·Clinical Research·

A study of retinal parameters measured by optical coherence tomography in patients with multiple sclerosis

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Abstract

• **AIM: To investigate the difference of retinal nerve fiber layer (RNFL) thickness and macular fovea thickness/volume between multiple sclerosis (MS) patients and healthy normal individuals using optical coherence tomography (OCT) and assess its association with visual field parameters.**

• **METHODS: Thirty consecutive MS patients and 28 healthy controls were recruited in this prospective study. Comprehensive standardized ophthalmic examinations included visual acuity, cycloplegic refraction, intraocular pressure, gonioscopy, visual field, and RNFL thickness and macular fovea thickness/volume detection using Humphrey OCT. Mean values for the thickness of the peripapillary RNFL and macular volume were calculated. Associations between visual field parameters and RNFL thickness/macular volume were analyzed by Pearson correlation analysis.**

• **RESULTS: The RNFL thicknesses in each quadrant, the average macular thickness, and the average macular volume in MS patients were all less than those in healthy controls, with statistically significant differences. The RNFL thickness and macular fovea thickness/volume were greater in eyes without optic neuritis than in eyes with optic neuritis. The average visual field parameters had positive correlations with the RNFL thickness and negative correlations with macular parameters in MS patients.**

• **CONCLUSION: OCT measurements can effectively identify the nerve changes of MS patients, which provide more data for the diagnosis of MS.**

• **KEYWORDS:** multiple sclerosis; retinal nerve fiber layer thickness; macular volume; visual field; optical coherence tomography

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INTRODUCTION

Multiple sclerosis (MS) is an inflammatory-demyelinating disease of the central nervous system, in which myelin sheaths around axons of the brain and spinal cord are damaged, leading to loss of myelin and scarring. Axon and nerve degeneration is considered to be the concomitant characteristic of MS and is related to the pathological process inducing permanent disability [1]. The retina, a distinctive part of the central nervous system, lacks myelin but contains ganglion cells and their respective axons. Therefore, the retina is considered as an ideal visual structure with neurodegenerative, neuroprotective, and even potential neurodegenerative characteristics.

Spectral domain optical coherence tomography (SD-OCT) is an emerging noninvasive, noncontact, and highly sensitive ophthalmic diagnostic imaging technology that can provide an *in vivo* objective and precise measurement of macular and retinal nerve fiber layer (RNFL) thickness [2-4]. In particular, the prominent advantages of SD-OCT in the diagnosis of macular diseases have been described in depth elsewhere [5-7]. In addition, the repeatability and accuracy of RNFL thickness measurements using SD-OCT have been widely recognized[8,9].

In the present study, we measured the retinal parameters of MS patients and age-matched controls using SD-OCT under free-living conditions, and assessed the association of retinal parameters and visual field parameters among MS patients. The purpose of this study was to provide a basis for defining the SD-OCT features of MS patients and promote the accurate diagnosis of MS.

SUBJECTS AND METHODS

Subjects Thirty MS patients (60 eyes) with a mean age of 58.00±9.24 years old and 28 healthy adults (56 eyes) with a mean age of 55.00 ±2.10 years old were enrolled in this study. The diagnosis of MS was made according to the diagnostic criteria for MS: 2010 Revisions to the McDonald Criteria [8]. A definite diagnosis of MS was made on all 30 patients by neurologists. Among these 60 eyes from MS patients, 41 eyes had suffered optic neuritis in which 12 eyes

had a relapse, while 19 eyes had never suffered optic neuritis. The 28 healthy volunteers met the following criteria: 1) the best corrected visual acuity (BCVA) of their eyes was ≥1.0; 2) intraocular pressure (IOP) measured by Goldmann applanation tonometry was ≤21 mm Hg; 3) high myopia was excluded; 4) there was no family history of glaucoma or other disorders of the inner eye and optic nerve. All subjects completed ocular examinations, including BCVA, refraction, IOP, gonioscopy, visual field, and indirect ophthalmoscopy. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, and informed consent was obtained from all subjects in this study according to the Delaration of Helsinki.

Methods

Optical coherence tomography measurements We applied Humphrey OCT (OCT-3000, Carl Zeiss) to detect the RNFL thickness and macular fovea thickness/volume. Before detection, the pupil was dilated to a diameter of approximately 5 mm using 1% tropicamide eye drops. Images were generated with a Zeiss OCT camera, which uses an internal fixation source and centers on the subject's fovea. Subjects stared at a point of fixation in the camera. We scanned the RNFL thickness around the optic disc using the fast RNFL thickness scanning mode; when a clear image was obtained, the results could be trusted. Three trusted images in every scan were stored, and the RNFL thickness was analyzed by the RNFL thickness program. The macular volume was measured by the fast macular thickness map scanning mode. The scanning center was the fovea and the scanning depth was 300 μm, with diameters of 1, 3, and 6 mm linear scanning. There were six radial linear sweeps, and the angle between each line was 30°. The mean macular volume was analyzed by the retinal thickness/volume analysis software provided with the instrument. All data were performed by the same operator under the same conditions.

Visual field measurements The visual field measurement was performed by the Humphrey Automatic Perimeter 30-2 full threshold test. Each subject was tested at least twice. Detection reliability was determined using the standard criteria of fixation loss rate (FL), false positive rate (FP), and false negative rate (FN) less than 25%. The mean deviation (MD) and corrected pattern standard deviation (PSD) of the visual field measurements were recorded.

Statistical Analysis We used SPSS 13.0 software to perform the statistical analysis. Comparison between the groups was performed using an independent sample *t*-test. We adopted Pearson correlation analysis to analyze the relationship among RNFL, macular parameters, and visual field measurements. We adopted the *t*-test to perform the gender comparison. A *P* value less than 0.05 was considered to be a statistically significant difference.

Table 1 Comparison of peripapillary RNFL thickness between multiple sclerosis patients and healthy controls

RNFL thickness (μm)	Controls	MS group
Superior quadrant	136.64±13.96	110.70±28.25[b]
Inferior quadrant	130.50±14.64	109.43±34.72[b]
Nasal quadrant	68.11±15.11	65.03±18.57[b]
Temporal quadrant	86.89±19.19	62.08±19.42[b]

RNFL: Retinal nerve fiber layer; MS: Multiple sclerosis; [b]$P<0.01$.

Table 2 Comparison of macular parameters between multiple sclerosis patients and healthy controls

Parameters	Controls	MS group
Macular volume (mm^3)	6.99±1.00[b]	6.97±0.42
Macular thickness (μm)	195.38±48.30[b]	179.82±31.76

[b]$P<0.01$.

Table 3 Relationship between the peripapillary RNFL thickness and the visual field

RNFL thickness (μm)	Mean deviation of visual field detection	Corrected pattern standard deviation of visual field detection
Superior quadrant	0.597[b]	-0.450[b]
Inferior quadrant	0.343[b]	-0.188[b]
Nasal quadrant	0.424[b]	-0.323[b]
Temporal quadrant	0.410[b]	-0.022

RNFL: Retinal nerve fiber layer; [b]$P<0.01$.

RESULTS

Among the 60 eyes from MS patients, 6 had mild refractive errors (-1.25 to +0.75 D) and the others had no ocular diseases. The BCVA was >1.0 in 1 eye, ranged between 1.0 and 0.3 in 20 eyes, ranged between 0.3 and 0.05 in 23 eyes, was <0.05 in 14 eyes, and there was no light perception in 2 eyes.

As shown in Table 1, the RNFL of the MS patients in each quadrant was thinner than that of the healthy controls.

Table 2 shows that the macular volume and foveal thickness of MS patients were both less than those of the controls. The relationship among measured RNFL values of MS patients in each quadrant and visual field parameters is shown in Table 3.

Correlation analysis indicated that there was a positive relationship between RNFL thickness and visual field among MS patients ($P<0.01$). However, there was no correlation between foveal thickness/macular volume and visual field among MS patients, as shown in Table 4. We also compared all parameters between eyes with and without optic neuritis. The macular volume, foveal thickness, and RNFL thickness in each quadrant were all greater in eyes without optic neuritis than in eyes with optic neuritis (Table 5).

DISCUSSION

In the current study, we found that the RNFL thickness and macular volume/thickness were all less than those parameters of healthy controls and that a positive correlation was found for the RNFL thickness and visual field of MS patients. This finding is interesting because it indicates that OCT plays an important role in assistance in making a correct MS diagnosis.

Table 4 Relationship between macular parameters and the visual field

Parameters	Mean deviation of visual field detection	Corrected pattern standard deviation of visual field detection
Macular volume (mm^3)	-0.114	-0.082
Macular thickness (μm)	-0.076	-0.009

Table 5 Comparison of macular parameters between patients with and without optic neuritis

Parameters (μm)	Patients with optic neuritis (n=41)	Patients without optic neuritis (n=19)
Macular volume (mm^3)	6.91±0.11	7.02±0.02[a]
Macular thickness	173.30±1.23	180.24±2.19[b]
Superior RNFL thickness	108.52±3.46	111.51±31.08[a]
Inferior RNFL thickness	107.95±12.28	110.26±11.21[b]
Nasal RNFL thickness	64.26±36.11	65.97±20.03[a]
Temporal RNFL thickness	60.27±5.71	64.01±36.71[a]

[a]P <0.05; [b]P <0.01.

MS is a chronic inflammatory and degenerative disease of the central nervous system that involves the white and gray matter pathways. Its diverse clinical manifestations include changes in vision, motor abilities, sensory organs, cognition, and emotion. MS has been considered primarily a demyelinating disease for a long time, but the relationship between axonal and neuronal pathology in MS and the final disability of MS patients makes axonal loss a main focus of research [1]. It can be expected in the early course of the disease that axons will be gradually lost. However, unfortunately, insufficient neuroscience testing and treatment usually lead to permanent disability in MS patients. Currently, magnetic resonance imaging technology is the primary method of detecting axonal loss of MS patients, but this technique in the diagnosis and monitoring of demyelinating disease has certain limitations. It has been shown previously that MS subtypes can be identified by evaluating the severity of RNFL thinning by OCT [10,11]. In particular, more severe retinal pathologies play an active role in promoting further changes in MS patients[12]. SD-OCT can provide high resolution characteristics of incised surface structures in living tissue. Therefore, we used this technology to perform imaging in the macular area of MS patients. We analyzed the change of macular thickness as well as the correlation between visual field and RNFL thickness and macular parameters in MS patients.

In addition, optic nerve demyelination and axonal degeneration have been recognized to occur in MS patients, especially those with optic neuritis [13]. Thus, it is very important to detect RNFL changes when MS occurs. The use of SD-OCT makes it possible to accurately measure RNFL thickness and macular volume. SD-OCT uses laser lower coherence interference measurements and can measure tissues and distances with a resolution of ≤10 μm. Currently, SD-OCT is the best method to measure RNFL thickness and macular parameters. It has been confirmed that the RNFL thickness is obviously thinner in glaucoma patients than in controls by OCT measurements [14,15]. Likewise, SD-OCT can also be used to help diagnose and evaluate nervous system diseases, especially MS-induced optic nerve damage. It has been reported that RNFL defects can be detected in the early stage of MS, even earlier than the changes of visual acuity and the optic disc [16,17]. Considering the measurement values obtained from SD-OCT are prone to be affected by the limited database sample, local race, age and gender, we have matched the age and gender of these subjects recruited in our study. Moreover, Gonzalez-Garcia *et al* [5] have investigated the repeatability of RNFL thickness by SD-OCT and proved the good repeatability of SD-OCT measurement. Therefore, we believe that SD-OCT can provide beneficial data for assistance in making a correct diagnosis and evaluating disease development by observing RNFL changes measured by SD-OCT.

As is well known, RNFL has a damage threshold of approximately 75 μm. If the axon loss reaches a certain level (damaged RNFL thickness >75 μm), the visual function will be reduced[18]. In the current study, we found that MS patients with a history of optic neuritis had a more obviously reduced RNFL thickness, although patients without a history of optic neuritis also had an abnormally reduced RNFL thickness. These results indicate that axonal loss can occur before the presence of clinical symptoms, which is likely to be an early manifestation of MS[19]. Our findings also confirmed that MS patients had a thinner RNFL thickness, which was consistent with the above-mentioned study.

Macular volume can reflect the integrity of retinal ganglion cells. Based on the study of Pulicken *et al* [20] and Kallenbach *et al* [21], 11% of MS patients with optic neuritis had a reduced macular volume compared with controls. In our study, we found that the macular parameters in MS patients were less than those in controls, and these parameters in eyes with optic neuritis were also less than in eyes without optic neuritis. The negative correlation between visual field and macular parameters may be explained by the fact that the macula is mainly responsible for central vision, while the visual field mainly reflects peripheral nerve function.

In summary, our study showed that SD-OCT may be a useful adjunct or a method to monitor possible progression of MS. In future work, we plan to conduct a study using larger sample sizes and perform regular follow-ups, which will contribute to a better understanding of RNFL thickness and macular parameters using SD-OCT in patients with MS.

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