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Comparison of optic coherence tomography results in patients with diagnosed epilepsy: Findings in favor of neurodegeneration☆,☆☆

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ABSTRACT

Background: Epilepsy is a chronic neurological disease characterized with recurrent seizures. Progressive neuronal degeneration is a common consequence of long-term and/or recurrent seizure activity in epilepsy. Optical coherence tomography (OCT) is a new medical imaging technique that displays biological tissue layers as high-resolution tomographic sections. The aim of our study was to evaluate OCT findings in patients with epilepsy and to compare OCT findings in terms of disease duration, presence of status, seizure frequency, and drug use.
Methods: Forty-three patients who had epilepsy according to the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) in 2010 and 40 healthy controls were recruited for the study. Disease duration, seizure frequency, status history, and multiple drug use were noted. Retinal nerve fiber layer (RNLF), ganglion cell layer (GCL), inner-plexiform layer (IPL), and choroid thinning were analyzed by using spectral OCT.
Results: The mean RNFL values are 101.48 ± 11.33 in the patient group and 108.76 ± 8.37 in the control group ($p = 0.001$). The mean GCL thickness values in the patient and control groups are 1.14 ± 0.12 and 1.22 ± 0.05, ($p < 0.001$). The mean IPL thickness is 0.93 ± 0.09 in the patient group and 0.97 ± 0.05 in the control group ($p = 0.02$). Choroid thickness is significantly increased in the patient group ($p < 0.001$).
Conclusions: Demonstration of RNFL, IPL, and GCL thinning might indicate neurodegeneration, and choroid thickening indicates neuroinflammation. We found no association between disease duration, seizure frequency, status history, and multiple drug use and OCT parameters. Further studies with larger patient groups should clarify the matter.

1. Introduction

Epilepsy is a chronic neurological disease that is commonly seen worldwide, characterized with recurrent seizures occurring as a result of excessive electrical discharges in a group of brain cells. Seizures are characterized by brief episodes involving a part of or the entire body and occasionally may be accompanied by loss of consciousness or involuntary loss of control over bowel or bladder. Epilepsy can be classified into two main clinically defined categories: focal and nonfocal epilepsy [1]. Epilepsy shows a wide range of age and geographic distribution. It affects 1% of the world population for those over 20 years of age and 3% of the population for those over 75 years of age [2]. New onset cases usually occur in infants and the elderly in developed countries and in children and young adults in developing countries [3]. Established risk factors for epilepsy are classified into two main categories as inherited and acquired risk factors; however, the cause is not known in some cases [4]. Progressive neuronal degeneration is a common consequence of long-term and/or recurrent seizure activity in epilepsy, and it is suggested to occur as a result of calcium overload caused by glutamate-mediated excitotoxicity or activation of proapoptotic molecular cascade. Excitotoxicity activates proapoptotic pathways. Hypoxia and local hypoxia may contribute to ictal neurodegeneration [5]. Additionally, accumulating evidence suggest that chronic use of antiepileptic drugs (AEDs) such as valproic acid, phenytoin, and carbamazepine may increase production of free radicals and consequently oxidative damage in neurons [6]. Status epilepticus (SE) is a medical emergency characterized tonic–clonic seizures, which is defined as seizure activity lasting 5 min or more or a series of seizures without

☆ The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and was approved by the Ethical Committee of the Adıyaman University Hospital. Informed consent was obtained from the participants after the nature of the procedures had been fully explained.
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recovery between them; SE-induced pathological outcomes include neurodegeneration, neuroinflammation, abnormal hippocampal neurogenesis, and epileptogenesis [7].

Optical coherence tomography (OCT) is a new medical imaging technique that displays biological tissue layers as high-resolution tomographic sections [8], which is a noninvasive, safe, and practical method that can be used to measure axonal and neuronal loss [9]. The retinal nerve structure is formed of 3 layers of ganglion cells; these are the retinal nerve fiber layer (RNFL) made up of the ganglion cell axons, the ganglion cell layer (GCL) made up of the ganglion cell bodies, and the inner-plexiform layer (IPL) made up of ganglion cell dendrites. The combination of these three layers is called the ganglion cell complex (GCC). Since the retina is an extension of the brain, evaluation of retina and optic nerve using OCT opens a window into the brain. Retinal changes may occur in parallel with neuroinflammation and degeneration.

Several studies are available in the literature reporting reduced RNFL thickness in neurological diseases including Alzheimer disease (AD), Parkinson disease (PD), multiple sclerosis (MS), essential tremor (ET), and migraine [10–13]. Particularly, demonstration of retinal myelin loss on OCT has been an evidence of degeneration [11]. Thus, retina layer has become an important anatomic structure for monitoring degeneration. Spectral domain OCT (SD-OCT) is a technology used to obtain a 1-mm lower resolution compared with conventional OCT devices. This enhanced resolution allows discrimination of RNFL, GCL, and IPL.

As far as we know, there is no study that investigates the effects of seizure frequency, disease duration, AEDs, and presence of status epilepticus in epilepsy on GCL, IPL, and choroid volume in existing literature [14,15]. The OCT findings may contribute to elucidating the neurodegenerative process and inflammation in epilepsy and may be a potential biological marker for the disease besides providing relevant information about progression and drug selection.

2. Material and methods

2.1. Protocol

This is a prospective case study comparing a group of patients with epilepsy and a control group. The study included 43 male and female (22 M, 21 F) patients with epilepsy 18–57 years of age who were followed up at Adiyaman University Neurology Outpatient Clinic, and 40 healthy male and female controls (20 M, 20 F) 18–60 years of age. The Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) in 2010 was applied for diagnosis of epilepsy. Sociodemographic characteristics (age, gender, marital status, etc.) of both groups were noted. Disease duration, seizure frequency, seizure type, AEDs used, and the presence of epileptic status of the patient group were questioned and recorded. The patients were grouped according to seizure frequency in the last one year: minimum 2 seizures per week — very frequent; more than once a month — frequent; more than once in 6 months — rare; and no seizures for at least one year. All patients underwent routine biochemical testing. Subjects in the patient or control groups who had diabetes mellitus, hypertension or any metabolic disease, history of stroke, multiple sclerosis, malign disease, or cerebral trauma were excluded — additionally, with glaucoma, pseudo exfoliation syndrome, high myopia, anomalous optic disc, age-related macular degeneration, peripheral vasospasm, sleep-related breathing disorder, history of ocular trauma, previous intraocular surgery like cataract, and corticosteroid use. Subjects with a history of epilepsy or suspected seizures were excluded from the control group. The patients with secondary epilepsy were excluded. Both case and control groups underwent ophthalmologic examination at the ophthalmology clinic; visual acuity (best correct visual acuity — BCVA), intraocular pressure, and dilated-pupil fundus examination using slit-lamp biomicroscopy were performed. Patients with normal findings on ophthalmologic examination and the control group were included in the study. Subjects

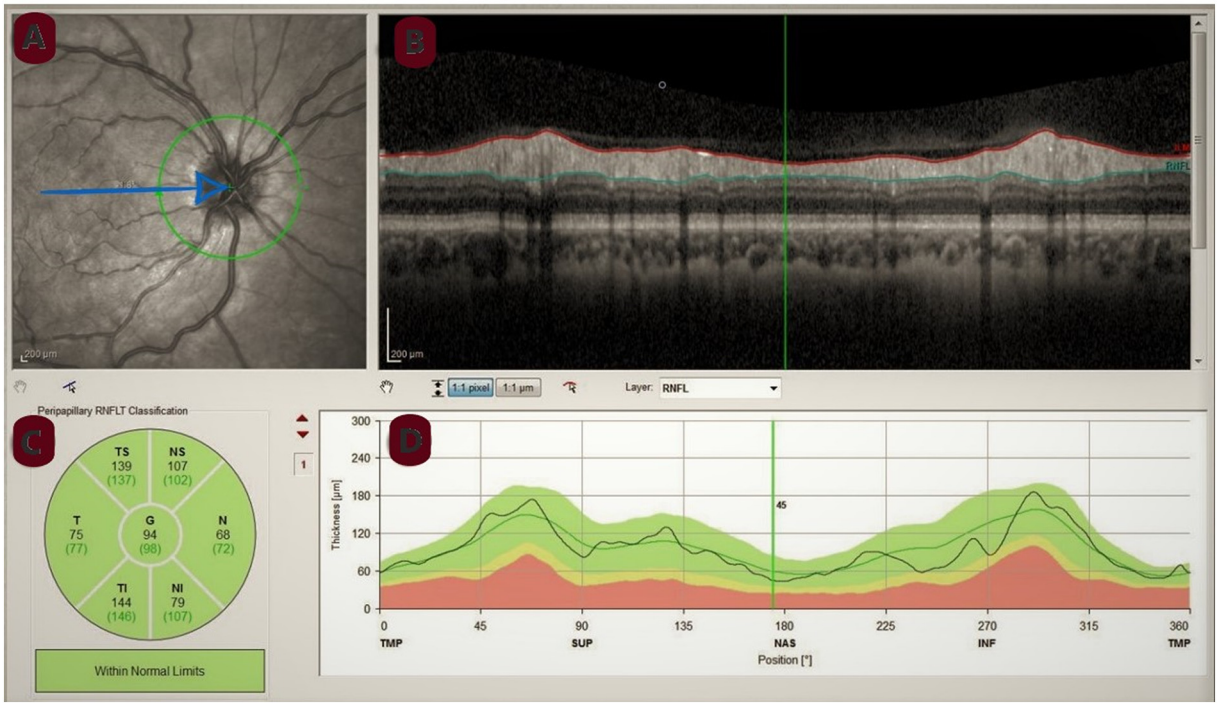

Fig. 1. Measurement of retinal nerve fiber layer (RNFL) thicknesses with spectral optic coherence tomography (OCT). a A circle is drawn around the optic disc to measure peripapillary RNFL thickness. b A Picture demonstrating the RNFL. c Seven measurements are performed for each eye, providing the RNFL thicknesses of the temporosuperior (TS), temporoinferior (TI), temporal (T), nasal superior (NS), nasal inferior (NI), nasal (N), and global (G) sectors. d RNFL thickness map.

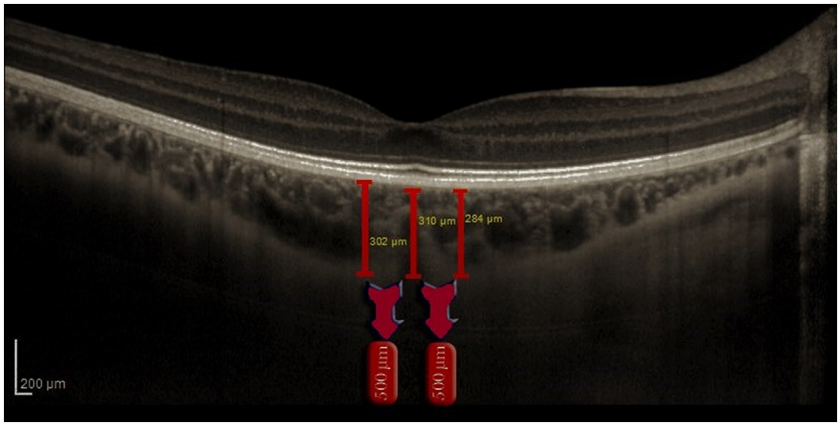

Fig. 2. Measurement of the choroidal thickness by spectral optic coherence tomography (OCT). A perpendicular line (middle yellow line) is drawn subfoveal from the outer edge of the retinal pigment epithelium to the choroid-sclera junction. Two additional lines are drawn at the nasal and temporal sides at 500-mm intervals from the subfoveal line. The mean value of these 3 measures was accepted as the choroidal thickness.

in both groups underwent OCT imaging performed by the Adiyaman University Medical School Department of Ophthalmology. Measurement of choroid thickness and mean estimation were performed by the same physician. Additionally, measurement of the RNFL, which is one of the lower layers of the GCC, and GCL thickness after GCC segmentation were measured by the device and recorded. This study was approved by Ethical Committee of Adiyaman University Medical School. Signed consent study participation was obtained from objects in both groups.

2.2. OCT measurement

The RNFL measurements, three-point measurements of choroid structure and their mean values, and GCL structures of right and left eyes were measured using Heidelberg Engineering Announces 85,000 Hz OCT2 Next Generation SPECTRALIS OCT Module device, and all measurements were recorded. The RNFL layer has temporal (T) and nasal (N) main segments. Each are also evaluated as subquadrants; superior quadrant (TS, NS), and inferior (TI, NI) quadrant. All layers were separately measured in each eye and analyzed. Therefore, total of 12 regions with 6 regions in each eye (N, NS, NI, T, TS, TI) plus mean RNFL for both eyes (right eye mean and left eye mean) were measured and compared.

Choroid thickness is another measurement that we compared using OCT. Subfoveal choroid thickness measurement was performed manually using the measuring tool of OCT software, by measuring the distance between a line that starts from the outer margin of retinal pigment epithelium and runs perpendicular to this margin that is brought to choroid–sclera margin. Measurements were performed at fovea and at 3 different points from fovea up to 1500-µm distance every 500 µm in nasal and temporal directions. In our study, we measured choroid thickness at 3 different areas and estimated their mean, and presence of difference between groups was analyzed. Finally, segmentation of the GCC structure was performed, the structure called GCL, axonal extension RNFL, and IPL formed of dendrite layer were compared separately. Measurements of OCT parameters are shown in Figs. 1–3.

2.3. Statistical analysis

To describe the data, frequency (percent), mean ± standard deviation (SD), median, and range were used. We assessed distribution of data using the Shapiro-Wilk test. Independent samples t-test was used in comparisons of normally distributed data and Mann–Whitney testing was used for comparison of non-normally distributed data. Chi-square test was used to compare differences between groups in categorical variables. Both eyes of a subject were analyzed individually and to compare groups while considering the correlation of eyes in one subject, generalized estimating equation (GEE) analysis was used. Multiple regression analysis was used to determine factors influencing OCT values. p value less than 0.05 was considered as statistically significant. All statistical analyses were performed by SPSS software (Version 21.0, Microsoft Co., Chicago, IL, USA).

3. Results

The study included 43 patients who were admitted to the neurology clinic of our hospital and were on follow-up and 40 healthy subjects as the control group. The patient group consisted of 22 male (51.2%) and

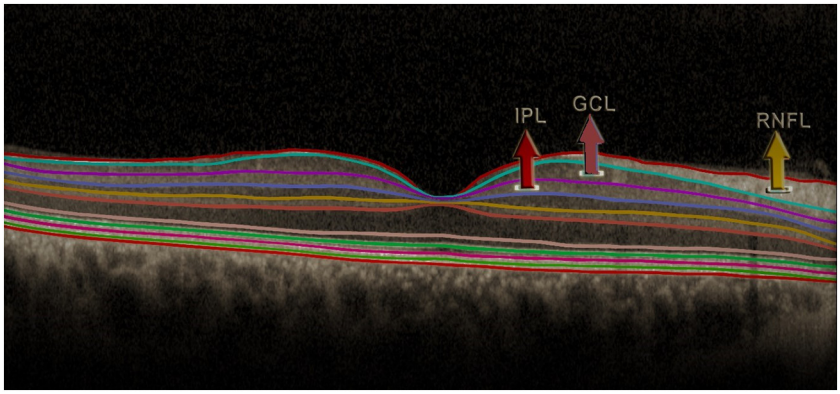

Fig. 3. Measurement of the ganglion cell layer (GCL) and inner-plexiform layer (IPL) thicknesses with spectral optic coherence tomography (OCT).

21 female (48.8%) patients. The control group consisted of 20 male (50%) and 20 female (50%) subjects. Mean age was 29.30 ± 10.97 years (range 18–60 years) in the patient group and 29.78 ± 9.65 years (range 18–57 years) in the control group. Sociodemographic characteristics are shown in Table 1. In the patient group, mean duration of epilepsy was 12.02 ± 8.96 years. Two patients (4.7%) had very frequent seizures, 11 (25.6%) had frequent, 17 (39.5%) had rare seizures, and the remaining 13 (30.2%) had no seizures for at least one year. History of status was present in 15 (34.9%) patients. The drugs used by the patients were carbamazepine (n = 11, 25.6%), valproic acid (n = 16, 37.2%), levetiracetam (n = 21, 48.8%), oxcarbazepine (n = 11, 25.6%), phenytoin (n = 3, 7%), lamotrigine (n = 3, 7%), (n = 2, 4.7%), zonisamide (n = 2, 4.7%), and lacosamide (n = 2, 4.7%). Twenty patients (46.5%) were using multiple drugs. Seizure frequencies and drugs used by the patient group are shown in Table 2.

Mean RNFL values were 101.48 ± 11.33 in the patient group and 108.76 ± 8.37 in the control group (p = 0.001). Mean GCL thickness values in the patient and control groups were 1.14 ± 0.12 and 1.22 ± 0.05, respectively (p < 0.001). Mean IPL thickness was 0.93 ± 0.09 in the patient group and 0.97 ± 0.05 in the control group (p = 0.02). Meanwhile, choroid thickness, which indicates vascularization, was found significantly increased in the patient group (p < 0.001). The OCT data are shown in Table 3.

Effects of disease duration, seizure frequency, status history, and multiple drug use on OCT parameters was evaluated in a regression model; no statistically significant relation was found for these factors. These comparisons are shown in Table 4. According to correlation analysis there was a negative correlation between GCL and duration of the disease, it was still non significant (r = −0.28, p = 0.07). The other correlations between OCT findings and seizure frequency, status history, and multiple drug use were not statistically significant (p > 0.05).

4. Discussion

Epilepsy affects the nervous system as a result of both the nature of the disease and the seizures [4,6]. Using medicines further increase this effect [16–20]. The relation between epilepsy and neurodegeneration is known [16,17]. Many recent studies using OCT technology have demonstrated that parameters provided by OCT are accurate to detect retinal or optic nerve pathologies. In the last decade, OCT has also been applied in several areas in neurology especially neurodegenerative diseases, such as MS, PD, ET, or AD [12]. Although there are limited studies conducted with specific drug groups, there is no study evaluating neurodegeneration of the nervous system in patients with epilepsy particularly using many OCT parameters. The aim of our study was to evaluate OCT findings in patients with epilepsy and to compare OCT findings in terms of disease duration, presence of status, seizure frequency, and drug use. Therefore, we had the opportunity to investigate the effects of these factors on neurodegeneration in the brains of patients with epilepsy. Our study indicated that RNFL, GCL, and IPL layers were thinner in the patient group, which may indicate neurodegeneration in the brain. On the other hand, choroid thickness was significantly increased in the patient group. Thickening of the choroid layer indicates increased vascularization, which may be a sign of increased neuroinflammation. However, our study failed to show that disease duration, seizure frequency, presence of status, and multiple drug use had effects on OCT parameters. Although a weak correlation was found between seizure frequency, no statistical significance was detected. This is potentially due to the small patient group included in the study.

Majority of the previous studies that have been conducted up to date are on the effects of drug use [18–21]. In 2006, in a study conducted in adolescents, Verrotti et al. have evaluated ocular effects of valproic acid and carbamazepine [18]. Although they found impaired color perception, macular changes were not detected during one year of follow-up. Lobefalo et al. in their study published in the same year have not detected any difference in RNFL and macular thickness of patients using carbamazepine or valproate [19]. Vigabatrin is definitely the most studied drug in relation to ocular effects in patients with epilepsy [22–30]. Besides many studies defining ocular toxicity of vigabatrin, OCT findings specific to vigabatrin were also demonstrated. Lawtown et al. have found that nasal quadrant RNFL thinning was a specific finding associated with vigabatrin use. They have recommended following up the thickness of RNFL for monitoring vigabatrin toxicity [25]. Although these studies were based on drug use, they found thinner RNFL in a similar manner to our study. In a study in which other OCT parameters such as GCL were evaluated, the patient group was evaluated within itself [31]. Tugcu et al. evaluated GCL with OCT in vigabatrin-exposed patients. They found thinner GCL in the patient group [32]. Another parameter that we assessed in our study was choroid thickness. Choroidal thickness is very variable. Differences may be observed in races and genders. In a study conducted in our country, it was found as 291.3 ± 53.1 μm in men, and as 252.7 ± 40.9 μm in women [33]. Choroidal layer is the most vascular layer of the retina, and it helps the nourishment of the retina. Thus, it is affected from any systemic event, which affects blood circulation [34]. Although initially cell death was associated with ischemia related to ictal vasospasm, observation of hyperemia in subsequent studies has changed this opinion [5]. In later studies, it was found that hyperemia can exacerbate hypoxia when vasospasm occurs in capillaries, leading to heterogeneous blood flow within capillary beds. A recent study by Leal-Campanario et al. indicates that irregular capillary blood flow due to mural cell dysfunction, combined with hyperemia, can exacerbate cell death in epilepsy [5].

Table 1
Demographic characteristics.

	Patient group	Control group
Age (years)	29.30 ± 10.98	29.78 ± 9.65
Sex		
Male	22 (51.2%)	20
Female	21 (48.8%)	20

Table 2
Features of the patient group.

Patient group	N = 43
Duration of epilepsy (years)	12.02 ± 8.96
Seizure frequency	
Very frequent	2 (4.7%)
Frequent	11 (25.6%)
Rare	17 (39.5%)
No seizure for at least one year	13 (30.2%)
History of status	
Yes	15 (34.9%)
No	28 (65.1)
Medications	
Carbamazepine	11 (25.6%)
Valproic acid	16 (37.2%)
Levetiracetam	21 (48.8%)
Oxcarbazepine	11 (25.6%)
Phenytoin	3 (7%)
Lamotrigine	3 (7%)
Zonisamide	2 (4.7%)
Lacosamide	2 (4.7%)

Table 3
Comparison of OCT subgroups.

	Patients (N = 43)	Controls (N = 40)	p value*
Choroidal thickness	338.99 ± 62.63	272.50 ± 72.49	<0.001
GCL	1.14 ± 0.11	1.22 ± 0.04	<0.001
IPL	0. 93 ± 0.08	0.97 ± 0.04	<0.002
RNFL	101.47 ± 11.33	108.76 ± 8.37	<0.001

GCL: Ganglion cell layer, IPL: Inner-plexiform layer, RNFL: Retinal nerve fiber layer.
* Independent Sample Test.

Table 4
Effects of disease duration, seizure frequency, status history, and multiple drug use on OCT parameters.

	Disease duration		Seizure frequency		Status history		Multiple drug use	
	B	p value*	B	p value*	B	p value*	B	p value*
Choroidal thickness	0.01	0.99	12.42	0.12	4.12	0.86	−22.80	0.30
GCL	0.00	0.89	−0.02	0.10	0.47	0.26	0.02	0.57
IPL	0.00	0.82	−0.02	0.15	0.04	0.22	0.01	0.80
RNFL	0.31	0.18	−1.88	0.19	0.90	0.83	−3.84	0.33

* Multivariate regression analysis.

Maybe this hypothesis can explain the thicker choroid that we found in the current study.

There are some limitations in this study: fist OCT values were not compared with types of epilepsy and drug groups due to the small number of patients, even if we had the data. However, as far as we know, there is no study evaluating RNFL, IPL, GCL, and choroid layer concomitantly in epilepsy.

Demonstration of RNFL, IPL, GCL thinning might indicate neurodegeneration and choroid thickening indicates neuroinflammation. Further studies with larger patient groups that can provide an opportunity to compare types of epilepsy and relationship with the drugs should clarify the matter.

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Conflict of interest statement

None of the authors has any conflict of interest to report.

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