ABSTRACT

Purpose. To report vision recovery in a single case of Leber’s hereditary optic neuropathy (LHON) (mtDNA14484/ND6 mutation) with longitudinal documentation of retinal ganglion cell layer by ocular coherence tomography (OCT) that includes the pre-onset, acute, and chronic stages of vision loss.

Case Report. We report LHON in a 16-year-old male patient with Type 1 diabetes and known and documented family history of LHON. The patient presented with best-corrected visual acuities of right eye 20/150 and left eye 20/25. His retinal nerve fiber layer had thinned compared with baseline measures obtained 19 months before the onset of vision loss. Vision rapidly reduced to “hand movements” vision in each eye over the following 2 months. Despite OCT-documented significant recalcitrant loss of ganglion cell layer, visual acuity remarkably recovered to right eye 20/40+ left eye 20/50+ 16 months after onset of neuropathy.

Conclusions. A selective loss of ganglion cells and nerve fiber layer can be documented in LHON. Significant recovery of visual acuity can occur without apparent structural recovery.

Key Words: Leber’s hereditary optic neuropathy (LHON), mitochondrial mutation, 14484, OCT

CASE REPORT

A 16-year-old Caucasian male patient presented in August 2013 for a previously recommended diabetic retinal examination that had been advocated to monitor for retinal changes potential from Type 1 diabetes mellitus diagnosed 2 years previously. The patient and his younger half-brother had been under regular optometric evaluation from infancy due to a family history of LHON (mtDNA/ND6 mutation) with significant vision recovery after initial severe vision loss without corresponding structural recovery.
Previous eye examination, 17 months before this presentation (January 2012), documented uncorrected visual acuity of 20/15 in each eye with normal examination findings. Fundus photos and ocular coherence tomography (OCT) (Zeiss HD-Cirrus 500) scans of both macula and optic nerve head regions had been taken as baseline to allow future monitoring.

The patient reported intermittently blurred vision in the preceding few months, which he attributed to fluctuating blood sugar levels. He was managing his diabetes with Novorapid insulin delivered by an infusion pump but reported that his blood glucose level had been high in the preceding month (up to 30 mmol/L (540 mg/dL)) due to a fault with the pump. After repair, the pump

FIGURE 1.
Pedigree of patient’s family (LHON TAS002) (mt14484)1. The black star indicates the presented patient. The black triangle indicates his maternal uncle who did not recover significant vision. Circles indicate women (carriers) and squares men. Black symbols indicate family members who have manifest optic neuropathy and severe vision loss.

FIGURE 2.
Retinal photographs of right eye (A) and left eye (B), at time of initial vision loss.
had operated effectively over the previous week, with blood glucose levels back in the range of 4 to 10 mmol/L (72–180 mg/dL). He was on no other systemic medications and had no other known health concerns.

Uncorrected visual acuity measured 20/150 in the right eye and 20/25− in the left eye. Pupils had sluggish reaction to light and accommodation and a trace afferent defect was noted in the right eye. Extraocular muscle motility was normal and cover test indicated orthophoria ocular alignment. Cycloplegic refraction determined low hyperopic refractive error (right eye and left eye +1.00DS), which gave no change in visual acuity. Anterior eye examination was unremarkable. Ophthalmoscopic examination of the posterior pole was unremarkable (90D, 20/30D lenses) and the optic discs appeared normal (see Fig. 2).

Computerized perimetry with Humphrey Field Analyzer (HFA) 24-2 found a 5 to 7 dB loss in central visual field more marked in the right eye (see Fig. 3). The presence of the central loss of sensitivity and reduced acuity caused inaccurate fixation (31%, 60% fixation loss), which is noted as an unreliable outcome. The patient was able to complete SITA-standard strategy for left eye testing; however, the protocol for the right eye was changed to SITA-Fast to allow completion of the test in a time that did not lead to further fatigue. Further perimetric examination with 10-2 protocol was attempted, but was aborted due to patient fatigue and frustration with inability to detect targets.

Fundus examination and OCT scans showed no indication of macular edema or vascular anomaly secondary to diabetes that would explain the marked reduction in acuity for the right eye. Although LHON was the provisional diagnosis for vision loss due to the known genealogy, referral to a neuro-ophthalmologist was made for confirmatory blood tests and to exclude alternative and potentially treatable causes of optic neuropathy. Magnetic resonance imaging of orbits and brain with and without contrast, and blood tests to investigate for signs of infectious or inflammatory markers (full blood examination (CBC), ESR, liver function tests, ACE, ANA, ENA, anti-DNA, ANCA, and serum electrophoresis), were ordered and all returned normal outcomes. Genealogical DNA tests confirmed 14484 mtDNA mutation.

OCT scans showed significant change from baseline with changes in retinal layer thickness measures compared with scans obtained 17 months before. Optic disc scans showed that the retinal nerve fiber layer had thickened compared with previous measure (average 107–127 μm: right eye and 107–112 μm: left eye). The average macula ganglion cell layer + inner plexiform layer thickness decreased from 84 to 77 μm right eye and from 82 to 78 μm left eye (see Table 1). Four days after the initial finding of vision loss, visual acuity in the right eye had reduced to “hand movements”; within 2 weeks, the right eye had stabilized at “hand movements” and the left eye started to decline to 6/24 (20/80) with deterioration to “hand movements” vision in both the right eye and left eye over the next 2 months.

Eleven months after initial identification of vision loss, visual acuity was <20/400 in both eyes. Computerized perimetry documented a deep central scotoma (HFA 24-2) with a mean defect of −26.15 dB. OCT Macular Cube scans showed significant loss of combined ganglion cell layer + inner plexiform layer (average thickness 49 μm right eye, 45 μm left eye compared with 84 μm right eye, 84 μm left eye in pre-neuropathy scans); optic disc scans showed reduction in peripapillary retinal nerve fiber layer (right eye 71 μm; left eye 62 μm) with a global narrowing of neural retinal rim and concomitant increase in cup-to-disc ratio.

Sixteen months after initial vision loss, the patient reported a sense of improvement in vision over the preceding month.

FIGURE 3.
Longitudinal computerized perimetry results for the right and left eyes measured at initial onset of vision loss, severe vision loss and time of vision recovery (Humphrey Field Analyzer 24-2 Central Threshold).
Remarkably, visual acuity had recovered to right eye 20/40+, left eye 20/50+, binocular 20/25+. Despite this marked improvement in acuity, computerized perimetry found modest shrinkage in the central scotoma with a mean deviation of \( j \) 14.74 dB in the right eye and \( j \) 19.7 dB in the left eye (see Table 1). OCT scans found persistent loss of ganglion cell layer + inner plexiform layer and retinal nerve fiber layer thickness (see Figs. 4 and 5). Table 1 shows visual acuity, mean computerized perimetry outcomes, and OCT parameters at the baseline visit 19 months before onset of vision loss, at time of vision loss and at subsequent visits 11 months and 16 months after initial vision loss.

**DISCUSSION**

LHON is a maternally inherited neuropathy that results in profound, bilateral central vision loss. Although mutations in mitochondrial DNA predispose mitochondrial dysfunction, the vast majority of affected individuals do not develop LHON vision loss, and currently there is no way of predicting who might lose vision.\(^1\,6\) Loss of retinal ganglion cells is the predominant structural consequence.\(^8\) The mtDNA mutations associated with LHON alter polypeptides of the mitochondrial oxidative phosphorylation chain, which may lead to inhibition of cellular energy production.\(^9\) An increase in the production of free radicals is thought to occur, which promote oxidative cellular damage, and the retinal ganglion cells in the papillomacular bundle are most susceptible to these free radicals.\(^6\)

It is not yet known why male carriers are more susceptible than females, or why vision recovery is more likely in patients who are younger at onset of vision loss. In contrast to the case presented, the patient’s uncle, who was 20 years of age at onset of vision loss, did not experience remarkable recovery of vision with visual acuity 20 years post-neuropathy stable at right eye 20/400 and left eye 20/100. This difference in visual outcome between related cases exemplifies a correlation between good visual outcome and age that has been previously noted, with patients whose onset was before 20 years of age having a higher likelihood of a final visual acuity better than 20/80 as opposed to those with later onset.\(^2\) Improvement in electrophysiological responses have been reported to accompany recovery of acuity and visual fields in LHON.\(^10\) Although the mechanism for vision recovery is not fully understood, the intractable loss of ganglion cell layer in this case supports a suggestion that a subset of retained but viable previously inactive retinal ganglion cells may be responsible.\(^10\)

A recessive X-linked susceptibility gene that works in concert with the mitochondrial mutation or hormonal influence has been hypothesized to explain the greater incidence of LHON in male

<table>
<thead>
<tr>
<th></th>
<th>Visual acuity</th>
<th>Computerized perimetry (Humphrey VFA 24-2)</th>
<th>OCT OHN RNFL thickness analysis (µm)</th>
<th>OCT macular ganglion cell analysis (average GCL + IPL thickness µm)</th>
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<tr>
<td></td>
<td>RE</td>
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<td></td>
<td>RE</td>
<td>LE</td>
<td>Onset of vision loss</td>
<td>MD = 2.62 dB VFI 92%</td>
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<tr>
<td></td>
<td>RE</td>
<td>LE</td>
<td>Onset of vision loss</td>
<td>MD = 14.74 dB VFI 59%</td>
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RE, right eye; LE, left eye; GCL, ganglion cell layer; RNFL, retinal nerve fiber layer; IPL, inner plexiform layer; MD, mean deviation; VFI, Visual Field Index; Av, average; S, superior; N, nasal; I, inferior; T, temporal.
FIGURE 4.
Longitudinal OCT of the optic nerve head and peripapillary zone measured as baseline before neuropathy, at initial onset of vision loss, severe vision loss, and time of vision recovery. Increase in superior and inferior RNFL thickness from baseline is seen at onset of neuropathy, followed by chronic reduction. A, right eye. B, left eye.

FIGURE 5.
OCT change in macular thickness from scans obtained at time of vision loss to 15 months later when vision had shown remarkable recovery. A, right eye. B, left eye.
carriers. Estrogens in females are thought to modify the defective synthesis of ATP, oxidative stress, and apoptosis of mitochondrial dysfunction.

Environmental factors such as heavy tobacco smoking, high alcohol consumption, and nutritional deficiencies have been implicated as triggers for vision loss in LHON carriers, in none of which were present in the case presented. A limited number of reports also suggest an association between LHON and diabetes mellitus, with the supposition that diabetes may place undue metabolic stress on mitochondria function. In the case presented, blood glucose level was poorly controlled immediately before onset of vision loss, raising the premise that metabolic stress precipitated the neuropathy.

There may be few ocular signs accompanying the severe loss of vision, which can be down to <6/120 (~20/400). However, it has been proposed that if seen early enough in the course of the disease, two phases can be recognized that result in changes to the optic discs—an acute and a chronic phase. In the acute phase, the optic disc may be mildly swollen with dilated peripapillary capillaries and hyperemia, which can also be seen in female carriers. In the chronic phase, the disc is typically flat, pale, and atrophic, and visual field testing finds a dense central scotoma with no peripheral field loss. Asymptomatic carriers have been shown to have thicker retinal nerve fiber layer, predominantly in the temporal peripapillary quadrant, and show greater variability in thickness measures than controls. Longitudinal OCT studies have shown a characteristic pattern of change in the peripapillary retinal nerve fiber layer in the acute phase, with thickening involving the four quadrants, with temporal and inferior sectors being the first affected, consistent with early involvement of the papillomacular bundle. In addition to variable thickness measures in phases of the neuropathy within subjects, differences have been noted between mtDNA etiology groups, with the 11778 group showing more prominent retinal nerve fiber layer atrophy of superior, nasal, and inferior quadrants than in those of the 14484 group. In this case, an initial increase in average retinal nerve fiber layer thickness of 20 μm was recorded in the right eye, from 107 μm 19 months before vision loss to 127 μm at the time of initial vision loss. Average retinal nerve fiber layer thickness in the right eye had dropped to just 62 μm 15 months after neuropathy onset (see Table 1 and Fig. 5).

Current medications for LHON are experimental or off-label. Antioxidants such as idebenone, which are said to decrease intracellular free radicals and the associated oxidative damage, have shown the most encouraging results; however, there has been no definitive clinical trials that show this can prevent visual loss or restore vision after loss. A recent isolated trial of a new experimental drug, EPI-743, has been reported. This drug is purported to act by reducing cellular oxidative stress and may provide some protection for retinal ganglion cells. The trial examined the use of EPI-743 in two siblings who had LHON (mtDNA mutation 14484) with the drug provided to the younger sibling, who developed a significantly better visual outcome than the older sibling who had no treatment. LHON is a genetic disorder, and thus genetic therapies are being developed and examined. Clearly, further investigations into the efficacy of these drugs and therapies are required in the form of randomized, controlled trials before they can be shown to have significant beneficial effects. Our patient and his family decided, with advice from the neuro-opthalmologist, not to proceed with idebenone or any other experimental treatments for his condition at present.

Patient management is predominantly supportive, recognizing that the sudden and severe loss of vision will impact the individual’s psychological state and have a significant negative impact on quality of life. All females with a mitochondrial DNA mutation, even those who do not develop LHON, will pass this genetic defect on to their children. It is, therefore, vital to ensure that adequate support channels are available to LHON patients, including genetic counseling for themselves and their female relatives who are carriers of the mitochondrial disorder. Such support requires a team approach, and it is important for all professionals involved in such care to maintain open communication between each other, for the best outcome for the patient and his family. In addition to genetic counseling, low vision aids and devices such as near optical and electronic magnifiers and telescopic systems for distance viewing are of significant benefit.

In the present case, the low vision appraisal suggested handheld video magnifiers and closed-circuit television magnification systems to assist with near tasks and voice recognition software for educational computers; orientation and mobility training were not required due to intact peripheral vision.

This case documents the changes in retinal tissue and changes in visual function at both the acute and chronic phases of LHON and reports that despite profound recalcitrant loss of retinal cells, notable recovery of visual acuity can occur.

Received August 26, 2015; accepted June 9, 2016.

REFERENCES

7. See JH, Hwang JM, Park SS. Comparison of retinal nerve fibre layers between 11778 and 14484 mutations in Leber’s hereditary optic neuropathy. Eye (Lond) 2010;24:107–11.

Optometry and Vision Science, Vol. 93, No. 12, December 2016

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