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The Visual Outcome of LHON due to m.3460G>A Depends on Genetic, Environmental, and Therapeutic Influences

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LETTER TO THE EDITOR

The interesting article about 5 patients with Leber's hereditary optic neuropathy (LHON) by Yang, *et al*., [Yang, H. K. *et al*., 2024] requires further discussion.

The first point is that the number of patients is too low and the design of the study is inappropriate to conclude that the visual prognosis is poor in Asian LHON patients carrying the mtDNA variant m.3460G>A, as expressed in the title [Yang, H. K. *et al*., 2024]. The study included only 5 patients and was a national single-centre study that did not include patients from across Asia.

The second point is that several factors that could be responsible for the poor outcome were not discussed. The first factor affecting the outcome is the heteroplasmy rate. At least in some cases, heteroplasmy rates correlate with disease severity, rate of progression, and outcome [Yang, H. K. *et al*., 2024]. The higher the heteroplasmy rates, the more severe the phenotype and the poorer the outcome. However, heteroplasmy rates in the 5 included patients were not reported. The second factor is the haplotype. Because haplotypes vary significantly between regions and ethnicities, and because haplotypes can influence phenotypic expression, it would have been crucial to know them for the 5 patients A third factor is the risk factors for the penetrance of the m.3460G>A variant. Since penetrance depends on alcohol, tobacco, agricultural pesticides and probably other toxins [Sadun, A. A. *et al*., 2003], it would have been imperative to know which toxins these patients were chronically exposed to and what their eating habits were.

The third point is that LHON plus was not considered as a factor determining the outcome. LHON can manifest not only in the retinal arteries, retinal ganglion cells, and optic nerve, but also in other organs such as the brain [Ren, H. *et al*., 2022] or myocardium [Becker, L. *et al*., 2014]. Cerebral manifestations of LHON may include Harding's disease, dystonia, or epilepsy and cardiac manifestations may include hypertrophic or dilated cardiomyopathy. If the number of white matter lesions is high, the visual impairment may be simply not resolve due to impairment of the cerebral visual pathways.

The fourth point it that none of the five patients received idebenone [Yang, H. K. *et al*., 2024]. Since idebenone can improve vision, at least in some cases, the use of this drug would have been mandatory.

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