Assessment of the lamina cribrosa in attention-deficit hyperactivity disorder

Serkan Akkaya, Döndü M Ulusoy[1], Hatice Doğan[2], Mahmut E Arslan[1]

Purpose: The aim of this study was to determine the usefulness of the lamina cribrosa thickness (LCT) and lamina cribrosa depth (LCD) in adolescence with attention-deficit hyperactivity disorder (ADHD) and compare with those receiving methylphenidate (MPH) and healthy controls. **Methods:** Fifty-five children with ADHD (9.23 ± 1.92 years, mean ± standard deviation), 41 children with ADHD given MPH (9.24 ± 1.84 years), and 86 healthy controls (9.95 ± 2.16 years) were recruited for the study. All subjects were subjected to a complete eye exam and optical coherence tomography (OCT) was used to assess LCT and LCD. The severity of ADHD symptoms was evaluated by using parent-report measures, including Conners's Parent Rating Scale–Revised: Short Form (CPRS-R: S) and the Strengths and Difficulties Questionnaire: Parent Form (SDQ: P). **Results:** The study showed a significant finding between the research groups with regard to LCT. LCT was shown to be significantly increased in ADHD subjects given MPH compared with the controls. However, LCD was not significantly different between cohorts. Also, a significant inverse correlation was found between the SDQ: P–Emotional Problems Subscale and LCT ($r = -0.253$; $P = 0.030$) in ADHD patients. **Conclusion:** Changes in lamina cribrosa (LC) in ADHD children receiving MPH suggest that the mechanism of action for MPH may target developing LC structures. More studies to define the relationship between MPH medications and the LC variations are defensible.

Key words: Attention-deficit hyperactivity disorder, lamina cribrosa thickness, methylphenidate

Attention-deficit hyperactivity disorder (ADHD) is a common neural condition in adolescence, and its frequency is between 6.7% and 7.8%.[1] Although the cause(s) of ADHD is not fully understood, the current literature indicates a combination of environmental and genetic influences.[2]

Psychopharmacological treatment has been used and seems to be useful to treat ADHD and can be combined with behavioral therapy.[3,4] A neurotransmitter imbalance (i.e. dopamine and norepinephrine) within the prefrontal cortex have been hypothesized to cause ADHD; and administration of methylphenidate (MPH) and amphetamines have been used to help correct this imbalance.[5,6] MPH inhibits the reuptake of dopamine and noradrenaline in the synaptic cleft. MPH has been shown to have side effects, including insomnia, appetite and weight loss, and abdominal pain.[5,6] According to the Summary of Product Characteristics, there have been some secondary effects on the eye such as dryness, mydriasis, and blurred vision.

MPH is not recommended in glaucoma patients because there is the potential for transient intraocular pressure (IOP) elevation.[7] However, this recommendation is a precaution that has resulted from the possible action of MPH on IOP progression.[8,9]

Lamina cribrosa (LC) is the area where the nerve fibers of the eye exit the posterior sclera and the central retinal vessels pass. In glaucoma, LC has been determined to be the primary site of retinal ganglion and axon injury.[10] Optical coherence tomography (OCT) is noninvasive and can be used to collect *in vivo* cross-sectional images of the retina[11] and LC.[10]

The retina and the nerves of the optic disk have been shown to spread from the diencephalon throughout development and are considered part of the central nervous system (CNS).[12] Neuroimaging has shown structural/functional brain dissimilarities in kids with and without ADHD.[13-15] Gehricke *et al.*,[16] in their study evaluating the structural brain anatomy and connectivity in ADHD, found significant associations between ADHD diagnosis and changes in the maturation of white matter fiber bundles and gray matter density in the brain, such as structural shape changes (incomplete maturation) of the middle and superior temporal gyrus, and frontobasal portions of both frontal lobes. They stated that ADHD diagnosis in an adult and especially childhood symptoms are associated with widespread micro- and macrostructural changes. Additionally, they asserted that the superior longitudinal fasciculus and corticolimbic findings suggest complex audio-visual, motivational, and emotional dysfunctions associated with ADHD in young adults.

Based on these findings, we hypothesized that the LC would be affected by MPH treatment in ADHD children because of the theoretical literature related to the relationship between MPH and glaucoma. To our knowledge, no reports have been documented in the literature analyzing the LC in ADHD.

In this report, we aimed to investigate the LC using SD-OCT (spectral-domain OCT) in ADHD subjects and compared LC thickness (LCT) and LC depth (LCD) in children

Department of Ophthalmology, Ankara Training and Research Hospital, Ankara, [1]Departments of Ophthalmology and [2]Child and Adolescent Psychiatry, Kayseri Training and Research Hospital, Kayseri, Turkey

Correspondence to: Dr. Serkan Akkaya, Department of Ophthalmology, Ankara Training and Research Hospital, Ankara - 06230, Turkey. E-mail: drsakkaya@gmail.com

with and without ADHD as well as ADHD subjects receiving MPH. Clinical outcomes data were used to determine the associations between LCT and ADHD symptom severity.

Methods

Participants

Subjects were enrolled from the Departments of Ophthalmology and Child and Adolescent Psychiatry in the single tertiary referral hospital between September 2019 and January 2021. The first group consisted of patients with ADHD and no treatment. The second group included children with ADHD receiving MPH treatment for a minimum of 3 months before enrolling. The third group included healthy controls given a regular eye examination with no known complications or history of ocular disease (except for refractive errors), psychiatric disorder, and no medication usage. Approval was obtained through the ethics committee, and all experiments were done according to the tenets of the Helsinki Declaration. Before enrollment, informed consent was collected from the subjects and parents. Following consent, parents were tasked with completing the Conners's Parent Rating Scale–Revised: Short Form (CPRS-R: S) and Strengths and Difficulties Questionnaire: Parent Form (SDQ: P).

All subjects included in this study were assessed by a psychiatrist specializing in children and adolescents using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version–Turkish Version (K-SADS-PL-T).[17,18]

All included subjects underwent dilated fundoscopic examinations. Patients with a best-corrected visual acuity (BCVA) equal or greater than 20/20, a refractive error (SE) of ± 2 diopters, and an IOP of less than 21 mmHg were included in the study. Exclusion criteria were as follows: not being able to complete the OCT exam, previous intraocular surgery, glaucoma, organic eye diseases, cataract, laser treatment, any conditions of the retina, and having any systemic illness, immune disorder, or neurological disease.

Procedures

Every included subject was given 1% cyclopentolate (three drops, Cyclogyl; Alcon Couvreur, Belgium) every 5 minutes, and cycloplegic refraction was performed 45 minutes following the initial treatment. Each subject had five autorefractor readings within 0.25 D of the other via a Tonoref II autorefractor/tonometer (Nidek Co. Ltd.). SE was calculated by spherical sum + 1/2 cylindrical error.

All subjects were subjected to other clinical assessments such as BCVA, extraocular movements, slit-lamp analysis, IOP, average central keratometry, and central thickness of the cornea (Scheimpflug camera, Wetzlar, Germany). In addition, the IOL (intraocular lens) Master was used to measure the eye's axial length.

OCT measurements

An SD-OCT (HEYEX software 6.0, Spectralis, Heidelberg Engineering Inc., Heidelberg, Germany) was used to measure LCT and LCD. The collected images were omitted if the visual quality was less than 20 or if the fundus or LC border was not clear. Optic nerve head (ONH)–enhanced depth imaging using SD-OCT has been previously described.[19] Briefly, the SD-OCT was centered on the optic disc to record a 15 × 10 degree rectangle. The image was allocated into 65 segments that comprised 100°CT frames on average for each individual segment. The horizontal B-scans were used to collect three frames (center, midinferior and -superior) passing through the ONH, and the factors were calculated for each frame. During the thickness calculation, we gave full weight to the LC center plate. Fig. 1 shows an OCT image from a child with ADHD receiving MPH and a control participant's LC border and Bruch's membrane opening, which connects both ends. The distance was calculated using a line perpendicular to the reference. The dimensions were recorded using the vertical center of the ONH. Temporal side dimensions were logged, if a vessel trunk blocked the ability for an accurate measure. LC boundaries were demarcated based on the anterior/posterior edges of the ONH in horizontal SD-OCT sections. The LCT was determined based on the distance between these borders. The
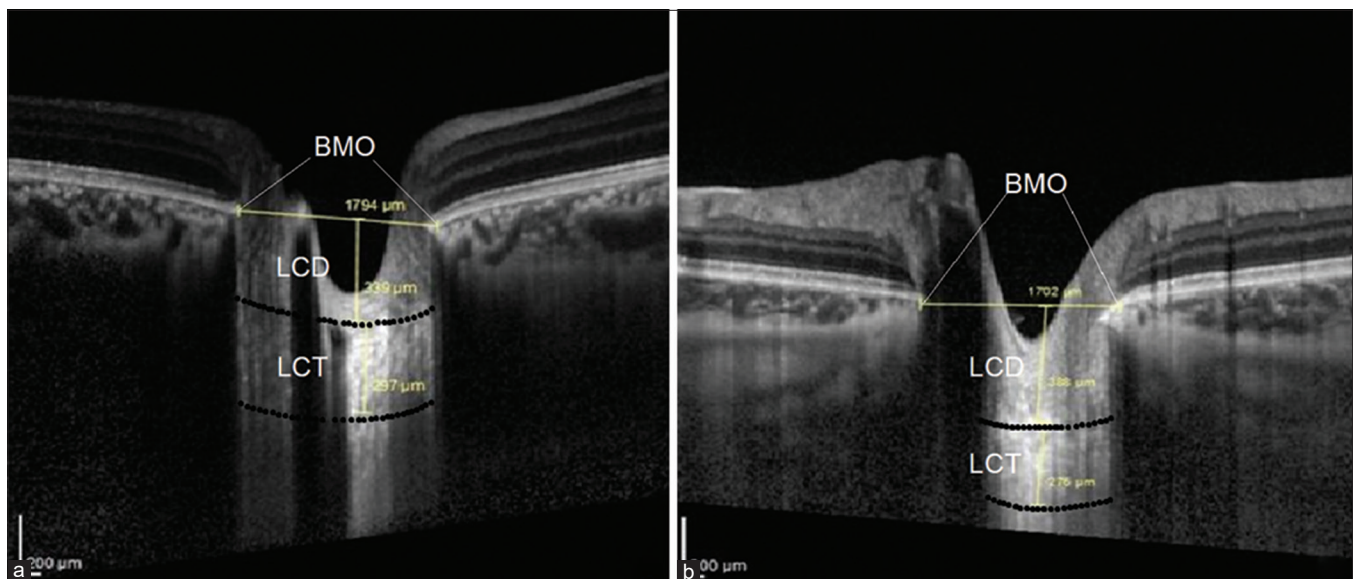
Figure 1: Images (OCT) from a child with ADHD (9-year-old) on regular methylphenidate (MPH) treatment and a control child (9-year-old). Horizontal scans: (a): The eye of the child with ADHD on regular methylphenidate treatment; LCT = 297 μm and LCD = 339 μm; (b): The eye of the control child; LCT = 276 μm and LCD = 388 μm. OCT = optical coherence tomography, ADHD = attention-deficit hyperactivity disorder, LCT = lamina cribrosa thickness, LCD = lamina cribrosa depth, BMO = Bruch's membrane opening

best image of the LC was obtained by adjusting the contrast settings, which helped identify the best quality. The distance from the Bruch's membrane opening and the LC anterior border was recorded as the LCD.

Assessment of ADHD symptoms

CPRS-R: S has been routinely used to measure ADHD. A guardian/parent was asked to rate the 27 items on a severity scale of problematic behavior, including 1 = Oppositional, 2 = Hyperactivity, 3 = Inattention, and 4 = ADHD Index, for their child using a 4-point Likert-type scale; ranges were from 0 (*false*) to 3 (*absolutely true*).[20] The Turkish version of the CPRS-R: S has been determined to be reliable and valid.[21]

SDQ: P has been used a screening questionnaire to measure parents' observation about their child's prosocial and difficult behaviors.[22] The questionnaire has 25 items, five in each subscale (5 total), which included 1 = Emotional Complications, 2 = Conduct, 3 = Hyperactivity, 4 = Peer Issues, and 5 = Behavior. The first four items are used for the Total Difficulties Scale. The Turkish version has been tested for reliability and validity.[23]

Statistical analysis

The analyses were performed with SPSS Version 22. Data were presented as mean, standard deviation, and percentage. A Kolmogorov–Smirnov test was used to determine variable distribution. A Chi-square test was used to compare the categorical variables.

A one-way analysis of variance (ANOVA) was performed to assess variable group differences. Associations for clinical/ocular parameters were assessed by correlation analysis. Pearson's correlation coefficient was used to evaluate statistical significance among LCT and LCD values with the CPRS-R: S and SDQ: P. A P value of less than 0.05 was considered statistically significant.

Results

The subject cohorts consisted of 55 children with treatment-naive ADHD (37 boys and 18 girls; Group 1), 41 children diagnosed with ADHD who had been under regular MPH treatment for at least 3 months (31 boys and 10 girls; Group 2), and 86 children who served as healthy controls (59 boys and 27 girls; Group 3). Table 1 contains the demographic/clinical variables as well as scores on the CPRS-R: S and SDQ: P for each group. The mean age was 9.23 ± 1.92 years for Group 1, 9.24 ± 1.84 years for Group 2, and 9.95 ± 2.16 years for Group 3. Age and sex were not found to be significantly different across the groups.

Table 2 summarizes the measured ocular parameters of the groups. The mean IOP was 15.85 ± 3.14 mmHg in Group 1, 16.53 ± 3.77 mmHg in Group 2, 15.50 ± 3.18 mmHg in Group 3. No significant difference in IOP between the groups was found (P = 0.366, ANOVA).

The LCT was significantly increased in Group 2 (300.06 ± 31.78 μm) compared with Group 3 (271.79 ± 37.93 μm, P = 0.002), but not Group 1 (285.92 ± 40.05, P = 0.239). In addition, no difference was determined between the controls and Groups 1 and 2 in terms of LCD (P = 0.081 and 0.821, respectively). Moreover, other measurement parameters were not significantly different among the three groups (P > 0.005).

In the ADHD group, correlations for LCT and the CPRS-R: S and SDQ: P scores were evaluated [Table 3]. A negative correlation was determined for LCT and SDQ: P–Emotional Problems scores (r = −0.253; P = 0.030). No other correlations were determined.

Discussion

In this report, OCT was used to assess LCT and LCD in children with ADHD and those receiving MPH compared with healthy controls. Compared with controls, ADHD kids that received MPH had thicker LC. No significant changes were observed within the groups based on LCD. Our study is the first to report on LCT in ADHD.

Alpha-adrenergic and anticholinergic drugs may cause acute angle-closure glaucoma secondary to mydriasis.[24] MPH, a sympathomimetic amine, is an indirect agonist that inhibits reuptake of dopamine and norepinephrine and

Table 1: Demographics and characteristics of the study participants

	ADHD (*n*=55) (Group 1)	ADHD + MPH (*n*=41) (Group 2)	Controls (*n*=86) (Group 3)	*P*	Group 1 vs. Group 2	Group 1 vs. Group 3	Group 2 vs. Group 3
Age (years)	9.23±1.92	9.24±1.84	9.95±2.16	0.083	0.977	0.104	0.158
Sex (Female/Male Ratio)	18 (32.7%) /37 (67.3%)	10 (24.4%) /31 (75.6%)	27 (31.4%) /59 (68.6%)	0.644	0.374	0.869	0.417
CPRS-R: S							
Oppositional	11.21±2.70	9.92±3.33	5.59±2.62	0.001	0.071	0.001	0.001
Inattention	12.32±2.49	11.41±2.97	3.20±2.21	0.001	0.180	0.001	0.001
Hyperactivity	11.87±2.96	9.46±3.40	3.47±2.59	0.001	0.001	0.001	0.001
ADHD Index	26.72±5.00	24.14±5.27	9.62±5.44	0.001	0.049	0.001	0.001
SDQ: P							
Emotional Problems	5.67±1.33	5.00±2.42	3.29±1.05	0.001	0.090	0.001	0.001
Conduct Problems	6.09±2.05	5.19±2.35	2.44±1.39	0.001	0.053	0.001	0.001
Hyperactivity	7.16±1.21	6.07±1.76	3.07±1.27	0.001	0.001	0.001	0.001
Peer Problems	6.23±1.52	5.85±2.01	3.18±1.01	0.001	0.409	0.001	0.001
Prosocial Behavior	7.92±1.29	8.04±1.78	9.05±1.76	0.001	0.930	0.001	0.004
Total Difficulties	25.47±5.18	22.02±6.66	11.98±3.51	0.001	0.002	0.001	0.001

ADHD=Attention-deficit hyperactivity disorder; MPH=Methylphenidate, CPRS-R: S=Conners's Parent Rating Scale-Revised: Short Form, SDQ: P=Strengths and Difficulties Questionnaire: Parent Form

Table 2: Comparison of the measurement parameters (mean±standard deviation) of ADHD, ADHD+MPH and control groups

	ADHD (n=55) (Group 1)	ADHD + MPH (n=41) (Group 2)	Controls (n=86) (Group 3)	P	Group 1 vs. Group 2	Group 1 vs. Group 3	Group 2 vs. Group 3
LCT (μm)	285.92±40.05	300.06±31.78	271.79±37.93	0.002	0.239	0.143	0.002*
LCD (μm)	330.78±53.61	349.27±59.87	357.07±65.25	0.098	0.397	0.081	0.821
Axial Length (mm)	22.83±0.91	22.93±0.65	23.13±0.78	0.121	0.840	0.112	0.448
SE (Diopter)	0.05±0.78	−0.23±0.57	−0.06±0.85	0.200	0.172	0.732	0.558
CCT (μm)	555.30±34.14	553.41±30.30	549.06±30.68	0.628	0.970	0.644	0.802
Keratometry (Diopter)	43.35±1.85	43.50±1.47	43.47±1.52	0.911	0.918	0.930	0.995
IOP (mmHg)	15.85±3.14	16.53±3.77	15.50±3.18	0.366	0.612	0.865	0.340

ADHD=Attention-deficit hyperactivity disorder; LCT=Lamina cribrosa thickness; LCD=Lamina cribrosa Depth; MPH=Methylphenidate; RNFL=Retina nerve fiber layer; SE=Spherical equivalent; CCT=Central corneal thickness; IOP=Intraocular pressure. *$P<0.05$

Table 3: The correlation of LCT and LCD values with the CPRS-R: S and SDQ: P

	LCT		LCD	
	r	P	r	P
CPRS-R: S				
Oppositional	0.100	0.394	0.004	0.974
Inattention	0.115	0.329	0.103	0.382
Hyperactivity	−0.105	0.375	−0.105	0.374
ADHD Index	0.057	0.628	0.017	0.885
SDQ: P				
Emotional Problems	−0.253	0.030*	0.122	0.300
Conduct Problems	−0.099	0.402	−0.105	0.371
Hyperactivity	−0.039	0.739	−0.127	0.282
Peer Problems	−0.132	0.261	0.128	0.276
Prosocial Behavior	0.199	0.093	0.160	0.179
Total Difficulties	−0.166	0.164	−0.022	0.857

ADHD=Attention-deficit hyperactivity disorder; LCT=Lamina cribrosa thickness; LCD=Lamina cribrosa depth; CPRS-R: S=Conners' Parent Rating Scale-Revised: Short Form; SDQ: P=Strengths and Difficulties Questionnaire: Parent Form. r=correlation coefficient. *$P<0.05$

may cause closure of the angle and increase IOP; therefore, it is classified as an adrenergic agonist and contraindicated theoretically in patients with glaucoma.[25] Nevertheless, this recommendation is only hypothetically based on the potential action of MPH.[8,9]

Previous reports have investigated the link between MPH and IOP, and no association was found.[25-27] Larrañaga-Fragoso et al.[25] examined the IOP in children with ADHD receiving MPH and found no IOP changes at 3 or 9 months. Güvenmez et al.[26] also found no significant change in IOP before treatment and after 1- and 6-month treatment periods in children with ADHD. Duman et al.[27] showed no IOP changes in children with ADHD receiving MPH.

In this report, no significant differences in IOP measurements were observed for subjects with ADHD or those receiving MPH when compared with controls. Our study is consistent with the aforementioned studies.

Moreover, structural and histological changes of LC in ocular diseases and in some systemic diseases with ocular involvement are under investigation. Considering that it plays a role in the pathogenesis, changes of LC have specifically been investigated in patients with glaucoma.[28,29] It has been suggested that quantitative changes determined by OCT can be used as biomarkers for predicting glaucoma-related injury.[30] Early detection of LC changes would enable early diagnosis of glaucoma.[31] Increased severity of glaucoma has been found to be associated with decreased LCT values.[32]

In the present study, higher LCT values in the eyes of the children with ADHD on regular MPH treatment suggested low risk for glaucoma, or MPH medications used for ADHD may not cause glaucoma damage in children with ADHD. However, although the difference between healthy children and ADHD children on MPH treatment was significant, it should be kept in mind that it may not hold clinical implications, as the changes are small. On the other hand, increased LCT may protect children with ADHD receiving MPH from glaucoma, and this may be useful in children with ADHD and glaucoma.

On the other hand, previous reports have shown lower retinal nerve fiber layer (RNFL) thickness in subjects with Alzheimer's disease,[33] Parkinson's disease,[34] and multiple sclerosis.[35] Retinal tissue loss has been linked to neurodegeneration, cognitive decline, and disease worsening.[36] Our recent study also revealed reduced LCD in multiple sclerosis eyes specifically with optic neuritis, and its association was shown to coincide with disease severity.[37] In the present study, we also found that increased LCT thicknesses was associated with decreased disease symptom severity – SDQ: P–Emotional Problems Subscale in children with ADHD.

Multiple studies[38,39] have investigated RNFL thickness in ADHD patients and showed that RNFL thickness was not different in ADHD patients. Hergüner et al.[38] concluded that ADHD involves a lag in cortical maturation, and this is measurable in the retina as the ADHD group had significantly lower RNFL thickness in the nasal quadrant than the controls. This may be due to the fact that ADHD is a neurodevelopmental disorder and not degenerative.[38,39] In terms of RNFL thickness, there might be no risk for glaucomatous damage for children with ADHD.[38,39]

The limitation of the study is the cross-sectional design, and further investigations are required to define the relationship between MPH medications and the development of glaucoma.

This study also provided evidence for the retina as a snapshot of the brain using eye research in CNS disorders from an LCT perspective.

Conclusion

In conclusion, children with ADHD receiving MPH may be impacted by the mechanism of action of MPH on the development of LC structures. Increased LCT in children with ADHD receiving MPH may be protective from glaucoma damage, and MPH may be safely used in children with ADHD and glaucoma when viewed from the LC perspective.

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Conflicts of interest

There are no conflicts of interest.

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