

# Autonomic Symptoms in Migraineurs: Are They of Clinical Importance

## Migrenlilerde Otonomik Semptomlar: Klinik İçin Önemli midir? Importance

Aysel Milanlıoğlu, Temel Tombul, Refah Sayın, Ömer Faruk Odabaş, Musa Şahin\*

Yuzuncu Yıl University, Faculty of Medicine, Department of Neurology, Van, Turkey

\*Yuzuncu Yıl University, Faculty of Medicine, Department of Cardiology, Van, Turkey

### Abstract

**Aim:** The aim of this study was to evaluate the presence of autonomic symptoms in migraine patients with and without aura and to investigate whether there is an association between expression of autonomic symptoms and disease duration, headache side, attack duration and frequency.

**Methods:** The study sample comprised 82 subjects in headache-free phase including 20 migraine with aura patients and 62 - without aura; 61 were females (74.39%) and 21 were males (25.61%). The mean headache frequency was 2.63±1.29 per month and the mean duration of headache occurrence was 10.04±7.26 years from the first episode.

The subjects were asked whether or not they had autonomic symptoms like diaphoresis, diarrhea, eyelid oedema, pallor, flushing, syncope or syncope-like episode, constipation, palpitation, diuresis, blurred vision, sensation of chills and coldness during each migraine headache.

**Results:** Of all 82 migraine patients, 50 (60.98%) experienced at least one of the autonomic symptoms during the attack periods. The most common symptom was flushing (39.2%). Among the autonomic symptoms, syncope or syncope-like episode was significantly more in patients without aura compared to those with aura ( $p<0.05$ ). In this study, patients who experienced autonomic symptoms during their headache attack had statistically significantly higher attack frequency ( $p=0.019$ ).

**Conclusion:** This result indicate that migraine patients with autonomic nervous system involvement have more frequent headaches, therefore these patients should be particularly and cautiously investigated. (*The Medical Bulletin of Haseki 2011; 49: 62-6*)

**Key Words:** Migraineurs, autonomic symptoms, autonomic nervous system

### Özet

**Amaç:** Bu çalışmanın amacı aural ve aurasız migrenli hastaların ataklarına eşlik eden otonomik fonksiyonların değerlendirilmesi ve bu semptomların baş ağrısı tarafı, sıklığı ve süresi ile ilişkili olup olmadığının gösterilmesidir.

**Yöntemler:** Çalışmada 20 aural ve 62 aurasız 82 hasta baş ağrısız dönemde değerlendirildi. Migrenlilerden 61 hasta (%74.39) bayanlardan 21 hasta (%25.61) ise erkeklerden oluşmaktaydı. Ortalama aylık baş ağrısı sıklığı 2.63±1.29 iken ilk epizottan sonraki baş ağrısı süresi 10.04±7.26 yıldır.

Hastalara her baş ağrısı ataklarında terleme, diyare, göz kapağı ödemi, solukluk, flushing, senkop veya senkop benzeri epizot, kabızlık, çarpıntı, diürez, bulanık görme, titreme ve soğukluk hissi gibi otonomik semptomlara sahip olup olmadıkları soruldu.

**Bulgular:** Hastaların %60.98'i (n=50) ataklarına en az bir otonom fonksiyonun eşlik ettiğini ifade etti. Otonomik semptomlar arasında en sık olanı flushing olarak bulundu (%39.2). Senkop veya senkop benzeri epizotun aurasız migrenli hastalara istatistiksel olarak daha fazla eşlik ettiği görüldü ( $p<0.05$ ). Ataklarına otonomik semptomların eşlik ettiği hastaların atak sıklıklarının eşlik etmeyen hasta grubuna göre anlamlı derecede daha fazla olması dikkat çekiciydi ( $p=0.019$ ).

**Sonuç:** Bu sonuç otonom sinir sistemi ve migren arasındaki bu ilişkinin daha dikkatli ve daha ayrıntılı değerlendirilmesi gerekliliğini ortaya koymaktadır. (*Haseki Tıp Bülteni 2011; 49: 62-6*)

**Anahtar Kelimeler:** Migrenliler, otonomik semptomlar, otonom sinir sistemi

### Introduction

Migraine is a disorder with multiple manifestations which affects the circulation, gastrointestinal tract and central nervous system (1). Despite the increased knowledge about migraine

that has accumulated in recent years, the pathophysiological basis of this disease is not still entirely known.

It is assumed that the autonomic nervous system (ANS) is involved in the pathophysiological mechanism of migraine, because autonomic symptoms are common during acute

**Address for Correspondence/Yazışma Adresi:** Aysel Milanlıoğlu

Yuzuncu Yıl University, Neurology, Van, Turkey

Tel.: +90 432 216 47 11 Fax: +90 432 210 17 46 E-posta: ayselmilanlioglu@yahoo.com

**Geliş Tarihi/Received:** 01 Aralık 2010 **Kabul Tarihi/Accepted:** 24 Şubat 2011

Haseki Tıp Bülteni,  
Galenos Yayınevi tarafından basılmıştır.

*The Medical Bulletin of Haseki Training and Research Hospital,  
published by Galenos Publishing.*

migraine headaches (2). Autonomic symptoms including nausea, vomiting, photophobia, phonophobia, abnormal pupillary reaction, diarrhea, cutaneous vasoconstriction (pallor), vasodilatation (flushing), piloerection and diaphoresis frequently occur in migraine patients (3).

Clinical practice and several studies have shown an overlap of autonomic symptoms in cluster headache and migraine. The clinically observed good response to triptans in this disease may be associated with large-scale recruitment of peripheral neurovascular 5-HT 1B/1D receptors specifically blocking plasma extravasation from blood vessels in the dura mater (4). This finding also supports the involvement of ANS in migraine disease.

The aim of this study was to evaluate the presence of autonomic symptoms during the headache phase in migraine patients and to assess whether the expression of autonomic symptoms is more pronounced in migraine patient with aura compared those without aura. Moreover, we tried to identify whether headache side, attack frequency or duration in migraine patients with autonomic symptoms are different compared to those parameters in non-autonomic migraine patients.

## Materials and Methods

82 patients with migraine (20 migraine with aura and 62 without aura) diagnosed according to the International Headache Society 2004 criteria were enrolled in the study (5). The patient group was chosen randomly from the patients who attended the headache clinic between December 2007 and 2008. The sample of migraineurs consisted of 61 females (74.39%) and 21 males (25.61%). Patients aged 20-53 years who had suffered from migraine for at least 1 year were included in the study. Headache frequency ranged between one to five per month (mean frequency:  $2.63 \pm 1.29$  per month), and the mean duration of headache occurrence was  $10.04 \pm 7.26$  years from the first episode.

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

The evaluation of subjects' medical condition was based on full medical history and complete physical and neurological examination. 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. The subjects

were asked whether or not they had autonomic symptoms like diaphoresis, diarrhea, eyelid oedema, cutaneous vasoconstriction (pallor), cutaneous vasodilatation (flushing), syncope or syncope-like episode, constipation, palpitation, diuresis, bilateral blurred vision, sensation of chills and coldness during each migraine attack of headache. These symptoms were not suggesting a different subtype of cephalalgias. Patients who reported at least one of the above symptoms during the attack period were considered migraineurs having autonomic symptoms, while the remaining patients were considered migraineurs without autonomic symptoms. Nausea, vomiting, photophobia and phonophobia are frequently seen during migraine headache, so these symptoms were excluded from the study. 50 patients (60.98%) reported that they regularly experienced at least one of these symptoms during their attacks.

We assigned the patients into five groups according to the side of headache: (i) patients having always right-sided headache, (ii) patients having always left-sided headache, (iii) patients having predominantly right-sided headache (having sometimes left-sided), (iv) patients having predominantly left-sided headache (having sometimes right-sided) and (v) mixed type (sometimes having right-sided sometimes left-sided). Of the 82 migraine patients, 4 patients (4.88%) reported having always right, 4 patients (4.88%) reported having always left-sided headache; 19 patients (23.17%) reported having predominantly right-sided; 13 patients (15.85%) reported having predominantly left-sided and 42 patients (51.22%) reported having mixed type headache during their migraine attack.

## Statistical Analyses

Statistical evaluation of the data was performed using SPSS 15.0 for Windows (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean values  $\pm$  standard deviation. Data from migraine patients with aura-without aura and having-not having autonomic symptoms were compared using the chi-square and Student's t-test. A p-value of less than 0.05 was considered statistically significant.

## Results

Gender, age, duration of disease, location and frequency of headache, and numbers of autonomic symptoms were similar in both migraineur populations-with aura and without aura. However, patients without aura had significantly longer attack duration than those with aura (the mean of the attack duration was  $20.10 \pm 11.43$  vs.  $12.00 \pm 5.62$  hours;  $p=0.003$ ). Test results are given in Table 1.

**Table 1.** Comparison of clinical and demographic characteristics in migraine patients with and without aura

	Migraine Patients Without Aura	Migraine Patients With Aura	P-value
Males (n, %)	15 (18.29%)	6 (7.32%)	0.605
Females (n, %)	47 (57.32%)	14 (17.07%)	
Age (mean, years)	35.23±8.50	32.60±8.60	0.234
Duration of migraine (mean, years)	10.71±7.38	7.95±6.59	0.140
Frequency of migraine (per month)	2.71±1.31	2.40 ±1.23	0.354
Duration of headache attack (mean, hour)	20.10±11.43	12.00±5.62	0.003
Always right-sided headache	2 (2.44%)	2 (2.44%)	
Always left-sided headache	4 (4.88%)	0 (.00)	
Predominantly right-sided headache	13 (15.85%)	6 (7.32%)	0.065
Predominantly left-sided headache	8 (9.76%)	5 (6.10%)	
Mixed type	35 (42.68%)	7 (8.54%)	
Numbers of autonomic symptoms	2.48±2.23	1.95±1.90	0.303

**Table 2.** Distribution number of autonomic symptoms in patients with migraine

	n=193	(%)
Diaphoresis	25	30.49
Palpitation	28	34.15
Sensation of chills	25	30.49
Cutaneous vasodilatation (flushing)	32	39.02
Constipation	0	0.00
Diarrhea	2	2.44
Diuresis	6	7.32
Blurred vision	2	2.44
Cutaneous vasoconstriction (pallor)	28	34.15
Sensation of coldness	10	12.20
Eyelid oedema	8	9.76
Syncope or syncope-like episode	27	32.93

The most common autonomic symptom which patients experienced was bilateral flushing of the face (39.02%). Distribution number of autonomic symptoms that patients had during migraine attacks is shown in Table 2.

Migraine patients without aura had significantly more often syncope or syncope-like episode as autonomic symptoms during their headache attack than the patients with aura (38.71% vs. 15.00%;  $p < 0.05$ ).

There were no significant differences in baseline demographic and disease characteristics between migraine patients with and without autonomic symptoms, except for frequency of attacks per month. Migraine patients with autonomic symptoms experienced significantly higher attack frequency compared with the patients without autonomic symptoms (mean frequency:  $2.90 \pm 1.28$  vs.  $2.22 \pm 1.21$  per month;  $p = 0.019$ ). Results are summarized in Table 3.

## Discussion

The major findings of the present study were that significant proportion of migraine patients (60.98%) experienced autonomic symptoms during the headache attacks and additionally, that migraine patients with autonomic symptoms had significantly more frequent headache attacks compared to those who had no autonomic symptoms. These results display a possible role of ANS involvement in the pathophysiology of migraine. Our findings indicate that the frequency of attacks increases in patients who experience autonomic symptoms, therefore, this condition must be investigated particularly.

Headache specialists are acquainted with the occurrence in clinical practice of autonomic symptoms in patients with migraine which seem to be much more common than generally assumed. It is possible that the development of autonomic symptoms might include functional alterations in the hypothalamic or brainstem circuits and also in the trigeminovascular system. In the trigeminovascular system, there are functional connections between trigeminal affer-

**Table 3.** Comparison of clinical and demographic characteristics in migraine patients with and without autonomic symptoms

	Patients without autonomic symptoms	Patients with autonomic symptoms	P-value
Males (n, %)	10 (31.25%)	11 (22.00%)	0.349
Females (n, %)	22 (68.75%)	39 (78.00%)	
Age (mean, years)	34.28±7.97	34.78±8.97	0.798
Duration of migraine (mean, years)	9.63±7.49	10.30±7.17	0.684
Frequency of migraine (per month)	2.22±1.21	2.90±1.28	0.019
Duration of headache attack (mean, hour)	17.31±9.08	18.64±11.92	0.592
Always right-sided headache	3 (9.38%)	1 (2.00%)	
Always left-sided headache	1 (3.13%)	3 (6.00%)	
Predominantly right-sided headache	5 (15.63%)	14 (28.00%)	0.303
Predominantly left-sided headache	4 (12.50%)	9 (18.00%)	
Mixed type	19 (59.38%)	23 (46.00%)	
Presence of aura	9 (28.13%)	11 (22.00%)	0.529

ences and parasympathetic efferences. Trigeminal autonomic reflex is most strongly expressed in the pathophysiological origin (6).

Studies investigating migraine and ANS function have shown that there is an association between migraine and ANS. It has been suggested that these inconsistent findings may be explained by varied autonomic dysregulation, probably resulting from imbalance between the sympathetic and parasympathetic nervous systems (7).

In our study, we aimed to design and validate a clinical instrument able to noninvasively approximate the diagnosis of clinical autonomic dysfunction. Question-based diagnostic tools were utilized to determine whether or not the subject had autonomic dysfunction. One of the limitations of the present study was that some symptoms were quite non-specific and mainly subjective by nature.

We concluded that the duration of attack was prolonged in migraine patients without aura than in those with aura. This result may be explained by the fact that patients suffering from migraine without aura much more frequently had involvement of the ANS. However, we could not support this finding with the evaluation of other parameters. Therefore, further studies with large patient groups are needed to investigate whether or not the presence or absence of aura influences the autonomic responses in migraine patients.

Although there was no significant difference between patients with aura and those without aura regarding the number of accompanying autonomic symptoms during the headache attack, syncope or syncope-like episode was reported significantly more often by the patients without aura (38.71%).

Various types of balance disorders, such as rotational vertigo, positional vertigo, dizziness, syncope, syncope-like episode, intolerance to head movement, and other less common findings, have been detected during headache attack in migraine patients (8,9,10).

The association of migraine with syncope has been previously highlighted in the CAMERA study, where syncope was more prominent in adults with migraine than in controls. The lifetime prevalence of syncope was 41% in all participants and was greater in women (45% vs. 32%;  $p=0.02$ ). Compared with control subjects, migraineurs had higher lifetime prevalence of syncope (46% vs. 31%;  $p=0.001$ ), syncope frequency (five or more attacks) (13% vs. 5%;  $p=0.02$ ), and orthostatic intolerance (32% vs. 12%;  $p<0.001$ ). However, there was no association between ANS symptoms and severity of migraine or migraine subtype (11).

In the present study, we investigated also the relationship between headache side and presence or absence of autonomic symptoms in migraine sufferers. However, we could not find any significant association on that basis and it is one of the limitations of our study. Avnon et al. have measured the trigemino-parasympathetic reflex in unilateral migraine patients by the vasodilator response of forehead skin bilaterally, and reported that left-sided migraineurs had higher bilateral parasympathetic vasodilatation and more pronounced bradycardia than the right-sided migraineurs in headache-free intervals. They mentioned that the autonomic control of brain is asymmetrical-the left hemisphere plays a predominant role in the parasympathetic functioning and the right

hemisphere is predominantly responsible for the sympathetic functioning (12). According to all these results we can say that right- and left-sided headache should be evaluated separately in future.

In conclusion, this study demonstrated that autonomic symptoms in patients with migraine are common, but in the past, this issue was widely underestimated. On the other hand, it was observed that migraine patients who had autonomic symptoms accompanying the headache attacks more frequently experienced pain than the non-autonomic group. Therefore, physicians have to pay more attention to understand the association between migraine and ANS.

Further studies with larger groups are needed to unravel the pathophysiological mechanism associated with migraine and the accompanying autonomic symptoms.

## References

1. Campbell JK. Manifestations of migraine. *Neurol Clin* 1990;8:841-55.
2. Welch KM. Migraine. A biobehavioral disorder. *Arch Neurol* 1987;44:323-7.
3. Rose FC. Handbook of clinical neurology. In Rose FC, ed. *Headache: Definitions and classifications*. New York: Elsevier Science, 1986: 4.
4. Goadsby PJ, Lipton RB. A review of paroxysmal hemicranias, SUNCT syndrome and other short lasting headaches with autonomic features, including new cases. *Brain* 1997;120:193-209.
5. Headache Classification Subcommittee of the International Headache Society. The International classification of headache disorders. *Cephalalgia* 2004;24:1-160.
6. Dora B. Migraine with cranial autonomic features and strict unilaterally. *Cephalalgia* 2003;23:561-2.
7. Shechter A, Stewart WF, Silberstein SD, Lipton RB. Migraine and autonomic nervous system function: a population-based, case-control study. *Neurology* 2002;58:422-7.
8. Kayan A, Hood JD. Neuro-otological manifestations of migraine. *Brain* 1984;107:1123-42.
9. Shepard NT. Differentiation of Menieres disease and migraine associated dizziness: a review. *J Am Acad Audiol* 2006;17:69-80.
10. Vuković V, Plavec D, Galinović I, Lovrenčić-Huzjan A, Budisić M, Demarin V. Prevalence of Vertigo, Dizziness, and Migrainous Vertigo in Patients With Migraine. *Headache* 2007;47:1427-35.
11. Thijs RD, Kruit MC, van Buchem MA, Ferrari MD, Launer LJ, van Dijk JG. Syncope in migraine: the population-based CAMERA study. *Neurology* 2006;66:1034-37.
12. Avnon Y, Nitzan M, Sprecher E, Rogowski Z, Yarnitsky D. Autonomic asymmetry in migraine: augmented parasympathetic activation in left unilateral migraineurs. *Brain* 2004;127:2099-108.