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Frequency of Cranial Autonomic Symptoms in Patients with Migraine

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ABSTRACT

Background: Migraine is characterized by recurring incapacitating headache attacks accompanied by various symptoms, often including aura. **Objective:** To determine the frequency of cranial autonomic symptoms (CAS) in patients with migraine. **Methods:** This cross-sectional study was conducted at the Department of Neurology, Lady Reading Hospital, Peshawar, from January 2025 to June 2025. A total of 93 migraine patients aged 18–60 years, diagnosed for ≥1 year as per International Headache Society criteria, were enrolled using non-probability consecutive sampling. Demographic and clinical data were recorded, and CAS were assessed using a structured proforma. CAS were defined as ocular, nasal, facial, or aural autonomic features reported in ≥3 migraine episodes. Data were analyzed using SPSS v26, with p≤0.05 considered significant. **Results:** Of 93 patients, 64 (68.8%) females, with median age of 30 years (IQR 21.5–38.0). Migraine without aura was present in 72 (77.4%), and with aura in 21 (22.6%) patients. The median duration of migraine was 36.0 months (IQR 12.0–96.0), with a median frequency of 10 attacks per month (IQR 4.0–18.0). CAS were identified in 38 (40.9%) patients. Most frequent symptoms were lacrimation 22 (23.7%), conjunctival injection 20 (21.5%), nasal congestion 13 (14.0%), and aural fullness 11 (11.8%). Ptosis, eyelid edema, and facial sweating were significantly more frequent in older age groups (p=0.044). Conjunctival injection was more common in classical migraine with aura (38.1% vs 16.7%; p=0.035). **Conclusion:** CAS are frequent in patients with migraine, with lacrimation and conjunctival injection being the most commonly reported.

INTRODUCTION

Migraine is characterized by recurring incapacitating headache attacks accompanied by various symptoms, often including aura. The etiology of migraine is multifaceted, with rare monogenic variants contributing to its complexity [1]. Globally, approximately 12% of the population is affected by migraine, though the prevalence is higher in some regions. Chronic migraine, affecting 1% to 2% of the worldwide population, has become a notable health concern [2,3]. Recent data from 2019 indicates a global prevalence of 14,107.3 and an annual incidence of 1142.5 per 100,000, showing a steady rise since 1990 [3]. In Pakistan, migraine's prevalence is estimated to be around 30%, affecting women nearly twice as often as men [4, 5].

Cranial autonomic symptoms (CAS) are distinct cluster of symptoms experienced by a subset of migraineurs. These include conjunctival injection, lacrimation, nasal congestion, rhinorrhea, miosis, ptosis, facial sweating, facial flushing, eyelid edema, and aural fullness [6, 7]. Despite their relevance, CAS remain under-recognized in the context of migraine, and their prevalence and relationship with migraine remain subjects of ongoing research. CAS are typically associated with cluster headache (CH) and other trigeminal autonomic cephalalgias (TAC), and are rarely considered in the evaluation of migraine.[8] The literature reports varying CAS frequencies, ranging from 3.8% to 80% [4-7, 8, 10]. Togha et al., revealed that approximately 70% of chronic migraine subjects and 56.2% of episodic migraine subjects reported one or more CAS [11]. Local data revealed the frequency of CAS as 75.8% among migraine patients,[4] while regional data highlighted that among 200 patients, 74% exhibited at least one CAS, with 70% experiencing two or more [9]. The most frequently reported CAS included lacrimation (45.5%), conjunctival injection (34.5%), eyelid edema (34%), aural fullness (27.5%), and facial sweating (25%) [9].

Differentiating migraine from other common primary headache disorders, such as trigeminal autonomic cephalalgias, is challenging due to overlapping clinical presentations. Therefore, a comprehensive assessment of CAS prevalence and distribution within the local migraine population is essential for precise diagnosis and improved management. No prior study of this nature has been conducted in the Khyber Pakhtunkhwa region of Pakistan, leaving a critical gap in understanding CAS prevalence in the context of migraine. By addressing this gap, the study

can contribute important data to the global comprehension of migraine, and may also lay the groundwork for future research on migraine and its associated symptoms in Pakistan. The aim of this study was to determine the frequency of cranial autonomic symptoms in patients with migraine.

METHODS

This cross-sectional study was conducted at the Department of Neurology, Lady Reading Hospital, Peshawar, during January 2025 to June 2025. A non-probability consecutive sampling technique will be employed. The sample size was calculated using the WHO sample size calculator, keeping a 95% confidence interval, 4% absolute precision, and 4% frequency of ptosis [9], yielding a sample size of 93 patients. The inclusion criteria were patients of any gender, aged 18–60 years, and diagnosed with migraine for a period of at least one year. Migraine was labeled according to the International Headache Society Diagnostic Criteria (IHSD), as if the patient had experienced at least five headache attacks lasting 4–72 hours with at least two of the following characteristics: unilateral location, pulsating quality, moderate to severe intensity, or aggravation by or avoidance of routine physical activity. In addition, during the headache, patients must have had at least one of the following associated symptoms: nausea and/or vomiting, photophobia, or phonophobia, with exclusion of other secondary causes of headache. Patients were excluded if they had other causes of headache such as stress type headache, cluster headache, trigeminal neuralgia, or other secondary headaches, as well as those with cognitive impairment, a prior history of anxiety disorder, or conditions such as myasthenia gravis, cranial nerve palsy, Bell's palsy, head injury, space-occupying brain lesions, or autonomic dysfunction due to diabetes mellitus. Patients with previous eye or nasal surgery, allergic rhinitis, or conjunctivitis were also excluded.

This study commenced after obtaining ethical approval from the Institutional Review Board (Ref: No. 143/LRH/MTI, dated: 09/05/2024). Eligible patients were explained about the objectives, and methods of this research in detail, and written informed consent was obtained from those willing to participate. Demographic information including medical record number, age, gender, educational level, address, and body mass index (BMI) were recorded. Clinical information included the duration of chronic migraine in months, the frequency of migraine attacks per month, and the type of migraine (with or without aura). CAS was defined as the presence of any of the following features during migraine episodes: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, miosis, ptosis, facial sweating, facial flushing, eyelid edema, or aural fullness. Patients were considered CAS-positive if they self-report experiencing one or more of these symptoms during at least three migraine episodes. Patients were asked a series of structured questions about the presence of specific CAS during migraine attacks, including conjunctival injection, lacrimation, nasal congestion, rhinorrhea, miosis, ptosis, facial sweating, facial flushing, eyelid edema, and aural fullness. Responses were documented as "present" or "absent" based on the patient's self-report across their last three migraine episodes. To ensure objectivity and accuracy, each symptom was clearly explained with examples during the interview.

Data were analyzed using the IBM-SPSS, Statistics, version 26.0. For quantitative variables such as age, BMI, duration of migraine, and frequency of attacks, mean ± standard deviation (SD), or median and interquartile range (IQR) were calculated. For qualitative variables such as gender, education level, type of migraine, and the presence or absence of individual cranial autonomic symptoms, frequencies and percentages were reported. Stratification was performed to assess the effect of potential modifiers including age, gender, BMI, duration of migraine, and migraine type on the prevalence of CAS. Post-stratification, chi-square test or fisher's exact test was used to determine the associations between the prevalence of CAS and categorical variables, or independent sample t-test or Mann-Whitney U test for numeric data, with p-value ≤ 0.05 taken as statistically significant.

RESULTS

In a total of 93 patients, 29 (31.2%) were males, and 64 (68.8%) females, giving a female-to-male ratio of 2.2:1. The median age of participants was 30.0 years (IQR 21.5–38.0), while 86 (92.5%) were aged between 18–45 year. The median BMI was 23.8 kg/m^2 (IQR 22.0–25.8). There were 64 (68.8%) patients who belonged to urban areas of residence. The median duration of migraine was 36.0 months (IQR 12.0–96.0), with a median frequency of 10 attacks per month (IQR 4.0–18.0). Migraine without aura was the most common type, reported in 72 (77.4%) patients. CAS were present in 38 (40.9%) patients, while 55 (59.1%) reported no CAS. Comparison of CAS present and CAS absent patients revealed no statistically significant differences with respect to gender distribution (p=0.400), age groups (p=0.911), education status (p=0.264), residence (p=0.600), BMI (p=0.972), or types of migraine (p=0.222). No significant differences were observed between CAS and duration of migraine (p=0.866) or monthly frequency of attacks (p=0.672) (table-1).

Table 1

Association of CAS with demographic and clinical characteristics of patients with migraine (N=93)

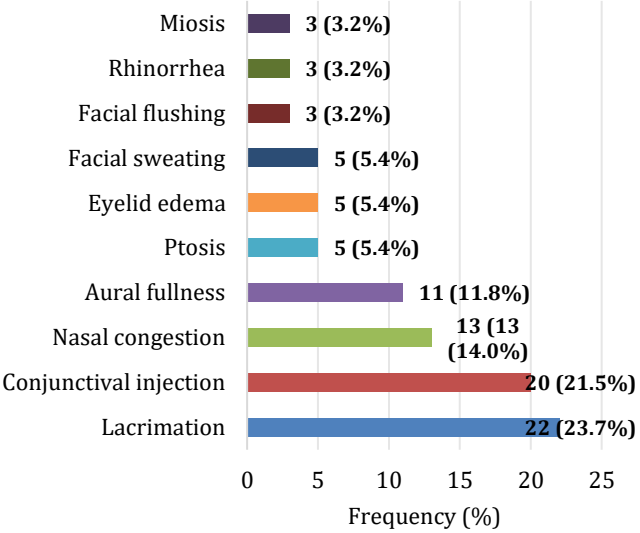
		Total (%)	CAS Absent (n=55)	CAS Present (n=38)	P-value
Gender	Male	29 (31.2%)	19 (34.5%)	10 (26.3%)	0.400
	Female	64 (68.8%)	36 (65.5%)	28 (73.7%)	
Age groups (years)	18-45	86 (92.5%)	51 (92.7%)	35 (92.1%)	0.911
	46-60	7 (7.5%)	4 (7.3%)	3 (7.9%)	
Education	Illiterate	28 (30.1%)	20 (36.4%)	8 (21.1%)	0.264
	Primary	9 (9.7%)	7 (12.7%)	2 (5.3%)	
	Middle	16 (17.2%)	8 (14.5%)	8 (21.1%)	
	Matriculation	17 (18.3%)	7 (12.7%)	10 (26.3%)	
	Intermediate	15	8	7	

	or graduation	(16.1%)	(14.5%)	(18.4%)	
	Masters	6 (6.5%)	3 (5.5%)	3 (7.9%)	
	Doctorate	2 (2.2%)	2 (3.6%)	-	
Residence	Rural	29 (31.2%)	16 (29.1%)	13 (34.2%)	0.600
	Urban	64 (68.8%)	39 (70.9%)	25 (65.8%)	
Body mass index (kg/m^2)	<25.0	65 (69.9%)	38 (69.1%)	27 (71.1%)	0.972
	25.0-29.9	20 (21.5%)	12 (21.8%)	8 (21.1%)	
	>29.9	8 (8.6%)	5 (9.1%)	3 (7.9%)	
Type of migraine	Classical migraine with aura	21 (22.6%)	10 (18.2%)	11 (28.9%)	0.222
	Migraine without aura	72 (77.4%)	45 (81.8%)	27 (71.1%)	
Duration of migraine (months)		36.0 (12.0-96.0)	30.0 (18.0-96.0)	36.0 (12.0-120.0)	0.866
Frequency of migraine attacks (monthly)		10.0 (4.0-18.0)	8.0 (18.0-34.0)	10.0 (4.0-18.0)	0.672

Among individual symptoms, lacrimation was the most frequent, reported in 22 (23.7%), followed by conjunctival injection in 20 (21.5%), nasal congestion in 13 (14.0%), and aural fullness in 11 (11.8%). Less frequently reported symptoms included ptosis (5, 5.4%), eyelid edema (5, 5.4%), facial sweating (5, 5.4%), facial flushing (3, 3.2%), rhinorrhea (3, 3.2%), and miosis (3, 3.2%) (Figure 1).

Figure 1

Frequency of CAS symptoms (n=93)



Analysis of individual CAS by gender distribution showed no statistically significant differences. Age distribution showed that individual CAS were comparable between age groups, in years group and 46–60 years group, except for ptosis (18–45 years: 3.5% vs 46–60 years: 28.6%; p=0.044) and facial sweating (3/86, 3.5% vs 2/7, 28.6%; p=0.044), which were significantly more frequent in older age group (table-2).

Table 2

Association of gender and age groups with CAS (N=93)

CAS symptoms	Gender		P-value	Age groups (years)		P-value
	Male	Female		18-45	46-60	
Lacrimation	6 (20.7%)	16 (25.0%)	0.650	20 (23.3%)	2 (28.6%)	0.750
Conjunctival injection	6 (20.7%)	14 (21.9%)	0.897	18 (20.9%)	2 (28.6%)	0.636
Nasal congestion	6 (20.7%)	7 (10.9%)	0.209	12 (14.0%)	1 (14.3%)	0.981
Aural fullness	1 (3.4%)	10 (15.6%)	0.163	10 (11.6%)	1 (14.3%)	0.834
Ptosis	2 (6.9%)	3 (4.7%)	0.645	3 (3.5%)	2 (28.6%)	0.044
Eyelid edema	1 (3.4%)	4 (6.3%)	0.579	4 (4.7%)	1 (14.3%)	0.330
Facial sweating	2 (6.9%)	3 (4.7%)	0.645	3 (3.5%)	2 (28.6%)	0.044
Facial flushing	-	3 (4.7%)	0.459	3 (3.5%)	-	0.615
Rhinorrhea	1 (3.4%)	2 (3.1%)	0.935	3 (3.5%)	-	0.615
Miosis	2 (6.9%)	1 (1.6%)	0.228	2 (2.3%)	1 (14.3%)	0.211

When analyzed according to migraine type, conjunctival injection was significantly more common in patients with migraine with aura compared to migraine without aura (p=0.035). Other symptoms such as lacrimation (p=0.077), nasal congestion (p=0.446), and aural fullness (p=0.261) showed relatively higher frequencies in patients with aura, although the differences did not reach statistical significance, and the details are given in table-3.

Table 2

Association of types of migraine with cranial autonomic symptoms (N=93)

CAS symptoms	Types of migraine		P-value
	Classical migraine with aura	Migraine without aura	
Lacrimation	8 (38.1%)	58 (80.6%)	0.077
Conjunctival injection	8 (38.1%)	12 (16.7%)	0.035
Nasal congestion	4 (19.2%)	9 (12.5%)	0.446
Aural fullness	4 (19.0%)	7 (9.7%)	0.261
Ptosis	1 (4.8%)	4 (5.6%)	0.887
Eyelid edema	2 (9.5%)	3 (4.2%)	0.315
Facial sweating	-	5 (6.9%)	0.584
Facial flushing	1 (4.8%)	2 (2.8%)	0.540
Rhinorrhea	2 (9.5%)	1 (1.4%)	0.127
Miosis	1 (4.8%)	2 (2.8%)	0.540

DISCUSSION

This study showed the frequency of CAS as 40.9% in patients with migraine. The present findings align more closely with Christensen et al.,[8] from Denmark, who reported CAS in 44% of patients when validated by interview, and with Zeliha and Ozlem in paediatric migraine patients, where 40% demonstrated CAS [12]. These parallels suggest that around half of migraine patients consistently report such symptoms, reinforcing CAS as a clinically important but variably expressed component of migraine. The proportion of CAS in this study is lower than that reported by another local study by Nasir et al., where 75.8% of patients experienced CAS, and by Tiwari et al., in India, who observed 74% of their cohort

to be CAS-positive [4, 9]. Both those studies applied less stringent criteria, requiring only one positive episode, whereas the present study required symptoms to be consistently reported in at least three migraine episodes. This methodological difference may explain the comparatively lower prevalence.

Lacrimation was the most frequent individual symptom (23.7%), followed by conjunctival injection (21.5%). Tiwari et al., identified lacrimation in 45.5% and conjunctival injection in 34.5% of Indian migraine patients, while a local study by Fatima et al., reported lacrimation in 56% and conjunctival injection in 31% [9, 13]. Although frequencies differ, lacrimation and conjunctival injection consistently emerge as the two dominant CAS. In the current study, their comparatively lower prevalence may again reflect stricter diagnostic thresholds. Clinically, this supports the importance of asking targeted questions regarding ocular autonomic symptoms, as they are the most frequently reported across diverse populations [14, 15].

Nasal congestion and aural fullness were observed in 14.0% and 11.8% of patients, respectively. These rates are somewhat lower than the 31% for nasal congestion reported by Fatima et al., and 25% for aural fullness reported by Karsan et al., in a tertiary UK cohort [6, 13]. Recognition of these symptoms in practice is important, as these may often be mistaken for sinus or ear disease, leading to unnecessary investigations [16].

The less common symptoms of ptosis (5.4%), eyelid edema (5.4%), facial sweating (5.4%), facial flushing (3.2%), rhinorrhea (3.2%), and miosis (3.2%) occurred at considerably lower frequencies than those reported by Tiwari et al., who described eyelid edema in 34%, facial sweating in 25%, and ptosis in 4% [9]. The divergence is most likely related to population differences, reporting bias, and the requirement of multiple episode confirmation in this study. These findings underline the need for international standardisation of CAS diagnostic criteria [17]. Christensen et al., suggested appendix criteria to unify definitions in epidemiological studies, which, if adopted, could improve comparability between populations [8].

Gender distribution did not influence the occurrence of CAS in this study. This contrasts with Nasir et al., who found a higher incidence in females ($p<0.049$), and with Fatima et al., where facial sweating was more common in women [4, 13]. Age-related analysis demonstrated that ptosis (28.6% vs 3.5%, $p=0.044$) and facial sweating (28.6% vs 3.5%, $p=0.044$) were more frequent among patients aged 46–60 years compared with those aged 18–45 years. This observation is supported by Togha et al., who reported thatocular and facial symptoms are more common in chronic migraine and in older patients [11]. The age effect may represent cumulative disease burden and progressive autonomic dysfunction with chronicity, indicating that older patients should be specifically assessed for subtle CAS such as ptosis [18, 19].

The presence of CAS was not significantly associated with duration of migraine or attack frequency in this study. This contrasts with Nasir et al., who reported that CAS prevalence increased with longer disease duration (58.8% with ≤1 year vs 74.2% with 4–5 years; $p=0.002$) [4]. Karsan et al., described a positive correlation between baseline headache frequency and number of CAS reported ($p=0.047$) [6]. The absence of such associations here may be related to a relatively narrower disease duration range and relatively smaller sample size. Larger multicentre cohorts with stratification by chronicity are required to clarify this temporal relationship.

With respect to migraine subtype, conjunctival injection was significantly more common in patients with aura (38.1% vs 16.7%; $p=0.035$). Togha et al., showed that CAS are more frequent in chronic migraine and in patients with neurologically complex forms such as aura [11]. Other symptoms, including lacrimation ($p=0.077$), nasal congestion ($p=0.446$), and aural fullness ($p=0.261$), were more frequent in patients with aura but without reaching statistical significance. This pattern suggests that aura may represent a phenotype with greater parasympathetic activation, which has implications for both pathophysiology and clinical management [20, 21].

The clinical implications of these findings are considerable. The recognition that around 40% of migraine patients exhibit CAS underscores the need for clinicians to include CAS in routine history-taking [22, 23]. Failure to do so risks misdiagnosis, particularly with trigeminal autonomic cephalalgias, where CAS are considered diagnostic hallmarks [24]. The association of CAS with aura and older age suggests that these subgroups may represent more severe disease phenotypes, necessitating closer monitoring and potentially more aggressive treatment. Identifying CAS early can prevent unnecessary otolaryngological referrals, reducing both patient burden and healthcare costs.

This study has certain limitations. The single-centre design and relatively modest sample size restrict the generalisability of results. Although the use of structured interviews with detailed descriptions aimed to minimise this, prospective headache diaries would provide a more objective method for future studies. Another limitation is the absence of headache severity scales, which have been shown in other studies to correlate with CAS frequency. Incorporating validated pain scales and quality-of-life instruments could better delineate the clinical impact of CAS. Future research should focus on multicentre, larger-scale studies using standardised diagnostic criteria, as well as longitudinal designs to assess the evolution of CAS with migraine chronicity.

CONCLUSION

CAS are frequent in patients with migraine, with lacrimation and conjunctival injection being the most commonly reported. Their presence was significantly associated with migraine with aura and with older age for certain symptoms. These findings highlight the importance of systematic CAS evaluation during migraine assessment, both for improving diagnostic accuracy and for identifying patients with potentially more severe disease phenotypes. Recognition of CAS may not only prevent misclassification with trigeminal autonomic cephalalgias but also guide more individualised treatment approaches.

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