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Clinical Study

Reduced retinal nerve fiber layer and macular thickness in patients with multiple sclerosis with no history of optic neuritis identified by the use of spectral domain high-definition optical coherence tomography

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ABSTRACT

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS), with both inflammatory and degenerative components. The visual system is frequently involved, often in the form of visual loss from optic neuritis (ON). Retinal nerve fiber layer (RNFL) loss has been demonstrated in individuals with MS, not only in those with previous ON but also in absence of historical evidence of previous acute inflammation/demyelination of the optic nerve. Peripapillary RNFL measurements of all quadrants, central macular thickness, and average macular thickness were performed in 32 eyes of healthy volunteers and 60 eyes of individuals with a diagnosis of relapsing remitting MS using high definition spectral domain optical coherence tomography (HD-OCT). Both the Macular Cube 512 × 128 scan and RNFL measurement by the Optic Disc Cube 200 × 200 protocol were performed on all eyes. Eyes of individuals with MS with no previous ON had significantly decreased overall RNFL thickness (89.1 μm) compared to controls (98.0 μm) ($p < 0.05$). MS mainly affected the temporal quadrant (56.6 μm *versus* [*vs.*] 67.8 μm) ($p < 0.05$), and inferior quadrant (117.9 μm *vs.* 132.1 μm) ($p < 0.05$), respectively. Also, the patients with MS demonstrated significantly decreased average macular thickness (280 μm) compared to the control group (287 μm) ($p < 0.05$). A significant correlation between RNFL and average macular thickness was also found in eyes of patients with MS ($r = 0.69$, $p < 0.01$). HD-OCT is a quick, inexpensive and promising tool to detect subclinical changes in RNFL and macular thickness in individuals with MS. Longitudinal studies should be encouraged to examine disease progression over time in individuals with MS.

1. Introduction

Multiple sclerosis (MS) is a chronic immune-mediated disease of the central nervous system (CNS) with both inflammatory and degenerative components. The visual system is frequently involved in MS, with more than 50% of individuals experiencing optic neuritis (ON) at some point during their disease.[1] Axonal loss of the anterior visual pathways is often a consequence of ON. It can be identified as thinning of the retinal nerve fiber layer (RNFL) through computerized imaging technologies such as optical coherence tomography (OCT).[2]

OCT is a non-invasive, simple-to-use, cost-effective tool, which provides *in vivo* cross-sectional images of the retina using the reflectivity of light waves. It can identify loss of the peripapillary RNFL, optic disc and macular thickness.[3] The RNFL corresponds to axons of the ganglion cells that converge to form the optic nerve. OCT is commonly used to evaluate a variety of ocular conditions including macular diseases, glaucoma and optic neuropathy.[4,5] Different from visual evoked potentials (VEP) that evaluate the functional integrity of the anterior visual pathway, OCT performs structural measurements of the retinal tissue, through high resolution images. The RNFL is an ideal location to evaluate neuronal loss – an important pathophysiologic component of disability in MS – as the axons of ganglion cells within the retina are not myelinated. This offers a way to measure the neuronal compartment exclusively, free of the thickness of myelin. The current OCT technology utilizes the spectral domain (SD), which offers improved reproducibility and accuracy over the previous time-domain modality. There are several different SD–OCT machines commercially available, such as RTVue (Optovue, Fremont, CA, USA), Spectralis OCT (Heidelberg Engineering, Dossenheim, Germany), and Cirrus SD–OCT (Carl Zeiss Meditec, Dublin, CA, USA). Due to differences in RNFL detection algorithms the results obtained through different

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SD–OCT instruments should not be used interchangeably.[6] MS has traditionally been evaluated by clinical parameters and brain MRI.[7] Studies in individuals with MS have shown a correlation between reduction of RNFL thickness and MRI documented brain atrophy[8,9] and also between RNFL thickness and level of disability measured by the Kurtzke's Expanded Disability Status Scale (EDSS) score.[8,10] This offers both structural CNS and functional associations to this retinal tissue change. A decrease in RNFL and macular thickness has been identified also in progressive types of MS to include both primary progressive MS and secondary progressive MS when compared to healthy controls.[11] RNFL thinning has also been documented in individuals with MS who have not experienced previous clinical episodes of ON,[11–14] suggesting other mechanisms of axonal loss. The objective of this study was to examine the RNFL, central macular thickness, and average macular thickness using Cirrus High Definition-OCT (Cirrus HD-OCT) in patients with MS without a history of ON and to compare them to those of healthy controls.

2. Methods

2.1. Participants

Patients from the MS Center of Oklahoma were recruited on the original day of their office visit and the testing was part of routine clinical assessments. All patients had a diagnosis of clinically definite MS using the McDonald diagnostic criteria[15] and had to be within the age range of 18 to 64 years of age. Healthy controls were recruited from Mercy Health Center and surrounding areas. Exclusion criteria included a history of neuromyelitis optica, ON, refractive errors of greater than ±5.0 diopters, coexisting ocular disease such as glaucoma, diabetes, and any other neurologic diseases. For the cohort with MS, an EDSS score of $\geqslant$5.0 was also exclusionary. All HD-OCT scans were performed by the same experienced technician. The protocol was reviewed and approved by the Institutional Review Board, and all participants had to sign an informed consent prior to participating in the study.

2.2. Research design

This study used a cross-sectional design with a control group (C, $n = 16$) and a group with MS (MS, $n = 30$), and all were assessed at one time point. Demographic data such as age, gender, and ethnicity were obtained during medical history questioning. Height and weight of all participants were measured from a stadiometer and a scale (Detecto scale, Cardinal Scale Manufacturing Company, Webb City, MO, USA). Body mass index (BMI) was calculated as weight (kg)/height squared (m^2).

2.3. Protocol of acquisition

All scans were performed on undilated pupils using the Cirrus HD-OCT (Model 4000) (Carl Zeiss Meditec, Dublin, CA, USA) for all measurements. This HD OCT obtains three-dimensional images, instead of two, due to the increased speed of 70 times faster than the conventional time-domain OCT, allowing for a larger set of actual data points and consequent accurate spatial correlations, and mapping of individual retinal layers over a larger area in a shorter time. All eyes had both Macular Cube 512 × 128 scan and RNFL measurement by the Optic Disc Cube 200 × 200 protocols done. Only scans that reached a signal strength of at least $\geqslant$6 (out of a maximum of 10), which indicate a high-quality scan, were accepted in the analyses. Peripapillary RNFL thickness was measured in each eye as an average (360°) and by quadrants (superior, nasal, inferior and temporal). Average and central macular thickness were also recorded for both right and left eyes.

2.4. Statistical analyses

The results of all descriptive analyses were reported as mean ± standard error for the group. The independent *t*-test was conducted to determine group differences for total RNFL thickness, RNFL by quadrants, average macular thickness, and central macular thickness. Analysis of covariance (ANCOVA), adjusting for age, was used to compare the two groups for total RNFL thickness, RNFL quadrants, average and central macular thickness. A Pearson product moment correlation coefficient was calculated to establish the correlation between RNFL and macular thickness. All statistical analysis was performed using the Statistical Package for the Social Sciences, version 16.0 (SPSS, Chicago, IL, USA). Statistical significance was defined as a p value <0.05.

3. Results

3.1. Participant characteristics

We studied 32 eyes of 16 normal participants and 60 eyes of 30 individuals with MS. The mean age was 32.7 ± 2.5 years and 42.2 ± 2.2 years respectively. All individuals in both cohorts were Caucasians. No statistically significant differences were found between the group with MS and control groups in terms of height (in centimeters), body weight (in kilograms), or body mass index (BMI) (kg/m^2) ($p > 0.05$). A significant difference in age was found between the two groups, with the group with MS being significantly older than the control group ($p < 0.05$) (Table 1).

Eyes of individuals with MS with no previous ON had a significantly decreased average RNFL thickness (89.1 μm) compared to controls (98.0 μm) ($p < 0.05$), (Fig. 1). When evaluated by sectors, the decrease in the RNFL was identified in the temporal quadrant (56.6 μm *versus* [*vs.*] 67.8 μm) ($p < 0.05$), and the inferior quadrant (117.9 μm vs. 132.1 μm) ($p < 0.05$) (Fig. 2). Also, the MS group demonstrated a significant decrease in the average macular thickness (280 μm) compared to the control group (287 μm) ($p < 0.05$), (Fig. 3). A significant correlation between RNFL and average macular thickness was also found in the eyes of patients with MS ($r = 0.70$, $p < 0.01$). After adjusting for age in the analysis, there still was a significant difference in average RNFL thickness, RNFL thickness in the temporal and inferior quadrants, and average macular thickness ($p < 0.05$) between the two groups.

4. Discussion

There is great need to identify objective, quantitative ways of evaluating disease progression in MS that have high sensitivity and good specificity. OCT is a non-invasive, easy-to-perform, relatively inexpensive procedure that has been correlated with brain atrophy by MRI and has the potential to identify structural

Table 1
Characteristics (mean ± standard error) of participants with or without multiple sclerosis (MS)

	MS ($n = 30$)	Controls ($n = 16$)
Age (years)	42 ± 2*	33 ± 3
Height (cm)	172 ± 0.1	170 ± 0.0
Weight (kg)	78 ± 3	74 ± 4
Body mass index (kg/m^2)	26 ± 1	25 ± 1
Ethnicity (Caucasian)	30 ± 0	16 ± 0

* Significantly different from control group ($p < 0.05$).