Letter to the Editor

Diagnose Leber’s Hereditary Optic Neuropathy in Multiple Sclerosis upon the Phenotype and Presence of Pathogenic mtDNA variants

JOSEF FINSTERER, MD, PHD
Klinik Landstrasse, Messerli Institute, Vienna, Austria

*Corresponding Author
JOSEF FINSTERER, MD, PHD

Article History
Received: 09.08.2021
Accepted: 20.08.2021
Published: 30.08.2021

Keywords: mtDNA, mitochondrial, respiratory chain, multiple sclerosis, pathogenicity.

With interest we read the article by Beckmann et al., (2021) about a study of 11 patients with multiple sclerosis (MS) with atypical optic neuropathy (ON) (Beckmann, Y. et al., 2021). Atypical ON was defined as bilateral ON, sequential ON, progressive visual loss, or no response to corticosteroid respectively plasmapheresis treatment (Beckmann, Y. et al., 2021). Five of the 11 patients carried an mtDNA variant (Beckmann, Y. et al., 2021). Only one primary Leber’s hereditary optic neuropathy (LHON) mutation (m.14484T>C) was detected in one of the five patients (Beckmann, Y. et al., 2021). It was concluded that MS with atypical ON should undergo investigations for LHON mutations (Beckmann, Y. et al., 2021).

We have the following comments and concerns.

The main limitation of the study is that the pathogenicity of the non-primary LHON variants m.14325A>G, m.3644T>C, m.14841A>G, m.9041A>G, and m.9448A>G was not demonstrated. Segregation of these variants with the phenotype within in a family or evolutionary conservation were not proven. Biochemical investigations attributable to these variants, or trans-mitochondrial cybrid studies were not carried out (Finsterer, J. et al., 2018). As long as this information is lacking, pathogenicity remains unproven.

Another limitation of the study is that heteroplasmy rates of the mtDNA variants were not provided in the five MS patients who carried an mtDNA variant. Though primary LHON mutations are commonly in the homoplasmic state in LHON patients, occasionally these variants can be heteroplasmic. Knowing heteroplasmy rates and the tissue in which they have been obtained is crucial as they may strongly influence the phenotype, the outcome and genetic counselling of these patients. Missing in addition to heteroplasmy rates are mtDNA copy numbers.

A further limitation is that results of clinical and genetic investigations of first degree family members of the five patients carrying mtDNA variants were not provided. Knowing if other family members were clinically or subclinically affected is crucial for assessing if the variant has to be classified as pathogenic or benign.

A further limitation is that the five patients carrying mtDNA variants were not systematically investigated for multisystem disease (Beckmann, Y. et al., 2021). Since MIDs are frequently multisystem diseases (Liskova, A. et al., 2021), either already at onset or with progression of the disease, it is crucial that all MID patients are systematically screened for multisystem involvement at onset and repeatedly during follow-up. Knowing the number of organs affected and the degree of affection is crucial for assessing the outcome of these patients. Even LHON may manifest not only in the eyes but also in various other organs (LHON plus) (Shemesh, A. et al., 2020).
Application of idebenone to all five MS patients carrying an mtDNA variant is not comprehensible. First the effect of idebenone in LHON patients is poor, second idebenone is expensive, and third the diagnosis LHON remains unproven in the 5 MS patients carrying mtDNA variants.

Lastly, MS features on MRI in patients with a mitochondrial disorder (MID) are not unusual and have been early recognised as Harding’s syndrome (Parry-Jones, A. R. et al., 2008). MS features on imaging in MID patients are potentially attributable to affection of immune cells by the mitochondrial defect, by an immune response against mutated mitochondrial proteins, or by the accidental co-occurrence of MS and a MID.

Overall, the study is appealing but has several limitations, which challenge the results and their interpretation. These limitations should be addressed to strengthen the conclusions.

Declarations
Acknowledgement: none
Statement of ethics: was in accordance if ethical guidelines
Conflicts of interest: none
Funding sources: no funding was received
Author contribution: JF: design, literature search, discussion, first draft, critical comments, final approval,
Informed consent: not applicable
The study was approved by the institutional review board

REFERENCES