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Optical Coherence Tomography Findings in Bipolar Disorder Patients and the Related Factors

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ABSTRACT

Background: This study's purpose is to determine the effects of current episode and the mood stabilizers on chorioretinal layer thicknesses of bipolar disorder (BD) patients using spectral-domain optical coherence tomography (SD-OCT).

Methods: Sixty-seven patients were diagnosed with BD I and using lithium (Li) or valproic acid (VPA), of whom 20 were manic, 24 were depressive, and 23 were in remission, and 49 healthy individuals were included in the study. Peripapillary retinal nerve fiber layer (RNFL), ganglion cell layer, and macular thicknesses of the participants were measured automatically using SD-OCT, and their choroid layer thicknesses were measured manually using the depth imaging mode of SD-OCT. Statistical analysis of the data was performed using Statistical Package for the Social Sciences version 23.0.

Results: The patient group's mean age was 39.78 ± 11.78, and the control group's mean age was 42.06 ± 12.10. The mean disease duration was 13.22 ± 8.23 in the patient group, and 26 patients were using Li. While peripapillary RNFL thicknesses were lower in the patient group ($P < .05$), other layer measurements were similar between the groups. Moreover, the episodes experienced by BD patients did not affect chorioretinal SD-OCT measurements. The patients on VPA had significantly lower RNFL thicknesses compared to the control and the Li groups, and all chorioretinal measurements were similar between the Li and the control groups.

Conclusion: As a result of the study, it was established that neurodegenerative processes play a role in the pathophysiology of BD and the usage of Li is protective against the neurodegeneration of RNFL. Retinal changes measured with SD-OCT can be used for the diagnosis and prognosis of BD and for evaluating responses to mood stabilizers.

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INTRODUCTION

Bipolar disorder (BD) is a chronic and recurrent disease that can progress with manic, depressive, and mixed episodes and that can present psychotic, affective, behavioral, and cognitive impairment symptoms and progresses with social and occupational devastation.[1] The lifelong incidence of BD is between 3% and 5%.[2] However, it has been reported that different clinical manifestations that can be seen in the progression of the disease may cause delays in its diagnosis and treatment, and this in turn causes resistance to the treatment and increases the frequency and severity of the attacks, thereby negatively affecting the prognosis.[3,4]

It has been suggested that, in addition to genetic and environmental factors, neurodegeneration also plays a role in the etiology of BD. It has been demonstrated in studies performed on BD patients that, while there are no reductions in the total brain volume,[5] there are reductions in gray matter, particularly in the prefrontal, temporal, and parietal cortexes, enlargements in the ventricles, and regional gray matter reductions in the anterior cingulate cortex in the early stages of BD and during the onset of attacks.[6,7] Similar to white matter, the retina also originates from neuroectoderm and it is directly connected to the brain via the optical nerve, and it is possible to observe the pathological changes that occur in the brain in certain neuropsychiatric diseases via the retina.[8]

Spectral-domain optical coherence tomography (SD-OCT) is a quick, inexpensive, and easily applicable imaging method that is used to examine retinal pathologies. Although SD-OCT is a method that is used to diagnose ophthalmological diseases that progress with degeneration, it has recently come into use in the diagnosis of neuropsychiatric diseases. In these studies, the fact that there is a thinning in the retinal nerve fiber layer (RNFL) of Alzheimer's disease (AD),[9] Parkinson's disease (PD),[10] and schizophrenia patients[11] comes to the forefront as the most consistent piece of information.

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Similarly, a significant portion of the SD-OCT studies carried out on BD patients have demonstrated decreases in the thicknesses of RNFL and ganglion cells, and findings support the role of neurodegeneration in the pathophysiology of BD.[12,13] In all of these studies, BD patients were included without paying any consideration to the stage of their illnesses. In addition to there being different clinical manifestations for manic and depressive episodes, it is also possible that there are different pathophysiological processes in their development, and this situation decreases the reliability of the study results. Each episode of BD patients can be devastating for the patient. A depressive episode and a manic episode can cause different destructions in the brain. In order to detect these possible different effects, it was aimed to compare the patients in different episodes of the illness. Lithium (Li) and valproic acid (VPA) are agents that are commonly used in BD as mood stabilizers (MS). Conflicting results have been reported regarding the neuroprotective effects of these agents in in vivo and in vitro studies regarding diseases with neurodegeneration, such as mild cognitive impairment (MCI), AD, and PD.[14,15]

We propose that neurodegeneration plays a role in the etiopathogenesis of BD and that this will be reflected in the thicknesses of the chorioretinal layer. We claim that Li and VPA, which are MS, may affect this neurodegeneration. To this end, we seek to compare the chorioretinal layer thicknesses of BD patients with the data of the control group using the SD-OCT method. Moreover, we have planned a study that will enable us to evaluate the possible effects of certain variables regarding BD patients, such as the disease duration, disease severity, the MS that is being used, and the episode that is being experienced on the chorioretinal layer.

MATERIAL AND METHODS

Patient and control groups: Patients who were followed up and treated in Niğde Ömer Halisdemir Training and Research Hospital psychiatry polyclinics and services between March 15, 2020 and December 15, 2020, who were diagnosed with BD I between the ages of 18 and 65 and who have been using Li or VPA in the last 6 months and have agreed to participate, were included in the study. Bipolar disorder patients were divided into 3 groups, which are manic, depressive, and remission. The control group was composed of healthy individuals from the employees of the hospital who were matched with the patients in terms of age and gender, fit the same exclusion criteria, and agreed to participate in the study. The data obtained from the 3 patient groups and the control group were compared. Additionally, the patients were grouped based on whether they were using Li or VPA.

MAIN POINTS

- According to the results of this study, while peripapillary retinal nerve fiber layer (RNFL) thickness was lower in bipolar disorder (BD) group, other layer measurements were similar between BD and control groups.
- The ongoing episode experienced by BD patients did not affect the chorioretinal optical coherence tomography (OCT) measurements.
- The patients on valproic acid had significantly lower RNFL thicknesses compared to the control and the lithium (Li) groups, and all chorioretinal measurements were similar between the Li and the control groups.
- The neurodegenerative processes that play a role in the pathophysiology of BD can be observed in the OCT measurements, and Li has protective effects against this neurodegenerative process.

Exclusion Criteria

(i) For the study group, those who suffer from intellectual disability, substance abuse, or comorbid psychiatric diseases (ii) For the bipolar remission group, those who have experienced attacks in the last 6 months; (iii) those with neurodegenerative diseases, such as AD, PD, or multiple sclerosis; (iv) those with glaucoma, retinal laser or surgical intervention histories, or uveitis; (v) those with spherical values of ±3.0 diopter and/or a cylindrical value of more than ±2.0 diopters in auto refractometer measurements; (vi) those with ocular tension values higher than 21 mm/Hg; (vii) those with systematic diseases that affect retinal and choroid thicknesses, such as diabetes mellitus (DM) and hypertension (HT). (viii) For the control group, those with diagnosed psychiatric diseases and (ix) those with a signal quality of 6 or less in the SD-OCT.

Ethical Considerations

Ethics committee approval for the study was obtained from Niğde Ömer Halisdemir University Rectorate Ethics Committee (March 2, 2020 decision no-2020/02-07). A protocol was signed between the hospital management and the researchers to conduct the study at Niğde Ömer Halisdemir Training and Research Hospital. All the doctors who participated in the study signed the Helsinki Declaration. All patients and control groups who agreed to participate in the study were given detailed information about the study. Their written and verbal consent was obtained and an informed consent form was signed.

Psychiatric Evaluation

Detailed psychiatric evaluations of the patients and the individuals comprising the control group were performed by experienced psychiatry experts. The BD I diagnoses were made via semi-structured interviews based on the Diagnostic and Statistical Manual of Mental Disorders-5[16] diagnosis criteria. In addition to the interviews with the patients, hospital records and information obtained from patients' relatives were also used to ascertain the diagnoses. Sociodemographic and clinical information of the patients were recorded using the form prepared by the researchers. Young Mania Rating Scale (YMRS) and/or

Hamilton Depression Scale (HDS) were used to evaluate the symptom severity of BD patients. The validity and reliability study of YMRS for Turkey was conducted by Karadağ et al.[17] The validity and reliability study of HDS for Turkey was conducted by Akdemir et al.[18]

Eye Examination

Detailed eye examinations of the patients and the control group were conducted by experienced doctors and the results were recorded. Auto refractometer measurement was performed on all participants. Their intraocular pressures were measured using Goldmann applanation tonometry, and biomicroscopic and fundus examinations were performed. Their ophthalmological histories were taken. The participating patient and control groups' retinal layer thicknesses were measured using a Zeis Cirrus 400 model optical coherence tomography (OCT) device. Zeis Cirrus 400 is an advanced device with characteristics similar to those used in recent international studies. It can take spectral-domain images, has a scan speed of 27000 A-scan/second, A-Scan depth of 2 mm, an axial resolution of 5 µm, and a transverse resolution of 15 µm.

Spectral-Domain Optical Coherence Tomography Imaging

Peripapillary RNFL, ganglion cell layer (GCL), and macular thicknesses (MT) used in the study were measured automatically by the device, and the choroidal layer was measured manually. In the study, the HD 5 Line Raster protocol, which is composed of 6 mm parallel lines with 1024 A-Scan/B-Scan features and a 0.25 mm interval, was reduced to a single line and the imaging was performed. The choroidal layer was imaged using SD-OCT with the enhanced depth imaging (EDI) mode. By using an EDI mode that uses a longer wavelength of light, EDI-OCT allows rapid and precise measurement of choroidal thickness.[19] Fovea-centric macular sections were obtained for each eye and measurements were taken. The first measurement was taken in a manner that ensured that it was located underneath the fovea centralis by magnifying the image obtained from the macular section. Regarding the measurement locations, the end of the hyperreflective band of the retina pigment epithelium (RPE) was determined to be the starting point, and the boundary at the choroid-scleral junction point was determined to be the ending point. By using the ruler feature available in the device, the distance between these 2 points was measured by the user vertically in microns. Afterward, a total of 6 similar measurements, 3 at the temporal direction and 3 at the nasal direction, were taken on the RPE hyperreflective band at 500-micron intervals up to 1500 microns by employing the ruler feature of the device. Additionally, these measurements were taken in a manner that ensures that this first point of measurement remained fixed. The mean choroidal thickness values of the nasal and temporal areas were obtained by taking the measurement values at 500, 1000, and 1500 microns and dividing them by 3, which is the total number of measurements. Choroid thicknesses at nasal-temporal-subfoveal areas were used when making comparisons. Choroid thickness measurements were taken separately by 2 different ophthalmologists who were not informed of which group the patient belonged to. In order to prevent diurnal variations in the choroid thicknesses, the SD-OCT imaging procedures were carried out by the aforementioned experts between the hours of 11:00 and 12:00 AM each day. Moreover, the patients were not allowed to smoke in the 3 hours prior to OCT imaging, as smoking before the OCT imaging may affect choroidal thicknesses.[20]

Statistics Analysis

Statistical analysis of the data was performed with the Statistical Package for the Social Sciences version 23.0 program (IBM SPSS Corp.; Armonk, NY, USA). Normality was checked using the Shapiro-Wilk test. Since all numerical values were normally distributed, the mean ± standard deviation was calculated. Since a normal distribution assumption was achieved, the means of the 2 independent groups (study--control) were compared using the independent samples *t*-test. Paired samples *t*-test was used to compare the SD-OCT data of right and left eyes. Means of more than 2 independent groups (Manic-Depressi on-Remission-Control and Li-VPA-Control) were compared using the 1-way analysis of variance test. Gabriel test was employed to carry out pairwise comparisons of post hoc analyses. Pearson correlation analysis was used to examine the relationship between sociodemographic factors, disease data, and SD-OCT measurements. Chi-square analysis was used to compare the categorical data like sex, marital status, and education between groups. A statistical significance level of 0.05 was used for all comparisons.

RESULTS

A total of 80 patients diagnosed with BD I were included in the evaluation. Of these patients, 3 were excluded due to bilateral glaucoma, 3 due to high myopia, 2 due to senile macular degeneration, and 5 patients were excluded because of poor OCT scan quality. The remaining 67 patients, of whom 33 (49.3%) were male, were included in the study. Twenty patients (29.9%) were manic, 24 (35.8%) were depressive, and 23 (34.3%) were in remission phase. A total of 49 individuals, of whom 31 (63.3%) were male, were included in the study as the control group. The patient group's mean age was 39.78 ± 11.78 and the control group's mean age was 42.06 ± 12.10. No significant differences were observed between the groups in terms of age, sex, marital status, tobacco usage, and intraocular pressure averages. However, the control group's average level of education was significantly higher. The descriptive statistics of the patient and control groups are shown in Table 1.

Table 1. Descriptive Statistics of Study and Control Groups

		Study Group	Control Group	*P*
		n (%)	n (%)	
Age/mean (SD)		39.78 (11.775)	42.06 (12.104)	.310
Sex	Female	34 (50.7)	31 (63.3)	.191
	Male	33 (49.3)	18 (36.7)	
Marital status	Married	39 (58.2)	30 (61.2)	.903
	Single	21 (31.3)	15 (30.6)	
	Widow/divorced	7 (11.5)	4 (8.2)	
Education	No education	4 (6)	0 (0)	.020*
	Primary	33 (49.2)	12 (24.5)	
	High school	18 (26.9)	15 (30.6)	
	University	12 (17.9)	22 (44.9)	
Smoking	Yes	31 (46.3)	16 (32.7)	.181
	No	36 (53.7)	33 (67.3)	

n, number; *P*, confidence interval; SD, Standard deviation.
*$P < .05$

The mean disease duration of the patients was 13.22 ± 8.23 years. The mean number of episodes experienced by the patients was 3.92 in the manic patient group, 4.11 in the depressive patient group, and 4.03 in the remission group, and there was no statistically significant difference between them. The mean YMRS score of the manic patients was 27.15 ± 7.43, while the mean HDS score of the depressive patients was 21.92 ± 6.20. The mean YMRS and HDS scores of the patients in remission were 1.48 ± 1.97 and 2.78 ± 1.28, respectively. Of the patients, 41 (61.1%) were using VPA as a MS, and 58 (87%) of these patients were using an additional antipsychotic agent in addition to a MS medication (Table 2).

According to the results of the study, RNFL thicknesses in both eyes were measured to be statistically significantly thinner in the BD patient group in comparison to the control group ($P < .05$). All retinal and choroid layer measurements other than the RNFL thickness were similar in the patient and control groups. The detailed comparison of the SD-OCT measurements of the groups is shown in Table 3.

Table 2. Clinical and Treatment Data of Patient Groups

		Mania Group (n=20)		Depression Group (n=24)		Remission Group (n=23)	
		Mean	SD	Mean	SD	Mean	SD
Illness duration		16.60	9.16	10.96	6.45	12.65	8.43
Number of attacks		3.92	2.63	4.11	2.75	4.03	2.55
YMRS score		27.15	7.43	-	-	1.48	1.97
HDS score		-	-	21.92	6.20	2.78	1.28
		n	%	n	%	n	%
MS	Li (n=26)	6	30	10	35.7	10	43.5
	VPA (n=41)	14	70	14	64.3	13	56.5
AP	Yes (n=58)	19	95	20	83.3	19	82.6
	No (n=9)	1	5	4	16.7	4	17.4

AP, antipsychotic; HDS, Hamilton Depression Scale; Li, lithium; MS, mood stabilizer; n, number; *P*, confidence interval; SD, standard deviation; VPA, valproic acid; YMRS, Young mania rating scale.

Table 3. Comparison of the Chorioretinal Layer Thicknesses of Study and Control Groups

	Group	n	Mean ± SD	*t*	*P*
Right tonus	Study	67	15.57 ± 3.15	−0.043	.966
	Control	49	15.59 ± 2.96		
Right nct	Study	67	263.24 ± 51.10	−0.807	.422
	Control	49	271.29 ± 55.69		
Right sfct	Study	67	299.79 ± 43.44	−0.714	.477
	Control	49	305.90 ± 48.17		
Right tct	Study	67	268.75 ± 47.88	−0.757	.451
	Control	49	275.67 ± 49.77		
Right RNFL	Study	67	87.16 ± 12.04	−2.272	**.037***
	Control	49	91.57 ± 8.18		
Right cmt	Study	67	250.96 ± 23.83	0.902	.369
	Control	49	247.10 ± 21.10		
Right GCL	Study	67	78.10 ± 8.59	0.496	.621
	Control	49	77.20 ± 10.38		
Left tonus	Study	67	15.57 ± 2.79	0.802	.424
	Control	49	15.14 ± 2.86		
Left nct	Study	67	263.07 ± 50.77	−1.642	.103
	Control	49	278.29 ± 47.12		
Left sfct	Çalışma	67	293.07 ± 50.10	1.463	.146
	Control	49	306.29 ± 45.07		
Left tct	Study	67	264.81 ± 45.55	−1.403	.163
	Control	49	277.39 ± 50.52		
Sol cmt	Study	67	251.27 ± 25.86	0.961	.339
	Control	49	246.92 ± 21.41		
Left RNFL	Study	67	86.52 ± 11.78	−2.542	**.012***
	Control	49	91.49 ± 8.11		
Left GCL	Study	67	77.19 ± 9.96	−0.368	.713
	Control	49	77.88 ± 9.76		

Cmt, centrale macular thickness; GCL, ganglion cell layer; n, number; nct, nasal choroid thickness; *P*, confidence interval; RNFL, retinal nerve fiber layer; SD, standard deviation; sfct, subfoveal choroidal thickness; *t*, t value; tct, temporale choroidal thickness.

Paired samples *t*-test was employed to compare the right and left eye SD-OCT measurements of a total of 116 individuals in the study and control groups. No statistically significant differences between the right and left eye tones, choroidal thicknesses, central MT, GCL thicknesses, and RNFL thicknesses were found as a result of this test ($P > .05$) (Table 4).

The results of the study did not indicate any statistically significant differences between mania, depression, remission, and control groups in terms of the mean of all retinal and choroidal layer thickness measurements on the right and the left ($P > .05$).

Table 4. The Comparison of Both Eye OCT Measurements

	n	Mean	SD	t	df	p
Right tonus	116	15.58	3.06			.563
Left tonus	116	15.39	2.81	0.581	115	
Right nct	116	266.64	52.99			.367
Left nct	116	269.50	49.63	-0.906	115	
Right sfct	116	302.37	45.39			.199
Left sfct	116	298.66	48.28	1.293	115	
Right tct	116	271.67	48.59			.593
Left tct	116	270.12	47.91	0.536	115	
Right RNFL	116	88.60	10.67			.979
Lef RNFL	116	88.62	10.64	-0.026	115	
Right cmt	116	249.33	22.70			.919
Left cmt	116	249.43	24.08	-0.102	115	
Right GCL	116	77.72	9.35			.702
Left GCL	116	77.48	9.84	0.384	115	

To compare the measures of right and left eyes paired samples t test was used.cmt, centrale macular thickness; df, differentiation factor; GCL, ganglion cell layer; n, number; nct, nasal choroidal thickness; P, confidence interval; RNFL, retinal nerve fiber layer; SD, standard deviation; sfct, subfoveal choroidal thickness; t, t value; tct, temporale choroidal thickness.

In the comparison made by dividing the patients into groups according to whether they use Li or VPA, while the RNFL thicknesses were significantly lower in the VPA patients than in the control group, no differences were detected in terms of the RNFL thickness between the Li group and the control group. Moreover, the VPA patient group had a lower thickness of RNFL when compared to the Li patient group, and the difference between the left-side RNFL thicknesses of these groups was significant. Conversely, no effect of MS medication type was detected on the choroid layer, GCL, and MT (Table 5).

No relationships were detected between HDS and YMRS scores and retinal and choroid layer measurements as a result of the correlation analysis. However, a weak negative correlation was detected between age and right and left eye temporal choroid thickness (TCT) and subfoveal choroid thickness (SFCT). Additionally, a weak negative correlation was detected between the duration of disease and all choroid layer thickness measurements (r = −0.267, P = .004 for left TCT; r = −0.283, P=.002 for right SFCT; r = 0.335, P < .001 for the left nasal choroid thickness). Right and left CMT measurements were significantly lower in women in comparison to men (right CMT=243.42 ± 22.81 vs 256.86 ± 20.39, P = .001; left CMT=242.45 ± 23.38 vs 258.33 ± 22.13, P < .001)

Table 5. The Comparison of the Chorioretinal Layer Measurements of Lithium and Valproic Acid Groups

	MS Group	n	Mean ± SD	F	*P*
Right nct	Lithium	26	253.73 ± 50.84	1.010	.367
	VPA	41	269.27 ± 50.96		
	Control	49	271.29 ± 55.69		
Right sfct	Lithium	26	295.96 ± 43.76	0.403	.669
	VPA	41	302.22 ± 43.60		
	Control	49	305.90 ± 48.17		
Right tct	Lithium	26	259.65 ± 45.26	1.032	.360
	VPA	41	274.51 ± 49.14		
	Control	49	275.67 ± 49.76		
Right RNFL	Lithium	26	90.42 ± 10.11	3.576	**.031***
	VPA	41	85.10 ± 12.80		
	Control	49	90.57 ± 8.18		
Right cmt	Lithium	26	254.23 ± 23.56	0.848	.431
	VPA	41	248.88 ± 24.05		
	Control	49	247.10 ± 21.10		
Right GCL	Lithium	26	75.96 ± 11.51	1.252	.290
	VPA	41	79.46 ± 5.84		
	Control	49	77.20 ± 10.38		
Left nct	Lithium	26	255.92 ± 51.86	1.795	.171
	VPA	41	267.61 ± 50.18		
	Control	49	278.29 ± 47.12		
Left sfct	Lithium	26	287.46 ± 54.97	1.355	.262
	VPA	41	296.63 ± 47.10		
	Control	49	306.29 ± 45.07		
Left tct	Lithium	26	257.08 ± 44.80	1.543	.218
	VPA	41	269.71 ± 45.89		
	Control	49	277.39 ± 50.52		
Left RNFL	Lithium	26	90.85 ± 11.62	7.318	**.001***
	VPA	41	83.78 ± 11.17		
	Control	49	91.49 ± 8.11		
Left cmt	Lithium	26	254.42 ± 21.83	0.824	.441
	VPA	41	249.27 ± 28.20		
	Control	49	246.92 ± 21.41		
Left GCL	Lithium	26	75.23 ± 11.22	0.913	.404
	VPA	41	78.44 ± 8.99		
	Control	49	77.88 ± 9.76		

Left RNFL [(Li-VPA=7.07 ± 2.53); P=.017), (Li-control=−0.64 ± 2.45); P=.991), (VPA-control=−7.71 ± 2.14); P=.01)]. Right RNFL [(Li-VPA=5.5.33 ± 2.62); P=.123), (Li-control=−0.15 ± 2.53; P=1.000), (VPA-control=−5.47 ± 2.21; P = .043)].
Cmt, centrale macular thickness; F, Fisher's constant; GCL, ganglion cell layer; MS, mood stabilizers; n, number; nct, nasal choroid thickness; *P*, confidence interval; RNFL, retinal nerve fiber layer; SD, standard deviation; sfct, subfoveal choroidal thickness; tct, temporale choroidal thickness; VPA, valproic acid.

DISCUSSION

As a result of this study, the RNFL thicknesses were measured to be thinner in the patient group than in the control group. No significant differences were detected between other chorioretinal measurements. The BD patients were divided into 3 groups, which were manic, depressive, and remission and were compared to the control group. As a

result of the literature review, we have concluded that, to the extent of our knowledge, this is one of the first studies that grouped patients according to their current episode, and there was no difference between the groups in terms of chorioretinal layer thicknesses. Moreover, the effects of MS medications used by the patients, namely Li and VPA, on neurodegenerative processes were also examined. While the RNFL thicknesses of the patients who are using Li showed similarities to the control group, it was determined that the RNFL thicknesses of the patients using VPA were thinner than both the Li group and the control group.

It was demonstrated as a result of the study that the BD patient group had significantly reduced thickness of RNFL than the control group. Examination of the literature on this subject indicates that the thinning of the RNFL is the clearest piece of information arising out of the SD-OCT studies on BD patients. As a matter of fact, this result was replicated in 8 of 9 studies.[12,13,15,21-25] The fact that RNFL thicknesses decrease in diseases such as AH, PH, MS, and schizophrenia was proven by many studies, and it is widely accepted that this thinning occurs due to neurodegenerative processes involved in the pathophysiology of these diseases.[9-11] The fact that RNFL thicknesses were reduced was demonstrated repeatedly supports the idea that neurodegeneration also plays a role in the pathophysiology of BD. No significant correlations were detected in the study between sociodemographic factors such as age and gender, factors such as the disease duration, the severity of symptoms, the current episode of the patient, and RNFL thickness. Previous SD-OCT studies have also demonstrated that there are no correlations between age, gender, disease severity, and RNFL thickness.[22,26] In a meta-analysis that included SD-OCT studies on BD and schizophrenia patients, it was reported that there was no significant relationship between RNFL thicknesses and sociodemographic, disease, and treatment-related factors.[27] In contrast to this study, there are also studies which have reported that RNFL thicknesses decrease as the duration of the disease increases.[13,21,24] As a matter of fact, it has been proposed that RNFL thickness decreases even in the first episode stage of BD patients, and because of this reason, RNFL thicknesses can be used in the early diagnosis of BD disease and in the follow-up of its progression.[21]

Another parameter that has been evaluated in this study was the GCL thickness. It has been determined as a result of the study that the GCL layer thicknesses of the patient and control groups were similar. However, in contrast to this study, some other studies have determined that GCL layer thicknesses in the BD patient group were significantly thinner in comparison to the control group.[12,13,22,28,29] In this study, the GCL thicknesses were measured as a single segment. However, in other studies, the GCL was evaluated by dividing it into many segments. Because of this segmentation, while certain segments have shown similar results in other studies, other segments have demonstrated significant differences. The reason why there are no significant differences between groups in our study may be related to the fact that only a single GCL measurement was taken. Total thickness may fail to demonstrate the whole picture in certain circumstances, and in-depth analyses, such as segmentation and the evaluation of certain layers in unison, may provide us with a more detailed picture.[13] As a result of the correlation analysis, no relationship was found between sociodemographic, disease and treatment data, and GCL thicknesses.

This study is one of the first studies which divided BD patients into 3 groups (manic, depressive, and remission) based on their current episode, and compared them with the control group. As a result of the study, no significant difference was found between the groups in terms of chorioretinal layer thickness. In conclusion, it can be argued that a patient's current episode does not have a significant effect on RNFL and other layer thicknesses. This result is similar to the results of Cokunlu et al.[29] Most of the previous studies were carried out without considering the current episode of the patients or solely on patients in remission. There is a possibility that inflammatory processes that progress during an acute episode may cause retinal layers to thicken, thereby masking the thinning of the RNFL and other layers.[30] This effect of inflammation made it difficult to interpret the results obtained from the studies that were performed. The results of this study can be interpreted as inflammation masking changes in chorioretinal layer thicknesses.

As a result of the comparison of the patients to the control group according to the type of MS that they are using (Li or VPA), it was determined that the RNFL thicknesses of the VPA group were lower in comparison to the Li group and the control group, and the Li group and the control group had similar measurements. According to these results, it might be stated that the usage of Li in BD is protective against the thinning that may occur in the retina. It has been put forward that the changes in the glycogen synthase kinase 3β (GSK-3β) levels observed in the white matter may be reflected in the retina.[31] In laboratory mice inflicted with BD via genetic modifications, the changes in the GSK-3β enzyme altered the retinal rod cell responses in electroretinography.[32] In 2 studies performed with individuals at high risk for the development of BD, it was determined that retinal rod cell b-wave amplitude was decreased and its latency was delayed.[33,34] Jin et al[35] examined the effects of Li and VPA on GSK-3β-mediated cell death in brain cells of laboratory mice.As a result, it has been demonstrated that Li decreases the number of cell deaths by inhibiting GSK-3β, while VPA has no effect on this enzyme and even triggers cell death. Lithium's neuroprotective effect on RNFL might occur via the inhibition of the pathway of GSK-3 on the retina.

Similar to this study, the study by Alıcı et al[23] compared the RNFL and GCL thicknesses of Li and VPA patients and determined that VPA patients had thinner RNFL and GCL thicknesses than Li patients. In their study on BD patients, Silverstone et al[36] demonstrated that the usage of Li increased the levels of N-acetyl aspartate, which has the effect of increasing neuronal vitality and functionality, while VPA did not cause such an increase.[36] In another study carried out by Bersani et al[37] on patients with BD, it was determined that Li patients had higher episodic memory and cognitive functions in comparison to the patients who are using other MS medications. It has been suggested that this neuroprotective effect is more prominent in the hippocampal region.[38] Another study compared the hippocampal volume of BD patients, both Li users and non-Li users, to a healthy control group. As a result, it was determined that, while the Li group had similar hippocampal volumes to the control group, the non-Li BD group had significantly lower volumes.[39] In a review performed by Galila et al,[40] it was indicated that a lower dose of Li was effective in treating MCI and AD-related dementia, and it slowed the progression of Huntington's disease. The studies presented above demonstrate Li's neuroprotective effects both in BD and in other neurodegenerative diseases. In this study, the fact that the Li group had similar RNFL measurements to the control group and had higher thicknesses than the VPA group supports Li's neuroprotective effects.

In contrast to this study, however, the study conducted by Kalenderoğlu et al[15] determined that the VPA group had higher RNFL thicknesses when compared to the Li and other MS groups.However, 32 of the participants in the study in question were VPA users, while 5 were Li users, and 6 were using other MS medications. The severe imbalance in the distribution of patients in terms of MS type may have caused a different result. In another SD-OCT study performed on BD patients, a positive correlation was detected between RNFL thickness and serum VPA levels. The results of the study of Keles-Altun et al[26] do not contradict the results of this study. According to these results, it might be suggested that the neuroprotective effects of VPA may only appear at higher dosages. However, since our study did not measure the serum levels of Li and VPA, it is not possible to perform a valid comparison.

In this study, no significant difference was found between the patient and control groups in terms of MT. While there were differences between the groups in terms of RNFL thicknesses, MT were measured to be similar. This may be due to the fact that, while the RNFL is only a single layer of the retina, the macula is the region that contains all layers of the retina. Any thinning that may have occurred in the RNFL in the macular region may be hidden by the simultaneous thickening of other layers. Similar to this study, no significant differences were detected between the groups in the only prior study which compared the MT of BD patients to healthy individuals.[26] As a matter of fact, in the meta-analysis of 12 studies carried out by Lizano et al,[27] which compared the chorioretinal thicknesses of schizophrenia and BD patients using SD-OCT, it was reported that there were no significant differences between patient and control groups in terms of MT. In the same meta-analysis, no significant relationship was demonstrated between clinical and sociodemographic factors and MT. However, in this study, MT in both eyes were found to be significantly thinner in women than in men. However, this piece of information needs to be re-evaluated in future studies.

No significant differences between the patient and control groups were detected in this study in terms of choroid thicknesses. Factors that may have an effect on choroidal thicknesses were taken into account while planning the study. Those who had systemic diseases that may affect choroid thicknesses were excluded from the study. Likewise, age and tobacco usage statuses were similar between the groups and no smoking was allowed in the 3 hours prior to the measurements. Additionally, all measurements were taken between 11:00 and 12:00 AM to avoid diurnal variations. Similar to this study, no significant differences were detected between patient and control groups in terms of choroid thicknesses in the previous 2 SD-OCT studies carried out on BD patients.[13,15] Likewise, in SD-OCT studies conducted on schizophrenia patients, no difference was found between the patient and control groups in terms of choroid thicknesses.[41] The reason for this may be the different structural characteristics of the retinal and choroidal layers. While the retina is comprised of the body, axon, and dendrites of the ganglion cells, approximately 70% of the choroid layer consists of blood vessels.[42] While RNFL thicknesses decrease in BD and schizophrenia patients compared to the control group, there may be no change in choroidal thickness due to this reason. Based on the findings of this study, as well as the findings of other studies based on BD and schizophrenia patients, it might be claimed that the choroid layer is not affected by neurodegenerative processes in these diseases.

Joe et al[43] compared the choroid layer thicknesses of a total of 6 schizophrenia and BD patients, all of whom were showing psychotic symptoms, to the data of 18 healthy individuals, and, in contrast to this study, a statistically insignificant thinning of the choroid layer thickness was observed in the patient group with psychotic symptoms. However, certain factors, such as SD-OCT imaging hours not being specified, the low number of patients, lack of detailed information regarding the eye examinations of the patients, and the thinning detected at the end of the study not being statistically significant decrease the reliability of the results of this study.

It was demonstrated that, in certain diseases that progress with neurodegeneration such as MCI, AD, and PD, the choroid layer is also affected by the process in question.[44-46]

This may be caused by the fact that pathophysiological mechanisms that cause neurodegeneration in schizophrenia and BD are different from those that do so in neurological diseases.[47,48] Moreover, diseases such as AD and PD are conditions that generally appear at very advanced ages and the studies carried out in this context indicate that the choroid thickness decreases by 2.98 µm each year.[49] Therefore, while the choroid thickness is being affected by diseases such as AD and PD, it may not be affected in diseases such as BD and schizophrenia. The fact that a negative correlation was detected between choroid thickness and age in this study is also supportive of this hypothesis. In the study, it was demonstrated that choroidal thickness decreased as the disease duration increased. This may be related to the fact that the disease duration increases as age increases. Similar relationships between choroid thickness and disease duration were detected in prior studies on BD and schizophrenia patients.[41] In contrast to this, however, in 2 studies evaluating choroid thicknesses in BD patients, no relationship was discovered between disease duration and choroid thickness.

Limitations

A factor which makes it difficult to interpret the results of this study is the fact that RNFL, GCL, and MT were calculated as a single measurement. In other studies, however, RNFL, GCL, and macula were divided into 8-9 segments to carry out an evaluation. The total thickness may not always allow the observation of pathologies. Dividing layers into segments or evaluating some layers in unison may be more effective in reflecting changes in the retina.[13]

In our study, 87% of the patients were using antipsychotic medications in addition to MS medications. Therefore, it is possible that the study results will be affected by antipsychotic medications. However, prior studies have reported that RNFL thinning observed in BD patients is independent of the use of antipsychotic medications or the type of antipsychotic that is used.[12,15]

This study has demonstrated that neurodegeneration plays a role in the etiopathogenesis of BD, that this neurodegeneration is being reflected in the SD-OCT measurements as a decrease in the thickness of RNFL, and that Li has a protective effect against the neurodegeneration that is reflected on the RNFL. Lithium might be considered an alternative agent in the treatment of diseases that progress with neurodegeneration. Retinal changes measured with SD-OCT can be used for the diagnosis and prognosis of BP and for evaluating responses to MS.

Ethics Committee Approval: This study was approved by Ethics Committee of Niğde Ömer Halisdemir University (Approval No: 2020/02-07, Date: March 2, 2020).

Informed Consent: Verbal andwritten informed consent was obtained from the patients who agreed to take part in the study.

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