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ABSTRACT

Objectives. Migraine is a prevalent debilitating neurological disorder manifested by frequent episodes of pounding headache. Cranial autonomic symptoms are frequently reported in patients of trigeminal autonomic cephalgias, but various studies also documented these cranio-autonomic symptoms in migraine patients as well. The primary objective of our study is to evaluate the prevalence of cranio-autonomic symptoms (CAS) amongst the patients suffering from migraines.

Material and methods. This study was conducted as a descriptive, cross-sectional survey involving patients attending the neurology clinic at Dow University Hospital. 132 patients met the inclusion criteria (according to ICHD-III) and were assessed for the frequency of cranio-autonomic symptoms.

Outcomes. The mean age recorded was 26.37 ± 6.31 years, while the mean duration of diagnosis was 23.54 ± 16.52 months. The frequency of cranio-autonomic symptoms was observed among 55% of the patients suffering from migraines in our study. The prominent symptom observed was lacrimation (56%), followed by nasal congestion (31%) and rhinorrhea (28%). The least prevalent symptom was ptosis (4%). Lacrimation was found more likely to be associated with the male gender ($p = 0.096$), while forehead/ facial sweating was found more prevalent in females ($p = 0.162$). The ciliary injection was frequent in conjunction with unilateral rather than a bilateral headache in the migraine patients ($p = 0.055$), while lacrimation was the most common symptom in the 21-30 years of age group followed by ciliary injection which was exclusively conspicuous in the same age category ($p = 0.020$).

Conclusions. Cranio-autonomic symptoms were detected prevailing in our study population, and may present as a confounding factor in physician's daily practice to diagnose migraine.

Keywords: migraine, autonomic, headache, trigeminal, frequency

INTRODUCTION

Migraine is a frequent, chronic, and incapacitating disease [1]. It constitutes a second predominant cause of headache burden [2]. The prevalence of migraine is proclaimed between 2.6% and 21.7%, with an expected value of 12% [3]. In Pakistan, the prevalence of migraine is 30%, conventional in females [4]. Cranio-autonomic manifesta-

tions are induced by trigeminal autonomic reflex along with its efferent fibers. Contrarily, bilateral cranio-autonomic symptoms are induced by the intermingling of parasympathetic fibers in the brainstem [5-8].

Diagnostic criteria utilized for detection of migraine is International Classification of Headache Disorders (ICHD-3rd edition) [9], implying the following clinical manifestations to be denoted as an

attack of migraine: 1. headache, unilateral and pulsating in origin with moderate to severe pain potentiated by the negligence with daily physical mobility; 2. headache prevailing for 4-72 hours; 3. headache associated with nausea and/or vomiting, fear of lights and noise and not favored by another ICHD-3 differential; 4. five episodes of headache meeting criteria 1 and 3. Patients of migraine are seldomly triggered by auras, most commonly visual auras (floaters, beams of light, moving or increasing zig-zag patterns, a decline in the vision leading to blind spots), sensory auras like tingling and numbness involving the arm, face, hand, lips, and tongue of the unilateral side of the body [10,11].

According to the international classification of headache disorders (ICHD-3rd edition) [9], unilateral cranio-autonomic manifestations comprise of conjunctival injection, lacrimation, eyelid edema, forehead/ facial sweating, facial flushing, rhinorrhea, nasal congestion, sense of ear fullness, miosis and/or ptosis, and are usually encountered by patients with cluster headache, short-lasting unilateral neuralgiform headache episodes (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), and paroxysmal hemicrania.

Cranial autonomic manifestations are documented to be encountered by three-fourths of migraine sufferers [1,12,13]. Trigeminal autonomic

cephalgia (TAC's) comprising of cranial-autonomic symptoms and migraine have a common pathophysiological pathway comprising of overstimulation of trigeminal autonomic reflex constituting a network of brainstem between the trigeminal nerve and facial parasympathetic flow [14-16]. In sufferers of migraine frequent emergence of cranio-autonomic symptoms contribute to misdiagnosis of a sinus headache or ocular issues, leading to irrelevant examinations and delayed care [17].

The prevalence of cranial autonomic symptoms in sufferers of migraine is reported by multiple studies [1,16-19], as summarized in Table 1. Few studies also reported cranio-autonomic symptoms strictly relevant to a specific variant of migraine [20,21]. Lacrimation is the single most frequent entity amongst all of the cranio-autonomic symptoms with the highest specificity, sensitivity, and positive predictive value. The most common bilateral symptom detected was forehead/facial sweating [4,22]. Allodynia was significantly associated with familial hemiplegic migraine [20]. Singh et al. reported about 16.7% prevalence of autonomic symptoms in the subtype of status migrainosus [22]. Migraine patients with autonomic features are reported to have a severe intensity of pain and are more likely to be suffering unilateral pain in comparison to those patients without autonomic symptoms [23,24].

TABLE 1. Overall prevalence of cranio-autonomic symptoms amongst migraine patients along with the frequency of specific symptoms, as quoted by previous studies in various populations

S.no	Cranio-autonomic symptoms	Reisco, et al.	Barbanti, et al.	Lai, et al.	Shin, et al.	Singh, et al.	Nasir, et al.	Obermann, et al.	Guyen, et al.	Gupta, et al.	Gelfand, et al.
1.	Overall prevalence amongst migraine patients	82%	37.4%	55.85%	-	70%	70.5%	26.9%	41.39%	73.07%	69.6%
2.	Lacrimation	49%	62.89%	44.2%	12.09%	24%	31.4%	91%	57.14%	43.58%	24.0%
3.	Eyelid edema	39%	47.70%	15.6%	11.57%	8%	16.2%	36%	66.23%	25.64%	8.0%
4.	Nasal congestion / rhinorrhea	20%	38.16%	46.68%	9.75%	24%	45.8%	41%	25.97%	10.25%	24.0%
5.	Conjunctival injection	44%	7.06%	23.8%	15.47%	22%	21.9%	57%	51.94%	35.89%	21.6%
6.	Sensation of ear fullness / Tinnitus	30%	-	-	20.15%	28%	-	-	-	-	28.0%
7.	Ptosis	42%	-	-	13.00%	18%	-	44%	-	-	17.6%
8.	Forehead / facial sweating	-	-	51.7%	12.87%	-	41%	-	-	-	24.0%
9.	Facial flushing	-	-	-	-	24%	-	-	-	-	

OBJECTIVE

The primary objective of our study is to evaluate the prevalence of cranio-autonomic symptoms amongst the patients suffering from migraines in our sample population. The secondary objectives are to correlate those symptoms with the onset of the disease, gender, age, and site of headache.

MATERIALS AND METHODOLOGY

This study was aimed to determine the frequency of cranio-autonomic symptoms in migraine conducted as a descriptive, cross-sectional study including the patients attending the neurology clinic at Dow University Hospital between January 2019 and December 2019. All patients who met the inclusion criteria were included in the study and assessed for their frequency of cranio-autonomic symptoms.

The patients were diagnosed with migraine according to the criteria of the International Classification of Headache Disorders (ICHD-3rd edition) [9]. The diagnosis was reaffirmed with clinical evaluation (history taking and physical examination) of all the patients by a specialized neurolo-

gist. The age group included was between 15 and 40 years. This study excluded all those patients either not fulfilling the criteria of migraine or exhibited other etiologies of cranio-autonomic symptoms, most importantly trigeminal autonomic cephalalgias (cluster headache, paroxysmal hemicrania, SUNCT, and SUNA) along with other origins of headache like glaucoma, meningitis, tension-type headache, ocular causes, refractive errors, head injury, allergic rhinitis/sinusitis, and autonomic neuropathy secondary to diabetes were also ruled out. A total of 132 individuals met the inclusion criteria and were inducted into the study by non-probability consecutive sampling. All analysis was conducted by using the Statistical Package for Social Science (SPSS) version 25.

RESULTS

The demographic characteristics of the study population are stated in Table 2. The mean age of the study population was 26.37 ± 6.31 years with a range from 15-40 years. The mean duration of diagnosis was 23.54 ± 16.52 months with a range of 6-60 months. While amongst CAS positive pa-

TABLE 2. Demographic data of the study population (n = 132)

S.no	Characteristics	Mean \pm Standard deviation	p-value
1	Mean age in years (n = 132)	26.37 \pm 6.31	0.264
	Males (n = 23)	25.13 \pm 5.65	
	Females (n = 109)	26.64 \pm 6.43	
	CAS positive (n = 73)	26.06 \pm 6.09	0.535
	CAS negative (n = 59)	26.76 \pm 6.59	
2	Duration of diagnosis in months (n = 132)	23.54 \pm 16.52	0.021
	In males (n = 23)	17.47 \pm 12.39	
	In females (n = 109)	24.82 \pm 17.03	
	In CAS positive (n = 73)	22.43 \pm 15.39	0.401
	In CAS negative (n = 59)	24.91 \pm 17.85	
3	Number of CAS positive (n = 73)	2.27 \pm 1.27	0.504
	Males (n = 13)	2.07 \pm 1.11	
	Females (n = 60)	2.31 \pm 1.30	
4	Number of CAS with unilateral headache (n = 53)	2.22 \pm 1.25	0.621
	Number of CAS with bilateral headache (n = 20)	2.40 \pm 1.35	
5	Duration of diagnosis in months with unilateral headache (n = 97)	24.18 \pm 16.28*	0.475*
	With CAS positive (n = 53)	22.30 \pm 15.26**	
6	Duration of diagnosis in months with bilateral headache (n = 35)	21.77 \pm 17.28*	0.906**
	With CAS positive (n = 20)	22.80 \pm 16.12**	

All values are computed through an independent t-test.

* Comparison among localization of headache and duration of diagnosis in the study population (n = 132).

** Comparison of localization with the duration of diagnosis amongst CAS positive patients (n = 73).

tients, the mean age was 26.06 ± 6.09 years, and the mean duration of diagnosis 22.43 ± 15.39 months (no significant difference). 4/5th of the study population comprised of females. No significant difference was detected among both genders in lieu of the number of CAS suffered by an individual. The frequency of cranio-autonomic symptoms was observed among 55.3% of the patients with migraine in our study. Amongst the individuals suffering from CAS, 1/3rd were only having 1 symptom, while 2/3rd were suffering from more than 1 symptom. The most common symptom observed was lacrimation (56%), followed by nasal congestion (31%), rhinorrhea (28%), ciliary injection (26%), and facial sweating (26%). The least prevalent symptom was ptosis, observed in only 4%. The study population comprised of unilateral headache (73.48%) more than bilateral headache (26.51%), while amongst the CAS positive patients, 72.60% were suffering from unilateral headache and the rest 27.39% from bilateral headache. The frequency and correlation of cranio-autonomic symptoms amongst gender are summarized in Table 3.

Lacrimation was predominantly associated with the male gender ($p = 0.096$), while forehead/facial sweating prevailed in females ($p = 0.162$). Around 55% of the study population was categorized between 21 and 30 years. Among all the cranio-autonomic symptoms, ciliary injection manifested in unilateral rather than a bilateral headache in the migraine patients ($p = 0.055$), shown in Table 4. The ciliary injection was found exclusively common in the same age group ($p = 0.020$), as shown in Table 5.

DISCUSSION

Migraine is a prevalent debilitating neurological disorder represented by frequent episodes of pounding headache along with sequences of neurological, gastrointestinal, and autonomic manifestations [25-27]. Significant studies quoted the connection between migraine episodes and the appearance of cranio-autonomic symptoms and even depicted the same pathogenesis [28,29]. In lieu of these studies, we calculated the frequency of cranio-autonomic manifestations among sufferers of

TABLE 3. Frequency of cranio-autonomic symptoms specified by gender ($n = 73$)

S.no	Symptoms	n (%)	Male (n = 13)	Female (n = 60)	p-value
1	Lacrimation	41(56.16)	10 (76.92%)	31 (51.66%)	0.096*
2	Nasal Congestion	23(31.50)	3 (23.07%)	20 (33.33%)	0.533**
3	Rhinorrhea	21(28.76)	2 (15.38%)	19 (31.66%)	0.323**
4	Ciliary injection	19(26.02)	5 (38.46%)	14 (23.33%)	0.303**
5	Forehead/facial sweating	19(26.02)	1 (7.69%)	18 (30.00%)	0.162**
6	Ear fullness	16(21.91)	2 (15.38%)	14 (23.33%)	0.720**
7	Facial flushing	14(19.17)	3 (23.07%)	11 (18.33%)	0.705*
8	Eyelid edema	10(13.69)	1 (7.69%)	9 (15.00%)	0.679**
9	Ptosis	3(4.10)	0 (0.00%)	3 (5.00%)	0.630**

* denotes values computed through Chi-square test

** denotes values computed through Fisher's exact test

TABLE 4. Correlation of cranio-autonomic symptoms with localization of headache

S.no	Symptoms	Localization of headache		p-value
		Unilateral (n = 53)	Bilateral (n = 20)	
1	Lacrimation	31 (58.49%)	10 (50.00%)	0.514*
2	Nasal Congestion	16 (30.18%)	7 (35.00%)	0.693*
3	Rhinorrhea	13 (24.52%)	8 (40.00%)	0.193*
4	Ciliary injection	17 (32.07%)	2 (10.00%)	0.055*
5	Forehead/facial sweating	12 (22.64%)	7 (35.00%)	0.283*
6	Ear fullness	10 (18.86%)	6 (30.00%)	0.349**
7	Facial flushing	9 (16.98%)	5 (25.00%)	0.509**
8	Eyelid edema	7 (13.20%)	3 (15.00%)	1.000**
9	Ptosis	3 (5.66%)	0 (0.00%)	0.557**

* denotes values computed through Chi-square test

** denotes values computed through Fisher's exact test

TABLE 5. Correlation of cranio-autonomic symptoms with different age groups

S.no	Symptoms	Age groups			p-value
		15-20 (n = 25)	21-30 (n = 73)	30-40 (n = 34)	
1	Lacrimation	4 (16.00%)	26 (35.61%)	11 (32.35%)	0.126*
2	Nasal Congestion	5 (20.00%)	13 (17.80%)	5 (14.70%)	0.883**
3	Rhinorrhea	4 (16.00%)	12 (16.43%)	5 (14.70%)	1.000**
4	Ciliary injection	1 (4.00%)	16 (21.91%)	2 (5.88%)	0.020**
5	Forehead/facial sweating	4 (16.00%)	10 (13.69%)	5 (14.70%)	0.934**
6	Ear fullness	2 (8.00%)	10 (13.69%)	4 (11.76%)	0.861**
7	Facial flushing	4 (16.00%)	7 (9.58%)	3 (8.82%)	0.559**
8	Eyelid edema	3 (12.00%)	4 (5.47%)	3 (8.82%)	0.461**
9	Ptosis	2 (8.00%)	1 (1.36%)	0 (0.00%)	0.093**

* denotes values computed through Chi-square test

** denotes values computed through Fisher's exact test

migraine visiting our clinics for a checkup. In our study, we established the prevalence of cranio-autonomic symptoms in 55% of patients with migraine. Nonetheless, the results of studies mentioned in the table above have a prevalence of cranio-autonomic manifestations ranging from 26-82% by utilizing International criteria for headache disorders (ICHD) [1,4,13,16-19,21-24].

Lacrimation, the most prevalent cranio-autonomic symptom recognized by numerous studies of migraine, was recorded as 56% in our study population suffering from CAS correlating with other studies [1,13,17,22], a greater ratio was detected in many studies [4,16,18,21] and lesser when corresponded with results of one study [23]. The prevalence of lacrimation was characteristic in the Western population [23], and not frequent in inhabitants of South Korea [16]. Conjunctival injection, the second most common cranio-autonomic symptom of migraine was found in 26% of our study population, which was similar to numerous studies [4,16,18,21,22,24], but reported decreased incidence in others [1,13,23]. Barbanti et al. demarcated a decreased prevalence of conjunctival injection when correlated with our study, stating it less prevalent in the inhabitants of Rome [17]. The prevalence of nasal congestion/rhinorrhea was 28-31% in our study population which is in approximation with few studies [1,13,18,21] and less frequent when corresponded with other studies [4,16,18,23]. South Koreans were prominent with a limited incidence of nasal congestion within their population [16]. Eyelid edema was recorded in 13.69% of our study participants, an outcome resembling to various studies [4,16,18,21,22], but few studies showed its higher incidence than ours [1,13,17,23]. United States of America (USA)

manifested markedly low occurrence of eyelid edema as a cranio-autonomic symptom of migraine [21], while it is a common manifestation in the population of Turkey [13,25]. Around 73% of our study population encountered localized unilateral headache in approximation with outcomes of limited studies, while the rest complained of bilateral headaches [17,21,22]. Only one study conducted in the pediatric population conferred bilateral headaches more common than unilateral in migraines [30]. The Incidence of a sensation of air fullness/tinnitus was detected in 22% of our population which is synchronous with many studies [1,16,18,21]. Contrastingly, this symptom was absent in results conducted by various other studies [4,13,16,17,22,23]. Increased prevalence was reported in the population of Spain [1]. Ptosis, another cranio-autonomic manifestation in sufferers of migraine had the least frequency recorded with only 4% in our sample size, corresponding with some studies [16,21], but was found higher in few other studies [1,18,23]. Nonetheless, it was absent in countable studies [4,13,17,22]. Incidence of forehead/facial sweating was reported as 22.6% in CAS positive patients, which is parallel with negligible studies [16,18]. Higher prevalence was recorded in a population of Taiwan [22], and presented as a common symptom in the population of Pakistan previously [4], when compared with other studies [1,13,17,21,23]. The occurrence of facial flushing was detected 19% in sufferers of migraine with CAS positive symptoms mirroring the outcome of an insignificant study conducted in Rochester, USA [21]. While a pediatric study reported a similar combined facial sweating/flushing frequency of 24% [18].

In our study, Lacrimation was a prevalent symptom in males while forehead/ facial sweating was predominant in females. However, previous studies suggested forehead/ facial sweating as the most common bilateral symptom [4,18,22], meanwhile, in our study ciliary injection had a prominent association with a unilateral headache rather than a bilateral headache, in contrast to ptosis having an association with unilateral headache [18]. Another study reported nasal symptoms to be bilateral even in patients with a unilateral headache [19].

In our study, the frequency of occurrence of 1 cranio-autonomic symptom was calculated as 34%, contrasting to 43.6%-45.6% reported in previous studies [18, 30], 2 cranio-autonomic symptoms as 30%, 3 cranio-autonomic symptoms as 17%, 4 cranio-autonomic symptoms as 11%, and the rest 7% reported more than 4 symptoms. Studies with results approximating with outcomes of our study were Nasir et al. stating 52% occurrence of more than 1 cranio-autonomic symptoms, and forehead/ facial sweating being frequently manifested symptom [4]. Guven et al. concluded his findings with 35% as a combined percentage for the occurrence of 1 to 2 cranio-autonomic symptoms along with 24.5% having 3 cranio-autonomic symptoms synchronizing with our results [13]. Lai et al. calculated greater than 1 cranio-autonomic symptom in 56% of participants which is greater than our calculated results, with forehead/ facial sweating as a common cranio-autonomic symptom and least common being eyelid edema [22]. Obermann et al. concluded their results with 26.9% suffering from 1 cranio-autonomic symptom, 34.3% suffering from 2 cranio-autonomic symptoms, 15.4% suffering from 3 cranio-autonomic symptoms, and 4.9% suffering from 4 cranio-autonomic

symptoms, along with only 2% people suffering from more than 5 cranio-autonomic symptoms, contradicting the outcomes of our study [23]. Barbanti et al. quoted the prevalence of 1 cranio-autonomic symptom as 53%, 2 cranio-autonomic symptoms as 38.2% while 3 or more cranio-autonomic symptom as 8.8% [17]. Gelfand et al. conferred 44% of patients with 1 cranio-autonomic symptom and the rest 56% having more than 1 cranio-autonomic symptoms, which when further elaborated had 28% individuals with 2 symptoms, 14% had 3 symptoms, 6% had 4 symptoms, and 9% had more than 4 cranio-autonomic symptoms [18]. Lastly, a study conducted in Turkey documented unilateral headache in 62.9% of sufferers of migraines with CAS, while 37.1% with a bilateral headache, when approximated with our study [25].

CONCLUSIONS

Cranio-autonomic symptoms were found frequent in our population, along with many factors elaborated contrasted to previous studies. The overall frequency was in approximation to various studies conducted in the past, and significant differences among gender, age groups, duration of disease, and a number of symptoms in an individual were found comparable with the literature. These cranio-autonomic symptoms may present as confounding factor in the physician's daily practice to diagnose migraine in lieu of overlapping signs and symptoms with trigeminal autonomic cephalgias, hence a thorough clinical examination and proper history taking can guide neurologist towards accurate diagnosis and subsequent relevant treatment.

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