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Natural History of Conversion of Leber's Hereditary Optic Neuropathy

A Prospective Case Series

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Purpose: To illustrate the natural history of Leber's hereditary optic neuropathy (LHON).

Design: Prospective observational case series.

Participants: The Soave-Brazil pedigree of m.11778G>A/ND4 mitochondrial DNA LHON mutation.

Methods: A prospectively acquired database of the Soave-Brazil pedigree was reviewed. Data from 285 individuals were included in the database over a 15-year period. The pedigree was reviewed for unaffected mutation carriers who converted to affected status, 6 patients with LHON were identified. The medical records were reviewed 1 year preconversion to 1 year postconversion for visual acuity (logarithm of the minimum angle of resolution [logMAR]), Humphrey Visual Field (HVF) mean deviation (MD), and retinal nerve fiber layer (RNFL) thickness, as measured by Cirrus (Carl Zeiss, Oberkochen, Germany) optic coherence tomography (OCT). The RNFL thickness values were normalized for age. Visual acuity, HVF, and processed RNFL data from each of the 12 eyes were then sorted into 2-month time periods relative to the date of conversion, within which they were averaged.

Main Outcome Measures: The main outcome measures were visual acuity, HVF MD, and RNFL thickness.

Results: Decreased visual acuity preceded conversion by up to 2 months and then declined up to 8 months postconversion. Decrease in HVF MD occurred at least 4 months preceding conversion, after which values decreased until plateau at 6 to 8 months. Average RNFL thickness was above normal baseline thickness in all 4 quadrants as measured by OCT at the time of conversion. Increase in RNFL thickness preceded conversion as early as 4 to 6 months, peaked at conversion, and decreased until individual plateaus. The temporal quadrant was first to be involved, then the inferior and superior quadrants, and the nasal quadrant showed the latest and least changes.

Conclusions: Subclinical changes preceded the date of conversion and may reflect the complicated nature of identifying the date of conversion in LHON. Early increases in RNFL preceding conversion suggest that structural changes precede clinically significant vision loss. Asynchronous quadrant involvement supports a previously published mathematical model. The natural history of LHON is not a subacute process, as previously believed, but progresses more slowly, taking up to 8 months to plateau. *Ophthalmology 2017;■:1–8 © 2017 by the American Academy of Ophthalmology.*

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Leber's hereditary optic neuropathy (LHON) is a maternally inherited genetic disorder that has been characterized as a subacute asynchronous severe bilateral loss of vision that is classically seen in young adult men in the second to third decades of life. This rapid loss of vision is associated with a dense central scotoma sometimes presaged by dyschromatopsia and diminished contrast sensitivity at high spatial frequencies.[1] Three mitochondrial DNA mutations at nucleotide positions m.11778 G>A, m.3460G>A, and m.11484T>C account for 95% of LHON cases by disrupting subunit genes of complex I (ND4, ND1, and ND6 respectively), which is involved in mitochondrial oxidative phosphorylation.[2]

Mutation at the nucleotide position 11778 was first described by Wallace et al[3] and is the single most common mutation site seen in approximately 75% of patients with LHON, including the Soave-Brazil pedigree. The penetrance rate of LHON is highly variable with differences between mutations and even within the same pedigrees, as well as differing severity of clinical expression among individuals. Of note, penetrance in men is higher, at approximately 50% versus 10% of women despite sharing the same mitochondrial DNA mutation.[1]

Vision loss in LHON presents initially as a relative central scotoma in 1 eye and progresses to a large, dense

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Table 1. Patient Demographics

	Gender	Age of Conversion (Yrs)	Year of Conversion
1	Male	46	2003
2	Male	15	2011
3	Male	15	2003
4	Male	35	2001
5	Male	20	2011
6	Female	43	2006

centrocecal scotoma. Involvement of the second eye occurs within weeks to months after the first eye, a pattern almost pathognomonic of LHON. Circumpapillary telangiectatic microangiopathy and nerve fiber layer swelling around the disc on funduscopic examination have been reported at the time of conversion.[2,4] However, although such fundus changes have been described around the time of conversion, there have been no published studies that include changes long preceding conversion. A 15-year longitudinal study of a large pedigree (>300 subjects) allowed us an unparalleled opportunity to follow the natural history in unaffected mutation carriers and affected patients with LHON. We report the first set of prospectively collected data providing the natural history of conversion in 6 patients whose clinical, psychophysical, and funduscopic changes were recorded for more than 1 year preconversion and postconversion.

Methods

A previously described prospective database containing examinations of the Soave-Brazil pedigree from 2001 was reviewed for this

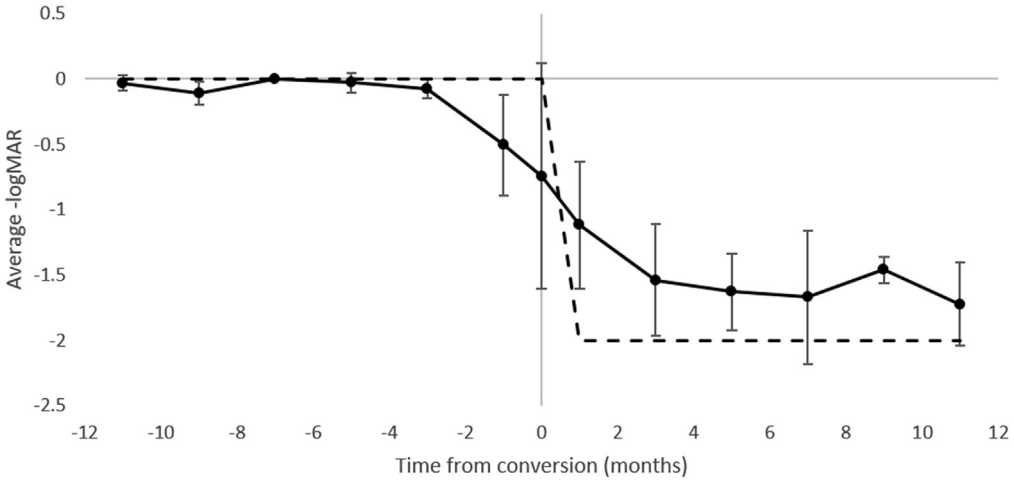

Figure 1. Average visual acuity (−logarithm of the minimum angle of resolution [logMAR]). *Dashed*: Hypothetical line depicting the presumed subacute nature of Leber's hereditary optic neuropathy (LHON). *Solid*: Average −logMAR values with standard deviation. Visual acuity decrease was noted up to 2 months preceding the date of conversion. After conversion, visual acuity gradually decreased at a rate slower than that of the previously presumed subacute progression of LHON. Plateau of −logMAR at complete loss of vision occurred 4 to 6 months after conversion.

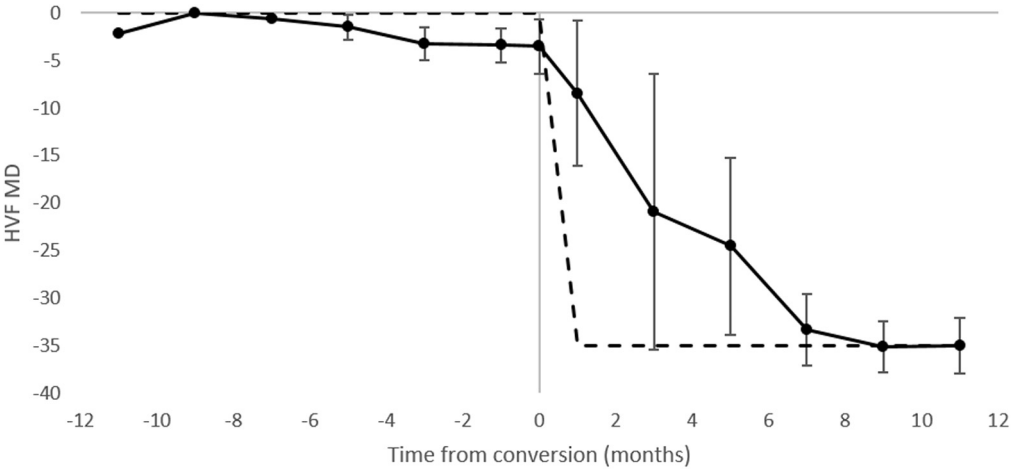

Figure 2. Average Humphrey Visual Field (HVF) mean deviation (MD). *Dashed*: Hypothetical line depicting the presumed subacute nature of LHON. *Solid*: Average HVF MD values with standard deviation. Decrease in HVF MD was noted as early as 2 to 4 months preceding the date of conversion. After conversion, values continued to gradually decrease until plateauing 6 to 8 months after conversion.