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Multimodal Imaging and Electroretinography in Long-Chain 3-Hydroxyacyl Coenzyme A Dehydrogenase Deficiency

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Abstract

Purpose—To report a case of pigmentary retinopathy in long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD) deficiency using multimodal imaging techniques.

Methods—Case report.

Results—An 8 year old boy with a history of failure to thrive and a diagnosis of LCHAD deficiency was referred for examination. Exam revealed a pigmentary retinopathy with macular atrophy; electroretinography (ERG) results were consistent with a rod-cone dystrophy. Fundus autofluorescence and optical coherence tomography (OCT) revealed RPE atrophy. Follow up exam findings showed increased severity of retinopathy on ERG, with OCT angiography revealing enhanced visualization of choroidal vessels.

Conclusion—This report reveals that LCHAD deficiency can be characterized as a progressive rod-cone dystrophy, with multi-modal imaging techniques used to describe this condition. In particular, OCT angiography can be used to further characterize this condition.

Keywords

LCHAD deficiency; chorioretinopathy; OCT angiography

Introduction

The oxidation of long chain fatty acids occurs primarily in mitochondria, which is an important source of energy during periods of fasting and metabolic stress. When there is a defect in fatty acid oxidation, systemic anomalies can occur. Long chain 3 hydroxy-acyl-CoA dehydrogenase (LCHAD) deficiency is an autosomal recessive disease that has features of retinopathy along with systemic manifestations of hypoketotic hypoglycemia, hepatic

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steatosis, cardiomyopathy, and rhabdomyolysis.¹ In 1996, the description of pigmentary retinopathy became pathognomonic in its association with LCHAD deficiency among those presenting with concurrent fasting induced hypoketotic hypoglycemia.²

To our best knowledge, this is the first case report that documents the retinal findings of LCHAD deficiency using optical coherence tomography (OCT) angiography, which along with multimodal imaging modalities and diagnostic techniques establishes it as a treatable rod-cone dystrophy.

Case Report

An 8 year-old boy was referred to the clinic with deteriorating vision and complaints of worsening night blindness over the past year. This patient, from non-consanguineous Caucasian parents, was born at 37 weeks with a low birth weight. At 4 months of age, he was hospitalized for an episode of failure to thrive, experiencing problems with feeding and lethargy. During this hospitalization, the patient was noticed to improve with intravenous 10% dextrose solution, and was also found to have cardiomyopathy. Genetic testing confirmed LCHAD deficiency; he was a compound heterozygote with G1528C in one allele and a 1 bp deletion (delta A2059) in exon 19. Because of poor feeding, a gastrostomy tube was placed and a low fat, high medium chain triglyceride diet with carnitine and docosahexaenoic acid (DHA) supplementation was initiated.

Ophthalmologic evaluation at the initial visit revealed 20/50 best corrected visual acuity in both eyes, with a refraction of $-4.00 +1.75 \times 90$ in the right eye (OD) and $-4.00 +1.50 \times 90$ in the left eye (OS). There was no afferent pupillary defect and the globes were bilaterally soft by palpation. Anterior segment exam was unremarkable. Dilated fundus exam revealed bilateral vascular tortuosity and macular atrophy with pigment mottling and intra-retinal pigment migration in the periphery (Figure 1a). Fundus autofluorescence showed multiple hypo-autofluorescent round shaped areas of macular retinal pigment epithelium (RPE) atrophy (Figure 1b). Spectral domain OCT revealed a hyper-reflective choroid secondary to RPE atrophy (Figure 1c). Full field electroretinogram (ERG) was performed according to international standards using skin electrodes, showing noisy but detectable responses, with decreased 30-Hz flicker peak amplitudes to approximately 20 microvolts (normal 131 ± 80) and 28 milliseconds implicit time (normal 24 ± 4). Dark adaptation to obtain scotopic responses at that time was not performed. 2 years later the patient had a follow up ERG that showed decreased scotopic response (approximately 25% of normal) and decreased 30-Hz flicker response (approximately 45% of normal).

Follow up exam 4 years later revealed a marked decrease in best corrected visual acuity to 20/150 in the right eye and 20/100 in the left eye, with a significant myopic shift in refraction ($-11.00 +2.00 \times 90$ OD and $-11.25 +2.75 \times 90$ OS). While the anterior segment examination remained unchanged, the dilated fundus exam revealed increased macular retinal and RPE atrophy (Figure 2a). Fundus autofluorescence showed marked spread in hypo-autofluorescent areas (Figure 2b), while OCT revealed more diffuse areas of RPE thinning now with outer retinal tubulations (Figure 2c). Additionally, OCT angiography revealed enhanced visualization of the choroidal vasculature secondary to RPE atrophy

(Figure 3). ERG at this time revealed loss of scotopic response yielding a flat wave, decreased maximal response with apparent electronegative curve with 11.5 candela-seconds per meter squared intensity flashes, as well as delayed (33 milliseconds) and decreased 30-Hz flicker responses (approximately 25 microvolts of peak amplitudes bilaterally) (Figure 4). While it was not optimal to correlate the earlier ERG performed with skin electrodes to this one given that it was recorded with Dawson-Trick-Litzkow (DTL) electrodes, it was apparent that the patient had a significant progressive decline in photoreceptor responses, with primary loss of rod responses.

Discussion

LCHAD is a mitochondrial, membrane bound enzyme that is specific for long chain substrates. The enzyme is part of the mitochondrial trifunctional protein (MTP), an enzyme complex consisting of four alpha and four beta subunits.³ These subunits are bound to the inner mitochondrial membrane that catalyzes steps in the β -oxidation of dietary long chain fatty acids. The subunits are encoded by the HADHA and HADHB genes, respectively.³ Patients with LCHAD deficiency have a G to C substitution at position 1528 of the cDNA encoding the alpha subunit, resulting in a glutamate to glutamine transition.³ LCHAD deficiency causes a greater number of different complications among all fatty acid oxidation disorders. Compound heterozygotes have been shown to have greater severity,³ as our patient had the G1528C mutation in one allele and a 1 bp deletion (delta A2059) in exon 19. The latter frameshift mutation has been shown to be damaging with a confidence of 85.8% (<http://sift.bii.a-star.edu.sg>).

Pigmentary retinal changes are seen by 2 years of age in about 50% of individuals.⁴ The cause and fundamental pathophysiology of this dystrophy has not yet been fully elucidated, but it is likely that degeneration of the RPE is the primary defect. Tyni et al⁵ measured fatty acid oxidation from cultured porcine RPE cells, with immunoblotting revealing expression of the MTP and enzyme assay showing activity of LCHAD in the cells. This study supported the hypothesis that mitochondrial fatty acid β -oxidation occurs in RPE cells, which provides a mechanism by which damage occurs when there is a defect in the metabolic pathway. Furthermore, histological examination of the retina has revealed macrophage infiltration of the RPE layer and evidence of RPE cell death, which eventually leads to photoreceptor loss.⁶ The role of fatty acid oxidation within the RPE has further been demonstrated by a study using LCHAD deficiency patient-specific RPE monolayers resulting in lipid accumulation leading to reduced oxidant scavenging potential, lipid toxicity, and loose blood-retina barrier.⁷ The marked spread of hypo-autofluorescent areas representing loss of RPE cells on fundus autofluorescence of our patient demonstrated that the disease primarily affects the RPE, with atrophy leading to hyper-reflectivity and increased visibility of the choroid on OCT and OCT angiography.

The typical pigmented fundus appearance in patients with LCHAD deficiency has been described in previous reports, in which it was noted that while some patients had pigmentation in the macular areas, others had initial subtle pigmentation spread in the mid-periphery but not in the macular areas.^{8,9} These patients may also be myopic, as noted in our patient who became progressively significantly more myopic at follow up.¹ Some

patients have even been described to have fibrotic chorioretinal changes, bare sclera, and staphyloma.⁹ To categorize severity of disease, a staging system has been described, ranging from stage 1 with a normal appearing fundus/diffuse hypopigmentation and normal visual performance to stage 4 with atrophy of the posterior pole and loss of the central photoreceptors and macular vision, with our patient representing a case of stage 4 disease.¹ Of peculiar interest is that our patient had vascular tortuosity with no evidence of familial arterial tortuosity syndrome, which has not been seen in other cases of LCHAD deficiency reported in the literature.

The sparing of the peripheral fundus may be explained by the susceptibility of the central fundus given its active metabolism, exposure to light damage, by the greater risk to cones compared to rods, or by the differences in anatomy in the RPE in the posterior pole.¹ Our case indicated a rod-cone dystrophy given that rod responses were more attenuated than cone responses. This was in contrast to a previous report of retinopathy in LCHAD deficiency which did not find that cone and rod responses on ERG were significantly diminished.¹⁰ Instead, our findings were more consistent with the diminished ERG recordings found by Tyni et al¹, which by the time patients reached their early teenage years no longer had recordable responses.

The electronegative ERG in our patient likely originated from dark-adapted cones, exposed in the presence of extinguished rod photoreceptor function. This is consistent with the so-called “photopic hill” and probably does not reflect inner retinal rod system dysfunction. In the cone system, increasing the stimulus intensity initially results in an increase in both photopic a-wave and photopic b-wave, but with further increase in stimulus intensity, the b-wave starts to reduce and hits a plateau, giving an electronegative waveform.¹¹

Screening for LCHAD deficiency has become more widely adopted. Now all states in the U.S. perform newborn screening through acylcarnitine profiling in dried blood spots, with confirmation involving enzyme assays, fatty acid oxidation probe studies in cultured patient fibroblasts obtained by skin biopsy, or gene sequencing and mutation identification.³ Treatment is with low fat intake and supplementation of medium chain triglycerides, including DHA.

This is the first case report detailing the progression of retinopathy seen in LCHAD deficiency as viewed using novel multi-modal imaging technologies, further describing it as a rod-cone dystrophy. Early diagnosis, treatment, and decreasing the number of metabolic crises are associated with a slower progression of retinopathy.⁸ Thus, it is important for the ophthalmologist to recognize the diagnostic and clinical findings seen in LCHAD deficiency among other numerous inherited disorders of metabolism associated with retinal dystrophy, as it is a preventable cause of death.

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Summary statement

We present a case of an 8 year old boy with rod-cone dystrophy secondary to long-chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency, characterized using electroretinography and imaging modalities such as optical coherence tomography angiography.

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Fig 1.

A, Color fundus montage photographs at presentation showing vascular tortuosity and macular atrophy with pigment mottling and intra-retinal pigment migration in the periphery.

B, Fundus autofluorescence showing hypo-autofluorescent round shaped areas of RPE atrophy. **C,** OCT showing areas with attenuated outer retinal layers and hyper-reflective choroid secondary to RPE atrophy.

Fig 2.

A, Color fundus montage photographs 4 years later showing increased macular atrophy with pigment mottling and intra-retinal pigment migration in the periphery. **B,** Fundus autofluorescence showing increased areas of hypo-autofluorescence. **C,** OCT showing increased attenuation of outer retinal layers and outer retinal tubulations with hyper-reflective choroid secondary to RPE atrophy.

Fig 3.
6 × 6 mm en-face OCT angiography at the level of the choriocapillaris showing enhanced visualization of choroidal vasculature.

Fig 4.

ERG at 4 years follow up (DTL) showing an extinguished scotopic response, decreased maximal response, decreased single flash photopic response, and delayed and decreased 30-Hz flicker (note decreased scale compared to normal in patient's ERG for single flash photopic and 30-Hz flicker).