Clinical Manifestations of Retinoschisis in a consanguineous family: a case report and review of literature

Ngoy KD1, Katumba NW2*

1Ariel Clinic, Kinshasa, Democratic Republic of Congo
2Department of Life Sciences, College of Agriculture and Environmental Sciences, University of South Africa (UNISA), Johannesburg, South Africa

Summary

Retinoschisis is the splitting (schisis) of the retinal layers leading to visual impairment and visual loss in a severe form of the condition. Causes are genetic mutations in variable expression, with X-linked recessive pattern being the most predominant. While males are the most vulnerable during the first decade of life, females are carriers and can also suffer to a lesser extent from this condition, which can be single or associated with coloboma. Consanguinity is the most prevalent cause in either retinoschisis alone or associated with coloboma. Mutations are numerous, but homogeneous mutations in the RS1 gene are the most consistent in this recessive pattern. No treatment is available reason why the accent is on prevention against, at least, consanguineous marriages. Boys are more affected than girls, unlike in this reported case similarly to three females from the same family affected with frameshift mutations in a Colombian sturdy.

Keywords: Retinoschisis-gender-pathogenesis-outcomes

Introduction

Neural plate develops in various steps as depicted in Carnegie classification until reaching the neural tube's complete closure between 26-28th day post fecundation1. During embryogenesis, eye development can be altered alone or in a syndromic fashion, producing optic coloboma between 7mm and 14mm stages2. When coloboma, defined as a closure defect of chorioid or optic fissure, is associated with anophthalmia, it usually displays a wide range of malformations leading to 10-15% of congenital blindness child population2,3. We report a case of a patient born in a consanguineous family and presenting with retinoschisis. The present case is an unusual case of retinoschisis in a young female patient (figure 1), similar to another rare report of three females from the same family affected with frameshift mutations in a Colombian sturdy4.

Case Observation

An eight-year-old girl was brought to our Out-Patients Clinic by her mother for the loss of nocturnal vision accompanied by pain for one year. Her past medical history has a history of consanguinity, and her siblings were on treatment for pulmonary tuberculosis. Clinical examination was unremarkable. On ophthalmological assessment, she had a visual acuity of 03 on the left and 02 on the right eye. Fundus examination showed the following: “appearance of bilateral macular hole, whitish speckled with black dots on the periphery of both eyes giving the appearance of retinitis pigmentosa” (figure 1).

Discussion

Retinoschisis, also known as macular degeneration, is more common in males than in females because of its X-linked chromosome5, even though females are carriers4. It is recessively inherited and characterised by a bilateral...
Figure 1: bilateral macular hole, whitish speckled with black dots on the periphery

Figure 2: Optical coherence tomography (OCT) showing cystoid macular oedema and thinning of the outer nuclear ellipsoid (disappeared in the periphery).

Figure 3: The vessels and the epiretinal membrane were normal.

Laboratory findings were as follows: WCC:6,800/mm, neutrophils:61, lymphocytes:24, monocytes:10, eosinophils:5 and sedimentation rate:36mm/h. Serology tests were also performed: VDRL: 0.234 (<0.9), TPH<1/80, CEA:3.17(<5ng/ml) and IDRT:10mm (positive).

presentation and progressive vitreoretinal atrophies. According to Lesch and colleagues, its prevalence is between 1:5,000 and 1:25,000, whereas optic coloboma prevalence is approximately 2 to 14 per 100,000 live births.

Pathogenesis

The pathogenesis of this condition is genetically dependent on RS1 gene mutations (Xp22.2-p22.1), the only known structure so far, identified in 1997 by Sauer and colleagues. Many reports have highlighted the role of the RS1 gene as the genetic basis of this disease. RS1 gene encodes retinochisin, a secretable extracellular adhesion protein (i.e., a 224 amino-acid protein) present in
photoreceptors in bipolar cells and which is involved in cell adhesion cell-cell interactions on membranes surfaces. This gene has three components: an RS1 domain (RS1D, 39AA) which has a secretory layer (LS, 23 AA); a discoidin domain and a C-terminal segment (5AA). Therefore, the fundamental structure of the RS gene is the discoidin domain (157 AA), which is crucial for the normal development of the retina. Hence, any lesion on that structure will lead to retinal splitting in its layers. This observation found credence in Molday and colleagues’ report. From their experimental studies, mutations in the discoidin domain cause “severe protein misfolding and retention in the endoplasmic reticulum (ER)”, in addition to signal sequencing disorders that lead to aberrant proteins synthesis and mutations in the surrounding discoidin domain, causing defective disulphide-linked subunit assembly. According to Slavonitek and colleagues’ findings, mutations, either monogenic or chromosomal, are responsible for 25-30% of cases of retinoschisis, leaving the remaining unresolved questions to further research. In that regard, we failed to determine the genetic basis in this patient in identifying mutations in the RAX gene, which are the genetic etiology. The RAX gene is known to house the phenotype in eye development. It is a ‘paired-like homeobox-containing gene initially expressed in the anterior region of developing embryos and later in the ventral hypothalamus and retina. Based on this anatomic specification, Xiu and colleagues advance by quoting Pan and colleagues’ animal experiments on Xenopus and Zebrafish, that alterations on the RAX gene in the early embryonic phase led to microphthalmia or anophthalmia. In contrast, alterations in the mature retina could induce photoreceptor degeneration. Clinical characteristics are mostly blurred vision and a reduction in visual acuity with sometimes loss of peripheral vision that may lead to blindness in severe form.

From George and colleagues’ findings, retinoschisis is often clinically associated with strabismus, nystagmus, axial hyperopia, and defective colouration, also known as red-green dyschromatopsia, and fovea ectopy. The disease commonly affects young boys (<10 years) who then will present with visual disturbances or reading difficulties with mild to a severe loss of visual acuity.

Clinical features

The disease is characterised by splitting the macula layers (or schisis) and microcystic changes of the macula area as early as the third month of life and most commonly during the first decade of life. These changes give a spoke-wheel pattern with different forms, among which the severe form leads to blindness consequent to full retinal detachment. According to Roesch and colleagues, the more advanced stage manifests with vitreous haemorrhage, retinal detachment, and neurovascular glaucoma, leading to blindness.

Diagnostic investigations

High suspicion index in the presence of a young infant male patient with complaints of visual acuity disturbance should raise the diagnosis of retinoschisis, like in the Hungarian study on X-linked young retinoschisis. So, in assessing these patients, an ophthalmologic examination should include a few investigations to ascertain this diagnosis: the fundus examination, the electroretinogram (ERG) and the optical coherence tomography (OCT). Fundoscopy is not specific because it can be normal or abnormal, showing “a-waves characteristics of photoreceptor function or even more often, b-waves that originate from the retinal cells activity”.

Nevertheless, it is worth recalling significant findings like in fundoscopy. As described by Tantri and colleagues, “radially oriented intraretinal foveomacular cysts present in the spoke-wheel pattern, with the absence of foveal reflex in most cases, whereas in some other cases, one can see bilateral peripheral retinoschisis in the inferotemporal part of the retina”. Besides these investigations, genetic screening is mandatory to determine the molecular and gene mutations (e.g., missense mutations, insertion mutations, or frameshift). Molecular analysis through DNA extraction on peripheral blood of family members, direct sequencing to amplify the axons components via polymerase chain reaction (PCR) and haplotype analysis using microsatellite markers will help in identifying the common haplotypes, the recurrent mutations and eventually the novo-mutations.

Altogether, these investigations assist in the determination of different lesions encountered in this pathology like foveal schisis on fundoscopy, waves characteristics (a and b-waves) on ERT and macular laminar splitting on OCT. In this present case report, OCT was used and confirmed the presence of macular schisis.

The specific findings were “cystoid macular oedema, thinning of the outer nuclear ellipsoid disappeared in the periphery (figure 2). The vessels and the epiretinal membrane were normal” (figure 3). They were slightly different from the ones described elsewhere, such as nerve fibre (NFL), ganglion cell (GCL), inner nuclear (INL), outer plexiform (OPL) and photoreceptor layers (PRL).

The next step would be to proceed with the genetic screening when we get a sizable sample because one single case is not sufficient to conclude how frequently this pathology may be in our population.

Conclusion

Retinoschisis is an uncommon genetic disease characterised by vision reduction and even vision loss in severe cases, like in this report. The central structure is retinochisin, an amino acid protein encoded by the RS1 gene
on chromosome Xp22.2-22.1. Notwithstanding the lack of genetic screening, this case raises the need to systematically undertake molecular analysis to describe specific variants in Congolese patients with XLRS and correlate these findings with clinical manifestations.

References


10. Wu WW, Molday RS. Defective discoidin domain structure, subunit assembly, and endoplasmic reticulum processing of Retinoschisin are primary mechanisms responsible for X-linked retinoschisis. Journal of Biological Chemistry. 2003 Jul 25;278(30):28139-46.


