FEATURED INSIGHT
A CASE REPORT OF PAPILLEDEMA SECONDARY TO HEMANGIOBLASTOMA

FABRY DISEASE WITH VALSALVA RETINOPATHY

RETAINED ANTERIOR CHAMBER IATROGENIC INTRAOCULAR FOREIGN BODY FOLLOWING UNCOMPPLICATED PHACOEMULSIFICATION

POINT-COUNTERPOINT: LASER PERIPHERAL IRIDOTOMY FOR PRIMARY ANGLE-CLOSURE GLAUCOMA

Photo credit: Kiera B. Jeschke, OD
Welcome to the inaugural issue of *Clinical Insights in Eyecare*. The American Academy of Optometry is excited to provide this new platform to receive practical information, useful in everyday clinical practice, through a case report format.

Our Sections and Special Interest Groups (SIGs) will be instrumental in composing and responding to practice controversies. This month highlights a point-counterpoint discussion from the Glaucoma Section addressing management of angle-closure glaucoma.

Each month’s publication will also feature “journal scans,” in synopsis-style reporting, from journal articles in the American Academy of Ophthalmology’s flagship journal, *Ophthalmology*, and their subspecialty journals. These journals are not open access, so we are pleased to be able to provide this feature within each of our issues.

A special thank you to our topical editors, reviewers, and especially our writers/authors for their many contributions. There are several individuals and groups to thank for their support in launching this first issue. Our Academy Board Liaison Andrew Mick, Academy President Sue Cotter, emeritus OVS Editor-in-Chief Michael Twa, staff managing editor Kayla Ritten, Academy CEO Trish Shomion, Academy staff members Betty Taylor, Rich Jones, and Ian Mitchell, our publisher Scholastica, and our copyeditor J&J Editorial were all collectively instrumental by offering their expertise and guidance.

Please consider submitting a case report for future issues of the journal (https://clinicalinsightsineyecare.scholastic-ahq.com/for-authors). Because our emphasis is on case reports, we will publish original, previously unpublished case reports and series that are highly relevant to clinical eye-care. The case report should highlight a diagnostic dilemma, an application of clinical technology, and/or treatment effects/considerations. Please remember, case reports do not have to highlight rare events. Your submission might describe a clinical entity that is seen periodically in most clinics, but the current understanding of the pathophysiology, the diagnostic thought process, the evidence-based treatment options, and the clinical trials that help to define standards of care are not universally known in our community.

We look forward to offering our readers these clinical updates and hope to hear your comments on how we might improve with each issue.

We hope you enjoy the first issue!

Joseph P. Shovlin, OD, FAAO
Editor-in-Chief

Raman Bhakhri, OD, FAAO
Associate Editor
Case Reports

A Case Report of Papilledema Secondary to Hemangioblastoma

Kiera B. Jeschke¹, Kelly A. Malloy¹, Ryan M. Keenan¹

¹ Optometry, Salus University

Keywords: Cerebellum, Fourth ventricle, Hemangioblastoma, Medulla oblongata, Papilledema

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Introduction

Central nervous system hemangioblastomas are slow-growing vascular neoplasms representing 2% of intracranial tumors. Although benign nonmetastasizing tumors, central nervous system hemangioblastomas can cause significant neurologic disability owing to mass effect. Central nervous system hemangioblastomas most often occur in the posterior fossa and are therefore likely to cause signs and symptoms associated with increased intracranial pressure as well as both cerebellar and brainstem compression. Because they are slow growing with periods of arrested growth, symptoms of central nervous system hemangioblastomas can be ignored or attributed to other causes before a diagnosis is finally made.

Case Report

An 18-year-old man presented for an eye examination with a history of acid reflux, emesis, and recent difficulty swallowing with associated weight loss. Dilated examination demonstrated papilledema suggestive of increased intracranial pressure. Cursory neurologic examination revealed absent soft palate elevation, dysphagia, and tongue weakness/fasciculations indicative of medullary cranial nerve IX-XII damage. These findings, combined with cerebellar signs of ataxia, are concerning for a large posterior fossa mass encompassing the fourth ventricle with associated obstructive hydrocephalus.

Conclusion

An intracranial mass can cause varied systemic symptoms that initially erroneously guide the workup and subsequently delay an accurate diagnosis. Thorough history-taking combined with detailed clinical examination is key to understanding, localizing, and ultimately diagnosing a pathologic presentation such as a central nervous system hemangioblastoma. Eyecare providers need to understand the eye-brain connection, be able to perform a cursory neurologic examination to explain nonocular symptoms, and be capable of anatomically localizing neurologic lesions.

INTRODUCTION

Central nervous system hemangioblastomas are benign, slow-growing vascular neoplasms and represent approximately 2% of intracranial tumors and 7% of posterior fossa tumors, making them the most common primary intra-axial tumor.¹-⁶ Central nervous system hemangioblastomas are characteristically very vascular structures and tend to arise infratentorially.⁵ They have specifically been shown to most commonly occur around the cerebellum and fourth ventricle (76%). Approximately 9% of central nervous system hemangioblastomas arise from the cerebral hemispheres, whereas 7% arise from the spinal cord. Of the spinal cord hemangioblastomas, thoracic hemangioblastomas are most common.⁵,⁷ Only 5% of central nervous system hemangioblastomas arise from the brainstem. On neuroimaging, hemangioblastomas are often solid, solid-cystic, or mainly cystic masses with solid enhancing nodule; there can be internal and peripheral feeding vessels.⁵

CASE REPORT

INITIAL EXAMINATION

An 18-year-old man presented for initial eye examination without ocular or visual complaints. He had a history of acid reflux, with associated emesis, which started 2 years prior. He had several unrevealing abdominal ultrasounds. His symptoms were somewhat improved by famotidine. Within the last few months leading up to this examination, he reported difficulty swallowing and was only eating soft foods. He reported associated weight loss. These symptoms continued to be attributed to a gastroenterologic issue.

On examination, the patient’s best-corrected visual acuity was 20/20 in the right eye and 20/20 in the left eye. Confrontation fields were full to finger counting in both eyes,
although an enlarged blind spot was questioned. Pupils demonstrated physiologic anisocoria with no evidence of an afferent pupillary defect. Color vision was normal in both eyes. Ocular motilities were full in both eyes and cover testing revealed only a small, two prism diopter, comitant esphoria. He demonstrated fusion with Worth-4-dot testing.

Anterior segment health was unremarkable. Intraocular pressures were 17 mm Hg in each eye. Posterior segment examination revealed significantly edematous and hyperemic optic discs with vessel obscuration, temporal Paton’s lines, and loss of the physiologic cup bilaterally (Figure 1). Ancillary testing, including optical coherence tomography, Humphrey visual fields, and fundus photos, was performed. Optical coherence tomography of the optic nerve demonstrated an elevated neuroretinal rim and retinal nerve fiber layer of both eyes consistent with papilledema. Ganglion cell analysis revealed 360-degree thinning bilaterally with evidence of serous macular detachment in each eye (Figure 2). A 24-2 Humphrey visual field demonstrated an enlarged blind spot with superior central/ceccocentral defect and apparent inferior nasal step in the right eye and enlarged blind spot with central/ceccocentral defect in the left eye (Figure 3).

Cursory neurologic examination revealed abnormal function of the glossopharyngeal nerve (cranial nerve IX) and the vagus nerve (cranial nerve X) as evidenced by absent soft palate elevation, difficulty with swallowing (dysphagia), and abnormal speech (dysarthria). Poor tongue protrusion and tongue fasciculations indicated abnormal hypoglossal nerve (cranial nerve XII) function. The patient demonstrated mild finger-to-nose ataxia, ataxic gait, difficulty with tandem gait, and a positive Romberg sign concerning for cerebellar dysfunction.

The combination of bilateral optic disc edema, ataxia, and involvement of multiple lower cranial nerves was suspicious for a large fourth ventricular mass with medullary and cerebellar compression as well as obstructive hydrocephalus. The patient was immediately sent to the hospital emergency room where magnetic resonance imaging of the brain and orbits with contrast (Figure 4) demonstrated an enhancing solid and cystic mass centered within the floor of the fourth ventricle, with significant associated mass effect, including effacement of the medulla and fourth ventricle. The presence of panventricular enlargement confirmed obstructive hydrocephalus secondary to this posterior fossa mass. Magnetic resonance venography ruled out venous sinus thrombosis. Lumbar puncture was contraindicated secondary to the large posterior fossa mass. The next day he underwent suboccipital craniotomy with mass resection; pathology findings were consistent with hemangioblastoma.

A Case Report of Papilledema Secondary to Hemangioblastoma
Figure 2. Despite the difficulty localizing the optic nerve, optic nerve head, and retinal nerve fiber layer, optical coherence tomography from the first examination demonstrated significantly elevated neuroretinal rim and retinal nerve fiber layer in the right and left eye. The ganglion cell was thin 360 degrees with evidence of serous macular detachment in the right and left eye. At the 2-month follow-up examination, there was improvement but residual elevation of the neuro-retinal rim and retinal nerve fiber layer of the right and left eye. The ganglion cell layer was within normal limits in the right eye and mildly thick temporally in the left eye. There appeared to be resolution of the serous macular detachment in both eyes. At the second follow-up examination, there was almost complete resolution of neuroretinal rim and retinal nerve fiber layer elevation in both eyes. Ganglion cell analysis demonstrated an area of borderline superior nasal thinning in the right eye and superior nasal thinning in the left eye, which may suggest mild postpapilledema atrophy.
Figure 3. Humphrey automated 24-2 visual fields from the initial examination demonstrate an enlarged blind spot inferiorly with superior central/ceccocentral defect and apparent inferior nasal step in the right eye and an enlarged blind spot superior and inferiorly with central/ceccocentral defect in the left eye. Visual fields had poor reliability secondary to high fixation losses and false negative errors. Humphrey automated 24-2 visual fields from the 2-month follow-up examination demonstrated an enlarged blind spot, small cephalocentral defect, and inferior nasal defects in the right eye, as well as an enlarged blind spot superiorly, central/ceccocentral defect, and a few nasal defects in the left eye. At the second follow-up examination, there was improvement in the blind spot enlargement, a mild inferior nasal step, and cephalocentral defects in both eyes, which may suggest postpapilledema atrophy.
FOLLOW-UP EXAMINATION

Two months later, while still undergoing outpatient rehabilitation, the patient denied balance issues and reported much improvement with only mild residual speech and swallowing difficulty. Best-corrected visual acuity was 20/20-1 in the right eye and 20/20-1 in the left eye. Repeat 24-2 Humphrey visual field testing demonstrated improvement in each eye, now with less blind spot enlargement, and less dense central/ceccocentral and nasal defects in each eye as compared with the initial testing (Figure 3). All other afferent and efferent testing was unchanged and remained normal. Posterior segment examination demonstrated definitely improved, but still significant, residual optic disc edema bilaterally. Obscuration of the retinal vessels at the disc margin was still appreciated in both eyes, but Paton’s lines were now only present in the left eye. There was no evidence of a spontaneous venous pulsation in either eye. Small cupping was now visible in both eyes (Figure 1).

Updated optical coherence tomography of the optic nerve demonstrated residual, but significantly improved, neuroretinal rim and retinal nerve fiber layer elevation in both eyes. Ganglion cell analysis showed no evidence of thinning (Figure 2).

Cursory neurologic examination revealed the following abnormalities, which were all improved from the initial examination: dysfunction of cranial nerves IX, X, and XII, mild finger-to-nose ataxia, difficulty with tandem gait, and a positive Romberg test.

SECOND FOLLOW-UP EXAMINATION

After another 2 months, the patient reported complete resolution of symptoms. Best-corrected visual acuity was 20/20 in each eye. Repeat 24-2 Humphrey visual field testing showed continued improvement in blind spot enlargement, and residual central/ceccocentral and nasal defects bilaterally (Figure 3). Afferent and efferent testing was otherwise unremarkable and stable. Undilated examination demonstrated optic discs with distinct margins, resolution of disc edema, and small cupping bilaterally. There was no longer any evidence of vessel obscurations or Paton’s lines in either eye (Figure 1). A spontaneous venous pulsation was now noted in the left eye, suggestive of normalized intracranial pressure. Optical coherence tomography of the optic nerve demonstrated almost complete resolution of neuroretinal rim and retinal nerve fiber layer elevation in both eyes. Ganglion cell analysis demonstrated borderline superior nasal thinning in the right eye and definite superior nasal thinning in the left eye (Figure 2). Both the optical coherence tomography and Humphrey visual field findings suggest possible mild postpapilledema atrophy.
secondary to chronic papilledema. Cursory neurologic examination demonstrated continued improvement, now only noting residual dysfunction of cranial nerve XII and mild finger-to-nose ataxia.

DISCUSSION

Central nervous system hemangioblastomas tend to arise in the region of the fourth ventricle and have the capacity to cause severe neurologic deficits either by direct compression of nearby structures or by increasing intracranial pressure secondary to a restriction of cerebrospinal fluid outflow.\(^8\) Because they are slow growing with periods of arrested growth, symptoms can be attributed to other causes before a correct diagnosis is finally made. Prior to the patient's eye examination, this patient's symptoms were initially thought to be associated with acid reflux. An eye examination with cursory neurologic examination was critical in revealing not only papilledema, suggestive of increased intracranial pressure, but also cranial nerves IX, X, and XII involvement suggestive of medullary damage and ataxia suggestive of cerebellar damage. These findings, along with understanding the function of key anatomical structures, allowed accurate localization of the lesion, recognition of the emergent nature of the presentation, and selection of the appropriate care team to handle the patient's care.

Papilledema can be defined as bilateral optic disc edema secondary to elevated intracranial pressure. High intracranial pressure may be idiopathic or may be secondary to a pathologic process including, but not limited to, intracranial mass, intracranial hemorrhage, or venous sinus thrombosis.\(^9\) Regardless of etiology, any increase in intracranial volume will result in increased intracranial pressure.\(^9,10\) As in this case, a tumor situated within the floor of the fourth ventricle would block drainage of cerebrospinal fluid, thereby causing obstructive hydrocephalus and associated enlarged ventricles, the most common neuroimaging finding in patients with central nervous system hemangioblastomas.\(^1,11\) Other common neuroimaging findings associated with increased intracranial pressure include posterior scleral flattening, optic nerve tortuosity, and enlarged optic nerve sheath diameter.\(^12\) Cerebrospinal fluid buildup within the optic nerve sheath is a precursor to the presence of bilateral optic disc edema on funduscopic examination.\(^9\)

Patients with papilledema may initially demonstrate enlarged blind spots with visual field testing because of the enlarged size of the edematous optic disc. If left untreated, increased intracranial pressure has the potential to cause irreversible vision loss by way of direct compression of, and damage to, the axonal optic nerve fibers within the subarachnoid space. This increased pressure along the optic nerve axons disrupts or halts axoplasmic flow and causes intraneuronal ischemia.\(^9\)

Other ocular signs related to increased intracranial pressure may include unilateral or bilateral abduction deficits. Increased intracranial pressure can cause compression of the abducens nerve as it runs over the petrous ridge of the temporal bone and through Dorello's canal. This can cause impairment resulting in unilateral or bilateral abduction deficits with corresponding eso deviation on cover testing. There may be corresponding symptoms of double vision, particularly on lateral gazes.\(^13\)

Once papilledema has been identified, it is critical to determine the cause. As seen in this case, cursory neurologic examination allowed us to identify several dysfunctional cranial nerves, which in the context of papilledema, allowed for localization of the lesion to the region of the fourth ventricle. Recall, cranial nerves IX, X, and XII are paired cranial nerves that arise from the nucleus ambiguous in the medulla oblongata of the brainstem.\(^14\) After exiting the medulla, their course through the cranial cavity is short. They exit the brainstem ventrally and pass through the cerebellopontine angle. Cranial nerves IX and X exit the skull via the jugular foramen, and cranial nerve XII exits the skull via the hypoglossal foramen. They then travel on to innervate structures involved in the execution of swallowing, taste, speech, heart rate, blood pressure control, and peristalsis. Dysfunction of these nerves characteristically results in dysphagia, dysphonia, dysarthria, and aspiration.\(^15\)

Among the many functions of cranial nerve IX, it most notably supplies the stylopharyngeus muscle, allowing for elevation of the pharynx during swallowing and speech.\(^14\)\(^16\) If nonfunctional, patients will describe symptoms of dysphagia. Thorough history-taking allowed this symptom to be uncovered in this case; it had previously been attributed to gastroenterologic problems. Additionally, cranial nerve IX also acts in the stimulation of the upper pharynx to help elicit the swallowing, gagging, and vomiting reflexes.\(^14\) Damage to these areas can often result in nausea and emesis as seen in the patient presented here.\(^16\)

Cranial nerve X also has widespread connections to the head, neck, and thorax.\(^14\) Specifically, this nerve innervates the levator veli palatini, which is responsible for elevation of the soft palate.\(^14\) Functionality can be easily assessed by having the patient stick their tongue out and say "ahh" to evaluate for palatal weakness or paralysis of the constrictor muscles. Depending on what side is lesioned, the examiner may observe palatal droop ipsilateral to the lesion and deviation of the uvula contralateral to the lesion.\(^14\) As seen in this case, however, there was an inability of the soft palate to elevate on either side, which suggested bilateral cranial nerve X damage.

Assessing for, let alone differentiating, a cranial nerve IX from a cranial nerve X palsy is difficult as they both have similar functions and are often lesioned together based on proximity. As both function in the production of speech, it is important to ask about dysphonia and dysarthria when suspecting impairment. This may be assessed by having the patient recite a phrase for the examiner to listen for hoarseness or vocal tone abnormalities.\(^14\) Weight loss is another concerning finding as these cranial nerves make up the nucleus solitarius, which is involved in integrating the perception of satiety and taste. It is thought that compression of the nucleus solitarius, in the medulla, can lead to reduced appetite and subsequent weight loss.\(^16\) In this case, the patient's weight loss is likely multifactorial and related to both appetite loss and dysphagia.
The nucleus solitarius also has connections to the brainstem reticular formation that is responsible for arousal as well as emesis. The reticular formation is a brainstem structure that is made up of a diffuse network of neurons projecting from multiple brainstem nuclei to the cortex. The vomiting center, also known as the area postrema or chemoreceptor trigger zone, is a part of the reticular formation that is located in the dorsal lateral medulla. Compression of the vomiting center also likely contributed to this patient’s symptoms of emesis.

In contrast to the previously mentioned cranial nerves, cranial nerve XII is solely responsible for movement of the tongue during speech, food manipulation, and swallowing. It innervates all tongue muscles aside from the palatoglossus muscle, which is innervated by cranial nerve X. Dysfunction of cranial nerve XII may present as diminished mobility, fasciculations, or wasting of the tongue. This can be tested by having the patient stick their tongue straight out. If a unilateral lesion is present, the tongue will deviate toward the affected side. Fasciculations or wasting may arise in chronic lower motor neuron lesions. As seen in this case, bilateral dysfunction of the hypoglossal nerve was demonstrated by bilateral tongue fasciculations.

It is important to note that the accessory nerve (cranial nerve XI) also originates at the level of the low medulla in the nucleus ambiguous, with cranial nerves IX and X, and exits the skull via the jugular foramen, again with cranial nerves IX and X. Cranial nerve XI is responsible for innervation of the sternocleidomastoid and trapezius muscles. The functionality of this nerve can be tested by having the patient shrug their shoulders against force or by having them turn their head against resistance. Dysfunction is often displayed as fasciculations or wasting. Given that these three cranial nerves run so closely together, it is likely that there may have been some apparent damage to this nerve as well. However, no definite dysfunction was noted during the examination.

Recall, the patient also demonstrated ataxia suggestive of cerebellar damage. The cerebellum is known to regulate posture, balance, coordination, and eye movements. It resides in the posterior cranial fossa and is separated from the brainstem by the fourth ventricle. The cerebellar folioluminal lobe is generally responsible for equilibrium, ocular movements, and vestibulo-ocular reflexes. The anterior lobe of the cerebellum regulates tone and posture, whereas the posterior lobe controls voluntary movements. The central vermis is responsible for receiving auditory, visual, and vestibular input as well as sensorimotor input from the head, trunk, and proximal limbs.

Those with dysfunction of the cerebellum often present with impaired gait and ataxia but could also demonstrate abnormal coordination of limbs, dysmetria (inability to control distance/speed/motion of movement), and nystagmus. Difficulty with balance is often seen in early stages of cerebellar disorders, and difficulty with walking is seen later in the disease state. Assessment of cerebellar function often starts with testing for ataxic gait, which often has a "drunken appearance" and may be characterized by widened stance, unsteadiness, lateral veering, and clumsy-ness with poor coordination of the legs and feet. There may also be reduced walking speed, cadence, step stride length, and swing phase with an increase in base width, stride time, step time, stance phase, and double limb support. Tandem gait, having the patient walk heel-to-toe in a straight line, is another common assessment. Those with cerebellar ataxia would find this difficult.

Romberg testing is another easy way to assess for cerebellar dysfunction. During this test, the patient is to stand, with closed eyes, and maintain their balance without oscillating or falling. Those with cerebellar damage may have difficulty maintaining their balance in this way, demonstrating postural body tremor. Asynergia, the inability to create fluid motion, can also be evaluated with finger-to-nose testing. Patients with cerebellar dysfunction may demonstrate dysmetria, overshoot of a target, or may present with "intention" or "kinetic" tremor. Kinetic tremor is an oscillatory movement that will progressively increase in amplitude during the terminal phase of voluntary movement and will disappear with rest. Dysdiadochokinesia, impaired rapid alternating movement, may also be seen. From an ocular perspective, those with cerebellar dysfunction may also present with downbeat nystagmus, gaze-evoked nystagmus, and periodic alternating nystagmus. Patients may also exhibit square wave jerks, microsaccades, saccadic intrusions, and slowed saccades.

CONCLUSION

Central nervous system hemangioblastomas, although benign and nonmetastasizing, can cause significant neurologic disability due to mass effect on the brainstem and cerebellum as well as blockage of cerebrospinal fluid and subsequent increased intracranial pressure. As seen in this case, mass compression of critical brain structures can cause an array of symptoms that may delay accurate diagnosis. The ability to recognize papilledema allows eye-care providers to be the first member of the health care team to relate a patient’s symptoms to a more ominous process. This, along with thorough history-taking and cursory neurologic examination, is key to understanding the clinical presentation, determining specific anatomic localization, and recognizing the need for emergent workup and treatment.

No identifiable health information was included in this case report.

TAKE HOME POINTS

- An intracranial mass, depending on the location, can cause varied systemic symptoms that can delay an accurate diagnosis.
- Thorough history taking and detailed clinical examination, including cursory neurologic examination, are key to understanding and localizing a pathologic presentation.
- It is important that eye care providers understand the eye-brain connection and be able to perform a cur-
CONFLICTS OF INTEREST

The authors declare no conflicts of interest.
REFERENCES


Case Reports

Case Report: Retained anterior chamber iatrogenic intraocular foreign body following uncomplicated phacoemulsification.

Andrew Gurwood¹, Nicholas Karbach¹
¹ Pennsylvania College of Optometry, Salus University

Keywords: iatrogenic, cilium, phacoemulsification, immune privilege, inflammation

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Introduction
Retained natural and foreign materials may be discovered in the anterior, middle and or posterior chambers of the eye following any penetrating injury or penetrating surgical procedure. Following cataract surgery, the commonly seen objects are retained remnants of uncollected lens material, however, cilia, suture material or other debris (a wisp of cotton from a used applicator) from the surgical field are plausible. Retained foreign material has the potential to produce both signs and/or symptoms through inflammatory induction via the object itself or allergens (flora/fauna) resting on the object. These reactions can be suppressed and eliminated by the effects of both the pre-operative and post-operative topical medical regimen (topical antibiotic, topical steroid) anti-inflammatory and topical non-steroidal anti-inflammatory. The ultimate management (removal or monitoring) is based on the personal experience of surgeon and the evolution of the clinical scenario.

Case report
A 64-year-old African American woman presented for her 1-month post-operative examination following cataract surgery, OD without signs or symptoms and good uncorrected vision. She had a retained intraocular foreign body in the anterior chamber: a cilia (presumably hers).

Given the immune privileged nature of the anterior chamber there was a clear absence of inflammation. There was no indication of infection (endophthalmitis). Even with the possibility of anaphylactic or delayed hypersensitivity reactions, in the setting of presenting ophthalmic co-morbidities, the decision was made to educate the patient regarding the finding and adopt a strategy of monitoring the condition for signs and symptoms of beginning, evolving or worsening inflammation at 6-month intervals.

Conclusion
The literature recognizes that the incidence of retained intraocular foreign materials is rare. It supports the idea of observation; generating a working plan for removal based upon the individual experience and preference of the treating clinician as well as the trending clinical signs.

INTRODUCTION
Retained natural and foreign materials may be discovered in the anterior, middle, and or posterior chambers of the eye following any penetrating injury or penetrating surgical procedure. Following cataract surgery, the commonly seen retained objects are remnants of uncollected lens material; however, other things such as cilia, suture material, or other debris from the surgical field are plausible. These objects may produce the following: (1) no signs or symptoms; (2) inflammation from allergens resting on the object; (3) inflammation based on the allergenic response to the object itself; or (4) infection from microorganisms resting on the object. These reactions may be suppressed and eliminated by the effects of both the preoperative and postoperative topical medicinal regimen (topical antibiotic, topical steroid) anti-inflammatory and topical nonsteroidal anti-inflammatory.

CASE REPORT
A 64-year-old African American woman presented for a 1-month postoperative examination following right eye cataract surgery. She was compliant with her pre- and postoperative care and had finished all of her topical postoperative medications. She reported seeing well and had no
symptoms of lost function or pain. She denied trauma, history of systemic diseases, or allergies of any kind.

Her best-corrected entering visual acuities were 20/20 in her right eye and 20/20 in her left eye at distance and through a refraction of plano in both eyes at distance and +3.00 D sphere at near. Her external examination was unremarkable with normal extraocular motilities, normal confrontational visual fields, and no evidence of afferent pupilary defect. Biomicroscopic examination of the right eye uncovered a single retained cilium in the anterior chamber (Figure 1).

There was no evidence of inflammation or infection (no cell/flare/hypopyon). Biomicroscopy of the left eye revealed a clear, well-centered posterior segment intraocular lens. Goldman intraocular pressures measured 14 mm Hg, in both eyes. Her undilated 90 D posterior segment findings were normal for both eyes, with normal nerves with small cups and quiet retinas with no macular pathology.

The diagnosis was an iatrogenically retained foreign body (cilium), following uncomplicated phacoemulsification with intraocular lens implantation in the right eye. In the setting of the absence of inflammatory or infectious signs, symptoms, or loss of function, a plan of monitoring was developed (6-month intervals), educating the patient to return immediately should adverse signs or symptoms (redness, lost vision, pain) begin.

DISCUSSION

Retained natural and foreign materials may be discovered in the anterior, middle, or posterior segments of the eye following any penetrating injury or surgical procedure. These phenomena are commonly seen following traumatic globe rupture. Iatrogenic foreign body in the anterior chamber following cataract extraction may result from retained remnants of uncollected lens material, "implanted" cilia, a cilium that "self-inoculates" via interaction with one of the created wounds, suture material, or other debris from surgical instruments or the surgical field. Iatrogenic "intraocular foreign bodies" have been documented to produce variable ocular comorbidities. Patients may present asymptotically or with unexplained painful visual interruption secondary to spontaneous corneal edema, intraocular inflammation, raised intraocular pressure, cystic macular edema, and endophthalmitis.

PATHOPHYSIOLOGY

The purpose of an immune response is reparative and protective. The eye is regarded as an "immune privileged" site. This term refers to the immunosuppressive and anti-inflammatory mechanism, which is mediated by resident ocular cells residing in tissues, the aqueous humor, and the anterior chamber. This evolutionary architecture assists in preventing unnecessary and unwanted damage to the eye, which, via an aggressive infiltrating inflammatory reaction, might otherwise create large-scale tissue disorganization leading to lost function (permanent visual loss or blindness).

The properties of immune privilege make it possible for the eyes to regulate the intraocular innate and adaptive immune responses. This permits reduced rates of rejection for ocular transplanted tissues over extended periods of time. In contrast, other body sites have a high affinity for rejecting such transplants and grafts.
To achieve immune privilege, the eye has multiple mechanisms that allow it to regulate potentially sight-threatening inflammatory responses.6-9 One of the mechanisms that creates peripheral tolerance to eye-derived antigens is known as the “anterior chamber-associated immune deviation.”6,8,9

Antigenic materials that invade the anterior chamber generate a systemic immune response that creates clonally expanded regulatory T-cells and B-cells that secrete large concentrations of immunoglobulin A.6-9 This is a non-complement-fixing antibody.6-8 The process is guided by regulatory T cells and ocular resident cells, which include corneal endothelial cells, ocular pigment epithelial cells of the anterior uvea and retina.6-8 There is also innate immune support from the aqueous humor itself.6-8

The reaction of an eye to a cilium is unpredictable, ranging from nothing to endophthalmitis.4,6,10 However, a cilium in the anterior chamber often remains inert.4,5,10-19 When a cilium enters the anterior chamber, the antigen presenting cells that become immunotolerant following exposure to naturally occurring transforming growth factor β in the anterior chamber engulf the cilium.6-9 The now immunotolerant antigen presenting cell leaves the anterior chamber through the trabecular meshwork, moving into the bloodstream, where it travels to the spleen to initiate the generation of regulatory T cells.6-9 Two populations of these immunoregulatory cells consist of regulatory CD4+ T cells (the afferent regulators), capable of suppressing the initial activation and differentiation of naïve T cells into Th1 effector cells, and regulatory CD8+ T cells (efferent regulators), capable of inhibiting the local expression of Th1-mediated immune responses, such as delayed hypersensitivity, at the local site.6,8,9 These regulatory T cells secrete immunosuppressive cytokines such as transforming growth factor β, which promotes the generation of non-complement-fixing antibodies such as immunoglobulin A.6-8

Furthermore, the regulatory T cells induced by ocular pigment epithelial cells, which constitutively express the transcription factor Foxp3, are indispensable for immune tolerance and homeostasis.6,9 They aid in the suppression of excessive immune responses that may be harmful to the host’s intraocular microenvironment.5,9

In contradistinction, materials “not of the body” introduced to the eye such as plant or organic matter, metals, or wood typically produce swift, severe complications such as nongranulomatous and granulomatous uveitis, epithelial iris cysts (keratin pearl cyst), cataractogenesis, corneal edema, sympathetic ophthalmia, and endophthalmitis via the cellular immune system.4-8,10 Acute inflammation/infection as a response to an offending allergen or microbe commonly begins within days to months of inoculation/introduction. In contradistinction, by personal experience and supported by the literature, eyelashes and cortical remnants are often tolerated for years without an adverse response.5,9

It can be hypothesized that there was another reason why the iatrogenically introduced eyelash remained inert during the postoperative cataract extraction healing period.

Although the eyelash may have introduced allergens or microbes (normal flora) into the anterior chamber, the immune reaction may have initially masqueraded as part of the postoperative surgical inflammatory response. In addition to natural physiology, this process was already being suppressed and neutralized by the effects of the pre- and postoperative regimen of topical antibiotic, topical steroidal, and topical nonsteroidal anti-inflammatory medications.

Today, most cataract surgeons deploy topical antibiotic and topical non-steroidal anti-inflammatory agents 3 to 7 days preceding the procedure to reduce the risk of the postoperative infection and postoperative retinal inflammation (cystoid macular edema Irvine-Gass syndrome).10,11 These agents may have provided an immune regulatory prophylaxis that reduced inflammatory exaggeration secondary to this peculiarity.10,11

DIAGNOSIS/DIFFERENTIAL DIAGNOSIS

Because a cilium was identified by direct observation, a differential diagnosis list is unnecessary.

MANAGEMENT

Removal of a retained eye lash is controversial. Some maintain a posture that no intervention is required in the absence of infection or lost function.4-9,12-19 Others prefer a preventive approach (especially when the location of a lash makes access to it easy, not requiring a trip to the operating room). The personal preference of an operating physician, even in quiet eyes, may opt for immediate removal to lessen the risk of future complications and late endophthalmitis.5,12-19

If it is decided that the lash is well placed so as to facilitate an uncomplicated biomicroscopic removal, a small, self-sealing corneal incision can be created adjacent to the lash’s vertical border. This is followed by viscoelastic dissection of the cilium from the iris surface. The procedure is completed with subsequent eyelash removal via sterile forceps.4 So long as the endothelium is undisturbed, the prognosis has an excellent record.

Following the procedure, topical fluorinated quinolone antiobiotic drops four times a day along with topical steroid drops (prednisolone acetate 1%) four times a day and over-the-counter oral pain medication (acetaminophen or ibuprofen) can be prescribed as necessary for 7 days to prevent postoperative infection, hasten recovery from inflammation, and mitigate residual discomfort.10,11 Follow-up evaluation to ensure appropriate healing should occur 1 day after the procedure to ensure that there are no adverse or idiosyncratic reactions and that no endophthalmitis is evolving. A final follow-up visit can be scheduled for 7 to 10 days after surgery. The patient should be instructed to return to the office immediately should the eye present with increased redness or become more painful or if vision becomes reduced in either eye (sympathetic ophthalmia).
CONCLUSION

This patient was not having any difficulties, so it was decided by the surgeon to approach things conservatively, monitoring her recovery by educating the patient about the signs and symptoms of decompensation and reevaluating the situation at regular biannual intervals; the cilium will be removed immediately if signs or symptoms arise.

Retained natural and foreign materials can be deposited in the anterior, middle, or posterior chambers of the eye following any penetrating injury or surgical procedure. The anterior chamber is a common location for retained lens remnants that were too risky to remove during cataract surgery; although rare, other things such as cilia, suture material, or debris from the surgical field can be incarcerated as well. These objects may be discovered serendipitously, evoking no signs or symptoms and producing no inflammation, infection, or loss of function. Management (removal or monitoring) is based on the combination of the personal preference of the surgeon and the observable clinical picture.

TAKE HOME POINTS

- Retained intraocular foreign bodies, such as cilia, can be found in the anterior chamber after a penetrating injury or intraocular surgery.
- The inflammatory response to these foreign bodies can vary widely, ranging from endophthalmitis to no response.
- Management options range from surgical removal to non-interventional monitoring based on the presence or absence of an inflammatory reaction to the foreign body.
- If the foreign body is inert, patient education and monitoring is an acceptable management option.

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Case Reports

A Case Report on Fabry Disease with Valsalva Retinopathy

Patricia Salazar

Keywords: Fabry disease, α-galactosidase A, glycosphingolipid, cornea verticillata, Valsalva retinopathy

Clinical Insights in Eyecare
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Introduction

Fabry disease (FD) is an X-linked lysosomal storage disease that results in the deficiency of the enzyme α-galactosidase A and over-accumulation of glycosphingolipids in the cells of various bodily systems. The hallmark of FD is a whorl-like pattern on the cornea that has been described using a variety of terms including cornea verticillata, whorl keratopathy, vortex keratopathy, hurricane keratopathy, or Fabry keratopathy. Less commonly, vomiting associated with FD-related gastrointestinal distress can lead to Valsalva retinopathy.

Case Report

A 21-year-old African American female presented with complaints of a sudden-onset black spot in her vision in the right eye that was noticed after experiencing gastrointestinal pain and vomiting that morning. Best corrected visual acuities were 20/20 in both eyes with slit lamp examination revealing bilateral corneal verticillata and fundus exam showing a small vitreous hemorrhage in the right eye. Based on her history and exam findings she was referred for laboratory testing which was positive for FD.

Conclusion

This case of FD represents a unique opportunity for eye care practitioners to aid in the early detection of a potentially fatal genetic condition. A thorough case history and ocular examination can assist in the differential diagnosis of FD. Although rare, valsalva retinopathy should raise suspicion for FD when found in conjunction with corneal verticillata.

INTRODUCTION

Fabry disease is a rare, underdiagnosed X-linked metabolic condition with potentially fatal systemic consequences. Fabry disease is characterized by two recognized phenotypes: the classic, early-onset type is found in the pediatric population and associated with neuropathic pain, whereas the later-onset type is predominantly associated with cardiac manifestations.1 Fabry disease often presents with unique ocular manifestations identifiable during a routine eye examination. Clinical ocular findings most commonly include corneal opacities (referred to as cornea verticillata for the remainder of this case report) and less commonly as conjunctival vascular abnormalities, lens opacities, and retinal vascular abnormalities.1 Eye care providers can play a critical role in helping patients with undiagnosed Fabry disease by recognizing the cornea verticillata that is pathognomonic for Fabry disease and referring patients with ocular findings for genetic testing.1-3

This case describes a patient previously undiagnosed with Fabry disease who presented with classical ocular and systemic signs and symptoms and introduces vitreous hemorrhage as a presenting ocular sign of Fabry disease. A general overview of the disease with emphasis on the importance of early detection of Fabry disease for optimal disease management is also discussed.

CASE REPORT

INITIAL VISIT

A 21-year-old African American woman presented at Navy bootcamp with complaints of a sudden-onset black spot in her right eye that occurred immediately after vomiting earlier that day. Aside from a complaint of acute gastrointestinal pain, the patient's medical history was unremarkable. Visual acuity was 20/20 in each eye. Confrontation visual fields were full to finger counting in both eyes. Extraocular muscle and pupil testing were unremarkable. Slit lamp biomicroscopy was remarkable for diffuse brownish corneal epithelial deposits with a central whorl-like pattern in both eyes (Figure 1). Intraocular pressures were right eye 13 mm Hg and left eye 12 mm Hg by noncontact tonometry. Dilated fundus evaluation was remarkable for vessel tortuosity in both eyes and a small vitreous hemorrhage inferior-nasal to the optic disc in the right eye (Figure 2). Posterio
segment findings of the optic nerve, macula, and periphery were otherwise normal in both eyes.

Blood pressure measured 118/72. The patient denied floaters, flashes of light, or curtain or veil in her vision. She also denied history of ocular trauma or surgery to either eye, and she had no known history of any systemic conditions. Further questioning exposed a strong family history of cardiovascular disease, cerebrovascular disease, and kidney failure. The patient’s gastrointestinal pain had waxed and waned over the previous few weeks, but this was the first instance of vomiting or associated ocular symptoms.

The patient was diagnosed with bilateral whorl keratopathy and Valsalva retinopathy in the right eye. Given the clinical presentation and genetic predisposition with gastrointestinal pain and history of vomiting, she was referred for blood work specific for Fabry disease. The patient was educated on the self-resolving nature of the vitreous hemorrhage and that vessel tortuosity and vomiting put her at increased risk for its occurrence. No retina referral was recommended at this visit, but the patient was told to avoid blood thinners and to return in 1 week for a follow-up visit.

DIFFERENTIAL DIAGNOSES OF SUPERFICIAL CORNEAL DEPOSITS

- **Cornea Verticillata:** whorl-like brown or white opacities within the epithelial basement membrane. This is the primary differential diagnosis based on the examination findings.
- **Amiodarone Keratopathy:** amiodarone, an anti-arrhythmic agent used to treat various cardiac dysrhythmias, causes whorl keratopathy in 70%-100% of patients. Chloroquine, hydroxychloroquine, indomethacin, and tamoxifen use can result in a similar presentation of whorl keratopathy. This patient had no history of amiodarone or other medication use.
- **Hudson-Stahli Line:** an iron deposition line in the corneal epithelium and typically seen inferiorly in a linear pattern. The clinical presentation in this patient was more extensive than a single linear or ring-like pigment deposit, ruling out Hudson-Stahli as a diagnosis.
- **Spheroidal Degeneration:** a degeneration of the cornea and/or conjunctiva characterized by bilateral, translucent spherules in the cornea. Our patient presented with a corneal pattern inconsistent with translucent spherules.

DIFFERENTIAL DIAGNOSES FOR VITREOUS HEMORRHAGE

- **Valsalva Retinopathy:** vomiting or coughing resulting in preretinal hemorrhaging. A positive and recent history of vomiting with no known systemic conditions makes this the lead differential diagnosis in this patient.
- **Terson Syndrome:** associated with sudden elevated intracranial pressure. Terson syndrome hemorrhaging can present in the subhyaloid space or subinternal limiting membrane, both of which are considered vitreous hemorrhages. The patient did not suffer from elevated intracranial pressure, so this condition was ruled out.
- **Retinal Macroaneurysm:** focal dilations of retinal arterial branches. Bleeding can be subretinal, intraretinal, sub–internal limiting membrane, or within the subhyaloid space. Patients with retinal macroaneurysm typically have hypertension; this patient had normal blood pressure in-office.

DIFFERENTIAL DIAGNOSES FOR RETINAL VESSEL TORTUOSITY

- **Hypertensive Retinopathy:** a retinal disorder that can result in scattered flame-shaped hemorrhages within the posterior pole, specifically within the retinal arcades, and notable retinal vessel tortuosity. The patient did not have hypertension.
FOLLOW-UP VISIT #1

At the 1-week follow-up appointment, the patient reported an improvement in symptoms and that the spot had faded in the right eye. Visual acuity was stable in both eyes, as was entrance testing. Anterior segment findings and intraocular pressures were stable in both eyes. Because the patient was a Navy recruit in a high-volume in-processing clinic, repeat dilation was not performed. The vitreous hemorrhage, as observed with undilated posterior segment evaluation, was noted to be resolving due to its smaller size.

The patient was reeducated on the self-resolving nature of the vitreous hemorrhage given its improvement both objectively and subjectively. She was asked to return to the clinic in 1 week.

FOLLOW-UP VISIT #2

At the 2-week follow-up appointment, the patient reported that the spot was gone and denied any other ocular or visual complaints. Vision and slit lamp findings were stable in both eyes. Undilated fundus evaluation was remarkable for mild vessel tortuosity in both eyes and complete resolution of the vitreous hemorrhage in the right eye (Figure 3).

Blood plasma testing confirmed a below-normal level of α-galactosidase A consistent with heterozygous Fabry disease. Upon receiving the confirmatory laboratory results, the patient was educated about the disease and treatment options, including enzyme replacement therapy. She was medically discharged from the Navy, referred to her primary care physician, and advised to return annually for eye examinations or sooner if any changes in vision were noted.

DISCUSSION

Fabry disease is a rare, X-linked lysosomal storage disorder that affects anywhere from 1:40,000 to 1:117,000 individuals; these are likely underestimations owing to missed or overlooked clinical signs and symptoms.\textsuperscript{4,6,7} Presentation of classical Fabry disease includes neuropathy, gastrointestinal disturbances (abdominal pain), hypohidrosis (sweating abnormalities), and angiokeratoma (skin abnormalities).\textsuperscript{7-9} Symptoms typically begin in adolescence (approximately age 10) and can lead to severe multiorgan dysfunction and premature death if not detected. The disease stems from deficiency of the enzyme α-galactosidase A that leads to an accumulation of glycosphospholipids. α-galactosidase A catalyzes a breakdown of globotriaosylceramide to galactosylceramide, the lack of which results in accumulation of globotriaosylceramide in lysosomes and triggers a cascade of inflammation in affected tissues.\textsuperscript{7} Fabry disease is diagnosed with confirmed low α-galactosidase A levels via fluorometry, a method for detecting fluorescence that uses ultraviolet light to stimulate the enzyme.\textsuperscript{7}

Fabry disease affects male patients at a younger age and more severely compared with female patients.\textsuperscript{2} Heterozygous male patients present with the classical variant, whereas heterozygous female patients have a wider spectrum of disease presentation, likely because of lyonization, where one X chromosome is inactivated.\textsuperscript{1} "Classic Fabry disease" was initially described in male patients with a severe clinical phenotype due to either the absence or significant reduction of α-galactosidase A activity. It was associated with childhood onset and progressive, irreversible multiorgan failure.\textsuperscript{7,8} Heterozygous female patients may find that clinical manifestations appear 10 years later on average than those in male patients.\textsuperscript{9}

Ocular findings in Fabry disease include eyelid swelling, conjunctival vessel varicosities, cornea verticillata, cataract, central retinal artery occlusion, visual field defects, internuclear paralysis of extracocular muscles, and occasional edema of the optic disc and retina. Cornea verticillata, cataract, and vascular tortuosity of the conjunctiva and retina have been most documented with Fabry disease\textsuperscript{10} and have a high specificity for Fabry disease.\textsuperscript{9}

Corneal verticillata affects the corneal epithelium and basement membrane, excluding stromal and endothelial involvement.\textsuperscript{2} This finding is the most common ocular manifestation of Fabry disease, affecting up to 88% of female and 95% of male patients.\textsuperscript{3,10} It often occurs bilaterally, symmetrically, and with a vortex pattern of pigmented subepithelial or intraepithelial globotriaosylceramide deposits that are taken up by the lysosomes of limbal epithelial cells that differentiate and migrate centrally, forming a whorl pattern.\textsuperscript{4} A fundamental optical property of the cornea is transparency; however, verticillata neither affects visual acuity nor causes visual symptoms.\textsuperscript{2}

There are conflicting data on the correlation of cornea verticillata to disease severity as well as changes to cornea...
verticillata over time. Pitz et al. identified cornea verticillata as a predictor for severity of Fabry disease. Using the Fabry Outcome Survey database, a correlation was made between prevalence of ocular change in patients with Fabry disease and disease severity. Their analysis suggests that patients with Fabry disease with ocular findings have higher disease severity than those without ocular findings. Conversely, Moiseev et al. found that although there was a strong association of Fabry disease with ocular presentation of cornea verticillata, there was no association between cornea verticillata and severity of Fabry disease. A retrospective cross-sectional study by Mete et al. also found no association between cornea verticillata and disease severity.

Sivley and Benjamin investigated whether cornea verticillata can worsen over time or improve with treatment. All untreated patients had observable changes of keratoconus, whereas stability or improvement was noted in patients undergoing treatment for the duration of the study. Although corneal involvement is variable over time among these studies, cornea verticillata does have a strong general association with Fabry disease. Samly created a table of questions to ask a patient with cornea verticillata (Table 1) to aid in diagnosis determination. These questions help strengthen the suspicion for Fabry disease if answered positively and can influence whether to order laboratory work that ultimately confirms a diagnosis of Fabry disease.

Other ocular findings of Fabry disease include less visible conjunctival vascular abnormalities, cataracts, and retinal vessel tortuosity. Although the isolated presence of tortuous vessels without lens or corneal findings is not specific to Fabry disease, their presence with corneal findings may indicate more significant disease severity. Posterior subcapsular opacities associated with Fabry disease, known as "Fabry cataracts," are more rare but also more specific for Fabry disease. Retinal vascular tortuosity occurs secondary to substrate accumulation in the vascular endothelium. Unique to this case is the presentation of vitreous hemorrhage. Vitreous hemorrhages are supplied by the central retinal artery and present within the vitreous anterior. The mechanisms for the pathogenesis of vitreous hemorrhage can include retinal vascular disorders with or without associated ischemia, breakthrough vitreous hemorrhage, or rupture of blood vessels (i.e., neovascularization). Blood in the vitreous occurs as an inflammatory reaction formed from polymorphonuclear neutrophils that break down fibrin macrophages then phagocytose red blood cells and cellular debris. Increased intra-abdominal pressure associated with an absence of valves in the venous system anterior to the heart leads to an increase in intraocular pressure and subsequent rupture of superficial retinal capillaries. The presentation of a vitreous hemorrhage in this case was likely due to the patient’s gastrointestinal distress, which is consistent with Fabry disease, and subsequent vomiting/Valsalva maneuver.

There are no documented cases of Fabry disease with Valsalva retinopathy. The Valsalva maneuver, otherwise known as hemorrhagic retinopathy of Valsalva, is the rupture of superficial capillaries secondary to an increase in retinal venous pressure following a sudden change in intrathoracic or intra-abdominal pressure. A rapid rise of intraocular venous pressure can cause spontaneous rupture of the superficial retinal capillaries, potentially leading to sudden and painless decrease in visual acuity in an otherwise healthy eye. Vessel tortuosity may have also put this patient at increased risk for hemorrhaging owing to weaker vasculature. Depending on the size of the vessel affected, Valsalva retinopathy can vary in presentation. It is largely self-limiting in nature but can require surgical intervention if larger or if resolution is not seen after 3 weeks of observation. In this case, gastrointestinal distress associated with Fabry disease was the presumed cause of this episode of vomiting, and the hemorrhage resolved without treatment.

The diagnosis of Fabry disease is largely based on clinical signs and symptoms. Organ involvement can be diagnostic, and impaired kidney function tests or echocardiography can confirm the diagnosis. Laboratory testing for α-galactosidase A deficiency should be performed in cases of suspected Fabry disease. Molecular genetic testing can also be performed and confirmed in the presence of the galactosidase α gene. Upon diagnosis, patients with Fabry disease should receive genetic counseling and family screening. These interventions are helpful in identifying additional familial cases, provide the patient with a better understanding of their condition, and identify the risk of offspring inheriting the disease. Where applicable, psychosocial, economic, insurance, and family planning considerations should be discussed with patients in their counseling sessions.

Table 1. A list of questions eye care providers can ask a patient with cornea verticillata to help with differential diagnosis. In this case, the patient answered "yes" to the questions in bold.

<table>
<thead>
<tr>
<th>Questions to ask a patient with cornea verticillata&lt;sup&gt;10&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Have you ever experienced recurrent tingling or burning sensations in your extremities?</td>
</tr>
<tr>
<td>• Have you ever experienced intermittent episodes of extreme pain of unknown cause, often accompanied by fever, and perhaps exacerbated or brought on by stress, illness, or lack of sleep?</td>
</tr>
<tr>
<td>• Do you have trouble sweating or exercising?</td>
</tr>
<tr>
<td>• Do you find heat or cold hard to tolerate?</td>
</tr>
<tr>
<td>• Do you have intermittent gastrointestinal symptoms such as pain and bloating after eating, nausea, cramps, or diarrhea?</td>
</tr>
<tr>
<td>• Do you have any small raised reddish-purple spots on your skin, especially in the “bathing trunk” area?</td>
</tr>
<tr>
<td>• Does anyone in your family have kidney failure of unknown cause?</td>
</tr>
<tr>
<td>• Have you had any heart disease at a relatively early age of unknown cause, specifically cardiac arrhythmia or hypertrophic cardiomyopathy?</td>
</tr>
<tr>
<td>• Have you had a stroke at a relatively early age?</td>
</tr>
</tbody>
</table>
Although analgesics or carbamazepine can be prescribed for pain management, treatment of Fabry disease is focused on replacing the absent or deficient α-galactosidase A enzyme by means of enzyme replacement therapy.\(^8,^{16}\) Introduced in 2001, enzyme replacement therapy was approved by the United States Food and Drug Administration in 2003. There are two forms of recombinant α-galactosidase A: Agalsidase α (Replagal) is produced by continuous human cell lines; Agalsidase β (Fabrazyme) is a recombinant form of the deficient enzyme produced by Chinese hamster ovary cells transduced with the α-galactosidase A gene. The United States Food and Drug and Administration has approved Fabrazyme for Fabry disease. The recommended dosage is 1 mg/kg of body weight, administered every 2 weeks as an intravenous infusion.\(^1,^{16}\) In 2014, another agalsidase β, Fab gal, was approved for use in South Korea.\(^17\)

Enzyme replacement therapy is considered the standard of care for patients with Fabry disease and has been found to have a positive impact on both systemic and ocular complications. Enzyme replacement therapy studies show promising results; improvements in pain level, cardiovascular function, and renal function have all been noted.\(^16\) A study by Germain et al. showed the predictive importance of younger age and absence of organ damage when enzyme replacement therapy is initiated.\(^18\) Fiedelius et al. found that 41% of patients who were observed over 10 years following initiation of enzyme replacement therapy showed a reduction of cornea verticillata without an effect on visual acuity over the study period.\(^19\) When treated with enzyme replacement therapy for 10 years, patients showed stabilization or slowing progression of the disease.\(^16\) No studies have provided a definitive recommendation for the duration of enzyme replacement therapy, but because the drug is rapidly depleted in the body, treatment is believed to be lifelong.\(^8\)

Due to the cost and complexity of intravenous infusion delivery treatment, other therapies are being investigated. Chaperone drugs can aid in patients with unstable variants of the mutant α-galactosidase A enzyme. Migalastat (Galafold) is the only oral chaperone drug Federal Drug Administration approved for Fabry disease treatment. The drug has shown an effect comparable to that of enzyme replacement therapy on renal function and cardiac outcomes in a clinical trial, but only for eligible patients with specific mutations.\(^17\) A small molecule, the chaperone does not induce antidrug antibodies like enzyme replacement therapy does, making it more effective at crossing the blood-brain barrier.

Plant-derived enzyme replacement therapies are designed to enhance efficacy by increasing plasma half-life and reducing immunogenicity.\(^16\) Substrate reduction therapy is an alternative means of enhancing enzyme efficacy. Substrate reduction therapy is a small molecule iminosugar that carries similar benefits to chaperone therapy like Galafold; it has shown potential in patients with Fabry disease.\(^16\) Gene therapy aims to add a normal α-galactosidase gene to the patient’s DNA, theoretically inducing the ability to produce normal enzyme. Systemic messenger RNA therapy carries some advantages over enzyme replacement therapy but also requires repeated administration to remain effective. Last, heart transplantation followed by enzyme replacement therapy is a potential treatment option for select patients but presents its own risks and is prone to a Fabry disease effect on the donor graft.\(^16\)

Treatment with enzyme replacement therapy should be combined with supportive management to address each patient’s systemic symptoms and complications. Preventive measures such as stroke prophylaxis and lifestyle modifications (smoking cessation, dietary salt restriction, and treatment of hypertension and dyslipidemia) are also important recommendations. Last, periodic comprehensive ocular health examinations are an important part of thorough management.\(^20\)

**CONCLUSION**

This case represents a unique opportunity for eye care practitioners to play a vital role in the early detection of a potentially fatal genetic condition. Vitreous hemorrhage presenting as Valsalva retinopathy in the presence of more classic ocular signs of Fabry disease has not been previously noted in the literature but should be considered a potential presenting sign of the condition. Identifying such signs and symptoms should raise suspicion of Fabry disease and prompt a referral for the appropriate testing and treatment.

**CONFLICTS OF INTEREST**

No identifiable health information was included in this case report. The author declares no conflict of interest.

**TAKE HOME POINTS**

- Fabry disease is a potentially fatal condition that presents with unique ocular findings that can be identified with a routine eye examination.
- Whorl keratopathy (cornea verticillata) in the absence of other systemic conditions or medication use is highly suggestive of Fabry disease.
- Knowing the systemic manifestations of Fabry disease, such as gastrointestinal distress leading to valsalva retinopathy, can also point in the direction of appropriate lab work for confirmation of the disease.

**ACKNOWLEDGMENTS**

Many thanks to David Malchow, OD, who took part in this patient’s care. Thank you also to Raman Bhakhri, OD, for his mentorship.

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A Case Report on Fabry Disease with Valsalva Retinopathy
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Point-Counterpoint

**Point-Counterpoint: Laser Peripheral Iridotomy for Primary Angle-Closure Glaucoma**

Pathik Amin, OD, FAAO, Lisa Young, OD, FAAO

Clinical Insights in Eyecare

Vol. 1, Issue 1, 2023

**POINT: DR. PATHIK AMIN**

Primary angle-closure glaucoma affects more than 20 million people worldwide and is known to have a greater likelihood of bilateral irreversible blindness compared with primary open-angle glaucoma. The standard treatment for decades has been laser peripheral iridotomy, which is indicated to prevent or treat a suspected pupillary block by opening an alternative pathway for aqueous flow, thereby equalizing the pressure between the anterior and posterior chambers. Using a classification system for primary angle-closure disease spectrum is important for management considerations. Table 1 outlines the modern classification system for primary angle-closure disease.

In the setting of an acute angle-closure crisis with a pupillary block mechanism, laser peripheral iridotomy is a well-established treatment. This should be performed once the intraocular pressure is adequately lowered through medical glaucoma therapy, which can serve to improve clarity of the media and increase safety. The fellow eye of a patient with acute angle-closure crisis should also be evaluated for a prophylactic laser peripheral iridotomy. 50% of patients will suffer an acute angle-closure attack in the fellow eye within 5 years.

In primary angle-closure suspect eyes, laser peripheral iridotomy increases angle width and has a good safety profile; approximately 96% of patients do not need additional intervention. Although the Zhongshan Angle-Closure Prevention (ZAP) trial found an overall low risk of angle closure in this subset of patients with observation alone, there was significant effect for prophylactic laser peripheral iridotomy—reducing the risk of progression to primary angle closure by 50%. Given that the population was purely Chinese, the results may not be generalizable to patients of other racial and ethnic groups.

**COUNTERPOINT: DR. LISA M. YOUNG**

Laser peripheral iridotomies have long been the gold standard to prevent angle closure-related pupillary block. Historically, this procedure has been the primary intervention used throughout the entire spectrum of primary angle closure, theoretically increasing the angle width in order to prevent acute angle-closure events, lower intraocular pressure, and decrease risk of glaucoma progression. Although this procedure still plays a critical role in the angle-closure spectrum, the historically low threshold for its application has been recently challenged and requires us to evolve our thinking about laser peripheral iridotomy.

Although the literature suggests that this laser is most beneficial in primary angle-closure suspects, it has also been suggested that laser peripheral iridotomy may be overperformed, even for this particular subset. Data from the 6-year Zhongshan Angle-Closure Prevention trial demonstrated that we would need to treat 44 patients in order to prevent one conversion to primary angle closure, and the 14-year data suggest that we would need to treat 12.55 patients to prevent that one conversion. Given this low rate of progression, observation is now considered as a

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**Table 1. Classification system for primary angle-closure disease spectrum**

<table>
<thead>
<tr>
<th>Stage</th>
<th>ITC &gt;180</th>
<th>Elevated IOP or PAST</th>
<th>Glaucomatous neuropathy?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACS</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>PAC</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>PACG</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

Abbreviations: IOP, intraocular pressure; ITC, iridotrabecular contact; N, no; PAC, primary angle closure; PACG, primary angle-closure glaucoma; PACS, primary angle-closure suspect; PAS, peripheral anterior synechiae; Y, yes.
reasonable approach for the majority of primary angle-closure suspects. Subsequently, it has been recommended that laser peripheral iridotomy should be considered merely for high-risk populations, including those with higher intraocular pressure at baseline, a shallower limbal anterior chamber depth, or a smaller central anterior chamber depth or those living in regions with inadequate access to health care.

Laser peripheral iridotomy is less likely to suffice as the lone therapy for patients with primary angle closure, acute primary angle closure, and primary angle-closure glaucoma. These patients continue to need close monitoring following laser peripheral iridotomy, and many require subsequent treatments in order to adequately control progression of the disease. Recently, the EAGLE study demonstrated that clear lens extraction shows superior intraocular pressure lowering when compared with laser peripheral iridotomy plus subsequent topical therapy for patients with primary angle closure and primary angle-closure glaucoma, with 21% needing further treatment after clear lens extraction as compared with 61% of those that had laser peripheral iridotomy and continue to be treated with at least one glaucoma drop. In fact, patients undergoing initial clear lens extraction are 10× more likely to maintain drop-free good intraocular pressure control than those with initial laser peripheral iridotomy, subsequently leading to less need for surgical intervention. Not surprisingly, after having cataracts removed, clear lens extraction also improved visual function and spectacle independence, as well as provided an overall better quality of life for these patients, which as providers should resonate with us all.

The goal continues to be safe, efficacious, and cost-effective therapy in order to prevent optic nerve damage and progression of glaucoma. It is no longer justified to indiscriminately use laser peripheral iridotomy as a band-aid for the primary angle-closure spectrum. Literature now supports monitoring the majority of patients with primary angle-closure suspects, performing laser peripheral iridotomy only as indicated in high-risk primary angle-closure suspect cases, and performing clear lens exchange for patients with elevated intraocular pressure and/or optic nerve damage secondary to angle closure.

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COMPARISON OF 10-2 AND 24-2 PERIMETRY TO DIAGNOSE GLAUCOMA USING OCT AS AN INDEPENDENT REFERENCE STANDARD


Question: How do 24-2 and 10-2 compare as diagnostic strategies across the spectrum of glaucoma severity?

Glaucoma has historically been felt to affect the peripheral visual field prior to the central field, and as such, the 24-2 visual field has typically been favored as monitoring strategy in all but advanced stage disease, where emphasis on central field loss leads to wide spread use of 10-2. More recent studies call this into question and suggest that macular changes may occur early in the disease process, a concept that is concerning for early monitoring as the 24-2 SITA devotes so few data points to fixation. The authors of this study used both circumpapillary retinal nerve fiber layer thickness and macular ganglion cell layer thickness as determined by optical coherence tomography to stage glaucoma by structural loss and then compared the ability of indices of both the 24-2 and 10-2 to match staging. More than 1300 paired visual fields of 339 patients were used.

CLINICAL VALUE/IMPLICATIONS

In all stages of disease (as determined by either circumpapillary retinal nerve fiber layer or macular ganglion cell layer defects) along all visual field indices, 24-2 performed better as a diagnostic strategy than 10-2. Even when disease severity was defined by macular ganglion cell layer, which would generally indicate increasing sensitivity of the more central field—specific 10-2, the 24-2 performed better. This difference was most prominent in early stages, and the two tests performed most similarly at late stages. A limitation of this study was that the definition of different stages of glaucoma was purely based on structural changes on optical coherence tomography. As no formal consensus for staging glaucoma based on optical coherence tomography deficits exists, the authors simply divided the optical coherence tomography into four groups (1 being mildest tissue loss on optical coherence tomography, 4 being the most severe). This obviously will not correlate precisely with clinical staging, which often relies partially on visual field defects. Furthermore, best corrected visual acuity worse than 20/40 was an exclusion criterion. In theory at least, patients with more central involvement, and thus worse best corrected acuity, may be predicted to have more to gain with the central emphasis of 10-2. Finally, the authors conclude that although 24-2 outperformed 10-2, neither test was very sensitive at detecting early deficits, and so, they point out that greater reliance on structural analysis may be appropriate for early-stage disease.

FELLOW-EYE RETINAL DETACHMENT RISK AS STRATIFIED BY HYALOID STATUS ON OCT

Wallsh JO, Langevin ST, Kumar A, et al. Ophthalmology 2023;130:624-630

Question: Can evaluation of the hyaloid status by optical coherence tomography at the time of a rhegmatogenous retinal detachment predict the risk of a rhegmatogenous retinal detachment occurring in the fellow eye?

BACKGROUND/SUMMARY OF FINDINGS

This was a retrospective chart review of patients having a diagnosis of a rhegmatogenous retinal detachment whose bilateral posterior hyaloid status was captured on optical coherence tomography at the time of the unilateral rhegmatogenous retinal detachment. Optical coherence tomography imaging involved obtaining a 20° by 15°/6 mm macular scan with 19 sections. Additionally, baseline characteristics, including lattice degeneration, refractive error, prior ocular laser, lens status, and family history of retinal detachment, were recorded. The posterior hyaloid status was defined by the presence or absence of a posterior vitreous detachment. The primary outcome measurements were the development of a fellow eye rhegmatogenous retinal detachment and the time it took to develop after the initial rhegmatogenous retinal detachment in the first eye. The authors also evaluated the development of and time to develop a posterior vitreous detachment in eyes whose posterior hyaloid face was attached at the initial optical coherence tomography capture.

Over 5.7 years, 1049 patients with an initial rhegmatogenous retinal detachment were followed; 14.6% developed a sequential rhegmatogenous retinal detachment in the fellow eye. Optical coherence tomography from 582 fellow eyes was available; 229 eyes had posterior vitreous detachments and 353 had attached hyaloid. Rhegmatogenous retinal detachments occurred in only 3% of eyes having a posterior vitreous detachment but occurred in 7.9% of those with hyaloid attachment. In eyes in which a posterior vitreous detachment developed, 23.7% (28 eyes) were also found to have concurrent rhegmatogenous retinal detachment,
and 21 eyes (17.8%) were found to have retinal tears (these were treated prior to any development of rhegmatogenous retinal detachment). Baseline hyaloid attachment carried a 160% risk of fellow eye rhegmatogenous retinal detachment, and baseline lattice degeneration carried a 50% increased risk. The authors noted that the retrospective nature of the study was a limitation and that although macular scans are often sufficient to assess when a posterior vitreous detachment has achieved completion, additional confirmation with optic nerve scans is optimal. Additionally, rhegmatogenous retinal detachments can occur even without complete posterior vitreous detachment owing to underlying peripheral retinal pathologies, so separation of the hyaloid face on macular scans does not preclude the development of rhegmatogenous retinal detachment.

CLINICAL VALUE/IMPLICATIONS

Optical coherence tomography is a widely used technology in clinical practice, and this study shows the possible prognostic use of macular scans in fellow eyes having already undergone a rhegmatogenous retinal detachment. Although a rhegmatogenous retinal detachment can be a result of multiple factors, the ability to simply and noninvasively assess the attachment or detachment of the hyaloid at the macula may enhance our ability to predict the likelihood of a rhegmatogenous retinal detachment and subsequently detect retinal damage early enough to prevent any threat to vision.

HAPTIC EROSION FOLLOWING SUTURELESS SCLERAL-FIXATED INTRAOCULAR LENS PLACEMENT


Question: What is the prognosis of a haptic erosion following placement of a sutureless intrascleral fixated intraocular lens?

BACKGROUND/SUMMARY OF FINDINGS

Intraocular lens placement in eyes with widely compromised capsular bag complexes has traditionally been accomplished with anterior chamber intraocular lenses. Potential compromise of both angle anatomy and corneal endothelium, with subsequent risk of glaucoma and corneal decompensation, have been long-term risks with anterior chamber intraocular lenses and have led to exploration of alternative techniques of intraocular lens fixation in these eyes. Sutureless intrascleral fixation, where the haptics of a three-piece intraocular lens are embedded through the scleral wall, presents one such alternative and has been gaining popularity steadily since Yamane et al. published the seminal report on their technique 6 years ago. Haptic erosion externally through the conjunctiva is a possible complication of sutureless intrascleral fixated intraocular lenses.

This multicenter review of sutureless intrascleral fixated intraocular lenses examined haptic erosions from nine different centers among 19 different surgeons and assessed the repair and prognosis of this erosion.

CLINICAL TRIAL FOR AUTOLOGOUS CULTIVATED LIMBAL EPITHELIAL CELL SHEET TRANSPLANTATION FOR PATIENTS WITH LIMBAL STEM CELL DEFICIENCY.

Oie Y, Sugita S, Yokokura S et al. Ophthalmology 2023 130:608-14

Question: Are sheets of cultivated autologous limbal stem cells viable treatments for limbal stem cell deficiency?

BACKGROUND/SUMMARY OF FINDINGS

At its surgical stages, limbal stem cell deficiency is a difficult problem to treat with guarded surgical prognoses. In the case of allogenic transplants (i.e., those derived from nonhost organisms of the same species), the requirement for potent immune modulatory therapy to prevent allograft rejection of the nonimmune privileged limbal tissue remains a real barrier to treatment. Host-derived limbal transplants avoid this immunologic burden but are limited by the fellow eye’s ability to withstand substantial areas of limbal tissue. This small, Japan-based, multicenter, uncontrolled study examined clinical response to sheets of au-
tologous (patient derived) cultivated limbal epithelial cell in patients with limbal stem cell deficiency. In this study, 3 mm² of limbal stem tissue was removed from the uninvolved fellow eye. This tissue was then cultivated into a sheet. The sheet was subsequently transplanted onto the diseased eye after surgical dissection of conjunctivalized corneal epithelium and placed under a bandage soft contact lens.

Sixty percent of patients responded positively to treatment with follow-up over 2 years. Evaluation of clinical response was performed by a second- or third-party cornea specialist who analyzed slit lamp and fluorescein photos anonymously and randomly. This measure compares favorably to other cultivated limbal stem cell treatment reviews and is superior to allogenic limbal stem cell therapy, in which improvement over 2 years was determined in one review to be 15%.

CLINICAL VALUE/IMPLICATIONS

Cultivated limbal stem cell sheets are interesting approaches for the future management of limbal stem cell dysfunction. This technique appears superior to allogenic (donor derived) approaches because it avoids most of the immunologic implications of transplanting foreign limbal cells and is minimally disruptive to the donor eye as only a small zone of limbus is removed. However, it is important to be aware that this approach is only available for patients with unilateral pathology as the fellow eye’s limbus needs to be healthy enough to donate 5 mm² of limbus tissue and so would not be an option for patients with severe bilateral disease, as seen with congenital aniridia. Furthermore, availability of this process is currently limited to Japan.

MENDELIAN RANDOMIZATION IMPLICATES BIDIRECTIONAL ASSOCIATION BETWEEN MYOPIA AND PRIMARY OPEN-ANGLE GLAUCOMA OR INTRAOCULAR PRESSURE


Question: Is there a causal genetic link between myopia and glaucoma or myopia and increased intraocular pressure?

BACKGROUND/SUMMARY OF FINDINGS

Possible associations between myopia and glaucoma and myopia and elevated intraocular pressure have been made previously; however, several studies of these associations have called them into question. Further, variations from normal retinal nerve fiber layer and subjective visual field testing among highly myopic eyes may confound the ability to differentiate from truly glaucomatous optic neuropathy, making any clinical relationship difficult to establish.

Mendelian randomization involves establishing a causal relationship between variation of normal genes within a population, exposure to a risk, and an associated outcome. This review applies several models of Mendelian randomization to large, publicly available, genetic databases of both European and Asian populations to identify genetic associations between primary open-angle glaucoma, intraocular pressure, and myopia.

Clinical Value/Implications: Researchers found a strong bidirectional genetic association between both myopia and primary open-angle glaucoma. This link appears to be primarily mediated by the even stronger link between elevation in intraocular pressure and myopia. The authors go on to speculate that this link appears strong enough that treating patients with myopia who have ocular hypertension even prior to a clear diagnosis of glaucoma may be worthwhile. Further, the fact that these relationships were found to be bidirectional at least suggests that efforts to prevent myopia genesis may have additional benefit in reducing risk of glaucoma as well, although both points were speculative and not specifically studied.

INTRAVITREAL THERAPY FOR UVEITIC MACULAR EDEMA—RANIBIZUMAB VERSUS METHOTREXATE VERSUS THE DEXAMETHASONE IMPLANT: THE MERIT TRIAL RESULTS

The Multicenter Uveitis Steroid Treatment Trial Research Group

Acharya N, Vitale A, Sugar E, et al. Ophthalmology 2023;1-10

Question: Is there a difference in the comparative effectiveness of dexamethasone implant, intravitreal methotrexate, and intravitreal ranibizumab in reducing the central subfield thickness in patients with minimally active or inactive uveitis and persistent macular edema in one or both eyes after 12 weeks of treatment?

BACKGROUND/SUMMARY OF FINDINGS

Macular edema is the most common complication of uveitis and can result in loss of vision. The current treatment standard in cases with persistent uveitic macular edema is repeated intravitreal corticosteroid injections. Although these injections often result in resolution, upward of 40% of cases will relapse. The potential risks associated with repeat corticosteroid injections necessitate exploring the value of noncorticosteroid agents in uveitic macular edema management. In this study, patients with persistent macular edema, defined by a central subfield thickness of >300 μm for Zeiss cirrus or Topcon spectral domain optical coherence tomography or >520 μm for Heidelberg Spectralis, were randomized 1:1:1 to receive dexamethasone 0.7 mg implant, methotrexate 400 μg/0.1 mL, or ranibizumab 0.5 mg/0.05 mL. Retreatment schedule protocols differed based on which interventions the patients were randomized to.

After 12 weeks, all three groups demonstrated statistically significant reduction in central subfield thickness relative to baseline measurements. Dexamethasone had a greater percentage reduction in central subfield thickness
than methotrexate or ranibizumab (35% vs 11% vs 22% reduction, respectively). The dexamethasone group also had a significantly greater gain in visual acuity than the other two therapies. Both the dexamethasone and ranibizumab groups had improved NEI-VFQ-25 scores; the methotrexate group did not improve. The incidence of intraocular pressure elevations to 30 mm Hg was significantly higher in the dexamethasone group than in the methotrexate or ranibizumab (10% vs. 1% and 1%, respectively). Overall ocular and systemic side effects were infrequent.

CLINICAL VALUE/IMPLICATIONS

Dexamethasone was superior to both ranibizumab and methotrexate, with methotrexate not achieving any clinically meaningful improvement in central subfield thickness. Although known side effects exist, intraocular corticosteroids remain the most effective way to treat persistent uveitic macular edema, when not absolutely contraindicated. Optimally, corticosteroid-sparing agents would successfully treat this condition with substantially diminished side effects; however, none have been shown to supplant steroids at this time.