DOI: 10.4274/jbuch.galenos.2024.28159
J Dr Behcet Uz Child Hosp 2024;14(2):81-90

Original Article

Evaluation of Autonomic Dysfunction in Pediatric Migraine Patients

Pediatrik Migrenli Hastalarda Otonomik Disfonksiyonun Değerlendirilmesi

Duygu Aykol[1], Nurhak Demir[2], Ayşe İpek Polat[1], İbrahim Öztura[2], Uluç Yiş[1], Ayşe Semra Hız[1]

[1]Dokuz Eylül University Faculty of Medicine, Department of Pediatric Neurology, İzmir, Turkey
[2]Dokuz Eylül University Faculty of Medicine, Department of Neurology, İzmir, Turkey

ABSTRACT

Objective: Headache during childhood is a common condition. Although recent studies have shown that the autonomic nervous system (ANS) in adult migraine patients is affected, there are few studies evaluating this relationship in children. Adult migraine patients demonstrate no abnormal ANS function in either the sympathetic or parasympathetic nervous system but there can be sympathetic/parasympathetic hypofunction/hyperfunction. The aim of this study is to investigate autonomic dysfunction in pediatric migraine patients.

Method: The study evaluated tests for autonomic functions such as the orthostatic test, 30: 15 ratio, cold-pressor test, heart-rate responses to deep and normal breathing, valsalva ratio (VR), blink reflex (BR), and sympathetic-skin-response with thirty pediatric migraine patients in interictal period. Patients in control group were selected from children that had not any other disease or headhache.

Results: Consistent with sympathetic hypofunction, there was more frequent orthostatic hypotension in migraine group (p=0.019) and negative correlation between average disease duration, migraine attack duration and orthostatic tests results. Consistent with parasympathetic hyperfunction, the migraine group had higher VRs (p=0.035). There was a negative correlation between analgesic use rate and normal respiratory-RR-interval variability and between attack rate and deep and normal-R-R interval (R-wave peak to R-wave peak in electrocardiograms) variability. There was a positive correlation between average disease duration and BR R2 and R2′ latency in migraine group (p=0.028 and p=0.027).

Conclusion: Our study revealed that ANS functions are affected in pediatric migraine and balance between sympathetic and parasympathetic nervous system is distrupted.Our study demonstrates decreased sympathetic responsiveness during the interictal period. Our results suggest hypofunction in the parasympathetic nervous system of migraine patients as attack rate and pain density elevate.

Keywords: Migraine, autonomic nervous system, blink reflex, sympathetic skin response

ÖZ

Amaç: Çocukluk çağında baş ağrısı sık karşılaşılan bir yakınmadır. Son yıllarda migrende otonom sinir sistemi fonksiyonunun etkilendiğini gösteren erişkin çalışmaları mevcut olmasına karşın çocukluk çağında bu alanda yapılmış çalışma sayısı kısıtlıdır. Bu çalışmanın amacı migrenli çocuklarda otonomik disfonksiyonun araştırılmasıdır.

Yöntem: Çalışmada otonom fonksiyonlar için baş ağrısız dönemde otuz migren hastasında "ortostatik test, 30/15 oranı, buz testi, derin ve normal solunumda elektrokardiyogramda RR (R-wave peak to R-wave peak in electrocardiograms) aralık değişkenliği, valsalva oranı, göz kırpma refleksi, sempatik deri yanıtları" değerlendirilmiştir. Kontrol grubundaki çocuklar ise baş ağrısı veya herhangi bir hastalık öyküsü olmayan sağlıklı bireylerden seçilmiştir.

Bulgular: Migren grubunda sempatik hipofonksiyonu gösterecek şekilde ortostatik hipotansiyon (p=0,019) daha sık ve ortalama hastalık süresi ile ortostatik test sonuçları arasında negatif korelasyon saptandı. Parasempatik hiperfonksiyonu destekleyecek şekilde migren grubunda valsalva oranı daha yüksek bulundu (p=0,035). Analjezik kullanım sıklığı ile normal solunum RR aralık değişkenliği arasında ve atak sıklığı ile derin ve normal solunum RR aralık analizi arasında negatif korelasyon saptandı. Ortalama hastalık süresi ile göz kırpma refleksi R2 ve R2′ latansı arasında pozitif korelasyon saptanmıştır (sırasıyla p=0,028; p=0,027).

Sonuç: Çalışmamızda pediatrik migrende otonom sinir sistemi fonksiyonlarının etkilendiği, sempatik ve parasempatik sinir sistemi arasındaki dengenin bozulduğu saptanmıştır. Çalışmamız interiktal dönemde azalmış sempatik yanıtı göstermektedir. Sonuçlarımız pediatrik migren hastalarında atak sıklığı ve ağrı yoğunluğu arttıkça parasempatik hipofonksiyonun olduğunu göstermektedir.

Anahtar kelimeler: Migren, otonom sinir sistemi, göz kırpma refleksi, sempatik deri yanıtı

Received: 14.03.2024
Accepted: 09.04.2024

Corresponding Author
Duygu Aykol
Dokuz Eylül University Faculty of Medicine, Department of Pediatric Neurology, İzmir, Turkey
d_aykol@hotmail.com
ORCID: 0000-0001-5328-3460

Cite as: Aykol D, Demir N, Polat Aİ, Öztura İ, Yiş U, Hız AS. Evaluation of Autonomic Dysfunction in Pediatric Migraine Patients. J Behcet Uz Child Hosp. 2024;14(2):81-90

Copyright© 2024 The Author. Published by Galenos Publishing House on behalf of Izmir Children's Health Society and Izmir Dr. Behcet Uz Children's Hospital.
This is an open access article under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

INTRODUCTION

Headache is common during childhood and patients are often referred to a neurologist. The most important and frequent cause of recurrent episodic headache is migraine. The prevalence of a headhache complaint is 37-51% in seven-year-old children and increases to 57-82% in adolescents[1]. Autonomic dysfunction can be seen in both ictal and interictal periods in patients with migraine. The pathophysiologic mechanisms of migraine are complex and yet to be fully understood. The autonomic nervous system (ANS) regulates entire unconscious homeostatic mechanism of the human body and modulate physiological pain responses including migraine. Besides the sympathetic pathways, the cranial parasympathetic system also plays a role in the migraine response[2]. Stimulation of the trigeminocervical complex of the trigeminal nucleus caudalis and spinal cord dorsal horns causes reflex activation of cranial parasympathetic fibers and chemicals such as acetylcholine, calcitonin gene related protein, vasoactive intestinal peptide are released from these particular regions[3]. Although recent studies have shown that the ANS in adult migraine patients is affected by headache, there are few studies that evaluate this relationship in children[4-9].

MATERIALS and METHODS

Thirty pediatric migraine patients who were followed in the Pediatric Neurology Department in between 2013-2015 and twenty-healthy controls were included. The study was approved by Local Ethic Committee of Dokuz Eylül University Faculty of Medicine (approval number: 2013/18-06, date: 20.05.2013). We diagnosed the patients as migraine according to International Classification of Headache Disorders (ICHD)-II, published by the International Headache Society in 2004[10]. ICHD-III diagnostic criteria are currently used for the diagnosis of migraine. There is no difference between ICHD-II and ICHD-III in terms of migraine without aura diagnostic criteria. We included pediatric patients aged 7-18 years with migraine without aura, who did not have prophylactic treatment. They had no chronic diseases including obesity, hypertension, hyperlipidemia, thyroid function abnormalities, renal disorders, diabetes mellitus, autoimmune disorders, hepatic disorders, cardiovascular disorders, infectious disorders and neurological disorders. All the individuals had a normal neurological examination and gave consent to participate in the study. Inclusion criterias for the migraneurs are listed in Table 1. Demographic features, anthropometric measurements, localization of headache, headache attack-frequency, duration, number of emergency service admission, analgesic usage, response to analgesics, triggering factors, family history of migraine were recorded. Pediatric Migraine Disability Assessment Score (PedMIDAS) questionnaire was applied to evaluate the effects of migraine attacks on the quality of life[11]. The tests were done to evaluate autonomic functions including the orthostatic test, cold-pressor-test, blink reflex (BR), sympathetic-skin-response (SSR) tests, 30:15 ratio, heart-rate responses to deep and normal breathing and valsalva ratio (VR). All of the participants were tested in the attack free period. Electrophysiological studies were performed by the same neurophysiologist using the same electrodes in a semi-dark room with a temperature between 24-26 °C using the Keypoint EMG (Medtronic, Minneapolis, USA). During the tests, they were performed at the same time of the day (13:30-17:00) in order to prevent diurnal variation, paying attention to the absence of any external stimuli that could affect the recordings. Parents have accompanied by the cases during all tests.

Orthostatic Test

Right upper extremity blood pressure (BP) was recorded after 15 minutes of rest in the supine position, just before standing up, immediately after standing up, and one, five and ten minutes after standing up. A decrease of 20 mmHg in systolic blood pressure (SBP) and 10 mmHg in diastolic blood pressure (DBP) was accepted as orthostatic hypotension[4-6,12,13].

Cold Pressor Test (CPT)

While the patient was monitored for BP and heart rate (HR) at 24 °C room temperature, the change in HR and arterial BP was recorded during the application of cold water at a temperature of 5 °C to the dorsum of the right hand for 1 minute after 2 minutes of rest[6].

Table 1. Inclusion criterias for the migraineurs ($p<0.05$)
Diagnosed as migraine without aura according to ICHD-II criterias
No chronic disease or chronic medication usage
Normal physical and neurological examination
Exclusion of secondary headache causes
7-18 ages
No medication usage at least 5 days prior to admission to the study
No exposure to alcohol/nicotine at least 72 hours prior to admission to the study
SD: Standard deviation, ICHD: International Classification of Headache Disorders

Blink Reflex

Recording is performed simultaneously from both sides of the face using a two-channel recording apparatus. Surface recording electrodes are placed over the inferior orbicularis oculi muscles bilaterally. For recording the orbicularis oculi muscle, the active recording electrodes (G1) are best placed below the eye just lateral and inferior to the pupil at mid-position. The corresponding reference electrodes (G2) are placed just lateral to the lateral canthus bilaterally. The filter settings are the same as for a motor conduction study (10 Hz, 10 kHz). Once supramaximal stimulation is achieved, four to six responses are obtained on a rastered tracing and superimposed to determine the shortest response latencies. With several traces superimposed, the shortest R2-latency is selected. It is extremely important that the patient be in a relaxed state to eliminate any signal noise, which could obliterate or confound one or both components of the BR (especially R2)[14-17].

Sympathetic Skin Response

Measurement of the SSR is a non-invasive technique for assessment of sympathetic fiber impairement. SSR measurement was recorded after cleaning the skin with alcohol while the patient was lying. Surface electrode placed on the palm of the hand or sole of the foot serves best as the active electrode (E1), with the reference electrode (E2) on the dorsal surface of the same limb. In the measurement phase, basal sympathetic tone was recorded first and followed by recording SSR of the upper and lower extremities with superficial stimulation of the median nerve at the level of the left wrist. SSR latency was accepted as the starting point of negative deflection, and for amplitude, between the peaks of negative and positive deflections[18,19].

Autonomic Cardiovascular Tests

The RR (R-wave peak to R-wave peak in electrocardiograms)-Analysis, VR and 30:15 Ratio

The RR interval-test was used to examine the condition of the parasympathetic nervous system. The time between the R-peaks in the electrocardiogram (ECG) of two consecutive heart beats was measured. Measurements were recorded in rest and in deep-breathing, during valsalva-maneuver and when standing up with surface plate electrodes[5,9,13].

Normal Breathing

After the patient is advised to relax, recordings were made at rest and in supine position. Regular interval rate variation (RRIV) was calculated using the formula;

RRIV=(RR maximum-RR minimum)x100/RR mean

Deep Breathing

The patient was advised to inhale for 5 seconds, then exhale for 5 seconds. It was repeated for a few times to get a good deep respiration rhythm. When deep breathing was obtained at 6 frequencies per minute, recordings were taken in the supine position. The heart beat frequency variation is most obvious in children and young people. ECG was recorded in limb lead-II for one minute with patient breathing deeply as instructed. RRIV was calculated using the same formula with normal breathing test.

Valsalva Ratio

Patients were advised to lie down and rest for at least 10 minutes. And patients were advised to stand up when they heard the signal. ECG was recorded continuously during and after the valsalva maneuver. VR was calculated using the longest RR-interval recorded after the maneuver and the shortest RR-interval-ratio recorded during the maneuver.

Cardiovascular Response to Standing-Up and 30:15 Ratio

After 15 minutes of rest in the supine position, the RR-interval at the 15th and 30th heart beats of the patients who underwent ECG monitoring after standing up was recorded.

Statistical Analysis

All statistical calculations were performed using SPSS 22.0 for Windows. Whether the distributions of continuous variables were normally or not being determined by the Shapiro-Wilk test. The assumption of homogenecity of variances was examined using the Levene-test. Descriptive statistics for continuous variables were expressed as mean ± SD or median ± (25th-75th) percentiles, where appropriate. The Mann-Whitney U test and Student's t-test were used for the comparison of parameters. The chi-square-test was used for categorical variables. The significance level was accepted as $p<0.05$. Data analysis was performed using SPSS Statistics version-22.0 software. Mann-Whitney U test was used to compare the mean values of the groups. While the differences among categorical groups were evaluated by chi-square-test. The Pearson's correlation analysis was performed to determine the correlation between the different variables.

RESULTS

There were no statistically differences between the groups regarding age and sex (p=0.803, p=0.804).

Nineteen patients (66%) in the migraine group had a family history of migraine. No statistically significant difference was found between groups regarding body weight, height and body mass index (p=0.699, 0.172 and 0.976, respectively). Mean of SBP and DBP values were similar (p=0.639 and p=0.590, respectively). Demographic features, BP values and anthropometric measurements are given in Table 2. Number of the triggering factors including sound, light, hunger, stress, physical activity, insomnia, drug use, food intake, infection and seasonal characteristics were found as 5.7±1.0. Disease information of migraneurs are given in Table 3.

Autonomic Dysfunction Test Results

Orthostotic hypotension was detected in 10 migraneurs and one patient in the control group. This difference was statistically significant (p=0.019). There was no statistically significant difference between groups regarding other orthostotic test findings including SBP, DBP and HR during supine position, standing, one minute, 5 minute and 10 minute later standing up (Table 4).

No statisticall significant difference was found between the two groups in terms of SBP, DBP and HR before and after CPT (Table 4).

There was no statistical difference between migraine and control groups regarding latans and amplitudes which were recorded in right hand and foot of the individuals (Table 4).

No statistically signicifant difference was found between the two groups in terms of left R1, R2, R2' and right R1,R2, R2'-responses (Table 4).

No statistically difference was detected between groups in terms of 30:15 ratio and RRIV. VR was found to be higher in migraineurs than control group and the difference was statistically significant (p=0.035) (Table 4).

Table 2. Demographic features and antropometric measurements of migraneurs and healthy subjects (p<0.05)

	Migraine group (n=30)	Control group (n=20)	p-value
Age (years) (mean ± SD)	13.2±2.6	12.7±3.5	0.803
Male gender (n%)	10 (30%)	6 (%)	0.804
Systolic blood pressure (mmHg)	113.0±12.0	114.6±8.7	0.639
Diastolic blood pressure (mmHg)	68±6.9	69.3±5.6	0.590
Body weight (kg) (mean ± SD)	49.2±15.2	49.8±16.4	0.699
Height (cm) (mean ± SD)	151.9±11.1	155.4±16.4	0.172
BMI (kg/m^2) (mean ± SD)	20.7±4.7	19.9±3.7	0.976

SD: Standard deviation, BMI: Body mass index

Table 3. Disease features of migraneurs (p<0.05)

	n (%) or (mean ± SD)	min.-max.
Migraine disease duration (months)	19.3±16.2	2-60
Attack frequency	6.1±3.8	1-16
Number of attacks with a need of analgesic usage (per month)	4.6±3.3	1-12
Attack duration (hours)	6.6±7.9	1-24
Number of emergency department admissions (per year)	1.1±2.3	0-10
Complete response to analgesic	5 (16.7%)	
Partial response to analgesic	24 (80%)	
PedMIDAS score (median) Grade 1 (0-10) Grade 2 (11-30) Grade 3 (31-50) Grade 4 (>50)	12 10 (33.3%) 14 (46.7%) 3 (10%) 3 (10%)	2-96

SD: Standard deviation, PedMIDAS: Pediatric Migraine Disability Assessment Score, min.-max.: Minimum-Maximum

Table 4. Comparision of orthostotic test, cold pressure test, sympathetic skin response test, blink reflex test and 30:15 ratio, valsalva ratio and RR interval variability test results in migraine and control groups ($p<0.05$)				
Orthostatic test results		**Migraine group (n=30)**	**Control group (n=20)**	**p-value**
Orhostatic hypotension		10 (33.3%)	1 (5%)	0.019
Supine position	Systolic BP	115.6±12.5	116.9±8.8	0.736
	Diastolic BP	69.2±8.0	68.5±5.7	0.866
	Heart rate	87.4±13.6	88.3±12.9	0.866
After standing up	Systolic BP	111.8±14.6	107.7±11.5	0.125
	Diastolic BP	68.5±7.1	70.1±6.5	0.599
	Heart rate	96±14.8	94.6±14.9	0.789
1 minute later standing up	Systolic BP	114.0±11.3	112.5±12.4	0.706
	Diastolic BP	70.3±10.6	68.1±8.5	0.677
	Heart rate	94.6±14.3	98.0±13.7	0.326
5 minutes later standing up	Systolic BP	111.6±10.5	112.8±8.5	0.592
	Diastolic BP	71.2±7.5	68.5±6.6	0.469
	Heart rate	95.9±12.1	94.1±12.7	0.721
10 minutes later standing up	Systolic BP	109.4±12.4	110.1±9.1	0.835
	Diastolic BP	70.2±8.7	70.1±7.0	0.953
	Heart rate	94.4±10.8	94.3±12.5	0.858
Cold pressure test results				
Before cold pressure test	Systolic BP	106.0±14.7	107.0±8.5	0.764
	Diastolic BP	68.4±6.8	71.0±7.8	0.233
	Heart rate	91.2±10.3	94.2±13.8	0.412
After cold pressure test	Systolic BP	108.6±10.3	109.0±7.3	0.858
	Diastolic BP	67.9±6.7	68.7±6.2	0.696
	Heart rate	92.0±11.0	95.0±14.7	0.455
Sympathetic skin responses test results		**Migraine group (n=30)**	**Control group (n=20)**	**p-value**
Right hand	Latans (ms)	1399.8±358.45	1366.7±264.69	0.709
	Amplitude (mV)	2.65±1.56	2.29±1.39	0.406
Right foot	Latans (ms)	1795.27±380.8	1818.3±324.16	0.820
	Amplitude (mV)	1.18±0.94	0.96±0.70	0.334
Blink reflex test results				
Left R1 latans (ms)		9.89±0.64	9.91±0.82	0.940
Left R2 latans (ms)		30.92±3.31	31.27±3.93	0.750
Left R2' latans (ms)		32.73±3.78	32.6±4.32	0.960
Right R1 latans (ms)		9.63±1.72	9.85±0.97	0.574
Right R2 latans (ms)		31.80±3.44	32.48±3.35	0.491
Right R2' latans (ms)		33.62±4.38	34.51±3.73	0.443
30:15 ratio test results				
30:15 ratio		1.12±0.16	1.08±0.11	0.201
Valsalva ratio test results				
Valsalva ratio		1.63±0.36	1.46±0.35	0.035
RR interval variability in normal and deep breathing				
Normal breathing		36.5±15.6%	32.7±16.7%	0.525
Deep breathing		53.0±13.5%	54.7±10.6%	0.898

BP: Blood pressure, SD: Standard deviation, RR: R-wave peak to R-wave peak in electrocardiograms

Table 5. Correlation analysis results RR interval variability		
	Migraine attack frequency r*	**p-value**
RRIV during normal breathing	-0.528	0.003
RRIV during deep breathing	-0.354	0.055
	Disease duration r*	**p-value**
SBP in supine position	-0.449	0.013
SBP 5 minute later standing up	-0.399	0.029
Right R2	0.402	0.028
Right R2′	0.403	0.027
	Migraine attack duration r*	**p-value**
SBP 10 minute later standing up	-0.366	0.047
DBP 10 minute later standing up	-0.397	0.030
SBP before cold pressure test	-0.512	0.004
DBP before cold pressure test	-0.380	0.038
DBP after cold pressure test	-0.394	0.031
Heart rate after cold pressure test	-0.370	0.044
	Analgesic usage r*	**p-value**
RRIV during normal breathing	-0.375	0.041
	PedMIDAS score r*	**p-value**
Heart rate before cold pressure test	-0.399	0.029
Heart rate after cold pressure test	-0.395	0.031

r*: Rate, RR: R-wave peak to R-wave peak in electrocardiograms, SBP: Sistolic blood pressure, DBP: Diastolic blood pressure, RRIV: RR interval variability, PedMIDAS: Pediatric Migraine Disability Assessment Score

Correlation Analysis

There was a negative correlation between migraine attack frequency and RRIV. A negative correlation was found between disease duration and SBP measured in supine position and 5 minutes later standing up during the orthostotic test. A positive correlation was found between disease duration and right R2 latancies of BR test. There was a negative correlation between migraine attack duration and SBP and DBP which were measured 10 minute later standing up during orthostatic test. A negative correlation was found between the duration of migraine attack and SBP, DBP measured before CPT and DBP, HR measured after the CPT. There was a negative correlation between analgesic usage and RRIV during normal breathing. A negative correlation was detected between PedMIDAS-score and HR before CPT and HR after CPT (Table 5). There was a positive correlation between average disease duration and BR-R2 and R2′ latency in migraine group (p=0.028 and p=0.027; Figure 1).

DISCUSSION

Sympathetic and parasympathetic dysfunction play a significant role in migraine pathogenesis. Our study demonstrates decreased sympathetic responsiveness during the interictal period in migraneurs. Our results suggest hypofunction in the parasympathetic nervous system of migraine patients as attack rate and pain density elevate.

Sympathovagal imbalance that affects cranial vascular system that can elucidate many systemic migraine phenomena such as irritability, odor, noise, and light sensitivity, which are frequent in the prodrome period[20]. The presence of at least one cranial autonomic symptom was 27-73% in adult patients with migraine and 62% of pediatric patients[21].

Adult migraine patients demonstrate no abnormal ANS function in either the sympathetic or parasympathetic nervous system but there can be sympathetic/parasympathetic hypofunction/hyperfunction.

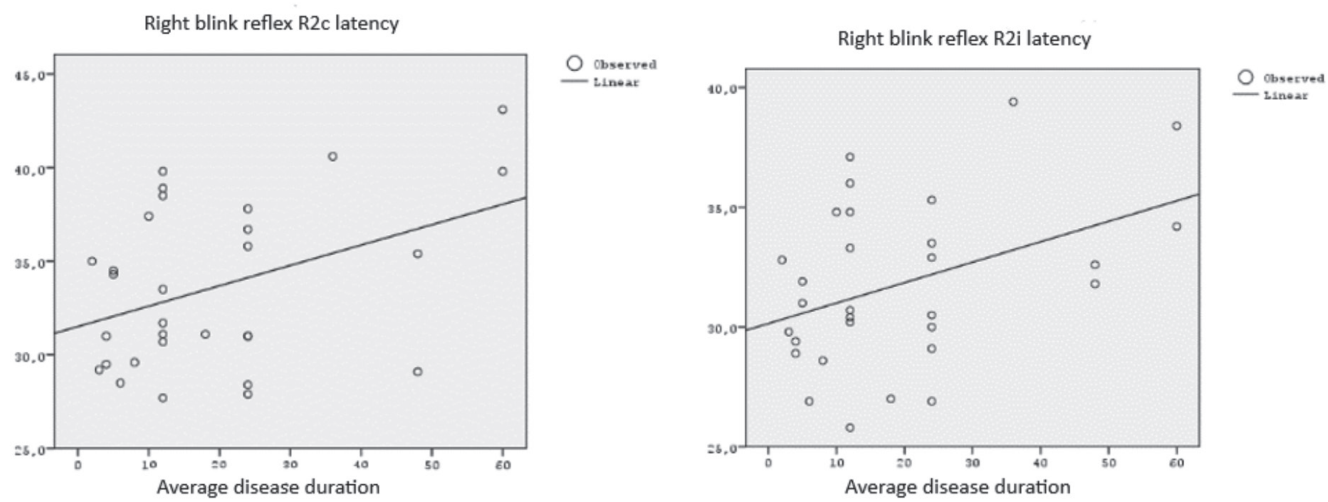

Figure 1. Positive correlation between average disease duration and blink reflex R2 and R2′ latency

In our study there were no statistically significant differences based on results of the resting BP. In the literature, some studies suggest that there is sympathetic nervous system hyperfunction in patients with migraine. Shechter et al.[22] showed that adult migraine patients had higher resting BP measured than a control group and they described this as increased sympathetic nervous system activity. Yildiz et al.[19] identified sympathetic nervous system hypofunction and hyperfunction in a re-evaluation performed 72 hours following attacks, based on SSR during attacks and the symptomatic period in adult migraine patients. Generally, most of studies demonstrate increased sympathetic nerve system activation during the ictal-period and decreased sympathetic nerve activation in interictal period in migrane group. In our study, negative correlation between SBP and DBP measured at the 10th minute during the orthostatic test and the duration of migraine attack was found. These results may show that lower SBP in patients with longer attack periods is associated with sympathetic nervous system hypoactivation. The central autonomic network (CAN) and its connections with the pain system are affected in migraine. The CAN is a system of interconnected nuclei in the cortex and brainstem that help regulate visceromotor, neuroendocrine, respiratory, and pain responses, among other functions. Important areas of the CAN that are also thought to be involved in the transmission of migraine pain include the periaqueductal gray (PAG) of the midbrain. PAG also play an important role in cardiovascular control[2]. The presence of orthostatic intolerance in migraine may be explained by this mechanism. Yakinci et al.[5] examined orthostatic test in pediatric migraine patients and showed higher systolic and diastolic BP than control group. These results suggest that sympathetic nervous system hyperactivity in migraneurs[5]. Peroutka[23] published results consistent with sympathetic nervous system hypofunction based on measurements during the asymptomatic period, in supine and upright positions, as well as evaluating plasma norepinephrine levels after the CPT. In the present study there was a negative correlation between average disease duration and SBP checked at the 5th minute and not in an upright position during the orthostatic test. Since there was a correlation with DBP, this result may linked to minimal hypoactivity in the sympathetic nervous system. In our study there was a negative correlation between SBP and DBP measured at the 10th minute during the orthostatic test and migraine attack duration. These results show that lower SBP in patients with longer attack periods may be linked to sympathetic nervous system hypoactivation. In many studies, sympathetic hypofunction was determined according to plasma norepinephrine level, cardiovascular reflex responses, and HR recovery indices, sustained handgrid tests and valsalva maneuver-phase 4[20] beat-to-beat blood pressure responses to the Valsalva maneuver, sustained handgrip, cold pressor test, and head-up tilt and tests of parasympathetic function (heart rate responses to deep breathing and the Valsalva maneuver. There was a negative correlation between average disease period and SBP and DBP measured before and after the CPT and between DBP and HR. This also shows sympathetic nervous system hypofunction since there was no HR increase and adequate BP level after the ice-test. There was a negative correlation between PedMIDAS scores and SBP and HR before and after the ice-test. This also shows that there was no significant HR increase response to the ice-test in patients whose life quality deteriorated because of headache and that they had sympathetic nervous system hypofunction. Havanka-Kanniainen et al.[24] found lower RRIV in deep and normal breathing, which could support parasympathetic hypofunction. In the same study, the valsalva maneuver, orthostatic, and isometric exercise test had results were consistent with sympathetic nervous system hypofunction[24]. There are many studies that have also identified sympathetic nervous system hypofunction[4,19,23-28]. All of these studies show that migraine is a chronic sympathetic nervous system disease as we demonstrated in our study.

In the literature, some studies suggest that there is parasympathetic nervous system hypofunction in patients with migraine. Pogacnik et al.[12] found lower spectral-frequency dependent measurements of heart-rate-variability, which supported parasympathetic hypofunction in migraine. A study demonstrated parasympathetic hypofunction in RRIV and identified autonomous symptoms indicating ANS dysfunction[22]. Havanka-Kanniainen et al.[24] found lower RRIV in deep and normal breathing, which could support parasympathetic hypofunction. In the same study, the valsalva maneuver, orthostatic, and isometric exercise test had results were consistent with sympathetic nervous system hypofunction. These results similar to our study Mikamo et al.[28], however, established a significant difference in deep and normal breathing RRIV between migraine and control group, suggesting that parasympathetic nervous system functions were protected. Nevertheless, an orthostatic test from the same study suggested that there was sympathetic nervous system hypofunction in migraine patients, since this group had lower BP and basal plasma norepinephrine levels[28]. In the current study, there was a negative correlation between analgesic use rate and normal respiratory RRIV and between attack rate and deep and normal breathing RRIV. These results also suggest hypofunction in the parasympathetic nervous system of migraine patients as attack rate and pain density elevate.

A few studies associate migraine with parasympathetic system hyperfunction in literature. In the study conducted by Yakinci et al.[5], 25 children with migraine were evaluated during the headache-free-period and the rate of valsalva measuring parasympathetic activity was found to be higher 30:15. Gotoh et al.[29] found hyperactivity of parasympathetic nervous system based significantly on differences in Aschner's-test. In our study significantly increased valsalva-rate may suggest that parasympathetic nervous system hyperfunction in migraineurs.

There are also studies in literature demonstrating that parasympathetic nervous system functions are protected[4,7].

The BR is an objective neurophysiological method used to evaluate facial nerve and lateral medulla functions. In our study, there was no statistically significant difference between the control and migraine groups in terms of left R1, R2, R2′ and right R1, R2, R2′-responses however there was a positive correlation between average disease duration and right R2, R2′-latencies of BR components. This suggests that exposure in the trigeminovascular system (TVS) increases the length of migraine periods. Normal R1-latency in BR, which is useful for evaluating trigeminovascular pathway functions, indicates that the oligosynaptic arc is protected. Longer R2, R2′-latencies show that the brain stem interneuron is suppressed and the polysynaptic pathway forming R2-response is affected. In a study conducted with migraine patients during the headache-free-period by Bánk et al.[15] R1-latency was within normal intervals in control and patient groups, but R2 and R2′-latency were statistically and significantly higher in the migraine group. They interpreted this result as indicating that the oligosynaptic pathway was protected, but there could be exposure in the trigeminal afferent and/or polysynaptic pathway[15]. In a study conducted by Yildirim et al.[17], R2-latency was higher in migraine patients and they suggested that there was a suppression of activity in brain stem interneurons.

Study Limitation

Our study has some limitations, such as the small number of patients. Recent studies have showed the ANS impairment in migraine patients. The results of ANS-tests, which are sensitive measurements, can be found very different in migraine studies. In the literature many studies, in which different methods are used to evaluate ANS, showed that patients suffering from headache have diverse physiological response to pain. The reason for the different results of the studies in the literature can be mentioned as age, gender, diversity of antopometric measurements, presence of either episodic or chronic migraine, presence of aura, other migraine features, ictal/interictal period in each study group. Considering this situation, studies with more homogeneous study groups are needed, so we used more restrictive inclusion criteria in our study.

CONCLUSION

In conclusion, while parasympathetic hyperfunction was detected with an increased rate of valsalva in the migraine group, the presence of hypofunction in the parasympathetic system was observed as the attack frequency and headache intensity increased. The fact that orthostatic hypotension was observed more frequently in the migraine group, the insufficient cardiovascular response to the ice test, the negative correlation between the PedMIDAS-score and the ice-test, the average disease duration and the negative correlation between the parameters evaluated during the orthostatic test with the migraine attack, suggested sympathetic hypofunction in migraine. Considering the positive correlation between the average disease duration and the right R2 and R2'-latencies, which are BR components, in the correlation analysis, it can be said that the effect on the TVS increased over time during the migraine disease.

As a result, ANS functions are affected in migraine, the balance between the sympathetic and parasympathetic nervous system is disrupted, and the TVS functions are affected by the increase in the mean duration of disease in migraine.

Ethics

Ethics Committee Approval: The study was approved by Local Ethic Committee of Dokuz Eylül University Faculty of Medicine (approval number: 2013/18-06, date: 20.05.2013).

Informed Consent: All the individuals had a normal neurological examination and gave consent to participate in the study.

Author Contributions

Design: A.İ.P., İ.Ö., U.Y., A.S.H., Data Collection and Processing: D.A., N.D., Analysis and Interpretation: D.A., N.D., Literature Search: D.A., Writing: D.A.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Bille BS. Migraine in school children. A study of the incidence and short-term prognosis, and a clinical, psychological and electroencephalographic comparison between children with migraine and matched controls. Acta Paediatr Suppl (Upps). 1962;136:1-151. https://pubmed.ncbi.nlm.nih.gov/13869189/
2. Miglis MG. Migraine and autonomic dysfunction: which is the horse and which is the jockey? Curr Pain Headache Rep. 2018;22(3):19. doi: 10.1007/s11916-018-0671-y
3. Cernuda-Morollón E, Martínez-Camblor P, Alvarez R, Larrosa D, Ramón C, Pascual J. Increased VIP levels in peripheral blood outside migraine attacks as a potential biomarker of cranial parasympathetic activation in chronic migraine. Cephalalgia. 2015;35(4):310-6. doi: 10.1177/0333102414535111
4. Havanka-Kanniainen H, Tolonen U, Myllylä VV. Cardiovascular reflexes in young migraine patients. Headache. 1986;26(8):420-4. doi: 10.1111/j.1526-4610.1986.hed2608420.x
5. Yakinci C, Mungen B, Er H, Durmaz Y, Karabiber H. Autonomic nervous system function in childhood migraine. Pediatr Int. 1999;41(5):529-33. doi: 10.1046/j.1442-200x.1999.01101.x
6. Ebinger F, Kruse M, Just U, Rating D. Cardiorespiratory regulation in migraine. Results in children and adolescents and review of the literature. Cephalalgia. 2006;26(3):295-309. doi: 10.1111/j.1468-2982.2005.01039.x
7. Torun E, Gursoy E, Guler S, Kolukisa M, Tatli B. Characteristic features of migraine in schoolchildren and adolescents and its relationship with autonomic nervous system disorders. Neuropediatrics. 2013;44(5):252-6. doi: 10.1055/s-0033-1347934
8. Rabner J, Caruso A, Zurakowski D, Lazdowsky L, LeBel A. Autonomic dysfunction in pediatric patients with headache: migraine versus tension-type headache. Clin Auton Res. 2016;26(6):455-9. doi: 10.1007/s10286-016-0385-3
9. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J. 1996;17(3):354-81. doi: 10.1161/01.CIR.93.5.1043
10. Olesen J, Steiner TJ. The international classification of headache disorders, 2nd edn (ICDH-II). J Neurol Neurosurg Psychiatry. 2004;75(6):808-11. doi: 10.1136/jnnp.2003.031286
11. Hershey AD, Powers SW, Vockell AL, LeCates S, Kabbouche MA. PedMIDAS: Development of a questionnaire to assess disability of migraines in children. Neurology. 2001;57(11):2034-9. doi: 10.1212/WNL.57.11.2034
12. Pogacnik T, Sega S, Pecnik B, Kiauta T. Autonomic function testing in patients with migraine. Headache. 1993;33(10):545-50. doi: 10.1111/j.1526-4610.1993.hed3310545.x
13. Cortelli P, Pierangeli G, Parchi P, Contin M, Baruzzi A, Lugaresi E. Autonomic nervous system function in migraine without aura. Headache. 1991;31(7):457-62. doi: 10.1111/j.1526-4610.1991.hed3107457.x
14. Marucco E, Lisicki M, Magis D. Electrophysiological characteristics of the migraine brain: current knowledge and perspectives. Curr Med Chem. 2019;26(34):6222-35. doi: 10.2174/0929867325666180627130811
15. Bánk J, Bense E, Király C. The blink reflex in migraine. Cephalalgia. 1992;12(5):289-92. doi: 10.1046/j.1468-2982.1992.1205289.x

16. Avramidis TG, Podikoglou DG, Anastasopoulos IE, Koutroumanidis MA, Papadimitriou AL. Blink reflex in migraine and tension-type headache. Headache. 1998;38(9):691-6. doi: 10.1046/j.1526-4610.1998.3809691.x
17. Yildirim G, Sayin R, Cögen EE, Odabas FO, Tombul T. Randomised, controlled blink reflex in patients with migraine and tension type headache. J Pak Med Assoc. 2011;61(10):978-82. https://pubmed.ncbi.nlm.nih.gov/22356030/
18. Gutrecht JA. Sympathetic skin response. J Clin Neurophysiol. 1994;11(5):519-24. doi: 10.1097/00004691-199409000-00006
19. Yildiz SK, Yildiz N, Korkmaz B, Altunrende B, Gezici AR, Alkoy S. Sympathetic skin responses from frontal region in migraine headache: a pilot study. Cephalalgia. 2008;28(7):696-704. doi: 10.1111/j.1468-2982.2008.01574.x
20. Mosek A, Novak V, Opfer-Gehrking TL, Swanson JW, Low PA. Autonomic dysfunction in migraineurs. Headache. 1999;39(2):108-17. doi: 10.1046/j.1526-4610.1999.3902108.x
21. Gelfand AA, Reider AC, Goadsby PJ. Cranial autonomic symptoms in pediatric migraine are the rule, not the exception. Neurology. 2013;81(5):431-6. doi: 10.1212/WNL.0b013e31829d872a
22. Shechter A, Stewart WF, Silberstein SD, Lipton RB. Migraine and autonomic nervous system function: a population-based, case-control study. Neurology. 2002;58(3):422-7. doi: 10.1212/wnl.58.3.422.
23. Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. Headache. 2004;44(1):53-64. doi: 10.1111/j.1526-4610.2004.04011.x
24. Havanka-Kanniainen H, Tolonen U, Myllylä VV. Autonomic dysfunction in adult migraineurs. Headache. 1986;26(8):425-30. doi: 10.1111/j.1526-4610.1986.hed2608425.x
25. Mosek A, Novak V, Opfer-Gehrking TL, Swanson JW, Low PA. Autonomic dysfunction in migraineurs. Headache. 1999;39(2):108-17. doi: 10.1046/j.1526-4610.1999.3902108.x
26. Yerdelen D, Acil T, Goksel B, Karatas M. Heart rate recovery in migraine and tension-type headache. Headache. 2008;48(2):221-5. doi: 10.1111/j.1526-4610.2007.00994.x
27. Cortelli P, de Carolis P, Sturani A, Ligabue A, Lugaresi A, Agati R, et al. Cardiovascular and biochemical assessment in migraine patients submitted to tilt test. Funct Neurol. 1986;1(3):285-90. https://pubmed.ncbi.nlm.nih.gov/3609861/
28. Mikamo K, Takeshima T, Takahashi K. Cardiovascular sympathetic hypofunction in muscle contraction headache and migraine. Headache. 1989;29(2):86-9. doi: 10.1111/j.1526-4610.1989.hed2902086.x
29. Gotoh F, Komatsumoto S, Araki N, Gomi S. Noradrenergic nervous activity in migraine. Arch Neurol. 1984;41(9):951-5. doi: 10.1001/archneur.1984.04050200057018