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Letter to the Editor

Altered Structural Network Architecture in LHON Brains may not only Reflect 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 an investigation of 15 patients with Leber's hereditary optic neuropathy (LHON) due to the variant m.11778G>A by means of an ultra-high field 7T-MRI and analysis of diffusion tensor imaging (DTI) data to reconstruct whole-brain, structural, neural networks [1]. It was concluded that the progression of LHON is accompanied by alterations within the brain network structure and its efficiency [1]. The study is appealing but raises the following comments and concerns.

LHON is a multisystem mitochondrial disorder (MID) not only affecting the retinal ganglion cells (RGCs) [2]. Organs/tissues affected in addition to the RGCs are the brain, ears (hypoacusis), endocrine organs (diabetes, thyroid dysfunction, and pituitary adenoma), the heart (cardiomyopathy, noncompaction, arrhythmias, heart failure, and sudden cardiac death), the kidneys (renal insufficiency), bone marrow (anemia), and the arteries (aortic stiffness), and the peripheral nerves (polyneuropathy) (LHON plus) [2]. Cerebral manifestations include epilepsy, leuco-encephalopathy, migraine, ataxia, chorea, dementia, and posterior reversible encephalopathy syndrome (PRES) [2]. Thus, we should know how many of the 15 patients had LHON plus and in how many of them was there evidence for clinical or imaging involvement of the brain other than the described network structure abnormalities.

Though the m.11778G>A variant is usually present in the homoplasmic state in LHON patients, we should know the individual heteroplasmy rates of each included patient. If heteroplasmy rates <100% were detected they may have influenced the phenotype and thus the data presented and may have caused inhomogeneity of the investigated cohort. Study results may also depend on mtDNA copy number and capacity of ROS detoxification pathways, why these parameters should be considered in the evaluation.

According to the method section, an exclusion criterion was a negative family history for neuropsychiatric disease [1]. However, in 75% of the cases mtDNA related MIDs are transmitted via the maternal line [3]. Thus, we should know if the variant m.11778G>A truly occurred spontaneously in all 15 included patients and was not maternally transmitted. Were all 15 mothers truly negative for the causative mutation?

Since visual impairment may strongly influence the cerebral network architecture [4] and the degree of visual impairment varies between individual LHON patients, we should know if any of the nodal parameters or the minimum spanning tree algorithm metrics correlated with the degree visual impairment in the 15 patients.

Missing are follow-up data to assess if nodal parameters changed over time. Missing are also data about the reproducibility of test results.

Idebenone is the standard treatment of LHON today but surprisingly none of the 15 included LHON patients was on idebenone [1]. We should know the reason why none of the patients took idebenone and if idebenone was stopped prior to the investigation or if all patients truly did not take this drug.

Since all the above mentioned points are highly determined by measurement reliability it is crucial to optimise measurement reliability by appropriate means [5]. This will improve the reliability of test results and facilitate interpretation of data and drawing conclusions.

Overall, the interesting study has some limitations, which should be addressed before attributing alterations of cerebral network structures only to progression of LHON. We need to know heteroplasmy rates, mtDNA copy numbers, ROS-detoxification capacity, results of genetic tests of first-degree relatives, correlations between visual acuity and nodal

parameters, and discussion why none of the patients took idebenone.

Declarations

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