Molecular characterization of a rare phenotype of X-linked retinoschisis with angle-closure glaucoma

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A 11-year-old boy presented with complaints of blurred vision and on evaluation was found to have X-linked retinoschisis (XLRS) with angle-closure glaucoma. Clinical and genetic evaluation of first-degree family members was done. His brother had a milder form of XLRS with shallow anterior chamber. Topical dorzolamide 2% and timolol 0.5% were used to control intraocular pressure. Genetic analysis revealed a novel three base pair deleterious mutation (c. 375_377 del AGA) in exon-5 of the RS1 gene in three members of the family.

Key words: Angle-closure glaucoma, dorzolamide, foveoschisis, *RS1* mutation, X-linked retinoschisis

X-linked retinoschisis (XLRS) is an inherited disorder characterized by splitting within the neurosensory retina. It is usually detected at school age.[1] According to Deutman, foveoschisis is characteristic of XLRS and occurs in 98%–100% of them, while Kellner *et al*. reported that though macular changes may be seen in all, the typical foveoschisis is found

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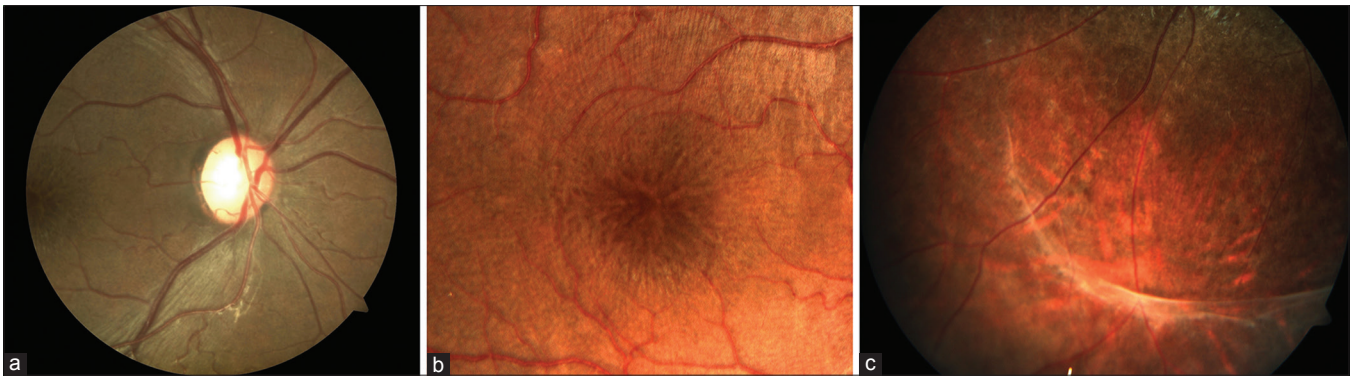

Figure 1: Images of the proband of right eye. (a) Fundus photograph showing glaucomatous disc of cup-disc ratio 0.7:1. (b) Spoke-wheel appearance of macula (foveoschisis). (c) Inferotemporal peripheral retinoschisis

only in 70%. Peripheral retinoschisis is seen in up to 50% of the patients.[2,3] Other ocular manifestations of XLRS include hypermetropia, strabismus, neovascularization, vitreous veils, vitreous hemorrhage, retinal detachment, etc.[1] More than 196 mutations of *RS1* gene in chromosome Xp22.2 have been shown to contribute to XLRS.[4] The disease phenotype is highly variable in that even patients of same genotype manifest different severities. The glaucoma usually associated with XLRS is the neovascular type.[5] We report here an uncommon association of XLRS with angle-closure glaucoma.

Case Report

A 11-year-old boy presented with slowly progressive decrease in vision both eyes (BE) over 1 year. On examination, his visual acuity (VA) was 6/18 BE with no further improvement on refraction (RE + 1DC@180° and LE-1DC@75°). Baseline intraocular pressure (IOP) was 30 and 32 mmHg, pachymetry 484 and 490µ in right eye (RE) and left eye (LE), respectively. Slit-lamp biomicroscopy showed shallow anterior chamber (Van-Herick II) and occludable angles on gonioscopy BE. A +90D fundus examination revealed cup-disc ratio (CDR) of 0.7 and 0.8:1 in RE and LE, respectively, with spoke-wheel appearance of macula BE. Indirect ophthalmoscopic examination revealed bilateral inferotemporal retinoschisis [Fig. 1]. Macular optical coherence tomography (OCT) showed multilevel foveoschisis in BE with central macular thickness (CMT) of 406 and 337µ RE and LE, respectively [Fig. 2]. Biometry was done to rule out lens-induced angle-closure, which revealed the axial lengths (AL) to be 21.43 and 22 mm, lens thicknesses 3.30 and 3.51 mm, anterior chamber depths 2.96 and 2.61 mm in RE and LE, respectively.

The child was started on a combination of topical dorzolamide and timolol maleate. After 1-week, his IOP was 12 mmHg BE. The family members of the patient were screened. His elder sibling (13-year-old male) had an unaided VA of 6/6 RE and 6/60 LE with no further improvement on refraction. Examination of the sibling showed BE shallow AC with occludable angles and peripheral retinoschisis, with macular spokes in LE. However, his IOP was 14 mmHg and CDR 0.3:1 with healthy rim BE. His refraction showed RE emmetropia and LE + 3DS. His AL was 22.53 and 21.18 mm, pachymetry 580 and 579µ in RE and LE, respectively. Macular OCT showed very few paracentral schitic cavities in LE, and CMT 332µ, not justifying the visual loss. Hence, a diagnosis

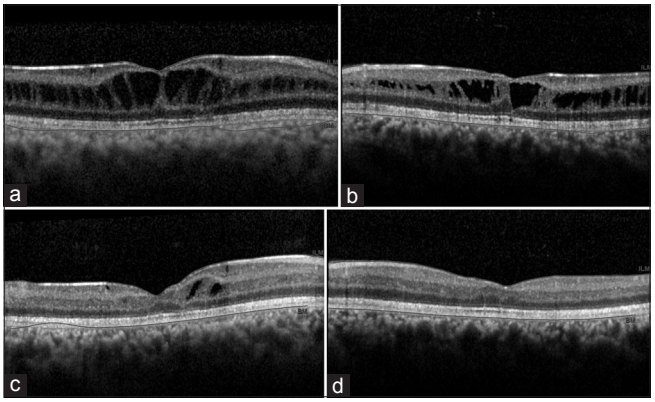

Figure 2: Macular OCT, (a and b) showing baseline multilevel foveoschitic cavities in RE and LE, respectively. (c and d) showing significant decrease in schitic cavities and central macular thickness of RE and LE respectively, after 6 weeks of topical dorzolamide therapy

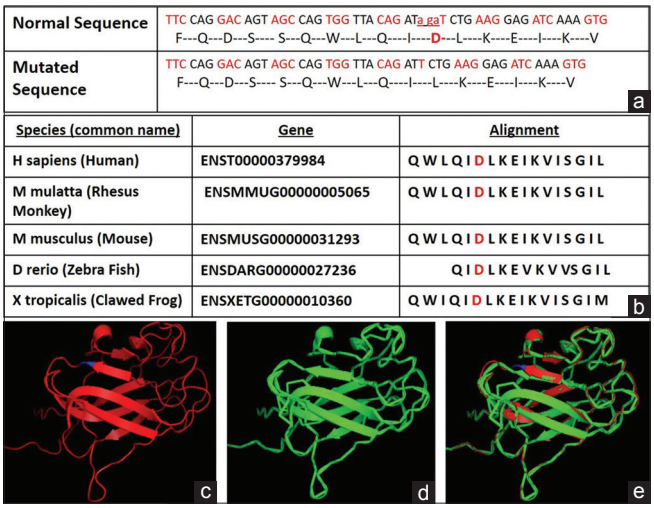

Figure 3: *In silico* and structural analysis of RS1 protein (a). Homozygous deletion of nucleotides 'AGA' leading to frameshift disrupting aspartic acid codon thereby deleting 'D' from mutated protein. (b). Multiple sequence alignment of *RS1* nucleotide sequences in different species showing conservation of 'D' (highlighted) in all orthologs (c, d and e) show computational analysis of *RS1* delAGA mutation. (c). Normal protein monomer showing amino acid 'D' (blue) with disrupted codon due to AGA deletion. (d). Mutant protein with absent 'D' amino acid. (e). Superimposed structural analysis of normal and mutant protein

of BE XLRS and angle-closure suspect with LE anisometropic amblyopia was made. Ocular examination of the father also showed LE anisometropic amblyopia, while the mother's eyes were normal.

After 6 weeks of medication, the proband's IOP was 12 mmHg BE and CMT decreased to 249 and 243μ in RE and LE respectively with significant collapse of the schitic cavities [Fig. 2]. However, there was no change in best corrected VA.

An informed consent was taken from the parents and peripheral venous blood sample was drawn for molecular investigations from both children and parents. Genomic DNA was extracted using standard salting-out protocol and subjected to polymerase chain reaction amplification of RS1 gene using 70–100 ng DNA, 1.25mM $MgCl_2$, 0.25 mM of each of the dNTPs (Invitrogen), 5 μM of each primer and 0.5 units of Taq Polymerase (Invitrogen) in 25 μl volume mixture using thermocycler ABI 9700 (Applied Biosystems).

All the amplified products were purified using Qiagen kits (Qiagen, GmbH), sequenced using BigDye Terminator Mix version 3.1 (Applied Biosystems), and analyzed on ABI-3100 Genetic Analyzer. The nucleotide sequences were compared with the published cDNA sequences of RS1 (GenBank accession number ENSG00000102104) gene.

Direct sequencing of RS1 gene revealed a novel three base pair deletion (c. 375_377 del AGA) in exon-5 in three family members [Fig. 3]. The proband and his brother were hemizygous, while their mother was heterozygous for the mutation. The father had a normal genotype. Assessment for pathogenicity using MutationT@ster predicted the mutation to be deleterious. Structural analysis revealed that the 'AGA' deletion led to disruption of the downstream codon, resulting in protein lacking amino acid 'D' at position 126. Sequence alignments of *RS1* revealed the D residue to be highly conserved over several species [Fig. 3].

Discussion

Peripapillary retinoschisis in acquired optic nerve head (ONH) cupping has been shown in a spectrum of glaucoma patients.[6] Advanced glaucomas have also been associated with macular schisis.[7,8] The pathophysiology attributed is liquid vitreous seeping through holes in the thin tissue overlying ONH cup, causing peripapillary retinal edema, and subsequently schisis. This fluid flow is accentuated by increased IOP.[7,8] However, the above mechanism was not the cause of foveoschisis in our patient. The sibling also showed foveoschisis but did not have glaucoma. Likewise, the peripheral retinoschisis in the proband could not have been due to glaucoma.

The presence of occludable angles and angle-closure glaucoma at such a young age seems to be genetically linked to *RS1* mutations. Low *et al*. reported a case of refractory angle closure glaucoma with XLRS in a 39-year-old man, that was treated by lens extraction.[9] Sonmez and Ozcan described a case of foveoschisis with angle-closure glaucoma secondary to nanophthalmos (axial length ≈ 16 mm) and cystinosis.[10] The anterior chamber depth, lens thickness, and axial length in our patient did not justify lens-induced glaucoma or nanophthalmos. Huang *et al*. described recurrent glaucoma in a case of retinoschisis with R102W *RS1* mutation.[11] However, the authors did not characterize the nature of the glaucoma in their patient. Pimenides *et al*. found that there was no correlation between disease severity and *RS1* mutation type.[12] Even within families, the severity varied and different patients of similar age and same mutation had varied phenotypic characteristics.

Topical carbonic anhydrase inhibitors like dorzolamide 2% have been shown to be beneficial in cases of XLRS, causing significant reduction in foveal cystic cavities.[13] Our proband, after 6 weeks of dorzolamide usage, showed significant reduction in the central macular thickness of both eyes (RE 39% and LE 29%), which sustained until last follow-up.

Conclusion

In conclusion, this case highlights the unusual association of XLRS with angle-closure glaucoma underscored by a novel *RS1* deleterious mutation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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