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Letter to the Editor

Changes in the Structural Network Architecture of LHON Patients' Brains may Reflect more than Just the Progression of the Disease

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Letter to the Editor

In their article "Aberrant Structural Network Architecture in Leber's Hereditary Optic Neuropathy: Minimum Spanning Tree Graph Analysis Application into Diffusion 7T MRI," Jonak *et al*. present and discuss the results of a study involving 15 patients with Leber's hereditary optic neuropathy (LHON) caused by the m.11778G>A variant. The study utilized ultra-high-field 7T MRI and diffusion tensor imaging (DTI) data analysis to reconstruct whole-brain structural neuronal networks (Jonak *et al*., 2020) [3]. The authors concluded that the progression of LHON is associated with alterations in brain network structure and efficiency (Jonak *et al*., 2020) [3]. While the study is of interest, it gives rise to the following observations and concerns.

LHON is a multisystemic mitochondrial disorder (MID) that affects more than just retinal ganglion cells (RGCs) (Finsterer & Zarrouk-Mahjoub, 2016) [1]. Organs and tissues affected in addition to RGCs include the brain, ears (hearing loss), endocrine organs (diabetes, thyroid dysfunction, and pituitary adenoma), the heart (cardiomyopathy, non-compaction cardiomyopathy, arrhythmias, heart failure, and sudden cardiac death), the kidneys (renal insufficiency), bone marrow (anemia), arteries (aortic stiffness), and peripheral nerves (polyneuropathy), a clinical presentation known as "LHON plus" (Finsterer & Zarrouk-Mahjoub, 2016) [1]. Cerebral manifestations include epilepsy, leukoencephalopathy, migraine, ataxia, chorea, dementia, and posterior reversible encephalopathy syndrome (PRES) (Finsterer & Zarrouk-Mahjoub, 2016) [1]. Therefore, it would be important to know how many of the 15 patients presented with a “LHON plus” form and how many showed evidence of clinical or imaging-detectable brain involvement extending beyond the described network structure anomalies.

Although the m.11778G>A variant typically presents in a homoplasmic state in LHON patients, the individual heteroplasmy levels of each enrolled patient should be known. If heteroplasmy levels of <100% were detected, these could have influenced the phenotype, and thus the presented data, as well as contributed to heterogeneity within the study cohort. Furthermore, the study results might depend on mtDNA copy number and the capacity of ROS detoxification pathways; consequently, these parameters should be taken into account during analysis.

According to the methods section, a negative family history regarding neuropsychiatric disorders served as an exclusion criterion (Jonak *et al*., 2020) [3]. However, given that mtDNA-associated MIDs are inherited via the maternal line in 75% of cases (Poulton, Finsterer & Yu-Wai-Man), it would be important to know whether the m.11778G>A variant actually arose spontaneously in all 15 enrolled patients rather than being maternally inherited. Were all 15 mothers indeed negative for the causative mutation?

Since visual impairment can significantly influence the architecture of cerebral networks (Hartcher-O'Brien, Levitan & Spence, 2010) [2] and the degree of visual impairment varies among individual LHON patients, it should be clarified whether any of the nodal parameters or the metrics derived from the "Minimum Spanning Tree" algorithm correlated with the degree of visual impairment in the 15 patients.

Longitudinal data are lacking to assess whether the nodal parameters changed over time. Information regarding the reproducibility of the test results is also missing.

Idebenone is currently considered the standard therapy for LHON; Surprisingly, however, none of the 15 LHON patients included in the study were treated with idebenone (Jonak *et al*., 2020) [3]. It would be informative to know why none of the patients were taking idebenone and whether its use had been discontinued prior to the examination or if the patients had never actually taken the drug.

Since all the aforementioned points depend significantly on measurement reliability, it is crucial to optimize this through appropriate measures (Zuo, Xu & Milham, 2019) [5]. This enhances the reliability of the test results and facilitates both data

interpretation and the drawing of conclusions.
Overall, this interesting study has certain limitations that should be considered before attributing changes in cerebral network structures solely to the progression of LHON. Information is required regarding heteroplasmy rates, mtDNA copy numbers, ROS detoxification capacity, the results of genetic testing of first-degree relatives, and correlations between visual acuity and nodal parameters. Furthermore, the reason why none of the patients were taking idebenone needs to be addressed.

Declarations

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