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Evaluation of the lamina cribrosa in patients with multiple sclerosis using enhanced depth imaging optical coherence tomography

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Abstract

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system. Optic neuritis (ON) is common clinical manifestation of MS. Spectral domain optical coherence tomography (SD-OCT) has been used as a useful tool to quantify the neuronal damage in the eyes of MS patients. The study aimed to evaluate the lamina cribrosa thickness (LCT) and lamina cribrosa depth (LCD) in patients with MS and their relationship with Expanded Disability Status Scale (EDSS) score. Fifty-two eyes of 26 relapsing-remitting MS patients and 39 eyes of 39 healthy age- and sex- matched participants were evaluated in this prospective, cross-sectional, observational study. There were two MS subgroups: 38 MS eyes without an ON history (MS−ON), and 14 MS eyes with an ON history (MS+ON). The LCT and LCD were measured with SD-OCT. Of the 26 participants with MS, 14 (53.8%) were female and the mean (SD) age was 35.1 (6.2) years; of the 39 healthy controls, 26 (66.7%) were female and the mean (SD) age was 36.7 (8.2) years (P=0.19 for sex and P=0.27 for age). The mean LCT was not significantly different between MS patients and healthy controls (272.66 ± 33.52 µm and 272.58 ± 35.97 µm, respectively, P=0.992). The mean LCD was 325.15 ± 67.07 µm for the MS+ON group, 409.71 ± 93.18 µm for the MS−ON group, and 427.64 ± 91.65 µm for the healthy control group. The LCD was significantly decreased in MS+ON group compared to MS−ON group (P=0.011) and healthy controls (P=0.002). EDSS score was negatively correlated with LCD in MS patients (r= -0.313, P=0.025). This study revealed decreased LCD in MS eyes particularly with optic neuritis, and its relationship with increased disease severity. Additional longitudinal studies are needed to confirm the use of LCD as an imaging biomarker in patients with MS.

Keywords: Lamina cribrosa thickness, lamina cribrosa depth, multiple sclerosis, enhanced depth imaging optical coherence tomography

Introduction

Multiple sclerosis (MS) is an inflammatory-demyelinating disease of the central nervous system. MS often affects the brain and nerve tissues as well as the eyes. It causes visual loss, particularly due to optic neuritis (ON). ON is an acute inflammatory demyelinating disorder of the optic nerve which is common in MS. 50% of patients with MS develop ON at some point during the course of their disease and 15-20% of patients with MS have ON as their presenting demyelinating event. [1–3].

The lamina cribrosa (LC) is a mesh-like, multilayered collagenous structure that bridges the scleral canal aperture and supports the structure of the retinal ganglion cell (RGC) axons [4]. The optical coherence tomography (OCT) devices have enabled visualization of the LC in vivo [5,6]. Lamina cribrosa thickness (LCT) and lamina cribrosa depth (LCD) are studied in optic nerve disorders, particularly in glaucoma [7,8]. In glaucomatous eyes, increased IOP compresses the optic disc, and causes the thinning of lamina cribrosa [9].

Recently, it has been reported that LCTs of the eyes with glaucomatous optic neuropathy and non-glaucomatous optic neuropathy were thinner than those of control group eyes [10]. ON, a common feature of MS, may affect blood perfusion of the larger ocular vessels and possibly damage visual acuity [11]. Recently, a method was developed of measuring local circulation using high-speed OCT to perform quantitative angiography. Using the split-spectrum amplitude-decorrelation angiography algorithm, optic nerve head perfusion can be quantified [12].

The recent study measured the microcirculation in the ONH of MS eyes with and without a history of ON compared with healthy control eyes, and found that the mean ONH flow index in MS+ON group was significantly lower than the healthy control and MS−ON groups (p=0.004 for both), while there was no significant difference between the healthy control and MS−ON groups (p=0.924) [13].

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To the best of our knowledge, evaluation of LCT and LCD using OCT in patients with MS has not been reported yet. In the present study we aimed to evaluate the lamina cribrosa thickness and the lamina cribrosa depth in MS patients with Enhanced Depth Imaging (EDI)-OCT. We also aimed to investigate the correlation of the LCT and LCD with disease duration and Expanded Disability Status Scale (EDSS) score.

Material and Methods

The study was approved by the local ethics committee and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants after a detailed information of the study design.

Subjects and Study Design

Fifty-two eyes of 26 patients with relapsing-remitting MS and 39 eyes of 39 age and sex matched healthy individuals were enrolled in this cross-sectional study undertaken at a single tertiary referral hospital between May 27, 2016, and February 28, 2017. The diagnosis of MS was given according to the revised McDonald criteria, based on clinical and radiologic findings [14].

A complete neurological examination was performed, and physical disability score was assessed using the Kurtzke Expanded Disability Status Scale (EDSS) for each patient with MS [15]. The scores for the EDSS range from 0 to 10, and a higher score points greater disability. The presence of previous episodes of optic neuritis as reported by the neurologist or the patient was also recorded. Patients with a history of ON 6 months prior to the study, diabetes mellitus, any other neurologic disorders, or any other coexisting systemic disease, previous ocular trauma or surgery, and glaucoma or contact lens use were excluded from the study. The age and sex matched healthy subjects compromised the control group. In MS group the eyes were categorised into two subgroups, with respect to presence of ON history, as patients without ON history were included in the MS-ON group, and those with ON history were included in the MS+ON group. Of the 26 patients with MS, 14 (53.8%) had a history of unilateral optic neuritis, and 5 of them had three, 4 of them had two, and 5 of them had one previous episodes of optic neuritis.

All participants underwent a complete ocular examination including slit-lamp biomicroscopy, fundus examination, gonioscopy, keratometry measurement using a Scheimpflug camera (Pentacam HR; Oculus GmbH, Wetzlar, Germany), central corneal thickness (CCT) measurement, and axial length (AL) using the IOL Master (Carl Zeiss Meditec, Dublin, California). The refraction of the participants was measured using a Tonoref II autorefractor/tonometer (Nidek Co. Ltd.). The spherical equivalent (SE) was defined as the sum of the spherical power and the half of the cylindrical error. Intraocular pressure (IOP) was measured using Goldmann applanation tonometry (GAT). Corrected IOP was calculated according to the formula reported by Kohlhaas et al [16]. In all participants, the Humphrey field analyzer using the central 24-2 fields and the Swedish Interactive Thresholding Algorithm (SITA) standard strategy tests were performed.

A fixation loss, false negative or positive test results less than 20% were accepted as reliable visual field results. The peripapillary retina nerve fiber layer (RNFL) thickness measurements were obtained using spectral-domain OCT (SD-OCT). The OCT scanning circle (diameter, 3.4 mm) was manually positioned at the center of the optic disc, and the mean peripapillary RNFL thickness was recorded.

Lamina cribrosa assessment

An SD-OCT (Spectralis, Heidelberg Engineering Inc., Heidelberg, Germany) was used to measure the LCT and the LCD of the participants. Obtained scans were excluded from the analysis, if the quality score was less than 20 or the provided image of the fundus and/or the border of the lamina cribrosa was unclear. The method for enhanced depth imaging of the optic nerve head with an SD-OCT device is published elsewhere [17]. The SD-OCT device was set to image a 15°× 10° rectangle centered on the optic disc. This rectangle was divided into approximately 65 sections, each comprising an average of 100 OCT frames. From these horizontal B scans, we selected three frames (center, mid-superior, and mid-inferior) that passed through the optic nerve head, and parameters were measured in each of these frames. During measurements of thickness, we assigned full weight to the center of the lamina cribrosa plate.Figure 1 demonstrates a representative OCT image of lamina cribrosa borders and Bruch's membrane opening in an MS patient. The Bruch's membrane opening corresponds to the line that connects both ends of Bruch's membrane. The distances were measured on the line perpendicular to the reference line. The measurements were obtained as close as possible to the vertical center of the optic nerve head. Temporal side measurements were recorded, if a vessel trunk made the measurement impossible. Lamina cribrosa borders were defined as the anterior and posterior borders of the highly reflective region at the vertical center of the optic nerve head in horizontal SD-OCT sections, and the LCT was measured as the distance between them.

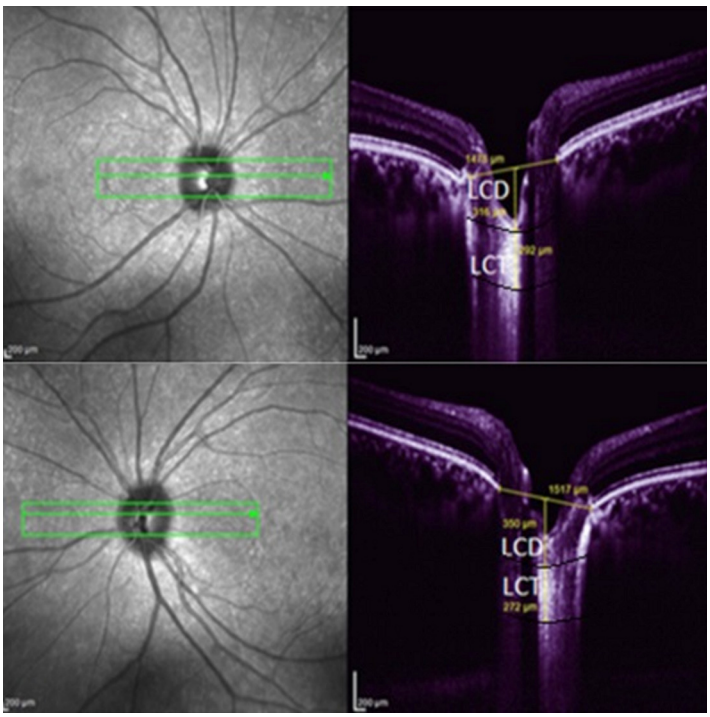

Figure 1. Optical coherence tomography images of a 33-year-old patient with multiple sclerosis (MS). Horizontal scans. (Top) Right eye with a prior optic neuritis (ON) history of the patient with MS. The thickness of the lamina cribrosa was 292 µm and depth of the lamina cribrosa was 316 µm. (Bottom) Fellow eye without ON history of the patient with MS. The thickness of the lamina cribrosa was 272 µm and depth of the lamina cribrosa was 350 µm

The clearest visualization of the lamina cribrosa was provided by the adjustment of contrast settings aided in the identification of

images. The distance between the Bruch's membrane opening and the anterior border of the lamina cribrosa was defined as LCD.

HEYEX software 6.0 (Heidelberg Engineering Inc., Heidelberg, Germany) were used to obtain the measurements. All images were analyzed by two independent researchers in a blinded fashion, who determined LCT and LCD twice. Hence, each LCT and LCD value was calculated four times, and the mean value was used in the primary analysis. Before the primary analysis, interexaminer and intraexaminer intraclass correlation coefficients were calculated using 15 randomly selected images to test the reproducibility of the LCT and LCD measurements.

Statistical analysis

Statistical analysis was performed using SPSS, version 21.0 (SPSS Inc., Chicago, IL, USA). Basic descriptive statistics were calculated on all the data gathered and are reported as the mean (SD) or median (interquartile range [IQR]), as appropriate. The normal distribution of the data was evaluated with the Kolmogorov–Smirnov test and Chi-square test was used to compare categorical parameters between MS and control group. A p value of less than 0.05 was accepted as statistically significant. The independent samples t test for normally distributed data and Mann-Whitney test for nonnormally distributed data were used to compare the measures between the MS patients and healthy controls. A 1-way analysis of variance test followed by the Tukey test or Kruskal-Wallis test and Mann-Whitney test with Bonferroni adjustment were used to compare the measures among subgroups according to patient history of optic neuritis. After Bonferroni adjustment, a p value less than 0.017 (equal to 0.05/3) was considered as statistically significant. Spearman correlation analysis was performed to evaluate the correlation of LCT and LCD with disease duration and EDSS score.

Results

A total of 52 eyes of 26 MS patients and 39 eyes of 39 healthy control subjects were evaluated. Table 1 summarized the patients' demographics and measured OCT parameters in both groups.

The mean (SD) age of the participants with 26 relapsing-remitting multiple sclerosis was 35.1 (6.2) years, and 14 (53.8%) of them were female. The mean (SD) age of the 39 healthy, age-matched controls was 36.7 (8.2) years, and 26 (66.7%) of them were female.

Intraexaminer intraclass correlation coefficient values (95% CIs for LCT and LCD were 0.895 (0.751–0.969) and 0.974 (0.916–0.992), respectively. Interexaminer intraclass correlation coefficients for LCT and LCD were 0.849 (0.761–0.979) and 0.943 (0.816–0.972), respectively.

There was no significant difference between MS and control groups with respect to age and sex (p = 0.27 and p = 0.19, respectively). The mean disease duration and the mean EDSS score of the MS patients was 6.92 ± 4.51 years, and 2.49 ± 1.01, respectively. The LCT was similar between MS and control groups (272.67 ± 33.53 µm , and 272.59 ± 35.97 µm, respectively, p = 0.92). However, the LCD was significantly lower in MS patients compared to control subjects (388.16 ± 94.29 µm and 427.64 ± 91.65 µm, respectively, p = 0.049). Moreover, the RNFL thicknesses were significantly decreased in MS group compared to those of control subjects (p < 0.05, except inferotemporal quadrant).

The subgroup analyses of the MS patients with respect to presence of ON were shown in Table 2.

The LCD was significantly decreased in MS+ON group (325.15 ± 67.07 µm) compared to MS-ON (409.71 ± 93.18µm, p = 0.011), and control groups (427.64 ± 91.65, p = 0.002). However, neither MS+ON, nor MS-ON groups were different than that of control subjects in terms of LCT (p = 0.970 and p = 0.994, respectively).

Spearman's correlation analyses revealed that EDSS score was negatively correlated with LCD in MS patients (r = -0.313, p = 0.025). LCD did not correlate with global retinal nerve fiber layer thickness (r = -0.021, p = 0.884) and disease duration (r = -0.193, p = 0.175).

Table 1. The comparison of the demographics and the measurement parameters (mean ± standard deviation) of multilpe sclerosis (MS) patients and controls

Parameters	Patients With MS (52 eyes)	Healthy Control Participant (39 eyes)	P value
Age (years)	35.1±6.22	36.79±8.3	0.270
Sex (Female/ Male)	28/24	26/13	0.190*
LCT (µm)	272.67±33.53	272.59±35.97	0.992
LCD (µm)	388.16±94.29	427.64±91.65	0.049
Temporal RNFL (µm)	59.75±17.67	74.41±13.41	<0.001
Superotemporal RNFL (µm)	115.96±28.85	138.33±20.02	<0.001
Superonasal RNFL (µm)	102.31±25.6	118.26±18.93	0.002
Nasal RNFL (µm)	68.92±15.33	78.87±10.82	<0.001
Inferonasal RNFL, median (IQR), (µm)	89.0 (80-101)	128.0 (110-142)	<0.001‡
Inferotemporal RNFL, median (IQR), µm)	126.0 (104-144)	134.0 (111-149)	0.241‡
Global RNFL (µm)	86.25±15.68	102.69±6.51	<0.001
Axial Length (mm)	23.43±0.74	23.3±0.62	0.358
SE, median (IQR), (Diopter)	-0.25 (-0.75-0.25)	-0.50 (-0.75-0.00)	0.252‡
CCT (µm)	533.69±24.58	550.36±26.91	0.003
Keratometry (Diopter)	43.25±1.12	43.07±1.03	0.434
IOP (mmHg)	13.73±1.99	14.92±2.64	0.016
Corrected IOP (mmHg)	14.43±1.75	14.92±2.60	0.288

LCT, Lamina Cribrosa Thickness; LCD, Lamina Cribrosa Depth; RNFL, Retina Nerve Fiber Layer; SE, Spherical equivalant; CCT, Central Corneal Thickness; IOP, Intra ocular pressure; IQR, interquartile range; *chi-square test; ‡ Mann-Whitney U test

Table 2. The comparison of the demographics and the measurement parameters (mean ± standard deviation) of MS With ON (MS+ON), MS Without ON (MS-ON) and control eyes

Parameters	Control (39 eyes)	Patients With MS		P Value		
		MS+ON (14 eyes)	MS-ON (38 eyes)	MS+ON vs MS-ON	MS-ON vs Control	MS+ON vs Control
Age (years)	36.79±8.3	32.85±5.73	35.87±6.26	0.391*	0.838*	0.203*
Sex(Female/Male)	26/13	8/6	20/18	0.940&	0.209&	0.406&
LCT (µm)	272.59±35.97	275.23±40.57	271.79±31.34	0.949*	0.994*	970*
LCD (µm)	427.64±91.65	325.15±67.07	409.71±93.18	0.011*	0.654*	0.002*
Temporal RNFL (µm)	74.41±13.41	60.92±22.56	59.34±16.02	0.950*	<0.001*	0.028*
Superotemporal RNFL (µm)	138.33±20.02	108.62±30.14	118.47±28.37	0.450*	0.003*	<0.001*
Superonasal RNFL (µm)	118.26±18.93	86.46±23.99	107.74±24.09	0.009*	0.096*	<0.001*
Nasal RNFL (µm)	78.87±10.82	62.62±10.28	71.08±16.26	0.125*	0.032*	<0.001*
Inferonasal RNFL, median (IQR), (µm)	128(110-142)	84.00(74-98)	91(80.75-102.75)	0.336‡	<0.001‡	<0.001‡
Inferotemporal RNFL, median (IQR), (µm)	134(111-149)	129(91.5-149)	124.5(104.75-142)	0.914‡	0.245‡	0.526‡
Global RNFL (µm)	102.69±6.51	81.38±18.33	87.92±14.56	0.237*	< 0.001*	<0.001*
Axial Length (mm)	23.3±0.62	23.44±0.8	23.43±0.73	0.998*	0.681*	0.791*
SE, median (IQR), (Diopter)	-0.5(-0.75-0)	-0.5(-1.12-0)	-0.12(-0.75-0.5)	0.146‡	0.081‡	0.516‡
CCT (µm)	550.36±26.91	536.15±24.66	532.84±24.83	0.915*	0.010*	0.202
Keratometry (Diopter)	43.07±1.03	43.1±1.43	43.3±1.01	0.825*	0.614*	0.997*
IOP (mmHg)	14.92±2.64	13.23±1.64	13.89±2.09	0.582*	0.127*	0.030*
Corrected IOP (mmHg)	14.92±2.60	13.83±1.32	14.63±1.85	0.642*	0.174*	0.061*
EDSS score, median (IQR),	NA	2.50(2.0-3.0)	2.50(1.50-3.0)	0.517#		
Disease duration, median (IQR), (years)	NA	7(4-14.5)	5(3-10)	0.329#		

LCT, Lamina cribrosa thickness; LCD, Lamina Cribrosa Depth; RNFL, Retina nerve fiber layer; SE, Spherical equivalant; CCT, Central corneal thickness; IOP, Intra ocular pressure; EDSS, Expanded disability status scale; IQR, interquartile range; NA, not applicable; *One-way analyses of variance test followed by Tukey test; &chi-square test;‡ Kruskal-Wallis test followed by Mann-Whitney test with Bonferroni adjustment. (P < 0.017 [equal to 0.05/3] is considered statistically significant.); #Mann-Whitney U test

Discussion

Multiple sclerosis is a neurodegenerative, inflammatory, demyelinating, and progressive disease of the central nervous system.

Although MS generally affects the brain and spinal nervous system, it can also cause ON in the eye. ON may be an early sign of MS. The loss of retina nerve fiber and axons occur due to neurodegeneration in MS [18].

OCT was used as a useful tool to quantify the neuronal damage in the eyes of MS patients [19]. To the best of our knowledge, the present study is one of the first to study to evaluate the LCD, and LCT in patients with MS. We found that the LCT was similar between MS and healthy control subjects. However, the LCD was significantly decreased in MS patients, particularly with the presence of ON.

The lamina cribrosa is a mesh-like structure that supports the axons of retinal ganglion cells [20]. It has been reported that posterior displacement of lamina cribrosa precedes early loss of RNFL and structural damage [21,22]. Particularly in patients with glaucoma, lamina cribrosa depression occurs before RNFL loss [23]. Xu et al. demonstrated that the optic disc surface becomes depressed before RNFL thinning in glaucoma [23]. Kim et al. reported that the lamina cribrosa morphology may help to predict the disease outcome in suspected glaucoma [24]. Omadoka et al. reported that LCT was significantly thinner in patients with glaucoma [25]. In the present study the LCT was similar between MS and control groups.

We suggest that LCT is not affected as reported in previous studies on glaucomatous eyes. In glaucoma, the lamina cibrosa might be vulnerable to IOP changes resulting lamina cribrosa thinning compared to MS patients.

In the pathogenesis of glaucoma, increased IOP cause RNFL damage, results with enlargement of the cup to disc ratio. LCD is a potential indicator of lamina cribrosa morphology, since it is well correlated with the magnitude of deformation of the posterior lamina cribrosa [26]. Similar to that of occurs in glaucoma, ON may cause axonal loss and lamina cribrosa changes. The nutrients and oxygen pass through the laminar collagenase matrix to the lamina cribrosa [10]. Any cause including increased IOP, ocular ischemia, and inflammation may damage retina ganglion cell axons via impeding the axoplasmic flow [9]. Thitiwichienlert et al. [10] suggested that both glaucomatous and non-glaucomatous optic neuropathic eyes had similar mechanism of the loss of retinal ganglion cell axons. However, in the present study, the LCD was significantly lower in patients with MS.

In contrast to glaucomatous optic neuropathy, in the present study, normal IOP measurements in MS patients, may be one of the cause of the lower LCD values.

Secondly, since MS is a demyelinating inflammatory disorder, glial cell proliferation, and the composition of inflammatory

infiltrates of the optic nerve may mask the increase in LCD of MS patients [27]. In an experimental study, Ueda et al. reported that oligodendrocytes contribute remyelinization of the optic nerve even with the absence of viable retinal ganglion axons [28]. Moreover, various optic disc morphologies including cup to disc ratio, total optic disc diameter may also affect the LCD measurements [29].

Previous studies demonstrated that RNFL thickness was decreased in patients with MS [30,31]. We also found significant thinning in the RNFL thickness in MS patients. The thinning of the RNFL is more evident in MS patients with ON, but also determined in MS patients without ON history. Even in the absence of an optic neuritis episode /history in MS, RNFL loss can be observed [32].

An increase in the EDSS score shows the progression of MS. Saidha et al. reported that EDSS score is correlated with RNFL and retina ganglion cell inner layer complex in MS patients [33].

In the present study we found a mild negative correlation between LCD and EDSS score in MS patients. Since the population in our study is relatively small, the use of LCD as a prognostic factor for MS needs further studies with larger sample.

The present study has some limitations. First the number of patients are relatively low to make a definitive conclusion. Second, the lack of longitudinal follow up is the other weakness. Third, the lack of optic nerve head morphology parameters may also affect the results. The last, identifying the deeper border of the lamina cribrosa was relatively subjective, since the the contrast of the signals in deeper tissue is lower even with use of EDI-OCT.

Conclusion

In conclusion, our study showed that the LCD was decreased in MS patients with or without ON compared to healthy controls. Moreover, the LCD was mildly correlated with EDSS score in MS patients. EDI-OCT is a useful tool for documenting structural alterations of lamina cribrosa in MS patients. Further prospective, extensive, longitudinal studies with a larger sample size are warranted to define association between MS and the lamina cribrosa morphology.

Competing interests
The authors declare that they have no competing interest.

Financial Disclosure
The financial support for this study was provided by the investigators themselves.

Ethical approval
Before the study, permissions were obtained from local ethical committee.

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