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ORIGINAL PAPER

Evaluation of migraine patients with optical coherence tomography angiography

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Abstract
Purpose To compare optical coherence tomography angiography (OCTA) findings in cases with migraine and healthy controls.
Methods Thirty-eight eyes of 19 patients with migraine with aura and 38 eyes of 19 healthy subjects were enrolled in this prospective and comparative study. All patients and healthy controls were evaluated with OCTA (Triton, Topcon®, Tokyo, Japan). Central macular thickness (CMT), optic disc parameters (such as retinal nerve fibre layer [RNFL] thickness and rim and disc areas), foveal avascular zone (FAZ) and parafoveal superficial vessel density (VD) measurements were analysed.
Results The optic disc rim area was significantly larger in the migraine group compared to the control group ($p = 0.009$). In OCTA measurements, the FAZ area was significantly larger in migraine patients ($p = 0.001$). The parafoveal superficial VD measurements were found to be lower in the migraine patients in all quadrants, but not statistically significant. Weak negative correlations were found between superior parafoveal VD and disease duration in migraine patients.
Conclusion Migraine with aura was associated with optic disc rim changes, but without any remarkable foveal vascular decrements. It is possible for migraine to cause structural changes due to its chronic nature.

Keywords Migraine · Aura · Optical coherence tomography angiography

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Introduction

Migraine is a complex episodic neurovascular disease characterized by recurrent episodes of throbbing headache. The typical headache is most commonly unilateral, pulsating, and often moderate-to-severe that may last from hours to 2–3 days. Affecting around 15% of the population, migraine disease is the third most common disorder worldwide in both genders. Migraine contains two main entities: migraine with aura and migraine without aura [1].

It is suggested that combined neural and vascular factors are interacting; however, the underlying pathophysiological mechanisms are not entirely elucidated. Migraine, particularly migraine with aura, is

associated with micro- or macrovascular changes during the attack. Several hypotheses have been proposed about the pathogenesis of migraine, such as inherited alteration of brain excitability, intracranial arterial dilatation, recurrent activation and sensitization of the trigeminovascular pathway, and consequent structural and functional changes in genetically susceptible individuals [2–4].

Migraine episodes lead to the activation and sensitization of the trigeminal vascular system (TGVS). The pathway is responsible for regulating vascular tone and for the transmission of pain signals [2]. The TGVS innervates both intra- and extrameningeal blood vessels and the brainstem, also the extracranial tissues and the structures of the eyes [5].

According to the literature, migraine is a risk factor for ischaemic complications of the retina and optic nerve, such as ischaemic optic neuropathy and retinal artery and vein occlusions [6–10]. Ganglion cell death due to an alteration in the perfusion of the optic nerve head or the retina has been suggested in migraine patients [11]. Therefore, there are several studies that have evaluated retinal nerve fibre layer (RNFL) thickness differences in migraine patients [5, 11, 12].

Recently, optical coherence tomography angiography (OCTA), a new noninvasive imaging technique, permits detailed visualization of the retinal microvasculature. As a result of the movement of erythrocytes within the retinal capillaries occurs flow imaging in repeated B-scans. In different vascular diseases, OCTA device provides microvascular network evaluation and vessel density (VD) calculation [13].

To date, limited data were published about the features of VD in migraine using OCTA. In this study, we aimed to study retinal VD and RNFL thickness changes in migraine patients and healthy subjects.

Material and methods

This prospective, comparative study was performed at the Ankara Numune Training and Research Hospital. Each subject conferred written informed consent to take part in the study approved by the Institutional Review Board. The study was carried out in adherence to the ethical standards of the Declaration of Helsinki.

The subjects were divided into two groups: normal cases (control group) and migraine with aura having at least one visual symptom (study group). The study group comprised subjects older than 18 years old who were followed up in the Neuro-ophthalmology Department and had a migraine attack with aura within the last two weeks. The control group is comprised of healthy individuals with no eye disease. Exclusion criteria were ocular trauma history, posterior segment diseases (glaucoma, optic neuropathy), optical media opacities and any systemic diseases. Patients who were under 18 years old or had a poor fixation were also excluded.

All participants underwent complete ophthalmologic examination. Best corrected visual acuity (BCVA) was assessed using the decimal system. Slit lamp biomicroscopy, fundus examination, intraocular pressure (IOP) by air-puff tonometry, swept-source optic coherence tomography (SS-OCT) and OCTA scans were performed. All eyes were imaged with a Triton SS-OCT device (Topcon®, Tokyo, Japan) by the same experienced examiner. Central macular thickness (CMT) and optic disc parameters (RNFL thickness and rim area) were measured using SS-OCT. Parafoveal superficial VD measurements were measured using an OCTA device (RTVue XR Avanti; Optovue, Inc., Fremont, CA). The size of the OCTA scan was used as 3×3 mm. The superficial vascular layer was defined between the internal limiting membrane (ILM) and inner plexiform layer (IPL). The quadrant analyses were determined by the device software based on the Early Treatment Diabetic Retinopathy Study (ETDRS) sector map. The temporal, inferior, nasal and superior sectors of the parafoveal ring were compared with the normal group, excluding the central ring. Two eyes per subject were selected for the analyses.

Statistical data analysis was done with SPSS software ver. 18 (IBM Corp., Armonk, NY). The categorical variables were compared with the Chi-square test or Fisher's exact test. The normality of the variables was assessed using the Shapiro–Wilk test. One-way ANOVA was applied for normally distributed variables. For more than two groups, the Kruskal–Wallis test was applied for normally distributed variables. Dunn's test was applied for pairwise comparisons. P value less than 0.05 was considered significant.

Results

This study included 38 eyes of 19 healthy subjects and 38 eyes of 19 patients with migraine with aura. The migraine group included 17 female and 2 male subjects, with a mean age of 37.2 ± 12.8 years, while the control group included 17 female and 2 male subjects, with a mean age of 36.9 ± 11.5 years. There were no statistically significant differences between migraine patients and control eyes in terms of age and sex (p = 1.000 and p = 0.958, respectively).

Mean duration of the disease was 9,47 ± 7,57 years (range 0.5–25 years). The measurements and comparisons of BCVA, IOP, CMT, optic disc parameters (RNFL thickness and rim and disc areas) and parafoveal superficial VD (superior, inferior, temporal and nasal quadrants) are outlined in Table 1. There were no significant differences in the mean BCVA and IOP values between the two groups.

In SS-OCT measurements, RNFL thickness, CMT and the optic disc area were not statistically different between the two groups (p = 0.770, p = 0.951 and p = 0.817, respectively). The optic disc rim area was significantly larger in the migraine group compared with the control group (p = 0.009).

In macular OCTA measurements, the FAZ area was 0.326 ± 0.065 mm^2 in migraine patients, significantly larger than the control group (0.272 ± 0.070 mm^2, p = 0.001). The parafoveal superficial VD measurements were higher in the control group in all four quadrants, but not statistically significant (p values for the superior, inferior, temporal and nasal quadrants 0.358, 0.390, 0.551 and 0.135, respectively).

In correlation analyses, there were no correlations between disease duration and CMT or optic disc parameters. Parafoveal superficial VD measurements were not correlated with disease duration, except in the superior quadrant. There was a weak negative correlation between the superior parafoveal VD and disease duration (p = 0.048) (Table 2).

Discussion

Despite the indefinite pathophysiology of the migraine, neurovascular changes are likely to cause alterations in both cerebral and retinal circulation. This effect possibly results in damage to the brain and even the retina or optic nerve. In the current study, we found a larger FAZ and optic disc rim area in migraine patients. However, no significant differences were found in terms of RNFL thickness or parafoveal OCTA measurements. There are few studies that deal with the effects of migraine on retinal vasculature using OCTA. A study by Chang et al. showed a significantly enlarged FAZ area and reduced superficial foveal VD in migraine patients. They suggested that OCTA could be useful as a biomarker for migraine with aura [13].

Ulusoy et al.[14] reported a thinner average RNFL thickness and a larger FAZ area in migraine patients. They found lower superficial and deeper foveal VDs in OCTA, but not a significant difference in parafoveal VDs. They also indicated that deep foveal VD and average RNFL were significantly lower in patients with migraine with aura having brain white matter hyperintensities.

Table 1 Measurements in migraine and control groups

	Migraine	Control	p
BCVA	0.98 ± 0.05	1.00	0.083
IOP (mmHg)	13.5 ± 2.5	13.6 ± 2.3	0.885
CMT (μm)	254.9 ± 23.2	254.6 ± 25.5	0.951
RNFL average (μm)	113.2 ± 8.8	112.2 ± 17.2	0.77
Rim area (mm^2)	1.65 ± 0.48	1.41 ± 0.27	0.009
Disc area (mm^2)	2.05 ± 0.28	2.06 ± 0.31	0.817
FAZ (mm^2)	0.326 ± 0.065	0.272 ± 0.070	0.001
VD superior (%)	47.63 ± 2.69	48.14 ± 2.06	0.358
VD inferior (%)	46.73 ± 2.58	47.25 ± 2.56	0.390
VD temporal (%)	45.85 ± 2.11	46.13 ± 2.05	0.551
VD nasal (%)	44.63 ± 2.22	45.50 ± 2.73	0.135

BCVA Best corrected visual acuity, *CMT* Central macular thickness, *IOP* Intraocular pressure, *RNFL* Retinal nerve fibre layer, *VD* Vessel density, *FAZ* Foveal avascular zone

Table 2 Correlation between parameters and migraine duration

	r	*p*
CMT	0.162	0.330
RNFL thickness	0.100	0.550
Rim area	−0.030	0.858
Disc area	−0.056	0.738
VD superior	−0.323	0.048
VD inferior	−0.249	0.131
VD temporal	−0.104	0.534
VD nasal	−0.229	0.166

CMT Central macular thickness, *RNFL* Retinal nerve fibre layer, *VD* Vessel density

The enlarged FAZ area in migraineurs has been proposed as a supportive finding for retinal microvascular disease [13]. Several studies have indicated the relationship between migraine and cardiac ischaemic events or stroke [15, 16]. Thus, these FAZ changes could be a secondary result of ischemia or a systemic vasculopathy.

Recently, a case report has revealed that OCTA can provide important evidence during a migraine attack, such as temporary narrowing of retinal vessels and decreasing capillary densities. Restoration of vascular changes 3 h after the visual aura may explain why the vascular structure is not permanently affected [17].

In the present study, the optic rim area was significantly larger (1.65 ± 0.48 mm^2) in the migraine group compared to the control group (1.41 ± 0.27 mm^2), while the optic disc area was 2.05 ± 0.28 mm^2 in the migraine group and 2.06 ± 0.31 mm^2 in the control group. Previous studies have demonstrated the association between migraine and normal tension glaucoma [18]. Since the rim area reflects the amount of nerve fibres in the optic disc, it can be assumed as early damage due to the vascular alterations.

Some studies have reported thinning of the RNFL in migraine patients, which is explained by chronic ischaemic damage and suggested a relationship between glaucoma and migraine [5, 12]. Martinez et al. reported a normal average RNFL thickness in migraineurs with aura, except for the temporal quadrant. They found a strong correlation between migraine severity and RNFL thickness parameters [11]. A meta-analysis by Feng et al. [19] described a significant reduction in average RNFL thickness in patients with migraine. Demircan et al. [20] described significant thinning of the nasal sector RNFL and choroid in migraine patients. The selective partly RNFL involvement has been explained with differences in the vulnerability of retinal axons to ischemia [14]. In our study, we found the average RNFL thicknesses not statistically different between the two groups ($p = 0.77$). Similar to our findings, Tan et al. [21] detected no significant difference in the RNFL thickness of migraine patients. Simsek et al. [22] also found no significant difference in average RNFL thickness measurements in inter-group comparisons.

In OCT measurements, there was no significant difference in terms of CMT between the two groups. Yulek et al. [12] and Demircan et al. [20] also did not find any difference in CMT values between groups.

In the current study, we found a larger optic disc rim area in patients with migraine with aura. This finding might raise the question again about the association between migraine and glaucoma, although there was no difference in RNFL thickness. Despite the enlargement of the FAZ area, the parafoveal superficial VD measurements were not found to be significantly lower in the migraine group. It is likely that there may be a relationship between migraine and the structural brain and ocular changes.

The main limitations of our study are its small sample size and not being able to evaluate the patients during a migraine attack.

In conclusion, although the vascular involvement of migraine disease is a transient phenomenon, the relationship between migraine pathophysiology and ischemia could be supported with the alteration of retinal vascular densities using OCTA as a biomarker. Future studies will be supportive to determine the significance of OCTA in the management of migraine patients.

Declarations

Conflict of interest All authors disclosure no conflict of interest.

Ethical approval All procedures performed in this article involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in this study.

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