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Editorial

Improving the visual outcome in Leber's hereditary optic neuropathy: Framework for the future

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Leber's hereditary optic neuropathy (LHON) is a mitochondrial disease characterized by central vision loss and a poor visual prognosis.[1] LHON remains without cure; however, recent advances in understanding the natural history of disease have led to new insights and approaches to therapy.

Natural history of disease

Various studies have advanced our understanding of LHON pathophysiology. Until recently, the contribution of the microvascular supply to the pathogenesis of LHON was poorly understood.[1,2] Optical coherence tomography angiography (OCTA) has improved on previous imaging technologies through enhanced visualization of the optic disc and retinal microvasculature.[3] Balducci and colleagues used OCTA to detect significant peripapillary microvascular changes over the disease course of LHON.[4] Intriguingly, vessel attrition corresponded with loss of the retinal ganglion cell-inner plexiform layer (RGC-IPL) and preceded thinning of the retinal nerve fiber layer (RNFL).[4] In addition to the peripapillary vasculature, recent OCTA studies conducted by our laboratory revealed vascular pathology also in the macula for both chronic and acute disease stages of LHON.[1,5] Borrelli et al. showed quantitative differences in the macular retinal and choroidal circulation of chronic LHON patients. Specifically, vascular attenuation was localized to the macular region corresponding to the upstream portion of the papillomacular bundle (PMB).[1] More recently, our group observed vascular pathology as early as the acute and subacute stages of LHON. Intriguingly, OCTA of the subacute stage showed vascular attrition with marked enlargement of the foveal avascular zone. In contradistinction, the acute stage exhibited increased vascular perfusion with evidence of microangiopathy and vascular telangiectasias.[5] Similar to chronic LHON, these early vascular changes coincided with loss of the PMB,[6,7] which contains the smallest RGC fibers that are the most vulnerable to mitochondrial dysfunction.[8,9] Taken together, these studies provide new insight into the evolution of disease and introduce the clinical utility of vascular parameters as objective biomarkers for LHON.

Emerging therapies and neuroprotective strategies

LHON is a complex disease with a multifactoral phenotypic manifestation influenced by secondary genetic factors, environmental triggers and hormonal influences.[9,10] The current standard of treatment for LHON is idebenone. However, visual improvement typically does not occur until two or more years of idebenone therapy, and rarely occurs by one year.[11,12] Studies have shown that unaffected LHON mutation carriers and normal healthy controls have a higher mtDNA copy number compared to affected patients with LHON.[10] Agents such as estradiols that promote mitochondrial biogenesis may help compensate for dysfunctional mitochondria and enhance visual recovery in patients with LHON.

Protective role of estrogen

Recent *in vitro* studies have highlighted estrogen's role in increasing mitochondrial biogenesis and thus, preserving vision.[9,13] LHON fibroblasts treated with oestrogen derivatives not only increased mtDNA copy number, but also reduced ROS levels and improved cell survival.[10] Our group elucidated estrogen's mechanism of action in cybrids whereby activation of estrogen β receptor, which upregulates antioxidant enzyme production of superoxide dismutase-2, increases mitochondrial biogenesis, and enhances cellular energy competence.[9,13] These findings suggest the protective role of estrogen and could explain the marked bias of LHON vision loss in males and in menopausal women given the declining levels of estrogen.[9,13] On the contrary, smoking is a major risk factor for visual loss in LHON.

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Previous experiments in LHON fibroblasts have shown impaired mitochondrial biogenesis and decreased mtDNA copy number when exposed to cigarette smoke.[10] Given these in vitro findings that estrogen may promote mitochondrial biogenesis in LHON, our laboratory recently demonstrated the clinical utility of estrogen's protective role in LHON in vivo. Specifically, a perimenopausal woman receiving idebenone treatment exhibited accelerated visual recovery following supplementation with hormone replacement therapy.[14] Visual field and visual acuity markedly improved shortly after one month with complete visual recovery after eight months.[15] Idebenone treatment combined with HRT may have a synergistic effect in enhancing cellular bioenergetics and improving visual outcomes in patients with LHON.

Promyelinating agents

Promyelinating agents have shown some efficacy in demyelinating diseases such as multiple sclerosis (MS).[14,16] 4-aminopyridine (4-AP), an extended release lipophilic pyridine derivative, inhibits voltage-gated potassium channels thereby delaying repolarization, promoting remyelination, and restoring impaired action potential propagation.[14] Therapy with 4-AP has improved walking speed and increased lower extremities muscle strength in patients with MS.[14]

Pathological features of LHON also involve poor myelination.[14] Our laboratory recently explored the clinical utility of 4-AP in LHON. Affected LHON patients carrying the 11778, 14484, and 3460 mtDNA mutations that were long-term non-responders to idebenone alone showed improvements in visual acuity, color vision, and visual field examination following supplementation with 4-AP.[17] Future studies in larger cohorts may broaden the use of 4-AP as an adjunct to idebenone in LHON.

Gene therapy

Gene therapy for LHON has been proposed, with great fanfare. Given their non-pathogenic and intrinsically low immunogenicity, adeno-associated viruses (AAVs) have been exploited as vectors for gene transfer delivery to the retina.[18] Intravitreal injection of the recombinant AAV2 vector carrying the *ND4* gene (GS010) has overall shown to be safe and well tolerated in LHON patients.[19–22] Recent findings from GenSight Biologics RESCUE and REVERSE phase III clinical trials revealed trends in improved visual function at 48 weeks as measured by best corrected visual acuity (BCVA) and contrast sensitivity.[23] Secondary evaluation at 72 weeks showed continued improvement in visual function, although this was not statistically significant.[23] In addition, structural evaluation using OCT showed, small but statistically significant differences in RNFL and RGC-IPL thinning.[23]

Conclusion and final remarks

Despite the introduction of novel treatment modalities, the preservation of vision in LHON remains problematic. Current treatments for LHON have shown limited efficacy and response to therapy varies from patient to patient. Nevertheless, advances in understanding LHON pathophysiology, especially in the early stages, are necessary. New insights into the natural history of disease, as presented by this article, may serve as a framework for new treatment modalities and improved visual outcomes in the future.

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