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X-linked Juvenile sRetinoschisis in a Young Female

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ABSTRACT

X-linked juvenile retinoschisis has recessive inheritance which occurs due to RS1 gene mutation. We report an instance in a female managed with systemic and topical carbonic-anhydrase inhibitors.

18-year female presented with bilateral blurred vision for two years. Best corrected vision was 6/24 right eye and 6/12 left eye. Fundus examination, ocular coherence tomography and fundus fluorescein angiography supported the diagnosis. Systemic and topical carbonic-anhydrase inhibitors were advised and followed for six months with scrutinization of possible adverse drug reaction.

Juvenile retinoschisis being rare among females, prompt diagnosis and management helps for the restoration of the vision and foveal anatomy.

Keywords: Carbonic anhydrase inhibitors; female; retinoschisin ; X linked juvenile retinoschisis.

INTRODUCTION

X-linked juvenile retinoschisis (XLRS), was incipiently described by Haas in 1898, while X-linked inheritance was recognized by Mann and Mac-Rae in 1938.[1] It has prevalence of 1:5000-1:25000, exclusively in males. However, being exceedingly rare in females, only handful of cases have been reported.[1,2] Formerly, XLRS was regarded irremediable.[2] However, recent reports shows abatement in approximately two-thirds of patients when treated with carbonic anhydrase inhibitors (CAIs).[1,3-5]

We report a rare case of XLRS in a female diagnosed clinically and further supported by ocular coherence tomography (OCT)/ fundus fluorescein angiography (FFA). Patient was observed for visual acuity (VA) and central macular thickness (CMT) after treatment with systemic and topical CAIs over a duration of six months. We have also included a brief review of literatures.

CASE REPORT

An 18-year female with unremarkable medical history presented to vitreoretina clinic with blurring of central vision both eye (BE) for two years which was gradual in onset and progressive. No history of previous ocular trauma and any other inflammatory or infectious ocular conditions. There was lack of consanguity in the family. Older male sibling along with three generations in family pedigree remained unaffected which was confirmed upon proper history taking and posterior segment ocular examinations. At presentation, VA was 6/36 right eye (RE) and 6/60 left eye (LE). Anterior segment evaluation of BE were within normal limits.

Direct fundus evaluation revealed well circumscribed cart wheel like maculopathy of radiating cystoid spaces in macular area BE (Figure 1). Intraocular pressure was 13mm Hg RE and 15mm Hg LE. Spectral domain OCT (Topcon 3D OCT, 2000 series Japan) demonstrated splitting at the level of nerve fiber layer in the foveal area in BE (Figure 1). Subsequently, FFA was performed which showed cystic changes with hypo-fluorescence in all phases at the foveal area BE. Fluorescein leakage or staining of the macula was not appreciated in any phases (Figure 2).

Patient was started with oral tab acetazolamide 500mg BD for 2 weeks along with gtt dorzolamide 2% BE BD. Then patient was followed up at 1st and 2nd week after starting medications and meticulous supervision of the possible adverse drug effects such as paresthesia, nausea, diarrhea, anorexia, metallic taste were noted along with assessment of VA, BCVA (Table 1) and CMT measurements (Table 1, Figure 3). At 2nd week presentation, oral acetazolamide was ceased and continued only with gtt dorzolamide 2% BE BD and instructed to follow up after 2 weeks.

By the end of 4th week her BCVA was 6/12 BE with

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rebound increase in CMT BE when compared with baseline. Patient was then followed up at 6th month of continuing gtt dorzolamide 2% BE and required examinations were performed, which exhibited improved BCVA as correlated with baseline, that is in BE visual acuity achieved was 6/12 with -0.50 diopter sphere nevertheless CMT was slightly increased in RE and reduced in LE in contrast to baseline (Table 1). However, at the end of 6th month of therapy, patient was symptomatically improved and no adverse effects of the medications used was observed.

Table 1. VA, BCVA and CMT of BE at different examinations.

	Baseline			1st week			2nd week			4th week			6th month		
	VA	BCVA	CMT (µm)	VA	BCVA	CMT (µm)	VA	BCVA	CMT (µm)	VA	BCVA	CMT (µm)	VA	BCVA	CMT (µm)
RE	6/36	6/24	378	6/12	6/9	398	6/24	6/12	410	6/24	6/12	461	6/24	6/12	438
LE	6/60	6/24	488	6/36	6/12	390	6/60	6/18	380	6/60	6/12	490	6/60	6/12	445

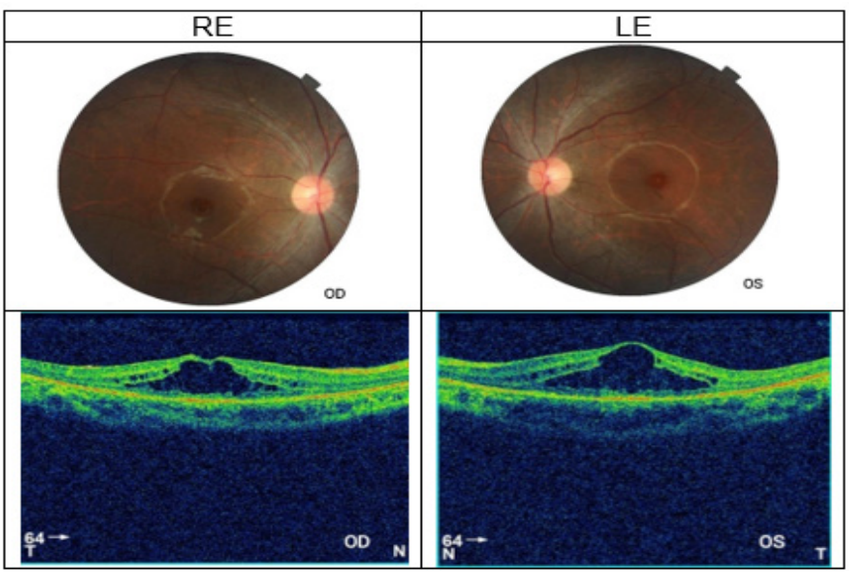

Figure 1. Fundus image showing spoke wheel like maculopathy BE at presentation. Baseline OCT image showing cystic spaces in middle retinal layers in foveal area with splitting in nerve fiber layer.

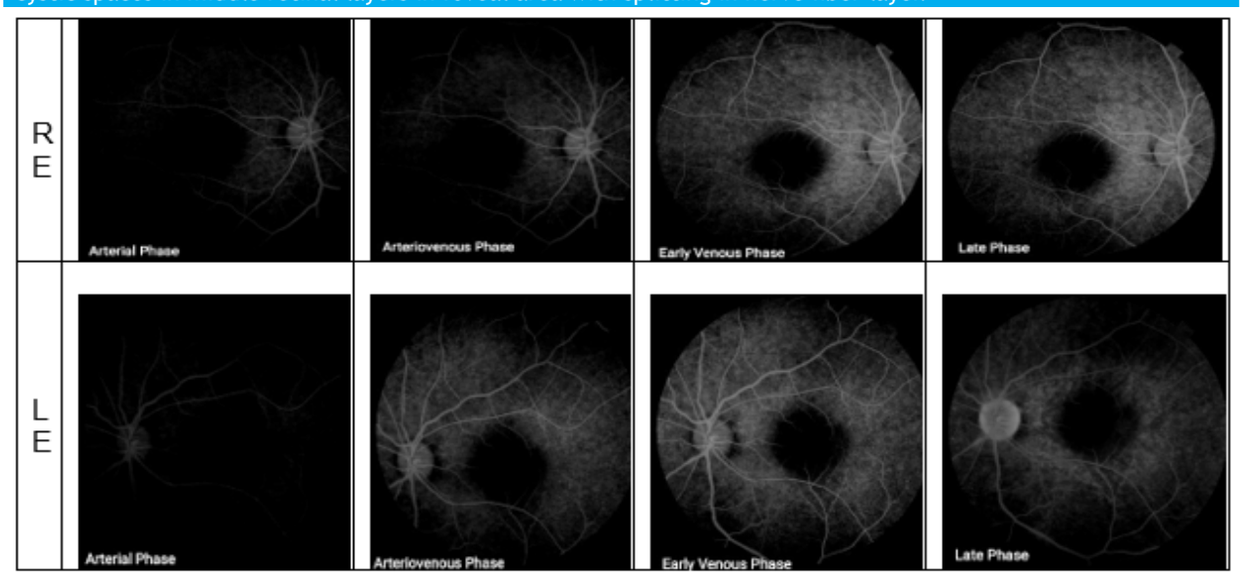

Figure 2. Hypo-fluorescein without leakage observed in macular area in FFA in BE.

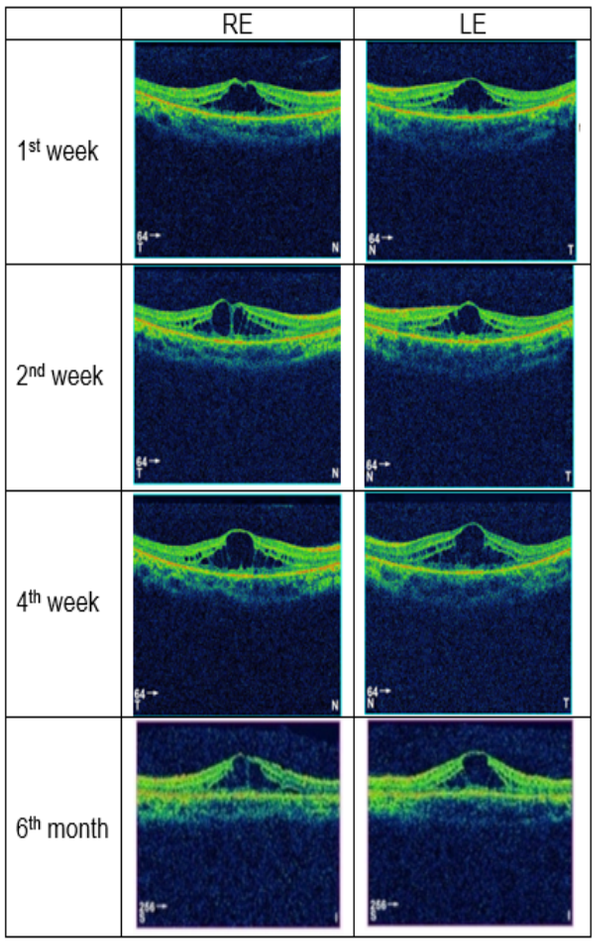

Figure 3. OCT image showing, BE cystic spaces in middle retinal layers in foveal area with splitting in nerve fiber layer at 1st, 2nd,4th week and 6th months of treatment with oral/topical CAIs.

DISCUSSION

XLRS is a vitreoretinal degeneration observed as bilateral foveal retinoschisis in nearly 100% of patients, whereas peripheral retinoschisis is present in 50% of patients.[6] Although rare, it has been described in all races.[7]

Clinically, patients with macular involvement have a definitive appearance which is attributable to splitting of macular nerve fiber layer, accordingly results in cystic spaces developing into a cartwheel-like pattern ('stellate' or 'bicycle-wheel' maculopathy), which is the cardinal sign as observed by OCT.[4] Unlike typical cystoid macular oedema, no leakage of dye is seen in posterior pole on FFA.[3] Consequently, OCT and FFA holds enormous appraisal in diagnosing XLRS as observed in our patient.

Mutations of RS1 gene in Xp22.2, encoding 24kDa retinoschisin is the sole cause behind XLRS.[5] Retinoschisin dysfunction holds three prime pathological mechanism; defective assembly of the disulfide linked subunit, abnormal folding of discoidin domain which has a role in retinal cell adhesion/interaction, inability to insert into the endoplasmic reticulum.[3] Gene mutation leads to absence of its secretion, causes reduced cohesion between the nervous fiber layer and the sensory retina, resulting cystic cavities.[6]

Juvenile retinoschisis, most frequently is associated with complications in deteriorated prognosis such as vitreous hemorrhage and retinal detachment.[2,6] Surgical intervention is advocated only in complicated instances of XLRS as described by Sikkink SK et al, Lomeo et al and Rosenfeld PJ et al.[2,8,9] Diverse group of studies have been conducted employing solid lipid nanoparticles, protamine, dextran or hyaluronic acids and plasmid in either mice or rats utilizing in vivo and in vitro techniques. Apaolaza PS et al and Delgado D et al have demonstrated the potential use of nonviral vectors for the treatment of retinal disorders, including XLRS.[10,11] However, such kind of therapeutic consequences are yet to be achieved in human inhabitants.

CAIs, in recent times have been frequently utilized as the treatment, as myriad of explications have been postulated for the mechanism of action, one of them could be the dorzolamide aided resorption of accumulated retinoschisin in foveal cystic spaces which is facilitated by retinal pigment epithelium(RPE).[4] Another mechanism is the inability of cells to secrete retinoschisin, which may be assisted by the use of CAIs.[12] The clinical effect is due to their action on the membrane-bound carbonic anhydrase receptors present in the RPE.[13] Moreover, other carbonic anhydrase receptors in different cells of the neural retina may also play a role.[14] As CAIs acts both on retinal and RPE cell function by acidifying the subretinal space, which tends to decrease the standing potential as well as raise the retinal adhesiveness, probably by increasing RPE fluid transport.[13]

Patients with XLRS have low visual acuity owing to foveolar retinoschisis, however most of the individuals retain relatively good vision until the fifth or sixth decades of life, when macular atrophy develops.[6]

In our case, vision has ameliorated in BE after 6th month. Patient is symptomatically better, though there is rebound increase in CMT BE after stopping oral acetazolamide at four weeks. However, by the end of 6th month when patient was maintained only on topical CAIs, rebound increase in CMT is observed in RE whereas decreased in LE. 'Rebound' increase implies to the CMT which have returned or increased than that of the baseline, also observed by Genead et al and Khandhadia S et al.[1,3] This could possibly result due to

various genetic mutations causing different retinoschisin protein dysfunction. It could be also dependable on the residual pumping mechanism of RPE cell function as CAIs has been shown to affect them. As mentioned by Genead MA et al, absence of response or rebound increase in CMT after treated with topical CAIs TDS for 6 months, it should be discontinued.[1] Nonetheless, in our patient rebound was observed upon discontinuation of systemic CAIs at the end of 4th week and improved vision was maintained, we advised the patient to continue topical CAIs for a timeframe of 6 months and affirmative outcomes were achieved. Association of XLRS has also been observed with Turners syndrome in literatures[15], nevertheless it is imperceptible in our patient.

XLRS, although being entirely rare is much rarer in females and only scant number of cases have been delineated in the literatures. There is neither any history of consanguinity nor other male sibling is being impacted in our patient, we believe our patient has sporadic origin, nonetheless molecular genetic analysis could luculent the inheritance pattern. Genetic testing for demonstration of RS1 gene would have much facilitated the case. However, it was deferred in our patient as a result of paucity of resources. In existence of such measures, genetic counselling could have enormous role in averting incidence of XLRS in country, such as ours.

CONCLUSIONS

Juvenile retinoschisis could have burdening consequences in the ailment bearing individuals, lack of dictated treatment further adds in. Nevertheless, CAIs have been counted as the possible therapy which is shown to have apted outcome. Scrutinous monitoring is mandatory to pin down potential rebound phenomenon.

Lastly, we believe that our case adds to the current pool of knowledge in understanding this rare entity. We recommend larger studies and involvement of multiple centers to make a definitive statement on the treatment outcome and prognosis, as our case report has these limitations. We strongly suggest the use of CAIs that might be conducted including substantial female cases of XLRS being treated with CAIs in whom molecular genetic analysis ought to be done to preclude the inheritance pattern along with efficacy of CAIs.

CONFLICT OF INTEREST

None

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