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Research Article

Ganglion Cell Layer, Inner Plexiform Layer, and Choroidal Layer Correlate Better with Disorder Severity in ADHD Patients than Retinal Nerve Fiber Layer: An Optical Coherence Tomography Study

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Abstract

Aim: To assess the thickness of the choroidal layer, inner plexiform layer (IPL), ganglion cell layer (GCL), and retinal nerve fiber layer (RNFL) in individuals with attention-deficit/hyperactivity disorder (ADHD).

Material and Methods: In this retrospective study, we used a spectral optical coherence tomography (OCT) device. The CPRS-48 was performed to the ADHD group.

Results: Both groups consisted of 60 subjects. There were significant differences in NS segment of RNFL (right p=0.039; left p=0.035). The mean right choroidal thickness of ADHD group was significantly lower than the control group (p=0.015). The left GCL and IPL volumes of ADHD group were significantly lower than the control group (p<0.05). In ADHD group, a significant correlation was found between right choroid and opposition (r=0.278, p<0.05) and conduct (r=0.373, p<0.01) subscales of CPRS-48; between age and right choroid (r=0.248, p<0.05). In control group, a significant correlation was found between age and right NS (r=-0.370, p<0.05), right TS (r=-0.381, p<0.05), right mean RNFL (r=-0.352, p<0.05), left NS (r=-0.397, p<0.05), right choroid (r=0.422, p<0.01), left choroid (r=0.443, p<0.01), right GCL (r=0.425, p<0.01), right IPL (r=0.446, p<0.01).

Conclusion: This study demonstrated that there is an association between disorder severity, duration of disorder, choroidal layer thickness, GCL, IPL and ADHD.

Keywords: Ganglion cell layer, retinal nerve fiber layer, inner plexiform layer, attention-deficit/hyperactivity disorder, optical coherence tomography

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD), which is characterized by problems in concentration, attention, activity, and impulse control, is a common, childhood-onset persistent developmental disorder with a prevalence of approximately 5% (1). The clinical appearance of ADHD is thought to be influenced by both hereditary and environmental variables, making it an etiologically multifactorial condition. It has been established that ADHD has a solid neurological basis, although the pathophysiology of the disorder is still poorly understood (2). Researchers have regularly employed various structural, functional neuroimaging, and neuropathological techniques to pinpoint certain anomalies connected to this illness (3). Another device used to increase our understanding of ADHD is optical coherence tomography (OCT) (4).

In 2018, Herguner et al. (5) have used the OCT to investigate the changes in 45 ADHD patients (mean age 8.6±1.9 years). They reported that ADHD group had significantly lower retinal nerve fiber layer (RNFL) thickness than the controls. The number of studies

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examining the association between ADHD and OCT has gradually expanded throughout the ensuing years. According to Ulucan Atas et al. (6), the healthy control group had much thicker RNFL in the nasal region and thicker macular tissue than the ADHD group did (mean age 9.5±2.2 years). Işık ve Kaygısız (7) demonstrated that the ganglion cell layer (GCL), global RNFL thickness, and central macular thickness of both eyes were not significantly different across treatment-naive children with ADHD (mean age 9.0±2.41 years), ADHD patients using methylphenidate (MPH) treatment, and healthy subjects. Akkaya et al. (8) reported that the ADHD patients (mean age 9.4±1.9 years) had a significantly higher mean choroidal thickness than the healthy controls. Bodur et al. (9) demonstrated that the GCL thickness of the ADHD group (mean age 111.62±27.05 months) was thinner than the control group. According to the study of Ayyildiz and Ayyildiz (10), corneal thickness was significantly higher in ADHD group (mean age 142.89±24.31 months) than in controls. Also, there was no discernible variation in RNFL thickness between groups. According to Tosun et al. (11), there was no discernible change in the GCL and RNFL thickness values between the control and ADHD (mean age, 9.902.15 years) groups.

The results of the investigations in the literature differ from one another, as is evident. More studies are needed to clearly reveal the ADHD-OCT relationship. In this research, we sought to examine the choroidal thickness, IPL, GCL, and RNFL of OCT in healthy controls and ADHD patients.

MATERIAL AND METHOD

The study was approved by the Clinical Research and Ethics Committee of the University of Health Sciences Antalya Training and Research Hospital, Antalya, Turkey (Date of Approval: 28.03.2019; Decision Number: 10/1).

Study Sample

In this retrospective study we compared the patients diagnosed with ADHD with a control group. The study was approved by the ethics committee.

Patients with ADHD who were diagnosed according to the DSM-5 (12) criteria were included. Patients who had organic pathologies were excluded. Mental retardation was excluded with the WISC-R (13). A spectral-OCT device was used.

Conners' Parent Rating Scale-48

Conners' Parent Rating Scale-48 (CPRS-48) consists of 48 items and four subscales ("opposition", "attention-deficit", "hyperactivity", "conduct") (14,15). The Turkish validity and reliability study of scale was performed by Dereboy et al. (16) Four-grade Likert type scale questions are answered by parents.

Statistical Analyses

SPSS 22.0 was used in statistical analyses. Two variables with normally distributed distribution were compared using an independent samples t-test, and two variables with non-normally distributed distribution were compared using the Mann-Whitney U test. In the ADHD group, a Pearson correlation analysis was done (p<0.05).

RESULTS

Both groups consisted of 60 people. There were 39 males (65.00%) and 21 females (35.00%) in patient group, 36 males (60.00%) and 24 females (40.00%) in the control group. The mean age was 9.61±2.38 in the patient group and 10.27±3.72 in the control group (p=0.322).

The data for RNFL and its sublayers were indicated in Table 1.

Table 1. The retinal nerve fiber layer thickness and sublayers

Parameters	ADHD (n=60) (Mean±SD)	Control (n=60) (Mean±SD)	p value
Right			
NS	112.61±20.57	124.35±35.26	**0.039***
N	75.57±14.46	78.15±21.09	0.473
NI	116.07±25.08	117.35±27.78	0.814
TI	137.25±20.76	146.50±20.83	**0.032***
T	72.05±9.81	74.00±9.57	0.330
TS	141.28±17.82	141.85±18.48	0.880
Mean	100.30±8.98	104.40±11.09	0.056
Left			
NS	119.96±21.39	142.10±68.02	**0.035***
N	69.23±12.72	83.10±39.54	**0.038***
NI	116.84±23.69	118.05±26.84	0.819
TI	141.20±17.64	140.30±29.01	0.842
T	71.69±10.31	73.00±14.61	0.915
TS	136.69±16.84	136.65±16.92	0.433
Mean	99.96±9.11	106.25±18.29	**0.042***

*p<0.05
Note: Unit is µm. ADHD: attention-deficit/hyperactivity disorder, SD: standard deviation, NS: naso-superior, NI: naso-inferior, N: nasal, TS: temporo-superior, TI: temporo-inferior, T: temporal

The data for choroidal thickness were indicated in Table 2. The data for GCL and IPL volumes were indicated in Table 2.

Table 2. Choroidal thickness, GCL, and IPL volumes of ADHD and control groups

Parameters	ADHD (n=60) (Mean±SD)	Control (n=60) (Mean±SD)	p values
Right Choroid	319.24±55.63	354.66±72.70	**0.015***
Left Choroid	328.39±57.93	346.03±66.37	0.339
Right GCL	1.13±0.08	1.16±0.08	0.084
Left GCL	1.10±0.09	1.15±0.07	**0.007***
Right IPL	0.91±0.06	0.94±0.07	0.065
Left IPL	0.89±0.07	0.94±0.06	**0.003***

*p<0.05
Note: Unit is µm. ADHD: attention-deficit/hyperactivity disorder, GCL: ganglion cell layer, IPL: inner plexiform Layer, SD: standard deviation

The results of correlation analysis of ADHD and control groups were given in Table 3 and Table 4.

Table 3. Correlation analysis of ADHD group in terms of CPRS-48 subscore

	Attention-Deficit	Hyperactivity	Opposition	Conduct
Right				
NS	0.099	-0.160	-0.057	-0.042
N	-0.035	-0.081	0.015	-0.067
NI	0.093	-0.231	-0.215	-0.107
TI	-0.137	0.009	-0.003	-0.122
T	-0.051	0.125	0.151	0.094
TS	-0.045	0.081	0.008	-0.044
Mean	-0.004	-0.114	-0.051	-0.104
Choroid	-0.015	0.082	**0.278***	**0.373****
GCL	-0.056	-0.123	0.010	0.099
IPL	-0.081	-0.166	-0.069	0.017
Left				
NS	0.001	-0.091	-0.085	-0.068
N	-0.071	-0.028	0.041	-0.035
NI	0.085	-0.215	-0.177	-0.069
TI	-0.048	-0.087	-0.079	-0.111
T	-0.056	-0.051	-0.018	-0.079
TS	-0.012	-0.020	-0.005	-0.108
Mean	-0.030	-0.137	-0.095	-0.129
Choroid	0.026	0.030	0.207	0.233
GCL	-0.061	0.008	0.052	0.147
IPL	-0.110	0.006	0.005	0.092

*p<0.05, **p<0.01
ADHD: attention-deficit/hyperactivity disorder, CPRS-48: conners' parent rating scale, NS: naso-superior, NI: naso-inferior, N: nasal TS: temporo-superior; TI: temporo-inferior; T: temporal; GCL: ganglion cell layer, IPL: inner plexiform layer

Table 4. Correlation analysis of ADHD and control groups in terms of age

	ADHD	Control
Right		
NS	.101	**-.370***
N	-.144	-.035
NI	-.027	-.204
TI	.125	-.114
T	-.008	-.073
TS	.113	**-.381***
Mean	.021	**-.352***
Choroid	.248*	**.422****
GCL	.194	**-.425****
IPL	.192	**-.446****
Left		
NS	.197	**-.397***
N	-.032	-.311
NI	-.176	-.132
TI	.178	.211
T	.021	.231
TS	.077	-.007
Mean	.050	-.289
Choroid	.132	**.443****
GCL	.166	-.147
IPL	.168	-.237

*p<0.05, **p<0.01
ADHD: Attention-Deficit/Hyperactivity Disorder; CPRS-48: Conners' Parent Rating Scale; NS: Naso-Superior; NI: Naso-Inferior; N: Nasal; TS: Temporo-Superior; TI: Temporo-Inferior; T: Temporal; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer

DISCUSSION

The RNFL was connected to our study's first significant finding. We have found significant thinning in nasal quadrant of RNFL between the ADHD group and healthy subjects. This finding related to RNFL was consistent with the studies of Herguner et al. (5) and Ulucan Atas et al. (6). The literature reported a delay in maturation in ADHD patients (Figure 1) (17). Considering the age of our patient group, it is acceptable that some RNFL parameters were significantly thinner than the control group (18). There are also studies that do not support our findings. Işık ve Kaygısız (7), Ayyildiz and Ayyildiz (10), Tosun et al. (11) found no significant RNFL differences between patient and control groups.

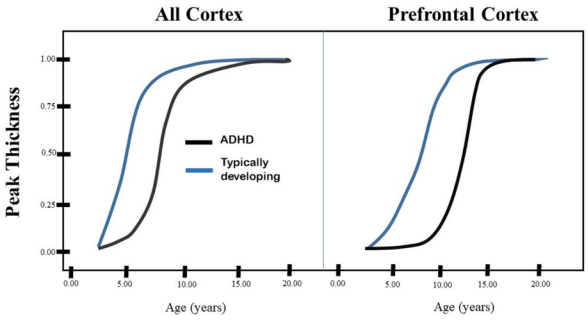

Figure 1. Development of cortex

Secondly, a significant thinning was found in patient group compared to the healthy subjects in terms of IPL and GCL volumes. Similar to our study, Bodur et al. (9) demonstrated that the GCL thickness of the ADHD patients was thinner than the control group. On the other hand, Işık ve Kaygısız (7), Tosun et al. (11) reported no alteration in GCL value. In our study, GCL and IPL parameters were found to be different in the left eye between the patient and control groups. Numerous studies have used spectral domain OCT to identify intra- and interocular differences in the OCT parameters in children. These studies were conducted to establish a standard reference range in different populations, age groups, and genders and have reached different values of OCT parameters. The researchers stated that the retinal asymmetry may be physiological up to some values, but in some cases this asymmetry may be pathological, and even this asymmetry may be used in the early diagnosis of some diseases (19, 20). Whether retinal asymmetry in our study is a limitation or is an important finding is the subject of further studies. Again, several studies reported anatomical and functional hemispheric asymmetries in ADHD brains (21, 22). Hale et al. (23) demonstrated increased right hemisphere (RH) activation in ADHD. However, some investigations found similarities between patients with RH damage and those with ADHD in the area of hemispheric processing (24). Neuroimaging studies provide additional support for the idea that RH dysfunction is one of the fundamental abnormalities in ADHD. Using MRI images, Almeida Montes et al. (25) found changes in the RH's cortical thickness (CT) exclusively between people with ADHD and controls. The degree of ADHD symptoms in this study was linked with the CT differences. In our investigation, it

was shown that the right eye's GCL and IPL had greatly diminished, whereas the left eye had not seen this change. These contradictory findings highlight the need for more research on this topic.

The basic assumption in ADHD is on maturation delay (17). Two meta analyses revealed that, the basal ganglia structural differences between individuals with ADHD and controls tended to disappear as people get older (26, 27). In animals, the majority of retinal neurons develop before birth, and the neurogenesis of RCGs—the retina's output neurons—is mostly governed by intrinsic factors (28). However, numerous additional investigations have also demonstrated that RGCs significantly refine their synaptic connections and dendritic morphology over the postnatal period. RGC dendrites in the IPL become significantly more narrowly stratified with subsequent maturation. These findings unequivocally show that targeted dendritic elimination and ramification, and ongoing dendritic development were all necessary for RGCs to develop their lamina-restricted dendritic pattern (29). In ADHD, these pre- and/or postnatal maturation changes of retina may have abnormalities (24). When the correlation of age and GCL, IPL volumes were examined, no significant correlation was found. This situation may be a finding that can support the hypothesis that delay in maturation decreases with time. However, there is a need for studies aiming at clarifying the potential normalization effects of age, disease severity, and medication.

Our third conspicuous finding was related to the choroidal layer thickness. One of the human body's most highly vascularized tissues is the choroid. Therefore, choroid tissue is indirectly proportional to cell number and is influenced by any inflammatory or autoimmune disorders that alter blood flow (4). Dopamine is also recognized to be involved in retinal function, but it is unclear how dopamine impacts the retina (30). The literature claims that dopamine enhances retinal vascular width and decreases flicker-induced alterations to the retinal vessels (31). Dopamine significantly improves the perfusion of the retina in people (32). We have shown that the left eye's choroidal layer thickness is noticeably thinner in the ADHD group. As opposed to that, Akkaya et al. (8) reported that the ADHD patients had a significantly higher mean choroidal thickness than the healthy controls. The disparity between the results of our study and the literature needs to be investigated further.

CONCLUSION

In conclusion, our findings are consistent with delay in maturation in ADHD and its neurodevelopmental feature. It is possible that the differences between studies in the literature are related to methods and limitations.

Limitations

The cross-sectional design of this study is its main limitation. Equal study subjects for men and women are required.

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Conflict of Interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *The study was approved by the Clinical Research and Ethics Committee of the University of Health Sciences Antalya Training and Research Hospital, Antalya, Turkey (Date of Approval: 28.03.2019; Decision Number: 10/1).*

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