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Letter to Editor

White matter lesions on diffusion tensor imaging may not only be genetic in asymptomatic LHON carriers

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Letter to the Editor

With interest we read the article [1] about a study of 14 asymptomatic Leber's hereditary optic neuropathy (LHON) carriers by means of diffusion tensor imaging (DTI) and retinal nerve fiber layer (RNFL) measurements [1]. Except for the right inferior quadrant, RNFL thickness was not different between LHON carriers and healthy controls [1]. On the contrary, fractional anisotropy (FA), was decreased and radial diffusion (RD) and mean diffusion (MD) were increased in LHON carriers [1]. We have the following comments and concerns.

Key words: optic atrophy; retinal ganglion cells; vision; white matter lesions; diffusion tensor imaging; mtDNA; oxidative phosphorylation; antioxidants.

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The main shortcoming of the study is that heteroplasmy rates of the three primary LHON mutations m.3460G>A (n=2), m.11778G>A (n=8), and m.14484T>C (n=4) were not provided. Since heteroplasmy rates may strongly influence the phenotype, we should be informed about the mutation load in each of the included LHON carriers. In a recent study of 4 patients and 28 carriers of the m.14484T>C variant, clinical manifestations occurred only at heteroplasmy rates >75% [2]. In case of low heteroplasmy rates, it is quite unlikely that the abnormal DTI findings in LHON carriers of the present study were truly attributable to the primary LHON variants.

A further shortcoming of the study is that the cardiovascular risk profile of each LHON carrier was not provided [1]. We need to know how many of the 14 carriers were smoking, had hyperlipidemia, diabetes, arterial hypertension, thyroid, dysfunction, carotid artery stenosis, atrial fibrillation, noncompaction, or systolic dysfunction. Cerebral microangiopathy or hypoxia due to the presence of any of these risk factors is the most frequent cause of cerebral white matter lesions (WMLs). In this respect we should also be informed about the current medication each of the included carriers was regularly taking. Noncompaction is a myocardial abnormality which has been occasionally described in LHON

patients [3] and is complicated by thrombo-embolism, heart failure, ventricular arrhythmias, and sudden cardiac death [4].

The authors speculated that white matter lesions (WMLs) in asymptomatic LHON carriers result from decreased oxygen consumption, decreased anti-oxidative capacity, decreased oxidative phosphorylation, and decreased ATP production [1]. However, they do not provide any data that would support these speculations. Lacking in this respect are functional and biochemical studies of affected and non-affected tissues which clearly show that LHON carriers truly manifest with reduced energy production or increased oxidative stress.

The structures predominantly affected in LHON are the retinal ganglion cells and the optic nerve [5]. However, RNFL thickness was not different between healthy subjects and the asymptomatic LHON carriers. On the contrary, DTI findings differed significantly between these two groups [1]. Why should there be subclinical involvement of the brain but absence of any retinal involvement in LHON carriers? This discrepancy should be addressed and may be attributed to the low number of included patients and variable heteroplasmy rates between affected and non-affected tissues.

Overall, the provided results do not support the conclusion that subclinical WMLs in asymptomatic LHON carriers are attributable to the genetic defect. As long as heteroplasmy rates are not provided and as long as the cardiovascular risk profile is not detailed, the conclusions drawn are not justified.

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