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

Kai Ching Peter Leung*, Tak Chuen Simon Ko

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.3,4 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 predicted 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
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 hypofluorescing 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
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.[3] 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.[4,5] The genotype–phenotypic correlation in ABCA4-related CORD, however, is heterogeneous and appears to have a wide clinical spectrum.[6]

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, XLR51, 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] XLR51 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.[8,21] A proband of childhood-onset CORD due to CRB1 mutation was also found to have MC.[5] 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
effect and complete resolution of bilateral cystic maculopathy after treatment with topical dorzolamide.\textsuperscript{33} Further studies are required to ascertain its efficacy in CORD.

**Conclusion**

We present a case of young-onset CORD secondary to an isolated \textit{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 \textit{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.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

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

**References**

1. Berger W, Kloekener-Gruissem B, Neidhardt J. The molecular basis of human retinal and vitreoretinal diseases. Prog Retin Eye Res 2010;29:335-75.
2. Hamel CP. Cone rod dystrophies. Orphanet J Rare Dis 2007;2:7.
3. Khan AO, Aldahmesh MA, Abu-Safieh L, Alkuraya FS. Childhood cone-rod dystrophy with macular cystic degeneration from recessive CRB1 mutation. Ophthalmic Genet 2014;35:130-7.
4. Salvatore S, Genead MA, Fishman GA. The prevalence of macular cysts in patients with clinical cone-rod dystrophy determined by spectral-domain optical coherence tomography. Ophthalmic Genet 2014;35:47-50.
5. Emfietzoglou I, Grigoropoulos V, Nikolaidis P, Theodossiadis G, Rouvas A, Theodossiadis P. Optical coherence tomography findings in a case of cone-rod dystrophy. Ophthalmic surgery, lasers & imaging: The official journal of the International Society for Imaging in the Eye 2010;41 Online:e1-3. doi:10.3928/15428877-20101124-10.
6. Fishman GA, Stone EM, Eliason DA, Taylor CM, Lindeman M, Derlacki DJ. \textit{ABCA4} gene sequence variations in patients with autosomal recessive cone-rod dystrophy. Arch Ophthalmol 2003;121:851-5.
7. Duroq D, Rozet JM, Gerber S, Perrault I, Barbet D, Hanein S, et al. The \textit{ABCA4} gene in autosomal recessive cone-rod dystrophies. Am J Hum Genet 2002;71:1480-2.
8. Klevering BJ, Blankenagel A, Mauger E, Cremers FP, Hoyng CB, Rohrschneider K. Phenotypic spectrum of autosomal recessive cone-rod dystrophies caused by mutations in the \textit{ABCA4} (ABCR) gene. Invest Ophthalmol Vis Sci 2002;43:1980-5.
9. Gass JDM. Müller Cell Cone, an Overlooked Part of the Anatomy of the Fovea Centralis. Arch Ophthalmol 1999;117:821. doi:10.1001/archopht.117.6.821.
10. Ganesh A, Sroth E, Manayah GJ, Al-Zuhairi S, Levin AV. Macular cysts in retinal dystrophy. Curr Opin Ophthalmol 2011;22:332-9.
11. Spalton DJ, Rahi AH, Bird AC. Immunological studies in retinitis pigmentosa associated with retinal vascular leakage. Br J Ophthalmol 1978;62:183-7.
12. Cox SN, Hay E, Bird AC. Treatment of Chronic Macular Edema With Acetazolamide. Arch Ophthalmol 1988;106:1190-5. doi:10.1001/archopht.1988.01060140350030.
13. Lingao MD, Ganesh A, Karthikeyan AS, Al Zuhairi S, Al Hosni A, Al Khayat A, et al. Macular cystoid spaces in patients with retinal dystrophy. Ophthalmic Genet 2016;37:377-83.
14. Cordovez JA, Traboulsi EI, Capasso JE, et al. Retinal Dystrophy with Intraretinal Cystoid Spaces Associated with Mutations in the Crumbs Homologue (CRB1) Gene. Ophthalmic Genetics 2015;36:257-64. doi:10.3109/13816810.2014.881505.
15. Strunnikova NV, Barb J, Sergeev YV, et al. Loss-of-function mutations in rab escort protein 1 (REP-1) affect intracellular transport in fibroblasts and monocytes of choroideremia patients. PLoS ONE 2009;4(12). doi:10.1371/journal.pone.0008402.
16. Soin EH, Chen FK, Rubin GS, Moore AT, Webster AR, MacLaren RE. Macular function assessed by microperimetry in patients with enhanced S-cone syndrome. Ophthalmology 2010;117:199-2060.
17. Genead MA, Fishman GA. Cystic macular oedema on spectral-domain optical coherence tomography in choroideremia patients without cystic changes on fundus examination. Eye (Lond) 2011;25:84-90.
18. Sauer CG, Gehrig A, Warneke-Wittrock R, Marquardt A, Ewing CC, Gibson A, et al. Positional cloning of the gene associated with X-linked juvenile retinoschisis. Nat Genet 1997;17:164-70.
19. Tepass U, Theres C, Knust E. crumbs encodes an EGF‑like protein with intraretinal cystoid spaces associated with mutations in the crumbs homologue (crb1) gene. Ophthalmic Genetics 2015;36:257‑64. doi:10.3109/13816810.2014.881505.
20. Stanga PE, Downes SM, Abuja RM, Chong NH, Antcliff R, Reck AC, et al. Comparison of optical coherence tomography and fluorescein angiography in assessing macular edema in retinal dystrophies: Preliminary results. Int Ophthalmol 2001;23:321-5.
21. Weng J, Mata NL, Azarian SM, Tzekov RT, Birch DG, Travis GH. Insights into the function of Rim protein in photoreceptors and etiology of Stargardt’s disease from the phenotype in abcr knockout mice. Cell 1999;100:13-23.
22. Sheffield VC, Stone EM. Genomics and the Eye. Feero WG, Guttmacher AE, editors. New England J Med 2011;364:1932-42.
23. Rozet JM, Gerber S, Ghazi I, et al. Mutations of the retinal specific ATP binding transporter gene (ABCR) in a single family segregating both autosomal recessive retinitis pigmentosa RP19 and Stargardt disease: evidence of clinical heterogeneity at this locus. J Med Genetics 1999;36:447-51. doi:10.1136/jgm.36.6.447.
24. Martinez-Mir A, Paloma E, Allikmets R, Ayyuso C, del Rio T, Dean M, et al. Retinitis pigmentosa caused by a homozygous mutation in
26. Allikmets R, Singh N, Sun H, Shroyer NF, Hutchinson A, Chidambaram A, et al. A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy. Nat Genet 1997;15:236-46.

27. Vinores SA, Derevjanik NL, Ozaki H, Okamoto N, Campochiaro PA. Cellular mechanisms of blood-retinal barrier dysfunction in macular edema. Doc Ophthalmol 1997;97:217-28.

28. Fishman GA, Cunha-Vaz J, Salzano T. Vitreous fluorophotometry in patients with retinitis pigmentosa. Arch Ophthalmol 1981;99:1202-7.

29. Fishman GA, Rhee AJ, Blair NF. Blood-retinal barrier function in patients with cone or cone-rod dystrophy. Arch Ophthalmol 1986;104:545-8.

30. Miyake Y, Goto S, Ito I, Ichikawa H. Vitreous fluorophotometry in patients with cone-rod dystrophy. Br J Ophthalmol 1984;68:489-93.

31. Gelman SK, Gorin MB. Significant macular edema in a patient with cone dystrophy and improvement with acetazolamide treatment. Retin Cases Brief Rep 2014;8:300-5.

32. Scruggs BA, Chen CV, Pfeifer W, Wiley JS, Wang K, Drack AV. Efficacy of topical brinzolamide in children with retinal dystrophies. Ophthalmic Genet 2019;40:350-8.

33. Larrañaga-Fragoso P, Pastora N, Bravo-Ljubetic L, Peralta J, Abellanas-Gómez J. Topical carbonic anhydrase inhibitors in macular edema associated with Alström syndrome. Ophthalmic Genet 2016;37:427-9.