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Rapid Resolution of Retinoschisis with Acetazolamide

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Abstract

Purpose—To report the results of an acetazolamide (Diamox®) treatment regimen in a genetically confirmed case of X-linked Juvenile Retinoschisis (XLRS).

Methods—A patient with XLRS was prescribed acetazolamide (Diamox®) at a dose of 500 mg/day, then discontinued the treatment due to non-compliance for 4 days, and finally resumed the course of treatment. Best-corrected visual acuity, retinal structure, and function were monitored with autofluorescence (AF), spectral domain-optical coherence tomography (SD-OCT), adaptive optics scanning laser ophthalmoscopy (AOSLO), and full-field electroretinogram (ERG). Full-field ERG was performed using DTL recording electrodes and Ganzfeld stimulation according to ISCEV standards.

Results—Serial monitoring of the cysts by SD-OCT revealed a strong association between the effects of acetazolamide administration and the size of the schisis. A reduction in foveal cyst size was significant in as rapid as 6 days after acetazolamide initiation. AOSLO data revealed that the resolution of cone cell images improves as the foveal schisis decreases in size.

Conclusions—Efficacy of acetazolamide in patients with XLRS can be apparent in as rapid as a week of therapy. AOSLO can be a good method to evaluate the cone cells after acetazolamide treatment in the early stages of XLRS.

Keywords

retinoschisis; acetazolamide; OCT; AOSLO

Introduction

X-linked Juvenile Retinoschisis (XLRS) is a rare, hereditary retinal disorder with an estimated prevalence of 1 in 5,000 to 20,000 males worldwide [1]. The onset of XLRS has

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been attributed to pathogenic mutations in the retinoschisin gene (*RS1*) on the X chromosome, which encodes an extracellular protein responsible for the architectural integrity of retina layers [1–2]. Affected individuals in early or pre-clinical stages exhibit cystic changes in the fovea resembling a spoke wheel pattern caused by the separation of the neurosensory retina [3]. Progression to later stages results from the coalescing of these cysts leading to non-specific atrophy of the macula and further deterioration of vision in both eyes.

While most XLRS patients typically present with foveoschisis, a small number of patients have been shown to exhibit the atypical phenotype of fine white dots in the macula instead; however, both phenotypes are associated with an electronegative bright-flash electroretinogram (ERG) configuration and abnormal pattern ERG findings [4]. The disease is initially confined to the macula, leading to early loss of central vision, but can lead to peripheral involvement with variable visual acuity. Progression of the disease has been documented from the presence of multiple small cysts that later coalesce into larger cysts, resulting in macular atrophy at a later disease stage. Disruptions in retinal lamination are attributed to Müller cell dysfunction, although more recent studies have indicated that photoreceptor and bipolar cells are the primary expression sites of the retinoschisin protein. The function of this disulfide-linked homo-octameric complex protein is the maintenance of retinal architecture integrity [5]. To date, no therapeutic treatment has been proven effective for this condition in humans.

Acetazolamide (Diamox®) is a carbonic anhydrase inhibitor that targets the membrane-bound carbonic anhydrase IV receptor in the basolateral membrane of the retinal pigment epithelium (RPE). It has been shown that the reduction in subretinal pH, changes in chloride flux, and RPE potential following acetazolamide administration can enhance RPE pumping capacity [6–8]. Previous studies have reported on the successful results of both oral and topical forms of carbonic anhydrase inhibitors as a treatment for cystoid macular edema in association with retinitis pigmentosa [9–15]; however, its efficacy across all conditions remains uncertain without further investigation. Herein, we report a positive outcome of cyst resolution through a patient undergoing a course of acetazolamide treatment with a genetically confirmed case of XLRS. Data collected throughout the treatment are also supplemented with adaptive optics imaging results prior to and after treatment.

Case description

A 19-year-old man diagnosed with XLRS presented with baseline best-corrected visual acuities (BCVA) of 20/80 and 20/70 in his right and left eye, respectively. Dideoxy chain-terminating sequencing of the *RS1* gene revealed a mutation, Arg213Trp, in exon 6. Figure 1 provides a timeline delineating treatment and imaging timepoints.

Fundus images prior to acetazolamide treatment are shown in Figure 2. Full-field ERG findings revealed amplitudinal reductions in both the rod and cone systems. Maximal ERG exhibited electronegative responses with preservation in a-wave amplitudes resulting from an inner retina conduction abnormality, which is consistent with typical findings in XLRS (Figure 3). The patient was treated with oral acetazolamide at a dosage of 500 mg/day.

Visual acuity, eye examination, and tracked SD-OCT scans over the same region were obtained and evaluated weekly following drug administration. Adaptive optics scanning laser ophthalmoscopy (AOSLO) (Canon Inc., Tokyo, Japan) data were obtained at three locations along the nasal and temporal meridians at measured distances of 0.5 mm, 1.0 mm, and 1.5 mm from the foveal center. After acquisition and processing, individual AOSLO images were manually mapped onto autofluorescence images collected simultaneously with SD-OCT by the TruTrack™ function on the Spectralis instrument (Heidelberg Engineering, Heidelberg, Germany). Images were collected prior to treatment and 13 days after treatment. Serial monitoring with SD-OCT revealed a strong efficacy of acetazolamide, as evidenced by a dramatic reduction in the patient's central foveal thickness and retinoschisis (Figure 4). The reduction of macular edema, as shown by SD-OCT, allowed for parafoveal cone resolution with AOSLO (Figures 5 and 6). Extensive schisis at baseline measurement affected (by blurring) the post-processing normalization of AOSLO images though numerous darkened areas interspersed throughout the cone mosaic were apparent. Figure 6 shows the corresponding locations between the AOSLO and the SD-OCT images. The SD-OCT images in Figure 4C show a marked increase in schisis volume and foveal thickness after the patient stopped acetazolamide treatment for four days, compared to when he was receiving treatment in Figure 4B. Six days after the patient resumed the acetazolamide treatment, SD-OCT images showed a mild yet noticeable decrease in schisis volume and foveal thickness (Figure 4D).

Discussion

The indication of acetazolamide in the management of non-specific macular edema provided the impetus for investigating its effects, though previous studies have only reported marginal success in terms of improved visual acuity and central foveal thickness [16–17]; however, reliable therapeutic resolution is still an unconquered challenge.

The current study presents a case of XLRS in which the effects of acetazolamide on macular schisis were observed to occur dramatically within one week of drug administration. Documented improvements in both visual acuity and central foveal thickness appeared to result from the treatment. Serial monitoring of the cyst by OCT revealed a strong association between acetazolamide administration and the size of the schisis. According to OCT images, the schisis regressed to its baseline size after the patient discontinued use of the drug for four days (Figure 4A,C). Foveal cysts were significantly decreased in size as soon as six days after restarting acetazolamide (Figure 4D). Because the mechanism of acetazolamide involves the facilitated removal and pumping of excess fluid by RPE cells and subsequent transport into the choroid, we hypothesize that the drug may respond differently at each stage of the disease in accordance with the condition of the patient's RPE. The drug may have a greater benefit on patients in early stages of the disease, when the cone mosaic is less affected by chronic cystoid changes. In patients with healthier RPE, the cysts can shrink more rapidly and the retinal structure can be maintained for a longer duration after administration of the drug. In patients with diseased RPE, the response to the medication will be slower or absent. Thus, the response of the cyst to acetazolamide treatment may give insight into the state of the RPE's health.

In our previous studies, AOSLO provided rare insight into the cellular organization of retinas in patients with chloroquine retinopathy, acute posterior multifocal placoid pigment epitheliopathy (APMPPE), enhanced S-cone syndrome, and X-linked retinitis pigmentosa (XLRP) [18–21]. Using AOSLO, Duncan et al. reported increased cone spacing and abnormal packing in the macula of XLRS patients [22]. Baseline images taken prior to treatment also exhibited qualitative abnormalities – dark spacing and mottling of the mosaic – when compared to a similar area in an unaffected control (Figure 5). Subsequent imaging of the patient following treatment revealed a mosaic that seemed comparable to that of a healthy mosaic though further, more extensive analysis may be necessary to assess whether these images reveal true structural improvements. Furthermore, a lower percentage of hexagonal cells (96.2% to 37.5%) were found after treatment, which may suggest irreversible morphological changes despite any possible structural recovery. If a real improvement of the cone mosaic were observed in AOSLO images before and after treatment, such results may support the view that photoreceptors are spared in the early stages of the disease. Thus, it can be inferred that treating XLRS patients before they develop irreversible cone photoreceptor loss from chronic cystoid changes may prolong or even prevent the development of macular atrophy, resulting in better prognoses and quality of life for XLRS patients.

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Fig. 1.

An abridged timeline of events in the treatment course of a patient with X-linked juvenile retinoschisis with acetazolamide.

Fig. 2.

Images of the XLRS patient's eyes at presentation: (A, B) Color fundus images of the right and left eyes, respectively, (C, D) 488nm reflectance images, (E, F) 488nm autofluorescence images. (G, H) spectral domain-optical coherence tomography scans across the fovea exhibiting small parafoveal spots seen on 488nm reflectance images, correlating with macular cysts that are less noticeable on color fundus and 488nm autofluorescence imaging.

Fig. 3.

Full-field electroretinogram results as compared to an age-matched control trace (bottom row). The patient exhibited electronegative maximal responses in both eyes. Scotopic rod specific ERG b-wave amplitudes were 64.5 microvolts in the right; 62.8 microvolts in the left, delayed implicit time of 120 ms was noted in both eyes. Maximal ERG a- and b-wave amplitudes were 233 microvolts and 177 microvolts in the right; 231 microvolts and 193 microvolts in the left. Photopic 30 Hz flicker ERG had implicit time and amplitudes of 28 milliseconds and 40 microvolts in the right; 31 milliseconds and 44 microvolts in the left. Transient photopic ERG b-wave amplitudes were 59 microvolts in the right; 56 microvolts in the left. Transient photopic ERG b-wave implicit times were 32 milliseconds in the right; 34 milliseconds in the left.

Fig. 4.

Apparent schisis resolution over time. Serial SD-OCT scans show various time points during the course of acetazolamide treatment. Between visits, the previous regions of interest were tracked and follow up SD-OCT scans were aligned at the center of the largest cyst. The initial OCT scan was taken before treatment began (Figure 4A). The follow-up examination occurred after 10 days of medication, in which the OCT revealed a decrease in the size of the foveal schisis of both eyes (Figure 4B). The next examination occurred 10 days later. Regression of the schisis to baseline was noted after the patient reported discontinued use of acetazolamide for four days (Figure 4C). A notable decrease in schisis was observed 6 days following the resuming of treatment (Figure 4D).

Fig. 5.

Parafoveal cones are visualized after acetazolamide treatment. Adaptive optics scanning laser ophthalmoscopy (AOSLO) images of the left eye at 1mm from the central fovea in the temporal direction were shown above. Compared with the normal control, the resolution of cones before treatment is low because the schisis hinders the resolution. Our second AOSLO images were taken after 13 days of treatment when the edema was significantly smaller than baseline. The resolution of cone cells was noticeably improved. The boundaries of the cone cells are much more defined in later courses of the treatment. Compared to the

AOSLO images of normal, age-matched males, the cone density and ratio of hexagons are decreased.

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Fig. 6.

The corresponding location between AOSLO and OCT. The vertical line marking cones 1mm from the central fovea in AOSLO images corresponds to the region of schisis reduction on OCT images. Comparing the target area of the AOSLO images before and after treatment, the OCT shows that the retinoschisis has almost subsided. Note: Post-treatment autofluorescence and AOSLO images were taken on days 11 and 13, respectively.