Foveal Retinoschisis: Case Report and Clinical Review

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Abstract
Clinicians often discover a retinoschisis during a peripheral retinal exam. However, the finding can occur within the posterior pole and surprise the examining provider. There are numerous etiologies of maculopathy associated with retinoschisis – also called foveoschisis. These include juvenile X-linked retinoschisis, myopic foveoschisis, optic disc pit maculopathy, autosomal recessive foveoschisis, medication induced foveoschisis, or even idiopathic classifications.

The following case report will describe a patient with unilateral foveoschisis. Though visually asymptomatic, the condition remained stable since 2013 and as such deferred any surgical intervention. It is important to recognize and understand the pathology, natural history, and prognosis of foveoschisis in order to monitor vision and potential complications. Regardless of the foveoschisis nature, the best diagnostic tool to monitor the condition is optical coherence tomography (OCT). Differentiating the cause will guide the examiner regarding an appropriate follow up schedule, monitoring for potential sequelae, and accurate education.

Introduction
Originally coined by Jager in 1953, the term "retinoschisis" has been described and studied as early as the late 19th century.1 Maculopathy associated with retinoschisis derives from a variety of etiologies, all resulting in the splitting of the inner foveal layers. Structurally, this anomaly is caused by either a defect in protein synthesis or more commonly the contraction of posterior cortical vitreous.2 Common causes of maculopathy associated with retinoschisis, also called foveoschisis, include juvenile X-linked retinoschisis, myopic traction maculopathy, optic disc pit maculopathy, and stellate nonhereditary idiopathic foveomacular retinoschisis (SNIFR). Other, less common causes include niacin or taxane induced foveoschisis and autosomal recessive S-cone syndrome.3

Treatment options for foveoschisis primarily include annual monitoring with dilated fundus exams or vitrectomy with tamponade and a combined internal limiting membrane peel. Despite the etiology of the foveoschisis, indications for treatment depend on the significance of the patient’s symptoms and other potential complications associated with the condition, including development of subretinal fluid.4,5,6 Expected outcomes of treatment are dependent on the patient’s initial presentation.7,8

Case Presentation
An 81-year-old African American male presented to the clinic in January 2020 for his yearly comprehensive eye exam complaining of mildly reduced vision through his habitual glasses at all ranges with both eyes. This patient also complained of increased glare at night and allergic conjunctivitis that was adequately controlled with occasional use of ketotifen fumarate .035%. Relevant ocular history included a longstanding unilateral foveoschisis and previous cataract extraction in the left eye (OS) only. No remarkable ocular history was noted for the right eye (OD). The only active medication reported by the patient was amlodipine for systemic hypertension. No known drug allergies were reported. Systemic and ocular family history were unremarkable.

Entering best corrected visual acuities (BCVA) were 20/20 OD and 20/40+2 OS. Amsler grid testing OS revealed metamorphopsia in all quadrants and no scotoma. Amsler grid testing was unremarkable for metamorphopsia or scotoma OD. Other chair skills including pupil testing and confrontation visual field testing were normal and unremarkable OD/OS. When testing best corrected vision with the left eye, the patient reported that the letters on the chart were "floating". This was a similar presentation reported at the previous comprehensive exam one year prior. Refractive findings were as follows:

<table>
<thead>
<tr>
<th>HABRx:</th>
<th>OD: -0.25-1.00x105</th>
<th>20/20-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OS: +1.25-0.50x083</td>
<td>20/40+2</td>
</tr>
<tr>
<td>Add:</td>
<td>+2.50</td>
<td>20/20 OU</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MRx:</th>
<th>OD: -0.50-1.00x105</th>
<th>20/20</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OS: +1.25-0.50x083</td>
<td>20/40+2</td>
</tr>
<tr>
<td>Add:</td>
<td>+2.50</td>
<td>20/20 OU</td>
</tr>
</tbody>
</table>
Slit lamp examination showed 1+ bulbar injection graded OD/OS. Both corneas were clear and intact apart from temporal scarring only in OS secondary to previous cataract surgery. Mild iris atrophy with temporal hypopigmentation was also noted only in OS. All other anterior segment findings were unremarkable OD/OS including open angles with Van Herrick assessment and quiet anterior chambers. Intraocular pressures measured at 9:59 a.m. via Goldmann applanation tonometry were 20 mmHg OD and 17 mmHg OS. The patient was dilated with two drops of tropicamide 1% OD/OS at 9:59 a.m.

Once dilated, the OD lens was assessed as having trace nuclear sclerosis with 1+ anterior cortical changes while the OS had a clear and centered posterior chamber intraocular lens. Upon clinical fundus examination, the optic nerves of each eye were assessed as having distinct margins and intact rim tissue with cup-to-disc ratios measured as 0.40 round OD and 0.35 round OS. Funduscopic presentation of the right macula was flat and intact, while the left macula presented with a diffuse puckered appearance extending to the temporal margins of the optic nerve (Figure 6). Blood vessel assessment was unremarkable, exhibiting a 2.3 artery-to-vein diameter ratio and 1:3 arteriolar light reflex in each eye. Peripheral retinal assessment was unremarkable for holes, tears, or detachments in all quadrants OD/OS.

OCT images were taken of the macula in both eyes, and of the optic nerve head (ONH) in the left eye only. The OD macula was flat, intact, and unremarkable while the OS macula showed significant retinal distension and cystic spaces. This can be seen below in Figures 1 and 2, respectively. The outer plexiform layer (OPL) is indicated with an orange arrow.

Comparatively, the ONH OCT of the left eye showed peripapillary retinal tissue distension extending nasally and temporally towards the macula. This can be seen below in Figure 3. The outer plexiform layer (OPL) is indicated with an orange arrow.

Management and Outcome
The patient was initially seen in July 2013, presenting with a recent onset of worsening vision in OS only. Fluorescein angiography (FA) was performed at that visit to rule out leakage or other abnormal staining patterns. Both arteries and veins demonstrated adequate perfusion and arm-to-retina times. No abnormal areas of hyperfluorescence or hypofluorescence were noted.

Following this initial exam, the patient was referred for a retinal consultation. The retina subspecialist hypothesized the localized retinoschisis to be from an optic disc pit. However, this hypothesis was unable to be confirmed at that time, and was ultimately ruled out. Thus, the resulting diagnosis of the condition was stated as retinoschisis in the peripapillary region of the left eye that extended to the macula.
From the patient’s initial exam in 2013 to his most recent one in 2020, the hypothesized nature of the schisis has been suggested to be idiopathic. No retinal surgery or other intervention has been recommended. Regular monitoring for posterior complications has been the preferred method of management for this case. Following cataract extraction in 2014, the patient’s OS BCVA has consistently measured between 20/30 and 20/40, and no additional complications associated with foveoschisis have been observed. The recommended period for monitoring this condition is yearly, or sooner if sudden visual decline is noticed.

Discussion
When a patient presents with a retinal foveoschisis, there are several different potential etiologies to consider. These include juvenile or X-linked retinoschisis, myopic foveoschisis, optic disc pit maculopathy, and idiopathic foveoschisis. Medication use or S-cone syndrome are other rare causes. Despite the etiology, the potential surgical options for foveoschisis and recommended indications for having them are sparse. The potential causes of the condition, treatment options, and visual prognosis of retinal foveoschisis will be discussed.

Juvenile (X-linked) Retinoschisis
Congenital X-linked retinoschisis (CXLRS) has been studied and reported on for over a century.9 One of the most common juvenile macular dystrophies, CXLRS has an estimated prevalence ranging from 1 in 5000 to 1 in 20,000 people and occurs almost exclusively in males.10 CXLRS is characterized by mutations in the RS1 gene that results in defective protein synthesis of retinoschisin and the splitting of inner retinal layers, particularly the RNFL.10 Current understanding suggests there are at least 191 unique variants of the RS1 gene that are associated with the CXLRS phenotype. However one study showed development of pediatric foveoschisis secondary to a defective CRB1 gene in infant twins conceived via artificial insemination.51 Most recent discussions of the condition follow specific classification criteria originally developed in September 2006 describing four distinct subtypes: Type 1 (foveal), Type 2 (foveolamellar), Type 3 (complex), and Type 4 (foveoperipheral).10 In this classification system, the term “foveal” is referring to a schisis that does not extend past what is observed clinically when imaged with OCT. The term “lamellar” refers to a schisis that is identifiable with OCT imaging, but is unable to be appreciated with clinical fundus exam. Type 1 CXLRS therefore describes a patient with a foveoschisis but without a peripheral schisis. Type 2 CXLRS refers to a patient with both lamellar and foveal schisis, but without a peripheral schisis. Patients with Type 3 CXLRS demonstrate foveal, lamellar, and peripheral involvement. Finally, a patient with Type 4 CXLRS will present with findings similar to Type 3 CXLRS, but without a schisis that is only detected with OCT imaging and unable to be appreciated clinically (“lamellar”).10 One study indicated that complex CXLRS (Type 3) was the predominant type in 71% of patients.10 This classification system is described below in Table I.

Overall, congenital X-linked retinoschisis displays stability up to five years after initial diagnosis in 83% of affected patients.12 The visual prognosis and natural progression of the condition vary considerably depending on the specific subtype and presence or absence of retinal exudation. It is unclear why some patients develop exudative changes when others do not, but the etiology of these findings is suspected to be due to vascular incompetence or resolving vitreous hemorrhages.1 Of the patients who develop complications from CXLRS, studies show that the majority of them likely have the complex (Type 3) phenotype. These complications can include retinal detachments and vitreous hemorrhages. Determining potential differential diagnoses for patients with juvenile retinoschisis depends heavily on differentiating between the exudative and non-exudative subtypes. For example, exudative changes in the retina due to CXLRS could mimic retinoblastoma, Coats disease, or complications stemming from posterior uveitis, among others. On the other hand, juvenile retinoschisis without exudation is often mistaken for pediatric retinal detachments. When observed with fluorescein angiography, central foveoschisis does not exhibit any active leakage associated with the inner retinal splitting, thus differentiating it from conditions such as diabetic or cystoid macular edema.3

Promising gene therapy advances have proven effective at replacing defective RS1 genes in mouse models. These treatments show improved gene expression in all retinal layers as well as restored b-wave amplitude on electroretinography (ERG), both characteristics principally affected in CXLRS.1 In cases of symptomatic retinal detachments or vitreous hemorrhages, complete vitrectomy with silicone oil tamponade is indicated. Peeling of the internal limiting membrane has been shown to increase risks of breaks or macular hole development post-surgery, and is thus a physician dependent choice that is decided on a case-by-case basis. While some studies show only a temporary resolution of the foveoschisis after surgery, others have reported significant restoration of foveal depression, collapse of schisis cavities, and improved visual acuity in up to 80% of studied eyes. However, some cases required a second surgery to achieve improved visual and anatomical results.13,14

It is highly unlikely that the patient mentioned in the case was born with congenital X-linked retinoschisis. If the patient’s history is accurate, the gradual vision loss in his left eye began.

Table I. CXLRS Classification

<table>
<thead>
<tr>
<th>CXLRS Type</th>
<th>Foveal Schisis</th>
<th>Lamellar Schisis</th>
<th>Peripheral Schisis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1: Foveal</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Type 2: Foveo-lamellar</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Type 3: Complex</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Type 4: Foveo-peripheral</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>CXLRS = congenital X-linked retinoschisis</td>
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in his early seventies. The unilateral presentation is an even stronger indication that this is an acquired finding rather than a congenital, bilateral condition caused by mutated genotypes.

**Myopic Foveoschisis**

Degenerative changes in the eye account for another major subset of retinoschisis. Often, these degenerative findings are a result of pathological myopia, defined as a myopic refractive error of at least six diopters with degenerative fundus changes and an axial length of greater than 26.5 millimeters. The root cause of degenerative myopic changes involves congenital scleral weakness which leads to progressive globe enlargement, axial lengthening, and finally the formation of a posterior staphyloma. In many patients with pathological myopia, focal retinoschisis in the macula can develop. This finding is termed myopic foveoschisis (MF). In three recent large scale population studies with just under 15,000 participants from predominantly Asian countries, MF was observed in 1-3% of eyes with axial lengths greater than 26.5 millimeters. A study conducted by Wu et al sought to uncover the specific pathophysiology of MF development and found the culprit to be contraction of cortical vitreous caused by progressive thinning of the sclera and the respective resistance to stretch by the inner retinal layers and retinal vessels. Univariate analysis showed significant association of increasing age and presence of posterior staphyloma with development of MF.

The severity of the myopic foveoschisis varies depending on the presence of other factors, such as epiretinal membranes that cause inner retinal traction. A retrospective case series of 29 eyes by Gaucher et al found the presence of epiretinal membranes on OCT testing resulted in slow visual decline and further splitting of the inner retinal layers. These retinal findings, and thus progression of visual loss, were found in 20 out of 29 eyes studied. As previously mentioned, scleral ectasia associated with increased axial length increases the risk of MF formation. However, it is not most likely the sole etiology because axial length is known to stabilize before 30 years of age, while the onset MF occurs later in life, typically around age 50. Therefore, it is most appropriate to conceive that tractional forces by the cortical vitreous on an already weakened retina result in the development of myopic foveoschisis.

Potential complications of pathological myopia range from early onset posterior subcapsular cataracts to the development of a choroidal neovascular membrane (CNV). Anti-VEGF injections are indicated in the event of CNV formation. In other instances of vision threatening complications such as retinal detachments, macular holes, or unstable myopic foveoschisis, pars plana vitrectomy (PPV) with silicone oil tamponade is indicated. Surgeons must also determine the necessity for an internal limiting membrane (ILM) peel. Marked progression of symptoms including a reduction in visual acuity or increased metamorphopsia signifies an "unstable" foveoschisis.

A 2005 study published in the British Journal of Ophthalmology evaluated nine eyes in patients who had been treated with complete vitrectomy without ILM peel after foveal detachment secondary to myopic foveoschisis. The study found a mean improvement in visual acuity of 3.6 lines on Snellen vision testing and a mean decrease in the height of foveal detachment from 505 μm preoperatively to 21 μm postoperatively. OCT imaging revealed complete resolution of the foveoschisis with reattachment in 77.8% of the studied patients. Another study evaluating the success of retinal surgery found that postoperative success was dependent on the preoperative status of the foveoschisis. Complete vitrectomy with or without ILM peel has been shown to benefit patients with preoperative foveal detachment the most (81%), while patients with preoperative macular hole without overlying foveal tissue were least likely to have improvements in visual symptoms (45%). Surgical success was measured as improved visual acuity with Snellen acuity testing and a decreased height of the foveoschisis measured on OCT. The foveal status, duration of visual symptoms, the patient’s age, and preoperative best corrected visual acuity are key factors in determining postoperative success.

Complete chart review of the patient in the case indicated that pathologic myopia was not the culprit. No posterior retinal findings consistent with pathological myopia including staphyloma were noted on dilated fundus exam in either eye. The patient's refractive error was also unremarkable for significant myopia. The preoperative refractive error taken in July 2014 before unilateral cataract extraction of the left eye is below:

**MRx:** OD: -0.25-1.00x105
**OS:** +1.25-0.50x083
**Add:** +2.50

Axial length measurements were not recorded in the preoperative note or in any other exam chart from the initial visit in July 2013 until the most recent in January 2020.

**Optic Disc Pit Maculopathy**

Apart from genetics or degenerative myopia, another potential cause of foveoschisis is the presence of congenital optic pits. Optic disc pit maculopathy (ODP-M) is a complication of optic disc pits that is estimated to occur in anywhere from 25% to 75% of people diagnosed with optic pits. Optic disc pits are relatively rare findings with an estimated prevalence of 1 in 5,000 and present as round, darkly pigmented depressions of the optic nerve tissue on fundus examination. The exact cause of optic disc pit development is uncertain and no other associations with systemic or ocular conditions have been revealed. Other than ODP-M, other potential complications include visual field abnormalities such as enlarged blind spots or paracentral arcuate scotomas. The exact cause of ODP-M is postulated to potentially be a result of leaky blood vessels, posterior vitreous detachments, choroidal leakage, or even cerebrospinal fluid. The exact cause of fluid accumulation leading to foveoschisis, however, has not been fully uncovered.
Diagnostically, two factors that play a pivotal role in confirming the presence of optic disc pits are FA and OCT imaging. Optic pits will exhibit hyperfluorescence in the early phase of fluorescein angiography and staining of the optic disc pit in the late phase.

On OCT imaging, optic pits will demonstrate a dense hyporeflective area within the area of the optic nerve head. A typical OCT scan of an optic pit can be seen below in Figure 5. The optic pit in both the infrared image and horizontal cross section is indicated with an orange arrow.

Originally documented and recognized clinically in the late 19th century, there are surprisingly no known triggering factors that cause the development of ODP-M. While ODP-M can develop at any age in patients with optic disc pits, they have been observed most often to develop in the third or fourth decade. While patients with optic disc pits and no maculopathy are commonly asymptomatic, complications of ODP-M can include significant and progressive visual disturbance. Another optic nerve anomaly that some researchers have questioned as potential causes of foveoschisis is significant enlargement of the optic nerve cup. A 2007 study conducted by Zumbro et al evaluated five patients with enlarged cup-to-disc ratios (C/D ratios) and foveoschisis who did not have any other abnormal ocular findings that could be contributory towards the schisis. The minimum C/D ratios in the study were measured as 0.6 round and normally associated with glaucomatous cupping. Similar to the etiological cause in optic pits, the authors believed the cause to be vitreous fluid leaking through the expanded pores of the thinned laminar tissue of the cup.

The currently accepted treatment approach for visually significant and progressive ODP-M is PPV with combination laser treatment, gas tamponade, and possible ILM peel depending on the surgeon’s discretion. A comprehensive review of PPV treatment with other combined techniques to treat OPD-M showed a roughly 50% success rate, defined as any improvement in anatomical status or visual acuity after surgery.

The patient mentioned in the case report was found not to have an optic pit in the left eye on OCT analysis. Enhanced depth imaging (EDI), a technique that allows for greater imaging of the choroid and deep laminar tissue, was not performed on any of the scans, however. Also, FA confirmed no active leakage, vessel abnormalities, or any areas of hyperfluorescence or hypofluorescence. These results, combined with the grossly unremarkable optic nerve assessment on dilated fundus exam, effectively ruled out an optic disc pit as a potential etiology of the patient’s unilateral foveoschisis.

**Idiopathic Foveoschisis and Rarer Causes**

A foveoschisis is considered idiopathic in the absence of juvenile X-linked retinoschisis, pathological myopia, congenital optic disc pits, or other gross ocular abnormalities. Idiopathic foveoschisis has been shown to demonstrate retinal splitting in the outer plexiform layer with a stellate tractional appearance on dilated fundus exam. Termed as stellate nonhereditary idiopathic foveomacular retinoschisis (SNIFR), this condition is most often observed unilaterally and commonly exhibits stable visual acuity of 20/40 or better. The fundus presentation of the patient’s left eye exhibiting a typical presentation of SNIFR is shown below in Figure 6.

In rare cases, a foveoschisis can develop from extended use of niacin, a complex B vitamin, or taxane derived drugs, which are chemotherapy agents. These cases have been shown to be acute and usually resolve after discontinuing the medication. Also, patients with autosomal recessive enhanced S-cone syndrome exhibit severe foveoschisis with significant night blindness from childhood as well as early onset cataracts and retinal pigment epithelium alterations. As with congenital X-linked retinoschisis, this condition would most likely present bilaterally and in childhood. The patient in question was on neither of these medications and exhibited longstanding stability of visual symptoms that initially began in adulthood.
In a retrospective case series examining the eyes of 17 individuals with SNIFR, a stable average visual acuity of 20/40 was noted except in one subject with significantly reduced vision of 20/200 after developing subretinal fluid. No preexisting retinal anomalies or family history of congenital ocular conditions were reported, as well as no exact gender predication or specific association with either the right or left eye. The most common refractive error among these individuals was myopia without any clinical findings of pathological myopia. However, another study examining only five patients with idiopathic foveoschisis reported the most common refractive error as being hyperopia. Overall, these findings are likely inconclusive due to the low number of patients studied. Also, FA of SNIFR reveals no active leakage or other abnormalities, consistent with the initial presentation of the patient in this case report.

The clinical presentation on both fundoscopy and OCT imaging combined with the lack of any other attributable etiology suggests that the patient’s unilateral foveoschisis is likely idiopathic in nature. Regular examination of SNIFR is indicated to monitor for progression of the foveoschisis or development of subretinal fluid.

**Conclusion**

Upon reviewing the patient’s case history, fundus presentation, and diagnostic testing, the etiology was determined to be SNIFR. A complete investigation into the cause of a foveoschisis is important in order to rule out other potential complications, e.g. CNV formation in pathological myopia or visual field abnormalities secondary to optic disc pits. Regular monitoring of foveoschisis is necessary to track stability of the posterior segment and potential development of subretinal fluid. Overall, accurately determining the etiology of a foveoschisis is essential, both for monitoring potential sequelae of the condition and for accurate patient education.

**References**

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1. What are the structural causes of maculopathy associated with retinoschisis?
□ Defect in protein synthesis
□ Cone-Rod dystrophy
□ Contraction of the posterior cortical vitreous
□ Both A and C

2. Which of the following is NOT a common cause of maculopathy associated with retinoschisis?
□ Autosomal recessive S-cone syndrome
□ Juvenile X-linked retinoschisis
□ Myopic Traction maculopathy
□ Optic disc pit maculopathy

3. Congenital X-linked retinoschisis has an estimated prevalence ranging from which of the following?
□ 1 in 15,000 to 1 in 60,000
□ 1 in 10,000 to 1 in 40,000
□ 1 in 5,000 to 1 in 20,000
□ 1 in 20,000 to 1 in 80,000

4. Which subtype of congenital X-linked retinoschisis is best described as: ‘a schisis that does not extend past what is observed clinically when imaged with OCT’?
□ Type 4 (foveoperipheral)
□ Type 3 (complex)
□ Type 2 (foveolamellar)
□ Type 1 (foveal)
5. Which of the following is not a key factor in determining postoperative success in patients with myopic foveoschisis?
- Foveal status
- Patient gender
- Duration of visual symptoms
- Preoperative best correct visual acuity

6. Myopic foveoschisis typically presents around what age?
- 60
- 50
- 40
- 30

7. The cause of optic disc put maculopathy has postulated to be a result of which of the following?
- Leaky blood vessels
- Cerebrospinal fluid
- Posterior vitreous detachments
- All of the above

8. Regardless of the etiology of schisis, what diagnostic tool has been shown to be the best in monitoring the condition?
- OCT
- Fluorescein angiography
- Fundus autofluorescence
- CT

9. Stellate non-hereditary idiopathic foveomacular reitinoschisis (SNIFR) commonly presents unilaterally and exhibits a stable visual acuity of which of the following?
- 20/15 or better
- 20/20 or better
- 20/40 or better
- 20/60 or better

10. Patients with autosomal recessive enhanced S-cone syndrome exhibit foveoschisis, often bilateral, alongside all the following co-morbidities except:
- Retinal pigment epithelium alterations
- Night blindness from childhood
- Early cataracts
- Glaucoma