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ORIGINAL ARTICLE

Assessment of intraocular pressure, macular thickness, retinal nerve fiber layer, and ganglion cell layer thicknesses: ocular parameters and optical coherence tomography findings in attention-deficit/hyperactivity disorder

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Objective: To compare intraocular pressure (IOP) and macular, retinal nerve fiber layer (RNFL), and ganglion cell layer (GCL) thicknesses in treatment-naive children with attention-deficit/hyperactivity disorder (ADHD), children with ADHD on regular methylphenidate (MPH) treatment for at least 3 months, and healthy controls.
Methods: A total of 58 treatment-naive children with ADHD, 45 children with ADHD on regular MPH treatment, and 44 healthy controls were enrolled in this study. All participants underwent a comprehensive eye examination. Optical coherence tomography (OCT) was used to assess global RNFL thickness, central macular thickness, and GCL thickness in both eyes.
Results: Separate univariate analysis of covariance (ANCOVA) on the outcome variables revealed a significant difference among the research groups with respect to IOP in the left eye. Post-hoc univariate analyses indicated that left IOP was significantly higher in children with ADHD under MPH treatment than among healthy controls. However, global RNFL thickness, central macular thickness, and GCL thickness of both eyes, as well as IOP in the right eye, were not significantly different across groups.
Conclusion: Further longitudinal follow-up studies are needed to determine whether MPH treatment has any effect on IOP or OCT findings.

Keywords: Attention deficit hyperactivity disorder; ganglion cell layer; intraocular pressure; methylphenidate; retinal nerve fiber layer

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a multifactorial neurodevelopmental disorder. Many factors have been implicated in its etiology, including genetics and environment. The incidence of ADHD was reported to be 12.4% in a multicenter nationwide study in Turkey.[1] Although ADHD is quite common, its etiology has yet to be fully explained. Many scientists continue to search for biological markers that might guide the diagnosis of ADHD and elucidate its etiology.[2] For this purpose, researchers have frequently used different neuroendocrine and neuroimaging techniques to define particular abnormalities related to this disorder.[2-5] There is general agreement regarding the atypical brain structure findings associated with ADHD on neuroimaging.[6] Global decreases in total brain volume, most prominent in the prefrontal cortex, basal ganglia, cerebellum, and parietotemporal areas, have been reported in volumetric analyses.[7,8] In one prospective study of young subjects, Shaw et al., showed that prefrontal cortical development was delayed in ADHD compared to typical participants.[9]

As stated above, brain-imaging studies have endorsed the presence of biological markers of ADHD. Since the eyes are considered a prolongation of the central nervous system, peripheral biomarkers such as the retinal nerve fiber layer (RNFL) and macular thickness promise a fresh pathway into investigation of brain development.[2] A recent article outlined the significant benefits of a methodology using assessment of RNFL and macular thickness, which is particularly attractive considering the similarities between the brain and retina from an embryological point of view and the relatively simple and accessible nature of retinal examination compared to brain scans.[10,11] For centuries, the retina has been known to provide insight into the status of the brain, suggesting the suitability of retinal research to explore bipolar disorder, schizophrenia, major depressive disorder, and ADHD.[5,12-15]

Optical coherence tomography (OCT) is a comparatively new, noninvasive, and contactless imaging technique that

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was first used in the field of ophthalmology.[16] The use of OCT to study axonal structural abnormalities has increased in recent years. Notably, OCT has been used in a few studies to evaluate patients with ADHD.[2,5,15] Hergüner et al. investigated macular thickness, macular volume, and RNFL thickness in children with ADHD and a control group.[5] They found lower RNFL thickness only in the nasal quadrant in a patient with ADHD compared to the control group; in the other quadrants, RNFL thickness was not significantly different.[5] In another study, Bodur et al. compared RNFL thickness, ganglion cell layer (GCL), and optic nerve thickness in patients with ADHD, ADHD plus oppositional defiant disorder (ODD), and controls.[15] The authors found no difference in RNFL thickness between the groups, but significantly lower GCL and optic nerve thickness in the patient groups than in controls.[15]

The abovementioned studies examining the relationship between OCT and ADHD only included ADHD and control groups; to date, no studies have compared drug-treated ADHD patients, drug-naive ADHD patients, and healthy controls. The aim of the present research was to compare intraocular pressure (IOP), macular thickness, RNFL, and GCL thickness in treatment-naive children with ADHD, children with ADHD on regular methylphenidate (MPH) treatment for at least 3 months, and healthy controls.

Methods

Participants and procedure

Three groups of participants were recruited from the Department of Ophthalmology and the Department of Child and Adolescent Psychiatry of Yozgat City Hospital in Yozgat, Turkey. Group 1 was composed of subjects who had been diagnosed with ADHD but not yet treated; Group 2 consisted of patients diagnosed with ADHD who had been under treatment with oral methylphenidate hydrochloride for at least 3 months before enrollment in the study. Group 3, the control group, comprised subjects who presented to the ophthalmology department for regular eye examination, had no history of ocular disease except for refractive errors, had no psychiatric disorder, and did not use any medication. The procedures were explained to the participants, and, prior to enrollment, written informed consent was obtained from all subjects and their parents.

All participants were evaluated with the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version-Turkish Version (K-SADS-PL-T)[17,18] and examined by a child and adolescent psychiatrist through clinical interviews. Both the participants' parents and teachers completed psychological questionnaires for assessing ADHD and levels of disruptive behavior. Parents completed the Turgay DSM-IV-Based Child and Adolescent Behavioral Disorders Screening and Rating Scale (T-DSM-IV-S)[19,20] and the Conners' Parent Rating Scale-Revised Short (CPRS-RS),[21] while teachers completed the T-DSM-IV-S alone.

All participants underwent a comprehensive eye examination by one of the authors (MK), who was unaware of group allocation. The examination included assessment of best corrected visual acuity (BCVA), ocular motility, intraocular pressure (IOP) measurement, visual field examination, and fundus photography, and was performed in the Department of Ophthalmology, Yozgat City Hospital. Only participants with BCVA $\geqslant$ 20/20, refractive error (myopia, hypermetropia, or astigmatism) of no more than $\pm$ 1 diopter, and IOP $<$ 18 mmHg were included. Participants with primary eye diseases (glaucoma, retinal diseases, etc.), a history of ocular inflammation or surgery, a history of head injury with loss of consciousness, or neurological, immune, or other systemic illnesses were excluded.

OCT was performed using a CIRRUS™ HD-OCT 500 scanner (Zeiss). Global RNFL thickness, central macular thickness, and GCL thickness were measured in both eyes.

Statistical analyses

Data were analyzed in SPSS version 22.0. The Kolmogorov-Smirnov test was used to evaluate the assumption of normality. Variables were described as the number (n), percentage (%), or mean $\pm$ standard deviation (SD). The chi-square test or one-way analysis of variance (ANOVA) were used to evaluate group differences in variables, as suitable. Multivariate analysis of covariance (MANCOVA) was conducted for possible confounding variables. These analyses were conducted with adjustments for age and sex, which were identified as significant factors ($p < 0.05$). The associations between the clinical and ocular parameters were determined through correlation analysis. Nonparametric or parametric methods (Spearman's *rho* or Pearson's *r*) were used as appropriate to test for correlation. P-values < 0.05 (two-tailed) were considered significant. Where stated, post-hoc Bonferroni tests were conducted with corrections for multiple testing.

Ethics statement

The study protocol was approved by the Bozok University Medical Faculty ethics committee. All procedures were carried out in accordance with the Declaration of Helsinki.

Results

The study population consisted of 58 children with treatment-naive ADHD (41 boys and 17 girls; Group 1), 45 children diagnosed with ADHD who had been under regular MPH treatment for at least 3 months (32 boys and 13 girls; Group 2), and 44 children who served as healthy controls (21 boys and 23 girls; Group 3). Table 1 presents and compares the descriptive and clinical variables of the groups. The mean age was 9 ± 2.41, 9.02 ± 2.19, and 10.85 ± 2.21 years in Groups 1, 2, and 3, respectively (Table 1). Age and sex differed significantly across the three groups. Table 1 also presents participants' scores on the CPRS-RS and T-DSM-IV-S.

One-way MANCOVA was performed with each of the three diagnostic groups as the independent variable,

Table 1 Demographics and characteristics of the study participants

Variable	ADHD (n=58) (Group 1) n	ADHD + MPH (n=45) (Group 2) n	Controls (n=44) (Group 3) n	Statistical analysis			Post-hoc comparisons*
				χ^2	df	p-value	
Male/female ratio	41/17	32/13	21/23	7.166	2	0.028	-
	Mean (SD)	Mean (SD)	Mean (SD)	F	df	p-value	
Age (years)	9 (2.41)	9.02 (2.19)	10.85 (2.21)	9.894	2	< 0.001	3 > 2, 3 > 1
Parent T-DSM-IV-S							
AD	15.56 (6.58)	15.33 (5.89)	5.9 (5.45)	38.404	2	< 0.001	1 > 3, 2 > 3
HA/I	13.24 (7.87)	13.08 (6.23)	3.9 (5.49)	29.137	2	< 0.001	1 > 3, 2 > 3
OD	9.58 (5.84)	9.95 (5.92)	5.77 (5.34)	7.480	2	0.001	1 > 3, 2 > 3
CD	3.06 (4.45)	3.57 (4.51)	1.04 (2.35)	5.143	2	0.007	1 > 3, 2 > 3
Teacher T-DSM-IV-S							
AD	14.75 (6.07)	13.71 (6.33)	5.75 (3.34)	37.754	2	< 0.001	1 > 3, 2 > 3
HA/I	9.68 (7.49)	9.13 (7.62)	1.59 (4.03)	21.305	2	< 0.001	1 > 3, 2 > 3
OD	7.08 (6.03)	6.31 (5.91)	3.84 (3.18)	4.894	2	0.009	1 > 3
CD	2.96 (4.58)	2.73 (3.79)	0.40 (0.97)	7.194	2	0.001	1 > 3, 2 > 3
CPRS-RS							
OD	8.01 (4.63)	8.37 (4.46)	7.04 (4.83)	0.987	2	0.375	-
CP-I	11.15 (4.88)	11.22 (4.61)	2.9 (3.51)	53.812	2	< 0.001	1 > 3, 2 > 3
HA	7.24 (4.92)	7.64 (4.55)	2.25 (3.12)	21.956	2	< 0.001	1 > 3, 2 > 3
ADHD Index	20.7 (7.7)	22.2 (7.07)	9.86 (7.29)	37.759	2	< 0.001	1 > 3, 2 > 3

AD = attention deficit; ADHD = attention-deficit/hyperactivity disorder; CD = conduct disorder; CPRS-RS = Conners Parent Rating Scale-Revised Short; CP-I = cognitive problems-ınattention; HA = hyperactivity; HA/I = hyperactivity-ımpulsivity; MPH = methylphenidate; OD = oppositional defiant behavior.
* Bonferroni, $p < 0.05$.

while only age and sex were used as covariates. This analysis showed no significant overall group differences in ocular parameters between research groups ($V_{Pillai's\ trace}$ = 0.114, $F_{14,272}$ = 1.023, p = 0.432, η_p^2 = 0.057). Separate univariate ANCOVAs on the outcomes variables disclosed a significant difference among the research groups with respect to IOP in the left eye ($F_{2,142}$ = 4.068, p = 0.019, η_p^2 = 0.054). Post-hoc univariate analyses indicated that left IOP was significantly higher in the ADHD + MPH group than in the healthy control group. However, global RNFL thickness, central macular thickness, and GCL thickness of both eyes, as well as IOP in the right eye, were not significantly different across groups (Table 2).

For the entire patient sample, correlations between ocular parameters and the CPRS-RS and parent- and teacher-rated T-DSM-IV-S scores were also evaluated. Negative correlations were found between left RNFL thickness and teacher-rated T-DSM-IV-S oppositional defiant scores (r = -0.240, p = 0.015). No other associations were found.

Discussion

This study investigated ocular parameters in children with treatment-naive ADHD, children with ADHD under MPH treatment, and healthy controls. The analyses demonstrated that intraocular pressure in the left eye was significantly higher in children with ADHD who had been receiving MPH treatment than in healthy controls, regardless of potential confounders, including age and sex. No significant differences were found across groups with respect to global RNFL thickness, central macular thickness, and GCL thickness.

Few studies have explored RNFL thickness in psychiatric disorders (including schizophrenia[13,14] and bipolar disorder[12]). These studies have found that decreased RNFL thickness may be an indicator of progressive neural degeneration.[12,14] In the present study, we found no significant difference in RNFL thickness in treatment-naive patients with ADHD or methylphenidate-treated patients with ADHD as compared with controls. To the best of our knowledge, only two prior studies have investigated RNFL thickness in ADHD patients. Their findings were consistent with ours, in that global RNFL thickness was not significantly different in ADHD patients compared to controls in either study.[5,15] This could be because ADHD is not neurodegenerative, but rather a neurodevelopmental disorder. However, in our study, we only measured the global RNFL, not the other segments individually. If other segments were measured, different results could be obtained. Therefore, more extensive research including other segments should provide a more accurate interpretation of the results.

Central macular thickness did not differ across groups in our sample. In recent years, few studies have explored macular thickness in ADHD.[2,5] In line with our findings, a recent study analyzed macular thickness in children with ADHD and found no significant difference in the ADHD group as compared to controls.[5] However, in another study, Bae et al. found increased macular thicknesses in the ADHD group.[2] This inconsistency might be related to the use of different tools for macular thickness measurement.

Likewise, we found no significant differences in GCL thicknesses across groups. To the best of our knowledge, only one previous study examined GCL thicknesses in

Table 2 Group comparisons of OCT findings and IOP measurement

Variable	ADHD (n=58) (Group 1) Mean (SD)	ADHD + MPH (n=45) (Group 2) Mean (SD)	Controls (n=44) (Group 3) Mean (SD)	ANOVA		ANCOVA*			Post-hoc comparisons†
				$F_{2,144}$	p-value	$F_{2,142}$	p-value	η_p^2	
Right IOP	11.56 (1.99)	11.71 (1.85)	11.15 (1.98)	0.971	0.381	1.083	0.342	0.015	-
Left IOP	12.10 (2.25)	12.86 (2.32)	11.40 (2.14)	4.699	0.011	4.068	0.019	0.054	2 > 3
Right macular thickness	246.60 (20.78)	242.44 (29.10)	244.97 (23.52)	0.369	0.692	0.403	0.669	0.006	-
Left macular thickness	245.03 (24.05)	242.68 (28.44)	245.15 (26.05)	0.133	0.876	0.121	0.886	0.002	-
Right RNFL	96.10 (10.92)	97.40 (10.98)	98 (10.28)	0.420	0.658	0.310	0.734	0.004	-
Left RNFL	95.75 (10.23)	98 (11.20)	96.70 (8.67)	0.623	0.538	0.668	0.514	0.009	-
Right GCL	83.89 (6.58)	83.28 (4.94)	83.31 (5.90)	0.176	0.838	0.228	0.797	0.003	-
Left GCL	83.53 (5.80)	83.75 (5.78)	82.88 (5.35)	0.285	0.752	0.477	0.622	0.007	-

ANOVA = analysis of variance; ANCOVA = analysis of covariance; ADHD = attention-deficit/hyperactivity disorder; GCL = ganglion cell layer; IOP = intraocular pressure; MPH = methylphenidate; RNFL = retinal nerve fiber layer; SD = standard deviation.
* Analysis of covariance (ANCOVA) was used after adjustment for age and sex for comparisons between groups.
† Bonferroni, $p < 0.05$.

ADHD.[15] In contrast to our findings, Bodur et al. demonstrated reduced GCL thickness bilaterally in patients with ADHD. Several studies have investigated the relationship between GCL thicknesses and psychiatric disorders.[12,22] In one of these studies, Kalenderoglu et al. measured GCL thicknesses in 43 euthymic patients with bipolar I disorder and 43 healthy controls, and detected lower GCL thicknesses in the patient group.[12] In another study, Celik et al. measured GCL thicknesses in 40 treatment-refractory patients with schizophrenia, 41 treatment-responsive patients, and 41 controls, and found reduced GCL thicknesses in the patients with schizophrenia than in controls.[22] These studies suggest that decreases in GCL thicknesses may reflect neuronal atrophy, and may be associated with neurodegeneration.[12,22] Since ADHD is not a neurodegenerative disorder, no change in GCL thicknesses were to be expected.

MPH is used as a first-line treatment for ADHD. Insomnia, loss of appetite, abdominal pain, and weight loss are among the most common adverse effects.[23,24] MPH also has some ocular side effects, including dry eye, mydriasis, impaired accommodation, and blurry vision. MPH is contraindicated in patients with glaucoma due to the possibility of transient IOP elevation.[25] However, this contraindication is only theoretical, resulting from the mechanism of action of MPH.[26] In recent years, studies investigating the relationship between MPH treatment and IOP did not find any association.[27,28] Larrañaga-Fragoso et al. investigated the effects of MPH treatment on IOP in children with ADHD, and found no significant change in IOP from baseline at 3 or 9 months.[28] Duman et al. also demonstrated no alterations in IOP in children with ADHD who had been receiving MPH.[27] In contrast to these results, children in our sample who had been receiving MPH for at least 3 months had significantly higher IOP in the left eye compared to controls. Although the increase was not clinically significant, it is important that clinicians remain alert to the possibility of glaucoma in patients receiving MPH for ADHD. Nevertheless, in our study, IOP was not measured at baseline. Therefore, the finding of high IOP in the MPH group may have been incidental, and not associated with MPH use at all. Further research is needed to clarify the potential interaction between MPH and IOP.

Our findings should be interpreted in light of the limitations of this study. First, the cross-sectional design precludes any causal inference. Second, the sample size was relatively small, which makes it difficult to generalize our results. Third, the ADHD group under MPH treatment did not have baseline IOP or OCT measurements, which makes it impossible to interpret whether MPH treatment had an effect on these parameters. Finally, the groups could not be matched in terms of age and gender, but we did control for age and gender in statistical analyses. To decrease the risk of false-positive results due to multiple comparisons, we performed Bonferroni corrections.

In conclusion, we found no difference in OCT parameters between treatment-naive children with ADHD, children with ADHD receiving MPH treatment, or healthy controls. However, left global RNFL thickness correlated negatively with teacher-rated T-DSM-IV-S oppositional

defiant scores, and left-eye IOP was higher in children receiving MPH than in controls. Further longitudinal follow-up studies are needed to determine whether MPH treatment has any effect on IOP and OCT parameters, and whether any differences exist in these parameters between patients with ADHD and controls.

Disclosure

The authors report no conflicts of interest.

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