Ocular microvascular alterations in epileptic patients

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Abstract:

PURPOSE: The brain and eye are linked by the same nerves and arteries, presenting a hemodynamic continuity. Alterations in ocular perfusion may have an impact on the visual function or the neurodegenerative process. We aimed to assess whether there is a relationship between epilepsy and ocular microvasculature in the adult population by optical coherence tomography angiography (OCTA).

METHODS: This observational, cross-sectional study included 22 epilepsy patients (epilepsy group), and 21 healthy controls (control group). OCTA analysis of the vessel density (VD) of the retinal superficial capillary plexus, deep capillary plexus, foveal retinal thickness (FRT), foveal avascular zone (FAZ) areas, and the radial peripapillary capillary, and retinal nerve fiber layer (RNFL) thickness were evaluated.

RESULTS: Age, gender, central corneal thicknesses, and mean intraocular pressure levels were similar between the groups (P>0.05 for all). Superficial and deep retinal capillary VD, FRT, and FAZ areas were not significantly different between the groups. However, significantly lower superior quadrant RNFL thicknesses and lower optic disc whole and peripapillary capillary VD were detected in the epilepsy group when compared to the control group (P = 0.026, P < 0.001, and P = 0.006, respectively).

CONCLUSION: Besides the neurological basis of epilepsy, vascular dysfunction seems to be another risk factor in the pathophysiology of epilepsy. OCTA may be suggested as a potentially useful biomarker for ocular microvascular alterations in epileptic patients.

Keywords:

Epilepsy, microvasculature, optic disc, optical coherence tomography angiography, retina

Introduction

Epilepsy is a frequent chronic neurological disease characterized by sudden paroxysmal episodes of neuronal electric discharges.[1-3] The blood–brain barrier dysfunction and microvascular changes are likely present in epilepsy.[1,2] In this regard, the pathophysiology of epilepsy also includes destroyed cerebral microvasculature in which vascular endothelial growth factor plays an important role.[1] Moreover, reduced cerebral blood flow and decreased cerebral glucose metabolism have been identified in epileptic patients also treated with antiepileptic drug therapy.[4-7]

The brain and eye are linked by the same nerves (the sympathetic nervous system) and arteries (the carotid arterial network), presenting a hemodynamic continuity. The ocular microvasculature may be affected by cerebral hemodynamic disorder described in epileptic children.[2] Alterations in ocular perfusion may have an impact on the visual function or the neurodegenerative process.[2,8] The microvascular structure of the different retinal layers and also the peripapillary region of the optic nerve head can be shown using the noninvasive imaging technique of optical coherence tomography angiography (OCTA).[2,3]

There are several studies about ocular perfusion characteristics in epileptic children.[2,3] However, to our knowledge, there is no study investigating the OCTA findings in adult epileptic patients. Therefore, we aimed to evaluate the microvascular changes of the optic nerve head and retina using OCTA in the adult epileptic population and compare the OCTA findings with age and sex-matched healthy controls.

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Methods

This submission has received review board/ethics committee approval (2024/04). The study adhered to the tenets of the Declaration of Helsinki. This observational, cross-sectional study included 22 epilepsy patients (epilepsy group) who were diagnosed with epilepsy in the neurology clinic of our hospital and 21 healthy controls (Control Group) who were admitted to the ophthalmology outpatient clinic for a general eye check-up without known epilepsy disease, ocular pathology and surgery, and additional systemic diseases. Patients with a neurologic disease other than epilepsy, systemic diseases such as diabetes, hypertension were excluded from the study. Patients with previous ocular surgery, ocular trauma, and other ocular diseases such as uveitis, cataracts, or glaucoma were also excluded from the study. A full ophthalmologic examination was performed in both eyes of all subjects. Demographic findings and disease durations of patients were noted.

All measurements of the patients were performed during the attack-free period. All subjects underwent full ophthalmologic examination, including best-corrected visual acuity, biomicroscopic anterior segment, and fundus examination. Intraocular pressure (IOP) and central corneal thickness (CCT) measurements were assessed by noncontact tonometer. The OCTA images were obtained by a single technician using AngioVue OCTA software (Avanti RTVue-XR 100, Optovue Inc, Fremont, CA). The OCTA image protocol involved two raster scans acquired by repeated B-scans at 304 raster positions, and each B-scan consisted of 304 A-scans covering a 6 mm × 6 mm area centered on the macula and 4.5 mm × 4.5 mm area centered in optic nerve head. Motion artifacts, including residual axial motion and transverse saccadic motion, were removed by three-dimensional orthogonal registration and by merging the pair of scans using the contained software (ReVue, version 2014.2.0.15; Optovue Inc.). Shadow graphic projection artifacts were removed with a slab-subtraction method, reducing inner retinal projection onto the outer retinal angiogram. Foveal retinal thickness, vessel density (VD) in the fovea of superficial and deep capillary plexus, and 300 μm width area around the foveal avascular zone (FAZ) were measured. FAZ was defined as the area without vessels that covers the center of the fovea. The fovea was defined as an annulus centered on the FAZ with inner and outer ring diameters of 1 mm. Flow areas of choriocapillaris were noted, too. Radial peripapillary capillary (RPC) densities (including whole image, inside disc, and peripapillary capillary plexus densities), and retinal nerve fiber layer (RNFL) thickness were also obtained. The peripapillary region was automatically defined by the software as a 1.0-mm-wide round annulus extending from the optic disc. OCTA scans with a quality level < 8, artifacts, or decentered were not used in the study. All measurements were taken at the same hour of the day (10:00 AM–12:00 PM) in all groups to rule out the effect of diurnal variations on OCTA values. Both eyes of the individuals were analyzed for statistical analysis.

Statistical analysis

Statistical analyses were performed with IBM SPSS for Windows Version 21.0 software (SPSS, IBM Corp, Armonk, NY, USA). Numerical variables were expressed as mean ± standard deviation or range as appropriate. Categorical variables were summarized as numbers and percentages. The normality of the distribution of continuous variables was evaluated with the aid of the Kolmogorov–Smirnov test. Independent samples *t*-test was used to determine the difference between two independent subgroups. Pearson's correlation coefficient was used for the correlations between variables, and $P \leq 0.05$ was considered to reflect statistical significance.

Results

Forty-four eyes of 22 epilepsy patients and 42 eyes of 21 control subjects were enrolled. The mean ages of the epilepsy group and control group were 35.2 (18–77) years and 36.9 (23–63) years, respectively ($P = 0.678$). Gender, best-corrected visual acuities, mean IOP levels, and CCT levels were similar between the groups. The comparisons of demographic and clinical characteristics between the groups are shown in Table 1. Eight of the epilepsy patients were diagnosed with generalized epilepsy and 14 of them with focal epilepsy. All of the epilepsy patients were receiving antiepileptic drug monotherapy (levetiracetam, $n = 14$; carbamazepine, $n = 4$; lamotrigine, $n = 3$; and valproic acid, $n = 1$). There was no significant difference regarding average and inferior, nasal, temporal quadrant RNFL thicknesses, FAZ and flow areas, and superficial and deep retinal VD. However, significantly lower superior quadrant RNFL thicknesses, lower optic disc whole, and peripapillary capillary VD were detected in epilepsy group than the control group (129.04 ± 12.7 μm vs. 135.92 ± 15.3 μm, $P = 0.026$, 49.05 ± 1.7% vs. 50.65 ± 2.0%, $P < 0.001$, 51.27 ± 2.3% vs. 52.64 ± 2.1%, $P = 0.017$, respectively). OCTA images of a subject from the epilepsy group and control group were presented in Figures 1 and 2, respectively. The outcomes of retina and optic disc OCTA

Table 1: Comparison of demographic and clinical characteristics between the groups

Characteristics	Epilepsy group (*n*=44 eyes)	Control group (*n*=42 eyes)	*P*
Number of subjects	22	21	
Age (years), mean (range)	35.2 (18–77)	36.9 (23–63)	0.678
Gender, *n* (%)			
Female	15 (68.2)	12 (57.1)	0.537
Male	7 (31.8)	9 (42.9)	
BMI (kg/m^2), mean±SD	24.7±3.9	25.8±4.2	0.405
CCT (μm), mean±SD	539.4±26.9	549.3±27.5	0.134
IOP (mmHg), mean±SD	16.9±3.5	16.3±2.0	0.326
Duration of epilepsy (year), mean (range)	5.05 (0.08–18)	-	
Attacks (year), mean (range)	3 (0–6)	-	
FRT (μm), mean±SD	244.2±27.5	245.9±16.5	0.738

BMI: Body mass index, SD: Standard deviation, FRT: Foveal retinal thickness, IOP: Intraocular pressure, CCT: Central corneal thickness

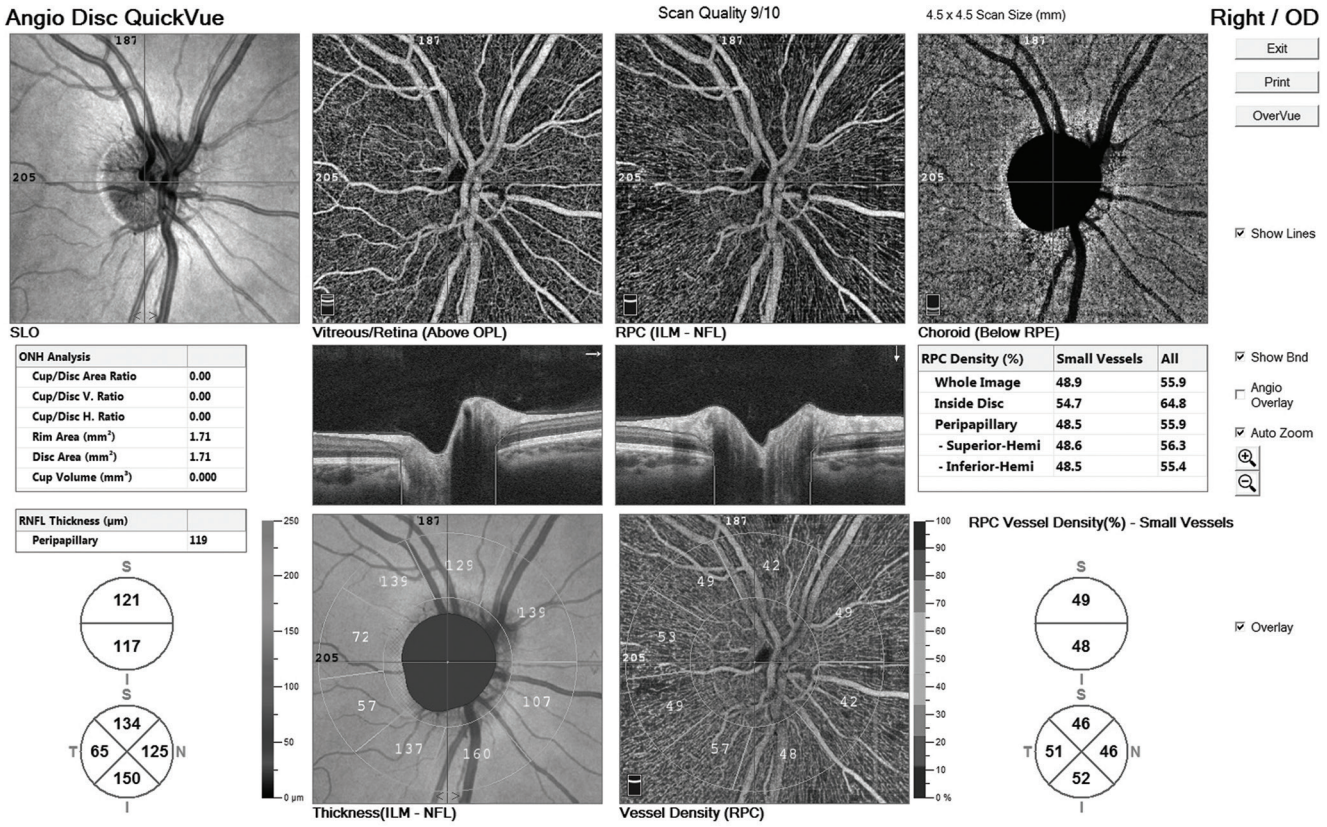

Figure 1: Optical coherence tomography angiography image (radial peripapillary capillary density) of a 30-year-old female subject from the epilepsy group. OCTA: Optical coherence tomography angiography

Table 2: The outcomes of retina parameters by optical coherence tomography angiography

	Epilepsy group (*n*=44 eyes)	Control group (*n*=42 eyes)	*P*
Superficial VD (%)			
Whole image	50.7±3.3	51.8±3.2	0.114
Fovea	20.1±7.5	21.1±6.1	0.486
Parafovea	53.7±4.0	54.9±3.6	0.168
Perifovea	51.4±3.3	52.4±3.4	0.177
Deep VD (%)			
Whole image	53.7±7.1	54.4±6.4	0.611
Fovea	38.3±8.2	38.5±8.4	0.922
Parafovea	58.0±5.1	56.7±5.0	0.665
Perifovea	56.4±6.7	56.5±6.9	0.924
FAZ area (mm²)	0.29±0.1	0.28±0.1	0.801

OCTA: Optical coherence tomography angiography, FAZ: Area of 300 µm width around the foveal avascular zone, SD: Standard deviation, VD: Vessel density

parameters of the groups are shown in Tables 2 and 3, respectively. Disease duration and attacks/year did not show any significant correlations with OCTA values.

Discussion

To our knowledge, there is no study investigating the OCTA findings in adult epileptic patients. In this study, significant lower superior quadrant RNFL thicknesses, lower optic disc whole, and peripapillary capillary VD were detected in the epilepsy group when compared to the control group. The observation of a reduction in superior quadrant RNFL levels and optic disc VD may strengthen the link between hypoperfusion, ischemia, inflammation, and the neurovascular basis of epilepsy disease.

Vascular endothelial damage and inflammation play a role in VD. In our study, no significant difference between groups regarding superficial and deep retinal VD was found. It can be explained by the fact that the retina is affected later, or it is more resistant to hypoxia and inflammation than the optic disc. On the other hand, there was a significant difference between the groups in terms of optic disc whole and peripapillary microvasculature. The optic disc may be more sensitive to capillary blood circulation changes. In addition, perhaps, neurodegenerative changes may play an early role in optic disc VD then macular retinal VD. Epileptic seizures may induce an immune response in the eye.[9] Herein, the optic nerve head may show early immune response than the retina by the brain inflammation through the eyes.

Hilton *et al*.[4] mentioned that patients with epilepsy exhibit reduced neuroretinal capillary blood flow, volume, and velocity compared with normal subjects. A reduction in ocular perfusion may have implications for visual function in people with epilepsy.

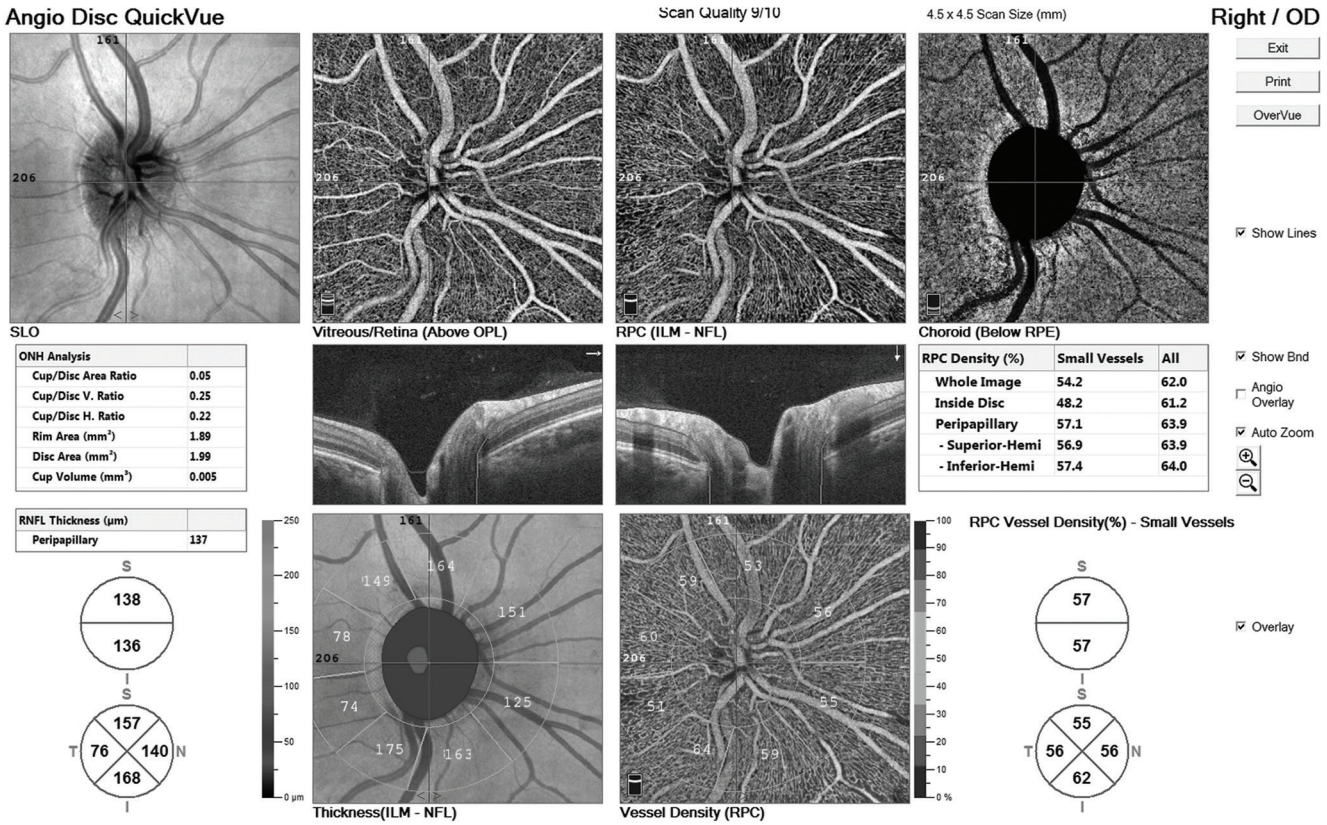

Figure 2: Optical coherence tomography angiography image (radial peripapillary capillary density) of a 30-year-old female subject from the control group. OCTA: Optical coherence tomography angiography

Table 3: The outcomes of optic disc parameters by optical coherence tomography angiography

	Epilepsy group (n=44) eyes	Control group (n=42) eyes	*P*
RNFL thickness (µm), mean±SD	110.2±10.3	112.8±11.2	0.271
Inferior quadrant	141.5±17.6	140.7±14.5	0.828
Superior quadrant	129.0±12.7	135.9±15.3	0.026
Temporal quadrant	72.9±10.1	73.8±9.0	0.690
Nasal quadrant	100.5±15.1	103.8±18.4	0.368
RPC density (%), mean±SD			
Whole image	49.0±1.7	50.6±2.0	<0.001
Inside disc	50.8±4.7	51.2±3.9	0.690
Peripapillary	51.2±2.3	52.6±2.1	0.006

OCTA: Optical coherence tomography angiography, RNFL: Retinal nerve fiber layer, RPC: Radial peripapillary capillary, SD: Standard deviation

In a study, VD of the RPC and the SCP and DCP of the macula were mentioned as similar results between the newly diagnosed epileptic children and control groups.[2] The fact that there is no effect on OCTA findings at the early ages of epilepsy makes us understand the importance of follow-up these children.

There several studies about the relationship between epilepsy and OCT findings.[10-13] In a study of Torun *et al*.,[11] structural alterations in the retina and choroid tissue of epilepsy patients and subtypes using enhanced depth imaging OCT. They mentioned that epilepsy disease has effects on the posterior segment of the eye. In another OCT study, authors reported that adults with epilepsy have a significantly thinner retina than healthy persons.[12] They mentioned that especially people with many big seizures and lots of medications have a thinner retina, and measurement of the retina can be useful as a marker of disease severity and to inform patient management. Bayraktar Bilen *et al*.[14] showed that epileptic patients taking antiepileptic drugs have reduced ganglion cell complex and RNFL thickness compared to healthy controls. This can be related to the neuro-ophthalmic process of epilepsy as a brain disorder affecting the eye. In our study, different from these studies, we evaluated OCTA images.

The present study has some limitations. First, the number of patients in the groups was relatively small. The observational design of our study cannot determine the causality. Second, choroidal perfusion from the microcirculation is found to be lower in epileptic children in several studies.[2,3] We could not evaluate choroidal perfusions. Third, evaluating the visual-evoked potential of epileptic patients[15] and the correlation with OCTA results could also give us valuable information. In addition, subgroup analysis according to seizure type (generalized/focal) could also be useful, but the size of the groups was small. Other larger studies can be made for these issues. Finally, all epilepsy patients were receiving antiepileptic drug therapy monotherapy. Bayraktar Bilen *et al*.[14] showed that epileptic patients taking antiepileptic drugs have reduced

ganglion cell complex and RNFL thickness compared to healthy controls related to the epileptic process in the brain. Medication with antiepileptic drugs may lead to thinner RNFL values, however, macular and radial peripapillary VD were not affected, as mentioned in the study of Gultutan *et al*.[3]

Conclusion

In conclusion, besides the neurological basis of epilepsy, vascular dysfunction seems to be another risk factor in the pathophysiology of epilepsy. Alterations in optic nerve head perfusion may occur in epilepsy. OCTA may be used as a useful tool for measuring and monitoring ocular microvascular alterations in epileptic patients. In this context, early diagnosis of ocular microvascular problems is important in preventing potential vision impairment. Further and larger researches are needed to evaluate the pathophysiology of the epileptic process in retinal microvasculature.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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