis: a reappraisal of terminology, classification and staging. Clin Experiment Ophthalmol. 2008;36(8):786-95.

3. Harooni H, Schoenfield LR, Singh AD. Current appraisal of conjunctival melanocytic tumors: classification and treatment. Future Oncol. 2011;7(3):435-46.

4. Colby KA, Nagel DS. Conjunctival melanoma arising from diffuse primary acquired melanosis in a young black woman. Cornea. 2005;24(3):352-5.

5. Lin SM, Ferrucci S. Primary acquired melanosis of the conjunctiva. Optometry. 2006;77(5):223-8.

6. Shields CL, Fasiuddin AF, Mashayekhi A, Shields JA. Conjunctival nevi: clinical features and natural course in 410 consecutive patients. Arch Ophthalmol. 2004;122(2):167-75.

7. Anonubi CC, Akinsola FB, Abdulkareem FB, et al. Conjunctival melanoma in a 55 year old male Nigerian: a case report. Niger Postgrad Med J. 2006;13(4):366-9.

8. Hu DN, Yu G, McCormick SA, Finger PT. Population-based incidence of conjunctival melanoma in various races and ethnic groups and comparison with other melanomas. Am J Ophthalmol. 2008;145(3):418-423.

9. Shields CL, Shields JA. Tumors of the conjunctiva and cornea. Surv Ophthalmol. 2004;49(1):3-24.

10. Zembowicz A, Mandal RV, Choopong P. Melanocytic lesions of the conjunctiva. Arch Pathol Lab Med. 2010;134(12):1785-92

11. Shields JA, Shields CL, Mashayekhi A, et al. Primary acquired melanosis of the conjunctiva: experience with 311 eyes. Trans Am Ophthalmol Soc. 2007;105:61-71; discussion 71-2.

12. Shields JA, Shields CL, Mashayekhi A, et al. Primary Acquired Melanosis of the Conjunctiva: Risks for Progression to Melanoma in 311 Eyes. The 2006 Lorenz E. Zimmerman Lecture. Ophthalmology. 2008;115(3):511-519.e2

13. Brownstein S. Malignant melanoma of the conjunctiva. Cancer Control. 2004;11(5):310-6.

14. Ackerman AB, Sood R, Koenig M. Primary acquired melanosis of the conjunctiva is melanoma in situ. Mod Pathol 1991;4(2):253-63.

15. Shields CL, Shields JA, Gunduz K, et al. Conjunctival melanoma: risk factors for recurrence, exenteration, metastasis, and death in 150 consecutive patients. Arch Ophthalmol. 2000;118(11):1497-507.

16. Köklü S, Gültuna S, Yüksel I, et al. Diffuse gastroduodenal metastasis of conjunctival malignant melanoma. Am J Gastroenterol. 2008;103(5):1321-3.

17. Savar A, Ross MI, Prieto VG, et al. Sentinel lymph node biopsy for ocular adnexal melanoma: experience in 30 patients. Ophthalmology. 2009;116(11):2217-23.

18. Corcoran KT, Marsich MM, Ward DC. Potentially life-threatening primary acquired melanosis. Clin Eye Vis Care. 2000;12(3-4):185-8.

19. Anandajeya WV, Corrêa ZM, Augsburger JJ. Primary acquired melanosis with atypia treated with mitomycin C. Int Ophthalmol. 2009;29(4):285-8.

20. Oellers P, Karp CL. Management of pigmented conjunctival lesions. Ocul Surf. 2012;10(4):251-63.

21. Shildkrot Y, Wilson MW. Conjunctival melanoma: pitfalls and dilemmas in management. Curr Opin Ophthalmol. 2010;21(5):380-6.

22. Kalski RS, Lomeo MD, Kirchgraber PR, Levine MR. Caruncular malignant melanoma in a black patient. Ophthalmic Surg. 1995;26(2):139-41.

23. Medina Mendez CA, Singh AD. Multifocal Melanoma of the Conjunctiva in an African American Patient With Neurofibromatosis Type 1. Cornea. 2014 Apr 2. [Epub ahead of print]

PTERYGIUM

Signs and Symptoms

Pterygium (plural: pterygia) is typically discovered upon routine ocular evaluation in asymptomatic individuals, or in patients who present with a cosmetic concern about a tissue "growing over the eye." In some instances, the vascularized pterygium may become red and inflamed, motivating the patient to seek immediate care. In others, the irregular ocular surface can interfere with the stability of the precorneal tear film, creating a symptomatic dry eye syndrome. Pterygia of significant magnitude can induce irregular tractional forces on the cornea, inducing astigmatism and higher-order aberrations.[1] In advanced cases, the visual axis can be obscured, resulting in substantially diminished acuity.[2,3]

Clinical inspection of pterygia reveals a raised, whitish, triangular-shaped wedge of fibrovascular tissue whose base lies within the interpalpebral conjunctiva and whose apex encroaches on the cornea. The leading edge of this tissue often displays a fine, reddish-brown iron deposition line (Stocker's line). More than 90% of pterygia occur nasally.[4]

These lesions are more commonly encountered in warmer climates, or in patients who are otherwise chronically exposed to outdoor elements or smoky/dusty environments. The association between outdoor work, sun exposure and pterygium formation is significant.[2,4-9] Use of UV-blocking sunglasses has been seen to reduce the incidence.[6] One study showed that pterygia occurred three times more frequently in patients of African descent than Caucasians.[9] Men are affected somewhat more frequently than women.[8,9]

Pathophysiology

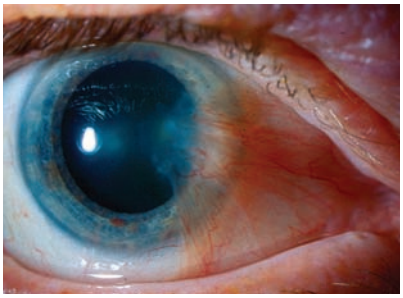
Ultraviolet light exposure—UV-A at 315nm to 400nm wavelengths and especially UV-B at 280nm to 315nm—

appears to be the most significant contributory factor in the development of pterygia.[5-11] This may explain why the incidence is vastly greater in populations near the equator and in persons who spend a great deal of time outdoors.[11] Other agents that may contribute to the formation of pterygia include allergens, noxious chemicals and irritants (e.g., wind, dirt, dust, air pollution). Heredity may also be a factor.[10]

While the etiologies are varied and likely multifactorial, pterygia in all cases represent a degenerative condition of the conjunctival stroma with replacement by thickened, tortuous, elastotic fibers. Activated fibroblasts in the leading edge of the pterygium invade and fragment Bowman's layer as well as a variable amount of the superficial corneal stroma. It has been suggested that multipotential stem and progenitor cells may be involved in pathogenesis through their differentiation into fibroblasts and vascular endothelial cells.[12]

The detection of T-lymphocyte infiltration in pterygium epithelium strongly supports the suggestion that cellular immunity plays an important role in pterygium formation.[13] Epidermal growth factors have been localized in pterygium tissue, and are significantly induced by UV-B in pterygium-derived epithelial cells. This may be the means by which UV irradiation influences the pathogenesis of pterygium.[14]

Histologically, pterygia are identical to pingueculae, and their development resembles actinic degeneration of the skin. Surface cells in pterygia exhibit squamous metaplasia with increased goblet cell density. These changes are most pronounced directly over the pterygium surface.[15] Stocker's line represents corneal iron deposition in a linear pattern at the leading edge of the lesion. It is derived from tear film lactoferrin and is presumably due to abnormal iron metabolism. The presence of Stocker's line along the advancing head



A large, nasal pterygium encroaching the visual axis.

of the pterygium may signify a lack of growth potential.[15]

Pterygia often persist after surgical removal; these lesions appear as a fibrovascular scar arising from the excision site. These "recurrent pterygia" probably have no relationship to ultraviolet radiation, but rather may be likened to keloid development in the skin.[16]

Management

Before initiating management, the clinician must be certain that the diagnosis is correct. A clear distinction must be made between the potentially progressive pterygium and the less threatening pinguecula. When large, pingueculae may be very difficult to differentiate from pterygia. Typically, pingueculae are more yellow in coloration and lie within the interpalpebral space, but do not encroach beyond the limbus.[17] Pingueculae also lack the wing-shaped appearance of pterygia, the former being more oval or amoeboid in appearance. It is also crucial to differentiate pterygia from any potentially malignant ocular surface lesions, such as carcinomatous intraepithelial neoplasia or invasive squamous cell carcinoma. Any question as to the exact diagnosis warrants referral to an experienced ocular oncologist or oculoplastic specialist for evaluation and biopsy.

Because pterygium development and proliferation appears to be linked to environmental exposure, management of asymptomatic or mildly irritating pterygia involves UV-blocking spectacles and liberal ocular lubrication especially if dellen develop. Patients should be advised to avoid smoky or dusty areas as much as possible. More inflamed or irritated pterygia may be treated with topical corticosteroid drops (e.g., prednisolone acetate 1% or loteprednol etabonate 0.5% QID for several days or until symptoms adequately resolve).

Surgical intervention may be indicated for cases of pterygia that present with: (1) unacceptable cosmesis, (2) significant, uncorrectable astigmatism or other aberrations, (3) chronic, peripheral corneal non-wetting or diminished stability, or (4) significant ingrowth to the visual axis, compromising or threatening to compromise visual acuity.

Surgical excision involves dissection and removal of the fibrous tissue down to the level of Tenon's capsule. Conjunctival autograft—a technique which involves excision of the pterygium and covering of the resulting bare sclera with a free conjunctival graft harvested from an uninvolved site of the ocular surface—is typically used to prevent recurrence.[11,18,19] The use of fibrin glue has advanced the utility of conjunctival autografts by eliminating the need for suturing, thus reducing both operating time and postoperative pain and inflammation.[20]

An alternative to conjunctival autograft involves the use of cryopreserved amniotic membrane transplantation (e.g., AmnioGraft, BioTissue).[21-23] Amniotic transplants typically are reserved for patients with recurrence following conjunctival autograft and those with insufficient viable conjunctival tissue, or those with glaucoma who may need the superior conjunctiva preserved for future trabeculectomy. Unfortunately, amniotic membrane transplantation has been associated with a higher rate of recurrence and generally poorer cosmetic outcome.[24]

Medical adjuncts in the form of the antimetabolites mitomycin-C and 5-fluorouracil may be used in order to reduce a pterygium's potential for recurrence.[25-27] Unfortunately, these antimetabolites can have attendant complications and are therefore typically reserved for cases of previous surgical failure. Topical cyclosporine (Restasis, Allergan) has also been shown in multiple clinical trials to help diminish the rate of pterygium recurrence after surgery.[28-30] Beyond medical adjuncts, single-dose beta-irradiation remains the simplest procedure following bare sclera surgery. It is an effective and safe treatment that reduces the risk of primary pterygium recurrence.[31]

Recent studies have evaluated the use of anti-VEGF drugs such as bevacizumab in the management of pterygia.[5,32] In theory, the ability of these medications to induce regression of abnormal blood vessel growth might help to retard the progression of pterygia; however, the clinical effects seen in these trials has been inconsistent and inconclusive. Despite safety, these studies have shown limited impact on growth and, as in other instances where they are used, a need for repeated injections in order to maintain the therapeutic effect.

Clinical Pearls

- The word pterygium is ultimately derived from the Greek word *pteryx*, meaning "wing" and indicative of the characteristic triangular shape of this lesion. In the Latin-American community where the incidence of pterygium can be quite high, the condition is often referred to as *carnosidad*, which means "fleshy." The name actually derives from the Spanish word *carne*, meaning "meat."
- Pterygia do have the capacity to affect vision if left unchecked. The corneal degradative effects of any pterygium appear to extend approximately three millimeters beyond the leading edge, or head, of the lesion.[33] This means that the pterygium need not cover the visual axis to inflict significant visual compromise. In our collective experience, we have witnessed seemingly benign pterygia at least two millimeters off the visual axis that have induced in excess of 10 diopters of irregular corneal astigmatism, and resulted in a best-corrected acuity of 20/80.
- It is not wise to wait until a pterygium impacts the visual axis or vision before recommending surgical excision. Since healthy corneal tissue beyond the leading edge of the pterygium must be resected during excision, waiting until the visual axis is affected virtually guarantees permanent visual reduction. Pterygia should not be allowed to progress beyond the midway point between the limbus and the pupil.
- Follow-up on medium to large sized pterygia should be performed at least once or twice yearly. It should include a manifest refraction, corneal topography, slit lamp evaluation and photodocumentation with measurement of the pterygium.

1. Zare M, Zarei-Ghanavati S, Ansari-Astaneh MR, et al. Effects of pterygium on ocular aberrations. Cornea. 2010;29(11):1232-5.

2. Al-Bdour M, Al-Latayfeh MM. Risk factors for pterygium in an adult Jordanian population. Acta Ophthalmol Scand. 2004;82(1):64-7.

3. Yaacov-Peña F, Jure D, Ocampos J, et al. Prevalence and causes of blindness in an urban area of Paraguay. Arq Bras Oftalmol. 2012;75(5):341-3.

4. Alqahtani JM. The prevalence of pterygium in Alkhobar: A hospital-based study. J Family Community Med. 2013;20(3):159-61.

5. Mauro J, Foster CS. Pterygia: pathogenesis and the role of subconjunctival bevacizumab in treatment. Semin Ophthalmol. 2009;24(3):130-4.

6. Nemesure B, Wu SY, Hennis A, Leske MC; Barbados Eye Studies Group. Nine-year incidence and risk factors for pterygium in the Barbados eye studies. Ophthalmology. 2008;115(12):2153-8.

7. Vojnikovic B, Njiric S, Coklo M, et al. Sunlight and incidence of pterygium on Croatian Island Rab—epidemiological study. Coll Antropol. 2007;31 Suppl 1:61-2.

8. Liu L, Wu J, Geng J, Yuan Z, Huang D. Geographical prevalence and risk factors for pterygium: a systematic review and meta-analysis. BMJ Open. 2013;3(11):e003787.

9. Luthra R, Nemesure BB, Wu SY, et al. Barbados Eye Studies Group. Frequency and risk factors for pterygium in the Barbados Eye Study. Arch Ophthalmol. 2001;119(12):1827-32.

10. Di Girolamo N, Chui J, Coroneo MT, et al. Pathogenesis of pterygia: role of cytokines, growth factors, and matrix metalloproteinases. Prog Retin Eye Res. 2004;23(2):195-228.

11. Todani A, Melki SA. Pterygium: current concepts in pathogenesis and treatment. Int Ophthalmol Clin. 2009;49(1):21-30.

12. Ye J, Song YS, Kang SH, et al. Involvement of bone marrow-derived stem and progenitor cells in the pathogenesis of pterygium. Eye. 2004;18(8):839-43.

13. Beden U, Irkec M, Orhan D, et al.. The roles of T-lymphocyte subpopulations (CD4 and CD8), intercellular adhesion molecule-1 (ICAM-1), HLA-DR receptor, and mast cells in etiopathogenesis of pterygium. Ocul Immunol Inflamm. 2003;11(2):115-22.

14. Nolan TM, DiGirolamo N, Sachdev NH, et al. The role of ultraviolet irradiation and heparin-binding epidermal growth factor-like growth factor in the pathogenesis of pterygium. Am J Pathol. 2003;162(2):567-74.

15. Detorakis ET, Spandidos DA. Pathogenetic mechanisms and treatment options for ophthalmic pterygium: trends and perspectives (Review). Int J Mol Med. 2009;23(4):439-47.

16. Singh H, Thakur AS, Sharma BL. Primary pterygium – comparsion of limbal conjunctival autografting surgery versus intraoperative mitomycin-C (0.02%) after exicision of primary pterygium. Nat J Comm Med. 2011;2(3): 331-4.

17. Dong N, Li W, Lin H, et al. Abnormal epithelial differentiation and tear film alteration in pinguecula. Invest Ophthalmol Vis Sci. 2009;50(6):2710-5.

18. Frau E, Labetoulle M, Lautier-Frau M, et al. Corneoconjunctival autograft transplantation for pterygium surgery. Acta Ophthalmol Scand. 2004;82(1):59-63.

19. Chaidaroon W, Wattananikorn S. Conjunctival autograft transplantation for primary pterygium. J Med Assoc Thai. 2003;86(2):111-5.

20. Bahar I, Weinberger D, Gaton DD, et al. Fibrin glue versus vicryl sutures for primary conjunctival closure in pterygium surgery: long-term results. Curr Eye Res. 2007;32(5):399-405.

21. Tananuvat N, Martin T. The results of amniotic membrane transplantation for primary pterygium compared with conjunctival autograft. Cornea. 2004;23(5):458-63.

22. Sangwan VS, Murthy SI, Bansal AK, et al. Surgical treatment of chronically recurring pterygium. Cornea. 2003;22(1):63-5.

23. Huang Y, Li H, Huang Z, et al. Application of amnion membrane transplantation combine with mitomycin C in the treatment of pterygium. Yan Ke Xue Bao. 2004;20(2):74-6.

24. Li M, Zhu M, Yu Y, et al. Comparison of conjunctival autograft transplantation and amniotic membrane transplantation for pterygium: a meta-analysis. Graefes Arch Clin Exp Ophthalmol. 2012;250(3):375-81.

25. Segev F, Jaeger-Roshu S, Gefen-Carmi N, et al. Combined mitomycin C application and free flap conjunctival autograft in pterygium surgery. Cornea. 2003;22(7):598-603.

26. Akarsu C, Taner P, Ergin A. 5-Fluorouracil as chemoadjuvant for primary pterygium surgery: preliminary report. Cornea. 2003;22(6):522-6.

27. Nabawi KS, Ghonim MA, Ali MH. Evaluation of limbal conjunctival autograft and low-dose mitomycin C in the treatment of recurrent pterygium. Ophthalmic Surg Lasers Imaging. 2003;34(3):193-6.

28. Yalcin Tok O, Burcu Nurozler A, Ergun G, et al. Topical cyclosporine A in the prevention of pterygium recurrence. Ophthalmologica. 2008;222(6):391-6.

29. Turan-Vural E, Torun-Acar B, Kivanc SA, Acar S. The effect of topical 0.05% cyclosporine on recurrence following pterygium surgery. Clin Ophthalmol. 2011;5:881-5.

30. Özülken K, Koç M, Ayar O, Hasiripi H. Topical cyclosporine A administration after pterygium surgery. Eur J Ophthalmol. 2012;22 Suppl 7:S5-10.

31. Jurgenliemk-Schulz IM, Hartman LJ, Roesink JM, et al. Prevention of pterygium recurrence by postoperative single-dose beta-irradiation: a prospective randomized clinical double-blind trial. Int J Radiat Oncol Biol Phys. 2004;59(4):1138-47.

32. Sarac O, Demirel S, Oltulu R. Efficacy of intralesional bevacizumab administration in primary pterygium: a quantitative analysis. Eye Contact Lens. 2014;40(1):46-50.

33. Bahar I, Loya N, Weinberger D, et al. Effect of pterygium surgery on corneal topography: a prospective study. Cornea. 2004;23(2):113-7.

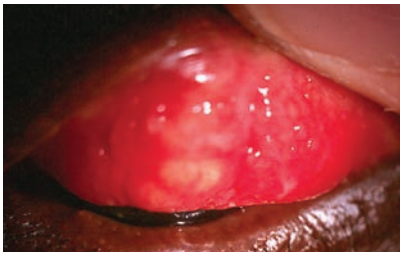
ATOPIC KERATOCONJUNCTIVITIS

Signs and Symptoms

Atopy is a genetic predisposition to develop an allergic reaction.[1] Systemic examples include allergic rhinitis and atopic dermatitis. The ocular correlate is atopic conjunctivitis. Patients with atopic keratoconjunctivitis (AKC) invariably have a personal or family history of allergic disease.[2] This may include atopic dermatitis, asthma, hayfever, food allergies and/or urticaria.[2-4] Patients are usually male, older than 20 years, with the peak incidence occurring between ages 30 and 50.[2–5] The condition is variable, with exacerbations and remissions; a large number of patients never seek medical care.[6] The disease has a reputation of provoking more symptoms during the winter months.[2–7]

Symptoms associated with AKC consist of bilateral itching with associated hyperlacrimation. Patients may also complain of a stringy or ropy mucoid discharge.[2-5] Eyelid swelling may be substantial, with burning eyelids and periocular skin. Inspection of the eyelids reveals characteristically scaly, indurated and wrinkled skin, with the possibility of fissure development at the lateral canthi associated with chronic ocular rubbing and epiphora.[2–7]

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.[2–7] Notable corneal involvement may also be encountered, including punctate keratitis, persistent epithelial erosions, "shield ulcers;" mucus plaque formation, corneal pannus and neovascularization.[2,8] The associated corneal involvement may represent the primary inflammatory process, or can be secondary to disrupted tear chemistry and lid function.



Large, cobblestone papillae in a teenager with atopic keratoconjunctivitis.

The chronic inflammation associated with AKC has the capacity to impart cicatricial changes within the conjunctiva and cornea.[8] Subepithelial conjunctival fibrosis, symblepharon (with subsequent entropion), corneal lipid deposition and pannus are not uncommon.[7-9] Primary corneal ectasias, such as keratoconus and pellucid marginal degeneration, may also occur in association with AKC. These corneal changes occur secondary to chronic mechanical stress, which produces associated astigmatic changes and scarring with subsequent visual impairment. Interestingly, cataract development is also possible in AKC. Anterior subcapsular opacities (sometimes called "shield cataracts") are thought to result from the complications of atopic inflammation.[4,7,9] Keratoconus has been associated with eyelid rubbing in atopic patients.

Pathophysiology

Atopy is the predisposed allergic reaction via the elevated production of immunoglobulin E upon exposure to an environmental antigen that is either inhaled or ingested.[1] AKC is believed to manifest elements of both Type I and Type IV hypersensitivity reactions.[10] Type I represents an immediate or anaphylactic reaction by the innate immune system secondary to an exposure that the body has been preprogrammed to eradicate. It involves the sudden degranulation of mast cells local to the region of exposure mediated by IgE antibodies.[2] This is the response seen in acute allergic conjunctivitis.

A Type IV reaction, also known as a delayed or cell-mediated hypersensitivity reaction, involves the slower adaptive immune system. Here, plasma cells, B-cells, T-lymphocytes and associated lymphokines respond following multiple exposures to varying loads of the antigen. Type IV reactions include contact dermatitis and phlyctenulosis. The measurement of released tear-specific inflammatory markers, such as histamine, tryptase, interleukins (IL-4, IL-5) and eotaxin, may be useful in confirming the diagnosis and monitoring ocular allergy.[11] New technologies such as multiplex bead assays, membrane-bound antibody array and proteomic techniques are being used to characterize and quantify the distribution of a wide range of these bioactive proteins in tears.[11]

Histopathologic evaluation of conjunctival samples from patients with AKC reveals elevated levels of mast cells, lymphocytes, eosinophils and basophils.[2,3] 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.[8,11] In addition, degranulation of eosinophils releases numerous toxic/inflammatory proteins, such as eosinophil cationic protein, eosinophil peroxidase, and eosinophil-derived neurotoxin.[9,11] These proteins

not only induce cicatricial changes in the conjunctiva; they have also been shown to cause cytotoxic disruption in corneal epithelial cells, suggesting a possible mechanism for the extensive corneal pathology seen in chronic AKC.[8,13] Matrix metalloproteinase is another eosinophil product associated with fibrosis and scarring.

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.[11,12] Research has identified several specific genes that may be responsible supporting the strong role of family history in atopic disease.[12]

Management

In the mildest forms, AKC is a seasonal nuisance disease. It can be treated easily with palliative methods (tears, cold compresses, lubricants) and mild topical anti-allergy medications (vasoconstrictors, antihistamine/mast cell stabilizers). Oral non-sedating antihistamines can be used to concurrently manage accompanying non-ocular and adnexal symptoms.[14] When possible, the patient should be instructed to avoid the environmental and chemical agents that are known to provoke the process.

In more severe cases, AKC can induce chronic debilitating symptoms along with tissue destruction capable of permanently affecting function.[2,8] Topical non-steroidal anti-inflammatory drugs (NSAIDs) can also be used to mitigate signs and symptoms.[15] Here, dosage and length of use must be monitored. Documented cases of keratolysis have been reported associated with increased frequency of administration and extended use.[16,17]

Because the pathology of AKC involves inflammation, topical corticosteroids may be required to suppress an aggressive inflammatory response. Prednisolone acetate 1% and difluprednate emulsion 0.05% are topical ophthalmic steroids that can be prescribed for chronic forms of the disorder. While they are effective agents, consideration must be given for intraocular pressure elevation with chronic use. Loteprednol etabonate 0.5% is a potent topical steroid with a reputation for having less propensity to raise IOP, though this response may occur with chronic use. It should be considered as an option for patients who require long-term corticosteroid therapy with close observation.[18,19]

The dosing of topical steroids should vary depending on the individual case; QID-Q2H for severe cases, with BID-QD dosing for cases requiring long-term maintenance. In cases demonstrating raised IOP where the topical therapy must be continued, aqueous suppressants can be added. Finally, topical steroids used for less than two weeks generally can be discontinued without tapering. In cases that induce the formation of corneal shield ulcer, topical cycloplegia and broad-spectrum antibiotic prophylaxis should be added.[2]

Patients with AKC who are inadequately controlled with topical corticosteroids or those who experience negative sequelae warranting discontinuation of steroids may require topical or systemic immunomodulatory therapy (oral, sublingual or subcutaneous routes).[20-26] 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.[20,21] Early research using cyclosporine 2% in maize oil demonstrated a distinct benefit.[22] However, clinical studies involving 0.05% cyclosporine emulsion have shown mixed results.[20-25] Oral steroids are only considered in non-responsive situations.

Atopic dermatitis involving the lids, in addition to palliative treatments and oral antihistamines, may require corticosteroid creams or ointments. Options include over-the-counter hydrocortisone 10%, fluorometholone ointment, triamcinolone acetonide 0.1% or clobetasone butyrate 0.05%. The immediate satisfaction topical steroids can produce encourages patients to use them liberally or without consulting a professional. This relapsing behavior by the patient is sometimes known as "topical steroid addiction." Since topical steroids can raise IOP and thin the dermis, patients must be educated that unapproved use is not a sound strategy. In lieu of steroids, topical tacrolimus 0.1% ointment (Protopic, Astellas Pharma) has demonstrated equivalent safety and efficacy in a head-to-head clinical study.[26,27]

Clinical Pearls

- Patients using topical steroids for long periods of time should also be monitored for glaucoma and cataractogenesis.
- It is important to distinguish between AKC and vernal keratoconjunctivitis (VKC). VKC is seen in younger males (age three to 25 years) and has a tendency to become exacerbated during warmer months and in warmer climates.
- AKC must also be differentiated from contact eyelid dermatitis. Contact dermatitis presents with acute, pitting edema (that can be pushed in), erythema and pronounced itching of the adnexa. Corneal and conjunctival involvement is rare and signals additional toxic exposure.
- Topical NSAIDs can provide analgesia in the management of AKC but the dosage and length of use must monitored as keratolysis has been associated with increased or prolonged regimens.
- Oral antihistamines have diminished bioavailability to the ocular tissues; however, their positive effect on the adnexa mandates consideration in AKC treatment.

• Consultation and comanagement with an allergist, dermatologist and corneal surgeon should be considered in patients with ongoing or worsening exacerbations.

1. Merriam Webster Online Dictionary. Available at: www.merriam-webster.com/dictionary/atopy. Accessed 2-23-14.

2. Rubenstein JB, Virasch V. Allergic conjunctivitis. In: Yanoff M, Duker JS. Ophthalmology. Mosby-Elsevier, St. Loius, MO 2009:237-240.

3. Butrus S, Portela R. Ocular allergy: Diagnosis and treatment. Ophthalmol Clin North Am 2005;18(4):485–92.

4. Bielory L. Allergic and immunologic disorders of the eye. Part II: Ocular allergy. J Allergy Clin Immunol 2000;106(6):1019–32.

5. Ono SJ, Abelson MB. Allergic conjunctivitis: Update on pathophysiology and prospects for future treatment. J Allergy Clin Immunol 2005;115(1):118–22.

6. Azari AA1, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment. JAMA. 2013;310(16):1721-9.

7. Zhan H, Smith L, Calder V, et al. Clinical and immunological features of atopic keratoconjunctivitis. Int Ophthalmol Clin 2003;43(1):59–71.

8. Mehta M, Siddique SS, Gonzalez-Gonzalez LA, Foster CS. Immunohistochemical differences between normal and chronically inflamed conjunctiva: diagnostic features. Am J Dermatopathol. 2011;33(8):786-9.

9. Bonini S. Atopic keratoconjunctivitis. Allergy 2004;59(S78):71–3.

10. Faraj HG, Hoang-Xuan T. Chronic cicatrizing conjunctivitis. Curr Opin Ophthalmol 2001;12(4):250–7.

11. Leonardi A. Allergy and allergic mediators in tears. Exp Eye Res. 2013;117:106-17.

12. Abelson MB, Chapin MJ, Leonardi A. AKC: Current and future treatments. Rev Ophthalmol 2001;8(4):100–2.

13. Leonardi A, Borghesan F, Faggian D, et al. Tear and serum soluble leukocyte activation markers in conjunctival allergic diseases. Am J Ophthalmol 2000;129(2):151–8.

14. Gane J, Buckley R. Leukotriene receptor antagonists in allergic eye disease: a systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2013;1(1):65-74.

15. Li Z, Mu G, Chen W, et al. Comparative evaluation of topical pranoprofen and fluorometholone in cases with chronic allergic conjunctivitis. Cornea. 2013;32(5):579-82.

16. Demirel S, Sarac O. Late corneal perforation with topical diclofenac sodium use after radiotherapy. Eye Contact Lens. 2012;38(3):197-9.

17. Feiz V1, Oberg TJ, Kurz CJ, et al. Nepafenac-associated bilateral corneal melt after photorefractive keratectomy. Cornea. 2009;28(8):948-50.

18. Calder VL, Jolly G, Hingorani M, et al. Cytokine production and mRNA expression by conjunctival T-cell lines in chronic allergic eye disease. Clin Exp Allergy 1999;29(9):1214–22.

19. Novack GD, Howes J, Crockett RS, Sherwood MB. Change in intraocular pressure during long-term use of loteprednol etabonate. J Glaucoma 1998;7(4):266–9.

20. Whitcup SM, Chan CC, Luyo DA, et al. Topical cyclosporine inhibits mast cell–mediated conjunctivitis. Invest Ophthalmol Vis Sci 1996;37(13):2686–93.

21. Pucci N, Caputo R, Mori F. Long-term safety and efficacy of topical cyclosporine in 156 children with vernal keratoconjunctivitis. Int J Immunopathol Pharmacol. 2010;23(3):865-71.

22. Hingorani M, Moodaley L, Calder VL, et al. A randomized, placebo-controlled trial of topical cyclosporin A in steroid-dependent atopic keratoconjunctivitis. Ophthalmol 1998;105(9):1715–20.

23. Akpek EK, Dart JK, Watson S, et al. A randomized trial of topical cyclosporin 0.05% in topical steroid-resistant atopic keratoconjunctivitis. Ophthalmol 2004;111(3):476–82.

24. Daniell M, Constantinou M, Vu HT, Taylor HR. Randomised controlled trial of topical ciclosporin A in steroid dependent allergic conjunctivitis. Br J Ophthalmol 2006;90(4):461–4.

25. Settipane RA1, Peters AT, Borish L.Chapter 17: Immunomodulation of allergic sinonasal disease. Am J Rhinol Allergy. 2013;27 Suppl 1:S59-62.

26. Nivenius E, van der Ploeg I, Jung K, et al. Tacrolimus ointment vs. steroid ointment for eyelid dermatitis in patients with atopic keratoconjunctivitis. Eye 2007;21(7):968–75.

27. Tzu JH, Utine CA, Stern ME, Akpek EK. Topical calcineurin inhibitors in the treatment of steroid-dependent atopic keratoconjunctivitis. Cornea. 2012;31(6):649-54.

VIRAL CONJUNCTIVITIS

Signs and Symptoms

The two frequently encountered forms of viral conjunctivitis are pharyngoconjunctival fever (PCF) and epidemic keratoconjunctivitis (EKC).[1–11] Pharyngoconjunctival fever is characterized by a fever, sore throat, history of recent upper respiratory infection (URI) and follicular conjunctivitis.[1,2,4,7,9-11] The condition may be unilateral or bilateral, but classically presents in one eye and is spread to the other.[1–8] This may explain why some epidemics are centered around community activity areas like swimming pools.[4,7,8] The cornea is rarely affected and infiltrates are uncommon.[5] Preauricular lymph nodes may be palpable and tender. The virus has an infectious period of 14 to 30 days that is self-limiting.[7,8] The condition is contagious through the entire clinical period.

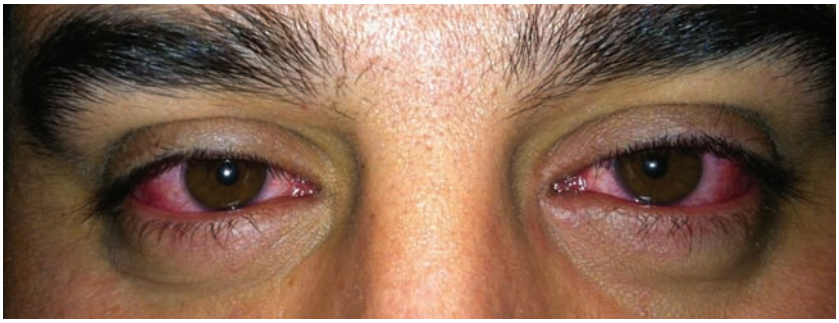
The principal symptoms include diffuse conjunctival redness, watery discharge, epiphora sometimes leading to a lateral canthal fissure (splitting of the skin at the lateral juncture of the upper and lower eyelids) and irritation.[1–11]

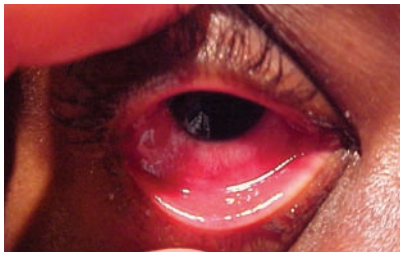
Epidemic keratoconjunctivitis presents as a unilateral or bilateral inferior palpebral follicular conjunctivitis with epithelial and subepithelial keratitis.[12,13] While the entity has a reputation for preserving corneal sensation, recent investigations have demonstrated that transient decreased sensitivity over the middle course of the infection is possible.[12-14] Subepithelial infiltrates (SEI) do not occur in every instance. When observed, they are typically concentrated in the central cornea, uniquely sparing the periphery.[12–15] These localized gatherings of leukocytes can persist for months or longer; the pockets they create underneath the corneal epithelium are capable of producing permanent corneal opacities.[15,16]

Diffuse conjunctival injection, tearing, watery discharge, red and edematous eyelids, pinpoint subconjunctival hemorrhages, pseudomembrane (with occasional true membrane) formation on the upper and palpebral conjunctiva and palpable painful swelling of the preauricular, submandibular or submental lymph nodes are fundamental clinical signs.[12–17] In severe cases, conjunctival desiccation can initiate scarring of the palpebral and fornix conjunctiva.[17] This condition is also contagious.[9–12] In many instances, patients present with a history of contact with a person who had red eyes or an upper respiratory infection.

Pathophysiology

Viral conjunctivitis can be caused by a number of different organisms.[1–18] Most produce mild, self-limiting disease, while others have the potential to produce severe, disabling symptoms.[1-18] Viral conjunctival infections are thought to be transmitted either by airborne respiratory droplets or direct transfer from fingers to the conjunctival surface.[1-4,7-16] After an incubation period of five to 15 days, the disease enters an acute phase, during which inciting particles trigger cytokines and chemoattractants, which initiate conjunctival hyperemia, tissue edema and follicle formation.[19-21] Follicles are not just reservoirs for extracellular fluid and lymph. Conjunctiva-associated





Above: A typical presentation of diffuse conjunctival injection and red, edematous eyelids in a patient with epidemic keratoconjunctivitis.

At right: Close-up view of severe epidemic keratoconjunctivitis, with more pronounced conjunctival injection, in another patient.

lymphoid tissue (CALT) plays a key role in the protection of the ocular surface by initiating and regulating immune responses.[19]

Scattered throughout the lamina propria and consisting of components that include immunoglobulins, macrophages, dendritic cells and B-cells, conjunctival follicles enlarge when exposed to toxins, bacteria, viruses and allergens.[19] Lymphoid cells (T-cells and B-cells) migrate to these locals from other mucosal regions (mucosal associated lymphoid tissues, or MALT) when defense is required.[19]

Pharyngoconjunctival fever is commonly caused by adenovirus types 3 and 5, and occasionally by adenoviruses 4 and 7.[10] Epidemic keratoconjunctivitis is also caused by adenovirus. Of the 41 serotypes of adenovirus, 19 can produce viral conjunctivitis.[21] Types 1-11 and 19 are most common, responsible for the mildest form of EKC.[12,21] Acute hemorrhagic conjunctivitis (viral/follicular conjunctivitis with subconjunctival hemorrhage) is a variant produced by adenovirus types 19 and 37 and the picornavirus.[15,17]

Adenoviruses also have the ability to exert effects on the respiratory, genitourinary and gastrointestinal tracts.[1-3] Adenoviruses account for 5% to 10% of respiratory illnesses in children.[9,10] Adenovirus 7a has the potential to cause community epidemics via transmission through children.[10] There is evidence that adenovirus type 8 can produce a more aggressive response, resulting in extensive keratitis, subepithelial opacities, subconjunctival hemorrhage and pronounced lymphadenopathy.[21]

Subepithelial infiltrates are caused by viral antigens and lymphocytes collecting in the shallow anterior stroma, just beneath the central epithelium.[1-3,23] Confocal biomicroscopic examination provides evidence of an inflammatory response localized to the basal epithelium and anterior stroma of the central cornea.[8,23] Some EKC variants include conjunctival membrane formation. Histologically, conjunctival membranes that develop in prolonged cases consist of fibrin, leukocytes, fibroblasts, collagen deposition, elements of the innate and acquired immune response, angiogenic factors and proliferating endothelial cells.[24] Pseudomembranes are differentiated from true membranes by the ease with which they are removed, pseudomembrane being distinguished by easier removal.[15,24-26]

Membrane removal is distinguished by profuse and oozing bleeding, though pseudomembrane removal will also often cause bleeding.[24-26] In both instances, as these components accumulate they interdigitate on a cellular level with the palpebral conjunctiva. As a result, when they are stripped from the conjunctival surface, they produce trauma to the underlying membrane, resulting in bleeding.[24-26] Cicatrization may ensue following removal, leading to significant permanent mechanical alterations.[24,26] The end result is fibrosis.[24,26]

Management

Differentiating the various causes of conjunctivitis can be challenging. The Rapid Pathogen Screening Adeno Detector (AdenoPlus, Nicox) point-of-care diagnostic test uses technology based on lateral flow immunochromatography to uncover the presence of adenoviral antigens.[27,28] This test can minimize misdiagnosis. The detector works by capturing virus in the testing tool and presenting it to antigen-specific monoclonal antibodies inside the apparatus. The sample collector transfers ocular fluid 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.[27,28] 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.[23] 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.[28]

Viral conjunctivitis is contagious and self-limiting. The primary goal of management is to increase patient comfort by relieving symptoms. The secondary goal is to educate patients so as to limit spread of the condition.[21-29-31] Patients should stay home from work or school until the

discharge is eliminated.[1-3] They should be warned against sharing utensils, glasses, linens or washcloths. Medical management may range from supportive cold compress and tears to topical vasoconstrictors, topical NSAIDs and topical steroids BID to QID.[21,29-31] 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 therapy QID can be employed following the removal of the inflammatory membrane.[15,21,29-31]

Currently, no specific topical antiviral medication is recognized as an effective treatment for viral conjunctivitis.[25] Ganciclovir gel (Zirgan, Bausch + Lomb), an antiviral option used in the treatment of herpes simplex dendritic keratitis, has been used successfully to limit the course and expedite healing in these cases, though this is an off-label use.[30] Prescribed four to five times a day and then tapered to TID, alone or in combination with other therapies, the agent is gaining acceptance as an option.[30] In stubborn cases, a povidone-iodine 5% (Betadine) rinse can be offered. Here, the eye is anesthetized with a topical drop and the patient reclined. Povidone-iodine is placed into the palpebral fissure bathing the conjunctivae for 10 to 30 seconds, then rinsed away. Discomfort is common afterwards and the patient may require analgesia. Patients should be well educated and give consent to this treatment.

Researchers have also been experimenting with off-label povidone-iodine eye drops with or without an incorporated topical steroid for hastening recovery and lessening symptoms.[32,33] In the worst cases, cycloplegia can be used for comfort.

Clinical Pearls

- When patients present with what is suspected to be viral conjunctivitis, the waiting room, magazines, office equipment and instruments should be sanitized so they do not become a flashpoint for outbreak.
- Most practitioners reserve topical steroidal therapy for the severely symptomatic, those exhibiting severe SEI, decreased acuity from lacrimation or SEI on the visual axis, cases exhibiting pseudo- or true membrane formation, and cases recalcitrant to nonsteroidal management.
- Epidemic keratoconjunctivitis infiltrates typically resolve without scarring the cornea. Patients should be told to expect their condition to worsen over the first seven to 10 days with slow improvement following over a three- to six-week period.
- Steroids should be tapered slowly as the condition remits so that rebound inflammation can be avoided.
- The URI that preceded the red eye should not be discounted or ignored; consider referral to the internist.

1. Azari AA, Barney NP. Conjunctivitis: a systematic review of diagnosis and treatment. JAMA. 2013;310(16):1721-9.

2. Kaufman HE. Adenovirus advances: new diagnostic and therapeutic options. Curr Opin Ophthalmol. 2011;22(4):290-3.

3. Kinchington PR, Romanowski EG, Jerold Gordon Y. Prospects for adenovirus antivirals. J Antimicrob Chemother 2005;55(4):424–9.

4. Aoki K, Tagawa Y. A twenty-one year surveillance of adenoviral conjunctivitis in Sapporo, Japan. Int Ophthalmol Clin 2002;42(1):49–54.

5. Marangon FB, Miller D, Alfonso E. Laboratory results in ocular viral diseases: implications in clinical-laboratory correlation. Arq Bras Oftalmol 2007;70(2):189–94.

6. Lenaerts L, Naesens L. Antiviral therapy for adenovirus infections. Antiviral Res 2006;71(2-3):172–80.

7. D'Angelo LJ, Hierholzer JC, Keenlyside RA, et al. Pharyngoconjunctival fever caused by adenovirus type 4: Report of a swimming pool–related outbreak with recovery of virus from pool water. J Infect Dis 1979;140(1):42–7.

8. Harley D, Harrower B, Lyon M, et al. A primary school outbreak of pharyngoconjunctival fever caused by adenovirus type 3. Commun Dis Intell 2001 ;25(1):9–12.

9. Chen HL, Chiou SS, Hsiao HP, et al. Respiratory adenoviral infections in children: A study of hospitalized cases in southern Taiwan in 2001–2002. J Trop Pediatr 2004;50(5):279–84.

10. Mitchell LS, Taylor B, Reimels W, et al. Adenovirus 7a: A community-acquired outbreak in a children's hospital. Pediatr Infect Dis J 2000;19(10):996–1000.

11. Meyer-Rüsenberg B1, Loderstädt U, Richard G, et al. Epidemic keratoconjunctivitis: the current situation and recommendations for prevention and treatment. Dtsch Arztebl Int. 2011;108(27):475-80.

12. Schrauder A, Altmann D, Laude G, et al. Epidemic conjunctivitis in Germany, 2004. Euro Surveill 2006;11(7):185–7.

13. Uchio E, Takeuchi S, Itoh N, et al. Clinical and epidemiological features of acute follicular conjunctivitis with special reference to that caused by herpes simplex virus type 1. Br J Ophthalmol 2000;84(9):968–72.

14. Ozturk HE, Sonmez B, Beden U. Corneal sensitivity may decrease in adenoviral epidemic keratoconjunctivitis--a confocal microscopic study. Eye Contact Lens. 2013;39(4):264-8.

15. Murrah WF. Epidemic keratoconjunctivitis. Ann Ophthalmol 1988;20(1):36–8.

16. Janićijević-Petrović MA, Srećković S, Petrović N, Sarenac T. Epidemic keratoconjunctivitis. Srp Arh Celok Lek. 2011;139(5-6):282-5.

17. Karki DB, Shrestha CD, Shrestha S. Acute haemorrhagic conjunctivitis: An epidemic in August/September 2003. Kathmandu Univ Med J (KUMJ) 2003;1(4):234–6.

18. Chang CH, Sheu MM, Lin KH, et al. Hemorrhagic viral keratoconjunctivitis in Taiwan caused by adenovirus types 19 and 37: Applicability of polymerase chain reaction-restriction fragment length polymorphism in detecting adenovirus genotypes. Cornea 2001;20(3):295–300.

19. Steven P, Gebert A. Conjunctiva-associated lymphoid tissue - current knowledge, animal models and experimental prospects. Ophthalmic Res. 2009;42(1):2-8.

20. Kaneko H, Kondo T, Fujiwara T, et al. Clinical and virological studies of nosocomial conjunctivitis infection caused by adenovirus type 37 variant. Nippon Ganka Gakkai Zasshi 2005;109(8):489–96.

21. Rubenstein JB, Virasch V. Allergic conjunctivitis. In: Yanoff M, Duker JS. Ophthalmology. Mosby-Elsevier, St. Loius, MO 2009:237-240.

22. Chang C, Sheu M, Chern C, et al. Epidemic keratoconjunctivitis caused by a new genotype of adenovirus type 8 (Ad8)—a chronological review of Ad8 in Southern Taiwan. Jpn J Ophthalmol 2001;45(2):160–6.

23. Alsuhaibani AH, Sutphin JE, Wagoner MD. Confocal microscopy of subepithelial infiltrates occurring after epidemic keratoconjunctivitis. Cornea 2006;25(9):1102–4.

24. Chintakuntlawar AV1, Chodosh J. Cellular and tissue architecture of conjunctival membranes in epidemic keratoconjunctivitis. Ocul Immunol Inflamm. 2010;18(5):341-5.

25. Rashid S, Dana MR. Cicatrizing and autoimmune diseases. Chem Immunol Allergy 2007;92:195–202.

26. Uchio E. New medical treatment for viral conjunctivitis. Nippon Ganka Gakkai Zasshi 2005;109(12):962–84.

27. Rapid pathogen screening. Point-of-Care Diagnostic Services Adeno Detector instructional insert. RPS Insert 2006:1–2.

28. Sambursky R1, Trattler W, Tauber S, et al. Sensitivity and specificity of the AdenoPlus test for diagnosing adenoviral conjunctivitis. JAMA Ophthalmol. 2013;131(1):17-22.

29. Wilkins MR, Khan S, Bunce C, et al. A randomised placebo-controlled trial of topical steroid in presumed viral conjunctivitis. Br J Ophthalmol. 2011;95(9):1299-1303.

30. Yabiku ST, Yabiku MM, Bottós KM, et al. Ganciclovir 0.15% ophthalmic gel in the treatment of adenovirus keratoconjunctivitis. Arq Bras Oftalmol. 2011;74(6):417-21.

31. Skevaki CL, Galani IE, Pararas MV,et al. Treatment of viral conjunctivitis with antiviral drugs. Drugs. 2011;71(3):331-47.

32. Trinavarat A1, Atchaneeyasakul LO. Treatment of epidemic keratoconjunctivitis with 2% povidone-iodine: a pilot study. J Ocul Pharmacol Ther. 2012;28(1):53-8.

33. Pelletier JS1, Stewart K, Trattler W, et al. A combination povidone-iodine 0.4%/dexamethasone 0.1% ophthalmic suspension in the treatment of adenoviral conjunctivitis. Adv Ther. 2009;26(8):776-83.

FUCHS' ENDOTHELIAL CORNEAL DYSTROPHY

Signs and Symptoms

First described by Austrian ophthalmologist Ernst Fuchs in 1910, the endothelial disorder that bears his name is a bilateral—though often asymmetric—condition, and relatively common in older adults.[1,2] While it may occasionally be diagnosed earlier based upon biomicroscopic findings, Fuchs' dystrophy is rarely symptomatic before 50 years of age. Patients typically present 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, hyperreflective 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 men, by a ratio of about 3:1.[2] A variety of ocular conditions have been postulated to occur in association with Fuchs' dystrophy as well, including hypermetropia and shallow anterior chambers, open-angle glaucoma, keratoconus and age-related macular degeneration.[3-10] None of these associations has been conclusively proven, however.

Pathophysiology

Fuchs' dystrophy stems from a primary malfunction of the corneal endothelium, which is likely inherited via an autosomal dominant mechanism with incomplete penetrance.[11,12] This leads to widespread loss of endothelial cells and subsequent disruption of the endothelial pump mechanisms, which are responsible for maintaining normal stromal hydration.[13] The consequence is an excessive influx of aqueous fluid, leading to corneal stromal edema and a physiologically and optically compromised tissue.

Corneal guttae are the hallmark of Fuchs' dystrophy.

The clinical and histopathological progression of Fuchs' dystrophy has been well described in numerous prior publications. A clinical staging scheme was proposed many years ago, and is now widely accepted; usually, these stages span a period from 10 to 20 years.[2,14,15]

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 coalescence of the guttae with a resultant 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' endothelial 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, symptoms that can be significantly exacerbated when the bullae rupture.[2] 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.[15] The corneal bullae dissipate at this point, as do the painful episodes experienced by patients. Unfortunately, profound vision loss accompanies the scarring.

Management

Treatment of Fuchs' endothelial dystrophy varies depending upon the severity of the disease. Patients with early stromal and/or epithelial edema may be treated conservatively with sodium chloride 5% solution throughout the day (e.g., Muro 128 every two to six hours) and sodium chloride 5% ointment overnight. These hypertonic agents serve to diminish corneal edema and improve vision.

Another historical noninvasive measure intended to deturgesce the cornea involves the use of a hair dryer, held at arm's length and directed toward the eyes.[14] Drying the cornea for five to 10 minutes upon waking may improve vision for some time, although caution should be taken not to burn the eye.

As patients become more symptomatic with regard to pain and/or reduced vision, additional treatment options may be employed. Topical nonsteroidal anti-inflammatory drugs (NSAIDs, e.g., Acuvail, 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.[16]

Historically, ocular hypotensive agents have been advocated for those with Fuchs' dystrophy, even for those patients in whom intraocular pressure is within normal limits.[17] It is hypothesized that by reducing the anterior chamber fluid volume, stress on the endothelial pump mechanisms is decreased, and this subsequently helps to diminish corneal edema; unfortunately, there are no conclusive, prospective studies to support this position to date. Additionally, one class of ocular hypotensives that should specifically be avoided in patients with Fuchs' dystrophy is the carbonic anhydrase inhibitors (i.e., dorzolamide, brinzolamide, acetazolamide), as these may actually disrupt the endothelial Na-K-ATPase pump.[18]

Therapeutic (bandage) soft contact lenses may also serve to alleviate patient discomfort in cases of advanced Fuchs' dystrophy. A flatly fit, high-water content lens helps to mask the irregular astigmatism and diminish pain associated with epithelial bullae.[13,17] Silicone hydrogel lenses have also been used in this capacity with some success.[19]

Despite medical treatment, most patients with Fuchs' dystrophy will ultimately require surgical intervention.[20] Until about 15 years ago, penetrating keratoplasty was the procedure of choice; however, with the advent of deep lamellar keratoplasty, patients now have a surgical option that is less invasive and painful, necessitates a shorter recovery time, and results in fewer instances of rejection.[21] In Descemet's membrane endothelial keratoplasty (DMEK) or Descemet's stripping endothelial keratoplasty (DSEK)/ Descemet's stripping automated endothelial keratoplasty (DSAEK), only the posterior aspect of the cornea is removed and replaced with donor tissue in an effort to restore a functional endothelial layer.

DMEK may offer better vision and may indeed become the preferred surgical procedure, but currently this extremely thin donor tissue is very fragile and difficult to handle. Consequently, the currently favored surgical technique is DSEK, which selectively peels away approximately 150µm (about 25%) of the posterior stroma, including Descemet's membrane and the endothelium.[22] The donor button of posterior stroma, Descemet's membrane and endothelium are then implanted.[23] DSEK has the advantage of a smaller, potentially self-sealing incision, a smoother recipient interface for the donor tissue and a more rapid rate of visual recovery than penetrating keratoplasty.[22]

Clinical Pearls

- The presence of excessive central guttae in the absence of corneal edema is commonly referred to as *endothelial cell dystrophy*.[13] This condition 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 entities are known as *Hassall–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 lubricant uses high colloidal density rather than osmotic pressure from salts to address epithelial edema. It also 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 in this condition.[24]

1. Eghrari AO, Gottsch JD. Fuchs' corneal dystrophy. Expert Rev Ophthalmol. 2010;5(2):147-159.

2. Elhalis H, Azizi B, Jurkunas UV. Fuchs endothelial corneal dystrophy. Ocul Surf. 2010;8(4):173-84.

3. Buxton JN, Preston RW, Riechers R, Guilbault N. Tonography in cornea guttata. A preliminary report. Arch Ophthalmol. 1967;77(5):602-3.

4. Pitts JF, Jay JL. The association of Fuchs's corneal endothelial dystrophy with axial hypermetropia, shallow anterior chamber, and angle closure glaucoma. Br J Ophthalmol. 1990;74(10):601-4.

5. Loewenstein A, Geyer O, Hourvitz D, Lazar M. The association of Fuch's corneal endothelial dystrophy with angle closure glaucoma. Br J Ophthalmol. 1991;75(8):510.

6. Lipman RM, Rubenstein JB, Torczynski E. Keratoconus and Fuchs' corneal endothelial dystrophy in a patient and her family. Arch Ophthalmol. 1990;108(7):993-4.

7. Orlin SE, Raber IM, Eagle RC Jr, Scheie HG. Keratoconus associated with corneal endothelial dystrophy. Cornea. 1990;9(4):299-304.

8. Jurkunas U, Azar DT. Potential complications of ocular surgery in patients with coexistent keratoconus and Fuchs' endothelial dystrophy. Ophthalmology. 2006;113(12):2187-97.

9. Rao GP, Kaye SB, Agius-Fernandez A. Central corneal endothelial guttae and age-related macular degeneration: is there an association? Indian J Ophthalmol. 1998;46(3):145-7.

10. Ali ZK, Whitson JT, Mootha VV, et al. Glaucoma in patients with corneal endothelial dystrophy. Eye Contact Lens. 2011;37(6):332-6.

11. Sundin OH, Jun AS, Broman KW, et al. Linkage of late-onset Fuchs corneal dystrophy to a novel locus at 13pTel-13q12.13. Invest Ophthalmol Vis Sci. 2006;47(1):140-5.

12. Sundin OH, Broman KW, Chang HH, Vito EC, Stark WJ, Gottsch JD. A common locus for late onset Fuchs corneal dystrophy maps to 18q21.2-q21.32. Invest Ophthalmol Vis Sci. 2006;47(9):3919-26.

13. Seitzman GD. Cataract surgery in Fuchs' dystrophy. Curr Opin Ophthalmol. 2005;16(4):241-5.

14. Adamis AP, Filatov V, Tripathi BJ, Tripathi RC. Fuchs' endothelial dystrophy of the cornea. Surv Ophthalmol. 1993;38(2):149-68.

15. Waring GO 3rd, Bourne WM, Edelhauser HF, Kenyon KR. The corneal endothelium. Normal and pathologic structure and function. Ophthalmology. 1982;89(6):531-90.

16. Asai T, Nakagami T, Mochizuki M, et al. Three cases of corneal melting after instillation of a new nonsteroidal anti-inflammatory drug. Cornea. 2006;25(2):224-7.

17. Borboli S, Colby K. Mechanisms of disease: Fuchs' endothelial dystrophy. Ophthalmol Clin North Am. 2002;15(1):17-25.

18. Egan CA, Hodge DO, McLaren JW, Bourne WM. Effect of dorzolamide on corneal endothelial function in normal human eyes. Invest Ophthalmol Vis Sci. 1998;39(1):23-9.

19. Kanpolat A, Ucakhan OO. Therapeutic use of Focus Night & Day contact lenses. Cornea. 2003;22(8):726-34.

20. Afshari NA, Pittard AB, Siddiqui A, Klintworth GK. Clinical study of Fuchs corneal endothelial dystrophy leading to penetrating keratoplasty: a 30-year experience. Arch Ophthalmol. 2006;124(6):777-80.

21. Price MO, Price FW. Descemet's stripping endothelial keratoplasty. Curr Opin Ophthalmol. 2007;18(4):290-4.

22. Nanavaty MA, Wang X, Shortt AJ. Endothelial keratoplasty versus penetrating keratoplasty for Fuchs endothelial dystrophy. Cochrane Database Syst Rev. 2014;(2):CD008420.

23. Price FW, Jr, Price MO. Descemet's stripping with endothelial keratoplasty in 50 eyes: A refractive neutral corneal transplant. J Refract Surg. 2005;21(4):339-45.

24. Wilson SE, Bourne WM, Brubaker RF. Effect of dexamethasone on corneal endothelial function in Fuchs' dystrophy. Invest Ophthalmol Vis Sci. 1988;29(3):357-61.

HERPES SIMPLEX VIRUS EPITHELIAL KERATITIS

Signs and Symptoms

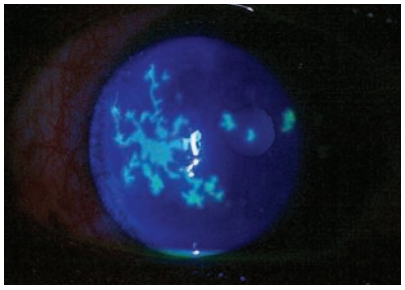
The herpes simplex virus (HSV) is a common pathogen in developed regions of the world and a frequent source of ocular infection. Nearly 60% of the American population is seropositive for HSV-1 and another 17% is seropositive for HSV-2.[1] Initial ocular infection by HSV tends to be seen in younger patients, with an approximate average age of 24 years.[1,2]

Recurrence of the HSV infection may occur at any age and while the Recurrence Factor Study (RFS) of the Herpetic Eye Disease Study (HEDS) II did not conclude any specific trigger factors to be associated with the development of signs and symptoms, other reports in the literature have identified causative factors, which 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.[3-7] There is no recognized racial or gender predilection in HSV keratitis.[1]

Epithelial keratitis is actually the second most common ocular manifestation of HSV; in a series of patients with herpetic ocular infection, epithelial keratitis was encountered in 12.2% overall, while stromal keratitis was noted in 25.4%.[8,9]

HSV epithelial keratitis typically presents as a unilateral red eye with a variable degree of pain or irritation. Associated photophobia and epiphora are common. Vision may or may not be affected, depending upon the location and extent of the corneal lesion. Bilateral HSV keratitis may be encountered in a small percentage of cases, though it is more common in children and those with immune or atopic disease.[10,11]

The hallmark finding in HSV keratitis involves a dendritic ulceration of the corneal epithelium, which may be accompanied by a stromal keratitis in more severe presentations. These lesions often begin as a nondescript, punctate keratopathy but quickly coalesce to form the familiar branching patterns (arborizing, dendritic) that stain brightly with sodium fluorescein dye. Also, because



A classic dendritiform lesion seen in herpes simplex epithelial keratitis.

the virus invades and compromises the epithelial cells surrounding the ulcer, the leading edges (the so-called "terminal end-bulbs") tend to exhibit staining with rose bengal and/or lissamine green dye. Secondary anterior uveitis is often encountered with the keratitis, particularly when treatment is delayed.[9] Other epithelial manifestations include geographic ulcers and marginal ulcers.

Rarely, a vesicular skin rash affecting the ocular adnexa or a follicular conjunctivitis may accompany the epithelial keratitis, although these findings are more typical of the initial, primary infection and less common with recurrent HSV.[9] One initial non-ocular manifestation that is seen is a vesicular papillomacular rash that sometimes affects the skin of the lids but more commonly results in a "fever blister" or "cold sore" in or around the mouth; this is referred to as *herpes labialis*.

Pathophysiology

HSV keratitis can be caused by either Type-1 or Type-2 herpes simplex. Infection by HSV-1 predominantly affects the upper half of the body (e.g., eyes and mouth) whereas HSV-2 is mainly associated with diseases of the lower half of the body (e.g., genitalia and perianal region).[12] The virus is transmitted via bodily fluids and affects the skin and mucous membranes of the infected host.[1] Primary herpetic infections are generally encountered in children and young adults.[1,2]

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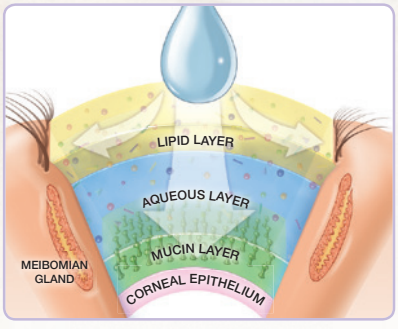

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References: 1. Akpek EK, Smith RA. Overview of age-related ocular conditions. *Am J Manag Care.* 2013;19 (5 suppl):S67-S75. **2.** Korb DR, Blackie CA, Meadows DL, Christensen M, Tudor M. Evaluation of extended tear stability by two emulsion based artificial tears. Poster presented at: 6th International Conference on the Tear Film and Ocular Surface: Basic Science and Clinical Relevance; September 22-25, 2010; Florence, Italy.

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HSV is a pathogen that establishes what is known as a lytic and latent infection.[13] Reactivation from latency occurs intermittently and chronically, serving as a life-long source of recurrent infection. In this complex process, HSV has the capability of simultaneously triggering and neutralizing innate immunity, creating a dynamic equilibrium between the virus and the innate immune system; when the immune system prevails, the signs and symptoms are negligible. When the virus prevails, more substantial signs and symptoms ensue.[13]

After resolution of the initial infection, the herpes virus migrates along local nerves to regional ganglia and remains dormant until reactivated by specific stimuli.[14] On average, patients experience recurrences at a rate of 0.6 episodes per year.[15] HSV infection can affect any of the three branches (ophthalmic, maxillary, mandibular) of the trigeminal nerve (cranial nerve V). This can then lead to latency in the trigeminal ganglion. While it is traditionally thought that reactivation spreads down the nerve axon from the ganglion to the corneal epithelium, interneuronal spread of the virus within the ganglion can cause ocular disease (epithelial keratitis) without primary infection in the cornea.

While many of the ocular manifestations related to HSV are immune (e.g., delayed hypersensitivity reaction) or inflammatory in nature (e.g., stromal and disciform keratitis, iridocyclitis), epithelial keratitis represents infection by live virus.[16,17] Cytokines characteristic of Th1 cells (in particular IFN-γ and IL-2) have been shown to dominate in HSV keratitis in addition to mechanisms by nonspecific, antigen-independent effector cells such as neutrophils, basophils and monocytes. More recently, the migration and maturation of dendritic cells within the corneal stroma of patients with HSV keratitis have been recognized as contributors to recurrent disease, suggesting a role for delayed type hypersensitivity in the immunopathogenesis of HSV keratitis.[17]

Viral replication in most cases is confined to the corneal epithelium, with stromal invasion impeded by early responding nonspecific defense mechanisms.[13,17] These are rapidly complemented by the specific, mainly cellular, immune response.[13,17,18] As the epithelial cells die, a dendritic ulcerative keratitis results. After several recurrences, the corneal stroma may become involved.[16,17] Disciform stromal scarring, conjunctivitis and uveitis are natural sequelae to the corneal inflammation.[17]

Management

HSV epithelial keratitis must be managed quickly and aggressively to prevent penetration into deeper corneal tissues with subsequent scarring and vision loss. The treatment of choice consists of topical and oral antiviral therapies. For over 30 years, the only readily available topical treatment for this condition has been trifluridine 1% ophthalmic solution (Viroptic, Monarch Pharmaceuticals). In most instances, the initial dosage of trifluridine is one drop every two hours up to nine times daily for HSV epithelial keratitis; as regression of the dendrites ensues, the dosage may be tapered to Q3-4H until complete resolution is seen, over a period of seven to 10 days.[19,20]

More recently, ganciclovir 0.15% ophthalmic gel (Zirgan, Bausch + Lomb) has emerged as an alternative to trifluridine; the advantage of this medication is less frequent initial dosing at just five times daily (approximately every three hours while awake) until the corneal ulcer heals, and then three times per day for another seven days. Additionally, ganciclovir demonstrates greatly reduced corneal toxicity as compared to trifluridine, primarily because it is only taken up by virus-infected cells.[16,21,22] Gentle debridement of the ulcer bed to remove active viral particles has been advocated as an adjunctive therapy to topical antiviral agents, as it may hasten the speed of resolution.[19] Cycloplegia (homatropine 2% TID-QID or even atropine 1% BID) may be initiated, depending upon the severity of the uveitic response and the patient's subjective discomfort.

Oral antiviral agents can also effectively treat HSV epithelial keratitis, and may be used in a variety of scenarios.[23-25] Oral medications should be considered in patients who lack the dexterity to independently instill eye drops with regular frequency, where there is a history of toxicity or other adverse response to topical antiviral therapy, or where the topical preparations are cost prohibitive. The oral antiviral agents work because they are able to generate pharmacotherapeutic levels in the tears. Options for managing HSV epithelial keratitis include acyclovir 200mg to 400mg five times daily, valacyclovir 500mg three times daily or famciclovir 250mg to 500mg two to three times daily for 21 days; of these, generic acyclovir is typically the least expensive.

The Acyclovir Prevention Trial (APT of the HEDS II) demonstrated that oral antiviral medications may further serve a preventative role by reducing the frequency and severity of recurrent infective outbreaks.[26,27] Acyclovir 400mg BID is the most commonly used regimen for prophylactic suppression, but valacyclovir 500mg once daily may be used for those who are intolerant of acyclovir.[28]

It is well established that the herpes simplex virus replicates more rapidly in the presence of certain immunosuppressive agents, hence worsening the course of the disease. Indeed, reports of corticosteroids exacerbating HSV ocular infections date back 50 years or more.[29] For this reason, topical steroids are generally considered a contraindication when managing active HSV epithelial keratitis. However, the Stromal Keratitis Not on Steroids (SKN) arm of HEDS I demonstrated that judicious topical steroid use can be a beneficial adjunct

when used under the umbrella of topical or oral antiviral agents, following several days of effective antiviral therapy; this is particularly true in cases of associated stromal inflammation.[30,31]

When managed appropriately, HSV epithelial keratitis resolves without scarring, although there is potential for subtle epithelial irregularities and progressive corneal hypoaesthesia with recurrent attacks.[32] Should stromal keratitis develop secondary to the epitheliopathy, the potential for corneal opacification increases dramatically. Penetrating or lamellar keratoplasty may be indicated in such cases.[33,34]

It should be noted that while treatment of this condition is often straightforward when identified and managed early, HSV remains the most common infectious cause of unilateral blindness in the developed world.[35]

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) must make the practitioner suspicious for HSV keratitis, particularly if the individual has a previous history of similar infections.
- Recurrent episodes induce greater damage to the corneal nerves, leading to hypoesthesia. The cotton-wisp test used for measuring corneal sensitivity is positive in cases of HSV keratitis when one cornea is less sensitive to the touch of the wisp then the other. It should be used whenever HSV is suspected.
- Consider a history of prolonged sun exposure or extreme psychological stress to be significant in diagnosing HSV epithelial keratitis.
- The majority of adverse steroid-related outcomes in HSV epithelial keratitis have arisen from improper diagnosis where topical steroid (alone or in combination) 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. 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 or a neurotrophic keratopathy.
- Not every case of HSV epithelial keratitis manifests in a classic dendritic appearance, especially early in the disease course. Factors such as duration since onset, medication use, atopic disease or a history of corneal transplantation can significantly alter the presentation. Always consider HSV in the differential of atypical or unusual epitheliopathies.
- At the initial presentation of HSV epithelial keratitis, we educate patients about the role of long-term suppressive therapy with low-dose oral acyclovir and give the patient this option. At the second outbreak, we more strongly recommend ongoing suppressive therapy.

1. Farooq AV, Shukla D. Herpes simplex epithelial and stromal keratitis: an epidemiologic update. Surv Ophthalmol. 2012;57(5):448-62.

2. Uchio E, Hatano H, Mitsui K, et al. A retrospective study of herpes simplex keratitis over the last 30 years. Jpn J Ophthalmol. 1994;38(2):196-201.

3. Shtein RM, Stahl RM, Saxe SJ, et al. Herpes simplex keratitis after intravitreal triamcinolone acetonide. Cornea. 2007;26(5):641-2.

4. Barequet IS, Wasserzug Y. Herpes simplex keratitis after cataract surgery. Cornea. 2007;26(5):615-7.

5. Miyajima S, Sano Y, Sotozono C, et al. Herpes simplex keratitis after ophthalmic surgery. Nippon Ganka Gakkai Zasshi. 2003;107(9):538-42.

6. Rezende RA, Uchoa UB, Raber IM, et al. New onset of herpes simplex virus epithelial keratitis after penetrating keratoplasty. Am J Ophthalmol. 2004;137(3):415-9.

7. Dios Castro E , Maquet Dusart JA . Latanoprost-associated recurrent herpes simplex keratitis. Arch Soc Esp Oftalmol. 2000;75(11):775-778.

8. Xu F, Sternberg MR, Kottiri BJ, et al. Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. JAMA. 2006;296(8):964-73.

9. Miserocchi E, Fogliato G, Bianchi I, et al. Clinical Features of Ocular Herpetic Infection in an Italian Referral Center. Cornea. 2014 Jun;33(6):565-70.

10. Chong EM, Wilhelmus KR, Matoba AY, et al. Herpes simplex virus keratitis in children. Am J Ophthalmol. 2004;138(3):474-5.

11. Souza PM, Holland EJ, Huang AJ. Bilateral herpetic keratoconjunctivitis. Ophthalmology. 2003;110(3):493-6.

12. Garweg JG, Halberstadt M. The pathogenesis of herpetic keratitis. Klin Monatsbl Augenheilkd. 2002; 219(7):477-86.

13. Ma Y, He B. Recognition of herpes simplex viruses: toll-like receptors and beyond. J Mol Biol. 2014 Mar 20;426(6):1133-47.

14. Saini JS, Agarwala R. Clinical pattern of recurrent herpes simplex keratitis. Indian J Ophthalmol. 1999;47(1):11-4.

15. Rowe AM, St Leger AJ, Jeon S, et al. Herpes keratitis. Prog Retin Eye Res. 2013;32(1):88-101.

16. Sahin A, Hamrah P. Acute Herpetic Keratitis: What is the Role for Ganciclovir Ophthalmic Gel? Ophthalmol Eye Dis. 2012;4:23-34.

17. Hawthorne KM, Dana R, Chodosh J. Delayed type hypersensitivity in the pathogenesis of recurrent herpes stromal keratitis. Semin Ophthalmol. 2011;26(4-5):246-50.

18. Garweg JG, Halberstadt M. The pathogenesis of herpetic keratitis. Klin Monatsbl Augenheilkd. 2002; 219(7):477-86.

19. Wilhelmus KR. Therapeutic interventions for herpes simplex virus epithelial keratitis. Cochrane Database Syst Rev. 2007;24(1):CD002898.

20. Labetoulle M. The latest in herpes simplex keratitis therapy. J Fr Ophtalmol. 2004;27(5):547-57.

21. Matthews T, Boehme R. Antiviral activity and mechanism of action of ganciclovir. Rev Infect Dis. 1988;10 Suppl 3:S490-4.

22. Croxtall JD. Ganciclovir ophthalmic gel 0.15%: in acute herpetic keratitis (dendritic ulcers). Drugs. 2011;71(5):603-10.

23. Higaki S, Itahashi M, Deai T, et al. Effect of oral valaciclovir on herpetic keratitis. Cornea. 2006;25(10 Suppl 1):S64-7.

24. Sozen E, Avunduk AM, Akyol N. Comparison of efficacy of oral valacyclovir and topical acyclovir in the treatment of herpes simplex keratitis: a randomized clinical trial. Chemotherapy. 2006;52(1):29-31.

25. Wilhelmus KR. Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis. Cochrane Database Syst Rev. 2010;(12):CD002898.

26. Herpetic Eye Disease Study Group. Oral acyclovir for herpes simplex virus eye disease: effect on prevention of epithelial keratitis and stromal keratitis. Arch Ophthalmol. 2000;118(8):1030-6.

27. Langston DP. Oral acyclovir suppresses recurrent epithelial and stromal herpes simplex. Arch Ophthalmol. 1999;117(3):391-2.

28. Miserocchi E, Modorati G, Galli L, Rama P. Efficacy of valacyclovir vs acyclovir for the prevention of recurrent herpes simplex virus eye disease: a pilot study. Am J Ophthalmol. 2007;144(4):547-51.

29. Crompton DO. Corticosteroids exacerbate ocular herpes simplex. Med J Aust. 1964;2(12):950-4.

30. Barker NH. Ocular herpes simplex. Clin Evid. 2006;(15):917-23.

31. Knickelbein JE, Hendricks RL, Charukamnoetkanok P. Management of herpes simplex virus stromal keratitis: an evidence-based review. Surv Ophthalmol. 2009;54(2):226-34.

32. Hamrah P, Sahin A, Dastjerdi MH, et al. Cellular changes of the corneal epithelium and stroma in herpes simplex keratitis: an in vivo confocal microscopy study. Ophthalmology. 2012;119(9):1791-7.

33. Li J, Ma H, Zhao Z, et al. Deep anterior lamellar keratoplasty using precut anterior lamellar cap for herpes simplex keratitis: a long-term follow-up study. Br J Ophthalmol. 2014;98(4):448-53.

34. Wu SQ, Zhou P, Zhang B, et al. Long-term comparison of full-bed deep lamellar keratoplasty with penetrating keratoplasty in treating corneal leucoma caused by herpes simplex keratitis. Am J Ophthalmol. 2012;153(2):291-299.e2.

35. Pepose J, Keadle T, Morrison L. Ocular herpes simplex: changing epidemiology, emerging disease patterns, and the potential of vaccine prevention and therapy. Am J Ophthalmol. 2006;141(3):547-57.

MOOREN'S ULCER

Signs and Symptoms

Mooren's ulcer represents an idiopathic, inflammatory, marginal or peripheral ulceration of the cornea. There are two recognized presentations, which were initially described by Wood and Kaufman in 1971.[1] The first of these is the typical or benign type, which tends to be unilateral, mild to moderate with regard to symptoms, and more commonly seen in elderly Caucasian individuals. The second variety is atypical or malignant, and tends to be bilateral in 75% of patients, progressive and more severe in terms of presentation and symptomology; it is encountered more frequently in younger patients and those of African descent.[2,3] Overall, the condition is slightly more common in men than in women.[4]

Patients with Mooren's ulcer typically present with variable levels of discomfort, ranging from foreign body sensation to excruciating and incapacitating pain. Photophobia is also common. On presentation, the involved eye will display hyperemia, tearing and blepharospasm in more severe cases. Vision may be impacted in association with progression of the ulcer toward the visual axis, or from the development of secondary astigmatism.

Biomicroscopically, Mooren's ulcer begins with patchy, peripheral stromal infiltrates, usually affecting the nasal or temporal cornea.[5] Eventually these infiltrates will coalesce, with subsequent dehiscence of the overlying epithelium. Ultimately, the condition progresses to involve active thinning of the anterior third to half of the stroma, often inferiorly and extending to the limbus. It is not uncommon to see quiescent regions adjacent to active, inflamed areas.

A classic finding in Mooren's ulcer is a steep, overhanging edge to the lesion, which is quite characteristic of the disease.[6] Associated findings may include anterior uveitis, hypopyon, glaucoma and cataract in extreme instances.[7] The greatest associated risk in Mooren's ulcer is progression to corneal perforation, which can result from minor trauma and occurs in up to 36% of cases.[7]

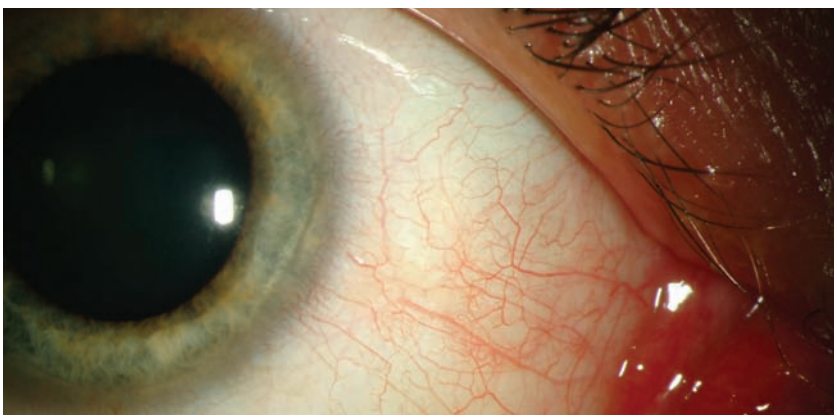
Pathophysiology

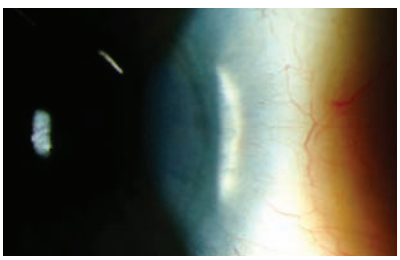
The precise etiology of Mooren's ulcer is unknown; however, genetic and environmental factors for the disease have been proposed.[6] Suggested environmental causes include an antecedent history of trauma or surgery as well as exposure to viral and parasitic infections, including helminthiasis. Human leukocyte antigens (HLAs) may also confer susceptibility to Mooren's ulcer.[8-10]

Whatever the basis, it is widely held that Mooren's ulcer is an autoimmune disease that solely impacts the cornea, without expression in other tissues of the body.[11] This is in direct contrast to the condition we know clinically as *peripheral ulcerative keratitis*, which is associated with systemic disease in the vast majority of cases, including such disorders as rheumatoid arthritis, granulomatosis with polyangiitis (i.e., Wegener's granulomatosis), polyarteritis nodosa, relapsing polychondritis, systemic lupus erythematosus, hepatitis and syphilis.[12]

Management

Therapy for Mooren's ulcer generally follows a stepladder approach, moving from less to more invasive based upon the severity of the condition. The goal is to arrest the inflammation and ulcerative process, thereby helping to facilitate corneal reepithelialization. In most cases, topical corticosteroids (e.g., difluprednate 0.05% Q2H-QID) are employed early, along with strong cycloplegia (e.g., scopolamine 0.25% BID-TID) and antibiotic prophylaxis (e.g., besifloxacin 0.6% TID). Additional topical therapies that have been attempted with modest success include cyclosporine 1% drops and acetylcysteine 10%.[6,13] Artificial tears and bandage contact lenses may be helpful as a supportive therapy to





Above: A 43-year-old male with Mooren's ulcer secondary to Lyme disease.

At left: The same patient one month after treatment with Lotemax and doxycycline.

(Both images courtesy of Christine Sindt, OD, University of Iowa Carver College of Medicine.)

further reduce discomfort and promote healing. In cases where topical steroids are contraindicated or ineffective after seven to 10 days, oral pulse therapy (e.g., prednisone 60mg to 100mg daily) may be attempted.

Should the condition be recalcitrant to topical and oral therapy, however—which is often the case—surgical excision of the perilimbal conjunctiva and episclera is indicated.[2,6] This helps to eliminate the inflammatory impetus, which is believed to stem from the vasculature located at the corneal margin. In more severe cases or in those with impending corneal perforation, lamellar keratoplasty may be required.[6] The use of amniotic membrane transplantation in patients with Mooren's ulcer has shown mixed results.[11,14,15] A variety of other systemic immunomodulatory therapies have also been documented in association with surgical therapy, including oral cyclosporine, methotrexate, interferon alpha-2b, infliximab and adalimumab.[6,16-20]

Clinical Pearls

• Mooren's ulcer is considered by some to be an idiopathic form of peripheral ulcerative keratitis, and in fact, the two may be clinically indistinguishable. A careful history is required in order to differentiate these conditions. In acute cases presenting without a known systemic history, medical testing is indicated to identify or rule out any associated systemic disorders.

• Likewise, Mooren's ulcer must be differentiated from other forms of progressive, peripheral corneal thinning, such as Terrien's marginal degeneration or pellucid marginal degeneration. Aside from having different courses and etiologies, the primary distinction between these entities and Mooren's ulcer is that the degenerations are characteristically painless and bilateral, whereas Mooren's is typically painful and often unilateral.

• Before initiating any topical therapy for presumed Mooren's ulcer, first be sure to rule out perforation. Should a Seidel test reveal leakage of aqueous from the wound indicating perforation, immediate referral to a board-certified cornea specialist is in order. Some might even argue that, since surgical intervention is virtually inevitable, all cases of suspected Mooren's ulcer should be referred to a corneal surgeon.

1. Wood TO, Kaufman HE: Mooren's ulcer. Am J Ophthalmol 1971;71(1 Pt 2):417-22.

2. Cellini M, Fresina M, Strobbe E, et al. Corneoscleral graft in Mooren's ulcer: a case report. Cases J. 2009;2:180.

3. Chow CY, Foster CS. Mooren's ulcer. Int Ophthalmol Clin. 1996;36(1):1-13.

4. Tuft S. Mooren's Ulcer. In: Johnson GJ, Minassian DC, Weale RA, West SK, eds. Epidemiology of Eye Disease, 2nd edition. London:Arnold, 2003. 209-11.

5. Kanski JJ. Clinical Ophthalmology: A Systematic Approach, 5th Edition. Philadelphia:Butterworth-Heinemann, 2003. 117-9.

6. Alhassan MB, Rabiu M, Agbabiaka IO. Interventions for Mooren's ulcer. Cochrane Database Syst Rev. 2014;(1):CD006131.

7. Sangwan VS, Zafirakis P, Foster CS. Mooren's ulcer: current concepts in management. Indian J Ophthalmol. 1997;45(1):7-17.

8. Zhao JC, Jin XY. Immunological analysis and treatment of Mooren's ulcer with cyclosporin A applied topically. Cornea 1993;12(6):481-8.

9. Taylor CJ, Smith SI, Morgan CH, et al. HLA and Mooren's ulceration. Br J Ophthalmol. 2000;84(1):72-5.

10. Zelefsky JR, Taylor CJ, Srinivasan M, et al. HLA-DR17 and Mooren's ulcer in South India. Br J Ophthalmol. 2008;92(2):179-81.

11. Schallenberg M, Westekemper H, Steuhl KP, Meller D. Amniotic membrane transplantation ineffective as additional therapy in patients with aggressive Mooren's ulcer. BMC Ophthalmol. 2013;13:81.

12. Galor A, Thorne JE. Scleritis and peripheral ulcerative keratitis. Rheum Dis Clin North Am. 2007;33(4):835-54, vii.

13. Zhao JC, Jin XY. Immunological analysis and treatment of Mooren's ulcer with cyclosporin A applied topically. Cornea. 1993;12(6):481-8.

14. Ngan ND, Chau HT. Amniotic membrane transplantation for Mooren's ulcer. Clin Experiment Ophthalmol. 2011;39(5):386-92.

15. Chen KH, Hsu WM, Liang CK. Relapsing Mooren's ulcer after amniotic membrane transplantation combined with conjunctival autografting. Ophthalmology. 2004;111(4):792-5.

16. Stammen J, Althaus C, Sundmacher R. Mooren ulcer. 4 severe bilateral disease courses with systemic cyclosporin A therapy. Klin Monbl Augenheilkd. 1997;211(5):306-11.

17. Wilson SE, Lee WM, Murakami C, et al. Mooren-type hepatitis C virus-associated corneal ulceration. Ophthalmology. 1994;101(4):736-45.

18. Fontana L, Parente G, Neri P, et al. Favourable response to infliximab in a case of bilateral refractory Mooren's ulcer. Clin Experiment Ophthalmol. 2007;35(9):871-3.

19. Saw VP, Cornelius N, Salama AD, et al. Infliximab therapy for aggressive mooren ulceration. Arch Ophthalmol. 2008;126(5):734.

20. Ashar JN, Mathur A, Sangwan VS. Immunosuppression for Mooren's ulcer: evaluation of the stepladder approach—topical, oral and intravenous immunosuppressive agents. Br J Ophthalmol. 2013 Nov;97(11):1391-4.

TRAUMATIC CORNEAL LACERATION AND PERFORATION

Signs and Symptoms

Traumatic corneal lacerations and perforations are invariably accompanied by a recent history of ocular injury. Typically, this involves a sharp object such as a knife, hand tool, tree branch or glass shard, although cases have been documented involving some very obscure items, including fish hooks, plastic toys, ninja stars and the talons from a bird of prey.[1-4] Although fingernail scratches typically do not generate enough force to lacerate the cornea, this etiology has been documented in the literature; hence, it is important to rule out laceration in all cases of corneal trauma.[5] Lacerations may also result from penetration by a high-velocity projectile or may occur secondary to severe blunt injury.[6]

Patients with corneal laceration typically report intense pain at the onset, although this may diminish over time due to severing of the corneal nerves. Additional symptoms may include photophobia, lacrimation and variably reduced vision. According to the database of the United States Eye Injury Registry (USEIR), corneal injuries are five times more likely in males than females, and are also more common in active, younger age groups.[7]

Typically, there will be pronounced ocular injection, secondary blepharospasm and pseudoptosis secondary to pain and photophobia. The corneal laceration may be obvious if it is large or irregularly shaped. One may observe a jagged defect that extends from the corneal epithelium into and through the underlying stroma. Small, linear

breaks may be more difficult to visualize, because the opposing surfaces of the wound may close like a "flap-valve" under the sustained intraocular pressure of the eye. If the laceration is full thickness, the anterior chamber may be shallow or even flat, again depending upon the extent of the injury.

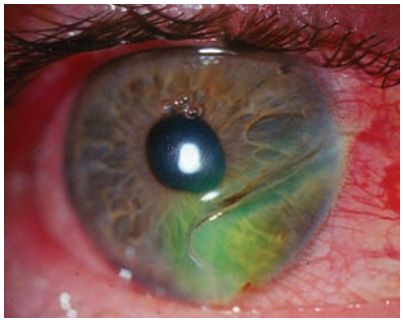
Aqueous can be visualized percolating from the edge of the wound when fluorescein is painted across the wound (Seidel's sign). The intraocular pressure may be substantially reduced in cases of full-thickness lacerations and perforations, sometimes reaching as low as 0mm Hg to 2mm Hg, depending upon the timing of the evaluation compared to the time of injury.

One finding that is particularly diagnostic of a perforating corneal injury is the presence of air bubbles within the anterior chamber. Other key signs include corectopia and iris prolapse into or through the wound as internal ocular pressure forces tissue forward to plug the wound. Accompanying pathology related to the inciting trauma is also common; subconjunctival hemorrhage, hyphema, iridodialysis, lens dislocation, cataract, vitreous hemorrhage and rarely vitreous incarceration are all possible findings.[4]

While corneal lacerations typically encompass significant area, perforations do not and can easily be missed during the clinical exam. Corneal perforations typically involve a foreign object penetrating the cornea, such as a needle or tree twig, or a small projectile entering the cornea and lodging within the eye. Corneal perforations can partially or fully self-seal. As such, there may be no hypotony, the chamber may be shallow but formed, and there may be no Seidel sign.

Pathophysiology

The cornea possesses great tensile strength and is generally resistant to penetration by blunt perpendicular forces; however, tangential injuries of sufficient force—particularly those induced by sharp objects—have the potential to cause the lamellar sheets of the corneal stroma to separate, allowing for entry into the tissue.



Traumatic corneal laceration.

A laceration refers to a wound produced by the tearing of a bodily tissue; it is usually traumatic, irregularly shaped and induced by a foreign object. Lacerations may vary in thickness. When the cornea is penetrated through all layers into the anterior chamber, it is referred to as a *full-thickness laceration*. A cleft that does not completely traverse the stroma and endothelium is considered a *partial-thickness laceration*.

The obvious danger in a full-thickness corneal laceration is the subsequent extrusion of intraocular contents through the wound or introduction of harmful matter or infectious microorganisms. Numerous cases of endophthalmitis have been documented, in some cases involving highly unusual organisms.[8-10] As the pressure in the anterior chamber drops, the pressure from the vitreous body forces the lens and iris forward. That excessive manipulation or further trauma may induce a prolapse of these tissues through the laceration.

Management

From a primary care point of view, the management of corneal laceration involves basic first aid. The clinician must make a definitive diagnosis as quickly as possible using the least amount of manipulation or intervention.

To aid examination in cases of corneal trauma, it is often advantageous to instill a topical anesthetic. This helps to alleviate patient discomfort and permits the clinician to perform a more thorough evaluation of the eye, including visual acuity assessment, pupillary evaluation and biomicroscopy.

The downside of using a topical anesthetic—or any topical agent—in cases of corneal laceration is the potential for deep tissue toxicity or introduced infection. With a compromised cornea, topically applied drugs achieve intraocular concentrations much greater than normally intended. This can lead to unwanted sequelae. Hence, any topical agents should be used sparingly if at all, and preservative-free options, where available, are preferred.

To differentiate corneal abrasions and partial-thickness lacerations from full-thickness lacerations, perform the Seidel test. Fluorescein is applied directly to the wound, and then carefully inspected under cobalt blue illumination, either with a Burton lamp or at the biomicroscope. In cases of corneal perforation, aqueous will slowly percolate from the lesion, creating a dark-appearing area with a steady flow of fluid to the inferior fluorescent tear lake. As some small perforations can at least partially self-seal, the Seidel test may be negative.

If a high-speed impact has caused trauma, a negative Seidel test does not rule out corneal perforation. In these cases, a pressure Seidel test should be performed. The corneal defect is painted with fluorescein and mild pressure is applied to the globe through the sclera or eyelid while the patient is at the biomicroscope. If there is a self-sealing perforation, the additional light pressure will turn a negative Seidel test into a positive result. Otherwise, tonometry, gonioscopy and other procedures requiring pressure on the globe should be deferred if there is any known ocular perforation.

Once the diagnosis is established, the primary goal is to stabilize the eye and ensure that no further damage occurs. An eye shield should be gently placed to protect the globe; however, the use of a pressure patch or bandage contact lens is ill-advised in large corneal lacerations, primarily due to the manipulation required to apply these measures. In the event that material is lodged in the wound, it should not be removed as it may actually be plugging the wound. Immediately refer to a cornea specialist to initiate surgical repair of the laceration. Patients must be instructed not to eat or drink before the surgical consultation, because this may delay a surgical procedure. If the patient is nauseous or overly anxious, consider prescribing an antiemetic agent such as meclizine 25mg PO to prevent vomiting.

Repair of corneal lacerations involves a variety of efforts. Partial-thickness and self-sealing lacerations may be treated with nothing more than topical antibiotics, cycloplegics and a bandage contact lens, with close observation for any signs of ensuing endophthalmitis. Larger wounds or those that are prone to leakage may sometimes be managed with fibrin glue or cyanoacrylate tissue adhesive in lieu of surgical repair.[11-15] Additionally, scleral patch grafts and amniotic membranes, often with adjunctive fibrin glue and cyanoacrylate adhesive, have been recently used with success.[16-20] However, many corneal lacerations often require suturing to restore corneal integrity.

Clinical Pearls

- With a corneal laceration, the patient may be tearing so heavily it renders the Seidel test inaccurate. In these cases, a shallow or flat anterior chamber, hypotony, or the presence of bubbles within the anterior chamber indicates a breach in the corneal integrity.
- For full-thickness corneal lacerations, the less done in the office the better. Assess the injury, arrange for the appropriate referral and shield the eye gently for protection while the patient is in transit to the surgeon.
- The patient should be educated that the entering acuity may represent the best vision that can be expected after surgical repair. Of course, acuity may improve following surgery; however, it is best not to elevate patient expectations.
- A fresh, previously unopened bottle of topical anesthetic is preferred when a full-thickness corneal laceration or globe rupture is suspected to avoid ocular contamination.
- Any eye injury from a high-speed projectile should be considered a perforation until proven otherwise. In some cases, ultrasound may be necessary to rule out intraocular foreign body.
- Small corneal perforations may partially self-seal, giving a negative Seidel result.
- Progressively worsening vision, pain, hypotony, shallow anterior chamber depth and hypopyon are indications of a corneal perforation and developing endophthalmitis.

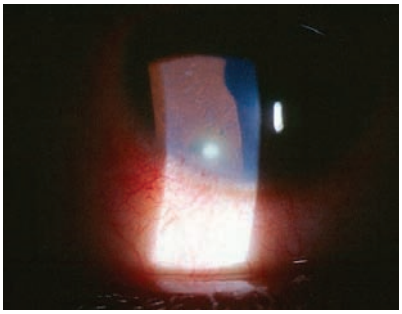
1. Muller L, Kohnen T. Scleral and corneal laceration with iris prolapse caused by an eagle claw. Graefes Arch Clin Exp Ophthalmol 2005;243(4):377-9.
2. Alfaro DV 3rd, Jablon EP, Rodriguez Fontal M, et al. Fishing-related ocular trauma. Am J Ophthalmol 2005;139(3):488-92.
3. Jeng BH, Steinemann TL, Henry P, et al. Severe penetrating ocular injury from ninja stars in two children. Ophthalmic Surg Lasers 2001;32(4):336-7.
4. Segev F, Assia EI, Harizman N, et al. Corneal laceration by sharp objects in children seven years of age and younger. Cornea 2007;26(3):319-23.
5. Taneja S, Arora R, Yadava U. Fingernail trauma causing corneal laceration and intraocular cilia. Arch Ophthalmol 1998;116(4):530-1.
6. Baker RS, Flowers CW Jr, Singh P, et al. Corneoscleral laceration caused by air-bag trauma. Am J Ophthalmol 1996;121(6):709-11.
7. Hamill MB. Corneal and scleral trauma. Ophthalmol Clin North Am 2002;15(2):185-94.
8. Ryan EH Jr, Cameron JD, Carpel E. Intraocular molluscum contagiosum after a corneoscleral laceration. Am J Ophthalmol 1997;124(4):560-1.
9. Sharma S, Saffra NA, Chapnick EK. Post traumatic polymicrobial endophthalmitis, including Neisseria subflava. Am J Ophthalmol 2003;136(3):554-5.
10. Moinfar N, Smiddy WE, Miller D, et al. Posttraumatic Aspergillus terreus endophthalmitis masquerading as dispersed lens fragments. J Cataract Refract Surg 2007;33(4):739-40.
11. Hamill MB. Cornea. In: Kuhn F, Pieramici DJ, eds. Ocular Trauma: Principles and Practice. New York: Thieme, 2002:95-109.
12. Celis J, Mesa D, Avendaño E, González-Valle F. Intracameral fibrin glue in spontaneous corneal perforation. Arch Soc Esp Oftalmol. 2012 Dec 21. pii: S0365-6691(12)00447-9.
13. Por YM, Tan YL, Mehta JS, Tan DT. Intracameral fibrin tissue sealant as an adjunct in tectonic lamellar keratoplasty for large corneal perforations. Cornea. 2009;28(4):451-5.
14. Khalifa YM, Bailony MR, Bloomer MM, et al. Management of nontraumatic corneal perforation with tectonic drape patch and cyanoacrylate glue. Cornea. 2010;29(10):1173-5.
15. Sharma A, Kaur R, Kumar S,et al. Fibrin glue versus N-butyl-2-cyanoacrylate in corneal perforations. Ophthalmology. 2003;110(2):291-8.
16. Sharma A, Mohan K, Sharma R, Nirankari VS. Scleral Patch Graft Augmented Cyanoacrylate Tissue Adhesive for Treatment of Moderate-Sized Noninfectious Corneal Perforations (3.5-4.5 mm). Cornea. 2013 Aug 22. [Epub ahead of print].
17. Samoila O, Totu L, Calugaru M. Methods for sealing of corneal perforations. Oftalmologia. 2012;56(2):34-9.
18. Grau AE, Durán JA. Treatment of a large corneal perforation with a multilayer of amniotic membrane and TachoSil. Cornea. 2012;31(1):98-100.
19. Chan E, Shah AN, O'Brart DP. "Swiss roll" amniotic membrane technique for the management of corneal perforations. Cornea. 2011;30(7):838-41.
20. Kim HK, Park HS. Fibrin glue-assisted augmented amniotic membrane transplantation for the treatment of large noninfectious corneal perforations. Cornea. 2009;28(2):170-6.

MARGINAL KERATITIS

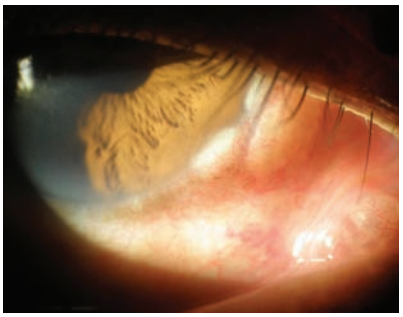
Signs and Symptoms

Marginal keratitis is defined as a peripheral corneal inflammatory response.[1-4] The condition is also known as *sterile keratitis*, *infiltrative keratitis*, *peripheral keratitis*, *peripheral ulcerative keratitis*, *contact lens–induced peripheral ulcer* (CLPU) and *contact lens–related infiltrates*. It can follow chronic exposure to an antigen (e.g., make-up, chemical exposure, pathogens), a chronic mechanical stimulus (e.g., debris, eyelid or eyelash), induced hypoxia (e.g., contact lens related) or can be a sequelae of vasculitic systemic disease (e.g., engraftment syndrome after hematopoietic stem cell transplantation, leukocytoclastic vasculitis).[1-14]

Patients with marginal keratitis may range in presentation from completely asymptomatic to severely symptomatic, depending on the extent and duration of the reaction.



Peripheral corneal infiltrates in a contact lens wearer with marginal keratitis.



Marginal keratitis associated with Stevens-Johnson syndrome.

When present, symptoms are graded as mild, moderate and severe, and may also be acompanied by ocular discomfort (e.g., burning, foreign body sensation, grittiness), photophobia and chronic tearing.[6] Vision generally remains unaffected.[1-7]

Typically, bulbar conjunctival injection is mild to absent. In the Fuchs' variation, a pseudopterygium with mild corneal thinning may be noted.[14] The palpebral conjunctiva may demonstrate subtle conjunctival chemosis.[11-13] The key diagnostic sign is one or more focal areas of grayish, subepithelial infiltrate near the limbus, usually located in the inferior cornea and particularly where the cornea interacts with the lower eyelid margin.[1,2,13-15] When the overlying epithelium is compromised, the defect is usually seen as an interrupted stippling much smaller than the area of infiltrate. This is in contradistinction to microbial keratitis, which demonstrates a continuous area of epithelial defect virtually equal to the area of stromal infiltrate.[16]

Characteristically, there are zones of unaffected limbal cornea.[9] In rare instances, marginal keratitis may be accompanied by other inflammatory ocular sequelae, such as mild anterior uveitis or folds in Descemet's membrane associated with corneal edema.

Blepharitis and its variants (seborrheic, psoriasiatic, acne rosacea, *Demodex*) are major contributors secondary to their effects on the lid margin.[2,11,12,13,17-19]

Patients with marginal keratitis may have a history of other ocular surface disease, such as chronic dry eye or allergic conjunctivitis. Inflammatory autoimmune disorders—including Terrien's marginal degeneration, Stevens-Johnson syndrome, rheumatoid arthritis, granulomatosis with polyangiitis, Behçet's disease and Churg-Strauss syndrome—are also known to produce marginal keratitis.[1,2,8-12, 13,15,16,19-21]

Pathophysiology

Classic marginal keratitis represents as a localized immune response, believed to be driven by antigen-antibody complexes that deposit in the peripheral corneal stroma.[11,20-23] Generically, the mechanism is that an inflammatory process initiates a cascade that results in the influx of leukocytes and plasma molecules to the site of the tissue damage.[1,24,25] The inciting etiology will dictate the specific cellular response.[15,16,25-27]

Initially, the overlying epithelium remains intact; however, as inflammatory cells accumulate to neutralize the offending reaction, collagenolytic enzymes released from these cells induce noninfectious ulceration (infiltrate in the presence of an overlying corneal break).[15,28] Matrix metalloproteinase-9 (MMP-9) appears to be a prominent player in the initiation of the epithelial basement membrane degradation that precedes corneal ulceration.[28]

Historically, bacterial exotoxins from staphylococcal organisms are considered the primary etiology.[11,13,15,20,22] While bacterial overgrowth associated with chronic blepharitis remains a significant cause of marginal keratitis, clearly not all cases are caused by microbial flora.[4-9] Other causes include systemic autoimmune disorders, mechanical events and hypersensitivity reactions to foreign substances and topical drugs including phenylephrine, gentamicin, atropine, pilocarpine and dorzolamide.[2,3-11,15,16,26,27]

Corneal hypoxia and bacterial biofilm associated with soft contact lens wear represent yet another potential etiology, although in these instances clinicians tend to use the term *contact lens-induced peripheral ulcer* (CLPU).[5]

Management

The treatment strategy for marginal keratitis must address both extinguishing the inflammatory response and removing or controlling the causative etiology.[2-27] In cases where microbial flora are implicated, aggressive control of eyelid and ocular surface bacteria can be accomplished using topical and oral antibiotics.

Mechanical cleaning of the eyelids to soften and remove debris/microbes should be employed, using warm compresses and commercially available lid cleansers such as OcuSoft (Cynacon) or generic "no-more-tears" baby shampoos, two to four times daily.[29]

Metronidazole ointment BID along with oral ivermectin, dosed once and repeated in seven days if necessary, are indicated in cases of suspected *Demodex* infestation.[30] In cases of rosacea (meibomian gland dysfunction), oral tetracycline 500mg BID PO, doxycycline 100mg BID PO or azythromicin (Z-pack) can be prescribed.[31,32] Generic staphylococcal blepharitis can be treated with traditional topical fluoroquinolone antibiotic drops and or ointments QID.

Since inflammation is an integral portion of the entity's histopathology, its mitigation can be accomplished with either topical antibiotic-steroid combination drops or ointments BID-QID or the addition of a topical steroid such as fluorometholone, prednisolone acetate, loteprednol etabonate or difluprednate to the topical antibiotic.[2-27] Since topical steroids may increase intraocular pressure (IOP), any prolonged course should include IOP monitoring. In cases with significant anterior segment inflammation or symptoms, cycloplegia may be warranted.

Marginal keratitis associated with drug hypersensitivity necessitates discontinuing the noxious agent and controlling inflammation as aforementioned.[26,27] Cases of contact lens-induced peripheral ulcer warrant temporarily discontinuing lens wear, protecting the cornea with a topical antibiotic or antibiotic-steroid combination and rehabilitating the ocular surface. Wear can continue following a reevaluation of the fit, lens material and disinfection system.[5]

Management options associated with systemic autoimmune diseases require a team approach. Correspondence with systemic specialists such as dermatology, infectious disease or rheumatology are critical.[6-10,13,15,16] In these cases, the classic topical regimen will require oral or intravenous supplementation, including systemic corticosteroids and immunomodulating agents, to attack the underlying disease process.[6-10]

Clinical Pearls

- Common examples of marginal keratitis are "sterile corneal infiltrates" or "sterile ulcerations" on the periphery of the cornea.
- Marginal keratitis itself is not an infectious process. It is an inflammatory response to a local toxic (chemical or microbial), mechanical, hypoxic or systemic inflammatory stimulus.
- The principal differential diagnoses for marginal keratitis include microbial keratitis, Mooren's ulcer, Terrien's marginal degeneration, and peripheral keratolysis (peripheral ulcerative keratitis—sometimes referred to as *corneal melting*).
- Microbial keratitis, as opposed to marginal keratitis, is characteristically: (1) located centrally or paracentrally, (2) composed of a singular large lesion, (3) secondary to a unilateral process, (4) produces an aggravated inflammatory response (significant cell and flare seen in the anterior chamber), (5) can be very painful and (6) produces symptoms which include tearing, photophobia and decreased vision.
- Mooren's ulcer is a painful, rapidly progressive keratitis that results in generalized peripheral corneal thinning, sometimes leading to perforation.
- Terrien's degeneration is a bilateral, painless, progressive degeneration of the peripheral cornea occurring in the setting of an otherwise white and quiet eye.
- Corneal scrapings and cultures in marginal keratitis are generally nonproductive and unnecessary, even when the condition is associated with staphylococcal blepharitis. Cultures should only be considered if the condition does not improve within the first 48 to 72 hours of intervention.

1. Zheng Y, Kaye AE, Boker A, et al. Marginal corneal vascular arcades. Invest Ophthalmol Vis Sci. 2013;54(12):7470-7.

2. Gupta N, Dhawan A, Beri S, D'souza P. Clinical spectrum of pediatric blepharokeratoconjunctivitis. J AAPOS. 2010;14(6):527-9.

3. Pereira MG, Rodrigues MA, Rodrigues SA. Eyelid entropion. Semin Ophthalmol. 2010;25(3):52-8.

4. Babu K, Maralihalli RE. Insect wing tarsal foreign body causing conjunctival granuloma and marginal keratitis. Indian J Ophthalmol. 2009;57(6):473-4.

5. Sweeney DF, Jalbert I, Covey M, et al. Clinical characterization of corneal infiltrative events observed with soft contact lens wear. Cornea. 2003; 22(5):435-42.

6. Li Yim JF, Agarwal PK, Fern A. Leucocytoclastic vasculitis presenting as bilateral marginal keratitis. Clin Experiment Ophthalmol. 2007;35(3):288-90.

7. Dai E, Couriel D, Kim SK. Bilateral marginal keratitis associated with engraftment syndrome after hematopoietic stem cell transplantation. Cornea. 2007;26(6):756-8.

8. Aust R, Kruse FE, Volcker HE. Therapy refractory marginal keratoconjunctivitis in a child. Wegener's granulomatosis in a child with initial manifestation in the eye. Ophthalmologe. 1997; 94(3):240-1.

9. Glavici M, Glavici G. Marginal keratitis in Behcet's disease. Oftalmologia. 1997; 41(3):224-7.

10. Bawazeer AM, Jackson WB. Marginal infiltrative ulcerative keratitis secondary to Churg-Strauss syndrome: a case report. Cornea. 2000; 19(3):402-4.

11. Jayamanne DG, Dayan M, Jenkins D, Porter R. The role of staphylococcal superantigens in the pathogenesis of marginal keratitis. Eye. 1997; 11(Pt 5):618-21.

12. Viswalingam M, Rauz S, Morlet N, Dart JK. Blepharokeratoconjunctivitis in children: diagnosis and treatment. Br J Ophthalmol. 2005;89(4):400-3.

13. Robin JB, Dugel R, Robin SB. Immunologic disorders of the cornea and conjunctiva. In: Kaufman HE, Barron BA, McDonal MB, eds. The Cornea, 2nd edition. Boston: Butterworth-Heinemann, 1998; 551-95.

14. Keenan JD, Mandel MR, Margolis TP. Peripheral ulcerative keratitis associated with vasculitis manifesting asymmetrically as Fuchs superficial marginal keratitis and terrien marginal degeneration. Cornea. 2011;30(7):825-7.

15. Bouchard CS. Noninfectious keratitis. In: Yanoff M, Duker JS. Ophthalmology. Mosby-Elsevier, St. Louis, MO 2009:454-65.

16. McLeod SD. Infectious keratitis. In: Yanoff M, Duker JS. Ophthalmology. Mosby-Elsevier, St. Louis, MO 2009:466-91.

17. Sobolewska B1, Zierhut M. Ocular rosacea. Hautarzt. 2013 Jul;64(7):506-8.

18. O'Reilly N, Gallagher C, Reddy Katikireddy K, et al. Demodex-associated Bacillus proteins induce an aberrant wound healing response in a corneal epithelial cell line: possible implications for corneal ulcer formation in ocular rosacea. Invest Ophthalmol Vis Sci. 2012;53(6):3250-9.

19. Bernardes TF, Bonfioli AA. Blepharitis. Semin Ophthalmol. 2010;25(3):79-83.

20. Thygeson P. Marginal corneal infiltrates and ulcers. Trans Am Acad Ophthalmol. Otolaryngol 1947; 51(1):198-207.

21. Bachmann B, Jacobi C, Cursiefen C. Inflammation of the eye in systemic inflammatory disorders: keratitis. Klin Monbl Augenheilkd. 2011;228(5):413-8.

22. Chignell AH, Easty DL, Chesterton JR, Thomsitt J. Marginal ulceration of the cornea. Br J Ophthalmol 1970; 54(7):433-40.

23. Stern GA, Knapp A. Iatrogenic peripheral corneal disease. Int Ophthalmol Clin. 1986; 26(4):77-89.

24. Pararajasegaram G. Mechanisms of uveitis. In: Yanoff M, Duker JS. Ophthalmology. Mosby-Elsevier, St. Louis, MO 2009:1105-12.

25. Hazlett LD, Hendricks RL. Reviews for immune privilege in the year 2010: immune privilege and infection. Ocul Immunol Inflamm. 2010;18(4):237-43.

26. Radian AB. Erosive marginal keratitis due to pilocarpine allergy. Oftalmologia. 1999; 47(2):83-4.

27. Taguri AH, Khan MA, Sanders R. Marginal keratitis: an uncommon form of topical dorzolamide allergy. Am J Ophthalmol 2000; 130(1):120-2.

28. Fini ME, Girard MT, Matsubara M. Collagenolytic/gelatinolytic enzymes in corneal wound healing. Acta Ophthalmol Suppl. 1992;70(202):26-33.

29. Liu J, Sheha H, Tseng SC. Pathogenic role of Demodex mites in blepharitis. Curr Opin Allergy Clin Immunol. 2010;10(5):505-10.

30. Czepita D, Kuźna-Grygiel W, Czepita M, Grobelny A. Demodex folliculorum and Demodex brevis as a cause of chronic marginal blepharitis. Ann Acad Med Stetin. 2007;53(1):63-7.

31. Layton A, Thiboutot D. Emerging therapies in rosacea. J Am Acad Dermatol. 2013;69(6 Suppl 1):S57-65.

32. Akhyani M, Ehsani AH, Ghiasi M, Jafari AK. Comparison of efficacy of azithromycin vs. doxycycline in the treatment of rosacea: a randomized open clinical trial. Int J Dermatol. 2008;47(3):284-8.

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References: 1. Liew M, Zhang M, Kim E, et al. Prevalence and predictors of Sjögren's syndrome in a prospective cohort of patients with aqueous-deficient dry eye. *Br J Ophthalmol.* 2012;96:1498-1503. **2.** Kassan SS, Moutsopoulos HM. Clinical manifestations and early diagnosis of Sjögren syndrome. *Arch Intern Med.* 2004;164(12):1275-1284. **3.** Sjögren's Syndrome Foundation. Sjögren's Syndrome Foundation. 2013. Available at http://www.sjogrens.org. Accessed September 5, 2013. **4.** Shen L, Suresh L, Lindemann M, et al. Novel autoantibodies in Sjögren's syndrome. *Clin Immunol.* 2012;145:251-255.

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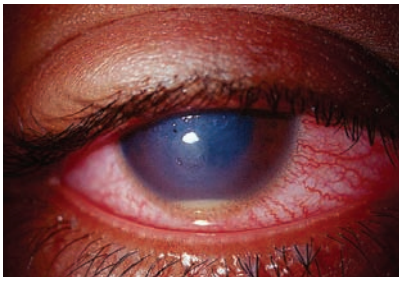
ENDOPHTHALMITIS

Signs and Symptoms

Due to its numerous potential routes of inoculation, endophthalmitis has no typical age, gender or racial predilection. Patients often manifest pain and significant vision loss upon presentation; visual deterioration may be rapid from the onset of the condition. There is also rapidly progressing diffuse bulbar hyperemia and chemosis of the affected eye. Common associated signs include hypopyon, hypotony, a shallow or flat anterior chamber (suggesting ocular perforation or surgical wound leak), anterior chamber cells and flare, fibrin, pupillary fibrin membrane formation, corneal infiltration, corneal edema, vitritis, retinitis, periphlebitis, retinal detachment and loss of the ophthalmoscopic red reflex.[1-3] Often, funduscopic evaluation cannot be accomplished due to media opacification from pupillary fibrin membrane formation or vitritis.

Endophthalmitis can occur either endogenously or exogenously. Patients developing endogenous endophthalmitis typically have a predisposing systemic condition that allows the spread of infection to the eye from a distant site. The most common conditions associated with endogenous endophthalmitis are diabetes, cardiac disease, endocarditis, cancer, HIV/AIDS, hepatitis C, iatrogenic immunosuppression following cancer chemotherapy or organ transplantation, recent hospitalization, recent non-ocular surgery and indwelling catheters.[4-8]

Infection in virtually any distant body part and microbial sepsis are also strong causative factors for endogenous endophthalmitis.[9] Additionally, intravenous drug use can serve as a portal of entry into the bloodstream for microbial pathogens, which can then reach the eye.[10] Rarely are patients with endogenous endophthalmitis systemically healthy.



Hypopyon as seen in endophthalmitis.

In contrast, patients with exogenous endophthalmitis have a pathogenic inoculation directly into the eye. The portal of entry in these cases is either a traumatic penetrating injury or other open-globe injury—often with a retained intraocular foreign body—or through ocular surgery.[11-15] The most common surgical procedure resulting in exogenous endophthalmitis is cataract surgery, though any penetrating ocular procedure, including intravitreal injections, can result in endophthalmitis.[16,17] Late-onset trabeculectomy bleb leaks are also a cause of exogenous endophthalmitis.[18]

Pathophysiology

Endophthalmitis represents significant inflammation of the vitreous and anterior chamber. Rarely, endophthalmitis may be sterile, resulting from a non-infectious toxin or retained antigenic lens fragments after surgery. Typically, however, endophthalmitis begins when a pathogenic inoculum reaches the eye. Numerous bacteria and fungi have been identified in endophthalmitis. Either a blood-borne pathogen in endogenous endophthalmitis or an organism introduced through the external eye in penetrating trauma or surgical incision reaches the vitreous or anterior chamber, replicates, and establishes a colony. This initiates an antigen-antibody response with subsequent breakdown of the blood/ocular barrier, releasing inflammatory cells with resultant anterior chamber reaction, fibrin, hypopyon and vitritis.

As the organism overcomes host defenses, toxins are released. Depending upon the infective organism, these may include cytolysin, gelatinase, serine protease, pneumolysin, autolysin, alpha-toxin or beta-toxin. This causes further tissue destruction, especially in the retina, and results in significant morbidity.[2]

Prognosis varies greatly, depending upon the virulence of the infective organism, time of first diagnosis and route of inoculation. Bacterial endophthalmitis typically presents acutely, though chronic inflammation and mild symptoms may occur if a bacterium of low virulence is involved. Cases involving fungal pathogens tend to run a more indolent course, and are commonly encountered in immunocompromised patients. Patients with ocular postoperative endophthalmitis often are infected with their own normal skin flora, typically coagulase-negative *Staphylococci*.[4] Most cases of post-op endophthalmitis are identified within six days of surgery.[2,4] Endophthalmitis can also present long after a surgical procedure; this is termed *delayed endophthalmitis*.

Features associated with better visual acuity outcomes include a better presenting visual acuity, infection with a low-virulence organism, and the absence of retinal detachment.[12] In penetrating globe injuries, the most common organisms identified are coagulase-negative *Staphylococci* and *Streptococcus* species as well as *Bacillus* species. In these cases, duration until wound closure is a significant factor; the quicker the globe is repaired, the greater the likelihood of better visual outcome.[19]

However, exogenous endophthalmitis caused by open-globe injury and retained foreign body tends to have the poorest prognosis.[11-13,19] Clinical diagnosis of exogenous endophthalmitis arising from penetrating injury is often delayed due to its initial similarities with traumatic acute inflammatory reactions, which further postpones antibiotic treatment.[3]

Management

For patients undergoing ocular surgery, endophthalmitis prophylaxis is crucial to a good postoperative outcome.[20] This is best accomplished through presurgical and perisurgical antibiosis. For in-office procedures such as intravitreal injection, povidone-iodine irrigation reduces the risk of endophthalmitis.[17] The European Society of Cataract and Refractive Surgeons has reported that intracameral injection of 1mg cefuroxime (10mg/mL) at the end of cataract surgery reduced the incidence of postoperative endophthalmitis fivefold.[21,22]

In any case of endophthalmitis, it is imperative to swiftly begin antimicrobial therapy, identify the causative organism, and then adjust the therapy if warranted by the microbiologic results. The Endophthalmitis Vitrectomy Study (EVS) was designed to determine the roles of immediate pars plana vitrectomy vs. vitreous tap biopsy and systemic antibiotic treatment in the management of postoperative endophthalmitis. The study found no difference in final visual acuity or media clarity with or without the use of systemic antibiotics. In patients whose initial visual acuity was hand motion or better, there was no difference in visual outcome whether or not an immediate vitrectomy was performed. However, in the subgroup of patients with initial light perception-only vision, vitrectomy produced a significantly better visual outcome than vitreous tap biopsy. Thus, it has long been advocated that early vitrectomy is beneficial for those who present with light perception-only vision.[23]

Vitrectomy confers many benefits, including the provision of microbiologic samples for culturing and the removal of intraocular foreign bodies, infective organisms and retinotoxic endotoxins.[3] Additionally, vitreous tap biopsy may not adequately sample a localized infection, yielding a false-negative culture result.

Intravitreal injection, either following a vitrectomy procedure or vitreous tap biopsy, is the mainstay of treatment. Antibiotics include vancomycin, ceftazadime, cefazolin, amikacin, cefuroxime or gentamicin.

Should cultures identify the presence of fungal infection, oral fluconazole or voriconazole or intravitreal amphotericin B are often used.

Clinical Pearls

- When evaluating post-op patients, the mnemonic "RSVP" can help identify patients developing early endophthalmitis: **R**edness, **S**ensitivity to light, **V**ision loss and **P**ain.
- In the early postoperative period, endophthalmitis must be distinguished from toxic anterior segment syndrome, which is characterized by corneal edema, mild vitreous inflammation and a positive response to steroids.
- The development of hypopyon, vitritis, retinitis, periphlebitis, corneal infiltration, increasing redness and pain with progressive vision loss should raise suspicion for endophthalmitis.
- Prognosis for endophthalmitis of any type is guarded. It is universally agreed that virulence of the infecting organism is the greatest predictor of final visual outcome.
- If endophthalmitis is suspected, referral to a retina specialist is most appropriate.

1. Cornut PL, Thuret G, Creuzot-Garcher C, et al. Relationship between baseline clinical data and microbiologic spectrum in 100 patients with acute postcataract endophthalmitis. Retina. 2012;32(3):549-57.

2. Combey de Lambert A, Campolmi N, Cornut PL, et al. Baseline factors predictive of visual prognosis in acute postoperative bacterial endophthalmitis in patients undergoing cataract surgery. JAMA Ophthalmol. 2013;131(9):1159-66.

3. Gokce G, Sobaci G, Ozgonul C. Post-Traumatic Endophthalmitis: A Mini-Review. Semin Ophthalmol. 2014 Feb 27. [Epub ahead of print].

4. Asencio-Egea MA, Huertas-Vaquero M, Carranza-González R, et al. Endogenous endophthalmitis: case report and brief review of a serious ocular disease. Rev Chilena Infectol. 2013;30(5):516-21.

5. Ness T, Pelz K, Hansen LL. Endogenous endophthalmitis: microorganisms, disposition and prognosis. Acta Ophthalmol Scand. 2007;85(8):852-6.

6. Sridhar J, Flynn HW Jr, Kuriyan AE, et al. Endogenous fungal endophthalmitis: risk factors, clinical features, and treatment outcomes in mold and yeast infections. J Ophthalmic Inflamm Infect. 2013;3(1):60.

7. Barge S, Rothwell R, Varandas R, Agrelos L. Enterococcus faecalis Endogenous Endophthalmitis from Valvular Endocarditis. Case Rep Ophthalmol Med. 2013;2013:174869. Epub 2013 Jul 1.

8. Lamaris GA, Esmaeli B, Chamilos G, et al. Fungal endophthalmitis in a tertiary care cancer center: a review of 23 cases. Eur J Clin Microbiol Infect Dis. 2008;27(5):343-7.

9. Sharma A, Sharma V. From the toe to the head: metastatic endophalmitis following staphylococcal purpura fulminans. Trop Doct. 2014;44(1):46-7.

10. Patel SN, Rescigno RJ, Zarbin MA, et al. Endogenous endophthalmitis associated with intravenous drug abuse. Retina. 2014 Jan 13. [Epub ahead of print].

11. Wykoff CC, Flynn HW Jr, Miller D, et al. Exogenous fungal endophthalmitis: microbiology and clinical outcomes. Ophthalmology. 2008;115(9):1501-7.

12. Lieb DF, Scott IU, Flynn HW Jr, et al. Open globe injuries with positive intraocular cultures: factors influencing final visual acuity outcomes. Ophthalmology. 2003;110(8):1560-6.

13. Yang CS, Lu CK, Lee FL, et al. Treatment and outcome of traumatic endophthalmitis in open globe injury with retained intraocular foreign body. Ophthalmologica. 2010;224(2):79-85.

14. Asencio MA, Huertas M, Carranza R, et al. A case-control study of post-operative endophthalmitis diagnosed at a Spanish hospital over a 13-year-period. Epidemiol Infect. 2014 Mar 11:1-6. [Epub ahead of print].

15. Jindal A, Pathengay A, Mithal K, et al. Endophthalmitis after open globe injuries: changes in microbiological spectrum and isolate susceptibility patterns over 14 years. J Ophthalmic Inflamm Infect. 2014;4(1):5.

16. Schwartz SG, Flynn HW Jr. Endophthalmitis Associated with Intravitreal Anti-Vascular Endothelial Growth Factor Injections. Curr Ophthalmol Rep. 2014;2(1):1-5.

17. Shimada H, Hattori T, Mori R, et al. Minimizing the endophthalmitis rate following intravitreal injections using 0.25% povidone-iodine irrigation and surgical mask. Graefes Arch Clin Exp Ophthalmol. 2013;251(8):1885-90.

18. Song A, Scott IU, Flynn HW Jr, Budenz DL. Delayed-onset bleb-associated endophthalmitis: clinical features and visual acuity outcomes. Ophthalmology. 2002;109(5):985-91.

19. Al-Omran AM, Abboud EB, Abu El-Asrar AM. Microbiologic spectrum and visual outcome of posttraumatic endophthalmitis. Retina. 2007;27(2):236-42.

20. Asencio MA, Huertas M, Carranza R, et al. Impact of changes in antibiotic prophylaxis on postoperative endophthalmitis in a Spanish hospital. Ophthalmic Epidemiol. 2014;21(1):45-50.

21. Barry P, Seal DV, Gettinby G, et al. ESCRS study of prophylaxis of postoperative endophthalmitis after cataract surgery: Preliminary report of principal results from a European multicenter study. J Cataract Refract Surg. 2006;32(3):407-10.

22. Beselga D, Campos A, Castro M, et al. Postcataract surgery endophthalmitis after introduction of the ESCRS protocol: a 5-year study. Eur J Ophthalmol. 2013 Dec 16:0. doi: 10.5301/ejo.5000417. [Epub ahead of print].

23. Endophthalmitis Vitrectomy Study Group. Results of the Endophthalmitis Vitrectomy Study. A randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. Endophthalmitis Vitrectomy Study Group. Arch Ophthalmol. 1995;113(12):1479-96.

MALIGNANT GLAUCOMA

Signs and Symptoms

Malignant glaucoma, also referred to as *aqueous misdirection syndrome* or *ciliary block glaucoma*, occurs without racial or gender predilection.[1-6] Patients typically have hyperopic and small (nanophthalmic) eyes. Most significantly, there is a history of antecedent ocular surgery (typically, glaucoma surgery) with complications beginning shortly after. Malignant glaucoma occurs most commonly after trabeculectomy, glaucoma drainage device implantation, peripheral iridectomy or iridotomy, and cataract surgery.[1-6] Frequently, there may have been a period of hypotony due to over-filtration following glaucoma surgery. Initially, malignant glaucoma may present with statistically normal, though rising, intraocular pressure (IOP) with concurrent anterior chamber shallowing.[1,7]

Biomicroscopically, there will be a shallow or flat anterior chamber in the presence of an intact iridectomy or iridotomy.[8-10] Frequently, there is a preoperative history of anatomically narrow angles, as well as prior miotic therapy.[9] For instance, plateau iris syndrome, which is often medically treated with miotics, may predispose such patients to postoperative malignant glaucoma.[11] Patients who develop significant inflammation, such as that seen with scleritis, may also develop malignant glaucoma. Trauma, retinal detachment surgery, panretinal photocoagulation and central retinal vein occlusion have also been reported in association with the development of malignant glaucoma.[12]

Progressive flattening of the anterior chamber following surgery, with progressive IOP rise, is the hallmark of malignant glaucoma.[9] Further, there will be no iris bombé or evidence of supraciliary effusion.[1,9,13,14] Should IOP elevate abruptly, classic signs and symptoms similar to those seen in acute angle-closure glaucoma may occur.

Pathophysiology

Malignant glaucoma is actually an imprecise description, as there is no malignancy associated with the condition. The term was introduced because the condition was historically poorly understood, difficult to treat and often resulted in significant visual morbidity. Likewise, *aqueous misdirection syndrome* is also a misnomer in that it is not universally accepted that the aqueous is actually misdirected in every case.[9,13-15]

The ciliary body in eyes with malignant glaucoma tends to be thinner and more anteriorly rotated.[16] An accepted theory holds that the ciliary body and ciliary processes form a tight apposition to the peripheral lens as well as to the anterior vitreous—this may occur following ocular surgery, through a natural predisposition or, paradoxically, following a period of hypotony. It prevents the aqueous from flowing into the anterior chamber. Subsequently, the aqueous is diverted into the vitreous cavity, increasing its volume.

An abnormally impermeable anterior hyaloid face may play a role by preventing aqueous from diffusing through the vitreous into the anterior chamber, thus causing an increase in the volume of the vitreous. This expansion of the vitreous secondarily pushes the lens and iris towards the cornea with subsequent shallowing and flattening of the anterior chamber and closure of the angle.

The classic appearance is that of a shallow anterior chamber axial depth (lens-cornea distance) along with an accompanying shallow peripheral anterior chamber depth (iris-cornea distance).[1,15,17] In contradistinction, a patient with acute pupil-block primary angle closure will have a normal axial depth and a shallow peripheral depth. In pupil-block glaucoma, a peripheral iridotomy will lead to deepening of the chamber; however, iridotomy has no effect in malignant glaucoma. The hallmark is a closed angle with a shallow chamber, no plateau iris configuration and narrow axial depth that remains despite patent iridotomy or iridectomy.

Management

Intervention begins medically, with the goal of breaking the apposition of the ciliary body and processes to the lens (in phakic situations) and/or anterior vitreous in aphakic situations. This is accomplished by relaxing the ciliary body and lens zonules using a potent cycloplegic such as atropine, allowing the lens to release posteriorly.[1,7,18]

Aqueous suppressants can be used to temporize the intraocular pressure and topical steroids to ameliorate any inflammation. Miotics are contraindicated, as they can precipitate or worsen the condition. Oral carbonic anhydrase inhibitors and hyperosmotic agents can be used to dehydrate and shrink the vitreous.

Medical control is effective in a moderate number of cases and represents the safest first option.[1,15] Medical therapy appears to be most effective in phakic eyes, while pseudophakic eyes and refractory cases require a step-wise surgical approach.[19]

Should medical control not be effective, surgical options must be employed. Relieving malignant glaucoma and aqueous misdirection caused by increased resistance to aqueous flow anteriorly through the ciliary body/zonules/lens capsule complex requires the establishment of a conduit to allow fluid passage.[20]

The first of the surgical options is hyaloidotomy, which is designed to disrupt the anterior hyaloid face of the vitreous and allow aqueous to escape from the ballooning vitreous cavity. This option attempts to redirect aqueous into the anterior chamber rather than the posterior chamber. The most common method involves Nd:YAG laser photodisruption of the anterior vitreous face through an iridectomy or iridotomy

hole or through the pupil. Once accomplished, the pre-existing opening may then serve as the conduit for aqueous to reach the anterior chamber.[1,9]

A more invasive method of surgically correcting malignant glaucoma is through core vitrectomy.[20-23] Here, the anterior vitreous is "debulked," giving the iris a chance to relax and the anterior chamber to deepen. Further, pockets of aqueous within the vitreous are removed and the anterior vitreous face is disrupted, potentially removing the blockage that prevented the aqueous from ultimately getting through the pupil.

All surgical options are designed to establish a communication between the vitreous cavity and anterior chamber.[22,23] Diode laser cyclodestruction has been used as a complementary treatment in managing the IOP in cases of refractory malignant glaucoma.[2,24]

More recently, several procedures used in combination have been seen as successful. One combination includes partial pars plana vitrectomy, hyaloidozonulectomy and peripheral iridectomy.[25] Combined phacoemulsification/IOL implantation/posterior capsulorhexis/anterior vitrectomy surgery is considered a safe and effective method for treating patients with phakic malignant glaucoma.[26] The necessary combination of multiple procedures to effect a surgical cure seems to underscore a poor overall understanding of the exact pathogenesis of malignant glaucoma.

Unfortunately, even after successful treatment of malignant glaucoma, the angle may remain closed due to extensive peripheral anterior synechiae. If more than half of the angle remains closed, IOP will remain permanently elevated despite successful treatment of the underlying cause. In this case, the surgeon may try to break the peripheral anterior synechiae with a goniosynechialysis, or the patient may require some form of permanent medical therapy.

Clinical Pearls

- Pupillary block is the most common condition mimicking malignant glaucoma. Laser iridotomy will relieve pupil block angle closure but will have no effect on malignant glaucoma. However, laser iridotomy must be done to help differentiate the two conditions.
- Choroidal effusion with a shallow anterior chamber, particularly after glaucoma filtration surgery, is the second most common differential diagnosis for malignant glaucoma. Large effusions will be seen ophthalmoscopically. Small suprachoroidal effusion can cause an anterior rotation of the ciliary body and precipitate this condition. Small effusions are typically only detected with the use of ultrasound biomicroscopy.
- After glaucoma surgery, such as trabeculectomy, a flat anterior chamber and low IOP is suggestive of either overfiltration or bleb leakage. If the anterior chamber is flattening and shallowing while the IOP is rising, malignant glaucoma should be considered the cause.

1. Greenfield DS, Tello C, Budenz DL, et al. Aqueous misdirection after glaucoma drainage device implantation. Ophthalmology. 1999;106(5):1035-40.

2. Muqit MM, Menage MJ. Malignant glaucoma after phacoemulsification: treatment with diode laser cyclophotocoagulation. J Cataract Refract Surg. 2007;33(1):130-2.

3. Stan C. Bilateral malignant glaucoma--case report. Oftalmologia. 2005;49(4):33-4.

4. Martínez-de-la-Casa JM, García-Feijoó J, Castillo A, et al. Malignant glaucoma following combined Ahmed valve implant and phacoemulsification surgery for chronic angle-closure glaucoma. Arch Soc Esp Oftalmol. 2005;80(11):667-70.

5. Przybylska-Rybczyńska I, Kłosowska-Zawadka A, Pecold-Stepniewska H. Malignant glaucoma following trabeculectomy--case report. Klin Oczna. 2004;106(1-2 Suppl):261-2.

6. Arya SK, Sonika, Kochhar S, et al. Malignant glaucoma as a complication of Nd:YAG laser posterior capsulotomy. Ophthalmic Surg Lasers Imaging. 2004;35(3):248-50.

7. Burgansky-Eliash Z, Ishikawa H, Schuman JS. Hypotonous malignant glaucoma: aqueous misdirection with low intraocular pressure. Ophthalmic Surg Lasers Imaging. 2008;39(2):155-9.

8. Valtot F. What should be done when laser iridotomy does not physically eliminate angle closure? J Fr Ophtalmol. 2006;29 Spec No 2:61-6.

9. Schroeder W, Fischer K, Erdmann I, et al. Ultrasound biomicroscopy and therapy of malignant glaucoma. Klin Monatsbl Augenheilkd. 1999;215(1):19-27.

10. Razeghinejad MR, Amini H, Esfandiari H. Lesser anterior chamber dimensions in women may be a predisposing factor for malignant glaucoma. Med Hypotheses. 2005;64(3):572-4.

11. Prata TS, Dorairaj S, De Moraes CG, et al. Is preoperative ciliary body and iris anatomical configuration a predictor of malignant glaucoma development? Clin Experiment Ophthalmol. 2013;41(6):541-5.

12. Theelen T, Klevering BJ. Malignant glaucoma following blunt trauma of the eye. Ophthalmologe. 2005;102(1):77-81.

13. Calugaru M, Marin C. Current concepts in malignant glaucoma. Oftalmologia. 1990;34(1):15-25.

14. Wang N, Zhou W, Ouyang J, et al. Pathogenesis and clinical classification of the malignant glaucoma. Yan Ke Xue Bao. 1999;15(4):238-41.

15. Hu N, Gong Q, Guan H. Mechanism and treatment of malignant glaucoma. Zhonghua Yi Xue Za Zhi. 1998;78(3):225-6.

16. Wang Z, Huang J, Lin J,et al. Quantitative Measurements of the Ciliary Body in Eyes with Malignant Glaucoma after Trabeculectomy Using Ultrasound Biomicroscopy. Ophthalmology. 2013 Dec 6. pii: S0161-6420(13)01041-5. doi: 10.1016/j.ophtha.2013.10.035. [Epub ahead of print]

17. Liu L, Wang T, Li Z. Studies of mechanism of malignant glaucoma using ultrasound biomicroscope. Zhonghua Yan Ke Za Zhi. 1998;34(3):178-82.

18. Zhang WZ, Huang L, Ma J, et al. Retrospective clinical analysis of 118 cases with malignant glaucoma. Zhonghua Yan Ke Za Zhi. 2013;49(2):126-9

19. Dave P, Senthil S, Rao HL, Garudadri CS. Treatment outcomes in malignant glaucoma. Ophthalmology. 2013 May;120(5):984-90.

20. Sharma A, Sii F, Shah P, et al. Vitrectomy-phacoemulsification-vitrectomy for the management of aqueous misdirection syndromes in phakic eyes. Ophthalmology. 2006;113(11):1968-73.

21. Byrnes GA, Leen MM, Wong TP, et al. Vitrectomy for ciliary block (malignant) glaucoma. Ophthalmology. 1995;102(9):1308-11.

22. Chaudhry NA, Flynn HW Jr, Murray TG, et al. Pars plana vitrectomy during cataract surgery for prevention of aqueous misdirection in high-risk fellow eyes. Am J Ophthalmol. 2000;129(3):387-8.

23. Sharma A, Sii F, Shah P, et al. Vitrectomy-phacoemulsification-vitrectomy for the management of aqueous misdirection syndromes in phakic eyes. Ophthalmology. 2006;113(11):1968-73.

24. Bresson Dumont H, Ballereau L, Lehoux A, et al. Diode laser in "Malignant Glaucoma" treatment. J Fr Ophtalmol. 2006;29 Spec No 2:73-7.

25. Bitrian E, Caprioli J. Pars plana anterior vitrectomy, hyaloido-zonulectomy, and iridectomy for aqueous humor misdirection. Am J Ophthalmol. 2010;150(1):82-87.

26. Liu X, Li M, Cheng B, et al. Phacoemulsification combined with posterior capsulorhexis and anterior vitrectomy in the management of malignant glaucoma in phakic eyes. Acta Ophthalmol. 2013;91(7):660-5.

FUCHS' HETEROCHROMIC IRIDOCYCLITIS

Signs and Symptoms

Patients with Fuchs' heterochromic iridocyclitis present as young adults with variable vision loss, anterior chamber reaction and iris heterochromia.[1-3] There appears to be no racial or gender predilection. Initial vision

loss is caused by cataract and vitreous opacities. Progressive vision loss can be due to secondary open- or closed-angle glaucoma. Symptoms typical of acute anterior uveitis (e.g., pain, photophobia, lacrimation, redness) are rarely reported.[2,4] Approximately 90% of cases are unilateral, but bilateral cases have been reported.[1-3,5,6]

Heterochromia, long held as the main diagnostic criteria for this condition, is not invariably present. In patients with dark irides, heterochromia may be absent or overlooked.[6] In patients with blue eyes, the affected eye will appear darker. If the condition is bilateral, heterochromia will be absent or minimal at best. There is often loss of iris detail.

While clinically apparent heterochromia is not a universal sign, iris stromal atrophy (particularly within the crypts), which is the cause of the heterochromia, *is* invariably present.[4] There is a fragility to the iris and anterior chamber angles, and a high likelihood of hemorrhage following surgery or seemingly insignificant trauma such as gonioscopy due to a fine network of neovascularization.[7] These vessels commonly rupture during cataract surgery when the paracentesis is performed, leading to hyphema; such an event is highly suggestive of this condition. Common but often overlooked iris findings are Busacca and Koeppe nodules.[3,6]

A mild anterior chamber reaction and fine stellate keratic precipitates are hallmarks of this disease.[1,4,6,8] The reaction is not true inflammation, but a breakdown of the blood/aqueous barrier, likely from the fragile iris vessels and neovascularization. The keratic precipitates are small to medium in size and nongranulomatous. Posterior synechiae, commonly seen in true uveitis, is not a feature of this condition, nor is cystoid macular edema, as the condition is not predominately inflammatory.[9]

Cataract and glaucoma occur in approximately 80% and 15% to 25% of cases, respectively.[1-4,10,11] While not common, Fuchs' heterochromic iridocyclitis accounted for over 8% of endogenous uveitis in a large study.[12] Fuchs' is an underdiagnosed cause of uveitis.

Pathophysiology

There is no clear consensus regarding the etiology of Fuchs' heterochromic iridocyclitis. An infectious etiology has been strongly considered. There has been a significant association between Fuchs' heterochromic iridocyclitis and ocular toxoplasmosis.[5,13-15] However, it is not clear if there is a causal relationship between the conditions.

Further strengthening the assertion of an infectious etiology behind Fuchs' heterochromic iridocyclitis is the discovery of herpes simplex virus DNA in the aqueous humor of an eye with the condition.[16] Recent evidence also points to a possible association with the rubella virus.[8,17,18] Additionally, it seems that the *Chikungunya* virus has been associated.[19] An autoimmune etiology has also been proposed due to the association between Fuchs' heterochromic iridocyclitis and retinitis pigmentosa. Since autoimmune phenomena have been described in patients with retinitis pigmentosa, it is conceivable that it may increase the risk for the development of Fuchs' heterochromic iridocyclitis.[20,21]

The cellular response is predominately lymphocytes and plasma cells, along with few mast cells and eosinophils.[3] There are rarely posterior synechiae; however, anterior synechiae have been known to occur and contribute to the formation of glaucoma. Causes of glaucoma include secondary angle closure as a result of inflammation with peripheral anterior synechiae, rubeosis, lens-induced angle closure and secondary open-angle glaucoma as a result of recurrent spontaneous hyphema.[10]

Visually significant cataract occurring secondary to chronic inflammation accounts for the majority of the visual impairment. Vitreous opacities and inflammatory debris as well as advanced glaucoma can also cause vision loss.

Management

Correct diagnosis is especially important, to avoid ineffective treatments and give the clinician an awareness of the prognosis. In many cases, patients with Fuchs' heterochromic iridocyclitis are initially misdiagnosed with anterior uveitis or pars planitis.[3] Though anterior chamber reaction and stellate keratic precipitates characterize the condition, it is not responsive to steroids in any form.[8,22] Fuchs' heterochromic iridocyclitis does not cause a severe anterior chamber reaction. Most eyes have minimal anterior segment response for years, with some becoming entirely cell free.

Many eyes with Fuchs' heterochromic iridocyclitis receive chronic topical steroid therapy due to misdiagnosis, contributing to cataract formation and glaucoma.[23] Chronic, mild anterior chamber reactions can often be tolerated without morbidity and thus a lack of a viable treatment is not detrimental. Unfortunately, the chronic accumulation of keratic precipitates, vitreous debris and cataract over time can diminish vision, with the formation of peripheral anterior synechiae eventually leading to glaucoma.[23]

Visual rehabilitation can be easily accomplished through cataract extraction, with minimal complications. Eyes with Fuchs' heterochromic iridocyclitis tolerate phacoemulsification with posterior chamber lens implantation well.[24-27] In patients with visually significant vitreous debris, pars plana vitrectomy—either separately or in conjunction with cataract surgery—will benefit most patients.[26,28]

Glaucoma carries the most risk of significant ocular morbidity in Fuchs' heterochromic iridocyclitis, and must be managed aggressively. Aqueous suppressants are the topical treatment of choice. Miotics should be avoided.

Restasis®
(Cyclosporine Ophthalmic Emulsion) 0.05%

For patients with decreased tear production presumed to be due to ocular inflammation associated with Chronic Dry Eye

THE DRY EYE TREATMENT SHE NEEDS TODAY. BECAUSE TOMORROW MATTERS.

RESTASIS® twice a day, every day, helps patients experience increased tear production

Increased tear production was seen at 6 months.[1]

Indication and Usage

RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

Important Safety Information

Contraindications

RESTASIS® is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

Warnings and Precautions

Potential for Eye Injury and Contamination: To avoid the potential for eye injury and contamination, individuals prescribed RESTASIS® should not touch the vial tip to their eye or other surfaces.

Use With Contact Lenses: RESTASIS® should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion.

Adverse Reactions

In clinical trials, the most common adverse reaction following the use of RESTASIS® was ocular burning (upon instillation)—17%. Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

Please see Brief Summary of the full Prescribing Information on adjacent page.

Reference: 1. RESTASIS® Prescribing Information.

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RESTASIS® (Cyclosporine Ophthalmic Emulsion) 0.05%

BRIEF SUMMARY—PLEASE SEE THE RESTASIS® PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION.

INDICATION AND USAGE

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WARNINGS AND PRECAUTIONS

Potential for Eye Injury and Contamination

To avoid the potential for eye injury and contamination, be careful not to touch the vial tip to your eye or other surfaces.

Use with Contact Lenses

RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, the most common adverse reaction following the use of **RESTASIS®** was ocular burning (17%).

Other reactions reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

Post-marketing Experience

The following adverse reactions have been identified during post approval use of **RESTASIS®**. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Reported reactions have included: hypersensitivity (including eye swelling, urticaria, rare cases of severe angioedema, face swelling, tongue swelling, pharyngeal edema, and dyspnea); and superficial injury of the eye (from the vial tip touching the eye during administration).

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C

Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), cyclosporine oral solution, USP, was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 5,000 and 32,000 times greater (normalized to body surface area), respectively, than the daily human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses in rats and rabbits are approximately 3,000 and 10,000 times greater (normalized to body surface area), respectively, than the daily human dose.

Offspring of rats receiving a 45 mg/kg/day oral dose of cyclosporine from Day 15 of pregnancy until Day 21 postpartum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 7,000 times greater than the daily human topical dose (0.001 mg/kg/day) normalized to body surface area assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (2,000 times greater than the daily human dose).

There are no adequate and well-controlled studies of **RESTASIS®** in pregnant women. **RESTASIS®** should be administered to a pregnant woman only if clearly needed.

Nursing Mothers

Cyclosporine is known to be excreted in human milk following systemic administration, but excretion in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of **RESTASIS®** ophthalmic emulsion, caution should be exercised when **RESTASIS®** is administered to a nursing woman.

Pediatric Use

The safety and efficacy of **RESTASIS®** ophthalmic emulsion have not been established in pediatric patients below the age of 16.

Geriatric Use

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low-dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 80 times greater (normalized to body surface area) than the daily human dose of one drop (approximately 28 mcL) of 0.05% **RESTASIS®** twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Mutagenesis: Cyclosporine has not been found to be mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE).

Impairment of Fertility: No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 2,000 times the human daily dose of 0.001 mg/kg/day normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.

PATIENT COUNSELING INFORMATION

Handling the Container

Advise patients to not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion. To avoid the potential for injury to the eye, advise patients to not touch the vial tip to their eye.

Use with Contact Lenses

RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that if contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of **RESTASIS®** ophthalmic emulsion.

Administration

Advise patients that the emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Rx Only

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Prostaglandin analogs should be considered as a last medical option. While the disease often responds well to medical therapy, trabeculectomy is frequently needed. Compared to uncomplicated open-angle glaucoma, the surgical outcome is less favorable and similar to outcome statistics seen in uveitic glaucoma.[22] Antimetabolites are used to optimize surgical results.[10,11,29]

Clinical Pearls

- Despite the clinically apparent anterior chamber reaction, do not treat patients with Fuchs' heterochromic iridocyclitis with topical steroids, as they are ineffective. Accept that no treatment may be the best treatment for the cellular reaction. Instead, concentrate management efforts at the comorbid glaucoma and cataract.
- Consider Fuchs' heterochromic iridocyclitis in patients with anterior uveitis unresponsive to steroid therapy. In fact, unresponsiveness to topical steroids can be a diagnostic sign of Fuchs' heterochromic iridocyclitis.
- Its name notwithstanding, do not rely upon heterochromia to make a diagnosis of Fuchs' heterochromic iridocyclitis. Many patients will not manifest heterochromia. Instead, examine carefully for iris atrophy (especially within the crypts) and iris nodules.

1. Velilla S, Dios E, Herreras JM, et al. Fuchs' heterochromic iridocyclitis: a review of 26 cases. Ocul Immunol Inflamm. 2001;9(3):169-75.

2. Fearnley IR, Rosenthal AR. Fuchs' heterochromic iridocyclitis revisited. Acta Ophthalmol Scand. 1995;73(2):166-70.

3. Jones NP. Fuchs' Heterochromic Uveitis: a reappraisal of the clinical spectrum. Eye. 1991;5 (Pt 6):649-61.

4. La Hey E, Baarsma GS, De Vries J, et al. Clinical analysis of Fuchs' heterochromic cyclitis. Doc Ophthalmol. 1991;78(3-4):225-35.

5. Ganesh SK, Sharma S, Narayana KM, et al. Fuchs' heterochromic iridocyclitis following bilateral ocular toxoplasmosis. Ocul Immunol Inflamm. 2004;12(1):75-7.

6. Arellanes-Garcia L, del Carmen Preciado-Delgadillo M, Recillas-Gispert C. Fuchs' heterochromic iridocyclitis: clinical manifestations in dark-eyed Mexican patients. Ocul Immunol Inflamm. 2002;10(2):125-31.

7. Ward DM, Hart CT: Complicated cataract extraction in Fuchs's heterochromic uveitis. Br J Ophthalmol 1967; 51:530-8.

8. Gordon L. Fuch's heterochromic cyclitis: new clues regarding pathogenesis. Am J Ophthalmol. 2004;138(1):133-4.

9. Tandon M, Malhotra PP, Gupta V, et al. Spectrum of Fuchs uveitic syndrome in a North Indian population. Ocul Immunol Inflamm. 2012;20(6):429-33.

10. Jones NP. Glaucoma in Fuchs' Heterochromic Uveitis: aetiology, management and outcome. Eye. 1991;5 (Pt 6):662-7.

11. La Hey E, de Vries J, Langerhorst CT, et al. Treatment and prognosis of secondary glaucoma in Fuchs' heterochromic iridocyclitis. Am J Ophthalmol. 1993;116(3):327-40.

12. Pivetti-Pezzi P, Accorinti M, La Cava M, et al. Endogenous uveitis: an analysis of 1,417 cases. Ophthalmologica. 1996;210(4):234-8.

13. Schwab IR. The epidemiologic association of Fuchs' heterochromic iridocyclitis and ocular toxoplasmosis. Am J Ophthalmol. 1991;111(3):356-62.

14. La Heij E, Rothova A. Fuchs's heterochromic cyclitis in congenital ocular toxoplasmosis. Br J Ophthalmol. 1991;75(6):372-3.

15. Jad A, C Céline T, BahramB, et al. Fuchs' heterochromic cyclitis: a post-infectious manifestation of ocular toxoplasmosis? International Ophthalmology 2013; 33(2),189-94.

16. Barequet IS, Li Q, Wang Y, et al. Herpes simplex virus DNA identification from aqueous fluid in Fuchs heterochromic iridocyclitis. Am J Ophthalmol. 2000;129(5):672-3.

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18. Suzuki J, Goto H, Komase K, et al. Rubella virus as a possible etiological agent of Fuchs heterochromic iridocyclitis. Graefe's Archive for Clinical and Experimental Ophthalmology 2010; 248(10):1487-91.

19. Mahendradas P, Shetty R, Malathi J, Madhavan HN. Chikungunya virus iridocyclitis in Fuchs' heterochromic iridocyclitis. Indian J Ophthalmol. 2010;58(6):545-7.

20. Chowers I, Zamir E, Banin E, et al. Retinitis pigmentosa associated with Fuchs' heterochromic uveitis. Arch Ophthalmol. 2000;118(6):800-2.

21. Lichtinger A, Chowers I, Amer R. Usher syndrome associated with Fuchs' heterochromic uveitis. Graefe's Archive for Clinical and Experimental Ophthalmology 2010;248(10):1481-5.

22. Jones NP. Fuch's heterochromic uveitis: An update. Surv Ophthalmol 1993; 37(4):253-72.

23. O'Connor GR. Heterochromic iridocyclitis. Trans Ophthalmol Soc UK 1985; 104:219-31.

24. Cheng B, Liu Y. Phacoemulsification in eyes with Fuchs' heterochromic iridocyclitis. Yan Ke Xue Bao. 2000;16(2):97-8.

25. Budak K, Akova YA, Yalvac I, et al. Cataract surgery in patients with Fuchs' heterochromic iridocyclitis. Jpn J Ophthalmol. 1999;43(4):308-11.

26. Soheilian M, Karimian F, Javadi MA, et al. Surgical management of cataract and posterior chamber intraocular lens implantation in Fuchs' heterochromic iridocyclitis. Int Ophthalmol. 1997;21(3):137-41.

27. Kosker M, Sungur G, Celik T, et al. Phacoemulsification with intraocular lens implantation in patients with anterior uveitis. Journal of Cataract & Refractive Surgery 2013; 39(7):1002-1007.

28. Scott RA, Sullivan PM, Aylward GW, et al. The effect of pars plana vitrectomy in the management of Fuchs heterochromic cyclitis. Retina. 2001;21(4):312-6.

29. You Y, Wu Y, Hu S. Surgical management of secondary glaucoma in Fuchs' heterochromic iridocyclitis. Graefe's Archive for Clinical and Experimental Ophthalmology 2013; 251(7): 1785-90.

GLAUCOMATOCYCLITIC CRISIS

Signs and Symptoms

The initial precipitating event in glaucomatocyclitic crisis (GCC) is the acute onset of a mild, self-limiting uveitis followed by a disproportionately large intraocular pressure (IOP) elevation. Glaucomatocyclitic crisis typically occurs between ages 20 and 50.[1-3] It is considered uncommon after age 60 and before age 20, though there have been instances of children with the condition.[4]

Glaucomatocyclitic crisis is typically recurrent and unilateral, with a duration of attack from a few hours to several weeks, though, most resolve within days.[5-7] When it recurs, it afflicts the same eye. Bilateral, simultaneous involvement is highly uncommon.[8, 9]

Patient complaints include mildly blurred vision, as well as ocular and periorbital discomfort; however, they may possibly report no symptoms at all.[5-7, 10] There may be a slightly injected eye with a mild anterior chamber inflammatory reaction and centrally located keratic precipitates.[1,2] Flare, though common in uveitis, is not common in GCC. Synechiae typically do not form. Classic uveitic symptoms of pain, photophobia and lacrimation are absent in GCC. There is a markedly elevated IOP, ranging between 30mm Hg and 40mm Hg, although there have been cases where IOP has exceeded 70mm Hg.[1,2,6,7,10] The elevated IOP serves to disrupt the sodium-potassium pump on the corneal endothelium, with resultant corneal edema and associated symptoms of blurred vision and halos.

As far back as 1947, GCC was identified and classically described by Drs. Posner and Schlossman.[1] Their description was so thorough and accurate, standing the test of time, that the condition has been also synonymously known as Posner-Schlossman syndrome. Their historic, insightful description characterized the condition as follows:

Centrally located keratic precipitates in an eye with glaucomatocyclitic crisis.

(1) Elevated intraocular pressure appears nearly simultaneously with inflammatory cells in the anterior chamber, followed by one to 20 unpigmented keratic precipitates on the corneal endothelium. Posterior synechiae are never formed.

(2) The eye is white or there may be minimal dilation of the conjunctival vessels without ciliary flush.

(3) The anterior chamber angles are open gonioscopically.

(4) The condition is unilateral. *(Today, bilateral cases—while rare—are recognized as possible.)*

(5) The presenting symptoms include slight discomfort, colored halos, visual blurring and an absence of frank pain. The patient may also be completely asymptomatic.

(6) The attacks last from hours to one month, but typically spontaneously resolve within two weeks.

(7) The episodes may recur with varying frequency and are unpredictable and unprovoked.

Pathophysiology

Glaucomatocyclitic crisis has long been considered an idiopathic inflammatory disease preferentially affecting the trabecular meshwork. Both herpes zoster and cytomegalovirus (CMV) have been associated with glaucomatocyclitic crisis.[11-13] Additionally, aqueous samples

aspirated from patients in glaucomatocyclitic crisis have been positive for genomic fragments of herpes simplex virus (though no live virus has been sampled), whereas no such genetic material is found in normal patients.[14] Currently, there is ample evidence of viral involvement in GCC, particularly for CMV.[15-17] However, CMV is not invariably present in the aqueous humor of all eyes with GCC; thus, the understanding of the pathophysiology of this syndrome remains incomplete.

The trabecular meshwork is innervated by the trigeminal nerve (V1), which serves as a conduit for virus to reach the eye. It has been postulated that viral-induced inflammation of the trabecular meshwork (acute trabeculitis) impedes the tissue's aqueous processing ability. This is supported by GCC's status as a nongranulomatous uveitic syndrome with no pronounced inflammatory cellular response causing mechanical obstruction of the trabecular meshwork, nor synechiae development leading to angle closure. The inflammatory cells visible in GCC are mononuclear phagocytes.[6]

During GCC episodes, there is a measurable increase in prostaglandin levels in the aqueous, particularly prostaglandin E, which correlates particularly well with IOP elevation. During periods of remission, there is a marked decrease in the level of aqueous prostaglandins as well as an increased outflow facility.[18] A likely hypothesis is that prostaglandin E incites the trabecular meshwork inflammation.[14] Further, prostaglandins serve to increase the permeability of the ciliary blood vessels, leading to fluid diffusion from the ciliary body and increased aqueous production.[19]

Fluorescein flow studies demonstrate that during the acute phase of GCC, there is increased flow of aqueous into the anterior chamber compared to the normal fellow eye. There is also decreased aqueous production when an eye is not in crisis. This indicates that the rise in IOP is due not only to reduced aqueous drainage but also increased aqueous humor production.[18]

Studies using confocal scanning laser tomography to measure optic disc topography during and after GCC episodes postulate a theory of plasticity. Patients demonstrated significant decreases in glaucomatous disc topography following IOP reduction. There were also significant increases in disc rim area and volume following cessation of the attack. These studies noted that there can be an increase in cupping during attack and that a reversal of cupping and optic disc topography improvement can be achieved with IOP reduction.[20,21]

Management

As GCC is an inflammatory condition, the most effective treatment for both the inflammation and the secondary IOP elevation is a topical steroid.[1,5-8] In that the inflammation is mild, doses of a steroid such as prednisolone acetate 1% greater than hourly are not necessary. As synechiae are unlikely to occur and patients are only minimally uncomfortable, cycloplegia is also usually unnecessary. However, the use of a mild cycloplegic agent is not contraindicated and may be employed on a case-by-case basis.

Successful reduction of intraocular pressure in glaucomatocyclitic crisis has been documented with carbonic anhydrase inhibitors, topical beta-blockers and alpha-2 adrenergic agonists.[22-24] However, all medications employed to reduce intraocular pressure should only be used adjunctively with anti-inflammatory therapy. Obviously, since GCC is an inflammatory condition, miotics and prostaglandin analogs should be avoided as they can exacerbate inflammation. Additionally, laser trabeculoplasty should be avoided due to the potential to further inflame the trabecular meshwork. In extremely recalcitrant cases, trabeculectomy remains a viable option in IOP management.[25,26]

There are some controversies and peculiarities involving GCC. While it has been considered that GCC is a benign and self-limiting disease, that clearly is not always the case.[2,27] While permanent glaucomatous damage is not typical, it can occur, especially in patients with frequent recurrences and prolonged attacks, and there appears to be a positive association with primary open-angle glaucoma development.[1,2,5,28] There have also been instances of non-arteritic anterior ischemic optic neuropathy (NAAION) developing during GCC episodes.[29,30] It has been postulated that the markedly elevated IOP in patients with small, crowded discs further compromises blood flow. Optic atrophy has also been reported following recurrent GCC episodes, presumably from a similar pathophysiology.[31]

As it has been shown that a significant number of eyes with GCC likely have a viral etiology such as herpes or CMV, anti-viral therapy remains a consideration. Recently, it has been shown that valganciclovir (Valcyte, Genentech), an oral anti-CMV agent, is effective both at managing the acute form of the syndrome as well as suppressing recurrent outbreaks. It is noted that these results were in eyes that demonstrated CMV in the aqueous humor with no other virus present or had failed previous acyclovir therapy.[32,33] The dosage was 900mg BID for two weeks, followed by 450mg BID as long-term suppression therapy. Cessation of therapy usually resulted in recurrence.

Because it has never been proven that all cases of GCC are due to CMV or any virus, blanket recommendation of using oral antiviral medications to manage or suppress GCC has no evidenced-based support.

Clinical Pearls

- In most cases, GCC is a benign, self-limiting disease. Occasionally, however, it is not.

- The initial presentation of GCC is easily missed. Often, a patient will present with a unilaterally elevated IOP with no apparent or obvious cause. A mild anterior chamber reaction can initially be missed in a cursory evaluation.
- Always address management preferentially towards inflammation control and secondarily towards IOP reduction. In that the pressure elevation is secondary to inflammatory processes, steroids will have the added benefit of reducing IOP in this condition.
- Many cases of GCC with modest pressure elevations can be successfully managed with steroids alone.
- Patients with moderate to heavy anterior chamber reactions, ocular pain and redness who are otherwise moderately symptomatic probably do not have GCC, but rather uveitic glaucoma that may require more aggressive management and systemic testing.
- GCC is not only idiopathic but idiosyncratic as well. That is, the patient may have extremely elevated IOP but will be minimally symptomatic and unlikely to manifest immediate permanent glaucomatous damage. We have seen GCC patients present with IOP in excess of 70mm Hg yet be only mildly bothered by slightly blurred vision. A patient with a similar IOP rise from acute angle-closure glaucoma will be significantly ill and risk profound vision loss, which may perhaps be permanent.
- There is strong support for a viral etiology in many eyes with GCC, but there are no controlled clinical studies examining the use of oral acyclovir as a suppressant therapy. Even so, acyclovir may be a safe option to try in patients with vision loss from multiple or prolonged recurrences.

1. Posner A, Schlossman A. Syndrome of unilateral recurrent attacks of glaucoma with cyclitic symptoms. Arch Ophthalmol 1948; 39:517-35.

2. Jap A, Sivakumar M, Chee SP. Is Posner Schlossman syndrome benign? Ophthalmology. 2001;108(5):913-8.

3. Ritcher R, Shields MB, Krupin T. The Glaucomas. St Louis; Mosby 1989:1205-20.

4. Burnstein Y, Shelton K, Higginbotham EJ. Glaucomatocyclitic crisis in a child. Am J Ophthalmol 1998;126(1):136-7.

5. Harrington JR. Posner-Schlossman syndrome: A case report. J Am Opt Assoc. 1999:70;11:715-23.

6. Harstad HK, Ringold A. Glaucomatocyclitic crises (Posner-Schlossman syndrome): a case report. Acta Ophthalmologica 1986; 64(2):146-51.

7. Raitta C, Vannas A. Glaucomatocyclitic crisis. Arch Ophthalmol 1977; 95(4):608-12.

8. Levatin P. Glaucomatocyclitic crises occurring in both eyes. Am J Ophthalmol 1956; 41:1056-9.

9. Puri P, Verma D. Bilateral glaucomatocyclitic crisis in a patient with Holmes Adie syndrome. J Postgrad Med; 1998; 44(3): 76-7.

10. Hahn IH, Stillman MC. A case of glaucomatocyclitic crisis in the emergency department. Ann Emerg Med. 2006; 47(2):167-9.

11. Bloch-Michel E, Dussaix E, Cerqueti P, et al. Possible role of cytomegalovirus infection in the etiology of the Posner-Schlossman syndrome. Int Ophthalmol 1987; 11(2):95-6.

12. Tanaka Y, Harino S, Hara J. Cellular immunity as judged by varicella skin test in Posner Schlossman patients. Folia Jpn 1985; 36:972-6.

13. Teoh SB, Thean L, Koay E. Cytomegalovirus in aetiology of Posner-Schlossman syndrome: evidence from quantitative polymerase chain reaction. Eye. 2005;19(12):1338-40.

14. Yamamoto S, Pavan-Langston D, Tada R, et al. Possible role of herpes simplex virus in the origin of Posner-Schlossman syndrome. Am J Ophthalmol 1995; 119(6):796-98.

15. Li J, Ang M, Cheung CM, et al. Aqueous cytokine changes associated with Posner-Schlossman syndrome with and without human cytomegalovirus. PLoS One. 2012;7(9):e44453.

16. Yang SY, Chen MJ, Chen KH,et al. Cytomegalovirus and herpes simplex virus as causes of bilateral anterior uveitis in an immunocompetent patient. J Chin Med Assoc. 2011;74(1):48-50.

17. Rodier-Bonifas C, Cornut PL, Billaud G, et al. Cytomegalovirus research using polymerase chain reaction in Posner-Schlossman syndrome. J Fr Ophtalmol. 2011;34(1):24-9.

18. Grant WM. Clinical measurements of aqueous outflow. Arch Ophthalmol 1951; 46:113-24.

19. Eakins K. Increased intraocular pressure produced by prostaglandins E1 and E2 in the cat eye. Exp Eye Res 1970; 10:87-92.

20. Park KH, Hong C. Reversal of optic disc topography in patients with glaucomatcyclitic crisis after remission of attack. J Glaucoma 1998;7(4):225-9.

21. Darchuk V, Sampaolesi J, Mato L, et al. Optic nerve head behavior in Posner-Schlossman syndrome. Int Ophthalmol. 2001;23(4-6):373-9.

22. Hung PT, Chang JM. Treatment of glaucomatocyclitic crises. Am J Ophthalmol 1974; 77(2):169-72.

23. Ohno S, Ichiisi A, Matsuda H. Hypertensive effects of Carteolol on intraocular pressure elevation and secondary glaucoma associated with endogenous uveitis. Ophthalmologica 1989;199:41-5.

24. Muthusamy P. Apraclonidine in the management of glaucomatocyclitic crisis. Eye 1994; 8(3):367-8.

25. Dinakaran S, Kayarkar V. Trabeculectomy in the management of Posner-Schlossman syndrome. Ophthalmic Surg Lasers. 2002; 33(4):321-2.

26. Zhong Y, Cheng Y, Liu X, Feng P. Trabeculectomy in the management of glaucomatocyclitic crisis with visual field defect. Ocul Immunol Inflamm. 2010;18(3):233-6.

27. Theodore F. Observations on glaucomatocyclitic crisis (Posner-Schlossman syndrome). Br J Ophthalmol 1952;36:207-10.

28. Kass MA, Becker, B, Kolker AE. Glaucomatocycltic crisis and primary open angle glaucoma. Am J Ophthalmol 1973;75:668-73.

29. Irak I, Katz BJ, Zabriskie NA, et al. Posner-Schlossman syndrome and nonarteritic anterior ischemic optic neuropathy. J Neuroophthalmol. 2003;23(4):264-7.

30. Kim R, Van Stavern G, Juzych M. Nonarteritic anterior ischemic optic neuropathy associated with acute glaucoma secondary to Posner-Schlossman syndrome. Arch Ophthalmol. 2003;121(1):127-8.

31. Kim TH, Kim JL, Kee C. Optic disc atrophy in patient with Posner-Schlossman syndrome. Korean J Ophthalmol. 2012;26(6):473-7.

32. Sobolewska B, Deuter C, Doycheva D, Zierhut M. Long-term oral therapy with valganciclovir in patients with Posner-Schlossman syndrome. Graefes Arch Clin Exp Ophthalmol. 2014;252(1):117-24.

33. Wong VW, Chan CK, Leung DY, Lai TY. Long-term results of oral valganciclovir for treatment of anterior segment inflammation secondary to cytomegalovirus infection. Clin Ophthalmol. 2012;6:595-600.

PEDIATRIC AND CONGENITAL GLAUCOMA

Signs and Symptoms

Pediatric glaucoma is a term that includes any form of glaucoma that presents between birth and age 18 years.[1,2] Pediatric glaucomas can be either primary or secondary and the angle may be open or closed. However, there is confusing and overlapping terminology. Primary congenital and primary infantile glaucoma occur secondary to trabeculodysgenesis, a developmental angle anomaly. This can be diagnosed any time between birth and early childhood. *Pediatric developmental glaucomas* are also classified by the time that they appear in a patient; *primary congenital glaucoma* occurs between birth and two months of age, *primary infantile glaucoma* between two months and two years of age, and *late-onset primary infantile glaucoma* (also known as *juvenile glaucoma*) after two years of age.[1]

Primary infantile glaucoma overlaps with *juvenile-onset open-angle glaucoma* (JOAG), a non-developmental glaucoma similar to primary open-angle glaucoma in adults, which develops late in childhood in the absence of angle anomalies.[1,2] It is most commonly accepted

that the term *primary congenital glaucoma* refers to patients in all three age groups in the presence of developmental anterior chamber angle abnormalities.[1,3]

Patients with primary congenital and infantile glaucoma typically manifest a classic triad of photophobia, lacrimation and blepharospasm.[1,3,4] These occur due to corneal changes such as edema secondary to elevated intraocular pressure (IOP). Buphthalmos develops from the distensibility of immature collagen within the infant corneal stroma. Horizontal breaks in Descemet's membrane known as Haab's striae commonly occur. These findings strongly suggest the presence of primary congenital glaucoma; they are not present if glaucoma develops after the age of three. In older children, glaucoma is diagnosed in the same way it is in adults; that is, by observing optic disc damage, elevated intraocular pressure and structural and functional changes consistent with glaucoma, in the absence of trabeculodysgenesis.

In patients with primary congenital glaucoma, abnormalities in the anterior chamber angle are diagnostic. The iris and ciliary body are anteriorly located, with iris tissue inserting into and overlapping the trabecular meshwork, impeding the outflow of aqueous.

Primary congenital glaucoma is the most common form of pediatric glaucoma.[1-4] The second most common form occurs in aphakic or pseudophakic children following congenital cataract surgery.[1,5-12] The mechanism in aphakic glaucoma is unclear, but gonioscopy may reveal a blockage of the trabecular meshwork secondary to an acquired repositioning of the iris against the posterior trabecular meshwork. There is often associated abnormal pigmentation and synechiae formation within the meshwork.[5] Beyond these conditions, glaucoma can occur in a pediatric patient from a number of other causes, including but not limited to trauma, inflammation, episcleral venous pressure elevation (as seen in Sturge-Weber syndrome), tumor, pupil block from subluxation, retinopathy of prematurity and infectious disease.[1,13-18]

Pathophysiology

The totality of pediatric glaucoma results in a diverse pathophysiology due to the wide range of possible associated conditions. Primary congenital and infantile glaucoma, however, clearly results from a developmental arrest of the iris and ciliary body in the seventh month of gestation.[19] These structures insert in an anterior location with iris tissue overlapping the trabecular meshwork, impeding aqueous outflow resulting in subsequent IOP elevation.[1,19] There is also developmental immaturity of the trabecular meshwork, with thickened trabecular tissue and an abnormal ground matrix.[1]

Primary congenital glaucoma appears to be autosomal recessive.[3] Two genetic loci—GLC3A and GLC3B—have been identified in a majority of hereditary cases.[20,21] An autosomal dominant JOAG has been linked to the GLC1A gene. Mutations in the trabecular meshwork inducible glucocorticoid response protein (TIGR) gene have also been identified in families with JOAG.[3,22]

Management

Proper management of any pediatric glaucoma begins with accurate diagnosis and categorization of the glaucoma. In older children with JOAG, IOP measurement, disc analysis, visual field testing and diagnostic retinal nerve fiber layer imaging can all be beneficial. In infants and younger children, these tests may not be possible or practical. In such cases, IOP measurement, along with observation of corneal clouding, corneal diameter measurement and inspection for Haab's striae become more important. Examination under sedation or general anesthesia may be necessary. Gonioscopy is critically important, as recognizing abnormal angle anatomy (trabeculodysgenesis) plays a significant role in the development of the management plan.

Primary congenital glaucoma is best managed surgically, with medications only used adjunctively. The most performed and successful surgeries for primary congenital glaucoma are the angle surgeries—goniotomy and trabeculotomy. The former involves inserting a goniotomy knife into the anterior chamber and incising the anterior aspect of the middle third of the trabecular meshwork over 120°.[1] In trabeculotomy, an external dissection of Schlemm's canal is performed over 180° of the anterior chamber angle.[1]

Goniotomy and trabeculotomy are typically very successful for primary congenital glaucoma. Goniotomy is performed when a clear cornea allows angle visualization, while trabeculotomy is preferred in cases involving a cloudy cornea. However, these procedures are less successful for cases of pediatric glaucoma other than primary congenital and infantile forms. In these cases, trabeculectomy with adjunctive antimetabolite application is a common procedure. In refractory cases, combined trabeculectomy with glaucoma drainage implant devices offer the most successful and predictable option.[23-30]

More recently, deep sclerectomy and circumferential trabeculotomy have met with success in managing congenital and childhood glaucoma.[31,32] Even more recently, transscleral cyclophotocoagulation and endoscopic cyclophotocoagulation have been seen to be safe, effective and comparable treatments that may be considered first-line therapy to achieve control of IOP in all forms of pediatric glaucoma. These procedures, when effective, can allow the patient to avoid a penetrating procedure.[33]

While surgery is the preferred treatment for pediatric developmental glaucoma, there are times where medi-

cations may be necessary, either prior to or adjunctively with surgery. For the majority of glaucoma meds, pediatric use is considered off label and safety and efficacy have not been studied; clinical guidance has been obtained through case series and retrospective analyses. Topical beta-blockers have been deemed safe and effective when used in children.[34-36] Prostaglandin analogs are safe and well tolerated, but unfortunately not very effective in the pediatric glaucoma population. Older children with JOAG demonstrate the best efficacy response.[37-39]

When used in children, topical carbonic anhydrase inhibitors (CAIs) are safe and effective in lowering IOP.[40,41] Brimonidine, though effective in lowering IOP in children, crosses the blood/brain barrier and can potentially affect the central nervous system. This medication has demonstrated an unacceptable level of adverse events in children and should be avoided if possible.[42-44]

Upon lowering IOP in infants, reversal of cupping as well as corneal clearing has been observed. However, once buphthalmos has occurred, the globe will not return to normal size.[4,45]

Clinical Pearls

- Aphakic and pseudophakic children must be followed life-long for the development of glaucoma. However, the presence of an intraocular lens seems to reduce the incidence of glaucoma development, though the reasons are unclear.
- IOP does not have to be dramatically high in a child for glaucoma to develop. IOP above 20mm Hg is concerning.
- Congenital, infantile and developmental glaucoma implies trabeculodysgenesis. A child with glaucoma but without angle abnormalities has JOAG or another secondary glaucoma.
- In rare instances where topical glaucoma medications in children are indicated, preferences include CAIs and beta-blockers. Prostaglandins are reserved only for cases involving older children with JOAG. Brimonidine should always be avoided.

1. Beck AD. Diagnosis and management of pediatric glaucoma. Ophthalmol Clin North Am. 2001;14(3):501-12.
2. Luntz MH. Congenital, infantile, and juvenile glaucoma. Ophthalmology 1979; 86(5):793-802.
3. Ho CL, Walton DS. Primary congenital glaucoma: 2004 update. J Pediatr Ophthalmol Strabismus. 2004;41(5):271-88.
4. DeLuise VP, Anderson DR. Primary infantile glaucoma (congenital glaucoma). Surv Ophthalmol 1983;28(1):1-19.
5. Walton DS. Pediatric aphakic glaucoma: a study of 65 patients. Trans Am Ophthalmol Soc. 1995;93:403-13.
6. Magnusson G, Abrahamsson M, Sjostrand J. Glaucoma following congenital cataract surgery: an 18-year longitudinal follow-up. Acta Ophthalmol Scand. 2000;78(1):65-70.
7. Chen TC, Walton DS, Bhatia LS. Aphakic glaucoma after congenital cataract surgery. Arch Ophthalmol. 2004;122(12):1819-25.
8. Egbert JE, Christiansen SP, Wright MM, et al. The natural history of glaucoma and ocular hypertension after pediatric cataract surgery. J AAPOS. 2006;10(1):54-7.
9. Asrani S, Freedman S, Hasselblad V, et al. Does primary intraocular lens implantation prevent "aphakic" glaucoma in children? J AAPOS. 2000;4(1):33-9.
10. Trivedi RH, Wilson ME Jr, Golub RL. Incidence and risk factors for glaucoma after pediatric cataract surgery with and without intraocular lens implantation. J AAPOS. 2006;10(2):117-23.
11. Bhola R, Keech RV, Olson RJ, et al. Long-term outcome of pediatric aphakic glaucoma. J AAPOS. 2006;10(3):243-8.
12. Brady KM, Atkinson CS, Kilty LA, Hiles DA. Glaucoma after cataract extraction and posterior chamber lens implantation in children. J Cataract Refract Surg. 1997;23 Suppl 1:669-74.
13. Di Rocco C, Tamburrini G. Sturge-Weber syndrome. Childs Nerv Syst. 2006;22(8):909-21.
14. Sijssens KM, Rothova A, Berendschot TT, et al. Ocular hypertension and secondary glaucoma in children with uveitis Ophthalmology. 2006;113(5):859.e1-2.
15. Freedman SF, Rodriguez-Rosa RE, Rojas MC, et al. Goniotomy for glaucoma secondary to chronic childhood uveitis. Am J Ophthalmol. 2002;133(5):617-21.
16. Kafkala C, Hynes A, Choi J, et al. Ahmed valve implantation for uncontrolled pediatric uveitic glaucoma. J AAPOS. 2005;9(4):336-40.
17. Taylor RH, Ainsworth JR, Evans AR, et al. The epidemiology of pediatric glaucoma: the Toronto experience. J AAPOS. 1999;3(5):308-15.
18. Awad AH, Mullaney PB, Al-Mesfer S, et al. Glaucoma in Sturge-Weber syndrome. J AAPOS. 1999;3(1):40-5.
19. Maumenee AE. Further observations on the pathogenesis of congenital glaucoma. Trans Am Ophthalmol Soc 1963; 55: 1163-76.
20. Sarfarazi M, Akarsu AN, Hossain A et al. Assignment of a locus (GLC3A) for primary congenital glaucoma (Buphthalmos) to 2p21 and evidence of genetic heterogeneity. Genomics 1995; 30(2): 171-7.
21. Sarfarazi M, Stoilov I. Molecular genetics of primary congenital glaucoma. Eye 2000; 14:422-8.
22. Richards JE, Ritch R, Lichter PR, et al. Novel trabecular meshwork inducible glucocortocoid response mutation in an eight-generation juvenile-onset primary open angle glaucoma pedigree. Ophthalmology 1998;105:1698-1707.
23. Tesser R, Hess DB, Freedman SF. Combined intraocular lens implantation and glaucoma implant (tube shunt) surgery in pediatric patients: a case series. J AAPOS. 2005;9(4):330-5.
24. Englert JA, Freedman SF, Cox TA. The Ahmed valve in refractory pediatric glaucoma. Am J Ophthalmol. 1999;127(1):34-42.
25. Sidoti PA, Belmonte SJ, Liebmann JM, et al. Trabeculectomy with mitomycin-C in the treatment of pediatric glaucomas. Ophthalmology. 2000;107(3):422-9.
26. Tanimoto SA, Brandt JD. Options in pediatric glaucoma after angle surgery has failed. Curr Opin Ophthalmol. 2006;17(2):132-7.
27. Ishida K, Mandal AK, Netland PA. Glaucoma drainage implants in pediatric patients. Ophthalmol Clin North Am. 2005;18(3):431-42.
28. Al-Hazmi A, Awad A, Zwaan J, et al. Correlation between surgical success rate and severity of congenital glaucoma. Br J Ophthalmol. 2005;89(4):449-53.
29. Morales J, Al Shahwan S, Al Odhayb S, et al. Current surgical options for the management of pediatric glaucoma. J Ophthalmol. 2013;2013: 763735: Epub 2013 Apr 24.
30. Ou Y, Caprioli J. Surgical management of pediatric glaucoma. Dev Ophthalmol. 2012;50:157-72.
31. Al-Obeidan SA, Osman Eel-D, Dewedar AS, et al. Efficacy and safety of deep sclerectomy in childhood glaucoma in Saudi Arabia. Acta Ophthalmol. 2014;92(1):65-70.
32. Girkin CA, Marchase N, Cogen MS. Circumferential trabeculotomy with an illuminated microcatheter in congenital glaucomas. J Glaucoma. 2012;21(3):160-3.
33. Kraus CL, Tychsen L, Lueder GT, Culican SM. Comparison of the Effectiveness and Safety of Transscleral Cyclophotocoagulation and Endoscopic Cyclophotocoagulation in Pediatric Glaucoma. J Pediatr Ophthalmol Strabismus. 2014 Feb 18:1-8.
34. Hoskins HD Jr, Hetherington J Jr, Magee SD, et al. Clinical experience with timolol in childhood glaucoma. Arch Ophthalmol. 1985;103(8):1163-5.
35. McMahon CD, Hetherington J Jr, Hoskins HD Jr, et al. Timolol and pediatric glaucomas. Ophthalmology. 1981;88(3):249-52.
36. Zimmerman TJ, Kooner KS, Morgan KS. Safety and efficacy of timolol in pediatric glaucoma. Surv Ophthalmol. 1983;28 Suppl:262-4.
37. Enyedi LB, Freedman SF. Latanoprost for the treatment of pediatric glaucoma. Surv Ophthalmol. 2002;47 Suppl 1:S129-32.
38. Enyedi LB, Freedman SF, Buckley EG. The effectiveness of latanoprost for the treatment of pediatric glaucoma. J AAPOS. 1999;3(1):33-9.
39. Urban B, Bakunowicz-Lazarczyk A, Mrugacz M, et al. The effectiveness of latanoprost for the treatment of pediatric glaucoma. Klin Oczna. 2004;106(1-2 Suppl):243-4.
40. Ott EZ, Mills MD, Arango S, et al. A randomized trial assessing dorzolamide in patients with glaucoma who are younger than 6 years. Arch Ophthalmol. 2005;123(9):1177-86.
41. Rehurek J, Spicarova R, Vancurova J. Effect of Trusopt on normal intraocular pressure values in children. Cesk Slov Oftalmol. 2000;56(6):366-9.
42. Al-Shahwan S, Al-Torbak AA, Turkmani S, et al. Side-effect profile of brimonidine tartrate in children. Ophthalmology. 2005;112(12):2143.
43. Enyedi LB, Freedman SF. Safety and efficacy of brimonidine in children with glaucoma. J AAPOS. 2001;5(5):281-4.
44. Berlin RJ, Lee UT, Samples JR, et al. Ophthalmic drops causing coma in an infant. J Pediatr. 2001;138(3):441-3.
45. Quigley HA. The pathogenesis of reversible cupping in congenital glaucoma. Am J Ophthalmol 1977; 84:358-70.

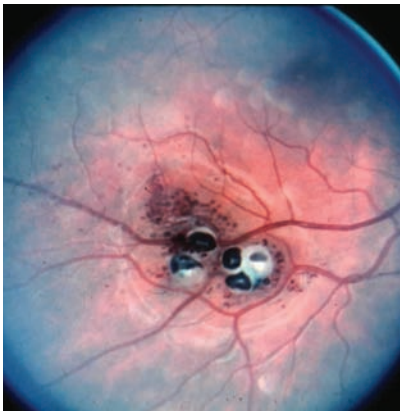
CAVERNOUS HEMANGIOMA

Signs and Symptoms

Cavernous hemangioma of the retina (CHR) and the optic disc are typically considered to be uncommon lesions. Their precise frequency in the general population is unknown, but both genders and all ethnic groups are susceptible.[1] They represent asymptomatic, congenital malformations of the retinal blood vasculature that are typically nonprogressive and most often unilateral.[2] Since CHRs 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 is a source of exudation or intraocular hemorrhage.[1-5] When they do produce spontaneous vitreous bleeding, without intervention the episodes are often recurrent and significant.[1]

CHRs are easily recognized by their characteristic saccular "grape-like" appearance, along with an associated grayish-white epiretinal membrane in some cases.[1-5] Optical coherence tomography may provide additional information and help in the differentiation of these lesions, which show lobulated, hyper-reflective masses in the inner retina that correspond to the aneurysms.[6,7]

Most individuals with CHR have a single lesion (consisting of multiple saccular components) in one eye with no other ocular or systemic anomalies; however, on occasion the disturbance can be found demonstrating multiple lesions in one retina along with abnormal vascular lesions of the skin and central nervous system.[1] While CHR are generally considered to be static and not capable of growth, the literature documents several cases of cavernous hemangioma of the optic nerve that demonstrate an increase in size.[8] There is even a documented case of cavernous hemangioma interfering with oculomotor nerve function, causing ophthalmoparesis, ptosis and visual impairment via a compressive etiology.[9]



Cavernous hemangioma of the retina.

Cavernous hemangioma of the retina, optic nerve or choroid may serve as the ocular component of neuro-oculocutaneous phacomatosis syndrome, sometimes referred to as *cavernoma multiplex*.[10,11] Choroidal hemangiomas are regularly associated with Sturge-Weber syndrome.[12]

Fluorescein angiographic features of CHR were described in 1975 by Lewis and associates.[13] These include: (1) a normal arterial and venous supply, (2) extraordinarily slowed venous drainage, (3) a lack of arteriovenous shunting and no disturbance in vascular permeability, (4) no secondary retinal exudation and (5) the unique formation of isolated clusters of vascular globules, with plasma/erythrocyte sedimentation surrounding the main body of the malformation.[13]

Pathophysiology

Cavernous hemangioma of the retina is considered a hamartoma. The word *hamartoma* originates from the Greek *hamartia*, meaning "a tragic flaw." In medical terms, it refers to a benign overgrowth of mature cells derived from tissues normally present in the locality of the mass, but of improper proportion and distribution. CHR may be sporadic in the population, or may display an autosomal dominant inheritance pattern in some families.[1,3]

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.[1,2,4] As the tumor evolves, it displaces and replaces the sensory retina in that zone. There is no recognized malignant potential.[1]

Management

Since CHRs do not commonly progress or leak, these lesions rarely require therapeutic intervention.[1-5] Moreover, they do not necessitate any restriction of activity or change in lifestyle.[1] However, because of their vascular nature and potential to serve as markers for additional lesions in alternate locations, there is always some risk of additional hemangiomas being present, carrying a more ominous prognosis.[9,10] While rare, the possibility of intracranial hemorrhage must be viewed as a life-threatening sequela.[10] For these reasons, individuals with CHR should be referred for neurological consultation and possibly neuroimaging.[1,3,14] Advice should also be offered to family members so that they can be properly evaluated as well.[3]

When CHR interferes with functional vision due to impingement, hemorrhage or exudation, shrinkage and/or closure should be attempted. Verteporfin-based photodynamic therapy (PDT) has been demonstrated to exhibit some success in achieving closure of large retinal capillary hemangiomas.[15,16] In clinical studies examining treatment options, CHR either shrunk in size or experienced complete closure with resultant mitigation of excessive exudation and hemorrhage following PDT.[15,16] In most instances, PDT successfully improved the visual acuity, but

tractional macular puckering has been noted.[16] Tractional macular pucker carries with it the risk of macular hole formation. Patients with this presentation can be instructed to monitor their status using the home Amsler grid. Other modalities that have been used successfully include focal laser photocoagulation and systemic infliximab (Remicade).[17,18]

Clinical Pearls

- Cavernous hemangiomas of the retina are considered to be stable intraretinal lesions. However, the same tumor occurring on the optic disc has the potential for growth—causing vitreous hemorrhage—and therefore should be closely monitored.
- The presence of either retinal cavernous hemangioma or choroidal hemangioma should alert the clinician to search for features suggestive of systemic and familial involvement.
- The principal differential diagnoses include exudative retinal telangiectasias, Coats' disease, the vascular von Hippel-Lindau tumor and the arteriovenous malformation racemose hemangioma (Wyburn-Mason syndrome).

1. Augsberger JJ, Bornfeld N, Correa ZMS. Hemangiomas of the retina. In: Yanoff M, Duker JS. Ophthalmology 2nd ed. Philadelphia, Mosby 2004:1089-92.

2. Knutsson KA, De Benedetto U, Querques G, et al. Primitive retinal vascular abnormalities: tumors and telangiectasias. Ophthalmologica. 2012;228(2):67-77.

3. Chen L, Huang L, Zhang G, Gordon L. Cavernous hemangioma of the retina. Can J Ophthalmol. 2008;43(6):718-20.

4. Turell ME, Singh AD. Vascular tumors of the retina and choroid: diagnosis and treatment. Middle East Afr J Ophthalmol. 2010;17(3):191-200.

5. Singh A. Intraocular vascular tumors. Saudi J Ophthalmol. 2007; 21(1):25-34.

6. Heimann H, Jmor F, Damato B. Imaging of retinal and choroidal vascular tumours. Eye (Lond). 2013;27(2):208-16.

7. Andrade RE, Farah ME, Costa RA, Belfort R Jr. Optical coherence tomography findings in macular cavernous haemangioma. Acta Ophthalmol Scand. 2005;83(2):267-9.

8. Kushner MS, Jampol LM, Haller JA. Cavernous hemangioma of the optic nerve. Retina. 1994;14(4):359-61.

9. Mirzayan MJ, Capelle HH, Stan AC et al. Cavernous hemangioma of the cavernous sinus, skin, and retina: hemodynamic changes after treatment: case report. Neurosurgery. 2007;60(5): E952; discussion E952.

10. Sarraf D, Payne AM, Kitchen ND, et al. Familial cavernous hemangioma: An expanding ocular spectrum. Arch Ophthalmol. 2000;118(7):969-73.

11. Mosca L, Pileggi S, Avemaria F, et al. De novo MGC4607 gene heterozygous missense variants in a child with multiple cerebral cavernous malformations. J Mol Neurosci. 2012;47(3):475-80.

12. Ray R, Foroozan R. Uveo-meningeal syndromes. Int Ophthalmol Clin. 2007;47(4):131-49.

13. Lewis RA, Cohen MH, Wise GN. Cavernous haemangioma of the retina and optic disc. A report of three cases and a review of the literature. Br J Ophthalmol. 1975;59(8):422-34.

14. Patikulsila D, Visaetsilpanonta S, Sinclair SH, Shields JA. Cavernous hemangioma of the optic disk. Retina. 2007;27(3):391-2.

15. Javellana JA, Drouilhet JH, Kokame GT et al. Retinal capillary angioma in familial exudative vitreoretinopathy treated with photodynamic therapy. Am J Ophthalmol. 2004;137(4):780-2.

16. Aaberg TM, Aaberg TM, Martin DF et al. Three cases of large retinal capillary hemangiomas treated with verteporfin and photodynamic therapy. Arch Ophthalmol. 2005;123(3):328-32

17. Gass JD. Cavernous hemangioma of the retina. A neuro-oculo-cutaneous syndrome. Am J Ophthalmol. 1971;71(4):799-814.

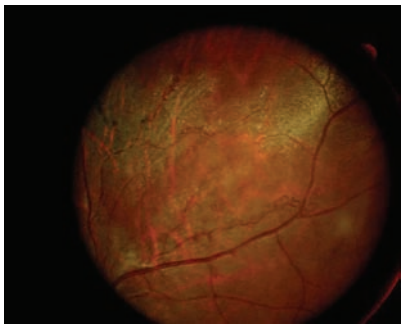
18. Japiassú RM, Moura Brasil OF, de Souza EC. Regression of Macular Cavernous Hemangioma with Systemic Infliximab. Ophthalmic Surg Lasers Imaging. 2011;42(6):E1-E3.

COMMOTIO RETINAE

Signs and Symptoms

Commotio retinae, formerly known as Berlin's edema, presents as an area of retinal pallor following direct blunt ocular trauma. Symptoms are associated with the location and extent of the retinal bruising along with the collateral consequences of the blunt trauma.[1-18] Any amount of retinal disruption located centrally can cause patients to observe metamorphopsia or reduced visual acuity without decreased red or brightness saturation.

The associated findings from blunt trauma may range from mild diffuse injection, chemosis, subconjunctival hemorrhage, photophobia and pain upon ocular motility to orbital fracture, iridodialysis, lens luxation, traumatic iritis, vitreous hemorrhage and globe rupture.[2-13] While specific data for ocular injuries have fluctuated over the last 10 years, one thing has remained constant: injury rates are consistently highest among males of all ages.[6-11]



Retinal whitening associated with commotio retinae.

Pathophysiology

The classic work of Sipperly, Quigley and Gass demonstrated that the predominant retinal abnormality in commotio retinae was disruption of the photoreceptor outer segments caused by hydraulic ocular distention induced by blunt force trauma, and not actually retinal edema.[15] This mechanism altered the hydrodynamics of the intraretinal and choroidal vascular systems, creating fluid leakage.

The condition is not merely an accumulation extracellular fluid, as originally postulated by Berlin.[1-4,14,15] It has been documented in animal models that the predominant pathophysiology is destruction of the vulnerable and delicate photoreceptor outer segments along with the concomitant imbibition of multiple intraretinal cellular elements (RPE, axons of the photoreceptor cells, Müller cells and selected ganglion cells) with intracellular fluid.[1-4,14,15] Visual disability depends upon the degree and location of permanently lost photoreceptors. Interestingly, the RPE's response to traumatic photoreceptor damage seems similar to that observed in experimental retinal detachment and light-induced retinal damage.[13,14]

Recent in-vivo investigations using spectral-domain optical coherence tomography (SD-OCT) confirm what was postulated by histological studies: commotio retinae is a disruption and fragmentation of the photoreceptor outer

segments with resultant fluid incursion and collateral damage to retinal elements.[1-4,14-17] The location of the commotio injury is traditionally in the contrecoup position, or directly opposite the site of the impact.[1,18]

SD-OCT imaging has been used to create a grading scale for macular commotio retinae based upon four distinct photoreceptor morphologic features that have been consistently observed:[4]

Grade 1: An increase in inner segment-outer segment (IS-OS) junction reflectivity with the disappearance of the thin hyporeflective optical space.

Grade 2: Cone outer segment tip (COST) defects only.

Grade 3: COST and IS-OS junction defects.

Grade 4: COST defects, IS-OS junction and external limiting membrane (ELM) defects.

Eyes with higher grades at baseline had significantly worse visual and anatomic outcomes.[4]

Cystoid macular edema (CME) is a classical complication of ocular inflammation and is a possible comorbidity of commotio retinae.[21] CME can result either from an insult to the inner or outer blood/ocular barrier.[12,21]

Management

There is no treatment for commotio retinae.[12-14] Management consists of attending to accompanying damage (facial or orbital fractures, tissue lacerations, corneal abrasion, traumatic uveitis, subconjunctival hemorrhage) and emotionally supporting the patient when vision is reduced. Acuity monitoring, Amsler grid testing, interferometry and SD-OCT can provide comparative data indicating progress of recovery.[1-4,14-17] Patients can be counseled that in the absence of associated damage to the cornea, lens and macula, visual recovery typically returns to pre-injury levels.[16-18] In the event it does not, the majority of incompletely resolved cases return to levels better than 20/30.[18]

Complications such as premature cataractogenesis and the symptoms associated with epiretinal membrane formation, posterior vitreous detachment and macular hole formation should also be mentioned as possible sequelae of the inciting blunt ocular trauma.[1,3,5,6,11-13]

Facial fractures should be prophylactically medicated with an oral antibiotic. Lacerations and abrasions to the epidermis, conjunctiva and cornea should be protected with topical antibiotic. Concurrent iritis should be treated using a topical cycloplegic and a topical corticosteroid. Hyphema should be managed with bed rest, elevated head position to promote blood settling with the additions of a nasal decongestant, stool softener and ocular hypotensives as necessary. Topical nonsteroidal and steroidal medications along with oral carbonic anhydrase inhibitors and injected steroidal depots have been used to manage recalcitrant cases of CME with variable results.[20]

Clinical Pearls

- Commotio retinae should be used as an indicator to carefully examine all ocular structures post-trauma.
- A 360˚ subconjunctival hemorrhage carries the risk of ruptured globe.
- Significant blunt ocular trauma mandates the consideration of imaging to rule out facial and orbital fracture.
- Blunt trauma cases should be monitored for late glaucoma over the patient's lifetime.
- In cases of peripheral commotio retinae with no visual loss or coexistent ocular damage, the best management is simple observation and patient reassurance.

1. Mansour AM, Green WR, Hogge C. Histopathology of commotio retinae. Retina. 1992;12(1):24-8.

2. Liem AT, Keunen JE, van Norren D. Reversible cone photoreceptor injury in commotio retinae of the macula. Retina. 1995;15(1):58-61.

3. Rubsamen PE. Posterior segment ocular trauma. In: Yanoff M, Duker JS. Ophthalmology. Mosby-Elsevier, St. Louis, MO 2009:1007-12.

4. Ahn SJ, Woo SJ, Kim KE, et al. Optical coherence tomography morphologic grading of macular commotio retinae and its association with anatomic and visual outcomes. Am J Ophthalmol. 2013;156(5):994-1001.

5. McGwin G Jr, Owsley C. Ocular morbidity associated with airbag deployment: a report of seven cases and a review of the literature. Arch Ophthalmol 2005;23(5):662-6.

6. Park JY, Nam WH, Kim SH, et al. Evaluation of the central macula in commotio retinae not associated with other types of traumatic retinopathy. Korean J Ophthalmol. 2011;25(4):262-7.

7. Chen AJ, Linakis JG, Mello MJ, Greenberg PB. Epidemiology of infant ocular and periocular injuries from consumer products in the United States, 2001-2008. J AAPOS. 2013;17(3):239-42.

8. McGwin G Jr, Xie A, Owsley C. Rate of eye injury in the United States. Arch Ophthalmol. 2005;123(7):970-6.

9. McGwin G Jr, Owsley C. Incidence of emergency department-treated eye injury in the United States. Arch Ophthalmol. 2005;123(5):662-6.

10. Scruggs D, Scruggs R, Stukenborg G, et al. Ocular injuries in trauma patients: an analysis of 28,340 trauma admissions in the 2003-2007 National Trauma Data Bank National Sample Program. J Trauma Acute Care Surg. 2012;73(5):1308-12.

11. Parver LM, Dannenberg AL, Blacklow B, et al. Characteristics and causes of penetrating eye injuries reported to the National Eye Trauma System Registry, 1985-91. Public Health Rep 1993;108(5):625-32.

12. Conn JM, Annest JL, Gilchrist J, et al. Injuries from paintball game related activities in the United States, 1997-2001. Inj Prev 2004;10(3):139-43.

13. Kiel J, Chen S. Contusion injuries and their ocular effects. Clin Exp Optom 2001;84(1):19-25.

14. Meyer CH, Rodrigues EB, Mennel S. Acute commotio retinae determined by cross-sectional optical coherence tomography. Eur J Ophthalmol 2003;13(9-10):816-8.

15. Sipperley JO, Quigley HA, Gass DM. Traumatic retinopathy in primates. The explanation of commotio retinae. Arch Ophthalmol 1978;96(12):2267-73.

16. Itakura H, Kishi S. Restored photoreceptor outer segment in commotio retinae. Ophthalmic Surg Lasers Imaging. 2011;3(42):e29-31.

17. Oh J, Jung JH, Moon SW, et al. Commotio retinae with spectral-domain optical coherence tomography. Retina. 2011;31(10):2044-9.

18. Blanch RJ, Good PA, Shah P, et al. Visual outcomes after blunt ocular trauma.Ophthalmology. 2013;120(8):1588-91.

19. Brouzas D, Charakidas A, Papagiannakopoulos D, et al. Elastic cord-induced ocular injuries. Injur 2003;34(5):323-6.

20. Ball DC, Bouchard CS. Ocular morbidity associated with airbag deployment: a report of seven cases and a review of the literature. Cornea 2001;20(2):159-63.

21. Guex-Crosier Y. The pathogenesis and clinical presentation of macular edema in inflammatory diseases. Doc Ophthalmol 1999;97(3-4):297-309.

LATTICE DEGENERATION

Signs and Symptoms

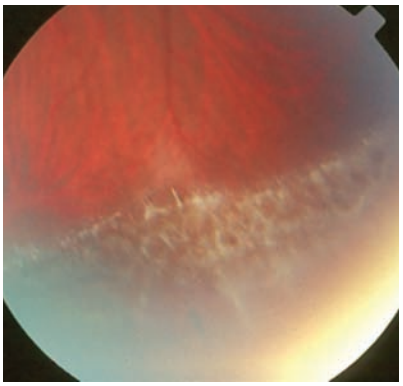
Lattice degeneration of the retina is named for its resemblance to a fine, white, linear criss-cross lattice pattern seen in the peripheral neurosensory retina.[1-15] The condition is common to

7% to 10% of adult eyes, with affected patients usually diagnosed over the age of 20.[1-5,12-15] The condition is predominantly seen in the superior quadrants, with less frequency in the horizontal meridans.[1] Axially myopic patients seem to have a higher incidence of lattice degeneration.[1,6-11] There appears to be no racial predilection, although there is some controversy in the literature.[1-11,12]

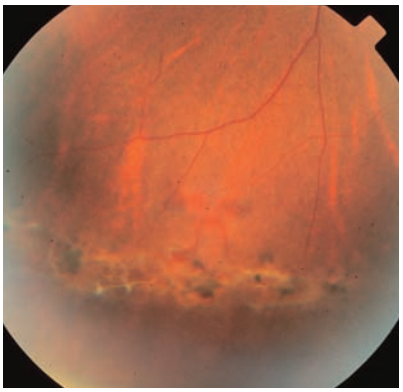
Lattice degeneration classically runs circumferentially between the equator and the ora serrata, parallel to the vitreous base.[1-10,13] The individual lesions usually measure from 0.5 disc diameter (DD) to 6 DD and can run 360° around the eye. Most of the time, the lesions are observed in discontinuous patterns, with the majority of lesions in the vertical meridians.[1,13] Lattice degeneration is typically bilateral.[12,13]

Sometimes, retinal pigment epithelial hyperplasia associated with significant retinal thinning or the physiology of healing (secondary to micro-injury) conceals the lattice lines.[1,12-15] This is often termed *pigmented lattice degeneration*. The retinal thinning causes overlying vitreous degeneration with subsequent accumulation of small pockets of liquid vitreous, known as lacunae, residing over top of the lesions.[12-17]

When atrophic holes develop, liquid vitreous can seep under the neurosensory retina to produce a shallow retinal detachment. The majority of shallow lattice-related detachments are asymptomatic. However, when a prominently lifted edge of a hole or linear tear along a lesion edge interacts with adherent vitreous, mechanical forces are translated into electrical retinal stimuli that are perceived by the patient as flashing lights (photopsia).[1] These forces can also create larger holes or tears that may be symptomatic.[1,6-8] Tractional retinal tears along the edge of lattice degeneration have the highest association with the development of retinal detachment arising from lattice retinal degeneration.[1,6-8]



Extensive lattice degeneration of the inferior retina.



Pigmented lattice degeneration with atrophic holes.

Pathophysiology

The etiology of lattice degeneration remains unclear. Recent research has hypothesized that the condition may occur secondary to genetic variants in the COL4A4 gene.[5] Pathophysiologically, lattice degeneration occurs as the result of dropout of peripheral retinal capillaries, with resulting ischemia and subsequent thinning affecting all layers of the retina.[15-17] The acellular thickening and sclerosis of the lumens of these peripheral retinal arterioles is what creates the characteristic linear appearance.[17]

Profound retinal thinning has several effects: first, the overlying vitreous becomes disturbed, resulting in a pocket of liquefaction overlying the lattice lesion, known as a lacuna; second, the vitreous along the edges of the lattice lesion maintains its adhesions, creating forces on the retina. Finally, the ischemia and retinal thinning may disturb the retinal pigment epithelium, resulting in RPE hyperplasia and a pigmented appearance.[16,17] Fluorescein angiography of lattice lesions demonstrates zones of avascularity.[17]

In one study, using optical coherence tomography, four characteristic changes of the retina and vitreous were seen in 13 eyes with lattice degeneration: (1) anterior/posterior U-shaped vitreous traction around the lesion, (2) retinal breaks, (3) the presence of focal retinal thinning and (4) vitreous membrane with evidence of traction, thought to be fibrosis from extracellular products of cell breakdown.[15] The morphologic appearance of vitreous traction and retinal breaks imaged in cases were concluded to be consistent with known histologic reports.[15]

The process becomes more significant when the thinning becomes profound, to the point of development of full-thickness atrophic holes in lattice lesions.[15-17] There exists the potential for overlying liquefied vitreous to pass through a hole into the subretinal space and possibly lead to rhegmatogenous retinal detachment. While the published data from larger studies demonstrate a wide range of prevalence, all generally agree that this is uncommon (0.5% to 3% over a five- to 11-year span).[12-17]

In some eyes (predominantly myopic ones), a slow build-up of fluid can occur in conjunction with posterior vitreous detachment (PVD).[17] These eyes seem to be at greatest risk of developing rhegmatogenous retinal detachment.[17] If a PVD occurs, vitreoretinal traction along the posterior edge of the lattice degeneration lesion may result in a tractional tear adjacent to the lesion. When these tears develop, they are typically created at the posterior boundary of the lesion.[17] This greatly increases the risk of rhegmatogenous retinal detachment.[17,18]

Management

The main concern with lattice degeneration is the risk of progression to rhegmatogenous retinal detachment.[1-19] When lattice degeneration with holes is detected, several factors can be used to determine if prophylactic treatment is required. These include a history of retinal detachment from lattice degeneration in the same or fellow eye, a family history of retinal detachment, axial myopia of greater than six diopters, presence of significant subretinal fluid under the edges of the hole and concurrent photopsia. Additionally, if the holes are large, the patient is pseudophakic or is planning to undergo cataract surgery, or the patient has an active, high-impact lifestyle, prophylactic treatment can be recommended.[7-23]

However, most lattice cases, even those presenting with associated retinal holes, are simply monitored, with visits every six to 12 months. Atrophic holes within lattice degeneration in phakic eyes without any complicating factors as previously mentioned do not generally require prophylactic treatment as the risk of progression to detachment is small.[2-20] These lesions need only periodic monitoring, with the patient educated on the signs and symptoms of retinal detachment.

When high-risk tractional retinal breaks associated with lattice degeneration are detected, the area can be prophylactically sealed with barrier laser photocoagulation or cryoretinopexy.[2,4,20,21] Cryoretinopexy uses an externally applied transscleral/conjunctival probe to deliver directed cold pressure to the area contacted, destroying the integrity of the choriocapillaris, RPE and outer retina. This induces RPE hyperplasia, creating an adhesion between the area of the tear and the healthy, attached, adjacent retina.[2,19-21] This prevents liquid vitreous from gaining access to the subretinal space.[2,19-21]

Advantages of cryoretinopexy over laser photocoagulation are that it can be applied to the retina of an eye with media opacities that preclude the use of laser photocoagulation (cataract or vitreous hemorrhage), ease of procedure performance and its suitability if the pupil size cannot be adequately enlarged. It is also the treatment of choice if the retinal lesion is anteriorly located in the eye close to the ora serrata.[19] Retinal adhesion with cryoretinopexy takes up to three weeks to mature.[19] Adverse effects of cryoretinopexy include inflammation, choroidal detachment, reduced accommodation, discomfort and raised intraocular pressure.[19]

Laser photocoagulation applies varying wavelengths of light (argon green, argon blue-green, krypton red) via a biomicroscope or binocular indirect delivery system to the retina to create a similar tissue adhesion. Unlike cryoretinopexy, the adhesion is immediate and matures within 10 days.[2,19] Laser photocoagulation, which is more commonly employed than cryoretinopexy, has fewer side effects, can be applied to more posterior lesions and can be more accurately placed.[2,19]

Clinical Pearls

- Lattice degeneration with or without atrophic holes is generally benign and often simply monitored.
- Tractional tears at the posterior border of lattice lesions can be difficult to see ophthalmoscopically. These tears can become apparent upon scleral depression, making the procedure a prudent exercise in the examination of these individuals.
- When unsure, use three-mirror or a non-contact fundus lens and biomicroscope to more closely evaluate the lesion.
- Patients should be educated regarding the signs and symptoms of retinal detachment.
- Standard follow-up in asymptomatic patients should be at six- to 12-month intervals for a dilated exam.
- Any tears along lattice lesions should be referred for further evaluation and treatment.
- While both cryoretinopexy and laser photocoagulation of retinal breaks are efficacious, most patients today are treated with the latter.

1. Tasman WS. Peripheral retinal lesions. In: Yanoff M, Duker JS. Ophthalmology. Mosby-Elsevier, St. Louis, MO 2009:711-15.

2. Greven CM. Retinal breaks. In: Yanoff M, Duker JS. Ophthalmology. Mosby-Elsevier, St. Louis, MO 2009:716-19.

3. Oyster CW. The retina in vivo and the optic nerve. In: Oyster CW. The human eye structure and function. Cinaur Associates Inc. Sunderland, MA 1999: 701-51.

4. Wilkinson CP. Interventions for asymptomatic retinal breaks and lattice degeneration for preventing retinal detachment. Cochrane Database Syst Rev. 2012;3:CD003170.

5. Meguro A, Ideta H, Ota M, et al. Common variants in the COL4A4 gene confer susceptibility to lattice degeneration of the retina. PLoS One. 2012;7(6):e39300.

6. Jamil MH, Farooq N, Khan MT, Jamil AZ. Characteristics and pattern of rhegmatogenous retinal detachment in pakistan. J Coll Physicians Surg Pak. 2012;22(8):501-4.

7. Mitry D, Singh J, Yorston D, et al. The predisposing pathology and clinical characteristics in the Scottish retinal detachment study. Ophthalmology. 2011;118(7):1429-34.

8. De Keyzer TH, De Veuster I, Smets RM. Stickler syndrome: an underdiagnosed disease. Report of a family. Bull Soc Belge Ophtalmol. 2011;(318):45-9.

9. Bansal AS, Hubbard GB 3rd. Peripheral retinal findings in highly myopic children < or =10 years of age. Retina. 2010;30(4 Suppl):S15-9.

10. Martín Sánchez MD, Roldán Pallarés M. Myopia: frequency of lattice degeneration and axial length. Arch Soc Esp Oftalmol. 2001;76(5):291-6.

11. Celorio JM, Pruett RC. Prevalence of lattice degeneration and its relation to axial length in severe myopia. Am J Ophthalmol. 1991;111(1):20-3.

12. Semes LP, Holland WC, Likens EG. Prevalence and laterality of lattice retinal degeneration within a primary eye care population. Optometry. 2001;72(4):247-50.

13. Semes LP. Lattice degeneration of the retina and retinal detachment. Optom Clin. 1992;2(3):71-91.

14. Lewis H. Peripheral retinal degenerations and the risk of retinal detachment. Am J Ophthalmol. 2003;136(1):155-60.

15. Manjunath V, Taha M, Fujimoto JG, Duker JS. Posterior lattice degeneration characterized by spectral domain optical coherence tomography. Retina. 2011;31(3):492-6.

16. Byer NE. Long-term natural history of lattice degeneration of the retina. Ophthalmology. 1989;96(9):1396-401.

17. Brinton DA, Wilkinson CP. Pathogenesis, epidemiology and natural course of retinal detachment. In: Brinton DA, Wilkinson CP. Retinal detachment principles and practice. New York, NY, Oxford press 2009:9-37.

18. Mastropasqua L, Carpineto P, Ciancaglini M, et al. Treatment of retinal tears and lattice degenerations in fellow eyes in high risk patients suffering retinal detachment: a prospective study. Br J Ophthalmol. 1999;83(9):1046-9.

19. Fraser S, Steel D. Retinal detachment. Clin Evid (Online). 2010;2010: pii: 0710.

20. Shunmugam M, Ang GS, Lois N. Giant retinal tears. Surv Ophthalmol. 2014;59(2):192-216.

21. Haug SJ, Bhisitkul RB. Risk factors for retinal detachment following cataract surgery. Curr Opin Ophthalmol. 2012;23(1):7-11.

22. Corrales G1, Curreri A. Eye trauma in boxing. Clin Sports Med. 2009;28(4):591-607.

23. Gupta OP, Benson WE. The risk of fellow eyes in patients with rhegmatogenous retinal detachment. Curr Opin Ophthalmol. 2005;16(3):175-8.

NON-EXUDATIVE (DRY) MACULAR DEGENERATION

Signs and Symptoms

Age-related macular degeneration (AMD) is the leading cause of acquired legal blindness in the United States for persons over the age of 65.[1-11] By 2020, AMD is expected to affect 2.95 million individuals in the US alone.[5] AMD is present in approximately 10% to 18% of the population over the age of 52 and in up to 33% of individuals over the age of 75.[8]

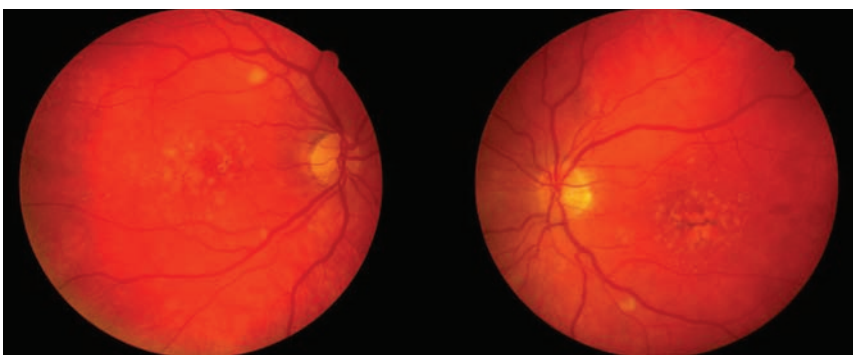
The disease involves complex interplay between genetic, environmental and metabolic factors.[6,7,12,13] Smoking, hypertension, obesity, suboptimal nutrition (e.g., increased cholesterol, low dietary intake of carotenoids, alcohol consumption), older age, sunlight exposure and family history are all risk factors.[6,7,12-14]

New evidence supports hypotheses implicating systemic inflammation and immune system involvement.[6] All AMD variants begin in the subretinal tissues under the retinal pigment epithelium (RPE). The non-exudative (dry) form develops from pathology that takes root in the RPE/Bruch's membrane complex and matures to involve the photoreceptors.[1-5,12,15]

The earliest clinical manifestations of AMD are hard and soft drusen (focal thickenings of Bruch's membrane) and macular pigmentary atrophy.[15,16] The presence of drusen does not alone indicate AMD, but may serve as a precursor.

AMD is bilateral in 55% of cases.[17] Visual symptoms associated with AMD depend on the severity and type of disease. The more common dry, atrophic form (with no choroidal neovascularization) tends to be less severe, producing a gradual, painless distortion and loss of central vision, although many patients maintain excellent visual acuity.[12,15] Some patients complain of color distortion. The clinical signs of non-exudative AMD include drusen of the posterior pole, granular clumping and disorganization of the RPE in the macular area, macular RPE hyperplasia and degeneration of the outer retinal layers with circumscribed areas of geographic atrophy of the RPE as the disease progresses.[15,16]

In individuals with advanced, late-stage dry AMD, approximately one third will develop geographic atrophy.[9-11]



Non-exudative age-related macular degeneration.

This advanced dry stage is characterized by single or multiple well-demarcated areas of partial or complete depigmentation of the RPE, with loss of adjacent choriocapillaris and photoreceptors.[9-11] Clinically, it appears as hypopigmented, circular patches where the choroidal vasculature is visible.[9-11] When these changes involve the macula, the effects on acuity are significant.

Pigment epithelial detachment (PED) is another non-exudative complication of the advancing process.[18] PEDs are defined by their discrete, subretinal, yellow, nodular appearance. They are seen adjacent to drusen and result from the movement of protein-laden fluid between Bruch's membrane and the RPE.[15-18] Patients who develop a PED in the vicinity of the macula will often experience significant reduction of acuity.[18] Their appearance often marks disease progression, and may precede the formation of choroidal neovascularization and conversion to the "wet" form of the disease.[18]

Pathophysiology

All forms of AMD begin with alterations in the macular RPE.[15-21] While the mechanisms and processes are poorly understood, it is postulated that these changes are initiated by isolated regions of choriocapillaris vascular dysfunction.[19-21] This occurs in conjunction with genetic, vascular and lifestyle risks as the choroid naturally thins with age (after 50 to 60 years of age, choroidal thickness has been shown to progressively decrease by 4µm to 5µm each year).[19,23,24] The process is hastened in the setting of missing natural protectants (macular pigment density and carotenoids such as zeaxanthin, mesozeaxanthin and lutein).[1-4,8,19,24,27]

Natural age-related thinning of the choroid is mirrored by reduction in oxygen and metabolite supply to the RPE and outer retina.[20,25] Exposure to ultraviolet light in the absence of natural RPE construction and in the setting of inadequate quenching by antioxidants creates reactive oxygen species (ROS),

which alter biomolecules, including proteins, nucleic acids and lipids.[27]

New pathophysiologic hypotheses categorize the damage into three distinct stages:

(1) Initial RPE oxidative injury, caused by any number of endogenous or exogenous oxidants resulting in extrusion of cell membranes (blebs). This occurs in concert with decreased activity of matrix metalloproteinases (MMPs) and the incomplete digestion of constantly shed photoreceptor outer segments, promoting elemental accumulation under the RPE as basal laminar deposits.[15,28]

(2) RPE cells under the influence of various plasma-derived molecules and hormones subsequently stimulate increased synthesis of MMPs and other molecules responsible for extracellular matrix turnover, decreasing collagen production. This affects both RPE basement membrane and Bruch's membrane, leading to linear basal laminar deposits and the formation of drusen via the admixture of the formed blebs into Bruch's membrane.[15,28] This contributes to the formation of drusen and the propagation of oxidative stress.[28] In this stage, a new basement membrane forms under the RPE, trapping these deposits within the Bruch's membrane.

(3) Macrophages are recruited via inflammatory mediators, growth factors or other substances to the sites of RPE injury and deposit formation.[15]

The recruitment of non-activated or scavenging macrophages may remove the deposits without further injury. In this instance, no loss of function is realized. In the disease state, however, the pathology reaches clinical threshold, creating visual loss.[15,28] As the RPE fails under stress, photoreceptor loss becomes progressive with the inner nuclear layer collapsing and contacting Bruch's membrane, initializing the degeneration of the outer retinal layers.[1-4,8]

Investigators have determined that increased choroidal thickness may be protective, as individuals with thicker choroids have been reported to retain better visual function.[24,26]

Management

Patients at risk for AMD should be educated on its associated risk factors and preventative measures.[1-31] While the genetic susceptibilities that accompany having a family history of AMD or a pedigree for cardiovascular disease or dyslipidemia cannot be altered, lifestyle changes—such as practicing good dietary choices, wearing UV light protection, not smoking and taking evidence-based supplements—can.[1-4,6,7,29] Semiannual eye examination with dilated funduscopy is critical to uncovering the early changes associated with the disease's development and progression.

Home therapy aimed at early detection of AMD using an Amsler grid permits at-risk patients to home monitor for stability. New early detection instrumentation includes dark adaptometry as cone and rod dark adaptation may be biomarkers for early AMD (AdaptDx, MacuLogix), macular pigmentary density evaluation as missing protective macular pigment may increase the vulnerability to short wavelength light (MPS II detector, Elektron Technology) and fundus autofluorescence, a technology that takes advantage of the fluorescent properties of drusen (early subretinal lesion detection, grading, progression, monitoring).[30-32]

Researchers have indicated that oral antioxidant supplements containing vitamins C, E, beta-carotene, copper and zinc appear to play a role in reducing retinal damage by limiting the chemical reactions initiated by the free radicals created by retinal metabolism.[34-37] Ordinary multivitamins, zinc, beta-carotene or products specifically designed for AMD are aimed at distributing the correct combinations of these ingredients and have been shown to be a useful tool for slowing the progression of non-exudative AMD and preventing the conversion to the exudative form.[34-37] Consider these supplements for patients with intermediate size drusen (64µm to 124µm), one or more large druse (>125µm), non-central geographic atrophy in one or both eyes, or AMD with vision loss in one or both eyes without the contraindication of smoking.[34-37]

The original Age-Related Eye Disease Study (AREDS1) formulation multivitamin (vitamins C, E, beta-carotene, zinc and copper), taken as directed, has been reported to reduce the risk of progression of non-exudative AMD by 25% over a five-year period.[36] People with dry AMD taking these supplements during the same time period were less likely to lose 15 or more letters of visual acuity.[34] No evidence for an effect of supplementation was seen in smaller trials of shorter duration.[37] Since beta-carotene is associated with increased lung cancer in former smokers, lutein/zeaxanthin may serve as a replacement to provide additional beneficial effects beyond the effects of the original AREDS1 formulation.[35,36] In addition, a randomized clinical trial of B vitamins demonstrated a beneficial effect with the vitamin B complex.[36]

The objective of the lutein antioxidant supplementation trial (LAST) was to determine whether nutritional supplementation with lutein or lutein together with antioxidants, vitamins and minerals, improved visual function and symptoms in atrophic AMD.[38,39] While the LAST trial suggested improved function may be plausible, results released by the AREDS2 study group supported the change of beta carotene to lutein and zeaxanthin because of their safer profile with smokers, but stopped short of endorsing any effectiveness over the AREDS1 formula.[35,39] The Central Retinal Enrichment Supplementation Trial (CREST) aims to follow up on the results of AREDS2 by investigating the potential impact of macular pigment

enrichment following supplementation with a formulation containing 10mg lutein, 2mg zeaxanthin and 10mg mesozeaxanthin on visual function in normal subjects and in subjects with early age-related macular degeneration.[37]

Dietary omega-3 long-chain polyunsaturated fatty acid (LCPUFA) intake and increased fish consumption (broiled or baked) have both been associated with protecting against the conversion of dry AMD to wet AMD.[40] Both oral docosahexaenoic acid (DHA) and oral eicosapentaenoic acid (EPA) in supplementation form have demonstrated protective effects against nonexudative AMD conversion to exudative AMD.[41] Rare reported spontaneous remissions from AMD suggest the retina has a regenerative capacity.[42] Researchers are currently investigating the potential for over-the-counter oral resveratrol (Longevinex, Resveratrol Partners).[42]

In cases where bilateral central visual acuity has been lost, low vision and vision rehabilitation specialists may be able to offer training with optical and non-optical devices to improve quality of life and functioning.

Clinical Pearls

- The risk of patients with dry AMD progressing to wet AMD, for any given five-year period, is approximately 14% to 20%.
- While geographic atrophy is commonly associated with AMD, other causes include adult-onset foveomacular vitelliform dystrophy, pattern dystrophy, choroideremia, central areolar choroidal sclerosis and degenerative myopia.
- While vitamins offer hope for stability and improvement, excessive use can be harmful. Zinc can produce yellow skin color and has been associated with pathological mechanisms related to metal dyshomeostasis in Alzheimer's disease. Beta carotene has been associated with increased risk of lung cancer in smokers. Prescribing supplementation should be treated carefully, gathering a full history and consulting with the patient's internist.

1. Bowes Rickman C, Farsiu S, Toth CA, Klingeborn M. Dry age-related macular degeneration: mechanisms, therapeutic targets, and imaging. Invest Ophthalmol Vis Sci. 2013;54(14):68-80.

2. van Lookeren Campagne M, LeCouter J, Yaspan BL, Ye W. Mechanisms of age-related macular degeneration and therapeutic opportunities. J Pathol. 2014;232(2):151-64.

3. Machalińska A. Age-related macular degeneration as a local manifestation of atherosclerosis — a novel insight into pathogenesis. Klin Oczna. 2013;115(1):74-8.

4. Turlea C. New aspects in age related macular degeneration. Oftalmologia. 2012;56(1):36-44.

5. Akpek EK, Smith RA. Overview of age-related ocular conditions. Am J Manag Care. 2013;19(5 Suppl):S67-75.

6. Cheung LK, Eaton A. Age-related macular degeneration. Pharmacotherapy. 2013;33(8):838-55.

7. Sin HP, Liu DT, Lam DS. Lifestyle modification, nutritional and vitamins supplements for age-related macular degeneration. Acta Ophthalmol. 2013;91(1):6-11.

8. Zarbin MA. Current concepts in the pathogenesis of age-related macular degeneration. Arch Ophthalmol 2004; 122(4):598-614.

9. Biarnés M, Monés J, Alonso J, et al. Update on geographic atrophy in age-related macular degeneration. Optom Vis Sci. 2011;88(7):881-9.

10. Lindblad AS, Lloyd PC, Clemons TE, et al. Age-Related Eye Disease Study Research Group. Change in area of geographic atrophy in the age-related eye disease study: AREDS report number 26. Arch Ophthalmol. 127(9):1168–1174.

11. Lujan BJ, Rosenfeld PJ, Gregori G, et al. Spectral domain optical coherence tomographic imaging of geographic atrophy. Ophthalmic Surg Lasers Imaging. 2009;40(2):96-101.

12. Nano ME, Lansingh VC, Pighin MS, et al. Risk factors of age-related macular degeneration in Argentina. Arq Bras Oftalmol. 2013;76(2):80-4.

13. Shahid H, Khan JC, Cipriani V, et al. Age-related macular degeneration: the importance of family history as a risk factor. Br J Ophthalmol. 2012;96(3):427-31.

14. Cougnard-Grégoire A, Delyfer MN, Korobelnik JF, et al. Elevated high-density lipoprotein cholesterol and age-related macular degeneration: the alienor study. PLoS One. 2014;9(3):e90973.

15. Mettu PS, Wielgus AR, Ong SS, Cousins SW. Retinal pigment epithelium response to oxidant injury in the pathogenesis of early age-related macular degeneration. Mol Aspects Med. 2012;33(4):376-98.

16. Bhutto I, Lutty G. Understanding age-related macular degeneration (AMD): relationships between the photoreceptor/retinal pigment epithelium/Bruch's membrane/choriocapillaris complex. Mol Aspects Med. 2012;33(4):295-317.

17. Alexander LJ. Exudative and Nonexudative Macular Disorders. In: Alexander, L.J. Primary Care of The Posterior Segment. East Norwalk, CT, Appleton and Lange 1994:277-344.

18. Cukras C, Agrón E, Klein ML, Ferris FL 3rd, et al. Natural history of drusenoid pigment epithelial detachment in age-related macular degeneration: Age-Related Eye Disease Study Report No. 28. Ophthalmology. 2010;117(3):489-99.

19. Ding X, Li J, Zeng J, et al. Choroidal thickness in healthy Chinese subjects. Invest Ophthalmol Vis Sci. 2011;52(13):9555-60.

20. Manjunath V, Taha M, Fujimoto JG, et al. Choroidal thickness in normal eyes measured using Cirrus HD optical coherence tomography. Am J Ophthalmol. 2010;150(3):325-329.

21. Ikuno Y, Kawaguchi K, Nouchi T, et al. Choroidal thickness in healthy Japanese subjects. Invest Ophthalmol Vis Sci. 2010;51(4):2173-6.

22. Wu L, Alpizar-Alvarez N. Choroidal imaging by spectral domain-optical coherence tomography. Taiwan Journal of Ophthalmology. 2013;3(1):3-13.

23. Zhang L, Lee K, Niemeijer M, et al. Automated Segmentation of the Choroid from Clinical SD-OCT. Invest Ophthalmol Vis Sci.2012;53(12):7510-9.

24. Wei WB, Xu L, Jonas JB, et al. Subfoveal choroidal thickness: the Beijing Eye Study. Ophthalmology. 2013;120(1):175-80.

25. Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. Am J Ophthalmol. 2009;47(5):811-5.

26. Lee JY, Lee DH, Lee JY, et al. Correlation between subfoveal choroidal thickness and the severity or progression of nonexudative age-related macular degeneration. Invest Ophthalmol Vis Sci. 2013;54(12):7812-8.

27. Tokarz P, Kaarniranta K, Blasiak J. Role of antioxidant enzymes and small molecular weight antioxidants in the pathogenesis of age-related macular degeneration (AMD). Biogerontology. 2013;14(5):461-82.

28. Wiktorowska-Owczarek A, Nowak JZ.Pathogenesis and prophylaxis of AMD: focus on oxidative stress and antioxidants. Postepy Hig Med Dosw (Online). 2010l 28(7);64:333-43.

29. Sin HP, Liu DT, Lam DS. Lifestyle modification, nutritional and vitamins supplements for age-related macular degeneration. Acta Ophthalmol. 2013;91(1):6-11.

30. Gaffney AJ, Binns AM, Margrain TH. The effect of pre-adapting light intensity on dark adaptation in early age-related macular degeneration. Doc Ophthalmol. 2013;127(3):191-9.

31. Schachar IH, Zahid S, Comer GM, et al. Quantification of fundus autofluorescence to detect disease severity in nonexudative age-related macular degeneration. JAMA Ophthalmol. 2013;131(8):1009-15.

32. Kaya S, Weigert G, Pemp B, et al. Comparison of macular pigment in patients with age-related macular degeneration and healthy control subjects - a study using spectral fundus reflectance.Acta Ophthalmol. 2012;90(5):e399-403.

33. García-Layana A, Recalde S, Alamán AS, Robredo PF. Effects of lutein and docosahexaenoic Acid supplementation on macular pigment optical density in a randomized controlled trial. Nutrients. 2013;5(2):543-51.

34. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol. 2001;119(10):1417-36.

35. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA. 2013;309(19):2005-15.

36. Chew EY. Nutrition effects on ocular diseases in the aging eye. Invest Ophthalmol Vis Sci. 2013;54(14):42-7.

37. Akuffo KO, Beatty S, Stack J, et al. Central Retinal Enrichment Supplementation Trials (CREST): Design and Methodology of the CREST Randomized Controlled Trials. Ophthalmic Epidemiol. 2014;21(2):111-23.

38. Evans JR, Lawrenson JG. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. Cochrane Database Syst Rev. 2012;11:CD000254.

39. Richer S, Stiles W, Statkute L, et al. Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial). Optometry. 2004;75(4):216-30.

40. SanGiovanni JP, Chew EY, Clemons TE, et al. The relationship of dietary lipid intake and age-related macular degeneration in a case-control study: AREDS Report No. 20. Arch Ophthalmol. 2007;125(5):671-9.

41. Souied EH, Delcourt C, Querques G, et al. Oral docosahexaenoic acid in the prevention of exudative age-related macular degeneration: the Nutritional AMD Treatment 2 study. Ophthalmology. 2013;120(8):1619-31.

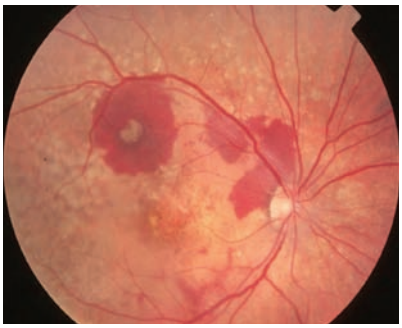
42. Richer S, Stiles W, Ulanski L, et al. Observation of human retinal remodeling in octogenarians with a resveratrol based nutritional supplement. Nutrients. 2013;5(6):1989-2005.

EXUDATIVE (WET) MACULAR DEGENERATION

Signs and Symptoms

Age-related macular degeneration (AMD) is a complex, progressive degenerative disease involving multiple genetic, lifestyle, systemic and environmental factors.[1-15] It is the leading cause of acquired blindness in elderly individuals living in western countries.[1-5] As the disease progresses through the non-exudative (dry) form, metabolic conditions arise that trigger processes which result in the release of vascular endothelial growth factors (VEGF).[1,13-19] This produces the choroidal neovascularization that defines exudative (wet) AMD.[6-10] Approximately 30% of adults aged 75 years or older have some signs of dry AMD with 6% to 8% of these individuals progressing to significant vision loss via advanced stages.[7]

All variants of the process begin in the subretinal tissues under the retinal pigment epithelium (RPE).[1-12] The non-exudative stages develop from pathology that takes root in the RPE/Bruch's membrane, maturing to involve the photoreceptors.[1-12] The earliest observable manifestations of AMD are visible hard and soft drusen (focal thickenings of Bruch's membrane).[12,13] Macular pigmentary changes and geographic atrophy follow and are observed as pigment mottling and clumping.[12,13,15]



Extensive subretinal hemorrhaging in wet macular degeneration.

As the disease progresses, chronic oxidative stress and inflammation ultimately lead to degeneration of the RPE with visible large coalesced soft drusen. This drives the process into an imbalance between antiangiogenic and proangiogenic factors that ultimately produces choroidal neovascularization.[14-16] Here, yellow subretinal, protein-laden fluid, yellow-white exudate and subretinal blood, seen as an amorphous reddish-brown accumulation under the retina/RPE, catastrophically disrupt function.[1-14]

The visual symptoms associated with exudative AMD depend on its severity, location and distribution. The vision loss that occurs in both symptomatic wet and dry disease is painless. The dry form produces subtle losses with gradual metamorphopsia and color alterations. As it advances more significant losses of acuity occur.[17] The wet form produces severe, sudden losses (in many cases, resulting in visual loss of six Snellen lines or more), dark adaptation dysfunction and a positive scotoma upon facial or formal Amsler grid testing.[17,18]

The clinical retinal signs of advanced exudative AMD include the disorganization of the RPE in the macular area, macular RPE hyperplasia, degeneration of the outer retinal layers with circumscribed areas of geographic atrophy of the RPE, subretinal bleeding, subretinal serosanguinous fluid accumulation, circular-shaped multilayered fibrovascular scarring (disciform scarring), intraretinal hemorrhage and, in severe cases, preretinal or vitreous hemorrhage.[1-19] Choroidal neovascular membranes (CNVM) not obscured by blood or fluid may appear to the observer as a grayish-green subretinal hue.[1-16]

Retinal angiomatous proliferations (RAP) and polypoidal choroidal vasculopathy (PCV) are considered subsets of exudative AMD.[20,21] In retinal angiomatous proliferations, neovascularization originating in the retina extends posteriorly into the subretinal space, eventually communicating with either the choroidal vasculature or sub-retinal CNV.[20] RAP is a manifestation of end-stage AMD.[21] Polypoidal choroidal vasculopathy (PCV) is a retinal disease typically seen more commonly in Asian and African populations. It is characterized by subretinal polypoidal lesions with or without a branching vascular network. The clinical features of PCV include recurrent subretinal hemorrhage, serosanguinous PED subretinal exudation and serous retinal detachment.[21]

Pathophysiology

The essential features of dry AMD (drusen, RPE changes, aging, choroidal thinning, vitreoretinal adhesion, genetic influences, cardiovascular disease, obesity, UV light exposure, smoking) prime the tissues for hypoxic stress, resulting in hypoxia and VEGF accumulation.[19-24] These proceedings cause the RPE to degenerate, resulting in photoreceptor loss. As the photoreceptors disintegrate, the inner nuclear layer collapses, causing it to contact Bruch's membrane, initializing the degeneration of the outer retinal layers.[2-5] UV-induced oxidation and free radical formation within these structures occurs concurrently.[25] Genetics, diet, smoking and many cardiovascular factors are linked with this disease, with increasing evidence that long-term oxidative stress, impaired autophagy and mediated inflammation are involved in the pathogenesis.[1]

Wet AMD results when the RPE/Bruch's barrier becomes compromised by new, weak and leaky blood vessels that grow from the choriocapillaris. Linked to isolated regions of choriocapillaris vascular failure, when hypoxic levels cross the threshold, fluid effusion and neovascularization result.[19,22-24] These occult (i.e., boundaries poorly defined) or classic (i.e., boundaries well defined) subretinal choroidal neovascular membranes leak serosanguinous fluid, causing RPE detachment, sensory retinal detachment, subretinal or intraretinal bleeding, fibrovascular disciform scarring and geographic choroidal atrophy.[1-25]

Studies have identified that interference with retinal oxygen metabolism by confluent drusen, serous or hemorrhagic retinal detachment, retinal edema and vitreoretinal adhesion advance the disease process.[19] Drusen and serous retinal elevation increase the distance between the choriocapillaris and retina and vitreoretinal adhesion reduces the diffusion of oxygen towards hypoxic retina, both contributing to retinal hypoxia.[19] Hypoxia-inducible-factor (HIF) is a cytokine known to exist in subretinal neovascularization; hypoxia being the main stimulus for HIF production along with the release of VEGF.[1,19] These features alone are not by themselves capable of producing enough hypoxia and VEGF accumulation to stimulate wet AMD, but when they combine the impetus is present.[19]

VEGF is naturally secreted by the RPE and serves as a protective surviving factor for the choriocapillaris, Müller cells, neuronal cells and RPE cells.[1] When pooled in elevated levels in combination with defects in Bruch's membrane and other cytokines, the potential for CNVM growth increases.[1,19] Choroidal ischemia in AMD has also been demonstrated to decrease oxygen delivery to the outer retina.[19,26-28] Tractional or serous retinal elevation and choroidal ischemia can combine forces to critically reduce oxygen delivery to the outer retina, creating retinal hypoxia.[19] Once the hypoxic cycle is started, VEGF production increases and retinal effusion follows, initiating the cascade of retinal detachment, intraretinal edema, increasing retinal hypoxia and increased VEGF production.[19]

Management

The best management for wet AMD is prevention. This strategy includes early detection via semiannual dilated fundus exams, patient self-monitoring of vision, lifestyle counseling and oral supplement recommendations in high-risk patients.[29,30]

Researchers have demonstrated that oral antioxidants like vitamins C, E and oral zinc may play a role in reducing early drusen formation by terminating the chemical reactions initiated by free radicals.[29,30] Advanced formulations containing carotenoids such as zeaxanthin and mesozeaxanthin along with polyunsaturated fish oils have also been advocated.[31] Multiple vitamins, oral zinc or products specifically designed for this purpose, such as Ocuvite (Bausch + Lomb), Icaps (Alcon) and Preservision (Bausch + Lomb), to name just a few, have been shown to be useful in slowing the progression of AMD from the dry to wet forms.[29-31]

Smokers or patients with a history of smoking must be advised to use the smokers supplement formulation.[29,30,32] Beta carotene has been shown to increase the risk of lung cancer and has been replaced in these formulations.[29,30,32] Smoking cessation should be discussed with patients.

The treatment of exudative AMD depends on the type, location and size of the lesion.[33,34] In the 1980s and 1990s, laser therapy was guided by the Macular Photocoagulation Study.[34] This strategy employed the use of intravenous fluorescein angiography and indocyanine green angiography to locate focal argon laser photocoagulation to destroy neovascular complexes with heavy confluent burns that extended outside the boundaries of well-defined CNVMs.[34] Unfortunately, poorly defined (i.e., occult) membranes could not be fully and thoroughly treated and frequent recurrence was documented, causing protracted intervention.[33,34]

Photodynamic therapy (PDT) offered new hope via a photosensitive dye (verteporfin) designed to bind with the CNVM and involute it when exposed to a standard wavelength of laser light.[35] While the procedure was far less damaging than photocoagulation, it offered limited, temporary improvement in function and required multiple procedures to maintain a diminishing effect.[33,35] Additionally, it was thought that PDT caused an upregulation of VEGF that could actually prove worse for the patient long term. The Submacular Surgery Trial demonstrated that surgical removal of CNVM was not beneficial compared to photocoagulation.[36]

Currently, the most effective approach to treating exudative AMD relies on vascular endothelial growth factor inhibitors such as bevacizumab, (Avastin, Genentech), ranibizumab, (Lucentis, Genentech) and aflibercept (Eylea, Regeneron) as monotherapy or in combination with laser and PDT.[33] By interfering with VEGF effects (e.g., increased vascular permeability, angiogenesis, induced microvessel formation), disease progression can be limited and even regressed.[33,37]

Studies have concluded that these intravitreally injected agents are superior to PDT in the treatment of predominantly classic CNVM.[37] Other studies (ANCHOR, MARINA, PIER) have demonstrated effectiveness compared to sham treatment for minimally classic or occult CNVM in AMD.[37] Monthly injections are generally well tolerated and induce low rates of ocular or systemic adverse events.[37] Less frequent dosing has been evaluated in a strategy

known as "treat and extend" with the goal of reducing the inconvenience, risk and cost of monthly injections.[37] In the landmark Comparison of Age-related Macular Degeneration Treatments Trial (CATT), monthly monitoring with retreatment as needed (treat and extend) was found equivalent to monthly treatment for vision gain at one year while reducing the number of injections (and the related cost) by approximately half.[38]

In head-to-head comparisons, aflibercept administered bimonthly was non-inferior to ranibizumab administered monthly (VIEW 1 and 2), bevacizumab administered monthly was equivalent to ranibizumab administered monthly and bevacizumab administered as needed was equivalent to ranibizumab administered as needed.[37,38] This was important because bevacizumab has been widely used off-label for economic reasons, providing evidence-based flexibility for the interchangeable use of these agents.[37]

In cases where bilateral central visual acuity has been lost, low vision and vision rehabilitation specialists may be able to offer training, optical devices and non-optical devices which improve patients' quality of life.

Clinical Pearls

- In patients who have already lost one eye to wet AMD, over the course of five years the risk of developing wet stage disease in the fellow eye is 10% for patients whose fellow eye has neither large drusen or pigment clumps, 30% for fellow eyes containing either large drusen or pigment clumps and 50% for fellow eyes with both pigment clumps and large drusen present.
- Genetic testing for AMD is available (e.g., RetnaGene, ArcticDx) for family members of high-risk patients. This test may offer an advantage in predicting the likelihood of being affected, affording these individuals the opportunity for closer follow-up care as well as early, proactive lifestyle modifications.
- Despite the tremendous advancements in anti-VEGF therapy, exudative AMD still carries a guarded prognosis. Sustained interruption to the anti-VEGF regimen can allow AMD to progress. Also, repeated injections may increase the risk of geographic atrophy or increase the risk of endopthalmitis or pigment epithelial detachment.

1. Klettner A, Kauppinen A, Blasiak J, et al. Cellular and molecular mechanisms of age-related macular degeneration: from impaired autophagy to neovascularization. Int J Biochem Cell Biol. 2013;45(7):1457-67.

2. Bowes Rickman C, Farsiu S, Toth CA, Klingeborn M. Dry age-related macular degeneration: mechanisms, therapeutic targets, and imaging. Invest Ophthalmol Vis Sci. 2013;54(14):68-80.

3. van Lookeren Campagne M, LeCouter J, Yaspan BL, Ye W. Mechanisms of age-related macular degeneration and therapeutic opportunities. J Pathol. 2014;232(2):151-64.

4. Machalińska A. Age-related macular degeneration as a local manifestation of atherosclerosis - a novel insight into pathogenesis. Klin Oczna. 2013;115(1):74-8.

5. Turlea C. New aspects in age related macular degeneration. Oftalmologia. 2012;56(1):36-44.

6. Akpek EK, Smith RA. Overview of age-related ocular conditions. Am J Manag Care. 2013;19(5 Suppl):S67-75.

7. Tranos P, Vacalis A, Asteriadis S, et al. Resistance to antivascular endothelial growth factor treatment in age-related macular degeneration. Drug Des Devel Ther. 2013;7(1):485-90.

8. Maguire MG, Daniel E, Shah AR, et al. Incidence of choroidal neovascularization in the fellow eye in the comparison of age-related macular degeneration treatments trials. Ophthalmology. 2013;120(10):2035-41.

9. Novack GD. Pharmacotherapy for the treatment of choroidal neovascularization due to age-related macular degeneration. Annu Rev Pharmacol Toxicol. 2008;48 (1):61-78.

10. Costa RA, Jorge R, Calucci D, et al. Intravitreal bevacizumab (Avastin) in combination with verteporfin photodynamic therapy for choroidal neovascularization associated with age-related macular degeneration (IBeVe Study). Graefes Arch Clin Exp Ophthalmol. 2007;245(9):1273-80.

11. Nano ME, Lansingh VC, Pighin MS, et al. Risk factors of age-related macular degeneration in Argentina. Arq Bras Oftalmol. 2013;76(2):80-4.

12. Mettu PS, Wielgus AR, Ong SS, Cousins SW. Retinal pigment epithelium response to oxidant injury in the pathogenesis of early age-related macular degeneration. Mol Aspects Med. 2012;33(4):376-98.

13. Bhutto I, Lutty G. Understanding age-related macular degeneration (AMD): relationships between the photoreceptor/retinal pigment epithelium/Bruch's membrane/choriocapillaris complex. Mol Aspects Med. 2012;33(4):295-317.

14. Kinnunen K, Petrovski G, Moe MC. Molecular mechanisms of retinal pigment epithelium damage and development of age-related macular degeneration. Acta Ophthalmol. 2012;90(4):299-309.

15. Roth F, Bindewald A, Holz FG. Key pathophysiologic pathways in age-related macular disease. Graefes Arch Clin Exp Ophthalmol. 2004;242(8):710-6.

16. Holz FG, Pauleikhoff D, Klein R, Bird AC. Pathogenesis of lesions in late age-related macular disease. Am J Ophthalmol. 2004;137(3):504-10.

17. Smith AG, Kaiser PK Emerging treatments for wet age-related macular degeneration. Expert Opin Emerg Drugs. 2014;19(1):157-64.

18. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic Atrophy: Clinical Features and Potential Therapeutic Approaches. Ophthalmology. 2014:S0161-6420(13)01102-0.

19. Stefánsson E, Geirsdóttir A, Sigurdsson H. Metabolic physiology in age related macular degeneration. Prog Retin Eye Res. 2011;30(1):72-80.

20. Yannuzzi LA, Negrão S, Iida T, et al. Retinal angiomatous proliferation in age–related macular degeneration. 2001. Retina. 2012;32 (Suppl 1):416-34.

21. Wong RL, Lai TY. Polypoidal Choroidal Vasculopathy: An Update on Therapeutic Approaches. J Ophthalmic Vis Res. 2013;8(4):359-371.

22. Ding X, Li J, Zeng J, et al. Choroidal thickness in healthy Chinese subjects. Invest Ophthalmol Vis Sci. 2011;52(13):9555-60.

23. Manjunath V, Taha M, Fujimoto JG, et al. Choroidal thickness in normal eyes measured using Cirrus HD optical coherence tomography. Am J Ophthalmol. 2010;150(3):325-329.

24. Ikuno Y, Kawaguchi K, Nouchi T, et al. Choroidal thickness in healthy Japanese subjects. Invest Ophthalmol Vis Sci. 2010;51(4):2173-6.

25. Tokarz P, Kaarniranta K, Blasiak J. Role of antioxidant enzymes and small molecular weight antioxidants in the pathogenesis of age-related macular degeneration (AMD). Biogerontology. 2013;14(5):461-82.

26. Wei WB, Xu L, Jonas JB, et al. Subfoveal choroidal thickness: the Beijing Eye Study. Ophthalmology. 2013;120(1):175-80.

27. Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. Am J Ophthalmol. 2009;47(5):811-5.

28. Lee JY, Lee DH, Lee JY, et al. Correlation between subfoveal choroidal thickness and the severity or progression of non-exudative age-related macular degeneration. Invest Ophthalmol Vis Sci. 2013;54(12):7812-8.

29. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol. 2001;119(10):1417-36.

30. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial. JAMA. 2013;309(19):2005-15.

31. SanGiovanni JP, Chew EY, Clemons TE, et al. The relationship of dietary lipid intake and age-related macular degeneration in a case-control study: AREDS Report No. 20. Arch Ophthalmol. 2007;125(5):671-9.

32. Chew EY. Nutrition effects on ocular diseases in the aging eye. Invest Ophthalmol Vis Sci. 2013;54(14):42-7.

33. Moutray T, Chakravarthy U. Age-Related Macular Degeneration: Current Treatment and Future Options. Ther Adv Chronic Dis. 2011; 2(5): 325–331.

34. Macular photocoagulation study group. Argon laser photocoagulation for neovascular maculopathy. Five-year results from randomized clinical trials. Macular Photocoagulation Study Group. Arch Ophthalmol. 1991;109(8):1109-14.

35. Bressler NM, Arnold J, Benchaboune M, Blumenkranz MS, et al. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Arch Ophthalmol. 2002;120(11):1443-54.

36. Bass EB, Gilson MM, Mangione CM, et al. Surgical removal vs observation for idiopathic or ocular histoplasmosis syndrome-associated subfoveal choroidal neovascularization: Vision Preference Value Scale findings from the randomized SST Group H Trial: SST Report No. 17. Arch Ophthalmol. 2008;126(12):1626-32.

37. Frampton JE. Ranibizumab: a review of its use in the treatment of neovascular age-related macular degeneration.Drugs Aging. 2013;30(5):331-58.

38. Maguire MG, Daniel E, Shah AR, et al. Incidence of choroidal neovascularization in the fellow eye in the comparison of age-related macular degeneration treatments trials. Ophthalmology. 2013;120(10):2035-41.

FACIAL NERVE PALSY

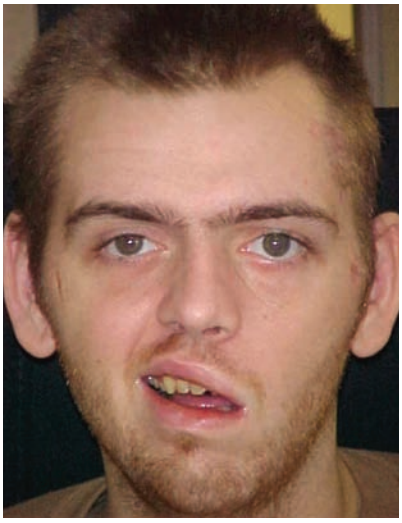
Signs and Symptoms

The seventh cranial nerve (CN VII, facial nerve) is responsible for the voluntary motor innervation to the muscles of facial expression, the stapedius muscle of the inner ear and for sensory innervation to the anterior two-thirds of the tongue.[1–7] The orbicularis oculi, responsible for eyelid closure, is under the control of CN VII.[1–6] Supranuclear pathway lesions (central or upper motor neuron) affect the contralateral lower face.

Damage either to one of the CN VII nuclei or fascicles, or interruption to its peripheral course (lower motor neuron), 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 trauma, diabetes, pregnancy, herpetic viral infection, ischemic vascular disease and family history.[2,6]

Facial nerve palsy can either 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 (buccinator muscle) and squeeze the eyes tightly closed (orbicularis oculi).



Left-sided, complete cranial nerve VII palsy associated with trauma.

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] 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, each of 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 30mm 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. This structure 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 work-up. Sensory afferents from the external auditory meatus and a small area of skin behind the ear transmit pain, temperature and touch information.[2,3]

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]

The term *Bell's palsy* is often used to describe idiopathic CN VII dysfunction, and is considered to be the most common diagnosis associated with facial nerve palsy.[2,12,13] Bell's palsy is a diagnosis of exclusion.[1–13] It is currently thought to be related to idiopathic inflammation secondary to the reactivation of herpes simplex virus isoform 1 (HSV-1) and/or herpes zoster virus (HZV) from the geniculate ganglia.[13]

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]

Management

Care 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, secondary epitheliopathy (sodium fluorescein staining) and tear quantity (Schirmer tear testing).

Since Bell's palsy is a diagnosis of exclusion, medical evaluation should be considered for patients with new-onset facial nerve palsy in an attempt to elicit a cause. The evaluation may include laboratory testing (Lyme titer, rheumatoid factor, erythrocyte sedimentation rate, antinuclear antibody, fluorescent treponemal antibody absorption test, HIV titer), echocardiogram, chest X-ray and contrast-enhanced MRI dependent upon the patient profile, presentation of the palsy, and associated signs and symptoms.[1–6]

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 or bedtime eyelid taping 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] Partial tarsorraphy can be completed in extreme cases.

Treatment for peripheral facial weakness and facial nerve palsy depends upon the underlying etiology. Should none be found definitively, and the cause is determined to be Bell's palsy, there are options designed to speed recovery, though typically the condition will resolve in several weeks to months.

There has been controversy regarding the role of oral antivirals in the management of acute Bell's palsy. Some have shown that there is a limited benefit to oral antiviral medications.[14,15] However, the prevailing thought is that oral antivirals alone are not superior to placebo and have no role in management. If they are considered at all it should be done in conjunction with oral steroids.[16-18] While oral antiviral medications may have no effect, the prevailing thought is that oral steroids are the mainstay of therapy for Bell's palsy with strong recommendations to begin treatment within 72 hours of palsy onset.[12-14,17,19] The recommended dosing is prednisolone, 60mg/d for five days, with the dosage then tapered for five days.[17]

Alternate therapies have shown some benefit. These include acupuncture, hyperbaric oxygen therapy and physical therapy.[20-22] While there is evidence of benefit, there does not exist enough controlled clinical research to warrant recommending these therapies, though

patients who express interest should not be summarily discouraged. In persistent cases of symptomatic facial paralysis, oculoplastic surgery can improve function.[23]

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.
- Bell's palsy will typically recover within several weeks to months. Persistence beyond three months requires re-evaluation.
- The number-one concern is corneal protection, using artificial tears, punctal plugs, moisture chambers, internal or external weights or complete or partial tarsorrhaphy.
- When a patient presents with acute-onset facial nerve palsy, do not immediately diagnose Bell's palsy. Instead, perform a thorough history and physical and consider medical and neuroradiologic evaluation to identify a potential cause. Remember, Bell's palsy is a diagnosis of exclusion.

1. Gurwood AS. The eyelid and neuro-ocular disease. In: Blaustein BH (ed.) Ocular Manifestations of Neurologic Disease, Philadelphia: Mosby, 1996:127–51.

2. Gurwood AS, Tasca JM, Kulback E. A review of cranial nerve VII palsy with emphasis on Bell's palsy. South J Optom 1996;14(3):13–17.

3. May M, Galetta S. The facial nerve and related disorders of the face. In: Glaser JS (ed.), Neurophthalmology (2nd ed.), Philadelphia, J. B. Lippincott Co., 1990:239–77.

4. Savino PJ, Sergot RC. Neuroophthalmology: Isolated seventh nerve palsy. In: Rhee DJ, Pyfer MF, The Wills Eye Manual (3rd ed.), Philadelphia, Lippincott Williams & Wilkins 1999:290–4.

5. Bajandas FJ, Kline LB. Seven Syndrome of the Seventh (Facial) Nerve. In: Bajandas FJ, Kline LB (eds.), Neuro-ophthalmology Review Mannual (3rd ed.), Thorofare, NJ: Slack, 1988:151–6.

6. Danielides V, Skevas A, van-Cauwenberge P, et al. Facial nerve palsy during pregnancy. Acta Otolaryngol Belg 1996;50(2):131–5.

7. Zwick OM, Seiff SR. Supportive care of facial nerve palsy with temporary external eyelid weights. Optom 2006;77(7):340–2.

8. Sensat ML. Mobius syndrome: A dental hygiene case study and review of the literature. Int J Dent Hyg 2003;1(1):62–7.

9. Salinas RA, Alvarez G, Ferreira J. Corticosteroids for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2004;18(4):CD001942.

10. Allen D, Dunn L. Aciclovir or valaciclovir for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2004;1(3):CD001869.

11. Gilbert SC. Bell's palsy and herpesviruses. Herpes 2002;9(3):70–3.

12. Baugh RF, Basura GJ, Ishii LE, et al. Clinical practice guideline: Bell's palsy. Otolaryngol Head Neck Surg. 2013;149(3 Suppl):S1-27.

13. Zandian A, Osiro S, Hudson R, et al. The neurologist's dilemma: A comprehensive clinical review of Bell's palsy, with emphasis on current management trends. Med Sci Monit. 2014;20:83-90.

14. Albers JR, Tamang S. Common questions about bell palsy. Am Fam Physician. 2014;89(3):209-12.

15. Hato N, Sawai N, Teraoka M, et al. Valacyclovir for the treatment of Bell's palsy. Expert Opin Pharmacother. 2008;9(14):2531-6.

16. Hato N, Yamada H, Kohno H,et al. Valacyclovir and prednisolone treatment for Bell's palsy: a multicenter, randomized, placebo-controlled study. Otol Neurotol. 2007;28(3):408-13.

17. Axelsson S, Berg T, Jonsson L, et al. Bell's palsy - the effect of prednisolone and/or valaciclovir versus placebo in relation to baseline severity in a randomised controlled trial. Clin Otolaryngol. 2012;37(4):283-90.

18. Lockhart P, Daly F, Pitkethly M,et al. Antiviral treatment for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev. 2009;(4):CD001869.

19. Berg T, Bylund N, Marsk E, et al. The effect of prednisolone on sequelae in Bell's palsy. Arch Otolaryngol Head Neck Surg. 2012;138(5):445-9.

20. Teixeira LJ, Valbuza JS, Prado GF. Physical therapy for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev. 2011;(12):CD006283.

21. Chen N, Zhou M, He L, et al. Acupuncture for Bell's palsy. Cochrane Database Syst Rev. 2010 Aug 4;(8):CD002914.

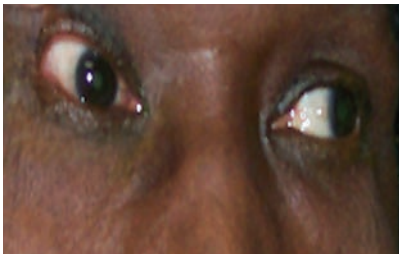
22. Holland NJ, Bernstein JM, Hamilton JW. Hyperbaric oxygen therapy for Bell's palsy. Cochrane Database Syst Rev. 2012 Feb 15;2:CD007288.

23. Sira M, Norris JH, Nduka C, Malhotra R. Transcaruncular Medial Canthal Tendon Plication with Lower Eyelid Suture Sling in Facial Nerve Palsy. Orbit. 2014 Feb 25. [Epub ahead of print].

INTERNUCLEAR OPHTHALMOPLEGIA

Signs and Symptoms

Internuclear ophthalmoplegia (INO) can present in either the young or old and can be due to various etiologies. Patients with INO generally report a painless visual disturbance involving horizontal diplopia in lateral gaze, but typically no diplopia in primary gaze.[1-4] Those who complain of diplopia in primary gaze typically have a concurrent skew deviation.[5]



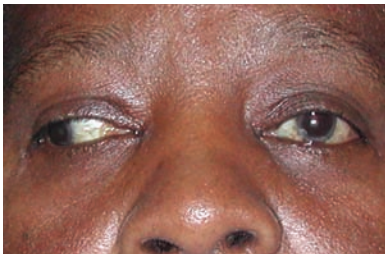
Adduction deficit and abducting nystagmus with right internuclear ophthalmoplegia.

Clinically, the patient will manifest a relative adduction deficit on the involved side, as well as a nystagmus of the fellow eye in extreme abduction (abducting nystagmus). The adduction deficit may range from a complete inability to move the eye beyond the midline to a subtle limitation of adducting capacity. Cover testing in lateral gazes can help identify a non-comitant deviation; a greater exo deviation away from the eye with the adduction deficit would be seen in INO. The differential diagnosis for this pattern could include a cranial nerve III palsy and myasthenia gravis, though the abducting nystagmus will identify INO. Some patients with INO will be able to converge their eyes while others will not; this ability or inability can localize the area of the causative lesion.

Several variations of INO may be encountered clinically, four of which are profiled below.

The first is *bilateral internuclear ophthalmoplegia* (BINO), in which both eyes are affected by the same underlying dysfunction. Patients with BINO demonstrate an adduction deficit in both eyes and contralateral abducting nystagmus of the each of the fellow eyes on lateral gaze.

Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO) is a syndrome in which a BINO is superimposed on a concurrent exotropia; hence, the patient presents with a divergent ocular posture in primary gaze (from involvement of CN III nucleus) as well as the adduction deficits and abducting nystagmus.[5,6]



Left internuclear ophthalmoplegia and skew deviation.

Skew deviation often accompanies INO, but it is less likely seen with BINO.[5] In skew deviation, the eyes demonstrate a vertical misalignment as well as torsion. The higher eye will be intorted, and the lower eye will be extorted. Patients with skew deviation will complain not only of horizontal diplopia in lateral gaze but also of vertical diplopia in primary gaze.

Finally, *one-and-a-half syndrome* describes a rare form of ophthalmoparesis in which the patient demonstrates conjugate horizontal gaze palsy in one direction (i.e., the eyes do not move at all), combined with INO in the opposite direction.[7] Upon attempted lateral gaze, one eye will remain essentially "frozen in space," while the other will only be able to turn outward with an associated nystagmus. However, the gaze palsy may not be complete. There may also be additional associated nystagmus occurring beyond the abducting nystagmus characteristic of INO; this may include upbeat or downbeat nystagmus. [8-10]

Pathophysiology

As the name implies, INO is an ophthalmoplegia that occurs secondary to a disruption of communication between two nerve nuclei; namely, the abducens nerve (in the pons) and the oculomotor (in the mesencephalon). The interaction and communication of cranial nerves III and VI to produce synchronous horizontal eye movements is accomplished via the medial longitudinal fasciculus (MLF), a neural pathway that interconnects these cranial nerve nuclei. The MLF can be considered to be a neural highway that connects the horizontal gaze control center in the pons with the medial recti subnuclei in the mesencephalon some distance away.

In INO, one or more lesions disrupt this pathway, interrupting communication between the cranial nerves VI and III, responsible for horizontal eye movements through control of the lateral rectus and medial rectus, respectively.[11,12]

To illustrate: In the case of a right INO, for a patient attempting to gaze to the left, the left supranuclear control center of horizontal eye movements (paramedian pontine reticular formation, or PPRF) must signal the left cranial VI nucleus to contract the left abducens muscle to turn the left eye outwards. At the same time, the PPRF must signal the right cranial nerve III nucleus, via the right MLF, to contract the right medial rectus so that it simultaneously turns the right eye inward. A lesion of the right MLF effectively prevents the neural impulse from reaching the right medial rectus. In that case, the left eye would abduct but the right eye would not adduct with it. This additionally forces the left eye into an abducting nystagmus. Note that an INO is named for the eye with the adducting deficit—a right INO indicates a right adduction issue.

Most MLF lesions are located in the pons, or caudal mesencephalon. The center for convergence is in the midbrain. So, if convergence is affected, the lesion is more likely in the midbrain. This is considered an anterior INO or BINO.[14] On the other hand, an INO with intact convergence ability means the midbrain is not affected, so the lesion is more likely in the pons. This is considered a posterior INO or BINO.[13]

In one-and-a-half syndrome, the PPRF or CN VI nucleus and MLF are both involved. On attempted gaze to the affected side, there is no abduction on the involved side or adduction of the fellow eye, hence a gaze paresis. On attempted gaze opposite the lesion, the fellow eye will abduct and demonstrate abducting nystagmus while the other eye does not move. Thus, there is a total gaze paresis on the involved side and an INO when looking opposite.

The most common cause of INO is vascular infarction of the brainstem, followed by demyelinating disease such as multiple sclerosis (MS). In older patients with INO, the most common etiology is vascular infarction.[7,15] In younger patients, MS is the most common etiology of INO.[2,16-18] In fact, INO is the most prevalent ocular motility dysfunction encountered in those with MS.[18] MS can cause a bilateral presentation, whereas ischemic vascular infarction tends to cause a unilateral presentation.[19] Other possible causes include brainstem and fourth ventricular tumor, viral infection, trauma, syphilis, Lyme disease, systemic lupus erythematosus, drug intoxication (phenothiazines and tricyclic antidepressants) and subdural hematoma.[20-24]

Recently, a cerebral vascular accident localized to the top of the basilar artery was reported to cause tegmental midbrain infarction resulting in BINO and WEBINO.[25,26] Also, myasthenia gravis can produce a pseudo-INO with a motility pattern identical to true INO.[27-29]

Management

There is no direct treatment for patients with any form of internuclear ophthalmoplegia. Optimal management of INO involves identifying the underlying cause, followed by appropriate medical treatment of the discovered etiology. Diagnostic testing is critical in disclosing the cause. Typically, patients without a known, pre-existing illness should undergo an MRI of the brainstem (with and without contrast media) including pons and mesencephalon.

Other work-up items may include blood pressure evaluation, diabetes testing, a complete blood count with differential and platelets, syphilis testing, Lyme assay and toxicology screen.

In INO secondary to ischemic vascular infarction, the motility pattern almost invariably returns to normal with time. In a study of 30 INO patients with brainstem infarction, 100% of subjects recovered within one year, and nearly 77% resolved within one month of onset.[30]

In persistent cases, medial rectus resection can be performed to relieve symptoms.[31] However, this typically is not needed, as any form of INO from either vascular infarct or demyelination will resolve over time.

Clinical Pearls

• Beyond MRI studies to rule out a compressive lesion, infarct and MS, patients require medical evaluation for underlying ischemic vascular diseases such as diabetes and hypertension. Fortunately, cases of INO associated with ischemia typically resolve rapidly.

• Always remember that myasthenia gravis can mimic the motility pattern of INO. The key to proper diagnosis is remembering that myasthenia tends to be variable from day to day and usually worsens at the end of the day. By contrast, INO generally is a sudden-onset disorder that remains static at least for days to weeks before showing gradual resolution. The abducting nystagmus can also help in differentiation.

• Abduction deficit from isolated medial rectus palsy is extremely rare. In cases where there is solely an abduction deficit, examine the fellow eye closely for an abducting nystagmus indicative of INO. Most cases of isolated "medial rectus palsy" are in reality INO.

1. Cogan DG. Internuclear ophthalmoplegia, typical and atypical. Arch Ophthalmol 1970;84(5):583-9.

2. Obuchowska I, Mariak Z. Internuclear ophthalmoplegia--causes, symptoms and management. Klin Oczna. 2009;111(4-6):165-7.

3. Rizzo JL, Lloyd M, O'Hara MA. Pediatric internuclear ophthalmoplegia. J Neuroophthalmol. 2013;33(2):134-6.

4. Rismanchi N, Crawford JR. Bilateral internuclear ophthalmoplegia associated with pediatric brain tumor progression: a case series and review of the literature. J Neurooncol. 2013;115(3):487-91.

5. Tsuda H, Kamata K, Tanaka K, Kishida S. WEMINO syndrome with skew deviation and facial palsy. Intern Med. 2011;50(20):2435-6.

6. McGettrick P, Eustace P. The WEBINO syndrome. Neuroophthalmol 1985;5(3):109-15.

7. Wall M, Wray SH. The one-and-a-half syndrome—a unilateral disorder of the pontine tegmentum: A study of 20 cases and review of the literature. Neurol 1983;33(8):971-80.

8. Shaikh AG, Ghasia FF, Rasouli G,et al. Acute onset of upbeat nystagmus, exotropia, and internuclear ophthalmoplegia--a tell-tale of ponto-mesencephalic infarct. J Neurol Sci. 2013;332(1-2):56-8.

9. Choi JH, Jung NY, Kim MJ, et al. Pure upbeat nystagmus in association with bilateral internuclear ophthalmoplegia. J Neurol Sci. 2012;317(1-2):148-50.

10. Jeong SH, Kim EK, Lee J, et al. Patterns of dissociate torsional-vertical nystagmus in internuclear ophthalmoplegia. Ann N Y Acad Sci. 2011;1233:271-8.

11. Pierrot-Deseilligny C. Nuclear, internuclear, and supranuclear ocular motor disorders. Handb Clin Neurol. 2011;102:319-31.

12. Bae YJ, Kim JH, Choi BS, et al. Brainstem pathways for horizontal eye movement: pathologic correlation with MR imaging. Radiographics. 2013;33(1):47-59.

13. Keane JR. Internuclear ophthalmoplegia: Unusual causes in 114 of 410 patients. Arch Neurol 2005;62(5):714-7.

14. Bolanos I, Lozano D, Cantu C. Internuclear ophthalmoplegia: causes and long-term follow-up in 65 patients. Acta Neurol Scand 2004;110(3):161-5.

15. Chen CM, Lin SH. Wall-eyed bilateral internuclear ophthalmoplegia from lesions at different levels in the brainstem. J Neuroophthalmol. 2007;27(1):9-15.

16. Kamogawa K, Toi T, Okamoto K, Okuda B. Case of multiple sclerosis with WEBINO syndrome. Rinsho Shinkeigaku. 2009;49(6):354-7.

17. Obuchowska I, Mariak Z. Internuclear ophthalmoplegia in course of multiple sclerosis and head trauma. Presentation of 2 cases. Klin Oczna. 2009;111(4-6):156-9.

18. Jacobs DA, Galetta SL. Multiple sclerosis and the visual system. Ophthalmol Clin North Am 2004;17(3):265-73.

19. Gass A, Hennerici MG. Neurological picture. Bilateral internuclear ophthalmoplegia in multiple sclerosis. J Neurol Neurosurg Psych 1997;63(5):564.

20. Abel MP, Murphy FT, Enzenauer RJ, Enzenauer RW. Internuclear ophthalmoplegia (INO): An unusual presentation of neuropsychiatric lupus erythematosus. Binocul Vis Strabismus Q 2003;18(1):29-30.

21. Cook FF, Davis RG, Russo LS Jr. Internuclear ophthalmoplegia caused by phenothiazine intoxication. Arch Neurol 1981;38(7):465-6.

22. Deleu D, Ebinger G. Lithium-induced internuclear ophthalmoplegia. Clin Neuropharmacol 1989;12(3):224-6.

23. Shinoda K, Matsushita T, Furuta K, et al. Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO) syndrome in a patient with neuromyelitis optica spectrum disorder and anti-aquaporin-4 antibody. Mult Scler. 2011;17(7):885-7.

24. Rodríguez Calvo de Mora M, Rodríguez Moreno G, España Contreras M. Webino syndrome caused by meningovascular syphilis. A rare entity with an unexpected cause. Arch Soc Esp Oftalmol. 2012: S0365-6691(12)00532-1.

25. Sierra-Hidalgo F, Moreno-Ramos T, Villarejo A, et al. A variant of WEBINO syndrome after top of the basilar artery stroke. Clin Neurol Neurosurg. 2010;112(9):801-4.

26. Arai D, Nakajima M. "Top of the basilar" occlusion causing bilateral internuclear ophthalmoplegia. Intern Med. 2011;50(5):527-8.

27. Bandini F, Faga D, Simonetti S. Ocular myasthenia mimicking a one-and-a-half syndrome. J Neuroophthalmol 2001;21(3):210-1.

28. Bogdan I, Crisanda V. Pseudo-internuclear ophthalmoplegia in myasthenia gravis. Oftalmologia. 2011;55(3):70-3.

29. Ito K, Mizutani J, Murofushi T, Mizuno M. Bilateral pseudo-internuclear ophthalmoplegia in myasthenia gravis. ORL J Otorhinolaryngol Relat Spec 1997;59(2):122-6.

30. Kim JS. Internuclear ophthalmoplegia as an isolated or predominant symptom of brainstem infarction. Neurol 2004;62(9):1491-6.

31. Adams WE, Leavitt JA, Holmes JM. Strabismus surgery for internuclear ophthalmoplegia with exotropia in multiple sclerosis. J AAPOS. 2009;13(1):13-5.

NEUROMYELITIS OPTICA

Signs and Symptoms

Neuromyelitis optica (NMO) was first described by Albutt in 1870, but the term was not applied until 1894 by Devic; hence the alternate name *Devic's disease*.[1,2] It wasn't until 2004 that a serologic marker was identified, allowing NMO to be differentiated from multiple sclerosis (MS) rather than being considered a subset of the condition.[3]

Patients will manifest signs and symptoms characteristic of demyelinating disease, including the clinical hallmarks of optic neuritis and transverse myelitis. The painful vision loss seen in NMO is quite severe, with acuity typically worse than 20/200; recovery is less complete than as seen in MS. In contrast to optic neuritis seen in adults with MS, bilaterality is common.[4] Other findings associated with NMO include weakness and paresthesia of the limbs, severe radicular back pain, spastic diplegia, bladder paralysis, loss of sphincter control, paroxysmal painful spasms of the limbs and trunk, intractable nausea and intractable hiccups.

Respiratory failure is the main cause of death in patients with NMO.[1] Within five years of onset, 50% of NMO patients are bilaterally blind and cannot walk unassisted.[5]

There are numerous autoimmune conditions associated with NMO, including myasthenia gravis, celiac disease, ulcerative colitis, sclerosing cholangitis, systemic lupus erythematosus, rheumatoid arthritis, antiphospholipid antibody syndrome, Sjögren's syndrome, autoimmune hypothyroidism, immune thrombocytopenic purpura, pernicious anemia, narcolepsy, pemphigus foliaceus, alopecia areata, psoriasis, scleroderma, dermatitis herpetiformis, polymyositis, chronic inflammatory demyelinating polyneuropathy, paraneoplastic disorders, insulin dependent diabetes mellitus, autoimmune encephalitis and sarcoidosis.[6,7]

NMO has a female predilection, with a ratio of women to men of 9:1.[5] There is also a higher incidence in people of color.[5] While NMO is considered within the spectrum of demyelinating diseases, the median age of onset is 39 years, which is approximately 10 years later than in MS. However, NMO has been known to develop both in children and the elderly.[2,6]

NMO can follow either a monophasic or relapsing course. In the monophasic course, optic neuritis will concurrently accompany transverse myelitis or the two conditions will develop within a short period of time of each other. This then may be the only manifestation of the disease. Should no other occurrences develop within three years, the patient is considered to have a monophasic course. In the relapsing form, patients will have recurrences of the autoimmune inflammation and subsequent accumulation of disability. Approximately 80% to 90% of patients will manifest the more severe relapsing form of NMO.[5] The five-year mortality rate of relapsing NMO is 32% compared to 10% for the monophasic form of the disease.[8]

Pathophysiology

Neuromyelitis optica is an immune-mediated, chronic inflammatory disorder of the central nervous system (CNS) affecting both white and gray matter, preferentially attacking the myelin of the optic nerve and spinal column. It is thought to be triggered by an environmental factor such as infection in genetically susceptible individuals.[8]

Once considered a variant of MS, NMO is now recognized as a separate demyelinating disorder with pleiotropic presentations, due to the identification of a specific autoantibody response against the astrocyte water channel aquaporin-4 (AQP4) in the majority of individuals with the disease.[3,9-11]

Aquaporin is the predominant water channel in the CNS, regulating the flow of water in cells. The aquaporin protein is in high concentration in the optic nerves, spinal cord, hypothalamus and periventricular regions of the brain. AQP4 is expressed in astrocytes and astrocytic processes surrounding small blood vessels. The AQP4 autoantibodies, also commonly known as NMO-IgG antibodies, bind to the astrocytic foot processes, recruiting and activating humoral immune system including the complement system, which leads to the mobilization of polymorphonuclear cells, inflammation and tissue edema.[5,6]

In contrast to multiple sclerosis episodes, NMO attacks are mediated by B-cells rather than T-cells, further differentiating the two conditions. The cellular infiltration initiated by NMO-IgG antibodies target the astrocytes in the CNS, causing cytopathic destruction of these cells. Additionally, vascular destruction, tissue necrosis, demyelination, and gliosis will accompany the inflammatory process.[5,6,8-13] The subsequent inflammatory reaction in the optic nerves gives rise to optic neuritis and the spinal cord damage results in transverse myelitis. The non-ocular physical signs and symptoms will be dictated by which spinal cord segments are involved.

Management

Proper diagnosis of NMO and differentiation from MS is crucial to proper management, especially since the two diseases are treated differently and some MS treatments may worsen the course of NMO. Contrast-enhanced magnetic resonance imaging (MRI) of the brain and entire spinal cord is obligatory in the diagnostic evaluation. During an acute attack, MRI will show an enhancing central cord lesion extending over three or more cord segments. There will also be enhancement of the optic nerves if an optic neuritis is present.

It is currently accepted that a diagnosis of NMO can be made with high specificity if two absolute criteria—optic neuritis and acute myelitis—are present, and additionally two of the following three supporting criteria: (1) normal brain MRI or MRI brain abnormalities not consistent with MS, (2) spinal cord MRI with contiguous T2-weighted signal abnormality extending over three or more vertebral segments, (3) NMO-IgG serpositivity.[1,5,6]

There exist some patients with recurrent optic neuritis or recurrent longitudinally extensive myelitis alone who are also positive for NMO-IgG antibody. Additionally, they may also have abnormal brain MRI indicative of brainstem encephalopathy but do not meet the classic diagnostic criteria of NMO. Due to the NMO-IgG seropositivity and often eventual progression to classic NMO in many cases, these individuals are considered to be within the NMO-spectrum disorder classification.[14,15]

Optical coherence tomography (OCT) can be helpful diagnostically, demonstrating thinning of the retinal nerve fiber layer (RNFL). OCT shows more severe retinal damage with thinner average RNFL, particularly of the superior and inferior quadrants after optic neuritis episodes in neuromyelitis optica than in relapsing-remitting multiple sclerosis.[16-18]

There is no cure for NMO and no FDA-approved therapies, though several immunomodulators have demonstrated effectiveness in managing the disease. The treatment goals for NMO involve rescue therapy for the acute phase of the disease and long-term disease-modifying immunomodulatory therapy to reduce neurologic disability.

During an acute attack of optic neuritis and myelitis, prompt rescue therapy with intravenous corticosteroids may reduce the degree of permanent tissue damage and neurological disability. Typical therapy involves 1gm/day of methylprednisolone for five days. If the patient's status does not improve, the next immediate step is five to seven cycles of therapeutic plasma exchange (TPE). This is crucial to prevent neurogenic respiratory failure. While corticosteroids exert global anti-inflammatory and immunosuppressive effects, TPE removes autoantibodies, immune complexes and inflammatory mediators from the patient's plasma.[1,6,8,19]

Beyond rescue therapy for the acute phase of the disease, there exists an immediate need for immunomodulatory therapy to reduce the accumulation of neurologic disability. Numerous reports indicate the effectiveness of azathioprine (Imuran) in reducing the relapse rate and ameliorating the neurologic disability in patients with NMO. As such, azathioprine is considered the first-line immunomodulatory therapy for NMO. The full effect of azathioprine may be delayed for several months. For this reason, oral steroids are typically used concurrently.

Rituximab (Rituxan) has shown good effect and is generally considered to be the second-line agent for NMO. Additionally, other non-specific immunosuppressant drugs, such as methotrexate, tacrolimus, mycophenolate mofetil and mitoxantrone have demonstrated effectiveness.[8-11,13,19-24] Standard MS therapies, including beta-interferons and glatiramer acetate, have been used in patients with NMO, but to little effect. In fact, it appears that interferon beta may worsen the course of NMO, underscoring the importance of differentiating the conditions.[1]

Clinical Pearls

- Bilateral simultaneous optic neuritis should raise suspicion for NMO.
- Incomplete recovery of visual function from MS-suspected optic neuritis should raise suspicion for NMO.
- NMO should be considered in patients who have repeated attacks of optic neuritis yet fail to show MRI brain lesions consistent with MS.
- Optic neuritis arising from MS does not necessarily need corticosteroid therapy, but optic neuritis arising from NMO does.

1. Argyriou AA, Makris N. Neuromyelitis optica: a distinct demyelinating disease of the central nervous system. Acta Neurol Scand. 2008;118(4):209-17.

2. Marrie RA, Gryba C. The incidence and prevalence of neuromyelitis optica: a systematic review. Int J MS Care. 2013;15(3):113-8.

3. Lennon VA, Wingerchuk DM, Kryzer TJ, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet. 2004;364(9451):2106-12.

4. Levin MH, Bennett JL, Verkman AS. Optic neuritis in neuromyelitis optica. Prog Retin Eye Res. 2013;36:159-71.

5. Cross SA. Rethinking neuromyelitis optica (Devic disease). J Neuroophthalmol. 2007;27(1):57-60.

6. Trebst C, Jarius S, Berthele A, et al. Neuromyelitis Optica Study Group (NEMOS). Update on the diagnosis and treatment of neuromyelitis optica: recommendations of the Neuromyelitis Optica Study Group (NEMOS). J Neurol. 2014;261(1):1-16.

7. Iyer A, Elsone L, Appleton R, Jacob A. A review of the current literature and a guide to the early diagnosis of autoimmune disorders associated with neuromyelitis optica. Autoimmunity. 2014 Feb 10. [Epub ahead of print].

8. Bienia B, Balabanov R. Immunotherapy of neuromyelitis optica. Autoimmune Dis. 2013;2013:741490. doi: 10.1155/2013/741490. Epub 2013 Dec 25.

9. Kowarik MC, Soltys J, Bennett JL. The treatment of neuromyelitis optica. J Neuroophthalmol. 2014;34(1):70-82.

10. Wingerchuk DM. Diagnosis and treatment of neuromyelitis optica. Neurologist. 2007;13(1):2-11.

11. Nandhagopal R, Al-Asmi A, Gujjar AR. Neuromyelitis optica: an overview. Postgrad Med J. 2010;86(1013):153-9.

12. Levy M, Wildemann B, Jarius S, et al. Immunopathogenesis of neuromyelitis optica. Adv Immunol. 2014;121:213-42.

13. Jarius S, Wildemann B, Paul F. Neuromyelitis optica: clinical features, immunopathogenesis, and treatment. Clin Exp Immunol. 2014 Jan 13. doi: 10.1111/cei.12271. [Epub ahead of print].

14. Sato DK, Lana-Peixoto MA, Fujihara K, de Seze J. Clinical spectrum and treatment of neuromyelitis optica spectrum disorders: evolution and current status. Brain Pathol. 2013;23(6):647-60.

15. Jacob A, McKeon A, Nakashima I, et al. Current concept of neuromyelitis optica (NMO) and NMO spectrum disorders. J Neurol Neurosurg Psychiatry. 2013;84(8):922-30.

16. de Seze J, Blanc F, Jeanjean L, et al. Optical coherence tomography in neuromyelitis optica. Arch Neurol. 2008;65(7):920-3.

17. Ratchford JN, Quigg ME, Conger A, et al. Optical coherence tomography helps differentiate neuromyelitis optica and MS optic neuropathies. Neurology. 2009;73(4):302-8.

18. Naismith RT, Tutlam NT, Xu J,et al. Optical coherence tomography differs in neuromyelitis optica compared with multiple sclerosis. Neurology. 2009;72(12):1077-82.

19. Fujihara K. Treatment of neuromyelitis optica. Nihon Rinsho Meneki Gakkai Kaishi. 2012;35(2):129-35.

20. Costanzi C, Matiello M, Lucchinetti CF, et al. Azathioprine: tolerability, efficacy, and predictors of benefit in neuromyelitis optica. Neurology. 2011;77(7):659-66.

21. Uzawa A, Mori M, Kuwabara S. Neuromyelitis optica: concept, immunology and treatment. J Clin Neurosci. 2014;21(1):12-21.

22. Nomura K. Treatment of neuromyelitis optica. Nihon Rinsho. 2013;71(5):829-38.

23. Kim SH, Huh SY, Lee SJ, et al. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. JAMA Neurol. 2013;70(9):1110-7.

24. Ramanathan RS, Malhotra K, Scott T. Treatment of neuromyelitis optica/neuromyelitis optica spectrum disorders with methotrexate. BMC Neurol. 2014;14:51.

BRAIN AND ORBITAL TUMOR

Signs and Symptoms

Brain and orbital tumors may either be primary lesions or the result of metastasis from primary tumors originating elsewhere. Brain tumors can directly and indirectly affect the systemic and visual systems.[1-4] They can occur spontaneously and idiopathically or as part of a genetic hereditary syndrome.[1-3] When they grow large enough, intracranial masses have the ability to displace or compress functional elements inside the cranium (both tissue and vascular) impacting structure and function.[1-4] Depending upon the tumor location, different functions may be affected. For example, patients with brain tumors may experience aphasia, ataxia, weakness, memory loss and hallucinations, among other things.[5-9] When a tumor impacts the visual pathway, visual acuity or visual field loss will ensue.[3-10]

These defects occur in seven cardinal locations, with variations:

(1) Unilateral optic nerve location, resulting in ipsilateral central acuity and field loss.

(2) Anterior chiasmal location, resulting in ipsilateral optic nerve and crossing contralateral nasal retinal axon impingement creating an ipsilateral central loss in conjunction with a contralateral temporal hemifield defect.

(3) Chiasmal location, creating the classic bitemporal hemianopic defect, denser superiorly.

(4) Posterior chiasmal syndrome, which can have three presentations: central bitemporal, bitemporal denser inferiorly, and incongruous homonymous hemianopia.

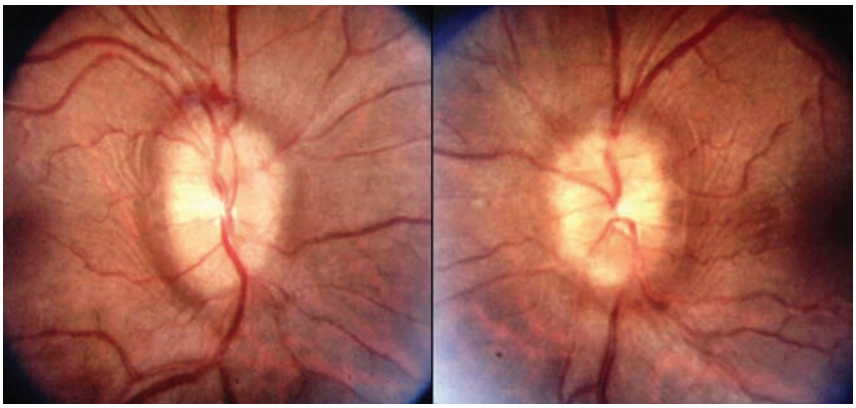
(5) Parietal lobe location, creating a contralateral, relatively incongruous, inferior homonymous quadrantanopia sometimes referred to as "pie on the floor."

(6) Temporal location, creating a contralateral superior homonymous quadrantanopia sometimes referred to as "pie in the sky."

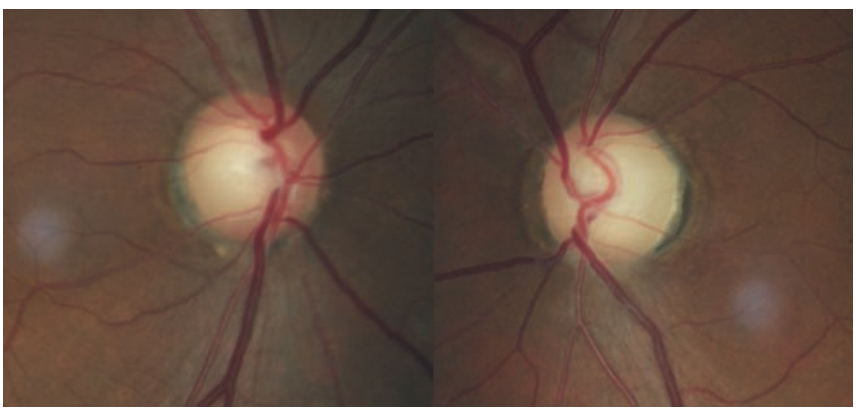
(7) Occipital lobe location, creating contralateral congruous homonymous quadrantanopia or hemianopia with or without macular sparing depending upon the location.

As tumors enlarge inside the closed cranial vault, they compress brain tissue and may elevate intracranial pressure either directly or through ventricular blockage, with resultant hydrocephalus.[11,12] This can create symptoms of increased intracranial pressure such as nausea, vomiting, headache (often waking the patient from sleep, or worsening throughout the day), transient visual obscurations and pulsatile tinnitus (in the ears). The most telling sign of increased intracranial pressure is bilateral optic disc edema (papilledema).

Tumors requiring formidable vascular supply can induce anemia or ischemic cerebrovascular accident (ischemic stroke CVA) along with all of its systemic and ocular sequelae.[14,15] If they or their vascular supplies hemorrhage, they can induce hemorrhagic cerebrovascular accident (hemorrhagic stroke CVA) along with its consequences.[13,16,17]



Bilateral papilledema from intracranial mass lesion.



Unilateral disc pallor OS from compressive lesion in the anterior visual pathway.

Diplopia and ophthalmoplegia occurring from cranial nerve III, IV or VI palsy, Horner syndrome, internuclear ophthalmoplegia, nystagmus and skew deviation, to name a few, may occur from an intracranial mass lesion impinging on various structures. Orbital tumors may present with loss of visual acuity, dyschromatopsia, relative afferent pupillary defect and proptosis.

Pathophysiology

The common brain tumors affecting the eye and visual pathway include pituitary adenoma, meningioma, glioma/astrocytoma and neurofibromas and hemangioblastoma (Von Hippel-Lindau vascular tumors).[1,2]

Pituitary adenomas can be either non-secreting or secreting in nature. The vast majority are non-secreting. Those that are secreting are traditionally named for the hormone that is errantly excreted when they grow. Prolactinomas (growth hormone adenomas) are among the most common types of hormone-secreting pituitary adenomas.[18,19] Patients with secreting pituitary adenomas may present initially with symptoms of endocrine dysfunction such as infertility, decreased libido and galactorrhea with or without neurologic symptoms such as headache and visual changes.[18,19] Patients with non-secreting tumors typically have no endocrine dysfunction.

Oversecretion of hormones from a dysfunctional pituitary gland may result in classic syndromes, the most common of which are hyperprolactinemia (from oversecretion of prolactin), acromegaly (from excess growth hormone) and Cushing's disease (from overproduction of adrenocorticotropic hormone).[18,19] Prolactinomas are more common in men.[19] Amenorrhoea is a common occurrence in women.[19] Acromegaly (gigantism, enlargement of the tongue) occurs in growth hormone-secreting tumors.[20]

When pituitary tumors bleed, they pose a life-threatening emergency known as *pituitary tumor apoplexy*.[21] The clinical features include abrupt onset of severe headache, nausea, vomiting, deteriorating consciousness, cranial neuropathies with ophthalmoplegia, visual impairment and endocrine deficiency.[21]

Meningiomas are tumors of the meninges.[22-24] Optic nerve sheath meningiomas (ONM) account for one third of all intrinsic tumors of the optic nerve.[22-24] Despite being histologically benign, they often cause progressive visual loss that can lead to blindness if left untreated.[22,23] Optic atrophy and optic disc collateral vessels are other presenting signs. Diffuse segmental optic nerve sheath thickening or globular growth is noted upon imaging.[23] Calcification is a sign that the tumor is slow growing.[23] OMN with posterior components have the potential for intracranial extension. Younger sufferers often demonstrate faster growth.[23]

Gliomas and astrocytomas are named for their cell types.[26-29] Both are common tumors of the central nervous system (CNS).[24] These tumors constitute a heterogeneous class of related neoplasms that are associated with a variety of molecular abnormalities affecting angiogenesis and the extracellular matrix.[25] Both tumors (glioma>astrocytoma) have been associated with neurofibromatosis type 1 (NF-1) and may be seen with or without the classic skin lesion known as the "café-au-lait" spot.[26] Any time optic nerve glioma is diagnosed, testing for NF-1 is advised.[26-28]

Astrocytomas are documented as being able to "seed" the retina, leading to retinal astrocytoma.[29] There are several grades of astrocytomas, from the least aggressive (grade 1) to the most aggressive (grade 4)—notably glioblastoma multiforme (GBM), which is a rapidly growing and spreading grade 4 tumor that may not produce symptoms until it is very large. Its infiltrative nature prevents complete surgical removal, giving GBM a very grim prognosis.

Hemangioblastomas (HB) are rare, indolent CNS vascular tumors that may occur sporadically or in association with von Hippel-Lindau (VHL) disease with associated lesions occurring in many organs.[30-35] VHL disease is characterized by the occurrence of primary hemangioblastic tumors in the nervous system.[30] While the origin has not yet been entirely clarified, patients with VHL carry an autosomal dominant germline mutation tumor-suppressor gene.[31]

Dysfunction of the VHL protein causes accumulation and activation of hypoxia-inducible factor (HIF), which is followed by expression of VEGF, erythropoietin, nitric oxide synthase and glucose transporter 1 in VHL-deficient tumor cells.[31] The result is endolymphatic sac tumors, which arise from proliferation of endolymphatic duct/sac epithelium.[30,32] These tumors may originate in or extend into the brain.[30] The tumors typically grow in the young adult population.[33]

The disease is associated with renal carcinoma, pheochromocytoma, paraganglioma, pancreatic neuroendocrine tumor and retinal capillary hemangioma, and is seen as discrete, circumscribed, orange-red vascular lesions found in either the peripheral or juxtapapillary retina.[34] These hemangiomas constitute one of the diagnostic criteria of VHL.[34]

Despite being slow growing—if they grow at all—the retinal lesions are capable of causing significant visual morbidity via exudative or tractional effects (tumor induces retinal striae and distortion) on the surrounding retina.[34]

Management

Neurologic diseases can be diagnosed by the company they keep. Proper understanding of anatomical correlates and advancing signs and symptoms can permit approximate localization of the lesion. Clinicians armed with this knowledge can direct neuroimaging to the specifically suspected location. Neuroimaging can be completed with or without the use of intravenous contrast-enhancing dyes. Computed tomography (CT), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and magnetic resonance venography (MRV), under the guidance provided by the practitioner, can correctly concentrate on the proper anatomic area of suspicion. Once the lesion is located it can be identified based upon patient profile, neuroimaging features, systemic signs and symptoms, appearance, behavior, location or cell type if biopsy is possible.

Once the lesion is identified, treatment can begin. Generally, there are five strategies for the treatment of tumors:

(1) Monitor and treat symptoms; small, slow-growing non-malignant tumors may not require removal or modification, as their rate of change is so slow they may never impact a patient's quality of life. Here, patients are educated to report for annual imaging and clinical examinations to reassess the size, location and functional impact of the tumor. Patients whose tumors impact the visual system can be monitored with serial automated perimetry, photography and neuroimaging, and can be given home-based tools such as an Amsler grid to monitor themselves for changes in acuity or field.[18,19]

(2) Surgical removal; resection must be done with great care, as collateral damage may impact quality of life as much as or more than allowing the tumor to remain.[29]

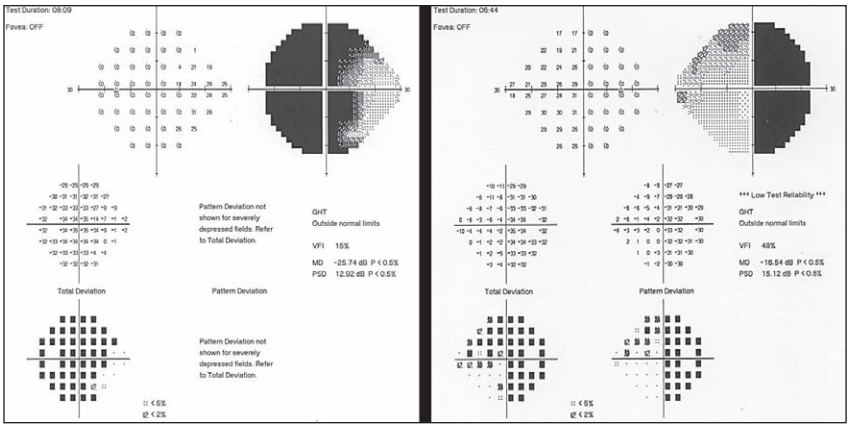
(3) Irradiation; accurately aimed internal beam radiation systems have the ability to thermally destroy tumors inside the cranium without being surgically invasive. Computer-driven systems direct tumor destruction with minimal collateral damage.[22,23]

(4) Medical therapy; chemotherapy is a traditional avenue for tumor treatment when surgical resection is not possible due to location or patient frailty. It works by selectively attacking tumor cells chemically. The great trick to the engineering of chemotherapeutic agents is building them so they attack bad cells while leaving the good (the magic bullet). The biggest drawback of this approach is that the medications induce substantial side effects, including hair loss, loss of appetite, fatigue, wasting and opportunistic infection. In some instances, medications exist that stabilize or stop tumor advancement. Other medications, for slow-growing tumors, are designed to reduce symptoms.[18-21]

(5) Deprive the blood supply; vascular endothelial growth factor (VEGF) inhibitors can involute tumor vascular systems and are effective for some tumors, with minimal side effects.[31-35]

Clinical Pearls

- Altered mentation, slurred speech and facial droop are classic signs of stroke, requiring emergent investigation and hospitalization. They are also signs of tumor, making neuroimaging a necessary diagnostic test.
- Screening visual fields are excellent tools for uncovering gross neurological visual losses.
- Automated perimetry should be completed for all patients known to have brain injury (tumorous or other). The test establishes baseline parameters; subsequent evaluations will chart improvements, stability or regression.
- Any time bilateral disc edema is seen, neuroimaging is indicated. Lumbar puncture cannot be performed until a space-occupying mass lesion is ruled out. Lumbar puncture in the presence of an intracranial tumor can cause life-threatening brain herniation through the foramen magnum, with subsequent respiratory arrest.
- Retinal hemangiomata from VHL can be treated with observation or tumor disruption via laser photocoagulation, cryotherapy, photodynamic therapy, radiation or surgical tumor excision.
- Vomiting can be seen as a response meant to dehydrate the body and relieve intracranial pressure.



Bitemporal defect from chiasmal tumor.

1. Louis DN, von Deimling A. Hereditary tumor syndromes of the nervous system: overview and rare syndromes. Brain Pathol. 1995;5(2):145-51.

2. de Ribaupierre S, Vernet O, Vinchon M, Rilliet B. Phacomatosis and genetically determined tumors: the transition from childhood to adulthood. Neurochirurgie. 2008;54(5):642-53.

3. Lanphear J, Sarnaik S. Presenting symptoms of pediatric brain tumors diagnosed in the emergency department. Pediatr Emerg Care. 2014;30(2):77-80.

4. Jardón J, Delgado L, Izquierdo NJ. Neuroophthalmology meets oncology: a case report. Bol Asoc Med P R. 2012;104(4):41-4.

5. Kundu B, Penwarden A, Wood JM, et al. Association of functional magnetic resonance imaging indices with postoperative language outcomes in patients with primary brain tumors. Neurosurg Focus. 2013;34(4):6.

6. Czapiewski P, Szmuda T, Dzierżanowski J. Pseudostroke manifestation of multiple myeloma: a report of two cases with literature review. Folia Neuropathol. 2013;51(1):87-91.

7. Lim A, Weir P, O'Brien TJ, Kaye AH. Complex visual hallucinations as a presentation of temporal low-grade glioma. J Clin Neurosci. 2011;18(1):157-9.

8. Lee TS. Transient and spontaneously-remitting complex hallucinations in a patient with melanoma and brain metastases. Psychosomatics. 2010;51(3):267-70.

9. Kan E, Kan EK, Atmaca A, et al. Visual field defects in 23 acromegalic patients. Int Ophthalmol. 2013;33(5):521-5.

10. Obuchowska I, Mariak Z. Homonymous hemianopsia. Klin Oczna. 2012;114(3):226-9.

11. Rajajee V, Vanaman M, Fletcher JJ, Jacobs TL. Optic nerve ultrasound for the detection of raised intracranial pressure. Neurocrit Care. 2011;15(3):506-15.

12. Passi N, Degnan AJ, Levy LM. MR imaging of papilledema and visual pathways: effects of increased intracranial pressure and pathophysiologic mechanisms. AJNR Am J Neuroradiol. 2013;34(5):919-24.

13. Tamhankar MA, Biousse V, Ying GS, et al. Isolated third, fourth, and sixth cranial nerve palsies from presumed microvascular versus other causes: a prospective study. Ophthalmology. 2013;120(11):2264-9.

14. Anila KR, Nair RA, Koshy SM, Jacob PM. Primary intravascular large B-cell lymphoma of pituitary. Indian J Pathol Microbiol. 2012;55(4):549-51.

15. Iglesias P, Castro JC, Díez JJ. Clinical significance of anaemia associated with prolactin-secreting pituitary tumours in men. Int J Clin Pract. 2011;65(6):669-73.

16. Gempt J, Gerhardt J, Toth V, et al. Postoperative ischemic changes following brain metastasis resection as measured by diffusion-weighted magnetic resonance imaging. J Neurosurg. 2013;119(6):1395-400.

17. Sattler MG, Vroomen PC, Sluiter WJ, et al. Incidence, causative mechanisms, and anatomic localization of stroke in pituitary adenoma patients treated with postoperative radiation therapy versus surgery alone. Int J Radiat Oncol Biol Phys. 2013;87(1):53-9.

18. Lake MG, Krook LS, Cruz SV. Pituitary adenomas: an overview. Am Fam Physician. 2013;88(5):319-27.

19. Delgrange E, Raverot G, Bex M, et al. Giant prolactinomas in women. Eur J Endocrinol. 2013;170(1):31-8.

20. Jallad RS, Bronstein MD. The place of medical treatment of acromegaly: current status and perspectives. Expert Opin Pharmacother. 2013;14(8):1001-15.

21. Zieliński G, Witek P, Koziarski A, Podgórski J. Spontaneous regression of non-functioning pituitary adenoma due to pituitary apoplexy following anticoagulation treatment - a case report and review of the literature. Endokrynol Pol. 2013;64(1):54-8.

22. Shapey J, Sabin HI, Danesh-Meyer HV, Kaye AH. Diagnosis and management of optic nerve sheath meningiomas. J Clin Neurosci. 2013;20(8):1045-56.

23. Saeed P , Rootman J, Nugent RA, et al. Optic nerve sheath meningiomas. Ophthalmology. 2003;110(10):2019-30.

24. Hallinan JT, Hegde AN, Lim WE. Dilemmas and diagnostic difficulties in meningioma. Clin Radiol. 2013;68(8):837-44.

25. Nicholas MK, Lukas RV, Jafri NF, et al. Epidermal growth factor receptor - mediated signal transduction in the development and therapy of gliomas. Clin Cancer Res. 2006;12(24):7261-70.

26. Curless RG, Siatkowski M, Glaser JS, Shatz NJ. MRI diagnosis of NF-1 in children without café-au-lait skin lesions. Pediatr Neurol. 1998;18(3):269-71.

27. Chateil JF, Soussotte C, Pédespan JM, et al. MRI and clinical differences between optic pathway tumours in children with and without neurofibromatosis. Br J Radiol. 2001;74(877):24-31.

28. Segal L, Darvish-Zargar M, Dilenge ME, et al. Optic pathway gliomas in patients with neurofibromatosis type 1: follow-up of 44 patients. J AAPOS. 2010;14(2):155-8.

29. Cohen VM, Shields CL, Furuta M, Shields JA. Vitreous seeding from retinal astrocytoma in three cases. Retina. 2008;28(6):884-8.

30. Vortmeyer AO1, Falke EA, Gläsker S, et al. Nervous system involvement in von Hippel-Lindau disease: pathology and mechanisms. Acta Neuropathol. 2013;125(3):333-50.

31. Capitanio JF, Mazza E, Motta M, et al. Mechanisms, indications and results of salvage systemic therapy for sporadic and von Hippel-Lindau related hemangioblastomas of the central nervous system. Crit Rev Oncol Hematol. 2013;86(1):69-84.

32. Pavesi G, Feletti A, Berlucchi S, et al. Neurosurgical treatment of von Hippel-Lindau-associated hemangioblastomas: benefits, risks and outcome. J Neurosurg Sci. 2008;52(2):29-36.

33. Maher ER, Neumann HP, Richard S. von Hippel-Lindau disease: a clinical and scientific review. Eur J Hum Genet. 2011;19(6):617-23.

34. Wong WT1, Chew EY. Ocular von Hippel-Lindau disease: clinical update and emerging treatments. Curr Opin Ophthalmol. 2008;19(3):213-7.

35. Hawasli AH, Rubin JB, Tran DD. Antiangiogenic agents for nonmalignant brain tumors. J Neurol Surg B Skull Base. 2013;74(3):136-41.

HEMIFACIAL SPASM

Signs and Symptoms

Hemifacial spasm (HFS) is a facial nerve disorder characterized by episodic involuntary ipsilateral facial muscle contraction. Patients with HFS are typically acutely aware of a painless facial contracture. 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. It may be severe enough to prevent eyelid opening. Patients are often predominantly concerned with cosmetic appearance.

Hemifacial spasm frequently affects individuals age 40 to 60.[1] In one study of 230 patients, 6.5% had young-onset HFS and 21.7% had older onset HFS; the remaining patients in the study were uncategorized because onset took place during the classically recognized 40 to 60 age bracket. In young-onset HFS, the mean age of onset of symptoms was 26 years, with a range of six to 30 years. The average age of onset appears to be 45 to 46 years.[3,4] Eighty percent of the cases occurred in women.

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] One large study failed to identify a greater incidence associated with hypertension. Stress has been noted to be the main aggravating factor and sleep the prime relieving factor.[4]

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).[5-10] 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.[1,2,11-20]

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.[6,7]

There is considerable evidence that primary hemifacial spasm (HFS) is, in almost all cases, related to microvascular compression of the facial nerve at its root within the exiting region of brainstem (root exit zone).[16-19] 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.[16-19]

Clinical and electrophysiological features suggest the presence of mechanical influences 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.[9,12,16] Measured lateral spread responses (LSR) elicited by excessive stimulation of the facial nerve branches testify to the existence of these electrophysiological disturbances.[11,12] Although vascular compression is accepted as a main producer of HFS, facial nucleus supersensitivity is also deemed to be a cause of emphatic HFS.[16]

Management

Treatment of HFS contractures is aimed at addressing the underlying cause. Detailed evaluation is mandatory in all patients with newly acquired 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.[21,22] When HFS spasm is produced by neoplastic compression, the area can be surgically decompressed.[2,13-16] Gamma knife radiosurgery, a relatively new modality, has been recently used in a patient with HFS secondary to an intracanalicular vestibular schwannoma.[10,11] The resolution of the spasm and cessation of the tumor's growth were achieved with a single session of gamma knife radiosurgery.[10]

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BRIEF SUMMARY OF PRESCRIBING INFORMATION.

FOR ADDITIONAL INFORMATION REFER TO THE FULL PRESCRIBING INFORMATION.

INDICATIONS AND USAGE

PATADAY® Solution is indicated for the treatment of ocular itching associated with allergic conjunctivitis.

DOSAGE AND ADMINISTRATION

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

DOSAGE FORMS AND STRENGTHS

Ophthalmic solution 0.2%: each ml contains 2.22 mg of olopatadine hydrochloride.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

For topical ocular use only.

Not for injection or oral use.

Contamination of Tip and Solution

As with any eye drop, to prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep bottle tightly closed when not in use.

Contact Lens Use

Patients should be advised not to wear a contact lens if their eye is red.

PATADAY® (olopatadine hydrochloride ophthalmic solution) 0.2% should not be used to treat contact lens related irritation.

The preservative in **PATADAY®** Solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses **and whose eyes are not red**, should be instructed to wait at least ten minutes after instilling **PATADAY®** (olopatadine hydrochloride ophthalmic solution) 0.2% before they insert their contact lenses.

ADVERSE REACTIONS

Symptoms similar to cold syndrome and pharyngitis were reported at an incidence of approximately 10%.

The following adverse experiences have been reported in 5% or less of patients:

Ocular: blurred vision, burning or stinging, conjunctivitis, dry eye, foreign body sensation, hyperemia, hypersensitivity, keratitis, lid edema, pain and ocular pruritus.

Non-ocular: asthenia, back pain, flu syndrome, headache, increased cough, infection, nausea, rhinitis, sinusitis and taste perversion.

Some of these events were similar to the underlying disease being studied.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic effects: Pregnancy Category C

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Rx only

Reference: 1. IMS Health, IMS National Prescription Audit, August 2010 to October 2013, USC 61500 OPHTH ANTI-ALLERGY.

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Microvascular decompression (MVD) is potentially curative.[23-25] In this procedure, a sponge or other barrier is placed between a compressing vessel and the facial nerve.[12] In a study of 33 patients, LSR disappeared with vascular decompression in 23 patients, with no evidence of LSR upon surgical closure.[12] The other 10 patients had evidence of LSR following the surgical conclusion. 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.[12] 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 and acquired neural hyperactivity are generated by the neurovascular compression.[11,12] Today, MVD is about 8% to 90% successful in relieving HFS.[24-25]

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.[14] The procedure has achieved good results for patients with facial paralysis from Bell's palsy, herpes zoster oticus, infection, hemifacial spasm, temporal bone fracture and tumors.[14] Access occurs through the mastoid, middle cranial fossa and retrolabyrinthine fossa.[14]

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.[15]

More recently, botulinum toxin A (Botox, Allergan) injection has been used to treat HFS.[3,24,26-28] Botulinum toxin A injections have been seen to be safe and well tolerated, but the effects are transient and require increased subsequent dosing. True relief seems only to be effected by MVD, though botulinum toxin A injections have no adverse effect on this procedure if done first.[28]

Clinical Pearls

- Chronic, slowly progressive HFS with the development of or conversion to facial nerve palsy suggests a space-occupying lesion or demyelination.
- The presence or a parotid mass suggests tumor of the gland.
- *Tardive dyskinesia* (late twitching secondary to exposure to antipsychotic medications) can produce symptoms similar to HFS.
- *Facial synkinesis,* abnormal movements created by aberrant sprouting of axons after injury (similar to the "jaw wink" phenomenon), is a separate entity.
- *Hemifacial spasm* should be differentiated from the more common benign eyelid myokymia, which presents as a continuous contraction of the lower eyelid only and is so minor that it is not typically grossly noticeable.

1. Tan EK, Chan LL. Young onset hemifacial spasm. Acta Neurol Scand 2006;114(1):59–62.

2. Nakamura T, Osawa M, Uchiyama S. Arterial hypertension in patients with left primary hemifacial spasm is associated with neurovascular compression of the left rostral ventrolateral medulla. Eur Neurol 2007;57(3):150–5.

3. Wang L, Hu X, Dong H, et al. Clinical features and treatment status of hemifacial spasm in China. Chin Med J (Engl). 2014;127(5):845-9.

4. Batla A, Goyal C, Shukla G, Hemifacial spasm: clinical characteristics of 321 Indian patients. J Neurol. 2012;259(8):1561-5.

5. Gurwood AS. The eyelid and neuro-ocular disease. In: Blaustein BH (ed.) Ocular Manifestations of Neurologic Disease, Philadelphia, Mosby, 1996:127–51.

6. Gurwood AS, Tasca JM, Kulback E. A review of cranial nerve VII palsy with emphasis on Bell's palsy. South J Optom 1996;14(3):13–17.

7. May M, Galetta S. The facial nerve and related disorders of the face. In: Glaser JS (ed.), Neurophthalmology (2nd ed.), Philadelphia, J. B. Lippincott Co., 1990:239–77.

8. Bajandas FJ, Kline LB. Seven Syndrome of the Seventh (Facial) Nerve. In: Bajandas FJ, Kline LB (eds.), Neuro-ophthalmology Review Manual (3rd ed.), Thorofare, NJ: Slack, 1988:151–6.

9. Jowi JO, Matende J, Macharia MI, et al. Hemifacial spasm: Case report. East Afr Med J 2006 ;83(7):401–4.

10. Peker S, Ozduman K, Kiliç T, et.al. Relief of hemifacial spasm after radiosurgery for intracanalicular vestibular schwannoma. Min Invas Neurosurg 2004;47(4):235–7.

11. Sindou MP. Microvascular decompression for primary hemifacial spasm. Importance of intraoperative neurophysiological monitoring. Acta Neurochir (Wien) 2005;147(10):1019–26.

12. Hatem J, Sindou M, Vial C. Intraoperative monitoring of facial EMG responses during microvascular decompression for hemifacial spasm. Prognostic value for long-term outcome: A study in a 33-patient series. Br J Neurosurg 2001;15(6):496–9.

13. James ML, Husain AM. Brainstem auditory evoked potential monitoring: When is change in wave V significant? Neurol 2005;2265(10):1551–5.

14. Pulec JL. Total facial nerve decompression: Technique to avoid complications. Ear Nose Throat J 1996;75(7):410–5.

15. Liu Z, Fang G. Mind-refreshing acupuncture therapy for facial spasm, trigeminal neuralgia and stubborn facial paralysis. J Tradit Chin Med 2004;24(3):191–2.

16. Suthipongchai S, Chawalparit O, Churojana A, et al. Vascular loop compressing facial nerve in hemifacial spasm: demonstrated by 3D-phase contrast magnetic resonance angiography in 101 patients. J Med Assoc Thai 2004;87(3):219–24.

17. Abbruzzese G, Berardelli A, Defazio G. Hemifacial spasm. Handb Clin Neurol. 2011;100:675-80.

18. Yaltho TC, Jankovic J. The many faces of hemifacial spasm: differential diagnosis of unilateral facial spasms. Mov Disord. 2011;26(9):1582-92.

19. Chiaramonte R, Bonfiglio M, D'Amore A, Chiaramonte I. Developmental venous anomaly responsible for hemifacial spasm. Neuroradiol J. 2013;26(2):201-7.

20. Harrison AR. Chemodenervation for facial dystonias and wrinkles. Curr Opin Ophthalmol 2003;14(5):241–5.

21. Tan EK, Chan LL, Lim SH, et al. Role of magnetic resonance imaging and magnetic resonance angiography in patients with hemifacial spasm. Ann Acad Med Singapore 1999;28(2):169–73.

22. Ho SL, Cheng PW, Wong WC, et al. A case-controlled MRI/MRA study of neurovascular contact in hemifacial spasm. Neurol 1999;53(9):2132–9.

23. Zhong J, Zhu J, Sun H, et al. Microvascular decompression surgery: surgical principles and technical nuances based on 4000 cases. Neurol Res. 2014 Mar 5:1743132814Y0000000344. [Epub ahead of print]

24. Rosenstengel C, Matthes M, Baldauf J, et al. Hemifacial spasm: conservative and surgical treatment options. Dtsch Arztebl Int. 2012;109(41):667-73.

25. Miller LE, Miller VM. Safety and effectiveness of microvascular decompression for treatment of hemifacial spasm: a systematic review. Br J Neurosurg. 2012;26(4):438-44.

26. Ababneh OH, Cetinkaya A, Kulwin DR. Long-term efficacy and safety of botulinum toxin a injections to treat blepharospasm and hemifacial spasm. Clin Experiment Ophthalmol. 2013 Jul 12. doi: 10.1111/ceo.12165. [Epub ahead of print].

27. Wu CJ, Shen JH, Chen Y, Lian YJ. Comparison of two different formulations of botulinum toxin A for the treatment of blepharospasm and hemifacial spasm. Turk Neurosurg. 2011;21(4):625-9.

28. Wang X, Thirumala PD, Shah A,et al. Effect of previous botulinum neurotoxin treatment on microvascular decompression for hemifacial spasm. Neurosurg Focus. 2013;34(3):E3.

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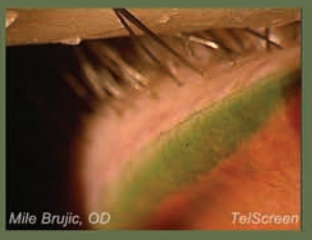

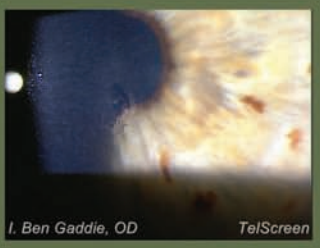

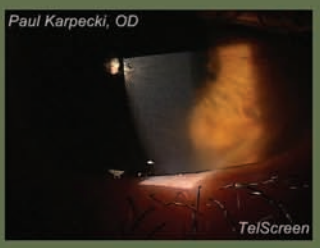

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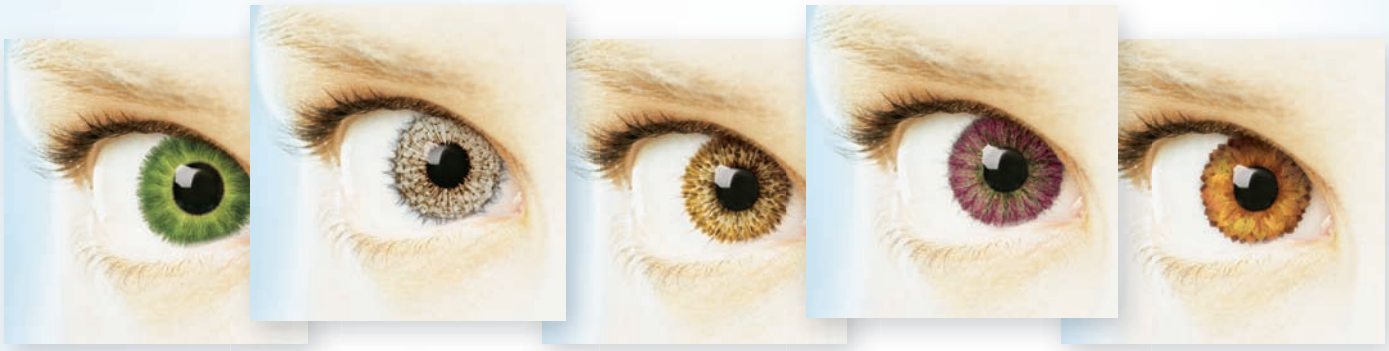

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INDICATION AND DOSING

PATADAY® Solution is a mast cell stabilizer indicated for the treatment of ocular itching associated with allergic conjunctivitis. The recommended dose is one drop in each affected eye once a day.

IMPORTANT SAFETY INFORMATION

PATADAY® Solution is for topical ocular use only. It is not for injection or oral use.

To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding areas with the dropper tip of the bottle. Keep the bottle tightly closed when not in use.

Patients should be advised not to wear contact lenses if their eyes are red.

PATADAY® Solution should not be used to treat contact lens-related irritation. The preservative in PATADAY® Solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and **whose eyes are not red** should be instructed to wait at least ten minutes after instilling PATADAY® Solution before they insert their contact lenses.

Symptoms similar to cold syndrome and pharyngitis were reported at an incidence of approximately 10%.

For additional information about PATADAY® Solution, please refer to the brief summary of prescribing information on adjacent page.

References: 1. IMS Health, IMS National Prescription Audit™, August 2010 to November 2013, USC 61500 OPHTH ANTI-ALLERGY. **2**. PATADAY® Solution package insert. **3**. Formulary data provided by Pinsonault Associates, LLC, PathfinderRx, November 2013.

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