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Retinal Changes in Panic Disorder Patients

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ABSTRACT

Aim: Optical coherence tomography (OCT) is a novel method that allows high resolution cross-sectional imaging of biological tissues. It was suggested that changes in the cranial structure or functions would be reflected in the retina. OCT has been an important method in the diagnosis and follow-up of diseases via morphometric or quantitative retinal measurements. Panic disorder (PD) is an anxiety disorder, where free radicals, inflammatory processes and neurotransmitter transmission disorders play a role in the etiology. The present study aimed to demonstrate neurodegeneration in PD by the comparison of PD patient and control OCT data.

Material and Method: The study group included 21 PD patients who met the study criteria. The control group included 21 healthy individuals without any known psychiatric or organic disease, including eye disease, and gender-matched to the patient group. All participants underwent detailed psychiatric and eye examinations. Central macular thickness (CMT), macular volume (MV), mean and retinal nerve fiber layer thickness (RNFL), ganglion cell layer thickness (GCLT), and central choroidal thickness (CCT) were measured in both eyes of all participants with OCT. A sociodemographic data form, Clinical Global Impression Scale (CGIS), and Panic Disorder Severity Scale (PDSS) were administered to the participants.

Results: In the study, it was determined that the CMT values of the PD patients were lower when compared to the controls in the OCT examination. There was a statistically significant difference between the CMT of the PD patient group and the control group; the CMT was lower in the patient group. There were no significant differences between the groups based on GCLT, RNFL superior, RNFL inferior, RNFL nasal, RNFL temporal, and CCT. There was no significant correlation between CGIS, PDSS scores and OCT measurements.

Conclusion: This is the first study in the literature where patients with a PD diagnosis were analyzed based on the OCT method. OCT, which is a simple, noninvasive and relatively inexpensive method that the patient could easily adapt to during imaging, could be employed as a supplementary method in the diagnosis and follow-up of PD patients.

Introduction

Panic Disorder (PD) has been classified as an anxiety disorder in the DSM-5 (American Psychiatric Association. and American Psychiatric Association 2013). Its prevalence is 3.4–4.7% in general population (Quagliato and Nardi, 2018). It was demonstrated that the free radicals, inflammatory processes, and neurotransmitter transmission problems play a role in PD etiology (Quagliato and Nardi, 2018, Kuloglu et al., 2002, Herken et al., 2006). It is known that free radicals could lead to psychiatric diseases due to neurodegeneration (Kuloglu et al., 2002, Herken et al., 2006, Bilici et al., 2001).

Optical coherence tomography (OCT) is a medical imaging method that displays biological tissue layers based on high resolution tomographic cross-sections (Fujimoto et al., 2000). It was developed by Huang et al. in 1991 (Huang et al., 1991). In the technique, cross-sectional images are obtained by measuring the coherence of the light reflected on the tissues (Fujimoto et al., 2000). It provides visuals of anatomical regions such as the retinal optic disc and macula and allows the examination of the intraretinal structures such as retinal nerve fiber, retinal pigment epithelium, and photoreceptors (Fujimoto et al., 2000). The retina and brain are connected via the optic nerve and originate in the ectoderm; they share common biological origins neurodevelopmentally (Lee et al., 2013). Thus, the retina is considered as a part of the central nervous system that opens to the outside world. It was

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suggested that cranial structure or function changes would be reflected on the retina (Chu et al., 2012). Certain studies demonstrated that visual pathways were the ideal tissue to investigate neurodegeneration (London et al., 2013). OCT imaging has been employed as a prominent method in the diagnosis and follow-up of diseases in recent years through morphometric or quantitative retinal measurements (Celik et al., 2016). In the literature, the number of studies that investigated retinal and neural network alterations with the OCT method has been increasing. These studies were mostly conducted on neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, and multiple sclerosis, and retinal degeneration was identified, consistent with the clinical presentation of the disease (Kemenyova et al., 2014, Almarcegui et al., 2010, Lu et al., 2010, Inzelberg et al., 2004). Thus, the retinal layer has been considered a significant anatomical structure where degeneration could be monitored (Kemenyova et al., 2014, Almarcegui et al., 2010, Lu et al., 2010, Inzelberg et al., 2004).

Recent studies reported that retinal OCT analysis could be a valid, easily accessible and non-invasive method for the investigation of cranial pathology in neuropsychiatric disorders (Celik et al., 2016, Kalenderoglu et al., 2016, Khalil et al., 2017, Schönfeldt-Lecuona et al., 2018, Schonfeldt-Lecuona et al., 2016).

In this study, we hypothesized that the OCT findings of patients with PD would be different from those of healthy controls. The aim of this study is to compare the OCTs of patients with PD and those of healthy controls to show the difference between the two and show that OCT can be a method that can be used in the diagnosis of PD.

Material and Methods

The study was carried out in the Psychiatry and Ophthalmology outpatient clinics of our University between June 2018 and January 2020 after the decision of the university local ethics committee (31.05.2018-10/19). The study was conducted in accordance with the Declaration of Helsinki (Riis, 2000).

Participants

Patients

Twenty-four patients who were admitted to the psychiatry outpatient clinic and diagnosed with PD based on the DSM-5 criteria (American Psychiatric Association. and American Psychiatric Association 2013) were invited to participate in the study. Two patients declined. One patient was excluded from the study due to preexisting conditions. The study group included 21 PD patients met the study criteria. The patients who were 18 and 65 years old, diagnosed with PD based on DSM-5, without a neurological disease or any important physical pathology or physiological disease that would affect the psychiatric symptoms were included in the study. Exclusion criteria included the presence of any psychiatric or physiological disease excluding PD, any eye disease that would affect OCT findings [intraocular pressure (IOP) greater than 21 mmHg, glaucoma, amblyopia, uveitis, ocular trauma, age-related macular degeneration, optic neuropathy, ocular surgery, hypertension, diabetes mellitus], the presence of opacity, refractive errors greater than ± 2.0 diopters of spherical equivalence that could prevent OCT examination. All patients were on a drug regimen that included a selective serotonin reuptake inhibitor (SSRI) for the treatment of PD.

Controls

The control group included 21 healthy individuals without any known organic disease, including any psychiatric or eye disease, who met the study criteria and matching the patient group based on gender. After the anamnesis was obtained from the control group members, the hospital system data were scanned, and the patient candidates underwent a psychiatric evaluation conducted by a psychiatrist and an eye examination conducted by an ophthalmologist to confirm that they did not have any psychiatric, ophthalmologic or other organic diseases.

Detailed psychiatric evaluation of all participants was conducted by a senior psychiatry assistant (AK), and detailed ophthalmological examinations that included visual acuity, refraction, anterior segment biomicroscopic and intraocular pressure examinations were conducted by an ophthalmologist (HY).

All participants signed the written informed consent form. A semi-structured sociodemographic data form, Clinical Global Impression Scale (CGIS), and Panic Disorder Severity Scale (PDSS) were administered to the participants.

Questionnaires

Sociodemographic and Clinical Data Form

The Sociodemographic and Clinical Data Form used was prepared taking into consideration the aims of the study and appropriate information obtained from the scanned literature and clinical experience. This form was a semi-structured form including sociodemographic information such as age, gender marital status, level of education, occupation, economic status and clinical data such as duration of the disease, number of hospitalizations, and presence of psychosocial support.

Clinical Global Impressions Scale

CGIS is a three-dimensional Likert-type ordinal scale that identifies the severity of the disease, or the degree of improvement based on the clinician's judgment. The severity of the disease is determined in the first dimension, recovery in the second dimension, and the severity of the adverse drug effects in the third dimension of the scale. In the present study, seven-point form of the disease severity scale was employed (Busner and Targum, 2007).

Panic Disorder Severity Scale

The scale were developed by Shear et al. (Shear et al., 1997) that measures the severity of PD, the frequency of panic attacks, episodes with limited symptoms, the severity of anticipatory anxiety, phobic avoidance, and functional impairment. It includes 7 items. Each item is scored between 0 and 4 points and the total score is obtained by adding item scores.

OCT Measurements

OCT measurements were performed using Cirrus HD-OCT 5000 Software version 6.5 (Carl Zeiss Meditec, Dublin, CA) by the same experienced author (HY). Right and left eye, macular volume, central macular thickness, retinal nerve fiber layer, choroidal and ganglion cell layer thickness measurements were performed with the OCT device. Five measurements were performed for the RNFL measurement in each eye: nasal (n), inferior (i), superior (s), temporal (t), and global. Signal strength of all participants above 6 were included in the study. The choroidal thickness were compared using OCT. This measurement was made by using the OCT device measurement tool. Manually, a vertical line was drawn from the outer layer of the retinal pigment epithelium to the choroid-sclera border, and its length was recorded. Three different measurements were performed from the fovea to the nasal and temporal poles with 500-μm intervals. We calculated the mean choroidal thickness from separate measurements of three regions.

Statistical Analysis

Data were expressed as mean ± standard deviation. The statistical analyses were made with IBM SPSS for Windows, version 25.0 (IBM statistics for Windows version 25, IBM Corporation, Armonk, New York, USA). The normality of the distribution of values was assessed using the Kolmogorov–Smirnov test. According to this test, Independent-Samples T test, Mann-Whitney U test, One-way ANOVA test with Tukey HSD and Kruskal-Wallis test were used to compare the groups. The value of

p<0.05 was considered statistically significant.

Results

The mean age of the PD group was 39.48±10.64, and the mean age of the control group was 28.71±4.76. There was a significant difference between the mean ages of the groups, and the mean age was higher in the PD group (p<0.05). There were 12 female (57.1%) and 9 male (42.9%) patients in the PD group. The control group included 13 female (61.9%) and 8 male (38.1%). There was no difference between the groups based on gender (p>0.05).

The mean disease duration was 2 years in the PD group. Twelve patients (57.1%) in the PD group and 2 participants (9.5%) in the control group were smokers. There was a statistically significant difference between the groups based on the number of smokers, and there were more smokers in the PD group (p=0.002). The some sociodemographic data are presented in Table 1.

There was a statistically significant difference between CMT of the patient group and the control group, and CMT was lower in the patient group (243.86±18.02, 251.79±21.07 respectively; p=0.020, based on the Mann-Whitney U-Test). There were no significant differences between the groups based on the GCLT, RNFL-s, RNFL-i, RNFL-n, RNFL-t, and CCT (p>0.05). OCT findings are presented in Table 1.

Table 1
Some sociodemographic and OCT data of the groups.

	n	Panic disorder (21)		Control (21)		p
		Mean	SD	Mean	SD	
Age		***36,48***	***10,512***	***28,71***	***4,71***	***<0,001****
Height		168,05	10,338	167,38	8,93	0,680*
Weight		70,95	14,968	64,95	12,05	0,073*
Body Mass Index		***25,4100***	***4,88621***	***23,17***	***3,99***	***0,016****
Age at onset		***30,90***	***9,916***	***0,00***	***0,00***	***<0,001****
Beck Depression Inventory		***20,52***	***12,907***	***1,24***	***1,95***	***<0,001****
Panic Disorder Severity Scale		14,10	5,983			
Central Macular Thickness	***42***	***243,86***	***18,016***	***251,79***	***21,07***	***0,020****
Macular Volume	42	10,129	,4910	10,20	0,48	0,532†
Ganglion Cell Layer Thickness	42	83,33	5,634	82,45	6,17	0,496†
Retinal Nerve Fiber Layer Thickness-Superior	42	122,73	16,509	122,07	13,56	0,845†
Retinal Nerve Fiber Layer Thickness-Inferior	42	130,70	15,699	128,71	18,03	0,597†
Retinal Nerve Fiber Layer Thickness-Nasal	42	72,75	11,460	70,29	10,94	0,322†
Retinal Nerve Fiber Layer Thickness-Temporal	42	66,00	11,345	67,36	9,89	0,396*
Central Choroidal Thickness	42	391,58	64,778	380,10	67,52	0,435†

OCT: Optical Coherence Tomography, SD: Standard Deviation
* Independent Sample T test
† Mann-Whitney U test

There was no significant correlation between both CGIS and PDSS scores and OCT measurements (p>0.05) (Table 2).

Discussion

In the present study, it was determined that the CMT values in PD patients were lower when compared to the controls. Panic disorder is a psychiatric disease the etiology of which is characterized by oxidative stress, inflammatory responses and neurotransmitter dysfunction, and where morphological and functional disorders are observed in related regions of the central nervous system (Kuloglu et al., 2002, Herken et al., 2006, Bilici et al., 2001, Asami et al., 2018, Oliva et al., 2021, Dean et al., 2009, Liu et al., 2008, Hovatta et al., 2010, Masood et al., 2008, Kuloglu et al., 2002, Gaeta and Hider, 2005).

Since the brain consumes about 20% of basal oxygen, it is susceptible and very sensitive to oxidative stress (Inoue et al., 2003). Oxygen ions and various free radicals are released by the oxygen metabolism (Inoue et al., 2003). Free radicals could damage normal cell structure and lead to cellular dysfunction (Inoue et al., 2003). Literature demonstrated that oxidative stress may be associated with various psychological disorders such as obsessive-compulsive disorder, social phobia, major depression, posttraumatic stress disorder, and panic disorder (Herken et al., 2006, Bilici et al., 2001, Dean et al., 2009, Liu et al., 2008, Hovatta et al., 2010, Kuloglu et al., 2002, Gaeta and Hider, 2005). In vitro studies reported that oxidative stress was induced in the hypothalamus and amygdala, which are the centers that play a role in the pathogenesis of PD, by glutathione inhibition, and oxidative stress directly leads to anxiety behavior (Masood et al., 2008, Salim et al., 2010). Kuloglu et al. (Kuloglu et al., 2002) reported that antioxidant serum levels decreased in PD and led to an increase in lipid peroxidation. Similarly, Yasunari et al. (Yasunari et al., 2006) also determined a significant correlation between free radicals and anxiety in hypertensive rats. In the present study, the CMT values were lower in PD patients when compared to the controls, which was attributed to the involvement of oxidative stress in the pathogenesis of PD and brain damage and retinal alterations induced by oxidative stress, where the latter was considered an extension of the brain. Studies that investigated the etiopathogenesis in anxiety disorders reported that inflammatory processes play a role in the pathogenesis. It was demonstrated that anxiety symptoms were associated with high cytokine levels, particularly C reactive protein (CRP), and the association was significant in males (Liukkonen et al., 2011, Vogelzangs et al., 2013). Clinical trials evidenced increased inflammatory activation in PD (Hoge et al., 2009). A recent review also indicated the role of inflammatory processes in the pathogenesis of PD, reporting that the study findings demonstrated increased inflammatory markers such as IL-6, IL-1β and IL-5 in PD (Quagliato and Nardi, 2018). OCT findings have been analyzed in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, multiple sclerosis, and Lewy body dementia with OCT (Kemenyova et al., 2014, Almarcegui et al., 2010, Lu et al., 2010, Inzelberg et al., 2004). In recent studies, OCT findings in psychiatric disorders such as schizophrenia, bipolar disorder, depressive disorder, obsessive-compulsive disorder, alcohol and multiple substance use disorder were different when compared to those of the healthy controls (Schönfeldt-Lecuona et al., 2018, Schonfeldt-Lecuona et al., 2016, Özen et al., 2019, Yıldız et al., 2016, Fountoulakis et al., 2005, Ozsoy and Alim, 2020, Kulu et al., 2021). The common denominator in the etiopathogenesis of both groups of diseases is the involvement of inflammatory processes in the pathogenesis (Kemenyova et al., 2014, Almarcegui et al., 2010, Lu et al., 2010, Inzelberg et al., 2004, Schönfeldt-Lecuona et al., 2018, Schonfeldt-Lecuona et al., 2016, Kuloglu et al., 2002, Özen et al., 2019, Yıldız et al., 2016, Kalenderoglu et al., 2016). Since it is known that inflammatory processes are also involved in the pathogenesis of PD suggested that OCT findings of the PD patients would differ when compared to those of the healthy controls. Another important factor that plays a role in the etiology of anxiety disorders is the dysregulation in dopamine and especially serotonin

Table 2
Bivariate correlations between the clinical characteristics of PD and OCT results.

Spearman	N (42)	Central macular thickness	Macular volume	Ganglion cell layer thickness	Retinal nerve fiber layer thickness superior	Retinal nerve fiber layer thickness inferior	Retinal nerve fiber layer thickness nasal	Retinal nerve fiber layer thickness temporal	Central choroidal thickness
Age	rho	-0,346	-0,598	-0,392		-0,491	-0,496	-0,501	-0,462
	p	0,025	0,000	0,010		0,001	0,001	0,001	0,003
Gender	rho	0,320	0,397	0,342	0,353		0,501		0,409
	p	0,039	0,009	0,026	0,026		0,001		0,009
Height	rho		0,427	0,319	0,321	0,394			0,343
	p		0,005	0,040	0,044	0,012			0,030
Weight	rho		0,563	0,322		0,472	0,466		
	p		0,000	0,037		0,002	0,002		
Marital status	rho	0,384	0,533	0,314				0,379	
	p	0,012	0,000	0,043				0,016	
Economic status	rho	-0,415	-0,412	-0,386			-0,374		
	p	0,006	0,007	0,012			0,017		
Occupation	rho	0,320							
	p	0,039							
Smoking	rho	-0,306							
	p	0,049							
Age at onset	rho	-0,322	-0,523	-0,341		-0,356	-0,413	-0,449	-0,379
	p	0,038	0,000	0,027		0,024	0,008	0,004	0,016
Number of hospitalizations	rho	-0,468	-0,646	-0,632	-0,523	-0,764	-0,465		
	p	0,002	0,000	0,000	0,001	0,000	0,002		
Additional organic disease	rho	0,311	0,313			0,523			0,475
	p	0,045	0,044			0,001			0,002
History of psychiatric treatment	rho	0,429				0,342			
	p	0,005				0,031			

PD: Panic Disorder, OCT: Optical Coherence Tomography

transmission. Lavoie et al. demonstrated that deviations in dopamine and serotonin transmission affected the electroretinogram (ERG) measurements. This finding suggested that the problems in ERG could be associated with central monoaminergic dysfunction (Schönfeldt-Lecuona et al., 2018). Electrooculography also revealed correlations between electrophysiological abnormalities and psychometric evaluations (Fountoulakis et al., 2005). It was shown that neurotransmitters, especially serotonin, which plays a key role in the development of PD, also play a role in retinal processes (Schwitzer et al., 2015). The above-mentioned data suggested that neurotransmitter dysfunction, which plays a role in the etiology of PD, also plays a role in retinal abnormalities, and retinal evaluation of patients with PD would yield different findings when compared to healthy controls.

One of the factors that could not be excluded in the study was treatment. The patients were on a SSRI group antidepressant. Previous studies reported that there were differences in electrophysiological measurements of retinal parameters in depression patients, and these findings normalized with antidepressant treatment (Bubl et al., 2010, Bubl et al., 2012). However, it is known that SSRIs could cause adverse effects on the eye such as mydriasis, elevated intraocular pressure, angle closure glaucoma, maculopathy, branch retinal vein occlusion, and cataracts. High serotonin levels were associated with ischemic optic neuropathy (Schmitt et al., 2002). Optic nerve head vessels may be affected by transient vasospasm that occasionally occurs due to hemodynamic alterations, leading to ischemic optic neuropathy (Schmitt et al., 2002). Serotonin could induce optic nerve ischemia via platelet aggregation, especially in atherosclerotic plaques, triggering vasospasm in ocular blood vessels (Schmitt et al., 2002). In a study that analyzed OCT findings in patients in SSRI treatment, it was demonstrated that there was a correlation between SSRI use and reduced ganglion cell complex and RNFL thickness (Guclu et al., 2018). In the present study, the lower CMT value in patients with PD when compared to healthy controls suggested the impact of SSRIs employed in eye and retina treatment. In the study, a significant difference was determined between the mean age of the PD group and the control group, where the mean age was higher in the PD group. Certain studies in the literature reported that certain OCT parameters decreased with increasing age (Ooto et al., 2015). In the present study, a significant difference was determined between the PD group and the control group based on smoking, where a higher number of PD patients smoked. The fact that the nicotine is a sedative with tension-relieving properties could have led to higher levels of smoking as self-medication among PD patients (Cosci et al., 2010). It was shown that smoking induced a decrease in OCT measurements (Dervisogullari et al., 2015). The inclusion of participants of the same age and smoking behavior in the control and PD groups in future studies may reduce the confounding impact of these factors.

The fact that the other OCT parameters in the study were not different from the OCT parameters in the control group and the lack of correlation between the scale scores and OCT values could be due to the small sample size. Studies with a higher sample size would produce stronger data for the analysis of the differences between the groups.

Limitations

The present study had certain limitations. The sample size was relatively small. The study was a cross-sectional study. Studies in the prospective design may contribute further to the analysis of progressive neurodegeneration. Confounding conditions such as medicine treatment, smoking, nutrition and exercise could not be excluded. The present study was the first in the literature to analyze the OCT in PD patients. Thus, it could contribute to the literature. It could also serve as an preliminary study for similar studies. These were the strengths of the present study.

Conclusion

In the study, CMT findings were lower in PD patients when compared to the controls. OCT, a simple, noninvasive and relatively inexpensive

method that the patient could easily adapt to during imaging, could be employed as an supplementary method in the diagnosis and follow-up of PD patients. Future prospective studies that could be conducted with larger groups would provide further data and contribution.

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