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Original Article / Özgün Araştırma

Retinal Thickness Alterations in Patients with Migraine

Migren Hastalarındaki Retina Kalınlık Değişiklikleri

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Abstract

Objective: To investigate the alterations in macula, ganglion cell complex (GCC), ganglion cell layer (GCL), macular and peripapillary retinal nerve fiber layer (pRNFL) thickness values in patients with migraine and to elicit the correlation between thickness and clinical characteristics of migraine disease.

Materials and Methods: One hundred sixty-two eyes of 81 patients with migraine (76 eyes of 38 patients with aura and 86 eyes of 43 patients without aura) and 90 eyes of 45 healthy volunteers as the control group were recruited in the study. Macula, GCL, GCC, and RNFL thickness values were measured using optical coherence tomography (OCT).

Results: The mean ages of the aura (+) group, aura (-) group, and the control group were 32.5±7.7, 35.2±7.9, and 33.7±7.7 years, respectively (p=0.751). The mean follow-up time of patients with migraine were 6.3±3.1 years. The central macular thickness, inner inferior macular thickness, central quadrant of macular RNFL thickness, mean of outer segment GCL thickness, inner inferior and temporal, mean of outer nasal quadrant GCL thickness measurements were found to be thinner in both aura (+) and aura (-) patients with migraine when compared with healthy subjects (p<0.01, p=0.01, p<0.01, p<0.01, p=0.04, p=0.04, p<0.01 and p=0.01, respectively).

Conclusion: Although a specific OCT marker for migraine cannot be detected, alterations of pRNFL, GCC, GCL, macular RFNL and macular thickness obtained with OCT may contribute to the understanding of migraine pathophysiology and aid in the assessment of treatment effectiveness.

Keywords: Macular thickness, retinal nerve fiber layer, optical coherence tomography, migraine

Öz

Amaç: Migren hastalarında makula, gangliyon hücre kompleksi (GHK), gangliyon hücre tabakası (GHT), makular ve peripapiller retina sinir lifi tabakası (pRSLT) kalınlığı değişikliklerini incelemek ve kalınlıklar ile migren hastalığının klinik özellikleri arasındaki ilişkiyi ortaya çıkarmaktır.

Gereç ve Yöntem: Çalışmaya 81 migren hastasının 162 gözü (38 auralı hastanın 76 gözü) ve 43 aurasız hastanın 86 gözü ve kontrol grubu olarak 45 sağlıklı gönüllünün 90 gözü dahil edildi. Makula, GHT, GHK ve RSLT kalınlık değerleri optik koherens tomografi (OKT) ile ölçüldü.

Bulgular: Yaş ortalaması aura (+) grup, aura (-) grup ve kontrol grubu için sırasıyla 32,5±7,7, 35,2±7,9 ve 33,7±7,7 yıldı (p=0,751). Hastalar ortalama 6,3±3,1 yıldır migren tanısı ile takip edilmekte idi. Sağlıklı bireylerle karşılaştırıldığında hem aura (+) hem aura (-) migren hastalarında santral makula kalınlığı, iç inferior makula kalınlığı, santral makular RSLT kalınlığı, ortalama dış halka GHT kalınlığı ile iç inferior, iç temporal ve dış nazal GHT kalınlıkları; inferiotemporal pRSLT kalınlığı (p<0,01, p=0,01, p<0,01, p<0,01, p=0,04, p=0,04, p<0,01 ve p=0,01) daha ince bulundu.

Sonuç: Migren için kesin bir OKT belirteci tespit edilemese de OKT ile elde edilen peripapiller RSLT, GHT, GHK, makular RSLT ve makula kalınlık değişiklikleri migren patofizyolojisinin anlaşılmasına katkı sağlayabilir ve tedavi etkinliğini değerlendirmeye yardımcı olabilir.

Anahtar Kelimeler: Makula kalınlığı, retina sinir lifi tabakası, optik koherens tomografi, migren

Introduction

Migraine is a common neurovascular disorder characterized by recurrent severe headache attacks, and it is a disease that negatively affects the quality of life of patients due to neurologic, autonomic, and gastrointestinal findings that may accompany headache attacks (1). Migraine is classified as migraine without aura and with aura according to the latest "International Classification of Headache Disorders, 3rd Edition" (2,3).

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The pathophysiology of migraine has not yet been fully elucidated. Although many vascular, neurovascular, hypoxic, cellular, hormonal and genetic hypotheses are discussed, the neurovascular hypothesis is frequently emphasized (4,5,6,7). Especially in migraine with aura, the decrease in blood flow due to temporary vasospasm in the occipital region is an important hypothesis explaining the visual aura and headache (8). In addition, it has been reported that recurrent vasospasm occurring in cerebral and retrobulbar vascular structures may cause permanent damage to cerebral and retinal tissues in patients with migraine (9). Many studies have been conducted to demonstrate the effects of vascular abnormalities due to recurrent vasospasm and ischemia on the macula, choroid, and optic nerve head in patients with migraine (10,11,12).

Optical coherence tomography (OCT) is a non-invasive retinal imaging method that provides reliable, fast, reproducible and objective examinations. High-resolution retinal images are obtained with spectral-domain (SD)-OCT, which has been widely used in the clinic in recent years (13). With OCT, the thickness of the retina, optic nerve head, peripapillary retinal nerve fiber layer (RNFL) and ganglion cell complex (GCC) can be quantitatively and qualitatively evaluated, and it is used in the diagnosis and follow-up of many neuro-ophthalmologic diseases.

There are many studies in which peripapillary RNFL, GCC, macular and choroidal thickness are evaluated with OCT in patients with migraine and compared with healthy controls (14,15). We think that vascular changes due to vasospasm indicated in the pathogenesis of migraine may cause differences in retinal layers according to the clinical features of migraine disease. With this study, we aimed to examine macular thickness, GCC, macular and peripapillary RNFL thickness changes in the ganglion cell layer (GCL) and to evaluate the relationship between thickness measurements and clinical features of migraine.

Material and Method

Approval was obtained from the Clinical Research Ethics Committee of Ankara Yildirim Beyazit University Faculty of Medicine (no: 26379996/16.04.2018/90). Our study was a prospective study in which 81 patients with migraine aged 18-50 years without additional systemic disease who met the diagnosis criteria of migraine published in 2018 by the "International Headache Society" and 45 healthy volunteers matched for age and gender were included. The study was conducted in accordance with the Helsinki Declaration criteria by obtaining written informed consent forms from all patients.

Headache characteristics, time of diagnosis, frequency and duration of attacks were recorded for patients with migraine in the neurology clinic. After determining the type of migraine and examining the presence of accompanying aura in detail, the patients were evaluated in the retina unit of our ophthalmology clinic.

The OCT images of the patients were obtained using Heidelberg Spectralis SD-OCT (Spectralis Engineering Heidelberg, Germany). All shots were made by a single operator with experience in this field. Images with a signal strength >25 db and full central focus were included in the study.

Those with retinal pathology such as diabetic retinopathy, choroidal neovascularization, central serous chorioretinopathy, patients with glaucoma and uveitis, patients with previous intraocular surgery, and those with corneal and lens opacity that might affect imaging were excluded from the study. In addition, patients with refractive errors of ±6D and a history of systemic drug use were not included in the study.

Peripapillary RNFL (pRNFL) thickness was determined using the "disc circle scan" protocol with a 3.45-mm diameter ring centering the optic disc with an automatic computer algorithm without the need for a user or reference plane. The pRNFL was measured in 7 quadrants as temporal (T) and nasal (N) main segments, superior quadrant (TS, NS) and inferior (TI, NI) quadrant, as well as the central area (1 mm - central subfield pRNFL) (Figure 1).

GCC consists of three separate layers including RNFL, GCL, and inner plexiform layer. These three layers were segmented automatically with SD-OCT and measurement results were obtained (Figure 2). The GCC central circle (1 mm), inner (1-3 mm) ring and outer (3-6 mm) ring were evaluated with the "Early Treatment Diabetic Retinopathy Study (ETDRS)" guide (Figure 3). The inner and outer rings were evaluated in four quadrants as superior, nasal, temporal and inferior.

Macular thickness was measured according to the macula-map X-Y scanning protocol as the average thickness between the inner limiting membrane and retinal pigment epithelium. The macular thickness was divided into 9 quadrants [central (1 mm) circle and superior, nasal, temporal and inferior quadrants of inner (1-3 mm) and outer (3-6 mm) rings] according to the ETDRS guideline, and thickness values were recorded (Figure 2).

There were three groups: Patients with migraine with aura, patients with migraine without aura, and a control group

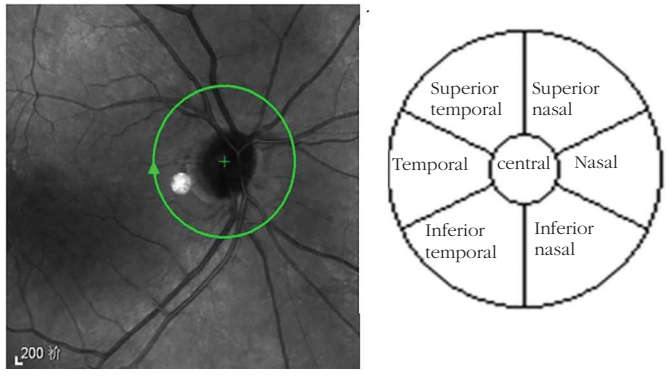

Figure 1. Optic disc circle protocol and peripapillary RNFL quadrants

RNFL: Retinal nerve fiber layer

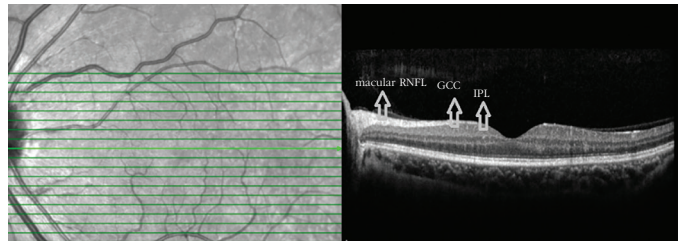

Figure 2. OCT section of GCC layers

GCL: Ganglion cell layer, IPL: Inner plexiform layer, OCT: Optical coherence tomography, RNFL: Retinal nerve fiber layer

consisting of healthy volunteers. OCT thickness measurements were made for all groups.

Statistical Analysis

While evaluating the findings obtained in the study, the statistical analysis of the data was performed using the SPSS 22.0 software (SPSS Inc. Chicago, USA). Continuous variables are expressed as mean ± standard deviation and categorical variables as frequency (%). The normality of the distribution of data was evaluated using the Kolmogorov-Smirnov test. Differences of parametric variables between groups were analyzed using the independent t-test. Groups of more than two were compared using single-sample ANOVA. The results were evaluated as a statistical significance level of $p<0.05$ and a further significance level of $p<0.01$ at a confidence interval of 95%.

Results

One hundred sixty-two eyes of 81 patients with migraine and 90 eyes of 45 age-sex matched controls were included in the study.

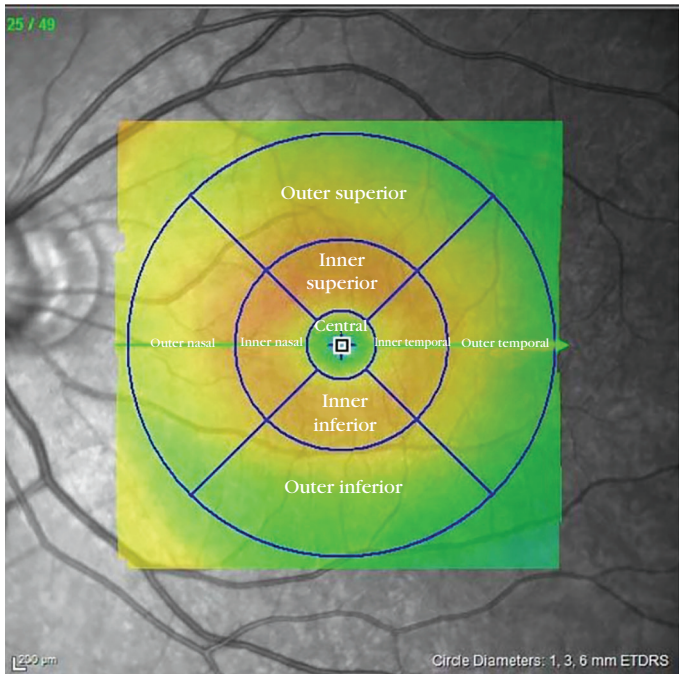

Figure 3. "Early Treatment Diabetic Retinopathy Study (ETDRS)" guide including central circle (1 mm), inner (1-3 mm) and outer (3-6 mm) rings

Eighty-one patients with migraine were divided into two groups as those with aura [aura (+), n=43] and those without [aura (-), n=38]. The mean age was 32.5±7.7 years in the aura (+) group, 35.26±7.9 years in the aura (-) group, 33.71±7.78 years in the control group. The mean age of the patients with migraine was 33.96±7.89 years, 79.0% (n=64) of them were female, and the mean duration of migraine disease was 6.34±3.1 years. The mean attack frequency of the patients was 4.8/month, and the mean attack duration was 10.64 hours (minimum-maximum: 1-72). It was found that 46.9% (n=38) of the patients experienced an aura before the attack. In the aura (+) and aura (-) groups, the mean duration of migraine were 5.86±3.1 and 6.77±3.13 years, respectively, and the mean attack frequencies per month were 5.37±3.67 and 4.44±3.06, respectively. Mean duration of migraine and frequency of attacks per month did not differ between the migraine groups ($p=0.800$ and $p=0.285$). There was no significant difference in terms of age and sex between the control and the patient groups ($p=0.751$ and $p=0.764$) (Table 1).

Central macular thickness and inner inferior macular thickness were thinner in both migraine groups compared with the control group [aura (-) $p<0.001$ and $p=0.046$, respectively; aura (+) $p<0.001$ and $p=0.003$, respectively]. In addition, inner nasal and internal temporal macular thickness values were lower in the aura (+) group than those of the control group ($p=0.03$ and $p=0.016$). There was no difference between groups in terms of macular thickness in other quadrants (Table 2).

Central macular RNFL thickness was thinner in the aura (+) and aura (-) groups compared with the control group ($p=0.006$ and $p<0.001$, respectively). In the aura (+) group, the mean outer ring, inner superior, outer superior and outer nasal macular RNFL thickness measurements were found to be lower than those of the control group ($p=0.017$, $p=0.005$, $p=0.020$, and $p=0.008$), and the macular RNFL thickness in the inner and outer superior quadrants was significantly thinner in the aura (+) group than in the aura (-) group ($p=0.025$ and $p=0.017$, respectively). There was no difference between the groups in terms of the other quadrants.

In the aura (-) and aura (+) groups, the mean outer ring, inner inferior, outer superior and outer nasal macular GCL thicknesses were thinner than those of the control group [aura (-) $p=0.001$, $p=0.022$, $p<0.001$ and $p<0.001$, respectively; aura (+) $p=0.036$, $p=0.037$, $p=0.039$, and $p<0.001$, respectively]. Also, central and internal nasal macular GCL thicknesses were thinner in the aura (-) group compared with the control group ($p=0.01$ and $p=0.041$, respectively). There was no difference in terms of macular GCL thickness in the other quadrants between the groups (Table 3).

Central, internal nasal, and inferior macular GCC thicknesses were found to be significantly thinner in the aura (-) group than in

Table 1. Group characteristics

	Migraine aura (-)	Migraine aura (+)	Control	p value
Age (years)	35.26±7.9	32.50±7.7	33.71±7.78	0.751
Sex (F/M)	35/8	29/9	33/12	0.207
Migraine duration (years)	6.77±3.13	5.86±3.1	-	0.800
Attack frequency/months	4.44±3.06	5.37±3.67	-	0.285
Attack duration (hours)	8.35±7.35	13.24±11.5	-	0.106

F: Female, M: Male

the control group (p=0.002, p=0.022 and p=0.029, respectively). In the aura (+) group, inner superior macular GCC thickness was thinner than in the control group (p=0.021). In addition, outer superior macular GCC thickness differed between the migraine groups; it was statistically significantly thinner in the aura (+) group (p=0.043). Macular GCC thickness profiles in the other quadrants did not differ between the groups (Table 4).

In the aura (+) group, superonasal, nasal, inferotemporal and temporal pRNFL thickness measurements were lower compared with the control group (p=0.009, p=0.006, p=0.012, and p=0.042, respectively). The superotemporal and inferotemporal pRNFL thicknesses were significantly thinner in the aura (-) group than in the control group (p=0.024 and p=0.006, respectively). In addition, peripapillary superonasal RNFL thickness was significantly thinner in the aura (+) group than the aura (-) group (p=0.046). There was no difference between the groups in terms of the other quadrants.

In the aura (+) group, there was a negative correlation between migraine duration and macular RNFL mean inner ring thickness (p=0.003). There was a negative correlation between the attack frequency and central retinal thickness in the aura (+) group (p=0.015). There was a negative correlation between outer temporal quadrant retinal thickness and duration of migraine in the aura (-) group (p=0.029).

Discussion

It is thought that retinal layers may be affected by possible ischemia occurring in migraine. In migraine attacks, the aura usually begins with a focal decrease in cerebral blood flow in the posterior regions of the brain. In some patients, this hypoperfusion

Table 2. Comparison of the mean macular thickness of the groups

	Macular thickness, µm, mean ± SD				Binary comparison, p value		
	Migraine aura (-) (n=43)	Migraine aura (+) (n=38)	Control (n=45)	p value	Aura (-) vs. control	Aura (+) vs. control	Aura (-) vs. aura (+)
Central	262.18±19.85	261.52±23.4	275.67±19.83	<0.001**	<0.001**	<0.001**	0.846
Inner superior	286.8±13.65	286.48±13.18	287.75±15.85	0.638	0.670	0.580	0.882
Inner nasal	340±15.64	330.9±52.4	344.64±15.73	0.042*	0.51	0.030*	0.148
Inner inferior	335.31±16.08	332.77±15.4	340.17±16.03	0.012*	0.046*	0.003*	0.308
Inner temporal	325.62±14.52	323.68±13.06	328.84±13.99	0.044	0.136	0.016*	0.374
Outer superior	308.86±22.37	305.17±15.58	305.76±15.09	0.712	0.282	0.803	0.231
Outer nasal	318.86±15.73	315.84±17.6	316.26±15.85	0.759	0.278	0.870	0.251
Outer inferior	310.62±31.08	301.26±34.96	307.58±16.07	0.471	0.420	0.127	0.073
Outer temporal	286.8±13.65	286.48±13.18	287.75±15.85	0.638	0.670	0.580	0.882

*p<0.05, **p<0.01, SD: Standard deviation

Table 3. Comparison of the mean macular GCL thickness of the groups

	Macular thickness, µm, mean ± SD				Binary comparison, p value		
	Migraine aura (-) (n=43)	Migraine aura (+) (n=38)	Control (n=45)	p value	Aura (-) vs. control	Aura (+) vs. control	Aura (-) vs. aura (+)
Central	15.75±5.92	17.02±13.2	18.04±5.74	0.022*	0.010*	0.509	0.422
Inner ring (1-3 mm/mean)	50.58±4.87	50.54±5.15	51.82±3.53	0.108	0.053	0.060	0.961
Outer ring (3-6 mm/mean)	39.76±3.02	39.38±4.01	40.19±3.22	0.007**	0.001**	0.036*	0.488
Inner superior	39.25±4.13	52.93±7.15	54.07±3.73	0.388	0.060	0.212	0.400
Inner nasal	51.22±5.83	51.53±6.42	52.91±5.04	0.020*	0.041*	0.125	0.741
Inner inferior	50.31±6.43	50.55±5.77	52.24±4.55	0.049*	0.022*	0.037*	0.805
Inner temporal	47.03±5.88	47.14±5.41	48.07±4.58	0.363	0.190	0.231	0.902
Outer superior	38.67±3.18	38.81±4.95	39.95±4.95	0.046*	<0.001**	0.039*	0.497
Outer nasal	40.08±3.69	40.14±4.31	38.01±3.35	<0.001**	<0.001**	0.000**	0.920
Outer inferior	41.05±4.28	40.34±4.77	39.94±3.97	0.229	0.075	0.559	0.316
Outer temporal	39.25±4.13	38.81±4.95	37.95±4.95	0.176	0.060	0.267	0.539

*p<0.05, **p<0.01, GCL: Ganglion cell layer, SD: Standard deviation

Table 4. Comparison of the mean macular GCC thickness of the groups

	Macular thickness, µm, mean ± SD				Binary comparison, p value		
	Migraine aura (-) (n=43)	Migraine aura (+) (n=38)	Control (n=45)	p value	Aura (-) vs. control	Aura (+) vs. control	Aura (-) vs. aura (+)
Central	57.26±7.42	58.75±14.88	60.77±7.26	<0.001**	0.002**	0.255	0.416
Inner ring (1-3 mm/mean)	80.58±4.87	80.54±5.15	81.82±3.53	0.108	0.053	0.060	0.961
Outer ring (3-6 mm/mean)	105.55±5.9	104.25±6.62	104.7±6.92	0.432	0.382	0.676	0.190
Inner superior	87.25±4.72	87.36±6.64	91.02±6.34	0.041*	0.537	0.021*	0.084
Inner nasal	102.01±7.54	102.35±8.45	104.52±6.84	0.042*	0.022*	0.070	0.785
Inner inferior	103.17±8.63	104.42±8.52	105.88±7.68	0.045*	0.029*	0.245	0.358
Inner temporal	94.05±5.9	94.13±6.05	95±5.14	0.479	0.260	0.319	0.938
Outer superior	106.79±7.77	104.13±8.81	106.3±5.9	0.012*	0.236	0.603	0.043*
Outer nasal	119.41±8.35	117.71±8.9	119.28±10.26	0.432	0.927	0.296	0.210
Outer inferior	108.75±6.87	107.82±7.25	108.43±7.58	0.714	0.768	0.603	0.405
Outer temporal	87.25±4.72	87.36±6.64	86.3±5.9	0.412	0.236	0.274	0.900

*p<0.05, **p<0.01, GCC: Ganglion cell complex, SD: Standard deviation

can be seen outside of the brain or additionally in the retina (16). It is thought that optic nerve and ganglion cells are affected due to hypoperfusion seen in migraine characterized by recurrent vasospasm and focal ischemia during attacks.

Ao et al. (17) found that inner inferior macular thickness was thinner in migraine with and without aura compared with a control group. Similarly, in our study, the inner inferior macular thickness and also the central macular thickness were significantly thinner in both migraine groups compared with the control group. Ischemic damage and eventually ganglion cell death that may be caused by impaired choroidal blood flow in migraine may explain the change in macular thickness measurements because the macula is the area where ganglion cells are most concentrated.

Ao et al. (17) showed that the thickness of the nasal pRNFL in patients with aura (+) migraine was thinner than in control and aura (-) groups, but no difference was observed in the other quadrants. Similarly, we found the superonasal pRNFL thickness was thinner in the aura (+) group compared with the control and migraine (-) aura groups. Nasal pRNFL was interpreted as thinner and more sensitive to neurodegenerative changes than other quadrants. However, in our study, the temporal quadrants were also affected; inferotemporal and temporal pRNFL thicknesses in the aura (+) group, and superotemporal and inferotemporal pRNFL thicknesses in the aura (-) group were thinner than those of the control group (17). Aksoy et al. (18) similarly showed that temporal pRNFL was thinner in patients with migraine compared with controls (18). Hypoperfusion developing at the optic nerve head secondary to vasospasm in the retrobulbar circulation including ophthalmic, posterior ciliary, and central retinal arteries during a migraine attack can explain the differences in pRNFL.

Although some authors found no relationship between migraine duration and pRNFL thickness, Feng et al. (19) showed that pRNFL was significantly thinner in patients who had migraines for longer than 15 years. In our study, an inversely proportional relationship was found between the mean RNFL thickness in the central area of 3 mm and the duration of migraine in patients with migraine with aura. Reggio et al. (20) found that there was a negative correlation between RNFL thickness and the frequency of migraine attacks. According to our data, central macular thickness was thinner in patients with aura (+) migraine who had frequent attacks. These findings support that the presence of aura and the frequency of attacks constitute an increased risk for hypoperfusion.

Gipponi et al. (21) showed that macular RNFL thickness in patients with migraine was thinner in the superior quadrant and Sorkhabi et al. (22) found it thinner in the nasal quadrant. Similarly, in our study, macular RNFL thickness was found thinner in the aura (+) group in the inner superior, outer superior and outer nasal quadrants than in the control group. Ekinci et al. (23), similar to our study, showed that the macular RNFL thickness in the inner and outer superior quadrants was thinner in the aura (+) group than the aura (-) group (p=0.025 and p=0.017, respectively). Ekinci et al. (23) found that the thickness of the GCC in the superior and inferior quadrants in patients with migraine was thinner compared with the control group. In our study, external nasal macular GCC thicknesses were thinner than the control group. Again, similar to the study by Ekinci et al. (23), outer superior macular GCC thickness differed between the migraine groups; it was statistically significantly thinner in the aura (+) group than in the aura (-) group (p=0.043). Altered choroidal blood flow can cause ischemic damage to retinal tissues, which can lead to photoreceptor dysfunction and ganglion cell death (23). Martinez et al. (24) showed that individuals with migraine with aura had lower mean and temporal RNFL thicknesses compared with patients with aura (-) migraine. Tan et al. (25) found no significant difference in terms of RNFL thickness between patients with migraine and a control group. The difference in the results may be due to the

selection of the patients examined in the studies, the number of samples, the male-female sex ratio, and the methods used.

Our findings can be interpreted as the ischemia risk may be higher in the aura (+) group.

Conclusion

The difference in OCT thickness measurements in many studies on migraine can be explained by the fact that migraine is a heterogeneous disease and the difficulty of classifying patients into subgroups. Although no definite OCT marker for migraine can be determined from our results, pRNFL, GCL, GCC, macular RNFL, and macular thickness measurements in OCT can contribute to understanding the pathophysiology of migraine and help evaluate the effectiveness of treatment. In addition, as the duration of migraine and the frequency of attacks increase, damage to neurons increases. Therefore, effective control of attacks should be ensured, especially in patients with migraine with aura.

Ethics

Ethics Committee Approval: Clinical Research Ethics Committee of Ankara Yildirim Beyazit University Faculty of Medicine (no: 26379996/16.04.2018/90).

Informed Consent: The study was conducted in accordance with the Helsinki Declaration criteria by obtaining written informed consent forms from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ş.Y., İ.E.E.T., Design: Ş.Y., Data Collection or Processing: D.E., Ş.Y., Analysis or Interpretation: Ş.Y., İ.E.E.T., Literature Search: Ş.Y., İ.E.E.T., Writing: Ş.Y.

Conflict of Interest: The authors have not declared any conflict of interest related to this article.

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