The Evaluation of the Retinal Nerve Fiber Layer in Multiple Sclerosis with Spectral-Domain Optical Coherence Tomography

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Key Words

Multiple sclerosis · Spectral-domain optical coherence tomography · Retinal nerve fiber layer thickness · Optic neuritis

Abstract

Background/Aims: Retinal nerve fiber layer (RNFL) thinning has been observed on histopathology and time-domain optical coherence tomography in many diseases of the central nervous system. In this study, with a higher resolution of spectral-domain optical coherence tomography (SDOCT), we detected RNFL changes in patients with multiple sclerosis (MS) in China, and compared RNFL thickness between eyes with and without optic neuritis (ON). **Methods:** In this retrospective, nonrandom case study, the patients were recruited from the Affiliated Sir Run Run Shaw Hospital of Zhejiang University. RNFL thickness was measured for each eye using SDOCT. The controls were recruited from the healthy population. **Results:** Peripapillary RNFL thickness of 24 eyes in 12 patients was detected by SDOCT. The average RNFL thickness of the MS patients was $81.9 \pm 17.8 \mu\text{m}$ compared to the control value of $102.1 \pm 8.1 \mu\text{m}$ ($p = 0.00$). The average RNFL of the patients with a history of ON was thinner than that of patients without ON ($71.8 \pm 19.2 \mu\text{m}$ vs. $92.0 \pm 8.5 \mu\text{m}$,

$p = 0.001$). **Conclusion:** The RNFL thinning in Chinese patients with MS can be detected by SDOCT. The SDOCT scan represents a high-resolution, objective, noninvasive and easily quantifiable in vivo biomarker of MS.

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Introduction

Multiple sclerosis (MS) is a neurodegenerative disease, and is considered to be a chronic inflammatory disease of the central nervous system (CNS). It may cause demyelination and axonal degeneration [1]. However, the pathogenetic mechanism of MS is still unknown. The retina is the only place where a tissue layer made up of unmyelinated axons can be imaged directly, so the changes in the retinal architecture require a unique model [2, 3]. Quantification of the retinal nerve fiber layer (RNFL) has the potential to open a diagnostic window for monitoring the axonal and neuron injury that occurs with neurodegeneration. Many studies have demonstrated thinning of the RNFL [4–8]. However, in China, there are only a few studies on the RNFL changes that occur with MS; a report on the RNFL changes of optic neuritis (ON) in early-stage MS came out only in 2011 [9].

As a noninvasive, high-resolution, noncontact technique which can quantify the retinal architecture objectively, including the peripapillary RNFL thickness and the macular volume, optical coherence tomography (OCT) has become an important instrument in neuro-ophthalmology [10]. Over the past 2 decades, the technique of OCT has developed tremendously. Spectral-domain optical coherence tomography (SDOCT) has been widely applied in clinical ophthalmology. Compared to the third generation, i.e. time-domain optical coherence tomography (TDOCT) which has significantly lower axial resolution and limited image acquisition, SDOCT, with axial resolutions of 2–3 μm , is characterized by markedly increased image acquisition speed and improved imaging quantification, and has been increasingly utilized for the evaluation of a variety of ocular diseases such as glaucoma, age-related macular degeneration, macular hole and diabetic macular edema [11, 12]. Bock et al. [13] demonstrated the difference between TDOCT and SDOCT technology on RNFL measurements. Based on the abovementioned facts, by utilizing SDOCT, we observed the RNFL changes that occur with MS in our country, and compared the RNFL thickness in patients with and without ON.

Material and Methods

This was a retrospective case series. Subjects were recruited between January 2009 and November 2012 from the Affiliated Sir Run Run Shaw Hospital of Zhejiang University, and the ocular evaluation was completed. All patients fulfilled the revised McDonald criteria [14]. Subjects with a diagnosis of MS were included, with or without ON. Eyes with other ocular diseases, such as glaucoma, atypical ON, ischemic optic neuropathy, neuromyelitis optica, uveitis, retinal vessels diseases and other CNS diseases were excluded. The patients with ON were excluded if the episode of ON lasted less than 6 months. The diagnosis of ON was based on the patient's description or clinician reports. Controls consisted of normal healthy hospital examinees. People with other ocular or CNS diseases were excluded.

This study was approved by the ethics committee of the Affiliated Sir Run Run Shaw Hospital of Zhejiang University. All participants received comprehensive ophthalmologic examinations, including best-corrected visual acuity (BCVA), noncontact ocular pressure, visual field (VF), dilated indirect slit-lamp examination of the anterior and posterior segment and peripapillary RNFL scanning.

Subjects underwent SDOCT scanning (Carl Zeiss Meditec, Dublin, Calif., USA) without pupillary dilation. OCT imaging generates cross-sectional tomograms of the retina. Scanning protocols included both a circular 3.4-mm scan centered on the optic nerve head with a scan density of 512×128 pixels in 3.5 s [10]. Only images with a signal-strength of ≥ 6 (maximum 10) were acquired. Images with large eye movements, disconnecting a large

Table 1. Demographic characteristics of MS patients with and without ON

	Eyes	
	ON (n = 16)	no ON (n = 12)
Age, years $\pm$ SD	43.6 $\pm$ 16.0	30.8 $\pm$ 8.6
Sex		
Female	7 (50%)	5 (35.7%)
Male	1 (7.1%)	1 (7.1%)
Duration, months $\pm$ SD	82.8 $\pm$ 82.0	61.0 $\pm$ 47.0
BCVA, eyes		
≤ 0.1	3	0
0.1–0.5	1	1
> 0.5	10	9
VF/defect, n (eyes)	13/11	10/0
RNFL scanning, n (eyes)	12	12

retinal vessel or black bands (caused by blinking) were rejected throughout the examination. OCT scanning was completed by two skilled operators. OCT parameters were calculated automatically by the equipment software. RNFL thickness measurements were taken using a circular (3.4 mm) peripapillary map. Mean RNFL thickness for 360° around the optic disc and for the superior, inferior, nasal and temporal quadrants around the optic nerve head were recorded for each eye of the patients and the healthy controls. A reliable standard automated perimetry test per eye was performed using a Humphrey Field Analyzer (Zeiss Humphrey Systems, Dublin, Calif., USA), with the 30-2 SITA standard strategy. If fixation losses were $> 15\%$ and false-positive or false-negative rates were $> 30\%$, the results of the VF were excluded. The BCVA was evaluated by the standard logarithmic visual acuity chart.

All statistical analyses were performed using SPSS 17.0. The Mann-Whitney U test was used to compare ages and disease duration between MS and healthy controls. Generalized estimating equation (GEE) models were used to compare RNFL thickness (the average and the 4 quadrants) between patients and controls, which allowed us to adjust age and intereye correlation. GEE models were also used to compare RNFL thickness in MS with or without VF defect. Statistical significance was defined as $p < 0.05$.

Results

In total, 28 eyes in 14 patients with MS were evaluated. Age ranged from 16 to 62 years (median 40.3 ± 17.3 years). There were 12 female (85.7%) and 2 male (14.3%) patients. The median age of patients with and without ON was 43.6 ± 16.0 and 30.8 ± 8.6 years, respectively. There were 8 patients (16 eyes, 57.1%) with ON and 6 (12 eyes, 42.9%) without ON (table 1). The RNFL thickness of 26 eyes was evaluated by SDOCT. Two eyes were excluded

Table 2. RNFL thickness comparisons between MS patients and healthy controls (μm)

	Eyes		p value
	MS patients (n = 24)	controls (n = 28)	
Average RNFL	81.9 $\pm$ 17.8	102.1 $\pm$ 8.1	0.00
Temporal	59.8 $\pm$ 20.2	75.4 $\pm$ 14.8	0.00
Nasal	61.8 $\pm$ 11.6	72.0 $\pm$ 9.5	0.001
Superior	105.9 $\pm$ 28.1	127.5 $\pm$ 13.5	0.00
Inferior	100.0 $\pm$ 25.0	132.9 $\pm$ 11.1	0.00
Rim area	1.3 $\pm$ 0.2	1.3 $\pm$ 0.2	0.18
RNFL symmetry	0.7 $\pm$ 0.2	0.9 $\pm$ 0.1	0.01

Table 3. RNFL thickness in MS comparisons between patients with and without ON (μm)

	Eyes		p value
	ON (n = 12)	no ON (n = 12)	
Average RNFL	71.8 $\pm$ 19.2	92.0 $\pm$ 8.5	0.001
Temporal	51.6 $\pm$ 22.8	68.1 $\pm$ 13.6	0.03
Nasal	58.9 $\pm$ 9.8	64.7 $\pm$ 13.0	0.2
Superior	91.3 $\pm$ 28.8	120.6 $\pm$ 18.7	0.002
Inferior	85.3 $\pm$ 25.2	114.7 $\pm$ 14.1	0.00
Rim area	1.2 $\pm$ 0.3	1.3 $\pm$ 0.2	0.45
RNFL symmetry	0.6 $\pm$ 0.3	0.8 $\pm$ 0.1	0.04

Fig. 1. There were significant differences in the RNFL thickness within the average RNFL and the superior, inferior, temporal and nasal quadrants between MS and healthy controls ($p = 0.00$, $p = 0.0$, $p = 0.001$, $p = 0.00$, $p = 0.00$, respectively, GEE models accounting for age and adjusting for within-patient intereye correlations).

on the basis of no objectively quantified data. Twenty-six eyes in 13 healthy controls were evaluated. The age range of the controls was 11–51 years (median 39.8 ± 10.4 years). There was no significant difference in age between MS patients and healthy controls ($p = 0.5$). No significant differences with regard to age or disease duration were found between eyes with and without ON.

The average RNFL thickness for individuals with MS was $81.9 \pm 17.8 \mu\text{m}$. Compared with the mean RNFL

thickness of healthy controls ($102.1 \pm 8.1 \mu\text{m}$), there was a significant difference ($p = 0.00$, GEE models accounting for age and adjusting for within-patient intereye correlations; table 2). With the rim area not being significantly different ($p = 0.18$), there were significant differences in the RNFL thickness within 4 quadrants and in RNFL symmetry (fig. 1). Meanwhile, compared to healthy controls, there were significant differences in average RNFL thickness, nasal and inferior RNFL thickness in MS patients without ON ($p = 0.001$, $p = 0.07$ and $p = 0.00$, respectively).

There was a significant difference in average RNFL thickness in patients with a history of ON and those without ($71.8 \pm 19.2 \mu\text{m}$ vs. $92.0 \pm 8.5 \mu\text{m}$, $p = 0.01$, table 3). There was also a statistical difference in the temporal, superior and inferior quadrants between the 2 groups ($p = 0.03$, $p = 0.002$ and $p = 0.00$, respectively, fig. 2).

Figure 3 shows the average RNFL thickness in patients with VF defect; this was thinner than in patients without VF defect ($61.1 \pm 12.6 \mu\text{m}$ vs. $93.7 \pm 9.0 \mu\text{m}$, $p = 0.00$). There was a significant difference in the temporal, superior and inferior quadrants ($p = 0.003$, $p = 0.00$ and $p = 0.00$, respectively). Also, the average RNFL thickness in patients with MS of a duration >24 months was thinner than that in patients with a disease duration of <24 months ($p = 0.02$, GEE models accounting for age and adjusting for within-patient intereye correlations).

Discussion

Neurodegenerative diseases, such as MS and Alzheimer disease, are characterized by axonal lesions throughout the CNS including the eye [15]. Frisen and Hoyt [16] had observed the RNFL changes subjectively by utilizing

Fig. 2. There were significant differences in average RNFL and the temporal, superior and inferior quadrants between MS with and without ON ($p = 0.001$, $p = 0.03$, $p = 0.002$, $p = 0.00$, respectively, GEE models accounting for age and adjusting for within-patient intereye correlations).

Fig. 3. The average RNFL thickness with VF defect was thinner than that without VF defect ($61.1 \pm 12.6 \mu\text{m}$ vs. $93.7 \pm 9.0 \mu\text{m}$, $p = 0.00$, GEE models accounting for age and adjusting for within-patient intereye correlations).

the direct ophthalmoscope 4 decades ago. Kerrison et al. [17] found peripapillary RNFL thinning in the temporal quadrant with histopathologic analysis. Parisi et al. [7], using an early generation of TDOCT technology, demonstrated reduced temporal and overall RNFL thickness

in MS eyes with and without ON when compared to the controls. Other investigators demonstrated that using SDOCT technology showed mean RNFL thinning in MS patients, and that eyes with a history of ON had thinner RNFL measurements than those without a history of ON [6, 8, 18]. In this study, our data demonstrated the thinning of RNFL in Chinese patients with MS. In a retrospective cross-sectional study, Trip et al. [19] reported no difference in RNFL between MS patients without ON and healthy controls; our study, however, demonstrated a significant difference ($p = 0.001$).

Some investigators evaluated the relationship between the loss of RNFL thickness and the loss of VF, and found a strong association between OCT and VF in all the sectoral measurements evaluated, particularly between the inferior optic disk quadrant and the corresponding VF loss in the superotemporal area [8, 20]. Our data showed that the average RNFL in patients with a VF defect was thinner than that in patients without a VF defect. Khanifar et al. [6] found that the peripapillary RNFL was thinning significantly over 5 years of disease, even in MS patients without a history of ON. Our results showed that the average RNFL thickness was thinner when the disease duration was >24 months. However, Henderson et al. [21], using TDOCT technology, reported that RNFL thickness had no significant association with the duration of progressive MS. The relationship between the duration of MS and the RNFL changes needs to be studied further.

Davies et al. [22] found there was characterized thinning of the ganglion cell layer in the eyes of MS patients, particularly in those with a history of acute ON. Similarly, our data demonstrated that the macular volume was thinner in eyes with ON (data not shown). However, only 2 eyes were observed, so further studies are needed on larger samples of Chinese patients with MS and the changes in the macular volume and the ganglion cell layer.

This study had some limitations. It was a retrospective case series, the sample number was small, so selective bias might have occurred. The possibility of recall bias was such that patients with a remote episode of ON could not be conclusively reported. However, the results measured were correct and objective.

In the future, large-sample, multicenter, prospective studies need to be launched. In order to better understand the retinal changes that occur with MS, we should attach importance to the longitudinal changes in MS subsets. In addition, the correlation between SDOCT and MRI findings needs to be studied.

Changes of the RNFL may be considered as one of the clinical manifestations of MS. In addition to MRI,

SDOCT retinal imaging represents a high-resolution, objective, noninvasive and easily quantifiable technology in vivo biomarker of MS with or without the presence of ON. It may also serve as a diagnostic adjunct for monitoring disease activity and responses to neuroprotective drugs.

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