Differences in Choroidal Vascularity Index Between Migraine Patients in the Attack-free Period and Normal Individuals

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ABSTRACT

Purpose: Migraine is a neurovascular disorder characterized by recurrent headaches. The relationship between migraine disease and the choroid, has been examined in an attempt to elucidate the underlying pathophysiological mechanisms. This study evaluated CT (choroidal thickness) and choroidal vascularity index (CVI) in chronic migraine patients.

Materials and Methods: In this prospective study, we compared CT and CVI values of 36 chronic migraine patients (30 women and 6 men) during an attack-free period with those of 36 healthy individuals (30 women and 6 men) with no systemic or ocular disease, including headache. All patients underwent a detailed eye examination. Migraine patients were grouped as those with and without aura and were asked to rate their headache severity on visual analog scale (VAS; range 1-10) and estimate their monthly migraine frequency.

Results: The mean subfoveal CT (SFCT) was 300.52 ± 88.30 µm in the migraine group and 262.85 ± 70.68 µm in the control group. The mean CVI was 71.8% ± 6.2% in the migraine group and 70.7% ± 5.3% in the control group. SFCT and CVI did not differ significantly between the migraine and control groups ($p>0.05$). VAS pain score was 8.17 ± 0.33 in the migraine group and was not correlated with SFCT (r=0, p=0.998) or CVI (r=-0.06, p=0.731). The monthly migraine frequency was 5.60 ± 3.60 and was not correlated with SFCT (r=-0.17, p=0.328) or CVI (r=-0.06, p=0.731).

Conclusion: CT and CVI showed no significant differences from controls in chronic migraine patients during an attack-free period.

Keywords: Choroidal vascularity index, Choroidal thickness, Migraine, Optical coherence tomography

INTRODUCTION

Migraine is a neurological disorder characterized by severe, recurrent unilateral headaches[1]. The diagnosis is based on the characteristics of the headache and associated neurological symptoms such as gastrointestinal and autonomic nervous system symptoms. These symptoms include photophobia, phonophobia, and vomiting, and the pain is usually aggravated by physical activity. One-third of migraine patients also experience transient visual, sensory, language, or motor disturbances before (or rarely, during) the headache, which are referred to as the aura[2].

The pathophysiology of migraine is not well understood and there is no consensus on existing theories. Vasogenic, neurogenic, and cortical spreading depression theories have been proposed to explain migraine pathophysiology[3]. The vasogenic theory attributes the headache to prolonged vasospasm followed by vasodilation whereas the neurogenic theory suggests that vascular changes in migraine occur as a result of neuronal dysfunction. In particular, the release of numerous vasogenic neuropeptides in the trigeminovascular region and the triggering of nociceptive impulses support that the pathophysiology of migraine may be of neurovascular origin[4, 5, 6]. Therefore, migraine is currently considered a neurovascular disease. Further, complex physiopathological changes in different stages of migraine complicate the understanding of the disease. Therefore, since all new knowledge obtained at all stages will be useful in understanding the pathophysiology, the CVI and CT of patients with chronic migraine in the attack-free period were compared with the healthy group.

The choroid receives most of the ocular blood flow,

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and understanding changes in its structure may provide insight into choroidal and ocular blood flow[7, 8]. Choroidal imaging was generally performed with indocyanine green angiography (ICGA) and contact B-scan ultrasound (US) before the introduction of spectral domain optical coherence tomography (SD-OCT) into clinical use[9]. Although choroidal imaging with SD-OCT was inadequate at first, the enhanced depth imaging technique (EDI-OCT) uses longer wavelengths and has enabled detailed visualization of the luminal and stromal structures of the choroidal layer[10]. Most recently, the increasing clinical use of optical coherence tomography angiography (OCTA) has allowed non-invasive examination of the deep and superficial retinal, choriocapillaris, and choroidal circulation[11].

Numerous studies using EDI-OCT to identify vascular changes in the pathophysiology of migraine have investigated choroidal thickness (CT)[12-17]. While measurement of CT may be helpful in clinical research, it is not a reliable parameter because it can be influenced by multiple factors, including diurnal variation, age, gender, and axial length[18, 19]. In addition, although CT has been evaluated in migraine patients before, CVI has not been evaluated. For this reason, we aimed to examine differences in CVI who diagnosed with migraine patients during an attack free period and healthy groups. Therefore, research focus has shifted to choroidal vascularity index (CVI), which is not affected by physiological factors and is determined as the ratio of luminal area to total choroidal area using special software[20-22].

MATERIALS AND METHODS

Thirty-six migraine patients (30 women and 6 men) who were being followed due to chronic migraine (three months or more) and were referred from the neurology clinic and 36 control subjects (30 women and 6 men) with no ocular or systemic disease and no headache complaints were compared. The study was approved by the Institutional Review Board and Ethics Committee and adhered to the Declaration of Helsinki. All participants provided informed consent to use their clinical data for this study.

The migraine patients were grouped as those with and without aura according to the Headache International Society criteria[23]. They were asked to rate their headache pain severity on last month using a visual analogue scale (between 0-10 points) and estimate their monthly headache frequency. All patients used nonsteroidal anti-inflammatory (NSAI) drugs for their migraine attacks. The patients were also asked how many times a month they used NSAI drugs. Patients with any disease that may affect choroidal flow (e.g., hypertension, diabetes mellitus, vasculitis, renal failure), smoking history, and use of drugs likely to affect CT (e.g., sildenafil, triptan, ergot alkaloids, antihistamines, decongestants) were not included in the study.

Ophthalmologic Examination

All participants in the control and migraine groups underwent a detailed ophthalmological examination by the same physician (M.B.). Best-corrected visual acuity (BCVA), fundoscopy, slit-lamp examination, and intraocular pressure measurement were performed in both groups.

Exclusion criteria included spherical and cylindrical refractive errors greater than +/-3 diopters (D), amblyopia, retinal or choroidal pathology, intraocular surgery, and media opacity that would prevent OCT imaging. The right eyes of all participants were evaluated in the study. SD-OCT scans were performed at the same time of day (9:00-10:00 am) to minimize the effect of diurnal variation on the choroid[24].

Choroidal Thickness Measurement

CT measurements were performed by two physicians blinded to the groups (M.B and S.T) using SD-OCT (Heidelberg Engineering, Heidelberg, Germany). A Spectralis OCT (Heidelberg Engineering) was used with a standardized imaging protocol. A 9-mm horizontal image centered on the fovea was obtained with an average of 100 B-scans in each section to improve the signal-to-noise ratio. Eye-tracking mode was also used. All subjects were examined with pupil dilation. CT was measured from the outer edge of the hyperreflective line corresponding to the retinal pigment epithelium (RPE) to the hyporeflective line corresponding to the choroidal-scleral interface. Measurements were made in three different regions, at the foveal center and 1000 μm nasal and temporal of the fovea.

Choroid Vascularity Index Assessment

Sonoda et al. used the image binarization technique to calculate CVI[23]. In this study we used the slightly modified technique described by Agrawal et al.[20]. Open-source ImageJ software was used for image processing (version 1.47; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA; http://imagej.nih.gov/ij/). Briefly, 1 × 1 pixel EDI-OCT images were opened in ImageJ and the scale was set to 200 μm. A total choroidal area (TCA) 1.5 mm in width and centered on the fovea was selected and marked using with the manual

plotting polygonal tool (Figure 1). The upper border of the choroid was marked at the RPE and the lower border was marked at the choroid-sclera junction. The entire length of the OCT B-scan was used for analysis. Then the EDI-OCT B scan was converted to 8-bit images using the default setting. Niblack's automated local threshold tool was applied to delineate the luminal area (LA) and stromal area (SA). The image was then converted back to an RGB (red, green, blue) image to enable computation of LA with the color threshold tool (Figure 2). Lastly, CVI was calculated as the ratio of LA to TCA. CVI measurements were performed by two physicians blinded to the groups (M.B and S.T).

Statistical Analysis

Statistical analysis was performed using SPSS software version 16.0 (SPSS, Inc., Chicago, IL, USA). The normality of data distributions was tested using Shapiro-Wilk test. Continuous variables were shown as median (min-max). Nominal data were analyzed by Pearson's chi-square or Fisher's exact test as appropriate. Differences between values in the three groups were analyzed using Kruskal-Wallis test. Mann-Whitney *U* test was used for pairwise comparisons of the groups. The correlation between SFCT and migraine variables was evaluated using Spearman's correlation coefficient. Statistical significance was defined as $p<0.05$.

RESULTS

Thirty-six right eyes of 36 participants in the migraine group (30 women, 6 men) and 36 right eyes of 36 participants in the control group (30 women, 6 men) were included in the study. The mean ages in the migraine and control groups were 34.7 ± 1.5 years (range 20-52) and 35.1 ± 1.4 years (range 23-51), respectively ($p=0.868$). The groups were also similar in gender distribution. The migraine group included 5 patients who experienced migraine with aura and 31 patients with migraine without aura. BCVA was 0.00 logMAR (20/20 Snellen equivalent) in all eyes. The mean refractive error was -0.07 ± 0.72 D (range -2.25 to +1.50 D) in the migraine group and -0.15 ± 0.74 D (range -2.50 to +1.50 D) in the control group (Table 1).

SFCT was 300.52 ± 88.30 µm in the migraine group and 262.85 ± 70.68 µm in the control group. There were no significant differences between the groups in SFCT or CT 1000 µm temporal and nasal of the fovea ($p>0.05$). The mean CVI was 71.8% ± 6.2% in the migraine group and 70.7% ± 5.3% in the control group ($p>0.05$). Mean CVI,

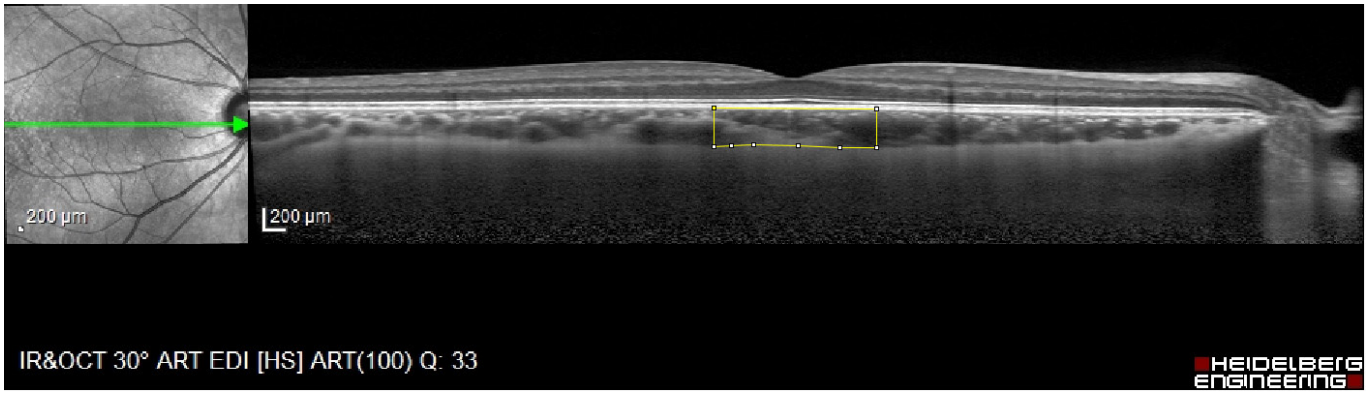

Figure 1: *A width of 1.5 mm centered at the fovea selected by manual plotting polygonal tool.*

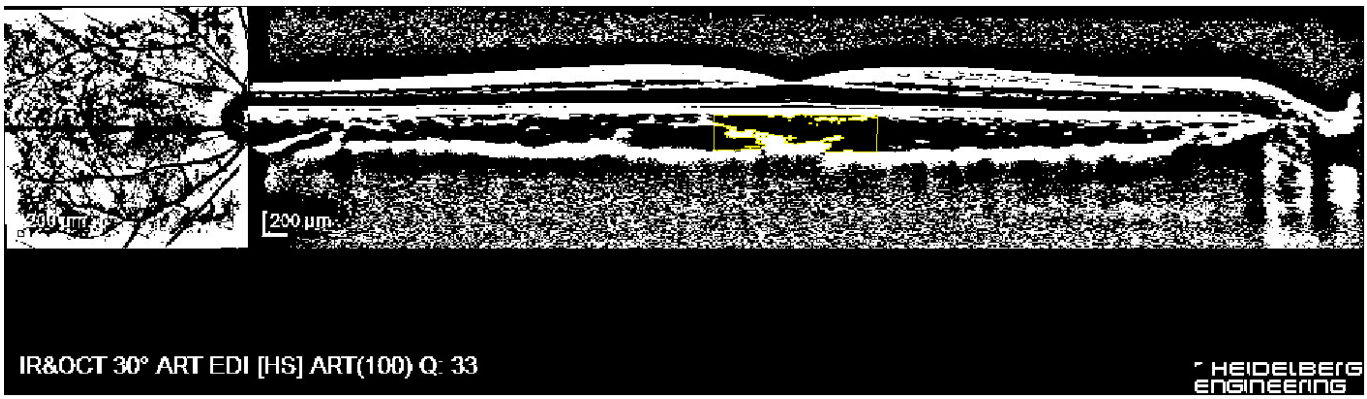

Figure 2: *Superimposed binarized image showing segmentation of the choroidal luminal and stromal structures.*

Table1: *Demographic data of patients and controls*			
Characteristics	Migraine group (n= 36)	Control group (n= 36)	*P* value
Age, years	34.7 ± 1.5	35.1 ± 1.4	0.868*
Gender, n (male/female)	6/30	6/30	
Refractive error, D	-0.07 ± 0.72	-0.15 ± 0.74	0.677**
VAS score (range)	8.17 ± 0.33 (1-10)		
Attacks per month (range)	5.60 ± 3.60 (1-14)		
* Student's t-test, ** Mann-Whitney U test VAS: Visual analogue scale			

TCA, LA, and SA did not differ significantly between the migraine and control groups (Table 2). There was also no significant difference in CVI between migraine patients with and without aura (p>0.05) (Table 3).

The mean VAS pain score in the migraine group was 8.17 ± 0.33 (range 1-10). VAS score was not correlated with SFCT or CVI (r=0, p=0.998 and r=-0.06, p=0.731, respectively). The mean monthly migraine frequency was 5.60 ± 3.60 and there was also no correlation between migraine frequency and SFCT or CVI (r=-0.17, p=0.328 and r=-0.06, p=0.731, respectively) (Table 4).

DISCUSSION

In this study, we observed no significant differences in SFCT and CVI between chronic migraine patients during an attack-free period when compared with the control group. Zengin et al. found that the mean CT was thinner in newly diagnosed (at least 3 months) migraine patients than in the control group (p=0.001). In the same study, they determined that CT decreased significantly in 5 patients during a migraine attack.[12] Reggio et al. also reported that CT was thinner in chronic migraine patients with and without aura compared to the control group (p<0.0001 for

Table 2: *Comparison of choroidal parameters between patients with migraine and the control group*			
Parameter	Migraine group mean ± SD	Control group mean ± SD	*P* value
Subfoveal CT (µm)	300.52 ± 88.30	262.85 ± 70.68	0.107**
N1000 CT (µm)	295.44 ± 91.25	263.84 ± 78.54	0.205**
T1000 CT (µm)	289.33 ± 93.48	263.92 ± 66.75	0.333**
Total Choroidal Area (mm^2)	0.715 ± 0.219	0.689 ± 0.183	0.580*
Luminal Area (mm^2)	0.516 ± 0.170	0.486 ± 0.130	0.395*
Stromal Area (mm^2)	0.199 ± 0.067	0.203 ± 0.069	0.964**
CVI (%)	71.8 ± 6.2	70.7 ± 5.3	0.316**
* Student's t-test, ** Mann-Whitney U test CT: Choroidal thickness, N1000: 1000 µm nasal of fovea, T1000: 1000 µm temporal of fovea, CVI: Choroidal vascularity index, VAS: Visual analogue scale			

Table 3: *Comparison of choroidal vascular index parameters in migraine patients with and without aura*			
	With aura (n=5)	Without aura (n=31)	*P* value
Total Choroidal Area (mm^2)	0.778 ± 0.20	0.704 ± 0.22	0.481*
Luminal Area (mm^2)	0.584 ± 0.18	0.505 ± 0.16	0.413*
Stromal Area (mm^2)	0.193 ± 0.02	0.199 ± 0.07	0.765*
CVI (%)	73.9 ± 7.5	71.5 ± 6	0.101**
* Student's t-test, ** Mann-Whitney U test CVI: Choroidal vascularity index			

Table 4: *Correlation between VAS score, monthly migraine frequency, choroidal thickness, and CVI in migraine patients*

	VAS score (range 1-10)		Attacks per month (range 1-14)	
	r	p	r	p
Subfoveal CT (µm)	0	0.998	-0.17	0.328
N1000 CT (µm)	0.06	0.733	-0.125	0.476
T1000 CT (µm)	-0.039	0.826	-0.128	0.465
Total Choroidal Area (mm^2)	0.183	0.293	-0.046	0.792
Luminal Area (mm^2)	0.152	0.382	0.044	0.800
Stromal Area (mm^2)	0.328	0.054	0.017	0.923
CVI (%)	-0.06	0.731	0.04	0.820

CT: Choroidal thickness, N1000: 1000 µm nasal of fovea, T1000: 1000 µm temporal of fovea, CVI: Choroidal vascularity index, VAS: Visual analogue scale

both eyes).[14] Likewise, Karaca et al. found that SFCT was thinner in the attack-free period in migraine patients with and without aura compared to the control group ($p<0.05$). However, CT was similar at all measured points between the migraine subgroups with and without aura ($p>0.05$).[15] Contrary to these studies, Gunes et al. found that CT was thicker in chronic migraine patients compared to the control group ($p<0.001$ for both eyes).[16] In their literature review, Ascado et al. summarized the different CT results obtained in migraine patients.[26] Therefore, a different parameter is needed due to the variable nature of CT. In our study, we determined that there was no statistically significant difference in CT and CVI between migraine patients and the normal healthy group. To the best of our knowledge, this is the first study evaluating the CVI in patients with chronic migraine.

Temel et al. investigated CVI in newly diagnosed migraine patients and reported that CVI was significantly decreased in patients with migraine.[27] However, limitations of their study are that it included a relatively small sample size. In studies, all agents that can cause arterial and venous vasoconstriction, especially ergot alkaloids and triptans should be questioned meticulously.[28, 29] Therefore, more studies are needed in migraine patients with CVI.

Many studies have shown that CT is affected by various factors, especially certain drugs such as sildenafil and antihistamines, smoking, age, and the axial length of the eye.[30-33] While choroidal thinning is seen in choroidal dystrophies and AMD, thickening occurs in diseases such as Vogt-Koyanagi-Harada, central serous retinopathy, and polypoidal choroidal vasculopathy.[34-36] In addition, CT measurements may differ due to examiner bias and interobserver variation.[21-37] On the other hand, CVI gives more reliable information than CT because LA (vascular), SA (interstitial), and TCA are determined from EDI-OCT images by special software using the binarization method.[20, 21] The rich vascular structure and changes in the connective tissue can be examined in more detail, providing more reliable data about the choroidal structure. For this reason, CVI is increasingly used instead of assessing choroidal structure only by its thickness.

EDI-OCT is a non-invasive method that enables detailed visualization of the choroid.[10] Although ICGA is still considered the gold standard imaging modality in choroidal pathologies such as PCV, its clinical use is declining because of its invasiveness.[38] With EDI-OCT, however, the effects of intraocular pressure and perfusion changes on the choroid can be assessed instantly and non-invasively. OCTA imaging has also seen more widespread clinical use in recent years because it allows non-invasive visualization of retinal and choroidal blood flow. This method uses special software to detect the movement of red blood cells in the vasculature and display vascular flow.[11] Güler et al. used OCTA to examine differences in retinal, peripapillary, and choriocapillaris blood flow between 26 patients with migraine without aura and a healthy control group. They observed no significant difference between the two groups in terms of blood flow in the superficial or deep retina, choriocapillaris, or choroid (choroidal flow area was 9.64 ± 0.44 and 9.65 ± 0.21 mm^2 in the migraine and control groups, respectively, $p=0.495$).[39] Özçift et al. examined optic disc perfusion, central macular perfusion, and central CT in 38 chronic migraine patients and reported no significant difference in perfusions or CT, although CT was negatively correlated with the duration of migraine disease ($r=-0.46$, $p=0.004$).[40]

OCT is excellent for visualizing the retinal and choroidal anatomy but provides no information about the vasculature

or circulation.[41] The fact that we detected no statistically significant difference in CVI values between the two groups in our study is consistent with previous studies indicating no change in choroidal flow on OCTA. The inconsistency between OCTA and CT studies may also be due to the relative subjectivity of CT measurement. According to Güler et al., there was no significant difference in retinal and choroidal blood flow in migraine patients, and retinal blood flow was determined by the dynamics of the vascular microenvironment.[39] Rather than CT, more OCTA and CVI data are needed to explain pathophysiological mechanisms, especially in a disease of unclear pathophysiology such as migraine.

Finally, we determined that mean VAS score (8.17 ± 0.33) and monthly attack frequency in the migraine group were not significantly correlated with CT or CVI. This is consistent with the results reported by Zengin et al., who observed no significant relationship between mean VAS score (5.55 ± 2.93) and CT.[12] However, Karaca et al. investigated the relationship between CT and VAS score, Migraine Disability Assessment Score, and Wong-Baker faces pain rating scale score and determined that CT moderately correlated with VAS score and Wong-Baker scores in patients with migraine without aura but not in patients with migraines with aura.[15] In this regard, it is clear that more studies are needed to understand the correlation between CT, CVI and different pain scores and migraine frequency.

The present study has some limitations. One important limitation of our study is that changes in CVI were not evaluated during migraine attacks. Different results may be obtained during a migraine attack due to the activation of different pathophysiological mechanisms. Another limitation is the small number of patients included in the study. Especially only 5 migraine patients belonged to aura type. The number of migraine patients with aura is of very limited representative value due to very small sample size. In addition, as in all CT studies, the manual determination of CT in our study is a limitation because manual segmentation remains a potential source of bias. Software-based automatic determination of CT is needed to eliminate this problem.

In conclusion, the results of this study suggest that CT and CVI do not differ significantly in chronic migraine patients during an attack-free period compared to healthy controls. However, considering the complex pathophysiology of migraine disease, more studies are needed to understand the relationship between migraine and CT.

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