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A Shift of the Pupillary Balance Towards the Parasymphathetic System in Migraine Patients with Aura

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ABSTRACT

Introduction: To analyze the static and dynamic pupillometrics in migraine patients with aura and compare these parameters to those in age– and sex-matched healthy participants.

Methods: This cross-sectional study included 34 patients with migraine and 37 healthy participants as a control group. The static pupillometrics consisted of scotopic pupil diameter (PD), mesopic PD, and low and high photopic PD. The dynamic pupillometrics were as follows: the initial diameter, amplitude of pupil contraction, latency of pupil contraction, duration of pupil contraction, velocity of pupil contraction, latency of pupil dilation, duration of pupil dilation, and velocity of pupil dilation. All participants were evaluated during a headache-free period. An automatic quantitative infrared pupillometry system was used to examine the pupillary characteristics of the eyes.

Results: The static and dynamic pupillary parameters except the latency of pupil contraction did not significantly differ between the migraine patients during an attack-free period and the healthy participants. The latency of pupil contraction was significantly statistically lower in migraine group than healthy subjects. Also, the scotopic PD differed significantly in the inter-eye comparison within migraine patients ($p<0.05$).

Conclusion: A significant inter-eye difference in scotopic PD values and the lower latency of pupil contraction in migraine patients with aura in the headache-free period might be attributed to a shift of the pupillary balance towards the parasymphathetic system.

Keywords: Dynamic pupillary parameters, latency of pupil contraction, migraine patients, scotopic pupil diameter, static pupillary parameters

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INTRODUCTION

Migraine is a common, chronic neurovascular disorder characterized by headache episodes that consist of a variety of clinical features with a mechanism that is not fully understood. The literature describes conflicting results on autonomic nervous system (ANS) activation in migraine patients. A wide variety of clinical signs and objective diagnostic data suggest that patients with migraine have sympathetic nervous system (SNS) dysfunction (1–3). Bremner suggested that migraine attacks could be prevented by modulation of the parasympathetic nervous system (4).

The evaluation of pupil diameter is a simple, useful, and non-invasive method to analyze the ANS (1). Some studies have been designed to evaluate the effect of migraine on pupillometric characteristics with different devices. The new generation non-invasive pupilometric devices, which standardize the amount of light in the media, perform quantitative measurements that are objective, repeatable and present statistical and dynamic parametric values (5–7).

The aim of this study was to evaluate pupillometry parameters in migraine patients with aura during a headache-free period using a newly developed automatic pupillometric device and to compare the results with control participants to understand the role of sympathetic or parasympathetic dysfunction, which might help elucidate the mechanism of migraine disorder.

Highlights

- **The pupil differences in migraine may be resulted from autonomic system shift.**
- **It was found lower intereye scoptic pupillary diameter in migraine group.**
- **Except scotopic PD value, all of the parameters in the migraine were similar.**

METHODS

This cross-sectional, prospective study was conducted between January and September 2019 in the Department of Neuro-ophthalmology at Ankara Ulucanlar Eye Training and Research Hospital. We enrolled 34 patients with migraine who were consecutively referred to our clinic by the neurology department. The control group consisted of 37 age– and sex-matched healthy participants with no systemic or ocular diseases. The study protocol was approved by the Ethics Committee of Ankara Keçiören Education and Research Hospital (Number: 15/1766). All of the

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study procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each individual participant.

The participants in both the study and control groups underwent a comprehensive ophthalmic examination including best-corrected visual acuity (BCVA) with a Snellen chart, refraction error, intraocular pressure measurement using a noncontact or Goldmann applanation tonometer, slit-lamp bio-microscopy, gonioscopy by Goldmann three-mirror lens, and fundus examination without mydriatics. The refractive error was recorded for all of the participants. The spherical equivalent was calculated by adding half of the cylinder to the sphere. Red-green color deficiency was evaluated with Ishihara plates. Eye movements in all of the participants' gazes were examined. To determine afferent pupillary defects, the swinging-flash light test was performed with a penlight.

All patients in migraine group had a medical diagnosis as having episodic migraine according to the criteria of the International Headache Society (8) and they were followed up in the Neurology clinic for at least 12 months. The demographic and clinical data of the patients were recorded. The type of migraine, accompanying symptoms (i. e., nausea, vomiting, photophobia, and phonophobia), duration of disease, number of migraine attacks per three months, duration of attacks were reviewed.

The patients who had refractive errors up to 3 diopters (D) for hyperopia or myopia and 1 D for astigmatism were included (9). Due to the effect of the premonitory period of migraine attacks, as guidance from the study by De Marinis et al. (10), we chose one week after the last migraine attack as the measurement period. Both the study and control groups consisted of participants who had no history of smoking or alcohol intake. The participants who had amblyopia, previous intraocular surgery, head or orbital trauma, systemic disease, or sleeping disorders and those who took prophylactic medications for migraine or chronic pain were excluded. In addition, patients who had iris and/or pupillary anomalies, such as synechia, sphincter tears, anisocoria, or colobomas, or who received topical or systemic medical treatment that may affect pupillary motility, such as tropicamide, cyclopentolate, pilocarpine, anti-depressants, and narcotic-derived medications were excluded from this study. Additionally, patients who ingested caffeine within the 4 hours before the test were not included in the study. We also excluded patients who had cataracts higher than grade two according to the Lens Opacities Classification System III (11). In order to distinguish migraine patients from intermittent angle closure, we examined the angle with the Goldmann three-mirror lens.

All of the measurements were performed by the same experienced technician using an automated quantitative pupillometry device (MonPack One, Vision Monitor System, Metrovision, Perenchies, France). The device was equipped with a near-infrared light-emitting and high-resolution camera (880 nm) system, and measurements were performed on both eyes simultaneously under complete darkness. The white stimulus was obtained from a full-field backlight combining blue (465 nm), green (523 nm), and red (632 nm) light-emitting diode sources.

Both dynamic and static pupillary functions can be clinically evaluated using this system, and the pupil size can be accurately measured (accuracy=0.1 mm) (12,13). Each participant was consecutively measured, and the data analysis revealed the average values. To minimize examiner-induced errors, measurements were performed with the automatic-release mode of the device, and only high-quality images were collected. To prevent the influence of daily variation in the pupillary response (14), all pupillary measurements were performed at the same time of day (i. e., between 12 to 15.00 pm) and in the same environmental conditions. Each patient was instructed to focus on a target in the center of the test field during the test in order to stabilize the fixation of the pupil (Figure 1a). Additionally, if the recordings were obtained when eyes were fixated within five degrees of the fixation axis of the optical system and infrared camera plane, the data were used for statistical analysis. The exclusive analysis software program of the device was used to automatically obtain the static and dynamic pupillometrics. The pupillary contours of the participants were automatically marked on the images to be accurately measured under specific lighting (Figure 1b).

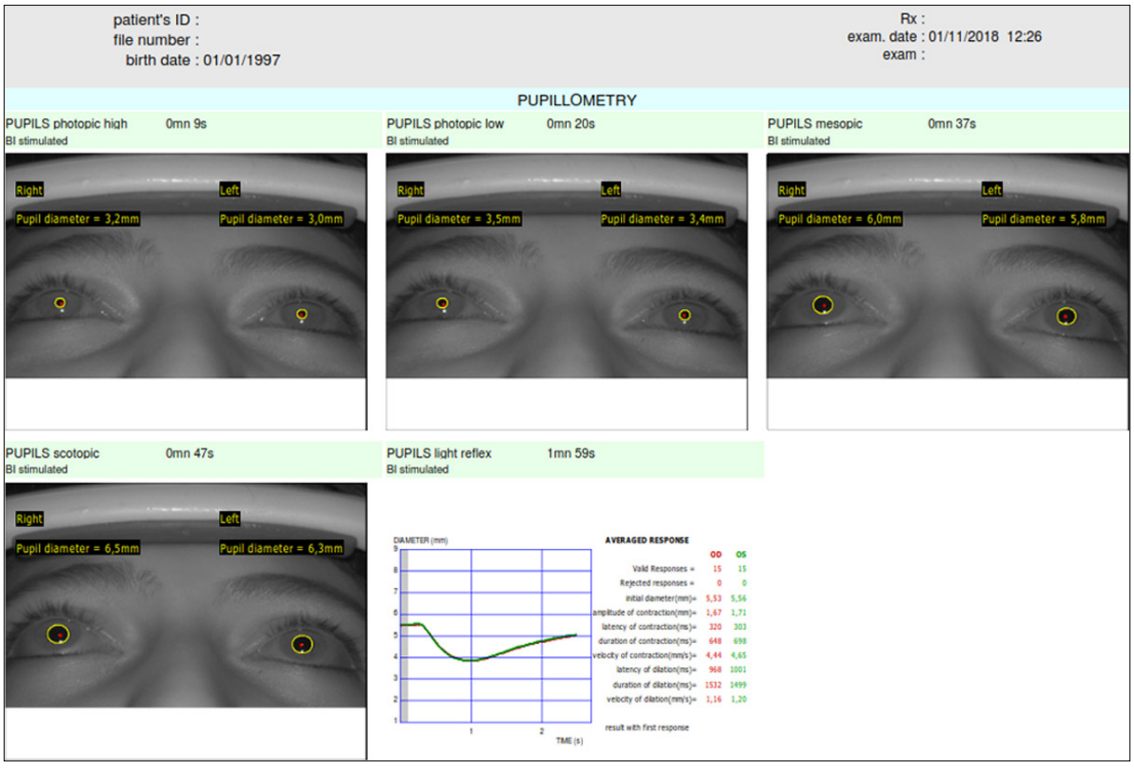
Thereafter, an analysis of the temporal and average responses to successive visual stimuli was performed with the software with automated quantification of the following parameters: the amplitude of contraction (mm); contraction and dilatation velocity (mm/s); latency and duration of contraction and dilation (ms); and minimum, maximum, initial, and mean PD (mm).

We first performed static pupillometry tests under several illumination levels to measure the pupil size in scotopic (0.1 cd/m^2), mesopic (1 cd/m^2), low photopic (10 cd/m^2), and high photopic (100 cd/m^2) vision conditions. Scotopic, mesopic, low photopic, and high photopic PD values were recorded separately. Dynamic pupillometrics were then obtained for a duration of 90 s following 5 min of darkness adaptation. The measurements were performed following stimulation with white light flashes (stimulation ON time, 200 ms; stimulation OFF time, 3.300 ms; total luminance, 100 cd/m^2; and total intensity, 20 lux). The images of both eyes were processed in real time (30 images per second) under luminance measured with a Minolta LS100 luminance meter (Vision Monitor System, Metrovision, Perenchies, France). The mean response to appropriate visual stimuli (i. e., light flashes) was quantified using the following parameters: the initial diameter, latency of pupil contraction, amplitude of pupil contraction, duration of pupil contraction, velocity of pupil contraction, latency of pupil dilation, duration of pupil dilation, and velocity of pupil dilation.

Statistical Analysis

The SPSS statistics software package version 22.0 for Windows (SPSS, Chicago, IL, USA) was used for statistical analysis. The sample size was calculated using PS software version 3.1.2 (Dupont & Plummer, 1997) based on the t test. To detect a difference of 0.1 mm in the pupil size with 80% power and an α of 0.05, the calculated sample size was 24 participants for each group. Continuous variables were reported as mean ± standard deviation, categorical variables were summarized with the use of frequencies. Due to the high degree of correlation between right and left eyes evaluated with Pearson correlation test for normally distributed parameters, and the Spearman correlation test for non-normally distributed parameters, the average of all measurements were used for both eyes in the group comparisons to avoid loss of statistical information. The normality of all data samples was controlled with the Kolmogorov–Smirnov test and Shapiro–Wilk test. An analysis of covariance (ANCOVA) was performed to compare pupillometric variables between two groups, controlling for gender, age, refraction. For inter-eye comparisons, normally distributed parameters were tested with the paired samples t test, and non-normally distributed parameters were calculated with the Wilcoxon Signed Rank test. A p-value <0.05 was accepted as statistically significant.

A



B

Figure 1. A, B. The image of the autonomic quantitative pupillary measurements system is shown **(A)**. The output of static and dynamic pupillometry via the autonomic quantitative pupillary measurement system is seen **(B)**.

RESULTS

The migraine patients consisted of 26 (76.5%) females and 8 (23.5%) males with a mean age of 36.7±9.4 years (20–63 years). The healthy participants consisted of 25 (67.6%) females and 12 (32.4%) males with a mean age of 35.2±10.3 years (18–55 years). The demographic and clinical characteristics of both groups are summarized in Table 1 and 2.

All of the static pupillometric parameters, including scotopic PD, mesopic PD, and low and high photopic PD, were compared between the groups. There was no statistically significant difference regarding the static pupillometry parameters between the two groups (ANCOVA test, p>0.05). The static pupillometry values of the migraine and healthy groups are summarized in Table 3. The dynamic pupillary parameters, except the latency of pupil contraction, did not significantly differ between the groups during the attack-free period (ANCOVA test, p>0.05). The latency of pupil contraction was lower in migraine group than control group (ANCOVA test, p=0.001). Box plot distribution of latency of pupillary contraction in migraine and healthy participants is shown in Figure 2. The dynamic pupillometry characteristics of the two groups are summarized in Table 4.

All of the static and dynamic pupillometry parameters were compared to each other in both eyes in migraine and control group. Regarding the static pupillometry parameters, only the scotopic pupillometry diameter was significantly different in both eyes of the migraine group (paired samples t test, p=0.041). Box plot distribution of scotopic pupillometry of migraine patients for right and left eye is shown in Figure 3. Table 5 summarizes the static pupillometry parameters of the right and left eyes of migraine and control subjects. None of the dynamic pupillometric values showed a statistically significant difference between the eyes of the migraine and control subjects (p>0.05). Dynamic pupillometry parameters of the right and left eyes of the migraine and control groups are shown in Table 6.

Table 1. Demographics and clinical characteristics of the migraine and healthy groups

Parameters	Migraine group (n=34) (min-max)	Healthy group (n=37) (min-max)	p value
Age, years (mean±SD)	36.7±9.4 (20 to 63)	35.2±10.3 (18 to 55)	0.527[ł]
Female/Male (n,%)	26(76.5%)/8(23.5%)	25(67.6%)/12(32.4%)	0.405[ł]
Refraction (D) SE (mean±SD)	-0.2±1.1 (-3 to 1)	-0.4±1.2 (-3.0 to 2)	0.173[s]

[ł]Independent t-test; [ł]Chi-square test; [s]Mann-Whitney U test.

Table 2. Clinical characteristics of the migraine subjects (n=34)

Parameters	Migraine group (min-max)
Disease duration (years) (mean±SD)	9.3±6.2 (2-23)
Number of attacks¶ (mean±SD)	3.9±1.7 (1-8)
Aura, n (%)*	34 (100%)
Photophobia	18 (53%)
Tinnitus	12 (35.3%)
Visual signs	10 (29.4%)

ł¶: per three months.

Table 3. Static pupillometry measurements of the migraine and healthy groups

Parameters (mm)/(mean±SD)	Migraine group (n=34) (min-max)	Healthy group (n=37) (min-max)	p*
Average Scotopic PD	6.4±0.8 (4.3-8.1)	6.4±1.1 (3.1-8.5)	0.406
Average Mesopic PD	4.7±0.7 (3.4-6.3)	5.0±0.9 (3.5-6.8)	0.596
Average Low Photopic PD	3.8±0.6 (2.6-4.8)	3.6±0.6 (2.7-5.3)	0.470
Average High Photopic PD	3.1±0.4 (2.4-4.2)	3.0±0.4 (2.2-3.7)	0.124

*p values after adjusting for age, sex and refractive error as confounders using analysis of covariance (ANCOVA).

Table 4. Dynamic pupillometry measurements of the migraine and healthy groups

Average Parameters mean±SD (min-max)	Migraine group (n=34)	Healthy group (n=37)	P value*
Initial diameter (mm)	5.8±0.7 (3.8 to 7.3)	5.8±0.8 (4.2 to 7.5)	0.650
Amplitude of pupil contraction (mm)	1.8±0.3 (1.2 to 2.4)	1.9±0.3 (1.5 to 2.7)	0.211
Latency of pupil contraction (ms)	253.3±46.5 (105 to 333)	276.3±33.5 (177 to 331)	***0.001***
Duration of pupil contraction (ms)	637.7±78.5 (528.5 to 919)	609.4±56.3 (540 to 766)	0.296
Velocity of pupil contraction (mm/s)	5.7±1.0 (3.7 to 7.6)	5.9±0.9 (4.3 to 8.2)	0.597
Latency of pupil dilation (ms)	889±55 (817 to 1012)	885±71 (799 to 1083)	0.448
Duration of pupil dilation (ms)	1571±55 (1448 to 1682)	1595±69 (1415 to 1699)	0.554
Velocity of pupil dilation (mm/s)	2.2±0.5 (1.5 to 3.6)	2±0.5 (1.5 to 3.6)	0.202

* p values after adjusting for age, sex and refractive error as confounders using analysis of covariance (ANCOVA)

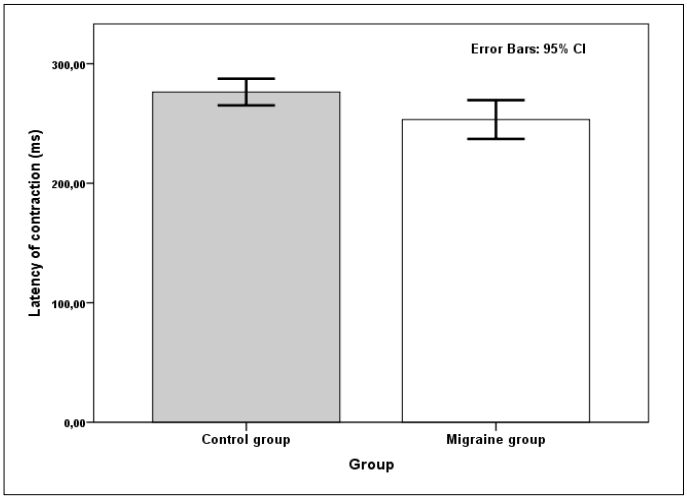


Figure 2. Box plot distribution of latency of pupillary contraction in migraine patients and healthy.participants.

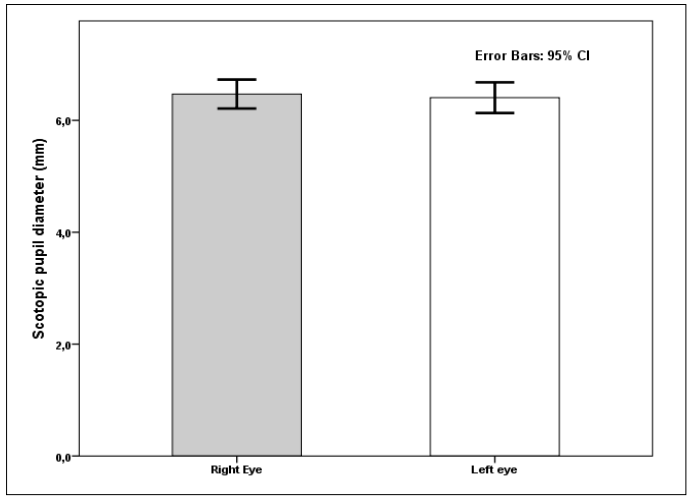


Figure 3. Box plot distribution of scotopic pupillometry of migraine patients for right eye and left eye.

Table 5. Static pupillometry parameters in right and left eyes of migraine and control participants

	Migraine group (n=34)			Control group (n=37)		
Parameters, mean±SD (range)	**Right eye**	**Left eye**	**p value***	**Right eye**	**Left eye**	**p value***
Scotopic PD (mm)	6.5±0.7 (4.3 to 8)	6.4±0.8 (4.2 to 8.1)	***0.041***	6.3±1.1 (3.1 to 8.5)	6.4±1.1 (3.1 to 8.4)	0.09
Mesopic PD (mm)	4.7±0.7 (3.4 to 6.4)	4.7±0.7 (3.3 to 6.2)	1.0	5.0±0.9 (3.5 to 6.7)	5.0±1.0 (3.4 to 6.9)	0.599
Low Photopic PD (mm)	3.8±0.6 (2.6 to 4.9)	3.8±0.6 (2.6 to 4.8)	0.474	3.6±0.6 (2.7 to 5.3)	3.6±0.6 (2.7 to 5.2)	0.413
High Photopic PD (mm)	3.1±0.4 (2.4 to 4.1)	3.2±0.4 (2.4 to 4.2)	0.203	3.0±0.4 (2.2 to 3.8)	3.0±0.4 (2.2 to 3.6)	0.442

*Paired t-test; PD: pupil diameter

Table 6. Dynamic pupillometry parameters in right and left eyes of migraine and control participants

	Migraine group (n=34)			Control group (n=37)		
Parameters, mean±SD (range)	**Right eye**	**Left eye**	**p value***	**Right eye**	**Left eye**	**p value***
Initial diameter (mm)	5.8±0.7 (7.4 to 3.9)	5.8 ± 0.8 (7.2 to 3.7)	0.905*	5.7±0.8 (4.2 to 7.5)	5.8±0.8 (4.2 to 7.4)	0.057*
Latency of pupil contraction (ms)	250±61 (69 to 330)	258±52 (79 to 336)	0.768*	277±31 (188 to 331)	275±38 (166 to 338)	0.884*
Amplitude of pupil contraction (mm)	1.8±0.3 (1.2 to 2.1)	1.8±0.3 (1.2 to 2.2)	0.516*	1.9±0.3 (1.2 to 2.5)	1.9±0.3 (1.4 to 2.6)	0.895**
Duration of pupil contraction (ms)	630±107 (507 to 919)	644±77 (534-827)	0.214*	604±55 (515 to 778)	615±70 (507 to 800)	0.33**
Velocity of pupil contraction (mm/s)	5.8±1.1 (3.6 to 7.8)	5.7±1.1 (3.7-8.4)	0.878*	5.9±0.9 (4.2 to 8.1)	5.9±1 (4.2 to 8.3)	0.925*
Latency of pupil dilation (ms)	885±72 (769 to 1034)	892.7±53 (804 to 1004)	0.388*	882±70 (766 to 1099)	888±80 (769 to 1131)	0.370**
Duration of pupil dilation (ms)	1576±81 (1334 to 1699)	1566±74 (1336 to 1699)	0.754*	1599±72 (1401 to 1734)	1591±97 (1245 to 1697)	0.856**
Velocity of pupil dilation (mm/s)	2.3±0.5 (1.6 to 3.6)	2.2±0.6 (1.3 to 3.6)	0.060*	2±0.6 (1.1 to 3.7)	2±0.5 (1.1 to 3.5)	0.330**

*Paired t-test; **Wilcoxon signed-rank test.

DISCUSSION

A recent systematic review and meta-analysis of community– and population-based studies revealed that migraine affects 11.6% of people globally (15). Despite many studies designed to determine the pathophysiology of migraines, the exact mechanism has not been revealed. The literature shows that pupil size and response abnormalities are associated with migraine patients during migraine attacks or an attack free-period (2,3,16,17). However, the role of ANS variations in migraine patients remains controversial.

Limited studies have been designed to investigate pupillometric characteristics with different infrared pupillometry devices. However, pupillometric studies based on different methodologies result in a wide range of conclusions and make comparison of the results of these studies challenging. The differences in ambient illumination, the intensity of the light stimulus, and errors depending on the examiner may cause significant variability in the evaluation of pupillary parameters (18).

The initial pupillary diameter is created by the balance between the opposing sympathetic and parasympathetic ANS (18). The initial diameter and the dilation velocity are considered to be markers of sympathetic activity (19,20) while the latency, velocity, and amplitude of pupillary contraction are markers of parasympathetic activity (19).

Nearly all of the previous studies had a common conclusion that the difference in the pupillary response that originates from ANS irregularities in migraine patients occurs within the first week following the headache attack. However, we observed lower latency of pupil contraction, and an inter-eye difference in the scotopic PD of migraine patients that was irrelevant to the effect of the acute attack. We included migraine patients with aura in this study to compare the dynamic and static pupillary parameters during a minimum 7-day attack-free period. Afterward, the data of the recorded parameters from these tests were compared to those of age and sex-matched healthy participants. We only found a lower latency of pupil contraction in migraine patients when compared to control group. We also analyzed the static and dynamic pupillometry parameters of each eye in migraine group. Except scotopic PD value, all of the static and dynamic inter-eye pupillometry parameters in the migraine group were similar. There was no difference in the initial diameter for each eye among the patients in the migraine group, although scotopic PD values of the left eye were smaller than those of the right. This finding was observed because there was an unequal inter-eye dilation among the migraine patients in darkness. Based on this finding, we might speculate that there is a subtle sympathetic hypofunction. A recent study from Yildiz et al. (21) has shown decreased oculosympathetic activity which resulted in decreased mean pupil size in patients with aura during the ictal period when compared to the interictal period. Besides, Cambran et al. (3) reported increased latency of pupillary contraction in migraine patients following the apraclonidine test, which can detect even subtle sympathetic pupillary hypofunctions. They have suggested that subtle autonomic sympathetic hypofunction occurs indirectly as an increased hypersensitivity response to the α-1 receptors in the pupil dilator muscle (3). As a result of this mechanism, the use of sympathomimetic agents by migraine patients stimulates different autonomic responses that are not observed in patients without migraine (16,22).

However, the information of stability in the parameters of the initial PD and dilatation velocity, which are primarily under the control of the SNS (19,20), makes explanation of the underlying problem with only sympathetic dysfunction challenging. In contrast to Cambron study (3), the migraine group had lower latency of pupillary contraction compared to the control group and we obtained this data without using a hypersensitivity test in

our study. As known, a latency of pupil contraction is present at the onset of pupil movement in reaction to stimulation by a light. A lower duration of this parameter indicates increased parasympathetic system activity. This finding suggested that there could be increased parasympathetic innervation activity of pupillary function in migraine patients.

A recent study revealed an increased parasympathetic response in patients with migraine. They used the cold pressor test to stimulate the peripheral SNS in migraine patients via physiological stress (23). A significant increase in the velocity of pupillary constriction at 5 min was present after the sympathetic stimulation in migraine patients, and its presence suggested that exaggerated parasympathetic activity follows sympathetic stimulation in the interictal phase (23). However, one of their inclusion criteria for the migraine group was at least a 48-hour headache-free period before or after measurement. In addition, they used a mono-ocular pupillometry device, which could show the variability of binocular measurements in the same participants (23).

In the migraine group, there was no inter-eye or intergroup difference in the duration of pupil dilation. As a result, we could not definitively associate the result of lower scotopic PD parameters with an inter-eye comparison in the migraine group with sympathetic hypofunction. However, those with atypical pupillometric recordings in scotopic conditions might have properties similar to those in patients with other types of headache disorders, which may be accompanied by subtle sympathetic hypofunction. Besides, taking into account the lower scotopic PD in the migraine group without initial diameter difference, and the lower latency of pupillary contraction in the migraine group during the headache-free period, we might speculate that there is a shift of the balance reflected in the pupillary diameter towards the parasympathetic system.

Some limitations of our study must be addressed. First, the patients were not examined during a migraine attack, as it may not be ethical to perform measurements during the aura period. In addition, it is difficult to examine patients during the aura period due to the phase typically lasting less than 30 min. Second, we did not perform any tests to stimulate either the SNS or the parasympathetic system to reveal an underlying hypersensitivity. However, we performed pupillometric tests in age and gender-matched groups at identical time intervals (12 to 15.00 pm) to limit the effect of age, gender, and diurnal variability (13,18).

In contrast to other studies in the literature, we were able to provide quantitative pupillometric parameters, which were obtained from measurements in different illumination conditions. In addition, all of the dynamic pupillometric values were obtained from the automatic, binocular infrared pupillometry device, which performs more accurate and sensitive measurements for small changes in autonomic imbalance. Further investigations are needed to differentiate the underlying mechanisms beyond the SNS and parasympathetic system on the pathophysiology of migraine-related pupillary dysfunction.

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Ankara Keçiören Education Research Hospital (Number: 15/1766, Date: 26.12.2018).

Informed Consent: Written informed consent was obtained from each individual participant.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- SKK, NHG; Design- SKK, NHG; Supervision- (-); Resource- (-); Materials- (-); Data Collection and/or Processing- DÖK, NHG; Analysis and/or Interpretation- SKK, PN; Literature Search- SKK, PN, DÖK; Writing- SKK, PN; Critical Reviews- SKK, PN, CK.

Conflict of Interest: The authors declared that there is no conflict of interest.

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REFERENCES

1. Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. Headache 2004;44:53–64. [Crossref]
2. Drummond PD. Disturbances in ocular sympathetic function and facial blood flow in unilateral migraine headache. J Neurol Neurosurg Psychiatry 1990;53:121–125. [Crossref]
3. Cambron M, Maertens H, Paemeleire K, Crevits L. Autonomic function in migraine patients: ictal and interictal pupillometry. Headache 2014;54:655–662. [Crossref]
4. Bremner F. Pupil evaluation as a test for autonomic disorders. Clin Auton Res 2009;19:88–101. [Crossref]
5. Zafar SF, Suarez JI. Automated pupillometer for monitoring the critically ill patient: a critical appraisal. J Crit Care 2014;29:599–603. [Crossref]
6. Hsieh YT, Hu FR. The correlation of pupil size measured by Colvard pupillometer and Orbscan II. J Refract Surg 2007;23:789–795. [Crossref]
7. Bootsma S, Tahzib N, Eggink F, de Brabander J, Nuijts R. Comparison of two pupillometers in determining pupil size for refractive surgery. Acta Ophthalmol Scand 2007;85:324–328. [Crossref]
8. Headache Classification Committee of The International Headache Society. The international classification of headache disorders: 3rd edition. Cephalalgia 2018;38:1–211. [Crossref]
9. Tekin K, Sekeroglu MA, Kiziltoprak H, Yetkin E, Doguizi S, Yilmazbas P. Static and Dynamic Pupillary Characteristics in Clinically Unilateral Pseudoexfoliation Syndrome. J Glaucoma 2018;27:552–557. [Crossref]
10. De Marinis M, Assenza S, Carletto F. Oculosympathetic alterations in migraine patients. Cephalalgia 1998;18:77–84. [Crossref]
11. Chylack LT Jr, Wolfe JK, Singer DM, Leske MC, Bullimore MA, Bailey IL, et al. The Lens Opacities Classification System III. The Longitudinal Study of Cataract Study Group. Arch Ophthalmol 1993;111:831–836. [Crossref]
12. Marcuti A, Cesaro M, Napoli D, Sorge RP, Ricci F, Mancino R, et al. Evaluation of pupillary response to light in patients with glaucoma: a study using computerized pupillometry. Int Ophthalmol 2014;34:1241–1247. [Crossref]
13. Aydogmus Y, Uzun S, Gundogan FC, Ulas UH, Ebiloglu T, Goktas MT. Is overactive bladder a nervous or bladder disorder? Autonomic imaging in patients with overactive bladder via dynamic pupillometry. World J Urol 2017;35:467–472. [Crossref]
14. Zele AJ, Feigl B, Smith SS, Markwell EL. The circadian response of intrinsically photosensitive retinal ganglion cells. PLoS One 2011;6:e17860. [Crossref]
15. Woldeamanuel YW, Cowan RP. Migraine affects 1 in 10 people worldwide featuring recent rise: A systematic review and meta-analysis of community-based studies involving 6 million participants. J Neurol Sci 2017;372:307–315. [Crossref]
16. Gotoh F, Komatsumoto S, Araki N, Gomi S. Noradrenergic nervous activity in migraine. Arch Neurol 1984;41:951–955. [Crossref]
17. Mylius V, Braune HJ, Schepelmann K. Dysfunction of the pupillary light reflex following migraine headache. Clin Auton Res 2003;13:16–21. [Crossref]
18. Tekin K, Sekeroglu MA, Kiziltoprak H, Doguizi S, Inanc M, Yilmazbas P. Static and dynamic pupillometry data of healthy individuals. Clin Exp Optom 2018;101:659–665. [Crossref]
19. Micieli G, Tassorelli C, Martignoni E, Marcheselli S, Rossi F, Nappi G. Further characterization of autonomic involvement in multiple system atrophy: a pupillometric study. Funct Neurol 1995;10:273–280. https://pubmed.ncbi.nlm.nih.gov/8837991/
20. Smith SA, Smith SE. Bilateral Horner's syndrome: detection and occurrence. J Neurol Neurosurg Psychiatry 1999;66:48–51. [Crossref]
21. Yildiz MB, Yildiz E, Balci S, Hasirci Bayir BR, Çetinkaya Y. Effect of migraine attack on pupil size, accommodation and ocular aberrations. Eur J Ophthalmol 2020:1120672120975334. [Crossref]
22. Boccuni M, Alessandri M, Fusco BM, Cangi F. The pressor hyperresponsiveness to phenylephrine unmasks sympathetic hypofunction in migraine. Cephalalgia 1989;9:239–245. https://journals.sagepub.com/doi/abs/10.1046/j.1468-2982.1989.0904239.x
23. Eren OE, Ruscheweyh R, Schankin C, Schöberl F, Straube A. The cold pressor test in interictal migraine patients - different parasympathetic pupillary response indicates dysbalance of the cranial autonomic nervous system. BMC Neurol 2018;18:41. [Crossref]