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Grand Rounds

A 5-year-old girl with decreased vision in the left eye

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History

A 5-year-old girl was referred to Greenlane Clinical Centre, Auckland, after community-based vision screening revealed decreased vision in her left eye. She was born at full term by normal vaginal delivery weighing 2.9 kg. Past ocular, medical, and family histories were unremarkable. Her parents reported no previous ocular trauma. She was not taking any medications regularly, and her immunizations were up to date.

Examination

On examination, her best-corrected visual acuity was 20/25 in the right eye and 20/30 in the left eye using a Snellen chart. Frisby stereotest measured stereopsis of 170 arcsec. Ocular motility examination was normal. There was no relative afferent pupillary defect. Anterior segment examination was normal in both eyes; both crystalline lenses were clear. The intraocular pressure was 19 mm Hg in the right eye and 20 mm Hg in the left eye by tonometry (Icare Finland Oy, Helsinki, Finland). Dilated fundus examination revealed a normal right macula and a vitelliform macular lesion in the left eye (Figure 1A, B). The optic nerve heads and peripheral retinae of both eyes appeared otherwise normal.

Ancillary Testing

Fundus fluorescein angiography was subsequently performed: no leakage or other abnormalities were detected in either eye (Figure 1C, D). Color fundus photographs were taken and spectral domain optical coherence tomography (SD-OCT) was performed (Figure 1E, F). Both parents had normal dilated fundus examinations.

Electrophysiological testing was performed according to ISCEV standards. Pediatric skin electrodes were used on the lower lids. The pattern electroretinogram (ERG) had well-defined P50 and N95 components, and the response to flash ERG identified normal rod and cone mediated function (Figure 2A, B). With electrooculography, no light rise was identified in either eye. The Arden ratio was 0.9 in the right eye and 1.4 in the left eye (normal ratio, >1.8; Figure 2C, D).

The reduced light rise in both eyes suggested a diagnosis of Best vitelliform macular dystrophy (BVMD). The clinical picture identified marked asymmetry with a normal clinical appearance and SD-OCT on the clinically uninvolved right eye and a typical vitelliform macular lesion in the left eye.

The patient had no family history of vitelliform maculopathy. Her parents had normal fundus appearance and did not want to pursue genetic testing for their daughter. The phenotype of Best vitelliform macular dystrophy is incompletely penetrant and approximately 5% of patients who carry an autosomal dominant *BEST1* mutation do not develop ophthalmoscopically visible retinal disease during the first 3 decades of life.[1] The mechanism of this incomplete penetrance is currently unknown.

Differential Diagnosis

A unilateral macular lesion in a 5-year-old child can be caused by an infection, tumor, trauma, or macular dystrophy. Based on clinical appearance alone, a coloboma of the macula could be possible because of the pale discoloration of the lesion. Infective chorioretinitis and pediatric retinal tumors such as retinoblastomas or retinomas could also cause elevated pale retinal lesions.

If we take into account the SD-OCT findings and the well-defined characteristic of the lesion, retinal dystrophies such as BVMD, North Carolina macular dystrophy, and juvenile Stargardt disease are more likely. Of

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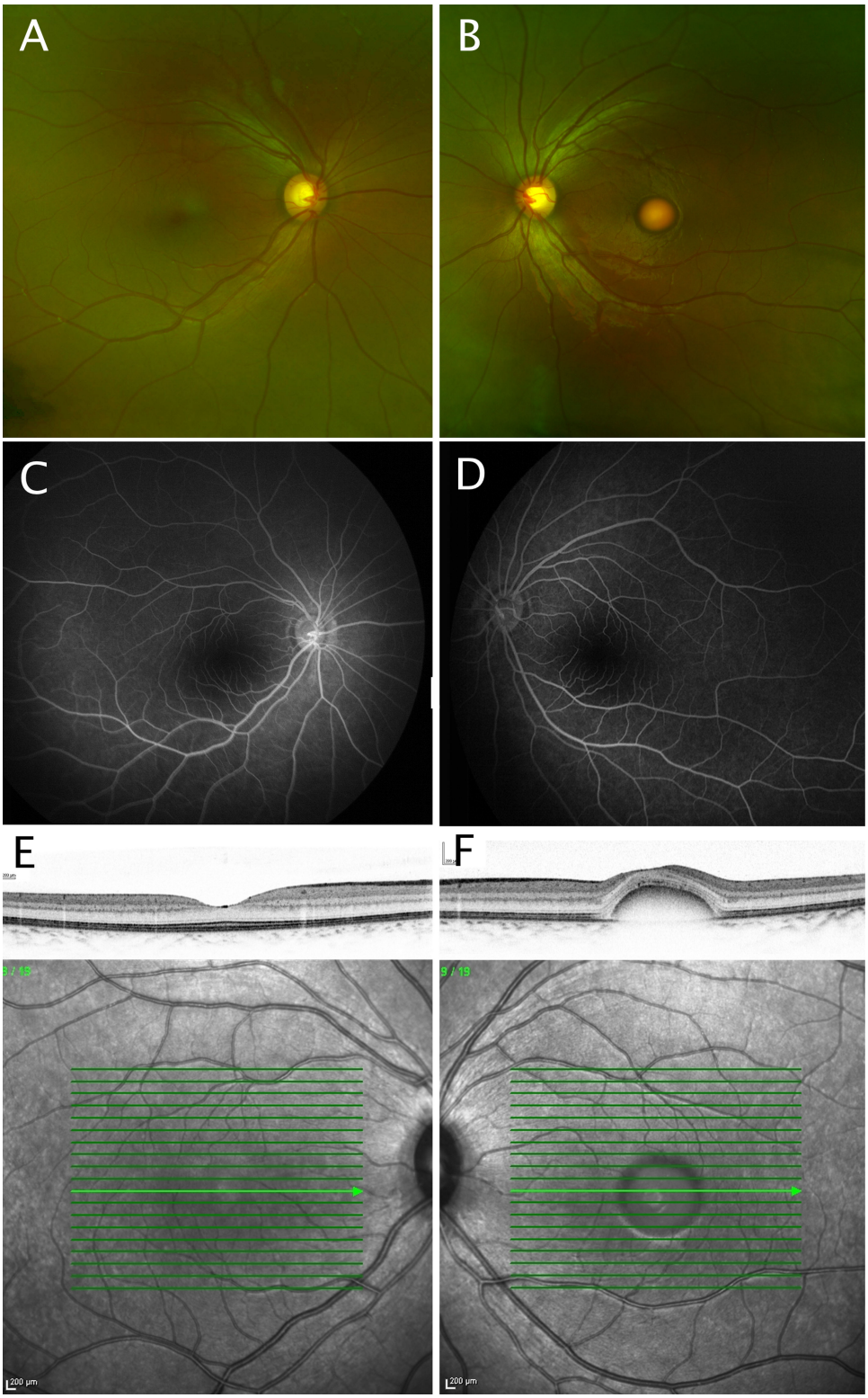

Figure 1. Color fundus photographs (A, B), late-stage fundus fluorescein angiogram (C, D) and infrared reflectance imaging with corresponding SD-OCT foveal cross section (E, F) of both the right and left eye, demonstrating asymmetric disease.

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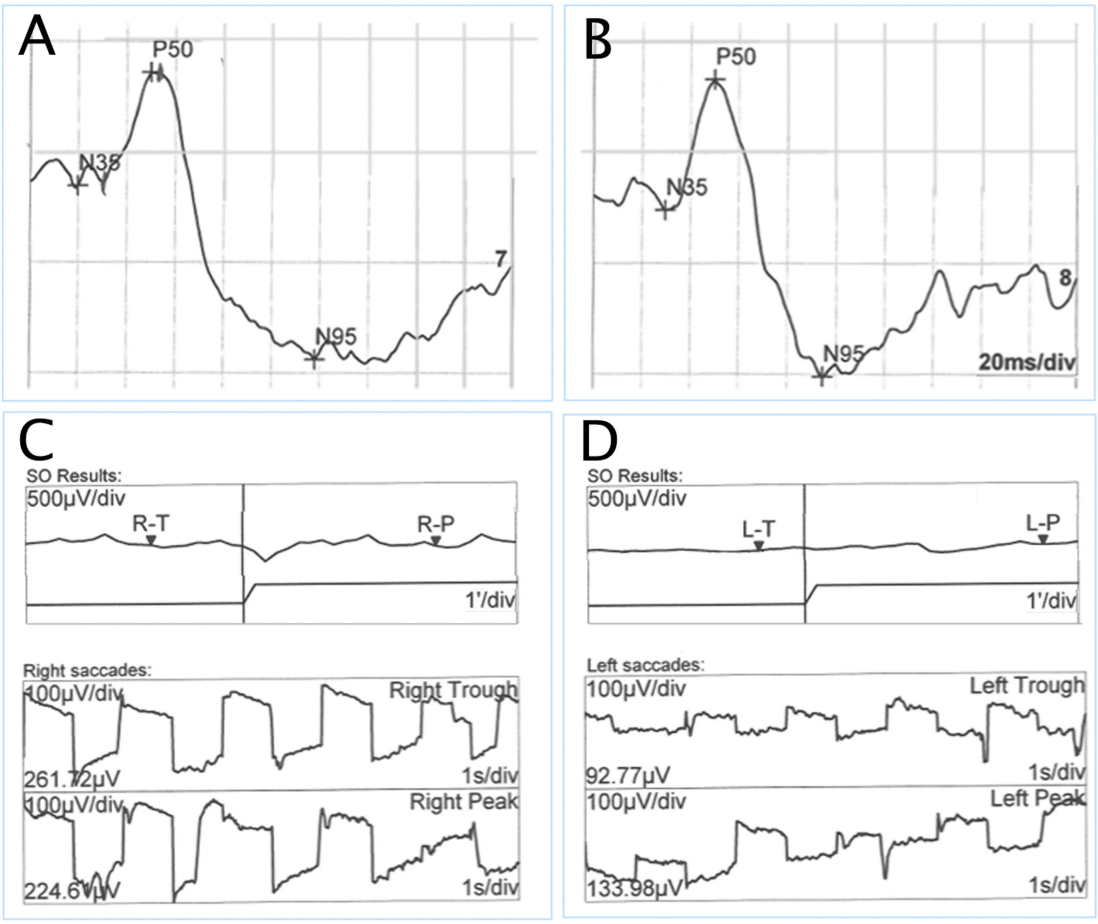

Figure 2. Electrophysiology encompasses several objective examination techniques that measure the function of the retina by measuring action potentials caused by particular patterns of light stimulation. Figure 2 shows a pattern ERG with well defined P50 and N95 components in both the right (A) and left (B) eyes, demonstrating symmetrical and normal macular function. Electrooculography measures the difference in electrical potential between the front and back of the eye, which is mostly a function of the retinal pigment epithelium. In this case, there are decreased light rise responses in both the right (C) and left (D) eyes. The Arden ratio (light to dark ratio) was reduced in both eyes.

these, BVMD is the most likely diagnosis and is supported by the electrophysiological tests.

Diagnosis and Discussion

A round, yellow lesion centered on the fovea characterizes Best vitelliform macular dystrophy. Although these lesions are typically bilateral, unilateral cases have been described in the literature.

Subash et al[2] published a retrospective case series of 6 patients with unilateral vitelliform maculopathy. The patients ranged in age from 30 to 68 years. In addition to performing ocular examination and obtaining ocular investigations, they acquired blood samples for DNA extraction and mutation screening of the *BEST1* and *PRPH2* genes. Molecular screening of both genes revealed no mutations in any patient. Interestingly, the electrooculography light-rise and full-field ERG were within normal limits for all of their patients. Our patient differed from the patients in their case series because she was much younger and had an abnormal electrooculogram.

Cascavilla et al[3] reported a similar case, involving an 8-year-old girl. She also presented with mildly reduced vision in the left eye and was discovered to have a round, yellow macular lesion in that eye. However, SD-OCT and fundus color photographs of the lesion showed more heterogeneity than in the present case. Additionally, their patient developed full-field ERG delayed rod and cone responses. On gene analysis, the patient was found to have a homozygous mutation in the *BEST1*

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gene, suggesting an autosomal recessive inheritance pattern.

The *BEST1* gene is virtually the only gene involved in BVMD. It encodes a 68-kDA protein bestrophin-1, which is thought to function as a chloride channel localized to the basolateral plasma membrane of the retinal pigment epithelium (RPE), which is critical for the phagocytosis of shed outer segments and is the site for the regeneration of the chromophore 11-cis-retinal. Over 200 different *BEST1* mutations have been described in families affected by BVMD.[1,4]

Previous studies have suggested that patients with an autosomal recessive pattern of inheritance in mutations of the *BEST1* gene have a phenotype that is different from those with autosomal dominant disease. The most commonly reported distinguishing features are extrafoveal and extramacular subretinal deposits. Kinnick et al[1] reported that patients with compound heterozygous mutations also have phenotypes that differ from classic dominant BVMD, in that macular deposits tended to be inferior to the fovea, and some degree of subretinal fibrosis was present. About half of their studied patients had small, round, yellow or white spots that were most prominent along the temporal vascular arcades.

Zhang et al[5] performed a post-mortem histological analysis on the macula of a patient with BVMD and found that the clinical finding of an elevated submacular yellow lesion corresponded histologically to RPE hyperplasia, accumulation of lipofuscin in the RPE, and deposition of granular material in the photoreceptors and macrophages. Kay and colleagues,[6] utilizing SD-OCT, suggested that the vitelliform material is located in the subretinal space and concluded that the disease is associated with diffuse photoreceptor outer segment abnormalities overlying a structurally normal RPE.

Acknowledgments

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