Vessel volume rendering quantifies disease conversion and progression in Leber hereditary optic neuropathy

Running head: Three-dimensional OCTA observation in LHON

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Leber hereditary optic neuropathy (LHON, OMIM 535000) is the most common primary mitochondrial optic neuropathy with an estimated prevalence of 1 in 31,000 to 1 in 50,000 in Northern Europe. The m.11778G>A mutation in the *MT-ND4* accounts for most cases of LHON worldwide with the proportion ranging from 60% to 90% depending on the population surveyed. LHON classically presents as painless, subacute, central vision loss in one eye, followed by the fellow eye within 3-6 months. LHON is categorized into four clinical stages: asymptomatic (carriers), subacute (<6 months), dynamic (6-12 months) and chronic (>12 months).[1] (X) Optic disc hyperaemia and swelling of the peripapillary retinal nerve fibre layer are characteristic features observed in the subacute stage of the disease. These are frequently accompanied by increased tortuosity of the central retinal vessels and peripapillary telangiectasia. There is rapid loss of retinal ganglion cells (RGCs) within the papillomacular bundle, which results in temporal pallor of the optic nerve head. During the transition to the chronic phase, RGC loss progresses further and the pallor becomes more prominent and diffuse. LHON is characterised by a poor visual prognosis with less than 15% of patients carrying the m.11778G>A mtDNA mutation experiencing any visual recovery, and with most remaining within the criteria for legal blindness.[1] The early vascular involvement in LHON makes it a suitable model for serial vascular imaging with non-invasive optical coherence tomography angiography (OCTA). OCTA allows visualisation of the retinal vascular supply, provides information on optic disc and peripapillary area perfusion, and it could potentially be used for assessing and monitoring disease progression. Previous studies involving OCTA imaging in LHON reported dilated peripapillary microvasculature in the acute stage and capillary dropout temporal to the disc in later stage of the disease.[2,3] However, these reports were only based on *en face* image representation in two dimensions, which cannot allow a spatial analysis of the vessels *per se*.

To overcome this constraint and expand the potential of OCTA vascular analysis, a 26-year-old woman with subacute LHON carrying the m.11778G>A mutation was reviewed

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prospectively to document the changes observed with a three dimensionally rendered and quantified OCTA method. At each clinic visit, a comprehensive evaluation was performed, including best corrected visual acuity (BCVA), contrast sensitivity and automated visual field testing (Humphrey Visual Field 30-2 threshold algorithm). The study protocol was explained and written consent for participation was obtained from the patient. This study adhered to the tenets of the Declaration of Helsinki and the study centre had the relevant ethical and institutional approvals.

Follow up OCTA volume scans of the optic nerve head were performed in each eye with spectral-domain OCTA (Cirrus HD-OCT, Carl Zeiss Meditec, Inc., Dublin, US,) version 9.0.0281). Each single volume OCTA scan provided a 3 mm x 3 mm x 2 mm optical specimen consisting of 245 x 245 x 1024 pixels. OCTA image postprocessing of the raw data and repeatability of the method have been demonstrated previously.[4] Briefly, planar *en face* OCTA images were exported as raw data, rendered and cropped as volume models. The binarized data were then measured for total vessel surface area and volume of each single volume. A schematic presentation of the method applied has been provided in Figure 1A.

The patient was first assessed 106 days following rapid central vision loss in her right eye (RE) and 49 days after disease onset in her left eye (LE). At the baseline examination, BCVA was <20/800 Snellen and 20/32 Snellen with contrast sensitivity of 0.00 logcs and 1.35 logcs in the RE and LE, respectively. Fundus examination showed hyperaemic optic nerve discs bilaterally with peripapillary telangiectasia and increased tortuosity of the central retinal vessels (Figure 1B). The patient had follow-up visits approximately 1.5 and 4.5 months later. As the disease progressed, qualitative 3D OCTA vessel analysis depicted: marked loss of the peripapillary radial vessel complex and thinning of the larger optic disc vessels (Figure 1C); a nasalization of the entry point of the central optic disc vessels; axial flattening of the optic disc and peripapillary vessel curvature (Figure 1D). Quantitative OCTA vessel analysis

was consistent with the qualitative results (Figure 2A). During the follow up visits, reduction of vessel volume and vessel surface area was observed in the RE. As the patient had a shorter disease duration in the LE, both vessel measurements were higher at the second visit compared with the first visit (Figure 1D, Figure 2A). OCTA vessel volume changed by -24.28% and -39.99% from baseline for the RE, and by +3.85% and -53.75% for the LE, respectively. Vessel surface area changed by -25.98% and -42.65% for the RE, and by +1.04% and -51.94% for the LE (Figure 1D). The clinical data, vessel volume and surface area measurements at each visit have been summarized in Figure 2

In this study, volume rendered OCTA imaging revealed similar findings described in previous studies. However, in the current case, capillary dropout temporal to the optic disc was documented when both eyes were still in the subacute stage, rather than in the chronic stage. As the patient's LE was affected about 2 months after the RE, the capillary dropout was subtle, limited to a small localised area compared with the RE (Figure 1C, arrow). With disease progression, the vessel dropout of the small peripapillary vessel complex increased in size and became more visible, and it corresponded with the visual field defects. This study brings new insights into the retinal vascular remodelling that occurs in LHON, highlighting a number of features, namely, the nasalization of the entry point of the central optic disc vessels and the axial flattening of the peripapillary vessel curvature. We were able to quantify vessel volume and vessel surface area by extending the standard 2D OCTA display method with a 3D vessel volume-rendering method for objective quantification of the raw data.[4,5] Additional studies with a larger group of LHON patients and automated data analysis are needed to confirm our observations.

To our knowledge, it is the first time that spatial vessel volume rendering of 3D OCTA scans has been applied serially to document disease progression in a patient with LHON. This imaging protocol could be used to spatially characterize, quantify, and capture retinal vascular

changes in LHON, with potential application as an outcome measure when evaluating treatment options, including gene therapy.

References

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Figure 1.

A – Schematic representation of vessel segmentation and quantification. Overlay of color fundus imaging with en face OCTA (left). Raw data were exported as 2D *en face* images without projection removal. Optic disc vessels above the retinal pigment epithelium were cropped and aligned (middle). All single images were stacked into a 3D OCTA volume from which the total vessel volume and vessel surface area were calculated (right).

B – Colour fundus photographs of right and left eye showing the characteristic appearance of the optic nerve head in the subacute stage of LHON, namely, hyperaemic optic disc, peripapillary retinal nerve fiber layer (RNFL) swelling (black arrows), telangiectasias (white arrows) and central retinal vessels tortuosity.

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C – Volume rendered OCTA (anterior view) and corresponding visual fields during the course of the disease. A relative dense peripapillary vessel system with vascular void areas (white arrows) were observed in the early subacute stage of LHON (Visit I). With disease progression, the temporal area within the papillomacular bundle in the right eye became less vascularised compared with the left optic disc area (Visit II). As the dynamic stage of the disease progressed into the chronic stage (Visit III), the large vessels narrowed and the vessel tree was shifted nasally and posteriorly in both eyes. Axial vessel outbowing was apparent that may not be visible in conventional 2D OCTA.

D – 3D OCTA (side view). Axial flattening of the retinal vessels, which was more pronounced in the left eye, was observed due to vessel drop-out as the disease progressed.

Figure 2.

A –Summary of clinical information and OCTA parameters (vessel volume and surface area) at each visit. BCVA – best-corrected visual acuity; CF – counting fingers; HM – hand movements; VFI – visual field index; MD – mean deviation; PSD - pattern standard deviation.

B – Changes in vessel volume and surface area with disease progression in both eyes. The arrow indicates the timepoint where the values start to decline.

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The two colours used – orange and red – are quite close to each other. Perhaps consider using red and another colour (e.g. dark blue or green) to make the difference more obvious.

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