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Original Article

Comparison of ocular posterior segment parameters in the pediatric population with migraine without aura and tension-type headache

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ABSTRACT

Background. This study aims to compare the posterior ocular structure parameters in children with migraine without aura (MWA), tension-type headache (TTH), and a healthy control group.

Methods. The study included 31 patients with MWA, 29 patients with TTH, and 38 healthy controls between 6 and 18 years of age. For all participants, the detailed eye examination and measurements including peripapillary retinal nerve fiber layer (pRNFL) thickness, central macular thickness (CMT), subfoveal choroidal thickness (SCT), macular vessel densities and foveal avascular zone (FAZ) parameters measured by optical coherence tomography (OCT) and OCT-angiography (OCTA), were obtained from the patient files.

Results. The mean age was 12.1±3.3 years in MWA patients, 12.4±2.8 years in TTH patients, and 11.9±3.8 years in the healthy controls (p=0.844). Among the groups, the mean pRNFL thickness, CMT, and SCT values were lowest in the MWA group. However, this difference was not statistically significant (p=0.621, p=0.854 and p=0.201, respectively). The mean and four-quadrant (superior, inferior, temporal, nasal) pRNFL thicknesses, the CMT, and the SCT were not statistically significant between the groups (p=0.621, p=0.500, p=0.186, p=0.565, p=0.744, p=0.854 and p=0.201, respectively). The macular vascular densities were lower in MWA patients than in the other two groups, and there was a statistically significant difference between the groups only in the nasal quadrant of the deep retinal capillary plexus (p = 0.014). There were also no statistically significant differences between the groups in the superficial and deep FAZ area parameters (p=0.652 and p=0.985).

Conclusion. This study suggested that differential diagnosis between MWA and TTH can be difficult in childhood, as these conditions, which can present with ocular symptoms, may also be characterized by changes in posterior segment parameters. Long-term studies incorporating OCT-A in larger patient populations may provide valuable insights into retinal changes associated with these two distinct headache spectrums.

Key words: pediatric migraine, pediatric tension-type headache, optical coherence tomography-angiography, macular vessel density, foveal avascular zone.

Headache is a common symptom, affecting nearly 52.0% of the population.[1] Headache is also common in the pediatric age group, with studies showing that various types of headaches can develop in 57-82% of children up to 15 years of age.[2] The average age of headache onset is 7.5 years.[3,4] The failure to diagnose and manage headache has a negative impact on the quality of life in childhood. The disability caused by chronic headaches in childhood has

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been shown to be similar to the loss in quality of life caused by cancer and arthritis.[5]

The most common types of primary headaches in the pediatric age group are migraine and tension-type headaches (TTH). The differential diagnosis depends on clinical symptoms, according to the International Classification of Headache Disorders, third edition (ICHD-III) of the International Headache Society (IHS).[6] The prevalence of migraine is 20 % in the 15-25 age group, however, the prevalance of TTH in young subjects varies between 0.9-72.3%.[7,8] It can be difficult to distinguish between these two spectra in children. Two theories explain the development of migraine: vascular and neurogenic. According to the vascular theory, migraine is triggered by activation of the trigeminal vascular system (TGVS), which maintains vascular tone and innervates blood vessels in the brainstem, extracranial tissues, and eyes.[9] The pathophysiology of TTH remains insufficiently understood. One theory suggests increased sensitivity of pain pathways in the central and peripheral nervous systems, and another hypothesis involves hyperactivation of myofascial nociceptors.[10,11]

Some ocular symptoms, such as photophobia, visual field loss, and periocular pain may develop in migraine and TTH patients.[12-14] However, the reason for these ocular conditions is not known. Some studies have reported changes in neuronal and vascular structures in the posterior segment on optic coherence tomography (OCT) and OCT-angiography (OCTA) imaging in migraine patients, and these studies demonstrated that migraine may cause impairment of retinal microcirculation, retinal nerve fiber layer (RNFL) thinning and ganglion cell loss in the retina.[15-17] However, there have been no studies of TTH using OCTA.

It is known that the cause of the ocular symptoms seen in both migraine without aura (MWA) and TTH cannot be fully explained. In addition, the difficulty of clinically differentiating these two types of primary headaches in children, increases the value of objective diagnostic tools. Therefore, this study aimed to comprehensively evaluate the posterior segment parameters concerning neural and vascular changes in MWA and TTH.

Materials and Methods

This retrospective study was conducted by the Pediatric Neurology and Ophthalmology Departments of Dr. Lütfi Kırdar Kartal City Hospital between May and June 2022. The study was approved by the Ethics Committee of Dr. Lütfi Kırdar Kartal City Hospital and conducted according to the tenets of the Declaration of Helsinki (Protocol Number: 2022/514/224/11). Written informed consent was not obtained from participants due to the retrospective nature of this study.

Thirty-one patients diagnosed with MWA and 29 patients diagnosed with TTH according to ICHD-III edition of the IHS, were included in the study, and 38 age- and gender-matched patients presenting to the Ophthalmology Department with minor symptoms such as refractive error were included as the healthy control group. The patients in this study consisted of those who were followed for at least 6 months due to headache before the differential diagnosis. The clinical and demographic data were collected from the medical records of all patients, including age, sex, diagnosis, age of onset, pain characteristics (including triggers and alleviating factors), associated symptoms (e.g., headache prodromes or a history of bruxism), disease duration following differential diagnosis, attack frequency and duration, treatments used, family history, and neurological and general physical examinations. Detailed eye examinations were also obtained for all patients including best corrected visual acuity (BCVA) with Snellen charts, slit-lamp biomicroscopy, fundus examination with a 78-diopter lens, and intraocular pressure (IOP) with Goldman applanation tonometry. For all participants, only the measurements of the right eye were examined due to the similarity of right and left eye analyses. In addition, all data such

as examinations and measurements were taken during the period when the patients were free of attacks.

Patients with previous ocular diseases (such as corneal and lens diseases, uveitis, and retinal diseases), a history of intraocular surgery, ocular or head trauma, ocular hypertension or glaucoma, drug or radiation treatment, and any systemic and neurological diseases except migraine and TTH were excluded from the study. Patients with BCVA ±4 D were also excluded from the study. In the healthy controls, patients were excluded if they had been diagnosed with any type of headache or reported having headaches for any reason in the previous six months. Patients were also excluded if they were under the age of four or over the age of eighteen, or if they were unable to cooperate with the measurements.

OCT images of all patients were obtained using a swept-source OCT device (DRI OCT Triton plus-Topcon, Japan) with a light source of 1050 nm wavelength and a scanning speed of 100,000 axial per second. Macular and optic nerve head parameters were assessed in a single scan with deep penetration wide-angle (12x9 mm) imaging at the posterior pole in OCT images (Fig. 1a, b). The central subfoveal choroidal thickness (SCT) was obtained by drawing a perpendicular line between the posterior edge of the retinal pigment epithelium and the choroid-sclera junction in the fovea region, using cross-sectional OCT-B scans by the same experienced technician. All SCT measurements were performed at the same time of the day (from 09.00 to 12.00 in the morning) to avoid daily variations.

OCTA images were measured by scanning a 3x3 mm^2 area on the fovea of the patients. The "en-face images" were taken from the superficial capillary plexus (SCP) and deep capillary plexus (DCP). The SCP is located from 2.6 μm below the internal limiting membrane (ILM) to 15.6 μm below the inner plexiform layer (IPL) while DCP is located between 15.6 μm and 70.2 μm below IPL. The quantitative analysis, including FAZ parameters and capillary density, was performed using the

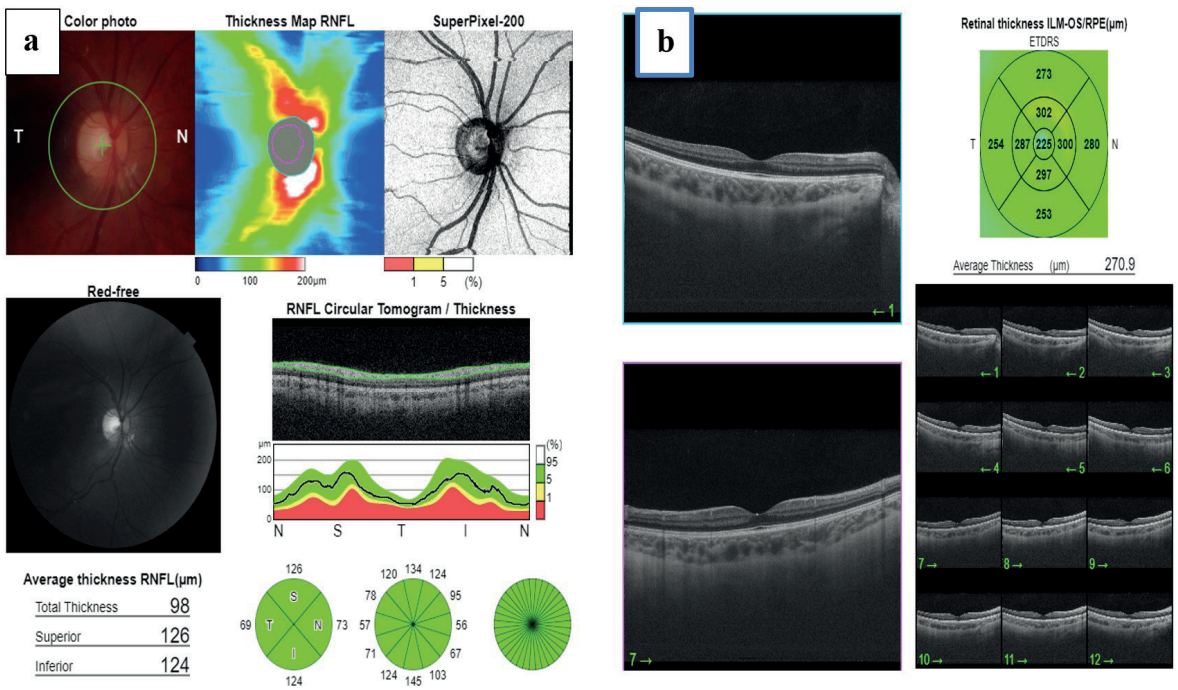

Fig. 1a. Optical coherence tomography images of the optic disc, **1b.** Optical coherence tomography images of the macula.

IMAGEnet program developed by Topcon (Tokyo, Japan). In addition, the FAZ area was measured manually (by the same experienced technician) in all study participants. The device automatically measured SCP and DCP, and the vessel density was determined as the percentage of the area occupied by the vessels. The device focused on two concentric circles with radii of 1 and 3 mm in the center of the fovea, dividing the area between them into four sections: superior, inferior, temporal, and nasal. The device also calculated the capillary densities in the superficial and deep plexus in 5 regions (Fig. 2).

Statistical analysis

The continuous variables were presented as mean+/-standard deviation or median (interquartile range) based on their distribution characteristics. The normality and homogeneity assumptions were assessed using the Shapiro-Wilk and Levene tests, respectively. The one-way ANOVA test was used to compare normally distributed and homogeneous data and the Kruskal-Wallis test was used to compare non-normally distributed continuous data. The Student's t-test was used to evaluate two groups with normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables, and the chi-square test for categorical variables. The Jamovi 2.2.5 statistical package program was used for statistical tests and $p<0.05$ was considered statistically significant.

Results

The study included 31 patients with MWA, 29 patients with TTH, and 38 healthy controls. The mean age was 12.1±3.3 years in MWA patients, 12.4±2.8 years in TTH, and 11.9±3.8 years in the healthy controls (p=0.844). 54.8% (n=17) of the patients in the MWA group, 72.4% (n=21) in the TTH group, and 60.5% (n=23) in the healthy controls were female (p=0.359). There was no statistically significant difference between the groups for age and sex. Also, there were no statistically significant differences between disease duration after differential diagnosis, age of onset, and frequency of attacks. The demographic and clinical characteristics of the groups are shown in Table I.

Biomicroscopic and dilated fundus examinations revealed no pathology in any of

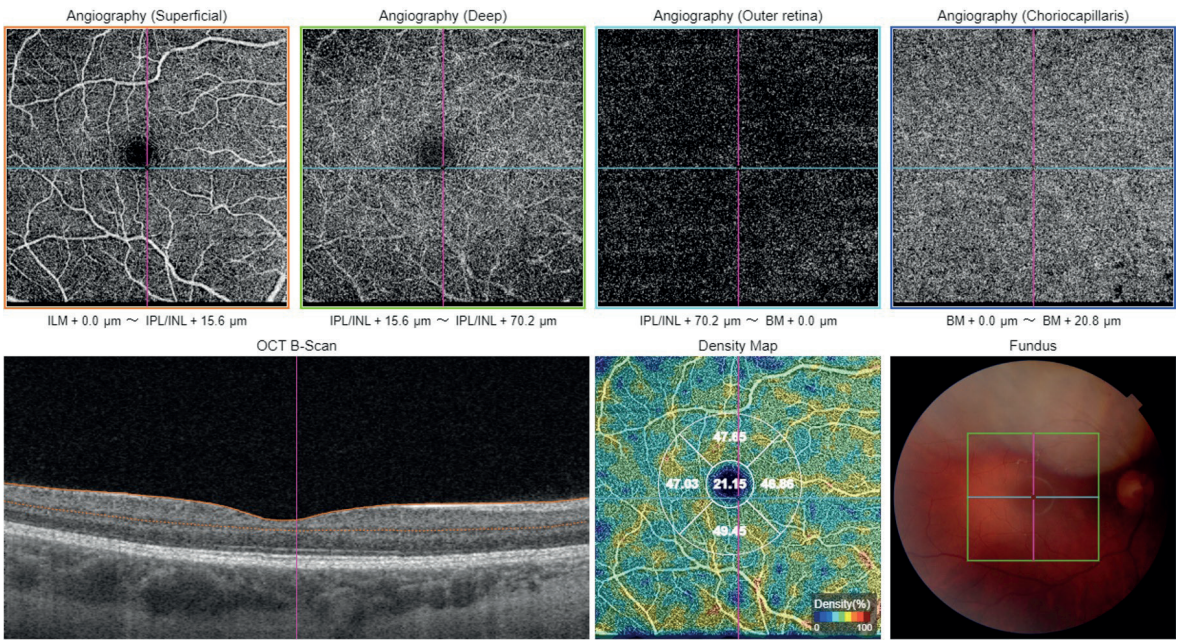

Fig. 2. Optical coherence tomography angiography images of the macula.

Table I. Clinical and demographic features of the groups.

	MWA	TTH	Healthy Controls	p
Age (years)	12.1 ± 3.3	12.4 ± 2.8	11.9 ± 3.8	0.844[K]
Gender (Female/Male)	17/14	21/8	23/15	0.359[C]
Refraction Error, SE, D	-0.82 ± 1.22	-1.41 ± 4.67	-1.26 ± 1.67	0.437[K]
Family history	61.3% (n=19)	37.9% (n=11)	-	0.071[C]
Disease duration (months)	19.2 ± 21.8	18.4 ± 10.5	-	0.336[U]
Attack frequency (per month) (range)	4.0 (1.5-6.0)	4.0 (2.0-6.5)	-	0.596[U]
Age of onset (months)	127.0 ± 40.0	134.0 ± 37.2	-	0.519[T]

C: Chi-square test, D: Diopter, K: Kruskal-Wallis test, MWA: Migraine without aura, SE: Spherical equivalent, TTH: Tension-type headache, T: student's t-test, U: Mann-Whitney u test.

the participants. Among the groups, the mean pRNFL thickness, central macular thickness (CMT), and SCT values were lowest in the MWA group. However, mean pRNFL thickness and the four-quadrant (superior, inferior, temporal, nasal) RNFL thicknesses were not statistically significant between groups (p=0.621, p=0.500, p=0.186, p=0.565, and p=0.744, respectively). The CMT and four-quadrant (superior, inferior, temporal, nasal) macular thicknesses were not statistically significant between MWA patients, TTH patients, and healthy controls (p=0.854, p=0.230, p=0.174, p=0.434, and p=0.333, respectively). SCT was also not statistically significant between groups (p=0.201). All parameters are listed in Table II.

According to macular vessel density parameters, there was no statistically significant difference between the groups in SCP and DCP measurements, except for the nasal quadrant of the DCP, although the vessel densities in both SCP and DCP were lower in MWA patients than in TTH patients and healthy controls (Table III). There was a statistically significant difference in the nasal quadrant of the DCP between the MWA patients, TTH patients, and the healthy controls (46.2±5.9, 48.8±3.2, and 49.5±3.1, respectively, p=0,014). It was observed that this difference was statistically significantly lower in the MWA patients than in the healthy controls. In addition, both the superficial and deep FAZ areas were larger in MWA patients than in both TTH patients and the healthy controls. However, there were no statistically significant differences between the superficial and deep FAZ area parameters between the groups (p=0.652 and p=0.985) (Table III).

Table II. Comparison of peripapillary retinal nerve fiber layer thickness, macular thickness, and subfoveal choroidal thickness values between the groups.

	MWA	TTH	Healthy Controls	p
Average RNFL (μm)	107 ± 8.3	109 ± 9.0	109 ± 7.1	0.621[A]
Superior quadrant RNFL (μm)	132.0 ± 11.7	135.0 +/- 11.5	134.0 ± 13.9	0.500[A]
Inferior quadrant RNFL (μm)	133.0 ± 13.5	141.0 ± 20.4	137.0 ± 12.9	0.186[A]
Temporal quadrant RNFL (μm)	78.4 ± 12.7	76.2 ± 9.0	79.6 ± 9.8	0.565[K]
Nasal quadrant RNFL (μm)	85.4 ± 12.2	83.3 ± 8.8	85.1 ± 12.2	0.744[A]
Central MT (μm)	236 ± 18.7	239 ± 23.8	238 ± 16.5	0.854[A]
Superior quadrant MT (μm)	310 ± 13.5	311 ± 19.0	317 ± 13.1	0.230[K]
Inferior quadrant MT (μm)	305 ± 12.8	304 ± 25.3	313 ± 14.1	0.174[K]
Temporal quadrant MT (μm)	294 ± 15.0	293 ± 38.2	295 ± 28.0	0.434[K]
Nasal quadrant MT (μm)	309 ± 18.6	313 ± 14.8	314 ± 16.7	0.333[K]
SCT (μm)	360 ± 72.3	395 ± 74.2	370 ± 80.2	0.201[A]

A: ANOVA test, K: Kruskal-Wallis test, MWA: Migraine without aura, MT: Macular thickness, RNFL: Retinal nerve fiber layer, SCT: Subfoveal choroidal thickness, TTH: Tension-type headache.

Table III. Comparison of macular vessel density of both superficial and deep plexus and foveal avascular zone area among the groups.

		MWA (n=31)	TTH (n=29)	Healthy Controls (n=38)	p
CVD superficial (%)	Parafoveal	20.3 ± 3.7	22.0 ± 4.1	20.6 ± 4.0	0.200
	Superior	45.2 ± 4.2	45.4 ± 4.3	47.3 ± 2.9	0.051
	Inferior	42.4 ± 4.6	43.1 ± 5.2	44.1 ± 4.2	0.252
	Temporal	45.6 ± 3.5	46.4 ± 3.5	46.6 ± 2.8	0.408
	Nasal	44.2 ± 4.0	45.3 ± 2.8	45.7 ± 2.9	0.169
CVD deep (%)	Parafoveal	18.3 ± 3.6	19.9 ± 3.9	19.4 ± 4.5	0.297
	Superior	48.7 ± 5.4	49.4 ± 4.5	51.1 ± 3.3	0.095
	Inferior	45.0 ± 5.8	46.4 ± 5.1	46.8 ± 4.6	0.346
	Temporal	47.8 ± 4.96	49.4 ± 4.0	50.0 ± 3.2	0.085
	Nasal	46.2 ± 5.9S	48.8 ± 3.2	49.5 ± 3.1S	0.014*
FAZ μm^2	Superficial	303.7 ± 97.1	281.8 ± 101.9	291.2 ± 78.9	0.652
	Deep	333.5 ± 83.7	333.2 ± 116.9	329.6 ± 105.0	0.985

*ANOVA test, CVD: Capillary vessel density, FAZ: foveal avascular zone, MWA: Migraine without aura, TTH: Tension-type headache.

Discussion

This study found a statistically significant difference in the nasal quadrants of the DCP between groups in the pediatric population, with MWA patients showing lower values compared to healthy controls. In addition, both the SCP and DCP parameters were lower in MWA patients than in both TTH patients and the healthy controls, but these changes were not statistically significant. The superficial and deep FAZ areas were larger in MWA patients, but not statistically significantly different between groups.

The symptoms of MWA and TTH frequently overlap in childhood. The diagnosis may also change over the years due to the development of complications and changing symptoms of primary headaches.[18,19] Kienbacher et al.[20] followed 227 patients with headache complaints in the pediatric and adolescent group for 6.6±1.6 years from the date of diagnosis. They showed that the headache complaint was resolved in 30% of the patients. In addition, the diagnosis changed in 20-25% of patients, from migraine to TTH or from TTH to migraine. The very similar epidemiological, clinical, and pharmacological features between migraine and TTH, make the differential diagnosis in children challenging. Some studies have aimed to evaluate the differences between migraine and TTH using quantitative sensory tests, brainstem excitability, laser-evoked potentials, temporal discrimination thresholds, and magnetic resonance imaging.[21-25]

There have been a few studies in the literature investigating the effect of migraine on retinal structures.[15,26,27] Kanar et al.[28] reported a statistically significant thinning in the mean pRNFL, superior and inferior pRNFL in adult patients with migraine compared to controls, only nasal quadrant of pRNFL was significantly thinner in patients with MWA than other groups. They proposed that these changes are associated with dysregulation of ocular blood flow, resulting from impaired autoregulation in individuals with migraine. Cankaya and Tecellioglu[29] reported that the retinal thickness of the fovea was thinner in adult patients in the migraine group compared with healthy controls, and they suggested that this was due to decreased blood flow in adult patients with migraine. Iyigundogdu et al.[15] showed no statistically significant difference in pRNFL and ganglion cell layer thickness in adult migraine patients compared to control

subjects. They attributed the difference between their results and other studies to differences in measurement techniques and participant characteristics. Nalcacioglu et al.[30] found no statistically significant difference between the migraine patient group and healthy controls in the pediatric group for pRNFL and macular thickness in the attack-free period. They related this situation to age-related changes in adult migraine patients, and the insufficiency of retinal and choroidal circulation due to the chronic nature of the disease in contrast to children. Rego-Lorca et al.[31] reported statistically significant reductions in RNFL thickness in the temporal and inferior-temporal in children with migraine with aura compared to patients with MWA. In addition, they detected negative correlations between the number of episodes per month and RNFL thickness.[31] On the other hand, there are few studies in the literature comparing adults with migraine and TTH. In one of them, Yener and Korucu[13] evaluated the visual field defects in adult patients with migraine and TTH and showed that adult patients with TTH have similar visual field defects as patients with migraine. The retinal changes such as pRNFL, macular thickness, and SCT were compared between adult patients with TTH and migraine in the study by Yener and Korucu, and they found no statistically significant difference.[32] In our study, no difference in mean pRNFL, four-quadrant RNFL, CMT, and four-quadrant macular thickness was observed between the groups during the attack-free period. We attributed this to the fact that the disease did not become chronic in children, considering the duration and number of attacks.

The choroidal thickness in patients with migraine has been evaluated in a few studies.[33,34] In the meta-analysis by Gouravani and colleagues, SCT was found to be reduced in individuals with migraine, particularly in those with aura compared to those without. This finding has been linked to the pathophysiology of migraine-related neovascularization.[33] Unlu et al.[34] demonstrated that SCT was thinner in adult patients with ≥5 migraine attacks per month than in healthy controls during the attack-free period and that the SCT was similar between migraine patients with ≤2 migraine attacks per month and the control group. They suggested that increasing disease frequency may contribute to decreased choroidal thickness through choroidal attenuation and vascular dysregulation. Nalcacioglu et al.[30] reported no statistically significant difference between the migraine patient group and healthy controls in the pediatric group for SCT in the attack-free period. Similarly, in this study, we observed that there was no statistically significant difference between the groups during the attack-free period. We attributed this to the fact that our study group was children and it was not yet a chronic process in terms of both MWA and TTH. Also, all measurements were taken during the attack-free period.

Additionally, some studies have demonstrated that migraine affects the vascular structures of the retina and optic nerve head. Kara et al.[35] reported an arterial resistance in the central retinal and posterior ciliary arteries using color-Doppler sonography in migraine patients compared with healthy controls. One study also implicated migraine as a risk factor for retinal vascular occlusion, ischemic optic neuropathy, and normotensive glaucoma.[36] Hamamci et al.[37] reported that in the macular OCTA measurements, SCP and DCP were significantly decreased, and FAZ area increased in the migraine with aura group compared to the control group in adult patients. There was also no statistically significant difference between the MWA group and the healthy control group in these measurements. Karahan et al.[26] also reported decreased macular DCP and increased deep FAZ area in patients with migraine with aura, which they attributed to the relationship between migraine pathophysiology and ischemia. Dereli et al.[38] reported no statistically significant changes in the macular and peripapillary microvascular densities measured by OCTA between the migraine patient and

healthy subjects during the nonattack period. They also showed that there was a negative correlation between the pediatric migraine disability assessment rating and optic disc OCTA parameters, and stated that there may be changes in the retina and optic disc vascular structures depending on the frequency, severity, and duration of attacks. Kurtul et al.[39] observed significantly lower values of all quadrants of SCP in pediatric MWA patients during the attack-free period compared with healthy controls, and no differences in FAZ area between MWA patients and healthy controls. They hypothesized that the low vascular density of the SCP is associated with hypoperfusion and ischemia. Our study observed a statistically significant reduction in the nasal quadrants of the DCP among groups in the pediatric population, with MWA patients showing particularly lower values compared to healthy controls. Furthermore, the MWA patients had lower mean SCP and DCP parameters than the TTH patients and the healthy controls, although these differences were not statistically significant. The superficial and deep FAZ areas were larger in MWA patients, but there was no statistically significant difference between the groups. We attributed this to the fact that the pathophysiology of MWA is different from that of TTH. In addition, vascular changes in MWA may originate from the nasal region.

The limitations of our study include its retrospective design, the lack of long-term outcome data for the patients, and the fact that the results cannot be generalized to all migraine patients, as the patients were selected from the MWA group during the attack-free period. Additionally, the inclusion of patients without visual symptoms and the inability to clearly specify the type of headache in the family history represent other limitations of the study. Although TTH can be classified into subtypes based on the ICHD-III edition of the IHS for adult patients, the challenges in applying these criteria to the pediatric population hindered the classification of TTH patients into subtypes, which constitutes a limitation of our study.

In summary, there was a statistically significant difference between the groups in terms of the DCP nasal quadrant, especially in patients with MWA, which was found to be lower than in healthy children. To the best of our knowledge, this is the first study to evaluate these parameters in pediatric patients with MWA, TTH, and healthy controls. We conclude that long-term follow-up studies in large patient populations using OCTA, a non-invasive, reproducible, and reliable imaging technique, may be extremely useful in understanding the pathogenesis of MWA and TTH. Additionally, OCTA could offer a unique advantage in providing objective, personalized measurements, which may be especially beneficial for pediatric patients who struggle to fully articulate their symptoms. This imaging technique could thereby enhance diagnostic accuracy and facilitate earlier identification, moving beyond reliance on subjective symptomatology. Furthermore, the findings of this study may contribute to a novel understanding of the differences between these two headache spectra, providing potential implications for future research and clinical practice.

Ethical approval

The study was approved by the Ethical Committee of İstanbul Kartal Dr. Lütfi Kırdar City Hospital (Protocol number: 2022/514/224/11).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: UK, MTK; data collection: UK, MTK, İK, İK; analysis and interpretation of results: İK; draft manuscript preparation: UK, MTK, İK. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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