tvst

https://doi.org/10.1167/tvst.8.6.42

Letters to the Editor

Heteroplasmy Rates of the m.14495A>G variant in *MT-ND6* May Not Predict the Phenotype of LHON

Josef Finsterer[1], and Rahim Aliyev[1]

[1]Krankenanstalt Rudolfstiftung, Messerli Institute, Vienna, Austria

Correspondence: Josef Finsterer, Postfach 20, 1180 Vienna, Austria. e-mail: fifigs1@yahoo.de

Dear Editor:

With interest, we read the article by Li et al.[1] about a Han Chinese family with Leber's hereditary optic neuropathy (LHON) due to the secondary LHON mtDNA variant m.14495A>G in *MT-ND6*. We have the following comments and concerns.

Though effective according to only a single study,[2] idebenone is a standard therapy for patients with LHON.[3] Thus, we ask why idebenone was not given to any of the clinically affected mutation carriers, and if this was due to unavailability of the drug in China, pecuniary considerations, or due to other reasons.

LHON may not only affect the retinal ganglion cells (RGCs) and the optic nerve, but also other structures, tissues, or organs (LHON plus).[4] In LHON plus not only the RGCs and the optic nerve are affected but also the central nervous system (CNS), ears, endocrine organs, heart, bone marrow, arteries, kidneys, or the peripheral nervous system.[4] Multiorgan involvement may start before or after onset of the visual compromise.[4] Thus, we ask if manifesting mutation carriers of the presented family were prospectively investigated for multisystem disease. Particularly, we should know the results of the cerebral MRI, echocardiography (ECG), and long-term ECG recordings. Recognizing multisystem involvement in LHON is crucial, as it may strongly determine genetic counseling and the outcome of LHON patients. Particularly CNS and cardiac involvement (seizures, arrhythmias, cardiomyopathy) in the disease should be recognized prior to the occurrence of a severe or fatal complication.

We do not agree with the conclusions "that heteroplasmy levels of LHON mutations in blood cells can be used as a diagnostic indicator of LHON risk."[1] According to Table 1 of the article,[1] the correlation between heteroplasmy and risk of developing LHON is poor. Two patients with heteroplasmy rates higher than 50% did not manifest clinically. The poor correlation could be explained by the fact that heteroplasmy rates were determined in a clinically unaffected tissue. Several studies demonstrated that clinically affected tissues have higher heteroplasmy rates than clinically less or unaffected tissues.[5]

The authors propose a heteroplasmy threshold of 50% above which carriers of the m.14495A>G manifest clinically.[1] We ask why the two individuals, IV-7 and V-5, did not manifest clinically despite heteroplasmy rates more than 50%. We ask if heteroplasmy rates were determined only with digital polymerase chain reaction.[1] Application of an alternative technique is crucial not to generate false-positive results.

It also should be explained why the copy number was more heterogeneous among nonmanifesting mutation carriers compared with clinically manifesting mutation carriers.

Overall, this interesting case study has a number of shortcomings, which need to be addressed before drawing final conclusions. It needs to be explained why idebenone was not applied, why affected patients were not prospectively investigated for LHON plus, and why the authors plead for heteroplasmy rates as an indicator for the risk of developing the disease.

Citation: Finsterer J, Aliyev R. Heteroplasmy rates of the m.14495A>G variant in *MT-ND6* may not predict the phenotype of LHON. Trans Vis Sci Tech. 2019;8(6):42, https://doi.org/10.1167/tvst.8.6.42

References

1. Li S, Duan S, Qin Y, Lin S, et al. Leber's hereditary optic neuropathy-specific heteroplasmic mutation m.14495A>G found in a Chinese family. *Transl Vis Sci Technol*. 2019;8(4):3.

2. Rudolph G, Dimitriadis K, Büchner B, et al. Effects of idebenone on color vision in patients with Leber hereditary optic neuropathy. *J Neuroophthalmol*. 2013;33:30–36.
3. Yu-Wai-Man P, Chinnery PF. Leber hereditary optic neuropathy. In: MP Adam Ardinger HH Pagon RA et al., editors. [eBook]. *GeneReviews*. Seattle, WA: University of Washington; 1993–2019. Available from http://www.ncbi.nlm.nih.gov/books/NBK1174/.
4. Finsterer J, Zarrouk-Mahjoub S. Leber's hereditary optic neuropathy is multiorgan not monoorgan. *Clin Ophthalmol*. 2016;10:2187–2190.
5. Bouchet C, Steffann J, Corcos J, et al. Prenatal diagnosis of myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome: contribution to understanding mitochondrial DNA segregation during human embryofetal development. *J Med Genet*. 2006;43:788–792.