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Microstructural Changes in Intraretinal Layers and Macular Structures of People with Epilepsy Measured Using Optical Coherence Tomography

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ABSTRACT

Introduction: Epilepsy is a network disorder that can cause alterations in retinal morphology due to microstructural changes in the brain. The aim of our study was to use spectral optical coherence tomography (OCT) to assess the possible effects of neuronal degeneration on the intraretinal layers and macular structures of people with epilepsy and epilepsy subgroups.

Methods: We enrolled 52 consecutive people with epilepsy (37 females, 15 males; mean age 29.8±9.9 years; range, 17–48 years) and 40 healthy volunteers (27 females, 13 males; mean age 33.3±10.2 years; range, 19–49 years) in this study. Both eyes of all participants were assessed by using spectral-domain OCT. Optical coherence tomography was used to assess the thickness of the peripapillary retinal nerve fiber layer (RNFL), ganglion cell layer-inner plexiform layer (GCC-IPL), central macula, and central macular volume.

Results: In comparison to healthy controls, people with epilepsy showed a thinner GCC-IPL in the superior and superior-nasal quadrants, as well as reduced macular thickness and macular volume ($p<0.05$). The thickness of the GCC-IPL layer in the superior and inferior subquadrants was negatively affected by frequent seizures (>5 seizures/year), polytherapy, and long-duration of epilepsy (≥10 years) ($p<0.05$). However, we did not find any other statistically significant associations between OCT measurements, age, sex, and epilepsy type (focal and generalized onset epilepsy).

Conclusion: Individuals with epilepsy exhibited microstructural alterations in the retinal layers, primarily in the superior and inferior quadrants. Frequent seizures, polytherapy, and long-duration of epilepsy may result in neuronal damage in the afferent visual system.

Keywords: Epilepsy, ganglion cell layer, neurodegeneration, optic coherence tomography, retinal nerve fiber layer

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INTRODUCTION

Epilepsy is a functional network disorder characterized by recurrent seizures and microstructural abnormalities and neuronal degeneration (1). Previous studies using diffusion tensor imaging and volumetric magnetic resonance imaging (MRI) have revealed widespread axonal loss due to alterations in the white matter network of individuals with epilepsy (2). Optical coherence tomography (OCT) is a noninvasive imaging technique that provides insight into retinal morphology. Retinal measurements assessed using OCT have been suggested to offer information about brain atrophy (3). Previous studies reported that retinal changes were associated with brain atrophy, cognitive impairment, and cerebral axonal integrity in different neurodegenerative and neuroinflammatory diseases (4). Therefore, alterations in retinal morphology may serve as an indirect measure of microstructural abnormalities, brain atrophy, and a biomarker of disease progression (5).

Optical coherence tomography evaluates retinal microstructure with high-resolution cross-sectional images and quantifies peripapillary retinal nerve fiber layer (RNFL) thickness (6). The optic nerve is unmyelinated at the level of the lamina cribrosa, thus allowing the assessment of axonal integrity (7). Few studies from individual centers have investigated the association between OCT abnormalities and clinical characteristics in individuals with epilepsy (8–11). Previous studies in individuals with epilepsy have shown that vigabatrin and valproic acid treatment have detrimental effects on RNLF thickness in children (12–14). A recent study in people with epilepsy with no previous exposure to vigabatrin suggested an association between RNLF thickness reduction, antiepileptic drug (AED) resistance, and possible disease severity (8). It remains unclear whether retinal thinning can serve as a biomarker of epilepsy-related neurodegeneration and disease severity.

In this study, we investigated the possible effects of neuronal degeneration in intraretinal layers and macular structures of people with epilepsy and epilepsy subgroups measured by spectral OCT.

Highlights

- **OCT detects microstructural abnormalities in the retinal layers of epilepsy patients.**
- **Epilepsy may produce neuronal damage in the afferent visual system.**
- **Frequent seizures, polytherapy, long-term disease are associated with retinal thinning.**

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METHODS

Study Population

This cross-sectional study included 52 consecutive people with epilepsy (37 females, 15 males, mean age 29.8±9.9 (range 17–48) years; mean duration of epilepsy 14.3±10.5 (range, 0.5–41) years) who were diagnosed and followed at neurology department between December 2020 and August 2020. Forty age– and sex-matched healthy volunteers (27 females, 13 males; mean age 33.3±10.2 years; range, 19–49) with no previous history of ophthalmologic, neurologic, major psychiatric diseases, drug or alcohol abuse, or nutritional deficiency, were recruited from hospital staff as the control group. This study was approved by the local ethics committee (reference number: 2019/420). Informed consent was obtained from all participants.

Epilepsy was defined as per the International League Against Epilepsy (ILAE) Executive Committee recommendations (15). Information regarding demographic data, age at onset, epilepsy duration, epilepsy etiology, AEDs, treatment response, seizure frequency, electroencephalography (EEG), and neuroimaging findings were collected from the medical records and interviews with the participants. The diagnosis of epilepsy was established through clinical history, video-EEG recordings, and neuroimaging findings. All patients underwent MRI. All MRI studies were performed using 1.5-T scanners with coronal, sagittal, and axial planes, including T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) images according to a standard epilepsy protocol and evaluated by neuroradiologists (16). Twenty-one channel EEG recordings with additional anterior temporal electrodes (FT9 and FT10) according to the international 10–20 system for at least a 30-minute duration were recorded from each patient. The EEG recordings were evaluated by experienced epileptologists. Epilepsy syndromes were classified according to the revised terminology and concepts for the organization of seizures and epilepsies of the ILAE Commission on Classification and Terminology 2017 (17). AED-resistant epilepsy was defined as 'failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained (>12 months) seizure freedom (18).

There were 14 (26.9%) patients with various structural causes of epilepsy (mesial temporal sclerosis (n=8, 15.4%), cortical dysplasia (n=5, 9.6%), and posttraumatic (n=1, 1.9%)); 15 (28.9%) people with focal epilepsy of unknown cause, 15 (28.9%) people with genetic generalized epilepsy, and eight (15.4%) patients with unknown etiology. Of the people with focal epilepsy, 15 had temporal lobe epilepsy, 4 had frontal lobe epilepsy, and 2 had parietal lobe epilepsy. There were no individuals with occipital lobe epilepsy in the study. Twenty-eight (53.9%) patients were classified as having AED-resistant epilepsy. At the time of the study, 23 (44.2%) patients were under monotherapy and 29 (55.8%) were under polytherapy. None of the patients was treated with vigabatrin. The baseline seizure frequency was calculated from the seizure calendars of the patients and their files. Twenty-five (48.1%) patients had more than one seizure per month, 11 (21.2%) patients had 1–11 seizures per year, and 16 (30.8%) patients had fewer than one seizure per year.

Study Design

All participants underwent a standard ophthalmologic examination including visual acuity, anterior and posterior segment evaluation, and measurement of intraocular pressure by an ophthalmologist. The exclusion criteria for participants were defined as having a history of corneal, retinal and/or macular disease, glaucoma, optic neuritis, orbital trauma, previous ocular surgery, coexisting diagnosis of multiple sclerosis, previous exposure to vigabatrin, and brain MRI evidence of visual pathway involvement. Subjects were also excluded if they were presented with a distance refractive error of >4.50 diopters or a spherical refractive error >2.5 diopters cylinder.

Optic Coherence Tomography

All participants were assessed using spectral-domain OCT imaging (Cirrus OCT; Carl Zeiss Meditec, Dublin, CA) by two experienced operators who were blinded to the group assignments in the ophthalmology department. Both eyes were examined for each participant without mydriasis. Macular scanning centered on the fovea was performed using the macular cube 200 × 200 protocol. Optic disc-centered peripapillary RNFL scanning was performed with the optical disc cube 200 × 200 protocol (Figure 1) (19). The ganglion cell complex (GCC) in the retina consists of three layers: the retinal nerve fiber layer (RNFL) consisting of unmyelinated axons of ganglion cells, ganglion cell layer (GCL) consisting of ganglion cell bodies, and inner plexiform layer (IPL) consisting of ganglion cell dendrites (Figure 1). Optical coherence tomography was used to assess the thickness of the RNFL in the peripapillary area (average and the four 90-degree quadrants; superior, temporal, nasal, and inferior), GCC-IPL (minimal, average, superior, superonasal, superotemporal, inferior, inferonasal, and inferotemporal regions), as well as central macula and central macular volume (Figure 2). Optical coherence tomography scans including artifacts due to eye movements and with signal strength <6 were not included in the study.

Statistical Analysis

The IBM Statistical Package for Social Sciences (SPSS) program version 22.0 (IBM corporation) for Windows was used for data analyses. Both eyes of the subjects were analyzed and averages of retinal thickness in both eyes were compared. For categorical variables, Chi-square tests or Fischer's exact test was used as appropriate. Continuous variables were analyzed using independent Student t-tests or the Mann–Whitney U test after testing for normal distribution of the data. Pearson or Spearman correlation tests were used for correlations as appropriate. Significance values were adjusted using Bonferroni correction for multiple comparisons. For all tests, a p-value of <0.05 was considered statistically significant.

RESULTS

In this study, OCT parameters in people with epilepsy were compared with healthy controls (Table 1). In epilepsy subgroups, associations of age, epilepsy duration, seizure frequency, multiple drug use, treatment response, epilepsy type, and structural MRI lesions with OCT parameters were evaluated (Table 2).

Peripapillary RNLF

The average RNLF and RNFL thicknesses in four quadrants were found similar in people with epilepsy and healthy controls (Table 1). The RNFL inferior quadrant was significantly thicker in patients with frequent seizures (>5 seizures/year) compared to those with less frequent seizures (≤5 seizures/year) (p=0.02). The RNFL inferior quadrant was significantly thicker in patients with treatment-resistant epilepsy compared with people with treatment-responsive epilepsy (p=0.04) (Table 2).

We found no significant associations between the average RNLF and RNFL thicknesses in four quadrants and other epilepsy subgroups (Table 2).

Retinal Thickness

The GCC-IPL thickness in superior and superior nasal quadrants was found to be significantly thinner in people with epilepsy compared with healthy controls (p<0.05) (Table 1). The average GCC-IPL and GCC-IPL thicknesses in inferior quadrants were not significantly different in people with epilepsy as compared with healthy controls (Table 1).

The average GCC-IPL thickness in all quadrants, GCC-IPL thickness in the superior nasal, superior temporal, inferior nasal, and inferior temporal quadrants were significantly reduced in people with epilepsy with

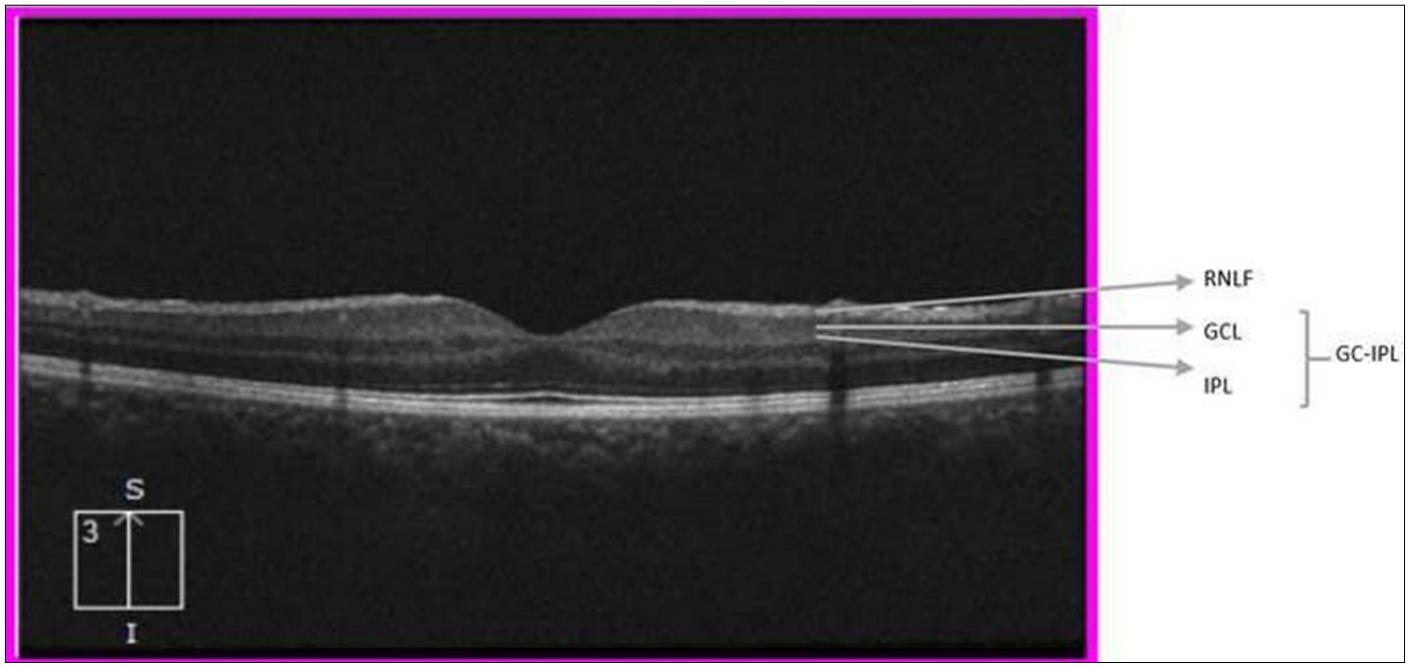

Figure 1. High-definition OCT with intraretinal layers of a patient with focal-type epilepsy. (OCT: optical coherence tomography, RNFL, retinal nerve fiber layer; GCL, ganglion cell layer; IPL, inner plexiform layer)

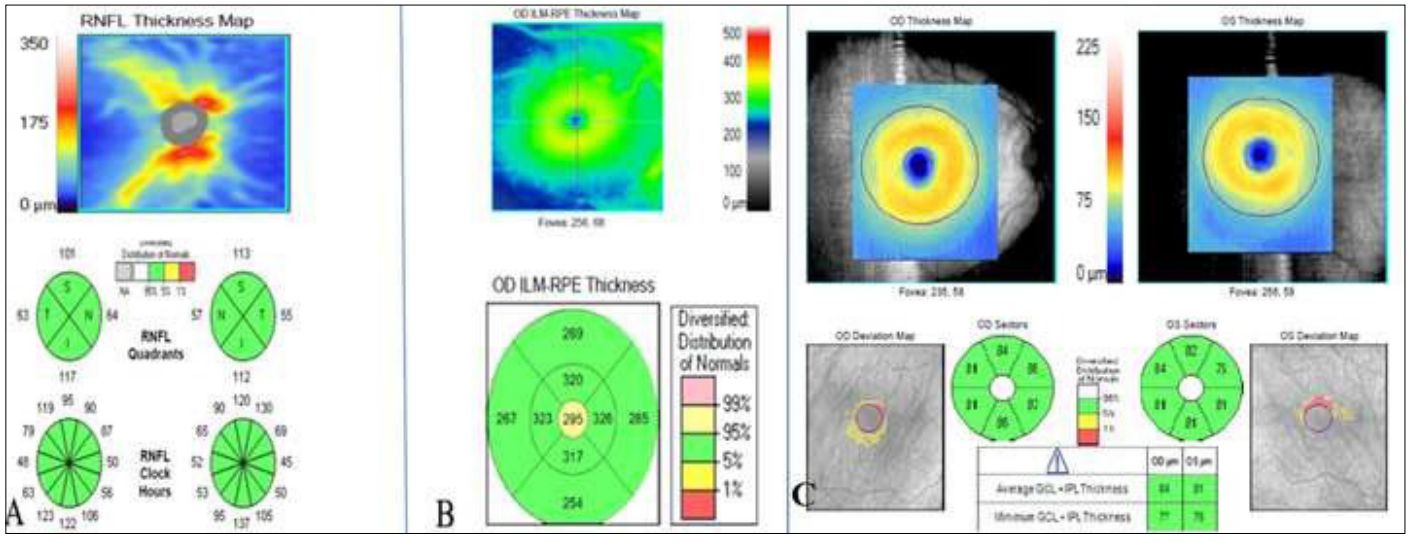

Figure 2. Spectral-domain OCT imaging (Cirrus OCT; Carl Zeiss Meditec, Dublin, CA) sample of a patient with genetic generalized epilepsy. A) Optical disc cube 200×200 protocol. B) Macular cube 200×200 protocol. C) Macular cube 512×128 protocol (Ganglion Cell Analysis). (ILM: Inner limiting membrane; OCT: optical coherence tomography; RNFL: Retinal nerve fiber layer; RPE: Retinal Pigment Epithelium).

frequent seizures (>5 seizures/year) compared to those with less frequent seizures (≤5 seizures/year) (p<0.05) (Table 2).

The average GCC-IPL thickness in all quadrants, GCC-IPL thickness in the superior nasal, superior temporal, inferior nasal, and inferior temporal quadrants were significantly reduced in people with epilepsy under polytherapy compared with those under monotherapy (p<0.05) (Table 2).

The GCC-IPL thickness in the inferior nasal quadrant was significantly reduced in people with epilepsy with longer duration epilepsy (≥10 years) compared with shorter duration epilepsy (<10 years) (p=0.04) (Table 2)

We found no significant associations between GCC-IPL thickness and structural MRI lesions in people with epilepsy (Table 2).

Central Macular Thickness

People with epilepsy showed decreased average central macular thickness cube compared with the healthy control group (p=0.04). The macular thickness central subfield was significantly thinner in people with epilepsy with structural MRI lesions compared with patients without MRI lesions (p=0.04) (Table 2). We found no other significant associations between central macular thickness and epilepsy subgroups.

Macular Volume

The total macular volume in people with epilepsy was significantly lower as compared with controls (p=0.02) (Table 1). We found no significant associations between total macular volume and epilepsy subgroups.

No other statistically significant relationships were found between OCT measurements and sex and epilepsy type (focal and generalized onset

Table 1. RNLF, GCC-IPL and macular thickness in epilepsy patients versus healthy controls

	Patients with epilepsy n=52	Healthy controls n=40	P value
Mean age (year ± SD)	29.8±9.9	33.3±10.3	0.1
Gender (F/M)	37/15	27/13	0.8
RNFL thickness*	n=35	n=34	
Quadrants (µm) (mean ± SD)			
Average thickness across 4 quadrants[1]	92.4±6.5	93.1±9.4	0.7
Superior[1]	114.4±13.0	114.0±16.8	0.9
Nasal[1]	68.9±8.1	70.1±7.6	0.4
Temporal[2]	66.7±13.6	64. 7±7.5	0.8
Inferior[1]	119.9±13	123.0±16.8	0.5
GCC-IPL thickness*	n=39	n=31	
Quadrants (µm) (mean ± SD)			
Average thickness across all quadrants[2]	76.3±9.4	79.6±15	0.05
Minimum[2]	65.9±17.3	71.9±19.7	0.05
Superior[2]	74. 2±14.7	80.7±15	**0.02**
Superior nasal[2]	75.3±12.3	80.4±14.8	**0.04**
Superior temporal[2]	76.7±9.4	80.1±14.9	0.05
Inferior[2]	76.7±9.3	77.9±14.8	0.5
Inferior nasal[2]	77.6±11.6	80.3±12.9	0.4
Inferior temporal[2]	77.2±10.2	77.2±19.7	0.3
Macular thickness*	n=43	n=39	
Quadrants (µm) (mean ± SD)			
Thickness average cube[2]	271.0±21.4	279.8±11.7	**0.04**
Thickness central subfield[1]	235.1±33.1	244.3±21.2	0.13
Volume cube[1]	9.9±0.4	10.1±0.4	**0.02**

CI: Confidence interval, F: Female, GCC-IPL: Ganglion cell complex– inner plexiform layer, n=number of patients, M: Male, RNFL: Retinal nerve fiber layer, SD: Standard deviation.
[1]Student's t test, [2]Mann-Whitney U test.
*OCT scans with signal strength <6 were not included. p value less than 0.05 are marked as bold.

epilepsy). We found no significant correlations between age, epilepsy duration, and OCT measurements (data not shown).

When correcting for multiple testing in epilepsy subgroups, however, only using polytherapy showed a significant association with the GCC-IPL thickness in the inferior nasal quadrant (p=0.009).

DISCUSSION

This study explored the pattern of peripapillary RNLF thickness, retinal GC layer integrity, and macular volume in people with epilepsy using spectral-domain OCT imaging. People with epilepsy showed a thinner GCC-IPL layer in the superior and superior-nasal quadrants and reduced macular volume and decreased average central macular thickness cube compared with the healthy controls. Frequent seizures (>5 seizures/year), polytherapy, and long-duration epilepsy (≥10 years) had detrimental effects on the thickness of the GCC-IPL layer superior and inferior subquadrants. Treatment-resistant epilepsy and frequent seizures were associated with thicker RNFL inferior quadrant. This is potentially due to the small patients subgroup included in this study. Only polytherapy was associated with the GCC-IPL thickness in multiple comparisons. No significant correlation was found between age, sex, epilepsy types, and OCT measurements.

The retina is a neural network layer that is an extension of the brain and originates from the same neuroectodermal origin as the brain. Due to 'transsynaptic degeneration,' neuronal damage that arises from the cortex or optic radiation is suggested to manifest structural changes in the retina (20). In the setting of transsynaptic degeneration, reduced peripapillary RNLF measurements are interpreted as representing axonal damage, and the loss of retinal GC integrity is interpreted as neuronal damage in the afferent visual system (20). In contrast to RNLF, GC-IPL analyses are not affected by axoplasmic stasis in the optic nerve, thus presenting early evidence of neuronal damage resulting from retrograde axonal degeneration and injury to the optic nerve or pathways (21,22). In people with multiple sclerosis, lower macular volume-associated RNLF thinning was interpreted to represent neuronal loss associated with retrograde degeneration from the lesions in the optic nerves, chiasms, or tracts (23).

Previous studies suggested that thinner GCL and thinner RNFL were associated with an increased risk of developing dementia (24). Apart from transsynaptic degeneration, accumulation of amyloid plaques was observed in the retina and brain of animal models of dementia, which suggested shared pathogenesis underlying the association between RNFL and dementia (24,25). Common neurodegenerative processes may also exist in epilepsies. Balestrini et al. (8) reported a significant relation between RNFL reduction, a longer duration of epilepsy, the presence of drug resistance, lower brain volume as assessed using brain MRI, and cognitive tests. Our study supports previous findings that have reported a reduction in the thickness of RNLF, GCL, and IPL layers in various groups of people with epilepsy compared with healthy controls (8,10,11).

Aza et al. (10) used OCT to investigate neurodegeneration in 43 individuals with epilepsy and 40 healthy controls. They found that the mean RNFL and GCL thicknesses were significantly lower in individuals with epilepsy compared to healthy controls.

Previous studies showed that some AEDs affected neurodegeneration in individuals with epilepsy. With its effects on the eye, vigabatrin, one of the best-known drugs, generated concentric visual field defects and reduction in RNFL thickness due to its accumulation in the retina (12,13,26). In 2015 Dereci et al. (14) reported that in children with epilepsy using valproic acid, the peripapillary RNFL superior quadrant was reduced compared

Table 2. Optic coherence tomography measurements in epilepsy subgroups

	Patients with infrequent seizures[i]	Patients with frequent seizures[o]	P	Patients under monotherapy[a]	Patients under polytherapy[b]	P	AED responsive epilepsy	AED resistant epilepsy	P	Focal onset epilepsy	Generalized onset epilepsy	P	Epilepsy with <10 years duration	Epilepsy with >10 years duration	P	MRI negative epilepsy	MRI positive epilepsy[c]	P
RNFL thickness*	N=16	N=19		N=15	N=20		N=18	N=17		N=20	N=11		N=13	N=22		N=27	N=7	
Quadrants (µm) (mean ± SD)																		
Average thickness across 4 quadrants	93.7±5.4	90.9±7.5	0.2[1]	92.6±6.8	92.3±6.4	0.9[1]	91.3±7.1	93.6±5.7	0.3[1]	93.2±5.5	92.2±8.3	0.6[1]	93.6±5.8	91.6±6.8	0.4[1]	91.9±6.1	95.6±7.4	0.2[1]
Superior	113.1±13.4	115.4±13.0	0.6[1]	115.1±11.1	113.9±14.6	0.8[1]	113.6±13.2	115.1±13.2	0.7[1]	114.2±13.9	116±11.8	0.7[1]	118.6±14.5	111.8±11.6	0.1[1]	114.6±12	116±16.7	0.8[1]
Nasal	67.8±8.5	69.8±7.8	0.5[1]	68.3±9	69±7.5	0.9[1]	68.5±8.9	69.2±7.3	0.8[1]	68.6±7.1	70.1±9.9	0.6[1]	67.7±8.3	69.5±8	0.5[1]	68.6±7.8	71.9±8.4	0.3[1]
Temporal	63.3±8.7	69.5±16.4	0.2[2]	64±6.9	68.7±17	0.3[2]	63.4±8	70.0±17.4	0.2[2]	68.9±16.1	63.1±10.3	0.3[2]	65.3±7	67.4±16.4	0.6[2]	64.1±8.1	76.1±25.3	0.3[2]
Inferior	116.1±15.8	123.2±9.2	0.02[2]	122.4±13.9	118.1±12.2	0.6[2]	116.7±15.2	123.3±9.1	0.04[2]	121.5±10.8	119.2±17.5	0.6[1]	119.1±9.8	120.4±14.6	0.7[1]	118.2±13.7	127.6±7.1	0.09[1]
GCC-IPL thickness*	N=19	N=20		N=16	N=23		N=20	N=19		N=20	N=13		N=12	N=27		N=30	N=8	
Quadrants (µm) (mean ± SD)																		
Average thickness across all quadrants	79±8.8	73.7±9.4	0.02[2]	80.1±7.3	73.7±9.9	0.01[2]	78. ±8.4	74.5±10.1	0.2[2]	74.8±9.5	79.5±6.3	0.2[2]	79.7±6.7	74.7±10	0.2[2]	77.2±8.7	72.4±12	0.3[2]
Minimum	70.8±13.9	61.2±19.2	0.1[2]	70.7±15	62.5±18.3	0.1[2]	67.6±16.2	64±18.6	0.6[2]	62.2±19.6	701±14.8	0.4[2]	69.1±18.8	64.3±16.6	0.6[2]	68±14.7	56.9±24.5	0.3[2]
Superior	77.3±13.6	71.3±15.4	0.1[2]	78.5±13.7	71.3±14.9	0.05[2]	74.9±15.6	73.6±13.9	0.5[2]	72.9±15.7	76±14.1	0.6[2]	77.7±14.1	72.6±14.8	0.5[2]	76.2±12.2	65.8±21.1	0.3[2]
Superior nasal	79.3±9.7	71.6±13.5	0.03[2]	79.7±10.4	72.3±12.8	0.02[2]	78.1±9.6	72.4±14.2	0.2[2]	72.4±13.7	80.3±7.7	0.06[2]	79.5±8.2	73.4±13.4	0.2[2]	76.6±12.2	70.4±13	0.3[2]
Superior temporal	79.3±9.3	74.2±9	0.02[2]	80.3±7.7	74.2±9.8	0.009[2]	78.0±9.7	75.3±9	0.1[2]	76±9	79.4±7.9	0.2[2]	80.7±5.6	74.9±10.1	0.07[2]	77.7±8.3	72.1±12.6	0.2[2]
Inferior	78.2±9.2	75.4±9.4	0.3[1]	79.6±8	74.8±9.7	0.1[1]	78±9.7	75.4±8.8	0.4[1]	75.4±8.7	79.9±7.3	0.1[1]	79.6±7.7	75.4±9.7	0.2[1]	77.1±8.6	75.3±12.4	0.8[1]
Inferior nasal	80.5±9.2	75±13.3	0.03[2]	82.3±6.8	74.4±13.2	0.006[2]	80.6±9.8	74.5±12.7	0.09[2]	75.7±13.2	82±6.2	0.1[2]	82.2±5	75.5±13	0.04[2]	77.4±11.7	78±12.7	0.9[2]
Inferior temporal	79.9±9.2	74.8±10.8	0.02[2]	80.4±8.3	75±11	0.05[2]	79±8.8	75.3±11.4	0.2[2]	76.4±10.7	79.9±7.3	0.4[2]	79.2±12.8	76.3±8.9	0.4[2]	78.4±8.3	72.5±15.9	0.4[2]
Macular thickness*	N=20	N=23		N=19	N=24		N=20	N=23		N=24	N=13		N=15	N=28		N=32	N=10	
Quadrants (µm) (mean ± SD)																		
Thickness average cube	272.2±9.5	270.1±28.1	0.7[2]	276.1±10.9	267.1±26.5	0.2[2]	273.3±8.7	269.1±28.2	0.7[2]	269.2±27.5	272.3±8.9	0.7[2]	274.1±11.7	269.4±25.1	0.9[2]	269.5±23.6	276.4±12	0.5[2]
Thickness central subfield	242.8±29.5	228.4±35.1	0.2[1]	245.3±29.3	226.9±34.2	0.07[1]	238.7±37.9	231.8±26.6	0.2[1]	227.1±34.5	245.6±31	0.1[1]	236.1±40.1	234.4±29.4	0.9[2]	242.4±27.3	210.7±41	0.04[1]
Volume cube	9.8±0.3	9.9±0.4	0.3[1]	9.9±0.4	9.8±0.4	0.3[1]	9.8±0.3	9.8±0.4	0.7[1]	9.8±0.4	9.8±0.3	0.5[1]	9.8±0.4	9.8±0.3	0.9[1]	9.8±0.3	9.9±0.4	0.5[1]

AED: Antiepileptic drug, CI: Confidence interval, GCC-IPL: Ganglion cell complex– inner plexiform layer, MRI: Magnetic resonance imaging; N: Number of patients, RNFL: Retinal nerve fiber layer, SD: Standard deviation.
[1]Student's t test, [2]Mann-Whitney U test.
* OCT scans with signal strength <6 were not included, [i](≤5 seizures/year) [o](>5 seizures/year) p values <0.05 are marked as bold.
[a]AED used: Levetiracetam n=11, Valproic acid n=4, Lamotrigine n=4, 1 Oxkarbazepine n=1.
[b]AED used: Levetiracetam n=23, Valproic acid n=10, Lamotrigine n=3, 1 Oxkarbazepine n=6, Primidone n=1, Lacozamide n=9, Carbamazepine n=7, Phenytoin n=1, Topiramate n=2, Zonisamide n=4, Ethosuximide n=1, Clobazam n=1.
[c]8 patients had mesial temporal sclerosis, 5 patients had cortical dysplasia, and 1 patients had posttraumatic lesion.

with healthy controls without loss of vision and visual field. However, another study comparing the effect of carbamazepine and valproic acid monotherapy on RNFL and macular thickness revealed no significant difference in retinal measurements after 1 year of treatment (27). In our study, only polytherapy showed an association with thinner GCC-IPL layers in multiple comparisons.

Optical coherence tomography is a fast, non-invasive, and inexpensive method to assess axonal integrity within the central nervous system. However, there is a lack of consistency and reproducibility in the interpretation of the results across different studies (5). The measurements may show significant differences among different OCT instruments (28). To minimize the effects of confounding factors, all of the participants in our study underwent a meticulous ophthalmologic assessment to exclude concomitant ocular pathologies. To minimize the effects of normal aging, only participants who were younger than 50 years were included in the study. All of the participants were assessed using the same spectral-domain OCT imaging (Cirrus OCT).

The limitations to this study are the relatively small sample size in the subgroup analyses and the lack of sufficient data regarding the effects of specific AEDs on the retina. We included all types of epilepsy; however, some syndromes and subgroups may have a greater predisposition for neurodegeneration and retinal changes.

Our study confirms that OCT detects microstructural abnormalities in the retinal layers of people with epilepsy, which may suggest neurodegeneration. Frequent seizures, polytherapy, and long-duration epilepsy may produce neuronal damage in the afferent visual system.

Declaration of Competing Interest

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Ethics Committee Approval: The study protocol was approved by Trakya University Faculty of Medicine Scientific Research Ethics Commitee (2019/420).

Informed Consent: The same researchers carried out the procedures after obtaining the participants written informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- LBK; Design- RG, LBK; Supervision- BG; Resource- BG; Materials- MMÇ; Data Collection and/or Processing- RG, MMÇ; Analysis and/or Interpretation- MMÇ; Literature Search- MMÇ; Writing- MMÇ; Critical Reviews- LBK, BG.

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