This is a non-final version of an article published in final form in Choi, Kai Yip, Wong, Horace Ho Yin, Chan, Henry Ho Lung. Utilizing Advanced Technology to Facilitate Diagnosis of Rare Retinal Disorders: A Case of Bietti Crystalline Dystrophy. Optometry and Vision Science 98(9):p 1031-1038, September 2021. DOI: 10.1097/OPX.0000000000001763. Optometry and Vision Science is available at https://journals.lww.com/optvissci/pages/default.aspx.

Title

Utilizing Advanced Technology to Facilitate Diagnosis of Rare Retinal Disorders - A Case of Bietti Crystalline Dystrophy

Authors

Choi, Kai Yip, PhD,[1] Wong, Horace Ho Yin, BSc, FAAO,[1] Chan, Henry Ho Lung, PhD, FAAO[1,2]

[1] Laboratory of Experimental Optometry (Neuroscience), School of Optometry, The Hong Kong Polytechnic University, Hong Kong

[2] Center for Eye and Vision Research, Hong Kong

Running title

Bietti crystalline dystrophy

Correspondence

Chan Henry Ho Lung (henryhl.chan@polyu.edu.hk)

School of Optometry, The Hong Kong Polytechnic University, 11 Yuk Choi Road, Hung Hom, Kowloon, Hong Kong

SIGNIFICANCE:

Optometrists, as primary eye care providers, encounter patients with rare ocular disease such as Bietti crystalline dystrophy from time to time. Utilizing the advanced technologies, which are also useful in manging common ocular conditions, to facilitate a prompt diagnosis is highly recommended.

PURPOSE:

This report describes a patient with clinically diagnosed Bietti crystalline dystrophy with findings on funduscopy, multimodal imaging, and visual electrophysiology.

CASE REPORT:

A 41-year-old Chinese female was referred to our clinic to test for retinitis pigmentosa, who had subjectively progressing dimmed vision (especially in the left eye) for 9 months. Best-corrected visual acuities were 6/6 and 6/7.6 in the right and left eye, respectively. Funduscopy revealed multiple crystalline deposits on the posterior pole in both eyes. The 30-2 perimetry displayed bi-infero-temporal scotoma (left > right eye). Scotopic flash electroretinogram (ERG) was normal, while photopic ERG was slightly attenuated. Electro-oculogram showed an abnormal adaptation time course of the retinal pigmented epithelium (RPE). Multifocal ERG revealed a decreased central retinal response, but para-central responses were relatively better preserved. Optical coherence tomography showed multiple patches of RPE atrophy, with disruption of the left ellipsoid zone. Outer retinal tubulations, hyper-reflective dots on RPE-Bruch's membrance interface, and intra-retinal bright spots were also identified.

CONCLUSIONS:

Rare ocular diseases like Bietti crystalline dystrophy can be encountered by optometrists. This case report shows the ophthalmic findings of a rare chorio-retinal dystrophy, and provides insight on how to better-utilize advanced equipment in an optometric practice to facilitate prompt diagnoses.

Bietti crystalline dystrophy is a rare tapeto-retinal disease that occurs as a result of an autosomal recessive genetic mutation in the CYP4V2 gene (Online Mendelian Inheritance in Man identifier, 210370).[1] Its prevalence has been reported to be 3% in patients with non-syndromic retinitis pigmentosa and is estimated to affect 1 in 67,000.[2] Bietti crystalline dystrophy is more commonly found in East-Asian countries, especially China, where over 21,000 cases have been reported, and Japan,[3] than Western countries where the incidence is 1 in 4,500,000,[4] where only 5,000 and 10-12 patients have been reported in the U.S. and Spain, respectively.

Bietti crystalline dystrophy was first described by Bietti in 1937 as the presence of characteristic multiple glistering crystals on the posterior pole of the fundus, which are associated with progressive retinal pigment epithelium atrophy and choroidal sclerosis. Superficial limbal-corneal crystalline deposit was also reported in approximately one-third of the patients with this condition.[5] Because of the clinical presentation, the differential diagnosis includes flecked retina syndrome, retinitis punctate albesens, cytinosis, drug (for example tamoxifen) toxicity, talc retinopathy, and retinopathy due to Sjogren-Larsson Syndrome. Patients experience decreased visual acuity, especially in their nocturnal vision, and scotomas in perimetry test depending on the stage of the disease. Currently, the disease is incurable and due to its progressive nature, the long-term prognosis may be blindness.

Optometric practices are often equipped with advanced tools to facilitate a prompt diagnosis and management of common ocular diseases, including, but not limited to, glaucoma, macular degeneration, and diabetic retinopathy. These tools, for instance,

imaging devices and electro-diagnostics, can also be utilized to aid the diagnosis in rare ocular conditions such as Bietti crystalline dystrophy.

CASE REPORT

No identifiable health information is included in this case report. LTY, a 41-year-old Chinese female, was referred to the university optometry clinic because of suspected retinitis pigmentosa. The patient reported slowly progressing vision loss in both night- and daytime, especially in the left eye, which became apparaent approximately 9 months ago (Figure 1). She reported an unremarkable family history and ocular history, except for an uneventful refractive surgery in 2003. Her pre-operative refractive error was reported to be approximately -6 D of myopia and 2 D of astigmatism. She was not taking any medications or suffered trauma to the eye.

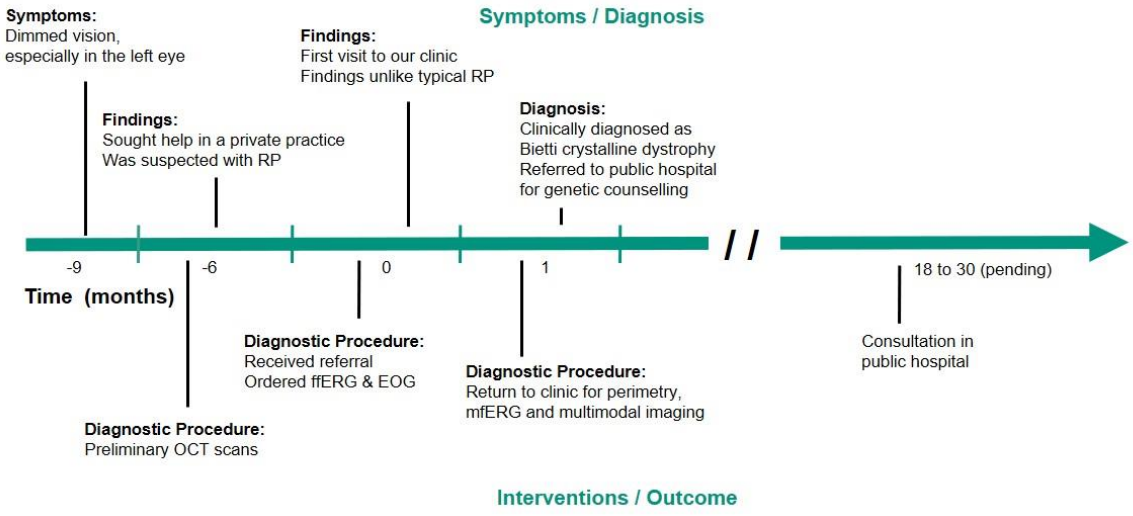


Figure 1. Clinical timeline of a 43-year-old Chinese female clinically diagnosed with Bietti crystalline dystrophy. Abbreviations: OCT = Optical coherence tomography, ffERG = Full-field electroretinogram, EOG = Electro-oculogram, mfERG = Multifocal electroretinogram, RP = Retinitis pigmentosa

On initial examination, the best-corrected visual acuity was 6/6 and 6/7.6 in the right and left eyes, respectively, measured by crowded line Sloan letters on a computerized acuity chart. The central and para-central fundus photographs are shown in Figure 2, in which multiple tiny glistening crystals cam be observed over the posterior pole in both eyes. However, her cornea did not exhibit any crystalline deposits. Full-field electroretinogram and electro-oculogram, following the International Society for Clinical Electrophysiology of Vision standards,[6, 7] were performed in the initial visit to evaluate the function of the retina in both photopic and scotopic conditions. The scotopic 0.01 and 3.0 rod responses

were normal (Figures 3A and B) while the photopic 3.0 cone response was slightly attenuated (Figure 3C), which was also indicated by 30 Hz flicker responses (Figure 3D). The full-field electroretinogram responses from both eyes were symmetrical. However, the electro-oculogram showed an abnormal adaptation time course of the retinal pigment epithelium, which was more severe in the left eye (Figure 3E).

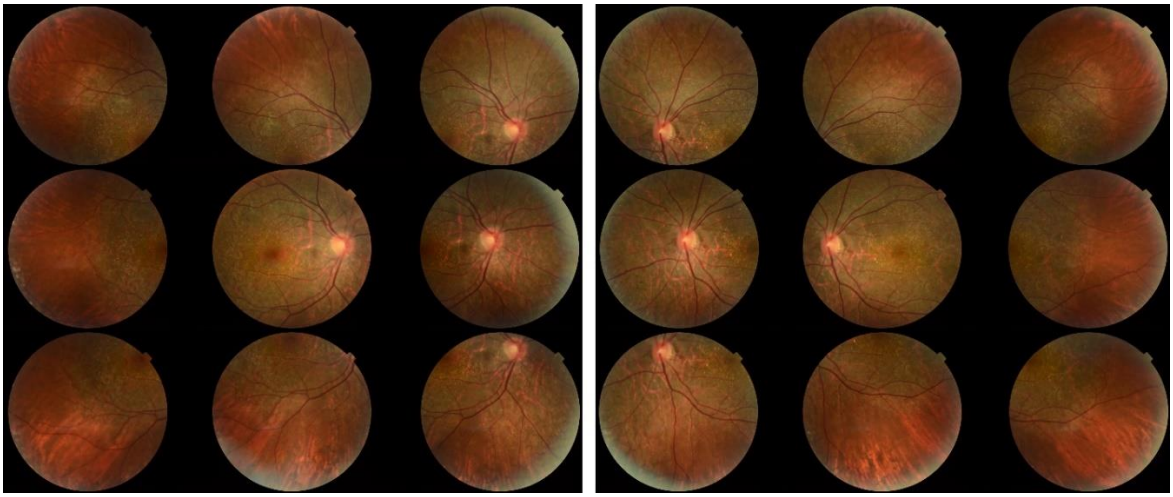


Figure 2. Central and para-central fundus photographs

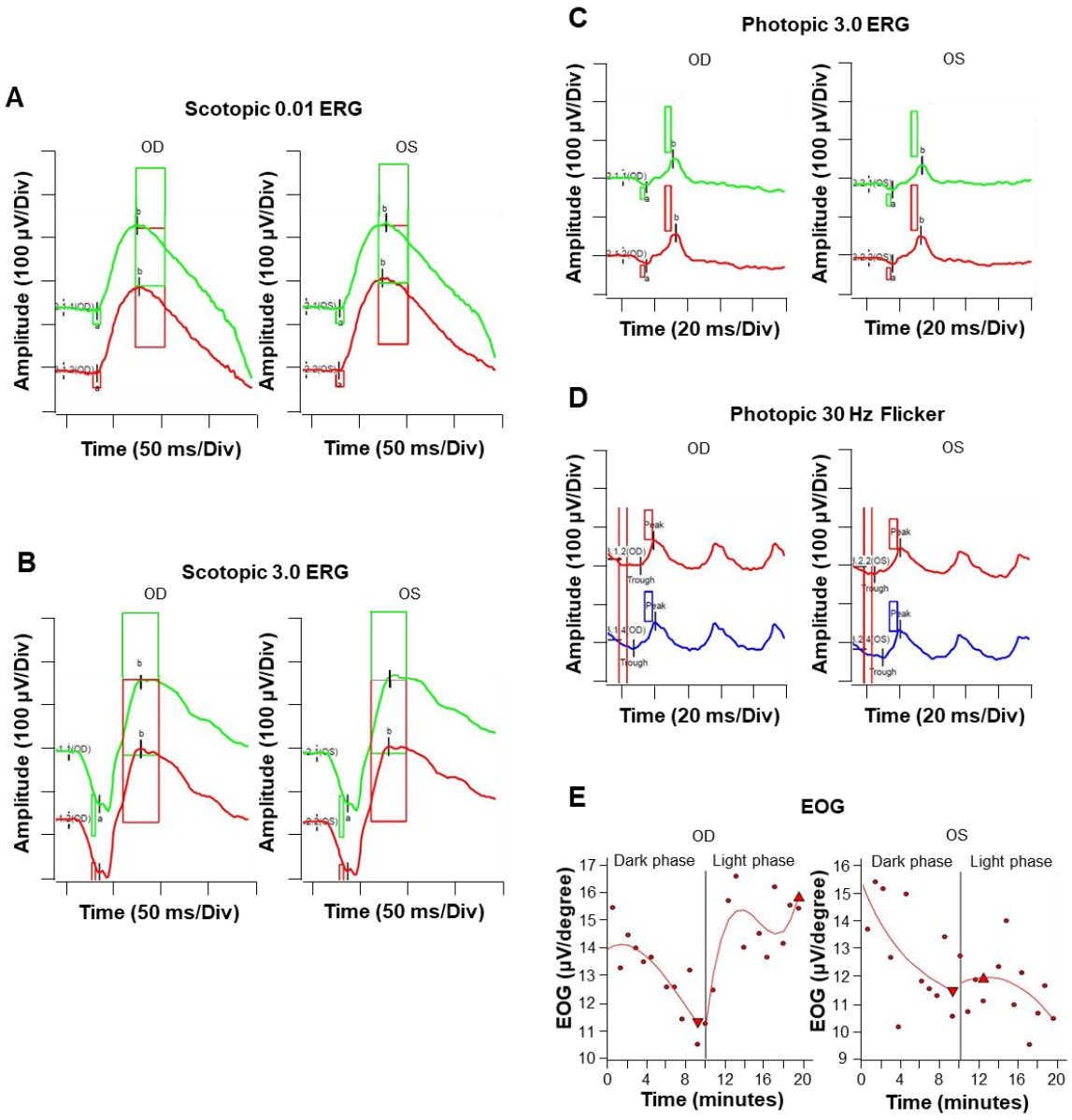


Figure 3. Full-field electroretinogram (A: Scotopic 0.01 response; B: Scotopic 3.0 response; C: Photopic 3.0 response; D: Photopic 30 Hz flicker responses) and E: Electro-oculogram

As the clinical and electrophysiological presentations were unlike retinitis pigmentosa, patient was asked to return for perimetry, multimodal imaging, and a multifocal electroretinogram. The 30-2 Swedish Interactive Thresholding Algorithm-Standard perimetry recorded a mean deviation and a pattern standard deviation of -7.55 dB and 10.08 dB in the right eye, and -7.07 dB and 9.46 dB in the left eye. A relative scotoma on the interior temporal quadrant was detected in both eyes, which was larger in the left eye. Spectra-domain optical coherence tomography imaging revealed multiple patches of retinal pigment epithelium atrophy (Figure 4), with disruption of the ellipsoid zone in the left eye. Outer retinal tubulations were identified, which grossly corresponded to the location of the perimetric scotoma (Figure 4B, white arrows). Hyper-reflective dots on retinal pigment epithelium-Bruch's membrane interface were found to correspond to crystalline deposits on the fundus (Figure 4B, yellow arrows). Intra-retinal bright spots were also observed (Figure 4C, blue arrows). Fundus auto-fluorescence imaging revealed hypo-fluorescence in areas with retinal pigment epithelium atrophy and multiple hyper-fluorescence dots over the posterior pole in both eyes (Figure 5A). The multicolour imaging allowed better visualization of the retinal crystalline deposits than conventional funduscopy (Figure 5B). No choroidal neovascularisation or blood vessel leakage was identified by optical coherence tomography-angiography. The multifocal electroretinogram revealed a decreased central retinal response, but a relatively better-preserved para-central retinal signal (Figure 6). The patient was clinically diagnosed with Bietti crystalline dystrophy and referred to a retinal specialist and for genetic counselling to look for a mutation in CYP4V2 gene. Familial checking was also advised. As the patient was experiencing relatively normal

visual acuity and acceptable visual field extent, visual rehabilitation was discussed, but not arranged at this stage.

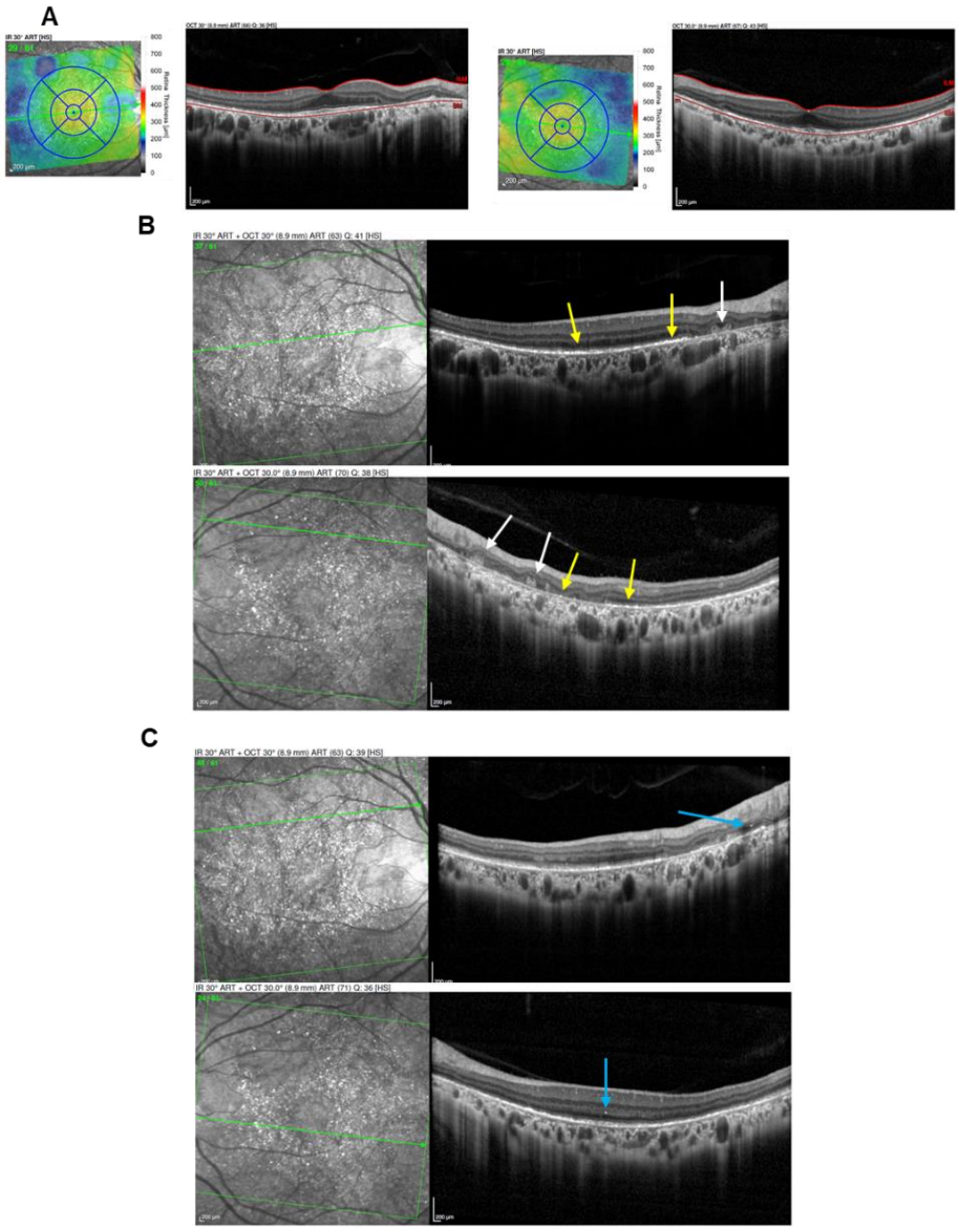
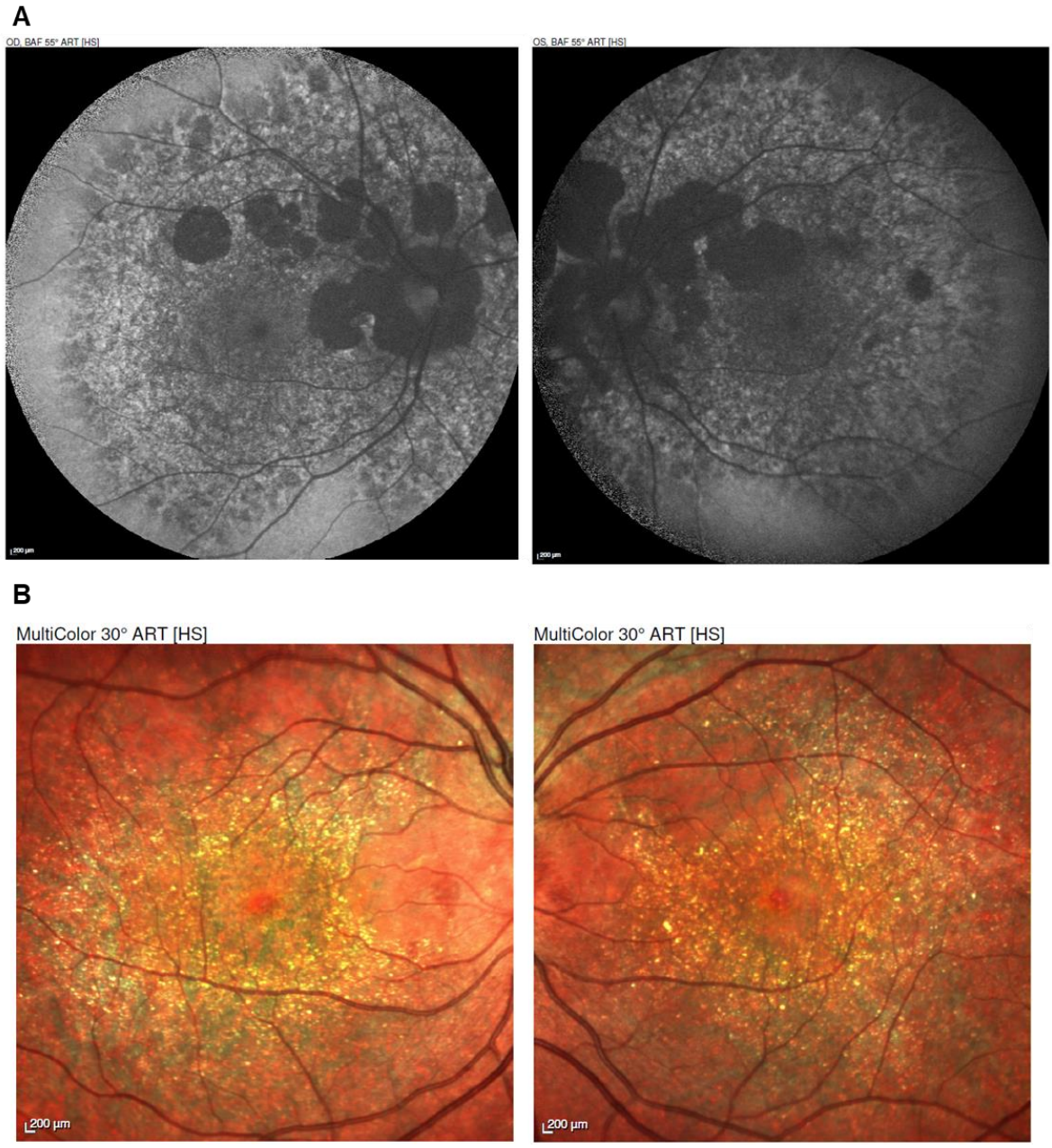


Figure 4. Spectral-domain optical coherence tomography. A: Volume scan with multi-patches of retinal epithelial atrophy; B: Outer retinal tubulations (white arrows) and hyper-reflective dots correspondent to crystalline deposits (yellow arrows); C: Intra-retinal bright spots (blue arrows)



134

135 Figure 5. Multimodal imaging. A: Fundus auto-fluorescence; B: Multi-colour imaging

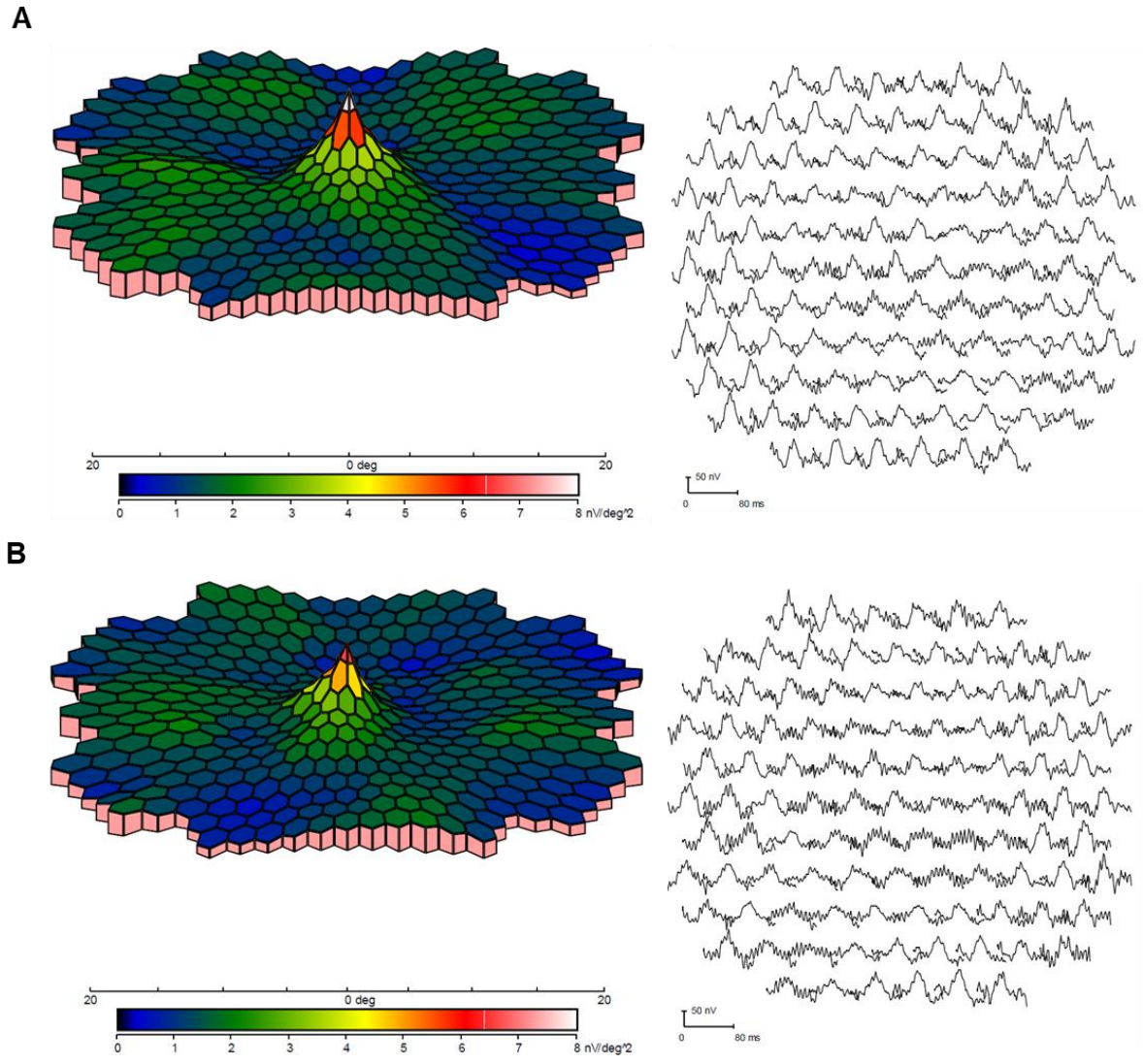


Figure 6. Multifocal electroretinogram with 3-dimensional plots of response density and trace arrays, with diminished central retinal response. A: Right eye; B: Left eye

DISCUSSION

This report presents a case of clinically diagnosed Bietti crystalline dystrophy in a 41-year-old Chinese female, in which the genetic testing for CYP4V2 mutation is required to further confirm the diagnosis.[1, 2]

The clinical findings are mostly consistent with previous reports of fundus appearance with multiple glistering crystals located on the retinal pigment epithelium -Bruch's membrane interface – observed using optical coherence tomography, as well as other optical coherence tomography findings, including retinal pigment epithelium atrophy, outer retinal tubulations, and intra-retinal bright spots.[9, 10] The absence of corneal crystals in this case was also in line with the previously reported high prevalence of purely retinal involvement in Asians.[3] The disruption of the foveal ellipsoid zone may explain the subjectively worse vision in the left eye, but it was not reflected in the generally symmetric full-field electroretinogram and multifocal electroretinogram responses. Whether structural deficit precedes functional deficits, or vice versa, warrants further study.

Although Bietti crystalline dystrophy often onsets between the second and fourth decades,[2] the disease progression rate varies between individuals but prognosis is poor as the condition may ultimately result in blindness.[4] Classically, the disease is categorized into three stages: (1) retinal pigment epithelium atrophy with fine-sized crystalline deposits near the macular area; (2) retinal pigment epithelium atrophic areas enlarged and extended beyond the posterior pole, while choriocapillaris atrophy is present on the posterior pole; (3) extensive retinal pigment epithelium -choriocapillaris atrophy over the fundus.[11] Despite the good visual acuity and full-field electroretinogram responses, this patient was currently

classified as stage 2, because the retinal pigment epithelium atrophy reached beyond the posterior pole.

Furthermore, the incurable nature of the disease may lead to a blinding prognosis. Recent research shed light on epigenetic factor modifications, as well as gene therapies to provide possible therapeutic effect on retinal dystrophies including Bietti crystalline dystrophy.[12-14] With a clinical database registry with genetic and lifestyle information, the epigenetic research could be accelerated to promote patient care and health care planning.[4]

An early diagnosis of Bietti crystalline dystrophy may sometimes be difficult because of the asymptomatic nature of the early stages.[4] As funduscopy findings can sometimes be misidentified as other less significant signs, such as scattered drusens, the use of proper clinical equipment can facilitate a more accurate diagnosis.[9, 10] In this case, the patient was referred to the clinic to check for retinitis pigmentosa, for which a full-field electroretinogram and electro-oculogram were ordered at the first visit, as in regular cases. However, her full-field electroretinogram appeared normal, especially in scotopic condition, while the electro-oculogram was compromised, which has previously been reported as an atypical form of electro-retinal responses found in Bietti crystalline dystrophy.[15] Hence, a multifocal electroretinogram was useful to detect localized changes, as it revealed a compromised central retinal function in this patient.

Optometrists, as primary eye care providers, are well capable of diagnosing and managing common ocular diseases such as glaucoma, macular degeneration, and diabetic retinopathy, which can also be aided with advanced diagnostic technologies. Occasionally, patients with rare ocular diseases could be encountered. In such cases, utilizing the advance diagnostic

tools may enhance eye care practitioners' competency and confidence in their diagnosis and management.[16] The techniques applied in the current case report, optical coherence tomography and electroretinography, are gaining importance in optometric practice, as they are useful for diagnosis of clinical conditions including glaucoma, macular degeneration, and diabetic retinopathy and for distinguishing symptomatically similar retinal and neurological disorders.[17, 18] In particular, due to the quantified nature of the outcomes, longitudinal monitoring of disease progression and comparison with normative data has highlighted their clinical significance. While the scope of practice of optometrists is rather diversified in different countries, ranging from only refractive corrections to therapeutic practice, most optometrists are eligible to use diagnostic drugs, including local anaesthetics, mydriatic, and cycloplegic agents.[19] In addition to slit-lamp biomicroscopy and funduscopy, access to advanced diagnostic ophthalmic equipment, for example the forementioned optical coherence tomography and electroretinography, has become more common,[20-22] aiding eye care providers in making a prompt diagnosis to benefit patients with respect to disease management and economic savings.[23] The increasing revenue generated for the practitioners in the past two decades may have also provided extra incentives for improved equipping of optometry practices in the private sector. According to the report, assuming the revenue per scan was USD44 each for 30 minutes in 8 hours per day, a 100% utilization of an optical coherence tomography device would generate USD200k every year. Even with a reduced utilization rate and other operational costs, the initial cost of the instrument of approximately USD60k, the return on capital would still be attractive to investors.[24]

With rapid technological developments, currently “advanced” equipment gradually becomes commonplace, enabling financial and spatially economic equipment,[25] which are capable of performing the same task as their bulky counterparts,[26] or combining multi-functions in a single piece of equipment. For instance, a handy and affordable visual electrodiagnostic tool was developed recently, which eliminated the need for complicated electrode setups, or even mydriasis.[27] The authors also speculate that the maturation of 3-dimensional printing technique and the use of open-source hardware[28] may accelerate the process of universalising the “advanced” diagnostic equipment in not only research institutes, but also primary eye care providers as end users.

In conclusion, Bietti crystalline dystrophy is a rare chorioretinal dystrophy, which can sometimes be difficult to identify and diagnose. Although the outcome for this patient may not differ from being diagnosed 1.5 years later in the public hospital, a prompter diagnosis can ameliorate patient anxiety, as well as improve patient loyalty. On the other hand, many other rare conditions would have the prognosis deteriorated with a delayed diagnosis and management. Utilizing the advanced diagnostic tools in optometric practices should be considered to maximize the scope of practice, which can be beneficial to both the optometrists and patients with ocular diseases.

ACKNOWLEDGEMENT

223 The authors thank the University Research Facilities in Behavioral and Systems
224 Neuroscience (UBSN), The Hong Kong Polytechnic University, for facility supports. The
225 authors also thank Dr. Maureen Boost to proofread the revised version of the manuscript.

REFERENCES

1. Li A, Jiao X, Munier FL, et al. Bietti Crystalline Corneoretinal Dystrophy Is Caused by Mutations in the Novel Gene CYP4V2. Am J Hum Genet 2004;74:817-26.
2. Abeshi A, Bruson A, Beccari T, et al. Genetic Testing for Bietti Crystalline Dystrophy. EuroBiotech J 2017;1:20-2.
3. Lin J, Nishiguchi K, Nakamura M, et al. Recessive Mutations in the CYP4V2 Gene in East Asian and Middle Eastern Patients with Bietti Crystalline Corneoretinal Dystrophy. J Med Genet 2005;42:e38.
4. García-García G, Martínez-Rubio M, Moya-Moya M, et al. Current Perspectives in Bietti Crystalline Dystrophy. Clin Ophthalmol 2019;13:1379.
5. Bagolini B, Ioli-Spada G. Bietti's Tapetoretinal Degeneration by Marginal Corneal Dystrophy. Am J Ophthalmol 1968;65:53-7.
6. McCulloch DL, Marmor MF, Brigell MG, et al. ISCEV Standard for Full-Field Clinical Electroretinography (2015 Update). Doc Ophthalmol 2015;130:1-12.
7. Constable PA, Bach M, Frishman LJ, et al. ISCEV Standard for Clinical Electro-Oculography (2017 Update). Doc Ophthalmol 2017;134:1-9.
8. Hood DC, Bach M, Brigell M, et al. ISCEV Standard for Clinical Multifocal Electroretinography (mfERG) (2011 Edition). Doc Ophthalmol 2012;124:1-13.
9. Oishi A, Oishi M, Miyata M, et al. Multimodal Imaging for Differential Diagnosis of Bietti Crystalline Dystrophy. Ophthalmol Retina 2018;2:1071-7.

10. Tiryaki Demir S, Keles Yesiltas S, Kacar H, et al. Optical Coherence Tomography and Optical Coherence Tomography Angiography Imaging in Bietti Crystalline Dystrophy. Ophthalmic Genet 2020;41:194-7.

11. Yuzawa M, Mae Y, Matsui M. Bietti's Crystalline Retinopathy. Ophthalmic Paediatr Genet 1986;7:9-20.

12. Herceg Z, Hainaut P. Genetic and Epigenetic Alterations as Biomarkers for Cancer Detection, Diagnosis and Prognosis. Mol Oncol 2007;1:26-41.

13. Hata M, Ikeda HO, Iwai S, et al. Reduction of Lipid Accumulation Rescues Bietti's Crystalline Dystrophy Phenotypes. Proceedings of the National Academy of Sciences 2018;115:3936-41.

14. Miraldi Utz V, Coussa RG, Antaki F, Traboulsi EI. Gene Therapy for RPE65-Related Retinal Disease. Ophthalmic Genet 2018;39:671-7.

15. Rossi S, Testa F, Li A, et al. An Atypical Form of Bietti Crystalline Dystrophy. Ophthalmic Genet 2011;32:118-21.

16. Ly A, Nivison-Smith L, Zangerl B, et al. Self-Reported Optometric Practise Patterns in Age-Related Macular Degeneration. Clin Exp Optom 2017;100:718-28.

17. Adhi M, Duker JS. Optical Coherence Tomography–Current and Future Applications. Curr Opin Ophthalmol 2013;24:213.

18. Wolpert K, Tsang S. Electroretinography. In. Electroretinograms: IntechOpen; 2011.

19. Padilla MA, di Stefano AF. A Snapshot of Optometry around the World: Optometric Scope of Practice is Literally All over the Map. . Rev Optom 2009;146:55-8.

20. Harper R, Creer R, Jackson J, et al. Scope of Practice of Optometrists Working in the UK Hospital Eye Service: A National Survey. Ophthalmic Physiol Opt 2016;36:197-206.

21. Bi H. Electrodiagnostics in Today's Practice. Rev Optom 2018;155:52-8.

22. Karpecki PM. It's All Primary Eye Care Today. Rev Optom 2018;155:16-7.

23. Windsor MA, Sun SJ, Frick KD, et al. Estimating Public and Patient Savings from Basic Research—a Study of Optical Coherence Tomography in Managing Antiangiogenic Therapy. Am J Ophthalmol 2018;185:115-22.

24. Swanson E. Estimates of Ophthalmic OCT Market Size and the Dramatic Reduction in Reimbursement Payments. OCT News 2012. http://www.octnews.org/articles/4176266/estimates-of-ophthalmic-oct-market-size-and-the-dr/

25. Cole J. How to Make a Big Impact on a Small Budget: From Digital Cameras to Used Equipment, Many Cost-Saving Options Are Available for Today's Optometry Practices. Rev Optom 2010;147:61-6.

26. Bursztyn L, Woodward MA, Cornblath WT, et al. Accuracy and Reliability of a Handheld, Nonmydriatic Fundus Camera for the Remote Detection of Optic Disc Edema. Telemed J E Health 2018;24:344-50.

27. Kato K, Kondo M, Sugimoto M, et al. Effect of Pupil Size on Flicker ERGs Recorded with Reteval System: New Mydriasis-Free Full-Field Erg System. Invest Ophthalmol Vis Sci 2015;56:3684-90.

28. Chagas AM. Haves and Have Nots Must Find a Better Way: The Case for Open Scientific Hardware. PLoS Biol 2018;16:e3000014.

FIGURE LEGENDS

Figure 1. Clinical timeline of a 43-year-old Chinese female clinically diagnosed with Bietti crystalline dystrophy. Abbreviations: OCT = Optical coherence tomography, ffERG = Full-field electroretinogram, EOG = Electro-oculogram, mfERG = Multifocal electroretinogram, RP = Retinitis pigmentosa

Figure 2. Central and para-central fundus photographs

Figure 3. Full-field electroretinogram (A: Scotopic 0.01 response; B: Scotopic 3.0 response; C: Photopic 3.0 response; D: Photopic 30 Hz flicker responses) and E: Electro-oculogram

Figure 4. Spectral-domain optical coherence tomography. A: Volume scan with multi-patches of retinal epithelial atrophy; B: Outer retinal tubulations (white arrows) and hyper-reflective dots correspondent to crystalline deposits (yellow arrows); C: Intra-retinal bright spots (blue arrows)

Figure 5. Multimodal imaging. A: Fundus auto-fluorescence; B: Multi-colour imaging

Figure 6. Multifocal electroretinogram with 3-dimensional plots of response density and trace arrays, with diminished central retinal response. A: Right eye; B: Left eye