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Assessment of Optical Coherence Tomography Findings in Adults with Attention Deficit Hyperactivity Disorder: A Case-Control Study

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ABSTRACT

Background: To assess retinal nerve fiber layer and ganglion cell-inner plexiform layer thickness using optical coherence tomography in attention deficit hyperactivity disorder adults on regular methylphenidate treatment, comparing them to healthy controls.

Methods: A total of 33 attention deficit hyperactivity disorder adults and 31 healthy subjects, matched for age, gender, and education (control group), were included in this study. Retinal nerve fiber layer and ganglion cell-inner plexiform layer thickness of both eyes were measured using optical coherence tomography, and symptom severity was evaluated using Adult Attention Deficit Hyperactivity Disorder Self-Report Scale and Wender Utah Rating Scale.

Results: There was no significant difference in retinal nerve fiber layer thickness between the attention deficit hyperactivity disorder and control groups ($P > .05$). Thinner ganglion cell-inner plexiform layer total ($P = .044$), inferior ($P = .012$), and inferior nasal quadrant thickness ($P = .049$) were observed in attention deficit hyperactivity disorder patients as compared to the controls.

Conclusion: Findings detected thinner ganglion cell-inner plexiform layer in some quadrants of attention deficit hyperactivity disorder adults, indicating an early disorder in retinal structure development. Whether retinal structures are sensitive attention deficit hyperactivity disorder biomarkers should be supported and investigated in future multimodal studies.

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KEYWORDS: ADHD, adult, ganglion cell-inner plexiform layer, optical coherence tomography, retinal nerve fiber layer thickness

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a chronic neurodevelopmental disorder, beginning in childhood and possibly continuing into adulthood, which is also characterized by symptoms of inattention, impulsivity, and hyperactivity.[1,2] Regarding its societal impact, studies have reported the ADHD prevalence in adults at a rate of 2.5-5%.[3,4] Notably, ADHD is also closely related to the difficulties experienced by the individual in academic, social, cognitive, and emotional areas.[5] In the predominantly combined presentation, which is the most common subtype in both genders, 3 core symptom groups of attention deficit, hyperactivity, and impulsivity are often presented together.[6,7]

The exact etiology and pathophysiology behind ADHD remain incompletely understood. Twin, family, and adoption studies have emphasized the importance of genetic factors in ADHD development.[8] However, specific genes associated with ADHD have yet to be identified.[9] Another suggestion from researchers posits that both genetic and environmental factors synergistically lead to the occurrence of the disorder, rather than working independently.[10,11]

Neurobiological evidence supports a brain basis for ADHD, with alterations in wide spread brain regions.[12] Neuroimaging studies have shown that ADHD children and adults have structural and functional differences as compared to healthy subjects.[12-16] Following the assumption that ADHD is a neurodevelopmental disorder, it is hypothesized that there is a cortical maturation delay in these individuals.[17] In studies supporting this hypothesis, prefrontal cortical maturation delay was indeed reported in ADHD children in comparison to healthy controls.[12,17] Imaging studies have found reductions in brain volume regions associated with executive functions in ADHD individuals as compared to healthy controls,[12-14] demonstrating a reciprocal correlation between structural and functional abnormalities in ADHD.[15,16,18-20]

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Dopamine, glutamate, and GABA: y-Aminobutyric acid are major neurotranmitters for post-ocular structures such as thalamus and visual cortex.[21] Dopamine, which is known to play a prominent role in the etiology of ADHD, also has multiple trophic roles in retinal function related to coupling of horizontal and amacrine cell lateral systems, the organization of the ganglion cell and bipolar cell receptive fields, and the modulation of the physiological activity of the photoreceptors. The retinal dopaminergic hypothesis claimed that there is a link between central and retinal dopamine, based on the extant literature.[22] Tannock et al[22] claimed that retinal and central dopamine levels are related and reciprocally influential, and contrast sensitivity, a measure of retinal dopamine, may be affected by central dopamine. Therefore, the retinal dopaminergic system influences light adaptation, color perception, contrast sensitivity, and spatial and temporal processing.[22,23] Studies examining the visual functions and features of ADHD patients have revealed that they had more frequent visual defects[24,25] and a higher rate of visual field abnormalities.[26] Other visual problems have also been reported in ADHD individuals, including depth perception, peripheral vision, visual search, and visual processing speed.[27] Retinal structures, in particular, are considered as central nervous system (CNS) components since the retina and optic nerve develop from the diencephalon during the embryonic development period. In ADHD, due to its nature as a neurodevelopmental disorder and the possible effects of structural retinal and visual functioning CNS changes, it has been suggested that visual problems accompany these patients more frequently.[21]

Optical coherence tomography (OCT) is a non-invasive, radiation-free imaging technique that provides in vivo cross-sectional retinal structure images. It can measure retinal nerve fiber layer (RNFL), ganglion cell-inner plexiform layer (GCIPL), and macular thickness (MT), as well as macular volume, which are all quantitatively sensitive enough in comparison to histological tissue samples.[28,29] Thus, OCT scans can potentially serve as a reliable diagnostic and follow-up tool in ophthalmologic disorders. Moreover, given that the retina's development comes from the same tissue as the brain, which is the neuroectoderm, this suggests that retinal changes measured using OCT may directly reflect structural and functional changes in the brain as well.[30,31] In fact, the effective use of OCT in clinical and research settings has facilitated the identification of neurodegenerative diseases, such as Alzheimer's, Parkinson's, and multiple sclerosis, and studies have reported a negative correlation between retinal and RNFL thickness with disease neurodegeneration, cognitive impairment, and severity index.[31-35]

Recently, the investigation of retinal changes has also become a research interest in psychiatry, wherein it has been reported that in some psychiatric disorders, such as schizophrenia and bipolar disorder (BD), there is a relationship between RNFL and MT thickness with disorder duration, providing more insights into these diseases.[29,30,36-39] Although there have been various studies in literature investigating the possible relationship between ADHD and retinal or optic nerve thickness in children and adolescents, we saw only 1 study conducted in adults with ADHD.[40-46] Therefore, in this study, it was aimed to compare the results of OCT measurements (RNFL and macular thickness, as well as macular volume) in adult ADHD patients and healthy controls. We also hypothesized that patients with ADHD would have thinner RNCL and that there would be an inverse relationship between retinal thickness and ADHD symptom severity.

MAIN POINTS

- Retinal structures, in particular, are considered as central nervous system (CNS) components since the retina and optic nerve develop from the diencephalon during the embryonic development period.
- In ADHD, due to its nature as a neurodevelopmental disorder and the possible effects of structural retinal and visual functioning CNS changes, it has been suggested that ocular problems accompany these patients more frequently.
- Optical coherence tomography (OCT) is a non-invasive, radiation-free imaging technique that provides in vivo cross-sectional retinal structure images.
- In this study, thinner ganglion cell-inner plexiform layer total, inferior, and inferior nasal quadrant thickness were observed in attention deficit hyperactivity disorder patients as compared to the controls. Hence, the quantitative and reproducible nature of Spectral Domain-OCT thickness measurements can be used as biomarkers in ADHD cases.

METHODS

Participants

The research sample was selected from consecutive cases of literate patients aged 18-45, who were followed in Izmir Bozyaka Training and Research Hospital's psychiatry outpatient clinic, including those diagnosed with "ADHD-combined presentation" following the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) criteria and healthy controls without any psychiatric or medical diagnosis. On the other hand, the exclusion criteria for this study were as follows: presence of a comorbid psychiatric disorder other than ADHD; mental retardation (according to clinical interview); preterm birth; psychomotor developmental alterations, including history of significant neurological illness, systemic diseases that may affect the CNS or retina (such as diabetes mellitus), or head trauma causing loss of consciousness; alcohol and/or substance abuse in the last 6 months; OCT adaptation problems; history of ocular surgery or trauma; ocular diseases (e.g., mature cataract, corneal opacity, uveitis, vitreous hemorrhage, glaucoma, and retinal vascular disease);

and refractive errors above 3 diopters. Written informed consent forms were signed and obtained from all subjects participating in the study, and approval for this study was obtained from the clinical research ethics committee of Izmir Bozyaka Training and Research Hospital in accordance with the Helsinki Declaration (Ethics committee date: September 19, 2018 number: 02).

Procedure

Study eligibility was evaluated by the same psychiatrist by performing a detailed psychiatric examination following the DSM-V ctieria (5th ed.; DSM-5; American Psychiatric Association, 2013; Elbir et al 2019).[47,48] Patients diagnosed with ADHD-combined presentation, using regular stimulant medication for at least 6 months, and those diagnosed with ADHD in childhood and/or adolescence were included in the study, and they were matched with a control group in terms of age, gender, and education. On the same day, the psychiatric evaluation and scales were applied. Afterwards, they underwent detailed eye examinations in the ophthalmology outpatient clinic, which was performed by the same physician who was blinded to the previous diagnosis and scale scores, and the OCT scans were taken thereafter.

Ocular Examination and OCT Measurements

Autorefractometer measurement, best-corrected visual acuity measurement, anterior segment examination using biomicroscopy, intraocular pressure measurement using a Goldmann applanation tonometer, and dilated fundus examinations (direct and indirect) were performed in the ADHD and control groups in the present study. The spherical equivalent of the patients was obtained by summing half of the cylindrical values with the spherical value, and the visual field for both groups was measured using an automatic perimeter. Peripapillary RNFL and GHIPL thickness measurements were performed by an experienced clinician using the Cirrus HD spectral domain OCT device (Carl Zeiss Meditec, model 4000, version 6.5, Dublin, CA, USA). Specifically, after pupil dilatation, a 6 × 6 mm cube optic disk scan was obtained from the 200-A scan for each 200-B scan. From this data cube, the device automatically determined the center of the disk, creating a 3.46-mm computing circle around it. Retinal nerve fiber layer layer thickness along this peripapillary circle was then analyzed and compared with normative data. Measurements with a signal strength of 7 or more were used for analysis in all subjects. In particular, RNFL layer analysis results were recorded by detecting the data of the 4 quadrants [superior (S), nasal (N), inferior (I), temporal (T)] for each eye, whereas GCIPL thickness was recorded in the 6 foveal region quadrants [superior (S), superior-temporal, superior-nasal, inferior (I), inferior temporal (IT) and inferior nasal (IN)] using the macular protocol (macula cube 512 × 128 protocol). Examples of peripapillary RNFL measurements at 4 quadrants (A) and GCIPL thickness measurements at 6 quadrants (B) are illustrated in Figure 1 (ADHD patient) and Figure 2 (healthy control).

Assessment of ADHD Symptoms

Adult ADHD Self-Report Scale: The Adult ADHD Self-Report Scale (ASRS) is a self-report scale developed by the World Health Organization, which has a total scale cut-off of 45 and contains 18 questions, with 6 questions in Part A and 12 questions in Part B. Scoring in these sections works similar to a 5-point Likert-type scale rated between "never" and "very often." Notably, Part A of the ASRS has been reported to be used for screening ADHD diagnosis, since stepwise logistic regression analysis showed that these questions were better predictive of ADHD diagnosis.[49] Turkish ASRS psychometric properties have even been determined on university students.[50]

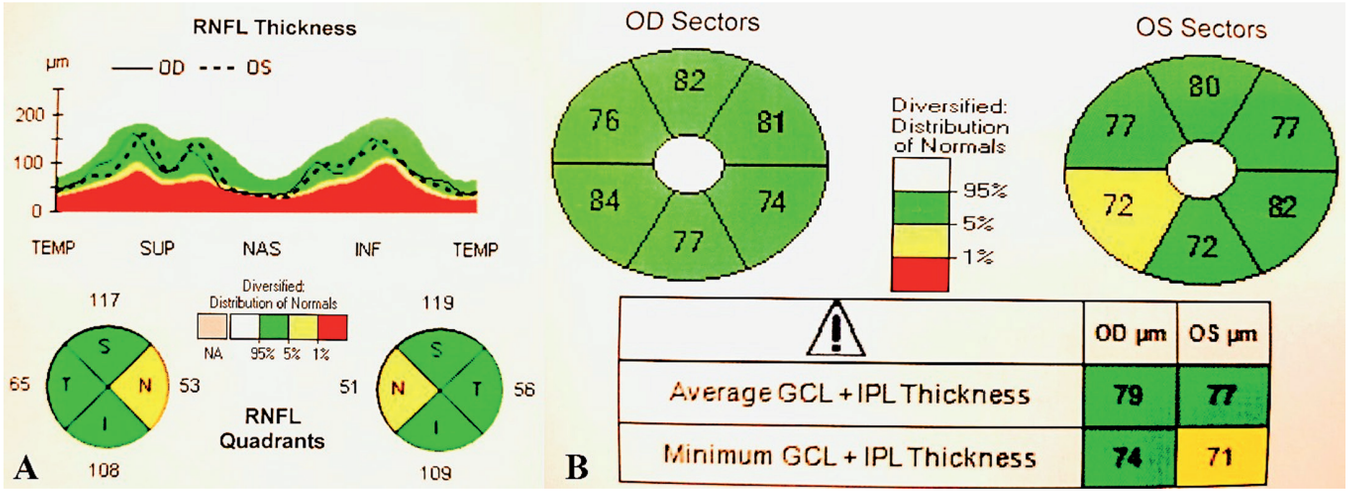

Figure 1. a,b. Measurements of RNFL thicknesses (a) and ganglion cell layer-inner plexiform layer thickness (b) using spectral domain-optical coherence tomography in an ADHD patient. Numbers directly on each sector name are the individual's mean RNFL thickness (µm). RNFL, retinal nerve fiber layer; ADHD, attention deficit hyperactivity disorder.

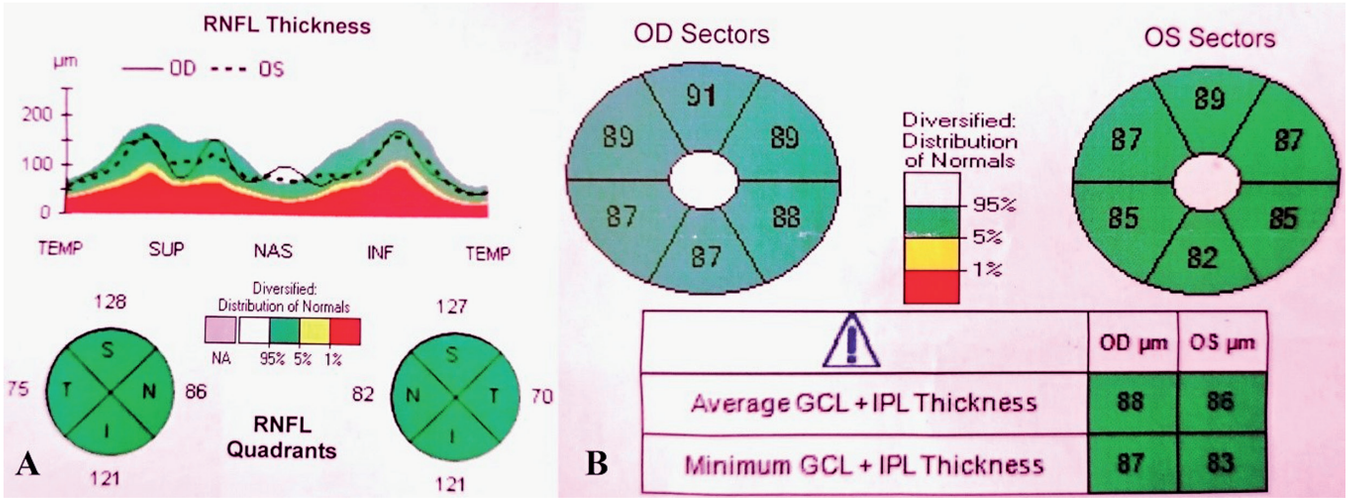

Figure 2. a,b. Measurements of RNFL thicknesses (a) and ganglion cell layer-inner plexiform layer thickness (b) using spectral domain-optical coherence tomography in a healthy control. Numbers directly on each sector name are the individual's mean RNFL thickness (μm). RNFL, retinal nerve fiber layer.

Wender Utah Rating Scale: The best-known scale for assessing ADHD adults is still the Wender Utah Rating Scale (WURS), which retrospectively assesses ADHD-relevant childhood behaviors and symptoms in adults. This scale originally consisted of 61 items reflecting ADHD signs and symptoms, but it was subsequently reduced to 25 items that distinguished ADHD patients from a non-patient comparison group.[51] Ratings in each WURS item was made on a 5-point scale ranging from 0 ("not at all or very slightly") to 4 ("very much"). Moreover, many studies have shown strong internal consistency and high test-retest reliability in this scale, wherein the ratings were made on a 5-point scale ranging from 0 ("not at all or very slightly") to 4 ("very much"). On testing the validity and reliability of the Turkish version, the cut-off score was determined 36.[52]

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM SPSS Corp.; Armonk, NY, USA). The Kolmogorov-Simirnov test was used to evaluate numeric variable distribution of numeric variables, which was found to be normal, and a chi-square test was used to compare categorical variables between groups. Student's *t*-test was used for independent groups A *P*-value < .05 was considered significant for all tests.

RESULTS

A total of 31 females (48.4%) and 33 males (51.6%), with a mean age of 25.5±8.02 (range: 18-45) years and 26.45±7.11 (range: 18-39) years for the ADHD and control groups, respectively, were included in the study. The average education duration was also noted to be 13.21±2.08 years in the ADHD group and 13.48±2.14 years in the control group. Moreover, there were no differences between the 2 groups in terms of age (z=-0.708; *P*=0.479), gender (z=0.063; *P*=.803), and education duration (z=-0.566; *P*=-0.571). Overall, ADHD scale scores in the experimental group were higher as compared to the control group (Table 1).

The ADHD and control groups were compared in terms of visual characteristics for both eyes (128 eyes) and OCT measurements, showing no difference between the intraocular pressure (z=-0.942, *P*=.346) and visual defects (z=-0.901, *P*=.367). On comparison of RNFL and GCIPL thickness measured using an OCT device in ADHD patients as compared to the control group, the GCIPL inferior quadrant (t=2.544, *P*=.012), inferior nasal quadrant (t=1.989, *P*=.049), and total GCIPL (t=2.034, *P*=.044) were found to be thinner. Additionally, the difference between the

Table 1. Sociodemographic Characteristics of Cases With and Without Comorbid ADHD

	ADHD (n=33)	Control (n=31)	x^2 or z (*P*)
Age (mean±SD)	25.52±8.02	26.45±7.11	-0.708 (*P*=.479)
Gender			
Male (%)	16 (48.5)	17 (54.8)	0.0063 (*P*=.803)
Female (%)	17 (51.5)	14 (45.2)	
Education (years, mean±SD)	13.21±2.08	13.48±2.14	0.566 (*P*=-.571)
Marital status			
Single or widowed (%)	28 (84.8)	25 (80.6)	0.656 (*P*=.747)
Married (%)	5 (15.2)	6 (19.4)	
WURS total score	46.91±12.79	21.87±10.69	−6.367 (*P*=.000)
ASRS total score	49.24±9.01	4.09±2.61	−6.886 (*P*=.000)

ADHD, attention deficit hyperactivity disorder; WURS, Wender Utah Rating Scale; ASRS, Adult ADHD Self-Report Scale.

Table 2. Comparison of OCT Measurements Between ADHD and Control Cases

	ADHD (n=33) (66 eye)	Control (n=31) (62 eye)	t^a	*P*
RSLT (μm)				
Superior	124.75±13.53	123.11±11.45	-0.740	.461
Nasal	73.30±13.10	73.80±11.61	0.229	.819
Inferior	127.98±12.05	129.46±14.19	0.638	.524
Temporal	64.87±7.80	66.74±10.48	1.144	.255
RSLT total	97.69±7.97	98.38±7.81	0.494	.622
GHIPT (μm)				
Superior temporal	83.15±5.02	85.24±4.55	1.959	.052
Superior	86.00±5.90	87.03±5.05	1.027	.306
Superior nasal	86.87±4.91	87.35±5.44	1.215	.227
Inferior temporal	85.78±5.53	86.69±5.10	1.598	.113
Inferior	84.24±5.42	86.32±5.54	2.544	.012*
Inferior nasal	85.36±5.63	86.87±5.99	1.989	.049*
GHIPT total	84.86±4.90	86.62±4.91	2.034	.044*

OCT, optical coherence tomography; ADHD, attention deficit hyperactivity disorder; RNFL, retinal nerve fiber layer; GCIPL, ganglion cell-inner plexiform layer; μm, microns. Student's *t*-test (*a*) was used for independent groups. *$P < .05$.

2 groups in the GCIPL superior temporal quadrant was close to statistical significance (t=1.959, $P=.052$). Detailed OCT measurement values of both groups are further described in Table 2.

When the correlation between ADHD scale scores and RNFL and GCIPL thickness was examined, no correlation was found between WURS and ASRS total scale scores and in any eye quadrant and OCT measurements (Table 3).

Table 3. Correlation Table Between Retinal Nerve Fiber Layer Thickness and WURS and ASRS Total Scale Scores

	WURS	ASRS
RSLT*		
Superior	-.034	.017
Nasal	.148	-.091
Inferior	.072	-.011
Temporal	.130	.061
Total ortalama	.099	-.022
GHIPT*		
Superior temporal	-.057	-.033
Superior	.131	-.043
Superior nasal	.151	-.066
Inferior temporal	-.040	.182
Inferior	.137	.097
Inferior nasal	.191	.011

*Pearson correlation coefficient, $P > .05$. WURS, Wender Utah Rating Scale; ASRS, Adult ADHD Self-Report Scale.

DISCUSSION

This cross-sectional study aimed to compare the RNFL thicknesses of ADHD adults who received treatment in childhood and adulthood with a matched healthy control group using OCT measurements. Although there was no significant difference in RNFL thickness between both groups, it was found that the 2 GCIPL quadrants (nasal and inferior nasal) and total GCIPL thickness were thinner in the ADHD group. Moreover, no relationship was found between ADHD symptom severity and retinal nerve fiber quadrants.

Currently, ADHD is one of the most common childhood neurodevelopmental disorders, with an increasing number of diagnosed children and adolescents, which has caught the attention and interest of researchers as focus becomes more directed toward the adult age group.[53,54] DSM provides a standard and ready-to-use diagnostic framework for psychiatric disorders, wherein clinical diagnosis and monitoring often depend on the clinical symptoms reported by patients (5th ed.; DSM-5; American Psychiatric Association, 2013).[47] In both the clinical and research settings, functional characteristics of mental disorders continue to be the therapeutic focus. In these researches, OCT has been commonly utilized, which is a rapid and non-invasive imaging device that captures high-resolution cross-sectional retinal images down to individual layers using near-infrared light. Particularly, regarding retinal development from the neuroectoderm, which is the same tissue as the brain, it has been suggested that retinal changes may have parallel structural and functional brain changes as well.[30] A study by Ahrendts et al[55] for one, compared 31 ADHD adults to healthy controls, and the decrease in bilateral visual cortex gray matter volume was interpreted as a representation of early developmental "sub-executive" attention mechanism impairment. Therefore, determining retinal biomarkers using non-invasive retinal imaging technologies such as OCT may provide researchers with an opportunity to reduce cost and time in clinical trials, thereby allowing clinicians to diagnose earlier, monitor disorder progression, and guide treatment of neuropsychiatric diseases such as ADHD.[30,56,57]

Retinal nerve fiber layer, consisting of retinal ganglion neurons and their unmyelinated axons that form the optic nerve origin, has been considered equivalent to cerebral gray matter.[21,58] In our study, the nasal, inferior nasal, and total GCIPL thickness were found to be thinner in the ADHD group as compared to the healthy control group. In previous studies, decreased retinal thickness has been associated with chronic axonal degeneration or abnormal neuronal development.[14,59] For example, findings regarding global retinal thinning in schizophrenia patients have drawn attention,[36,60-62] wherein peripapillary RNFL thinning was specifically observed in the nasal, inferior, and mostly superior quadrants.[61,62] In multiple BD studies, it was shown that there was statistically significant peripapillary RNFL

and global RNFL thinning.[37,63-65] In comparison with healthy controls, a statistically significant global RNFL thinning was even observed in euthymic BD patients.[63] Moreover, many studies have observed lower GCIPL and GCL volume in BD patients,[63,65,66] with a significant negative correlation between retinal thickness and disease severity and duration.[63]

On review of literature, the relationship between ADHD and retinal thickness has already been investigated in various studies involving child and adolescent age groups. Herguner et al[40] for one, compared 90 eyes of 45 ADHD children and 90 eyes of 45 controls, revealing that the ADHD group showed significantly lower RNFL nasal quadrant thickness as compared to the controls. The remaining RNFL quadrants, macular thickness, and macular volume were not significantly different between the groups, and an inverse correlation was noted between RNFL thickness and ADHD symptom severity.[40] The results of another study showed thinner bilateral GCIPL thickness in ADHD patients as compared to the controls.[67] In contrast, the results of another study showed no differences between children with and without ADHD in terms of RNFL and macular thickness.[41] Ababneh et al[43] additionally reported that there was no significant difference between 55 ADHD children and 55 healthy control subjects in terms of macular thickness, whereas Atas et al[42] detected thinner macula and RNFL nasal quadrant thickness in 37 ADHD children as compared to healthy controls. Similar to our results, thinning of the ganglion cell complex were reported in unmedicated adult ADHD patients.[46] In another recent study, a lower central macular thickness was observed in ADHD children and adolescents as compared to the controls, in which no difference was found in terms of ganglion cell complex or RNFL thickness. Although it was found that there was no difference between treated and untreated ADHD patients in terms of macular and ganglion cell thickness, the foveal thickness and 5/12 RNFL sectors were found to be thinner at the papillary level in the non-treated group of the same study.[44] This finding supports studies reporting that low-dose stimulants used in treatment contribute to the reduction of structural ADHD abnormalities or neurological anatomy and functioning normalization,[15,16] such as the anterior cingulate and cerebellar vermis.[68,69] Furthermore, Isik and Kaygisiz[45] compared ADHD children with and without methylphenidate (MPH) treatment to healthy subjects, finding no difference between the groups in terms of global RNFL, central macular, and GCL thickness in both eyes. Regarding the effect of psychostimulants on ADHD neurological development, Friedman and Rapoport[13] suggested that either the stimulant itself exerts a direct impact on normalizing brain development or that the stimulant supports anatomical normalization based on adequate function. This hypothesis may explain why the RNFL thickness of adult ADHD patients using stimulant therapy did not differ from healthy controls. However, studies with larger samples are needed to properly evaluate GCIPL total, nasal, and inferior-nasal quadrant thickness, which we have identified as a more sensitive region among the retinal structures.

To date and to our knowledge, this research is the first study examining the retinal layers in ADHD adults who received long-term psychostimulant treatment. Although it makes a significant contribution to the current literature, the study has certain limitations. First, our results cannot be generalized due to the small sample size, the fact that all patients were under medication and since the included participants may have had selection bias. Diagnosing adult ADHD with the current version of DSM-5 rather than the diagnostic interview (DIVA: Diagnostic Interview for Adult ADHD ACE: ADHD Child Evaluation) is one of our limitations. Attention deficit hyperactivity disorder is highly comorbid with other mental disorders, suggesting common neurobiological pathways. Excluding comorbid disorders in study samples makes difficult to understand whether a dysregulated or pathological evidence might be the actual link between ADHD and its comorbidities. If ADHD and the comorbid disorder are each associated with different correlates, a double dissociation between the clinical disorders can be obtained, that is, both disorders can be separated by the profile of their correlates.[70] Investigating the correlates of the comorbid group relative to the single-disorder groups may then highlight important issues of the etiology of comorbidity between the 2 disorders. Therefore, exclusion of comorbid conditions is one of our important limitations in this present study.

As stimulant treatment is widely prescribed in patients with ADHD of all ages, evaluating the effects of the therapeutic oral doses of stimulants on retinal structure and function in individuals with ADHD is in areas of clinical and scientific relevance. In a study examining the possible effect of MPH on contrast sensitivity which is a potential physiological marker for ADHD showed that contrast sensitivity is low in children with ADHD and increases significantly after OROS-MPH: Osmotic-Release Methylphenidate medication but still did not reach the levels of the children without ADHD.[71] On the other hand experimental researches in animals without ADHD modeling demonstrated that MPH could increase oxidative stress to cause cell toxicity via autophagy with increasing dose, providing the scientific rationale for the retinal structures caused by the MPH administration.[72,73] Due to the cross-sectional nature of our study and the difficulty of evaluating the possible effects of MPH treatment as a result of the absence of basal OCT measurements in ADHD cases, it is difficult to define our retinal findings as state or trait biomarkers. Lastly, the fact that retinal findings were not supported by structural or functional neuroimaging measurements can be considered as another limitation.

The abnormal connectivity findings observed in ADHD patients should be examined from a developmental perspective and supported by longitudinal, structural, and functional imaging studies. It would also be of interest to conduct studies with a longitudinal design and a larger sample size to confirm the present results, as well as a subanalysis thereof based on treatment and cerebral plasticity of adult ADHD. In particular, planning multimodal methodology studies that examine the hypothesis of neural network delays or altered maturation through the measurement of structural and functional connectivity will provide significant advances in the diagnostic and prognostic definition of developmental disorders such as ADHD.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Izmir BozyakaTraining and Research Hospital (Decision number: 02. Date: September 19, 2018).

Informed Consent: Informed consent was obtained from all participants who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept - E.E., D.H.D.; Design - E.E., D.H.D., K.O.; Supervision - E.E., D.H.D.; Resource - E.E., D.H.D.; Materials - E.E., D.H.D.; Data Collection and/or Processing - E.E., D.H.D., O.K.; Analysis and/or Interpretation - E.E., D.H.D., O.K.; Literature Search - E.E., D.H.D.; Writing - E.E., D.H.D., O.K.; Critical Reviews - E.E., D.H.D., O.K.

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