An Optical Coherence Tomography Study that Supports the Neurovascular Basis of Schizophrenia Disease

ABSTRACT

Objectives: Spectral domain optical coherence tomography (SD-OCT) is a non-penetrating, quick, and practical device which enables measurement of the chorioretinal layers. In this study, our purpose was to investigate the retinal nerve fiber layer (RNFL) and choroidal thickness in schizophrenia patients, using SD-OCT, and compare the findings with those of the control group.

Methods: For the study, 44 patients with a diagnosis of schizophrenia, and 41 age- and gender- matched healthy controls were enrolled. Both eyes of each participant were evaluated. RNFL was measured and analyzed automatically with optical coherence tomography. Scans for choroidal thickness were obtained with the enhanced depth imaging mode of the SD-OCT device and measured manually.

Results: The average age of schizophrenia patients was 47.82, and it was 45.5 for the control group. The mean illness duration of the patients was 24.79 years. According to the results of this study, all choroidal measures (nasal, subfoveal, and temporal) of both eyes, and the RNFL thickness of schizophrenia patients, were significantly thinner than that of healthy controls. The chorioretinal measures of both eyes were similar. The results showed that a weak negative correlation was present between illness duration and choroidal diameter.

Conclusion: In addition to demonstrating the thinning of RNFL in schizophrenia patients, as frequently reported in the literature, the results of this study show, for the first time, that choroidal thickness is considerably decreased in schizophrenia patients compared to the healthy controls, using SD-OCT. Keeping in mind that the choroid is a vascular layer, these results support the neurovascular hypothesis of schizophrenia.

Keywords: Clinical trials, psychiatric disorders, psychopathology, schizophrenia

Introduction

Schizophrenia is a chronic, ingravescent, usually devastating disease, with positive, negative, affective, and cognitive symptoms.[1] Although its etiopathogenesis is not completely understood, one of the proposed models is the neurodegeneration model.[2]

The brain and retina have many structural and functional similarities, such as both being derived from the neuroectoderm and having similar neural cells and layered structures. They are also connected with the optic nerve.[3] The retina is visible and can be examined using special instruments, and the pathologic changes occurring in the brain in several neurodegenerative diseases can also be seen in the retina.[4-6] Optical coherence tomography (OCT) has emerged as a non-penetrating, rapid, and easy-to-use method of retinal imaging which enables practitioners to examine the retina and its layers in high resolution. Although it is mainly used to study several degenerative ophthalmic diseases, many studies also show a decrease in retinal nerve fiber layer (RNFL) diameter in some neurodegenerative illnesses of the brain, like mild cognitive disturbance, Alzheimer's dementia (AD), Parkinson's disease (PD), multiple sclerosis (MS), and Huntington's disease (HD).[4-8]

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In the last decade, based on the consistent results related to neurodegenerative diseases and the neurodegenerative hypothesis on the etiology of schizophrenia, several studies have used OCT to evaluate the retinal layers and structures in schizophrenia patients. While many studies using OCT revealed that the RNFL in schizophrenia patients was considerably thinner than that of the control groups,[9-15] others reported no difference in RNFL thickness between the patient and control groups.[16,17]

Another hypothesis for schizophrenia pathogenesis is the microvascular changes in the brain vasculature.[18] In a postmortem study of schizophrenia patients, Uranova et al[19] found severe structural distortions and changes in the prefrontal and visual cortex capillaries. Long-term mild inflammation that has been related to increased vascular risk is reported in schizophrenia patients.[20,21] The choroid is composed of a vascular network, and its thickness can change in response to autonomic nervous system input and inflammation.[22]

The data about the structure and layers of the retina obtained from OCT support the data about functional changes in the retina obtained from electroretinography (ERG). A considerable association between the decrease in RNFL thickness in OCT and the low amplitude and late latency in ERG have been reported by some researches.[23] A few studies in schizophrenia patients have reported a decrease in RNFL thickness and a delayed latency in ERG, but the direct relationship between OCT and ERG has not been shown.[24]

We hypothesize that the choroidal layers of the schizophrenia patients may be affected by the neurovascular and neurodegenerative processes. To date, 2 studies have evaluated choroidal layers using OCT and both have reported conflicting results.[15,17] While there are many studies about RNFL thickness in schizophrenia patients, there is little research about the choroid layer in these patients. We hypothesize that the choroidal thickness and RNFL of schizophrenia patients are thinner than those of healthy individuals. The purpose of this research was to demonstrate in particular the difference between the choroidal thickness values of schizophrenia patients and healthy controls, using spectral domain optical coherence tomography (SD-OCT).

Methods

The study was conducted with patients diagnosed with schizophrenia or schizoaffective disorder, between the ages of 18 and 64, who were followed and treated between June 15, 2019, and December 15, 2019, in the outpatient or inpatient psychiatry clinics of Niğde Training and Research Hospital. An age- ($P = .270$) and sex-matched

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MAIN POINTS

- *For the first time, results of this study shows that choroidal thickness is significantly decreased in schizophrenia patients compared to the healthy controls using SD-OCT.*
- *Because of the intense vascular nature of choroid layer, choroidal thinning in schizophrenia patients support the neurovascular hypothesis of schizophrenia.*
- *There was a weak negative corelation between illness duration and choroidal thickness.*

($P = 1.000$) control group was formed of healthy individuals who accepted to participate in the study.

Exclusion criteria: (1) Patients who had mental retardation or comorbid psychiatric disorders, (2) Patients who had neurodegenerative diseases, such as AD, PD, or MS, (3) Patients with a history of uveitis, glaucoma, or invasive retinal interventions, (4) Patients who had diabetic retinopathy or hypertensive retinopathy on retinal examination, (5) Patients with a spherical refractive error greater than ± 3.0 D and/or cylindrical error greater than ± 2.0 D, (6) Patients with intraocular pressure greater than 21 mmHg in the ophthalmic examination, and (7) Patients with low-quality OCT scans (signal strength ≤ 6) were excluded from the study. Additionally, participants with psychiatric diseases were excluded from the control group.

The ethical confirmation of the study was received from the Ethics Committee of Niğde Ömer Halisdemir University (February 27, 2019/02-13). All researchers accepted to conduct the study according to the tenets of the Declaration of Helsinki. Detailed information about the study process was provided to all participants, and an informed consent form was signed by all participants and their legal guardians.

The diagnosis of schizophrenia was made using a semi-structured interview based on DSM-5 criteria.[25] Autorefractometry was performed for all participants, Goldmann applanation tonometry was used to measure intraocular pressure, and biomicroscopy and fundus examinations were performed. The sociodemographic, clinical, and ophthalmological data of the patients were recorded using the form prepared by the researchers. The Positive and Negative Syndrome Scale (PANSS) scale was used to survey the intensity of clinical symptoms in schizophrenia patients. Validity and reliability studies of the Turkish version of this scale were conducted.[26] The retinal layers of both groups were measured using the Cirrus HD-OCT device (Carl Zeiss Meditec Inc., Dublin, CA, USA).

The RNFL thickness was measured automatically by the device, while the choroidal layer thickness was measured manually. In this study, the images were obtained by following the HD 5 Line Raster protocol, consisting of 6 mm parallel lines with 1024 A-scan/B-scan and 0.25 mm spacing, which was reduced to single line. The choroidal layer was visualized in SD-OCT in the enhanced depth imaging (EDI) mode. The first measurement was made under the fovea. Then, keeping the first measurement point constant with the help of the device ruler function, 3 temporal and 3 nasal measurements were obtained in the same way from a total of 6 points in the temporal and nasal aspects, with 500 μm gaps up to 1500 μm on the hyperreflective RPE band. The mean values for nasal and temporal choroidal thickness were obtained by adding 500-, 1000-, and 1500-μm measurement values and dividing them by the total number of measurements. Three nasal-temporal-subfoveal choroidal thickness values were used for comparison. Two ophthalmologists blinded to the groups measured the choroidal thickness separately. To prevent diurnal variations in choroidal thickness, OCT scans were obtained between 11 AM and 12 PM, within one hour, everyday by the same experienced technician.

Statistical Analysis
SPSS version 23.0 (IBM Corp., Armonk, NY, USA) was used for statistical evaluation of the data obtained in our study. The skewness and kurtosis values and histogram graph of dependent variables were checked for patient and control groups while examining normality

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in grouped data. The boxplot graph was reviewed to examine the outlier values. An independent groups *t*-test was used in the analysis of the data in which the assumptions were met. A paired-samples *t*-test was performed to evaluate the intereye variability of the data obtained from right and left eyes. Chi-square tests were used for the analysis of categorical data like gender and systemic disease. Pearson correlation coefficient was used to investigate the correlation between variables. The margin of error (*P*-value) was accepted as .05 in this study. Power analysis was done by the G-power 3 test (Heinrich Heine University, Düsseldorf, Germany).

Results

In the study, 52 patients diagnosed with schizophrenia or schizoaffective disorder were enrolled. Two patients with bilateral glaucoma, 2 patients with high myopia, and 4 patients with low-quality OCT scan were excluded. Data were obtained from both eyes of the remaining 44 patients and the 41 healthy controls who were enrolled in the study. When an alpha value of 0.05 was obtained in the power analysis, it was found to be 0.9475 for choroidal thickness and 0.80 for the RNFL thickness.

The average age of the schizophrenia patients and healthy controls was 47.82 and 45.59, respectively, and the groups were

Table 1. Demographic and Clinical Data of the Patient and Control Groups

Group	Patient	Control	P
Age, mean (SD)	47.82 (9.44)	45.59 (9.92)	.270
	n (%)	n (%)	
Gender			1.000
Female	14 (31.8)	13 (31.7)	
Male	30 (68.2)	28 (68.3)	
Systemic disease			.904
Yes	9 (20.5)	7 (17.1)	
No	35 (79.5)	34 (82.9)	
Intraocular Pressure, mean (SD)			.190
Right	16.02 (4.26)	15.02 (2.57)	
Left	16.06 (3.64)	15.21 (2.45)	.210

Table 2. Clinical Data and Scale Scores of Patient Group

	n (%)
Diagnosis	
Schizophrenia	37 (84.1)
Schizoaffective disorder	7 (15.9)
Drugs	
AAP	32 (72.7)
AAP+MS	12 (27.3)
	mean (SD)
Disease duration	24.79 (15.22)
PANSS total	102.30 (16.56)
PANSS positive	23.32 (5.79)
PANSS negative	27.23 (6.84)
PANSS general	51.95 (8.26)

AAP, atypical antipsychotics; MS, mood stabilizers; PANSS, Positive and Negative Syndrome Scale.

similar in terms of age (*P* = .270) and sex (*P* = 1.000). Thirty-seven patients (84.1%) were diagnosed with schizophrenia. The average illness duration of the patients was 24.79 years. The measures of intraocular pressure and the contribution of the systemic disease (*P* = .904) between the patient and the control groups were similar. Thirty-four (77.3%) of the patients were from the outpatient clinic, and were in remission or partial remission; only 10 (22.7%) were inpatients and had new psychotic exacerbations. The detailed sociodemographic and clinical data of the groups are represented in Tables 1 and 2.

According to the results of this study, all choroidal measures (nasal, subfoveal, and temporal) of both eyes and the RNFL measures were statistically significantly lower in the schizophrenia patients than in the healthy controls. The comparison of the choroidal measurements between the groups is given in Table 3.

A paired-samples *t*-test was performed to evaluate the intereye variability of the data obtained from both eyes. According to statistical evaluation, there was no difference in the chorioretinal measurements between both the eyes. Detailed results are shown in Table 4.

Pearson correlation coefficient was obtained to examine the relationships between variables, and the detailed data are shown in Table 5. The PANSS evaluates the symptom severity of the disease. According to this study, there was a slight inverse relationship between the duration of illness and the measurements of the left nasal and left subfoveal choroidal thickness, but no correlation was found between the other retinal diameter measurements. While there was a slight positive relationship between PANSS total scores and choroidal thickness, the PANSS positive scores were independent of all measurements. Finally, a weak positive relationship was demonstrated between RNFL diameter and PANSS negative scores.

Discussion

The first parameter evaluated in this study was the RNFL thickness. We determined that the patients diagnosed with schizophrenia had significantly thinner RNFL than the control group. RNFL thinning in schizophrenia patients has been shown in many studies in the literature to-date, and there is almost a consensus on this issue.[9-11,13-15,27,28] Only 2 studies have reported similar RNFL measures between the groups.[16,17] The Stratus OCT device, with lower resolution than the current devices, was used in the study by Chu et al,[16] which reported that there was no diversity in terms of RNFL thickness between the patient and control groups. The study by Topçu-Yılmaz et al[17] included patients with an acute attack, and reported that the inflammatory process which may be seen in patients with acute attack may mask the thinning in the retinal nerve. In order to perform RNFL measurements with the OCT device in the follow-up of schizophrenia patients, it seems necessary to reveal whether RNFL is related to the illness duration and the intensity of the symptoms. Yılmaz et al[13] and Ascaso et al[12] could not find a correlation between RNFL thinning and illness duration in their studies. Schönfeldt-Lecuano et al[28] and Lee et al[11] found a negative correlation between the illness duration and RNFL in their studies. Similar to Yılmaz et al,[13] a relationship between illness duration and RNFL thickness was not determined in this study. Lee et al[11] could not detect a relationship between PANSS scores and RNFL. Thus, they reported that no relationship could be observed between disease symptoms and RNFL. Celik et al[14] detected a weak

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Table 3. Comparison of Retinal Nerve Fiber Thickness and Nasal, Temporal, and Subfoveal Choroidal Thickness in Patient and Control Groups

Variable	Group	n	Mean (SD)	P
Right nasal choroidal thickness (μm)	Patient	44	233.02 (41.59)	.004
	Control	41	262.87 (49.99)	
Right subfoveal choroidal thickness (μm)	Patient	44	266.70 (40.59)	<.001
	Control	41	300.78 (44.78)	
Right temporal choroidal thickness (μm)	Patient	44	229.75 (47.61)	<.001
	Control	41	271.19 (47.88)	
Left nasal choroidal thickness (μm)	Patient	44	243.54 (49.45)	.039
	Control	41	269.39 (63.95)	
Left subfoveal choroidal thickness (μm)	Patient	44	267.93 (48.02)	.001
	Control	41	304.75 (54.21)	
Left temporal choroidal thickness (μm)	Patient	44	237.11 (45.84)	<.001
	Control	41	279.95 (50.67)	
Right RNFL	Patient	44	87.04 (9.64)	.017
	Control	41	91.78 (8.13)	
Left RNFL	Patient	44	85.13 (7.20)	.003
	Control	41	90.58 (8.90)	

P < .05.
RNFL, retinal nerve fiber layer.

Table 4. Comparison of Retinal Nerve Fiber Thickness and Nasal, Temporal, Subfoveal Choroidal Thickness Right and Left Eye

Variable	Group	n	Mean (SD)	P
Nasal choroidal thickness (μm)	Right	85	247.42 (47.97)	.079
	Left	85	256.01 (58.08)	
Subfoveal choroidal thickness (μm)	Right	85	283.14 (45.74)	.511
	Left	85	285.69 (54.07)	
Temporal choroidal thickness (μm)	Right	85	249.74 (51.83)	.100
	Left	85	257.78 (52.56)	
RNFL	Right	85	89.33 (9.21)	.087
	Left	85	88.76 (8.47)	

P < .05.
RNFL, retinal nerve fiber layer.

other studies, there was a poor positive correlation between RNFL and PANSS negative scores.

In recent studies, it has been emphasized that the neovascular unit could potentially contribute to the pathophysiology of schizophrenia.[21,29,30] Neuroimaging studies reporting that the neurovascular unit is involved in schizophrenia have shown local or widespread hypoperfusion areas in the brain.[31-33] Burghardt et al[34] reported diffuse vascular endothelial cell disorder in patients with schizophrenia. In the same study, they stated that endothelium-derived nitric oxide, which increases blood flow by causing vasodilation, was decreased in schizophrenia patients. The negative effects of neuroinflammation on neurovascular unit function in patients with schizophrenia have been shown in many studies.[21]

inverse relationship between PANSS scores and RNFL, but there was a stronger correlation between the ganglion cell layer and the internal plexiform layer values and PANSS scores. In our study, as in the research of Lee et al,[11] we did not determine a statistically considerable relationship between RNFL and PANSS scores, but unlike the

In our study, in all choroidal thickness measurements (subfoveal, nasal, and temporal choroid layer thickness of both eyes), statistically significant thinning was detected in the schizophrenia patients compared to the healthy controls. Our study shows that the neurovascular unit is affected in patients with schizophrenia, which supports

Table 5. Investigation of Relationship of Retinal Nerve Fiber Layer and Choroidal Thickness with Disease Duration and PANSS Values in Patients

Pearson correlation analysis

	Disease Duration		PANSSt		PANSSp		PANSSn		PANSSg	
	r	P	r	P	r	P	r	P	r	P
Right nct	−0.17	.271	0.34	.025[a]	0.16	.293	0.37	.014[a]	0.28	.062
Right sfct	−0.29	.060	0.35	.019[a]	0.24	.109	0.32	.035[a]	0.28	.063
Right tct	−0.04	.792	0.27	.073	0.23	.128	0.18	.234	0.24	.109
Left nct	−0.37	.012[a]	0.38	.011[a]	0.16	.293	0.36	.015[a]	0.36	.016[a]
Left sfct	−0.37	.015[a]	0.48	.001[b]	0.26	.093	0.42	.004[b]	0.44	.003[b]
Left tct	−0.28	.62	0.48	.001[b]	0.27	.080	0.40	.007[b]	0.44	.002[b]
Right RNFL	−0.02	.894	0.26	.092	0.01	.941	0.33	.030[a]	0.19	.221
Left RNFL	−0.07	.634	0.22	.129	0.07	.634	0.35	.015[a]	0.14	.353

[a]*P* < .05; [b]*P* < .01.
nct, nasal choroidal thickness; scft, subfoveal choroidal thickness; tct, temporal choroidal thickness; RNFL, retinal nerve fiber layer; PANSS, Positive and Negative Syndrome Scale; *r*, Pearson correlation coefficient.

many previous studies. According to the literature review, this is the first research study to show that the choroidal layer is significantly thinner in schizophrenia patients than in healthy controls. In a previous study which reported a similar result, the choroidal thickness of 6 schizophrenia and bipolar disorder patients with psychotic symptoms were compared with the data of 18 healthy individuals matched for age and sex.[15] In their study, a statistically insignificant thinning in the choroidal layer was detected in patients with psychotic symptoms. However, the lack of time points at which the OCT examinations were performed in their study seems to be an important methodological problem because the thickness of the choroid layer is affected by diurnal variations.[33] Tan et al[35] reported that the thickness of the choroidal layer changes during the day. It is generally the thickest in the early hours, and diminishes later in the day. The low number of patients and the lack of detailed eye examination data are other issues that decrease the reliability of this results. In contrast to our study, Topcu-Yilmaz et al,[17] found no difference in the choroidal thickness between groups, in their study. They compared the choroidal diameter of 59 schizophrenia patients with acute exacerbation who were followed in the inpatient psychiatry clinic, with a control group of 36 healthy individuals matched for age and sex, while in our study, a significant proportion of the patients (34 patients, 77.3%) were in remission or partial remission and were followed up as outpatients. In a study by Ascaso et al,[12] the retinal layers of schizophrenia patients with acute exacerbation and of patients in remission or partial remission were compared with those of healthy controls using OCT, and there was no significant disparity in RNFL thickness measurements between the patients with acute exacerbation and those in the control group, while RNFL diameter was considerably diminished in patients in remission. The researchers attributed this to the ongoing inflammatory process in patients with acute exacerbation and claimed that inflammation led to the thickening of the retinal layers, which masks the thinning. Since Topcu-Yilmaz et al[17] conducted their study in patients with an acute attack of schizophrenia, the ongoing inflammatory processes may be responsible for the absence of disparity between the groups in terms of choroidal layer thickness.

We detected a weak inverse relationship between illness duration and choroidal diameter in this study. A similar correlation was shown in the study by Topcu-Yilmaz et al,[17] but no relationship was detected between the illness duration and choroidal diameter in the study by Joe et al[15] Moreover, a positive relationship was detected between the PANSS total and negative scores and the choroidal thickness in our study. The correlation was thought to be related to the PANSS negative scores, because there was no relationship between PANSS positive scores and the choroidal diameter.

The results of our study, together with the other studies using OCT in schizophrenia patients, give rise to hope that OCT can be used in the diagnosis and screening of neurodegenerative diseases such as schizophrenia, due to the scarcity of studies on choroidal thickness, especially on RNFL thickness. However, the lack of correlation between the severity and duration of the illness and the OCT findings reduces the possibility of using the OCT device for disease staging.

The use of atypical antipsychotic drugs by all patients in the study is a limitation of this research. However, the active ingredients of these drugs were different, and the profiles of the metabolic side effects of each drug differed. Therefore, it is not possible to exclude the effects of atypical antipsychotic drugs on retinal layers and vessels.

In our study, the RNFL thinning and the reduction in choroidal thickness in schizophrenia patients, determined by the SD-OCT device, support the claim that the neurovascular unit is affected in schizophrenia. If the role of neurovascular abnormalities in the neurobiology of schizophrenia can be fully explained, therapies to target these abnormalities may be promising.

In conclusion, while it has been repeatedly shown that RNFL thickness, measured by SD-OCT which is an easy-to-use, fast, and non-invasive imaging method, decreases in both neurological diseases and in psychiatric diseases like schizophrenia, this study has, for the first time, shown that choroidal thickness decreases significantly in schizophrenia patients. SD-OCT appears to be a beneficial method for the diagnosis and follow-up of schizophrenia. The investigation of chorioretinal abnormalities in schizophrenia patients with further well-planned future studies in this area may increase the value of this method.

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