Original Article

Optical coherence tomography in multiple sclerosis

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic neurodegenerative disease that damages myelinated fibers within the central nervous system. Data obtained using optical coherence tomography (OCT) have recently been identified as a potential biomarker for this disease. We aimed to measure circumpapillary retinal nerve fiber layer thickness (cpRNFLT) using OCT and to compare the results in healthy participants with those of individuals having clinically definitive MS with and without a history of optic neuritis.

Methods: This cross-sectional study recruited patients with clinically confirmed MS, with and without optic neuritis, and healthy individuals as a control group. We documented demographic characteristics, duration of MS, and time elapsed since the episode of optic neuritis. All participants underwent a thorough ocular examination and measurement of total, superior, and inferior cpRNFLT using swept-source OCT.

Results: In participants with MS, women outnumbered men in the subsets with (90%) and without (64%) optic neuritis. The control group comprised approximately similar numbers of men and women. There was a statistically significant difference in total, superior, and inferior cpRNFLT between study groups (all $P < 0.001$). Pairwise comparisons revealed significantly thinner total, superior, and inferior cpRNFLTs in patients having MS with and without (all $P < 0.001$) optic neuritis when compared with the controls. We found significantly higher total, superior, and inferior cpRNFLTs in women than in men (all $P < 0.05$). However, we found no significant correlation between total, superior, or inferior cpRNFLT and patient age, duration of MS, or time elapsed since the optic neuritis episode (all $P > 0.05$), except for a significant moderate inverse correlation between patient age and total cpRNFLT ($r = -0.41$; $P < 0.05$), indicating a loss of total cpRNFLT with age.

Conclusions: Patients with clinically confirmed MS, with or without optic neuritis, had a significantly decreased cpRNFLT compared to that of healthy individuals. There was a significant inverse correlation between age and total cpRNFLT and a difference in cpRNFLT between the sexes, indicating that age and sex may influence the measurement of cpRNFLT using OCT in patients with MS. As a screening tool, OCT should be used along with other existing diagnostic modalities for patients with definite or suspected MS. Further longitudinal studies including various classifications of MS with or without isolated episodes of optic neuritis, along with diagnostic accuracy studies, could provide more robust conclusions on the suitability of OCT as a biomarker of MS.

KEYWORDS

optical coherence tomography, biomarker, disseminated sclerosis, disseminated sclerosis, ms (multiple sclerosis), optic neuritides, nerve fiber, healthy participants

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INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune neurodegenerative disease that damages myelinated fibers in the central nervous system (CNS) [1]. MS is the leading cause of non-traumatic permanent disability among young adults and predominantly affects female individuals [2, 3]. The prevalence of MS in Iran is 29.3 cases per 100 000 individuals [3]. The most common symptoms are painful monocular vision loss (due to optic neuritis), paresthesia, weakness, and developmental coordination disorder [4].

MS is characterized by demyelination and loss of axons, producing diffuse, multifocal lesions within the white matter of the CNS [5]. Although evidence indicates that axonal damage and loss is the primary cause of disability in the later phases of MS, the correlation between axonal damage and disability in the early phases of MS is less clear [6].

A history of optic neuritis must be thoroughly investigated in patients with MS, as it may have diagnostic implications [7]. However, establishing a history of optic neuritis using visual function testing may be difficult because patients with optic neuritis may experience a nearly full recovery of visual function. A robust diagnostic modality is required to reliably establish a history of optic neuritis [7]; however, magnetic resonance imaging is inadequate for detecting early axonal damage and loss. Thus, other methods that contribute to the early diagnosis of MS are needed [8].

Optical coherence tomography (OCT) is a novel technique recently introduced as a potential biomarker of diabetic macular edema [9] and MS [10]. It offers highly reliable, reproducible depictions of the CNS neuroaxonal structure that correlate well with disease severity and progression of MS. OCT contributes to the evaluation of neurodegeneration in MS primarily by detecting thinning of the retinal nerve fiber layer (RNFL) [10]. Baseline RNFL thickness may predict MS progression [11]. OCT can demonstrate changes in the RNFL thickness before visual field defects appear [12]. Studies have proposed using OCT data as a potential biomarker for the progression of MS and other neurodegenerative diseases, and for follow-up and evaluation of treatment response [13, 14].

This study aimed to measure circumpapillary RNFL thickness (cpRNFLT) using OCT and to compare results in healthy individuals with those of patients having MS with and without a history of optic neuritis.

METHODS

This observational, analytical, cross-sectional study recruited patients having clinically definitive MS with and without a history of optic neuritis, and a control group of healthy individuals, from those referred to Alavi Hospital, Ardabil University of Medical Sciences, from January 1, 2022, to January 1, 2023. The Ethics and Research Committee of the Faculty of Medical Sciences of the Azad University of Ardabil, Ardabil, Iran, provided ethical approval for the study (approval code: IR.IAU.ARDABIL.REC.1401.144). After reviewing all pertinent study information, each participant provided written informed consent for participation.

We excluded patients with a history of other optic nerve diseases such as glaucomatous optic disc or ischemic optic neuropathy; those with a history of trauma, intravitreal injections, vitreoretinal surgeries, and retinal or macular laser therapy; those with a history of any medical or ocular disease other than MS; those with prior use of ocular or systemic medications with possible side effects of optic neuropathy, such as steroids and anti-tuberculosis treatment; those with a significant media opacity that precluded the capture of clear images; and lactating or pregnant women. For the control group, we recruited heathy individuals with normal ocular examination findings. Finally, using a convenience sampling technique, we allocated participants to one of three groups: clinically confirmed MS and a history of optic neuritis, clinically confirmed MS and no history of optic neuritis, and healthy individuals.

We reviewed medical records of the included patients with clinically confirmed MS from the neurology clinic. According to a checklist prepared by the researchers, the data collected included demographic characteristics, duration of MS, and time elapsed since the optic neuritis episode. All participants underwent thorough ocular examinations including best-corrected distance visual acuity measurements using a Snellen chart (LC1300B; AnnoTek, Shiraz, Iran), intraocular pressure measurement using Goldmann applanation tonometry (AT900; Haag-Streit, Koeniz, Switzerland), anterior segment examination using a slit lamp (SL 3C slit lamp; Topcon Inc., Tokyo, Japan), and fundus examination under a slit lamp using a Volk 90 D lens (Volk Optical Inc., Mentor, OH, USA). The cpRNFLT was measured using swept-source OCT (SS-OCT) (DRI-OCT Triton; Topcon Inc.) [15].

Following instillation of 1% tropicamide (Mydrax; Sina Daru, Tehran, Iran) to achieve a minimum pupil diameter of 5 mm, a skilled technician conducted SS-OCT for all participants using a wide-field scan protocol

to image a 12-mm × 9-mm area of the posterior pole. We disregarded scans with low image quality or noticeable misalignment of the measurement circle position. We recorded total, superior, and inferior cpRNFLT for further analysis. These data were provided in a standard SS-OCT printout [16].

The data were analyzed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro – Wilk test. Further analysis was performed using the Mann – Whitney U test, Kruskal – Wallis H-test followed Dunn's post-hoc test with the Bonferroni correction, and Spearman's rank correlation when applicable. The results with *P*-values < 0.05 were considered statistically significant.

RESULTS

A total of 42 individuals with MS were included, along with 25 individuals in the control group. Among the patients with MS, 20 patients had a history of optic neuritis and 22 patients had no such history. Table 1 presents the demographic characteristics of the study groups. In participants with MS, women outnumbered men in the subsets with (90%) and without (64%) optic neuritis. The control group comprised approximately similar numbers of men and women (Table 1).

As presented in Table 2, there were statistically significant differences in total, superior, and inferior cpRNFLT between study groups (all $P < 0.001$). Pairwise comparisons revealed a significantly decreased total, superior, and inferior cpRNFLT in patients having MS with ($P < 0.001$) and without ($P < 0.001$) optic neuritis compared with the healthy control participants.

Table 3 displays the associations between total, superior, and inferior cpRNFLT and sex in all participants. Our results indicate a significantly higher total, superior, and inferior cpRNFLT in women than in men (all $P < 0.05$).

Table 1. Demographic characteristics of the study groups

Variable	Study group	Value
Sex (Men/Women), n (%)	**MS with optic neuritis**	2 (10) / 18 (90)
	MS without optic neuritis	8 (36) / 14 (64)
	Control	11 (44) /14 (56)
Age (y), Mean ± SD (Range)	**MS with optic neuritis**	37.5 ± 7.8 (24 to 56)
	MS without optic neuritis	33.1 ± 5.4 (26 to 42)
	Control	49.5 ± 13.3 (13 to 66)
Duration of MS (y), Mean ± SD (Range)	**MS with optic neuritis**	8.2 ± 4.8 (0.5 to 18)
	MS without optic neuritis	5.9 ± 3.5 (1 to 18)
Time elapsed since the optic neuritis episode (y), Mean ± SD (Range)	**MS with optic neuritis**	6.3 ± 4.9 (0.50 to 18)

Abbreviations: n, number of participants; %, percentage; MS, multiple sclerosis; y, years; SD, standard deviation.

Table 2. Differences in cpRNFLT between study groups

Variable	Study group	Median (IQR)	*P*-value
cpRNFLT, total (μm)	**MS with optic neuritis**	85 (14)	**< 0.001**
	MS without optic neuritis	106 (13)	
	Control	117 (13)	
cpRNFLT, superior (μm)	**MS with optic neuritis**	109 (25)	**< 0.001**
	MS without optic neuritis	131 (19)	
	Control	146 (19)	
cpRNFLT, inferior (μm)	**MS with optic neuritis**	114 (30)	**< 0.001**
	MS without optic neuritis	139 (22)	
	Control	145 (22)	

Abbreviations: cpRNFLT, circumpapillary retinal nerve fiber layer thickness; μm, micrometers; IQR, interquartile range. Note: *P*-values < 0.05 are shown in bold; The IQR is the difference between the first quartile (Q1, the 25th percentile) and the third quartile (Q3, the 75th percentile): IQR = Q3 – Q1.

Table 3. Associations between the cpRNFLT and sex

Variable	Sex	Median (IQR)	*P*-value
cpRNFLT, total (μm)	**Men**	111 (14)	**0.029**
	Women	118 (9)	
cpRNFLT, superior (μm)	**Men**	144 (17)	**0.040**
	Women	147 (21)	
cpRNFLT, inferior (μm)	**Men**	139 (16)	**0.043**
	Women	149 (25)	

Abbreviations: cpRNFLT, circumpapillary retinal nerve fiber layer thickness; μm, micrometers; IQR, interquartile range. Note: *P*-values < 0.05 are shown in bold; The IQR is the difference between the first quartile (Q1, the 25th percentile) and the third quartile (Q3, the 75th percentile): IQR = Q3 – Q1.

Table 4. Correlations between cpRNFLT and characteristics of MS

cpRNFLT (μm)		Variable		
		Age	**Duration of MS**	**Time elapsed since the optic neuritis episode**
cpRNFLT, total	**Correlation Coefficient**	r = - 0.41	r = - 0.29	r = - 0.03
	P-value	***P* = 0.003**	*P* = 0.063	*P* = 0.877
cpRNFLT, superior	**Correlation Coefficient**	r = - 0.27	r = - 0.12	r = - 0.18
	P-value	*P* = 0.058	*P* = 0.851	*P* = 0.392
cpRNFLT, inferior	**Correlation Coefficient**	r = - 0.24	r = - 0.15	r = - 0.04
	P-value	*P* = 0.095	*P* = 0.363	*P* = 0.863

Abbreviations: cpRNFLT, circumpapillary retinal nerve fiber layer thickness; μm, micrometers; MS, multiple sclerosis. Note: *P*-value < 0.05 is shown in bold.

Table 4 indicates that there were no significant correlations between total, superior, or inferior cpRNFLT and patient age, duration of MS, or time elapsed since the optic neuritis episode (all $P > 0.05$), except for a significant moderate inverse correlation between patient age and total cpRNFLT (r = -0.41; $P = 0.003$) (Table 4), indicating loss of total cpRNFLT with age.

DISCUSSION

We found a significantly decreased total, superior, and inferior cpRNFLT in individuals with clinically definitive MS, with or without optic neuritis, compared with measurements in healthy controls. The total cpRNFLT decreased with age. However, we observed no other significant correlations between superior, inferior, or total cpRNFLT with patient age, duration of MS, or time elapsed since the optic neuritis episode.

We found that the total cpRNFLT decreased with age in individuals with MS. In contrast to this finding, a study by Palazon-Cabanes et al. [17] on 300 eyes of 150 healthy men and 150 healthy women revealed no significant relationship between age and RNFL thickness [17]. In agreement with our results, Bendschneider et al. [18] observed a 1.90-μm mean decrease in RNFL thickness with each decade of life [18]. Budenz et al. [19] reported that each 10-year increase in age was associated with an approximately 2.0-μm decrease in the mean RNFL thickness [19]. Thus, our observed correlation may be related to age rather than MS. Further studies are needed to clarify this possibility.

In this study, the total, superior, and inferior cpRNFLT were significantly higher in women than in men. Regarding this relationship, prior reports are contradictory. For example, Palazon-Cabanes et al. [17] found no significant correlation between the RNFL thickness and sex, as did Mauschitz et al. [20], Invernizzi et al. [21], and Budenz et al. [19]. However, Wang et al. [22] demonstrated an overall decreased RNFL thickness in boys [22]. This discrepancy between studies could be due to differences in sample size, age or ethnicity of participants, or other undiscovered confounders.

We observed no correlations between total, superior, or inferior cpRNFLT and the mean duration of MS. Khanifar et al. [23] studied 95 eyes of patients with MS and found a significantly lower mean RNFL thickness in patients with disease of > 60 months duration than in those with disease duration < 13 months. However, RNFL thicknesses were comparable in individuals with disease durations of 13 – 60 months and < 13 months [23]. Al-Hawasi [24] reported that RNFL thinning in patients with the benign form of MS, but not in those with

relapsing-remitting MS, had no significant correlation with disease duration [24]. However, Eslami et al. [25] studied 240 eyes of 120 patients with MS and found no significant differences in RNFL thickness between the subtypes of MS [25]. Garcia et al. [12] found that average RNFL thickness correlated with duration of MS and history of an optic neuritis episode [12]. These results suggest that severity and type of MS could significantly affect the correlation between RNFL thickness and disease duration. Thus, our results should be interpreted judiciously.

We analyzed two subgroups of patients having clinically confirmed MS—with versus without a history of optic neuritis—to investigate the effect of optic neuritis on cpRNFLT. Pairwise comparisons indicated no significant differences in total, superior, or inferior cpRNFLT between the subgroups; however, both demonstrated a significantly lower cpRNFLT when compared with healthy individuals. Al-Mujaini et al. [1] found that patients with MS and prior optic neuritis had greater RNFL thinning compared to those without prior optic neuritis. However, they found no significant difference in mean RNFL thickness between the groups [1]. As observed in our study, their patients with and without optic neuritis had a significant reduction in RNFL thickness over time compared to the control group [1]. Garcia-Martin et al. [12] found a significant decrease in RNFL thickness in patients having MS without a visual history compared to controls [12].

We found no significant correlation between the time elapsed since the optic neuritis episode and total, superior, or inferior cpRNFLT. Garcia-Martin et al. [26] measured the RNFLT of patients with MS annually for 5 years and observed progressive axonal loss and RNFL thinning [26]. In a longitudinal study, they noted a greater RNFLT decrease in eyes of patients having MS with or without prior optic neuritis than in eyes of healthy individuals [26]. Likewise, we found a significantly decreased total, superior, and inferior cpRNFLT in patients with or without optic neuritis compared to that of healthy controls. However, Balk et al. [27] reported no association between the number of optic neuritis episodes and the RNFL thickness. They observed a similar longitudinal change in cpRNFLT in patients with and without MS-related optic neuritis [27]. We observed no significant differences in total, superior, or inferior cpRNFLT in pairwise comparisons between participants with and without optic neuritis. Eyre et al. [28] found no significant correlation between the number of optic neuritis episodes and mean RNFL in patients with MS [28].

We included patients having clinically confirmed MS with and without a history of optic neuritis to analyze the structural optic nerve changes induced by optic neuritis. However, the study is limited by a small sample size and lack of longitudinal assessments. Moreover, we failed to include functional optic nerve assessments such as perimetry measurements [29] with the structural evaluations. Measuring both functional and structural changes could provide more evidence supporting cpRNFLT as a biomarker in patients with MS. Further studies addressing our limitations are necessary to investigate the performance of OCT as a biomarker for diagnosing and monitoring MS in clinical practice.

CONCLUSIONS

Patients having clinically confirmed MS with and without optic neuritis had significantly decreased cpRNFLT compared to that of healthy individuals. We found a significant inverse correlation between age and total cpRNFLT, along with sex-related differences in cpRNFLT, indicating that age and sex may influence the measurement of cpRNFLT using OCT. Considering the factors other than MS that influence cpRNFLT, we believe that OCT can serve as a screening tool along with other existing diagnostic modalities for patients with definite or suspected MS. Further longitudinal studies including various classifications of MS with or without isolated episodes of optic neuritis, along with diagnostic accuracy studies, could provide more robust conclusions regarding the suitability of OCT as a biomarker in patients with MS.

ETHICAL DECLARATIONS

Ethical approval: The Ethics and Research Committee of the Faculty of Medical Sciences of the Azad University of Ardabil, Ardabil, Iran, provided ethical approval for the study (approval code: IR.IAU.ARDABIL.REC.1401.144). After reviewing all pertinent study information, each participant provided written informed consent for participation.

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