ORIGINAL ARTICLE

Longitudinal Changes in Retinal Nerve Fibre Layer Thickness after an Isolated Unilateral Retrobulbar Optic Neuritis: 1-Year Results

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ABSTRACT

The objective of this study was to investigate the longitudinal changes in retinal nerve fibre layer (RNFL) thickness 1 year after an episode of unilateral acute optic neuritis. This prospective cohort study recruited consecutive patients with a first episode of isolated, unilateral acute optic neuritis from October 2010 to June 2013. RNFL thickness of the attack and normal fellow eyes was measured by optical coherence tomography on presentation and 3, 6, and 12 months post attack in both the treatment and non-treatment groups. The treatment group consisted of subjects that opted for systemic steroids to hasten recovery time. In 20 subjects, 11 received systemic steroids and 9 were treated conservatively. The baseline RNFL thickness was similar in the attack and fellow eyes ($p \geq 0.4$). Progressive RNFL thinning was seen in the attack eye over the 12-month period, with significant differences for baseline versus 3 months; baseline versus 12 months; and 3 versus 12 months (all $p < 0.0001$). At 12 months, the attack eye had a thinner average RNFL than the fellow eye (100.9 ± 6.1 versus $107.3 \pm 5.5 \mu\text{m}$; $p = 0.002$). The 12-month RNFL was similar between the treatment and non-treatment groups ($p \geq 0.6$). A single episode of optic neuritis triggered an accelerated, progressive RNFL thinning up to 6 months post attack. Initial treatment with systemic steroids did not seem to alter the degree of RNFL loss at 12 months.

Keywords: OCT, optic neuritis, optical coherence tomography, RNFL, steroid

INTRODUCTION

Acute optic neuritis commonly presents with pain, vision loss, and dyschromatopsia, followed by demyelinating axonal loss and later optic atrophy.^{1,2} Optical coherence tomography (OCT) enables high-resolution cross-sectional quantification of the retinal nerve fibre layer (RNFL), making it particularly useful to assess the rate and extent of axonal loss after optic neuritis and also help to differentiate between neuromyelitis optica (NMO) and multiple sclerosis (MS).^{3–8} Previous studies have shown that neither the use of systemic steroid nor interferon-beta altered the degree of RNFL thinning up to 4 months after

optic neuritis.^{9,10} The aim of this study was to assess the longitudinal changes in RNFL thickness after a first attack of optic neuritis and to investigate the impact of treatment on RNFL thinning at 1 year after the attack.

PATIENTS AND METHODS

The study was approved by Institutional Review Board of the Hospital Authority of Hong Kong, and informed consent was obtained prior to commencement of the study. The study was conducted in accordance with the Declaration of Helsinki.

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The authors declare no financial or proprietary interests. Parts of the study protocol have been previously described in another study investigating the early RNFL changes after an attack of optic neuritis.⁹ This was a prospective cohort study conducted at Caritas Medical Centre, Hong Kong Special Administrative Region, China, between October 2010 and June 2013. Consecutive, consenting adults, 18–60 years of age, diagnosed with a first episode of isolated unilateral acute optic neuritis presenting within 8 days of symptom onset were recruited and followed up for at least 12 months. The diagnosis of optic neuritis was made based on a compatible history involving ocular pain; clinical examination demonstrating impairment of optic nerve function including dyschromatopsia, visual acuity (VA) impairment, optic disc swelling (except for retrobulbar cases), or relative afferent papillary defect; as well as the absence of any space-occupying lesion on a computed tomography scan of the brain and orbit.

All subjects underwent neuro-ophthalmic examination by an ophthalmologist (S.K.Y.) and a neurologist (P.K.L.). All subjects underwent imaging for RNFL thickness via a spectral-domain OCT (Heidelberg Engineering, Carlsbad, CA, USA).

Contrast magnetic resonance image (MRI) scan of the brain and orbit was performed for all patients. Blood was taken for autoimmune markers and aquaporin-4 antibody to rule out other causes of optic neuritis. Subjects with known or confirmed diagnosis of MS, NMO, autoimmune disease, other optic neuropathies, myopic peripapillary atrophy, and glaucoma were excluded. The diagnostic criteria adopted for MS, NMO, and clinical isolated syndrome (CIS) has been described in an earlier publication by the authors.¹¹

Subjects who required a hastened visual recovery and who understood the risk and benefit of treatment were administered a systemic steroid treatment (intravenous methylprednisolone 250 mg every 6 hours for 3 days, followed by oral prednisone 1 mg/kg/day for 11 days) as per the Optic Neuritis Treatment Trial (ONTT) protocol (treatment group).¹² The non-treatment group did not receive any active medical treatment.

Measurement of the Peripapillary RNFL Thickness with OCT

The Spectralis OCT for RNFL was operated by a trained imaging technician who was masked to subjects' diagnosis. RNFL thickness was measured around the optic nerve head obtained using the fast RNFL thickness protocol. Scans were repeated three times and assessed for signal strength and centration. Scans with signal strength quality $Q \leq 16$ or poor centration were excluded. RNFL thickness was

analysed with the RNFL Single Exam Report OU with fovea-to-disc technology. The RNFL thickness of each of four quadrants and the average RNFL were recorded for the attack and non-attack fellow eyes at baseline (on presentation) and at 3, 6, and 12 months after the attack in all subjects (including both the treatment and non-treatment groups).

Statistics

The Mann-Whitney *U* test was used to assess for differences in the mean RNFL for the following groups:

- Treatment versus non-treatment eye at baseline
- Treatment versus non-treatment eye at 12 months post attack
- Attack versus fellow eye at 12 months post attack
- Attack versus fellow eye at baseline

The Friedman test with Dunn's multiple comparison test was performed to assess for differences in the average and four-quadrant RNFL thicknesses at the following time intervals: baseline and 3, 6, and 12 months after the initial attack. Data were expressed as mean $\pm$ standard deviation and statistical significance was defined as $p < 0.05$.

RESULTS

During the study period, 30 optic neuritis subjects presented to the Department of Ophthalmology, Caritas Medical Centre, Hong Kong. The aetiological distribution included 73.3% (22/30) CIS, 10% (3/30) developed MS, 10% (3/30) had NMO, and 6.7% (2/30) had NMO-spectrum disorder. Out of the 22 patients with CIS, 2 were excluded because they defaulted follow-ups. Twenty patients were included in the study. All subjects had a first episode of an isolated, unilateral, retrobulbar optic neuritis without papillitis. Those with other aetiologies of optic neuritis other than isolated optic neuritis were excluded from this study. The male-to-female ratio was 1:3. There were 11 right eyes and 9 left eyes. The mean age was 34.8 ± 12.1 years. All subjects were ethnic Chinese. Eleven subjects were in the treatment group and 9 were in the non-treatment group. There were no complications from the systemic steroid treatment. In all 20 subjects, the baseline quadrant and average RNFL thickness were statistically similar in the attack and fellow eyes ($p \geq 0.4$). Likewise, the baseline quadrant and average RNFL thickness were similar in both the treatment and non-treatment groups ($p \geq 0.1$).

The average RNFL in the attack eye at baseline was $108.4 \pm 5.9 \mu\text{m}$. Progressive thinning in the average RNFL was seen at each of the measured time points: 3 months ($103.9 \pm 6.0 \mu\text{m}$), 6 months ($101.7 \pm 5.9 \mu\text{m}$), and

12 months ($100.9 \pm 6.1 \mu\text{m}$) after the attack (Figure 1). The differences were statistically significant for baseline versus 3 months; baseline versus 12 months; and 3 months versus 12 months (all $p < 0.0001$). Similar changes were observed over all four RNFL quadrants. There were no significant differences between the 6-month and 12-month average or quadrant RNFL (Table 1).

For the uninvolved fellow eye, there was a mild thinning of the RNFL over the 12-month period ($107.3 \pm 5.5 \mu\text{m}$) compared with baseline ($108.1 \pm 5.9 \mu\text{m}$) ($p = 0.03$). There were no significant differences between the averages RNFL and the other measured time points in the fellow eye (all $p > 0.5$). At 12 months, the average RNFL in the attack eye ($100.9 \pm 6.1 \mu\text{m}$) was significantly thinner than the fellow eye ($107.3 \pm 5.5 \mu\text{m}$) ($p = 0.002$). The rate of average RNFL thinning was 6.9% and 0.7% in the attack and non-attack fellow eyes, respectively.

When comparing the RNFL thickness between the treatment and non-treatment groups at 12 months,

FIGURE 1 Changes in average RNFL thickness after an attack of isolated optic neuritis. Upper whisker = minimum; Lower whisker = maximum; Upper box line = upper quartile; Middle box line = median; Bottom box line = lower quartile.

there was no significant difference in the quadrant or average thickness ($p \geq 0.6$).

DISCUSSION

In an earlier study, we have established that a single, acute episode of optic neuritis was able to induce a significant RNFL thinning and that initial treatment with intravenous steroids did not alter the course of RNFL thinning up to 3 months after an attack.⁹ In this follow-up study, we investigated the changes in RNFL at 1 year after the optic neuritis. This is one of the few studies in the literature that provides a relatively longitudinal RNFL monitoring after optic neuritis in a Chinese population.

Over the 12-month period, we noted a physiological RNFL thinning of 0.7% over the normal fellow eye. In the attack eye, the rate of RNFL thinning was accelerated by close to 10 times (6.9%) over the 12-month period post attack. The bulk of RNFL thinning took place within the first 6 months of optic neuritis, as evident by the absence of further RNFL thickness differences between the 6-month and 12-month RNFL measurements. The thinning was generalised and evident in all four quadrants of the RNFL. Our findings were consistent with previous studies that reported significant RNFL thinning within the first 6 months after the acute optic neuritis and that no further significant interval changes were detected from 6 to 24 months.^{7,13} As all of our subjects did not present with papillitis, the amount of longitudinal RNFL thinning may not be as dramatic as other study populations^{14,15} that included subjects with initial papillitis, since papillitis would give rise to an initial paradoxical increase in RNFL thickness.

Initial treatment was systemic steroids did not confer any protective effect on the amount of average or quadrant RNFL loss at any time point up to 12 months post attack. Our findings were in agreement with a systemic review of the literature that demonstrated an absence of statistically significant benefit of systemic steroids in the treatment of acute optic neuritis.¹⁶ Subjects in this series opted for steroid

TABLE 1 Dunn's multiple comparison test of RNFL thickness in the attack eye at various time intervals.

Comparison	Difference in RNFL thickness between different time points following optic neuritis (μm)				
	Average	Superior	Nasal	Inferior	Temporal
Baseline versus 3 months	-4.5	-4.7	-4.7	-4.5*	-4.3
Baseline versus 6 months	-6.7*	-7.0*	-6.3*	-6.4*	-7.1*
Baseline versus 12 months	-7.5*	-7.8*	-7.0*	-7.3*	-8.0*
3 months versus 6 months	-2.2	-2.3*	-1.7*	-1.9	-2.8*
3 months versus 12 months	-3.0*	-3.1*	-2.4*	-2.8*	-3.7*
6 months versus 12 months	-0.8	-0.8	-0.7	-0.9	-0.9

*Statistically significant.

treatment to mainly increase the speed of visual recovery, as demonstrated by the ONTT.¹² The lack of effect of systemic steroids on RNFL loss has two important implications. First, this allows for the concomitant use of potential neuroprotective drugs in future clinical trials without fear that the effects of systemic steroid use would confound the degree of RNFL thinning. Secondly, the treatment effects of neuroprotective medication can be monitored with OCT, as previously proposed by Henderson et al.^{7,17}

This study had its limitations. Firstly, the assignment of treatment and non-treatment groups was not randomised, but the authors felt that it would be unethical to withhold treatment in those with a high visual demand when systemic steroids can hasten the visual recovery process. Secondly, a large sample size would enable us to further stratify the population by age, optic neuritis aetiologies, and disease duration.

In conclusion, an accelerated, progressive RNFL thinning was demonstrated to take place up to 6 months after an initial attack of optic neuritis. Initial treatment with systemic steroids did not seem to alter the degree of RNFL loss at 12 months after the attack.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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