By: Megan Alberts, OD, FAAO, Jennifer Sutter, OD, FAAO, and Kelli Payne, OD

Background

Retinoschisis means “splitting of neurosensory retina.”\(^1\) In the various forms of retinoschisis, patients may present with or without symptoms. The condition can be unilateral or bilateral and it can be peripheral or central. Acquired retinoschisis and X-linked (juvenile) retinoschisis are the major subtypes mentioned in the literature. Senile, acquired, degenerative, and peripheral retinoschisis are synonymous. Acquired retinoschisis tends to be unilateral, have a later age of onset, and be nonprogressive.\(^1\) There is no predilection for acquired retinoschisis based on gender or refractive error. Reticular retinoschisis is a subtype of acquired retinoschisis in which bullous elevation occurs in the peripheral retina.\(^1\) Typical retinoschisis is another subtype of acquired retinoschisis and it involves little to no elevation.

X-linked retinoschisis (XLRS) disproportionally affects males, tends to show up earlier in life and, most notably, shows foveoschisis clinically.\(^1\) A significant amount of information is available about the evolution of X-linked foveoschisis, but little is known about the pathological development of acquired retinoschisis.

Practicing optometrists can manage retinoschisis most efficiently by recognizing clinical presentation, utilizing imaging, and understanding retinal anatomy. This case report addresses the most common types of retinoschisis that an eyecare provider may encounter, and is appropriate for third- and fourth-year optometry students as well as optometric residents.

Student Discussion Guide

Case description

A 67-year-old Caucasian male presented as a new patient for a diabetic eye examination. He had been diagnosed with non-insulin-dependent diabetes mellitus (NIDDM) one year prior and the condition was well-controlled with use of metformin 500 mg twice daily. He had no new ocular or visual complaints. His best-corrected visual acuity was 20/20 OD (+1.25 sph) and 20/20 OS (+1.00 sph). No relative afferent pupillary defect was noted. Preliminary testing and anterior segment evaluation were both unremarkable OU.

During fundus examination of the left eye, a large segment of elevation was noted in the nasal portion of the posterior pole. The margins of this elevation were distinct and extended into the periphery. Binocular indirect ophthalmoscopy revealed an elevated, smooth dome of retinal tissue nasally from 7 to 11 o’clock (approximately 12-15 disc diameters) extending to the ora serrata. There was visible separation between the retinal layers, but scleral indentation revealed no obvious break or hole.
Upon further questioning, the patient admitted that he had a black spot on the side of his vision for the “past few weeks,” but assumed it was “just a floater.” Based on the examination findings, the patient was diagnosed with having 12-15 disc diameters of symptomatic reticular retinoschisis of unknown duration. A retinal consult was arranged, and the general ophthalmology staff offered the patient the next available appointment. Three weeks later, he called the clinic to report that his vision had significantly worsened and objects out of his left eye appeared to have a yellow tinge. The patient was directed to the emergency room where he could be examined by the on-call resident ophthalmologist.

The resident saw the patient that same day. Examination of the left eye showed Snellen visual acuity of 20/400 and a relative afferent pupillary defect secondary to a large, macula-off, retinal detachment. The patient was sent to the Brooke Army Medical Center for surgery the next morning. The patient underwent a pars plana vitrectomy with scleral buckle repair for the retinal detachment of the left eye. Best-corrected visual acuity stabilized around 20/80 six months after surgery. The patient continues to be followed yearly by the retina service to monitor for change.

Educational Guidelines

Key concepts

1. Recognize the clinical differences between the subtypes of acquired retinoschisis
2. Understand the importance of taking a good history
3. Be familiar with different types of ancillary testing to aid in diagnosis and management of the condition
4. Be aware of management options for all subtypes of retinoschisis
5. Be able to properly educate patients regarding diagnosis and prognosis of the condition

Learning objectives

At the conclusion of this case discussion, participants should be able to:

1. Recognize all types of retinoschisis from an anatomic standpoint
2. Identify major classifications of retinoschisis from a retinal detachment
3. Understand the typical patient demographic for both X-linked and acquired retinoschisis
4. Understand the risk factors in association with the clinical presentation to best manage the patient, including if/when referral is appropriate
5. Provide patient education regarding all management options and expectations for those options
6. Understand that treatment with oral or topical carbonic anhydrase inhibitors for foveoschisis have similar visual outcomes but varied side effects
7. Understand treatment options in cases of peripheral retinoschisis
8. Understand intravenous fluorescein angiography (IVFA) results in XLRS.

Discussion questions
1. Knowledge and concepts required for critical review of the case
   a. What are the typical clinical characteristics of peripheral retinoschisis?
   b. What are the typical clinical characteristics of X-linked retinoschisis?
   c. How can one distinguish retinoschisis from other peripheral retinal conditions?
   d. What would be the most appropriate management given the case provided?

2. Differential diagnoses
   a. What differential diagnoses make the most sense, given the clinical characteristics?
   b. What other factors need to be considered in this case?
   c. Are there any ancillary tests that would have been helpful in this diagnosis?

3. Disease management
   a. How would you monitor this patient, if at all?
   b. What timeline is most appropriate for this patient?

4. Patient education
   a. How would you educate the patient regarding this diagnosis?
   b. What is the long-term prognosis for this patient?
   c. How would you discuss visual outcomes with or without treatment?

5. Critical thinking
   a. How would you have managed this case?
   b. Do you feel more prepared to manage or co-manage this condition?

Learning assessment
1. Facilitate case discussion to achieve learning objectives
2. Knowledge base can be evaluated by comparing optical coherence tomography (OCT) scans and fundus photographs with case history
3. Knowledge base of the condition can be assessed by student presentations of differential diagnoses
4. Clinical thinking skills can be evaluated by case reports that are from a review of literature or hypothetical examples

Discussion
Retinoschisis is defined as splitting of the neurosensory retinal components. Retinoschisis can be large or small, flat or elevated (bullous), symptomatic or asymptomatic, central or peripheral, unilateral or bilateral, progressive or nonprogressive. Acquired retinoschisis and XLRS are two major types discussed in the scientific literature. Acquired retinoschisis is most commonly peripheral, unilateral, asymptomatic, and present in an older demographic. XLRS is usually bilateral, central, symptomatic, and present in a younger male demographic.
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1) Other forms of retinoschisis are myopic macular retinoschisis and tractional retinoschisis. Myopic macular retinoschisis (also known as myopic traction maculopathy or myopic foveoschisis) is a complication from high myopia. A posterior staphyloma is commonly associated with this type of retinoschisis.5 Tractional retinoschisis can occur in vitreomacular traction syndrome or proliferative diabetic retinopathy.6 The combination of clinical findings and patient symptoms determines the diagnosis, prognosis and management of the condition.

XLRS is a rare condition that can show characteristics at birth, but some children go years without a diagnosis. The clinical sign of XLRS is foveoschisis, which is retinoschisis that affects the fovea. This condition typically presents bilaterally but can be asymmetric. XLRS patients have reduced vision ranging from 20/40 to no light perception, depending on the type of mutation, location of the retinoschisis, and chronicity of relapses. As with all X-linked disorders, XLRS disproportionately affects males. The prevalence of XLRS is 1:5,000-25,000 males.7-11 Patients with XLRS can also independently develop acquired retinoschisis. Family history may or may not be helpful in assessing risk of development. Table 1 outlines differences between acquired retinoschisis and XLRS.

The repulsion of foveal components in XLRS has been studied in great depth.12 The gene involved with this foveal pathology is the retinoschisin gene, or RS1.7,12-15 Due to incomplete penetrance and expressivity of RS1, the clinical presentation of XLRS varies greatly. Gel electrophoresis, velocity sedimentation and mass spectrometry show that RS1 is a protein comprised of eight subunits, held together by disulfide bonds.15 The proteins made by the RS1 gene aid in retinal cell adhesion, help with cellular organization within the retina, act as an osmotic buffer between inner and outer cellular fluids, and provide general structural support.12,13 One of the most notable subunits is the discoidin domain, which helps adjust water balance between the intracellular and extracellular environment utilizing sodium/potassium ATPase. The lack of a functional discoidin domain may lead to fluid accumulation extracellularly, causing a divide between retinal layers and creating the potential for retinoschisis.13,15,16
In humans, retinoschisin has been found on the extracellular surfaces of the inner segments of rod and cone photoreceptors, bipolar cells, outer nuclear layer, and both inner and outer plexiform layers. Due to the wide distribution of the retinoschisin protein, any level of the retina can be affected.\textsuperscript{13,15}

XLRS causes a significant visual disturbance due to its presence within the fovea. Cystoid macular edema (CME) is visible with OCT.\textsuperscript{7,17} The CME has an atypical OCT appearance, as it involves retinoschisis with vertically elongated columns of stretched middle anatomy (Figure 1).\textsuperscript{18} Performing IVFA can further differentiate this retinoschisis from other cases of CME, as the cystoid intraretinal spaces in XLRS do not leak or stain (Figure 2).\textsuperscript{16,18} The cystoid spaces can be seen with indocyanine green (ICG) angiography.\textsuperscript{18}

It has been reported in the scientific literature that treating with a topical or oral carbonic anhydrase inhibitor (CAI) can decrease the size of the cysts and potentially increase visual acuity.\textsuperscript{17} Topical dorzolamide 2% ophthalmic solution (Trusopt, Merck) is dosed three times daily in the affected eye. Oral acetazolamide (Diamox, Duramed Pharmaceuticals) is taken as 125 mg twice daily. Dosing duration varies depending on how responsive the eye is to treatment. The exact mechanism of action of CAIs in retinoschisis is unknown, but CAIs are known to effect fluid transportation through the manipulation of bicarbonate ions to reduce intraocular pressure. It has been postulated that CAIs have similar effects within the macula. It has also been proposed that CAIs cause vascular dilation and increased blood flow by increasing tissue carbon dioxide concentrations and/or lowering tissue pH, leading to a more normal macular architecture.\textsuperscript{8,17,19}
A maintenance dose of 62.5 mg Diamox taken by mouth, or once daily/twice daily dosing of Trusopt in the affected eye have been shown to help decrease XLRS relapses. Unfortunately, relapses are still quite common even with chronic CAI use.\textsuperscript{3,17} Topical CAIs greatly reduce systemic absorption and are the preferred treatment of CME in XLRS. Although treatment with oral CAIs has been shown to produce equal visual acuity outcomes, it is associated with a significantly greater side-effect profile when compared with topical treatment.\textsuperscript{8,17,19}

Acute onset macular edema is more responsive to treatment than chronic edema. The longer the edema is present, the more difficult it is to recover proper anatomic orientation, which decreases the likelihood of a good visual outcome. In cases of chronic foveoschisis, granular retinal pigment mottling is often seen, and in some instances is described as being wheel/spoke-like in nature.\textsuperscript{11}

Both acquired retinoschisis and XLRS involve splitting of neurosensory retina; however, the mechanism that causes the split is vastly different. Research has been done to determine the impact of the retinoschisin gene on acquired retinoschisis. Interestingly enough, acquired retinoschisis does not occur because of any mutations in the RS1 gene. Research has not determined how or why acquired retinoschisis occurs.\textsuperscript{7,12}

Previously, it was thought that typical retinoschisis created retinal splitting in the outer plexiform layer, while reticular retinoschisis and XLRS both created a split in the nerve fiber layer. While these are still common locations for each, OCT has shown that retinal splitting can occur between other layers as well.\textsuperscript{3,13}

The most common type of retinoschisis is acquired retinoschisis. Acquired retinoschisis is usually benign and non-progressive. It is idiopathic, sporadic, usually less impactful upon vision, and most often affects the peripheral retina.\textsuperscript{1,10,12,14} Patients are typically asymptomatic despite the retinoschisis causing a true and absolute visual field defect. If a patient is symptomatic, the situation needs to be taken seriously.

Acquired retinoschisis is further divided into reticular or typical retinoschisis.\textsuperscript{1} Reticular
(bullous) retinoschisis produces elevation due to the presence of fluid between the neurosensory layers, which poses a higher risk of progression and potential complications. Typical retinoschisis tends to have a flatter appearance due to less fluid accumulation.\(^1\)

Acquired retinoschisis tends to emerge later in life, but cases of younger adults and children with this presentation have been seen. It most commonly affects peripheral inferotemporal retina, although reticular retinoschisis is seen in the nasal retina more frequently than typical retinoschisis.\(^1\)

Approximately 1% of all eyes have acquired retinoschisis, which shows bilaterality in 33% of those patients.\(^3\) Myopic patients are more likely to be progressive than hyperopic patients and there is no gender predilection.\(^2,3\) Neither cataract surgery nor posterior vitreous detachments have been shown to worsen retinoschisis.\(^21\)

There can be outer or inner wall breaks within the acquired retinoschisis.\(^20\) Outer wall breaks are usually larger and occur in up to 25% of all acquired retinoschisis cases. Outer wall breaks can have a characteristic ring of pigmentation surrounding the hole, which denotes chronicity (Figure 3).\(^{20-22}\) Inner wall breaks (chronic or acute) tend to be significantly smaller and have been described as mimicking the appearance of an atrophic hole.\(^21\) The presence of a hole (in either the inner or outer segment) is more strongly considered for surgical intervention, as retinal detachments are more common with either presentation.\(^1,3,21\) However, when there are no inner or outer retinal wall holes, reticular retinoschisis is typically benign and non-progressive and is commonly monitored.\(^2\)
Clinicians must be able to distinguish between a retinal detachment and peripheral retinoschisis using anatomical differences observed during funduscopic examination. Retinoschisis tends to be more translucent with visible vasculature, less flexible with well-demarcated borders, and have an overall smoother appearance than a retinal detachment. To complicate matters, a longer-standing retinal detachment can exhibit demarcation lines and retinal pigment epithelium (RPE) alterations, similar to how some retinoschises cases present. Furthermore, a patient can present with a combination of retinoschisis and detachment. A true detachment will have complete separation of neurosensory retina from underlying RPE with associated atrophy of the RPE. The advent of OCT has greatly improved the accuracy of diagnosis, as the photoreceptor integrity line is relatively easy to locate. Figure 4 shows a true retinal detachment, as the whole sensory retina is disconnected from the RPE. Figure 5 shows retinoschisis, as the RPE is still attached to outer retina, with the detachment located between the neurosensory retinal components.

Acquired retinoschisis most commonly occurs in peripheral retina, creating limitations to imaging with OCT. However, there is evidence of some success performing peripheral OCT through a modified slit lamp with a three-mirror contact lens, 78D lens and/or Heidelberg Spectralis ultra-widefield module lens. Scleral indentation (with or without B-scan echography) can also help differentiate between a retinoschisis and a retinal detachment. Scleral indentation will flatten areas of a true retinal detachment, but will not flatten a retinoschisis. However, highly bullous retinal detachments do not flatten, even with forceful
indentation.\textsuperscript{20,22} Similarly, a B-scan (with indentation) will show a decrease in the space between the retina and sclera in a true detachment but not with a retinoschisis. Performing a Humphrey Visual Field test can also be helpful.\textsuperscript{22} An absolute, irreversible defect will be seen in retinoschisis, while a relative defect may be seen in retinal detachment.\textsuperscript{21,22} In 1964, Okun and Cibis published an article describing how laser photocoagulation could be used to distinguish between these conditions, as it would cause a blanching effect on the retina in acquired retinoschisis but not in retinal detachment. These findings have since been refuted.\textsuperscript{20,22}

The efficacy of prophylactic laser barricade is debated.\textsuperscript{2-4,21} Options may include panretinal photocoagulation, argon laser treatment or retinal cryopexy. Drainage of the retinoschisis cavity is commonly done with laser demarcation treatments to help collapse the retinal layers in an attempt to achieve as close to a normal retinal contour as possible. This prophylactic treatment will not re-establish the neuronal integrity of the split retina; therefore, it does not reverse the absolute visual field defect caused by acquired retinoschisis.\textsuperscript{24} The goal is to help prevent a retinal detachment by creating a laser-induced chorioretinal scar around the affected area of retina.

Even after prophylactic treatment, progression may occur.\textsuperscript{21} Literature suggests that acquired retinoschisis progresses to a more serious retinal concern in about 15% of cases.\textsuperscript{1,3} If retinoschisis does progress to a retinal detachment, it is difficult to repair.\textsuperscript{2-4,21,24} Clinical presentation of the detachment determines which type of retinal procedure is pursued, but a scleral buckle, and/or pars plana vitrectomy are most commonly performed. Up to 40% require a second surgical repair.\textsuperscript{21,24}

Retinoschisis can present with a myriad of symptoms or none at all. The funduscopic examination is an important element in achieving the appropriate diagnosis. In the case reported here, the patient’s history, the unknown timeline and the dilated examination were considered for the most accurate diagnosis and appropriate management. The patient presented with a new “floater” in his peripheral vision, without central vision being affected. A dilated examination revealed a large reticular retinoschisis affecting the nasal retina that was first observed with a 78D lens. A referral was warranted given the features of this
symptomatic retinoschisis.

Doctors have different levels of comfort with diagnosing and managing acquired retinoschisis, but typically if no inner or outer wall holes are present, and the patient is asymptomatic, it is appropriate to monitor the condition. It is imperative that the clinician stresses the importance of follow-up visits. The patient must understand the severity of the condition and should return to the clinic with any change in or worsening of symptoms. A retinal consult is always an option should any of the conditions negatively change.

Conclusion

Over the past two decades, there have been extensive advancements in the understanding of all types of retinoschisis at the clinical, molecular, genetic and cellular level. Even with these developments, there is still more to be discovered. The clinical presentation of this patient and understanding of retinal anatomy is what prompted the referral. Patients who are not managed appropriately are at risk for permanent vision loss. Therefore, it is important that optometrists be well-versed in the newest treatments and theories surrounding this pathology.

References


