Original Article

Peripapillary and subfoveal choroidal vascular index in patients with tension-type headache and migraine

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Purpose: This study aimed to evaluate the choroidal vascular characteristics of patients followed up with different headache diagnoses. **Design:** Prospective comparative study. **Methods:** This study included 21 patients with migraine with visual aura (MwA), 20 with migraine without aura, 29 patients experiencing episodic tension-type headache, and 30 healthy participants. The participants was performed refraction values, axial length, and intraocular pressure were examined. Choroidal thickness was determined in all participants with HD-line optical coherence tomography (OCT) in the subfoveal, nasal, and temporal quadrants 500 µm from the fovea. Using special image processing software, luminal area (LA), stromal area, total choroidal area, and choroidal vascular index (CVI) values were calculated in both macular and peripapillary regions. OCT was also used to perform peripapillary retinal nerve fiber layer (pRNFL) thickness and optic disc head measurements. **Results:** Spherical refraction, axial length, and intraocular pressure values did not significantly differ among the four groups with similar gender and age distributions ($P > 0.05$). The LA values in both macular and peripapillary regions were found to be statistically significantly lower in the MwA group ($P = 0.007$ and $P = 0.005$, respectively). There was no statistically significant difference among the groups in terms of the remaining choroidal area parameters or CVI values ($P > 0.05$). The groups also did not show any significant difference in the pRNFL or optic disc head measurements performed in different quadrants ($P > 0.05$). **Conclusion:** While LA, one of the choroidal vascular parameters, was found to be lower in the MwA group in both the macular and peripapillary regions, there were no statistically significant differences between the groups in terms of the peripapillary or macular CVI values.

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Tension-type headache (TTH) and migraine are the common types of headaches seen across the world.[1] Although the pathophysiology of TTH is not yet clearly understood, it is considered to occur due to the hypersensitivity of peripheral nociceptors and the contraction of pericranial muscles. Along with this usually bilateral headache, individuals also describe a sensation of pressure that varies in intensity. It is known that there are different subtypes: infrequent episodic, frequent episodic, and chronic.[2,3]

Migraine is a very common, multifactorial, and neurovascular headache syndrome.[4,5] This condition is generally characterized by unilateral, recurrent attacks and may be accompanied by different symptoms.[6] Migraine subtypes are categorized based on the presence of aura. Visual, sensory, or motor phenomena, called aura, may be seen in some patients before the attack. The most accepted mechanism for migraine pathogenesis is changes in vascular tone and the transport of pain signals, associated with the trigeminal vascular system. Due to the rich vicinity of the trigeminal nerve and its wide innervation network, this nerve is of great importance in the development of migraine.[7,8]

Vasospasm-induced reduction in blood flow is reported in the occipital area in different types of headaches. Visual symptoms and headaches may occur due to decreased blood flow. Reduced blood circulation may affect not only the cortical regions, but also the ocular blood flow.[9,10] The retina is a vital tissue for the visual function of the ocular system. The central retinal artery and choroid are involved in the nourishment of the retina. The choroid is responsible for feeding the outer one-third of the retina; therefore, retinal damage may occur due to choroidal pathologies.[8]

The choroidal vascular index (CVI) is an important parameter that has received increasing popularity in recent years and has been evaluated in many diseases.[11] Although optical coherence tomography (OCT), which is a noninvasive, fast, effective, and reliable imaging method, does not offer detailed information about the choroidal tissue, it can be used to calculate CVI that provides data on the status of choroidal blood flow in different regions.[12]

Different visual symptoms and findings may be observed in patients with migraine and TTH. Although retinal layer and choroidal thicknesses in these patient groups, especially those with migraine, have been examined in many studies, to

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our knowledge, there is no research evaluating the structural and vascular properties of the choroid in individuals with TTH.[4-6,12] The fact that visual symptoms are seen especially in migraine patients with aura and the most accepted mechanism is cortical spreading depression necessitates investigation of ocular involvement.[7,8] The main hypothesis of this study is whether the choroid, which is rich in vascularization, is affected in migraine patients with aura. At the same time, the most accepted mechanism in the pathophysiology of TTH is pericranial contractions, and the possibility of the thickness and blood supply of posterior ocular structures getting affected in these contractions is another hypothesis of the study. We consider that the current study will make significant contributions to the literature since it is the first to evaluate peripapillary CVI in both patients with migraine and those with TTH. The aim of the study was to obtain more information on the ocular effects by detecting changes in choroidal vascular structures in different types of headaches.

Methods

After receiving ethics committee approval from Ethics Committee No. 1 of Ankara City Hospital, this prospectively designed study was conducted at the neurology and ophthalmology clinics of Yozgat City Hospital, taking into account the principles of the Declaration of Helsinki. Necessary consents were obtained from the participants.

The study included 41 patients followed up for migraine at the neurology clinic [21 patients with migraine with aura (MwA) and 20 patients with migraine without aura (MwoA)], 29 patients diagnosed with frequent episodic TTH, and 30 healthy controls. Patients in the MwA group had visual auras. The diagnoses of migraine and TTH were established based on the criteria outlined in the International Classification of Headache Disorders, third edition.[8]

Diagnostic criteria for MwA[8]:

1) At least two episodes (items 2 and 3 must be met)
2) Presence of fully reversible visual, sensory, speech and/or language, motor, brainstem, and retinal aura (must be at least one)
3) Gradual spread of at least one aura symptom for more than 5 min, aura duration of 5–60 min, at least one aura symptom being unilateral, aura accompanying headache (at least two of these four conditions must be present)
4) Transient ischemic attack and/or not better explained by another disease

Diagnostic criteria for MwoA[8]:

1) At least five episodes (must meet points 2 and 4)
2) Headache attacks lasting 4–72 h
3) Unilateral localization, pulsating quality, pain intensity moderate or severe, aggravated or avoided by routine physical activities (at least two of these conditions must be present)
4) Nausea and/or vomiting, photophobia, and phonophobia (must be at least one)
5) Not included in any other classification

Diagnostic criteria for frequent episodic TTH[8]:

1) At least 10 headache attacks over an average of more than 3 months (criteria 2 and 3 must be met)
2) Lasting between 30 min and 7 days
3) Bilateral localization, nonpulsatile quality, mild or moderate intensity, no aggravation with routine physical activity (must be at least two)
4) Absence of nausea, vomiting, photophobia, and phonophobia
5) Cannot be explained by other diagnostic criteria

In the ophthalmologic examination of all participants, spherical and cylindrical refractive values were determined using an autorefractometer (Nidek ARK-1; Nidek Co., Aichi, Japan). Intraocular pressure measurements were undertaken with an air puff tonometer (Nidek NT-510). Visual acuity was measured using the determined refractive values and the Snellen chart. Then, an anterior segment examination was performed with a biomicroscope. One patient who was found to have cataract onset during this examination was excluded from the study. After adequate dilatation was achieved, a detailed fundus examination was undertaken. Axial length was measured with the IOLMaster 500 (Carl Zeiss, Jena, Germany). OCT (Cirrus OCT; Carl Zeiss Meditec, Dublin, CA, USA) scans were obtained by an experienced health-care professional between 9 a.m. and 11 a.m. in the morning for all participants. OCT was performed with horizontal and vertical scans centered on the fovea and optic disc. This imaging was performed with 200 A-scans and 200 B-scans centered on the optic disc and based on an area of 6 mm^2. The peripapillary retinal nerve fiber layer (pRNFL) thickness profile was calculated automatically through the dataset after automatic determination of the center of the disc. pRNFL thicknesses were automatically measured by OCT separately for the superior, inferior, temporal, and nasal quadrants, as well as the mean values. Disc head measurements were obtained from a three-dimensional cube dataset with the end of Bruch's membrane as the boundary. Measurements of the optic disc included the rim area, disc area, cup volume, and mean and vertical cup/disc ratios. For the evaluation of choroidal thickness, the outer border of the retinal pigment epithelium and the choroidoscleral interface points were identified, and choroidal thickness values were recorded for the subfoveal quadrant (SFCT) and the nasal and temporal quadrants 500 µm from the fovea (N_{500}FCT and T_{500}FCT, respectively). The obtained macular HD-line OCT and peripapillary HD-line OCT images were evaluated using special software to calculate CVI. The limit for signal quality was accepted as >8/10.

Excluded from the study were individuals with spherical or cylindrical refractive errors of >±2 D, best-corrected visual acuity of <20/20 on the Snellen chart, intraocular pressure of >20 mmHg, or axial length of <22.5 mm to >24.5 mm; those with amblyopia, cataract, keratoconus, uveitis, pseudoexfoliation, glaucoma, papilledema, optic neuropathy, or retinal pathologies; those younger than 18; those with diabetes mellitus, systemic hypertension, cardiovascular disease, autoimmune diseases, cranial mass, trauma, ocular or systemic surgery history; pregnant or breastfeeding women; and smokers.

Using open-access image processing software (ImageJ 1.51; National Institutes of Health, Bethesda, MD, USA), image binarization was performed with the method described by Agrawal *et al*.[13] The retinal pigment epithelium was accepted as the reference line, and the choroid–scleral junction was identified using the Niblack method. The hue, saturation, and brightness were adjusted with the color threshold segment. Field was added for the image obtained based on yellow color. The total choroidal area (TCA) was calculated in a 1500-µm area centered around

the fovea from four directions [Fig. 1a]. This area was designated as the region of interest. Subsequently, the luminal area (LA) was calculated by selecting dark pixels and yellow colors using the color threshold. After the determination of LA and the region of interest through the software, they were combined and area measurements were performed. For calculation of the peripapillary CVI, the optic disc border was marked from the inner edge of the scleral ring and binarized with 1000-µm-wide scans in the superior, inferior, temporal, and nasal quadrants and the area values were determined[14] [Fig. 1b]. In both evaluations, the stromal area (SA) was calculated by subtracting the LA value from the TCA value. The ratio of the LA value to the TCA value was accepted as CVI, which was recorded for both macular and peripapillary regions. All measurements were performed twice, and inconsistent measurements were not included in the statistical analysis.

In the sample analysis performed before the study, it was estimated that a minimum of 20 participants was required for each group, totaling at least 80 participants, based on the values of 0.4 for the effect size, 0.01 for the type 1 error, and 80% for the power value. Only the right eye measurements of all participants were included in statistical analyses.

The data obtained were analyzed using the Statistical Package for the Social Sciences package program (IBM Corp., Armonk, NY, USA). The suitability of the data to the normal distribution was examined with the Shapiro–Wilk test statistically and with histograms visually. Kruskal–Wallis analysis of variance was used to analyze four different independent groups. In the presence of a significant difference according to the Kruskal–Wallis analysis of variance, Bonferroni correction was applied to determine the group from which this difference originated. In measurements where this correction was employed, $P = 0.05/6 = 0.008$ was accepted as the significance level for the P value. In all other comparisons, 0.05 was considered the significance level for the P value.

Results

The study included 100 eyes of 100 participants. Table 1 presents the age, gender, and ophthalmologic examination findings of patients according to the groups. The four groups had similar age and gender distribution. There were also no statistically significant differences between the groups in terms of spherical refractive error values, axial length, or intraocular pressure values ($P > 0.05$ for all).

The pRNFL thicknesses (mean and temporal, superior, nasal, and inferior quadrant values) and optic disc measurements (rim area, disc area, mean cup-to-disc ratio, vertical cup/disc ratio, and cup volume) of the cases are shown in Table 2. There were no statistically significant differences among the four groups in relation to the pRNFL thicknesses measured in any of the quadrants or any of the optic disc measurements ($P > 0.05$ for all).

Table 3 presents the distribution of the SFC, $N_{500}FC$, and $T_{500}FC$ thickness values, choroidal area measurements (LA, SA, and TCA), and the macular and peripapillary CVI parameters. Choroidal thicknesses were similar among the four groups in all three quadrants ($P > 0.05$ for all). The LA values in both macular and peripapillary regions were significantly lower in the MwA group than in the control group ($P = 0.007$ and $P = 0.005$, respectively). There were no statistically significant differences among the four groups in relation to the remaining choroidal area measurements, namely SA, TCA, and CVI, evaluated in the macular or peripapillary regions ($P > 0.05$ for all).

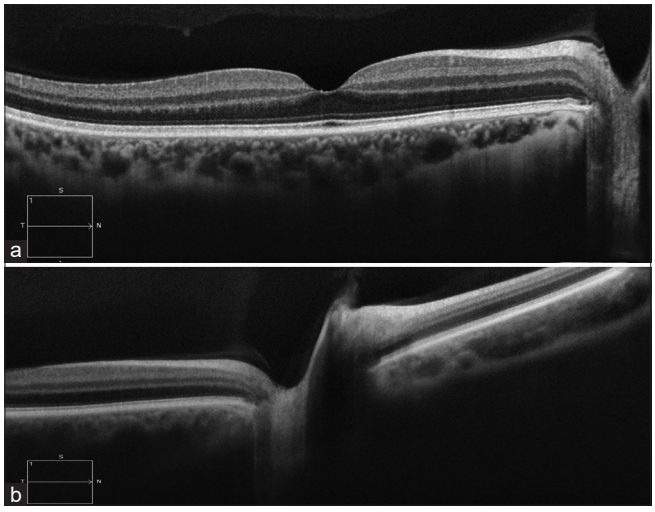

Figure 1: Choroidal images in the subfoveal (a) and peripapillary (b) areas

Discussion

It is known that pathologies characterized by chronic or recurrent attacks can potentially impact the blood flow of ocular structures such as the optic nerve head, retina, and choroid.[15] In this study, RNFL thicknesses, choroidal thicknesses, optic disc head measurements, and choroidal vascular parameters were evaluated in patients with migraine and frequent episodic TTH during pain-free periods. Patients with migraine were further divided into two groups according to their aura status, and their data were compared to those with TTH and healthy controls. The primary findings of the study indicate that while there were no significant differences between the groups in terms of RNFL thicknesses, choroidal thicknesses, or optic disc head measurements, among the choroidal vascular parameters, only the LA value was found to be significantly lower in the MwA group.

The retina and the choroid are two important neighboring ocular structures with anatomic and functional interactions. The choroid is responsible for the blood supply to a large part of the retina. The choroid itself is fed by trigeminal sensory innervation rich in calcitonin gene-related peptides.[16] Choroidal thickness can be evaluated quantitatively with OCT imaging. In addition, Agrawal *et al*.[13] introduced CVI in the literature, which they calculated using HD-line or enhanced-depth-image OCT slices through image processing software. Thus, information about the vascular structure of the choroid can be obtained through noninvasive, rapid imaging. While CVI has been examined in different diseases and conditions, it has been suggested that it can also serve as an important biomarker in pathologies involving the central nervous system.[17,18] Despite the presence of studies evaluating macular CVI in patients with migraine,[19,20] we did not find any research assessing peripapillary CVI. Furthermore, there is currently no study investigating choroidal vascular and structural characteristics in patients with TTH. Therefore, being the first study to evaluate different headache types in terms of CVI values in

Table 1: Distribution of the demographic and ophthalmologic findings of the cases

Parameter	MwA (*n*=21)	MwoA (*n*=20)	TTH (*n*=29)	Control (*n*=30)	*P*[a]
Age (years)	30.9±10.3	31.6±9.4	33.6±8.4	34.9±7.9	0.37
Gender (F/M)	19/2	16/4	25/4	25/5	0.65
Spherical refractive error (D)	-0.51±0.28	-0.62±0.33	-0.47±0.26	-0.41±0.21	0.25
Axial length (mm)	23.5±1.4	23.1±1.7	23.2±1.2	23.2±1.4	0.41
Intraocular pressure (mmHg)	12.4±2.6	12.9±3.1	13.2±2.8	11.7±1.9	0.55

MwA=migraine with aura, MwoA=migraine without aura, TTH=tension-type headache. [a]Kruskal–Wallis test

Table 2: Distribution of the pRNFL and optic disc head measurements across the groups

Parameter	MwA (*n*=21)	MwoA (*n*=20)	TTH (*n*=29)	Control (*n*=30)	*P*[a]
pRNFL (μm)					
Mean (μm)	99±9	98±7	97±8	97±8	0.88
Superior (μm)	122±16	121±14	122±17	121±14	0.98
Inferior (μm)	131±15	130±9	125±15	127±13	0.37
Temporal (μm)	66±9	69±10	65±10	69±11	0.44
Nasal (μm)	77±11	73±9	75±12	73±13	0.67
Rim area (mm^2)	1.39±0.23	1.42±0.24	1.43±0.28	1.48±0.30	0.72
Disc area (mm^2)	1.84±0.35	1.84±0.34	1.87±0.31	1.88±0.35	0.97
Mean cup/disc ratio	0.45±0.16	0.43±0.15	0.44±0.17	0.43±0.12	0.97
Vertical cup/disc ratio	0.42±0.15	0.41±0.15	0.42±0.15	0.41±0.11	0.99
Cup volume (mm^2)	0.13±0.13	0.12±0.11	0.11±0.10	0.09±0.06	0.48

MwA=migraine with aura, MwoA=migraine without aura, pRNFL=peripapillary retinal nerve fiber layer, TTH=tension-type headache [a]Kruskal–Wallis test

Table 3: Distribution of choroidal thickness and choroidal vascular parameters across the groups

Parameter	MwA (*n*=21)	MwoA (*n*=20)	TTH (*n*=29)	Control (*n*=30)	*P*[a]
SFCT (μm)	302±21	306±32	294±29	287±35	0.25
N500FCT (μm)	279±34	287±37	282±29	291±34	0.33
T500FCT (μm)	280±19	271±21	264±35	274±26	0.29
Macular LA (mm^2)	0.12±0.03	0.13±0.04	0.16±0.04	0.17±0.04	**0.007**
Macular SA (mm^2)	0.06±0.01	0.06±0.02	0.08±0.03	0.09±0.02	0.014
Macular TCA (mm^2)	0.19±0.04	0.20±0.07	0.25±0.07	0.25±0.09	0.009
Macular CVI	0.64±0.02	0.66±0.01	0.66±0.03	0.65±0.02	0.33
Peripapillary LA (mm^2)	0.11±0.02	0.13±0.02	0.15±0.04	0.16±0.02	**0.005**
Peripapillary SA (mm^2)	0.05±0.01	0.06±0.03	0.07±0.02	0.08±0.03	0.009
Peripapillary TCA (mm^2)	0.17±0.02	0.19±0.05	0.23±0.04	0.23±0.05	0.012
Peripapillary CVI	0.62±0.03	0.64±0.02	0.63±0.01	0.62±0.02	0.24

CVI=choroidal vascular index, LA=luminal area, m=macular, MwA=migraine with aura, MwoA=migraine without aura, N500FCT=nasal choroidal thickness measured 500 μm from the fovea, SA=stromal area, SFCT=subfoveal choroidal thickness, T500FCT=temporal choroidal thickness measured 500 μm from the fovea, TCA=total choroidal area, TTH=tension-type headache. [a]Kruskal–Wallis test with Bonferroni correction for pairwise comparisons; statistically significant at *P*<0.008

both macular and peripapillary regions, the current study will contribute to the literature concerning possible ocular effects in different headache syndromes.

The most accepted mechanism for the formation of an aura in migraines is cortical spreading depression.[17] This electrophysiologic wave originates from the occipital region. It is considered that the visual aura, in particular, develops due to changes in blood flow in this region.[21] *In vitro* and *in vivo* studies have detected a decrease in cortical blood flow in patients with MwA using functional magnetic resonance and single-photon emission computed tomography.[22,23] If this decrease occurs consistently in the presence of each aura, it may lead to ocular effects in patients with chronic migraine. Our study revealed that the LA values in both the macular and peripapillary regions were lower in the MwA group compared to the healthy control group. However, no significant difference was detected for the remaining choroidal area measurements. These findings are supported by the ocular effect mechanism described above.

The optic nerve, derived from the ectoderm, is part of the central nervous system. The pathway between the primary visual cortex and the retina is an example of transneuronal

retrograde neuronal degeneration. In studies conducted on animals, while atrophy was observed in ganglion cells and the optic nerve after occipital lobectomy, degeneration in the visual cortex was also reported.[24,25] These relationships have led researchers to examine retinal and optic disc parameters in patients with migraine. pRNFL is an important marker for the evaluation of the optic disc. Martinez *et al*.[4] compared this marker between migraine and healthy control groups and found no significant difference. In another study conducted with the same design with a smaller number of patients, no significant change was detected in RNFL.[5] In the current study, different from previous research, the pRNFL and optic disc head measurements were evaluated in patients with TTH, but no difference was found among the groups in pRNFL or optic disc head measurements.

The pathophysiology of TTH is not yet clearly known. The development of pain is believed to be caused by pericranial contractions, which is supported by changes in electromyography activity.[26] With the idea that these pericranial contractions may affect ocular blood flow, researchers have made quantitative evaluations using OCT and visual field tests in patients with TTH.[12,27] In one of these studies, RNFL thickness, retinal layer thickness, and optic disc head measurements obtained from OCT were compared between patients with migraine and healthy controls, and no significant difference was found,[12] which is consistent with our findings. In another study, Yener and Korucu[27] evaluated visual field findings in patients with migraine and TTH and reported visual field deficits in 44% of the former and 36% of the latter.

Many studies have evaluated choroidal thickness in patients with migraine, but reported varying results. It is considered that choroidal thinning or thickening may occur due to changes in retinal blood flow.[28,29] Conflicting results may be due to factors such as differences in study populations and the variability in migraine subtypes and disease duration. While choroidal thickness has been frequently investigated in patients with migraine, we found no similar study for patients with TTH. To the best of our knowledge, the current study is the first to evaluate choroidal thickness in this patient population. As in patients with migraine, we observed no significant difference in choroidal thickness in the three regions in patients with TTH. The absence of research investigating potential ocular effects in patients with TTH, except for two studies,[12,27] and the lack of data on the choroid in patients with TTH highlight the significance of our study.

Although migraine and TTH are considered different headache entities, it can be challenging to make a clinical distinction. Furthermore, 20%–25% of patients initially diagnosed with migraine or TTH may transition from migraine to TTH or from TTH to migraine. While symptoms of migraine include muscle tension and neck pain, photophobia may be observed in TTH.[30] Given the above-mentioned conditions, the diagnostic distinction between these two headache syndromes may become difficult, especially in young patients or in cases of chronic headache. It can be suggested that it is not possible to clearly differentiate between these two conditions based on the ocular effects revealed by the current findings. In contrast to previous reports indicating that choroidal area parameters (TCA, LA, and CVI) can be used as potential biomarkers in neurodegenerative pathologies,[17] only LA was found to be lower in the MwA group in the current study. Although Temel *et al*.[19] reported the CVI value to be lower in patients newly diagnosed with migraine, Torun *et al*.[20] detected no significant difference among the MwA, MwoA, and healthy control groups in terms of CVI values. In contrast to these studies, we also examined the choroidal area parameters of patients with TTH and observed no significant difference in the choroidal area parameters of these patients.

Among the limitations of our study, the most important are the small number of patients and the single-center design. Another limitation is that different aura types and other TTH subtypes were not included in the evaluation. The investigation focused solely on choroidal blood flow parameters derived from OCT data. Supporting these data with additional examinations will strengthen the findings. Furthermore, it is important to note that the results of this study do not provide information about ocular effects in the presence of headaches, since the evaluations were made during the pain-free periods of the participants.

Conclusion

The results of this study revealed no significant differences in RNFL thickness, optic disc head measurements, or choroidal thickness among migraine subgroups, patients with TTH, and healthy controls. While the LA value, one of the choroidal vascular parameters, was found to be lower in the MwA group than in the control group, no statistically significant difference was observed in terms of CVI values measured in the peripapillary and macular regions. The effects of both conditions on choroidal vascular structures can be better assessed by randomized studies with a larger series.

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