

## Sympathetic skin responses in migraineurs

### *Migrenlilerdeki sempatik deri cevapları*

Aysel Milanlıođlu, Temel Tombul, Refah Sayın

*Yüzüncü Yıl University, Department of Neurology, Van, Türkiye*

#### ABSTRACT

**Objectives:** The aim of this study was to compare the sympathetic nerve system profile of migraineurs during the headache-free periods to a group of normal subjects based on sympathetic skin response.

**Materials and methods:** 82 patients with migraine (20 migraine with aura and 62 without aura) and 35 healthy volunteers who are age-and sex-matched patients with migraine selected randomly from the hospital personnel as a control group were enrolled in the study. Patients reporting at least one of the autonomic symptoms during the attack periods regularly were considered migraineurs with having autonomic symptoms. Sympathetic skin response test was applied on both sides of the upper and lower limbs of all subjects.

**Results:** There were no subjects whose responses were absent for both right and left sides of upper and lower limbs. Patients with migraine had significantly longer sympathetic skin response latency than the control group. There was no significant difference between the mean latency and amplitude results in the migraine patients with and without aura or autonomic dysfunction or not ( $P>0.05$ ). Additionally, sympathetic skin response amplitude values were not significantly different between the three groups ( $P>0.05$ ).

**Conclusions:** Migraine patients exhibited significantly longer sympathetic skin response latency than controls, leading to suggest that sympathetic hypofunction occurred in patients with migraine during the headache-free period. *J Clin Exp Invest 2011; 2(1):16 -21*

**Key words:** Sympathetic skin response, migraine, autonomic nerve system

#### ÖZET

**Amaç:** Bu çalışmanın amacı sempatik deri yanıtını kullanarak baş ağrısız dönemdeki migren hastaları ile kontrol grubundaki bireylerin sempatik sinir sistemi profilinin karşılaştırılmasıdır.

**Gereç ve yöntem:** 82 migren hastası (20 auralı ve 62 aurasız) ile hastane personellerinden yaş ve cinsiyetle uyumlu olarak rastgele seçilen 35 gönüllünün olduğu kontrol grubu çalışmaya dahil edildi. Baş ağrısı ataklarına düzenli olarak en az bir otonomik semptomun eşlik ettiği hastalar otonomik semptomların olduğu hastalar olarak nitelendirildi. Tüm bireylere hem üst hem de alt ekstremitelerde sempatik deri cevabı testi uygulandı.

**Bulgular:** Hem sağ hem de sol üst ve alt ekstremitelerden elde edilen cevabın olmadığı hiçbir birey yoktu. Migrenli hastaların sempatik deri cevabı latansları kontrol grubuna göre anlamlı derecede daha uzundu. Ortalama latans ve amplitüd değerleri auralı-aurasız veya otonomik disfonksiyonun olduğu veya olmadığı hastalar arasında farklı değildi ( $P>0,05$ ). Ek olarak sempatik deri cevabı amplitüd değerleri de 3 grup arasında anlamlı derecede farklılık göstermedi ( $P>0,05$ ).

**Sonuç:** Migrenliler, baş ağrısız dönemde daha uzun sempatik deri cevabı latansına sahiptir ki bu durum migrenlilerde kontrollere göre sempatik hipofonksiyonun olduğunu ortaya koymaktadır. *Klin Deney Ar Derg 2011; 2(1): 16-21*

**Anahtar kelimeler:** Sempatik deri cevabı, migren, otonomik sinir sistemi

**Yazışma Adresi /Correspondence:** Dr. Aysel Milanlıođlu, Yüzüncüyıl University,  
Department of Neurology, Van-Türkiye E-mail: ayselmilanlioglu@yahoo.com

Geliş Tarihi / Received: 08.01.2010, Kabul Tarihi / Accepted: 13.01.2010

Copyright © Klinik ve Deneysel Arařtırmalar Dergisi 2011, Her hakkı saklıdır / All rights reserved

## INTRODUCTION

The past two decades have brought definite advances in our understanding of the pathophysiology of migraine. Examination of autonomic processes seems reasonable because of the well-known autonomic symptoms that occur during migraine attack and because of the various structural and functional connections between the central autonomic network and pain-processing systems. Thus, the possible significance of autonomic processes in migraineurs is a matter of discussion in experimental studies.<sup>1,2</sup>

In laboratory evaluation of the sympathetic nervous system (SNS) in migraineurs, various procedures including superior ophthalmic nerve stimulation by soapy or saline eye drops, pupillary functions, thermographic asymmetry, measurement of frontal blood flow, sweat estimation on frontal region, heart rate variability and eventually sympathetic skin response (SSR) were well developed. Among these procedures, SSR is an easy and non-invasive test to analyse SNS function.<sup>3</sup>

SSR reflects sympathetic cholinergic sudomotor function which induces changes in skin resistance to electrical conduction. SSR was first noted Tarchanoff who assigned the potential change to modification in the secretory activity of sweat glands independent of vascular reaction and Shahani et al.<sup>4</sup> first described applications of SSR in clinical neurophysiology.

The objective of this study was to compare SNS profile of migraineurs during the headache-free periods to a group of normal subjects based on SSR.

## MATERIALS AND METHODS

### Subjects

82 patients with migraine (20 migraine with aura and 62 without aura) diagnosed according to International Headache Society 2004 criteria were enrolled in the study.<sup>5</sup> Patient group were chosen

from the patients who came to the outpatient headache clinic of Yüzüncü Yıl University between December 2007 and December 2008. Thirty-five healthy volunteers who are age- and sex-matched patients with migraine selected randomly from the hospital personnel and took part as a control group in the study.

Exclusion criteria were any prophylactic headache treatment or any other regular medication during the last half-year, the presence of a headache subtype different from migraine or the presence of other diseases possibly affecting autonomic functions (e.g. any chronic pain disorder, thyroid dysfunction, anaemia, electrolyte imbalance, endocrinological, cardiovascular or other neurological diseases).

The evaluation of subjects medical condition was based full medical history and complete physical and neurological examinations. All patients were studied during the headache-free period. Informed consent was obtained from each subject and the study protocol was approved by the local ethics committee. Patients with migraine were asked whether having autonomic symptoms like diaphoresis, diarrhea, cutaneous vasoconstriction (pallor), cutaneous vasodilatation (flushing), syncope or syncope like episode, constipation, palpitation, diuresis, sensation of chilly and coldness in their migraine attacks of headache or not. Patients reporting at least one of the above symptoms during the attack periods regularly were considered migraineurs with having autonomic symptoms, while remaining were considered migraineurs without having autonomic symptoms. Nausea, vomiting, photophobia and phonophobia are frequently seen in migraine headache, so these symptoms were excluded from the study. 50 patients (61.0%) mentioned having at least one of these symptoms in their attacks regularly.

We assigned the patients into five groups according to the side of headache: patients having always right-sided headache, patients having al-

ways left-sided headache, patients predominantly having right-sided headache (having sometimes left-sided), patients predominantly having left-sided headache (having sometimes right-sided) and mixed type (sometimes having right-sided sometimes left-sided). Of these 82 migraine patients, 4 patients (4.9%) reported having always right, 4 patients (4.9%) reported having always left sided headache; 19 patients (23.2%) reported having predominantly right-sided; 13 patients (15.9%) reported having predominantly left-sided and 42 patients (51.2%) reported having mixed type headache during their migraine attacks.

### SSR recordings

SSR recordings were taken in a comfortable supine position in a quiet, well-lit air-conditioned room maintained at  $24\pm 1^{\circ}\text{C}$ . The skin temperature of each patient was  $>32^{\circ}\text{C}$ . All the subjects were instructed not to breathe deeply and fastly, cough, talk or move their head and limbs during the procedure. SSR recordings were performed with a Medelec Synergy electromyograph. The response was recorded using Ag-AgCl surface electrodes. The frequency bandpass was 0.2-100 Hz. The sweep duration was 5 s and the gain was  $500\ \mu\text{V}$  per division.

In the upper limb, the active electrode was placed on the palm, the reference electrode was placed on the dorsum of the hand. The ground electrode was placed near by. In the lower limb, the active electrode was on the sole while the reference electrode was on the dorsum of the foot. The electrical stimulation was applied over the opposite median nerve for the upper limb and posterior tibial nerve for the lower limb. We initially 5 mA intensity level with 0.1 ms duration and increased the level by 5 mA until reliable SSRs were recorded. The latency was measured from the onset of the stimulus artefact to the first deflection of the signal baseline and the amplitude was measured peak to peak.<sup>6</sup> The stimuli were delivered at irregular intervals to avoid the SSR habituation that will

lead to decrease of the response amplitude. At least successive five stimuli were delivered to each subject to make sure of the response and the mean latencies and amplitudes of responses were calculated. Subjects who showed no response on either side after receiving 10 consecutive electrical stimuli of an intensity of 100 mA were considered unresponsive. All subjects had SSRs on both sides of the upper and lower limbs.

### Statistical analysis

Statistical evaluation of the data was performed using SPSS 15.0 for Windows (Statistical Package of Social Sciences; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean values  $\pm$  standard deviation. Chi-square test was used for categorical variables. One-way analysis of variance (ANOVA) was used to compare differences among groups, followed by Bonferroni test. P-value  $<0.05$  was considered to be statistically significant.

## RESULTS

The sample of migraineurs consisted of 61 females (74.4%) and 21 males (25.6%). Inclusion criteria were patients with 20-53 years of age who had suffered from migraine for at least 1 year. Headache frequency ranged between one to five per month (mean frequency  $2.63\pm 1.29$  per month), and the mean time of headache was  $10.04\pm 7.26$  years from first episode.

In the present study, there were no subjects whose responses were absent for both right and left sides of upper and lower limbs. SSR latency and amplitude recorded from left and right sides were not significantly different ( $P>0.05$  for both). The mean latency and amplitude values of the patients with migraine and control group which were recorded separately from four limbs were shown in Table 1.

Patients with migraine had significantly longer latency than the control group but the mean ampli-

tude values of the responses were not significantly different between two groups.

There was no significant difference between the mean SSR latency and amplitude results in the migraine patients with and without aura ( $P>0.05$ ).

Mean latency and amplitude values of the responses were recorded from four different recording locations in migraineurs with and without autonomic symptoms in their headache attack periods and controls were summarized in Table 2.

SSR latencies of the migraineurs with and without autonomic symptoms in their headache attack periods were significantly longer than the controls except for left lower responses.

The mean right and left upper SSR latencies of the migraineurs with autonomic symptoms in their headache attack were longer than the mean latencies of the migraineurs without autonomic symptoms in their headache attack, but this difference was not statistically significant. Additionally, SSR amplitude values were not significantly different between the three groups ( $P>0.05$ ).

There was no correlation between age, sex, duration of disease, attack frequency per month, attack duration, number of autonomic symptoms accompanying headache attack, headache side and SSR latency and amplitude results.

**Table 1:** Comparison of mean latency and amplitude values of the responses recorded from right and left sides of upper and lower limbs in migraine patients and control group (Mean±Standard deviation).

		Migraine patients (n=35)	Control group (n=82)	P value
Latency (ms)	Right upper	1383.00±117.79	1277.57±137.55	<0.001
	Left upper	1412.88±124.80	1292.57±112.28	<0.001
	Right lower	2208.48±230.43	2068.51±184.25	0.002
	Left lower	2172.11±297.86	2061.17±165.45	0.041
Amplitude (µV)	Right upper	884.18±447.21	845.14±224.49	NS
	Left upper	1031.94±1231.92	848.49±238.82	NS
	Right lower	897.61±437.49	812.29±284.47	NS
	Left lower	930.65±397.19	794.60±268.53	NS

NS: Not significant

**Table 2.** The mean latencies and amplitudes of sympathetic skin responses in migraine patients with and without autonomic symptoms and those of control group.

		Control group	Migraineurs with autonomic symptoms (n=50)	Migraineurs without autonomic symptoms (n=32)	F	P value
Latency (ms)	Right upper	1277.57±137.55	1389.50±116.53	1378.84±119.58	8.877	<0.001
	Left upper	1292.57±112.28	1416.75±121.10	1410.40±128.27	12.005	<0.001
	Right lower	2068.51±184.25	2165.56±178.17	2235.94±256.35	6.140	0.003
	Left lower	2061.17±165.45	2152.13±160.87	2184.90±360.37	2.273	NS
Amplitude (µV)	Right upper	845.14±224.49	989.22±569.58	816.96±336.96	2.027	NS
	Left upper	848.49±238.82	1033.13±599.91	1031.18±1510.32	0.377	NS
	Right lower	812.29±284.47	990.78±542.22	837.98±347.98	2.031	NS
	Left lower	894.60±268.53	1039.16±482.56	861.20±317.58	2.181	NS

NS: Not significant

## DISCUSSION

Autonomic function in patients with migraine has been investigated in several studies, and most have analyzed cardiovascular reflex mechanisms, biochemical changes and pupillometry.

A wide variety of experimental data indicate that dysfunction of both sympathetic and parasympathetic nervous system exists in migraine sufferers. However, it has been reported that migraine is associated with sympathetic and parasympathetic hypofunction, hyperfunction or sympathetic instability.<sup>7</sup>

SSR is used commonly for the assessment of SNS function because of its easy, noninvasive application and reliable results. SSR is thought to originate from synchronized activation of sweat glands in response to a volley of discharges by efferent sympathetic nerve fibers. The final efferent pathway begins within the thoracolumbar cord and is mediated by the unmyelinated postganglionic sympathetic fibers.<sup>8</sup>

In our study, there was no non-responder subject both in the patient and control groups. Also, the migraine patients exhibited significantly longer SSR latency than controls, leading to suggest that sympathetic hypofunction occurred in patients with migraine during the headache-free period. To date, in the majority of the studies, sympathetic hypofunction was determined in migraine patients which are demonstrated like in our study. Unfortunately, we could not introduce this result in subgroups; aura-without aura and with autonomic dysfunction and without.

Drummond has suggested that this sympathetic deficit could be due to the compression of the sympathetic plexus surrounding the internal carotid artery in the carotid canal and also he has supported this suggestion by the finding of symmetrical sweating and flushing in the cheeks of unilateral migraine sufferers.<sup>9</sup>

According to the findings of the current studies, it seems sensible to consider that there is a localized sympathetic deficit on the side of the headache but we could not show this finding. If we had studied with unilateral patients during attack period perhaps we could have displayed unilateral sympathetic hypofunction in these patients. Therefore, this study has limitations namely it does not allow monitoring all the changes occurring in SSR in one cycle of headache composed attack and post-attack periods. Secondly, one of the important point is that even though the SSR test is reliable, some environmental factors and variables can easily affect confidence of this test.

Gruzelier et al.<sup>10</sup> have reported that left-sided pain is associated with under-responsiveness and fast habituation, right-sided pain with over-responsiveness and slow habituation in autonomic responsiveness in unilateral migraine sufferers. Avnon et al.<sup>11</sup> have measured the trigemino-parasympathetic reflex in unilateral migraine patients and reported that left-sided migraineurs have higher parasympathetic vasodilation than right-sided in headache-free period. They mentioned that the autonomic control of brain is asymmetrical, the left hemisphere affecting predominantly parasympathetic function and the right hemisphere affecting predominantly sympathetic function. These results lead us to consider that the patients with unilateral headache should be investigated separately in the future.

Consequently, SSR is a new, noninvasive method using for the evaluation of SNS function in different diseases surely.

## REFERENCES

1. Pietrobon D, Striessnig J. Neurobiology of migraine. *Nat Rev Neurosci* 2003; 4:386-398.
2. Benarroch EE. Pain-autonomic interactions: a selective review. *Clin Auton Res* 2001; 11:343-349.
3. Gutrecht JA. Sympathetic skin response. *J Clin Neurosci* 1994;11:519-524.

4. Vetrugno R, Liguori R, Cortelli P, Montagna P. Sympathetic skin response: Basic mechanisms and clinical applications. *Clin Auton Res* 2003;13:256-270.
5. Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. *Headache* 2004; 44:53-64.
6. Atasoy HT, Atasoy N, Unal AE, Sumer M. Sympathetic skin response in migraineurs and patients with medication overuse headache. *Headache* 2004;44:305-310.
7. Yakinci C, Mungen B, Er H, Durmaz Y, Karabiber H. Autonomic nervous system function in childhood migraine. *Pediatr Int* 1999;41:529-533.
8. Kanzato N, Komine Y, Fukiyama K. Sympathetic skin responses of the hand in normal subjects: shorter latency at distal phalanx. *Electroenceph Clin Neurophysiol* 1997;105:165-170.
9. Drummond PD. Effects of body heating and mental arithmetic on facial sweating and blood flow in unilateral migraine headache. *Psychophysiology* 1991;28:172-176.
10. Gruzelier JH, Nicolaou T, Connolly JF, Peatfield RC, Davies PT, Clifford-Rose F. Laterality of pain in migraine distinguished by interictal rates of habituation of electrodermal responses to visual and auditory stimuli. *J Neurol Neurosurg Psychiatry* 1987;50:416-422.
11. Avnon Y, Nitzan M, Sprecher E, Rogowski Z, Yarnitsky D. Autonomic asymmetry in migraine: augmented parasympathetic activation in left unilateral migraineurs. *Brain* 2004;127:2099-2108.