OCT-angiography is inappropriate to demonstrate causality of peripapillary hypodensity in LHON

Josef Finsterer, MD, PhD

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Letter to the Editor

In a recent article, Kousal et al. reported about a study of 6 individuals carrying primary LHON mutations by means of the optical coherence tomography angiography (OCTA)\(^1\). Three of the mutation carriers manifested clinically and three were asymptomatic. Five individuals carried the m.11778G>A variant, of whom 2 manifested clinically, and one carried the variant m.14484T>C who manifested clinically as well\(^2\). In the five affected eyes the capillary density of the peripapillary network of the retinal nerve fiber layer (RNFL) and the retinal ganglion cells (RGC) were reduced on OCTA\(^1\). We have the following comments and concerns.

It is well appreciated that primary LHON mutations not only manifest in the RGCs but also in the retinal peripapillary capillary network\(^3\). Particularly, viability of endothelial and vascular smooth muscle cells (VSMCs) has been hypothesised to lower the retinal blood flow in LHON\(^3\). In this respect, it would be interesting to know if nitric oxide (NO)-precursors, known to have a dilative, antispastic effect on cerebral arteries in patients with stroke-like episodes (SLEs)\(^4\), had ever been tried in any of the 3 clinically manifesting mutation carriers. Furthermore, we should be informed if the manifesting mutation carriers manifested also in organs other than the eyes. From LHON it is well known that in addition to the RGCs and the micro-vasculature, also other tissues / organs can be affected (LHON plus)\(^5\). Organs/tissues other than the RGCs and the retinal micro-vasculature include the brain (myoclonic epilepsy, leukoencephalopathy, MS-like lesions, psychomotor regression, posterior reversible encephalopathy syndrome, migraine, chorea, cerebellar ataxia, dementia), the ears (hypoacusis), the heart (dilated cardiomyopathy, noncompaction, arrhythmias, syncope, sudden cardiac death), endocrinological organs (diabetes, pituitary adenoma, thyroidism, hyperthyroidism), bone marrow (anemia), arteries, kidneys (renal failure), or the peripheral nervous system (polyneuropathy)\(^5\). Non-ophthalmologic manifestations in LHON may manifest before or after onset of visual impairment.

Another shortcoming of the study is that reproducibility of the results was not investigated. Since the application of OCTA to LHON patients is fairly new, it is crucial that reproducibility of the results and thus the reliability is systematically tested. It also needs to be carefully investigated if the inter-observer variability of OCTA was high or low. Since only a single investigator carried out the investigation and the group size was small, the interobserver variability remains unclear.

A further shortcoming of the study is that the peripapillary capillary network density was only subjectively assessed and not quantitatively. Quantitative assessment is required to demonstrate small changes over time at follow-up investigations to assess the effect of treatment or document spontaneous recovery or deterioration.

Since the penetrance of primary LHON mutations is low, we should be informed which factors could have contributed to the penetrance of the mutation in clinically manifesting carriers. Which was the mtDNA copy number and the number of “ancillary” mtDNA mutations in the 2 manifesting and the three non-manifesting m.11448G>A carriers?

Overall, this interesting study could be more meaningful if shortcomings such as small cohort size, missing quantification of OCTA results, missing assessment of interobserver variability, and missing assessment of the reproducibility would have been addressed. There is currently no evidence for a contribution of reduced peripapillary capillary network density to visual loss in LHON.

References


\(^1\) Krankenanstalt Rudolfstiftung, Messerli Institute, Veterinary University of Vienna, Vienna, Austria