Comparison of OCT findings of schizophrenia patients using FGA, Clozapine, and SGA other than Clozapine

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Abstract

Objective: The effect of antipsychotic (AP) drugs on optical coherence tomography (OCT) findings in schizophrenia has not yet been fully elucidated. In this study, we aimed to investigate the effects of APs (the first generation antipsychotic group [FGAG], the second generation antipsychotic group [SGAG], the clozapine group [CG]) on OCT findings in schizophrenia. **Methods:** The thickness of the retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), and choroidal thickness were measured using a spectral OCT device. **Results:** No significant difference was found between FGAG, SGAG, CG ($p > 0.05$) while there was a significant difference between the control group and the patients group in terms of RNFL, GCL, and IPL ($p < 0.05$). A significant difference between SGAG and CG, FGAG ($p < 0.05$); between control group and FGAG ($p < 0.05$) were found in terms of choroidal thickness. **Conclusion:** These findings suggested the deterioration of the metabolic parameters due to the SGA use. Thinner choroidal layer thickness in the CG compared to the SGAG and control group was thought to be related to the patients using clozapine had a resistance to the treatment.

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Keywords: Antipsychotics, Retinal Ganglion Cell, Choroid, Optical Coherence Tomography, Schizophrenia

Abbreviations

OCT: Optical Coherence Tomography; RNFL: Retinal Nerve Fiber Layer; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; FGA: First Generation Antipsychotic; SGA: Second Generation Antipsychotic

Introduction

Schizophrenia is a mental disorder that manifests symptoms and signs in almost all areas of the mental state, usually beginning in youth, leading to a significant loss of functioning and yet having no complete understanding of aetiology[1-3]. Although the pathogenesis is not clearly known, the literature demonstrating the relationship of neuronal degeneration with the disorder cannot be underestimated[4]. Cellular, molecular, and structural pathologies of the frontal and temporal lobes have been most commonly studied[5,6]. Additionally, decreases in the total brain volume, enlargement of the lateral ventricles, and reductions in the corpus callosum, thalamus, hippocampus volumes have been reported[6]. Reduced thalamic neuronal density and decreased body size and dendritic arborisation of neurons, as well as decreases in the numbers and functions of oligodendrocytes have been reported as pathological changes in the brains of patients with schizophrenia.[7] To investigate the possibility of progressive neuroanatomical changes during the course of the disorder, studies were performed starting from the first episodes[8,9]. Grey matter loss in schizophrenia has been demonstrated not only in chronic schizophrenia patients but also in the first episode and prodromal stage patients[9]. Different neuroimaging methods have been frequently used to identify schizophrenia-related brain abnormalities[6,7]. The retina is an anatomical extension of the brain, and retinal changes may occur in parallel with inflammation and central nerve system degeneration. In recent decade, optical coherence tomography (OCT) has been used by various researchers to investigate neuronal degeneration in schizophrenia[10].

OCT is a novel imaging method that can capture biological tissue layers by acquiring high-resolution sections. This technique measures the delay time and intensity of infrared light, which is transmitted to and reflected from different tissue layers. It gives cross-sectional images of tissues similar to, but with much higher resolution than ultrasonography[11]. Its use increased rapidly because it is a non-invasive and rapid method that can assess the macula thickness (MT), volume (MV) and retinal layers. Because OCT technology significantly enhances the imaging resolution, the segmentation of retinal layers, such as the ganglion cell layer (GCL), inner plexiform layer (IPL), and retinal nerve fiber layer (RNFL), is

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now possible. The RNFL involves axons of ganglion cells, the GCL involves bodies of ganglion cells, and the IPL involves dendrites of ganglion cells. Another parameter that can be measured with OCT is choroidal thickness. The choroid is among the most vascularized tissues in the human body, and it plays important roles in providing oxygen and nutrition to the outer retina, temperature regulation of the retina, disposition of waste products from the retina, and the release of growth factors. Thus, any vascular pathology can cause choroidal thinning[10-12].

Cabezon et al.[13]'s study in the field of schizophrenia revealed a significant reduction in the overall and superior quadrant RNFL thickness in schizophrenia patients compared with controls. Celik et al.[10] demonstrated reduced GCL and IPL volumes in schizophrenia patients compared with controls using spectral OCT. They also detected significant negative correlations between disorder severity parameters and GCL and IPL volumes. Using new spectral domain OCT, which yields a higher spatial resolution, Lee et al.[14] compared patients with schizophrenia with controls, and they observed decreased RNFL thickness in the patient group. They also found an inverse correlation between illness duration and RNFL thickness. Samani et al.[15] reported that total retinal and photoreceptor complex thickness was reduced in all regions in patients. Pan et al.[16] reported in a meta-analysis that average RNFL thickness in patients with schizophrenia was significantly reduced compared to that of healthy controls. García-Portilla et al.[17] suggested that the differences in the OCT results of schizophrenia studies found could be due more to the effect of the length of illness than to the disorder itself.

Increased access to health services and medications allows drug-naive schizophrenia patients to be rarely seen. The most commonly used drug group in the treatment of schizophrenia is antipsychotics (APs)[18]. There are several studies showing that the effects and side effects of APs, which have been frequently investigated since the time they were first discovered, may influence the structure and function of neurons by a number of mechanisms[19]. These mechanisms include neuronal plasticity in which gradual cellular changes develop in response to the environment; hydrolysis of cell membranes and neurotoxicity caused by an inflammatory response; and apoptosis characterized by nuclear fragmentation, condensation of the chromatin[20,21]. Neuroplasticity changes are due to increased cyclic adenosine monophosphate (cAMP) after dopamine 2 (D_2) receptor blockade. cAMP activates protein kinase A (PKA) which phosphorylates N-methyl-D-aspartate (NMDA) and other receptors. PKA is involved in the activation of transcription factors that regulate the expression of neuronal growth factor genes[22]. Increased neurotrophic nerve growth factor (NGF) was reported after AP use. NGF increase is associated with D_2 receptor blockade. In animal studies, use of haloperidol has been found to increase NMDA receptor binding levels in parietal and frontal lobes and increase NMDA density. Brain-derived neurotrophic factor (BDNF) is another neurotrophic factor affected by APs. Chronic olanzapine use in animal studies has been shown to be associated with increased BDNF in the hippocampus and dentate gyrus. Furthermore, in animal studies, olanzapine has been reported to normalize the decrease in BDNF levels due to haloperidol. In terms of second generation antipsychotics (SGAs), it is known to increase BDNF production by serotonin (5-HT) 2A receptor antagonism and to decrease BDNF by D_2 receptor antagonism. This explains the BDNF-stimulating effect of olanzapine[23]. Quetiapine, another SGA, induces fibroblast growth factor (FGF) and BDNF expression and reverses stress-induced BDNF reduction. First generation antipsychotics (FGAs), especially haloperidol, may have a neurotoxic effect by increasing the calcium inflow into neurons[24]. Andreassen et al.[25] showed that haloperidol increased the release of glutamate and increased the size of the glutamatergic terminals. In another neurotoxicity study, Sram et al.[26] reported that cell viability was lost due to haloperidol and deoxyribonucleic acid (DNA) repair was inhibited. Noh et al.[27]'s study of haloperidol has shown that cell death occurs within 24 hours without gliosis in DNA fragmentation and nuclear membrane cleavage and cortical cell cultures. Hieronymus et al.[28] reported that DNA degradation due to chlorpromazine use and cell death in lymphoblast occurred. Loeffler et al.[29] showed that clozapine causes neutrophil apoptosis. In animal studies, the use of olanzapine and clozapine has been shown to be associated with 30-50% B-cell lymphoma 2 (Bcl-2) messenger ribonucleic acid (mRNA) and protein increase in the frontal cortex[30]. Jarskog et al.[30] reported that patients with schizophrenia treated with APs had higher levels of cortical Bcl-2 than the group who did not use AP before. These studies are consistent with the information that SGAs shown in vitro have slowed apoptosis and that haloperidol from FGAs selectively increases pro-apoptotic Bcl-XS levels[31]. As a result, APs cause neuronal changes with various factors. Jeste et al.[32] emphasized the loss of striatal neurons due to AP use, increases in neuron size, and perforated synapses. Harrison[33] reported an increase in inhibitory synapses, dendritic changes and gliosis in the caudate nucleus due to AP use. Konradi and Heckers[34] stated that axon terminals increased and density and shape changes occurred in dendrites due to haloperidol use.

Although studies have shown that APs cause structural and functional changes in the brain, the effect of APs on OCT findings in schizophrenia has not been investigated yet. Therefore, one of the major limitations of the studies investigating the relationship between OCT and schizophrenia is that it is not known how the AP drug subgroups, which are known to have different effects on the brain, effect on retinal findings. Studies in the literature divide AP drugs into two groups, FGAs and SGAs[35]. However, there are studies evaluating clozapine as a separate group due to the receptor profile and side effects[36]. In this study, we aimed to investigate the effect of AP treatment subgroups on OCT findings of patients with schizophrenia. Our study is the first study to investigate the effect of AP treatment on OCT findings.

Methods

Study Sample

This case-control study compared patients with schizophrenia using FGA, SGA, and clozapine who were followed in the psychiatry department at our university medical school with a control group. Data of 483 schizophrenia patients in the study population were evaluated for this study. Twenty-one patients using clozapine, 34 patients using other SGAs and 22 patients using FGAs were included in the study. Care was taken to ensure that the medications used by the patients were in specific dose ranges: clozapine (300-900 mg/day), fluphenazine (1-2 mg/day), haloperidol (5-20 mg/day), zuclopenthixol (10-20 mg/day), amisulpride (200-800 mg/day), aripiprazole (10-30 mg/day), olanzapine (10-20 mg/day), paliperidone (3-15 mg/day), risperidone (1-8 mg/day), quetiapine (150-750 mg/day), chlorpromazine (100-300 mg/day), amisulpride (200-800 mg/day), pimozide (2-20 mg/day). In this retrospective study, the patient group was also divided into two groups as treatment-resistant schizophrenia (TRS) and non-treatment resistant schizophrenia (N-TRS). The criteria determined by Kane et al.[37] were based on TRS criteria. Sociodemographic data and psychometric scales obtained from the patient registration system were used. The healthy control group was selected from

people who had OCT but did not have any psychiatric or organic pathology and did not use drugs. OCT measurements were made in the Ophthalmology Department at the same centre and all measurements were made between 10 am – 14 pm due to the operating time of the device. Local ethics committee approval was obtained from a University (19.04.2018/2018/146).

Inclusion and Exclusion Criteria

Patients with schizophrenia who were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5)[38] criteria were included. In addition, schizophrenia patients for at least 5 years, using the same group of AP for at least 2 years, in remission was based on such criteria. Patients who had comorbid first axis diagnosis, hypertension, diabetes mellitus, severe neurological, drug use other than APs, immunological or systemic diseases (glaucoma or retinal diseases) were excluded. Patients with refraction errors ≥ 1 prism dioptre were also excluded. Both the patient and the control groups had been examined in the ophthalmology clinic and best corrected visual acuity, intraocular pressure, slit lamb bio-microscopy, and fundus examination by eye dilatation had been measured. Patients and controls with normal eye findings were included. The group of healthy controls did not have any first axis diagnosis, hypertension, diabetes mellitus, severe neurological, drug use other than APs, immunological or systemic diseases which may affect the results.

Data Collection

Age, gender, educational status, marital status, working status, duration of disorder, number of attacks, number of hospitalizations were questioned by a sociodemographic form.

The Clinical Global Impressions (CGI)[39] and the positive and negative syndrome scale (PANSS)[40] were used to determine the severity of the disorder. CGI consists of three parts, including severity of disorder, recovery and side effects. Based on two established psychiatric rating systems, the 30-item PANSS was conceived as an operationalized, drug-sensitive instrument that provides balanced representation of positive and negative symptoms and gauges their relationship to one another and to global psychopathology.

OCT Measurement

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), temporal superior (TS), temporal inferior (TI) and global (mean) segments. Therefore, 7 measurements were made for each eye (i.e., N, NS, NI, T, TS, TI, mean) (Figure 1). 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 3 measures was accepted as the choroidal thickness. All measurements were performed by the same author who was blinded to the diagnoses of the patients. The choroidal measurement method used with the spectral-OCT devices has been previously explained. Lastly, we measured the GCL and IPL volumes with an OCT device. (Figure 2).

Statistical Analyses

The mean ± standard deviation and percentages were used as descriptive statistics. In order to compare the groups, student t-test was used for continuous variables. Student t-test was used for intra-group comparisons for dependent variables. The chi-square test was used to compare the groups when the variables were categorical or nominal. The significance level (p value) was determined as 0.05 or less. SPSS 22.0 package program was used to evaluate the data.

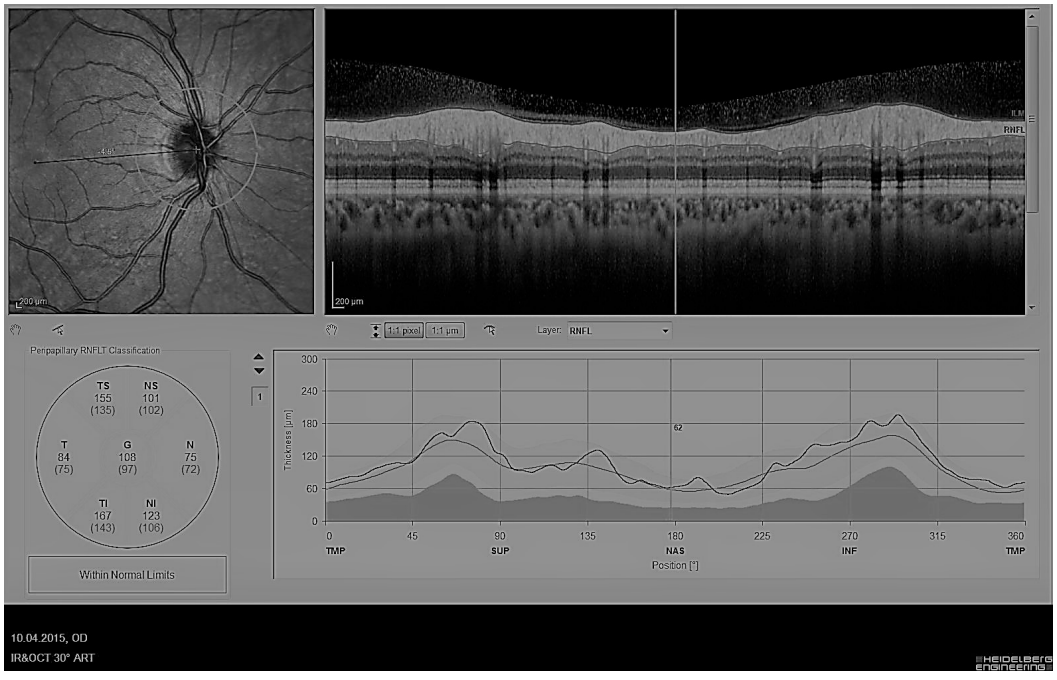

Figure 1. Measurement of RNFL thicknesses with spectral OCT

A. The circle is drawn around the optic disc to measure peripapillary RNFL thickness. B. Demonstration of RNFL. C. Seven measurements are performed for each eye, providing the RNFL thickness of the TS, TI, T, NS, NI, N, and G sectors. D. RNFL thickness map (OCT: Optical Coherence Tomography; RNFL: Retinal Nerve Fiber Layer; TS: Temporo-Superior; TI: Temporo-Inferior; T: Temporal; NS: Nasal Superior; NI: Nasal Inferior; N: Nasal; G: Global)

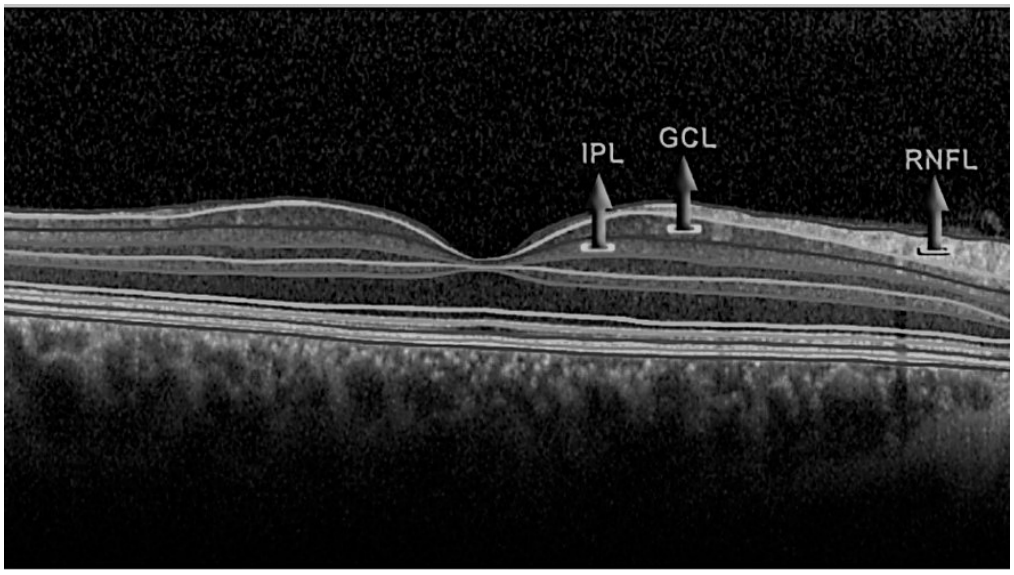

Figure 2. Measurement of the GCL and IPL thicknesses with spectral OCT
(GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; OCT: Optical Coherence Tomography)

Results

Sociodemographic Data

The socio-demographic features of the patients and controls are shown in Table 1. The study included 82 patients (female 18, male 64) and 50 healthy controls (female 18, male 32). The mean ages in the patient total, FGA group (FGAG, n = 22), SGA group (SGAG, n = 34), clozapine group (CG, n = 26), and control group were 36.76 ± 10.63 years, 41.36 ± 10.74 years, 36.67 ± 10.93 years, 33.00 ± 8.83 years, and 41.02 ± 13.69 years, respectively. There were no statistically significant differences between the patients and controls (p = 0.171), between the patient subgroups (p = 0.345) according to age. Thirty-eight of the patient group were determined as N-TRS and 44 as TRS. TRS patients with schizophrenia were more likely to be single or divorced, and their level of education was lower, their PANSS and CGI scores were higher, and their hospital admissions were more frequent compared with the N-TRS patients.

Features of Medication Use

Twenty (52.60%) patients were using olanzapine (Per Oral (PO)), 9 (23.70%) were using risperidone (PO), 2 (5.30%) were using quetiapine (PO), 6 (15.80%) were using haloperidol (PO) and 1 (2.60%) was using zuclopenthixol decanoate depot injection (intramuscular (IM)) in N-TRS group. Twenty-six patients (%59.10) were using clozapine (PO), 6 (%13.60) were using olanzapine (PO), 2 (%4.50) were using quetiapine (PO), 8 were using (%18.20) haloperidol (PO), 1 (%2.30) was using chlorpromazine (PO), 1 (2.30%) was using zuclopenthixol decanoate depot injection (IM) in TRS group. Eleven (28.90%) of the N-TRS group did not use a second drug. Five (13.20%) patients were using risperidone (PO), 1 (%2.60) was using risperidone depot injection (IM), 10 (26.30%) were using quetiapine (PO), 1 (2.60%) was using aripiprazole (PO), 1 (2.60%) was using paliperidone (PO), 2 (5.3%) were using amisulpride (PO), 4 (10.50%) were using chlorpromazine (PO), 3 (7.90%) were using zuclopenthixol decanoate depot injection (IM) as second drug in N-TRS group. Five (11.40%) of the TRS group did not use a second drug. Two (%4.50) were using olanzapine (PO), 6 (%13.60) were using risperidone (PO), 3 (6.80%) were using quetiapine (PO), 2 (%4.50) were using paliperidone (PO), 1 (%2.30) was using amisulpride (PO), 8 (%18.20) were using haloperidol (PO), 8 (%18.20) were using chlorpromazine (PO), 1 (%2.30) was using haloperidol decanoate depot injection (IM), 1 (%2.30) was using pimozide (PO), 7 (%15.90) were using zuclopenthixol decanoate depot injection (IM) as second drug in TRS group. Thirty-two (84.20%) of the N-TRS group did not use a third drug. Two (5.30%) were using risperidone (IM), 1 (2.60%) was using amisulpride (PO), 1 (2.60%) was using pimozide (PO), 2 (5.30%) were using zuclopenthixol decanoate depot injection (IM) in N-TRS group. Thirty-three (77.30%) of the TRS group did not use a third drug. Three (6.80%) were using quetiapine (PO), 1 (2.30%) was using aripiprazole (PO), 1 (2.30%) was using paliperidone palmitate depot injection (IM), 2 (4.50%) were using chlorpromazine (PO), and 3 (6.80%) were using zuclopenthixol decanoate depot injection (IM) TRS group.

OCT Findings

The RNFL thickness was statistically different at all measured regions (TS, TI, T, NS, NI, N, Global) in the N-TRS and TRS groups compared with the controls for both eyes ($p < 0.05$). There was no a significant difference between N-TRS and TRS in terms of RNFL sub parameters ($p > 0.05$). As seen in Table 2, there was no significant difference between the control group and the N-TRS group in terms of the choroid layer (right eye p = 0.831, left eye p = 0.923), the choroidal layer was thicker in the control group and there was a significant difference between the control group and the TRS group (right eye p = 0.001, left eye p = 0.004). There was a significant difference between TRS and N-TRS groups in terms of choroid layer thickness (right eye p = 0.000, left eye p = 0.002). There was a significant difference between TRS and N-TRS in terms of GCL and IPL ($p < 0.05$).

The RNFL thickness was statistically different at all measured regions in the FGAG, SGAG, and CG compared with the controls for both eyes ($p < 0.05$). There was no a significant difference between FGAG, SGAG, and CG in terms of RNFL sub parameters ($p > 0.05$). As seen in Table 3, there were significant difference between control group and CG (p = 0.042), between control group and FGAG (p = 0.015) in terms of the choroidal layer for right eye. There was significant difference between control group and FGAG (p = 0.016) in terms of the choroidal layer for left eye. In terms of the choroidal thickness that SGAG has the highest value for both

Table 1. Sociodemographic Features of Schizophrenia Patients and Healthy Controls

	Group (n)	Mean±SD or Number (%)	p
Age (years)	Control (n = 50)	41.02±13.69	0.171
	Patient (n = 82)	36.76±10.63	
	FGAG (n = 22)	41.36±10.74	0.345
	SGAG (n = 34)	36.67±10.93	
	CG (n = 26)	33.00±8.83	
Duration of Illness	FGAG (n = 22)	17.95±9.76	0.130
	SGAG (n = 34)	13.58±10.16	
	CG (n = 26)	12.73±8.02	
	N-TRS (n = 36)	12.36±9.84	0.065
	TRS (n = 44)	16.29 ± 9.01	
PANSS	FGAG (n = 22)	75.63 ± 11.64	0.099
	SGAG (n = 34)	69.91 ± 18.53	
	CG (n = 26)	78.88 ± 15.96	
	N-TRS (n = 36)	68.05 ± 16.06	0.001*
	TRS (n = 44)	79.68 ± 14.85	
CGI	FGAG (n = 22)	3.68 ± 1.35	0.093
	SGAG (n = 34)	3.05 ± 1.15	
	CG (n = 26)	3.65 ± 1.19	
	N-TRS (n = 36)	2.89 ± 0.92	0.000*
	TRS (n = 44)	3.86 ± 1.32	
Number of Hospitalizations	FGAG (n = 22)	4.68 ± 4.32	0.153
	SGAG (n = 34)	3.05 ± 2.50	
	CG (n = 26)	3.50 ± 2.33	
	N-TRS (n = 36)	2.73 ± 2.17	0.014*
	TRS (n = 44)	4.40 ± 3.54	
Number of Attacks	FGAG (n = 22)	5.92 ± 3.75	0.148
	SGAG (n = 34)	5.11 ± 2.87	
	CG (n = 26)	5.92 ± 3.75	
	N-TRS (n = 36)	4.44 ± 2.53	0.001*
	TRS (n = 44)	7.20 ± 4.34	
Education Status	Control (n = 50)		0.008*
	Patient (n = 82)		
	FGAG (n = 22)		0.639
	SGAG (n = 34)		
	CG (n = 26)		
	N-TRS (n = 36)		0.036*
	TRS (n = 44)		
Marital Status	Control (n = 50)		0.027*
	Patient (n = 82)		
	FGAG (n = 22)		0.598
	SGAG (n = 34)		
	CG (n = 26)		
	N-TRS (n = 36)		0.430
	TRS (n = 44)		
Working Status	Control (n = 50)		0.018*
	Patient (n = 82)		
	FGAG (n = 22)		0.854
	SGAG (n = 34)		
	CG (n = 26)		
	N-TRS (n = 36)		0.738
	TRS (n = 44)		

*p<0.05

PANSS: Positive and Negative Syndrome Scale; CGI: Clinical Global Impression; FGA: First Generation Antipsychotic Group; SGA: Second Generation Antipsychotic Group; CG: Clozapine Group; SD: Standard Deviation; N-TRS: Non-Treatment Resistant Schizophrenia; TRS: Treatment Resistant Schizophrenia

Table 2. Statistical Comparison of Choroid, GCL and IPL According to the Treatment-Resistance Variable

Dependent Variable	Diagnosis (I)	Diagnosis (J)	Mean Difference (I-J)	Standard Error	p
Right Choroid	Control	N-TRS	-3.89263	6.70072	0.831
		TRS	24.66000	6.43590	0.001*
	N-TRS	Control	3.89263	6.70072	0.831
		TRS	28.55263	6.89518	0.000*
	TRS	Control	-24.66000	6.43590	0.001*
		N-TRS	-28.55263	6.89518	0.000*
Right GCL	Control	N-TRS	0.08877	0.01719	0.000*
		TRS	0.14799	0.01651	0.000*
	N-TRS	Control	-0.08877	0.01719	0.000*
		TRS	0.05922	0.01768	0.003*
	TRS	Control	-0.14799	0.01651	0.000*
		N-TRS	-0.05922	0.01768	0.003*
Right IPL	Control	N-TRS	0.06248	0.01376	0.000*
		TRS	0.10153	0.01322	0.000*
	N-TRS	Control	-0.06248	0.01376	0.000*
		TRS	0.03904	0.01416	0.018*
	TRS	Control	-0.10153	0.01322	0.000*
		N-TRS	-0.03904	0.01416	0.018*
Left Choroid	Control	N-TRS	-2.81368	7.37815	0.923
		TRS	23.11455	7.08656	0.004*
	N-TRS	Control	2.81368	7.37815	0.923
		TRS	25.92823	7.59227	0.002*
	TRS	Control	-23.11455	7.08656	0.004*
		N-TRS	-25.92823	7.59227	0.002*
Left GCL	Control	N-TRS	0.09052	0.01792	0.000*
		TRS	0.14056	0.01721	0.000*
	N-TRS	Control	-0.09052	0.01792	0.000*
		TRS	0.05005	0.01844	0.021*
	TRS	Control	-0.14056	0.01721	0.000*
		N-TRS	-0.05005	0.01844	0.021*
Left IPL	Control	N-TRS	0.06174	0.01254	0.000*
		TRS	0.09245	0.01204	0.000*
	N-TRS	Control	-0.06174	0.01254	0.000*
		TRS	0.03072	0.01290	0.049*
	TRS	Control	-0.09245	0.01204	0.000*
		N-TRS	-0.03072	0.01290	0.049*

*p<0.05
N-TRS: Non-Treatment Resistant Schizophrenia; TRS: Treatment Resistant Schizophrenia; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer

Table 3. Statistical Comparison of Choroid, GCL and IPL According to the Drug Sub Group Variable

Dependent Variable	Diagnosis (I)	Diagnosis (J)	Mean Difference (I-J)	Standard Error	p
Right Choroid	Control	CG	20.39077	7.64094	0.042*
		SGAG	-3.89882	7.02469	0.945
		FGAG	24.52364	8.08503	0.015*
	CG	Control	-20.39077	7.64094	0.042*
		SGAG	-24.28959	8.23306	0.020*
		FGAG	4.13287	9.15450	0.969
	SGAG	Control	3.89882	7.02469	0.945
		CG	24.28959	8.23306	0.020*
		FGAG	28.42246	8.64679	0.007*
	FGAG	Control	-24.52364	8.08503	0.015*
		CG	-4.13287	9.15450	0.969
		SGAG	-28.42246	8.64679	0.007*

Right GCL	Control	CG	0.13025	0.01980	0.000*
		SGAG	0.09669	0.01820	0.000*
		FGAG	0.14595	0.02095	0.000*
	CG	Control	-0.13025	0.01980	0.000*
		SGAG	-0.03355	0.02133	0.398
		FGAG	0.01570	0.02372	0.911
	SGAG	Control	-0.09669	0.01820	0.000*
		CG	0.03355	0.02133	0.398
		FGAG	0.04925	0.02240	0.129
	FGAG	Control	-0.14595	0.02095	0.000*
		CG	-0.01570	0.02372	0.911
		SGAG	-0.04925	0.02240	0.129
Right IPL	Control	CG	0.09726	0.01565	0.000*
		SGAG	0.06380	0.01439	0.000*
		FGAG	0.09744	0.01656	0.000*
	CG	Control	-0.09726	0.01565	0.000*
		SGAG	-0.03346	0.01686	0.199
		FGAG	0.00017	0.01875	1.000
	SGAG	Control	-0.06380	0.01439	0.000*
		CG	0.03346	0.01686	0.199
		FGAG	0.03364	0.01771	0.233
	FGAG	Control	-0.09744	0.01656	0.000*
		CG	-0.00017	0.01875	1.000
		SGAG	-0.03364	0.01771	0.233
Left Choroid	Control	CG	19.85231	8.24851	0.081
		SGAG	-5.42824	7.58325	0.891
		FGAG	26.29636	8.72791	0.016*
	CG	Control	-19.85231	8.24851	0.081
		SGAG	-25.28054	8.88771	0.026*
		FGAG	6.44406	9.88241	0.915
	SGAG	Control	5.42824	7.58325	0.891
		CG	25.28054	8.88771	0.026*
		FGAG	31.72460	9.33434	0.005*
	FGAG	Control	-26.29636	8.72791	0.016*
		CG	-6.44406	9.88241	0.915
		SGAG	-31.72460	9.33434	0.005*
Left GCL	Control	CG	0.13266	0.02056	0.000*
		SGAG	0.09891	0.01890	0.000*
		FGAG	0.12784	0.02176	0.000*
	CG	Control	-0.13266	0.02056	0.000*
		SGAG	-0.03376	0.02216	0.426
		FGAG	-0.00483	0.02464	0.997
	SGAG	Control	-0.09891	0.01890	0.000*
		CG	0.03376	0.02216	0.426
		FGAG	0.02893	0.02327	0.601
	FGAG	Control	-0.12784	0.02176	0.000*
		CG	0.00483	0.02464	0.997
		SGAG	-0.02893	0.02327	0.601
Left IPL	Control	CG	0.09546	0.01423	0.000*
		SGAG	0.06524	0.01309	0.000*
		FGAG	0.07791	0.01506	0.000*
	CG	Control	-0.09546	0.01423	0.000*
		SGAG	-0.03023	0.01534	0.205
		FGAG	-0.01755	0.01705	0.733
	SGAG	Control	-0.06524	0.01309	0.000*
		CG	0.03023	0.01534	0.205
		FGAG	0.01267	0.01611	0.860
	FGAG	Control	-0.07791	0.01506	0.000*
		CG	0.01755	0.01705	0.733
		SGAG	-0.01267	0.01611	0.860

*p<0.05

GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; FGAG: First Generation Antipsychotic Group; SGAG: Second Generation Antipsychotic Group; CG: Clozapine Group

eyes; the choroidal layer thickness of control group, CG, and FGAG decreased with the same order. There was a significant difference between control group and CG, FGAG, SGAG in terms of GCL and IPL ($p < 0.05$), but not in drug sub groups ($p > 0.05$).

Choroid layers of N-TRS patients in SGAG and N-TRS patients in FGAG were compared and a statistically significant difference was found (right eye $p = 0.023$, left eye $p = 0.004$). GCL layers of N-TRS patients in SGAG and N-TRS patients in FGAG were compared and no statistically significant difference was found (right eye $p = 0.824$, left eye $p = 0.682$).

Choroid layers of TRS patients in CG, SGAG, and FGAG were compared and a statistically significant difference was not found (right eye $p = 0.298$, left eye $p = 0.711$). GCL layers of TRS patients in CG, SGAG, and FGAG were compared and no statistically significant difference was found (right eye $p = 0.114$, left eye $p = 0.520$).

Discussion

When our findings were evaluated and interpreted in the light of the literature, it is observed that our sociodemographic data support the loss of cognitive and social functioning due to schizophrenia. Resistance to treatment adversely affects the parameters associated with the disorder process. The fact that RNFL sub parameters were different in the patient group compared to the control group was considered as an indicator of axonal degeneration. Axonal degeneration can be responsible for decreases in the gray matter volume and also the thinning of the RNFL. However, there was no statistically significant difference between the TRS and N-TRS groups and between the CG, FGAG, and SGAG in terms of RNFL parameters. Previous studies have found that RNFL damage can be detected by ophthalmologic examination only after 50% of the ganglion cells were damaged. This shows that the sensitivity of RNFL is low and may explain the absence of any difference between the patient subgroups[41,42].

It was observed that schizophrenia caused thinning in GCL and IPL and there was a negative correlation between these parameters and resistance to treatment. There was a significant difference between TRS and N-TRS groups in terms of GCL and IPL. These findings suggest that schizophrenia is a neurodegenerative disorder and this neuronal degeneration correlated with the severity of the disorder. Although there is a need for a longitudinal study in a larger group of patients with drug monitoring, the absence of a significant difference between FGAG, CG, and SGAG in terms of GCL and IPL suggests that the course and severity of the disorder play an important role in the pathophysiology of neuronal degeneration, rather than the AP drugs used.

The control group was found to be significantly thicker than the TRS group in terms of choroid layers. There was a significant difference between TRS and N-TRS in terms of choroidal layer thickness. Celik et al.[10], similar to our study, choroidal layer thickness was found to be thinner in patients with TRS compared to N-TRS patients. There was a significant difference between the control group and CG and FGAG for right eye; between the control group and the FGAG for left eye. No significant difference was found between the control group and the SGAG for both eyes. While there was a significant difference between the CG and SGAG, there was no significant difference between CG and FGAG for both eyes in terms of choroid. The thickness of choroidal layer thickness was found to be thicker in SGAG than in the control group, CG and FGAG. A significant difference was found between FGAG and SGAG in terms of the thickness of the right and left eye choroid layers.

The choroid is one of the tissues with the most vascularization in the human body and is affected by any systemic event affecting the blood flow[41]. Recent studies suggest that the underlying pathogenesis mechanisms of neurodegenerative diseases and mental disorders may be related to neuronal inflammation[42]. Data have shown that microglia-mediated neuronal inflammation has a pathogenic role in schizophrenia[43]. In primary cell cultures, clozapine has been shown to inhibit microglial nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX_2, a superoxide producing enzyme) and protect dopaminergic neurons from inflammation-related damage[44]. In our study, all patients using clozapine were from the TRS group. Resistance to treatment was thought to be the most important cause of choroidal thinness. The transition to clozapine, which is recommended to be used as the third drug after two APs failed, has been shown to be delayed by 47.7 months in Europe and the United States. Side effects and follow-up difficulties lead to clinicians' delay in choosing clozapine and clozapine is used in clinical practice in later stages of schizophrenia. These delays are known to increase neuronal degeneration and loss of functionality in schizophrenia patients[45,46]. Another possible reason is the alpha 1 adrenoreceptor blockade and anticholinergic effects of clozapine and postural hypotension. It was thought that decreased choroidal blood flow due to clozapine use may be another reason of low choroidal layer thickness[47]. Scheepers et al.[48] showed that caudate nucleus volumes were reduced after clozapine treatment was started in patients using FGA. van Haren et al.[49] reported that superior frontal grey matter density was inversely correlated with the number of hospitalizations, and clozapine use slowed down this reduction. In the same study, this positive result was not seen in the use of FGA.

The results of the FGA-choroid layer relationship have been associated with the mechanism of drug action and/or the patient. FGAs cause more significant blood flow reduction in frontal cortex than SGAs[50]. van Haren et al.[49] reported that the use of SGA decelerated the decrease of superior frontal grey matter density, but this positive course was not observed in patients using FGA. According to the MRI studies, FGAs, especially haloperidol, may increase the calcium inflow into neurons and show a neurotoxic effect[26]. Sram et al.[26], Lieberman et al.[51] and Hieronymus et al.[28] reported that cell viability was lost due to haloperidol and DNA repair was inhibited. Considering the situations that may be associated with the patient, the stage and the severity of the disorder and the patient's functionality come to the forefront. Parks and colleagues[52] have shown that a ranking of AP usage preferences in psychiatric practice is as follows (not as a guideline): (I) SGA, which is neutral in weight gain, (II) FGA with one or more intermediate potencies, (III) At least one sedative SGA, (IV) High potency SGA, (V) One or more high potency long-acting FGA, (VI) Clozapine, (VII) One or more low potency FGA. In our study, the number of patients using FGA in the TRS group was high and there was no significant difference between FGAG and CG in terms of choroidal thickness and this result was evaluated with the above mentioned information[52].

Another important finding of our study is that the choroidal layer thickness in patients using SGAs other than clozapine is higher than CG and FGAG and is similar to the control group. SGAs are associated with increased weight gain, intra-abdominal obesity, hyperlipidaemia, dyslipidaemia, insulin resistance, type 2 diabetes mellitus, hypertension, and cardiovascular diseases. Especially olanzapine and clozapine were evaluated as drugs which may cause these side effects more[53]. In Saddichha et al.'s[53] study, the prevalence of metabolic syndrome risk was significantly increased after olanzapine was used in first episode psychosis patients. In a

study from Taiwan[54], it was shown that the use of SGA, including clozapine, was associated with a significant increase in metabolic syndrome according to FGA use. The literature stated that clozapine induces hypotension in the short term on blood pressure, but it causes long-term hypertension with significant weight gain, changes in lipid and cholesterol balance, and impaired glucose tolerance. On the other hand, more sedation of the SGAs than the FGAs and the resulting sedentary lifestyle may be considered as the other factors that maintain the metabolic syndrome[29,44,53]. There are findings in favour of neuronal degeneration, even in patients with first episode psychosis[19]. However, in our study, the choroidal layer thickness of SGAG is higher than the control group, although not significantly different and this indicates the obvious metabolic effects of SGAs.

As a result, comparison of FGA, SGA, and clozapine revealed insignificant results and this suggested that the course and severity of the disorder were more important than the drugs used in the pathophysiology of neuronal degeneration. In optimal conditions, assuming that the choroidal thickness of the control group is within normal limits, SGAs significantly affect the choroidal structure. The impaired metabolic parameters due to SGAs may have caused the thickening of the choroid layer by increasing the inflammatory process. Resistant patient profile, excessive neuronal loss, receptor profile and deterioration of tissue perfusion, anti-inflammatory effect of clozapine may be the cause of thin choroidal layer in CG. In view of the fact that FGAs have neurotoxic effects, decrease choroidal tissue perfusion secondary to the neurodegenerative process, are used as an interim treatment before switching to clozapine in schizophrenia without adequate response to SGAs, and even that FGAs are used in treatment-refractory patients who do not respond to clozapine, it is understandable that the choroidal layer thickness of FGAG is lower than the other groups.

Major limitation of this study is its cross-sectional design. There is a need for longitudinal studies starting from the early stages of the disorder and in particular the use of medication, with regular OCT shots. It is thought that these studies will reveal the effect of the disorder process and drug effects on the neuronal structure. The lack of knowledge of the blood levels of the drugs used by the patients is another important limitation. The drugs included in the drug subgroups are in the same group but different active substances. The effect of these drug differences on the results is unknown. 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. The fact that a structured clinical interview was not applied to patient and control groups made it difficult to exclude comorbidities. In addition to the patient groups and the control group, another group to be formed from drug-naïve patients. Smoking may have an impact on OCT measurements.

Significant outcomes

1. Optical coherence tomography is useful in detecting neurodegeneration in schizophrenia.
2. The second generation antipsychotics which can impair metabolic parameters may increase the choroid layer thickness by increasing the inflammatory process.
3. Resistant patient profile, excessive neuronal loss, receptor profile and deterioration of tissue perfusion, anti-inflammatory effect of clozapine effect the choroidal layer thickness in clozapine users.

Limitations

1. There is a need for longitudinal studies starting from the early stages of the disorder.
2. 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 optical coherence tomography as a tool in neuropsychiatric disorders.
3. In addition to the patient groups and the control group, another group to be formed from drug-naive patients.

Authors' Contributions

M.H.O.: 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; M.B.: Patient sampling, preparation of statistical analysis, and literature review; A.S.K.: examination and evaluation by means of optical coherence tomography; E.D.: Psychiatric examination of subjects, sample collection, statistical analysis.

Competing Interests

The authors declare that they have no competing interest.

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Ethical Consideration

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional guides on the care and use of laboratory animals.

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