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Treatment of Adult-Onset Acute Macular Retinoschisis in Enhanced-S Cone Syndrome with Oral Acetazolamide

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Abstract

Purpose—To report on the efficacy of the oral carbonic anhydrase inhibitor (CAI), acetazolamide, in treating macular retinoschisis (RS) in the rare vitreoretinal dystrophy best known as the enhanced S-cone syndrome (ESCS).

Design—Interventional case report.

Methods—Setting: University-based practice. Patient: A 48-year old Jewish Italian male with clinically, functionally and molecularly confirmed ESCS, due to homozygosity for the R311Q mutation in the *NR2E3* gene, presented with sudden visual acuity loss (20/200) and metamorphopsia in the left eye resulting from acute, late-onset, asymmetric macular RS. Intervention: Open-label, off-label treatment with the oral CAI acetazolamide. Main Outcome Measure(s): Best corrected visual acuity, retinal thickness and retinal microanatomy, assessed by Stratus optical coherence tomography (OCT) criteria.

Results—Following treatment, instituted one month after the acute-onset visual acuity loss, retinal thickness and microanatomic profile normalized in the affected eye, with restoration of 20/20 corrected visual acuity. The fellow eye, which had remained asymptomatic at 20/16 vision, had experienced mild paracentral macular RS evident by OCT criteria, which also resolved completely following oral CAI treatment. The outcome was maintained throughout the follow up period at a low maintenance dose.

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Conclusions—Taken together with other recent reported benefits of topical and oral CAIs in the treatment of macular RS in X-linked retinoschisis, this interventional case report shows that CAIs can be used to treat effectively macular RS in general, and also specifically in ESCS.

Introduction

Enhanced-S Cone Syndrome (ESCS)^{1–4} is a rare, autosomal recessive vitreoretinal dystrophy also known as Goldmann-Favre vitreo-retinopathy (GFVRD) or clumped pigmentary retinal dystrophy (CPRD),⁵ which are often mistaken for retinitis pigmentosa (RP). Clinically, macular and peripheral retinoschisis (RS) are commonly observed in ESCS, along with a variety of retinal changes, including nummular pigmentary deposits and retinal flecks, typically along the arcades.^{3–5} Macular RS is often present, causing reduced acuity in ESCS patients, and no successful treatment for this condition has yet been reported. Herein we report the unusual case of ESCS presenting with adult-onset acute macular RS, and document a positive response of this complication to the oral carbonic anhydrase inhibitor (CAI), acetazolamide, an established treatment modality utilized both orally and topically to manage cystoid macular edema in retinitis pigmentosa (RP),^{6–12} resulting in resolution of the macular RS, with normalization of macular microanatomy and restoration of visual acuity.

Methods

The functional work-up included full-field dark- (DA) and light-adapted (LA) flash electroretinograms (ERGs), recorded as previously described^{13, 14} with HK-loop conjunctival electrodes,¹⁵ and DA (500nm size-V stimuli) and LA [600nm size-V stimuli on a standard white background to estimate thresholds mediated by long- and middle- (L/M) wavelength-sensitive cones, and 440nm size-V stimuli on a bright yellow background to isolate short wavelength-sensitive (S) cones] monochromatic automated perimetry (MAP) across the entire field of vision, performed as previously described^{14, 16} according to the technique developed by Jacobson et al.^{4, 14, 17} Once the diagnosis of ESCS was established on clinical and functional criteria, the accuracy of this conclusion was verified through diagnostic molecular genetic testing for mutations in the *NR2E3* gene, which is known to underlie ESCS.¹⁸ Genomic DNA was extracted, PCR amplified, and sequenced according to standard procedures.

The intervention used in this case was an oral CAI regimen of acetazolamide 125 mg (half of a 250-mg Diamox tablet, Teofarma, Pavia, Italy) twice daily, and subsequently tapered to a single maintenance dose of 62.5 mg (one quarter of a tablet) daily, administered on an open-label basis for off-label use to treat acute macular RS. The main outcome measures used to evaluate response to this treatment regimen in this patient were: best corrected visual acuity, measured with ETDRS acuity charts; retinal thickness, expressed in microns (μ); and the overall retinal microanatomical profile, the latter two ascertained by means of conventional, time-domain Stratus OCT (Carl Zeiss Meditec, Dublin, CA).

Results

In this interventional case report, we illustrate the case of a 48-year-old man of Jewish-Italian descent who presented with a 1-month history of acute metamorphopsia, blurred and reduced visual acuity in the left eye, reported to have occurred after a strenuous gym exercise session. His history was remarkable for a life-long history of nyctalopia and, upon review of previous medical records and color fundus photos, retinal pigmentary changes that were present in both eyes. Corrected visual acuity of 20/20 or better had been documented at all previous eye exams with a mild myopic correction, in the absence of clinically detectable macular retinal cystic changes. The medical history of this patient was not contributory, and the family history was

significant for consanguinity. The diagnosis carried by this patient since the age of 8 was that of RP, believed by the treating physicians to have been recently complicated by macular edema.

At our initial examination in February 2006, corrected visual acuity was 20/16 in the right eye and 20/200⁺² in the left, with metamorphopsia on Amsler grid testing. Fundus exam (Figure 1) was remarkable for a bilateral, prominent ring of coalescent, nummular deep retinal (i.e., not bone spicule-like intraretinal) pigmentary deposits, accompanied by a band of atrophy at the arcades and whitish punctate flecks in the mid- to far periphery. Unlike RP, retinal vessels, which lie above the pigmentary deposits, were not attenuated and discs exhibited only minimal waxy pallor. Overt macular cystic changes, more severe nasally to fixation, were evident in the left macula both clinically (Figure 1) and by OCT criteria (Figure 2). Although the right eye was asymptomatic, the OCT showed a partial, kidney-shaped ring of perifoveal cystic changes, also more prominent nasally, leading to increased retinal thickness and an altered retinal profile. Despite these cystic changes, a fluorescein angiogram (performed by the referring ophthalmologist and reviewed at the time of referral, not shown) showed absence of any detectable pooling or leakage of the dye in the macular area of either eye. These findings suggested to us the possible diagnosis of ESCS.

Rod-driven ERGs were non-recordable, ERGs were electronegative in shape in response to both DA (mixed) and LA (cone-driven) bright stimuli, but were markedly reduced in size, and cone transient responses were also markedly delayed (not shown). These findings were again strongly suggestive of, but not completely diagnostic for ESCS.^{1-5, 19} Therefore, DA and LA MAP was performed (not shown). S-cone sensitivity was supernormal across most of the field, L/M-cone sensitivity varied from mildly to markedly depressed, and DA thresholds to 500nm stimuli, normally mediated by rods, were profoundly abnormal. These findings were diagnostic for ESCS. This conclusion was corroborated by diagnostic molecular genetic testing, which demonstrated the presence of a homozygous R311Q mutation in the *NR2E3* gene (see Supplemental Material available at AJO.com), the gene underlying ESCS, as well as GFVRD and CPRD.^{5, 18} Based on these findings, the cystic macular changes were interpreted as acute macular RS. Moving from the assumption that these cystic spaces were likely filled with endogenous interstitial retinal fluid undetectable to fluorescein angiography testing, the patient was placed on an oral regimen of acetazolamide 125 mg twice daily.

Treatment was very well tolerated and led to rapid improvement of visual acuity in the left eye from 20/200⁺² at baseline, to 20/30 at week 4 and to 20/20⁻¹ by week 12 of treatment (Figure 3). Acetazolamide dosing was therefore reduced to a maintenance dose of 62.5 mg twice daily, with sustained recovery of acuity and maintenance of a normal retinal profile throughout September 2007. These improvements in visual acuity were accompanied by progressive and ultimately complete normalization of the retinal microanatomical profile by OCT criteria (Figures 2 and 3). The incipient but asymptomatic macular RS in the right eye had already resolved by week 4, and this eye remained asymptomatic throughout follow-up. The patient was placed on further reduced oral acetazolamide maintenance dosing of 62.5 mg once daily and a topical CAI, 2% dorzolamide (Trusopt, Merk & Co., Inc., West Point, PA) twice daily in OU, with which visual acuity, retinal thickness and retinal morphology has remained essentially unchanged through the 24th month of follow-up. The patient has been counselled to utilize an Amsler grid test on a weekly basis to identify any change that may suggest a relapse in the macular RS.

Discussion

ESCS is a rare autosomal recessive disorder of retinal cell fate resulting from the erroneous development of retinal progenitor cells committed to becoming photoreceptors into Scones at the expense of rods, which are missing, and L/M-cones, which are diminished in number.^{18,}

²⁰ In the post-mortem retina of a patient homozygous for the same R311Q mutation presented by our patient, no rods were identified, whereas cones were increased approximately 2-fold. Of these, 92% were S cones, 15% expressed L/M cone opsin, and some of these co-expressed S cone opsin.²⁰ On functional grounds, this disorder results in congenital night blindness and relatively or absolutely enhanced S-cone-mediated retinal sensitivity.^{1–4, 19} Genetically, ESCS has been shown to share the same etiology as GFVRD and CPRD,⁵ which therefore represent different phenotypic facets of the same genetic spectrum.

Often, as in this case, these three allelic conditions are confused with RP. Considering that, unlike RP, they carry a risk of retinal detachment and that the course of the disease differs from that of typical RP,^{4, 20–22} diagnosing these patients correctly has importance beyond mere diagnostic accuracy. Although specialized functional testing may be indispensable to formulate the diagnosis of ESCS and molecular testing nowadays affords the opportunity of a diagnosis of certainty, clinical identification of ESCS, or its variants GFVRD and CPRD, is possible and in fact necessary to direct the functional and molecular diagnostic work-up. In our experience,²² certain fundus characteristics presented by our case exemplify one of the most classical clinical presentations of this disease spectrum, i.e., that of nummular, coalescent deep pigmentary deposits at the arcades, where normally rod photoreceptor density in the retina would be highest, typically accompanied by normal retinal vasculature overlying the pigmentary deposits. This presentation, noted as typical also by Sharon et al.⁵ and by Audo et al.,²³ whether or not accompanied by peripheral and/or macular RS, argues strongly against the diagnosis of RP and should raise the suspicion of ESCS, for which patients should be worked-up accordingly. It must also be noted that peripheral RS can be overt, sometimes conferring a “shredded” appearance to the peripheral retina due to degeneration of the inner leaflet of the schisis, but can also present far more subtly, with a micro-flecked appearance of the retinal anterior to the arcades, which may or may not be accompanied by true, clinically overt schitic changes.²² The latter was the case of our patient, and its identification aided further in ultimately formulating the correct diagnosis of ESCS.

Here we report, to the best of our knowledge for the first time, a case of acute, adult-onset macular RS and the successful resolution of this complication with the oral CAI, acetazolamide, in a middle-aged patient with a functionally and molecularly proven case of ESCS. It is unclear why this patient retained 20/20 or better visual acuity for his entire life until this complication occurred. This favorable functional status is not typically observed in ESCS patients in general,^{4, 21} and those with the R311Q mutation in particular,²⁰ who most often present with overt macular cystic changes and reduced visual acuity. While macular RS can disappear or attenuate spontaneously over the long term in patients with ESCS, unlike our patient, this phenomenon is gradual, and is typically associated with progressive degradation of retinal integrity and visual acuity decline.²¹ Also, hyperopic refractive defects are more commonly observed in patients with *NR2E3* mutations,^{5, 20, 23} including the R311Q one observed in our patient,²⁰ who instead had a mild myopic refractive status. Whether this played in any way a role in the delayed onset of macular RS and/or the unusually favorable functional status is unsure. Yet unknown genetic modifiers may also account for the milder than usual phenotype observed in our patient.

It is also unclear what precipitated the sudden development of macular RS. It is possible that the strenuous physical exertion and intense sweating sustained in the gym by the patient may have favored the RS by virtue of a “delamination” process through a Valsalva maneuver-like effect, or from acute dehydration of the vitreous body following in conjunction with the physical exercise, leading to sudden contraction of the vitreous gel. Further prospective or retrospective studies will be required to verify whether patients with ESCS may be at increased risk of developing RS, experiencing a worsening thereof, or incurring retinal rhegmatogenous

outcomes in conjunction with strenuous physical exertion, profuse sweating, and/or other special circumstances leading to acute vitreal dehydration and contraction.

Acetazolamide has been frequently and successfully used in the treatment of cystoid macular edema associated with RP^{6–12} as well as other disorders.^{10, 24–30} We reasoned that also in macular RS, and especially acute RS, the cystic spaces observed clinically and by OCT would be fluid-filled. We therefore determined that an off-label use of a CAI would be a reasonable treatment to try to promote resorption of this putative intraretinal fluid, regardless of its etiology. Consistent with this prediction, treatment with acetazolamide resulted in prompt and near complete recovery of visual acuity, and OCT demonstrated a strikingly rapid improvement in, and ultimately normalization of the macular microanatomical profiles as well. Benefit from the treatment was observed also in the fellow eye, which was subjectively asymptomatic but with incipient macular RS by OCT criteria. Visual acuity and retinal status have remained stable with a low maintenance dose of acetazolamide, presently combined with a topical CAI twice daily. It is presumed that the mechanism of action of CAIs in this setting is the same as in macular edema, i.e., the ability to facilitate trans-RPE drainage of fluid accumulated in the intraretinal cystic spaces.^{28, 31}

While this ESCS patient was being followed, Apushkin and Fishman³² and Ghajarnia and Gorin³³ have independently demonstrated improved macular RS and acuity with topical and oral CAIs, respectively, in the case of another hereditary vitreoretinal disorder, X-linked RS. Ghajarnia and Gorin³³ have also shown that, upon discontinuation of this treatment, macular RS relapses, thereby establishing a cause-effect relationship between the treatment and the resolution of macular RS. Taken together, their findings and ours indicate that macular RS can be treated successfully with CAIs. Our report shows that this treatment is effective also in ESCS, at least when the macular RS is of recent onset. A very recent report by Audo et al. suggests that acetazolamide may not be of benefit in ESCS patients with macular RS.²³ However, it is not clear from this report how many patients were treated, with what dosages, for how long, how was response to treatment assessed, or what was the duration and the extent of the schitic changes treated by these investigators. Unlike the report by Audo et al., we have observed partial regression of chronic macular RS and improvement in visual acuity in another patient with ESCS and long-standing, otherwise stationary macular cystic changes via a combined oral and topical CAI treatment regimen similar to the one used in the present report (Iannaccone 2008, unpublished observation). Hence, it is possible that oral and/or topical CAIs may successfully ameliorate also chronic macular RS, as it is more often observed in ESCS patients, at least in some cases. Further investigations in this area remain warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biography

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Dr. Iannaccone received his MD and did his Ophthalmology residency at the University La Sapienza of Rome, Italy, followed by fellowships at the Scheie Eye Institute, University of Pennsylvania, and at the University of Tennessee Health Science Center (UTHSC), where he joined the faculty in 1998. At UTHSC, he also obtained a MS in Epidemiology. He directs the Retinal Degeneration & Ophthalmic Genetics Service of the Hamilton Eye Institute, where he is an Associate Professor.

Figure 1.

Composite of the left eye of the patient with Enhanced-S Cone Syndrome and adult-onset acute macular retinoschisis. The fundus is remarkable for a prominent ring of coalescent, mainly nummular (i.e., not bone spicule-like intraretinal), deep retinal pigmentary deposits, accompanied by a band of atrophy of the retinal pigment epithelium at the arcades and whitish punctate flecks in the mid- to far periphery. Retinal vessels lie above the pigmentary deposits and are not attenuated. The optic disc exhibits minimal waxy pallor. Overt macular cystic changes, more severe nasally to fixation, can be observed clinically in this eye.

Figure 2.

Macular thickness maps and custom horizontal transfoveal OCT scans of the patient with Enhanced-S Cone Syndrome and adult-onset acute macular retinoschisis. Top row, baseline OCTs: In the asymptomatic right eye, an area of partial (scan), kidney-shaped (map) macular retinoschisis (RS) nasal to the fovea can be observed; in the left eye, the nasal, kidney-shaped area of macular RS was much more pronounced, involving and extending temporally to the fovea. Second row, OCTs obtained 4 weeks after treatment with acetazolamide: Modest retinal thickening nasal to fixation (map) persisted in the right eye due to persistent mild RS (scan); in the left eye, the area of RS was unchanged, but retinal thickness (map) had greatly diminished perifoveally and was near-normal foveally, although macular RS persisted throughout the area originally involved by the RS (scan). Third row, OCTs obtained 12 weeks after treatment with acetazolamide: The retinal thickness map and profile in the right eye have fully normalized; except for mild persistent retinal thickening in the outermost nasal ring quadrant (map), foveal thickness has become normal and the retinal profile shows no evidence of RS. Fourth row, 18-month follow-up OCT while on maintenance acetazolamide dosing of 62.5 mg twice daily: The retinal thickness maps and profiles are essentially within normal limits in both eyes. Bottom row, 24-month follow up OCT while on maintenance acetazolamide dosing of 62.5 mg daily and topical 2% dorzolamide twice daily, illustrating overall maintenance of the normal retinal thickness values and profiles observed at 18 months. T = temporal; N = nasal. The false color gradient bars atop the maps span the standard retinal thickness range of 0 to 500 μm .

Figure 3.

Plot of Snellen fraction of visual acuity (left-hand y-axis), mean retinal thickness and acetazolamide dosing (right-hand y-axis) as a function of time (x-axis) in the patient with Enhanced-S Cone Syndrome and adult-onset acute macular retinoschisis. The black arrow identifies the onset of acetazolamide treatment. The light grey arrow marks the onset of topical 2% dorzolamide treatment twice daily. Mean retinal thickness data area presented for the foveal (1.0-mm) central ring and for the nasal 3.0-mm quadrant. A visual acuity of 1.0 equals to 20/20.