Review Article

Insights into X-Linked Retinoschisis: Clinical Characteristics, Diagnostic Approaches and Therapeutic Considerations

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Abstract

X-linked retinoschisis (XLRS) is a bilateral hereditary macular disorder typically seen in males in the first decade of life. Affected males generally present with diminished vision during early school life. The pathogenesis of XLRS involves mutations in the RS1 gene. Typical clinical features include a honeycomb or spoke-wheel-like appearance. SD-OCT, fundus autofluorescence, and electroretinography are important diagnostic tools. Patient education and routine screening help in early diagnosis and management of sight-threatening complications like RD and VH. Genetic counseling is advisable for relatives at risk.

Keywords: X-linked retinoschisis, Hereditary macular disorders, Juvenile retinoschisis.

Introduction

X-linked retinoschisis (XLRS) is a bilateral hereditary macular disorder typically seen in males in the first decade of life. It may also be congenital, presenting as early as three months of age.[1,2] Affected males generally present with diminished vision during early school life with best corrected visual acuity (BCVA) ranging from 6/18 to 6/36. XLRS is one of the most common degenerative retinopathies found in approximately 1 in 5000 to 1 in 20,000 males worldwide.[1]

The slight deterioration in BCVA is seen during the first two decades of life, which is fairly stable until the fifth or sixth decade, when slowly progressive macular atrophy may occur.[3,4] The slow deterioration of vision in early life suggests that there is an optimal window of opportunity for treatment within the first three decades of life.

The pathogenesis of XLRS involves mutations in the RS1 gene which encodes a 224 amino acid protein called retinoschisin, that is expressed in bipolar and photoreceptor cells.[1,5] This protein is secreted into the extracellular space and is believed to play a critical role in cell-to-cell adhesion and neurosynaptic transmission.[1,6] Males are only affected because XLRS has an X-linked recessive pattern of inheritance. Females are mostly carriers and are generally asymptomatic. Some carrier females, however, may show minor changes on multifocal electroretinography (ERG).[1,7]

Clinical Presentation

Young males may present with diminished vision or, nystagmus or strabismus.

Typical clinical features include loss of the foveal reflex, radial striations, microcystic lesions, honeycomb or spoke-wheel-like appearance, pigment mottling, or atrophic patches[4] (Figure 1).

Retinal detachment (RD) may occur in about 5 to 22% of affected individuals. About 4 to 40% of individuals develop vitreous hemorrhage (VH) due to the shearing of retinal vessels that transverse the schisis cavity. XLRS is an important differential in a young boy with VH.

Female carriers are usually asymptomatic but may show peripheral flecks or areas of retinoschisis.

Differential Diagnosis

The presence of retinoschisis in an individual with a positive family history of XLRS establishes the diagnosis. In patients without a significant family history, the diagnosis is difficult.

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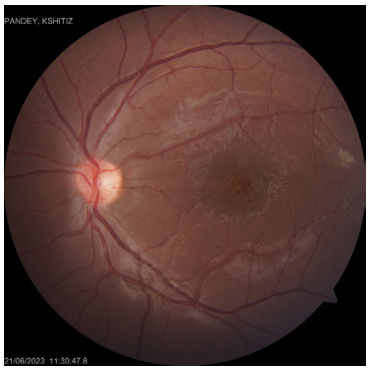

Figure 1: Fundus photo of the left eye of a patient with X-linked retinoschisis showing typical 'honeycomb or spoke-wheel' appearance at the fovea

Important differentials include

Hereditary disorders- X-linked congenital stationary night blindness, Goldmann-Favre vitreoretinal degeneration & enhanced S-cone syndrome, non-syndromic retinitis pigmentosa, Wagner syndrome & erosive vitreoretinopathy

Acquired disorders or disorders of an unknown genetic cause- cystoid macular edema, bilateral amblyopia, degenerative retinoschisis or RD.

Diagnostic Approaches

Role of fundus autofluorescence

Characteristic fundus autofluorescence (FAF) finding in XLRS is a spoke-wheel pattern of high- and low-intensity signals resulting from the displacement of the luteal pigment.[8]

Georgiou *et al*. 2022[9] identified four different patterns on FAF: (1) spoke-wheel pattern, (2) increased central signal, (3) central reduction in signal, and (4) ring of the increased signal (Figure 2).

Role of spectral-domain optical coherence tomography

Schisis involving different retinal layers (inner nuclear, outer plexiform and outer nuclear layer) is seen on Spectral-domain optical coherence tomography (SD-OCT). It is an important investigative procedure in children with hyperopic amblyopia to rule out early stages of XLRS.[10] Traction on retinal layers and schisis, which is not observed on fundus examination, is

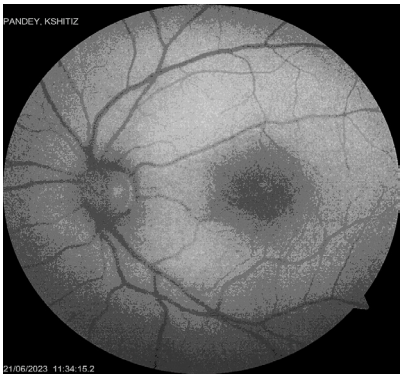

Figure 2: Fundus Autofluorescence of the left eye of a patient with X-linked retinoschisis showing a central reduction in signal

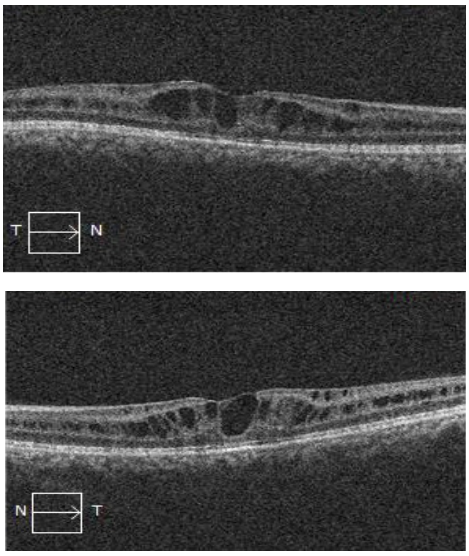

Figure 3: Shows macular schisis involving different retinal layers (inner nuclear, outer plexiform and outer nuclear layer), which extends beyond the foveal area in the right and left eye of a patient with X-linked retinoschisis

well determined on SD-OCT. It is also helpful in detecting retinal schisis extending up to the optic disc area and beyond.[11] The integrity of EZ and the photoreceptor outer layer on SD-OCT may be necessary for choosing optimal candidates for treatment and as potential structural biomarkers in future therapeutic studies[12] (Figure 3).

Role of ERG

It is confirmatory for XLRS. A negative waveform with b-wave amplitude reduction disproportionate to a-wave loss is typically seen.

Treatment Options

Patients are managed conservatively by refraction or amblyopia therapy. For those with severely compromised visual ability, low vision aids can be advised. Complications like RD and VH can be managed surgically by pars plana vitrectomy.

Successful ocular gene therapy has been proven in mouse XLRS models.[13,14] Human trials for gene therapy are currently going on.

Precautions

Patient education and routine screening help in early diagnosis and management of sight-threatening complications like RD and VH. Avoiding head trauma and high-contact sports is also recommended for the prevention of the above-mentioned risks. Genetic counseling is advisable for relatives at risk.

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