Retinal nerve fiber layer, macular thickness and anterior segment measurements in attention deficit and hyperactivity disorder

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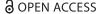Taha Ayyildiz [a] and Didem Ayyildiz [b]

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ABSTRACT

AIM: We aimed to explore whether there is difference in terms of Retinal Nerve Fiber Layer (RNFL) thickness, macula thickness and anterior segment structures of the eye between children and adolescents with ADHD and healthy controls.

METHOD: Children and adolescents aged 8–16 years who were admitted to the Child Psychiatry outpatient clinic of Ahi Evran University Hospital diagnosed with ADHD constituted the study group. Exclusion criteria included patients who had any systemic/ocular or psychiatric disorder other than ADHD and patients who had any psychopharmacological treatment. Participants in the control group were children and adolescents who applied to the outpatient clinic of Ophthalmology at the same hospital with no chronic medical or psychiatric disorder. Groups were compared in terms of central macular thickness, retinal nerve fibre layer thickness (RNFL), central corneal thickness, corneal diameter, mean corneal radius of curvature, anterior chamber depth, and axial length using Optical Coherence Tomography (OCT) and Optical Biometry.

RESULTS: Data obtained from the measurements of 60 eyes of 30 patients with ADHD and 60 eyes of 30 patients of the control group were evaluated. Groups were similar in terms of age and gender. Corneal thickness ($p = 0.001$) and axial length ($p = 0.04$) values were significantly higher in ADHD group while the mean corneal curvature radius ($p = 0.03$) was significantly lower in ADHD group than in controls. No significant difference was observed between groups in terms of RNFL thickness, macular thickness, the corneal diameter, and anterior chamber depth measurements.

CONCLUSION: In recent years, the use of OCT in neuropsychiatric diseases has increased the interest in identifying possible biomarkers and the elucidation of neurodegenerative and neurodevelopmental mechanisms that contribute to the nature of these diseases. Differences in the ophthalmic anatomical structures observed between healthy controls and cases with ADHD, which is a neurodevelopmental disorder, need to be supported by longitudinal studies with a larger sample and using OCT in connection with brain imaging.

Introduction

ADHD is the most common neurodevelopmental disorder in children and the worldwide prevalence of ADHD is reported to be 3.4% (2.6–4.5) [1]. Although genetics plays an important role in the occurrence of ADHD, the etiology is still not clear. The neurobiological hypothesis to explain ADHD suggests that there is a delay in cortical maturation in these cases [2]. Magnetic resonance imaging studies have shown that brain volume in individuals with ADHD is reduced in regions associated with executive functions such as four important brain lobes (frontal, temporal, parietal and occipital), cerebellum, corpus callosum and caudate [3–5].

Embryologically, eye and brain development are parallel to each other. The retina and cerebral cortex originating from the neuroectoderm are part of the central nervous system (CNS). The retina and the brain are connected by the optic nerve and the optic nerve loses myelin before it enters the eye. Retinal nerve fibres are unmyelinated axons of nerve cells and appear to be equivalent to the cerebral cortex [6]. CNS pathologies have ocular manifestations due to degeneration of the visual pathways; so, in neurodegenerative diseases such as Multiple Sclerosis, Parkinson's disease, retinal changes associated with changes in brain tissue have been shown [7–10].

Optical Coherence Tomography (OCT) is a non-invasive imaging technique which allows in vivo visualization of the retinal nerve fibre layer (RNFL) primarily used to monitor retinal changes in glaucoma [11]. In recent years, OCT has been used in evaluating retinal and macular differences in neuropsychiatric disorders to find out underlying pathophysiology. In

literature, there are many studies on retinal changes by using OCT in schizophrenia patients thought to be a neurodegenerative disease among psychiatric disorders [12–15]. As a result of a meta-analysis of case-control studies related to this issue and performed in 2018, it was stated that RNFL can be used as a diagnostic tool in schizophrenia [16]. In addition to studies about schizophrenia, there are researches that ocular findings have been evaluated by using OCT in patients with Major depressive disorder, ADHD and Anorexia nervosa [17–20].

To the best of our knowledge, there are only two studies evaluated the RNFL and macular thickness of eyes of children and adolescents with ADHD which is a neurodevelopmental disorder. Hergüner et al. found that the ADHD group's macular thickness did not differ from age-matched controls, but the RNFL thickness is reduced in the ADHD group [20]. In another study, children and adolescents with ADHD and Oppositional Defiant Disorder (ODD) accompanying ADHD compared to healthy controls, no significant difference was found in terms of RNFL but the ganglion cell layer of the retina was found to be thinner in ADHD and ADHD + ODD groups [21].

Detecting the anatomical differences in eye related to the extension of the brain in children with ADHD will help to clarify the neurodevelopmental process contributing to the presence of the disease. OCT, a noninvasive imaging method, may be a tool for the diagnosis and prognosis of the disease. In our study, it was aimed to show whether there is any difference in the measurements of central macular thickness, global RNFL thickness by using OCT and other anatomical structures as central corneal thickness, corneal diameter, mean corneal radius of curvature, anterior chamber depth, and axial length of the eye by using Optical biometry between children and adolescents with ADHD and healthy controls.

Method

The data obtained from the measurements of 60 eyes of 30 individuals free of any chronic medical or psychiatric diseases (control group) and 60 eyes of 30 patients with ADHD (study group). Patients were admitted to the Child Psychiatry outpatient clinic of Ahi Evran University Educational and Research Hospital in May-December 2017. Patients who were aged 8–16 years, first diagnosed with ADHD and have not received any treatment were included. The diagnosis of ADHD was clarified by Child and Adolescent Psychiatrist by using K-SADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version), a semi-structured diagnostic interview tool. In all cases, symptoms were consistent with the ADHD-combined subtype. The exclusion criteria were the presence of a comorbid psychiatric disorder or mental retardation (according to clinical interview), pervasive developmental disorders, and including the history of significant neurological illness or head injury leading to loss of consciousness. Alterations in ocular fixation and saccadic eye movements are known in children with ADHD [22–24]. Six of the 36 cases with ADHD were excluded from the study because they could not focus on the device for a sufficient period. Healthy controls without any psychiatric complaint were recruited from the Ophthalmology outpatient clinic in the same hospital. Children and adolescents with ADHD and healthy controls were evaluated by a specialist in the outpatient clinic of Ophthalmology. Detailed ophthalmologic examination including visual acuity, non-contact tonometry, intraocular pressure measurement, anterior and posterior segment evaluation was applied to all cases. Patients with visual acuity ≤ 20/20 and any ocular or systemic disease according to patient's detailed history were not included in the study. The research was carried out in accordance with Helsinki declaration rules and by receiving informed consent forms of patients.

Macular (μ) and RNFL (μ) measurements were made with Spectral Domain Optical Coherence Tomography (SD-OCT) (software version 6.3.3.0, Heidelberg Engineering Inc., Heidelberg, Germany). The device contained a superluminescent diode with a wavelength of 870 nm and could obtain 40.000 A-scans per second. The axial and transverse resolutions were 7 and 14 μm, respectively [12]. Measurements of Axial Length (AL) (mm), corneal diameter (mm) (white-to-white), Central Corneal Thickness (CCT) (μ), anterior chamber depth (mm), and corneal radius of curvature (diopter) were measured by Optical biometry (Haag-Streit LENSTAR 900, Koniz, Switzerland). It measures the axial dimensions of the eye in a single step. The technology is based on optical low-coherence reflectometry (OLCR), with an 820 μm superluminescent diode. In addition to axial length, the unit measures the central corneal thickness and aqueous depth, defined as the measurement from the corneal endothelium to the anterior lens surface. It also measures crystalline lens thickness and retinal thickness. The K readings are calculated by analyzing the anterior corneal curvature at 32 reference points orientated in 2 circles at approximately 2.30 and 1.65 mm optical zones. It also measures the size and centricity of the pupil [25]. The average of all values measured from the right and left eyes were evaluated.

Statistical analysis

The obtained data were analyzed using Statistical Package for Social Sciences-SPSS for IBM, 20.0. Since the axial length values did not show a normal distribution

(Kolmogorov-Smirnov), the difference between the two groups was assessed by the Mann-Whitney U test; other parameters with normal distribution were assessed by the independent t-test. The chi-square test was used to determine the gender distribution among the groups. The effect size also was calculated in order to determine whether the difference between groups was significant. For this purpose, the calculation method using mean and standard deviation values developed by Cohen was used. If the value of d is less than 0.2, it is assumed that the effect size is weak, and medium in the case of 0.5 and in the case of greater than 0.8, it is assumed to be strong [26]. Statistical significance was accepted as $p < 0.05$.

Results

Measurements of 60 eyes of 30 patients in the ADHD group and 60 eyes of 30 patients in the control group were evaluated. ADHD group has 19 boys and 11 girls; 15 of the control group were boys and 15 were girls. The mean age of the ADHD group was 142.89 ± 24.31 months while the mean age of the control group was 153.13 ± 24.73 months. The two groups were similar with respect to age and sex. There was no statistically significant difference between groups in terms of global RNFL thickness ($p = 0.1$), macular thickness ($p = 0.75$), the corneal diameter ($p = 0.93$) and anterior chamber depth ($p = 0.25$) parameters. Central Corneal Thickness (CCT) ($p = 0.005$) (cohen's $d = 0.756$) and Axial Length (AL) ($p = 0.04$) (cohen's $d = 0.769$) values were significantly higher in ADHD group while the mean corneal curvature radius ($p = 0.03$) (cohen's $d = -0.408$) was significantly lower in ADHD group (Table 1).

Discussion and conclusion

In this study, we examined whether the values obtained in the measurements of the RNFL thickness, macular thickness and anterior segment parameters of the eye by using OCT and optical biometry differ between the children and adolescents with ADHD and the age-matched control group. According to the result of our study, expected significant difference could not be shown between children and adolescents with ADHD and healthy controls in terms of the values of RNFL, macula thickness, corneal diameter and anterior chamber depth parameters measured by OCT and Optical biometry. It has been determined that the Central Corneal Thickness (CCT) and Axial length (AL) values were significantly higher in the ADHD group while the mean corneal curvature radius was significantly lower in the ADHD group.

Previous reports evaluated RNFL and macular thickness in schizophrenia patients by using OCT in literature are usually compatible with the decrease in RNFL and macular thickness compared to controls except one study showing that patients with schizophrenia and schizoaffective disorder have similar RNFL thickness and macular volume as controls [15]. The changes in the retina in schizophrenia thought to be caused by neurodegenerative mechanisms are assumed to be parallel to gray matter volume loss [12–15,27,28]. Several studies on this issue have found a relationship between reduction in RNFL and macular volume and duration of disease and emphasized that OCT may be a useful tool in the diagnosis of schizophrenia and monitoring disease progression [12,28,29]. In a study conducted in Turkey in 2018, choroidal structures in addition to RNFL and macular thickness were also investigated in adult schizophrenia patients. In this study, there was a significant decrease in macular thickness but RNFL and choroidal thickness were similar between patients with schizophrenia and controls [30]. Another psychiatric disorder in which retinal findings are investigated using OCT is major depressive disorder. No significant difference was found in the two studies in patients with Major depressive disorder [17,18]. In another study with 13

Table 1. Sociodemographic outcomes and mean values of measurements.

		Study group ($n = 30$)	Control group ($n = 30$)	p	Cohen's d
Age (month)		142.89 ± 24.31	153.13 ± 24.73	0,11[a]	
gender	girl	11	15	0.297	
	boy	19	15		
Macular thickness (μm)		256.46 ± 27.81	256.40 ± 16.89	0.75[a]	
RNFL (μm)		103.50 ± 8.96	105.86 ± 6.65	0.1[a]	
AL (mm)		23.61 ± 0.77	22.51 ± 1.87	*0.04*[*b]	0.769
Corneal diameter (mm)		12.23 ± 0.52	12.22 ± 0.40	0.93[a]	
Anterior chamber depth (mm)		3.08 ± 0.27	3.13 ± 0.23	0.25[a]	
Corneal curvature Radius (Dioptri)		43.06 ± 1.22	43.56 ± 1.23	*0.03*[*a]	−0.408
CCT (μm)		556.80 ± 40.26	530.40 ± 26.30	*0.005*[**a]	0.756

Mean values: Average of the measured values from right and left eyes.
Cohen's d: Value of effect size.
RNFL: Retinal nerve fibre layer thickness.
CCT: Central corneal thickness.
AL: Axial length.
Independent t- test[a].
Mann-Whitney U test[b].
$P < 0.05$ *.
$P < 0.01$**.

women with Anorexia nervosa, the macular thickness was found to be decreased in anorexia cases, while no difference was found in RNFL thickness between groups [19].

In the literature, only two studies investigated RNFL and macular thickness in children and adolescents with and without ADHD. Hergüner et al. found that the ADHD group's macular thickness did not differ from age-matched controls, but the RNFL is reduced in the ADHD group. They also suggested that there was a negative correlation between RNFL thickness and ADHD symptom severity [20]. In parallel with the previous result, we found RNFL thickness was lower in the ADHD group than in the control group, but this difference was not statistically significant. In the other study, children and adolescents with ADHD and Oppositional Defiant Disorder (ODD) accompanying ADHD compared to healthy controls, no significant difference was found in terms of RNFL but the ganglion cell layer of the retina was found to be thinner in ADHD and ADHD + ODD groups [21].

Other parameters investigated in this study were corneal structures. It was found; children with ADHD had higher CCT and lower corneal curvature diameters than the control group and their ALs, which described the anterior-posterior diameter of the eye to be higher. The obtained data were statistically significant. To the best of our knowledge, there is no study which explores the difference in the anterior segment measurements of the eyes of children and adolescents with or without ADHD and this is the first study in this area. Future studies in ADHD patients whose ocular imaging is evaluated in conjunction with brain imaging, involving more patients may contribute to define differences in anatomical structures of eyes as a neuroanatomic marker for ADHD.

Small sample size and cross-sectional design of the study are restrictions. Longitudinal studies with a large number of the sample will clarify whether progressive RNFL, macular thickness or other structures' changes. Another limitation is that the severity of the disease has not been evaluated; it has caused working with a heterogeneous group and may have affected the results. In addition, cognitive evaluations of patients could be performed with a standard test.

The neurodevelopmental hypothesis postulates that ADHD is caused by delayed cortical maturation which is supported by many structural and functional imaging studies. In previous cross-sectional structural MRI studies, it's been found that the age of attaining peak cortical thickness was delayed in patients with ADHD for most of the cortical points [31]. Considering that the retinal nerve fibres can be accepted as an extension of the brain in the embryological context; retinal imaging in neuropsychiatric disorders may contribute to the understanding of neurodegenerative and neurodevelopmental mechanisms leading to these disorders. Future studies will evaluate retinal differences using OCT in patients with ADHD between childhood and adulthood which will help in clarifying the neurobiological mechanisms thought to be the cause of ADHD.

Disclosure statement

No potential conflict of interest was reported by the authors.

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