

Lamina cribrosa thickness in children with hyperopic anisometropic amblyopia

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Abstract

• **AIM:** To determine lamina cribrosa thickness (LCT) in the optic nerve head region of the eyes in children with hyperopic anisometropic amblyopia and to compare this thickness with that of fellow eyes, hyperopic non-amblyopia, and age-matched controls.

• **METHODS:** Thirty-two patients (12.0 ± 1.8 y, mean \pm standard deviation) with hyperopic anisometropic amblyopia, 31 subjects with age- and refractive error-matched hyperopic non-amblyopia (10.7 ± 2.2 y), and 32 age-matched controls (11.2 ± 2.0 y) were included in this prospective, cross-sectional study. LCT was measured using an enhanced depth-imaging program of a spectral domain optical coherence tomographic instrument in all participants, and the correlation between LCT and axial length was calculated.

• **RESULTS:** The mean LCT was 180.9 ± 29.4 μ m in amblyopic eyes, 247.7 ± 19.0 μ m in fellow eyes, 251.6 ± 27.3 μ m in hyperopic non-amblyopic eyes, and 240.2 ± 15.8 μ m in control eyes. Lamina cribrosa in amblyopic eyes was significantly thinner than fellow, hyperopic non-amblyopic, and control eyes ($P < 0.05$). There was no significant correlation in LCT and axial length between amblyopic ($P = 0.16$) and control ($P = 0.31$) group.

• **CONCLUSION:** Lamina cribrosa of eyes with hyperopic anisometropic amblyopia is significantly thinner than that of fellow eyes, hyperopic non-amblyopia, and age-matched controls. The LCT profile in amblyopic eyes is different from that observed in fellow, hyperopic non-amblyopic, and control eyes.

• **KEYWORDS:** anisometropia; amblyopia; hyperopia; lamina cribrosa; optical coherence tomography.

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INTRODUCTION

Amblyopia is a visual system developmental disorder that is accompanied by reductions in unilateral or bilateral visual acuity (VA) even in cases with structurally normal eyes with no pathology that are receiving optimal refractive correction^[1]. The visual deficit is associated with the presence in early life of strabismus, anisometropia, or, less often, a visual axis obstruction (*e.g.* congenital cataract)^[2-3]. Among these, the most important risk factor for amblyopia is hyperopic anisometropia^[4].

Several animal and human studies have shown that visual deprivation after birth effects growth of cells in the lateral geniculate body^[5-6] and visual cortex^[7]; whether or not the choroid and/or retina are altered in amblyopic eyes is still being debated. Amblyopic eyes can be examined with optical coherence tomography (OCT), which determines the retinal morphology of the human eye and confirm whether or not the patient has a structurally normal retina. Recently, there have been several reports regarding the thickness of the retinal nerve fiber layer^[8-9], macular volume^[10], thickness of the retina^[11-13], and choroidal thickness^[14-15] in eyes with amblyopia. However, in human children, the relationship between lamina cribrosa thickness (LCT) and amblyopia has not yet to be determined.

The present study aimed to evaluate the LCT and lamina cribrosa depth (LCD) of eyes with hyperopic anisometropic amblyopia and to determine the differences between these parameters with fellow eyes, eyes with hyperopic non-amblyopia, and eyes of age-matched controls.

SUBJECTS AND METHODS

Patients This cross-sectional, comparative, non-interventional study conducted at the Kayseri Training and Research Hospital between July 2016 and February 2017. The study's protocol was written in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of University of Erciyes, Turkey. All participants (or parents/legal guardians, as applicable) consented for original measurements and review of their medical records.

Subjects were diagnosed as being amblyopic in cases where the best-corrected visual acuity (BCVA) of one eye was $\leq 20/30$ or was worse than the fellow eye by at least two Snellen VA lines. A difference of ≥ 2.00 diopters (D) in both eyes was classified as anisometropia.

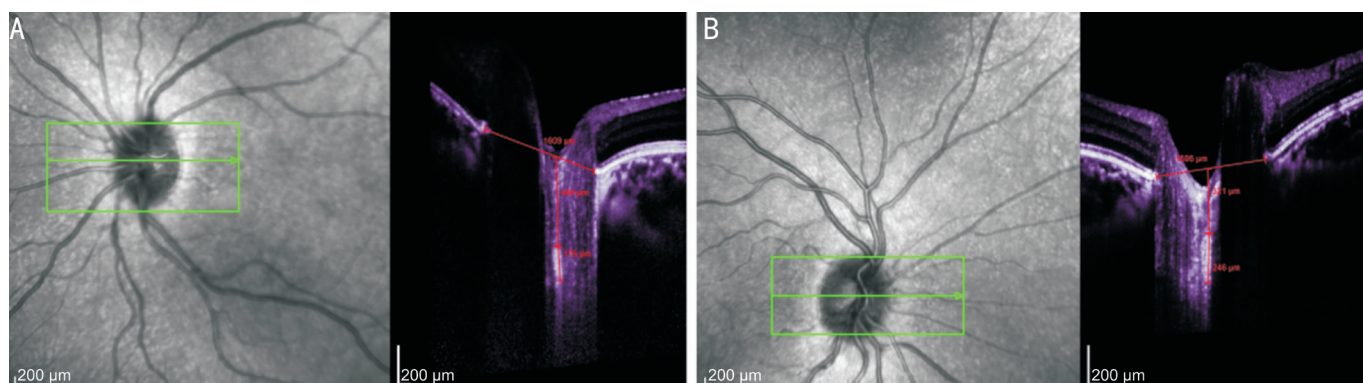


Figure 1 Images (OCT) from an amblyopic patient (9-year-old) Horizontal scans. A: Amblyopic eye with a BCVA of 1.0 logMAR units and the LCT of 176 μm ; B: Patient's fellow eye with a BCVA of 0 logMAR units and the LCT of 246 μm .

In total, 32 eyes with hyperopic anisometric amblyopia and their fellow eyes and 31 hyperopic non-amblyopic eyes were included the study. The mean patient age was $12.0 \pm 1.8\text{y}$ (range: 9-14y). All participants underwent dilated fundoscopic examinations. Patients were not included in the study who had a history of undergoing an intraocular surgery, strabismus, laser treatment, organic eye diseases, cataract, glaucoma, or any other retinal disorders. I also had to exclude any patient who could not cooperate for an OCT examination.

Thirty two right eyes of 32 control subjects ($11.2 \pm 2.0\text{y}$) who had VA that was either normal or corrected-to-normal [0 logarithm of the minimal angle of resolution (logMAR) units or better] in both eyes were included the study.

These age-matched controls were all between 8 and 13 years old and were visiting Kayseri Training and Research Hospital for regular visual screening. All of the controls had good VA with a spherical equivalent (SE) ranging from -0.50 square diopters (DS) to 0.87 DS and did not have any retinal diseases. The parents of the controls also provided informed consent after being told about the study and its procedures.

Ophthalmic Examination Each patient was given 3 drops of 1% cyclopentolate (Cyclogyl; Alcon Couvreur, Purrs, Belgium) at 5min intervals, and underwent cycloplegic refraction 45min later. I measured refraction using a TonorefII autorefractor/tonometer (Nidek Co., Ltd., Japan). Every study participant underwent 5 consecutive autorefractor readings, and each of these had to be within 0.25 D of one other. The following formula was used to calculate SE: sum of the spherical + 1/2 of the cylindrical error.

All of the patients also underwent other clinical examinations including BCVA, refractive error (SE), slit lamp examination, extraocular movements, ophthalmoscopic examination, intraocular pressure, central corneal thickness (*via* a Scheimpflug camera (Pentacam HR; Oculus GmbH, Wetzlar, Germany), and the eye's axial length *via* the IOL Master (Carl Zeiss Meditec, Dublin, California, USA). I used a standard Snellen chart to measure the VA of each patient, and VA decimal values were converted to logMAR units in order to undergo statistical analysis.

Optical Coherence Tomography A Heidelberg Spectralis spectral domain OCT (SD-OCT; Heidelberg Engineering, Heidelberg, Germany) with an enhanced depth imaging program determined the LCT of each patient from their images following pupillary dilation. I excluded all scans having a quality score <20 as well as those of inadequate quality (*e.g.* unclear fundus images, unclear LCT border).

Enhanced Depth Imaging SD-OCT of the Optic Nerve Head I used a previously described method for SD-OCT (EDI-OCT) enhanced depth imaging of optic nerve head (ONH)^[16]. In general, the instrument was set to image a $15^\circ \times 10^\circ$ rectangle centered on the optic disk. This rectangle was divided into approximately 65 sections, each of which had 100 OCT frames on average. From these horizontal B scans, three frames (center, mid-superior, and mid-inferior) that passed through the ONH were selected, and parameters were measured in each of these frames. The center of the lamina cribrosa plate was utilized to determine thickness during the measurements. The borders of the lamina cribrosa and the Bruch's membrane opening (BMO) are shown in an ONH OCT image in Figure 1. The BMO was defined as the line connecting both ends of Bruch's membrane. Every distance was determined on a line at a right angle to the reference line, and all parameters were measured as close to the perpendicular ONH center as possible. In cases where the measurements could not be made due to a vessel trunk, measurements were recorded at the temporal side. Lamina cribrosa borders were defined as the posterior and anterior borders of the highly reflective area at the ONH's perpendicular center in the horizontal SD-OCT cross-section. The thickness of the lamina cribrosa was defined as the distance between these two borders. I used image adjustments (*e.g.* contrast) in order to provide the clearest images of the lamina cribrosa. The distance between the BMO and the anterior border of the lamina cribrosa was defined as LCD.

HEYEX software 6.0 (Heidelberg Engineering Inc., Heidelberg, Germany) was used to obtain all measurements. Two examiners independently analyzed every image in this study. Both examiners independently determined both LCT and LCD

Table 1 Demographic and ocular characteristics of patients, hyperopic non-amblyopic eyes, and controls

Demographic information	Amblyopic eyes (n=32)	Fellow eyes (n=32)	Control eyes (n=32)	Hyperopic non-amblyopic eyes (n=31)	Amblyopia vs fellow	Amblyopia vs control	Amblyopia vs hyperopic non-amblyopia
Age (y)	12.0 ±1.8	12.0 ±1.8	11.2±2.0	10.7±2.2	P=1.0	P=0.58	P=0.15
Gender (F/M)	15/17	15/17	16/16	14/17	P=1.0	P=0.86	P=0.58
IOP (mm Hg)	13.3 ±1.05	13.2±2.01	13.5±1.9	13.4±1.5	P=0.99	P=0.97	P=0.99
VA (logMAR)	0.36±0.17	-0.07±0.08	-0.09±0.10	-0.06±0.08	P<0.001	P<0.001	P<0.001
SE (D)	5.62±1.14	1.26±0.61	0.34±0.39	5.27±0.80	P<0.001	P<0.001	P=0.84
AL (mm)	21.85± 0.98	22.56±0.83	22.55±0.39	21.97±0.58	P=0.051	P=0.056	P=0.94
CCT (µm)	558.89±21.17	557.10±21.68	562.33±23.57	562.74±15.86	P=0.99	P=0.94	P=0.91

IOP: Intraocular pressure; logMAR: Logarithm of the minimal angle of resolution; AL: Axial length; CCT: Central corneal thickness.

twice. Thus, each LCT and LCD value was obtained four times. The mean of these four values was used in the primary analysis. Before the primary analysis, intraexaminer, intraclass correlation coefficients were calculated using 15 randomly selected images to test the reproducibility of the LCT and LCD measurements.

Statistical Analyses All of the statistical analyses in this study were executed *via* statistical software (SPSS version 21.0; SPSS, Inc., Chicago, IL, USA). Pretest statistical power was 90%. Descriptive statistics for continuous variables were calculated as means±SD. SE was determined as follows: spherical power + 1/2 of the minus cylinder power. I used logMAR VA (converted from Snellen VA) for statistical analysis. Distributions of SE, VA of the amblyopic eye, VA of the fellow eye, axial length, LCT, and LCD were confirmed as normally distributed. One-way analysis of variance (ANOVA) was used to determine the significance of differences in values among amblyopic eyes, fellow eyes, hyperopic non-amblyopic eyes, and control eyes. LCT in the amblyopic eyes was compared with that in the fellow, hyperopic non-amblyopic eyes, and control eyes by using Tukey tests. Pearson's correlation coefficient was used to determine the significance of correlations among LCT and axial length, age, and SE. Significance was set at a *P* value of less than 0.05.

RESULTS

Table 1 presents the demographic and ocular characteristics of patients, hyperopic non-amblyopia, and controls. No significant differences were observed for age, sex, and intraocular pressure between groups (*P*>0.05). The mean BCVA was 0.36±0.17 logMAR units in amblyopic eyes, -0.07±0.08 logMAR units in fellow eyes, -0.06±0.08 logMAR units in hyperopic non-amblyopic eyes, and -0.09±0.10 logMAR units in control eyes. The amblyopic eyes had significantly worse mean BCVA than fellow eyes, hyperopic non-amblyopic eyes, and control eyes (all *P*<0.001).

The mean SE was 5.62±1.14 (range, 4.12-7.50) D in amblyopic eyes, 1.26±0.61 (range, 0.50-3.12) D in fellow eyes, 5.27±0.80

(range, 4.00-6.87) D in hyperopic non-amblyopic eyes, and 0.34±0.39 (range, -0.50-0.87) D in control eyes (*P*<0.001, ANOVA). There was no significant difference in SE value between amblyopic and hyperopic non-amblyopic eyes (*P*=0.84) however, there was significantly more hyperopia in amblyopic and hyperopic non-amblyopic eyes than fellow eyes (*P*<0.001) and control eyes (*P*<0.001). Fellow eyes had significantly more hyperopia than control eyes (*P*<0.001).

The mean axial lengths were as follows: 21.85±0.98 mm in amblyopic eyes, 22.56±0.83 mm in fellow eyes, 21.97±0.58 mm in hyperopic non-amblyopic eyes, and 22.55±0.39 mm in age-matched control eyes. There was no significant difference in this length among all groups (*P*=0.051, ANOVA).

The mean central corneal thickness was 558.89±21.17 µm in amblyopic eyes, 557.10±21.68 µm in fellow eyes, 562.74±15.86 mm in hyperopic non-amblyopic eyes, and 562.33±23.57 µm in age-matched control eyes. There was no significant difference in central corneal thickness among all groups (*P*=0.74, ANOVA).

The intra-examiner, intraclass correlation coefficient values [95% confidence interval (CI)] were as follows: LCT; 0.895 (0.751-0.969) and LCD; 0.974 (0.916-0.992). The inter-examiner, intraclass correlation coefficient values were as follows: LCT 0.849 (0.761-0.979) and LCD 0.943 (0.816-0.972). LCT and LCD of patients, hyperopic non-amblyopia, and controls are shown in Table 2.

The mean LCT was 180.9±29.4 µm in amblyopic eyes, 247.7±19.0 µm in fellow eyes, 251.6±27.3 µm in hyperopic non-amblyopic eyes, and 240.2±15.8 µm in age-matched control eyes. The lamina cribrosa was significantly thinner in amblyopic eyes than in fellow, hyperopic non-amblyopic, and age-matched control eyes [*P*<0.001, ANOVA; *P*<0.001 (95%CI: 86.8-46.7), *P*<0.001 (95%CI: 89.2-52.1), *P*<0.001 (95%CI: 78.2-40.2), respectively, Tukey test].

The mean LCD was 371.7±85.8 µm in amblyopic eyes, 272.1±51.6 µm in fellow eyes, 397.4±75.7 µm in hyperopic non-amblyopic eyes, and 391.1±87.7 µm in control eyes. The

Table 2 LCT and LCD of amblyopic, fellow, hyperopic non-amblyopic, and control eyes

Parameters	Amblyopic eyes (µm)	Fellow eyes (µm)	Control eyes (µm)	Hyperopic non-amblyopic eyes (µm)	Amblyopia vs fellow	Amblyopia vs control	Amblyopia vs hyperopic non-amblyopia
LCT	180.9±29.4	247.7±19.0	240.2±15.8	251.6±27.3	<i>P</i> <0.001	<i>P</i> <0.001	<i>P</i> <0.001
LCD	371.7±85.8	272.1±51.6	391.1±87.7	397.4±75.7	<i>P</i> <0.001	<i>P</i> =0.84	<i>P</i> =0.68

LCD: Lamina cribrosa depth; LCT: Lamina cribrosa thickness.

lamina cribrosa was located significantly posteriorly in the amblyopic eyes than in the fellow eyes but not the hyperopic non-amblyopic eyes, and the control eyes (*P*<0.001, ANOVA; *P*<0.001, *P*=0.68, *P*=0.84, respectively, Tukey test).

A significant negative correlation was noted between LCT and axial length in fellow eyes (*r*=-0.50, *P*=0.02) but not in amblyopic, hyperopic non-amblyopic, and control eyes (*r*=-0.33, *P*=0.16; *r*=0.18, *P*=0.36 and *r*=0.21, *P*=0.31, respectively; Pearson's correlation coefficient).

No significant correlations were observed among LCT, age, and SE in amblyopic, fellow, hyperopic non-amblyopic, and control eyes (*P*>0.05; Pearson's correlation coefficient).

However, a significant positive correlation was noted between LCD and age in amblyopic eyes (*r*=0.51, *P*=0.02) but not in fellow, hyperopic non-amblyopic, and control eyes (*r*=0.25, *P*=0.29; *r*=0.20, *P*=0.31 and *r*=0.37, *P*=0.07, respectively; Pearson's correlation coefficient).

Moreover, a significant negative correlation was observed between LCD and axial length in control eyes (*r*=-0.28, *P*=0.04) but not in amblyopic, hyperopic non-amblyopic, and fellow eyes (*r*=-0.20, *P*=0.39; *r*=0.05, *P*=0.77 and *r*=0.26, *P*=0.28, respectively).

Furthermore, no significant correlations were noted between LCD and SE among amblyopic, fellow, hyperopic non-amblyopic, and control eyes (*P*>0.05; Pearson's correlation coefficient).

DISCUSSION

Differences in Lamina Cribrosa Thickness of Amblyopic Eyes Analysis of this study shows that the lamina cribrosa was significantly thinner in amblyopic eyes than in fellow, hyperopic non-amblyopic, and age-matched control eyes. Numerous studies have examined the topography of amblyopic eyes, but these have examined only retinal and choroidal topography and not laminar topography. To the best of my knowledge, this study is the first to evaluate LCT of amblyopic eyes and compare the same with fellow, hyperopic non-amblyopic, and age-matched control eyes.

According to a previous study, in monkeys with advanced glaucomatous optic nerve damage, the lamina cribrosa was significantly thinner than in those with non-glaucomatous vascular optic nerve damage^[17]. Similarly, human studies have revealed that eyes with secondary angle closure glaucoma and advanced glaucomatous optic nerve damage have thinner

lamina cribrosa than normal eyes^[18-20].

The present study revealed that the lamina cribrosa of amblyopic eyes was significantly thinner than that of fellow, hyperopic non-amblyopic, and age-matched control eyes; this implies that amblyopic eyes may have an altered optic nerve, although a structurally normal appearance.

Histological studies performed in amblyopic animals have reported atrophy in ganglion cells, optic nerve fibers, and thinning of the inner plexiform layer^[21-22].

In a similar study, amacrine synapses were significantly increased in the inner plexiform layer of unilaterally visually deprived rats^[23]. In addition, atrophy of ganglion cells was demonstrated in the lateral geniculate nucleus of animals with unilateral lid suture^[24]. Histological studies have revealed changes in areas ranging from retina to visceral cortex in amblyopic animals^[6,21-24], suggesting that lamina cribrosa may be affected as well.

Guo *et al*^[25] aimed to demonstrate retinal and choroidal microstructural abnormalities in amblyopic eyes by using digital subtraction autofluorescence and split-spectrum amplitude-decorrelation angiography. In this study, choroidal thickness was increased in amblyopic eyes, but choroidal capillaries revealed atrophy.

The lamina cribrosa receives its primary blood supply from the choroidal circulation^[26]. Despite there is no study about choroidal circulation and LCT in the ophthalmology literature, as an inference of anatomical blood supply, choroidal circulation might play a role in LCT. It can be suggested that choroidal circulation might be a provocative factor in pathogenesis thinner lamina cribrosa in hyperopic amblyopic eyes. Either blood flow increase or decrease might affect LCT. The relation between choroidal blood flow changes and LCT may be an interesting subject of a study.

The factors LCD and LCT attracted the attention of glaucoma experts, given the known significant role of the lamina cribrosa in the development of optic neuropathy. My study assessed IOP in all subjects and its effect was eliminated. In this study, I also evaluated hyperopic non-amblyopic eyes and compare them with amblyopic eyes. The analysis demonstrated that LCT was decreased in amblyopic eyes independent of hypermetropia.

The present study has certain limitations. I studied only anisometric amblyopic patients and did not evaluate LCT in other types of amblyopia. Moreover, the study sample was

relatively small. Furthermore, LCT was determined manually as there is a lack of accessible automated software. Therefore, additional studies including larger samples and the ability to conduct deeper tissue imaging are warranted to confirm my findings. In conclusion, the lamina cribrosa was thinner in amblyopic eyes than in normal fellow, hyperopic non-amblyopic, and age-matched control eyes. The LCT profile in amblyopic eyes was different from that observed in fellow, hyperopic non-amblyopic, and control eyes.

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Conflicts of Interest: Akkaya S, None.

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