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A rare case of type 3 usher syndrome with bilateral cystoid macular edema treated with topical dorzolamide

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Abstract:

A 30-year-old female presented with gradually progressive diminution of vision for 1 month, with night blindness for the past 5 years and difficulty in hearing for the past 10 years. Her developmental history and family history were unremarkable. Ocular examination revealed visual acuity of 6/36 in both eyes. Fundus showed features of retinitis pigmentosa with bilateral macular edema. Audiometry revealed bilateral sensorineural hearing loss; although, her vestibular functions were preserved. Clinical diagnosis of Usher syndrome type 3 was made based on normal hearing at birth, delayed presentation of progressive visual and auditory impairment with normal vestibular function, and developmental milestones. Her macular edema resolved after 3 months of treatment with topical dorzolamide therapy. The unique feature of this case is the presence of bilateral macular edema in type 3 Usher syndrome, which is rarely reported in literature.

Keywords:

Macular edema, night blindness, retinitis pigmentosa, sensorineural hearing loss, usher syndrome

Introduction

Ushers syndrome (USH) comprises a group of autosomal recessive inherited disorders. Charles Usher, a British ophthalmologist, demonstrated the hereditary nature of this disease in 1914, and it was named after him.^[1] USH is the most common human syndrome involving combined visual and hearing loss, accounting for more than half of deaf-blindness cases.^[2] It has heterogeneous clinical and genetic presentation and three distinct subtypes of the syndrome have been described.^[3]

Usher syndrome type 1 (USH1) patients have a prevalence of about 40% and are characterized by profound sensorineural hearing loss (SNHL) at birth or during the 1st year of life, abnormal vestibular function,

and delayed motor development, as well as the prepubertal onset of progressive retinitis pigmentosa (RP).^[4,5] Hearing in the low frequencies is generally preserved, making these USH1 children ideal cochlear implant candidates.^[6-8] At least seven different loci have been mapped (USH1B-USH1H), but only five genes have been isolated, namely myosin VIIa (MYO7A), cadherin-23, protocadherin-15, harmonin (USH1C), and SANS (USH1G).^[3]

Usher syndrome type 2 (USH2) is less severe than Type 1 and have moderate-to-severe hearing loss from birth and normal vestibular function. It is the most common USH with a prevalence of around 60%. The onset of RP is in the first or second decades. The onset of the visual symptoms in Type 2 occurs usually several years later than for USH1. Three genetic loci (USH2A, USH2C, USH2D) and their corresponding genes have been identified. The most common

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mutations accounting for up to 85% of the USH2 cases is the USH2A gene on chromosome 1q41, which encodes for usherin.^[3]

Usher syndrome type 3 (USH3) is characterized by normal hearing at birth and undergo progressive hearing loss later with variable onset of RP, and variable impairment of vestibular function (normal to absent).^[9-11] In general, developmental motor milestones are normal in Type 3. USH3 is not as common as USH1 and USH2, with a prevalence of 2%–4% within all USH cases. It is caused by mutations in the USH3A gene mapped onto 3q21-q25 which encodes for clarin-1.^[3]

Even though macular edema has been reported in USH1 and USH2 before, the occurrence of cystoid macular edema (CME) in USH 3 has rarely been reported. CME has been reported to be present in 11%–20% of all USH and/or RP patients.^[12]

Herein, we report a case of clinically diagnosed USH3 with bilateral macular edema successfully treated with topical dorzolamide.

Case Report

A 30-year-old female, presented with bilateral gradually progressive diminution of vision for the past 1 month. She also complained of difficulty in seeing at night for the past 5 years. She is born out of a nonconsanguineous marriage and with normal developmental milestones. Her systemic history revealed gradually progressive difficulty in hearing for the last 10 years; although, she had normal hearing at birth and early childhood. Old records showed the past ophthalmic evaluation at 15 years of age was normal. Family history was noncontributory. Best-corrected visual acuity (BCVA) was 20/120 in both eyes (BE). Anterior segment and intraocular pressures were normal in BE. Fundus examination revealed clear media with bilateral arteriolar attenuation and bony spicule-like pigmentation in the mid periphery of BE. Waxy disc pallor and macular edema were also noted in BE [Figure 1a and b]. The overall clinical picture was consistent with RP.

Optical coherence tomography (OCT) revealed multiple hypo reflective cystoid spaces suggestive of CME in BE [Figure 2a and b] with the central macular thickness (CMT) of the right eye (RE) and left eye (LE) being 385 μ m and 433 μ m respectively. Full-field 120-point suprathreshold analysis revealed confluent mid-peripheral and central scotoma [Figure 3]. Pure tone audiometry revealed the bilateral absence of air-bone gap and an average hearing loss of 60db suggestive of moderately severe SNHL in both ears [Figure 4]. The assessment for the vestibular system was within the

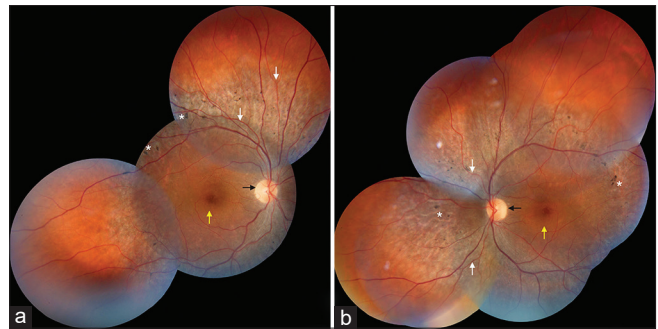


Figure 1: Fundus photo of right (a) and left (b) eye showing bilateral arteriolar attenuation (white arrow), bony spicule like pigmentation in the mid periphery (asterisk), waxy disc pallor (black arrow), and macular edema (yellow arrow)

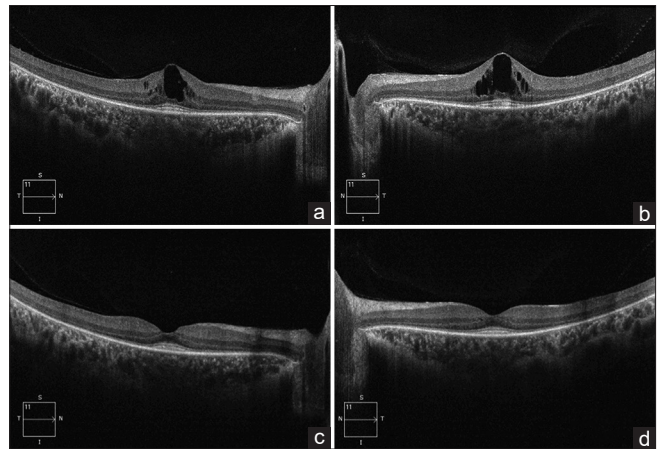


Figure 2: Optical coherence tomography revealed multiple hypo reflective cystoid spaces suggestive of cystoid macular edema in both eyes with the central macular thickness of (a) right eye being 385 μ m and (b) left eye being 433 μ m. Repeat optical coherence tomography after 3 months showed resolution of cystoid macular edema in both eyes-central macular thickness in (c) right eye decreased to 214 μ m and (d) left eye decreased to 216 μ m



Figure 3: Full-field 120-point suprathreshold analysis revealed confluent mid-peripheral and central scotoma in (a) right eye and (b) left eye

normal limits. A clinical diagnosis of Usher syndrome type 3 (USH3) with bilateral CME was made.

She was started on topical carbonic anhydrase inhibitor (CAI) (dorzolamide hydrochloride 2%) thrice daily in BE for macular edema and was advised a hearing aid for SNHL. She was further advised genetic

analysis and electroretinogram, which she declined. Educational and counseling sessions were also provided for the patient and her family. She was followed up, and after 3 months, her BCVA improved to 20/40 in RE and 20/30 in LE and a repeat OCT [Figure 2c and d] showed resolution of CME in BE. CMT in RE decreased from 385 μm to 214 μm and LE from 433 μm to 216 μm .

Discussion

USH consists of a group of autosomal recessive inherited disorders involving visual and audio-vestibular system.^[1-3] It is further sub-classified clinically into three types. Atypical clinical types have also been observed that do not adhere to this easy clinical classification. Some USH1 patients with MYO7A mutation had clinical features suggestive of USH3, and the only way to confirm this atypical clinical subtype is by genetic analysis.^[3] Progress on the molecular genetics and clinical research of USH has revealed broad genetic and clinical heterogeneity, but the genetic analysis is not needed to clinically classify the disease into one of the three classical types.^[3] Clinically, they can be distinguished depending on onset and severity of hearing loss, age of onset of RP, and the presence or absence of vestibular dysfunction. Of all the clinical features, the onset, grade, and progression of SNHL is the most consistent and prominent distinguishing feature among the three types of USH.^[13] Delayed onset of hearing impairment with moderate-to-severe SNHL in our case was the clincher that helped us to clinically diagnose it as type 3 USH. This diagnosis was supported by other clinical findings such as delayed visual impairment with preserved vestibular function and normal developmental milestones. The scope of genetic analysis was beyond the reach of our patients due to economic reason.

Although epiretinal membrane and CME have been reported as the most common macular abnormality in patients with USH type 1 and type 2, data regarding macular abnormality in type 3 USH patients are sparse in literature due to relative rarity of this group.^[2] No

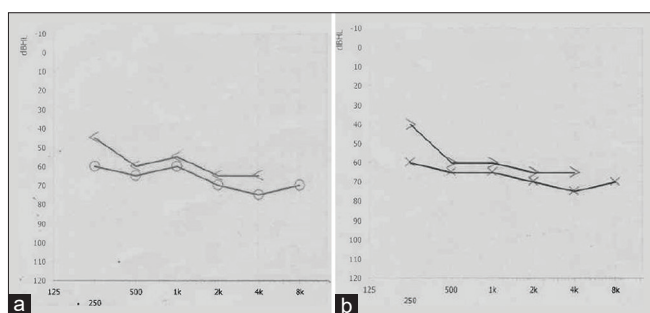


Figure 4: Pure tone audiometry revealed the bilateral absence of air-bone gap and an average hearing loss of 60db suggestive of moderately severe sensorineural hearing loss in both (a) right ear and (b) left ear

single etiology has been definitively established to cause RP CME. It is possible that RP CME may result from a combination of mechanisms, these may include the breakdown of the blood-retinal barrier, failure (or dysfunction) of the pumping mechanism in the RPE, Müller cell edema and dysfunction, antiretinal antibodies, and vitreous traction.^[14,15]

The diagnosis of CME was mostly based on slit-lamp biomicroscopy along with fluorescein angiography before the advent of OCT. Our clinically diagnosed USH 3 patient had CME as evidenced by funduscopy and OCT. Walia *et al.* have reported cystic macular changes in one-fourth of their USH 2 cohort, and highlighted that significant proportion of them did not have any macular changes on clinical funduscopy.^[13] The substantial number of RP patients with CME studied by Hajali and Fishman did not show cystic changes by direct ophthalmoscopy or contact lens biomicroscopy and CME was determined by OCT analysis. Awareness and knowledge of the high incidence for CME in such USH patients can help in identifying these individuals, to provide them with adequate early treatment strategies.^[16] Hence, it is necessary to screen RP patients by OCT to exclude the presence of CME.

Various authors have reported benefits of CAIs therapy (both oral acetazolamide and topical dorzolamide) in patients with CME with RP and USH (type 1 and 2) and they are considered as first-line therapy.^[17-19] Genead and Fishman used an OCT-guided strategy in USH1 and USH2 patients which showed decrease in central foveal thickness in most cases and improvement in visual acuity in one-third of cases.^[19] In patients not responding to CAI treatment, other modalities such as intravitreal steroids (triamcinolone acetonide and sustained-release dexamethasone implant), oral corticosteroid (deflazacort), intravitreal anti-vascular endothelial growth factor agents (ranibizumab and bevacizumab), grid laser photocoagulation, pars plana vitrectomy, or ketorolac have also been found to be effective in improving CME secondary to RP.^[20-23] Regardless of the choice of treatment, rebound of CME was commonly seen in the long term.^[24,25]

Our patient was also started on topical dorzolamide and after 3 months follow-up, CMT in BE reduced significantly with corresponding gain in visual acuity.

Conclusion

CME in type 3 USH is rarely reported in literature. Detailed systemic evaluation and fundus examination should be carried out in all suspected cases. OCT screening can help in excluding the presence of CME in RP patients. CME if present can be treated with

topical dorzolamide with favorable response. However, long-term follow-ups are required to monitor for recurrences. Early diagnosis, proper rehabilitation, and support programs are necessary for such patients to improve their quality of life.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her 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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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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