LETTER TO THE EDITOR

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

Variable response to Idebenone in LHON is multifactorial

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Keywords: mtDNA, LHON, respiratory chain, oxidative phosphorylation, Idebenone.

Dear Editor,

We read with interest the article by Mercuţ *et al.* about two patients with Leber's hereditary optic neuropathy (LHON), a 15-year-old male carrying the mitochondrial deoxyribonucleic acid (mtDNA) *m.3460G>A* variant in *MT-ND1* [patient (1)] and an 11-year-old male carrying the *m.11778G>A* variant in *MT-ND4* [patient (2)], in whom the morphological and functional response to Idebenone treatment was monitored in three months intervals over a period of one year [1]. Patient (1) experienced improvement of visual acuity, visual fields defects, and visually evoked potentials (VEPs) but no improvement was found regarding the retinal abnormalities, while patient (2) experienced neither functional nor morphological improvement of his abnormalities [1]. The study is appealing but raises concerns that should be discussed.

A limitation of the study is that heteroplasmy rates of the causative mtDNA variants were not provided [1]. Knowing heteroplasmy rates is crucial as they may contribute to the phenotypic expression of mtDNA variants and could be responsible for the variable treatment responses of the two index patients. It is conceivable that low heteroplasmy rates may favor a beneficial treatment response whereas high heteroplasmy rates may prevent a beneficial effect.

Another factor determining the phenotypic expression of mtDNA variants is the mtDNA copy number within mitochondria. Increased mtDNA copy number could represent a compensatory mechanism for the disturbed energy production. Therefore, it is conceivable that high mtDNA copy numbers favor a beneficial treatment response.

Another factor that may have led to the variable treatment response in both patients could be the adherence of the patients to take the study drug. We, therefore, should know how treating physicians monitored the correct intake of the study drug. Is it conceivable that patient (2) was less compliant than patient (1)?

LHON is often not only a disease of the retinal ganglion cells (RGCs) but can be occasionally a multisystem disease (LHON plus). We should be informed how involvement of organs other than the eyes was ruled out. Of particular interest are the results of the cerebral magnetic resonance imaging (MRI) and the results of cardiac investigations because affection of the brain or the heart may strongly determine the outcome of LHON patients.

Missing is the discussion about the possibility that improvement in patient (1) was due spontaneous recovery and independent of the treatment. Spontaneous recovery in patients carrying the *m.3460G>A* variant has been previously reported. Spontaneous recovery of visual impairment has been also reported in LHON due to other mtDNA variants.

Overall, the interesting study has limitations that challenge the results and their interpretation. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Based on the considerations outlined above, we disagree with the conclusions that the Idebenone effect in LHON depends on the underlying genetic defect.

Conflict of interests

The authors have no conflict of interests to declare.

Reference

[1] Mercuţ MF, Tănasie CA, Dan AO, Nicolcescu AM, Ică OM, Mocanu CL, Ştefănescu-Dima AŞ. Retinal morphological and functional response to Idebenone therapy in Leber hereditary optic neuropathy. Rom J Morphol Embryol, 2022, 63(1):213–219. https://doi.org/10.47162/RJME.63.1.24 PMID: 36074687 PMCID: PMC9593130

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Received: October 9, 2022 *Accepted: March 3, 2023*