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Juvenile Macular Degenerations

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Abstract

In this paper we review three common juvenile macular degenerations: Stargardt disease, X-linked retinoschisis, and Best vitelliform macular dystrophy. These are inherited disorders that typically present during childhood, when vision is still developing. They are sufficiently common that they should be included in the differential diagnosis of visual loss in pediatric patients. Diagnosis is secured by a combination of clinical findings, optical coherence tomography (OCT) imaging, and genetic testing. Early diagnosis promotes optimal management. While there is currently no definitive cure for these conditions, therapeutic modalities under investigation include pharmacologic treatment, gene therapy, and stem cell transplantation.

Introduction

Patients with a juvenile macular degeneration (JMD) may present initially to a neurologist or neuro-ophthalmologist with poor vision or nystagmus. Age at presentation is typically early childhood, but older or younger is possible. On the other hand, a child with JMD may be asymptomatic and the eye or vision problem may be identified on a pediatrician's or school screening exam. Family history may lead to identification and diagnosis, as each of the JMDs is a heritable condition.

The macula is a region of the central retina that represents approximately 5% of the total retinal area. Within the macula is a specialized region, the fovea, in which cone photoreceptors are packed tightly in an approximately 4° to 5° (1.5 mm) rod-free zone. The fovea is highly specialized, and mediates fine visual acuity.

Development of the fovea starts preterm and continues post-term into adolescence.^{1; 2; 3} The macula, including the fovea, is the last retinal region to reach maturity.^{2; 4; 5; 6} The

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specialized neurovascular structure makes this central retinal region vulnerable to disease. The types of disease that may affect the pediatric retina include the JMDs, developmental anomalies, and retinal disease in the setting of metabolic disorders. Among the more frequently seen developmental anomalies is foveal hypoplasia, as in albinism⁷ and *PAX6* gene mutation.⁸ Among the more frequently seen metabolic disorders is cobalamin C type methylmalonic aciduria and homocystinuria.⁹

There are some other uncommon macular degenerations including some forms of Leber congenital amaurosis^{10; 11; 12}, North Carolina macular dystrophy¹³, Sjögren Larsson syndrome¹⁴, Alagille syndrome¹⁵, and juvenile neuronal ceroid lipofuscinosis.¹⁶

The common juvenile macular degenerations are Stargardt disease, X-linked retinoschisis, and vitelliform macular dystrophy.^{17; 18}

Although each of these is much less common than strabismus or amblyopia, pediatric macular disorders affect a substantial number of children in the pre-school and school years and must be included in the differential diagnosis of visual loss in pediatric patients. The awareness of these conditions promotes an early diagnosis and optimal management.

Stargardt Disease

Stargardt disease (STGD) is the most common juvenile macular degeneration, with a prevalence of 1 in 10,000.¹⁹ A frequent cause is biallelic mutations in the *ABCA4* gene, which encodes for a rim protein located in the outer segment of the photoreceptors, both rods and cones; the protein is a transporter of vitamin A derivatives.²⁰ The malfunction of this transporter leads to accumulation of all-*trans* retinal, which results in increased concentration of a toxic byproduct, N-retinylidene-N-retinyl-ethanolamine (A2E), which is a major component of lipofuscin. Lipofuscin accumulates in the retinal pigment epithelium (RPE), causing RPE cell dysfunction, and consequent photoreceptor death.^{21; 22}

ABCA4 disease is inherited in an autosomal recessive manner. *ABCA4* is a large gene.²³ It is highly heterogeneous and many disease-causing variants have been described.²⁴ The clinical presentation is also heterogeneous, with a spectrum of conditions: maculopathy, generalized cone-rod dystrophy, and increased susceptibility to age related macular dystrophy. Other less frequent genetic causes of STGD are *PROM1*²⁵ and *ELOVL4*.²⁶ *PROM1* is autosomal recessive and *ELOVL4* is autosomal dominant.

Regardless of the genetic cause, STGD usually presents as bilateral symmetric decrease in visual acuity during the first or second decade. Generally speaking, early-onset progresses to lower final acuity (20/200)^{27; 28}; later onset has a better prognosis, and foveal structure and function may be preserved.^{29; 30; 31}

STGD is notorious for presenting with poor vision before any ophthalmoscopic changes are visible. The child may mistakenly be labelled a malingerer. Early signs by ophthalmoscopic examination may show atrophy of the RPE at the fovea (Fig. 1B) and flecks in the macula that may become more widespread over time. Flecks correspond to deposits of lipofuscin in the RPE and in later stages can be seen as localized RPE atrophy with foveolar reflex

blunted or absent. However, a third of the children with STGD do not have flecks on initial presentation.³²

Visual acuity is not the only visual function affected in STGD. Deficits in color vision³³ and central visual field³⁴ progressively increase typically accompanying a decrease in visual acuity.

Fluorescein angiography (FA) demonstrates that the accumulation of lipofuscin in the RPE block the choroidal fluorescence, producing a dark or silent choroid. This sign is seen in approximately 75% of cases.^{28; 35}

Both spectral-domain optical coherence tomography (SD-OCT) and fundus autofluorescence (AF) may show changes in the retina that are not identifiable by ophthalmoscopy and should be used in the initial evaluation.

The main OCT finding is a central loss of outer retinal layers (Fig. 2B); in the early-onset type, thickening of the external limiting membrane has been described.³⁶ We use OCT in our evaluation of young children with possible STGD because it is non-invasive and image acquisition is quite quick.

AF is abnormal in STGD. Flecks are initially hyperfluorescent, reflecting the accumulation of lipofuscin in the RPE. With the progression of the RPE atrophy, the flecks become hypofluorescent. The pattern of the AF at the presentation of the disease is related to the enlargement of the retinal atrophy over time.^{37; 38} AF has replaced the use of fluorescein angiography for evaluation of patients with suspected STGD.

Electrophysiological studies further characterized peripheral and central function in patients with STGD. Full field electroretinography (ffERG) results can be used to characterize peripheral function, while multi-focal electroretinography (mfERG) results can be used to characterize central function.^{39; 40; 41}

Several interventions for STGD have been proposed, including light deprivation⁴², regulation of Vitamin A^{43; 44; 45; 46}, gene-replacement therapy⁴⁴, and human stem cell transplantation.^{44; 47} Information about current clinical treatment trials can be accessed at [ClinicalTrials.gov](https://clinicaltrials.gov).

X-Linked Juvenile Retinoschisis

X-linked juvenile retinoschisis (XJR) is the leading inherited cause of macular degeneration in boys, with an estimated prevalence of 1 in 5,000 to 25,000 and accounts for approximately 5% of all childhood-onset, inherited retinal dystrophies.⁴⁸

XJR is caused by mutation in the *RS1* gene, which is located on the short arm of the X-chromosome. *RS1* encodes retinoschisin, an extracellular binding protein which is secreted by retinal cells and characterized as a disulphide-linked octamer.⁴⁹ Although all major classes of adult retinal neurons (with the possible exception of horizontal cells) express retinoschisin, *RS1* mRNA is expressed most abundantly in photoreceptor inner segments and in bipolar cells⁵⁰, and serves as an adhesion molecule to maintain the structural and

functional integrity of the retina, including the first synapse, that is, the synapse between photoreceptors and bipolar cells. This is a clue that the first synapse is likely critical to XJR pathology.⁵¹

There are three ways by which *RS1* mutations affect the function of retinoschisin.⁵² First, they alter the three-dimensional structure of the protein. Second, they impair the protein's ability to connect cells together (cell adhesion). And third, they cause the protein to be misplaced (i.e., trapped) within the retinal cells.

XJR affects young boys causing worsening vision over time, typically between the first and the second decade. It is usually bilateral; the ophthalmoscopic features may be asymmetric. The disease is clinically characterized by the formation of cavities within the retina, visible by ophthalmoscopy. The main clinical features are tiny splits within the retinal layers and, in the macula, a spoke-like pattern of cystic spaces between the outer plexiform and nuclear layers (Fig. 1C).⁵³ Peripheral cystic spaces are associated with the formation of vitreous veils. These retinal changes put the boy at risk for impaired peripheral vision, vitreous hemorrhage, retinal holes, retinal detachment, progressively worsening vision, and even blindness.⁵⁴

The affected boys may present with moderately high hyperopia. The decrease of visual acuity may also be associated with a defect in color vision function with or without predominant (red-green) axis.⁵⁵

OCT allows visualization of the macular and extra-macular regions to evaluate the presence of cystic spaces within the retinal layers (Fig. 2C). Some studies have shown that the outer plexiform layer (OPL) and inner nuclear layer (INL) are most affected.^{56; 57; 58; 59} Macular thickness (measured by OCT) may be used to monitor changes in the cavities. Retinal thickness is often asymmetric between the eyes, and not necessarily related to the visual acuity.⁶⁰ OCT is also useful to detect vitreo-retinal traction.^{61; 62}

In addition to the formation of cavities within the retinal layers, which is the clinical hallmark of XJR, diminished transmission of the visual signal across the first synapse, between the photoreceptor and bipolar cell, is recognized as an important element of XJR pathology.⁶³ This diminished transmission presents, electroretinographically, as a waveform with relatively greater attenuation of post-receptor responses (*b*-wave) than of photoreceptor responses (*a*-wave).⁶⁴ The cornea-positive *b*-wave is reduced disproportionately to the cornea-negative *a*-wave, resulting in a “negative ERG” in the early stage of XJR.

The biochemical mechanism of retinoschisin (RS) is not completely known. Treatment options continue to be evaluated, including both gene replacement and carbonic anhydrase inhibitors (CAIs). To date, all data pertaining to the efficacy of gene replacement in XJR has come from studies in the *RS1* “knockout” mouse^{65; 66; 67; 68}, but retroviral gene-replacement therapies in humans are currently in Phase I/II clinical trials (see [ClinicalTrials.gov](https://clinicaltrials.gov)). A CAI trial is also ongoing (see [ClinicalTrials.gov](https://clinicaltrials.gov)). CAIs may be helpful in decreasing the cavities and retinal thickness.⁶⁹ XJR eyes respond to CAIs with reduction in the volume of the cavities but show little improvement in acuity; it is unlikely that CAIs would provide direct treatment of the fundamental disease process. It is known that CAIs are effective therapies

for cation channelopathies, such as primary hypo- and hyperkalemic periodic paralysis (PPP).⁷⁰

Best Vitelliform Macular Dystrophy

Best vitelliform macular dystrophy (BVMD) is an early onset maculopathy with a characteristic deposit of a yellowish material, like egg yolk, in the macula.⁷¹

BVMD is caused by mutation in the *BEST1* gene located on chromosome 11q13.⁷² This gene is also known as *VMD2* gene and encodes a protein, bestrophin-1⁷³, located in the basolateral membrane of the retinal pigment epithelial (RPE) cells. This protein is a calcium sensitive chloride channel. The effect of the mutation on this protein is not completely understood, but it is associated with accumulation of lipofuscin in the RPE.

BVMD is inherited in an autosomal dominant mode with incomplete penetrance. The mutations produce variable phenotypes, including an adult-onset vitelliform dystrophy.⁷⁴

BVMD is usually a bilateral condition, but some cases with unilateral disease have been reported.⁷⁵ The presentation is highly variable, but typically presents during the first or second decade, with worsening of visual acuity. BVMD can be completely asymptomatic and discovered as an incidental finding on examination of the eyes. A slow decline in visual acuity may occur over the years.⁷⁶

Ophthalmoscopic findings vary as the disease progresses.⁷⁷ There are three main stages that characterize the disease: the vitelliform stage, the pseudohypopyon stage, and the vitelliruptive stage. In the vitelliform stage, the cyst is a dome-shaped deposit of vitelliform material under the macula. In the pseudohypopyon stage, the cyst is both vitelliform material and clear fluid. In the vitelliruptive stage, the cyst is both vitelliform material and clear fluid but in a mottled and disorganized distribution (Fig. 1D). In later stages chorioretinal atrophy may be present. Some patients develop choroidal neovascularization under the lesions.

OCT shows both hyperelective and hyporelective areas in the RPE and the ellipsoid zone (EZ). Hyperelective areas correspond with lipofuscin deposits seen by ophthalmoscopy. Hyporelective areas are “optically empty” spaces that are located between the RPE and the EZ (Fig. 2D). In later stages, loss of the EZ and thinning of all the retinal layers may be seen.^{78; 79}

A range of autofluorescence (AF) patterns is seen, including normal, hyperfluorescence, and hypofluorescence. Lipofuscin deposits correspond with areas of high AF.⁷⁸ The distribution of AF may be patchy, multifocal, or spoke-like.⁸⁰

A classical finding in patients with BVMD is abnormal electrooculogram (EOG), characterized by an absent or significantly decreased light rise (Arden ratio less than 1.5).⁸¹ Today, a combination of clinical findings, OCT results, and genetic testing secures the diagnosis.

BVMD typically progresses with a slow decrease in the visual acuity. If an abrupt decrease in visual acuity occurs, development of a neovascular choroidal membrane should be

suspected. The use of anti-vascular endothelial growth factor agents have been used in the treatment of this complication.⁸² Stem cell transplantation is also under investigation.⁷¹ (See ClinicalTrials.gov.)

Conclusion

We have reviewed three common juvenile macular degenerations: Stargardt disease, X-linked retinoschisis, and Best vitelliform macular dystrophy. Each condition typically presents during childhood, when vision is still developing. The juvenile macular degenerations are sufficiently common that they should be considered in the differential diagnosis of visual loss in childhood.

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Figure 1.

Fundus photos showing a normal macula and examples of the typical macular findings in common juvenile macular degenerations. A) Normal macula. B) STGD showing atrophic macular region. C) XJR showing the classical “spoke-like” pattern in the macula. D) BVMD showing vitelliform material and clear fluid in a mottled distribution in the macula. STGD: Stargardt’s disease; XJR: X-linked retinoschisis; BVMD: Best vitelliform macular dystrophy

Figure 2.

Spectral domain ocular coherence tomography (SD-OCT) scans showing a normal macula and examples of the typical macular findings in common juvenile macular degenerations. A) Normal macula showing all of the retinal layers. B) STGD showing absence of the outer retinal layers, with a significant thinning at the level of the fovea. C) XJR showing the presence of cystic spaces within the retinal layers. D) BVMD showing a heterogeneous material with hyperelective areas and some optical empty areas under the fovea. STGD:

Stargardt's disease; XJR: X-linked retinoschisis; BVMD: Best vitelliform macular dystrophy

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