Presymptomatic Visual Loss in Leber Hereditary Optic Neuropathy: A Therapeutic Window of Opportunity?

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An ironic, awesome paradox of contemporary scientific technology is that so apparently esoteric a discipline as abstract mathematics and so apparently dehumanized a device as a digital computer can be used to help clinicians improve the practical humanitarian art of patient care.


Leber hereditary optic neuropathy (LHON) is an inherited disorder caused by mutations in mitochondrial DNA (mtDNA). Patients typically present with severe bilateral sequential painless vision loss. Involvement of the second eye usually occurs weeks to months after vision loss in the first eye, with more than 97% of patients developing bilateral vision loss and optic atrophy within 1 year. Two point mutations in mtDNA account for 90% of LHON cases worldwide. The most common mutation is m.11778G>A in MF-NDM, which also happens to have the poorest visual outcome and the least chance of spontaneous recovery. It is not known why the visual loss occurs as an all-or-nothing event, why it is sharply confined to the central visual field, what factors produce the ictus, why it never recurs, or how central vision, once extinguished, can sometimes spontaneously improve. At the retinal ganglion cell level, it remains unclear whether the subacute visual loss of LHON represents a threshold phenomenon in a setting of progressive mitochondrial dysfunction or a sudden metabolic cascade leading inexorably to apoptosis and cell death.

In this issue of *Ophthalmology*, Hwang et al (see www.aaojournal.org/article/S0161-6420(16)30848-X/fulltext) analyze their prospectively acquired database from a unique 7-generation Soave-Brazil pedigree of patients with the 11778 LHON mutation. They provide the clinical and optical coherence tomography (OCT) findings in patients with symptomatic visual loss (termed conversion) from LHON. In following 285 individuals over 15 years, they chart the conversion of 6 patients. The authors detected thickening of the retinal nerve fiber layer (RNFL) on OCT, 4 to 6 months before conversion. Additionally, decrements on Humphrey visual field were noted 4 months before conversion, whereas a very mild decrease in visual acuity was detectable up to 2 months before the patients became symptomatic. At the point of conversion, there was a significant thickening of the RNFL followed by progressive atrophy over 8 to 10 months associated with the symptomatic worsening of vision.

This is the largest longitudinal OCT study of a cohort of patients with LHON beginning from a preclinical stage to conversion, which expands on 2 previous studies from the same cohort of patients. Sadun et al previously documented the conversion of 4 patients with LHON and found an increase in RNFL thickness on OCT leading up to symptomatic vision loss. The current study adds to the number of patients who underwent conversion and reports the subtle changes on visual fields and acuity leading up to conversion. Before the advent of OCT, Nikoskelainen et al documented the ophthalmoscopic findings in LHON and found an increase in peripapillary telangiectatic vessels and pseudoeeda of the RNFL long before symptomatic vision loss, which increased at the end of the presymptomatic stage. The current study extends these observations using OCT, a more sensitive and robust diagnostic method for detecting RNFL changes. Optical coherence tomography does not require an expert eye to detect the subtle peripapillary changes that were previously reported, and it allows for objective measurement of subclinical RNFL swelling that could indicate impending vision loss.

In interpreting these results, it is important to remember that the psychophysical and structural changes detected within the presymptomatic stage are subtle, making it difficult to distinguish them from the longstanding psychophysical and electrophysiologic aberrations described previously in asymptomatic carriers of LHON, which have been noted to wax and wane. Thus, the development of mild dyschromatopsia or small scotoma in an asymptomatic carrier could potentially be misinterpreted as signifying incipient vision loss. In addition, “conversion,” the major outcome measure of this study, is an imprecise parameter that is dependent on innumerable psychogenic and physiologic factors.

Despite these issues, this study provides additional evidence that the onset of LHON is more gradual than is classically thought, reflecting the notion that LHON is really a chronic disease at the mitochondrial level. These results suggest that conversion in LHON is a distinct physiologic event superimposed on a slow continuum of change. Even with the mtDNA mutation, however, retinal ganglion cells subserving the peripheral visual field typically remain fully functional, suggesting that their larger ratio of volume to surface area allows them to maintain the necessary bioenergetic reserve capacity to maintain axonal conduction and perhaps limit the production of reactive oxygen species.

Therefore, this lifelong axonal resilience suggests that targeted neuroprotective therapy also could preempt central visual loss.

This study comes at a pivotal point for LHON research because there are new promising advances in LHON treatment. Prior studies with mitochondrial modifying agents,
such as idebenone, have shown modest improvement in visual outcomes in some patients when given after the onset of visual loss. Gene therapy trial using intravitreal injection of an adenovirus vector for the treatment of the LHON 11778 mutation are now being offered. Prior work has demonstrated successful rescue of mutant animal models of LHON using this strategy. In 2015 and 2016, the initial phase 1 human clinical trials for LHON 11778 were completed, which demonstrated safety of the treatment. A dose-escalation trial is currently under way to evaluate different doses at various time points in the disease process (NCT02161380). Most recently, GenSight Biologics began enrolling patients for a randomized, double-masked, sham-controlled phase 3 clinical trial to evaluate the efficacy of gene therapy for LHON (NCT02652767 and NCT02652780).

Although gene therapy holds promise, its efficacy in the treatment for both the affected eye and the presymptomatic eye is yet to be determined. In addition, gene therapy may have only a short-term effect, as has been shown recently in some gene trials with RPE65 for Leber congenital amaurosis. The optimal timing of treatment will depend in part on the duration of its treatment effect. If the treatment is not permanent, then finding carriers on the verge of conversion becomes even more meaningful because restoring vision after significant vision and ganglion cell loss would unlikely to be as effective as treatment when a patient is on the verge of symptomatic vision loss. A latency period for diffusion of the virus vector and for successful integration and expression of the gene also might require that patients be treated early within the presymptomatic stage. However, it also remains possible that the onset of the presymptomatic stage may define a point at which the metabolic switch has been flipped and preventive treatment becomes ineffective. Last, although current gene therapy treatments for LHON would not prevent transmission of the disease to subsequent offspring, newer mitochondrial replacement therapy could eventually achieve this goal.

Ongoing advances in OCT may further refine the presymptomatic detection of patients destined for vision loss from LHON. A combination of RNFL thickening and ganglion cell layer thinning may be a red flag for imminent vision loss. Balducci et al. reported 2 patients who had ganglion cell layer thinning 6 weeks before symptomatic vision loss. Optical coherence tomography angiography is a newer diagnostic tool that may allow us to predict conversion, demonstrating dilated temporal peripapillary capillaries in eyes of unaffected preclinical patients, whereas eyes of symptomatic patients show the development of telangiectatic arterioles. Improvements in identifying patients at risk for impending vision loss combined with new therapies for LHON could provide hope for this visually devastating disease.

References


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