256550). In sialidosis type II, which has a worse prognosis, there is an early onset (<12 months of age) of symptoms, including coarse facies, dysostosis multiplex, hepatosplenomegaly, and macular cherry-red spots as well as psychomotor and developmental delay. Patients with type I sialidosis present later in life, with a mild form of the disease that is mostly confined to ophthalmologic features, myoclonus, and minor or absent neurologic manifestations.[2-4]

We describe the biochemical and clinical phenotype associated to two novel mutations. No effective therapy is yet available for this rare disease; therefore, treatment is focused on symptoms. This case illustrates the importance of early diagnosis of lysosomal storage diseases through the ophthalmological examination. Because the patient was in ophthalmological follow-up for retinopathy of prematurity, it was possible to trace the natural history of the onset of macular cherry-red spots in sialidosis type II. This sign, caused by the accumulation of storage material in the macula, should raise suspicion for a lysosomal storage disease, especially oligosaccharidosis. The differential diagnosis of macular cherry-red spots mainly involves GM2 gangliosidoses, GM1 gangliosidosis, sialidosis, metachromatic leukodystrophy, Niemann-Pick type A, and Farber lipogranulomatosis. Other typical ocular manifestations in sialidosis type II are corneal whorling or opacities. The presence of punctate lenticular opacities in our patient, which are grouped into a stellate-shaped lineal pattern resembling the pattern seen in alpha-mannosidosis, is, to our knowledge, the first report of this characteristic in a patient with sialidosis type II. Punctate opacities have recently been described in a 15-year-old boy with sialidosis type I.[5]

The finding of an altered urinary profile of oligosaccharides would indicate the subsequent enzymatic and/or genetic study to confirm the causing metabolic disorder. To date, at least 40 disease-causing mutations in the *NEU1* gene have been reported.

References

1. Caciotti A, Di Rocco M, Filocamo M, et al. Type II sialidosis review of the clinical spectrum and identification of a new splicing defect with chitotriosidase assessment in two patients. J Neurol 2009;256:1911-15.
2. Khan A, Sergi C. Sialidosis: a review of morphology and molecular biology of a rare pediatric disorder. Diagnostics (Basel) 2018;8(2):E29.
3. Seyrantepe V, Poupetova H, Froissart R, Zabot MT, Maire I, Pshezhetsky AV. Molecular pathology of *NEU1* gene in sialidosis. Hum Mutat 2003;22:343-52.
4. Lee BH, Kim GH, Lee BS, Kim CJ, et al. Histological, biochemical, and genetic characterization of early-onset fulminating sialidosis type 2 in a Korean neonate with hydrops fetalis. Brain Dev 2014;36:171-5.
5. Wang IH, Lin TY, Kao ST. Optical coherence tomography features in a case of type I sialidosis. Taiwan J Ophthalmol 2017;7:108-11.

Unilateral cone-rod dysfunction and retinal thinning in a child carrying the 14484 mutation of Leber hereditary optic neuropathy

Ahmed Kassem, MBBCh,[a] Rustum Karanjia, MD, PhD,[b,c,d,e] Collin McClelland, MD,[a] Alfredo Sadun, MD, PhD,[b,c] and Michael S. Lee, MD[a]

Leber hereditary optic neuropathy is a mitochondrial disorder that presents with bilateral, usually sequential, central vision loss from optic nerve damage. We report the case of an 11-year-old girl with the 14484 mutation who developed significant, unilateral visual loss secondary to retinal thinning and abnormal cone-rod responses on electroretinography, with no evidence of optic nerve damage. Patients carrying the 14484 mutation may also develop cone-rod dysfunction.

Leber hereditary optic neuropathy (LHON) is a mitochondrial disorder that presents as acute or subacute visual loss secondary to optic nerve dysfunction. Classically, rapid vision loss in one eye is followed, sometimes quickly, by involvement of the fellow eye within 1 year. Three primary mitochondrial DNA point mutations comprise over 90% of cases: 11778 (69%), 3460 (13%), and 14484 (14%).[1] Rarely, retinal dysfunction has been reported among patients carrying an LHON mutation.[2-4]

Case Report

An 11-year-old girl suffered syncope 7 weeks prior to presentation at the University of Minnesota. On awakening, she had noted poor vision in the left eye, which remained subjectively stable. She denied photopsias. Her presenting visual acuity was 20/20 in the right eye and 4/200 in the left eye. There was an afferent pupillary defect and decreased color vision in the left eye. Dilated fundus examination

Author affiliations: [a]Department of Ophthalmology and Visual Neurosciences, University of Minnesota, Minneapolis; [b]Doheny Eye Institute, Los Angeles, California; [c]Department of Ophthalmology, David Geffen School of Medicine at UCLA, Los Angeles, California; [d]Ottawa Eye Institute, University of Ottawa, Ottawa, Canada; [e]Ottawa Hospital Research Institute, Ottawa, Canada

Submitted May 26, 2018.
Revision accepted September 17, 2018.
Published online November 14, 2018.

Correspondence: Michael S. Lee, MD, 420 Delaware St SE, MMC 493, Minneapolis, MN 55455 (email: mikelee@umn.edu).

J AAPOS 2019;23:104-106.

1091-8531/$36.00
https://doi.org/10.1016/j.jaapos.2018.09.005

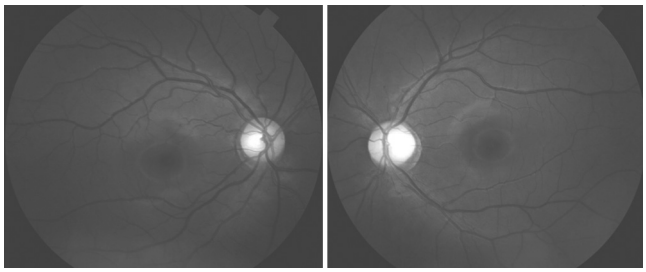

FIG 1. Fundus photographs showing pallor of the left optic nerve compared to the right; the macula appears unremarkable.

was unremarkable in the right eye and showed temporal optic nerve pallor in the left eye (Figure 1). Optical coherence tomography (OCT) of the retinal nerve fiber layer (RNFL) was normal and symmetric. Automated perimetry showed normal findings in the right eye and a central scotoma in the left eye. The following blood tests were normal: ACE, ANA, NMO-IgG, Lyme, and FTA-ABS. Magnetic resonance imaging of the brain and orbits with and without contrast was normal. There was no family history of sudden or unexplained vision loss. LHON testing revealed the 14484 point mutation.

On follow-up, automated segmentation of the macula revealed normal results in the right eye and, in the left eye, thinning of the inner plexiform, inner nuclear, outer plexiform, and outer nuclear layers (Figure 2). The ganglion cell layer (GCL), the ellipsoid, and the retinal pigment epithelium (RPE) of the left eye were normal. Full-field ERG showed normal results in the right eye. The left eye showed photopic abnormalities that exceeded scotopic abnormalities in amplitude and implicit time. The 30 Hz flicker and single photopic flash response demonstrated reduced amplitudes and prolonged implicit times (Figure 3). Pattern electroretinogram demonstrated normal findings in the right eye and reduced P50 amplitude and normal N95 amplitude in the left eye, consistent with the finding of an abnormal full-field ERG in that eye.

The patient was started on idebenone 900 mg daily and remained clinically stable on idebenone for 5 years, with no further changes in visual acuity (right eye, 20/20; left eye, 4/200), optic nerve appearance, automated visual field, GCL, or RNFL. It was presumed that the temporal pallor was an overcall, given the normal RNFL.

Discussion

To our knowledge, this is the first report of retinal thinning and cone-rod dysfunction associated with the 14484 mutation. Although optic nerve disease is much more common, there have been isolated case reports of primary or secondary mitochondrial mutations associated with LHON and retinal dysfunction. Salomão and colleagues[2] reported the electrophysiological findings of an extensive Brazilian family affected with LHON and harboring the 11778 mutation consisting of a carrier, her 2 brothers, and her son. Pattern-reversal visual evoked potential showed severely reduced P100 latencies and decreased N75-P100 peak in both eyes in the 3 affected members. The affected mother and her affected son both showed reduced peak-to-peak amplitude of single-flash cone response and 30 Hz flicker in both eyes; OCT findings were not reported.[2] Fenton and colleagues[3] reported outer retinal dysfunction in a 43-year-old woman found to be harboring the 15257 mutation, a rare mitochondrial mutation associated with LHON. They reported thinning of the outer retina on OCT. Multifocal electroretinography (mfERG), which measures cone function, showed markedly depressed p1 amplitudes of both eyes centrally. Heher and Johns[4] reported 3 cases harboring the 15257 mutation who had retinal findings similar to those of Stargardt's disease or

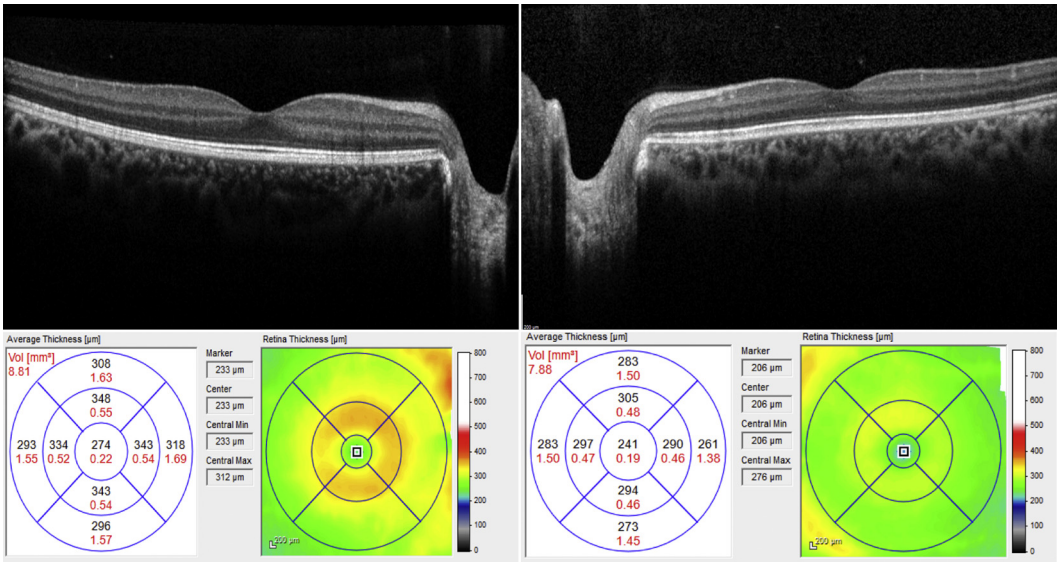

FIG 2. Optical coherence tomography showing a line scan and volume of macula of the right and left eyes.

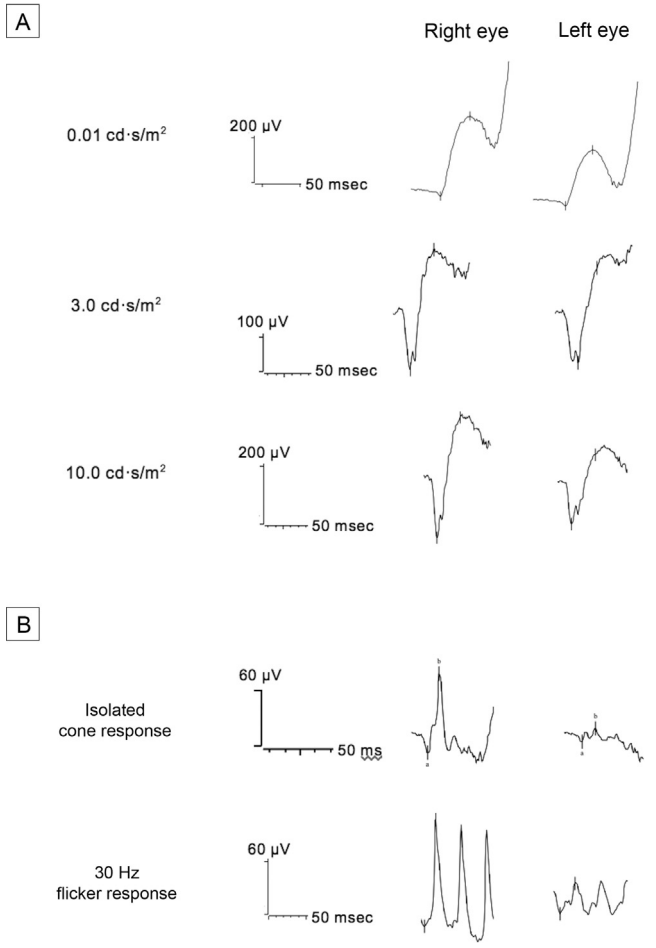

FIG 3. An ISCEV standard full-field flash electroretinogram (ERG) was preformed. A, Scotopic ERG responses to 0.01, 3.0, and 10.0 cd s/m^2 showing responses, including oscillatory potentials, within normal limits. B, Photopic ERG showing isolated cone response and reduced 30 Hz flicker response in the left eye.

other maculopathy in both eyes. At a recent meeting of the Upper Midwest Neuro-Ophthalmology Group, Abalem presented the case of a patient with central vision loss, temporal pallor, and bilateral central scotomas (Trobe JD. Neuroophthalmology 2017;41:335-8). The mfERG findings, which demonstrated prominent bilateral reduction of central macular signal amplitudes, delayed the ultimate diagnosis of 14484-mutation-positive LHON.

Our patient is unique in that visual loss occurred only in one eye, associated with photoreceptor dysfunction and the absence of RNFL thinning for 5 years. It is possible that the 14484 mutation did not cause visual loss in this patient; however, it is also possible that patients with unilateral retinal dysfunction do not get tested for LHON and hence may go undetected. It is also unclear what other disorder could have caused unilateral cone-rod dysfunction acutely in our patient. There were no symptoms of photopsias or signs of irregularities of the ellipsoid or RPE consistent with other outer retinopathies.

Based on the cases of bilateral cone-rod dysfunction reported and our patient, it would appear that retinal dysfunction may occur with various mutations of LHON. The exact pathophysiology of LHON remains elusive, but it may represent an interplay of genetic dysfunction of both mitochondrial and nuclear modifier genes and environmental factors causing mitochondrial dysfunction with ensuing reduced ATP synthesis, increased free radicals, and redox imbalance. The end result is ganglion cell dysfunction and apoptosis, causing optic nerve dysfunction.[5] Photoreceptors also experience very high ATP and energy demands,[6] yet only a few reports of retinal dysfunction exist. All cells carry varying degrees of abnormal mitochondria (heteroplasmy), and there may be selective segregation of these mitochondria in ganglion cells compared to photoreceptors. This heteroplasmy could theoretically explain the unilateral nature of our patient's vision loss. It is also possible that photoreceptor dysfunction may be more prevalent than reported, considering that clinicians do not routinely order retinal electrophysiologic testing in patients with LHON.

Ubiquinone analogues including co-enzyme-Q10 and idebenone have been used in the treatment of LHON. Recently, an international consensus statement recommends idebenone in the treatment of LHON.[7] Notably, our patient has not developed vision loss in the fellow eye on idebenone in 5 years of follow-up. It is unclear whether the idebenone has played a role in this or whether the fellow eye would have remained disease free without treatment.

Literature Search

A PubMed search was conducted in October 2017 using the following search terms: *Leber*, *retina*, *cone*, *rod*, *electroretinogram*, *photoreceptor*, and *segmentation*.

References

1. Newman NJ. Hereditary optic neuropathies: from the mitochondria to the optic nerve. Am J Ophthalmol 2005;140:517-23.
2. Salomão SR, Berezovsky A, Andrade RE, Belfort R Jr, Carelli V, Sadun AA. Visual electrophysiologic findings in patients from an extensive Brazilian family with Leber's hereditary optic neuropathy. Doc Ophthalmol 2004;108:147-55.
3. Fenton GL, Ho AC, Volpe NJ. Outer retinal dysfunction in a patient with the 15257 mitochondrial DNA mutation. Retin Cases Brief Rep 2011;5:104-7.
4. Heher KL, Johns DR. A maculopathy associated with the 15257 mitochondrial DNA mutation. Arch Ophthalmol 1993;111:1495-9.
5. Sadun AA, Karanjia R, Pan BX, Ross-Cisneros FN, Carelli V. Reactive oxygen species in mitochondrial optic neuropathies: comment. J Neuroophthalmol 2015;35:445-6.
6. Country MW. Retinal metabolism: a comparative look at energetics in the retina. Brain Res 2017;1672:50-57.
7. Carelli V, Caronelli M, de Coo IF, et al. International consensus statement on the clinical and therapeutic management of Leber's Hereditary Optic Neuropathy. J Neuroophthalmol 2017;37:371-81.