Assessment of the lamina cribrosa in attention-deficit hyperactivity disorder

Serkan Akkaya, Döndü M Ulusoy1, Hatice Doğan2, Mahmut E Arslan1

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 of MPH may target developing LC structures. More studies to define the relationship between MPH medications and the LC variations are defendable.

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 noradrenaline) 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 LCD depth (LCD) in children.
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 funduscopy 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.](image-url)
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 = Inattentiveness, 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 as 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).

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)     | ADHD + MPH (n=41) | Controls (n=86) | P                |
| Age (years)                    | 9.23±1.92       | 9.24±1.84        | 9.95±2.16       | 0.083 |
| Sex (Female/Male Ratio)        | /37 (67.3%)     | /31 (75.6%)      | /59 (68.6%)     | 0.644 |
| CPRS-R: S                      |                |                 |                 |                  |
| Oppositional                   | 11.21±2.70      | 9.92±3.33        | 5.59±2.62       | 0.001 |
| Inattentiveness                | 12.32±2.49      | 11.41±2.97       | 3.20±2.21       | 0.001 |
| Hyperactivity                  | 11.87±2.96      | 9.46±3.40        | 3.47±2.59       | 0.001 |
| ADHD Index                     | 26.72±5.00      | 24.14±5.27       | 9.62±5.44       | 0.001 |
| SDQ: P                         |                |                 |                 |                  |
| Emotional Problems             | 5.67±1.33       | 5.00±2.42        | 3.29±1.05       | 0.001 |
| Conduct Problems               | 6.09±2.05       | 5.19±2.35        | 2.44±1.39       | 0.001 |
| Hyperactivity                  | 7.16±1.21       | 6.07±1.76        | 3.07±1.27       | 0.001 |
| Peer Problems                  | 6.23±1.52       | 5.85±2.01        | 3.18±1.01       | 0.001 |
| Prosocial Behavior             | 7.92±1.29       | 8.04±1.78        | 9.05±1.76       | 0.001 |
| Total Difficulties             | 25.47±5.18      | 22.02±6.66       | 11.98±3.51      | 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                | 357.06±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 | | |
|-------------------|--|--|--|--|--|--|
| 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 concomitantly theoretically in patients with glaucoma.[8,9] 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.[30] examined the IOP in children with ADHD receiving MPH and found no IOP changes at 3 or 9 months. Güvenmez et al.[30] also found no significant change in IOP before treatment and after 1- and 6-month treatment periods in children with ADHD. Duman et al.[30] 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.[39] 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 glaucomatos 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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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