Original article

Optical coherence tomography findings in conversion disorder: are there any differences in the etiopathogenesis of subtypes?

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Abstract

Background: Optical coherence tomography is a contactless and fast neuroimaging method. Previous Studies have observed thinning of the ganglion cell layer and inner plexiform layer in many neurodegenerative diseases. **Objective:** The aim of this study was to compare the layers of ganglion cell complex in conversion disorder. **Methods:** This study involved 50 conversion disorder patients and 50 healthy volunteers as the control. The parameters were measured and recorded automatically by a spectral optical coherence tomography device. **Results:** There was no difference in the retinal nerve fiber layers between the conversion disorder group and the control group ($p > 0.05$). The left and right choroid layer thickness acquired from three regions of the choroid layer was higher in patients compared with controls ($p < 0.05$). The ganglion cell layer and inner plexiform layer volumes were also significantly lower in the patient group ($p < 0.05$). **Discussion:** These ganglion cell layer and inner plexiform layer findings suggest that neurodegeneration occurs during the course of conversion disorder especially in subtype involved motor component. The choroid seems to be more related to the sensory component and it may be used to determine the active stage of the disease and to monitor inflammatory process like other inflammation markers used in systemic inflammatory diseases.

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Keywords: Conversion disorder, ganglion cell layer, inner plexiform layer, neuron degeneration, optical coherence tomography

Introduction

Conversion Disorder (CD) "involves unexplained symptoms or deficits affecting voluntary motor or sensory function" that cannot be attributed to an organic neurological cause. The symptoms of CD are thought to be generated unconsciously, arising from trauma, daily stressors, or conflict[1]. Symptoms suggest a medical condition with a behavioral presentation mimicking various types of neurological symptoms. 30% of neurological patients have neurological symptoms that cannot be explained medically[2]. The psychiatric approach to conversion movement disorder and the neurological approach to the psychogenic movement disorders are both problematic. Neither neurology nor psychiatry has yet made a clear interpretation of the possible mechanisms underlying this disorder. For this reason, a number of neurobiological and neuroimaging studies have been conducted in recent years to explain the etiopathogenesis of CD[3].

Cellular, molecular, and structural pathologies of the limbic regions, amygdala, thalamus, and their interactions with different motor areas have been most commonly studied. These studies indicate abnormalities outside the core motor network, including the prefrontal cortex and anterior cingulate cortex. The results support the hypothesis of abnormal inhibition of motor systems by limbic regions or impairments of motor conceptualization. In addition, reduced thalamic, caudate, basal ganglia, and lentiform nuclei volume, increased amygdala activation have been reported in the cases of the CD. The studies suggested that patients with CD have smaller mean volumes of the right and left basal ganglia and smaller right thalamus, with a trend toward to smaller left thalamus compared to healthy controls. It is emphasized that this reduction may be important in understanding the pathophysiology of the CD. Brain volume loss has been observed in patients with CD, and these findings suggest that neurodegeneration accompanies with CD[4]. Another device that can be used to evaluate neurodegeneration is optical coherence tomography.

Optical coherence tomography (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. The OCT method was first described by Fujimoto et al. from the Massachusetts Institute of Technology. Then, its use in ophthalmology and in neurology was described. 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 now possible. The RNFL involves axons of ganglion cells, the ganglion cell layer (GCL) involves bodies of ganglion cells, and the IPL involves dendrites of ganglion cells[5,6].

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. More recently, its use was expanded to neurodegenerative diseases because the retina is an anatomical extension of the brain, and retinal changes may occur in parallel with inflammation and CNS degeneration[7,8]. OCT has shown retinal changes in neurodegenerative diseases, such as multiple sclerosis[8], Alzheimer's disease[9], Parkinson's disease[10], and restless leg syndrome[11] which correlated with the severity of clinical disease. A demonstration of retinal neuronal loss using OCT provides great evidence for degeneration. Research on multiple sclerosis patients has repeatedly shown an association between retinal thinning and gray matter damage in the brain. Therefore, the thickness of the retinal layers has become an important anatomical parameter to track neurodegeneration[12].

More recently OCT was used to detect neuronal degeneration in psychiatric disorders. Using time domain OCT Cabezon *et al.*[13] reported a significant reduction in the overall and superior quadrant RNFL thickness in schizophrenia patients compared with controls. The Spatial resolution of OCT devices increased with new spectral

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domain OCT and this enabled separation of other retinal sublayers such as GCL and IPL was shown to have better structure-function correlation in neurodegenerative diseases such as multiple sclerosis then RNFL[14]. Our group demonstrated reduced GCL and IPL volumes in schizophrenia patients compared with controls using spectral OCT[15]. We also detected significant negative correlations between disease severity parameters and GCL and IPL volumes. In our another study, it is suggested that the neurodegeneration occurred during the course of bipolar disorder may be demonstrated by decreased GCL at early stages, and as the disease progresses, the involvement of other retinal layers, such as the RNFL and IPL, maybe observed[16]. Again, our research team demonstrated that OCT finding of decreased GCL and IPL volumes supports previous research suggesting degeneration in major depressive disorder. According to this study, considering RNFL to be the latest layer that will be affected during the course of degeneration, GCL and IPL volumes appear to be better parameters follow. In addition, choroid may be an important structure to detect acute attack period and to follow the inflammatory process in major depressive disorder like in systemic inflammatory diseases[17]. To the best of our knowledge, no study has assessed the OCT parameters (RNFL, GCL, IPL, and choroidal thickness) in patients with CD.

Although not a subtype classification based on Diagnostic and Statistical Manual of Mental Disorders (DSM), some authors preferred to distinguish conversion disorder according to symptoms[18-20]. In these studies, there was information that conversion symptoms may have emerged with different etiopathogenesis. Our hypothesis was that the symptoms of conversion disorder could be separated with the structures of eye. The aim of this study was to compare the RNFL, GCL, IPL, and choroidal thickness of patients with motor CD (M-CD, abnormal movements such as tremor, dystonia or weakness such as paraplegia) with somato-sensorial CD (SS-CD, represents the symptoms of sensory loss such as not seeing, not hearing) with sensori-motor CD (SM-CD) and controls to assess the usefulness the usefulness of these measurements to demonstrate neurodegeneration in CD.

Material and methods

Study sample

This case-control study compared patients with CD who were followed in the Psychiatry Department at our University Medical School with a control group. The patients with CD were consecutive patients who were being followed at our outpatient clinic at least for the last 6 months. The CD group consisted of 50 patients (10 males and 40 females). In terms of subtypes; there were 19 M-CD patients, 20 SS-CD patients, and 11 SM-CD patients. After being seen during the baseline visit by the treating psychiatrist, each patient's eligibility for the study was evaluated, and if they were eligible, they were invited to participate in the study. The control group consisted of 50 healthy volunteers without a history of a CD who were recruited from the hospital staff. OCT measurements were made in the Ophthalmology Department at our University Medical School. All OCT measurements were made between 10 am – 14 pm due to the operating time of the device. Local ethics committee approval was obtained, and all study participants provided written informed consent (Protocol Number: 2016/2-7).

Inclusion and exclusion criteria

Patients with CD who were between 18 and 65 years of age and who were diagnosed according to the DSM-IV-TR criteria[1] were included. Patients who had comorbid first axis diagnosis, hypertension, diabetes mellitus, severe neurological, 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 were examined in the ophthalmology clinic and best corrected visual acuity, intraocular pressure, slit lamb bio-microscopy, and fundus examination by eye dilatation was 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, immunological or systemic diseases which may affect the results.

OCT measurements

A spectral-OCT device (SpectralisTM OCT, Version 6.0, Heidelberg Engineering, Germany) was used to assess the RNFL and choroid thicknesses and GCL and IPL volumes in both eyes. The RNFL includes temporal (T), nasal (N), temporo-superior (TS), temporo-inferior (TI) and global (G) segments. Therefore, 7 measurements were made for each eye (i.e., N, NS, NI, T, TS, TI, G) (Figure 1).

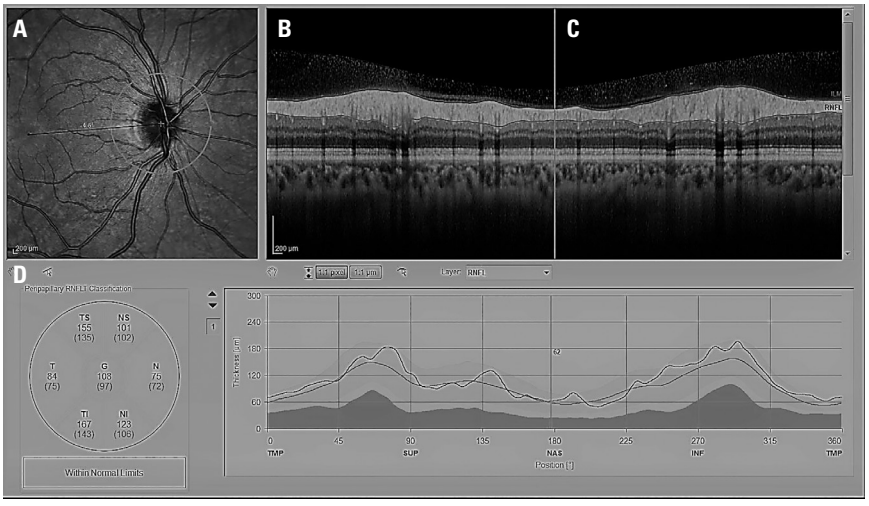

Figure 1. Measurement of RNFL thicknesses with spectral OCT.
A. The circle is drawn around the optic disc to measure peripapillary RNFL thickness. **B.** Demonstration of RNFL. **C.** Seven measurements are performed for each eye, providing the RNFL thickness of the TS, TI, T, NS, NI, N, and G sectors. **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.

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 (ASK) 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. Segmentation of the retina into 6 layers (GCL, IPL, RNFL, inner nuclear layer, outer plexiform layer, outer nuclear layer) was performed automatically with the device (Figure 2). Because the between-group comparisons provided similar results for the right and left eyes, only the results of the right eye are provided in the tables and discussed to decrease the complexity of the tables.

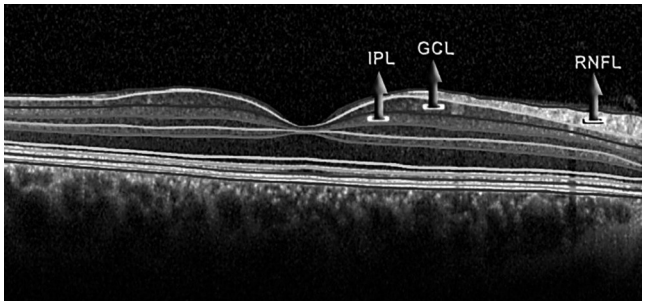

Figure 2. Measurement of the GCL and IPL thicknesses with spectral OCT. GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer; RNFL: Retinal Nerve Fiber Layer; OCT: Optical Coherence Tomography.

Statistical analyses

Statistical analyses were performed using SPSS 22.0 package program (IBM Corp). The mean ± standard deviation and percentages were used as descriptive statistics. The Chi^2 test was used to compare categorical variables. The normality of the data was tested using the Kolmogorov-Smirnov test. An independent samples t-test was used to compare 2 normally distributed variables and the Mann-Whitney U test was used to compare 2 non-normally distributed variables. ANOVA and post-hoc Tukey's B test were used to compare more than two normally distributed variables. The Kruskal-Wallis test was used to compare more than two non-normally distributed variables. $P < 0.05$ indicated statistical significance.

Results

Socio-demographic data

The mean patient ages in the CD group and control groups were 35.68 ± 12.03 and 37.96 ± 15.88 years, respectively and it was not significant ($p = 0.420$). The socio-demographic features of the patients and controls are shown in Table 1. There were no statistically significant differences between the groups, according to sex, marital status, and smoking. Education was significantly higher in the control group than in the patient group ($p < 0.05$). Occupation status was also significantly higher in the control group than in the patient group ($p < 0.05$). In the CD group, there were a family history in 9 (%18) patients and 41 (%82) not. The mean disease duration was 10.52 ± 9.10 in the CD group. Number of hospitalizations; none: 41 patients (%82), < 3: 6 (%12), and > 3: 3 (%6). When we divide the conversion patients into 3 subtypes according to the predominant symptom clusters. The number of M-CD patients was 19 (38%), the number of SS-CD patients were 20 (40%) and the number of SM-CD patients was 11 (22%).

OCT findings

When all the lower layers of RNFL were evaluated in both eyes; there was no difference in the RNFL layers between the CD group and the control group ($p > 0.05$) (Table 2).

The mean choroidal thickness, which is the mean value of the measurements from three regions, was significantly increased in the patients with CD compared with the controls ($p < 0.05$) (Table 2). The choroidal thickness of right eye in patients diagnosed with SS-CD was significantly higher than M-CD and SM-CD, but not significant for left eye's choroid thickness (Figure 3).

The GCL and IPL volumes were significantly decreased in the patients with CD compared with the controls ($p < 0.05$) (Table 3). We found significantly lower GCL and IPL volumes in M-CD and SM-CD patients ($p < 0.05$). But, GCL and IPL volumes were not significantly lower in SS-CD patients when compared with M-CD and SM-CD patients (Table 4). There was no a significant decrease in GCL and IPL volumes in SS-CD patients when compared with control group ($p < 0.05$) (Table 5) (Figure 4).

Discussion

We found 3 main findings in imaging studies done with OCT device in the CD patients. One of the most important findings of our study was the lower volume of GCL and IPL volumes in CD patients compared with the controls for both eyes. Somas of the ganglion cells form GCL, dendrites of ganglion cells form IPL, and their axons form RNFL[12,13]. So our finding implies degeneration in somas and dendrites of the neurons in the retina. Axonal degeneration can be responsible for decreases in the gray matter volume and also the thinning of the RNFL. Nerve axons in the retina make synapses at the mesencephalon, lateral geniculate nucleus, pretectum, and hypothalamus. We wanted to investigate the retina by OCT method to find clues for neurodegeneration. Because the retina is accepted as an extension of the brain by many anatomists due to the embryological development and cellular structure[7,21].

Table 1. Sociodemographic features of the patients and the control groups

	Patient		Control		P value
	N = 50	%	N = 50	%	
Sex					0.483
Male	10	20	14	28	
Female	40	80	36	72	
Education					**0.026**
No	5	10	5	10	
Primary school	21	42	7	14	
Secondary school	6	12	11	22	
High school	11	22	20	40	
University	7	14	7	14	
Occupation					**0.000**
No	17	34	18	36	
Worker	2	4	19	38	
Public servant	1	2	9	18	
Farmer	1	2	1	2	
Other (Housewife)	29	58	3	6	
Marital Status					0.641
Married	38	76	34	68	
Single	10	20	14	28	
Divorced	2	4	2	4	
Smoking					0.125
Yes	6	12	13	26	
No	44	88	37	74	

Table 2. Mean values for RNFL and choroid thickness

	Patients (Mean ± SD)	Controls (Mean ± SD)	P value
Right nasal superior/Left nasal superior	116,18 ± 23,51 µm/122,86 ± 27,91 µm	112,60±19,49 µm/124,88±20,43 µm	0.409/0.681
Right nasal inferior/Left nasal inferior	130,08 ± 23,40 µm/132,52 ± 25,24 µm	127,78 ± 27,32 µm/123,84 ± 27,11 µm	0,652/0.146
Right nasal/Left Nasal	84,40 ± 17,85 µm/83,28 ± 18,68 µm	83,54 ± 15,88 µm/78,02 ± 14,69 µm	0.800/0.121
Right temporal/Left temporal	72,86 ± 14,53 µm/71,54 ± 13,47 µm	75,34 ± 8,62 µm/73,348 ± 9,16 µm	0.302/0.402
Right temporal inferior/Left temporal inferior	147,60 ± 22,87 µm/149,12 ± 26,33 µm	154,70 ± 17,55 µm/154,24 ± 20,16 µm	0.085/0.278
Right temporal superior/Left temporal superior	145,52 ± 25,96 µm/144,68 ± 20,19 µm	145,76 ± 14,77 µm/146,78 ± 14,16 µm	0.955/0.548
Right global/Left global	106,32 ± 11,09 µm/106,94 ± 11,15 µm	107,32 ± 8,82 µm/106,92 ± 10,25 µm	0.619/ .993
Right choroid mean/Left choroid mean	310,60 ± 54,11 µm/298,90 ± 55,31 µm	249,16 ± 31,67 µm/247,66 ± 37,02 µm	**0.000/0.000**

RNFL: Retinal Nerve Fiber Layer, SD: Standard Deviation.

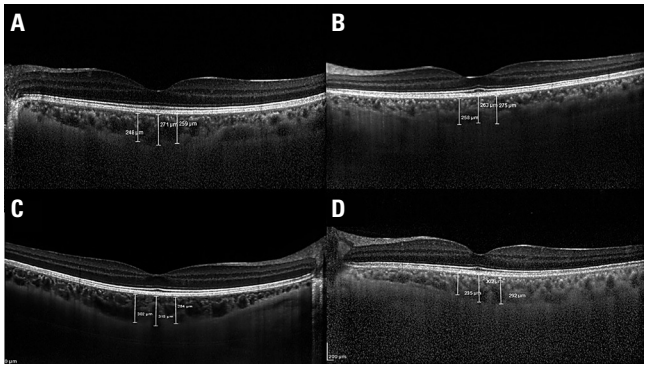

Figure 3. Comparison of choroidal thickness of CD subtypes.
Comparison of choroidal thickness of a patient with M CD (**A**), a patient with SM-CD (**B**), a patient with SS-CD (**C**), and a control (**D**) (CD: Conversion Disorder; M CD: Motor Conversion Disorder; SM-CD: Sensori-Motor Conversion Disorder; SS-CD: Somato-Sensorial Conversion Disorder).

In this study, we found a retinal nerve cell damage and neuronal degeneration in patients with CD. There are some studies that point to the findings of neurodegeneration in CD patients. Volumetric MR studies have found evidence for neurodegeneration in the brains of patients with CD[4]. Atmaca *et al.*[4] suggested that patients with CD have significantly smaller mean volumes of the left and right basal ganglia and smaller right thalamus, with a trend toward to smaller left thalamus compared to healthy controls. The demonstration of decreased activity in some areas of the brain in single photon emission computed tomography (SPECT) and functional magnetic resonance imaging studies is important in supporting neuropathological processes in the brain. In one of the studies related to cerebral blood flow, Czarnecki *et al.*[22] compared conversive tremor with essential tremor using SPECT at rest and during a tremor-inducing motor task (to bring a cup from a table to the face). During the motor task, patients with functional tremor had decreased regional cerebral blood flow in the ventromedial prefrontal cortex consistent with abnormalities of the default mode network, which were not observed in essential tremor. According to the study of Schrag *et al.*[23], psychogenic dystonia was associated with greater basal ganglia and cerebellar and decreased primary motor cortical blood flow, compared with healthy volunteers and patients with organic dystonia.

The second remarkable finding of our study is differences between subtypes of CD in terms of GCL and IPL. We found significantly lower GCL and IPL volumes in M-CD and SM-CD patients. But, GCL and IPL volumes were not significantly lower in SS-CD patients when compared with motor and SM-CD patients. There was no a significant decrease in GCL and IPL volumes in SS-CD patients when compared with control group. So; Neuronal degeneration in M-CD and SM-CD patients were found to be significantly higher than the control group, but no neuronal loss

Table 3. Mean GCL and IPL volumes of left and right eyes

	Patient (Mean ± SD)	Control (Mean ± SD)	P value
Right GCL	1.12 ± 0.99 µm	1.20 ± 0.47 µm	0.000
Left GCL	1.11 ± 0.97 µm	1.20 ± 0.47 µm	0.000
Right IPL	0.91 ± 0.73 µm	0.96 ± 0.50 µm	0.000
Left IPL	0.91 ± 0.75 µm	0.96 ± 0.50 µm	0.000

GCL: Ganglion Cell Layer, IPL: Inner Plexiform Layer, SD: Standard Deviation.

in SS-CD was found. This finding suggests that a more destructive etiopathogenesis is responsible for neuronal damage in the motor component dominant CD. Indeed, in the study of Voon *et al.*[24], some neurological findings were pointed out in CD patients with psychogenic movement disorder. The studies reveal abnormalities outside the core motor network, including the anterior cingulate cortex and prefrontal cortex. These findings support the hypothesis of impairments of motor conceptualization or abnormal inhibition of motor systems by limbic regions[25,26]. The result of all these studies suggests that neurological deficit is predominant in M-CD.

The third important finding of our study is changes in choroid thickness in CD patients. The choroid is one of the most vascularized tissues of the human body and it plays important roles in nutrition and oxygenation of outer retina, disposal of waste products out of retina and secretion of growth factors[27]. Choroid tissue is affected by any inflammatory or autoimmune conditions affecting blood flow. Research in some autoimmune diseases with retinal involvement (e.g. Behçet's disease) also demonstrated that choroid thickness increases during acute attack periods due to increased inflammation but then decreases with progressing disease[28]. We detected a significant increase in choroid thickness in CD patients who did not have any systemic disease that can disturb the vascular structure of affect blood flow when compared with. In addition, the choroidal thickness of right eye in patients diagnosed with SS-CD was significantly higher than M-CD and SM-CD, but not significant for left eye's choroid thickness. We suggest that an increase in choroid thickness results from the inflammatory process in the CD. Inflammatory process has been demonstrated in many psychiatric disorders such as obsessive compulsive disorder and depression. Because CD occurs in response to psychosocial stress, neural plasticity promises hope in explaining the effect of stress on brain[29]. One candidate mechanism that has been proposed as the site of possible flaw in signal transduction from monoamine receptors is the target gene for brain-derived neurotrophic factor. Deveci *et al.*[30] demonstrated that the serum BDNF level of the healthy control group was statistically higher than the level of the CD group. Inflammation in the central nervous system is known to cause glial degeneration and this process is blamed in the etiology of Alzheimer's disease, and Parkinson's disease. Studies in psychoneuroimmunology yielded strong evidence that the nervous and immune systems are in interaction reciprocally[31]. These intercorrections are mainly mediated by hormones, neural activations, and cytokines. Tiyekli *et al.*[32] suggested that lower TNF-α levels were found during acute conversion phase. They stated that stress associated with CD may suppress immune function in acute

Table 4. Comparison of GCL, IPL, and choroidal thickness in right and left eyes in conversion subtypes

	Subtypes (I)	Patient (Mean ± SD)	Subtypes (J)	Mean Difference (I-J)	P value
Right GCL	M-CD* (n = 19)	1.06 ± 0.42 µm	SS-CD	-0.14726	**0.000**
			SM-CD	-0.01254	0.645
	SS-CD* (n = 20)	1.21 ± 0.82 µm	M-CD	0.14418	**0.000**
			SM-CD	0.13777	**0.000**
	SM-CD* (n = 11)	1.07 ± 0.54 µm	SS-CD	-0.13473	**0.000**
			M-CD	0.01254	0.645
Left GCL	M-CD (n = 19)	1.05 ± 0.63 µm	SS-CD	-0.14418	**0.000**
			SM-CD	-0.00641	0.856
	SS-CD (n = 20)	1.20 ± 0.47 µm	M-CD	0.10242	**0.000**
			SM-CD	0.09491	**0.000**
	SM-CD (n = 11)	1.06 ± 0.12 µm	SS-CD	-0.13777	**0.000**
			M-CD	0.00641	0.856
Right IPL	M-CD (n = 19)	0.87 ± 0.65 µm	SS-CD	-0.10242	**0.000**
			SM-CD	-0.00751	0.724
	SS-CD (n = 20)	0.97 ± 0.21 µm	M-CD	0.09363	**0.000**
			SM-CD	0.09282	**0.000**
	SM-CD (n = 11)	0.87 ± 0.34 µm	SS-CD	-0.09491	**0.000**
			M-CD	0.00751	0.724
Left IPL	M-CD (n = 19)	0.87 ± 0.50 µm	SS-CD	-0.09363	**0.000**
			SM-CD	-0.00081	0.972
	SS-CD (n = 20)	0.97 ± 0.47 µm	M-CD	0.09363	**0.000**
			SM-CD	0.09282	**0.000**
	SM-CD (n = 11)	0.87 ± 0.50 µm	SS-CD	-0.09282	**0.000**
			M-CD	0.00081	0.972
Right Choroid	M-CD (n = 19)	288.94 ± 37.16 µm	SS-CD	-41,45263	**0.016**
			SM-CD	-23,05263	0.247
	SS-CD (n = 20)	330.40 ± 23.25 µm	M-CD	41,45263*	**0.016**
			SM-CD	18,40000	0.350
	SM-CD (n = 11)	312.00 ± 54.17 µm	SS-CD	-18,40000	0.350
			M-CD	23,05263	0.247
Left Choroid	M-CD (n = 19)	295.57 ± 57.34 µm	SS-CD	-7,92105	0.663
			SM-CD	-0.69378	0.974
	SS-CD (n = 20)	303.50 ± 32.74 µm	M-CD	7,92105	0.663
			SM-CD	7,22727	0.734
	SM-CD (n = 11)	296.27 ± 58.12 µm	SS-CD	-7,22727	0.734
			M-CD	0.69378	0.974

M-CD*: Motor Conversion Disorder; SS-CD*: Somato-Sensorial Conversion Disorder; SM-CD*: Sensori-Motor Conversion Disorder; SD: Standard Deviation; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer.

Table 5. Comparison of GCL and IPL Volumes of Somato-Sensorial Conversion Disorder Patients with Control Group

	SS-CD Patient (Mean ± SD)	Control (Mean ± SD)	P value
Right GCL	1.21 ± 0.54 µm	1.20 ± 0.47 µm	0.540
Left GCL	1.20 ± 0.97 µm	1.20 ± 0.47 µm	0.474
Right IPL	0.97 ± 0.52 µm	0.96 ± 0.50 µm	0.522
Left IPL	0.97 ± 0.60 µm	0.96 ± 0.50 µm	0.606

SS-CD: Somato-Sensorial Conversion Disorder; SD: Standard Deviation; GCL: Ganglion Cell Layer; IPL: Inner Plexiform Layer.

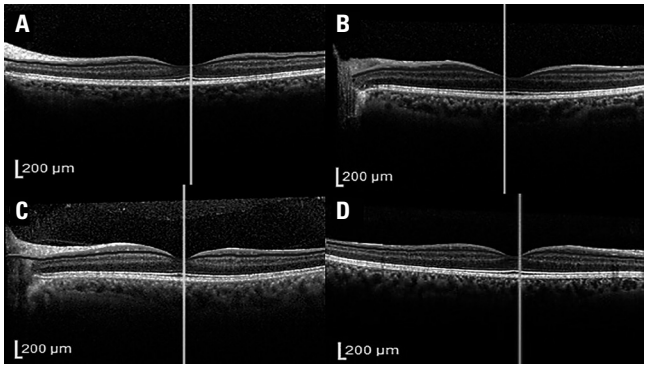

Figure 4. Comparison of GCL of CD subtypes.
Comparison of GCL volumes of a patient with M CD (A), a patient with SM-CD (B), a patient with SS-CD (C), and a control (D) (GCL: Ganglion Cell Layer; CD: Conversion Disorder; M CD: Motor Conversion Disorder; SM-CD: Sensori--Motor Conversion Disorder; SS-CD: Somato-Sensorial Conversion Disorder).

conversion phase and may have diagnostic and therapeutic value. We think that inflammatory process is active in patients with CD in symptomatic phase causing increased blood flow and increasing choroid thickness. Furthermore, the more significant increase in choroidal thickness in the somato-sensorial CD suggests that the inflammatory etiopathogenesis may play a more prominent role in the somato-sensorial subtype. The choroid thickening of the somato-sensorial CD and the direct retinal neuron damage of the motor CD and sensori-motor CD suggests the question of whether the subtypes differ in terms of etiopathogenesis. These results have led to the impression that the different clinical patterns of conversion disorder behave differently in terms of neurobiology. The cells involved in degeneration are mainly macrophages. Molecular inflammatory mediators such as cytokines, transcription factors, complement system, arachidonic acid metabolites, and oxidative stress parameters are also known to play a role in this mechanism[33]. Oxidative stress is mostly related to the increased formation of reactive oxygen and nitrogen species (ROS and RNS), which transmogrify the phospholipids and proteins leading to lipid peroxidation. These changes are considered to the change membrane permeability and configuration in addition to producing functional modification of various cellular proteins. Oxidative stress can cause to some cellular defects such as decreasing of the sarcolemmal Ca^{+2} ATP-ase pump and Na^{+}-K^{+} ATP-ase activities. These alterations lead to a decrease in the Ca^{+2} effluxes and an increase in the Ca^{+2} influxes, respectively. Oxidative stress has also been reported to suppress the sarcoplasmic reticulum Ca^{+2} ATP-ase pump and thus inhibits Ca^{+2} sequestration from the cytoplasm. ROS change the activity of Ca^{+2} regulatory mechanisms and this results in intracellular Ca^{+2} overload and cell death[34]. In these findings from different part of literature, somatic subtypes were thought to use more inflammatory processes, whereas motor subtypes were thought to use mechanisms that could lead to more direct neuronal damage. Though there is no significant difference in GCL and IPL volumes between the motor subtype and the sensori-motor subtype, the sensorimotor subtype was less affected than the motor type, suggesting that the thinning probably originated only from the motor component.

When all the lower layers of RNFL were evaluated in both eyes; there was no difference in the RNFL layers between the CD group and the control group. We have one possible explanation for this. Previous studies have found that RNFL damage can be detected by ophthalmologic examination only after 50% of the ganglion cells were damaged[35,36]. Therefore, RNFL damage may be expected to occur after more ganglion cell damage takes place. To detect such a process longitudinal studies should be performed in CD patients involving early-stage patients.

In conclusion, the findings of this study suggest that there is neuronal degeneration in CD and that it can be characterized by the thinning of the GCL and IPL. This thinning is more significant in CD patients involve motor component. Moreover, choroid may be used to determine the active stage of the disease and to monitor inflammatory process like other inflammation markers used in systemic inflammatory diseases.

Limitations

The major limitation of this study is its cross-sectional design. A prospective design starting from early periods of disease with regular follow-up OCT measurements would yield more convincing results about progressive degenerating nature of CD. There is a need for study that equals male and female subjects and control numbers. Another limitation of our study is lack of control measurements to increase validity and reliability of OCT to detect inflammation and degeneration. The 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 the utility of OCT as a tool in neuropsychiatric disorders. Separation of patients into subgroups is another limitation because there is no classification system, since it is connected to the psychiatrist. The OCT application time can be clearer. Deep chamber, thick lens and axial length parameters are considered to be able to influence the measurements made and their absence is considered as a limitation. The fact that the medical treatment of the patient group is not known clearly is a limitation of this study. Effects of psychotropic medications on OCT measurements has not been studied in detail previously. Direct effects of psychotropic medications on the retina cannot be excluded and this should be assessed in further studies.

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Conflict of Interest

The authors declare that they have no competing interest.

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References

1. American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders, 4th ed., Washington, DC: American Psychiatric Association [text revision].
2. Carson AJ, Ringbauer B, Stone J, McKenzie L, Warlow C, Sharpe M. Do medically unexplained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics. J Neurol Neurosurg Psychiatry. 2010;68:207-10.
3. Aybek S, Nicholson TR, O'Daly O, Zelaya F, Kanaan RA, David AS. Emotion-Motion Interactions in Conversion Disorder: An fMRI Study. PLoS ONE. 2015;10(4):e0123273.
4. Atmaca M, Aydin A, Tezcan E, Poyraz AK, Kara B. Volumetric investigation of brain regions in patients with conversion disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30:708-13.
5. Fujimoto JG. Optical coherence tomography for ultrahigh resolution in vivo imaging. Nat Biotechnol. 2003;21:1361-7.
6. Fujimoto JG, Hee MR, Huang D, et al. Principles of optical coherence tomography. In: Schuman JS, Puliafito CA, and Fujimoto JG, editors. Optical coherence tomography of ocular diseases. Thorofare, NJ: Slack Inc.; 2004. p. 3-20.
7. Schönfeldt-Lecuona C, Kregel T, Schmidt A, Pinkhardt EH, Lauda F, Kassubek J, et al. From imaging the brain to imaging the retina: optic coherence tomography in schizophrenia. Schizophr Bull. 2016;42(1):9-14.
8. Saidha S, Syc SB, Ibrahim MA, Eckstein C, Warner CV, Farrel SK, et al. Primary retinal pathology in multiple sclerosis as detected by optical coherence tomography. Brain. 2011;134:518-33.
9. He XF, Liu YT, Peng C, Zhang F, Zhuang S, Zhang JS. Optical coherence tomography assessed retinal nerve fiber layer thickness in patients with Alzheimer's disease: a meta-analysis. Int J Ophthalmol. 2012;5:401-5.
10. Cetin EN, Bir LS, Sarac G, Yaldizkaya F, Yaylali V. Optic disc and retinal nerve fibre layer changes in Parkinson's disease. J Neuroophthalmol. 2013;37:20-3.
11. Tak AZA, Celik M, Kalenderoglu A, Saglam S, Altun Y, Gedik E. Evaluation of optical coherence tomography results and cognitive functions in patients with restless legs syndrome. Arch Neuropsychiatry. DOI:10.5152/npa.2017.21598.
12. Saidha S, Al-Louzi O, Ratchford JN, Bhargava P, Oh J, Newsome SD, et al. Optical coherence tomography reflects brain atrophy in multiple sclerosis: a four-year study. Ann Neurol. 2015;78(5):801-3.

13. Cabezon L, Ascaso FJ, Ramiro P, Quintanilla MA, Gutieerrez L, Lobo A, et al. Optical coherence tomography: a window into the brain of schizophrenic patients. Acta Ophthalmol. 2012;90:0.
14. Saidha S, Syc SB, Durbin MK, Eckstein C, Oakley JD, Meyer SA, et al. Visual dysfunction in multiple sclerosis correlates better with optical coherence tomography derived estimates of macular ganglion cell layer thickness than peripapillary retinal nerve fiber layer thickness. Mult Scler. 2011;17(12):1449-63.
15. Celik M, Kalenderoglu A, Sevgi-Karadag A, Egilmez OB, Han-Almis B. Decreases in ganglion cell layer and inner plexiform layer volumes correlate better with disease severity in schizophrenia patients than retinal nerve fiber layer thickness: findings from spectral optic coherence tomography. Eur Psychiatry. 2016;19(32):9-15.
16. Kalenderoglu A, Sevgi-Karadag A, Celik M, Egilmez OB, Han-Almis B, Ozen ME. Can the retinal ganglion cell layer (GCL) volume be a new marker to detect neurodegeneration in bipolar disorder? Compr Psychiatry. 2016;67:66-72.
17. Kalenderoglu A, Celik M, Sevgi-Karadag A, Egilmez OB. Optic coherence tomography shows inflammation and degeneration in major depressive disorder patients correlated with disease severity. J Affect Disord. 2016;204:159-65.
18. Scott RL, Anson JG. Neural correlates of motor conversion disorder. Motor Control. 2009;13(2):161-84.
19. Stone J, Carson A, Aditya H, Prescott R, Zaubi M, Warlow C, et al. The role of physical injury in motor and sensory conversion symptoms: a systematic and narrative review. J Psychosom Res. 2009;66(5):383-90.
20. Watanabe T, Akiyama K. Conversion disorder with sensory symptom or defect. Ryoikibetsu Shokogun Shirizu. 2003;38:515-8.
21. Bora E, Fornito A, Pantelis C, Yucel M. Gray matter abnormalities in major depressive disorder: a meta analysis of voxel based morphometry studies. J Affect Disord. 2012;138:9-18.
22. Czarnecki K, Jones DT, Burnett MS, Mullan B, Matsumoto JY. SPECT perfusion patterns distinguish psychogenic from essential tremor. Parkinsonism Relat Disord. 2011;17:328-32.
23. Schrag AE, Mehta AR, Bhatia KP, Brown RJ, Frackowiak RS, Trimble MR, et al. The functional neuroimaging correlates of psychogenic versus organic dystonia. Brain. 2013;136:770-81.
24. Voon V, Cavanna AE, Coburn K, Sampson S, Reeve A, LaFrance WC Jr. Functional neuroanatomy and neurophysiology of functional neurological disorders (Conversion disorder). J Neuropsychiatry Clin Neurosci. 2016;28(3):168-90.
25. Burgmer M, Konrad C, Jansen A, Kugel H, Sommer J, Heindel W, et al. Abnormal brain activation during movement observation in patients with conversion paralysis. Neuroimage. 2006;29:1336-43.
26. Ward NS, Oakley DA, Frackowiak RS, Halligan PW. Differential brain activations during intentionally simulated and subjectively experienced paralysis. Cogn Neuropsychiatry. 2003;8:295-312.
27. Parver LM. Temperature modulating action of choroidal blood flow. Eye (Lond). 1991;5:181-5.
28. Coskun E, Gurler B, Pehlivan Y, Kisacik B, Okumus S, Yayuspayi R, et al. Enhanced depth imaging optical coherence tomography findings in Behcet disease. Ocul Immunol Inflamm. 2013;3:1-6.
29. Maes M. The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression. Neuro Endocrinol Lett. 2008;29:287-91.
30. Deveci A, Aydemir O, Taskin O, Taneli F, Esen-Danaci A. Serum brain-derived neurotrophic factor levels in conversion disorder: Comparative study with depression. Psychiatry Clin Neurosci. 2007;61:571-3.
31. Irwin MR. Human psychoneuroimmunology: 20 years of discovery. Brain Behav Immun. 2008;22:129-39.
32. Tiyekli UC¸ Aliyurt O, Tiyekli ND. Proinflammatory cytokine levels in patients with conversion disorder. Acta Neuropsychaitr. 2013;25(3):137-43.
33. Cámara-Lemarroy CR, Guzmán-de la Garza FJ, Fernández-Garza NE. Molecular inflammatory mediators in peripheral nerve degeneration and regeneration. Neuroimmunomodulation. 2010;17(5):314-24.
34. Parlakpinar H, Orum MH, Sagir M. Pathophysiology of myocardial ischemia reperfusion injury: A review. Medicine Science. 2013;2(4):935-54.
35. Honrubia F, Calonge B. Evaluation of the nerve fiber layer and peripapillary atrophy in ocular hypertension. Int Ophthalmol. 1989;13:57-62.
36. Quigley HA, Addicks EM. Quantitative studies of retinal nerve fiber layer defects. Arch Ophthalmol. 1982;100:807-14.