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Ophthalmic Findings in an Infant with Phosphomannomutase Deficiency

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Abstract

Introduction—We present the ocular features including full-field electroretinography (ff-ERG) and spectral domain optical coherence tomography (SD-OCT) in a 14-month-old infant with congenital disorder of glycosylation type 1a (PMM2-CDG). An infant with failure to thrive, bilateral neurosensory hearing loss, cerebellar hypoplasia, and pericardial effusions was referred to ophthalmic genetics for evaluation. The patient had fix and follow vision, an intermittent esotropia, moderate myopia, a hypopigmented macula, and mild attenuation of the retinal vasculature. Electroretinography showed severe reduction in both rod and cone-dependent responses with a negative waveform pattern. Handheld SD-OCT revealed severe attenuation of the outer retina throughout the macula, but with preservation of outer retinal structures in the fovea. PMM2-CDG is a rare congenital disorder for which both ff-ERG and SD-OCT were useful in demonstrating early changes of retinal architecture and function.

Keywords

Congenital Diseases of Glycosylation; Electroretinography; Negative waveform electroretinogram; Phosphomannomutase deficiency; Spectral domain optical coherence tomography

Introduction

Since the early 1980's, 45 types of congenital disorders of glycosylation have been described.[1] Although the exact prevalence is unknown, it has been estimated to be as high as 1:35,000 in some populations.[2] The most common form is congenital disorder of glycosylation type 1a (PMM2-CDG), which is an autosomal recessive disease associated with mutations in the *PMM2* gene on chromosome 16. Mutations at the *PMM2* gene locus result in a deficiency of phosphomannomutase, an enzyme responsible for the creation of precursors in the N-glycosylation pathway that play a fundamental role in cell signaling and protein folding pathways.[3]

The presentation of PMM2-CDG is highly variable, but most children have developmental delay and hypotonia, as well as other systemic signs that include failure to thrive, hepatic dysfunction, coagulopathy, hypothyroidism, hypogonadism, pericardial effusions, abnormal

fat pad distribution, seizures, stroke-like episodes, osteopenia, and cerebellar hypoplasia.[4] Ocular findings include nyctalopia, myopia, esotropia, nystagmus, yellow dots around the fovea, narrowed retinal vessels, retinitis pigmentosa, and decreased rod and cone function on electroretinography (ERG).[5–11] PMM2-CDG is diagnosed by clinical features, neuroimaging, transferrin isoform analysis, and genetic testing.

Case Report

A 14-month-old female was referred to our institution for evaluation of poor ability to fix and follow, nystagmus, intermittent esotropia, and foveal hypoplasia to determine if these findings were related to her underlying genetic condition. She was born at 39 weeks via an uncomplicated spontaneous vaginal delivery, and weighed 2.93 kg. However, in the newborn period she failed to thrive and eventually required permanent gastrostomy tube placement for feeding. In the first few months of life, she was diagnosed with bilateral neurosensory hearing loss and poor truncal muscle tone. Magnetic resonance imaging showed severe vermian and cerebellar hypoplasia. At 6 months of age, she was diagnosed with PMM2-CDG after her transferrin isoform assay showed severe hypoglycosylation. Three months later, she was found to have right and left ventricular hypertrophy and pericardial effusions on echocardiogram requiring a pericardectomy. Her past medical history was also notable for hypothyroidism and a chronic normocytic anemia. Genetic testing through the Emory Genetic Laboratory revealed one copy of a c.422G>A mutation in exon 5 and one copy of a c.652C>G change in exon 8. The c.422G>A mutation has been previously reported in patients with PMM2-CDG, but the c.652C>G nucleotide change is novel although it has not been observed in the general population.[12]

Complete ophthalmic examination was performed while awake and under anesthesia at the Casey Eye Institute using a propofol sedation protocol, as previously described.[13] Previous reports have demonstrated an approximately 50% reduction in scotopic ERG amplitudes as well as a 10% increase photopic single flash b-wave and 30Hz Flicker implicit time.[14] To account for this effect ERGs were compared to age matched controls also recorded under propofol sedation. She was found to have fix and follow vision with myopia (−3.5 D sphere) and an intermittent alternating esotropia. Fundoscopic exam revealed a poorly pigmented fundus and macula with mild attenuation of the retinal vessels in both eyes (Figure 1A).

Handheld SD-OCT images were obtained under anesthesia using the Envisu R2200-HR handheld SD-OCT device (Biotigen, Durham, NC). Both volume scans of the macula (10 mm width, 1000 a-scans/b-scan, 230 b-scans) and macular horizontal linear scans through the fovea (9 mm width, 900 a-scans/b-scan, 145 b-scans/stack) were obtained. Images were processed in a similar manner as previously described.[15] These showed attenuation of the outer retina throughout the macula, with relative preservation centrally (Figure 1B). In the left eye there was visible loss of the ellipsoid zone outside of the fovea.

Fullfield ERG (ff-ERG) was obtained under anesthesia using Burian-Allen bipolar contact lens electrodes according to the International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines.[16] Scotopic recordings demonstrated severely attenuated b-

wave amplitude (20% of age matched sedated normals) and prolonged timing to dim flashes (Figure 2). Bright Scotopic flashes revealed both a diminished a- and b-wave with a reduction of the b to a-wave ratio. Photopic single flash responses showed decreased amplitudes (50% of age matched sedated normals), prolonged timing, and loss of oscillatory potentials. Responses to 30 Hz flicker were additional diminished and prolonged compared to age-matched normal controls under a similar sedation protocol. Overall, the rod-driven responses were more affected than cones, resembling a generalized rod-cone dystrophy.

Discussion

Our patient demonstrated many of the typical features of PMM2-CDG including hypotonia, developmental delay, cerebellar hypoplasia, esotropia, nystagmus, myopia, and rod-cone dysfunction. The fundus exam demonstrated decreased pigmentation with visible choroidal vessels, as well as attenuated retinal vessels similar to previous published reports. The lack of pigmentary changes in our patient is likely due to the young age of presentation. To our knowledge, this is the first published evidence of handheld SD-OCT imaging in a patient with PMM2-CDG, which showed attenuation of the outer retina in the macula with relative preservation in the fovea, consistent with the results of ff-ERG showing a pattern of rod-cone degeneration. These results are supported by a prior postmortem study showing degeneration and loss of photoreceptors at the outer retina, as well as a longitudinal case report showing early rod-cone dysfunction and preservation of some cone function into adulthood.[5,7]

Several studies have published ERG results in patients with PMM2-CDG, which have varied from unrecordable to normal.[5,7,6,8–11] The majority of studies have shown decreased or absent scotopic b-wave amplitudes, but cone involvement has also been reported with absent photopic b-waves and decreased amplitude and prolonged timing for the 30 Hz flicker. Recently, Thompson et al. observed reduced b to a-wave ratios and absent photopic on-response b-waves in two patients with PMM2-CDG[11,10]. Similarly, our case also showed a decreased b to a-wave ratio consistent with synaptic dysfunction in addition to a rod-cone pattern of dysfunction.

Despite the growing body of literature on PMM2-CDG, its pathophysiology in the eye remains unclear. The decreased b to a-wave ratio suggests synaptic dysfunction between the photoreceptors and the bipolar cells, and Thompson et al. hypothesized that mutations associated with PMM2-CDG may disrupt depolarization of the on-bipolar cells at the outer plexiform layer of the retina [10,11]. In addition, Andreasson and colleagues have suggested that the etiology of retinal damage may involve a defect that affects opsin and interphotoreceptor retinoid-binding protein, which are both glycosylated.[5] Whatever the initial insult, the combined SD-OCT and ff-ERG data in this infant with PMM2-CDG suggests that there is an early predilection for rod outer retinal photoreceptor loss.

Our understanding of PMM2-CDG in the eye is still limited, and early diagnosis is dependent upon appropriate clinical suspicion and proper work-up. A child with developmental delay and hypotonia, who is referred for ophthalmic consultation should prompt one to rule out syndromes that include PMM2-CDG. Here we present evidence that

handheld SD-OCT is not only a useful adjunct to ff-ERG in the detection of retinal damage, but it is also useful in better characterizing the spectrum of ocular pathophysiology in PMM2-CDG.

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Figure 1.
 (A) Fundoscopic images showing diffuse hypopigmentation of fundus with attenuation of the retinal vessels. (B) SD-OCT revealing loss of the outer retina throughout the macula.

Figure 2. Scotopic and photopic responses from ff-ERG revealing generalized rod-cone dysfunction and diminished b to a-wave ratio to bright scotopic stimuli.