• Clinical Research •

Central choroidal thickness in children and adolescents with anxiety disorders: enhanced depth imaging optical coherence tomography findings

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Abstract

● **AIM:** To measure the central choroidal thickness (ChT) in children and adolescents with anxiety disorders.

● **METHODS:** Totally 41 anxiety patients (8-16y) and 35 healthy controls (age-matched) were evaluated. Complete ophthalmic examination was performed. Inclusion criteria were best corrected visual acuity ≥20/20, normal intraocular pressure (IOP; 10-21 mm Hg), and no systemic or ocular diseases according to history. The diagnosis of psychiatric disorders was determined using Schedule for Affective Disorders and Schizophrenia for School Aged Children Present-Lifetime Version (K-SADS-PL). Enhanced depth imaging optical coherence tomography (EDI-OCT) was used to measure the central ChT.

● **RESULTS:** The mean age was 12.18±3.24y in the patient group and 12.86±3.15y in the control group. Age and gender distribution of the two groups was similar. Central ChT mean value was 353.26±31.9 μm in anxiety patients while 318.75±60.9 μm in the control group. Mean central ChT was statistically significantly higher in the children and adolescents with anxiety disorders than healthy controls (*P*=0.002).

● **CONCLUSION:** The children and adolescents with anxiety disorders have significantly thicker central ChT than controls. In the larger sample, longitudinal studies will contribute to the use of choroidal differences as a clinical marker for monitoring anxiety disorders.

● **KEYWORDS:** anxiety disorders; choroidal thickness; spectral optical coherence tomography; children; adolescent
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INTRODUCTION

Anxiety is the emotional, cognitive, and physiologic reaction response to real or imagined threat that may occur in the future. Adaptive anxiety allows individuals to be prepared to cope with possible problems, and to decide and deal quickly in dangerous situation. Anxiety is defined as a "clinical disorder" when the anxious reaction becomes so intense that it causes impairments in academic, social, or family functioning[1]. Anxiety disorders are among the most common psychiatric disorders in childhood and adolescence. Although there are limited studies on the prevalence of anxiety disorders, studies conducted in the west have found that it is seen at a rate of approximately 5%[2]. Excessive fear and anxiety and related behavioral discomfort are common presentations in various anxiety disorders[3]. Children with anxiety often describe physical symptoms as well as changes in thoughts, feelings, and behaviors. These symptoms such as headaches, stomach aches, nausea, vomiting, diarrhea, and muscle tension are caused by the state of hyperarousal related to activation of the sympathetic nervous system.

The sympathetic adrenomedullary system (SAM) is activated in order to maintain the physiological homeostasis of the body under stress. In response to stress, corticotropin releasing hormone (CRH) is discharged from the hypothalamus, the release of adrenocorticotropic hormone (ACTH) from the pituitary gland is stimulated, and consequently the release of glucocorticoids from the adrenal cortex increases. As a result of this cycle called hypothalamic-pituitary-adrenal (HPA) axis, blood pressure, respiratory rate and blood flow to vital organs rises[4].

The choroid is highly vascularized layer formed of a dense capillary network and nourishes the outer two-thirds of retina[5]. It has been showed that the choroid thickness is changed with various factors such as age[6], myopia[7] and central serous chorioretinopathy (CSCR). CSCR is an ophthalmic disorder

associated with an increase in choroidal thickness due to increased blood flow through increased vascular permeability and hydrostatic pressure[8]. Rich autonomic innervation of choroidal structures may be affecting the choroidal thickness through regulation of blood flow and changes in smooth muscle tone[9]. The relationship between ocular disorders particularly CSCR and psychological factors has been investigated for a long time and it is thought that stress, anxiety or fear conditions affect the eye structures negatively by causing sympathetic discharge like cardiovascular diseases and type A personality disorder[10-15]. This relation is thought to be associated with increased levels of catecholamines that are released when SAM system is activated. Spectral optical coherence tomography (OCT), a non-invasive imaging technique, enables *in vivo* visualization of the eye structures[16]. Recently, OCT has been used to assess retinal, macular and choroid variations in psychiatric disorders such as schizophrenia[17-21], bipolar disorder[22], major depressive disorder (MDD)[23] and obsessive-compulsive disorder[24-25] which are thought to be associated with neurodegeneration and neuroinflammation. Enhanced depth imaging spectral-domain optical coherence tomography (EDI-OCT) is a method has been developed that allows *in vivo* cross-sectional imaging of the choroid[26].

In the study, we aimed to show whether there is a relationship between central choroidal thickness (ChT) of the eye measured by EDI-OCT and anxiety disorders known as stress-related illnesses in children and adolescents.

SUBJECTS AND METHODS

Ethical Approval The sociodemographic data of the whole sample were collected by the researcher using a detailed form and written informed consents were obtained. Ahi Evran University Medical Faculty Research Ethics Committee approved the study by the protocol number 2019-11/124.

Sample The sample included 41 patients with anxiety disorders (study group) and 35 healthy controls, aged between 8-16y. Patients who were applied to the child psychiatry outpatient clinic of Ahi Evran University Educational and Research Hospital in June-December 2018 and have newly diagnosed with at least one anxiety disorder were included. Receiving any treatment was the exclusion criteria. Age and gender matched healthy controls, who referred by the school administration for eye screening or brought by their parents for routine visual examination were recruited from ophthalmology outpatient clinic in the same hospital. Individuals have no chronic medical or psychiatric disorders according to history were included to control group.

Procedure Patients with anxiety disorders and healthy controls were examined by a senior ophthalmologist. Visual acuity with Snellen chart and intraocular pressure (IOP) measurement with non-contact tonometry was applied to all participants. Individuals with best corrected visual acuity ≥20/20 (visual acuity of at least 1.0, a refractive error less than 3 diopters) and any ocular or systemic disease were not included in the study. Cases with IOP 10-21 mm Hg, which are normal values for IOP, were included in the study. Axial length (AL; mm) parameter which was thought to affect the choroidal thickness was also measured by Optical Biometry (LE LS 900 HaagStreit, Köniz, Switzerland) in all participants.

The anxiety disorder diagnoses were determined by using Schedule for Affective Disorders and Schizophrenia for School Aged Children Present-Lifetime Version (K-SADS-PL) by a child and adolescent psychiatrist. The anxiety symptom levels of patients were evaluated with the Screen for Child Anxiety Related Emotional Disorders (SCARED) scale.

Spectral Domain Optical Coherence Tomography Spectral domain optical coherence tomography (SD-OCT; software version 6.3.3.0, Heidelberg Engineering Inc., Heidelberg, Germany) was used to determine the central ChT. The device which produces high-resolution images from low infrared light contains a super luminescent 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. ChT was measured manually with the caliper from the outer portion of the reflective line corresponding to the retinal pigment epithelium in the inner sclera border. Measurement were performed at the center of the fovea on EDI-OCT mode. ChT, AL and IOP measured from the right eye of each participant were analyzed. In our study, all examinations were made between 9:00 a.m. and 12:00 noon, to avoid the effect of diurnal variation on choroidal thickness[27].

K-SADS-PL The psychiatric diagnoses were determined by using Turkish version of K-SADS-PL. K-SADS, a semi-structured diagnostic interview is used to assess present and lifetime psychopathology in children and adolescents, according to the diagnostic and statistical manual of mental disorders (DSM-IV) criteria. K-SADS-PL was developed by Kaufman *et al*[28] in 1997 and validity and reliability study in Turkey were carried out by Gökler *et al*[29] in 2004.

SCARED Scale SCARED was developed by Birmaher *et al*[30] in 1997 to measure symptom levels of anxiety disorders in children. The validity and reliability study of the self-report scale was conducted by Karaceylan Çakmakçi[31]. The scale consisting of 41 items is scored between "0" (not right) and "2" (most of the time). Higher scores on the scale are indicative of a high level of general anxiety.

Optical Biometry Optical Biometry (Haag-Streit LENSTAR 900, Koniz, Switzerland), which works with the principle of low optical coherence reflectometry, is used to measure the distances inside the eye. In this technology, coherence

Table 1 Demographic data, IOP and SCARED scale values of the groups mean±SD (min-max)

Parameters	Patient group (*n*=41)	Control group (*n*=35)	χ^2/t	*P*
Gender, *n* (%)			0.013	0.99
Boy	14 (34.1)	12 (34.2)		
Girl	27 (65.9)	23 (65.8)		
Age (y)	12.18±3.24 (7-17)	12.86±3.15 (8-17)	-0.707	0.484
IOP (mm Hg)	14.57±1.57 (13-19)	15.15±2.23 (12-19)	-1.325	0.189
SCARED	38.78±13.12 (12-57)			

SD: Standard deviation; min-max: Minimum and maximum value of the average values; IOP: Intraocular pressure; SCARED: The Screen for Child Anxiety Related Emotional Disorders.

superposition of light waves occurs. The device uses an 820 nanometer superluminescent diode laser for AL, central corneal thickness, anterior chamber depth, aqueous depth and lens thickness measurements[32].

Statistical Analyses All statistical analyses were made using Statistical Package for Social Sciences (SPSS) for IBM, 20.0. Descriptive statistics were shown as mean±standard deviation, minimum and maximum values, or frequency (%). Kolmogorov-Smirnov test was used to assess the normal distribution of age, IOP, AL and central ChT values. Groups were compared by using independent *t*-test in terms of age, IOP, AL and central ChT values. Chi-Square test was used to evaluate the gender distribution of the groups. Significance was set at $P<0.05$.

RESULTS

In all, 76 children and adolescents (41 in the patient group and 35 in the control group) were included in the study. ChT, AL and IOP values measured from the right eye of each participant were analyzed. The mean age was 12.18±3.24y in the patient group and 12.86±3.15y in the control group. In the patient group, the rates of boys and girls were 34.1% (*n*=14) and 65.9% (*n*=27), respectively. Totally 34.2% of the control group was boy (*n*=12) and 65.8% was girl (*n*=23). The groups were similar regarding age (*t*=-0.707, *P*=0.484) and gender (χ^2=0.013, *P*=0.99). When the IOP values were assessed; mean IOP value was 14.57±1.57 mm Hg in the patient group and 15.15±2.23 mm Hg in the control group. The groups were similar in terms of IOP (*t*=-1.325, *P*=0.189; Table 1). In the study group, the mean score obtained from the SCARED scale was 38.78±13.12 (Table 1).

The prevalence of anxiety disorders subtypes in the patient group was general anxiety disorder (GAD; 88%), social anxiety disorder (40%), separation anxiety disorder (SAD; 8%) and panic disorder (8%). Totally 32% of the patient group had at least one psychiatric disorder other than anxiety disorders. Depressive disorder (16%), obsessive-compulsive disorder (12%), tic disorder (8%), attention deficit hyperactivity disorder (4%), trichotillomania (4%) and enuresis nocturna (4%) were the co-morbid psychiatric disorders (Table 2).

Table 2 Psychiatric morbidities in the patient group

Psychiatric diagnoses	Prevalence
MDD	16%
GAD	88%
Social phobia	40%
SAD	8%
Panic disorder	8%
OCD	12%
Trichotillomania	4%
EN	4%
ADHD	4%
Tic disorder	8%

MDD: Major depressive disorder; GAD: Generalized anxiety disorder; SAD: Separation anxiety disorder; OCD: Obsessive-compulsive disorder; EN: Enuresis nocturna; ADHD: Attention deficit hyperactivity disorder.

Central ChT mean value was 353.26±31.9 μm in the patient group while 318.75±60.9 μm was in the control group. Mean central ChT was statistically significantly higher in the children and adolescents with anxiety disorders than healthy controls (*t*=3.158, *P*=0.002). AL values were 23.11±0.9 mm and 22.87±1.3 mm in the study group and the controls, respectively. There was no statistically significant difference between groups in terms of AL (*t*=0.946, *P*=0.347; Table 3).

When the correlation between choroidal thickness and SCARED scale scores was investigated; no significant correlation was found.

DISCUSSION

We aimed to explore whether there was a difference in terms of central ChT by using EDI-OCT between patients with anxiety disorders and healthy controls in child and adolescent age group. Our main results demonstrated that central ChT was significantly higher in children and adolescents with anxiety disorder than the controls. Similarly, in a study conducted in adult patients with MDD, ChT measured by OCT was found to be higher in the acute phase of the disorder

Table 3 Choroidal thickness and axial length measurements mean±SD (min-max)

Parameters	Patient group	Control group	*t*	*P*
Central ChT (μm)	353.26±31.9 (300-410)	318.75±60.9 (165-420)	3.158	0.002[a]
AL (mm)	23.11±0.9 (21.5-25.3)	22.87±1.3 (21.5-24.4)	0.946	0.347

ChT: Choroidal thickness; AL: Axial length; [a]*P*<0.01.

than controls. Authors suggested that it may be associated with increased blood flow due to inflammation. It has been previously reported that inflammation is more active in the first episode than recurrent MDD[23]. The results of two studies, conducted recently in Turkey, were consistent with that ChT of the adult obsessive-compulsive disorder patients was significantly higher than controls[24-25]. It is known that pediatric neuropsychiatric autoimmune disorders associated with streptococcal infections (PANDAS) syndrome caused by anti-basal ganglia, anti-thalamus antibodies against group-A beta hemolytic Streptococcal agent is characterized by sudden exacerbation of obsessive-compulsive dissorder (OCD) symptoms and accompanying multiple tics. Because of clinic overlap between PANDAS and pure OCD, similar etiological mechanisms have been investigated and anti-basal ganglia and anti-thalamus antibodies were found to be associated with hyperglutamatergia in pure OCD[33]. In a study examining ChT in sleep bruxism, another disease thought to be particularly related to stress and anxiety, ChT was found to be increased in patients compared to the controls. It was suggested that this finding was associated with the neuroinflammatory process[34]. Previous reports regarding ophthalmological findings in theneuropsychiatric diseases, develops with neuroinflammatory mechanisms suggested that cytokines released in the inflammatory process may cause depression and anxiety by affecting the neurotransmitter metabolism, HPA axis or cortical circuits regulate emotion, fear or arousal[35-36].

There are also studies showed that ChT of the psychiatry patients is not thicker than the controls. In one study evaluating ChT in patients with psychosis, the value of ChT was lower than the controls. It was emphasized that although not statistically significant, this decrease in the ChT may be related to vascular dysfunction in the course of schizophrenia. Joe *et al*[37] suggested that ChT can also be affected by systemic conditions and some of the patients who participated in their studies had diabetes. In addition, in a recent study evaluating ChT in patients with anorexia nervosa (AN), ChT was reported to be thinner than controls[38]. It is known that medical complications involving many organs can be observed in AN cases[39], so the ChT may be influenced by systemic signs of the disorder.

Another finding we indicated in our study was that the axial length (AL) mean values were less than 24 mm in both groups and statistically not different. Tan and Cheong[40] found that ChT showed differences with spherical equivalent and AL in their study investigating factors affecting ChT in adults. Cases with spherical equivalent less than 3 diopters were included in our study. The advantages of our study were that the groups in our study were similar in terms of spherical equivalent and AL and the participants did not have a systemic and ophthalmic disorder that could influence main outcome of the study. However, small sample size, cross-sectional design and lack of SCARED scale data of healthy controls were limitations of our study.

In recent years, SD-OCT has become a focus of attention in terms of allowing the examination of eye structures such as retinal nerve fiber layer (RNFL), macula and choroid. Although ocular symptoms due to degeneration of the visual pathways or neuroinflammation often occurs as signs of central nervous system (CNS) abnormalities, studies on ocular findings in children and adolescents with psychiatric disorders whose etiology is thought to be inflammation are limited. Studies comparing findings from different subtypes and different episodes of the disease and using simultaneous magnetic resonance imaging (MRI) may provide more meaningful results for the use of ChT changes as a clinical marker in the diagnosis and follow-up of anxiety disorder.

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