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Is Ciliary Muscle Affected in Migraine Patients with Aura and without Aura?

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to compare spherical equivalents (SE) and spherical equivalents with cycloplegic (CSE) values of migraine patients with and without visual aura, with those patients without migraine complaints.

Material/Methods: We included patients over the age of 18 years, who had 20/20 uncorrected vision, and who did not have ocular pathology in their examination. The patients were divided into 3 groups: Group 1: 86 eyes of 43 migraine patients without aura, Group 2: 38 eyes of 19 migraine patients with aura, and Group 3: 60 eyes of 30 patients without migraine. Spherical equivalents and spherical equivalents with cycloplegic from the auto-refractometrical values of the patients were compared.

Results: The mean age of the migraine and control patients was 34.2±8.3 and 33.6±10.8 years, respectively. Forty-three (69%) of 62 migraine patients had migraine without aura and 19 (31%) had migraine with aura. The right and left eyes of the patients were evaluated together and a significant correlation was found between the groups. To evaluate the impact of cycloplegia in patients, SE and CSE values were obtained and differences between these values were evaluated. It was found that the change in Group 2 patients was significantly lower than the change in Group 3 patients (p=0.024).

Conclusions: We found that the cycloplegic spherical equivalents values of our patients with aura were lower than control patients. We need further studies to reveal whether migraine with aura is the trigger or the result of those attacks.

MeSH Keywords: Accommodation, Ocular • Migraine with Aura • Migraine without Aura • Refractive Errors

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Background

Migraine is a chronic disease of the brain that enhances morbidity with complains like photophobia, headache attacks, phonophobia, and nausea [1,2]. In the second edition of the headache classification by the International Headache Society, migraine is among the primary headaches and migraine without aura, migraine with aura, migraine cursors in childhood, retinal migraine, and migraine complications are grouped as potential migraines [1]. According to the results of the Turkish Headache Database, the number of female patients is 4 times that of male patients. There were 84% of the adults who were migraine without aura patients, and 14% who were migraine with aura patients. Although most of these patients have been found to have comorbidity with other diseases, eye diseases were excluded from those studies; however, photophobia is reported to be the most frequent accompanying symptoms [3]. The vision system is reported to play a role, especially in migraine with aura headaches [4]. One of 5 patients with a headache is directed to the department of eye diseases [5], mostly because almost all migraine with aura patients have visual auras [6]. The relationship between migraine and refractive errors has been studied for more than 100 years; however, conflicting results have emerged from those studies [7–9]. In this study, we compared the auto-refractometric values of migraine patients with and without visual aura, with those patients without migraine complaints.

Material and Methods

Patient groups

We prospectively compared the patients who consulted the Neurology policlinic between June 2013 and March 2014 with a headache complaint and diagnosed with migraine in accordance with the ICHD-2 criterion with the individuals of the same gender and age group with no headache complaint. This study adhered to the tenets of the Declaration of Helsinki and was carried out with the approval of the institution. The patients were given full detailed eye examinations and findings were noted. Out of these patients, those over age 18 years who had 20/20 uncorrected vision and who did not have ocular pathology in their examination were included in the study.

The patients were divided into 3 groups: Group 1: 86 eyes of 43 migraine patients without aura; Group 2: 38 eyes of 19 migraine patients with aura; and Group 3: 60 eyes of 30 patients without headache.

Patient examinations

The same ophthalmologist examined the patients in the period with no headache. The corrected and uncorrected vision of right eye and left and bilateral eye of all the patients were individually measured. Those patients whose uncorrected vision did not have 20/20 value for both eyes separately and bilaterally were excluded from the study. The 3-dimensional vision and eye movements of the patients were evaluated by the Worth 4-point test and those patients who failed this test were excluded from the study. Biomicroscopic and fundus examinations of the patients were carried out and the intraocular pressure values were measured with Goldmann applanation tonometry; those patients with ocular pathology were excluded from the study. Before the eye examination, the patients' auto-refractometry measurements were taken. Following the eye examinations, 45 minutes after the patients were given 1% cyclopentolate HCl drips 3 times with 5 minutes intervals, their auto-refractometry values were recorded again. The intended purpose of using the cyclopentolate with mydriatic and cycloplegic effect was that with the cycloplegic effect, ciliary muscles contraction was hindered and refractivity of the lenses increases through cambering; in other words, accommodation was hindered. Thus, we aimed to provide more accurate refractivity values for the eye structures [10]. In the study, spherical equivalents (SE) and cycloplegic spherical equivalents (CSE) from the auto-refractometrical values of the patients were used. Spherical equivalent is equal to the sum of the sphere value and half the cylindrical value, which were measured by the auto-refractometer device.

Statistical analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences) for Windows 17.0 software. For quantitative data to compare the groups with normal distribution of parameters, t-test and Mann-Whitney U test were used. Tukey test was used for post hoc analysis. Pearson chi-square was performed to compare qualitative data. The statistical significance was set at $p<0.01$ and $p<0.05$.

Results

The average age of the migraine patients included in our study was 34.2±8.3 years. Forty-three (69%) out of the total of 62 patients had migraine without aura and 19 of them (31%) had aura migraine. All the patients had 20/20 vision. The intraocular pressure value was 15.2±3.3 mmHg. Age, gender distribution, and auto-refractometrical values of the migraine and control patients are given in Table 1. The comparison of the 3 groups is given in Table 2. Although the cycloplegic spherical equivalents results of the right eyes were not statistically significant, statistical significance was found in the Tukey test between the migraine patients with aura and the control group ($p=0.05$). The right and left eyes of the patients were evaluated together and a significant correlation was found between

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Table 1. Comparison of migraine and control groups according to SE and CSE values.

	Number	M/F	Age (year)	SE of OD (Diopter)	SE of OS (Diopter)	CSE of OD (Diopter)	CSE of OS (Diopter)	SE of all eyes (Diopter)	CSE of all eyes (Diopter)
Migraine	62	10/52	34.2±8.3	–0.15±0.8	–0.05±0.8	0.5±0.7	0.6±0.8	–0.07±0.8	0.6±0.7
Control	30	4/26	33.6±10.8	0.01±0.6	0.04±0.6	0.8±0.7	0.8±0.7	0.03±0.6	0.8±0.7
P value			0.803	0.322	0.608	0.080	0.114	0.396	**0.030**

M – male; F – female; SE – spherical equivalent; CSE – cycloplegic spherical equivalent; OD – right eye; OS – left eye.

Table 2. Comparison of the 3 groups according to SE and CSE values.

	Age (year)	SE of OD (Diopter)	SE of OS (Diopter)	CSE of OD (Diopter)	CSE of OS (Diopter)	SE of all eyes (Diopter)	CSE of all eyes (Diopter)
Group 1	33.8±7.5	–0.13±0.9	–0.04±0.8	0.63±0.69	0.66±0.68	–0.08±0.86	0.65±0.68
Group 2	35.6±10.7	–0.13±0.4	0.03±0.7	0.26±0.70	0.42±0.86	–0.05±0.60	0.34±0.77
Group 3	33.6±10.9	0.01±0.6	0.04±0.6	0.81±0.69	0.84±0.70	0.03±0.56	0.83±0.69
P value	0.777	0.695	0.902	**0.064**	0.202	0.685	**0.014**

SE – spherical equivalent; CSE – cycloplegic spherical equivalent; OD – right eye; OS – left eye.

Table 3. Comparison of difference between CSE and SE values of the 3 groups.

	Group 1[1]	Group 2[2]	Group 3[3]	P	Post Hoc Tukey
CSE-SE value	0.68±0.86	0.35±0.44	0.78±0.58	**0.029**	p^1–p^2=0.077 p^1–p^3=0.694 **p^2–p^3=0.024**

the groups. It was also found through the Tukey test that the source of significance was patients with aura (p=0.010). When the refractive value differences between both eyes were evaluated, no significant difference was found in SE and CSE measurements (p=0.411 and 0.536). To evaluate the impact of cycloplegia in patients, SE and CSE values were obtained and differences between these values were evaluated. In the post hoc Tukey test, it was found that the change in Group 2 patients was significantly lower than the change in Group 3 patients (p=0.024). The differences between CSE and SE in all eyes in both groups are given in Table 3.

Discussion

Ninety-nine percent of migraine patients with aura had visual symptoms [6]. It was observed that since visual auras such as photopsy, scintillating scotoma, and hemianosmic changes in the foreground, especially in migraine with aura, the potential ocular problems in migraine pathogenesis have to be taken into account and the patients consulting with headaches were referred to ophthalmologists [5]. We give eye examination to the migraine patients referred to our policlinics from the Department of Neurology and evaluated their examination findings. The pathophysiology of migraine is still unclear. There are studies stating that migraine-related findings and refraction defects can trigger migraine. It was reported that migraine may impact the eyelids, conjunctiva, iris, pupil, optical nerve, retina, and extraocular muscles [11]. The relationship between the refractive errors and migraine has been researched since the beginning of the 20th century. Although these studies especially emphasized that anisometropia and astigmatism were the triggers of migraine, the value of their results were limited because they were not controlled studies and no statistical evaluation was made [7–9]. Harle et al. emphasized that blurry vision generated by astigmatism could create a hyperexcitability on the visual cortex and this could be a triggering factor for migraine [12]. When the migraine patients in our study were compared with the same age and gender groups, the spherical equivalents were found to be the same, but the cycloplegic spherical equivalents were significantly lower. When the migraine patients are divided into groups with and without

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aura and evaluated this way, while SE values of the patient group with aura were similar to the control group, their CSE values were significantly lower. However, a similar result was not found for the migraine patients without aura. Compatible with this finding, it was found that the changes in migraine patients with aura between the measurements before and after eye drops (1% cyclopentolate HCl) were significantly lower. Similar to our study, there are studies demonstrating that the refractive errors were not different in migraine patients and it was also suggested in these studies that binocular vision was important [13]. However, even though we found no significant difference in refractive values between the 2 eyes in our study, all the patients involved in the study had 3-dimensional and uncorrected 20/20 vision. The fact that the cycloplegic refraction values, especially in patients with aura, were found to be lower in comparison to healthy individuals could be an indication that these patients did not make sufficient accommodation. Since these patients could have blurry vision and difficulty focusing, it should be noted that this could be the trigger of a headache. On the other hand, no anisocoria was found in any of our patients; however, we failed to measure the pupil diameters since we did not have a pupillometer. It was reported that mydriasis might accompany migraines [14]. It is possible that lack of accommodation in addition to isochoric and mydriatic pupils may create an attack with the increase in the amount of light entering the retina. It was found in the previous studies that visual stimulus triggered a migraine in more than 1/3 of the patients and that the migraines triggered by light decreased in patients who were given colored lenses during the migraine attack [15,16]. Bright light was a triggering factor in 87% of the migraine patients with aura, and this rate was 76% in migraine patients without aura [17].

An alternative view is that our findings might be the result of the disease. There exists a particular condition known as ophthalmoplegic migraine. The general characteristic of this condition is that with the third cranial nerve the most affected, it is accompanied by ocular cranial nerve palsy together with the migraine-like headaches in the form of attacks [18]. In these situations, in which the pathophysiology is not fully understood in 75% of the patients, there was contrast increase and thickening in the MRI-scanned nerves during the attacks, and it was thought that there might be an accompanying migraine or independent neuropathy [19]. In another study, in a SPECT-scanned nerve area, a low level of blood flow was detected and it was thought that a temporary ischemic attack might follow [20]. In addition, ciliary ganglion cells or migraine-related elongated mydriasis might have occurred as a result of temporary dysfunctioning of postganglionic and parasympathetic fibers during a migraine attack. The researchers who coined the term *sillier gangliоplegic* for this particular situation stated that this might be another result of ophthalmoplegic migraine pathogenesis. According to this hypothesis, the cause of ophthalmoplegic migraine may also cause elongated mydriasis by clinging to the parasympathetic fibers [14]. In the same study, it was stated that, in theory, the pain stemming from the sillier ganglions may find its way to the ophthalmic region of the trigeminal nerve and may create a bilateral headache [14]. Based on this study, it is possible to conclude that innervation deterioration in the sillier ganglions into the sillier muscle in these patients may cause insufficient accommodation. However, it was not possible to evaluate these hypotheses in our study since there were insufficient numbers of migraine patients with aura; they were evaluated during the remission period and no MRI tests were carried out.

Conclusions

Different results emerged from many different studies. We are of the opinion that the main causes of these conflicting results are misdiagnosis of headaches, changes in the diseases classification due to the new diagnostic techniques, evaluation of all the migraine patients together, and the lump-sum evaluation of all the eye impairments and visual levels. To keep our study free of such handicaps, we only evaluated the patient with uncorrected 20/20 vision, dividing them into groups with and without aura. We found that the cycloplegic spherical equivalent values of our patients with aura were lower than in control patients. However, given the fact that our findings were obtained from the eye examinations of the patients during the remission period, it is not possible to determine whether migraine with aura is the trigger or the result of those attacks. However, the number of migraine patients with aura is less than those without aura and it is very difficult to detect by the patient's ophthalmologist during the attack period. In order to be more conclusive about this particular issue, the neurologist and ophthalmologist should be in communication and there is a need for more comprehensive studies with larger number of participants.

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