Original article / *Araştırma*

Comparison of optic coherence tomography results in patients diagnosed with OCD: findings in favor of neurodegeneration

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ABSTRACT

Objective: *Optic coherence tomography (OCT) is a contactless and fast neuroimaging method. Previous studies have observed thinning of the ganglion cell layer (GCL) and inner plexiform layer (IPL) in many neurodegenerative diseases. The aim of this study was to compare the GCL volume, retinal nerve fiber layer (RNFL), and IPL thickness in obsessive compulsive patients and controls using OCT to demonstrate neurodegeneration in obsessive compulsive disorder (OCD).* ***Methods:*** *This study involved 50 OCD patients who were being followed by the Psychiatry Department of Adiyaman University Medical School and 50 healthy volunteers as control. OCT measurements were performed for both groups. The RNFL, IPL thickness, and GCL volumes were measured and recorded automatically by a spectral OCT device.* ***Results:*** *The RNFL thickness was lower in patients compared with controls at all measured regions, and this decrease statistically significant in a few regions (left temporo-superior, left mean). The left and right choroid layer thickness acquired from three regions of choroid layer was higher in patients compared with controls. The GCL and IPL volumes were also significantly lower in the patient group. There was a significant negative correlation between the disease duration and OCT results.* ***Discussion:*** *These findings suggest that neurodegeneration occurs during the course of OCD. This degeneration may be demonstrated by decreased GCL at early stages, and as the disease progresses, involvement of other retinal layers, such as the RNFL and IPL, may be observed.* ***(Anatolian Journal of Psychiatry 2019; 20(2):166-174)***

Keywords: *choroid, neurodegeneration, obsessive compulsive disorder, optic coherence tomography, retina*

Obsesif kompulsif bozukluk hastalarında optik koherans tomografi sonuçlarının karşılaştırılması: Nörodejenerasyon lehine bulgular

ÖZ

Amaç: *Optik koherans tomografi (OCT), temassız ve hızlı bir görüntüleme yöntemidir. Önceki çalışmalarda birçok nörodejeneratif hastalıkta ganglion hücre tabakası (GCL) ve iç pleksiform tabakasında (IPL) incelme gözlemlemiştir. Bu çalışmanın amacı obsesif kompulsif bozuklukta (OKB) nörodejenerasyonun ortaya konulması amacıyla OKB hastalarında GCL hacmi, retina sinir lifi tabakası (İVFL) ve IPL kalınlığı ile OCT kullanılarak yapılan kontrollerin karşılaştırılmasıdır.* ***Yöntem:*** *Çalışmaya Adıyaman Üniversitesi Tıp Fakültesi Psikiyatri Anabilim Dalında tedavi edilen 50 OKB hastası ve 50 sağlıklı gönüllü kontrol olarak alındı. İki grup için de OCT ölçümleri yapıldı. RNFL, IPL kalınlığı ve GCL hacimleri, bir spektral OCT cihazı tarafından otomatik olarak ölçülmüş ve kaydedilmiştir.* ***Sonuçlar:*** *RNFL kalınlığı, tüm ölçülen bölgelerdeki kontrollere göre daha düşüktü ve bu, birkaç bölgede (sol temporo-superior, sol ortalama) istatistiksel olarak anlamlı bir düşüş gösterdi. Koroid tabakanın üç bölgesinden elde edilen sol ve sağ koroid tabaka kalınlığı, kontrol grubuna göre daha yüksekti. GCL ve IPL hacimleri de hasta grubunda anlamlı olarak*

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düşüktü. Hastalık süresi ile OCT sonuçları arasında anlamlı negatif korelasyon vardı. ***Tartışma:*** *Bu bulgular, OKB sürecinde nörodejenerasyonun meydana geldiğini düşündürmektedir. Bu dejenerasyon, erken evrelerde azalmış GCL ile gösterilebilir ve hastalık ilerledikçe, RNFL ve IPL gibi diğer retinal tabakaların katılımı gözlenebilir.* ***(Anadolu Psikiyatri Derg 2019; 20(2):166-174)***

Anahtar sözcükler: *Koroid tabaka, nörodejenerasyon, obsesif kompulsif bozukluk, optik koherans tomografi, retina*

INTRODUCTION

Several theories have been developed to explain obsessive compulsive disorder (OCD). The parts of the brain effected due to the obsessions and compulsions observed in OCD have not been completely explained yet. OCD is considered to have a neurological characteristic due to causes such as symptoms occurring despite the patient's conscious will, frequency of unclear neurological symptoms and presence of obsessive compulsive symptoms in some neurological disorders.[1-3] With the improvement in imaging methods in recent years, it has been stated that there are structural or functional deviations in the brain in many psychiatric disorders.[4] These findings acquired from brain imaging studies make it easier for us to understand the pathophysiology of the disease. Especially with functional brain imaging studies, it was shown that there is an abnormal operation in certain frontal-subcortical brain circuits in OCD.[5] Also the connection of OCD with Parkinson's disease and Tourette syndrome point out the basic role of basal ganglions in OCD pathogenesis.[6,7]

Magnetic resonance spectroscopy (MRS) is an effective technique which measures metabolites in the brain such as N-acetyl-aspartate (NAA, a marker of neuronal viability), glutamate ve glutamine, choline (CHO, a marker of cell membrane turnover), myo-inositol, and creatine-phosphocreatine (CRE, a marker of cellular energy).[8] Particularly, NAA is an indicator of axonal degeneration and neurodegeneration and decreases in the cingulate gyrus, left or right striatum, and medial thalamus of OCD patients.[8,9] Although the results acquired by different imaging methods are different, all these data show that OCD symptoms are caused by functional disorder in fronto-striato-thalamic circuits and especially the decrease in metabolites such as NAA/CRE and NAA/CHO demonstrate the decrease in hippocampal neuronal density or at least it may be the demonstrator of neuronal dysfunction in OCD patients.[10]

In many neurodegenerative diseases such as multiple sclerosis,[11] Alzheimer's disease,[12] Parkinson's disease,[13] and restless legs syndrome,[14] a severe myelin loss has been observed in retinal nerve fiber layer (RNFL) thickness in the eye with optical coherence tomography (OCT) in recent years. So, neurodegeneration follow-up was made with OCT measurements in many diseases with neurodegeneration and a significant relation was detected.[15-18] Because when the anatomical structure of retinal neural network is observed, ganglion cell and its branches make synapses and leave the eye after forming the optical nerve and connect with different parts of the brain. Nerve fibers coming from other sources in thalamus lateral geniculate body primarily form synapses and end up in occipital lobe. Activation occurs not only in the occipital lobe, but also in inferior temporal cortex, postero-infero-parietal cortex sections and some parts of frontal lobe.[19]

On the other hand, the main neurotransmitter of photoreceptors responsible for sight in retina physiology is glutamate and neurotransmitters such as serotonin, dopamine, g-amino butyric acid, glycine, acetylcholine and taurine were detected in amacrine cells.[19] But their functions have not been completely understood yet. So when the explanations of OCD symptoms through the functional disorder in fronto-striato-thalamic circuit and OCD physiopathology through serotonin and dopamine systems are considered, some changes may be expected in the mechanisms responsible for the neuronal structure and physiology of retina.[20,21]

More recently OCT was used to detect neuronal degeneration in psychiatric disorders.[22] Spatial resolution of OCT devices increased with new spectral domain OCT and this enabled separation of other retinal sublayers such as GCL and IPL was shown to have better structure function correlation in neurodegenerative diseases such as multiple sclerosis then RNFL.[23] Our group demonstrated reduced GCL and IPL volumes in schizophrenia patients compared with controls using spectral OCT.[24] We also detected significant negative correlations between disease severity parameters and GCL and IPL volumes. In our another study, it is suggested that the neurodegeneration occurred during the course of bipolar disorder may be demonstrated by decreased GCL at early stages, and as the disease progresses, involvement of other retinal layers,

such as the RNFL and IPL, may be observed.[25] Again, our research team demonstrated that OCT finding of decreased GCL and IPL volumes supports previous research suggesting degeneration in major depressive disorder. According to this study, considering RNFL to be the latest layer that will be affected during course of degeneration, GCL and IPL volumes appear to be better parameters follow. In addition, choroid may be an important structure to detect acute attack period and to follow inflammatory process in major depressive disorder like in systemic inflammatory diseases.[26]

The aim of this study was to compare the RNFL, GCL, IPL, and choroidal thickness of patients with motor OCD and controls to assess the usefulness of these measurements to demonstrate neurodegeneration in OCD.

METHODS

Study design

This case-control study compared patients with OCD who were followed in the Psychiatry Department at our University Medical School with a control group. The patients with OCD were consecutive patients who were being followed at our outpatient clinic at least for last six months. The OCD group consisted of 50 patients (20 males and 30 females). After being seen during the baseline visit by the treating psychiatrist, each patient's eligibility for the study was evaluated, and if they were eligible, they were invited to participate in the study. The control group consisted of 50 healthy volunteers (28 males and 22 females) without a history of an OCD who were recruited from the hospital staff. OCT measurements were made in the Ophthalmology Department at Adıyaman University Faculty of Medicine. Sociodemographic Data Form was filled for all study group. All study protocols were approved by the ethics committee of Adıyaman University Medical School (Dated 14 September 2015 and enumerated as 2015/06-2). All subjects provided written informed consent for OCT measurement. In strict accordance with the Declaration of Helsinki, the decision to have OCT was made by the experts in agreement with the free will of the patient and/or their family, completely independently from study participation.

Inclusion/exclusion criteria

Patients with OCD who were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria were included.[27] Patients who had comorbid first axis diagnoses (past or current diagnosis), severe neurological, immunological or systemic diseases, and primary ophthalmological diseases (glaucoma or retinal diseases) were excluded. Again, healthy subjects who had severe neurological, immunelogical or systemic diseases, and primary ophthalmological diseases (glaucoma or retinal diseases) were excluded. Patients and controls with risk factors (non-psychotropic drug use, cancer, alcohol and substance use-before or at the moment, pregnancy) that may have an impact on OCT measurements were not included. Smoking was not considered as an inclusion or exclusion criterion, nor was it questioned in the control group or the patient group. Patients with refraction errors >1 prism dioptre were also excluded. Both the patient and the control groups were examined in ophthalmology clinic and best corrected visual acuity (BCVA), intraocular pressure, slit lamb bio-microscopy, and fundus examination by eye dilatation were measured. Patients and controls with normal eye findings were included. The control group was similarly distributed to the patient group in regard to age and gender.

OCT measurements

A spectral-OCT device (SpectralisTM OCT, Version 6.0, Heidelberg Engineering, Germany) was used to assess the RNFL and choroid thicknesses and GCL and IPL volumes in both eyes. The RNFL includes temporal (T), nasal (N), temporo-superior (TS), temporo-inferior (TI), naso-superior (NS), naso-inferior (NI) and global (G) segments. Therefore, 7 measurements were made for each eye (i.e., N, NS, NI, T, TS, TI, G).

The choroid structure was also measured with OCT. The choroidal thickness was measured manually. A perpendicular line was drawn subfoveal from the outer edge of the retinal pigment epithelium to the choroid-sclera junction. Two additional lines were drawn at the nasal and temporal sides at 500 μm intervals from the subfoveal line. The mean value of these three measures was accepted as the choroidal thickness. All measurements were performed by the same author (ASK) who was blinded to the diagnoses of the patients. The choroidal measurement method used with the spectral-OCT devices has been previously explained.[28]

Lastly, we measured the GCL and IPL volumes with an OCT device. Segmentation of the retina into 6 layers (GCL, IPL, RNFL, inner nuclear layer, outer plexiform layer, and outer nuclear

layer) was performed automatically with the device. Because the between-group comparisons provided similar results for the right and left eyes, only the results of right eye are provided in the tables and discussed to decrease the complexity of the tables. Patients were taking medication (psychotropic drugs) when OCT was performed.

Statistical methods

To evaluate the assumption of normality in the data, the Kolmogorov-Smirnov test was used; and to describe the data, frequency (percent), mean±SD, median, and range were used. For evaluation of the differences between the two groups, we utilized t-test, Mann-Whitney U, and chi-square tests; and to compare groups while considering the correlation of eyes in one subject, generalized estimating equation (GEE) analysis was used. P-value less than 0.05 was considered as statistically significant. All statistical analysis was performed by SPSS software (Version 22.0, Microsoft Co., Chicago, IL, USA).

RESULTS

Sociodemographic data

The study group included 50 patients and 50 controls. The mean age of the patient group was 33.66±9.85, and that of the control group was 37.96±15.88. The patient group consisted of 20 males (40%) and 30 females (60%). The control group consisted of 28 males (56%) and 22 females (44%). The sociodemographic features of the patient and the control groups are given in Table 1. No significant difference was found between group according to age, sex, or marital status. The percentage of active workers was higher in the patient group than the control group (p=0.016).

OCT findings

The RNFL thickness was decreased at all measured regions (TS, TI, T, NS, NI, N) in the patients with OCD compared with the controls, and this difference reached the level statistical significance for the left TS and left mean RNFL thicknesses (Table 2) (Figure 1).

The mean choroidal thickness, which is the mean values of the measurements from three regions, was higher in all OCD patients group than controls (p<0.05) (Table 2 and 3) (Figure 2).

Both GCL and IPL volumes were smaller in OCD patients than controls (p<0.05).

We detected significant negative correlation disease duration and GCL volume. The mean

Table 1. Sociodemographic features of patient and control groups

	Patient (n=50)		Control (n=50)		
	n	%	n	%	p
Gender					0.108
Male	20	40	28	56	
Female	30	60	22	44	
Education (years)					0.542
No	0	0	5	10	
Primary	7	14	11	22	
Secondary	12	24	10	20	
High school	22	44	17	34	
College	9	18	7	14	
Job					0.016
Unemployed	32	64	18	36	
Worker	9	18	19	38	
Officer	3	6	9	18	
Farmer	5	10	0	0	
Housewife	1	2	3	6	
Other	0	0	1	2	
Marital status					0.151
Married	27	54	34	68	
Single	20	40	14	28	
Widow	3	6	2	4	
Age (Mean±SD)	33.66±9.85		37.96±15.88		0.108
Female	33.03±7.93		39.59±12.97		
Male	34.60±12.35		36.67±17.97		

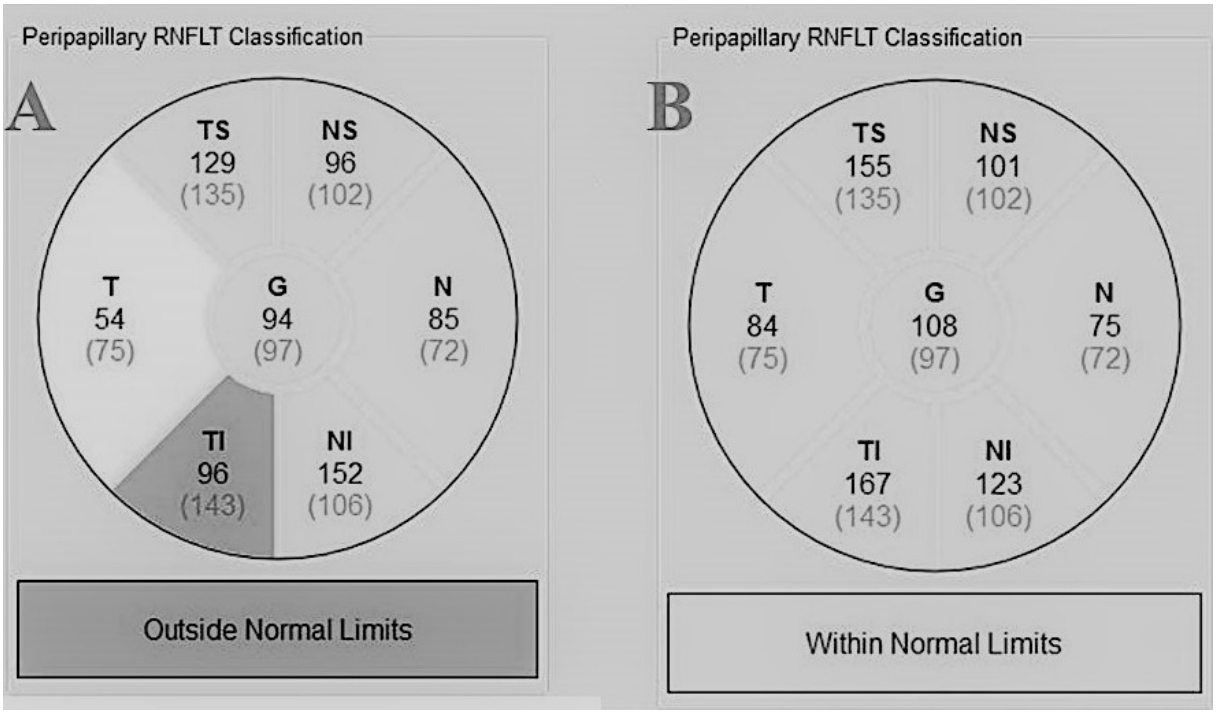

Figure 1. Comparison of retinal nerve fiber layer (RNFL) thicknesses measured at 6 regions using spectral optic coherence tomography (OCT) of obsessive compulsive disorder (OCD) patient (A) and a control subject (B).

Table 2. Mean measurement results of right RNFL-right choroid

	Group	Mean±SD	p
Right NS	Patient	110.22±17.07	0.518
	Control	112.60±19.49	
Right N	Patient	83.04±27.48	0.229
	Control	83.54±15.88	
Right NI	Patient	117.72±27.19	0.082
	Control	127.78±27.32	
Right T	Patient	74.18±10.79	0.554
	Control	75.34±8.62	
Right TI	Patient	148.38±22.76	0.123
	Control	154.70±17.55	
Right TS	Patient	138.22±27.09	0.230
	Control	145.76±14.77	
Right mean	Patient	103.74±9.80	0.152
	Control	107.22±8.82	
Right choroid mean	Patient	292.54±53.67	<0.001
	Control	249.16±31.67	

RNFL: Retinal nerve fiber layer; NS: Naso-superior; N: Nasal; NI: Naso-inferior; T: Temporal; TI: Temporo-inferior; TS: Temporo-superior

duration of disease was 8.58±5.74. r=-0.322, p=0.022 for right GCL and r=-0.389, p=0.005 for left GCL. On the other hand, there was not a correlation between disease duration and IPL and RNFL thickness (p>0.05).

DISCUSSION

Evidence from different lines of research has supported the finding of neurodegeneration in patients with OCD. While neuropsychiatric diseases are being investigated, radiological meth-

Table 3. Mean measurement results of left RNFL-left choroid

	Group	Mean±SD	p
Left NS	Patient	118.34±19.73	0.107
	Control	124.88±20.43	
Left N	Patient	75.36±13.65	0.255
	Control	78.02±14.69	
Left NI	Patient	112.38±27.66	0.164
	Control	123.48±27.11	
Left T	Patient	72.46±14.79	0.934
	Control	73.48±9.16	
Left TI	Patient	149.46±20.66	0.245
	Control	154.24±20.16	
Left TS	Patient	137.36±21.40	0.030
	Control	146.78±14.16	
Left Mean	Patient	105.78±27.98	0.034
	Control	106.92±10.25	
Left Choroid Mean	Patient	289.06±49.14	<0.001
	Control	247.66±37.02	

RNFL: Retinal nerve fiber layer; NS: Naso-superior; N: Nasal; NI: Naso-inferior; T: Temporal; TI: Temporo-inferior; TS: Temporo-superior

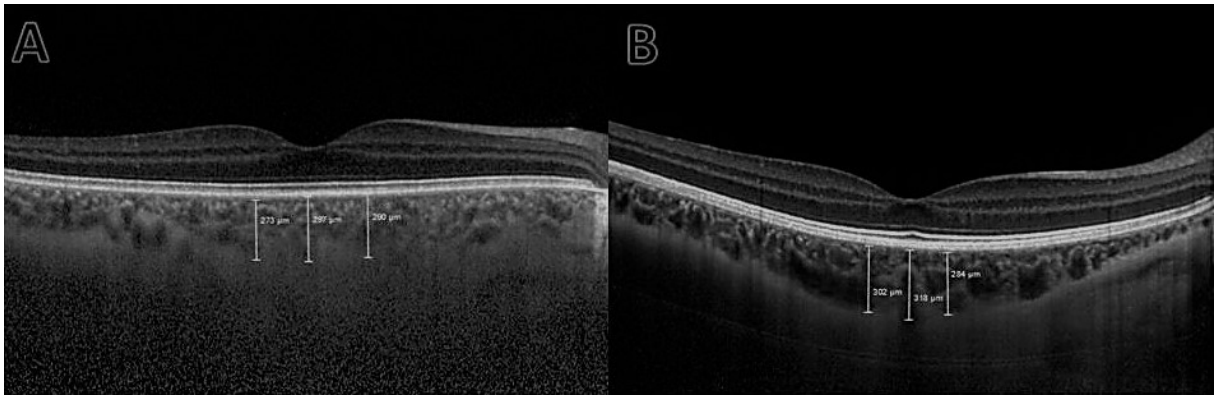

Figure 2. Comparison of choroidal thicknesses of a control subject (A) and of a patient with obsessive compulsive disorder (OCD) (B) measured by spectral optic coherence tomography (OCT) device.

ods like magnetic resonance spectroscopy are frequently used. In the studies on chemicals such as NAA, glutamine, CHO, creatine-phosphocreatine used for evaluating the neuronal structure, a decrease was observed in the ratio of these chemicals in the brain and this was interpreted as loss of neuron or axon in OCD patients and the possibility of a neuronal dysfunction in OCD pathogenesis was tried to be shown.[8,9]

We wanted to examine retinal neural network with OCT method to be able to demonstrate a possible neurodegeneration, since with its receptors, ganglion cells, glial support cells and axons, retina is regarded as an extension of brain by many anatomists. From this point of view, retina is regarded as an easily observable part of the brain. Although it doesn't contain myelin, retina is an ideal model of a nerve tissue in which degeneration can be observed with the ganglion cell neurons and axons it contains.[29-31] The basic finding in our study is the detection of a significant decrease in GCL and IPL thicknesses when patients diagnosed with OCD were compared with the healthy group. As a result, the decrease in IPL formed by the dendritic structure and GCL constituting the retinal neural structure soma is a demonstrator of a neuron loss. Another finding in our study was the fact that although there was a decrease in RNFL layer compared to the control group, this decrease was not significant when compared with the control

group (Table 2, 3). But it was detected that the significant decrease was in some sub-layers (left TS, left mean) of RNFL layer ($p<0.05$) (Table 3).

According to our hypothesis, there may be some reasons for GCL and IPL decreasing more significantly compared to RNFL sublayers constituting axonal structure. First, it is known that pro-inflammatory cytokines play a role in OCD pathogenesis.[32] This inflammatory phase in which cytokines play a role may have caused the delay of axonal degeneration by causing an increase in retinal blood flow and thus improving the retinal structure nourishment. So RNFL sublayers may be measured as a thicker layer than normal due to inflammation. According to our findings, it was detected that choroid layer thickness showing retinal blood flow increases significantly in patients diagnosed with OCD compared to the control group, although there is no systemic disease (Table 2, 3). Choroid is one of the most vascularized tissues of human body and it plays important roles in nutrition and oxygenation of outer retina, disposal of waste products out of retina and secretion of growth factors.[33] Choroid tissue is affected by any inflammatory or autoimmune conditions affecting blood flow. Research in some autoimmune diseases with retinal involvement (e.g. Behçet's disease) also demonstrated that choroid thickness increases during acute attack periods due to increased inflammation but then decreases with progressing disease.[34-36]

Secondly, in different studies, it was demonstrated that RNFL in which damage was detected with fundus examination and photos is possible only after 50% ganglion cell damage. So it can be anticipated that ganglion cell damage in a level which would cause a significant decrease or axonal degeneration did not occur in RNFL, but RNFL damage may also be observed in latter stages of the disease.[37,38] So a longitudinal OCT follow-up study is required in OCD patients.

When we observed the correlation of disease duration and OCT parameters, it was demonstrated that the thinning in GCL increased in correlation with disease duration ($r=-0.322$ and $p=0.022$ for right GCL; $r=-0.389$, $p=0.005$ for left GCL) and thus the conclusion that the area primarily effected in neuronal degeneration is ganglion cell soma can be reached from here. Finally, if we consider RNFL layer as one of the parameters which can be damaged last in advanced cases in degeneration follow-up, GCL and IPL appear to be more important parameters in the degeneration follow-up of the diseases in early phase.

As a result, we detected that neurodegeneration occurred in certain layers of retinal neural network which is an extension of the brain in patients diagnosed with OCD. In near future, OCT can be used as a new method in OCD patients for degeneration follow-up or for observing the progression of the disease.

Limitations

Major limitation of this study is its cross-sectional design. A prospective design starting from early periods of disease with regular follow-up OCT measurements would yield more convincing results about progressive degenerating nature of OCD. The diagnosis of patients were made clinically. In further studies, a scale can also be used when diagnosing. Again, we have not used a semistructured interview like structured clinical interview for DSM-5 or else. Another limitation of our study is lack of control measurements to increase validity and reliability of OCT to detect inflammation and degeneration. Inclusion of other neuroimaging methods such as magnetic resonance imaging to detect neurodegeneration and inflammatory markers such as interleukins or acute phase reactants to detect inflammation in future studies will provide better clues about utility of OCT as a tool in neuropsychiatric disorders. Direct effects of psychotropic medications on retina cannot be excluded and this should be assessed in further studies. Smoking may have an impact on OCT measurements.

Authors' contributions: *M.E.Ö.: carried out the design and coordinated the study, participated in the analysis, examination of subjects, last revisions; A.K.: patient sampling, preparation of statistical analysis, and literature review; A.S.K.: examination and evaluation by means of OCT; M.H.Ö.: psychiatric examination of subjects, sample collection*

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