AMERICAN ACADEMY™
OF OPHTHALMOLOGY

Characterization of Chorioretinopathy Associated with Mitochondrial Trifunctional Protein Disorders

Long-Term Follow-up of 21 Cases

Erin A. Boese, MD,[1] Nieraj Jain, MD,[2] Yali Jia, PhD,[1] Catie L. Schlechter, MS, CGC,[1] Cary O. Harding, MD,[3] Simon S. Gao, PhD,[1] Rachel C. Patel, BA,[1] David Huang, MD, PhD,[1] Richard G. Weleber, MD,[1] Melanie B. Gillingham, PhD,[3] Mark E. Pennesi, MD, PhD[1]

Purpose: To assess long-term effects of genotype on chorioretinopathy severity in patients with mitochondrial trifunctional protein (MTP) disorders.

Design: Retrospective case series.

Participants: Consecutive patients with MTP disorders evaluated at a single center from 1994 through 2015, including 18 patients with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) and 3 patients with trifunctional protein deficiency (TFPD).

Methods: Local records from all visits were reviewed. Every participant underwent a complete ophthalmic examination and was evaluated by a metabolic physician and dietitian. Nine patients underwent ancillary funduscopic imaging including optical coherence tomography (OCT) and OCT angiography.

Main Outcome Measures: The primary outcome measure was best-corrected visual acuity at the final visit. Secondary outcome measures included spherical equivalent refraction, visual fields, electroretinography B-wave amplitudes, and qualitative imaging findings.

Results: Participants were followed up for a median of 5.6 years (range 0.3–20.2 years). The median age of LCHADD participants at initial and final visits was 2.3 and 11.9 years, whereas that for TFPD participants at initial and final visits was 4.7 and 15.5 years, respectively. Four long-term survivors older than 16 years were included (3 with LCHADD and 1 with TFPD). The LCHADD participants demonstrated a steady decline in visual acuity from an average of 0.23 logarithm of the minimum angle of resolution (logMAR; Snellen equivalent, 20/34) at baseline to 0.42 logMAR (Snellen equivalent, 20/53) at the final visit, whereas TFPD patients maintained excellent acuity throughout follow-up. Participants with LCHADD, but not TFPD, showed an increasing myopia with a mean decrease in spherical equivalent refraction of 0.24 diopters per year. Visual fields showed sensitivity losses centrally associated with defects on OCT. Multimodal imaging demonstrated progressive atrophy of the outer retina in LCHADD, often preceded by the formation of outer retinal tubulations and choriocapillaris dropout. Electroretinography findings support the more severe clinical profile of LCHADD patients compared with TFPD patients; the function of both rods and cones are attenuated diffusely in LCHADD patients, but are within normal limits for TFPD patients.

Conclusions: Despite improved survival with early diagnosis, medical management, and dietary treatment, participants with the LCHADD subtype of MTP disorder continue to demonstrate visually disabling chorioretinopathy. Multimodal imaging is most consistent with choriocapillaris loss exceeding photoreceptor loss. *Ophthalmology 2016;■:1–13 © 2016 by the American Academy of Ophthalmology.*

Supplemental material is available at www.aaojournal.org.

Mitochondrial trifunctional protein (MTP) disorders are rare, recessively inherited conditions of impaired fatty acid metabolism. Affected patients typically seek treatment at an early age with episodes of hypoketotic hypoglycemia, cardiomyopathy, rhabdomyolysis, hepatomegaly, and sudden death.[1–5] Early recognition and initiation of treatment including dietary modifications have improved survival considerably, and many patients are now living into adulthood.[6,7] Despite these advances, most patients experience progressive and advanced visual disability.[8–12]

Mitochondrial trifunctional protein disorders result from mutations within the trifunctional protein (TFP), a protein complex that catalyzes 3 specific enzymatic activities in long-chain fatty acid metabolism: 2-3 enoyl

http://dx.doi.org/10.1016/j.ophtha.2016.06.048
ISSN 0161-6420/16

CoA hydrase, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), and 3-ketoacyl-CoA thiolase. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD; Online Mendelian Inheritance in Man identifier, 609016) is defined by the presence of the common mutation c.1582G→C in at least 1 allele of the *HADHA* gene, which yields a normal protein expression of the enzyme complex and a predominant deficiency of LCHAD activity with relative sparing of the other 2 enzymatic activities. Other mutations within the *HADHA* or *HADHB* genes are associated with decreased protein expression and more uniform deficiency of all 3 enzymatic activities, yielding so-called multifunctional TFP deficiency (TFPD; Online Mendelian Inheritance in Man identifier, 609015). Although resulting from a similar disruption in fatty acid metabolism, TFPD has several distinct differences, including the absence of liver pathologic features and a milder ocular phenotype.[1,2,13]

We previously reported the 5-year results of a prospective study correlating medical treatment and dietary patterns with chorioretinopathy progression in MTP disorders that demonstrated relative retention of retinal function among patients with improved dietary management and lower hydroxyl acylcarnitines.[6] Participants from this initial study, affected by either LCHADD or TFPD, are now among the longest known survivors with the disease. Herein we present long-term findings in 21 participants with up to 20 years of follow-up, exploring the effect of genotype on chorioretinopathy severity. We provide an in vivo structural assessment of the affected retina with multimethod imaging, including optical coherence tomography (OCT), OCT angiography, and fundus autofluorescence (FAF). Using serial electroretinography, we also demonstrate corresponding functional changes with time.

Methods

This was a retrospective case series of all patients seen at the Casey Eye Institute, Oregon Health & Science University (OHSU), between September 20, 1994, and August 18, 2015, with a diagnosis of either LCHADD or TFPD. All participants were followed up clinically or participated in various research protocols in the Department of Molecular and Medical Genetics of OHSU, as detailed previously,[6,7] and 13 of these participants were reported previously in a prospective open-label study evaluating the effect of diet treatment on chorioretinopathy progression.[6] Diagnosis of LCHADD or TFPD was based on the presence of at least 2 of 3 of the following: clinical findings, disease-specific acylcarnitine profiles, or enzymatic assays in cultured skin fibroblasts. All participants underwent molecular testing, which identified 2 deleterious mutations in the *HADHA* or *HADHB* genes in 18 of the 21 cases.

Approval from the OHSU Institutional Review Board for the study protocol and consent were obtained, and the study followed the tenets set forth by the Declaration of Helsinki. Each participant's legal guardian provided informed consent for obtaining outside records, and participants older than 7 years gave assent to participate.

Medical Clinical Evaluation

Participants were evaluated by a biochemical geneticist (C.O.H.) at Doernbecher Children's Hospital or at the Clinical and Translational Research Center of OHSU as part of routine clinical care or a clinical research study, respectively. Patients were asked to maintain a diet low in long-chain fatty acids and were supplemented with medium-chain triglycerides to minimize oxidation, as previously described by Gillingham.[7] Medical history and complete physical examination including neurologic evaluation were completed. Participants in a research study were asked to complete a 3-day diet record and to return the completed record to the investigators (M.B.G.) for analysis. Blood samples were collected after an overnight fast and were analyzed for plasma acylcarnitines by electrospray tandem mass spectrometry at the Biochemical Genetics Laboratory, Mayo Clinic.[14] Dietary intake was assessed by 24-hour dietary recall for patients evaluated clinically by the metabolic dietitian. Nonfasting blood samples were sent for plasma acylcarnitine analysis as described previously.

Ophthalmic Clinical Evaluation

Participants initially underwent a complete ophthalmic examination with cycloplegic refraction and full-field electroretinography (ffERG). Best-corrected visual acuity (BCVA) was measured with Snellen testing and was converted to logarithm of the minimum angle of resolution (logMAR) units. Nine participants underwent additional imaging, including spectral-domain OCT (Spectralis; Heidelberg Engineering, Germany), OCT angiography (Avanti RTVue XR; OptoVue, Inc., Freemont, CA), and wide-field FAF imaging (200Tx; Optos PLC, Freemont, CA) at the discretion of the treating ophthalmologist, often based on the availability of these tests and the patient's ability to cooperate. Severities of chorioretinopathy for and last documented visits were assessed by a retina specialist (N.J.) based on the previously described chorioretinopathy staging system.[12] Fundus images and clinical data were used to stage the chorioretinopathy. For visual acuity and refractive error analysis, our records were supplemented with outside ophthalmology records. Visual fields, including manual and automated kinetic perimetry (Octopus 101 or Octopus 900; Haag-Streit, Koeniz, Switzerland), were obtained from participants old enough to participate. Static visual fields were performed using the same perimeter, a radially designed, centrally condensed grid containing 164 test location[15]; the GATEi strategy[16,17]; and a 200-ms stimulus of size V on a white background of 10 cd/m^2. The reliability factor for the static perimetry was calculated as the sum of positive and negative catch trials divided by the total number of catch trials presented (designated as a percentage). The sensitivity values were imported into a custom software application (United States patent no. 8,657,446, Visual Field Modeling and Analysis, or VFMA, Office of Business and Technology of OHSU) to model the hill of vision. The volumetric indices (in decibel-steradian or dB-sr) of differential luminance sensitivity—V_{tot}, V_{30°, and V_{periph} ($V_{tot}-V_{30^\circ}$)—and defect space—D_{tot}, D_{30°, and D_{periph} ($D_{tot}-V_{30^\circ}$)—were measured from the model as described previously.[15]

En face OCT images of the outer retina and retinal pigment epithelium (RPE) were derived from the mean reflectance of slabs 25 to 45 μm above Bruch's membrane (BM) and 25 μm above BM to BM, respectively. The OCT angiography images were derived