American Journal of Ophthalmology Case Reports 8 (2017) 1–3

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: http://www.ajocasereports.com/

Case report

Treatment of cystic cavities in X-linked juvenile retinoschisis: The first sequential cross-over treatment regimen with dorzolamide

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ARTICLE INFO

Article history:
Received 19 January 2017
Received in revised form
3 July 2017
Accepted 19 July 2017
Available online 21 July 2017

Keywords:
X-linked juvenile retinoschisis
Macular cystic cavities
Natural history
Treatment
Topical carbonic anhydrase inhibitors

ABSTRACT

Purpose: To report the first sequential cross-over treatment with the longest ophthalmic follow-up in a case of X-linked juvenile retinoschisis (XLRS) successfully treated with topical dorzolamide.
Observations: A healthy 34 year-old man presented with one month history of decreased visual acuity in his left eye. Funduscopy was significant for a blunted and cystoid-like foveal reflex in both eyes. The macular OCT showed cystic foveal changes OU. The patient was diagnosed with XLRS and was observed. On two subsequent follow-ups, a significant decrease in the patient's visual acuity warranted the use of topical dorzolamide for treating the cystic foveal changes, which completely resolved two months post-treatment initiation.
Conclusion and importance: Previous reports showed the benefit of dorzolamide in treating foveal cystic cavities in XLRS. To our knowledge, this is the first case of XLRS demonstrating the benefits of topical dorzolamide based on a sequential cross-over treatment regimen. It may also represent a case with the longest ophthalmic follow-up providing, in consequence, long-term understanding of the natural history and complications of this rare disease After ruling out major causes of cystoid macular edema, XLRS patients presenting with worsening of their visual acuities due to larger cystic macular changes may benefit from an alternating ON/OFF regimen of topical dorzolamide, which offers a significant treatment advantage outweighing its well-known side effects. Our study consolidates the importance of "medication vacation" by showing its efficacy in providing anatomical and visual functional improvements in patients with chronic cystic macular changes.

1. Introduction

X-linked juvenile retinoschisis (XLRS) is the leading cause of juvenile macular degeneration affecting males during their school age.[1,2] Its prevalence ranges between 1:5000 and 1:20,000[1] and it is caused by mutations in the *RS1* gene.[3] All patients with XLRS have foveal schisis and can have a variable range of visual deterioration and/or disturbances depending on the extent of their pathologies.[2] Up to 50% of cases show infra-temporal peripheral schisis. Additionally, about 5% of patients present with vitreous hemorrhages and/or retinal detachment due to unsupported retinal vessels.[4]

2. Case report

A 34 year-old man was referred to our clinic after reporting one month of decreased visual acuity (VA) in his left eye. The patient did not report any previous medical problem. His ophthalmic history was only significant for refractive amblyopia in his right eye. At presentation, his VA was counting fingers (CF) OD and 20/100 OS. The anterior segment exam was within normal limits OU without noticeable keratic precipitates or cells. The fundus exam was significant for a blunted and cystoid-like foveal reflex in both eyes. Additionally, his left fundus exam revealed tractional folds in the infra-temporal peripheral quadrant. The foveal optical coherence tomography (OCT) showed diffuse retinal thickening with cystoid-like foveal cavities in both eyes (Fig. 1. A,B). There were no bone spicules, vitritis or vascular sheathing seen in either eye. The B-scans of both eyes were within normal limits. Due to the absence of inflammatory ophthalmic changes in this healthy young patient, a diagnosis of XLRS was attributed as the cause of the cystic-like

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http://dx.doi.org/10.1016/j.ajoc.2017.07.008

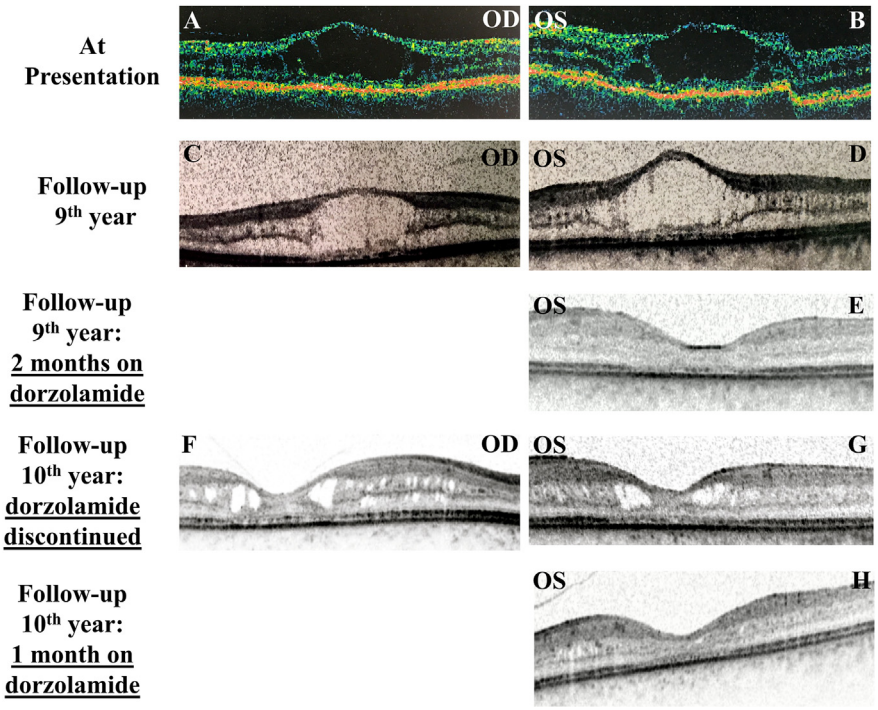

Fig. 1. Macular optical coherence tomography (OCT) of our 34-year-old patient with X-linked juvenile retinoschisis. **A.** OD foveal OCT at presentation showing diffuse retinal thickening due to cystoid-like foveal cavities. The amblyopic OD visual acuity was CF. **B.** OS foveal OCT presentation showing diffuse retinal thickening due to cystoid-like foveal cavities. The OS visual acuity was 20/100. **C.** OD foveal OCT at the 9th year of follow-up showing diffuse retinal thickening due to cystoid-like foveal cavities. The OD visual acuity was CF and the central foveal thickness (CFT) was 347 μm. **D.** OS foveal OCT at the 9th year of follow-up showing diffuse retinal thickening due to cystoid-like foveal cavities. The OS visual acuity worsened to 20/400 and the CFT was 463 μm. **E.** OS foveal OCT 2 months after starting topical dorzolamide TID (during the 9th year of follow-up) showing complete resolution of the cystic foveal thickening. The OS visual acuity improved to 20/70 and the CFT decreased by 50%–248 μm. **F.** OD foveal OCT at the 10th year of follow-up showing inner and outer retinal cystoid-like foveal cavities. The OD visual acuity was still at CF and the CFT was 323 μm. **G.** OS foveal OCT at the 10th year of follow-up showing recurrence of the cystic foveal thickening 6 months after stopping topical dorzolamide. The OS visual acuity dropped to 20/100 and the CFT increased to 288 μm. **H.** OS foveal OCT 1 month after starting topical dorzolamide TID (during the 10th year of follow-up) showing significant reduction of the cystic foveal thickening. The OS visual acuity improved to 20/60 and the CFT decreased by 35%–188 μm.

foveal cavities. After discussing the advantages and disadvantages of medical and surgical interventions with our patient, we elected to follow-up with observation to minimize and prevent any iatrogenic complications to his good seeing eye.

The patient's ophthalmic exam remained stable and unchanged two months after the initial presentation. The patient was then followed every six months during the first two years and then once yearly. During this follow-up period neither significant subjective nor objective changes were noted. Nine years after the initial presentation, the patient re-presented to our clinic complaining of a new onset of VA worsening in his left eye. The acuity was found to have dropped to 20/400. The VA in the amblyopic right eye was still at CF. Funduscopy was significant for larger foveal cystic changes in both eyes. The macular OCT showed diffuse retinal thickening OU. The OCT estimated central foveal thickness (CFT) was 347 μm OD and 463 μm OS (Fig. 1. C,D). Given the noticeable VA worsening in the left eye, which was likely caused by the larger cystic foveal cavities, we decided to start topical dorzolamide TID. Two months after treatment, the patient's OS VA significantly improved to 20/70 and the CFT decreased by 50%–248 μm (Fig. 1. E). The right eye remained stable and unchanged.

During the 10th year of follow-up, the patient's OS VA decreased to 20/100. The patient reported stopping dorzolamide 6 months prior to his 10th year follow-up appointment. The VA in his right eye remained stable at CF. The macular OCT was significant for inner and outer retinal cystoid-like foveal cavities in both eyes with CFT of 323 μm OD and 288 μm OS (Fig. 1. F,G). Dorzolamide TID was started again in the left eye. The patient was followed-up 1 month thereafter and reported a significant improvement in his OS VA which improved to 20/60. The CFT of his left eye decreased by 35%–188 μm (Fig. 1. H). Hence, a treatment regimen consisting of an extended period of “dorzolamide vacation” immediately followed by starting dorzolamide seemed to have resulted in noticeable anatomical and visual functional improvements.

3. Discussion

In 2006, Apushkin et al. were the first to study the effect of topical carbonic anhydrase inhibitors (CAI), particularly 2% dorzolamide, on cystic macular cavities in XLRS. The authors reported more than 7 letters VA gain within 2 months in about 50% of cases.[5] The treatment response was variable and was speculated to depend on the pathologic stage of the disease itself. Advanced cases of XLRS characterized by chronic cystic macular cavities are associated with irreversible retinal layers architectural disruptions and permanent visual acuity loss. These cases are thought to not respond to CAI therapy.[5] Other factors including duration and dosage as well as route of administration could modulate the treatment response.

The pathophysiological mechanism explaining the effect of CAI on XLRS foveal cystic cavities is still unclear. In 1988, Cox et al. studied the effect of the acetazolamide on chronic macular edema.[6] The authors reported that acetazolamide increased the rate of fluorescein disappearance and fluid transport from the vitreous based on membrane-bound carbonic anhydrase IV receptors in the

RPE layer.[7] In fact, CAI are thought to enhance adhesion between retina and RPE. XLRS patients with foveal cystic cavities unresponsive to or worsening on CAI may benefit from discontinuation for up-to 6 months ("medication vacation") and later retreatment with the same agent. The ON/OFF medication regimen is believed to allow the RPE "metabolic pump to partially recover and therefore facilitate the ability for a future response to treatment".[8]

XLRS is due to a mutation in *RS1* gene, which encodes retinoschisin. The latter is a 24 kDa protein tightly bound to the surface of photoreceptors and bipolar cells.[3,4] Retinoschisin was associated with cellular adhesion and the development and maintenance of retinal architecture.[9] In particular, retinoschisin is thought to regulate fluid balance within the photoreceptors and bipolar cells layers via its binding to NaK ATPase, which then affects the activity of the RPE osmotic homeostatic pump. Thus mutations in *RS1* gene can result in a non-functional retinoschisin protein and the subsequent formation of fluid filled cystic cavities in the extracellular retinal space.[10]

The existence of these macular cystic cavities was confirmed both histologically and on OCT thanks to the work of Eriksson et al. in 2004 and Xu et al. in 2009 on Rs1h knockout mice.[11,12] An amorphous eosinophilic PAS positive filamentous material of müllerian cellular origin was extracted from these cysts.[13] Furthermore, both cystatin C, which is a protease inhibitor involved in inflammation, and tenascin-C, which is an extracellular matrix protein implicated in wound healing, were extracted from the intraschisis fluid of an 8-month old child with XLRS.[14]

Anatomically, these cysts disrupt the normal retinal layers architecture causing a dysfunction in the photoreceptor-bipolar synaptic junction. This then can result in a negative ERG which is characterized by an a-wave that is larger than the b-wave.[15] Only 50% of XLRS patients display this negative ERG sign. The ERG in XLRS is in fact more variable than generally expected.[16,17] Hence, it is important to stress that a relatively normal ERG does not exclude XLRS.

The majority of XLRS patients show no or minimal worsening in their visual acuities.[4] In rare instance, some patients report worsening of their visual acuities with increasing age possibly due to larger cystic cavities and corresponding retinal layers disruption.[18] Our patient likely falls in this category. To our knowledge, this is the first case of XLRS demonstrating the benefits of topical dorzolamide based on a sequential cross-over treatment regimen.[1] It may also represent a case with the longest ophthalmic follow-up providing, in consequence, long-term understanding of the natural history and complications of this rare disease.

After ruling out major causes of cystoid macular edema, XLRS patients presenting with worsening of their visual acuities due to larger cystic macular changes may benefit from an alternating ON/OFF regimen of CAI, which offers a significant treatment advantages outweighing its well-known side effects. Our study consolidates the importance of this treatment regimen by showing its efficacy in providing anatomical and visual functional improvements in patients with chronic cystic macular changes. The benefit of continuous long-term treatment is yet to be determined but one can consider slowly tapering CAI to every other day dosing in order to prevent the recurrence of the cystic cavities and the possibility of irreversible visual loss. Finally, all XLRS patients should be regularly followed-up with visual acuity measurements, dilated fundus exams and OCTs.

[1] The term "cross-over" refers in this case to the pathological changes observed when the patient was on dorzolamide (ON regimen) compared to those observed when he was off dorzolamide (OFF regimen).

Patient consent: Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

Acknowledgements and disclosures

Funding: No funding or grant support.
Conflict of interest: RGC has no financial disclosures.
We have the following financial and/or commercial disclosures to disclose:

- M. A. Kapusta is a consultant for: Alcon Inc., Bayer Inc., Novartis Pharmaceuticals Inc. and ArcticDx Inc.

Authorship: Each of the authors has contributed to, read and approved this manuscript. All authors attest that they meet the current ICMJE criteria for Authorship.
Acknowledgements: None.

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