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Cranial Autonomic Features in Migraine and Migrainous Features in Cluster Headache

Migren'de Kraniyal Otonomik Bulgular ve Küme Başağrısında Migrenöz Özellikler

Derya ULUDUZ[1], Semih AYTA[2], Aynur ÖZGE[3], Osman Özgür YALIN[4], Turkish Headache Database Study Group[3], Gülhan ÖREKİCİ TEMEL[5], Bahar TAŞDELEN[5]

[1]Department of Neurology, İstanbul University İstanbul School of Medicine, İstanbul, Turkey
[2]Department of Pediatrics, Child Neurology Unit, Haseki Training and Research Hospital, İstanbul, Turkey
[3]Department of Neurology, Mersin University School of Medicine, Mersin, Turkey
[4]Department of Neurology, İstanbul Training and Research Hospital, İstanbul, Turkey
[5]Department of Biostatistics, Mersin University School of Medicine, Mersin, Turkey

ABSTRACT

Introduction: Limited data about the importance of cranial autonomic features of migraines and migrainous features of cluster headaches are available.

Methods: We enrolled 2955 patients with migraine and 93 patients with cluster headache. We explored the autonomic features, including ptosis, lacrimation, rhinorrhea, facial swelling, conjunctival injection, and pupil changes. The presence of migrainous features, such as nausea, vomiting, photophobia, and phonophobia, in cluster headache patients were noted.

Results: Migraine patients with underlying autonomic symptoms (MwuAS) and those without differed significantly. Unilaterality, periocular localization of headaches provoked by starvation, and history of

abdominal pain significantly increased the risk of MwuAS. The parameters with the highest sensitivity (94.38%) and specificity (99.89%) for the diagnosis of MwuAS were lacrimation, facial swelling, and conjunctival injection.

Conclusion: Migraine and cluster headache are considered two different entities with different pathophysiologies. The assessment of autonomic symptoms is essential, and specialists must consider such an overlap in clinical practice in order to obtain accurate prevalence rates. In particular, lacrimation, conjunctival injection, and facial swelling are widely experienced by migraineurs.

Keywords: Migraine, cluster headache, cranial autonomic symptoms, migrainous features, trigeminovascular system

ÖZ

Amaç: Migren hastalarında bulunan kraniyal otonomik bulgular ve küme başağrısında bulunan migrenöz özellikler ile ilgili bilgilerimiz kısıtlıdır.

Yöntem: Çalışmaya 29955 migren ve 93 küme başağrısı tanılı hasta dahil edildi. Migren hastalarında pitoz, göz yaşarması, rinore, fasyal ödem, konjunktival injeksiyon, ve pupil değişikliklerini içeren otonomik semptomların varlığı incelendi. Ayrıca küme başağrısı tanılı olgularda bulantı, kusma, fotofobi ve fonofobi gibi migrenöz bulguların varlığı kaydedildi.

Bulgular: Otonomik semptom bulunan ve bulunmayan migren hastalarında anlamlı farklılıklar saptandı. Unilateral başağrısı, periokuler lokalizasyon, açlıkla tetiklenme, ve karın ağrısı hikayesi otonom semptomların bulunma riskini anlamlı olarak artırdığı gözlendi. Otonom semptomla-

rın eşlik ettiği migren tanısında en yüksek duyarlılık (%94.38) ve özgünlüğe (%99.89) sahip bulgular lakrimasyon, fasiyal ödem ve konjunktival injeksiyon idi.

Sonuç: Migren ve küme başağrısı klinik ve patofizyolojilik olarak iki farklı antite olarak kabul edilmektedirler. Otonomik semptomların araştırılması tanıda önemlidir ve gerçek prevalanslarının saptanabilmesi için başağrısı uzmanlarının bu birlikteliği günlük pratikte sorgulamaları gerekmektedir. Özellikle lakrimasyon, konjunktival injeksiyon ve fasiyal ödem migren hastaları tarafından sık bildrilen otonom semptomlardır.

Anahtar Kelimeler: Migren, küme başağrısı, kraniyal otonomik semptomlar, migrenöz özellikler, trigeminovaskuler sistem

INTRODUCTION

Migraine, a severe form of headache that affects up to 16% of the adult population, can have a major impact on the quality of life (1). According to limited clinical data, cluster headache (CH) affects 0.1% of adults (2).

The International Headache Society (IHS) definitions make a clear distinction between migraine and CH (3). IHS criteria identify four main features distinguishing CH from migraine: unilaterality of short-duration attacks of pain, periodicity of the syndrome, accompanying ipsilateral autonomic features, and restlessness during pain. Unilateral cranial autonomic symptoms (uAS) are typical features of trigem-

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inal–autonomic cephalgia (4). uAS symptoms have also been reported in some patients with migraine accompanying other features of migraine attacks. On the other hand, migrainous features, such as nausea, vomiting, and photophobia, have been observed during some CH episodes (2,4,5). Some patients may present with characteristics of both headache types. These observations suggest that at least some patients experience clinical features shared by both conditions (4,5,6,7).

This study evaluated the prevalence of uAS in patients suffering from migraines and assessed the expression of these symptoms using a retrospective design. Additionally, the pain characteristics of migraine attacks experienced by pure migraine patients with and without autonomic features were compared.

METHODS
This study was part of an ongoing Turkish Headache Database Study investigating the clinical characteristics and outcomes of headache syndromes in the Turkish population. The Turkish Headache Database includes a total of 19488 patients since May 2013, with patients mostly diagnosed as having primary headaches. The study was approved by the local Ethics Committee of Mersin University, and informed consent was obtained from all participants (MEU.0.01.00.06/265, 20.10.2008). Of the 12036 patients enrolled in the larger study, 2955 consecutive patients with definite migraine with and without aura and 93 patients with CH were enrolled in the present study. Migraine patients were divided into two groups depending on the presence of at least one associated autonomic symptom: 89 migraine patients having uAS (MwuAS) and 2773 migraine patients who did not have uAS (MwouAS).

Classification of migraine and CH was based on The International Classification of Headache Disorders, 3rd edition beta version (Headache Classification Committee, 2013). Patients reporting at least one autonomic symptom during an attack were considered to be MwuAS. Personal identifiers were removed during the subject selection, and written informed consent was obtained by a representative of each center involved in this study before any data were included in database. Subjects younger than 18 years of age and those older than 65 years of age received headache diagnosis codes other than ICHD 1.1, 1.2, and 3.1; patients with "headache-plus" diagnoses (e.g., migraine plus tension type) and patients with incomplete headache data were not included.

Data on the socio-demographic and clinical characteristics, including age at onset, headache duration, headache frequency, presence of aura, headache characteristics, localization and intensity of pain, triggering factors, associated features, and medical and family history, were gathered from all patients by headache specialists in face-to-face interviews using a structured questionnaire drawn from a web-based database. The presence of autonomic symptoms (ptosis, lacrimation, rhinorrhea, facial swelling, conjunctival injection, and pupil changes) in migraineurs and the presence of migrainous features (nausea, vomiting, photophobia, and phonophobia) in CH patients were also noted.

Statistical analysis
Data were entered and analyzed in the Number Cruncher Statistical System (NCSS, 2007) and PASS 2008 Statistical Software (Utah, USA). For the classification and regression tree (CRT), the program STATISTICA®-6.0 was also used. After a descriptive analysis (mean, standard deviation, etc.), the groups were compared using the Kruskal–Wallis test, Mann–Whitney U test, or chi square test according to variable type. The clinical features and demographics of the patients with cranial autonomic symptoms were compared with those of the patients with

CH and migraine patients without autonomic symptoms. Risk factors for MwuAS were determined using multivariate analysis. A classification tree model was performed using CRT analysis. The most important variables were determined in the classification model. The prediction values in the terminal nodes of the classification tree were compared with the observed values (with or without autonomic symptoms), and sensitivity and specificity were estimated. Results are given as the 95% confidence interval (CI), and p<0.05 was accepted as significant.

RESULTS
The headache characteristics of patients are summarized in Table 1. Group I consisted of 89 patients with MwuAS (70 females; average age, 36.4±11.9 years); Group II consisted of 2773 patients with MwouAS (2397 females; average age, 41.6±13.2 years); and Group III consisted of 93 patients with CH (30 females; average age, 42.2±12.7 years).

The medical histories of the patients revealed that travel sickness, abdominal pain, and periodic vomiting were more common in patients with MwuAS (24.7%, 18%, and 6.7%, respectively) than in patients with MwouAS (8.2%, 2.3%, and 0.9%, respectively) (p<0.001) (Table 2). Co-morbid medical histories of diabetes mellitus (14.8%, p<0.001), coronary heart disease (13.4%, p<0.001), and smoking (27.9% vs. 23.6%, p<0.001) were significantly more common in patients with MwouAS. Family histories of headaches, hypertension, diabetes mellitus, and cardiac disease were significantly more common in patients with MwuAS (Table 2).

uAS in migraine patients and migrainous features in CH are summarized in Table 3. Among patients with MwuAS, lacrimation was noted in 63 patients (70.8%), conjunctival injection in 33.7% of patients, facial swelling in 12.4%, ptosis in 6.7%, and rhinorrhea in 4.5%. Of the migrainous features of CH patients, nausea accompanied CH in 38.7% of patients, although vomiting was less common (19.4%). Phonophobia was reported in 41.9% of patients, and photophobia was reported in 34.4%.

Multivariate analysis of the risk factors of MwuAS
Unilaterality increased the risk of MwuAS by a factor of 2.5 (p=0.001); periocular localization increased the risk by a factor of 4 (p=0.001); and starvation increased the risk by a factor of 3.9 (p=0.030). Individuals with a history including attacks of abdominal pain were almost 3.6 times (p=0.001) more likely to suffer from MwuAS.

CRT-a recent statistical method commonly used in algorithm analysis-demonstrated that the most sensitive parameters for MwuAS diagnosis were lacrimation, facial swelling, and conjunctival injection, with high sensitivity (94.38%) and specificity (99.89%), as shown in Figure 1 and Table 4.

CRT showed the list of the most important ways of defining uAS in migraine subjects. If a clinician has limited time for a patient interview, he or she should ask about lacrimation, facial swelling, and conjunctival injection as uAS. As shown in Table 4, this model performed the best at identifying MwouAS subjects.

DISCUSSION
Limited data are available about the frequency and importance of uAS in migraine patients compared with those in CH patients. Our study revealed a moderate frequency of uAS in migraine sufferers. Our model identified a high frequency of some associated features in the subjects with MwuAS compared with those with CH. It should be noted that certain common features of migraines and CH may overlap depending on how certain questions are posed in the clinical setting.

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Table 1. Clinical characteristics of the study patients

		MwuAS n=89 (%)	MwouAS n=2773 (%)	CH n=93 (%)	+p
Headache duration (month) Median (25–75% perc)		60 (24-120)	60 (24-120)	48 (12-120)	0.1076
Headache frequency (day) Median (25–75% perc)		8 (4-12.5)	6[a] (3-15)	20[b] (6.5-30)	0.0002
Headache Features	Stabbing	0 (0.0%)	48 (1.7%)	36 (38.7%)[a,b]	
	Blunt	0 (0.0%)	167 (6.0%)[a]	5 (5.4%)	
	Pressing	7 (7.9%)	399 (14.4%)	7 (7.5%)	
	Shock-like	0 (0.0%)	21 (0.8%)	4 (4.3%)[a]	<0.0001
	Throbbing	80 (89.9%)	2084 (75.1%)[a]	27 (29.0%)[a,b]	
Localization	Unilateral (yes)	56 (62.9%)	1173 (42.3%)[a]	76 (81.7%)[a,b]	<0.0001
	Unilateral (no)	33 (37.1%)	1600 (57.7%)	17 (18.3%)	
Trigger factors	Coughing	17 (23.9%)	315 (11.3%)[a]	1 (1.0%)[a,b]	
	Emotional stress	73 (82.0%)	2072 (74.7%)	39 (41.9%)[a,b]	
	Physical activity	52 (58.4%)	1402 (50.5%)	11 (11.8%)[a,b]	
	Alcohol	8 (9.0%)	8 (0.3%)[a]	24 (25.8%)[a,b]	<0.0001
	Starving	40 (44.9%)	211 (7.6%)[a]	6 (6.4%) [a]	

+aKruskal–Wallis, bChi square test
MwuAS: migraine with autonomic symptoms; CH: cluster headache; MwouAS: migraine without autonomic symptoms.

Table 2. Comparison of the migraine (with and without unilateral autonomic symptoms) and CH patients

	MwuAS n=89 (%)	MwouAS n=2773 (%)	CH n=93 (%)
Periodical vomiting	6 (6.7%)	25 (0.9%)[a]	0 (0.0%)[a]
Travel sickness	22 (24.7%)	228 (8.2%)[a]	5 (5.4%)[a]
History of abdominal pain	16 (18%)	64 (2.3%)[a]	0(0.0%)[a]
Diabetes mellitus	2 (2.2%)	410 (14.8%)[a]	10 (10.8%)[a]
Coronary heart disease	1 (1.1%)	372 (13.4%)[a]	11 (11.8%)[a]
Smoking	21 (23.6%)	773 (27.9%)	32 (34.5%)
Alcohol	0 (0.0%)	395 (14.2%)[a]	26 (28%)[a,b]
Family history of headache	42 (47.2%)	835 (30.1%)[a]	22 (23.7%)[a]

MwuAS: migraine with autonomic symptoms; CH: cluster headache; MwouAS: migraine without autonomic symptoms; DM: diabetes mellitus. Differences in groups aMwuAS; bMwouAS.

Table 3. Associated features of the migraine and CH patients

	MwuAS n=89 (%)	MwouAS n=2773 (%)	CH n=93 (%)
Nausea	78 (87.6%)	2235 (80.6%)	36 (38.7%)[a,b]
Vomiting	48 (53.9%)	1211 (43.7%)	18 (19.4%)[a,b]
Phonophobia	76 (85.4%)	2100 (75.7%)[a]	39 (41.9%)[a,b]
Photophobia	72 (80.9%)	1907 (68.8%)[a]	32 (34.4%)[a,b]
Lacrimation	63 (70.8%)	2 (0.1%)[a]	50 (58.8%)[b]
Ptosis	6 (6.7%)	0(0.0%)[a]	8 (15.1%)[b]
Rhinorrhea	4 (4.5%)	1 (0.0%)[a]	29 (41.4%)[a,b]
Facial swelling	11 (12.4%)	0 (0.0%)[a]	21 (32.3%)[a,b]
Conjunctival injection	30 (33.7%)	2 (0.1%)[a]	42 (52.5%)[a,b]
Pupil changes	3 (3.4%)	0 (0.0%)[a]	3 (6.1%)[b]

Differences in groups aMwuAS; bMwouAS.

The role of autonomic features accompanying migraines and migrainous features accompanying CH needs to be clarified (8). Migraine may be caused by trigeminovascular system activation leading to neurogenic inflammation (9). Activation of the trigeminovascular system may trigger the efferent parasympathetic arm of the trigeminoautonomic reflex in some patients with migraine (10). This study described uAS. However, migraine headaches are generally unilateral and severe in patients with uAS (7,11).

In the present study, the most sensitive parameters for detecting MwuAS were lacrimation (70.8%), conjunctival injection (33.7%), and facial swelling (12.4%). With regard to migrainous features in CH, nausea

occurred in 38.7% of the patients; although vomiting was less common (19.4%), phonophobia occurred in 41.9% of patients, and photophobia was reported by 34.4%. To the best of our knowledge, no report has yet been published about these ratios in clinical settings. However, the retrospective design of this study underscores the importance of continuing education about this topic for headache specialists; indeed, the scarcity of uAS may be related to the lack of physician attention to this condition. Additional studies for further development of the headache classification criteria and for clarification of the role of physician attention in the diagnostic process are thus warranted.

Unilateral and periocular localization, starvation (3.9 times as frequent), and history of abdominal pain (3.6 times as frequent) were found to be
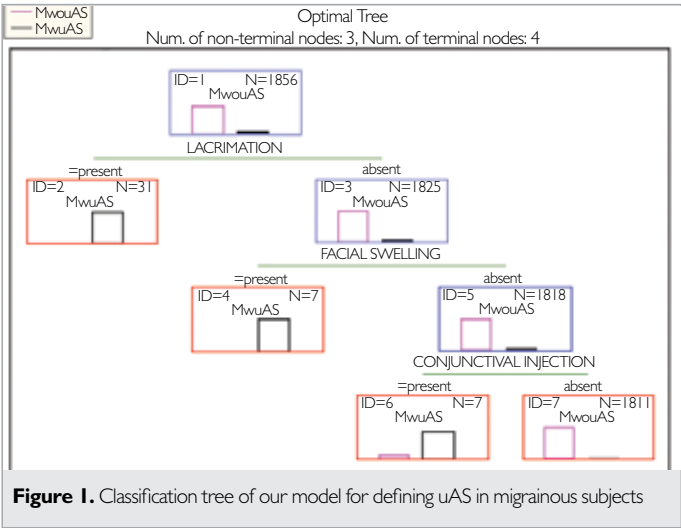
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MwouAS
MwuAS

Optimal Tree
Num. of non-terminal nodes: 3, Num. of terminal nodes: 4

ID=1   N=1856
MwouAS

LACRIMATION

=present   N=31
ID=2
MwuAS

absent
ID=3   N=1825
MwouAS

FACIAL SWELLING

=present   N=7
ID=4
MwuAS

absent
ID=5   N=1818
MwouAS

CONJUNCTIVAL INJECTION

=present   N=7
ID=6
MwuAS

absent
ID=7   N=1811
MwouAS

Figure 1. Classification tree of our model for defining uAS in migrainous subjects

Table 4. Classification matrix table of this model

		Observed Class		
		MwouAS	MwvuAS	Total
Predicted Class	MwouAS	1810	1	1811
	MwvuAS	2	43	45
Total		1812	44	1856

independent risk factors in migraine patients with uAS. The pain is unilateral in migraine patients, but it may be bilateral or start unilaterally and become generalized (12). In our migraine and CH groups, the headache was mostly unilateral (62.9% and 81.7%, respectively). The frequency of CH attacks can vary from one attack to up to eight attacks per week (12,13). In our study, the attacks occurred in bouts lasting between 6 and 30 days, during which CH occurred mainly during sleep. Among active migraineurs, the median attack frequency is 1.5 attacks per month, although 10% of migraineurs have weekly attacks (14,15). The mean attack frequencies among migraineurs with and without autonomic features were 4–12 and 3–15 attacks per month, respectively. The pain was mostly stabbing (38.7%) in CH patients and throbbing in patients with MwuAS and MwouAS (89.9% and 75.1%, respectively). A throbbing type of pain was also frequent in CH patients (29.0%). Although blunt and pressing type headaches were more frequent in patients with MwouAS, blunt pain was absent in patients with MwuAS, and the pressing pain rate was similar to that in patients with CH.

Patients with CH are restless during attacks of pain, or pain does not exacerbate during movement, which is the opposite in migraine patients. Previous studies mentioned that the pain of CH was made better by movement in 80% of cases, compared with 15% of migraineurs, whereas the pain was worse with movement in 20% of the patients with CH and 85% of those with migraine headache (16,17). We found a significantly higher frequency of these parameters in the subjects with MwuAS (58.4%) compared with MwouAS (50.5%) and CH (11.8%). However, the multivariate regression analysis did not identify this parameter as defining MwouAS. In this model, the aggravation by emotional stress had clinical importance. We found that 0.31% of 2862 migraineurs had unilateral autonomic features, and 19.4–41.9% of 93 patients in the CH group had migrainous features. Therefore, distinctions between related clinical syndromes are often artificial, and many patients may have clinical features that overlap several such categories.

Nausea is a common accompanying symptom in migraine (18). Studies have suggested that nausea and vomiting never accompany CH, but some authors claimed that nausea is present in half of the patients with CH, although vomiting remains less common. Nausea occurred in 38.7% and vomiting in 19.4% of our patients with CH. Photophobia and phonophobia occur in up to 90% of patients (19). The percentage of patients with CH who experience photophobia varies between 5% and 72% across studies. Ekbom (16) reported phonophobia in 39% of 105 patients. Of the 50 patients observed by Kudrow (19) during cluster attacks, 72% experienced photophobia with or without phonophobia. Phonophobia and photophobia were present in 41.9 and 34.4% of our patients with CH, respectively.

Detailed examination of the accompanying symptoms in migraine might help to understand its pathophysiology. Unilaterality suggests activation of the trigeminovascular system, a throbbing nature suggests vascular innervation, and aggravation by movement is a reflection of neurogenic inflammation (8). The presence of uAS suggests activation of the cranial parasympathetic system in migraineurs with uAS (10). Ocular symptoms might also be due to neurogenic inflammation (20). Our data suggested an overlapping pathophysiological process in two distinct diseases (migraine and CH) as reflected in the overlapping clinical features.

Unilaterality, periocular localization, starvation, and history of abdominal pain were independent risk factors for MwuAS patients. The most sensitive parameters for MwuAS diagnosis were lacrimation, facial swelling, and conjunctival injection, with high sensitivity and specificity.

The main limitation of this study is lower (3.1%) prevalence of MwuAS compared with that found in prospective clinical data. However, this is a retrospective study, and we did not expect our sample to be representative of the entire population of migraine patients examined via epidemiological or prospective designs.

The following major contributions of this study should be noted: It is the first large-sample database analysis of overlapping features of CH and migraine. It provides the first data defining the importance of overlapping features in a clinical setting. It is the first study to rank overlapping features (lacrimation, facial swelling, and conjunctival injection).

In conclusion, although migraine and CH are considered two different entities with different, but not-yet-fully-understood, pathophysiology, they may share a common pathophysiological step, probably functional alteration in the hypothalamic or brainstem circuits. The existence of this common mechanism could give a clue toward a specific agent for the treatment of migraine and CH attacks. Hence, assessing common clinical features, particularly autonomic symptoms, in CH and migraine is mandatory, and headache specialists have to consider this in their clinical practice to obtain true figures. Particularly, lacrimation, conjunctival injection, and facial swelling are widely experienced by migraineurs. Further comprehensive studies are needed to unravel the role of these accompanying autonomic symptoms in diagnosis and therapy.

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