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Original Article

Choroid and Retinal Effects of Epilepsy and Epilepsy Subgroups

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Abstract

Objectives: The objective were to evaluate structural alterations in the retina and choroid tissue of epilepsy patients and subtypes using enhanced depth imaging optic coherence tomography (EDI-OCT).

Methods: 46 epilepsy patients and 50 sex- and age-matched control patients were analyzed in the study. Patients' epilepsy types were recorded. The central macular thickness (CMT), retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and choroidal thickness (CT) were investigated through the Spectralis-OCT device (SD-OCT). Image-J program was used to calculate the total choroidal area (TCA), the luminal area (LA), stromal area (SA), and the choroidal vascularity index (CVI).

Results: CMT, TCA, LA, and SA outcomes were substantially reduced in epilepsy patients than in healthy controls. There was no significant difference between CT, RNFL, GCL, CVI results. There were no statistically significant differences between patients with partial and generalized epilepsy ($p>0.05$ for each).

Conclusion: According to the results of our study, epilepsy disease has effects on the posterior segment of the eye. To the best of our knowledge, our study is the first to evaluate CVI in patients with epilepsy and the epilepsy subgroups.

Keywords: Choroidal thickness, choroidal vascular index, epilepsy, generalized epilepsy, partial epilepsy, retinal nerve fiber layer.

Introduction

Epilepsy is a chronic disease that causes recurrent, unprovaked seizures. Within the brain, structural and cognitive loss both occur (1). There is a significant variance in the age and geographic distribution of epilepsy. For people over 20 years of age, 1% of the population is impacted (2). There are two main clinically identified types of epilepsy: focal and nonfocal epilepsy (3). Epilepsy is known to cause cognitive impairment, learning difficulties, and behavior problems. Although it is believed that the number, duration, and severity of seizures influence the extent of damage, the precise cause of brain volume loss in epileptic patients remains unknown (4).

Due to the retina's morphological, embryological, and physiological similarities to the brain, optical coherence tomography (OCT) analysis of the retina and optic nerves offers a window into the brain (5). OCT is a practical and noninvasive tool that helps us to evaluate neuronal and axonal loss (6). Numerous neurodegenerative conditions, such as multiple sclerosis, neuromyelitis optica, Parkinson's disease, and Alzheimer's disease, have been evaluated with OCT

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(7). In epilepsy, studies utilizing magnetic resonance imaging have disclosed extensive brain atrophy unrelated to seizure history, antiepileptic drug treatment, or epileptic focus. Considered a network disorder, epilepsy is characterized by extensive neuronal loss (8,9). Due to this, an OCT imaging investigation in epilepsy patients can reveal the retinal alterations caused by the disease.

In recent years, enhanced depth imaging-OCT (EDI-OCT) has been used to identify deep ocular structures such as the choroid. The choroidal vascularity index (CVI) is a novel evaluation tool for choroidal vasculature health. It is calculated using data acquired after image binarization and is defined as the ratio of the luminal area (LA) to the total choroidal area (TCA) (10). In numerous neurodegenerative illnesses, CVI calculation has been performed in previously published studies (11-13).

When reviewing the literature, we could not find any research about CVI in epilepsy patients. In this study, we aimed to compare CT, CVI, retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), and central macular thicknesses (CMT) of epilepsy patients with healthy controls of similar age and gender, using EDI-OCT. We also analyzed the outcomes of epilepsy patients in two subgroups generalized epilepsy and partial epilepsy. This is the first study to evaluate CVI in epilepsy patients and subgroups, as far as we are aware.

Methods

This observational and prospective study was performed at the Ophthalmology and Neurology Clinics of Sultan Abdülhamid Han Training and Research Hospital. 46 patients with epilepsy and 50 healthy controls were included. 23 of the epilepsy patients were diagnosed with generalized epilepsy and 23 of them with partial epilepsy. The study was authorized by the Human Research Ethics Committee at Haydarpaşa Numune Training and Research Hospital (HNEAH-KAEK 2022/KK139) and conducted in accordance with the Declaration of Helsinki. Before inclusion, we received informed and written consent from all individuals.

All subjects were examined between July 2022 and January 2023. A specialist neurologist working in the neurology clinic of our hospital diagnosed epilepsy patients. To exclude the effects of the drugs used in the treatment on the retina and choroid, patients with epilepsy diagnosed in the past 3 months were included in the study.

Our control group consisted of 50 patients of age and gender similar to the study group, who applied to the Ophthalmology Outpatient Clinic of Sultan Abdülhamid Han Training and Research Hospital for routine eye examination and did not have any neurological disease.

Complete ophthalmologic and neurological exams were performed on all individuals. All patients' detailed anamneses were noted. Slit-lamp biomicroscopic examinations, measurements of intraocular pressure (IOP), fundus examinations, and best-corrected visual acuity (BCVA) using a Snellen chart were all evaluated. To avoid the effects of diurnal variation, all evaluations were conducted between 10:00 AM and 12:00 PM. The individuals' only right eye was analyzed for statistical analysis.

All patients included in the study had refraction values within the range of +4/-4 diopters, IOPs below 21 mmHg, and BCVAs above 6/10. Patients with a history of ocular trauma, intraocular surgery, ocular laser, glaucoma, retinal disease, and ocular surface problems were excluded from the study across all categories.

Only patients between the ages of 18 and 55 were included in the study. Patients having a diagnosis of pregnancy, under medication for hypertension essential, diabetes mellitus, cardiovascular illness, or renal disease and smokers that could alter the vessel diameter in the choroid tissue were excluded from the study. Participants with other neurological diseases were excluded from the epilepsy group. Patients in the control group had no diagnosis of neurological illness. The medications and types of epilepsy in the epilepsy group were recorded.

CMT, CT, and RNFL were measured using the spectral-domain Heidelberg Spectralis OCT-instrument, (SD-OCT; Heidelberg Engineering, Heidelberg, Germany). To prevent bias, all scans were conducted by the same trained operator. After pupillary dilation, all OCT images were scanned in conditions of equal illumination. In addition, each scan included an internal fixation target and a visual tracking system that operated in real time.

To evaluate the CMT with OCT, the Retina application mode was selected. The CMT was automatically estimated by the OCT program The device's glaucoma application mode was used to calculate RNFL. This software provided a thickness profile for the temporal-superior-nasal-inferior temporal regions of the standard 12° circular scan, and the average thickness values were used for statistical analysis. To manually estimate the measurement of the choroid layer, horizontal B-scans were acquired on vertical lines extending from the outer retinal pigment epithelial border to the choroidoscleral junction using the Heidelberg Spectralis OCT software. Five locations in the subfoveal region, the fovea at 500 µm and 1500 µm in the nasal and temporal orientations were used to obtain measurements.

The choroidal region of the SD-OCT scan was binarized using Image J. Niblack's auto-local threshold technique was then utilized to distinguish between the luminal or vascular area (LA) and the stromal or interstitial area (SA). Each image's CVI was then measured. CVI is defined as the ratio of the LA to the choroidal area (Fig. 1).

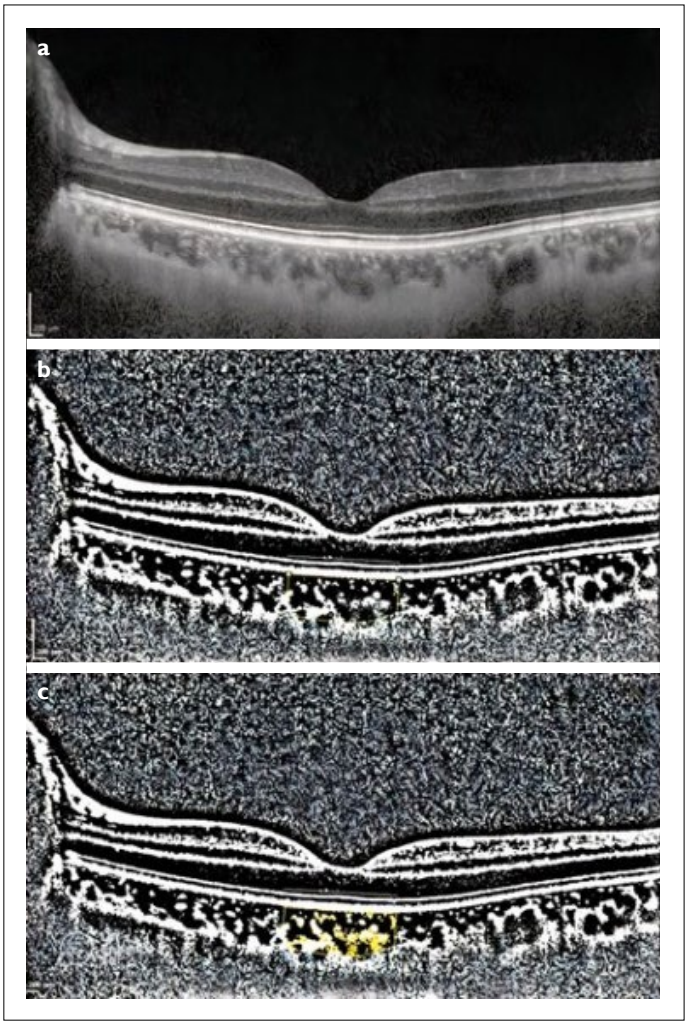

Figure 1. CVI calculation with EDI-OCT image binarization **(a)** EDI-OCT image of a patient. **(b)** The image was binarized using the auto-local threshold from Niblack. **(c)** The color threshold tool was used to select the dark pixels, representing the liminal area (yellow lines). Calculating the CVI involves dividing the luminal area by the total choroidal area.

Statistical Analysis

Statistical analysis was performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). In descriptive analyses, normally distributed variables are presented with means and standard deviations. Using the Kolmogorov–Smirnov and Shapiro–Wilk tests, the normality of the data distribution was analyzed. In group evaluations, non-parametric (Kruskal–Wallis test) tests were utilized when at least one variable exhibited a normal distribution within the groups, while parametric (analysis of variance) tests were utilized when all groups were normally distributed. A $p<0.05$ was statistically significant.

Results

This investigation included 46 epilepsy patients and 50 healthy participants. 23 patients in the epilepsy group had generalized epilepsy, whereas 23 had partial epilepsy. While there were 23 males (50%) and 23 females (50%) in the epilepsy group, there were 22 males (44.0%) and 28 females (56.0%) in the control group. The mean age was 31.28±10.9 (range 19–55 years) in the epilepsy group and 31.6±8.7 years (range 18–48) in the controls. There was no statistically significant difference between the groups in terms of mean age and gender ($p>0.05$) (Table 1).

While the CMT value was 221.87±21.8 µm in epilepsy patients, it was 254.5±28.3 µm in the control group. According to these findings, the epilepsy group had significantly thinner CMT than the control group (p=0.0001**).

In the epilepsy group, the mean RNFL thickness was 96.59±7.9 µm, whereas in the control group it was calculated 98.84±9.8 µm. According to the results, the average RNFL thickness of epilepsy patients was found to be thinner, but this lowerness was not statistically significant (p=0.219).

TCA outcome in the epilepsy group was 1.18±0.25 mm^2, and it was 3.87±2.63 mm^2 in the control group. TCA result was significantly lower in epilepsy patients (p=0.001*). In the epilepsy group, the LA result was 0.79±0.15 mm^2, when compared to the control group it was 1.01±0.32 mm^2; in the epilepsy group, the SA result was 0.38±0.12 mm^2, while in the control group, it was 2.77±2.63 mm^2. Both results indicate that the mean values of LA and SA in patients with epilepsy were significantly smaller than the control group (p=0.0001**, p=0.016*, respectively).

Five-point CT measurements, GCL thickness, and CVI measurements show no statistically significant differences ($p>0.05$ for each) (Table 2).

When comparing the findings of subgroups of epilepsy, there were no significant differences between patients with partial and generalized epilepsy ($p>0.05$ for each) (Table 3).

Table 1. Demographic characteristics of participants

	Epilepsy group (n=46)	Control group (n=50)	p
Gender (n)			
Male	n=23 (50%)	n=22 (44.0%)	0.556
Female	n=23 (50%)	n=28 (56.0%)	
Age			
Mean±SD	31.28±10.9	31.6±8.7	0.495
Range	(19–55)	(18–48)	

SD: Standard deviation.

Table 2. Structural OCT parameters in the study groups

	Epilepsy Group (n=46)	Control Group (n=50)	p
Mean RNFL Thickness (μm)	96.59±7.9 (82–114)	98.84±9.8 (74–120)	0.219
CMT (μm)	221.87±21.8 (184–269)	254.5±28.3 (197–318)	0.0001**
GCL (μm)	15.33±4.9 (6–28)	16.1±4.6 (7–27)	0.423
The CT of the point 500 μm temporal to the fovea (μm)	341.22±77.5 (209–542)	352.88±105 (164–561)	0.535
The CT of the point 1500 μm Temporal to the fovea (μm)	322.8±80.2 (146–503)	343.06±94.5 (151–544)	0.262
The subfoveal CT (μm)	349.83±73.7 (223–494)	363.38±110.7 (150–554)	0.479
The CT of the point 500 μm nasal to the fovea (μm)	337.48± 79.2 (193–518)	351.12±107 (140–555)	0.483
The CT of the point 1500 μm nasal to the fovea (μm)	280.72± 85 (131–465)	299.84±103.3 (111–527)	0.327
TCA (mm^2)	1.18± 0.25 (0.71–1.76)	3.87± 2.63 (0.62–3.86)	0.001**
LA (mm^2)	0.79±0.15 (0.49–1.15)	1.01±0.32 (0.45–1.70)	0.0001**
SA (mm^2)	0.38±0.12 (0.20–0.94)	2.77±2.63 (1.59–3.86)	0.016*
CVI (%)	0.68±0.04 (0.46–0.76)	0.68±0.11 (0.58–0.88)	0.74

Discussion

This study's objective was to investigate differences in CT, CVI, CMT, RNFL, and GCL thickness in epilepsy patients and epilepsy subgroups. The outcomes of 47 patients with epilepsy (n=23 with generalized epilepsy and n=24 with partial epilepsy) and 50 age- and sex-matched healthy controls were compared. The CMT, TCA, LA, and SA of epilepsy patients were substantially lower compared to the controls. When comparing the two subgroups, generalized and partial epilepsy, we found no statistically significant differences. As far as we are aware, this is the first study to compare CVI in patients with epilepsy and epilepsy subgroups.

There are few studies that investigate retinal changes in epilepsy patients. In these studies, epilepsy patients presented retinal changes related to neurodegeneration and drug use. In one of these studies, which was published by Balestrini et al., significant thinning of average RNFL thickness in epilepsy patients has been reported (14). Their hypothesis was thinner; RNFL is associated with longer epilepsy duration, drug resistance, and intellectual disability. In a different study, Gonzalez de la Aleja et al. found that the superior and inferior quadrant RNFL results of patients with genetic generalized epilepsy were thinner than the control group (15). Furthermore, another research made by Bayraktar Bilen et al. supports these results. They found the median and superior quadrant RNFL thickness outcomes of epilepsy patients were substantially lower (16). They hypothesized that these findings directly relate to neurodegeneration in epilepsy. To demonstrate whether RNFL decreasing in epilepsy reflects neurodegeneration, however, a longitudinal study estimated progressive RNFL thinning as a function of time is required. In this current study, although the mean RNFL thickness was found to

Table 3. Structural OCT parameters in epilepsy subgroups

	Generalized epilepsy subgroup (n=23)	Partial epilepsy subgroup (n=23)	p
Mean RNFL thickness (μm)	98.3±8.5 (83–113)	94.87±7.1 (82–114)	0.143
CMT (μm)	215.96±19.7 (184–256)	227.78±22.6 (190–269)	0.066
GCL (μm)	14.39±4.7 (6–23)	16.26±5 (9–28)	0.195
The CT of the point 500 μm temporal to the fovea (μm)	340.35±91.8 (209–498)	342.09±62.1 (253–542)	0.801
The CT of the point 1500 μm Temporal to the fovea (μm)	321.52±75.9 (208–474)	324.09±85.8 (146–503)	0.915
The subfoveal CT (μm)	343.35±78.9 (223–494)	356.3±69.4 (266–494)	0.557
The CT of the point 500 μm nasal to the fovea (μm)	331.13±85.3 (193–518)	343.83±74 (209–485)	0.592
The CT of the point 1500 μm nasal to the fovea (μm)	278.48±87.6 (131–465)	282.96±84.1 (155–432)	0.86
TCA (mm^2)	1.16±0.22 (0.85–1.76)	1.19±0.27 (0.71–1.75)	0.731
LA (mm^2)	0.79±0.14 (0.62–1.15)	0.79±0.17 (0.49–1.12)	0.767
CVI (%)	0.68±0.03 (0.63–0.74)	0.67±0.06 (0.46–0.76)	0.782
SA (mm^2)	0.37±0.08 (0.22–0.60)	0.38±0.14 (0.20–0.94)	0.621

be lower in the epilepsy group compared to the control group, no statistically significant difference was observed. This result may have been achieved because, in our study group, there were no drug-resistant epilepsy patients and no patients with mental retardation.

The CMT of epilepsy patients was found to be substantially thinner than the control group in our study. The findings of the Gomceli et al.'s study also support our results (17). The patients' CMT was significantly reduced in both eyes, according to their findings. In the study by Bayraktar Bilen et al., it was observed that the CMT of patients taking multiple antiepileptics was lower than patients who were taking a single antiepileptic (16). They claim that neurodegeneration in epilepsy patients with drug-resistant seizures is more frequent in polytherapy patients than in non-resistant patients. As a consequence, CMT reduction supports the neurodegeneration theory in epilepsy patients.

When analyzing the studies on choroidal thickness (CT) in epilepsy patients, Tak et al. found that CT in epilepsy patients was significantly increased (18). In the study of Gomceli et al., CT was measured to be higher in the juvenile myoclonic epilepsy group associated with photoparoxysmal response compared to juvenile myoclonic epilepsy without photoparoxysmal response group (17). Higher CT was found to be associated with neuroinflammation in epilepsy patients.

In another research, adolescents diagnosed with genetic generalized epilepsy were included in the study to see the effects of valproic acid on the retina. The CT results of newly diagnosed patients and patients using valproic acid for at least 1 year did not differ significantly (19).

In our study, no statistically significant difference was found between the epilepsy patients and the control group in the measurements made from the 5 points of the choroid.

There are few studies that calculate CVI in neurological diseases such as multiple sclerosis, migraine (12,20,21). In these studies, CVI was found to be reduced in migraine and multiple sclerosis patients. This result was thought to be due to neurodegeneration. Our research is the first one to calculate CVI in patients with epilepsy. In this current study, TCA, LA, and SA mean values were lower compared to the control group, while CVI values did not reach a statistically significant difference. Despite the CVI values were not lower, these findings provide further evidence in favor of the hypothesis that neurodegeneration is the underlying cause of epilepsy.

Several limitations exist in this study. There are few epilepsy patients who meet our inclusion criteria. In addition, long-term follow-up of the same patient group may give us solid clues about the hypothesis of neurodegeneration in the etiopathogenesis of the disease.

Conclusion

This current study showed that the mean CMT, TCA, LA, and SA values of epilepsy patients were found to be significantly lower. OCT may be used as a useful instrument for measuring and monitoring neurodegeneration in epilepsy. To evaluate the pathophysiology of the epileptic process in retina and choroid, further research is required.

Disclosures

Ethics Committee Approval: The study was authorized by the Human Research Ethics Committee at Haydarpaşa Numune Training and Research Hospital (HNEAH-KAEK 2022/KK139) and conducted in accordance with the Declaration of Helsinki.

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Conflict of Interest: None declared.

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