LETTER TO THE EDITOR

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# Retinal morphological and functional response to Idebenone therapy in Leber hereditary optic neuropathy

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Dear Editor,

We read with interest the letter [1] from Josef Finsterer & Sounira Mehri about our article regarding the morphological and functional response to Idebenone therapy in patients with Leber hereditary optic neuropathy (LHON), where two pediatric patients, genetically confirmed, were periodically followed-up over a period of one year after we initiated the treatment [2]. We thank them for the interest shown in this topic and we want to answer the questions they have formulated regarding our study.

The first concern was the fact that the heteroplasmy rates of the causative mitochondrial deoxyribonucleic acid (mtDNA) were not provided in our study. According to the symptoms, the ophthalmological examination, and the functional and morphological investigations, the two patients were suspected of LHON, they were genetically tested and confirmed. Because they fulfilled all the inclusion criteria, they were included in the National LHON Program and were eligible to receive the treatment with Idebenone. We considered that, being symptomatic carriers, our patients do not require this determination. It is already known that clinically manifesting carriers of one of the primary LHON mutations: *mtND1*: *m.3460G>A*, *mtND4*: *m.11778G>A*, *mtND6*: *m14484T>C*, usually, present a homoplasmic state of that variant [3, 4].

Regarding the mtDNA copy number, Giordano *et al.* observed that symptomatic carriers have a decreased rate of mtDNA copy number [5]. Baglivo *et al.* correlated, in their study, the amount of mtDNA and treatment response and hypothesized that in *m.3460G>A* variant a protective role of mitochondrial biogenesis could be considered since in *m.11778G>A* variant, there was no correlation between the mtDNA copy number and disease penetrance [6]. In our study, we obtained a good response to Idebenone in patient with *m.3460G>A* mutation and no response in patient with *m.11778G>A* mutation. Nevertheless, in Romania, neither the determination of heteroplasmy rates, nor the mtDNA copy number is performed routinely in public or private health systems.

A concern was about the patients' adherence to treatment and if we ensured the correctness of the treatment. The Idebenone therapy was initiated in the hospital, in the presence of a parent for each patient. We explained and monitored the treatment intake for the first three days and then the patients continued at home. Both the patients and their parents confirmed the correct intake of Idebenone, 300 mg, three times/day.

Another question was related to the presence of other signs and symptoms, especially neurological and cardiological, that could determine the presence of LHON plus syndrome. As it is written in the article, the brain magnetic resonance imaging was normal for both patients. Also, the patients were sent for complete neurological and cardiological examination before Idebenone initiation, and both were normal, so we excluded a LHON plus syndrome.

Regarding the spontaneous recovery in patient with *m.3460G>A* variant in *mtND1*, we considered the improvement in visual acuity and all the functional tests due to Idebenone therapy, because since the diagnosis until the treatment initiation there were 15 months in which the visual acuity and functional and morphological investigation showed a severe progression of the disease. In three months after we started the treatment, we obtained a good result which continued to improve during the treatment. There are reported cases of LHON patients with spontaneous recovery in visual function, but especially with *m.14484T>C* mutation [7–9]. On the other hand, patients with *m.3460G>A* mutations have not only a 4% chance of spontaneous recovery [10], but they also have a bad prognosis without treatment, and good response to Idebenone therapy [11, 12].

In conclusion, our study focused on the retinal changes due to Idebenone therapy in our two patients with LHON. We concluded that Idebenone may improve the retinal function, with no effect on the morphological tests, a fact that is

also sustained by other studies [13, 14]. Regarding the factors that influence the treatment, we consider that the genetic profile may have influenced the therapy response in our cases, but we did not state that it is the only factor which affects the retinal response to Idebenone.

**Conflict of interests**

The authors have no conflict of interests to declare.

## References

[1] Finsterer J, Mehri S. Letter to the Editor: Variable response to Idebenone in LHON is multifactorial. Rom J Morphol Embryol, 2023, 64(1):101. https://doi.org/10.47162/RJME.64.1.13 PMID: 37128798 PMCID: PMC10257775

[2] 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

[3] Poulton J, Finsterer J, Yu-Wai-Man P. Genetic counselling for maternally inherited mitochondrial disorders. Mol Diagn Ther, 2017, 21(4):419–429. https://doi.org/10.1007/s40291-017-0279-7 PMID: 28536827

[4] Yu-Wai-Man P, Howell N, Mackey DA, Nørby S, Rosenberg T, Turnbull DM, Chinnery PF. Mitochondrial DNA haplogroup distribution within Leber hereditary optic neuropathy pedigrees. J Med Genet, 2004, 41(4):e41. https://doi.org/10.1136/jmg.2003.011247 PMID: 15060117 PMCID: PMC1735729

[5] Giordano C, Iommarini L, Giordano L, Maresca A, Pisano A, Valentino ML, Caporali L, Liguori R, Deceglie S, Roberti M, Fanelli F, Fracasso F, Ross-Cisneros FN, D'Adamo P, Hudson G, Pyle A, Yu-Wai-Man P, Chinnery PF, Zeviani M, Salomao SR, Berezovsky A, Belfort R Jr, Ventura DF, Moraes M, Moraes Filho M, Barboni P, Sadun F, De Negri A, Sadun AA, Tancredi A, Mancini M, d'Amati G, Loguercio Polosa P, Cantatore P, Carelli V. Efficient mitochondrial biogenesis drives incomplete penetrance in Leber's hereditary optic neuropathy. Brain, 2014, 137(Pt 2):335–353. https://doi.org/10.1093/brain/awt343 PMID: 24369379 PMCID: PMC3914475

[6] Baglivo M, Nasca A, Lamantea E, Vinci S, Spagnolo M, Marchet S, Prokisch H, Catania A, Lamperti C, Ghezzi D. Evaluation of mitochondrial dysfunction and Idebenone responsiveness in fibroblasts from Leber's hereditary optic neuropathy (LHON) subjects. Int J Mol Sci, 2023, 24(16):12580. https://doi.org/10.3390/ijms241612580 PMID: 37628761 PMCID: PMC10454080

[7] Carelli V, Ross-Cisneros FN, Sadun AA. Mitochondrial dysfunction as a cause of optic neuropathies. Prog Retin Eye Res, 2004, 23(1):53–89. https://doi.org/10.1016/j.preteyeres.2003.10.003 PMID: 14766317

[8] Ventura DF, Gualtieri M, Oliveira AGF, Costa MF, Quiros P, Sadun F, de Negri AM, Salomão SR, Berezovsky A, Sherman J, Sadun AA, Carelli V. Male prevalence of acquired color vision defects in asymptomatic carriers of Leber's hereditary optic neuropathy. Invest Ophthalmol Vis Sci, 2007, 48(5):2362–2370. https://doi.org/10.1167/iovs.06-0331 PMID: 17460303

[9] Hsu TK, Wang AG, Yen MY, Liu JH. Leber's hereditary optic neuropathy masquerading as optic neuritis with spontaneous visual recovery. Clin Exp Optom, 2014, 97(1):84–86. https://doi.org/10.1111/cxo.12100 PMID: 23905692

[10] Mascialino B, Leinonen M, Meier T. Meta-analysis of the prevalence of Leber hereditary optic neuropathy mtDNA mutations in Europe. Eur J Ophthalmol, 2012, 22(3):461–465. https://doi.org/10.5301/ejo.5000055 PMID: 21928272

[11] Manickam AH, Michael MJ, Ramasamy S. Mitochondrial genetics and therapeutic overview of Leber's hereditary optic neuropathy. Indian J Ophthalmol, 2017, 65(11):1087–1092. https://doi.org/10.4103/ijo.IJO_358_17 PMID: 29133631 PMCID: PMC5700573

[12] Tonagel F, Wilhelm H, Richter P, Kelbsch C. Leber's hereditary optic neuropathy: course of disease in consideration of Idebenone treatment and type of mutation. Graefes Arch Clin Exp Ophthalmol, 2021, 259(4):1009–1013. https://doi.org/10.1007/s00417-020-05045-4 PMID: 33337510 PMCID: PMC8016777

[13] Yu-Wai-Man P, Soiferman D, Moore DG, Burté F, Saada A. Evaluating the therapeutic potential of Idebenone and related quinone analogues in Leber hereditary optic neuropathy. Mitochondrion, 2017, 36:36–42. https://doi.org/10.1016/j.mito.2017.01.004 PMID: 28093355 PMCID: PMC5644719

[14] Fantini M, Asanad S, Karanjia R, Sadun A. Hormone replacement therapy in Leber's hereditary optic neuropathy: accelerated visual recovery *in vivo*. J Curr Ophthalmol, 2018, 31(1):102–105. https://doi.org/10.1016/j.joco.2018.10.003 PMID: 30899856 PMCID: PMC6407313

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