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Retinal OCT changes in pediatric epilepsy: neurodegeneration and antiseizure medication effects

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ABSTRACT

Objective: This study aimed to evaluate peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell–inner plexiform layer (GCL+IPL) thickness in children with epilepsy using optical coherence tomography (OCT), and to compare these parameters with healthy controls. Additionally, the relationship between retinal structure and epilepsy duration, as well as antiseizure medication (ASM) exposure (notably valproate), was investigated.

Material and Methods: Fifty pediatric epilepsy patients and 50 healthy children aged between 6 and 18 years underwent spectral-domain OCT (Zeiss Cirrus HD-OCT 5000) to measure RNFL, GCL+IPL, and central subfield thickness (CST). Independent-samples t-test and Spearman correlation analysis were used to assess group differences and associations with clinical variables. Retinal thickness values were also compared across ASM subgroups (valproate, levetiracetam, carbamazepine, lamotrigine monotherapy, and polytherapy).

Results: Compared to controls, children with epilepsy had significantly thinner average RNFL (95.0±11.0 µm vs 101.0±9.0 µm; p = 0.020) and superior quadrant RNFL (125±15 µm vs 132±14 µm; p = 0.030). GCL+IPL thickness was also significantly reduced in the epilepsy group (80.0±5.5 µm vs 85.0±5.0 µm; p = 0.003), as was CST (240±22 µm vs 250±20 µm; p = 0.045). Longer epilepsy duration correlated negatively with RNFL (ρ = –0.300; p = 0.030) and GCL+IPL (ρ = –0.35; p = 0.010). While retinal thickness did not differ significantly across ASM subgroups, the valproate and polytherapy groups had numerically lower values.

Conclusion: Pediatric epilepsy is associated with subtle but significant thinning of RNFL and inner macular layers, suggesting subclinical neurodegenerative effects. The observed correlation with disease duration indicates a possible progressive impact. Although differences between ASM groups were not statistically significant, valproate may contribute to retinal changes. OCT appears to be a valuable noninvasive tool for assessing neuroaxonal integrity in pediatric epilepsy.

Keywords: Epilepsy, optical coherence tomography, pediatrics, retina, valproate

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, which may lead to progressive neurodegeneration over time due to repeated excitotoxic and metabolic stress (1,2). Although these effects are primarily observed in the brain, accumulating evidence suggests that the retina may also reflect such neuroaxonal injury (3,4).

The retina, as an extension of the central nervous system, shares both structural and embryological features with the brain. Optical coherence tomography (OCT) is a noninvasive imaging modality that enables quantitative assessment of retinal neuronal layers, especially the peripapillary retinal nerve fiber layer (RNFL) and the macular ganglion cell–inner plexiform layer (GCL+IPL) (5). Thinning of these layers has been reported in various neurodegenerative and neuroinflammatory disorders, including multiple sclerosis, Alzheimer's disease, and epilepsy (6,7).

Several studies have shown reduced RNFL and GCL thickness in patients with epilepsy, suggesting subclinical retinal involvement (8–11). However, it remains unclear whether these changes are caused by the disease itself or the long-term use of antiseizure medication (ASMs). Valproate, in particular, has been associated with potential retinal toxicity (12,13), whereas agents such as levetiracetam and lamotrigine are considered to have minimal ocular effects. In a pediatric OCT-based study,

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Durgut et al. (13) demonstrated that levetiracetam monotherapy did not significantly alter RNFL, GCC, or foveal thickness compared to healthy controls, suggesting a favorable retinal safety profile for this drug in children with epilepsy. In pediatric populations, available data are limited and inconsistent, and the relative contribution of epilepsy duration, seizure burden, and ASM exposure to retinal changes remains to be fully clarified (14,15).

However, recent pediatric OCT studies have shown thinning of both RNFL and GCL+IPL layers in children with genetic generalized epilepsy and chronic ASM exposure, particularly in valproate users, further supporting the hypothesis of early subclinical neurodegeneration (16,17).

In this study, we aimed to assess retinal structural changes using spectral-domain OCT in children with epilepsy. We compared RNFL, GCL+IPL, and central subfield thickness measurements between patients and healthy controls, and examined the relationship between these parameters and clinical variables such as disease duration, seizure onset age, and ASM regimen. We hypothesized that children with epilepsy would show measurable retinal thinning and that these changes might be associated with both epilepsy duration and specific treatment exposure.

MATERIALS and METHODS

Study design and participants

This prospective, cross-sectional study included 50 children diagnosed with epilepsy and 50 age- and sex-matched healthy controls, conducted between September 2023 and September 2024. Sample size was calculated based on a moderate effect size (Cohen's d = 0.6) derived from pilot data on RNFL differences, with $\alpha = 0.05$ and 80% power, requiring a minimum of 45 participants per group. Epilepsy patients were consecutively recruited from the Department of Pediatrics at Tokat State Hospital, and ophthalmic assessments were performed at the Department of Ophthalmology, Tokat Gaziosmanpaşa University Faculty of Medicine. Inclusion criteria for the epilepsy group were: age between 6–18 years, clinical diagnosis of epilepsy according to ILAE criteria, and ongoing treatment with one or more antiseizure medication (ASMs). Exclusion criteria included prior use of vigabatrin, any ocular pathology (e.g., glaucoma, optic neuritis), systemic diseases affecting the retina (e.g., diabetes), significant refractive error (±5.0 D sphere or >3.0 D cylinder), previous intraocular surgery or trauma, and any neurological comorbidity other than epilepsy.

Control participants were neurologically healthy children of similar age and sex, with no history of epilepsy or systemic illness. All participants had best corrected visual acuity of 20/25 or better, normal color vision, and no abnormalities on slit-lamp or fundus examination.

Ophthalmic evaluation and OCT imaging

All participants underwent detailed ophthalmological examination including anterior and posterior segment biomicroscopy, non-contact tonometry (mean of three measurements), autorefractometry, and best corrected visual acuity assessment. Only the right eye was included in the analysis unless scan quality required use of the left eye.

Spectral-domain optical coherence tomography (SD-OCT) was performed using the Zeiss Cirrus HD-OCT 5000 device. Peripapillary retinal nerve fiber layer (RNFL) thickness was measured with the Optic Disc Cube 200×200 scan protocol, evaluating average global RNFL and quadrant-specific values (superior, inferior, nasal, temporal). Macular ganglion cell–inner plexiform layer (GCL+IPL) thickness was recorded using the Macular Cube 512×128 protocol with the device's Ganglion Cell Analysis (GCA) software. Additionally, central subfield thickness (CST) was measured as the average retinal thickness in the central 1-mm diameter zone. Only scans with a signal strength of 7 or higher (out of 10) were accepted for analysis. All OCT scans were performed by a certified technician who was blinded to the participants' clinical group (epilepsy vs. control) during image acquisition.

Clinical data and ASM subgrouping

Clinical data collected for each patient included age at seizure onset, duration of epilepsy, and current ASM regimen. Patients were grouped based on treatment as follows: valproate monotherapy, levetiracetam monotherapy, carbamazepine monotherapy, lamotrigine monotherapy, or polytherapy (≥2 ASMs). No patients were receiving vigabatrin. MRI findings were reviewed to exclude patients with visual pathway involvement.

Statistical analysis

Statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as mean and standard deviation (SD). Normality was assessed with the Shapiro-Wilk test. Group comparisons for OCT parameters were made using independent samples t-tests. Spearman correlation analysis was performed to examine associations between retinal thickness and clinical variables such as epilepsy duration and age at seizure onset. For ASM subgroups, one-way ANOVA was used to compare RNFL and GCL+IPL thicknesses; post-hoc Tukey's test was applied if appropriate. A p-value of <0.050 was considered statistically significant. Bonferroni correction was used for quadrant-wise RNFL comparisons.

RESULTS

A total of 100 participants were included in the study, comprising 50 children with epilepsy and 50 healthy controls. The groups were well matched in terms of age and sex. The mean age was 12.5±3.2 years in the epilepsy group and 12.0±3.4 years in the

Table I: Demographic and clinical characteristics of study participants

Variable	Epilepsy Group	Control Group
Number of patients	50	50
Age (years)*	12.5±3.2	12.0±3.4
Gender (Male/Female)	26 / 24	25 / 25
Age at seizure onset (years)*	7.3±2.5	-
Duration of epilepsy (years)*	5.2±2.0	-

**: mean±SD*

Table II: Comparison of peripapillary RNFL thickness between groups

RNFL Region	Epilepsy Group	Control Group	p*
Number of patients	50	50	-
Average RNFL†	95.0±11.0	101.0±9.0	0.020
Superior RNFL†	125±15	132±14	0.030
Inferior RNFL†	126±16	131±15	0.070
Nasal RNFL†	84±12	86±11	0.350
Temporal RNFL†	68±10	70±9	0.400

**: Independent samples T test, †: mean±SD*

control group. The epilepsy group had a mean age at seizure onset of 7.3±2.5 years and a mean disease duration of 5.2±2.0 years (Table I).

Compared to the control group, children with epilepsy showed significantly lower mean RNFL thickness (95.0±11.0 µm vs 101.0±9.0 µm; p = 0.020; mean difference: –6.0 µm, 95% CI: –10.4 to –1.6 µm; Cohen's d =0.62). The most pronounced difference was observed in the superior quadrant (125±15 µm vs 132±14 µm; p =0.030). Differences in inferior, nasal, and temporal quadrants were not statistically significant (Table II).

Children with epilepsy also demonstrated significant thinning in the macular inner retinal layers. The mean GCL+IPL thickness was significantly lower in the epilepsy group (80.0±5.5 µm) compared to controls (85.0±5.0 µm), with a mean difference of –5.0 µm (95% CI:–8.0 to –2.0 µm; p =0.003; Cohen's d = 0.85). Additionally, the central subfield thickness (CST) was mildly reduced in the epilepsy group (240±22 µm vs 250±20 µm; p = 0.045) (Table III).

In the epilepsy group, longer epilepsy duration was significantly associated with reduced RNFL (ρ =–0.30, p =0.030) and GCL+IPL thickness (ρ =–0.35, p =0.010). Additionally, younger age at seizure onset correlated with greater thinning of both RNFL (ρ =+0.28, p =0.040) and GCL+IPL (ρ =+0.32, p =0.020) (Table IV).

When the epilepsy group was analyzed based on current ASM therapy, no statistically significant differences in RNFL or GCL+IPL thickness were found among subgroups (p = 0,426, p = 0.243). However, the valproate and polytherapy subgroups exhibited numerically lower values across both layers (Table V).

Table III: Comparison of macular GCL+IPL and central subfield thickness between groups

Parameter	Epilepsy Group	Control Group	p*
Number of patients	50	50	-
GCL+IPL Thickness†	80.0±5.5	85.0±5.0	0.003
Central Subfield Thickness†	240±22	250±20	0.045

**: Independent samples T test, †: mean±SD*

Table IV: Correlation between clinical variables and retinal layer thickness in the epilepsy group

Clinical Variable	RNFL (ρ)	p*	GCL+IPL (ρ)	p*
Epilepsy duration (years)	–0.30	0.030	–0.35	0.010
Seizure onset age (years)	+0.28	0.040	+0.32	0.020

**: Spearman correlation*

Table V: Retinal thickness parameters by antiseizure medication (ASM) subgroups

ASM Group	n	Average RNFL (µm)*	GCL+IPL Thickness (µm)*
Valproate	11	94±10	79±6
Levetiracetam	7	98±9	82±5
Carbamazepine	5	96±11	81±6
Lamotrigine	6	100±8	84±5
Polytherapy	21	92±11	78±7

**: mean±SD*

DISCUSSION

In this study, we demonstrated that children with epilepsy exhibit significant thinning of the peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell–inner plexiform layer (GCL+IPL) compared to healthy controls, even in the absence of visual symptoms. These findings may reflect early structural retinal alterations associated with epilepsy, possibly indicating broader neuroaxonal involvement within the central nervous system.

Our results are consistent with previous studies reporting reduced RNFL and inner retinal thickness in epilepsy. Tak et al. (5) showed approximately 7% RNFL thinning in adults with epilepsy, while González de la Aleja et al. (8) found significant superior and inferior RNFL thinning in patients with genetic generalized epilepsy. In our pediatric cohort, average RNFL and GCL+IPL thickness were reduced by approximately 6%, suggesting that retinal involvement is evident even at younger ages and earlier stages of disease.

The superior quadrant RNFL was the most significantly affected region in our cohort. This pattern aligns with prior observations suggesting increased vulnerability of vertical retinal fibers to metabolic stress, inflammation, or mechanical factors such as fluctuating intracranial pressure during seizures (8,9). Similarly, macular GCL+IPL thinning suggests a loss of retinal ganglion

cell bodies, analogous to cortical neuronal loss observed in epilepsy-related brain imaging studies (3,4).

We also identified a significant negative correlation between epilepsy duration and both RNFL and GCL+IPL thickness, indicating a cumulative neurodegenerative process. Earlier age at seizure onset was also associated with greater thinning, likely due to longer cumulative disease exposure. These findings support the use of OCT as a potential monitoring tool for tracking neuroaxonal damage over time.

Kaplan et al. (16) also reported that adolescents with genetic generalized epilepsy exhibited inner retinal thinning, even in the absence of visual complaints, supporting the notion of early subclinical involvement.

Importantly, although group comparisons did not reveal statistically significant differences between ASM subgroups, patients receiving valproate or polytherapy showed numerically lower retinal thickness values. This trend is in line with previous reports indicating potential retinotoxic effects of valproate (9,11). Xiong et al. (9) reported that valproate monotherapy was associated with significantly lower RNFL values compared to other ASMs or untreated patients, and meta-analytic data have confirmed RNFL thinning in pediatric patients using valproate, particularly in nasal and inferior quadrants (6). Sahin and Cirakli found that children treated with valproate had lower GCL+IPL and RNFL thickness compared to those receiving levetiracetam, further supporting our findings (17). Although our findings did not reach statistical significance—possibly due to limited subgroup sizes—they suggest that further investigation is warranted. Similarly, a recent pediatric OCT study found that children receiving valproate had significantly lower GCL+IPL and RNFL thickness compared to those on levetiracetam, suggesting a possible drug-specific retinal vulnerability (17).

In contrast, patients receiving levetiracetam or lamotrigine had relatively preserved retinal structure, consistent with their favorable neuro-ophthalmic safety profiles (13). Our data also do not support a strong effect of polytherapy per se, as the observed thinning may be confounded by longer disease duration or valproate inclusion within these regimens.

Chontos et al. (18) recently published a meta-analysis confirming consistent inner retinal thinning in epilepsy, with valproate exposure identified as a significant contributing factor. In another pediatric OCT study, Gultutan et al. (19) observed that retinal blood flow was reduced in children receiving valproate, in parallel with structural thinning. Moreover, a recent pharmacogenomic analysis by Boothman et al. (20) demonstrated that individuals exposed to vigabatrin experienced varying degrees of peripapillary RNFL loss depending on genetic susceptibility, highlighting the potential for personalized risk assessment in ASM-induced retinal toxicity. These findings, together with ours, underscore the importance of considering ASM-specific effects when interpreting OCT data in epilepsy populations.

From a clinical perspective, OCT may serve as a valuable, noninvasive biomarker for detecting early retinal changes in children with epilepsy. Its utility may extend beyond research into monitoring long-term neurotoxic effects of chronic ASM use, particularly in patients requiring long-term therapy or showing signs of cognitive decline. While retinal thinning alone may not impair visual function, it may reflect broader CNS involvement and help identify patients at risk of neurodevelopmental complications. Future studies integrating visual field testing or electrophysiological assessments are needed to clarify the functional consequences of these structural findings.

Our study has several limitations. Its cross-sectional design precludes evaluation of progression over time. The sample size was moderate and not powered to detect subtle inter-drug differences. Although OCT revealed structural alterations, functional visual testing (e.g., visual fields or electroretinography) was not performed. Therefore, the clinical implications of these structural findings in terms of visual function remain uncertain.

CONCLUSION

This study demonstrated that pediatric epilepsy is associated with subtle but statistically significant thinning of the peripapillary retinal nerve fiber layer (RNFL) and macular ganglion cell–inner plexiform layer (GCL+IPL) as measured by spectral-domain optical coherence tomography. These retinal structural alterations may reflect subclinical neuroaxonal damage linked to chronic epileptic activity. The observed negative correlations between disease duration and retinal thickness suggest a cumulative degenerative process, even in the absence of overt visual symptoms. Although no statistically significant differences were observed among antiseizure medication (ASM) subgroups, numerically lower values in the valproate and polytherapy groups raise the possibility of a medication-related effect that warrants further investigation. OCT may serve as a valuable, noninvasive biomarker for monitoring neurodegeneration in pediatric epilepsy. Prospective, longitudinal studies with larger cohorts are needed to validate these findings and determine their potential clinical implications in neurodevelopmental follow-up and therapeutic decision-making.

Ethics committee approval

This study was approved by the Tokat Gaziosmanpaşa University Clinical Research Ethics Committee (Decision No: 23-KAEK-195, Date: August 31, 2023).

Contribution of the authors

AG: Conceptualization, ophthalmologic examinations, OCT analysis, data interpretation, manuscript drafting, final approval. ***KG:*** Patient recruitment and follow-up, clinical data collection, coordination of pediatric evaluations, manuscript revision, final approval.

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Conflict of interest

The authors declare that there is no conflict of interest.

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