Case Report

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Childhood cone–rod dystrophy with macular cyst formation in *ABCA4* mutation identified by serial spectral-domain optical coherence tomography

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Abstract:

Cone–rod dystrophy (CORD) is a type of progressive hereditary retinal dystrophies that causes cone predominant photoreceptor degeneration characterized by wide genotypic and phenotypic heterogeneity. Macular cyst (MC) occurs very infrequently in the pediatric age group and has rarely been described in CORD. We report a case of young-onset CORD that was affected by an isolated *ABCA4* mutation complicated by the development of MC. Through serial spectral-domain ocular coherence tomography MC has been observed to persist for 24 months before its resolution, followed by retinal thinning and macular atrophy with corresponding visual acuity decline. The formation of MC and visual acuity appeared to be directly correlated in *ABCA4*-related CORD and its manifestation is invaluable in predicting eventual visual loss. We further speculate that dysfunctional outer blood–retinal barrier may play a role in the pathophysiology of MC development in CORD.

Keywords:

ABCA4, cone–rod dystrophy, cystoid maculopathy, macular cyst, ocular coherence tomography

Introduction

Cone–rod dystrophy (CORD) is a type of progressive retinal dystrophies that causes cone predominant photoreceptor degeneration and is characterized by wide phenotypic and genetic heterogeneity.[1,2] Macular cyst (MC) occurs very infrequently in the pediatric age group and has rarely been described in CORD.[3-5] We report a case of young-onset CORD secondary to an isolated *ABCA4* mutation, which presented with MC in the early stages of disease. Through serial spectral-domain optical coherence tomography (SD-OCT), we were able to diagnose and monitor changes of MC and conclude that its discovery predicated later visual drop.

Case Report

A 4-year-old girl of Chinese origin whose parents were non-consanguineous presented to the ophthalmology service with a 6-month history of vision loss and divergent squint. No family history of blindness was noted. Initial examination revealed best-corrected visual acuity of 0.6 bilaterally. Cycloplegic refraction showed hypermetropia +2.0 D bilaterally. Color vision was normal. Intermittent exotropia of 20 prism diopter was noted, and extraocular movements were full. The anterior segment examination was unremarkable. Fundal examination showed blunted foveal reflex without flecks, bony spicules, and spoke-wheel pattern [Figure 1a]. SD-OCT of macula showed bilateral cystoid

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maculopathy with intraretinal bridging strands and thickened central macula thickness of 349 μ and 346 μ for the right and left eye, respectively [Figure 1b]. X-linked juvenile retinoschisis *(XLRS1)* was initially suspected, but no pathological variant, gene duplication, or deletion for *RS1* gene was detected on sequencing and array comparative genomic hybridization. Subsequent follow-up at 6, 12, 18 and 24 months showed further decline in vision to 0.2 bilaterally and perifoveal thinning [Figure 1c]. SD-OCT showed an interval reduction of bilateral cystoid maculopathy with progressive retinal thinning of macula. Interruption at the photoreceptor, retinal pigment epithelium (RPE), and outer retina were also noticed [Figure 1d and f]. Fundus autofluorescence showed bilateral parafoveal ring hyposignaling representing Bull's eye pattern with peripapillary sparing [Figure 1e]. Full-field electroretinogram (ERG) was performed according to the International Society for Clinical Electrophysiology of Vision Standards and showed marked reduction of cone- and rod-mediated responses, with cone more severely affected (photopic response: right eye a-wave −9.761 uV duration 18 ms and b-wave 15.48 uV duration 25 ms; left eye a-wave −5.693 uV duration 10 ms and b-wave 6.81 uV duration 33 ms [norm a-wave voltage −62.54 ± 32.39 uV duration 12 + 0.2.26 ms and b-wave voltage 163.5 ± 111 uV duration 27.33 ± 2.46 ms]. 30 Hz Flicker: right eye 30.99 uV, trough 16 ms, peak 27 ms; left eye 13.85 uV, trough 10 ms, peak 32 ms [norm peak voltage 131 ± 82uV, trough duration 9.08 ± 2 ms, peak duration 24.17 ± 4 ms]) [Figure 2]. A diagnosis of CORD was made clinically. Further genetic testing of *CRB1* gene was negative. *ABCA4* genetic sequencing returned positive at another tertiary center. Unfortunately, no further information regarding *ABCA4* mutation could be provided. Our patient declined treatment with topical dorzolamide due to potential side effects. Visual rehabilitation was offered to the patient.

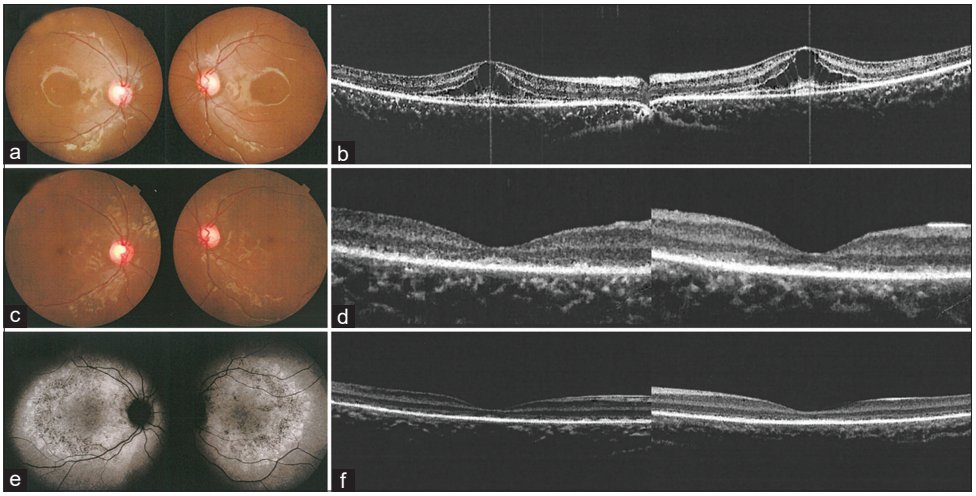

Figure 1: (a) Fundus photograph showing blunted foveal reflex without flecks and bony spicules in *ABCA4*-related cone–rod dystrophy. (b) Spectral-domain optical coherence tomography of the macula revealed bilateral macular cysts with bridging strands in *ABCA4*-related cone–rod dystrophy. (c) Fundus photograph showing progressive perifoveal thinning and early atrophy 1 year after onset. (d) Resolution of bilateral macular cysts 1 year after onset. (e) Bilateral fundus autofluorescence showing "Bull's eye" maculopathy. (f) Progressive bilateral foveal atrophy and retinal thinning at 2 years after onset

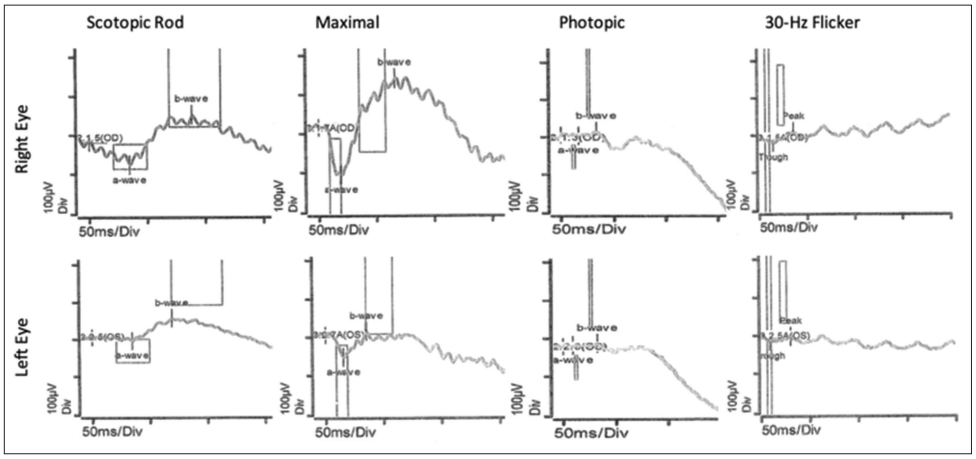

Figure 2: Full-field electroretinography finding displaying bilateral cone predominant abnormalities in *ABCA4*-related cone–rod dystrophy

Discussion

CORD is a type of generalized progressive retinal dystrophies that causes cone predominant photoreceptor degeneration.[2] Typically, CORD presents with loss of visual acuity, color vision deficits, and central visual field impairment, which are associated with fundoscopic features of RPE change, followed by perifoveal RPE atrophy in a ring fashion, resulting in "Bull's eye" maculopathy. In later stages, RPE atrophy tends to extend to the mid-peripheries accompanied by the attenuation of vessels and temporal pallor of optic disc.[1] Fundus autofluorescence and SD-OCT are essential in identifying subtle changes of RPE changes and to rule out other differential diagnosis. ERG is crucial in diagnosis of CORD, where cone response is found to be reduced predominantly. In the advanced stages of disease, both cone and rod response will eventually be diminished. To date, 21 genes have been identified to produce CORD, with *ABCA4* gene mutation found to cause autosomal recessive CORD.[6,7] The genotype–phenotypic correlation in *ABCA4*-related CORD, however, is heterogeneous and appears to have a wide clinical spectrum.[8]

The development of MC in the pediatric age group is commonly associated with hereditary retinal dystrophies and is divided into leaking and nonleaking subtypes based on their underlying pathophysiology.[9,10] In retinitis pigmentosa, leaking MC is believed to occur as a result of leakage of fluid from failing RPE pumps, vitreomacular traction, and nonimmune response from toxic products released from the degenerating retina.[6,11,12] Nonleaking MC is associated with mutations of genes that are related to the maintenance of retinal architecture, which includes *CHM*, *NR2E3*, *XLRS1,* and *CRB1*.[13] *CHM* at Xq21.2 encodes for Rab escort protein 1 (REP-1) that controls intracellular trafficking and outer disc membrane shedding of RPE, which is postulated to cause choroideremia and nonleaking MC.[14,15] *NR2E3* genetic mutation at 15q23 results in enhanced S-cone syndrome, Goldmann–Favre syndrome, and clumped pigmentary retinal degeneration.[16] MC formation in *NR2E3* mutation is believed to be related to the inability to form tight junctions between hybrid rod–cone cells, which results in MC and typically found located at outer plexiform and inner nuclear layer.[17] *XLRS1* gene at Xp22.1 is responsible for retinoschisin production, and mutations result in MC due to dysfunctional cellular adhesion.[18] *CRB1* gene at 1q31.3, which is known to cause retinitis pigmentosa, CORD, and Leber congenital amaurosis, is crucial in the development of photoreceptors and Drosophila crumbs protein function.[19] It is believed that MC formation is due to dysfunctional assembly of zonula adherens and maintenance of apical–basal polarity in epithelial cells.[20] CORD-associated MC is infrequent. MC was first identified in CORD with time-domain OCT in 2001 and later with SD-OCT on a 25-year-old male with clinical CORD.[5,21] A proband of childhood-onset CORD due to *CRB1* mutation was also found to have MC.[3] However, a large retrospective review of 36 CORD patients did not reveal the presence of MC, which included three patients with possible, likely or definite disease-causing sequence variations in *ABCA4* gene.[4]

We present the first case of young-onset CORD secondary to an isolated *ABCA4* mutation, which was complicated by the development of MC in the early stages of disease. *ABCA4* encodes for photoreceptor transmembrane protein that transports a visual cycle intermediate, *N*-retinylidene-phosphatidylethanolamine, from the inner to the outer leaflet of the disc membrane.[22] Dysfunctional *ABCA4* is responsible for a wide range of clinical findings as a result of different degrees of impact on RPE and photoreceptor, with mild genotype causing Stargardt disease, moderate genotype causing selective injury on cone cells to result in CORD, and severe genotype causing rod and cone injury, resulting in autosomal recessive retinitis pigmentosa.[6,23-26] The underlying etiology for MC development in *ABCA4*-related CORD remains elusive. We postulate that the pathophysiology of MC formation is linked to dysfunctional outer blood–retinal barrier.[27,28] This is evidenced by the fact that impairment of blood–retinal barrier, which is a contributing factor for the development of MC in retinitis pigmentosa, is also being demonstrated in CORD.[29,30] The relatively few prevalence of MC in CORD compared with other hereditary retinal dystrophies remains to be investigated.

The natural progression of MC in CORD has been observed in our study. Previous studies have shown an inconsistent correlation between visual acuity, size of cystoid spaces, and retinal thickness in hereditary retinal dystrophies. Our study has revealed a direct relationship between visual acuity and the appearance of MC. Serial SD-OCT monitoring has demonstrated gradual visual acuity deterioration upon MC resolution, a novel finding that has not been reported previously in CORD. The onset and resolution of MC, followed by retinal thinning and atrophy of the macular, took 24 months in our proband. The time of dissolution of MC allows the prediction of visual loss, which may be a useful prognostic indicator in *ABCA4*-related CORD.

The use of carbonic anhydrase inhibitor (CAI) in the preservation of retinal architecture, delaying visual decline, and atrophic maculopathy has been employed in different hereditary retinal dystrophies, resulting in variable success.[31,32] Studies on CAI on CORD-related MC are few but encouraging, with a case report showing

efficacy and complete resolution of bilateral cystic maculopathy after treatment with topical dorzolamide.[33] Further studies are required to ascertain its efficacy in CORD.

Conclusion

We present a case of young-onset CORD secondary to an isolated *ABCA4* genetic mutation, which was complicated by the development of MC. The formation of MC in CORD is rare, and its pathophysiology remains unclear, although impairment of outer blood–retinal barrier function has been speculated. Identification of MC with SD-OCT remains an important and useful tool for diagnosis, prognostic evaluation, and monitoring purposes. In our study, we have demonstrated that the MC lasted for 24 months from its onset until resolution in *ABCA4*-related CORD. The appearance of MC and visual acuity appeared to be directly correlated and is invaluable in predicting eventual visual loss in CORD.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for the patient's images and other clinical information to be reported in the journal. The guardian understands that the patient's name and initials will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

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

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