Enhanced depth imaging optical coherence tomography of the choroid in migraine patients: implications for the association of migraine and glaucoma

Zeynep Dadaci,[1] Fatma Doganay,[2] Nursen Oncel Acir,[1] Hacer Doganay Aydin,[3] Mehmet Borazan[1]

[1]Department of Ophthalmology, Mevlana University School of Medicine, Konya, Turkey
[2]Department of Neurology, Mevlana University School of Medicine, Konya, Turkey
[3]Department of Neurology, Konya Research and Training Hospital, Konya, Turkey

Correspondence to
Dr Zeynep Dadaci, Department of Ophthalmology, Mevlana University School of Medicine, Aksinne M., Esmetas S., No: 16, Meram, Konya 42040, Turkey; zdadaci@hotmail.com

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ABSTRACT

Aim To compare the choroidal thickness measurements obtained during the attack period and during the pain-free interval in migraine patients using enhanced depth imaging optical coherence tomography (OCT).

Methods 58 eyes of 29 subjects with a diagnosis of migraine with or without aura were enrolled in this observational, cross-sectional study. Two OCT scans were performed for each patient, one during the peak period of the migraine attack and the other during the headache-free interval, using the enhanced depth imaging mode. Choroidal thicknesses were measured at the fovea, at three locations nasal and at three locations temporal to the fovea at 500 μm intervals.

Results In patients with unilateral headaches, the choroidal thickness measurements obtained during the attack period were significantly increased only in the eyes on the headache side ($p<0.001$) compared to basal levels. At the fovea, the choroidal thickness measured in the pain-free interval was 373.45±76.47 μm (mean ±SD), which increased to 408.80±77.70 μm during the attack period ($p<0.001$). When the choroidal thickness measurements of patients with bilateral headaches were compared to basal levels, a statistically significant increase was observed at five out of the seven measured points in the right eyes ($p<0.05$) and at all seven measured points in the left eyes ($p<0.05$).

Conclusions Choroidal thickness was found to be significantly increased in migraine patients during the attack period when compared to basal levels. The possible implications of this finding on the association between migraine and glaucoma are discussed.

INTRODUCTION

Migraine is a chronic neurological disease and is widely encountered in the general population. According to data from the American Migraine Prevalence and Prevention study, the cumulative lifetime incidence of migraine was reported to be 43% in women and 18% in men.[1] Migraineurs usually have accompanying ocular complaints, such as periorbital pain, photophobia, or other visual disturbances. For this reason, ophthalmologists are often the first doctors to evaluate patients with migraine. Furthermore, migraine is a well-defined risk factor for the development of glaucoma.[2]

Migraine is a multifactorial, neurovascular syndrome characterised by attacks of recurrent headaches, which are precipitated by intrinsic or extrinsic factors in subjects with a genetic predisposition.[3] Although there are a considerable number of studies and theories on the pathophysiology of migraine, the exact nature of the condition is still considered to be unknown.[4] Currently, migraine is accepted as a neurovascular syndrome resulting from the activation of the nociceptors that innervate the meningeal blood vessels.[5]

Recent reports have demonstrated direct electrophysiological evidence for the activation of trigeminovascular neurons during a migraine attack.[6] The dura mater is largely innervated by the sensory nerve fibres originating from the trigeminal ganglion. Sensorial innervation of the eye is also supplied by the trigeminal nerve. Long and short ciliary nerves, which originate from the ophthalmic division of the trigeminal nerve, innervate various structures in the eye. Short ciliary nerves also carry autonomic nerve fibres, which innervate the choroidal vasculature.[7]

There are studies demonstrating decreased sensitivity in visual fields and retinal nerve fibre layer defects in migraine patients when compared to control subjects.[8 9] Additionally, a history of migraine is considered to be a risk factor for glaucoma. After increased intraocular pressure, vascular problems are the second most extensively studied factors in the pathogenesis of glaucoma.[10] Demonstrating the vessel structure of the eye during migraine attacks may provide insight into the association between migraine and glaucoma.

Optical coherence tomography (OCT) allows us to investigate whether vasodilation and/or plasma protein extravasation occurs in humans by showing the choroidal layer of the eye directly. Using this method, high resolution cross sectional images of the posterior segment of the eye can be obtained. In particular, OCT devices with enhanced depth imaging programmes can effectively evaluate the choroidal thickness.[11]

In this study we aimed to investigate the changes in the choroidal thickness during the attack period in migraine patients using enhanced depth imaging spectral domain OCT. To the best of our knowledge, there are no previous studies in the literature demonstrating choroidal thickness using this method in migraine patients.

METHODS

Study population

This observational, cross-sectional study involved 58 eyes of 29 patients with a diagnosis of migraine with or without aura according to the criteria of the Headache International Society (HIS).[12] All of

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the subjects were recruited between July and November 2013 and evaluated at the Mevlana University eye clinic. The study protocol was approved by the ethics committee (2013/239). The study was performed in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from each patient before enrolment in the study.

Study measurements

All subjects underwent full ophthalmological examinations, including best-corrected visual acuity obtained with a Snellen projection chart, refraction, slit-lamp biomicroscopy, intraocular pressure measurement with Goldmann applanation tonometry, gonioscopy, and fundus examination in the headache-free period. Subjects with any ocular pathology, including refractive disorders greater than ±3.0 D, were excluded. Additionally, patients underwent a complete neurologic examination, and subjects with neurological diseases other than migraines or with other types of migraine (ie, hemiplegic migraine, retinal migraine) were excluded. Subjects with a history of systemic diseases, such as diabetes, hypertension, collagen vascular disease, and/or consumption of drugs with potential vascular effects, as well as patients who were pregnant or smoked, were not included in the study.

Enhanced depth imaging OCT scans

All OCT scans were performed by the same experienced technician who was blind to the study protocol. Before the scan, it was verified that none of the patients had consumed drinks with caffeine or had taken analgesic medications, triptans or ergot alkaloids for at least 24 h previously. Two scans were performed for each patient, one during the peak period of the migraine attack and the other during the headache-free interval. To conclude the peak period of the migraine attack, we asked the patients to grade their headaches as mild, moderate, severe, or intense and called them for OCT scans during a period of severe or intense pain. Both scans were performed at the same time of day to avoid diurnal fluctuations and were obtained within 1 month for each patient.

OCT was performed with a spectral domain OCT machine (Cirrus HD-OCT, model 4000; Carl Zeiss Meditec, Dublin, California, USA) with the enhanced depth imaging mode. Cirrus HD-OCT has a light source with a 840 nm wavelength that can obtain 27 000 A-scans per second with an axial resolution of 5 μm in tissue. The scan pattern used by the Zeiss Cirrus HD-OCT instrument software V.6.5 is an HD 1-line raster, which is a 6 mm line consisting of 4096 A-scans. A high definition one line raster image is generated from 20 B-scans taken at a single location.

Choroidal thickness measurements

Choroidal thickness, defined as the distance between the outer portion of the hyperreflective line that corresponds to the retinal pigment epithelium and the inner surface of the sclera, was measured using the manual calliper function of the Cirrus HD-OCT software. Seven measurements perpendicular to the retina pigment epithelial layer were obtained for each scan: one at the fovea; three at 500, 1000 and 1500 μm nasal; and three located at 500, 1000 and 1500 μm temporal to the fovea. All measurements were made by two observers who were not involved in data analysis and were then averaged for analysis.

Statistical analysis

Statistical analyses were performed using SPSS V.17.0 (SPSS Science, Chicago, Illinois, USA). The mean age and distribution of sexes among the patients with unilateral and bilateral headaches were compared with the Mann-Whitney U test and χ^2 test, respectively. The Wilcoxon signed-rank test was used to test the differences in choroidal thickness. Values of $p<0.05$ were considered statistically significant.

RESULTS

Fifty-eight eyes of 29 subjects were investigated, of which 20 (two male, 18 female) patients had unilateral headaches and nine (two male, seven female) had bilateral headaches. The data were analysed separately for patients with unilateral (eight right-sided, 12 left-sided pain) and bilateral headaches. The mean ages of patients with unilateral and bilateral headaches were 31.70±8.77 years (range 18–53 years) and 35.33±11.89 years (range 20–55 years), respectively. There were no differences between patients with unilateral and bilateral headaches with respect to age ($p=0.52$) or sex ($p=0.76$).

In patients with unilateral headaches, compared to the measurements obtained during the pain-free interval, the choroidal thickness measurements obtained during the attack period were significantly increased in the eyes on the headache side ($p<0.001$), whereas the choroidal thickness did not differ at the contralateral eyes ($p>0.05$) in all measured points (table 1). At the fovea, the choroidal thickness measured in the pain-free interval was 373.45±76.47 μm (mean±SD), which increased to 408.80±77.70 μm during the attack period in the eyes on the headache side ($p<0.001$). Enhanced depth imaging OCT scans obtained during the migraine attack and pain-free intervals of the same patient in the eye on the headache side are shown in figure 1.

Choroidal thickness measurements in the right and left eyes were compared separately for patients with bilateral headaches.

Table 1 Choroidal thickness measurements (mean±SD in μm) in patients with unilateral headaches (n=20)

	Eye on the headache side			Contralateral eye		
	Attack	Baseline	p Value	Attack	Baseline	p Value
N3	329.20±72.17	303.55±73.66	<0.001	308.65±81.47	307.80±84.62	0.343
N2	365.55±73.90	337.30±78.13	<0.001	344.25±82.39	344.25±83.15	0.823
N1	390.75±77.29	358.20±77.23	<0.001	369.40±82.87	370.75±82.34	0.499
SF	408.80±77.70	373.45±76.47	<0.001	386.60±81.84	386.00±82.00	0.427
T1	406.45±75.92	375.75±75.53	<0.001	382.00±81.38	380.95±81.21	0.239
T2	390.75±81.42	360.95±77.58	<0.001	369.40±84.51	368.40±84.22	0.259
T3	368.25±88.08	335.90±79.75	<0.001	342.75±85.30	341.95±84.42	0.432

N1, choroidal thickness at 500 μm nasal to the fovea; N2, choroidal thickness at 1000 μm nasal to the fovea; N3, choroidal thickness at 1500 μm nasal to the fovea; SF, choroidal thickness at fovea; T1, choroidal thickness at 500 μm temporal to the fovea; T2, choroidal thickness at 1000 μm temporal to the fovea; T3, choroidal thickness at 1500 μm temporal to the fovea.

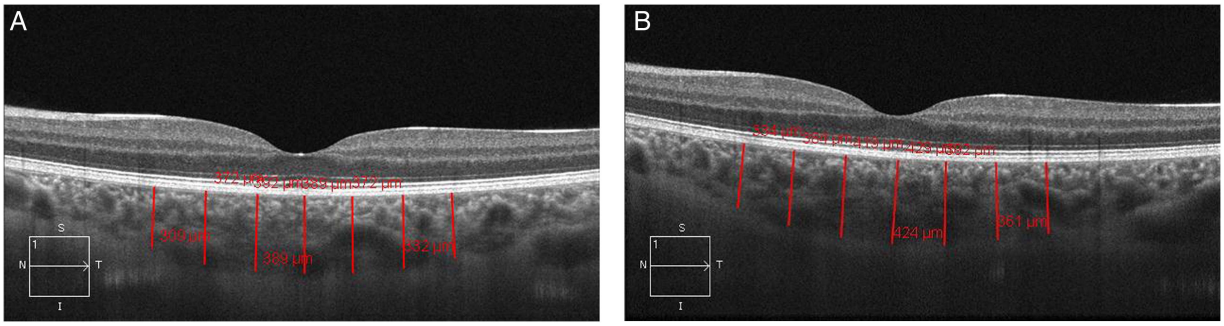

Figure 1 Choroidal thickness in a patient with a unilateral migraine using enhanced depth imaging optical coherence tomography. (A) Measurements obtained during the pain-free interval. (B) Measurements obtained during the migraine attack period.

Compared to the basal choroidal thickness measurements obtained during the pain-free interval, a statistically significant increase was observed at five out of seven measured points ($p<0.05$) in the right eyes and at all seven measured points in the left eyes during the migraine attack ($p<0.05$) (table 2).

DISCUSSION

Migraine is accepted as a neurovascular disorder of unknown aetiology. Because demonstrating microvascular changes in the human brain is not an easy task, most previous studies have been conducted in animals.[13] As far as we know, our study is the first investigation of choroidal thickness in migraine patients. Our findings can be valuable in understanding the pathophysiology of migraine and its association with glaucoma, as both the eyes and the meninges are innervated by the trigeminal nerve. In our study, we observed a statistically significant increase in the choroidal thickness during the migraine attack. This finding seems to be in accordance with most of the theories describing the pathophysiology of migraine.

According to the neurogenic inflammation theory,[14] some unknown stimulus triggers cortical spreading depression (CSD) within the brain that is responsible for the migraine aura and trigeminal activation. The electrical excitation of the trigeminal ganglion results in mast cell degranulation, vasodilatation and an increase in endothelial permeability, which results in plasma protein leakage from postcapillary venules in the dura mater. As a result, the sensitisation of trigeminovascular sensory fibres leads to the perception of pain. This neurogenic inflammation of the meninges is used to describe the migraine headache. In a previous study of the neurogenic inflammation model, albumin extravasation was demonstrated in both the dura and the retina of rats. However, in the second stage of the same study, when retinal angiography was used, no leakage of the dye was demonstrated in humans.[15] In another animal study, CSD was experimentally induced by the focal stimulation of the visual cortex, and the trigeminal nerves were shown to be stimulated.[6] As the trigeminal nerve also supplies the sensory innervation of the eye, this presumed neurogenic inflammation can also occur in the choroid and may result in our observation of increased choroidal thickness during a migraine attack.

Autonomic nervous system dysfunctions are frequently reported in patients with migraine.[16] Reflex autonomic activity related to trigeminovascular activation may provide another explanation for the increased choroidal thickness during the migraine attack, as observed in our study. In humans, the noxious stimulation of the eye induced vasodilation in the forehead circulation through the trigeminal–parasympathetic reflex.[17] In fact, cranial autonomic symptoms that were commonly ipsilateral to the headache were reported to be present in 73.1% of migraine patients, representing a hyperactivity of the trigeminal autonomic reflex.[18] An interesting theory considers migraine to be a chronic sympathetic nervous system disorder, based on a considerable amount of evidence implying systemic sympathetic dysfunction in migraine.[16] This sympathetic nervous system disorder hypothesis is also consistent with the well defined role of trigeminal activation in migraine. The sympathetic nervous system normally has an inhibitory effect on trigeminal activity; therefore, the exhaustion of sympathetic function after a period of increased demand, as in the case of stress, which has been accepted as an important factor in triggering migraine headaches, may lead to trigeminal activation and vasodilatation.[16]

Autonomic dysfunction has also been demonstrated in patients with primary open angle glaucoma (POAG) and

Table 2 Choroidal thickness measurements (mean±SD in µm) in patients with bilateral headaches (n=9)

	Right eyes			Left eyes		
	Attack	Baseline	p Value	Attack	Baseline	p Value
N3	304.00±104.85	289.89±95.23	0.012*	309.56±108.09	300.89±103.08	0.028*
N2	333.56±109.38	322.56±102.22	0.015*	354.00±115.11	340.67±112.76	0.011*
N1	350.00±109.15	342.67±98.65	0.161	371.11±118.23	359.78±118.42	0.012*
SF	364.89±108.32	353.67±103.33	0.063	383.44±119.74	370.56±122.86	0.017*
T1	357.56±106.98	343.44±102.56	0.021*	376.78±122.33	360.22±120.76	0.012*
T2	340.33±106.74	327.33±106.47	0.008*	358.11±114.84	343.33±116.99	0.011*
T3	319.78±106.26	306.22±108.48	0.011*	331.00±108.85	314.78±106.97	0.024*

*Significant difference between baseline and attack period.
N1, choroidal thickness at 500 µm nasal to the fovea; N2, choroidal thickness at 1000 µm nasal to the fovea; N3, choroidal thickness at 1500 µm nasal to the fovea; SF, choroidal thickness at fovea; T1, choroidal thickness at 500 µm temporal to the fovea; T2, choroidal thickness at 1000 µm temporal to the fovea; T3, choroidal thickness at 1500 µm temporal to the fovea.

normotensive glaucoma (NTG).[19 20] Procedures implicating autonomic nervous system disorders, such as the estimation of heart rate variability and cold pressor test, have been reported to be impaired in migraineurs[21 22] during headache-free periods and in patients with glaucoma.[19 20] Gherghel *et al*[20] reported a significant decrease in ocular blood flow and changes in blood pressure responses of patients with POAG compared with normal subjects in response to cold provocation, suggesting systemic autonomic failure and vascular dysregulation as an aetiologic factor in POAG. Our observation of increased choroidal thickness during the attack period only in the eyes on the side of the pain in patients with unilateral migraine can constitute direct evidence of disturbances in the autonomic activity.

Reduction in the retinal nerve fibre layer thickness has been reported in migraine patients and is most likely a consequence of retinal ischaemia.[9 23] In opposition to choroidal vessels, which have intense autonomic innervation, the intraocular part of the retinal vessels has no autonomic innervation. Retinal vessels also have a blood–retinal barrier similar to the blood–brain barrier of brain vessels. However, the circulation of the optic nerve head is somewhat different. The superficial layer of the optic nerve head is supplied by small branches originating from the central retinal artery, while the anterior part of the optic nerve is supplied mainly by the short posterior ciliary arteries and choroidal vessels.[24] Thus, alterations in these structures may be associated with diseases of the optic nerve. In fact, decreased blood flow in the ophthalmic and posterior ciliary arteries was shown to be associated with glaucoma progression.[25] Additionally, alterations in the ocular and systemic circulation have been demonstrated in patients with POAG and NTG.[26] Our observation of increased choroidal thickness during the migraine attack period may reflect an alteration of ocular circulation. Further research is needed to clarify the precise mechanisms through which alterations in the ocular and systemic circulation cause ganglion cell death.

We demonstrated a statistically significant increase in choroidal thickness during the migraine attack, especially in patients with unilateral headaches, but our study has some limitations. Our first limitation is the low number of study participants, especially in the bilateral headache group. To overcome this problem we measured multiple points for each patient and adhered to strict inclusion criteria. To eliminate factors that may have an effect on choroidal circulation, patients on systemic and topical medications, patients with a known systemic or ocular disease, smokers, and pregnant subjects were excluded. Additionally, both measurements were performed at the same time of day to avoid diurnal fluctuations. Secondly, we did not check for test–retest variation because it was difficult to call patients several times during the peak period of the migraine attack. Lastly, although the average measurements obtained by the two observers who were not involved in the data analysis were used for analysis, drawing the choroidal borders manually might have introduced measurement bias.

In conclusion, we found that the choroidal thickness was significantly increased in migraine patients during the attack period when compared to basal levels. Our study is a preliminary report. Further larger studies investigating the neurovascular structures of the eye in migraine patients may provide further insights into both the pathogenesis of migraine and the association between migraine and glaucoma.

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Competing interests None.

Patient consent Obtained.

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