

Are foveal thickness, pit depth, and slopes truly abnormal in unaffected carriers of the LHON variant m.11778G>G?

Josef Finsterer

Klinik Landstrasse, Messerli Institute, Vienna 1180, Austria

Correspondence to: Josef Finsterer. Postfach 20, Vienna 1180, Austria. Fifigs1@yahoo.de

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Dear Editor,

We read with interest the article by Liu *et al*^[1] about an optical coherence tomography (OCT) study of five patients (10 eyes) with Leber's hereditary optic neuropathy (LHON) due to the variant m.11778G>A in *MT-ND4* which were compared with 11 clinically unaffected carriers (22 eyes) of the variant and with 20 healthy controls. Thicker foveal thickness, thinner foveal pit depth, and flatter foveal slopes were found in LHON patients and unaffected carriers compared to controls^[1]. We have the following comments and concerns.

Missing in this study are the heteroplasmy rates of the m.11778G>A variant^[1]. Though most of the primary LHON mutations are found in a homoplasmic state, there are exceptions and even the m.11778G>A variant occurs in the heteroplasmic state and is nonetheless pathogenic^[2]. Thus, knowing heteroplasmy rates is crucial as they may strongly influence the OCT results. We should know how the authors excluded that any of the 20 control subjects was indeed an asymptomatic m.11778G>A carrier. We should know if the 20 healthy subjects had undergone genetic testing to exclude the presence of an asymptomatic m.11778G>A variant. We also should know the haplogroup of the investigated family since the haplotype may strongly determine the phenotypic expression of primary LHON mutations^[3].

Missing in the study is the information about who of the affected or unaffected carriers was a smoker. Since smoking is regarded as a putative trigger of LHON in asymptomatic carriers, it is worthwhile to know how many of the included m.11778G>A carriers were smoking or not.

A further limitation of the study is that it was not mentioned how many of the 5 LHON patients received antioxidants,

in particular idebenone (900 mg/d). The latter is the only approved drug for LHON and may exhibit a significant effect in some of the LHON patients^[4]. Since idebenone may strongly influence the test results, it is worthwhile to know how many of the 5 LHON patients received the drug or other antioxidants known to exhibit a beneficial effect.

Since some patients carrying the m.11778G>A variant may recover spontaneously^[5], it should be mentioned how many of the 5 LHON patients reported spontaneous remission or improvement over time. Spontaneous recovery may also strongly influence the study results. In all four sectors total retinal and RNFL thickness were, though not statistically significant, larger in unaffected carriers compared to controls. This finding contradicts thicker foveal thickness, thinner foveal pit depth, and flatter foveal slopes in unaffected carriers compared to controls. This discrepancy requires an explanation.

Overall, the presented study has a number of limitations, which need to be solved before final conclusions can be drawn. Considering factors influencing the expressivity of the m.11778G>A variant is crucial for interpretation of the study results. Whether allegedly asymptomatic carriers of the variant m.11778G>A are subclinically affected remains unproven.

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