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Original Study

Optic Nerve Head Changes in Patients with Optic Neuritis Secondary to Multiple Sclerosis: A Comparison of the Affected and Fellow Healthy Eyes

Multipl Skleroza Sekonder Optik Nöritli Hastalarda Optik Sinir Başı Değişiklikleri: Etkilenen ve Diğer Sağlıklı Gözlerin Karşılaştırılması

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ABSTRACT

Objective: *To evaluate the thickness of lamina cribrosa (LC) in patients with multiple sclerosis (MS) using optical coherence tomography (OCT) and the effect of optic neuritis (ON) attack on these measurements during the remission period.*
Methods: *The study included 20 cases diagnosed with relapsing-remitting MS with a history of ON attacks affecting one eye and in remission of MS and ON attacks for at least three months, and 28 randomly selected eyes of age- and sex-matched healthy controls. In the MS group, the eyes affected by ON attack were assigned as Group 1 (MS+ON), their fellow unaffected eyes as Group 2 (MS-ON), and healthy control eyes as Group 3. The LC, peripapillary retinal nerve fiber layer (ppRNFL), and subfoveal choroidal thickness measurements were made by using OCT in all cases, and results were compared between the groups.*
Results: *The mean LC thickness in MS+ON and MS-ON groups was significantly lower than the control group (p<0.001). There was no significant difference between MS+ON and MS-ON groups in terms of mean LC thickness (p=0.073). The mean ppRNFL in the MS+ON and MS-ON groups was statistically significantly lower than the control group (p=0.003, p=0.035, respectively).*
Conclusions: *It is noteworthy that LC is significantly affected in eyes with MS who have not had a history of ON attack. Evaluation of the LC measurements can be important for early detection of optic nerve damage in patients with MS.*

Keywords: *Lamina cribrosa, multiple sclerosis, optical coherence tomography, optic neuritis*

ÖZ

Amaç: *Multipl skleroz (MS) hastalarında optik koherens tomografi (OKT) ile yapılan lamina kribroza (LK) kalınlık ölçümlerinin ve optik nörit (ON) atağının bu ölçümlere olan etkisinin remisyon döneminde değerlendirilmesi.*
Yöntem: *Relapsing-remitting MS tanısı alan ve tek gözden ON atağı geçirme hikayesi olan, en az üç aydır MS ve ON atağı remisyonda olan 20 olgu ile yaş, cinsiyet uyumlu 28 sağlıklı olgunun rasgele seçilen gözü dahil edildi. MS'li grupta; ON atağından etkilenen gözleri Grup 1 (MS+ON), ON atağından etkilenmeyen diğer sağlıklı gözleri Grup 2 (MS-ON), sağlıklı bireylerin gözleri ise Grup 3 olarak değerlendirildi. Olgulara çekilen OKT görüntülerinden ortalama LK, peripapiller retina sinir lifi tabakası (ppRSLT) ve subfoveal koroid (SFK) kalınlık ölçümleri gruplar arasında karşılaştırıldı.*
Bulgular: *Ortalama LK kalınlığı MS+ON ve MS-ON gruplarında kontrol grubu ile karşılaştırıldığında anlamlı (p<0,001) olarak ince olduğu saptandı. MS+ON ve MS-ON grupları arasında ortalama LK kalınlık değeri karşılaştırıldığında ise anlamlı fark olmadığı görüldü (p=0,073). MS+ON ve MS-ON gruplarında ortalama ppRSLT kalınlığı kontrol grubu ile karşılaştırıldığında anlamlı düzeyde ince olduğu saptandı (sırasıyla, p=0,003, p=0,035).*
Sonuç: *Çalışmamızda ON atağı geçirmemiş olan MS'li gözlerde LK'nin anlamlı düzeyde etkilenmiş olması dikkat çekicidir. MS'te bu ölçümlerin değerlendirilmesi, hastalarda oluşan optik sinir hasarının erken tespiti için önemli olabilir.*

Anahtar kelimeler: *Lamina kribroza, multipl skleroz, optik koherens tomografi, optik nörit*

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INTRODUCTION

Multiple sclerosis (MS) is a chronic disease which is characterized by inflammation and demyelination. Autoimmunity plays an essential role in MS pathogenesis. Demyelination and neurodegeneration occur due to a T cell-driven inflammatory response against myelin in the central nervous system[1]. Optic neuritis (ON) appears as an acute inflammatory demyelinating clinical picture resulting from axonal degeneration of the optic nerve and can be the first clinical sign in 25% of the patients with MS[2].

Magnetic Resonance Imaging (MRI) is the primary method to evaluate the central nervous system damage in MS. The retina and optic nerve are parts of the central nervous system, and measurements of unmyelinated axons may indicate general neuronal degeneration associated with the disease. Recently, increasing number of studies have indicated that optical coherence tomography (OCT) can also be used to determine the degree of neuronal loss. Some studies reported that OCT is an essential imaging method for monitoring neurodegenerative diseases and MS. It was found that peripapillary retinal nerve fiber layer (ppRNFL) and macular thickness were associated with disease severity, cognitive and physical dysfunction in patients with MS[3-10].

Lamina cribrosa (LC) is a multi-layered collagen structure consisting of perforated rigid connective tissue and elastic fibers in the intraocular part of the optic nerve, through which the axons of retinal nerve fiber bundles pass where glial tissue is maximized[11]. With the enhanced depth imaging (EDI) mode in OCT devices, it has been possible better to visualize deep structures, such as choroid and LC, using lower signal intensity and resolution but with increased depth[12,13]. Previously, LC thickness was studied in optic nerve disorders, especially in glaucoma. It was reported that in glaucomatous eyes, increased intraocular pressure causes thinning of the LC by compressing the optic disc[14]. Besides ocular diseases such as glaucoma, LC has also been investigated in the central nervous system diseases affecting the optic nerve such as Parkinson's disease and MS. It was shown that this important structure which is related with retinal nerve fibers is also affected in patients with these disorders[15-17].

The choroid layer is a vascularized tissue, located between the retina and sclera. It provides oxygen and nutrient support to the outer retina. The choroidal layer might be affected by diseases characterized by systemic inflammation and vascular disorganization, such as MS[18].

In previously reported studies that evaluated LC and subfoveal choroid (SFC) thickness, the time of ON and MS attacks were not specified and we think that it is one of the reasons to explain the differences in measurements between studies. We hypothesized that these measurements might yield different results at different times of the ON attack, so we determined these measurements only in MS patients in remission and did not have an ON attack for at least three months. The current study aimed to investigate the measurements of LC, ppRNFL, subfoveal choroid (SFC) thickness, and the effect of ON attack on these measurements in relapsing-remitting MS patients in the remission period.

MATERIAL and METHODS

This study included 20 patients followed up in Ophthalmology Clinic and Neurology Clinic, diagnosed with relapsing-remitting MS as per the McDonald criteria with their clinical and radiological findings, and had a history of ON attack in only one eye, and 28 healthy controls. Participants were divided into three groups: Group 1 included the eyes affected with ON attack in patients with MS (MS+ON), Group 2 included their healthy fellow eyes (MS-ON), and Group 3 consisted of randomly selected eyes of healthy controls[19]. All participants provided written informed consent.

The study was conducted in accordance with the Declaration of Helsinki.

The inclusion criteria were as follows for MS group: The presence of unilateral ON history proven by visual field, contrast-enhanced orbital MRI and examination findings, being followed up in Neurology and Ophthalmology clinics, absence of ocular hypertension and glaucoma, best-corrected visual acuity (BCVA) 2/10, refractive error of -4 to +3 diopters spherical and 3≥ diopters cylindrical, no history of ocular disease other than ON and ocular surgery, systemic disease other than MS and surgery, remission of MS and ON attacks, systemic and topical corticosteroid use for at least three months.

The healthy control group included of 28 randomly selected eyes of healthy controls who were applied to the ophthalmology clinic for routine ophthalmologic examination and compatible with MS patients in terms of age and gender. Inclusion criteria were as follows: no history of ophthalmological pathology other than refractive error or cataracts, ocular hypertension and glaucoma, ocular or systemic diseases , surgery, topical corticosteroid use and the presence of BCVA ≥ 6/10, refractive errors of -4 and +3 diopters spherical and ≤3 diopters cylindrical,. For both groups, patients with optic media opacity (dense cataract, corneal opacity, pupillary anomaly, and vitreous opacities) that could affect OCT images were not included in the study.

Each participant underwent the Snellen test for the BCVA, slit-lamp biomicroscopy, intraocular pressure measurement (Goldmann applanation tonometry), axial length measurement (IOL Master, Carl Zeiss Meditec, Dublin, CA), gonioscopy, examination of pupillary reflexes and eye movements, visual field examination (Humphrey Visual Field Analyzer III, Carl Zeiss Inc., Dublin, CA) with central 24- 2 SITA (Swedish Interactive Thresholding Algorithm standard strategy), dilated fundus examination, and OCT (Heidelberg Engineering GmbH, Germany) imaging. In order to prevent diurnal changes, measurements were performed on images obtained at the same time of the day.

Measurement of the Lamina Cribrosa Thickness

Using the OCT images obtained in EDI mode, the

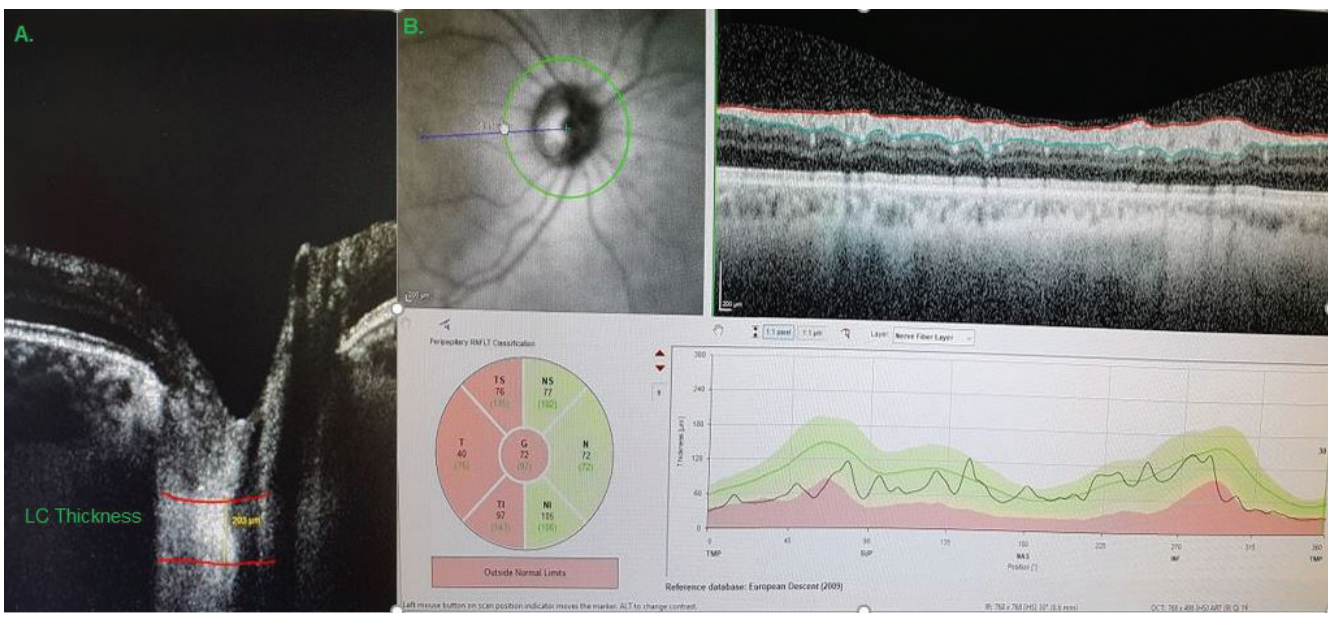

Figure 1. Measurement of lamina cribrosa (A) and retinal nerve fiber layer thicknesses (B) in a patient with multiple sclerosis who had an optic neuritis attack in the right eye.

LC thickness was measured using the device's manual measurement tool. Image quality was evaluated as per the signal-to-noise ratio (SNR). Scans with SNR 20 decibels (dB) or above were considered the best quality. The spectral-domain OCT (SD-OCT) was set to image a 15x10° rectangle centered on the optic disc. Approximately 45 frames were generated for each cross-sectional B-scan. In these horizontal B-scans, the central scans passing through the optic nerve head were selected. The scans passing through the center of the central retinal blood vessels were centered on the optic disc. In horizontal B-scan images, the region between outer and inner borders of the hyperreflective area within the optic disc's vertical center was considered as LC. LC thickness was measured using vertical lines extending between the hyperreflective area's inner and outer borders, as described by Park et al.[20] (Figure 1).

Measurement of the Choroidal Thickness

1024 A-scans were obtained on a 6 mm horizontal line passing through the center of the fovea. Choroidal thickness was determined using the digital calipers on the device in the subfoveal area on the vertical line extending from the outer border of the retinal pigment epithelium to the choroidoscleral junction. All measurements were performed by two independent investigators blinded to the patients' diagnoses. To determine the reliability and repeatability of the measurements, intra- and inter-observer correlation coefficients were calculated from 20 randomly selected images.

Measurement of Thickness of the Peripapillary *Retinal Nerve Fiber Layer*

The ppRNFL was measured around the optic disc in 768 A-scans using 16 averaged, circular B-scans (with 3.4-mm diameter) (12 degrees). The ppRNFL was automatically divided into segments using Spectralis software. Later on, the average, temporal, superotemporal, superonasal, nasal, inferionasal, and inferiotemporal values of the patients were recorded (Figure 1).

Statistical Analysis

The study results were analyzed using SPSS (Statistical Package for Social Sciences) version 22.0 (SPSS for Windows Inc., Chicago, USA). Descriptive statistics (mean, standard deviation, and percentage) were used for evaluating the study data. The Kolmogorov-Smirnov test was employed to assess the compatibility of data to normal distribution. The Mann-Whitney U test, the Kruskal-Wallis test, one-way analysis of variance (ANOVA), and the chi-square test were used to analyze the intergroup differences. $P<0.05$ was considered statistically significant.

RESULTS

No statistically significant difference was found between MS group and the control group participating in the study regarding age and gender distribution ($p=0.844$ and $p=0.861$, respectively). Table 1 shows the demographic characteristics and ophthalmic exam results of the groups (Table 1).

The mean LC thickness was found to be 180.6±40.5 µm, 197.0±26.4 µm and 246.5±33.2 µm, in MS+ON, MS-ON and the control groups, respectively. The LC layer was significantly thinner in MS+ON and MS-ON groups than the control group ($p<0.001$) (Table 2).

The temporal, inferotemporal and the mean ppRNFL were statistically significantly thinner in MS+ON and MS-ON groups than the control group ($p<0.05$). However, MS+ON and MS-ON groups did not significantly differ in terms of ppRNFL thickness ($p>0.05$) (Table 2). The intra- and inter-observer correlation coefficients for LC and SFC thickness measurements are shown in Table 3.

Table 1. Demographic characteristics and ophthalmic features of the groups.

	Group 1 MS+ON		Group 2 MS-ON		Group 3 Healthy Controls		
	mean±sd	median	mean±sd	median	mean±sd	median	p
Age	31.0±7.5	32.0			32.9±11.3	32.5	0.844[A]
Gender							
Female	11 (55.0%)				16 (57.14 %)		0.861[X²]
Male	9 (45.0%)				12 (42.85 %)		
Disease Duration (month)	56.6±83.5	12.0					
İOP (mmHg)	13.8±2.3	13.6	14.1±2.0	14.6	12.9±1.3	13.0	0.070[K]
CCT (µm)	557.6±8.0	555.5					
Refractive error (diopter)			560.6±12.0	560.0	572.1±19.8	565.5	0.052[K]
Spherical	-0.6±0.7	-0.5	-0.6±0.5	-0.4	-0.6±0.9	-0.4	0.184[K]
Cylindirical	-0.7±0.7	-0.5	-0.7±0.8	-0.5	-0.7±0.5	-0.5	0.256[K]
Axial length (mm)	23.44±0.7	23.0	23.45±0.8	23.0	23.44±0.8	23.0	0.321[K]
BCVA (Snellen)	0.60±0.36	0.80	1.00±0.0	1.00	1.00±0.0	1.00	0.001[K]

MS+ON; The eyes affected with ON attack in patients with MS, MS-ON; their healthy fellow eyes, BCVA; Best-corrected visual acuity, IOP; Intraocular pressure; CCT; Central corneal thickness
[A]ANOVA, K Kruskal-wallis, [m]Mann-whitney u test, X²Chi-square test.

Table 2. Lamina cribrosa thickness and peripapillary retinal nerve fiber layer thickness measurements in the groups.

					p[A]		
		Group 1 MS+ON mean±sd	Group 2 MS-ON mean±sd	Group 3 Healthy Controls mean±sd	Group 1-2	Group 1-3	Group 2-3
ppRNFLT (µm)	T	70.4±17.7	63.6±13.8	81.0±14.9	0.395	0.023	0.002
	ST	126.6±21.5	131.1±23.8	144.6±30.2	0.346	0.052	0.090
	IT	132.9±21.9	139.2±16.7	157.4±17.7	0.160	0.001	0.005
	N	66.4±17.3	78.4±21.0	82.1±27.9	0.154	0.062	0.566
	SN	106.4±23.7	105.3±21.9	111.8±28.6	0.800	0.699	0.640
	IN	94.4±29.4	108.4±20.2	114.6±24.9	0.148	0.052	0.371
	Avg.	90.5±15.3	96.4±15.2	106.8±12.6	0.223	0.003	0.035
LCT (µm)		180.6±40.5	197,0±26.4	246.5±33.2	0.073	0.000	0.000

LC; Lamina cribrosa thickness, ppRNFLT; Peripapillary retinal nerve fiber layer thickness, T; Temporal, ST; Superotemporal, IT; Inferotemporal, N; Nasal, SN; Superonasal, IN; Inferonasal, Avg.; Average.
[A]ANOVA (Tukey).
p values are statistically significant.

Table 2. Lamina cribrosa thickness and peripapillary retinal nerve fiber layer thickness measurements in the groups.

	Intraobserver ICC 95% CI	Interobserver ICC 95% CI	p
LCT (µm)	0.986 (0.951-0.997)	0.998 (0.987-1.000)	<0.001
SFCT (µm)	0.998 (0.994-1.000)	0.996 (0.994-1.000)	<0.001

LC; Lamina cribrosa thickness, SFCT; subfoveal choroidal thickness measurements.
p values are statistically significant.

DISCUSSION

This study has investigated the effect of ON on the anatomy of the optic nerve and choroid layers in both affected and unaffected eyes in patients with relapsing-remitting MS during the remission period. As a result, it was determined that the mean LC layer in the ON-affected eyes and the other healthy eyes of these patients were significantly thinner compared to the healthy controls. When ppRNFL was examined, the temporal, inferotem-

poral, and ppRNFL were found to be significantly thinner in MS groups than in the control group.

Lamina cribrosa is the intraocular part of optic nerve in which the axons of nerve fiber bundles pass through and where these nerve bundles reach the upper centers. This region is essential to provide the the integrity of the retinal nerve fibers. LC thickness was examined in glaucoma patients. It was reported that the laminar thickness was thinner in glaucomatous eyes than in the controls due to increased intraocular pressure[13]. Also, it was recently suggested that as compared to the eyes of healthy controls, LC thicknesses were lower in the eyes with non-glaucomatous optic neuropathy[17]. Increased intraocular pressure is thought to disrupt LC hemodynamics due to its mechanical effect on microcirculation in LC[14,15,21,22]. Recently, this anatomical structure in which retinal nerve fibers pass through has been investigated in neurodegenerative diseases affecting the optic nerve, which is considered as an extension of the brain[15,16,23]. Akkaya et al.[16] compared LC thickness between MS patients and the healthy controls, and did not report any significant difference, which is in contrast with our study. On the other hand, similar to our study, Kocamış et al.[23] found the mean LC thickness be significantly lower in MS group (171.86±62.81 μm) as compared to the control group (230.1±66.84 μm) ($p < 0.001$). As distinct from those studies, we investigated the ON attack's effect on these measurements and revealed that LC was significantly thinner in the eyes affected and unaffected by the ON attack than the healthy controls. The differences between the studies in terms of measurements may have resulted from disease durations, the length of remission periods, or the severity of attacks. Our study analyzed the measurements of thickness obtained from the scans of MS patients who had been in remission for at least three months. More prolonged attack or remission periods may explain the different measurements of thickness reported in those studies.

The OCT-angiography study was performed because ON attack may affect the perfusion of the vessels feeding the optic nerve. We measured the microcirculation of the optic nerve head of MS eyes with and without a history of ON compared to the healthy controls, we found that the mean flow index of the optic nerve head was significantly lower in eyes with MS, regardless of ON history[24]. The fact that optic nerve perfusion is affected, and inflammation is present in patients with MS may reduce the nutrient and oxygen transfer from the laminar collagen matrix in LC and may cause deformation of LC over time, which may consequently be thinning of LC in both affected and unaffected eyes affected by ON attacks.

Several studies are indicating decreased ppRNFL thickness in MS patients with or without ON[3,5,6]. Previous studies reported decreased ppRNFL thickness might be associated with optic radiation damage in eyes without ON[25,26]. The current study also showed that RNFL thickness was reduced in MS-ON and MS+ON groups than the controls. Moreover, previous studies comparing MS eyes with the healthy controls have reported the highest thinning in the temporal ppRNFL, which is in line with our study[3,4,27]. In MS, axonal loss specific to the temporal quadrant of ppRNFL has been associated with the region, which is responsible for central vision that consists of small parvocellular axons[28]. The retina is part of the central nervous system, and measurements of unmyelinated axons in the eye may indicate general neural degeneration associated with the disease[4]. Previously, a negative correlation was found between functional and cognitive impairment and ppRNFL thickness[10,27,29]. The measurements of RNFL thickness are important for the diagnosis and the follow-up of the disease.

Thinning of RNFL damaged by ON attacks and the structural changes in LC due to impaired microcirculation are expected results in MS. However, both ppRNFL and LC layers were thinner in the eyes of MS patients without ON attack than in the control group which was a noteworthy finding of

our study. It was demonstrated in studies utilizing OCT that there was thinning in ppRNFL of MS eyes without a history of ON. Although the reason could not be clearly explained, it has been related to the fact that ON results in retrograde degeneration and subsequently in the axonal loss[30]. Similarly, the presence of structural changes in LC-where retinal nerve fibers pass through-without an ON attack may result from the fact that inflammation or vascular perfusion disorders in MS patients decrease nutrients in LC, which leads to deformation even without an ON attack.

In this study, significant difference was not found between the study participants regarding the choroidal thickness ($p>0.05$). Doğan et al.[29] stated that measurements of choroidal thickness did not significantly differ between MS patients and the healthy controls, yet the choroidal layer was thicker in the group with ON than the group without ON. Esen et al.[31] reported thinner choroidal layer in all MS patients compared to healthy controls, regardless of ON history. It is observed that the choroidal thickness measurements of MS patients reported in the literature are different from each other. In the present study, choroidal thickness in MS patients was evaluated differently on OCT scans obtained when the patients were in remission and not receiving treatment. The drugs received by the patients during the scanning period, the difference between the average ages, and the disease duration can affect the measurements of choroidal thickness. These may be the reasons for the differences between studies in terms of choroidal thickness. Due to the controversial results regarding choroidal thickness, lower quality of evidence is available on the use of choroidal thickness measurements as an indicator of neurodegeneration and clinical progression in MS.

The small number of patients, relapsing-remitting MS being the inclusion criteria, and the inability to evaluate the progression of the patients' parameters examined in OCT over time are the limitations of this study.

CONCLUSION

In the current study, it was shown that LC and ppRNFL were thinner in MS patients than the controls regardless of the history of ON. We hypothesized that LC measurements can also be used to determine early damage of nerve fibers in patients with MS. Studies to be conducted with a higher number of patients, long-term follow-up of the measurements of thickness of LC and ppRNFL both before and after the attack, and more homogeneous groups in terms of MS subtypes may help to reach a better understanding of the role of LC structure in ON attack in cases of MS.

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