this work and should be considered as co–first authors.

Conflict of Interest Disclosures: None reported.

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Bietti Crystalline Retinopathy: Report of Retinal Crystal Deposition in Male Adolescent Siblings

Bietti crystalline dystrophy (BCD) is a genetically determined disorder characterized by progressive choriotinal degeneration, nystalopia, visual field constriction, and multiple intraretinal yellow-white crystalline deposits. Similar crystals can be seen at the corneoscleral limbus on slitlamp examination and in circulating lymphocytes on histological examination. Retinal crystals are observed predominantly at the posterior pole and in the superficial and deep retinal layers. They are associated with multiple, sharply demarcated areas of atrophy in the retinal pigment epithelium and loss of choriocapillaris; the crystals are less obvious as the disease advances. Bietti crystalline dystrophy is inherited as an autosomal recessive trait and is associated with mutations in the CYP4V2 gene (cytochrome P450, family 4, subfamily V, polypeptide 2). The CYP4V2 gene maps to chromosome 4q35, is expressed in a wide variety of tissues (including the retina and the cornea), and encodes an enzyme with a selective fatty acid ω-hydroxylase activity.1,2

The age at onset of BCD is typically after the second decade of life, and to our knowledge, only 2 pediatric cases with fundoscopic lesions in keeping with BCD have been reported3,4; neither had a confirmed molecular diagnosis. In our report, we present the clinical find-

Figure 1. Color fundus photographs of patient 1 (A; the proband) and patient 2 (B) showing multiple crystalline deposits that are more numerous at the posterior pole and peripapillary region than at the retinal periphery, which is relatively spared. The corresponding fundus autofluorescence images of patient 2 (C) are also shown.
ings regarding 2 brothers who presented in childhood with typical intraretinal crystalline deposits associated with compound heterozygous mutations in CYP4V2.

Report of a Case. Patient 1 (proband) was the fourth of 6 children born to healthy unrelated parents. He presented at the age of 5 years with amblyopia; his treatment required the use of spectacles and patching, and he was later discharged from his local hospital. At the age of 16 years, he was noted to have an abnormal retinal appearance during a routine eye test. On direct questioning, the patient reported that he could not see clearly at night (nyctalopia) but that he had no other visual problems. There was a family history of hearing impairment but not of any retinal disease. He was otherwise healthy. When examined at the age of 16 years, his visual acuity was 0.2 logMAR in the right eye and 0.5 logMAR in the left eye. Peripheral visual fields were full to confrontation, and a fundus examination revealed bilateral crystalline deposits and retinal pigmentation (Figure 1A). No corneal crystals were observed. Fundus fluorescein angiography revealed focal areas of choriocapillaris loss. Spectral-domain optical coherence tomography revealed hyperreflective lesions throughout the retina (Figure 2A), although many of these did not spatially associate with retinal crystals on fundus photographs. International-standard pattern and full-field electroretinograms (ERGs) revealed no evidence of macular or generalized retinal dysfunction (Figure 3). The proband was examined by a metabolic physician to exclude any other metabolic abnormality that could lead to crystalline deposition in the retina; the results of all the metabolic investigations proved to be negative. Following informed consent, blood samples were obtained for DNA extraction and subsequent mutation screening of the CYP4V2 coding region and intron-exon boundaries. Two mutations in the heterozygous state were identified: a previously reported missense change (c.83G>A, p.Gly95Arg)\(^3\) and a novel 5-base pair (bp) deletion (c.636_640delAGTA, p.Ser213X).

Two male siblings of the proband were available for examination. A younger brother (patient 2) who was 13 years of age also had a history of anisometropic amblyopia, and he had a logMAR visual acuity of 0.96 in the right eye and 0.00 in the left eye. Funduscopy revealed the presence of similar crystalline retinal deposits in both fundsi with increased pigmentation around the macular region (Figure 1B and Figure 2B). Genetic testing confirmed the presence of the same mutations in CYP4V2. Unfortunately, parental DNA samples were not available, and it was not possible to establish the phase of variants. A third brother (patient 3) who was 11 years of age was asymptomatic and had normal visual acuity, and the results of his fundus examination were normal.

Comment. Bietti crystalline (corneoretinal) dystrophy, first described in 1937, is characterized by the presence of crystalline deposits in the retina and cornea. Complex lipid inclusions have been demonstrated in corneal keratocytes, circulating lymphocytes, and conjunctival fibroblasts. The condition is associated with recessive mutations in CYP4V2, an 11-exon gene encoding a protein involved in fatty acid metabolism. A mutated CYP4V2 gene results in an abnormal lipid metabolism and intracellular retinal pigment epithelial crystalline deposits eventually leading to degeneration of the retinal pigment epithelium, followed by secondary photoreceptor loss.

Clinically, affected individuals experience reduced visual acuity, progressive night blindness, and visual field constriction, typically occurring around the third to fourth decades of life. Legal blindness is common in the fifth to sixth decade. Although patients with BCD have been described from Europe, North and South America, the Middle East, and Africa, the condition has been reported to be more common in...
East Asia, especially in Chinese and Japanese populations. Previous studies have documented full-field ERGs in affected adults ranging from normal to undetectable. There may be generalized dysfunction of both rod and cone systems with macular involvement evident on multifocal ERG or pattern ERG testing. Predominant or early rod-system dysfunction has also been reported, and significant ERG worsening of the condition can occur over time. Our 2 cases are unusual in that the condition was diagnosed during childhood for both patients, and it is evident that, at this early stage, the ERGs are normal despite there being extensive crystalline deposits.

To date, more than 40 mutations have been reported in CYP4V2, all associated with BCD. Herein, we report a novel 5-bp deletion in exon 5 resulting in a premature termination codon, p.Ser213X, that would be predicted to cause the p.Ser213X mutant messenger RNA to succumb to nonsense-mediated decay; however, if these mutations were translated, the protein product would be 312 amino acids shorter than wild type and would not contain the heme-coordinating helices, encoded in exon 7, that are important for enzymatic activity. This mutation was found in the heterozygous state and paired with a heterozygous missense mutation (p.Gly95Arg), significantly changing the polarity of a highly conserved amino acid. A similar heterozygous p.Gly95Arg has been previously reported in a Chinese patient with BCD.5

In summary, we report 2 siblings with crystalline retinal deposits and mutations in CYP4V2 presenting in their teenage years. Bietti crystalline dystrophy should be considered as a possible diagnosis for pediatric patients with crystalline deposits.

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**Figure 3.** Normal full-field electroretinograms (ERGs) and pattern ERGs (PERGs) from the right and left eyes of the proband and representative normal traces (bottom row). The ERGs were recorded under dark-adapted (DA) and light-adapted (LA) conditions according to the published standards of the International Society for Clinical Electrophysiology of Vision. The DA ERGs are shown for white flash strengths of 0.01 and 11.0 candela (cd) s m⁻². Standard LA full-field ERGs are shown for a flash intensity of 3.0 cd s m⁻² (mean [SD], 30 [2] Hz). The PERGs are recorded to an alternating checkerboard. The broken lines replace eye movement artifacts.

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Corrigendum

Error in Author's Name. In the Research Letters article titled “Intravitreal Bevacizumab for Peripapillary Choroidal Neovascular Membranes” by Davis et al, published in the August issue of the Archives (2012; 130[8]:1073-1075), Dr Sohn’s first name was spelled incorrectly. His name should have appeared as Elliott H. Sohn, MD. This article was corrected online.