



6-2016

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Recommended Citation

Nasir, Sadaf; Abrar, Naureen; Sher, Khalid; and Shahnaz, Shahnaz (2016) "Frequency of cranial autonomic symptoms (cas) in migraine patients," *Pakistan Journal of Neurological Sciences (PJNS)*: Vol. 11: Iss. 2, Article 4.

Available at: <http://ecommons.aku.edu/pjns/vol11/iss2/4>

FREQUENCY OF CRANIAL AUTONOMIC SYMPTOMS (CAS) IN MIGRAINE PATIENTS

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Date of submission: February 15, 2016 **Date of revision:** May 17, 2016 **Date of acceptance:** May 25, 2016

Background: The presence of cranial autonomic symptoms often leads to a misdiagnosis of sinus headache or ocular problems in adult migraineurs, leading to unnecessary investigations & delaying treatment. **Objective:** This study was done to determine the frequency of cranial autonomic symptoms (CAS) among migraine patients presenting to neurology ward of tertiary care hospital in Karachi. **METHODS:** This descriptive cross sectional study was conducted in duration of one year in Neurology Ward Jinnah Postgraduate Medical Center, Karachi. Total 105 patients of age 18-65 years, either gender, diagnosed cases of migraine of >1 year duration were consecutively selected. **RESULTS:** Mean \pm SD age was 35.08 ± 10.18 years. Mean \pm SD duration of migraine at was 3.68 ± 1.42 years. Majority of patients were females i-e; 59% (n=62). Frequency of CAS was more (75.8%) in patients of 21-40 years age compared to elder and very younger age patients (P value = 0.303). Female patients had very higher incidence of CAS (77.4%) compared to their male (P value < 0.049). Frequency of CAS was 58.82% with history of up to 1 year of migraine, 68.18% with history of 2-3 years & 74.24% with 4-5 years history of migraine. (P value 0.002). **CONCLUSION:** The CAS in migraine patients are very frequently present. All migraine patients should be evaluated for cranial autonomic symptoms from the day one of their diagnosis.

KEY WORDS: Migraine, Cranial autonomic symptoms.

INTRODUCTION

Of all the painful states that afflict humans, headache is undoubtedly the most frequent and common reason for seeking medical help. Headache has over 300 different types and different etiologies; migraine is one of them and continues being an under diagnosed condition in many of cases as it can be accompanied by symptoms commonly associated with other causes of facial pain. Out of 28 million people in USA who have history of headache and symptoms which mimic the typical migraine only 48% are diagnosed of migraine. In Pakistan the prevalence of migraine was found to be around 30%, and about twice as frequently in women as in men⁵. Migraine headaches, which are often, misdiagnosed as sinus or tension headaches affects work, social and leisure activities & has tremendous impact on a person's life⁶. WHO in 2004 released a report placing migraine on 19th rank with which migraine sufferers live years of their life with disability. ⁷These may occur as often as several times per week or as rarely as once or twice a year⁸. Cranial autonomic symptoms (CAS) are typically associated

with trigeminal autonomic cephalgias, such as cluster headache⁹. However they may also occur in patients with migraine. The frequency of symptoms is reported to vary widely from 27% to 73% in different studies.^{10,11,12} Recognition of CAS as a common component of migraine is important diagnostically and thus therapeutically. In a study conducted on pediatric patients, nearly 40%¹³ and in another study conducted on adult patients it was found that 52% were initially mislabeled as having sinus related headaches¹⁴. The international Classification of Headache Disorders, second edition (ICHD-II)¹⁵ includes conjunctival injection, lacrimation (or both), nasal congestion, rhinorrhea (or both), eyelid edema, forehead and facial sweating, forehead/ facial flushing and/or miosis & ptosis. In ICHD-III, a sense of aural fullness will be added as a cranial autonomic symptom.¹⁶ The international studies have documented variability in prevalence of CAS among migraine patients however no study was done at local level. The current study has evaluated and measured the burden of CAS among migraine patients in tertiary care hospital. Failure to recognize which, may lead to

unnecessary investigations and delaying appropriate migraine therapy.

MATERIAL AND METHODS

This was a descriptive cross sectional study carried out in Neurology department JinnahPostgraduate Medical Center, Karachi from 1st January 2015 to 31st December 2015. Estimated prevalence of CAS among migraine patients taken at rate of 15.6%¹², margin of error 7%, & level of significance 95% and using WHO's sample size calculator the calculated sample size came was 103 ~ 105. Non probability consecutive sampling technique was used to select sample. Informed consent was taken from the patients and purpose of study was explained to them. Diagnosed cases of migraine for at least >1 year, of either gender with age between 18 to 60 years and ready to participate in the study were included. Patients fulfilling criteria for Trigeminal autonomic cephalalgias, tension type headache, head injury, bell's palsy, space occupying lesion of brain, patients suffering from autonomic neuropathy due to diabetes mellitus, glaucoma, uveitis, recent ophthalmological and ENT surgery and patients having symptoms of allergic rhinitis and nasal obstructive symptoms were excluded from the study. Permission for the data collection was taken from Ethical committee of JPMC. The researcher collected data on a predesigned pro forma including demographic variables like name, age, gender and residence, further data regarding presence of CAS (conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, forehead/ facial sweating, forehead/ facial flushing and miosis or ptosis) were also collected. The data entry and analysis was done using SPSS version 19. Mean \pm SD was expressed for continuous variable like age, duration of disease & duration of migraine attack. Frequency & percentages were expressed for gender & residence (rural or urban), number of attacks of migraine & presence of CAS. The effect modification of outcome variable (frequency of CAS) due to age, gender, & duration of disease were analyzed by stratification of these variables followed by application of the chi-Square test with a P value significance of <0.05. Selection criteria were strictly followed to control for the potential confounders.

RESULTS

The current study assessed the frequency of cranial autonomic symptoms among migraine headache patients. Mean \pm SD age of patients was 35.08 ± 10.18 years with a range from 19-60 years. Mean \pm SD duration of migraine at time of presentation was

3.68 ± 1.42 years & minimum & maximum durations were 01 & 05 years respectively. (Table1).

Table: 1. Basic characteristics. (n= 105)

Variable	Minimum	Maximum	Mean	Standard deviation
Age of the Patient	19	60	35.08	10.18
Duration of Migraine (Years)	1	5	3.68	1.42
Duration of migraine attack (hours)	4	72	25.14	9.89

Further it was noted that mean \pm SD duration of attack of migraine headache was 25.14 ± 9.89 hours with the range of 4 to 72 hours. (Table1). It was observed that nearly two third of the patients (62.86%, n=66) were of 21-40 years of age, (29.52%, n = 31) were of age 41-60 years while remaining 7.62% (n= 8) were of age upto 20 years. Majority of patients were females i-e; 59% (n=62). Equal distribution was noted as far as residence was concerned. Urban residents were 49.5% (n= 52). Majority of patients (62.9%, n=66) had history of migraine for 4-5 years, other 21%, (n= 22) had migraine for 2-3 years while only 16.2% (n= 17) patients presented with upto 1 year history of migraine. Frequency of cranial autonomic symptoms (CAS) in migraine patients (the primary outcome) were detected among 70.48% (n= 74 out of 105). (Figure1) and forehead/ facial sweating was most common symptom. (Table:2)

Figure: 1. Frequency of cranial autonomic symptoms in Migraine patients. (n=105)

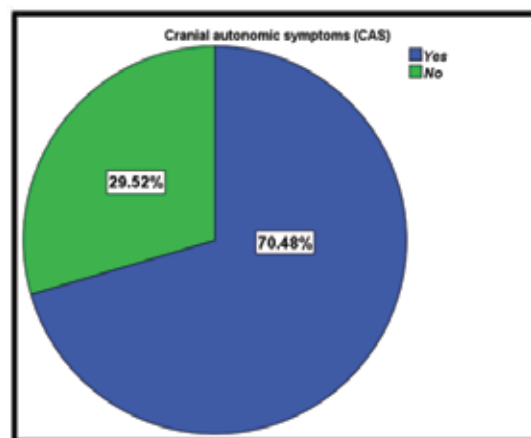


Table: 2. Frequency of different cranial autonomic symptoms.

Duration of disease	Frequency	Percentage
Forehead/ facial sweating	43	41
Lacrimation	33	31.4
Nasal congestion	26	24.8
Conjunctival injection	23	21.9
Rhinorrhea	22	21
Eyelid edema	17	16.2

To evaluate the effect modification of outcome variable by other variables we conducted the stratified analysis. It was found in this analysis that frequency of cranial autonomic symptoms (CAS) was more (75.8%) in patients of 21-40 years age compared to elder and very younger age patients (i-e; 61.3% in 41-60 years age group & 62.5% in upto 20 years age group). (P value = 0.303; Table: 3).

Table: 3 Effect of age on frequency cranial autonomic symptoms in Migraine patients.

Age of the Patient	Cranial Autonomic Symptoms		Total	P value
	Yes	No		
Upto 20 Years	5	3	8	0.303
	62.5%	37.5%	100.0%	
21-40 Years	50	16	66	
	75.8%	24.2%	100.0%	
41-60 Years	19	12	31	
	61.3%	38.7%	100.0%	
Total	74	31	105	
	70.5%	29.5%	100.0%	

It was significantly noted that female patients had very higher incidence of CAS (77.4%) compared to their male counterparts (60.5%). (P value < 0.049; Table: 4).

Table: 4. Effect of gender on frequency cranial autonomic symptoms in Migraine patients.

Gender	Cranial Autonomic Symptoms		Total	P value
	Yes	No		
Female	48	14	62	0.049
	77.4%	22.6%	100.0%	
Male	26	17	43	
	60.5%	39.5%	100.0%	
Total	74	31	105	
	70.5%	29.5%	100.0%	

Residence showed only minimal difference and urban patients had 71.2% frequency of CAS compared to 69.8% among rural patients. (P value 0.525). However; it was worth noting that longer the duration of disease, higher was the frequency of cranial autonomic symptoms (CAS) and the finding was significant. (P value 0.002). The frequency of CAS was 58.82% among patients with history of upto 1 year duration of migraine, 68.18% among patient with history of 2-3 years & 74.24% among 4-5 years history of migraine.

DISCUSSION

Migraine is a common and disabling neurological disorder.^{17,18} Daily many patients in our neurology OPD present with episodic severe throbbing headache which is diagnosed as migraine. It is characterized by recurrent attacks of headache and combinations of neurologic, gastrointestinal, and autonomic changes. Unilateral cranial autonomic symptoms (UAS) are features of cluster headache, paroxysmal hemicrania, and SUNCT.^{2,9,12,17} Studies have found an association between cranial autonomic symptoms and migraine attack, hypothesizing possible pathogenesis.^{10,12,19} On the basis of these considerations and on suggestion of a cranial parasympathetic activation in some migraineurs, we evaluated the frequency of cranial autonomic symptoms during cephalalgic attacks in patients presenting to our institute with the symptoms of migraine. Our study shows that in migraineurs, cranial autonomic symptoms are common. It was found that incidence of cranial autonomic symptoms (CAS) in migraine patients was 70.48%. Our results are correlating with similar results of other studies. However; the incidence of CAS reported by various studies range from 27% to

73%^{7,10,12,20,21,22}. Our study did not include the pediatric patients. But in a recent study²³ high frequency of cranial autonomic symptoms was found in pediatric migraineurs (i.e; 62%, which can rise to 70% with inclusion of new proposed International Headache Society criteria)¹⁶. We have not used the new proposed International Headache Society criteria otherwise the incidence rate might have been found at least 10% more. In a prospective study conducted on migraine patients, the prevalence of >1 CAS was 56%¹⁷. Likewise; in the current study we noted that about 52% patients had >1 CAS e.g; forehead/ facial sweating, lacrimation, nasal congestion, conjunctival injection, rhinorrhea, and eyelid edema. Presence of more than one CAS in migraine patients clearly directs its association with cranial autonomic symptoms. Lai TH, et al., reported that among migraine patients with CAS, forehead/ facial sweating was the most common (51.7%) followed by lacrimation (44.2%), nasal congestion (25.2%), conjunctival injection (23.8%), rhinorrhea (21.5%), and eyelid edema (15.6%)⁹. The current study found very similar pattern but the incidence of these symptoms was lesser. Accordingly; forehead/ facial sweating was the most common (41%) followed by lacrimation (31.4%), nasal congestion (24.8%), conjunctival injection (21.9%). Similarly; one study found that unilateral cranial autonomic symptoms occurred during migraine attacks in 81 patients (45.8%); during attacks, ocular symptoms (conjunctival injection, lacrimation, or eyelid edema) occurred alone in 33 patients and in combination with nasal symptoms (nasal stuffiness or rhinorrhea) in 37 patients. Isolated nasal symptoms occurred in 11 patients. Other studies from other populations have documented varying frequencies of these symptoms in migraine patients.^{10,12,24,25} Mean age of our patients was 35 years however; very young age i.e; 19 years old patients were also included & nearly two third patients (62.86%, n=66) were of 21-40 years. These findings do not match with other studies which is due to the fact that migraine is prevalent in all age groups & different studies focus different age groups^{11,18,21,26}. We had taken only the adult patients. Other demographic feature of our patients was the gender distribution. We noted that majority of patients were females i.e; 59% that agrees with findings of previous researchers^{10,11,20,22} But; in the current study, the stratified analysis significantly showed that the female patients had very higher incidence of CAS (77.4%) compared to their male counterparts (60.5%). (P value < 0.049). Regarding age the stratified analysis significantly showed that middle aged (21-40 years) patients had higher frequency of cranial autonomic symptoms compared to

elder and very younger age patients (P value = 0.303). Living in a rural or urban setting was also doubted to be an effect modifier but the current study ruled out it and found that residence showed only minimal difference as the urban living patients had CAS incidence of 71.2% compared to 69.8% in rural patients. (P value = 0.525). One important aspect of this study was evaluation of duration of migraine since its diagnosis and look for its association with incidence of cranial autonomic symptoms in our patients. We hereby document that it was a significant finding in our analysis that longer the duration of disease, higher was the frequency of CAS. (P value 0.002). Studies have documented that the patients with unilateral cranial autonomic symptoms present with more severe headaches (P value < 0.0002) and more strictly unilateral headaches (P value < 0.0004) than those without unilateral cranial autonomic symptoms, findings that suggest trigeminal-autonomic reflex activation.¹⁰ Apart from that it has been suggested that a general autonomic hyperactivity (especially parasympathetic) may also be found more frequent in different populations of CAS-positive migraineurs compared to CAS negative migraineurs^{5,8,15} but exploring these was beyond the scope of the current study. Although the study was of limited scope due to limited financial & time resources and smaller sample size yet it has investigated an important aspect of clinical pictures of migraine patients. The study also found the magnitude of burden of cranial autonomic symptoms in such patients which previously had been a neglected issue in our part of world. The current study suggests that more in depth and larger studies should be conducted on this aspect of migraine.

CONCLUSION

It is evidence based fact that cranial autonomic symptoms (CAS) such as lacrimation, conjunctival injection, eyelid edema and nasal congestion, which are the hallmark of trigeminal autonomic cephalalgias may also occur in migraine patients. The current study evaluated the magnitude of burden of these symptoms in local migraine affected patients. The study found that the cranial autonomic symptoms in migraine patients are very frequently present. Forehead/ facial sweating, lacrimation, nasal congestion, conjunctival injection, rhinorrhea and eyelid edema were the commonest symptoms. Female gender, middle age, and longer duration of disease are associated with higher incidence of CAS. The study recommends that all migraine patients should be evaluated for cranial autonomic symptoms from the day one of their

diagnosis. Failure to recognize CAS would lead to misdiagnosis or under diagnosis of a common treatable condition resulting in increment in patient's misery. Its early recognition could have therapeutic implications, given the potential large scale recruitment of peripheral neurovascular 5-HT 1B/1D receptors (the target of acute migraine treatment) in such patients.

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Conflict of interest: Author declares no conflict of interest.

Funding disclosure: 58

Author's contribution:

Sadaf Nasir: Study concept and design, protocol writing, data collection, data analysis, manuscript writing, manuscript review

Naureen Abrar: data collection, data analysis, manuscript writing, manuscript review