Original Article

Comparison of Peripapillary Retinal Nerve Fiber Layer Thickness in Patients with MS and Normal Population

Nahid Beladimoghadam [1], MD; Morteza Entezari *[2], MD ; Mostafa Asadollahi [1], MD; Mohammadhasan Seifi [2], MD; Maryam Nazari [1] MD; Soheil Naderi [3], MD; Mehdi Yaseri [4], PhD

1. Ophthalmic Research Center, Department of Neurology, Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Ophthalmic Research Center, Department of Ophthalmology, Imam Hossein Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3.Tehran University of Medical Sciences, Tehran, Iran.
4. Department of Epidemiology and Biostatistics, Tehran University of Medical Sciences, Tehran, Iran.

Corresponding Author: Morteza Entezari

Email: morteza_entezari@sbmu.ac.ir

Article Notes:

Received: May. 27, 2017
Received in revised form: Jul. 29, 2017
Accepted: Sep. 8, 2017
Available Online: Sep. 30,2017

Keywords:

Multiple sclerosis
Tomography
Optical Coherence
Optic Neuritis
Retinal
Nerve Fibers

Abstract

Purpose: To compare peripapillary retinal nerve fiber layer thickness (RNFLT) between patients with multiple sclerosis (MS) and healthy controls using optical coherence tomography (OCT).

Patients and Methods: In this prospective case control study, peripapillary RNFLT of 120 eyes from 60 patients with multiple sclerosis (MS) was compared to 120 eyes from 60 age and sex matched healthy controls using OCT. The RNFLT in 4 peripapillary quadrants and the mean RNFLT of all four quadrants were compared between the case and control groups. The relation between MS variables such as age of onset, type and duration of disease, history of optic neuritis (ON) and other non-ocular episodes with RNFLT was evaluated in the case group.

Results: The mean RNFLT of all four quarters was significantly lower in patients with MS compared to the controls ($P < 0.001$). Also RNFLT was significantly lower in each of 4 quadrants (superior, temporal, inferior; $P < 0.001$, nasal $P = 0.003$). There was no significant relation between RNFLT, the age of onset of MS disease, and history of non-ocular episodes. RNFLT had a significant relation with duration of the disease ($P < 0.001$), the type of MS ($P < 0.001$), history of ON ($P = 0.002$), and the number of ON episodes ($P = 0.021$).

Conclusion: We found that RNFLT decreases in MS patients and its reduction is related to the duration and type of disease as well as history and number of ON episodes. Therefore measuring RNFLT may help in estimating the progress of MS and can potentially be included as a part of patients' follow up protocol.

How to cite this article: Beladimoghadam N, Entezari M, Asadollahi M, Seifi MH, Nazari M, Naderi S, Yaseri M. Comparison of Peripapillary Retinal Nerve Fiber Layer Thickness in Patients with MS and Normal Population. Journal of Ophthalmic and Optometric Sciences. 2017;1(5):23-30.

Introduction

Multiple sclerosis (MS) is a primary demyelinating disease of the central nervous system (CNS) with a variety of clinical presentations. While myelin damage is the hallmark of MS, axonal degeneration is the final pathologic process, which leads to irreversible disabilities [1]. Therefore, evaluation of CNS axonal function is of value for assessment of the course of the disease and prognosis among MS patients.

Retinal nerve fiber layer (RNFL), which is the unmyelinated extension of the optic nerve, represents a part of CNS and the thickness of this layer is associated with changes in CNS axonal function [2-4]. Optical coherence tomography (OCT) is a noninvasive imaging technique that provides high-resolution cross-sectional images of the retina and automatic measurement of retinal thickness as well as retinal nerve fiber layer thickness (RNFLT). Because retina contains axons and glia without myelin and originates from CNS, RNFLT is valued as a sensitive and also non-invasive quantification of neurodegeneration and is used in evaluation of neurological disorders especially MS [3-6]. OCT was initially used for assessing changes in glaucoma and macular disorders [6], but at present it is used in evaluating neurological disorders such as MS [5, 7-11], Alzheimer's disease [12], Parkinson's disease [13], schizophrenia [14], and bipolar disease [15]. OCT measurements of RNFLT have also provided a window to follow the CNS axonal and neuronal loss in MS patients [2,16,17].

In the present study, we compared peripapillary RNFLT between patients with MS and healthy controls using optical coherence tomography (OCT) to evaluate the use of OCT as a monitoring tool of disease progression.

Patients and Methods

This prospective case-control study was carried out from July 2012 to December 2015. Sixty patients with diagnosis of MS were recruited from the neurology clinic of Imam Hossein Medical Center, Tehran, Iran, and entered the study as the case group. Also 60 controls were recruited from the healthy persons accompanying the patients in outpatient ophthalmology ward of the same hospital. The protocol was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran, and the study followed the tenets of the Declaration of Helsinki. Informed written consent was obtained from all participants prior to entering the study.

All patients with a history of neurologic and systemic diseases other than MS were excluded from the present study. Other exclusion criteria were significant refractive error, abnormal IOP, history of amblyopia, history of any retinal pathology other than MS, and corneal haziness. Also to eliminate the effect of acute inflammatory process on RNFLT, patients were excluded if less than 3 months had passed from their last optic neuritis (ON) attack.

The patients with MS underwent a complete neurological examination and definite MS diagnosis was based on McDonald criteria [18]. Variables such as age of onset, type of disease and its duration as well as history of ON and other non-ocular episodes were recorded for all patients with MS entering the study. ON was diagnosed based on precise history taking or documented previous examinations. Also the cases and controls underwent a complete ophthalmologic examination, including assessment of best-corrected visual acuity (BCVA), intraocular pressure (IOP) measurement, slit lamp biomicroscopy, and dilated fundus examination. Measurement of peripapillary RNFLT was performed for all participants in the study using OCT

(3D OCT-1000, Topcon Corporation, Tokyo, Japan) method. OCT was performed by an experienced optometrist who was masked to the participants' diagnosis. Scans with a quality factor lower than 60 and blinking during the scanning process were excluded. OCT was performed for every eye in a 3.4 mm wide circle around the optic disc in four superior, temporal, inferior and nasal quadrants. The thickness of each quadrant and the mean thickness of all four quadrants were used for analysis.

Statistical method

To present data, we used mean, standard deviation, median, range, percent and frequency. To compare the characteristics of the case and control groups we used t-test and Chi-Square test. To compare the RNFLT between the study groups we used generalized estimating equation (GEE) analysis. Also another GEE model was used to compare the groups adjusted for the age and gender. All statistical analysis was performed using SPSS Version 22 (Armonk, NY: IBM Corp.). All tests were two sided and a P value of less than 0.05 was considered statistically significant.

Results

In this prospective comparative case control study, we compared 120 eyes of 60 patients with diagnosis of MS to 120 eyes of 60 age and sex matched healthy individuals. The mean age of participants was 33 ± 10 and 34 ± 10 years in the case and control groups respectively. Ninety percent of both groups were female and 10 % were male (Table 1). Thirty six (60 %) MS patients had a disease duration of more than five years and only 7 (11.7 %) had disease duration of less than one year. Also sixty three percent of MS patients had a history of at least one ON attack with thirteen cases (21.7 %) experiencing ON in both eyes (Table 2).

The mean RNFLT of four quadrants was significantly lower in cases (90 ± 12 μm) compared to the controls (102 ± 9 μm) ($P < 0.001$) (Table 3). Also the mean RNFLT in each individual quadrant was significantly lower among cases in comparison to the controls (superior, temporal, inferior; $P < 0.001$, nasal $P = 0.003$) (Table 3).

Table 1: Demographic characteristics of participants in the case and control groups

Parameter		Total	Groups		P value
			MS	Control	
Age	Mean ± SD	33 ± 10	33 ± 10	34 ± 10	0.859*
	Median (range)	31 (15 to 68)	33 (19 to 68)	31 (15 to 57)	
	≤ 30	112 (46.7 %)	56 (46.7 %)	56 (46.7 %)	
	31-45	92 (38.3 %)	46 (38.3 %)	46 (38.3 %)	
	≥ 46	36 (15.0 %)	18 (15.0 %)	18 (15.0 %)	
Sex	Female	216 (90.0 %)	108 (90.0 %)	108 (90.0 %)	1†
	Male	24 (10.0 %)	12 (10.0 %)	12 (10.0 %)	

* Based on t-test.

† Based on Chi-square test.

Table 2: Disease variables among patients with MS

Parameter		
Age of onset	Mean ± SD	27 ± 9
	Median (range)	26 (16 to 55)
	≤ 25	30 (50.0 %)
	26-40	25 (41.7 %)
	≥ 41	5 (8.3 %)
Duration	Less than 1 year	7 (11.7 %)
	1-5 year	17 (28.3 %)
	More than 5	36 (60.0 %)
MS Type*	RRMS	51 (85.0 %)
	PPMS	5 (8.3 %)
	SPMS	2 (3.3 %)
	PRMS	2 (3.3 %)
Non-Ocular Episodes	Mean ± SD	2.3 ± 2.7
	Median (range)	1 (0 to 15)
Number	0	11 (18.3 %)
	1	21 (35.0 %)
	2 - 4	19 (31.7 %)
	≥ 5	9 (15.0 %)
Ocular Episodes (ON)	Mean ± SD	0.9 ± 1.1
	Median (range)	1 (0 to 7)
Number	0	22 (36.7 %)
	1	30 (50.0 %)
	≥ 2	8 (13.3 %)
Medicine	Rebif	8 (13.3 %)
	ReciGen	0 (0.0 %)
	Avonex	4 (6.7 %)
	CinnoVex	20 (33.3 %)
	Betaferon	9 (15.0 %)
	Others	10 (16.7 %)
	None	9 (15.0 %)
BCVA LogMAR	Mean ± SD	0.01 ± 0.03
	Median (range)	0 (0 to 0.2)
	10/10	75 (84.3 %)
	< 10/10	14 (15.7 %)

RRMS: Relapsing remitting multiple sclerosis
PPMS: Primary progressive multiple sclerosis
SPMS: Secondary progressive multiple sclerosis
PRMS: Progressive relapsing multiple sclerosis

There was no statically significant relation between RNFLT and the age of onset of MS disease (0.155) (Table 4). RNFLT had a statistically significant relation with the duration of the disease and patients with disease duration of more than 1 year had thinner RNFLT than those with disease duration of less than one year ($P < 0.001$) (Table 4). Also patients with secondary progressive MS had thinner RNFLT compared to those with other types of the disease ($P < 0.001$) (Table 4). Cases with a history of ON had thinner RNFLT (90 ± 13 µm) compared to those without a history of ON (95 ± 11 µm) ($P = 0.002$), and the number of ON episodes also showed a statistically significant relation with RNFLT ($P = 0.021$) (Table 4). Twenty three cases (38.3 %) had ON only in one eye. Among these patients the mean RNFLT was 83 ±12 µm for affected eye versus 97 ± 10 µm for the unaffected eyes ($P < 0.001$) (Table 4). No significant relation was observed between RNLFT and non-ocular episodes ($P = 0.286$) (Table 4).

Discussion

Evaluation of patients with demyelinating disease requires a reliable and sensitive imaging technique to investigate specific pathologic changes of the CNS [19]. These patients are routinely followed by size and number of the lesions in brain and spinal cord MRI, but there is no absolute correlation between disease severity and the extent of these lesions [11]. Therefore MRI is not necessarily an appropriate tool for patients follow up and prediction of disease progress [11]. Optic nerve involvement in form of ON is a common presentation of demyelinating diseases which occurs in 30-70 % of MS patients and may affect RNFLT [12,13]. Therefore assessment of RNFLT may provide useful information about

Table 3: Comparison of RNFLT between the case and control groups

Quadrant		Total	Groups		P value*	P value**
			MS	Control		
Superior	Mean ± SD	118 ± 18	111 ± 18	124 ± 14	0.000	< 0.001
	Median (range)	119 (56 to 162)	115 (56 to 143)	123 (84 to 162)		
Nasal	Mean ± SD	80 ± 16	76 ± 15	83 ± 16	0.004	0.003
	Median (range)	79 (33 to 146)	75 (33 to 116)	82 (52 to 146)		
Inferior	Mean ± SD	118 ± 19	108 ± 18	127 ± 14	0.000	< 0.001
	Median (range)	120 (54 to 155)	110 (54 to 147)	129 (95 to 155)		
Temporal	Mean ± SD	68 ± 13	64 ± 14	73 ± 11	0.000	< 0.001
	Median (range)	68 (34 to 99)	62 (34 to 99)	71 (55 to 99)		
The Mean of all four quadrants	Mean ± SD	96 ± 12	90 ± 12	102 ± 9	0.000	< 0.001
	Median (range)	97 (60 to 134)	92 (60 to 114)	102 (80 to 134)		

* Based on GEE analysis

** Adjusted for age and sex, based on GEE analysis

CNS axonal damage and has the potential to become a practical means of evaluating MS progression [7,8]. RNFLT can be directly visualized using OCT which is a noninvasive, convenient, fast, and precise technique.

According to the results of the present study, MS patients, with or without a history of ON, had significant thinning of RNFL measured by OCT compared to normal individuals. Patients with disease duration of 1 to 5 years showed more thinning of RNFL compared to those patients with disease duration of less than one year. Patients with history of ON had significantly thinner RNFL compared to those without ON episodes and RNFLT also correlated with the number of ON episodes. In addition, patients with a history ON in one eye had thinner RNFL in the affected eye compared to unaffected eye. Finally patients with secondary progressive MS had thinner RNFLT compared to those with other types of the disease.

Similar to our findings some previous studies have shown that subclinical RNFL thinning occurs in MS [21]. Frohman et al., [3] found that there is a strong association between RNFLT and low contrast visual acuity in MS [3]. Spain et al., [20] found an association between MS duration with both RNFLT and the expanded disability status scale (EDSS), but the relation was not statistically significant. In another study by Singer et al., [22] the mean RNFL thickness in MS patients was lower than normal controls and the degree of RNFL thinning was related to the amount of lesions detected in MRI T1 sequence. They also reported that RNFLT was

Table 4: The relation between MS variables and RNFLT

Parameter		Superior		Nasal		Inferior		Temporal		Mean of Four Quadrants	
		Mean ± SD	P value*	Mean ± SD	P value*	Mean ± SD	P value*	Mean ± SD	P value*	Mean ± SD	P value*
Age of Onset	<= 25	109 ± 20	0.235	79 ± 15	0.171	106 ± 19	0.482	63 ± 14	0.336	89 ± 14	0.155
	26-40	116 ± 17		85 ± 12		111 ± 13		65 ± 13		94 ± 10	
	41+	118 ± 11		80 ± 14		106 ± 18		67 ± 19		93 ± 14	
Duration	less than 1 year	128 ± 8	0.004	91 ± 12	0.009	118 ± 12	0.153	74 ± 11	0.007	103 ± 6	< 0.001
	1-5 year	114 ± 18		79 ± 13		109 ± 15		61 ± 12		91 ± 12	
	more than 5	109 ± 19		81 ± 14		106 ± 18		64 ± 15		90 ± 13	
MS Types†	RRMS	113 ± 18	0.297	81 ± 14	0.545	108 ± 16	< 0.001	65 ± 14	< 0.001	92 ± 13	< 0.001
	PPMS	120 ± 20		84 ± 15		112 ± 15		68 ± 10		96 ± 14	
	SPMS	89 ± 27		77 ± 4		88 ± 25		50 ± 10		76 ± 16	
	PRMS	116 ± 11		80 ± 7		110 ± 16		52 ± 5		89 ± 10	
History of Optic Neuritis	Yes	110 ± 19	0.011	80 ± 14	0.004	106 ± 18	0.016	62 ± 14	0.035	90 ± 13	0.002
	No	118 ± 17		83 ± 14		112 ± 13		68 ± 14		95 ± 11	
Eye Involvement in the same Patient	Not Involved Eye	120 ± 14	< 0.001	85 ± 13	0.001	114 ± 13	< 0.001	69 ± 13	< 0.001	97 ± 10	< 0.001
	Involved Eye	101 ± 19		75 ± 11		98 ± 18		57 ± 12		83 ± 12	
Number of Ocular Episodes	0	118 ± 17	0.158	83 ± 14	0.012	112 ± 13	0.037	68 ± 14	0.378	95 ± 11	0.021
	1	112 ± 20		82 ± 15		107 ± 18		64 ± 14		91 ± 13	
	2+	104 ± 18		76 ± 7		100 ± 18		55 ± 13		84 ± 12	
Non-ocular Episodes	No	116 ± 14	0.069	76 ± 12	0.864	112 ± 20	0.472	67 ± 14	0.358	93 ± 11	0.286
	Yes	109 ± 18		76 ± 15		108 ± 18		64 ± 14		89 ± 13	

*Based on GEE analysis. † RRMS: Relapsing remitting multiple sclerosis, PPMS: Primary progressive multiple sclerosis, SPMS: Secondary progressive multiple sclerosis, PRMS: Progressive with relapsing multiple sclerosis

significantly associated with disease duration and EDSS score [21]. Feng et al., [22] evaluated peripapillary RNFL thickness in 12 MS patients and compared it to healthy individuals using high quality spectral-domain OCT. They concluded that the mean RNFLT was significantly lower in patients with MS compared to controls. Also MS patients with ON had significantly thinner RNFL compared to those without ON.

Conclusion

We found that RNFLT decreases in MS patients and its reduction is related to the duration and type of disease as well as history and number of ON episodes. Therefore measuring RNFLT may help in estimating the progress of MS and can potentially be included as a part of patients' follow up protocol.

References

1. Bitsch A, Schuchardt J, Bunkowski S, Kuhlmann T, Brück W. Acute axonal injury in multiple sclerosis. Correlation with demyelination and inflammation. Brain. 2000;123(Pt 6):1174-83.

2. Costello F, Coupland S, Hodge W, Lorello GR, Koroluk J, Pan YI, et al. Quantifying axonal loss after optic neuritis with optical coherence tomography. Ann Neurol. 2006;59(6):963-9.

3. Frohman E, Costello F, Zivadinov R, Stuve O, Conger A, Winslow H, et al. Optical coherence tomography in multiple sclerosis. Lancet Neurol. 2006;5(10):853-63.

4. Ogden TE. Nerve fiber layer of the primate retina: thickness and glial content. Vision Res. 1983;23(6):581-7.

5. Frohman EM, Fujimoto JG, Frohman TC, Calabresi PA, Cutter G, Balcer LJ. Optical coherence tomography: a window into the mechanisms of multiple sclerosis. Nat Clin Pract Neurol. 2008;4(12):664-75.

6. Bock M, Paul F, Dörr J. Diagnosis and monitoring of multiple sclerosis: the value of optical coherence tomography. Nervenarzt. 2013;84(4):483-92. (Article in German)

7. Hassenstein A, Spital G, Scholz F, Henschel A, Richard G, Pauleikhoff D. Optical coherence tomography for macula diagnostics. Review of methods and standardized application concentrating on diagnostic and therapy control of age-related macula degeneration. Ophthalmologe. 2009;106(2):116-26. (Article in German)

8. Sergott RC, Frohman E, Glanzman R, Al-Sabbagh A; OCT in MS Expert Panel. The role of optical coherence tomography in multiple sclerosis: expert panel consensus. J Neurol Sci. 2007;263(1-2):3-14.

9. Sepulcre J, Murie-Fernandez M, Salinas-Alaman A, García-Layana A, Bejarano B, Villoslada P. Diagnostic accuracy of retinal abnormalities in predicting disease activity in MS. Neurology. 2007;68(18):1488-94.

10. Henderson AP, Trip SA, Schlottmann PG, Altmann DR, Garway-Heath DF, Plant GT, An investigation of the retinal nerve fibre layer in progressive multiple sclerosis using optical coherence tomography. Brain. 2008;131(Pt 1):277-87.

11. De Stefano N, Matthews PM, Fu L, Narayanan S, Stanley J, Francis GS, et al. Axonal damage correlates with disability in patients with relapsing-remitting multiple sclerosis. Results of a longitudinal magnetic resonance spectroscopy study. Brain. 1998;121(Pt8):1469-77.

12. Parisi V, Restuccia R, Fattapposta F, Mina C, Bucci MG, Pierelli F. Morphological and functional retinal impairment in Alzheimer›s disease patients. Clin Neurophysiol. 2001;112(10):1860-7.

13. Inzelberg R, Ramirez JA, Nisipeanu P, Ophir A. Retinal nerve fiber layer thinning in Parkinson disease. Vision Res. 2004;44(24):2793-7.

14. Ascaso FJ, Rodriguez-Jimenez R, Cabezón L, López-Antón R, Santabárbara J, De la Cámara C, et al. Retinal nerve fiber layer and macular thickness in patients with schizophrenia: Influence of recent illness episodes. Psychiatry Res. 2015;229(1-2):230-6.

15. Mehraban A, Samimi SM, Entezari M, Seifi MH, Nazari M, Yaseri M. Peripapillary retinal nerve fiber layer thickness in bipolar disorder. Graefes Arch Clin Exp Ophthalmol. 2016;254(2):365-71.
16. Trip SA, Schlottmann PG, Jones SJ, Altmann DR, Garway-Heath DF, Thompson AJ, et al. Retinal nerve fiber layer axonal loss and visual dysfunction in optic neuritis. Ann Neurol. 2005;58(3):383-91.
17. Huynh SC, Wang XY, Burlutsky G, Rochtchina E, Stapleton F, Mitchell P. Retinal and optic disc findings in adolescence: a population-based OCT study. Invest Ophthalmol Vis Sci. 2008;49(10):4328-35.
18. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol. 2005;58(6):840-6.
19. Henderson AP, Trip SA, Schlottmann PG, Altmann DR, Garway-Heath DF, Plant GT, et al. An investigation of the retinal nerve fibre layer in progressive multiple sclerosis using optical coherence tomography. Brain. 2008;131(Pt 1):277-87.
20. Spain RI, Maltenfort M, Sergott RC, Leist TP. Thickness of retinal nerve fiber layer correlates with disease duration in parallel with corticospinal tract dysfunction in untreated multiple sclerosis. J Rehabil Res Dev. 2009;46(5):633-42.
21. Singer AJ, Wang Z, McClain SA, Pan Y. Optical coherence tomography: a noninvasive method to assess wound reepithelialization. Acad Emerg Med. 2007;14(5):387-91.
22. Feng L, Shen J, Jin X, Li J, Li Y. The evaluation of the retinal nerve fiber layer in multiple sclerosis with special-domain optical coherence tomography. Ophthalmologica. 2013;230(3):116-20.

Footnotes and Financial Disclosures

Conflict of interest:

The authors have no conflict of interest with the subject matter of the present study.