Graefe's Archive for Clinical and Experimental Ophthalmology (2020) 258:2517–2521
https://doi.org/10.1007/s00417-020-04805-6

NEUROPHTHALMOLOGY

Evaluation of retinal vessel density and choriocapillaris flow in migraine patients with and without aura

Pınar Bingöl Kızıltunç[1] · Gökçen Özcan[1] · Ferhad Özer[1] · Canan Togay Işıkay[2] · Huban Atilla[1]

Received: 6 April 2020 / Revised: 4 June 2020 / Accepted: 15 June 2020 / Published online: 26 June 2020

Abstract

Purpose Migraine is thought to be a neurovascular disorder and increases the likelyhood to develop ischemic complications. Studies have shown that vascular disorders such as ischemic optic neuropathy, retinal artery and vein obstructions are more common in patients with migraine. This study aimed to evaluate the differences between retinal and optic disc microvasculature between migraine patients with and without aura and healthy controls using optical coherence tomography angiography (OCTA) imaging.

Methods Thirty-three patients with migraine and 28 healthy subjects were included in this prospective cross sectional study. Optical coherence tomography angiography imaging was performed for the macula and optic disc. Vessel densities (VD) and choriocapillaris flow values were compared between three groups: control group, migraine with aura (MWA), and migraine without aura (MWOA).

Results There was no difference between the three groups for the VDs of the foveal, perifoveal, parafoveal, and the whole area. The choriocapillaris flow of patients with MWA was significantly less than that of the MWOA and control groups. The VDs of the optic disc revealed no significant difference between the three groups.

Conclusion A lack of choriocapillaris autoregulatory mechanisms may be a possible cause of the decrease in choriocapillaris flow in patients with MWA.

Keywords Choriocapillaris · Migraine · Optical coherence tomography angiography · Vessel density

Introduction

Migraine is one of the main causes of headache worldwide, and it is considered a neurovascular disorder. Although the pathophysiology of migraine is not fully understood, two main theories are proposed: the trigemino-vascular model and cortical spreading depression (CSD) [1, 2]. In these two theories, cerebral hypo-perfusion develops. Therefore, migraine is more likely to cause the development of ischemic complications. Owing to these vascular disorders in migraine, a decrease in perfusion in the optic nerve head and retina can be observed. A few case reports with ocular vascular disorders such as ischemic optic neuropathy, retinal artery, and vein obstructions have been reported [3–5].

There are limited studies evaluating ocular vascular changes in migraine patients. In these studies, fundus photography and fundus video were used to evaluate the vascular changes [6, 7]. Optical coherence tomography angiography (OCTA) is an imaging method that provides detailed information about retinal microvasculature, and nowadays, with the introduction of this method, more detailed information about the microvasculature of the retinal and optic disc is obtained in vascular disorders. Few studies have examined retinal and optic disc microvasculature in patients with migraine using OCTA imaging [8, 9]. These studies evaluated only retinal microvasculature on macular OCTA, and the choriocapillaris layer was not evaluated.

This study aimed to evaluate the differences between retinal and optic disc microvasculature between migraine patients with and without aura and healthy controls using OCTA imaging. Additionally, it was aimed to evaluate microvascular differences of the choriocapillaris layer between these patients for the first time.

✉ Pınar Bingöl Kızıltunç
pinarbingol84@gmail.com

[1] Department of Ophthalmology, Ankara University School of Medicine, Ankara, Turkey

[2] Department of Neurology, Ankara University School of Medicine, Ankara, Turkey

Materials and methods

Patients selection

This study was approved by the Institutional Review Board Committee of the Ankara University (IRB Number: 05–396-19, Date: 11 March 2019) and was performed according to the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all participants after explanations of the nature and possible consequences of the study. Thirty-three consecutive migraine patients who were diagnosed at the migraine clinic of the neurology department were referred to the ophthalmology department and 28 age matched healthy volunteer subjects were included in this prospective cross sectional study. Patients with migraine were divided into two groups according to the presence of aura (MWA, migraine with aura and MWOA, migraine without aura).

The exclusion criteria were any ocular pathology, refractive error more than 3.5 diopters, and history of ocular surgery, systemic diseases other than migraine, and regular drug use.

Data acquisition and quantitative analysis

Each patient and healthy subject underwent full ophthalmic examination, including visual acuity and intraocular pressure (IOP) measurement and anterior and posterior segment examination. Optical Coherence Tomography (OCT) and OCTA imaging were performed using an Optovue RTVue XR Avanti spectral-domain OCT device with AngioVue software version 3.5 (Optovue Inc., Fremont, CA, USA). The average retinal nerve fiber layer (RNFL) thickness and ganglion cell complex (GCC) thickness were measured based on structural OCT scans [10].

Optical coherence tomography angiography images of the macula were acquired from a 6 × 6 mm cube and optic nerve were acquired from a 4.5 × 4.5 mm cube. Automatic segmentation of the retinal layers was applied to derive the en face slabs for each retinal capillary plexus. The superficial capillary plexus (SCP) was defined from the inner limiting membrane to 9 μm above the inner plexiform layer (IPL), the deep capillary plexus (DCP) was defined from 9 μm above the IPL to 9 μm below the outer plexiform layer, and the choriocapillaris layer was defined from 9 μm above and 30 μm below the Bruch membrane layer.

The angioflow vessel density (VD) was expressed as the percentage of vessel area with flowing blood over the total measurement area. In the foveal, parafoveal, and perifoveal regions, VDs were automatically calculated. A non-flow measurement on the superficial vascular plexus was selected for the foveal avascular zone (FAZ) and the software automatically calculated the area (in mm^2) by clicking on the center of the FAZ.

The OCTA images were evaluated in a reproducible manner by GÖ, who was blinded to the files of the patients. Optical coherence tomography and OCTA parameters were compared between the MWA, MWOA, and healthy control groups.

Statistical analysis

The statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 15.0. A Shapiro–Wilk test was performed for all variables to detect departures from a normal distribution. Because there were three different groups, the comparison of the variables was performed with analysis of variance (ANOVA) or Kruskal–Wallis test according to the distribution pattern. Bonferroni corrected results for ANOVA and Dunn's test results for Kruskal–Wallis tests were assessed for pairwise comparisons. P values < 0.05 were considered significant.

Results

In this prospective cross sectional study, there were 17 patients in the MWA group, 16 patients in the MWOA group, and 28 healthy subjects in the control group. All patients and healthy controls were female. Mean ages of all groups were similar (32.1 years for the MWA group, 30.4 years for the MWOA group, and 32.3 years for the control group).

Best corrected visual acuities of all patients and healthy subjects were 0.0 logMAR, and all of them had normal anterior and posterior segment evaluation. Mean IOP values were not significantly different between the three groups (14.5 mmHg for the MWA group, 13.7 mmHg for the MWOA group, and 14.2 mmHg for the control group). Refractive errors (mean ± SD) were similar for the three groups (−1.75 ± 0.75 for the MWA group, −1.50 ± 0.50 for the MWOA group, and −2.00 ± 0.75 for the control group). The average RNFL thickness and GCC thickness were similar for the three groups (p = 0.715 and p = 0.405, respectively, Table 1).

When VDs of macula for SCP and DCP were evaluated, there was no difference between the three groups for the VDs of the foveal, perifoveal, parafoveal, and the whole area. The choriocapillaris flow of patients with MWA was significantly less than the MWOA and control groups (p = 0.048), and the foveal avascular zone of the three groups were similar (p = 0.370) (Table 2).

Assessment of optic disc OCTA parameters revealed no significant decrease between the three groups (Table 2).

Table 1 Comparison of RNFL and GCC thickness between MWA, MWOA, and healthy control groups using OCT imaging

OCT parameter	MWA group	MWOA group	Control group	P value
RNFL thickness				
Average	99 (83–127)	105 (89–119)	100.5 (88–127)	0.715
Superior	123.5 (90–172)	124.5 (110–148)	119.5 (94–167)	0.309
Inferior	124 (101–160)	131 (105–145)	120 (107–149)	0.638
Temporal	77.8 (67.6–88)	76.1 (67.6–84.6)	77.7 (69.4–86)	0.859
Nasal	76.9 (65.2–88.6)	80.6 (69.9–91.3)	82.5 (70.8–94.2)	0.112
GCC thickness				
Average	99.1 (91.9–106.3)	101.5 (97.7–105.3)	98.7 (93.8–103.6)	0.405

GCC ganglion cell complex, *MWA* migraine with aura, *MWOA* migraine without aura, *OCT* optical coherence tomography, *RNFL* retinal nerve fiber layer

Discussion

In this study, in contrast to other studies, the choriocapillaris layer on macular OCTA was also evaluated and the choriocapillaris flows of patients with MWA were found to be less than those of patients with MWOA and the control group. This decrease had a statistically borderline significance ($p = 0.048$). There was no difference between the three groups for the VDs of the foveal, perifoveal, parafoveal, and the whole area for SCP and DCP. Additionally, RNFL and GCC thickness were similar for all groups.

Although the pathophysiology of migraine is not fully understood, migraine is considered a systemic neurovascular disorder, and ischemic events in migraine are not limited to the brain. Other systemic ischemic conditions such as stroke, angina, and myocardial infarction are also observed more in these patients than in healthy subjects [11–13]. Additionally, studies have shown that ischemic events are more common in migraine patients with aura than migraine patients without aura [13, 14].

Cortical spreading depression, which is the electrophysiological mechanism of aura, may be the cause of more ischemic events in migraine with aura. Increased risk of CSD development and cerebral ischemia was demonstrated in mice with human migraine mutations [15]. In this electrophysiological condition, significant ionic and water changes and increased energy metabolism are seen due to the changes in the blood–brain barrier. In the first stage, an increased blood flow is observed due to

Table 2 Comparison of OCTA parameters between MWA, MWOA, and healthy control groups

OCTA parameter	MWA group	MWOA group	Control group	P value
Superficial capillary plexus				
Whole	52.7 (47.0–54.5)	50.9 (32.3–55.7)	50.8 (41.3–54.2)	0.255
Fovea	21.8 (14.0–25.7)	19.7 (4.2–37.7)	18.1 (8.5–56.4)	0.275
Parafovea	53.1 (45.2–57.2)	52.9 (33.8–58.5)	51.9 (23.2–56.4)	0.257
Perifovea	53.3 (47.4–55.3)	51.7 (45.8–56.5)	51.7 (41.7–54.3)	0.249
Deep capillary plexus				
Whole	50.0 (41.7–56.5)	52.7 (38.6–62.7)	50.2 (36.4–60.3)	0.336
Fovea	40.8 (18.2–49.7)	35.8 (19.3–49.5)	36.6 (18.4–50.1)	0.180
Parafovea	55.2 (51.3–58.0)	56.6 (44.2–64.0)	56.2 (44.0–60.4)	0.399
Perifovea	50.8 (42.5–58.2)	53.4 (38.3–64.3)	51.1 (36.5–62.0)	0.425
FAZ	0.22 ± 0.05	0.26 ± 0.13	0.28 ± 0.10	0.370
Choriocapillaris non-flow	0.45 (0.32–0.58)	0.53 (0.1–0.787)	0.56 (0.34–0.88)	0.093
Choriocapillaris flow	19.8 (18.5–20.8)	20.5 (18.8–21.9)	20.9 (18.7–21.5)	**0.048**
Optic disc				
Whole disc	52.3 (48.7–52.9)	50.8 (45.4–54.0)	50.4 (45.6–54.4)	0.059
Inside disc	49.9 (43.1–52.4)	51.6 (44.2–53.1)	50.1 (42.1–52.6)	0.06
Peripapillary	53.1 (49.1–54.2)	52.8 (50.1–53.7)	54.1 (50.2–54.6)	0.08

FAZ foveal avascular zone, *MWA* migraine with aura, *MWOA* migraine without aura, *OCTA* optical coherence tomography angiography

the need for higher oxygen and glucose that is then followed by long-lasting hypoperfusion and impaired cerebrovascular reactivity. In this study, a decrease in choriocapillaris flow in patients with MWA may be due to the mechanism of CSD.

Few studies have evaluated the OCTA parameters of patients with migraine. Chang et al. [8] found that migraine patients with aura had a reduced vessel density of SCP and a superior peripapillary capillary when compared with migraine patients without aura. Foveal vessel densities of SCP and DCP were significantly less in migraine patients with and without aura in the study by Ulusoy et al. [9]. Our results were different from the results of these two studies. We did not find any difference in VDs of SCP and DCP. However, unlike other studies, we also evaluated choriocapillaris flow, and we found a statistically borderline significant decrease in choriocapillaris flow in migraine patients with aura. Retinal and choroidal circulation differ anatomically and functionally. One of the difference between these circulations is the presence of autoregulation mechanisms. It is known that there is an autoregulation mechanism in the retinal circulation. The autoregulation mechanisms enable the vascular bed to maintain a contant blood flow despite changes in perfusion pressure. However, choroidal circulation is poorly autoregulated, and it is affected by changes in blood flow and perfusion [16]. In our study, as a result of autoregulation, no change in vessel density was observed in SCP and DCP, which are part of the retinal circulation. However, due to the absence of autoregulatory mechanisms in the choroidal circulation, hypoperfusion and ischemic events in migraine with aura may have resulted in a decrease in the choriocapillaris flow.

Previously, we demonstrated diffuse narrowing of retinal vessels and a decrease in VDs of SCP, DCP and the radial peripapillary capillary in a patient during the visual aura [17]. These findings were recovered three hours after the aura. In this patient, these findings suggest that current autoregulatory mechanisms of retinal circulation may not be sufficient to prevent hypoperfusion due to the CSD mechanism during the attack. However, these autoregulatory mechanisms may provide continuity of retinal perfusion in periods without attack.

In previous studies regarding OCT findings in migraine patients, RNFL thickness, choroidal thickness and macular parameters such as ganglion cell layer (GCL) thickness and foveal thickness were evaluated. The RNFL thickness in the migraine patients was found to be thinner than that in the control groups [18–21]. In these studies, it was suggested that posterior cerebral hemisphere hypoperfusion occurs during the aura period, and this hypoperfusion causes subclinical ischemic lesions and neurodegenerative changes. Thinning in RNFL thickness may have occurred secondary to neurodegenerative changes [22, 23]. However, there have been controversial results regarding macular parameter changes. Some studies indicated significant changes in migraine patients [19, 20] and some found no change [24, 25]. Studies also evaluated the choroidal thickness and they found that migraine patients with and without aura had significantly lower choroidal thickness than healthy controls. In addition, patients with aura had significantly lower choroidal thickness than patients without aura [19, 20, 26, 27]. In our study, we did not find any difference regarding RNFL and GCC thickness between the three groups. Additionally, there was no difference between these groups in terms of VD of the SCP. As known, the blood supply of the RNFL layer and GCC derives from the SCP. No change in RNFL and GCC thickness is an expected finding demonstrating that RNFL and GCC will retain their physiological structure due to a similar blood supply.

There are some limitations of this study. One of them is the small sample size. In addition, we did not evaluate MWA patients during migraine aura. Since Optuvue OCT does not have an Enhanced Depth Imaging (EDI) mode, we did not evaluate the relationship between choroidal thicknesses and choriocapillaris flow because the measurement of choroid thickness would not be reliable. Further studies with larger study groups and during the migraine attack are needed to evaluate the vascular changes of these patients. Additionally, the relationship between choriocapillaris flow and choroidal thickness can be evaluated using EDI mode OCT and OCTA imaging at the same time.

In conclusion, this study found a borderline significant decrease in choriocapillaris flow in migraine patients with aura. This finding may be explained by the vascular autoregulatory mechanisms of the eye. While vascular autoregulatory mechanisms of retina ensure constant vascular density in migraine patients with aura, the absence of this mechanism in the choriocapillaris may be a possible cause of the decrease in choriocapillaris flow in these patients.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national 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 the study.

References

1. Brennan KC, Charles A (2010) An update on the blood vessel in migraine. Curr Opin Neurol 23:266–274. https://doi.org/10.1097/WCO.0b013e32833821c1
2. Schain AJ, Melo-Carrillo A, Strassman AM, Burstein R (2017) Cortical spreading depression closes paravascular space and impairs glymphatic flow: implications for migraine headache. J Neurosci 37:2904–2915. https://doi.org/10.1523/jneurosci.3390-16.2017
3. Benninger F, Saban T, Steiner I (2015) Central retinal vein occlusion in a migraine patient. J Clin Neurosci 22:1833–1834. https://doi.org/10.1016/j.jocn.2015.03.057

4. Christakis PG, Alon R, Brent MH (2018) Recurrent visual field defect associated with migraine resulting in a hemiretinal artery occlusion. Can J Ophthalmol 53:e92–e94. https://doi.org/10.1016/j.jcjo.2017.08.023
5. Lee AG, Brazis PW, Miller NR (1996) Posterior ischemic optic neuropathy associated with migraine. Headache 36:506–510. https://doi.org/10.1046/j.1526-4610.1996.3608506.x
6. Ota I, Kuroshima K, Nagaoka T (2013) Fundus video of retinal migraine. JAMA Ophthalmol 131:1481–1482. https://doi.org/10.1001/jamaophthalmol.2013.4686
7. Rose KM, Wong TY, Carson AP, Couper DJ, Klein R, Sharrett AR (2007) Migraine and retinal microvascular abnormalities: the atherosclerosis risk in communities study. Neurology 68:1694–1700. https://doi.org/10.1212/01.wnl.0000261916.42871.05
8. Chang MY, Phasukkijwatana N, Garrity S, Pineles SL, Rahimi M, Sarraf D, Johnston M, Charles A, Arnold AC (2017) Foveal and peripapillary vascular decrement in migraine with aura demonstrated by optical coherence tomography angiography. Invest Ophthalmol Vis Sci 58:5477–5484. https://doi.org/10.1167/iovs.17-22477
9. Ulusoy MO, Horasanli B, Kal A (2019) Retinal vascular density evaluation of migraine patients with and without aura and association with white matter hyperintensities. Acta Neurol Belg. https://doi.org/10.1007/s13760-019-01094-7
10. Jia Y, Tan O, Tokayer J, Potsaid B, Wang Y, Liu JJ, Kraus MF, Subhash H, Fujimoto JG, Hornegger J, Huang D (2012) Split-spectrum amplitude-decorrelation angiography with optical coherence tomography. Opt Express 20:4710–4725. https://doi.org/10.1364/oe.20.004710
11. Gryglas A, Smigiel R (2017) Migraine and stroke: What's the link? What to do? Current neurology and neuroscience reports 17:22. https://doi.org/10.1007/s11910-017-0729-y
12. Gudmundsson LS, Scher AI, Aspelund T, Eliasson JH, Johannsson M, Thorgeirsson G, Launer L, Gudnason V (2010) Migraine with aura and risk of cardiovascular and all cause mortality in men and women: prospective cohort study. BMJ 341:c3966. https://doi.org/10.1136/bmj.c3966
13. Kurth T, Schurks M, Logroscino G, Gaziano JM, Buring JE (2008) Migraine, vascular risk, and cardiovascular events in women: prospective cohort study. BMJ 337:a636. https://doi.org/10.1136/bmj.a636
14. Kruit MC, van Buchem MA, Hofman PA, Bakkers JT, Terwindt GM, Ferrari MD, Launer LJ (2004) Migraine as a risk factor for subclinical brain lesions. JAMA 291:427–434. https://doi.org/10.1001/jama.291.4.427
15. Eikermann-Haerter K (2014) Spreading depolarization may link migraine and stroke. Headache 54:1146–1157. https://doi.org/10.1111/head.12386
16. Delaey C, Van De Voorde J (2000) Regulatory mechanisms in the retinal and choroidal circulation. Ophthalmic Res 32:249–256. https://doi.org/10.1159/000055622
17. Bingol Kiziltunc P, Atilla H (2020) Vascular changes with optical coherence tomography angiography during aura of migraine: a case report. Eur J Ophthalmol. https://doi.org/10.1177/1120672119899900
18. Feng YF, Guo H, Huang JH, Yu JG, Yuan F (2016) Retinal nerve fiber layer thickness changes in migraine: a meta-analysis of case-control studies. Curr Eye Res 41:814–822. https://doi.org/10.3109/02713683.2015.1056373
19. Reggio E, Chisari CG, Ferrigno G, Patti F, Donzuso G, Sciacca G, Avitabile T, Faro S, Zappia M (2017) Migraine causes retinal and choroidal structural changes: evaluation with ocular coherence tomography. J Neurol 264:494–502. https://doi.org/10.1007/s00415-016-8364-0
20. Ekinci M, Ceylan E, Cağatay HH, Keleş S, Hüseyinoğlu N, Tanyildiz B, Cakici O, Kartal B (2014) Retinal nerve fibre layer, ganglion cell layer and choroid thinning in migraine with aura. BMC Ophthalmol 14:75. https://doi.org/10.1186/1471-2415-14-75
21. Yülek F, Dirik EB, Eren Y, Simavlı H, Uğurlu N, Çağıl N, Şimşek Ş (2015) Macula and retinal nerve fiber layer in migraine patients: analysis by spectral domain optic coherence tomography. Semin Ophthalmol 30:124–128. https://doi.org/10.3109/08820538.2013.833270
22. Kurth T, Slomke MA, Kase CS, Cook NR, Lee IM, Gaziano JM, Diener HC, Buring JE (2005) Migraine, headache, and the risk of stroke in women: a prospective study. Neurology 64:1020–1026. https://doi.org/10.1212/01.wnl.0000154528.21485.3a
23. Sacco S, Ricci S, Carolei A (2012) Migraine and vascular diseases: a review of the evidence and potential implications for management. Cephalalgia 32:785–795. https://doi.org/10.1177/0333102412451361
24. Gipponi S, Scaroni N, Venturelli E, Forbice E, Rao R, Liberini P, Padovani A, Semeraro F (2013) Reduction in retinal nerve fiber layer thickness in migraine patients. Neurol Sci 34:841–845. https://doi.org/10.1007/s10072-012-1103-0
25. Simsek IB (2017) Retinal nerve fibre layer thickness of migraine patients with or without white matter lesions. Neuroophthalmology 41:7–11. https://doi.org/10.1080/01658107.2016.1243131
26. Colak HN, Kantarcı FA, Tatar MG, Eryilmaz M, Uslu H, Goker H, Yildirim A, Gurler B (2016) Retinal nerve fiber layer, ganglion cell complex, and choroidal thicknesses in migraine. Arq Bras Oftalmol 79:78–81. https://doi.org/10.5935/0004-2749.20160024
27. Demircan S, Ataş M, Arık Yüksel S, Ulusoy MD, Yuvacı İ, Arifoğlu HB, Başkan B, Zararsız G (2015) The impact of migraine on posterior ocular structures. J Ophthalmol 2015:868967. https://doi.org/10.1155/2015/868967