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Letters to the Editor

Early macular thickness changes in Leber's hereditary optic neuropathy: case report

Leber hereditary optic neuropathy (LHON) is a disease caused by mutations in mitochondrial deoxyribonucleic acid, which is transmitted exclusively through maternal inheritance. LHON is known to have incomplete penetrance, meaning that not all mutation carriers will develop vision loss. Although the mechanisms involved have not been entirely elucidated, it appears the genetic and environmental factors play an important role. LHON is clinically characterized by painless and subacute loss of vision, which occurs either in both eyes simultaneously or in one eye before progressing to the other eye. It has a strong male preponderance (80%–90%). Symptom onset usually occurs in the second and third decades of life [1].

Advances in the understanding of LHON have been made possible by the introduction of optical coherence tomography (OCT). Studies involving the use of OCT have shown that the changes in the thickness of the peripapillary retinal nerve fiber layer (pRNFL) follow a specific pattern, i.e., early thickening and late thinning. Therefore, analyses of pRNFL cross-sectional thickness using OCT cannot detect optic atrophy in the initial edematous phase because opposite components of swelling and atrophy are superimposed in the pRNFL value. Atrophic progress of LHON may be better seen by retinal ganglion cells (RGC) analysis of the macula, because in this area the influence of pRNFL and vessels can be avoided by evaluating the RGC layer only [2].

Here we present the case of a patient with LHON, with the loss of RGC but without pRNFL atrophy, who underwent an OCT examination.

The patient was a 21-year-old male who presented with severe vision loss in the left eye (oculus sinister [OS]). He had no history of pain on eye movements or other ophthalmic or systemic conditions, and he had no pathological or family history of ocular disorders. On ophthalmologic examination, he presented with 20/25 visual acuity in the right eye (oculus dextrus [OD]) and hand movement acuity in the OS. Examination of ocular motility was normal. The left pupil was slow to react to light and had a relative afferent pupillary defect.

Fundoscopy was normal in the OD, but it showed a disk of hyperemia and telangiectasia in the vessels of the peripapillary retina in the OS. Fluorescein angiography did not reveal contrast leaks in either eye (oculus uterque [OU]). Computerized perimetry revealed a normal examination in the OD and a cecocentral scotoma in the OS (Fig. 1). An OCT examination of the OS using an RS-3000 device (Nidek Co., Ltd., Gamagori, Japan) showed increased pRNFL thickness and thinning of the inner macular layers, including the macular nervous fiber layer (mNFL), RGC layer, and inner plexiform layer (IPL) (Fig. 2).

This inner retinal thinning affected the inferior nasal area of the macula and was correlated with the superior temporal visual field defect. Moreover, in the normative database plot, it can be observed that the macular RGC atrophy area tracing an arc shape was consistent with the arrangement of nerve fibers in the papillomacular bundle. A nuclear magnetic resonance examination of the skull and orbit was performed, and it showed no changes.

Based on these results, a diagnostic hypothesis of LHON was proposed, and an investigation of mitochondrial mutations was requested. The results of the genetic test were positive for the primary mutation of 11778 G > A. Four months after the onset of clinical manifestations, the condition progressed to involve the contralateral eye. The final visual acuity was hand movement in OU.

In patients with LHON, OCT can show pRNFL thickening, particularly in the temporal and inferior quadrants, with involvement of the papillomacular bundle, which later progresses to progressive optic nerve atrophy. The temporal and inferior quadrants of the optic nerve show early involvement of edema (pseudoedema). In contrast, the nasal and superior quadrants are affected at a later stage, only reaching their maximum thickness after 3 months of onset, when the papillomacular bundle is already atrophic. The thickening of the pRNFL is likely dependent on a compensatory increase in mitochondrial biogenesis, axonal stasis along the fibers, or both; hence, optic atrophy may not be detected in the early stages of the disease [2].

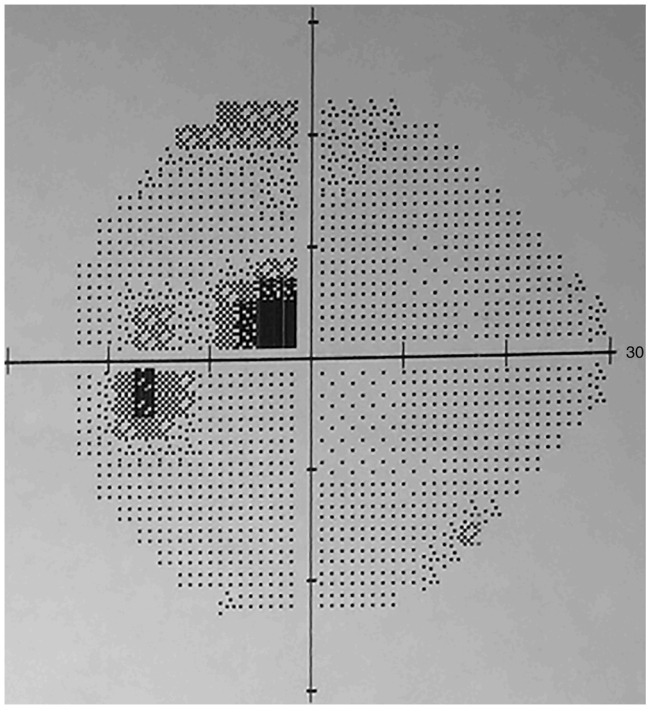

Fig. 1. Computerized visual field examination showing a cecocentral scotoma in the left eye.

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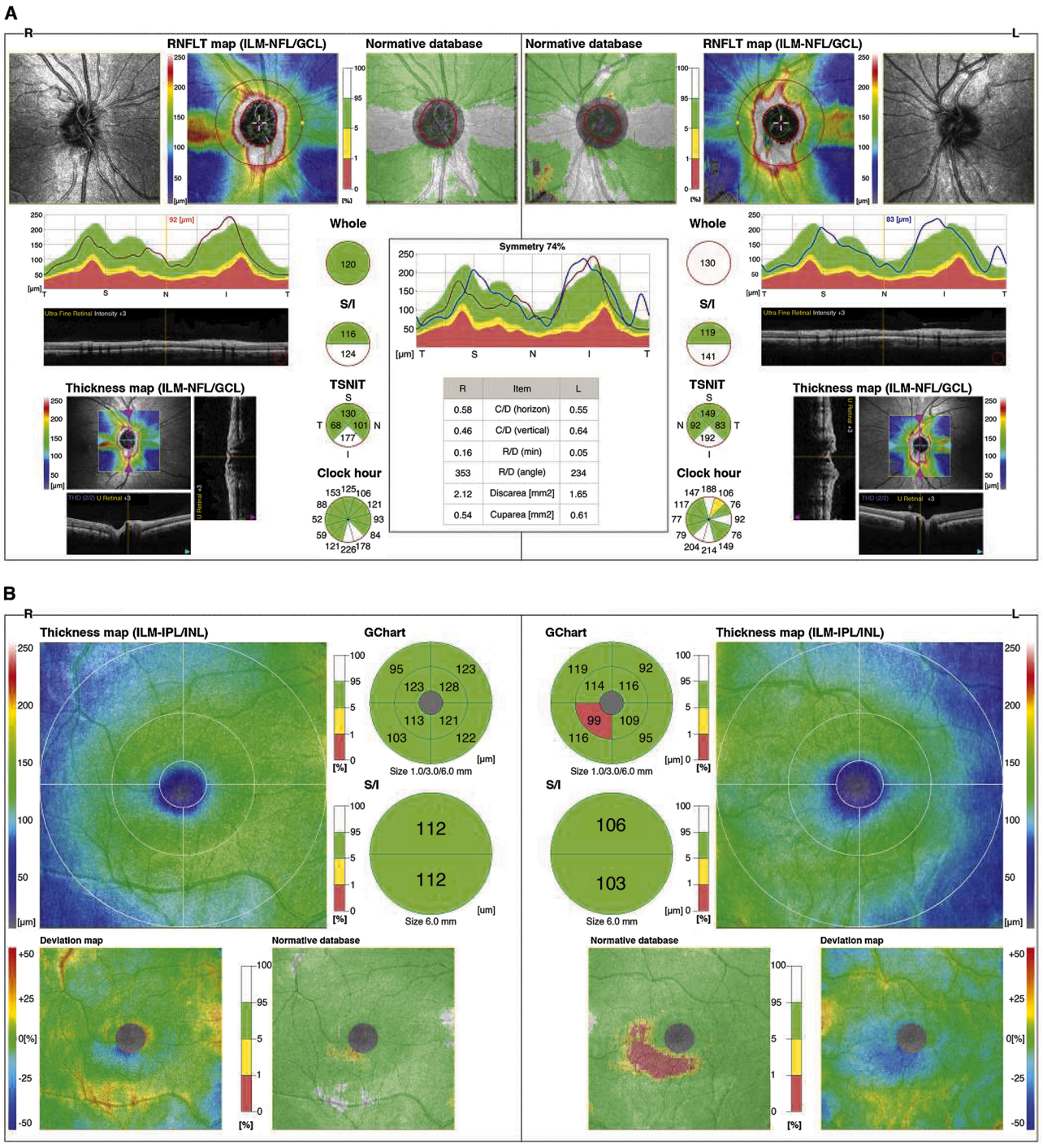

Fig. 2. Optical coherence tomography of both eyes. (A) Peripapillary retinal nerve fiber layer with normal thickness in both eyes. (B) Macular deviation map showing a defect in the inner ring of the inferior and superior nasal sectors in the left eye.

pRNFL edema (pseudoedema) prevents the detection of optic nerve atrophy detected by OCT in the early stages of the disease. Thus, in the early presymptomatic stage of LHON, the progression of atrophy is best represented by the analysis of the RGC-IPL of the macular sectors. Recent studies have proposed that these analyses can detect optic nerve damage in patients with LHON before the appearance of pRNFL changes. In contrast, in the mid- to long-term stages (3–12 months), mNFL and pRNFL thickness provide the most reliable information about disease progression [2–4].

Initial damage of the RGCL and IPL complex typically begins approximately 6 weeks before the onset of visual loss [2]. Reduction in RGCL–IPL thickness begins in the inner ring of the nasal sectors, where retinal ganglion cell bodies, which contribute to the fibres of the papillomacular bundle, are contained. Nerve fibre loss progresses in the following order: inner ring of the lower sector, outer ring of the nasal sector, inner ring of the temporal and upper sectors, outer ring of the temporal sector and outer ring of the upper and lower sectors [5,6].

Performing macular segmentation using OCT provided better knowledge about the RGC losses that preceded the changes in the pRNFL. Therefore, the main expectation is that OCT, which detects the onset of optic neuropathy in the presymptomatic phase in carriers of the mitochondrial mutation, will act as a disease biomarker for LHON. This

observation may be of fundamental importance for future therapeutic approaches in patients with LHON who are at a high risk of conversion to advanced stages and those with acute early LHON [7].

The findings of the present report are consistent with those in the literature, which show that in patients with LHON, OCT reveals an initial decrease in RGC-IPL, which is located in the inferior nasal sector of the macular region.

Conflict of interest

The authors declare no conflict of interest.

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