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Characterisation of thickness changes in the peripapillary retinal nerve fibre layer in patients with Leber's hereditary optic neuropathy

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ABSTRACT

Background Limited studies have identified the changes in peripapillary retinal nerve fibre layer (pRNFL) thickness in patients with chronic Leber's hereditary optic neuropathy (LHON) at different stages of the disease. We aimed to characterise the pRNFL thickness changes in patients with LHON having m.11778G>A (*MT-ND4*) mutation.

Methods This retrospective cross-sectional study included 221 eyes from patients with LHON (n=145)—classified into seven groups according to disease duration—and 52 eyes from healthy controls (n=26). All subjects underwent pRNFL examinations. pRNFL thickness of the superior, nasal and inferior, and temporal quadrants, and the 360° average were measured.

Results Within 3 months of onset, the temporal pRNFL thickness decreased significantly, whereas the remaining quadrants and the average pRNFL thickness initially increased. The temporal quadrant (p<0.01) and average pRNFL thickness (p=0.02) significantly decreased at 3–6 months. Excluding that in the nasal quadrant (p=0.93), pRNFL thickness significantly decreased in all other quadrants at 6–9 months. At 9–12 months, the average and individual quadrant pRNFL thicknesses continued to decrease. Compared with 12–24 months, the pRNFL thickness was thinner at 24–60 months and >60 months.

Conclusions The papillomacular bundle was affected first and preferentially in LHON. pRNFL thickness initially increased and then decreased, corresponding to the retinal ganglion cell swelling and apoptosis. pRNFL thinning first occurred in the temporal quadrant, followed by the inferior and superior quadrants, and finally, the nasal quadrant. pRNFL continued to thin slowly in some quadrants even after 60 months.

INTRODUCTION

Leber's hereditary optic neuropathy (LHON) is a hereditary mitochondrial disease characterised by symptoms of acute or subacute painless visual loss, which is often accompanied by central or cecentral scotomas, colour vision deficiency and optic nerve atrophy.¹ Patients with LHON having the m.11778G>A/*MT-ND4* mutation are the most prevalent and have the worse prognosis and hence were included in this study.

The pathogenesis of LHON begins with mutations in the mitochondrial DNA (mtDNA), which leads to dysfunction of the mitochondrial

respiratory chain complex I. This consequently results in an impairment of ATP production and overproduction of reactive oxygen species, thereby damaging the retinal ganglion cells (RGC) and their axons, and eventually causing optic nerve atrophy.² Peripapillary retinal nerve fibre layer (pRNFL) thickness, measured with optical coherence tomography (OCT), can be considered as one of the indicators for evaluating optic nerve injury. Some studies have reported that pRNFL thickness initially increases and then decreases along with the course of LHON, with significant thinning of the pRNFL in the chronic stage.^{3–5} However, only a few studies have focused on subsequent pRNFL thickness changes in patients with chronic LHON having different disease courses.

In this study, we investigated the natural pathological process of RGC by measuring the pRNFL thickness of patients with LHON with different disease durations and the m.11778G>A/*MT-ND4* mutation in mtDNA. Additionally, we divided patients with chronic LHON into three groups according to their disease durations—12–24 months, 24–60 months and >60 months—to compare the pRNFL thicknesses of chronic LHON patients at different stages of the disease. This information would help to understand the pathological progression of LHON in the RGC.

METHODS

Study subjects

A total of 145 (221 eyes) patients with LHON (with m.11778G>A/*MT-ND4* mutation) were enrolled between September 2017 and September 2018 in this cross-sectional study. All participants provided informed consent. The study was approved by the ethics committee of Tongji Hospital at the Tongji Medical College and was conducted in strict accordance with the regulations of the Declaration of Helsinki.

Inclusion criteria

Patients diagnosed with LHON based on clinical symptoms and signs, with genetic testing indicating m.11778G > A/*MT-ND4* mutation; age 6–65 years; without significant visual improvement (a change in best-corrected visual acuity (BCVA) ≥ 0.3 of the logarithm of the minimal angle of resolution (logMAR) was considered significant) within



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3 months or since the onset of the disease; who have not received any drug or therapy within 3 months or since the onset of the disease; who provided informed consent and who were willing to participate in the ophthalmic examinations and follow-up were included in the study.

Exclusion criteria

Patients with glaucoma and high myopia as well as those with retinal and optic nerve diseases other than LHON were excluded. The time point at which uncorrectable vision loss or visual dysfunction occurred was considered as the time point of onset for recording the course of the disease. Disease duration of both eyes was separately documented and classified into the corresponding group in our study.

Study grouping

Based on the international consensus statement, patients with LHON were grouped as follows: subacute stage, within 6 months of onset; dynamic stage, 6–12 months from onset and chronic stage, more than 12 months from onset.⁶ Considering the international consensus statement with our clinical practice, the patients were further subdivided as follows: 1st group, disease duration ≤ 3 months; 2nd group, disease duration 3–6 months; 3rd group, disease duration 6–9 months; 4th group, disease duration 9–12 months; 5th group, disease duration 12–24 months; 6th group, disease duration 24–60 months and 7th group, disease duration >60 months. We recruited age-matched and sex-matched healthy individuals as the healthy control group (both eyes of healthy controls ($n=26$; 52 eyes) were included in this study); the inclusion criteria for these participants included BCVA $>20/25$, refractive errors <6 dioptres sphere and 2 dioptres cylinder, intraocular pressure <21 mm Hg and lack of systemic or central nervous system diseases.

Instrumentation and procedures

The ophthalmic examination process was explained to the patients beforehand, and guidance was provided to them for their appropriate co-operation during the examination. All OCT scans were performed in a darkroom by experienced operators. The pRNFL thickness in patients with LHON was measured using Spectralis HRA+OCT (Heidelberg Engineering, Heidelberg, Germany). We recorded the RNFL thickness of the superior, inferior, temporal and nasal quadrants, and the 360° average value. Participants with pupil diameter <2 mm required pupil dilation. Measurements were repeated when the imaging quality was poor. The Spectralis HRA+OCT software automatically calculated all OCT data. Visual acuity tests were based on the BCVA, and

eye charts were standard logMAR charts (2.5 m; Star Kang Medical Technology, Wen Zhou, China). During measurement, the patients were positioned 2.5 m away from the visual acuity chart, and data were measured and recorded by the same physician. All patients were examined three times to confirm the changes in visual acuity, and the mean value was considered as the final visual acuity.

Data analysis

All the data are expressed as mean \pm SD and were analysed using SPSS (SPSS V.21.0; IBM Corp., Armonk, New York, USA). The pRNFL thicknesses in all groups were compared by one-way analysis of covariance, with sex and age as the covariates, followed by Bonferroni posthoc test for pairwise comparisons. P values <0.05 indicated statistically significant differences.

RESULTS

Patient demographic data

Table 1 shows the demographic data of the patients and healthy controls. A total of 145 patients with LHON (131 men and 14 women; $n=221$ eyes) were included in this study. The mean age of the patients was 19.58 ± 6.93 years (range, 6–50 years) and the disease mean duration was 37.21 ± 50.01 months (range, 1–312 months). The healthy control group consisted of 26 patients (13 men and 3 women; $n=52$ eyes) and had a mean age of 21.12 ± 4.32 years (range, 9–27 years). There were no significant differences in the age ($p=0.14$, Student's *t*-test) and sex distribution ($p=1.00$, continuity correction) between the patients with LHON and healthy controls.

Changes in pRNFL thickness within each group

Table 2 shows the pRNFL thicknesses of each quadrant for the healthy controls and patients with LHON with different disease durations. Compared with that in the healthy controls, the temporal pRNFL thickness in patients with LHON was less and was significantly different ($p<0.01$) within 3 months of disease onset; in contrast, pRNFL thickness in the remaining quadrants and the average RNFL thickness showed an initial increase, but without a significant difference except that in the nasal quadrant ($p=0.02$) (online supplemental material 1). pRNFL pseudoe-dema gradually disappeared, and by 3–6 months of onset, the pRNFL thickness of each quadrant and the average thickness had decreased; the decrease in pRNFL thickness in the temporal quadrant ($p<0.01$) and the average ($p=0.02$) reached significant differences (online supplemental material 1). With further death of the RGC and the consequent loss of axons, the RNFL thickness of each quadrant and the average thickness decreased by

Table 1 Demographic information of the patients in each group

Demographics	Within 3 months (1st group)	3–6 months (2nd group)	6–9 months (3rd group)	9–12 months (4th group)	12–24 months (5th group)	24–60 months (6th group)	>60 months (7th group)
Sex							
Male eyes	12	13	22	33	42	42	34
Female eyes	0	0	5	0	7	4	7
Age, years	19.42 \pm 6.57	17.77 \pm 4.07	15.00 \pm 4.73	18.61 \pm 5.79	17.67 \pm 4.41	20.24 \pm 5.26	25.20 \pm 8.34
Disease duration, months	1.75 \pm 0.97	4.31 \pm 0.48	7.70 \pm 1.14	11.00 \pm 0.87	18.51 \pm 4.08	39.11 \pm 8.74	118.76 \pm 67.20
BCVA (LogMAR)	1.65 \pm 0.44	1.58 \pm 0.44	1.71 \pm 0.37	1.79 \pm 0.42	1.64 \pm 0.51	1.75 \pm 0.39	1.49 \pm 0.36

BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle of resolution; 1st group, disease duration ≤ 3 months; 2nd group, disease duration 3–6 months; 3rd group, disease duration 6–9 months; 4th group, disease duration 9–12 months; 5th group, disease duration 12–24 months; 6th group, disease duration 24–60 months; 7th group, disease duration >60 months.

Table 2 Mean values of the average 360° RNFL thickness and the RNFL thickness in the superior, nasal, inferior and temporal quadrants in healthy controls and patients with LHON at different disease progressions

Group	Group control	Within 3 months (1st group)	3–6 months (2nd group)	6–9 months (3rd group)	9–12 months (4th group)	12–24 months (5th group)	24–60 months (6th group)	>60 months (7th group)
RNFL average thickness (µm)	103.10±9.11	109.92±27.39	84.77±32.61*	64.30±21.03*	51.36±13.77*	50.16±16.54*	39.83±10.31*	44.10±14.02*
RNFL S thickness (µm)	132.79±12.91	148.92±36.52	116.08±41.24	92.48±34.08*	69.30±22.65*	71.12±27.61*	50.13±17.36*†	61.90±25.40*
RNFL N thickness (µm)	57.48±8.63	72.50±15.61*	56.08±19.33	47.33±20.78	37.61±13.73*	35.51±16.63*	28.26±15.80*	28.10±16.14*
RNFL I thickness (µm)	134.02±20.96	147.92±40.91	118.31±48.47	80.04±29.32*	69.97±21.37*	63.37±21.72*	49.74±13.13*	56.71±17.50*
RNFL T thickness (µm)	87.67±14.78	69.33±30.23*	48.77±40.22*	37.19±13.44*	28.76±6.26*	33.57±8.66*	30.89±9.33*	29.51±6.96*

*P<0.05 when compared with healthy controls.

†P<0.05 when 6th group and 7th group were compared with 5th group, disease duration 12–24 months.

Data are shown as mean±SD. Values were compared by one-way analysis of covariance, followed by Bonferroni posthoc test. Sex and age were used as covariates in the analysis.

Group control, healthy control; I, inferior; LHON, Leber’s hereditary optic neuropathy; N, nasal; RNFL, retinal nerve fibre layer; S, superior; T, temporal; 1st group, disease duration ≤3 months; 2nd group, disease duration 3–6 months; 3rd group, disease duration 6–9 months; 4th group, disease duration 9–12 months; 5th group, disease duration 12–24 months; 6th group, disease duration 24–60 months; 7th group, disease duration >60 months.

6–9 months from disease onset, with all values showing a significant difference (p<0.01), except that in the nasal quadrant (p=0.93) (online supplemental material 1). As the disease progressed, further thinning of the pRNFL occurred, and the pRNFL thickness of each quadrant and the average pRNFL thickness in patients with LHON decreased further at 9–12 months, 12–24 months, 24–60 months and >60 months, all of which showed statistically significant differences (p<0.01). The data presented in table 2 also demonstrates that compared with those in the 12-month to 24-month disease duration group, the pRNFL thickness of each quadrant decreased in the 24-month to 60-month disease duration group, with the superior quadrant reaching a significant difference (p<0.01) (online supplemental material 1; online supplemental material 2). Furthermore, compared with the pRNFL thickness of the 12-month to 24-month disease duration group, that in each quadrant decreased in the >60-month disease duration group, with no significant differences in all quadrants (online supplemental material 1; online supplemental material 2).

Figure 1 shows the pRNFL thickness in each quadrant for the healthy controls and patients with LHON with different disease

durations. Compared with that in healthy controls, the temporal pRNFL in patients with LHON thinned within 3 months of disease onset (p<0.01) (online supplemental material 2), whereas it thickened in the remaining quadrants. As the disease progressed, the pRNFL in all quadrants became thinner, with the temporal quadrant showing the most severe thinning (from 87.67 µm to 29.51 µm; table 2). Figure 1A shows the progression of the thickening and thinning of the fibres and its topographical distribution. In the subacute stage (1st and 2nd groups), the temporal pRNFL became thinner, whereas that in the remaining quadrants first thickened and then became thinner. In the dynamic stage (3rd and 4th groups), the thickness of pRNFL in each quadrant was significantly reduced (online supplemental material 1). In the chronic stage (5th, 6th and 7th groups), the pRNFL in each quadrant continued to thin, but at a slower rate than that in the dynamic stage. Figure 1B shows the mean values of the average 360° RNFL thickness and the RNFL thickness in the superior, nasal, inferior and temporal quadrants in healthy controls and patients with LHON at different stages of disease progression. Figure 2 shows an OCT image of the pRNFL of healthy controls.

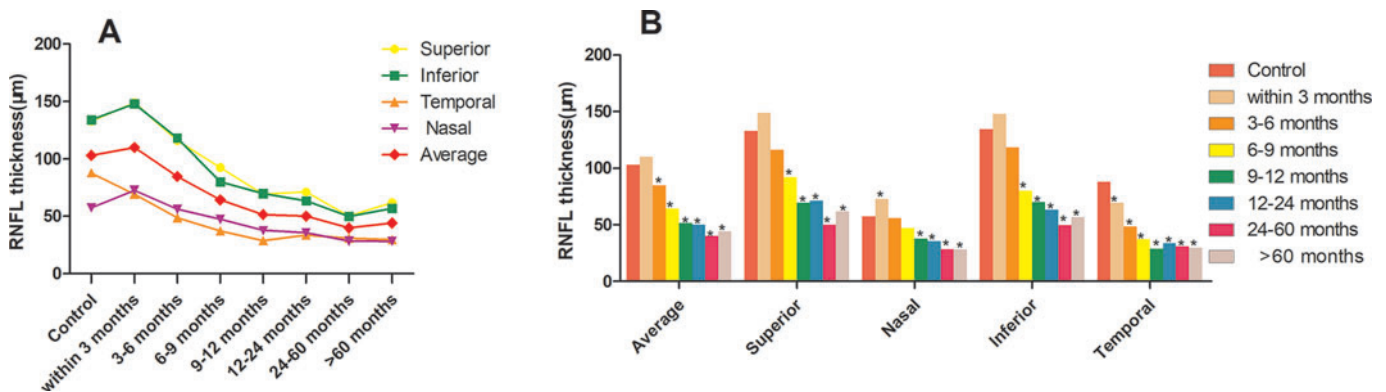


Figure 1 Disease progression in patients with Leber’s hereditary optic neuropathy (LHON). The peripapillary retinal nerve fibre layer (pRNFL) thickness in each quadrant and the 360° averages for the different time course groups and healthy control. (A) The figure shows that temporal pRNFL thickness decreased within 3 months of onset and gradually progressed, while the pRNFL in other quadrants thickened at first and then thinned. (B) The figure shows that compared with the healthy control group, the temporal pRNFL thickness decreased within 3 months of onset, with a statistically significant difference; in contrast, the superior, inferior, nasal and average pRNFL thickness showed an initial increase, with the pRNFL thickness in the nasal quadrant showing a statistically significant difference. As the disease progressed, the pRNFL thickness of all quadrants and the average pRNFL thickness continued to become thinner at 3–6 months, the average pRNFL thickness had decreased and showed a significant difference; at 6–9 months, the superior and inferior pRNFL thickness had decreased and showed a significant difference and at 9–12 months, the nasal pRNFL thickness had decreased and showed a significant difference. * P<0.05 when compared with healthy controls.

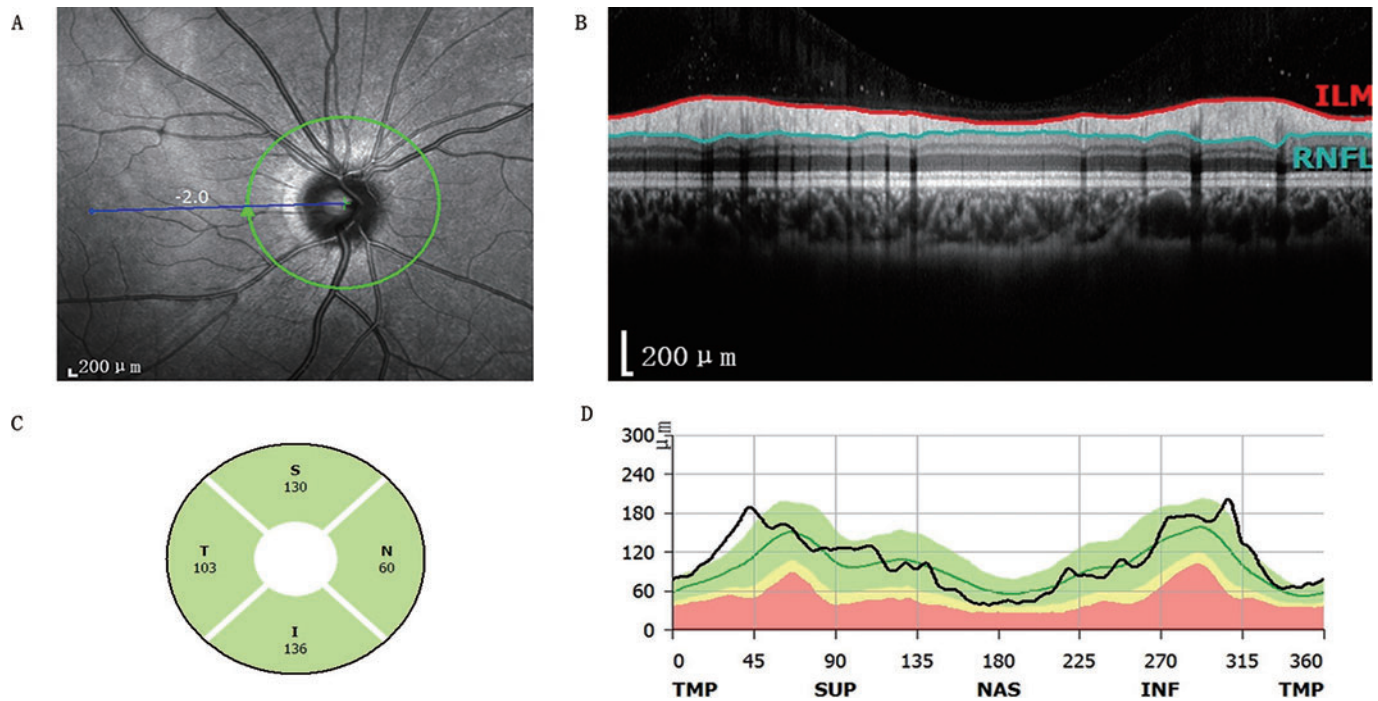


Figure 2 Representative 360°, circle scan (3.5 mm in diameter) centred on the optic disc, from a representative healthy subject (control group). (A) The location and range measured by optical coherence tomography (OCT). (B) The peripapillary retinal nerve fibre layer (pRNFL) was measured from the red line to the blue line. (C) The values from the quadrants of the peripapillary retinal nerve fibre layer measured by OCT. (D) The RNFL thickness in 360° circle scan and the corresponding peripapillary retinal nerve fibre layer areas. I, inferior; N, nasal; S, superior; T, temporal.

Table 3 shows the rate of difference versus group control and the comparison from the previous stage of the disease. The RNFL average thickness was significantly reduced in 2nd group (3–6 months) compared with that in 1st group (within 3 months) ($p=0.003$) and in 3rd group (6–9 months) compared with that in 2nd group (3–6 months) ($p=0.003$). The RNFL thickness of the superior quadrant was significantly reduced in 2nd group (3–6 months) compared with that in 1st group (within 3 months) ($p=0.029$), in 4th group (9–12 months) compared with that in 3rd group (6–9 months) ($p=0.049$) and in 6th group (24–60 months) compared with that in 5th group (12–24 months) ($p=0.004$). The RNFL thickness of the inferior quadrant was significantly reduced in

3rd group (6–9 months) compared with that in 2nd group (3–6 months) ($p<0.001$). The RNFL thickness of the temporal quadrant was significantly reduced in 2nd group (3–6 months) compared with that in 1st group (within 3 months) ($p=0.014$) (table 3).

DISCUSSION

In this study, pRNFL thickness was measured in 221 eyes of patients with LHON and 52 eyes of age-matched and sex-matched healthy controls. By comparing the pRNFL thickness of each quadrant in patients with LHON with increasing disease durations, we found certain patterns of pRNFL involvement in patients with LHON: first, the temporal pRNFL thins, followed

Table 3 pRNFL thickness change versus group control in the four quadrants and the 360° average

Group	1st group (within 3 months)	2nd group (3–6 months)	3rd group (6–9 months)	4th group (9–12 months)	5th group (12–24 months)	6th group (24–60 months)	7th group (>60 months)
RNFL average thickness change versus group control	6.61%	-17.78%*	-37.63%*	-50.18%	-51.35%	-61.37%	-57.23%
RNFL S thickness change versus group control	12.15%	-12.58%*	-30.36%	-47.81%*	-46.44%	-62.25%*	-53.39%
RNFL N thickness change versus group control	26.13%*	-2.44%	-17.66%	-34.57%	-38.22%	-50.84%	-51.11%
RNFL I thickness change versus group control	10.37%	-11.72%	-40.28%*	-47.79%	-52.72%	-62.89%	-57.69%
RNFL T thickness change versus group control	-20.92%*	-44.37%*	-57.58%	-67.20%	-61.71%	-64.77%	-66.34%

* $P<0.05$ when compared with the former group.

Date are shown as % change versus group control. Values were compared by one-way analysis of covariance, followed by Bonferroni posthoc test. Sex and age were used as covariates in the analysis.

Group control, healthy control; I, inferior; N, nasal; RNFL, retinal nerve fibre layer; S, superior; T, temporal; 1st group, disease duration ≤ 3 months; 2nd group, disease duration 3–6 months; 3rd group, disease duration 6–9 months; 4th group, disease duration 9–12 months; 5th group, disease duration 12–24 months; 6th group, disease duration 24–60 months; 7th group: disease duration >60 months.

by that in the inferior and superior quadrants, and finally, the nasal pRNFL (figure 1).

Within 3 months of onset, the temporal pRNFL (primarily composed of papillomacular bundle) significantly thinned in patients with LHON, and as the disease progressed, the thinning of the temporal pRNFL proved to be the most severe among those in all quadrants (table 2). This could be attributed to the small diameter of the papillomacular bundle that anatomically limits the axoplasmic transport of mitochondria,⁷ and the small volume-to-surface area ratio, leading to low productivity and high-energy requirements.^{8–9} Clinically, patients with LHON present with symptoms such as visual acuity loss and central or cecentral scotomas at onset, also indicating that the papillomacular bundle is the first and most severely damaged.

Within 3 months of disease onset, the superior, inferior, nasal and average pRNFL thickness had increased, and the thickening in the nasal quadrant showed a significant difference (table 2; online supplemental material 1). Clinically, normal pRNFL thickness is often considered as a sign of no optic nerve injury. However, when accompanied by a decrease in the patient's visual acuity and visual field index, this implies that the RGC are dysfunctional or even apoptotic, and therefore, a diagnosis of LHON should be considered. The pRNFL in patients with LHON may be completely normal or even thickened, which is also one of the pathological features of LHON.

The reasons for pRNFL thickening remain controversial. Some researchers believe that energy deficiency at disease onset may cause compensatory engorging of the vessels around the optic disc, which could lead to pRNFL thickening.¹⁰ Nevertheless, other researchers have suggested that pRNFL thickening may be related to impaired axoplasmic transport and a compensatory increase of mitochondrial biogenesis, which were caused by the energy defect and the overproduction of reactive oxygen species.^{11–13} Optic disc microangiopathy is a hallmark of LHON. Some researchers have tried to analyse the relationship between microangiopathy and fibre thickness changes and have found that microvascular changes in the temporal sector, implicating the papillomacular bundle, precede the RNFL and mirror the macular ganglion cell-inner plexiform layer (GC-IPL) changes. This argues in favour of an active role played by the retinal microvasculature in the process of disease during LHON conversion that leads to an irreversible wave of axonal injury (RNFL thickening) and an irreversible wave of RGC loss (GC-IPL thinning).¹⁴ However, this type of pRNFL thickening is distinct from true oedema and does not show leakage on fluorescein angiography; hence, it is known as pseudoedema, which must be clinically distinguished from true oedema caused by optic neuritis.

As the disease progresses, further apoptosis and axonal loss of the RGC occur. By 3–6 months from onset, compared to the healthy controls, the pRNFL thicknesses of each quadrant and the average thickness had decreased, and the changes in the temporal and average pRNFL thickness were significantly different (table 2; online supplemental material 1). This observation indicates that the pRNFL pseudoedema gradually disappeared and that the optic nerve atrophy was gradually exposed. Zhang *et al*³ and Borrelli *et al*¹² measured the pRNFL changes in each quadrant of patients with LHON with different disease durations and found that pRNFL first showed thickening, followed by thinning, during the course of LHON.^{4–5}

Further thinning of the pRNFL was observed in this study. By 6–9 months from onset, the thinning of the superior, inferior, temporal and average pRNFL had reached a significant difference (table 2; online supplemental material 1), and pRNFL in the

inferior quadrant showed more severe thinning (from 134.02 μm to 80.04 μm) than that in the superior quadrant (from 132.79 μm to 92.48 μm); this demonstrated that the inferior quadrant might be involved earlier than the superior quadrant in the course of disease progression. However, our study did not provide sufficient evidence, which necessitates further verification to validate this conclusion. By 9–12 months from onset, pRNFL thinning of all the quadrants and the average pRNFL thickness reached a significant difference (table 2; online supplemental material 1). A particular pattern could be observed in the changes of pRNFL thickness after the onset of LHON: thinning first occurred in the temporal pRNFL, followed by the inferior and superior pRNFL, and finally, the nasal pRNFL (figure 1). The sequence of RNFL thinning was consistent with the pattern previously observed by researchers in the natural course of LHON.^{5–15}

In the chronic stage, even at 60 months from onset, pRNFL thinning continued to occur in some quadrants (table 2; online supplemental material 1; online supplemental material 2). In this study, we found more pRNFL thinning in the 6th (24–60 months) and 7th groups (>60 months), when compared with that in the 5th group (12–24 months); moreover, pRNFL thinning in the superior quadrant showed a statistically significant difference ($p < 0.01$) (online supplemental material 1; online supplemental material 2). However, the pRNFL thicknesses changes in other quadrants were not statistically significant, probably due to the heterogeneity in the included patients (online supplemental material 2). Furthermore, we did not find more thinning in the 7th group (>60 months) when compared with that in the 6th group (24–60 months). The rates of RNFL thinning were extremely slow in the chronic stage after 12 months since disease onset, especially after 24 months, or alternatively, the thinning stabilised. However, we still need further evidence to validate this conclusion.

Our study has some limitations: only a cross-sectional observation of the changes in pRNFL thickness in patients was performed in this study. Binocular data were included in the statistics due to the rarity of patients with LHON, and therefore, the influence of binocular factors was not excluded.

Nevertheless, this study provides insights into treating LHON. In the chronic stage, even at 60 months from onset, pRNFL thinning continued to occur in some quadrants (table 2; online supplemental material 1; online supplemental material 2), suggesting the presence of viable RGC in these quadrants, which were still slowly and gradually undergoing apoptosis. This knowledge might help ophthalmologists to preserve a patient's visual function better and improve their quality of life. This is possible if patients with chronic LHON having longer disease durations are actively treated, which might preserve the remaining RGC.

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