Evaluation of Lamina Cribrosa Layer in Multiple Sclerosis

Multipl Sklerozda Lamina Kribroza Tabakasının Araştırılması

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ABSTRACT

Purpose: We aimed to measure lamina cribrosa thickness (LCT), lamina cribrosa depth (LCD) and retinal nerve fiber layer (RNFL) thickness in multiple sclerosis (MS) patients and compare the results with eyes of healthy subjects.

Materials and Methods: The eyes of multiple sclerosis patients were compared with the eyes of a healthy control group. A full ophthalmologic examination was conducted for both groups. Optic coherence tomography (OCT) was used to measure LCT, LCD, and RNFL thickness values. Correlation analysis was conducted between the Expanded Disability Status Scale (EDSS) score and disease duration of the MS patients and the LCT, LCD, and RNFL thicknesses.

Results: Mean LCT values were 171.86±62.81 µm in the MS group and 230.1±66.84 µm in the control group. LCT was statistically significantly lower in the MS group than the control group ($p<0.001$). Mean LCD value was 300.9±100.5 µm in the MS group and 279.68±99.78 µm in the control group with no statistically significant difference ($p>0.05$). Mean RNFL thickness was 96 µm in MS group and 100 µm in the control group and was statistically significantly lower in the MS group ($p<0.05$). A statistically significantly moderate relationship was found between disease duration and EDSS score in the MS group with Spearman correlation analysis ($r=0.468$, $p<0.01$). A statistically significantly moderate relationship was found between the RNFL thickness and both disease duration and EDSS score ($r=-0.574$, $r=-0.601$, respectively, $p<0.001$).

Conclusion: The intraocular nerve fiber layer was affected in multiple sclerosis patients. The LCT and RNFL thickness were thinner in MS patients than in the control group but there was no difference in terms of LCD values.

Key Words: Multiple Sclerosis, Lamina Cribrosa Thickness, RNFL, Optic Neuritis, LCD.

ÖZ

Amaç: Multipl skleroz (MS) hastalarında lamina cribrosa kalınlığı (LKK), lamina cribrosa derinliği (LKD) ve retina sinir lifi tabakası (RSLT) kalınlığını ölçmeyi ve sağlıklı gözlerin sonuçları ile karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Multipl skleroz hastalarının gözleri sağlıklı kontrol grubunun gözleri ile karşılaştırıldı. Her iki grup için tam oftalmolojik muayene yapıldı. LKK, LKD ve RSLT kalınlık değerlerini ölçmek için optik koherens tomografi (OKT) kullanıldı. MS hastalarının Genişletilmiş Engellilik Durum Ölçeği (GEDÖ) skoru ve hastalık süresi ile LKK, LKD ve RSLT kalınlıkları arasında korelasyon analizi yapıldı.

Bulgular: Ortalama LKK değerleri MS grubunda 171.86 ± 62.81 µm, kontrol grubunda 230.1 ± 66.84 µm idi. LKK MS grubunda kontrol grubundan istatistiksel olarak anlamlı derecede düşüktü ($p <0.001$). Ortalama LKD değeri MS grubunda 300.9 ± 100.5 µm, kontrol grubunda 279.68 ± 99.78 µm idi ve istatistiksel olarak anlamlı bir fark yoktu ($p>0.05$). Ortalama RSLT kalınlığı MS grubunda 96 µm, kontrol grubunda 100 µm idi ve MS grubunda istatistiksel olarak anlamlı derecede düşüktü ($p <0.05$). Spearman korelasyon analizi ile MS grubunda hastalık süresi ile GEDÖ skoru arasında istatistiksel olarak anlamlı bir ilişki bulundu ($r = 0.468$, $p <0.01$). RSLT kalınlığı ile hem hastalık süresi hem de GEDÖ skoru arasında istatistiksel olarak anlamlı bir ilişki bulundu ($r = -0.574$, $r = -0.601$, sırasıyla, $p <0.001$).

Sonuç: Göz içi sinir lifi tabakası multiple skleroz hastalarında etkilenmiştir. LKK ve RSLT kalınlığı MS hastalarında kontrol grubundan daha ince idi, ancak LKD değerleri açısından fark yoktu.

Anahtar Kelimeler: Multipl Skleroz, Lamina Kribrosa Kalınlığı, RSLT, Optik Nörit, LKD.

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INTRODUCTION

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disorder of the central nervous system (CNS). Optic neuritis (ON) is common in MS patients and visual symptoms are the initial symptom in approximately 20% of the cases. Post-mortem studies have revealed visual pathway lesions in 90% of this group so even MS patients without a history of ON are likely to have relevant lesions.[1,2] Visual impairment in MS is most commonly caused by ON, and is the result of optic nerve axonal degeneration following the demyelination process.[3]

The lamina cribrosa (LC) consists of porous connective tissue on the inner surface of the optic nerve head.[4] It provides mechanical support for retinal ganglion cell (RGC) axons passing through the scleral canal.[5] It serves as a pressure barrier between the intraocular and retrobulbar cerebrospinal fluid (CSF) cavities and helps to stabilize the intraocular pressure (IOP).[6] There is growing evidence that the laminar region of the optic nerve head is the first to be damaged in axonal loss such as glaucomatous optic neuropathy (GON); LC has also been shown to become thinner in glaucomatous nerve fiber damage with in vitro studies.[7,8] İnflammation, mechanical IOP stress and ischaemia act to interrupt axoplasmic flow, thence damaging RGC axons.[9,10] The subsequent loss of RGC axons leaves the pores of the LC open, resulting connective tissue damage appropriate to induce scarring. Scar formation, successively, leads to tissue shrinkage and laminar thinning. Both GON and non-GON eyes experience a loss of RGC axons; thence, the laminar thinning of non-GON eyes may result from similar mechanisms.

OCT measurements have revealed lower peripapillary retinal nerve fiber layer (pRNFL) thickness in MS patients, even when there is no history of ON.[11,12] Measurements of ocular unmyelinated axons can indicate the level of MS-related neural degeneration as the retina is part of the central nervous system (CNS).[13]

Our study was the first to evaluate LCT in MS patients, as far as we are aware. Our aim was to measure the LCT, LCD and RNFL thickness values in MS patients and compare them with a healthy control group.

MATERIALS AND METHODS

This a cross sectional study included 50 eyes of 25 MS patients and 50 eyes of 25 control group subjects consisting of healthy individuals of similar age and gender. The study was approved by the ethics committee of our institution and was conducted in accordance with the Helsinki declaration. The disease duration, Expanded Disability Status Scale (EDSS) score, and the ON history were obtained from the patient history and previous reports of the patients followed-up with a diagnosis of MS at the neurology outpatient department and the MS subgroups were determined. The eyes were divided into two subgroups as MS ON (18 eyes) and MS Non-ON (32 eyes). Patients with systemic hypertension, diabetic mellitus, history of cerebrovascular events, and a history of ocular or head trauma were excluded. Patients with degenerative brain disease, a glaucoma diagnosis or suspicion, optic nerve disease, retinal disease, cornea and ocular surface disease affecting the OCT measurement and media opacity were also not included in the study. Patients who had optic neuritis in the past six months were again not included. The control group consisted of subjects of a similar age and gender with no ocular or systemic disease. A full ophthalmologic examination including visual acuity with the Snellen chart, biomicroscopy, IOP measurement and fundus examination was conducted for both groups. Patients with a refractive error higher than spherical ± 4 D or cylindrical ± 3 D were not included in the study. Central corneal thickness (CCT) and axial length (AL) were measured with the Lenstar 900 (Haag-Streit AG, Köniz, Switzerland). LCT, LCD, and RNFL measurements were conducted with SD OCT (Heidelberg Engineering, Heidelberg, Germany).

Lamina cribrosa thickness and LCD measurements were performed at the optic disc center in the OCD-EDI mode. Figure 1 shows the LCT limits and the Bruch membrane opening (BMO) in ONH OCT images of a patient with MS. The line connecting the ends of the Bruch membrane was defined as the BMO. Distances on the line were measured perpendicular to the reference line. Anterior and posterior borders of the high-grade reflective region at the vertical center of the ONH at the horizontal SDOCT section were determined as the LCT boundaries and the distance between them was defined as the LCT. We adjusted the contrast settings to help in image identification and to optimize LCT. We defined the lamina cribrosa depth (LCD) as the distance from the BMO to the LCT anterior border. We were careful to use the center of the LC plate during the thickness

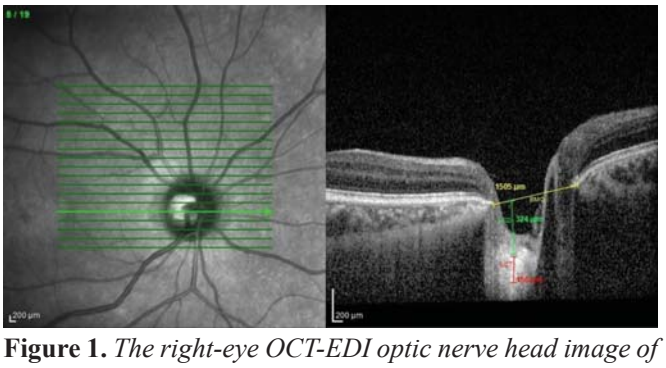

Figure 1. *The right-eye OCT-EDI optic nerve head image of a 32-year-old MS patient. BMO is shown with a yellow line, LCD a green line, and LCT a red line.*

measurement. All the final values we used were the mean of three measurements. All measurement were analyzed by one ophthalmologist (OK) in a blinded fashion.

STATISTICAL ANALYSIS

The SPSS 23.0 program was used for the statistical analysis. The distribution of the data was evaluated with the Shapiro-Wilks test. We used the Two Sample t-test in Independent Groups for variables distributed normally and the non-parametric Mann-Whitney U Test for variables not distributed normally in group comparisons. The Spearman correlation coefficient was used for correlation analysis. ANOVA was used in the comparison of more than two independent groups, and the Bonferroni and Tamhane tests were used for the analysis of the differences between the groups. The chi-square test was used for the analysis of categorical data. Scatter graphs were provided for the variables with a significant relationship between them as a result of correlation analysis. A p value <0.05 was accepted as statistical significance for all statistical analyses.

RESULTS

The mean age was 32.64±8.66 years in the MS patients and 36.6±8.46 years in the control group. MS patients consisted of 22 females and 3 males and the control group of 20 females and 5 males. No statistically significant difference was present between the two groups in terms of age or gender (p=0.109, p=0.440, respectively, table 1). No statistically significant difference was found between the axial length and central corneal thickness measurements of the two groups (p>0.05, table 1). The mean disease duration was 60 (48-156) months in patients in the MS ON group and 24 (3-132) months in the MS Non-ON group. Mean EDSS scores were 1 in the MS ON group and 2.5 in the MS Non-ON group. The clinical and demographic characteristics of the patients are presented in table 1. The mean LCT values were 171.86±62.81 µm in the MS group and as 230.1±66.84 µm in the control group. The mean LCT value was found to be statistically significantly lower in the MS group than the control group (p<0.001, table 2) but no statistically significant difference was found between the MS ON group and the MS Non-ON group (p>0.05, table 3). Mean LCD

Table 1. *Demographic characteristics of the MS and Control groups.*

	MS(n=50)	Control(n=50)	P
Age(y)	32.64±8.66	36.6±8.46	.109[t]
Gender(f/m)	22/3	20/5	.440[ki]
AL(mm)	23.37±0.65	23.24±0.79	.379[t]
CCT(µm)	532.5	536.5	.530[W]
	MS ON(18)	MS Non-ON(32)	
Duration(m)	60(48-156)	24(3-132)	.002[w]
EDSS	1(0-2.5)	2.5(0-7.5)	.023[w]

MS ON: Multiple sclerosis Optic neuritis, **MS Non-ON:** Multiple sclerosis Non Optic neuritis, **AL:** axial length, **CCT:** Central Corneal Thickness, **EDSS:** Expanded Disability Status Scale, [t]t test, [ki]Chi square, [w]Mann-Whitney. Y: year, m: month

Table 2. *LCT, LCD, RNFL thickness analyses of the MS and control groups.*

	MS ON(n=18)	MS Non-ON(n=32)	Control(n=50)	P
LCT(µm)	171.27±28.90	172.18±76.01	230.1±66,84	.000[A]
LCD(µm)	319.72±78.33	290.31±110.93	289.68±99.78	.351[A]
RNFL(µ)	82.77±15.02	100.25±8.99	100.76±2.26	.000[A]

LCT: Lamina cribrosa thickness, **LCD:** Lamina cribrosa depth, **RNFL:** Retinal nerve fiber layer
[a]Anova test

Table 3. *LCT, LCD and RNFL results of the MS ON and MS Non-ON groups*

	MS ON(n=18)	MS NON ON(n=32)	P
LCT(µm)	171.27±28.9	172.18±76	.952
LCD(µm)	319.72±78.33	290.31±110.93	.326
RNFL(µ)	82.77±15.02	100.25±8.99	.000

MS ON: Multiple sclerosis Optic neuritis, **MS Non-ON:** Multiple sclerosis Non Optic neuritis, **LCT:** Lamina cribrosa thickness, **LCD:** Lamina cribrosa depth, **RNFL:** Retinal nerve fiber layer,

measurements were 300.9±100.5 µm in the MS group and 279.68±99.78 µm in the control group with no statistically significant difference (p>0.05, table 2). We also found no statistically significant difference between the MS ON and MS Non-ON patients in terms of mean LCD measurements (p>0.05, table 3). Mean RNFL thickness was 96 µm in the MS group and 100 µm in the control group and was statistically significantly lower in the MS group (p<0.001, table 2). Mean RNFL thickness was statistically significantly lower in the MS ON group than the MS Non-ON group (p<0.001, table 3). A statistically significant moderate relationship was found between disease duration and the EDSS score in the MS group with Spearman correlation analysis (r=0.468, p<0.01, figure 2). A statistically significant moderate relationship was also found between the RNFL thickness values and both disease duration and EDSS (r=-0.574, r=-0.601, respectively, p<0.001, figure 3, 4). No relationship was found between the other parameters and disease duration or EDSS.

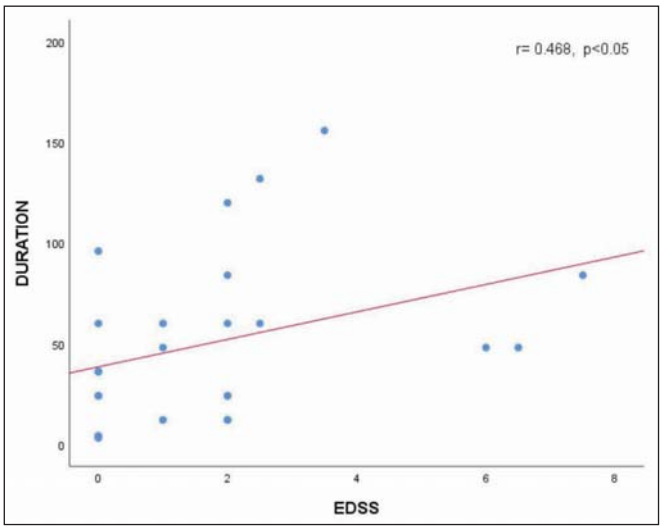

Figure 2. *Graphic of correlation between EDSS and disease duration in MS patients.*

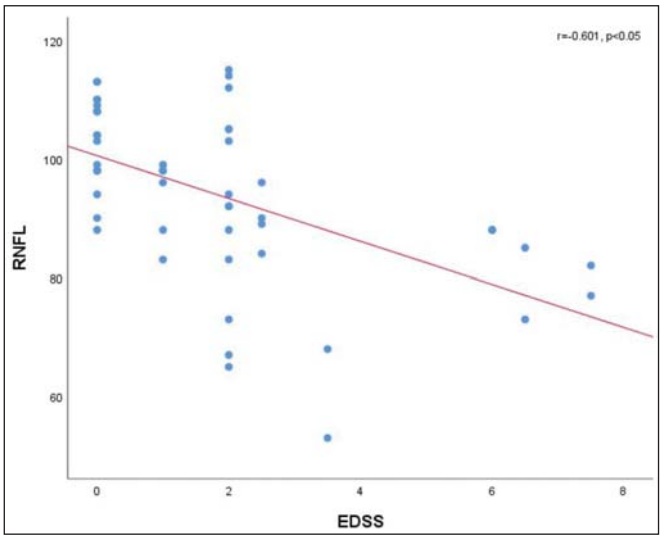

Figure 3. *Graphic of correlation between RNFL thickness and disease duration in MS patients.*

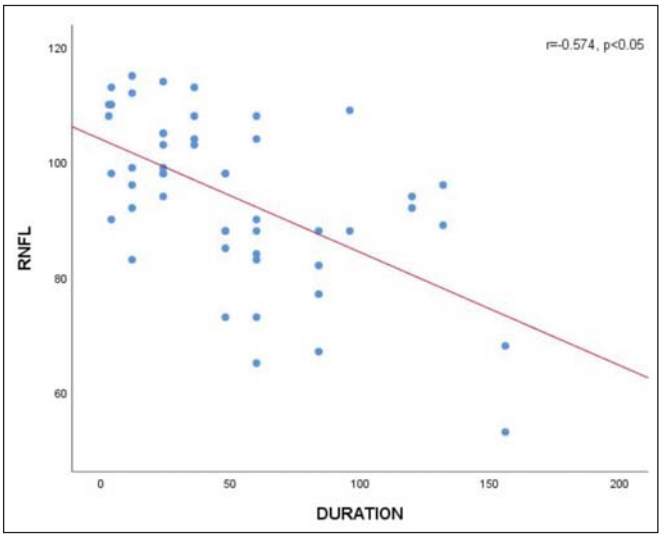

Figure 4. *Graph of correlation between RNFL thickness and EDSS values of MS patients.*

DISCUSSION

The LC is linked to the papillary area of the optic nerve head and receives its oxygen and nutrients from the laminar capillaries that pass through the laminar collagenase matrix. Mechanical IOP stress, inflammation and ischemia can interrupt the axoplasmic flow and thus damage RGC axons.[14,15] Subsequent loss of RGC axons can leave the LC pores open, and the connective tissue damage that eventually develops causes scarring. This scarring leads to tissue shrinkage and laminar thinning.

LCT measurements were found to be statistically significantly lower in MS patients than in the control group in this study. However, these values were not statistically significantly different between the MS ON group and the MS non-ON group. There was also no statistically significant difference between the MS patients and the control group for mean LCD measurements. The mean RNFL thickness measurements in MS patients were statistically significantly lower than in the control group. Mean RNFL thickness measurements in the MS ON group were also statistically significantly lower than in the MS Non-ON group.

The pathologic mechanism of the decreased ganglion cell inner plexiform layer (GCIPL) and RNFL thickness in MS patients with or without a history of neuritis is still unclear. It is possible that the ON resulting in retrograde degeneration and then in axonal loss could be the main mechanism. However, several different mechanisms are possible in MS patients with no clinical sign of ON but with typical RNFL and GCIPL loss of ~6.73 µm. [16]

Lower peripapillary RSLT values have been found in MS

patients with a history of ON compared to those without such a history or to healthy subjects.[11,17,18] RNFL thinning has also been reported in MS patients without previous retrobulbar ON in various studies.[11,19] A statistically significant decrease in RNFL has been reported by Kucharcuk et al. during MS, whether a history of ON is present or not.[20] We found the mean RNFL thickness to be statistically significantly lower in MS patients than the control group in our study. It was also statistically significantly thinner in the MS ON group than the MS Non-ON group. However, various studies have shown a significant decrease in RNFL and GCL in MS patients regardless of the history of an ON episode, in contrast to our study.[21-23] We did not find the decrease in RNFL and GCL thickness over 6 months to be significantly different between MS groups with or without ON although the values were significantly higher than that observed in controls. [24]

The lamina cribrosa is a dynamic structure. Previous studies have indicated a correlation between LCT and the risk of glaucomatous neuropathy.[4,25] Glaucoma surgery has been reported to lead to anterior LC displacement and prelaminar tissue thickening in addition to lowering the IOP in the Reis et al.[26] and Barrancos et al.[27] studies. Park et al.[28] have reported lower LCT values in normotensive glaucoma patients compared to normal eyes or those with primary open-angle glaucoma. We are not aware of any other studies evaluating LCT and LCD in MS patients. We found the LCT measurements in the MS group to be statistically significantly lower than in the control group. There was no statistically significant difference between the LCT measurements of the MS ON and MS Non-ON groups. Comparison of mean LCD measurements also did not reveal a statistically significant difference between MS patients and the control group.

Progressive axonal loss is known to be associated with the clinical parameters of disease duration and neurological disability. We found a moderate statistically significant relationship between the RNFL thickness values and both disease duration and EDSS score in our study ($r=-0.574$, $r=-0.601$, respectively, $p<0.001$). Some studies have reported a correlation between the RNFL thickness and EDSS, [29,30] but not others.[31] Bsteh et al.[32] observed a 3-fold increase in EDSS progression risk and 2.7-fold increase in cognitive decline over 3 years in MS patients with RNFL thickness <88 μm ($p < 0.001$).

Our study has certain limitations. Firstly, there is the possibility of measurement errors due to the manual LCT and LCD measurements. Secondly, we do not know the measurement values during the relapse period since all our MS patients were in remission.

In conclusion, while LCT measurements were thinner in the MS patients than in the control group, no difference was found between the MS subgroups. Mean RNFL measurements in both the MS ON and MS Non-ON groups were found to be lower than in the control group. It might be possible to use LCT measurements as an independent parameter to determine ocular involvement in MS patients. Larger long-term studies are required to support this notion.

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