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ORIGINAL ARTICLE

Evaluation of lamina cribrosa thickness and lamina cribrosa curvature index in patients with schizophrenia

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Abstract

Purpose: It has been reported that there is a decrease in lamina cribrosa thickness (LCT) in neurodegenerative diseases. However, patients with schizophrenia have not been evaluated before. In the current study, we aimed to assess the LCT and lamina cribrosa curvature index (LCCI) in patients with schizophrenia.

Methods: The study included 20 eyes of 20 patients with schizophrenia and 20 eyes of 20 healthy controls. After routine ophthalmological examination, the optic nerve head area was scanned using swept-source optical coherence tomography (OCT) (DRI OCT Triton, Topcon Inc., Tokyo, Japan) to examine the lamina cribrosa curvature depth (LCCD) and LCT. To determine the degree of the posterior bending of the lamina cribrosa, LCCI was calculated using the formula, lamina cribrosa curvature depth/curvature width × 100.

Results: The mean age of the patients was 35.4±8.2 years, and there were 18 males. The LCT values were 205.86±21.38 µm in the schizophrenia group and 229.72±25.84 µm in the control group and were found to be statistically significantly lower in the schizophrenia group (p=0.003). The LCCI value in the schizophrenia group was found to be 3.07±0.70 and was similar to the healthy control group (p=0.923). Furthermore, there was no significant difference between the two groups regarding the LCCD or lamina cribrosa curvature width (p=0.396 and 0.362).

Conclusion: OCT revealed that the lamina cribrosa was thinner in patients with schizophrenia. LCT can also be used to determine early damage to nerve fibers in these patients.

Keywords: Lamina cribrosa curvature index; lamina cribrosa thickness; neurodegeneration; schizophrenia.

Schizophrenia is a serious brain disease that impairs the ability of individuals to distinguish between real and unreal phenomena and prevents healthy thought flow, emotional control, and normal behavior.^[1] Within the realm of research on the etiology of schizophrenia, there is an

important conceptual debate about whether schizophrenia is a neurodevelopmental or neurodegenerative disease.^[2,3] Neurodegenerative diseases have been shown to reduce the thickness of the retinal nerve fiber layer (RNFL), as assessed by optical coherence tomography (OCT), which



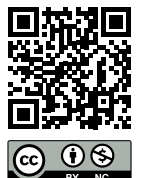
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correlates with findings from neuroradiological imaging.^[4-6] Being the only component of the central nervous system that can be directly examined with optical instruments, the retina provides a distinct model for studying neuronal changes in various neuropsychiatric conditions.^[7] Parallel to the reduction in gray and white matter volume in neuroimaging in patients with schizophrenia, RNFL thickness, ganglion cell thickness, and macular thickness have also been reported to decrease.^[8-11]

The lamina cribrosa is a mesh-like structure consisting of connective tissue and holes through which the axons of retinal ganglion cells (RGCs) pass while forming the optic nerve. The swept-source OCT has allowed for more detailed visualization of the lamina cribrosa.^[12] It has been reported that the diagnostic ability of lamina thickness is more sensitive than that of RNFL thickness.^[13] The lamina cribrosa curvature index (LCCI), which is used to measure the degree of curvature of the lamina cribrosa, has recently been proposed as a reliable parameter to quantify deformation in this structure. The deformation of the lamina cribrosa can exert mechanical stress on axons passing through the laminal pores, which can eventually lead to the apoptosis of RGCs.^[14] Glaucoma, the most common type of acquired optic neuropathy, is characterized by the progressive loss of RGCs and their axons. Studies have reported that lamina cribrosa thickness (LCT) decreases in glaucoma and that the LCCI increases in correlation with glaucomatous damage.^[14,15] However, no study in the literature has investigated LCCI in neurodegenerative diseases.

This study aimed to assess the LCT, lamina cribrosa curvature depth (LCCD), and LCCI in patients with schizophrenia and compare these measurements with those of a healthy control group.

Materials and Methods

The study included patients who were followed up due to schizophrenia according to the Diagnostic and Statistical Manual-V, the World Health Organization, and healthy controls. After obtaining the Haydarpasa Numune Research and Training Hospital ethics committee's approval, (Date: 23.10.2023, No: HNEAH-KAEK 2023/178) the study was conducted by the ethical standards outlined in the Declaration of Helsinki. All participants provided informed consent.

Twenty patients with schizophrenia and 20 healthy individuals were included. Patients with accompanying ocular diseases (uveitis, cataract, glaucoma, optic neuropathy, and retinal diseases), a history of intraocular

surgery or ocular trauma, those with >3D myopia, >3D hyperopia, >1D astigmatism, or comorbid psychiatric disorders other than schizophrenia; those using typical antipsychotic medications; and those with diabetes mellitus, hypertension, a history of cerebrovascular accident, or substance use (including smoking) were not included in the study. The control group was selected from healthy volunteers. For both groups, only the right eyes were included in the sample.

All participants underwent a comprehensive ophthalmic examination, including autorefractive measurements, best-corrected visual acuity evaluation, slit lamp biomicroscopy, intraocular pressure (IOP) measurement using Goldmann applanation tonometry, fundus evaluation, and axial length (AL) measurement (IOL Master, Carl Zeiss Meditec, Dublin, CA, USA), and visual field examinations. No participant had a glaucoma hemifield test result beyond the normal limits. All participants' mean and pattern standard deviation values were within normal limits.

OCT (Topcon Swept Source OCT DRI OCT Triton, Topcon Co., Japan) was performed to evaluate lamina cribrosa parameters. The LCT and LCCI were assessed using the OCT images of the optic disc head. Measurements were performed in six slices selected at 30° angle intervals (0°, 30°, 60°, 90°, 120°, and 150° clockwise) from radial B-scans centered on the optic disc. To calculate lamina cribrosa curvature width (LCCW), vertical lines were drawn from the endpoints of Bruch's membrane to the anterior surface of the lamina cribrosa. These two points were linearly connected. The LCCD was calculated as the vertical distance from the center of the lamina cribrosa curvature to the anterior lamina surface (Fig. 1). The LCCI was calculated using the following formula: $(LCCD/LCCW) \times 100$. The LCT was defined as the distance between the outer and inner borders of the hyperreflective zone at the vertical center of the optic disc head. Six measurements were performed, and their average was used for statistical analysis.

Two investigators conducted all measurements without access to the participants' clinical data (MBY, RB). To assess the reliability and consistency of the measurements, intra- and inter-observer correlation coefficients were computed for LCT and LCCI.

Statistical Analysis

The data were processed using IBM SPSS Statistics Standard Concurrent User v. 29. Descriptive statistics were given as the number and percentage (%) of units and mean \pm standard deviation. The normality of the data distribution for

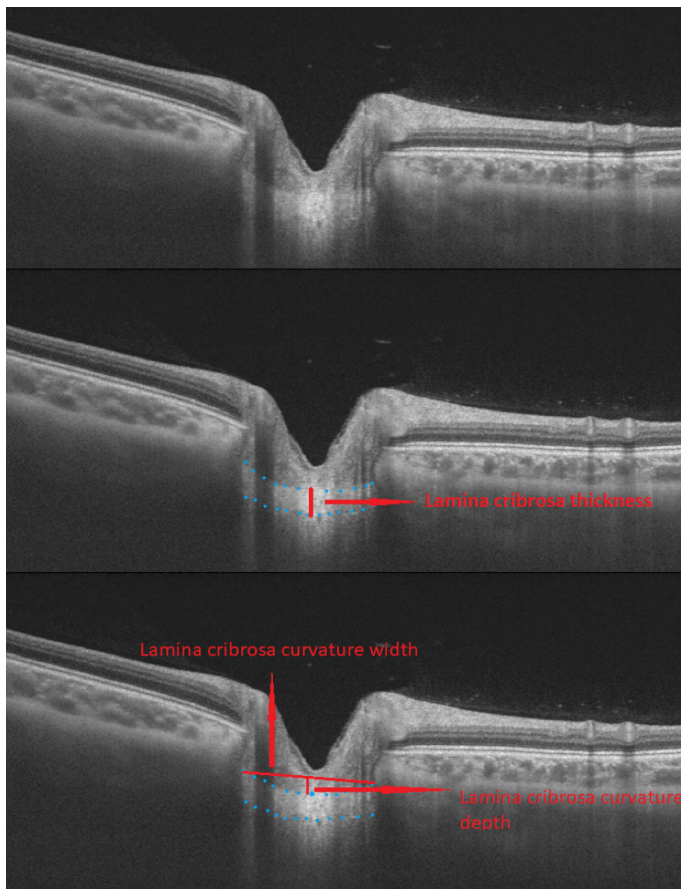


Fig. 1. Measurement of laminal parameters on the radial optical coherence tomography cross-section of the optic disc.

numerical variables was evaluated with the Shapiro–Wilk normality test. The homogeneity of the variance of the groups was analyzed with the Levene test. The comparisons between two groups for numerical variables were conducted using an independent samples t-test. A $p < 0.05$ was regarded as statistically significant.

Table 1. Demographic features of the study groups

	Groups		Test statistic	
	Schizophrenia n=20	Control n=20	Test value	p
Gender, n (%)				
Male	18 (90.0)	18 (90.0)	-	-
Female	2 (10.0)	2 (10.0)		
Age	35.4±8.2	36.3±8.7	0.341	0.738 [†]
Spherical equivalent (D)	-0.350±0.600	-0.336±0.456	0.080	0.937 [†]
IOP (mmHg)	13.80±1.58	14.40±1.82	1.115	0.272 [†]
CCT (μm)	549.5±7.8	555.8±15.6	1.631	0.111 [†]
Axial length (μm)	23.71±0.46	23.71±0.50	0.020	0.984 [†]

Numerical data are summarized as mean±standard deviation; [†]Independent-samples t-test; n: Number of patients; %: Column percentage; IOP: Intraocular pressure; CCT: Central corneal thickness.

The sample size was determined considering the effect size of the difference between the LCT of the groups, as reported by Omodaka et al.^[16] Accordingly, a total of 40 eyes (20/group) was calculated, considering an effect size of $f^2 = 1.19$, a 5% Type I error, and a statistical power of 95%.

Results

The study included a total of 40 participants, of whom 20 were in the schizophrenia group and 20 were in the control group. The mean age of the patients was 35.4±8.2 years, and there were 18 (90%) males. Gender, age, spherical equivalent, IOP, CCT, and AL were similar between groups ($p > 0.05$ for all) (Table 1).

The LCT values were 205.86±21.38 μm in the schizophrenia group and 229.72±25.84 μm in the control group and were found to be statistically lower in the schizophrenia group ($p = 0.003$). The LCCI value in the schizophrenia group was found to be 3.07±0.70 and was similar to the healthy control group ($p = 0.923$). Furthermore, there was no significant difference between the two groups regarding the LCCD or LCCW ($p = 0.396$ and 0.362) (Table 2).

To assess the reliability and repeatability of the measurements, intra- and interobserver correlation coefficients were computed for LC depth and LC thickness values and were found to be > 0.9 for all measurements.

Discussion

In this study, we found the lamina cribrosa to be thinner in patients with schizophrenia compared to the healthy control group. The LCCI and LCCD were similar between the two groups. To the best of our knowledge, no previous study has evaluated the LCT or LCCI in schizophrenia.

Table 2. Comparison of measurements of lamina cribrosa parameters between the study groups

	Groups		Test statistic	
	Schizophrenia n=20	Control n=20	Test value	p
LCCD (μm)	46.89 \pm 7.74	49.52 \pm 11.33	0.859	0.396 [†]
LCCI	3.07 \pm 0.70	3.09 \pm 0.60	0.097	0.923 [†]
LCT (μm)	205.86 \pm 21.38	229.72 \pm 25.84	3.181	0.003 [†]
LCCW (μm)	1547.6 \pm 178.7	1595.1 \pm 144.6	0.923	0.362 [†]

Numerical data are summarized as mean \pm standard deviation. [†]Independent-samples t-test. n: Number of patients; %: Column percentage; LCCD: Lamina cribrosa curvature depth; LCCI: Lamina cribrosa curvature index; LCT: Lamina cribrosa thickness; LCCW: Lamina cribrosa curvature width.

Several studies have reported retinal functional and structural abnormalities in patients with schizophrenia. [17] Lizano et al. [9] observed decreases in the peripapillary RNFL thickness, ganglion cell layer/inner plexiform layer thickness, and macular volume in patients with schizophrenia; however, they did not detect any change in choroidal or macular thickness. Budakoglu et al. [18] found temporal quadrant RNFL and temporal quadrant peripapillary vascular density values to be lower in patients with schizophrenia than in healthy controls. Ascaso et al., [19] who divided cases of schizophrenia into recent illness episode and non-recent illness episode groups, reported that only the latter showed a decrease in retinal thickness in all parameters. The authors attributed this to neuroinflammation and edema that might occur during the acute disease period, suggesting that this could mask symptoms of tissue loss. In another study, no significant difference was found between the schizophrenia and control groups to the RNFL or subfoveal choroidal thickness. Since the patients in this study were selected from the inpatient unit and were probably in an acute phase of the disease, the authors similarly drew attention to the possibility of neuroinflammation masking symptoms. [20] Although hospitalized patients with acute exacerbations were included in our study, the LCT was still found to be lower in patients with schizophrenia than in healthy controls.

Lamina cribrosa is important for transmitting neurotrophic factors from the lateral geniculate nucleus to RGCs and maintaining the structural integrity of nerve fibers. In neurodegenerative diseases, OCT studies have shown that, in addition to the thinning of the RNFL, there is also a decrease in the LCT, which also correlates with neuroradiological imaging. Eraslan et al. [21] found the average laminar thickness to be 209.4 \pm 40.2 μm in individuals with Parkinson's disease and 292.5 \pm 3.7 μm in healthy eyes, reporting a significantly lower value in

the patient group. Balcı et al. [22] evaluated patients with multiple sclerosis and measured the LCT as 180.6 \pm 40.5 in those who had an optic neuritis attack, 197.0 \pm 26.4 in those without an optic neuritis attack, and 246.5 \pm 33.2 in the healthy control group. The authors concluded that the lamina cribrosa was thinner in cases of multiple sclerosis, regardless of the presence of an optic neuritis attack. Lee et al. [23] determined that in eyes with primary open-angle glaucoma, the mean LCT was smaller than the breakpoint (<221.14 μm), and these eyes exhibited worse results in terms of not only global cognition but also visuospatial function and visual memory than in those with a larger mean LCT. In another study evaluating Alzheimer's disease, an elevated level of T-tau protein in cerebrospinal fluid was found to be associated with a thinner lamina cribrosa. [24]

Glaucoma, the most common type of acquired optic neuropathy, is defined by the progressive loss of RGCs and their axons. In glaucoma, RGC axon damage is considered to occur either due to direct axonal compression as it passes over the lamina cribrosa or as a result of disruption in the mechanical or nutritional support provided by glial cells and lamina cribrosa capillaries. The deformation of the lamina cribrosa has been shown to occur before detectable changes in RNFL thickness, as measured by spectral-domain-OCT in an experimental glaucoma model. [25] There are also studies reporting a thinner and deeper lamina cribrosa and higher LCCI in glaucomatous eyes than in control eyes. [14,15] However, Kim et al. [26] detected no change in lamina cribrosa morphology in autosomal dominant optic atrophy with primary RGC degeneration compared to normotensive glaucoma and the healthy control group. Furthermore, the LCD and LCCI have been reported to be similar between eyes with non-arteritic anterior ischemic optic neuropathy and healthy eyes. [27] Similarly, in the current study, intraocular pressure was normal in patients with schizophrenia, and the LCCD and LCCI values were similar between the groups.

The loss of retinal neurons in patients with schizophrenia has been proposed to be caused by retrograde transsynaptic degeneration.^[9,28] Cho et al.^[29] reported that thalamic connectivity was disrupted in schizophrenia. Another possible explanation is that retinal changes may occur secondary to the reduction in cortical gray matter volume, which has been associated with antipsychotic medication intake.^[30] Our study exclusively included individuals diagnosed with schizophrenia who were receiving atypical antipsychotic medications to reduce the effects of the drugs. However, currently, there is no direct evidence concerning the potential mechanism of retinal thinning in schizophrenia.

Our study has several limitations, the primary restriction being the small sample size. In addition, since no software was available for automatic measurements, the measurements of LCT and LCCD were performed manually. Furthermore, we could not evaluate whether there is a progressive change in lamina cribrosa parameters in patients with schizophrenia. Despite these limitations, this study is important as it is the first investigation of lamina cribrosa parameters in patients with schizophrenia.

CONCLUSION

In our study, we found that the LCT was thinner in patients with schizophrenia. Large-scale studies should validate this finding, and the possible underlying causes should be explored from a physiopathological standpoint. In light of our findings, we hypothesize that the LCT can also be used to assess early damage to nerve fibers in these patients.

Ethics Committee Approval: The Haydarpasa Numune Research and Training Hospital Ethics Committee granted approval for this study (date: 23.10.2023, number: HNEAH-KAEK 2023/178).

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