Findings of Optical Coherence Tomography of Retinal Nerve Fiber Layer in Two Common Types of Multiple Sclerosis

Gholamali Yousefipour[1], Zabihollah Hashemzahi[2], Masood Yasemi[3], and Pegah Jahani[4]

[1]Department of Neurology Sciences, Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[2]Department of Neurology Sciences, Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[3]Department of Ophthalmology, Poostchi Eye Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[4]Department of Medicine, Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran

Received: 12 Sep. 2015; Accepted: 28 Feb. 2016

Abstract- Multiple sclerosis (MS) is the most prevalent disease caused by the inflammatory demyelinating process that causes progressive nervous system degeneration over the time. Optical Coherence Tomography (OCT) is a non-invasive optical imaging technology, which can measure the thickness of retinal nerve fiber layer as well as the diameter of the macula. The purpose of the study is evaluation OCT findings in two common types of multiple sclerosis. For doing the cross-sectional study, 63 patients with two prevalent types of multiple sclerosis (35 patients with Relapse Remitting Multiple Sclerosis (RRMS) and 28 patients with Secondary Progressive Multiple Sclerosis (SPMS) were evaluated for 6 months. Exclusion criteria of the study were a history of optic neuritis, suffering from diabetes mellitus, hypertension, ocular disease, and the presence of other neurologic degenerative diseases. Then, the thickness of retinal nerve fiber layer (RNFL), as well as thickness and volume of the macula, were measured in the patients using OCT technology. The disability rate of patients was evaluated according to Expanded Disability Status Scale (EDSS). Finally, data was analyzed by means of SPSS software. Overall, 35 patients with RRMS (with mean age of 32.37+10.01, average disease period of 3.81+3.42 and mean EDSS of 1.84+0.45) and 28 patients with SPMS (with mean age of 39.21+9.33, average disease period of 11.32+5.87 and mean EDSS of 5.12+1.46) were assessed and compared in terms of retinal nerve fiber layer and size and thickness of macula. In all of these sections, the thicknesses were smaller in SPMS patients than patients with RRMS. But, there was a significant difference in total thickness (81.82µm versus 96.03µm with *P*=0.04) and thickness of temporal sector (54.5 µm versus 69.34 µm with *P*=0.04) of retinal nerve fiber layer and macular size at the superior sector of external ring (1.48 mm^3 versus 1.58 mm^3 with *P*=0.03), and nasal sector of external ring surrounding macula (1.53 mm^3 versus 1.66 mm^3 with *P*=0.03). No significant correlation was found among rising disability and reduced thickness of macula and optic nervous layer. Based on the study results, it can be said that OCT is a useful method for showing axonal degeneration severity and evaluation of various drugs effects on the course of MS disease, and thus we can change drugs based on OCT findings for achieving best results.

Acta Med Iran, 2016;54(6):382-390.

Keywords: OCT; Multiple sclerosis; Multiple sclerosis; Chronic progressive

Introduction

Multiple Sclerosis (MS) is one of the most common diseases caused by the inflammatory demyelinating process (1) that seems to be an immune-mediated disorder in Central Nervous System (CNS) (2,3). This chronic, progressive and degenerative disease of the CNS system is characterized by small demyelinating plaques in the brain and spinal cord, and it also leads to progressive degeneration of axons and loss of the neurons (4). This Progressive degeneration of neurons over the time has brought this disease as one of the most common causes of acquired neurologic disability (5).

In most of the patients, MS is presented with Relapse-Remitting courses (Relapse Remitting multiple sclerosis RRMS) and many of these patients later

Corresponding Author: Z. Hashemzahi
Department of Neurology Sciences, Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
Tel: +98 915 1493279, Fax: +98 71 36121065, E-mail address: zabih1966@yahoo.com

progress to Secondary Progressive Multiple Sclerosis (SPMS) 6).

Progression rate of the disease varies (7). A disability scale which is frequently employed in the study of disability among the patients is "Expanded Disability Status Scale" (EDSS) that is graded from zero for normal neurological examination and functions to ten for mortality caused by disease (1).

Etiology of MS disease is unknown (8,9). It has been referred to autoimmune and infectious mechanisms in its pathogenesis that eventually characterized by demyelination, gliosis, axonal damage and degeneration of neurons in the brain and spinal cord (10). Degeneration of neurons and axons are considered as the important presentation of multiple sclerosis that involves anterior optical pathway (11). Retinal Nerve Fiber Layer (RNFL) is made of axons of retinal ganglionic cells, which transfer optic data from retina to brain through the optic nerve and as long as it does not exit from the eye, it lacks myelin sheath so it can be directly visible. Thus, it may indicate us the affection of axons in various diseases. In the absence of optic neuritis, retrograde trans-synaptic degeneration of retinal ganglion cell due to multiple sclerosis lesions within the posterior optic pathways could cause RNFL loss (12,13).

In contrast to demyelinating process, degeneration of axons is irreversible, and it is assumed as the important cause of disability in the patients. It is demonstrated that degeneration of axons takes place at the primary phase of disease therefore the early use of neuroprotective medications is recommended in the disease (13).

Recently, OCT (Optical coherence tomography) technique has been utilized as a potential tool to explore axonal degeneration in patients with MS.

OCT is a non- invasive optical imaging technology in which the light near to infrared spectrum is employed for the preparation of sectional and or three dimensional images from the retina, and it can measure the thickness of retinal nerve fiber layers as well as macula (2).

Today, along with technological advancement, OCT imaging technique has been also subjected to change and development. In many previous studies, Time-Domain (TD-OCT) technique was utilized. Recently, Spectral- Domain (SD-OCT) method is available that provides high quality and higher- resolution images without wasting a lot of time (4,13). The thickness of RNFL and macula are measurable parameters in the OCT. The reduced thickness of these layers has been observed in eyes with or without a history of optic neuritis in MS- patients (4,13).

According to the previous studies, there is a significant relationship between the quantities measured by OCT in retinal atrophy with axonal degenerative parameters in MRI as well as parameters of disability and cognitive functions (4,14).

The periodic examination for axonal degeneration is considered as a priority in MS- patients and OCT are deemed as a sensitive, accurate, and non- invasive method in this regard (13).

Since the OCT may act usefully in the diagnosis of neuronal and axonal degeneration and with regard to the importance of early diagnosis of neuronal and axonal loss and insufficiency of the previous studies in the field thus, the current research was carried out to improve diagnostic trend and treatment plans of Multiple sclerosis (MS) diseases.

The differential aspect of this study from most of the previous studies in this regard is related to using OCT for measurement of thickness of Retinal Nerve Fiber Layer (RNFL) as well as thickness and volume of macula in two common types of multiple sclerosis (i.e. RRMS and SPMS), which have been separately evaluated according to different parts of these and finally determine correlation between these findings and rate of disability among the patients. since the axonal damage more frequently occurs in SPMS type than in RRMS type thus presence of significant relationship among OCT findings and clinical signs of this type of MS, one may express that OCT serves as an appropriate tool for evaluation of neuronal degeneration and at the same time it can be used for presentation of a favorable model to evaluate the effects of new treatments plans in multiple sclerosis, especially for neuroprotective drugs.

Materials and Methods

For doing the cross- sectional study, 35 patients with RRMS and 28 patients with SPMS types who had referred to Neurology center in southern Iran at the Chamran Hospital of Shiraz city were evaluated so that diagnosis of their disease was determined by an experienced neurologist based on previous file, history of disease, physical examination, and MRI findings. Then, the needed information was given to the patients about methods and goals of study as well as the lack of risk for this purpose, so the patients participated in the study with full awareness. The given questionnaire was filled out, and then OCT was done for them, and their findings were recorded. Inclusion criteria of the study were the patients with Relapse Remitting Multiple Sclerosis (RRMS) and Secondary Progressive Multiple Sclerosis (SPMS) types that were selected based on

McDonald Criteria (2010) (15) and was done by an experienced neurologist. The exclusion criteria of the study were a history of optic neuritis ,history of the recent attack of disease during last six months; suffering from diabetes mellitus, hypertension, and ophthalmic diseases (glaucoma and retinal diseases, etc.); the patients with a refractive error greater than 5diopters; suffering from other neurodegenerative disorder except MS. The previous history of optic neuritis was identified according to former medical evidence and self-reporting of patient or result of Visual Evoked Potential (VEP). Afterward, EDSS rate was measured in those patients, and a questionnaire was filled out for this purpose by a neurologist. Then, patients were referred to ophthalmology clinic for doing of OCT.

OCT test was done with the device of (Spectralis HRA+ OCT Heidelberg Engineering GmbH) via specific software (version 5.4) on both eyes of patients; that was done by a well-trained and experienced specialist in this field. The thickness of RNFL and volume and thickness of macula were measured in different sections (Figures 1,2).

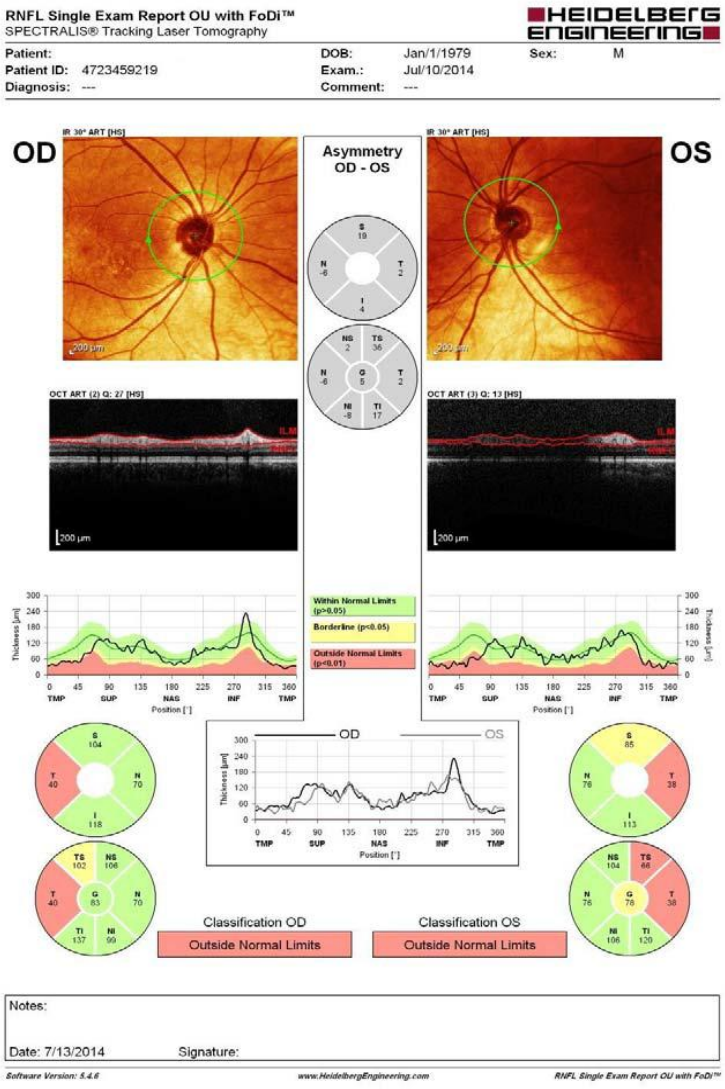

Figure 1. The figure shows image of optic nerve and thickness of its surrounding retinal nerve fiber layer in both eyes of a patient with thickness diagrams and thickness range of the layer. The circle in inferior of the figure shows thickness layer and thickness range of the layer based on µm. The mentioned ring divided to supranasal (NS), nasal (N), inferonasal (IN), inferotemporal (TI), temporal (T), supratemporal (TS) and G (indicate total thickness) parts that the thickness of each layer is expressed as a number and also, each layer is determined by a color including green, yellow and red that show layer thickness based on age and gender. Green, yellow and red colors showed normal, borderline and decreased the thickness of related parts, respectively.

.

Figure 2. The figure shows macular Image of both eyes with thickness and volume diagram of the macula in its different parts. The circle in the image has three rings in the inside: Central, internal and external rings with diameters of 1, 3 and 6 millimeters, respectively. Internal and external ring divided into 4 parts of superior, inferior, temporal and nasal (the area is adjacent to temporal part of optic disk). In the each part, thickness and volume based on micrometer and millimeter are determined, respectively. Also, total volume is mentioned in superior part of the diagram

The measured values were compared according to a normal database of the device and based on age and gender via device software. Scan protocol for RNFL was done as 3.4 mm ring around the end of the optic nerve and as three rings for macula (central ring with 1 mm diameter, internal ring with 3 mm diameter and external ring with 6 mm diameter around of macula center).

After doing of OCT, the given images and quantities were evaluated under the supervision of an experienced ophthalmologist, and if the images had low quality, they were tested again. Data from any patient for each eye were selected randomly for analysis, and then the given findings and quantities were recorded and finally analyzed.

Data was entered into SPSS software after collection. Descriptive statistics, t-test, a test of Analysis of Variance (ANOVA), Chi-Square test and Analysis of Covariance (ANCOVA) (for control of variables of age and period of the disease in both groups) were used for data analysis (Significance level was $P \leq 0.05$).

Results

Overall, 35 RRMS-patients (9 male and 26 female with mean age of 31.97+9.98) and 28 SPMS-patients (12 male and 16 female with mean age of 38.29+9.5) were studied. The average age for starting disease was 28.84 year in RRMS group and 27.89 years in SPMS patients.

The thickness of RNFL was measured for all of the patients by OCT. Since the parameters of the age and period of the disease have effects on the thickness of RNFL thus the statistical analysis of Covariance (ANCOVA) was used for two groups to control these variables. The results of both parts of RNFL and macula are separately shown in Tables 1 and 3.

The RNFL findings were calculated and recorded in two forms by OCT where one shows layer thickness in micrometer, and the other indicates the limit of layers thickness by the color coding pattern. The information was recorded in all parts around the optic disk in both

groups of patients (Table 1).

The thickness of RNFL in all measured sectors was smaller in SPMS patients than the thickness of this layer in RRMS patients, and there was a significant difference in the temporal sector and the total thickness of this layer between two groups.

Thickness and volume of different parts of macula were measured for 21 RRMS-patients and 22 SPMS-patients. The statistical analysis was done among two groups using Analysis of Covariance (ANCOVA) to control variables of age and duration of disease. The findings are shown in Tables 4 and 5.

Thickness in different parts of macula was smaller in SPMS-patients than in RRMS-patients; however, there was a significant difference only in the thickness of superior and nasal sector of external ring.

Also, macular volume was similar to its thickness in two groups; the volume in the measured parts of macula was smaller in SPMS-patients than in RRMS-patients. But, there was a significant difference only in the thickness of superior and nasal sector of external ring. So, there was no significant difference in total volume of macula between two groups.

The RRMS-patients had EDSS rate from 1 to 3 while this value ranged from 2 to 7 in SPMS patients (Table 2).

Correlation between RNFL thicknesses reductions and disability of patients was evaluated based on EDSS scale as well. Since the EDSS values ranged from zero to ten, and there was a high dispersion among these values compared to the studied population in any group, so these quantities were divided into three groups with mild disability (EDSS: 0-3), moderate disability (EDSS: 3-6), and severe disability (EDSS: 6-10). All RRMS patients were classified in the first group, and the comparison was not feasible practically. The analysis was done using Analysis of Variance (ANOVA) in SPMS group. Based on the values derived from OCT, in many parts of macula and RNFL, as EDSS rate was higher in a patient, the thickness of RNFL was smaller, but this relationship was not significant. Out of 28 SPMS patients, seven patients were placed in the first group, other seven patients were in the second group, and 14 patients were classified in the third group.

Table 1. Comparison of mean thickness of RNFL (μ) in both groups of RRMS and SPMS ANCOVA

Average thickness of RNFL	RRMS	SPMS	*P*. value
At superior sector of nasal quadrant	102.26	92.61	0.59
At nasal quadrant	73.51	62.14	0.06
At inferior sector of nasal quadrant	110.74	94.68	0.06
At inferior sector of temporal quadrant	140.20	119.21	0.1
At temporal quadrant	69.34	54.5	0.04
At superior sector of temporal quadrant	132.71	113.82	0.14
Average thickness of global section at	96.03	81.82	0.048

Table 2. Comparison of demographic traits in all patients in both groups of RRMS and SPMS

Variable	N=, RRMS	N=, SPMS
Quantity	35	28
Age (mean +SD)	32.37+10.01	39.21+9.33
Gender(percent)	Male: 14.28 Female: 41.26	Male: 19.04 Female: 25.39
Mean EDSS	1.84 + 0.45	5.12 + 1.46
Disease period (year)	3.81+ 3.42	11.32 +5.87

Table 3. Comparison of range of RNFL thickness in both groups of RRMS and SPMS

		RRMS	SPMS	*P*-Value
Average thickness of RNFL at superior the lobe of the nasal quadrant	Normal	94.28	92.85	1
	borderline level	5.71	7.14	
	Reduced	0	0	
Average thickness of RNFL at nasal quadrant	Normal	100	89.28	0.08
	borderline level	0	10.71	
	Reduced	0	0	
Average thickness of RNFL at inferior the lobe of the nasal quadrant	Normal	100	89.28	0.08
	borderline level	0	10.71	
	Reduced	0	0	
Average thickness of RNFL at inferior the lobe of the temporal quadrant	Normal	91.42	57.14	0.017
	borderline level	2.85	35.71	
	Reduced	5.71	7.14	
Average thickness of RNFL at temporal quadrant	Normal	82.85	57.14	0.003
	borderline level	14.28	7.14	
	Reduced	2.85	35.71	
Average thickness of RNFL at superior the lobe of the temporal quadrant	Normal	91.42	60.71	0.012
	borderline level	2.85	21.42	
	Reduced	5.71	17.85	
Average thickness of global section At RNFL	Normal	91.42	46.42	0
	borderline level	0	14.28	
	Reduced	8.57	39.28	

Table 4. Comparison of mean thickness (µm) of macula, internal and external surrounding rings in both groups of RRMS and SPMS

	RRMS	SPMS	*P*-Value
Central part of macula	257.86	256.68	0.98
Superior sector of interior ring surrounding of the macula	340.90	323.50	0.22
Nasal sector of interior ring surrounding of macula	338.76	323.59	0.36
Inferior lobe of interior rings surrounding of macula	336.05	320	0.30
Temporal sector of interior ring surrounding of macula	324.81	313.68	0.49
Superior sector of exterior ring surrounding of the macula	299.38	280.36	0.03
Nasal sector of exterior ring surrounding of macula	313.67	289.68	0.02
Inferior sector of exterior ring surrounding of the macula	290.81	273.05	0.13
Temporal sector of exterior ring surrounding of macula	285.95	270.05	0.06

Table 5. Comparison of average size (mm^3) of macula, internal and external surrounding rings in both groups of RRMS and SPMS without history of optic neuritis

	RRMS	SPMS	*P*-value
Central part of macula	0.2	0.201	0.98
Superior sector of interior ring surrounding of the macula	0.53	0.50	0.30
Nasal sector of interior ring surrounding of macula	0.53	0.50	0.33
Inferior sector of interior ring surrounding of macula	0.52	0.50	0.30
Temporal sector of interior ring surrounding of the macula	0.51	0.49	0.5
Superior sector of exterior ring surrounding of the macula	1.58	1.48	0.03
Nasal sector of exterior ring surrounding of macula	1.66	1.53	0.03
Inferior sector of exterior ring surrounding of the macula	1.54	1.44	0.12
Temporal sector of exterior ring surrounding of the macula	1.51	1.43	0.057
Macular total size	8.59	8.11	0.08

Discussion

Different aspect of the current research from many previous studies in the field is related to doing OCT to measure thickness of Retinal Nerve Fiber Layer (RNFL) and thickness and volume of macula in both common types of Multiple Sclerosis (SPMS and RRMS) in the patients without history of previous optic neuritis, which have been separately evaluated based on different parts of the eye and finally the given relation between the findings and rate of disability in the patients. Detail of thickness change of RNFL layers was not evaluated in any other study similar to the current research. The thickness of RNFL in all points of around of optic disk was smaller in SPMS group than in RRMS group in this study; however, a significant difference was seen only in total thickness and temporal sector thickness. Thickness in the temporal sector was 50.54µm in SPMS patients and 69.34µm in RRMS patients (*P*=0.04). Similarly, the total thickness of RNFL were 81.82 µm in SPMS patient and 96.03µm in RRMS patients (*P*=0.04). Therefore, these findings are aligned with the results of study that was done on types of multiple sclerosis by Pulicken *et al.,* (2007) (16). In their study, total thickness of retinal nerve fiber layer was 94.4µm and 81.8µm in patients with RRMS and SPMS types, respectively where it was significantly smaller than in control group. Likewise, these findings are consistent with the study results Oberwahrenbrock *et al*., (2012) (4) on 414 MS- patients and 94 healthy persons. In other words, regardless of type of disease and without history of optic neuritis, the patients with multiple sclerosis showed distinct reduction in thickness of RNFL and total volume of macula compared to control group (*P*<0.011) and total thickness of RNFL was smaller in type SPMS patients (83.14) than in type RRMS (92.03) (*P*=0.007).

Of course, these findings were not consistent with study of Fathi *et al*., (17), who compared the rate of RNFL thickness in three groups of RRMS, SPMS, and CIS (Clinically isolated syndrome) by means of OCT non- invasive test and they did not find significant difference between three groups in terms of RNFL thickness rate (*P*>0.05).

The results of our study are similar to the research of Noval *et al.,* (2010) (18) in OCT field among patients with MS and NMO (Neuromyelitis optica). According to that study, temporal lobe is the most vulnerable part in RNFL against process of MS disease and reduction in thickness of this region is often deemed as the only symptom which may differentiate between MS patients and healthy persons and the current study, in addition to showing the reduced thickness of RNFL in SPMS patients compared to RRMS patients, also, it demonstrated a significant difference in temporal lobe thickness compared with other regions. Also, this finding is consistent with the study results of Noval *et al.,* in terms of the highest involving part and the that involvement is prominent in SPMS type, so it can be

observed as more reduction in thickness of RNFL among SPMS patients in their OCT, a status that is similar to our study results.

So, based on the mentioned researches results, the current research shows this significant difference in temporal lobe further than other regions in addition to indicating reduced thickness of RNFL in SPMS patients compared with RRMS patients.

In terms of thickness range between two groups, more than of the patients with SPMS type had decreased or borderline RNFL thickness in the OCT compared with RRMS group; however, there was a significant difference among both groups in the thickness of inferior and superior temporal lobes and total thickness (Table 1).

Based on thickness and volume of different parts of the macula in results of the current study, it can be expressed that thickness in the measured points of the macula is smaller in SPMS patients than in RRMS group, but there was a significant difference only in the thickness of superior and nasal lobes in the external ring. Also, there was such a status between two groups in terms of volume, but no significant difference was found in the total volume of macula between two groups.

In the cross sectional study of Oberwahrenbrock *et al*., (4) on 414 patients affected by MS with 94 healthy persons by means of OCT technique, the macular total volume was 8.32 mm^3 in SPMS type compared to 8.54 mm^3 in RRMS type that is significantly smaller (P=0.039). Our study showed this significant difference only in some points of macula adjacent to the region of the temporal disk.

No other study was found in which the size and volume of macula were compared in these two types of multiple sclerosis while most of the studies had compared macular volume between MS patients with healthy persons. For instance, in a study in which Fjeldstad *et al*., (10) examined 30 RRMS patients by means of HD-OCT technique, the mean thickness of macula was 280µm in RRMS patients that were smaller than in control group (287 µm) (P<0.05). Similarly, in the study of Trip *et al.,* (19), who evaluated twenty five of patients with MS via OCT, the size of macula was reduced 11% further in patients with history of optic neurosis (6.10 mm^3) compared with its size in the control group (6.83 mm^3) and this reduction was 9% in the patients that suffered from disease compared to eye without disease (6.71 mm^3) (P<0.001).

In a study that was done by Khanifar (2010) (20) on eyes of 94 patients suffered from MS, he measured macular volume and RNFL by OCT and compared them with a control group where MS patients showed significantly reduced thickness in interior and external nasal lobe compared with the normal persons. The study is consistent with our survey in terms of region of reduced thickness, but no comparison was made between two types of multiple sclerosis in the study of Khanifar.

Correlation between thickness reduction of different part of RNFL and disability of patients was evaluated by using the EDSS disability scale (21,22). Since the EDSS values range from zero to ten and with regard to high dispersion of these quantities and small sample size in any group, we divided these values into three groups with low disability (EDSS:0-3), medium disability (EDSS:3-6), and high disability (EDSS:6-10). All of RRMS patients were classified in the first group (low disability), so this comparison was not practically feasible. Based on OCT findings, in many points of macula and NFL as patient's EDSS was higher, RNFL thickness was smaller, but there was generally no significant relationship among disability of patients with a reduction in thickness. Although there were not consistent results in the previous studies, it seems that with regard to the dispersion of EDSS values, the number of our patients to be small for this comparison so it requires a greater sample size for appropriate comparison in this regard.

Reduction of thickness and size of the macula in its nasal lobe complies with reduction of thickness in RNFL in the current study since papilla macular bundles are placed in the nasal lobe of the macula and, the macular thickness at this point of macula decrease with degeneration of RNFL (20).

Overall, this study indicated that total thickness of RNFL as well as its thickness in the temporal lobe and also thickness and size of the macula in its nasal lobe is significantly different among two RRMS and SPMS groups. These findings confirm the results of previous researchers, which showed the involvement of RNFL temporal lobe following to MS process and additionally they indicated that the maximum changes take place in this region as the disease progresses as well. Based on the study results adaptation with pathologic process of MS disease, it seems the maximum involvement of RNFL occurred at temporal lobe and given that to the existing significant difference between results of two groups, it can be implied that the OCT is assumed as an appropriate tool to display axonal degeneration in patients with multiple sclerosis and physician can evaluate the effect of different drugs on disease process with accurate selection of the patients and doing of OCT

in regular intervals and thereby formulate schedule for treatment of patients and select more efficient therapy for patients as it required.

Since the physicians play an essential role in counseling programs and interventions in training activities, thus they can reduce disability rate of the patients by improving awareness and information of patients for follow-up and early diagnosis of the MS disease. Reception of the patient and follow-up processes of treatment as well as prevention of side effects will be done better with the improvement of ability status and patients with MS, and their families may be less damaged so it seems OCT can play a helpful role in this regard.

References

1. Stone J, Carson A. Functional and dissociative (Psychologenic) neurological symptoms. In: Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, eds. Bradley's Neurologyin Clinical Practice. 6th ed. Philadelphia: Saunders, 2012:2336.
2. Saidha S, Syc SB, Ibrahim MA, Eckstein C, Warner CV, Farrell SK, et al. Primary retinal pathology in multiple sclerosis as detected by optical coherence tomography. Brain 2011;134:518-33.
3. Compston A, Coles A. Multiple sclerosis. Lancet 2008;372:1502-17.
4. Oberwahrenbrock T, Schippling S, Ringelstein M, Kaufhold F, Zimmermann H, Keser N, et al. Retinal Damage inMultiple Sclerosis Disease Subtypes Measured by High-Resolution Optical Coherence Tomography. Mult Scler Int 2012;2012:530305.
5. Costello FC, Klistorner A, Kardon R. Optical Coherence Tomography in the Diagnosis and Management of Optic Neuritis and Multiple Sclerosis. Ophthalmic Surg Lasers Imaging 2011;42:28-40.
6. Multiple Sclerosis In: Rowland LP, Pedley TA, editors. Merrit's neurology. 12th ed. Philadelphia: Lippincott Williams and Wilkins, 2009:1172.
7. Pfueller CF, Brandt AU, Schubert F, Bock M, Walaszek B, Waiczies H, et al. Metabolic changes in the visual cortex are linked to retinal nerve fiber layer thinning in multiple sclerosis. PLoS One 2011;6:e18019.
8. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med 2000;343:938-52.
9. Klistorner A, Arvind H, Nguyen T, Garrick R, Paine M, Graham S, et al. Axonal loss and myelin in early on loss in postacute optic neuritis. Ann Neurol 2008;64:325-31.
10. Fjeldstad C, BembenM, Pardo G. 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 . J Clin Neurosci 2011;18:1469-72.
11. Galetta KM, Calabresi PA, Frohman EM, Balcer LJ. Optical Coherence Tomography (OCT): Imaging the Visual Pathway as a Model for Neurodegeneration. Neurotherapeutics 2011;8:117-32.
12. Pueyo V, Martin J, Fernandez J, Almarcegui C, Ara J, Egea C, et al. Axonal loss in the retinal nerve fiber layer in patients with multiple sclerosis. Mult Scler 2008;14:609-14.
13. Petzold A, Boer JF, Schippling S, Vermersch P, Kardon R, Green A, et al. Optical coherence tomography in multiple sclerosis a systematic review and meta-analysis. Lancet Neurol 2010;9:921-32.
14. Nikanfar M, Talebi M, Bahrabar M, Sharifipour E, Bahrebar M, Kiavar A, et al. Optic coherence tomography findings in patients with relapsing-remitting multiple sclerosis of north-west Iran. Iran J Neurol 2013;12:81-6.
15. McDonnell G, Hawkins S. Clinical study of primary progressive multiple sclerosis in Northern Ireland, UK. J Neurol Neurosurg Psychiatry1998;64:451-4.
16. Pulicken M, Gordon-Lipkin E, Balcer LJ, Frohman E, Cutter G, Calabresi PA. Optical coherence tomography and disease subtype in multiple sclerosis. Neurology 2007;69:2085-92.
17. Fatehi F,Shaygannejad V, Kiani Mehr V, Dehghani A. Optical coherence tomography versus visual evoked potential in multiple sclerosis patients. Iran J Neurol 2012;11:12-5.
18. Noval S, Contreras I, Munoz S, Oreja-Guevara C, Manzano B, Rebolleda G. Optical Coherence Tomography in Multiple Sclerosis and Neuromyelitis Optica: An Update. Multi Scler Int 2011;2011:472790-472801.
19. Trip S, Schlottmann PG, Jones SJ, Li WY, Garway-Heath DF, Thompson A, et al. Optic nerve atrophy and retinal nerve fibre layer thinning following optic neuritis: Evidence that axonal loss is a substrate of MRI-detected atrophy. Neuroimage 2006;31:286-93.
20. Khanifar A, Parlitsis GJ, Ehrlich JR, Aaker GD, D'Amico DJ, Gauthier SA, et al. Retinal nerve fiber layer evaluation in multiple sclerosis with spectral domain optical coherence tomography. Clin Ophthalmol 2010;4:1007-13.
21. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33:1444-52.
22. Haber A, LaRocca NG, eds. Minimal Record of Disability for multiple sclerosis. New York: National Multiple Sclerosis Society, 1985.