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ORIGINAL COMMUNICATION

Microvascular involvement in migraine: an optical coherence tomography angiography study

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Abstract

Objective The aim of this study was to evaluate the microvasculature of the macula and the optic nerve in patients affected by migraine with aura (MA) and without aura (MO) by optical coherence tomography angiography (OCTA), comparing the findings with healthy controls (HC).

Methods We collected data from ocular and orthotic examinations, including eye motility, intraocular pressure measurement, best-corrected visual acuity (BCVA) measurement, objective refraction measurement, fundus examination, macular and optic disk OCTA examination. All subjects were imaged with solix fullrange OCT. The following OCTA parameters were recorded: macular vessel density (VD), inside disc VD, peripapillary VD, disc whole image VD, fovea choriocapillaris VD, fovea VD, parafovea VD, peripapillary thickness, fovea thickness, parafovea thickness, macular full retinal thickness, and foveal avascular zone (FAZ) parameters. Clinical and demographical data about migraine patients were collected by a neurologist.

Results We included 56 eyes from 28 patients with a diagnosis of MO, 32 eyes from 16 patients with a diagnosis of MA, and 32 eyes from 16 HC subjects. The FAZ area was 0.230 ± 0.099 mm^2 in the MO group, 0.248 ± 0.091 mm^2 in the MA group and 0.184 ± 0.061 mm^2 in the control group. The FAZ area was significantly larger in the MA group than in the HC group ($p = 0.007$). The foveal choriocapillaris VD was significantly lower in MA patients ($63.6 \pm 2.49\%$) when compared with MO patients ($65.27 \pm 3.29\%$) ($p = 0.02$).

Conclusion An impairment of retinal microcirculation can be detected in patients with MA, as demonstrated by the enlargement of FAZ. Moreover, the study of choroid circulation may reveal microvascular damage in patients with migraine with aura. OCTA is a useful non-invasive screening tool for the detection of microcirculatory disturbance in patients with migraine.

Keywords Migraine · OCTA · Aura · FAZ · Retinopathy · Retinal vessel density

Introduction

Migraine is an extremely common neurobiological disorder, ranking among the most disabling medical illnesses [5]. Migraine is a paroxysmal disease in which attacks recur

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cyclically with variable intensity and frequency [8]. Up to one-third of migraineurs experience aura, defined as a totally reversible phenomenon that expresses itself as a gradually developing disturbance of the sensory, speech, visual and motor sphere [1].

Although the pathogenesis of migraine is not yet completely clarified, it is proposed that combined neural and vascular factors interact. Migraine attacks cause activation and sensitization of the trigeminovascular system, which is the major efferent pathway responsible for pain transmission [9].

The pathophysiological mechanism for migraine aura is thought to be cortical spreading depression, a wave of depolarization that propagates across the cerebral cortex, where an initial brief hyperaemia is followed by cerebral hypoperfusion [9].

The introduction of a novel technique, optical coherence tomography angiography (OCTA), has allowed the non-invasive study of retinal and choroidal blood flow in several disorders [13].

Few studies assessed retinal vessel densities with OCTA in small cohorts of patients with migraine, demonstrating that migraine patients present a retinal vascular decrement [6, 10, 25].

Since the retinal and cerebral microcirculation share similar embryology and anatomy, and neurovascular mechanisms may underlie migraine pathogenesis, an association between migraine and retinal microvascular changes can be hypothesized [16]. Alterations of the retinal vascular system and ischemic complications of the retina and optic nerve have been reported in patients with migraine [3, 15]. However, only limited evidence supports the involvement of retinal microvasculature in patients with migraine, especially in the ones with aura.

We, therefore, analysed the microcirculation of the macula and the optic nerve in patients with a diagnosis of migraine with and without aura by OCTA, comparing the findings with healthy controls.

Methods

Study design and population

The present study is a prospective, observational, case–control study. We consecutively enrolled patients diagnosed with migraine admitted to the Headache Centre of the Neurology Outpatients Clinic of the Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome. Healthy controls were recruited among faculty and staff members. Patients and controls were enrolled from February 2021 to March 2022.

Inclusion criteria for patients with migraine were: patients between the age of 18 and 60 years; a diagnosis of migraine with aura (MA) or migraine without aura (MO) according to the International Classification of Headache Disorders 3 (ICHD3) [1].

Inclusion criteria for healthy controls (HC) were: patients between 18 and 60 years; no history of primary or secondary headache; no history of neurological and psychiatric diseases.

The age of 60 as a cutoff was chosen accordingly to data reported in the literature on OCTA parameters change with ageing [19].

Exclusion criteria for all groups (MA, MO, and HC) were: systemic diseases affecting the microcirculation, such as hypertension, diabetes mellitus, chronic kidney disease, and vasculitis; use of vasoactive medications such as beta-blockers and calcium channel blockers; myopic or hyperopic spherical equivalent refractive errors greater than 3.00 dioptres; other neurological diseases; disorders affecting the retina and the optic nerve, such as glaucoma; any history of intraocular surgery, including cataract extraction. All patients gave written informed consent.

The study was approved by the Ethical Committee of the Università Cattolica del Sacro Cuore (protocol ID 4155/2021).

Patients' demographic and clinical information

The following demographic information was collected: age, gender, and comorbidities.

For patients with migraine, the following data were gathered: type of migraine; mean monthly migraine frequency and mean monthly headache frequency; mean severity of pain through the visual analogue scale (VAS); type and number of acute medications intake; type of migraine prophylaxis; migraine-related disability assessed by the Head Impact test-6 (HIT-6) [14] and the Migraine Disability Assessment (MIDAS) scale [23].

Ophthalmologic examination

A complete ophthalmologic examination was carried out on all patients by a neuro-ophthalmologist. Clinical orthoptic and ophthalmological data were recorded, including ocular pressure, ocular motility, best corrected visual acuity (BCVA), objective refraction, fundoscopy, and macular and optic nerve OCTA.

Cover-uncover tests were carried out to highlight any alterations in eye alignment. A full refractive correction was used for all tests when required. Using the prism and the alternating cover test, the angle of deviation for distance (3 m) and near (33 cm) was evaluated and recorded in prismatic diopters. The fusional amplitude was assessed using the Berens prism bars. We used base-in prism for divergence and base-out prism for convergence. The fusional

convergence value was evaluated as the diopter power of the base-out prism in which exotropia happened and could not be compensated. A non-contact tonometer was used to measure eye pressure in both eyes. The best corrected visual acuity (BCVA) for the right and left eyes was assessed using the EDTRS tables. Auto refractometry was used to objectively assess refractive status. The refractive states (myopia, hyperopia and astigmatism) were recorded and quantified in diopters. The sum of the spherical power plus half of the cylindrical power was used to calculate the spherical equivalent (Seq). Myopia, astigmatism and farsightedness were expressed as SEq < 0.5 diopters (*D*), cylindrical error > 1.0*D* and SEq > 0.5*D*, respectively. Fundoscopy data and fundus photos were taken under pharmacological mydriasis and were accurately recorded.

OCTA

Through the Solix Fullrange OCT (Optovue Inc, Freemont CA, USA—version 2019 V1.0.0.305), an SD-OCTA (Spectral domain-optical coherence tomography angiography) device with very high scanning and acquisition speed, both eyes of the patients have been examined. The device can perform 120,000 scans/second with the division amplitude-spectrum decorrelation angiography (SSADA) algorithm. The optimization of the signal-to-noise ratio (SNR) permits, through a contrast between tissue statics and dynamics, the study of the blood flow in the capillary bed, following numerous B scans in the same retinal and choriocapillaris area [11].

The software applied motion correction technology (MCT) after completing volumetric data sets acquisitions, a 3D correction tool for image distortion in all directions, creating a very precise post-processing result. Only scans with good quality or with a signal strength ≥ 8 were collected. The same operator was involved for all scansions. The operator was blinded to the diagnosis of the patients. It was the operator's duty to examine and exclude all OCTA images that did not meet the pre-established quality standards or showed artefacts that could distort the study results. Through special tools present, the operator was authorized to make manual modifications of segmentation and propagation if the software had difficulty in autonomously recognizing the retinal areas to be examined. The same tools were used to delimit the foveal avascular zone (FAZ) area in case the software does not identify it or does it abnormally. 6 × 6 mm scan areas both centred on the fovea were used. After the scan process, the following data were collected: macular vessel density (VD), inside disc VD, peripapillary VD, peripapillary thickness, disc whole image VD, fovea choriocapillaris VD, fovea VD, parafovea VD, fovea thickness, parafovea thickness, macular full retinal thickness and FAZ parameters.

Statistical analysis

Statistical data were analysed with SPSS version 21.0 and Microsoft Office Excel (Microsoft, Redmond, Washington, USA). Summary statistics were reported as mean ± standard deviation (SD). Data normality was defined using the Kolmogorov–Smirnov test. The Kruskal–Wallis test was used to compare variables. Both eyes of a subject were analysed individually. The correlation between OCT values and migraine variables was studied through the Pearson or Spearman correlation coefficient as appropriate. A p value less than 0.05 was considered significant.

No statistical correction for multiple comparisons was done.

Results

Study population

We included 56 eyes from 28 patients with a diagnosis of MO, whose mean age was 30.9 ± 13.0 years, 32 eyes from 16 patients with a diagnosis of MA, whose mean age was 33.1 ± 12.2 years and 32 eyes from 16 healthy control subjects, whose mean age was 29.7 ± 9.3 years. The mean age did not differ among the groups ($p = 0.502$). None of the MA patients fulfilled the criteria for retinal migraine [1].

The clinical and demographic features of the migraine groups are reported in Table 1.

Refractive errors

Among MO patients, astigmatism was observed in 21 patients: mainly myopic astigmatism (20 patients), emmetropia in 1 patient, antimetropia in 3 patients, myopia in 19, and hypermetropia in 10 patients. In the MA group, 16

Table 1 Clinical and demographic characteristics of the migraine groups

	MO ($n = 28$)	MA ($n = 16$)
Sex (female)	22	12
	Mean ± SD	Mean ± SD
Age (years)	30.89 ± 13.01	33.06 ± 12.17
Disease duration (years)	12.58 ± 10.91	13.57 ± 10.43
Chronic migraine (*n*)	11	2
Medication overuse headache (*n*)	5	1
Monthly migraine frequency	4.60 ± 4.39	4.5 ± 4.27
Monthly headache frequency	9.13 ± 6.82	6.28 ± 8.05
Migraine attacks intensity (VAS)	7.22 ± 1.83	7.15 ± 1.34

MO migraine without aura, *MA* migraine with aura, *SD* standard deviation, *VAS* visual analogue scale

patients were astigmatic: mainly with myopic astigmatism (14 patients), 2 were emmetropic, 13 myopic, and 2 were hyperopic. In the HC group, astigmatism was observed in 15 patients: mainly myopic astigmatism (13 patients), myopia in 18 and hypermetropia in 3 patients. The degrees of refractive errors did not differ among the three groups significantly.

OCTA findings

The FAZ area was respectively 0.230 ± 0.099 mm^2 in the MO group, 0.248 ± 0.091 mm^2 in the MA group and 0.184 ± 0.061 mm^2 in HC group. The FAZ area was significantly larger in the MA group than in HC group ($p = 0.007$), and there were no significant differences between the MO and MA groups ($p = 0.7$) and between MO and HC groups ($p = 0.068$) (Fig. 1).

The foveal choriocapillaris VD was significantly lower in MA patients ($63.6 \pm 2.49\%$) when compared with MO patients ($65.27 \pm 3.29\%$) ($p = 0.022$). No significant differences emerged between MA and HC ($65.16 \pm 2.27\%$) and between MO and HC (Fig. 2).

Moreover, there was no significant difference among the MA, MO, and HC groups in macular whole-image VD, disc whole-image VD, inside disc VD, peripapillary VD, fovea and parafovea VD (Table 2).

Regarding the structural OCT measurements, including the foveal, parafoveal, and peripapillary thickness, no significant correlation emerged among the three groups (Table 2).

Correlations between clinical parameters and OCTA findings

Considering the migraine groups (MA and MO), a significant correlation was observed between peripapillary thickness and the mean age of the patients (Spearman $\rho = -0.256$, $p = 0.020$). No significant correlation was observed between peripapillary thickness and the mean age of the controls

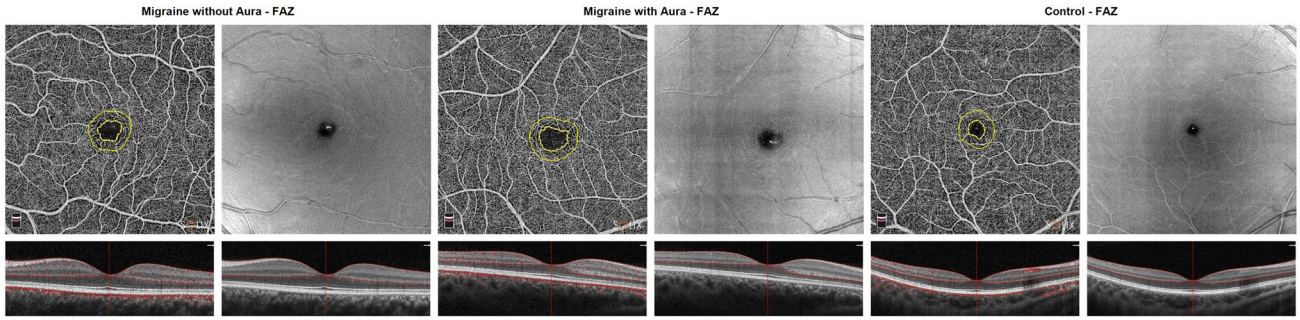

Fig. 1 Representative macular optical coherence tomography angiography (OCTA) scans of migraine with aura (MA), migraine without aura (MO), and healthy controls (HC) participants. The foveal avascular zone (FAZ) area is circled in yellow. The mean FAZ area was larger in the MA group, followed by the MO and HC groups. The FAZ area is significantly enlarged in the MA participant in comparison to the HC participants

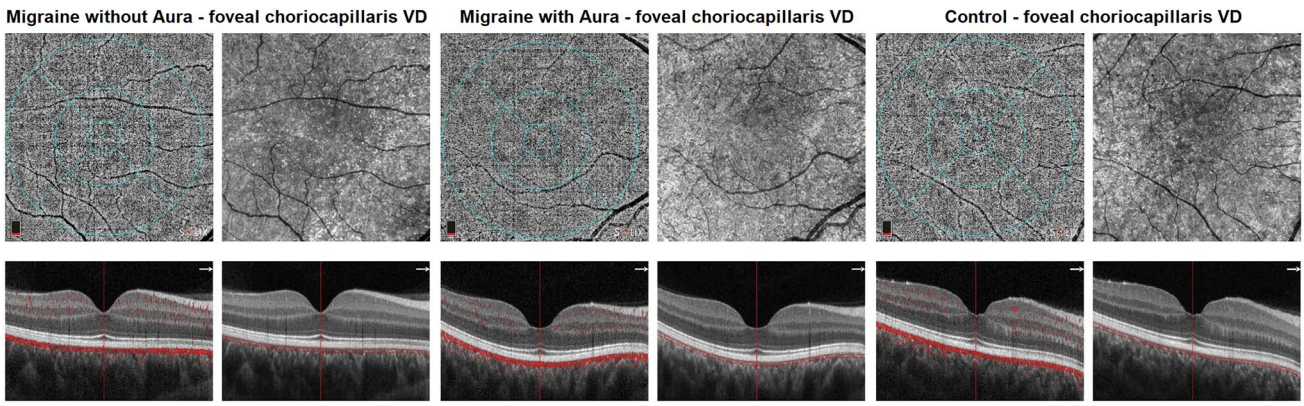

Fig. 2 Representative macular optical coherence tomography angiography (OCTA) scans of migraine with aura (MA), migraine without aura (MO), and healthy controls (HC) participants. The foveal choriocapillaris vessel density (VD) decreased in MA patients in comparison to MO patients

Table 2 Optical coherence tomography angiography (OCTA) findings in migraine with aura (MA), without aura (MO), and healthy controls (HC) and comparison among the three groups

	MO ($n=28$)		MA ($n=16$)		HC ($n=16$)		p
	Mean	SD	Mean	SD	Mean	SD	
IOP (mmHg)	15.5	2.92	14.87	2.78	15.06	2.69	0.464
FAZ (mm^2)	0.23	0.099	0.248	0.091	0.184	0.061	**0.007**
Disc whole image VD (%)	46.84	2.24	46.69	3.01	46.80	2.39	0.920
Inside disc VD (%)	50.30	5.50	49.06	5.64	50.86	3.80	0.517
Peripapillary VD (%)	50.14	5.99	49.33	3.08	48.93	2.55	0.614
Peripapillary thickness (mm)	93.49	12.32	90.20	7.91	90.47	6.54	0.502
Macular whole image VD (%)	56.44	2.83	55.83	2.20	55.81	2.64	0.165
Fovea VD (%)	37.30	5.52	36.20	5.10	38.38	4.56	0.181
Parafovea VD (%)	58.62	3.23	58.07	2.71	58.47	3.19	0.345
Fovea thickness (mm)	264.11	19.00	258.69	26.69	265.5	20.26	0.315
Parafovea thickness (mm)	328.88	14.11	325.38	13.30	327.5	14.67	0.571
Foveal choriocapillaris VD (%)	65.27	3.29	63.6	2.49	65.16	2.27	**0.022**

Statistical significant results ($p<0.05$) are shown in bold type

FAZ foveal avascular zone, *HC* healthy controls, *IOP* intraocular pressure, *MO* migraine without aura, *MA* migraine with aura, *SD* standard deviation, *VD* vessel density

(Spearman $\rho=-0.156$, $p=0.409$). We did not find significant correlations between the monthly migraine frequency, the monthly headache frequency, and the OCTA parameters.

Discussion

The main finding of this study was that MA, but not MO patients, had a significantly enlarged FAZ area in comparison with HC.

Moreover, the foveal choriocapillaris vessel density was significantly lower in MA patients in comparison to MO patients. No significant correlations emerged between clinical and vessel density parameters.

The FAZ is a round, capillary-free region within the macula. Enlargement of FAZ could be considered an indirect sign of microangiopathy. Previous studies showed that FAZ is enlarged in several systemic conditions, such as diabetic retinopathy [2] and lupus erythematosus [18].

A previous study by Chang et al. showed that the patients with migraine with aura had a significantly enlarged FAZ area compared to healthy controls. The same authors demonstrated a reduced superficial foveal vessel density and a significantly decreased peripapillary vessel density in the migraine with aura group compared with migraine without aura group and healthy controls [6].

Hamurcu et al. confirmed that the FAZ area was significantly larger in migraine with aura patients [10]. Still, their study population did not include patients with a diagnosis of migraine without aura. Another study correlated OCTA parameters with brain white matter hyperintensities [25]. The authors found that migraine with aura patients with white matter lesions had lesser deeper foveal and superior hemisphere vessel densities and significantly larger FAZ compared to the group without white matter lesions [25].

Conversely, a recent study did not find differences in retinal vessel density of the foveal, perifoveal, parafoveal, and the whole area between healthy controls and migraine patients with and without aura. However, the choriocapillaris flow of patients with migraine with aura was significantly lower than the other two groups [4].

Overall, our results on FAZ in migraine patients agree with the previous data available in the literature, but, to the best of our knowledge, the present study is the first one also evaluating the foveal choriocapillaris vessel density.

There is a substantial difference between retinal and choroidal circulation. Retinal circulation has a low blood flow, whereas the choroid has a high flow. Retinal circulation lacks autonomic innervation, is principally regulated by local factors and has efficient autoregulation. The choroidal circulation is innervated mainly by the sympathetic system and is poorly autoregulated. Due to poor autoregulation, choroidal circulation may be affected by changes in perfusion and blood flow [7]. In the present study, no changes in retinal vessel densities were observed. However, we recorded a decrease in the foveal choriocapillaris VD in MA patients compared to MO patients. We hypothesize that the modification in the foveal choriocapillaris VD may occur earlier than the vessel density changes in the retina.

A large body of evidence supports the link between migraine and vascular conditions, such as stroke, cardiac ischemic disease and vascular retinopathy [24]. It has been hypothesized that neurogenic inflammation, shifts in vascular diameter, hypoxia, and blood–brain barrier disruption related to migraine attacks may cause perturbation and damage to the vascular endothelium [24]. The

microcirculatory impairment found in our cohort of MA patients could be explicated by the endothelial dysfunction that the disease may induce.

In a study using orbital color Doppler sonography, patients with migraine showed lower interictal pulsatility and resistance indices in the posterior ciliary arteries compared to controls [12]. A study by Silvestrini et al. with transcranial Doppler ultrasonography on vascular reactivity to hypercapnia in the anterior and posterior cerebral vessels showed a significantly lower reactivity in the basilar artery of migraine with aura patients [22].

A study performed on a patient during an attack of migraine with visual aura showed narrowing of the retinal vessels and decreased radial peripapillary capillary density, superficial and deep foveal vessel density. These modifications improved three hours after the visual aura was resolved [4].

The association between retinal vascular involvement and migraine has been extensively analysed. A population-based study reported associations between migraine and retinal microvascular signs. Among participants without hypertension or diabetes, the association was stronger and significant for both migraines with and without aura. This association with aura persisted despite controlling for cardiovascular risk factors [21]. Thus, both temporary and persistent dynamic vascular changes also involving the retina may occur in patients with migraine and during the aura.

The increased FAZ area found in migraine with aura patients may suggest microangiopathy affecting the retina, which may result from perpetrated microvascular insult over time.

Moreover, our study first evaluated foveal choriocapillaris vessel density in patients with migraine, which could be considered a more sensitive and earlier marker of microvascular damage in patients with migraine with aura.

This hypothesis of microvascular involvement in migraine patients could also be confirmed because we find a significant correlation between peripapillary thickness and the age of migraineurs. Conversely, there was no correlation between age and peripapillary thickness in the controls. Some studies reported thinning of the retinal nerve fiber layer (RNFL) in migraine patients, particularly in chronic migraineurs, which could be explained by chronic ischemic damage [20]. In contrast, another study reported a normal average RNFL thickness in the migraine group [17].

The present study has some limitations. The participants were studied during the headache free-period, and even if we included a larger cohort of patients in comparison to the studies on OCTA reported in the literature, larger sample sizes are needed to draw conclusions.

Conclusion

Our data confirm that an impairment of retinal microcirculation can be detected in patients with migraine with aura. Moreover, the study of choroid circulation may reveal microvascular impairment in patients with migraine with aura, which could not be detected otherwise.

OCTA is a useful non-invasive screening tool for the detection of early microcirculatory disturbance in patients with migraine and might allow the individuation of a subgroup of migraineurs that may be at higher risk of vascular events. However, further studies are needed to evaluate these microvascular changes over time and to assess how they relate to the risk of development of vascular local and systemic complications.

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Declarations

Conflicts of interest No disclosures.

Ethical standard statement The study was approved by the Ethical Committee of the Università Cattolica del Sacro Cuore (protocol ID 4155/2021).

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