Cranial Autonomic Symptoms in Migraine: An Observational Study

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Objective: Our aim was to observe frequency of cranial autonomic symptoms (CAS) in migraineurs (primary) and its relation with laterality of headache or other factors, if any. Background: Migraine episodes have headaches with or without aura, and sometimes associated with systemic autonomic nervous system symptoms. Primarily presence of cranial autonomic symptoms suggests diagnosis of TACs. But many studies reported cranial autonomic symptoms (CAS) ranging from 26% to 80% in migraine patients. Material and Methods: Consecutive patients of migraine attending our headache clinic were included in our study. Presence of CAS was recorded with respect to ocular, nasal, facial and aural symptoms along with headache characteristics and laterality information. Detailed clinical examination was performed. We used ICHD 3 (beta version) criteria. Results: Our study cohort comprised of 200 patients having mean (± SD) age 31.12 (± 10.67) years. There were 157 (78.5%), females. Out of 200 patients, 148 (74%) were having at least one CAS, of which 70% were having 2 or more CAS. Frequency of CAS was lacrimation (45.5%), conjunctival injection (34.5%), eyelid edema (34%), nasal congestion (9%), rhinorrhea (5%) and ptosis (4%). Bilateral CAS was present in 129 (87%) and unilateral CAS in 19 (13%) (OR 35.31; 95% CI 9.19 to 135.7), (P < 0.0001). Sunlight as a trigger was present in all 148 (100%) patients. Conclusion: Our study showed that CASs in migraine is common and bilateral. Sunlight triggers headache in almost all CAS positive patients.

Keywords: Autonomic symptoms, CAS, migraine and CAS, parasympathetic cranial autonomic symptoms, sympathetic cranial autonomic symptoms, trigeminal autonomic reflex

INTRODUCTION

Migraine, the most common neurological cause of disability worldwide, needs awareness and attention from researchers, clinicians, and patients.[1] Systemic autonomic nervous system symptoms like vomiting, diarrhea, constipation, tachycardia, coldness of extremities, nausea, etc., are well described in migraine patients. But cranial autonomic symptoms (CAS) are mostly described with Trigeminal Autonomic Cephalalgias (TACs).[2-4]

Migraineurs have trigemino-vascular system abnormality and autonomic system disturbances, it is logical to expect CAS in migraineurs.[5] Initial studies have shown the predominance of unilateral CAS (like TACs) but also suggested the presence of bilateral CAS in migraine.[6-8] Kaup et al.[9] suggested that side-locked migraineurs with CAS may be a different group and may lie between migraine and trigeminal autonomic cephalalgias (TACs). Studies done so far, have reported CAS to be present in a range of 26% to 73%. This wide variation and fewer studies are reasons for less emphasis on CAS in research and clinical use. However, recent studies have suggested CAS as a common component of migraine rather than an exception.[10-13]

Several studies have shown that patients are misdiagnosed as sinus headaches, confused with TACs, and sometime subjected to sinus surgeries.[14-18] Misdiagnosis puts these migraineurs at risk of inappropriate treatments and procedures and delays appropriate treatment.

Knowing frequency of CAS in migraineurs or observing such endo-phenotype will be helpful in resolving the above problems. These phenotypes (clinical features) can also give an insight into the biotype (pathophysiology).

Hence the study was designed to observe frequency of CAS in migraineurs.

MATERIAL AND METHODS

Standard protocol approval, ethical clearance, and consent

For this prospective study approval and ethical clearance was taken from the ethical committee (IEC No. 45/15). We enrolled patients in the study from March 2016 to November 2017, after taking informed written consent.
Study design and population
We performed cross-sectional observation of headache characteristics in patients presenting to headache clinic of neurology department. Inclusion criteria were - 1) Patients of all age groups; 2) diagnosis of migraine according to ICHD-3 (beta version). Exclusion criteria were - 1) diagnosis that was not a migraine. Patients (and/or their attendants, if present) were interviewed for the presence of perceptual (e.g., sense of ear fullness, nasal congestion) and observable CAS during headache episodes since the onset of their migraine, findings were confirmed by a headache expert after first interview. CAS occurring in more than or equal to fifty percent of headache episodes was considered as CAS positive. Patient flow in the study is shown in flow chart [Figure S2, Supplementary material].

Determination of cranial autonomic symptoms and other features
Leading questions were asked about the presence of 1) conjunctival injection, 2) lacrimation (apart from crying), 3) eyelid edema 4) nasal congestion, 5) rhinorrhea, 6) sense of ear fullness or pressure, 7) ptosis, 8) miosis, and 9) forehead and facial sweating or flushing, during headache episodes. Miosis was not expected to be observed by patient or attendants so this was considered for patients presenting with headaches during visit.

Grouping of CAS and other features
Patients were asked about the laterality of CAS in relation to headache. Headache location clubbed as bilateral (global, alternating hemi cranial, bifrontal, bitemporal, occipital), right sided (right hemi cranial, right frontal/temporal/occipital), left sided (left hemi cranial, left frontal/temporal/occipital), vertex and neck. Patients with CAS were clubbed into bilateral, ipsilateral and unilateral groups. Presence of even single CAS on both sides was considered bilateral. CAS and headache occurring on the same side but both changing sides were kept in an ipsilateral group. CAS and headache fixed to one side were considered unilateral CAS. For ease of understanding autonomic symptoms was divided into four categories according to neuro-anatomical innervations: (a) Ocular (conjunctival injection, lacrimation, eyelid edema, ptosis, miosis), (b) nasal (nasal congestion, rhinorrhea), (c) facial (facial flushing, facial sweating), and (d) aural (aural fullness) symptoms.

Data analysis
All the analysis was carried out on SPSS 16.0 version (Chicago, Inc., USA). For the analysis, the x² (Chi-Square), Fisher exact, and Student t-tests were used as appropriate. For observing co-occurrence of cranial autonomic symptoms, Odds Ratio (95% Confidence interval) was calculated [Table S1, Supplementary material].

Results
Total 200 patients with primary headache fulfilling ICHD 3 (beta version) criteria for migraine were interviewed in the study. Four patients qualified as probable migraine; however, they were included in the analysis.

Demographic characteristics of the sample
Out of 200 patients in study 128 (64%) belonged to the age group of 20 to 40 years (range 13-70 years; mean ± SD: 31.12 ± 10.67 years, median 30 years). Female patients were 157 (78.5%), and female to male ratio was 3.65:1. A family history of migraine was present in 74 (37%) cases.

Headache characteristics of subjects
History of headache duration was longer in 178 (89%) patients (1-6 years 60.5%, 7-12 years 19%, >12 years 9.5%). Chronic migraine (>15 days per month) was diagnosed in 54 (27%) patients. 145 (72.5%) patients had episodic migraine (including four probable migraine, and one patient with status migrainosus). Bilateral headache (see the grouping of features in material and methods section) was observed in 151 (75.5%) whereas 21 (10.5%) right-sided, 17 (8.5%) vertex pain, 9 (4.5%) left-sided and 2 (1%) had neck pain. Aura was present in 8 (4%) patients. Associated features like nausea (87.5%), vomiting (58%), phonophobia (98%), photophobia (98.5%), and vertigo (1.5%) were also observed in shown frequencies. Headache aggravation was observed with sunlight (98.5%), noise (97%), fasting (23%), and travel (14.5%) [Table 1].

Three patients had a history of surgery for headache, 2 underwent sinus surgery, and one rhinoplasty for deviated nasal septum without any post-op improvement. Two patients out of these three improved with medications for migraine; one discontinued follow up.

Cranial autonomic symptoms
Frequency
Out of 200 patients, 148 (74%) reported at least one cranial autonomic symptom. Lacrimation (45.5%) was the most common symptom followed by conjunctival injection (34.5%), eyelid edema (34%), aural fullness (27.5%), nasal congestion (9%), rhinorrhea (5%) and ptosis (4%) [Figure 1].

Combinations
Ocular symptoms were observed in 125 (84.5%) patients (most common). Out of these, 51 had only ocular symptoms, whereas 74 had it along with other CAS. ‘Nasal only’ (3), ‘facial only’ (8), ‘aural only’ (8) symptoms were observed separately. Non-ocular symptom combinations observed were facial with auricular (3) and nasal with facial (1). We observed each patient for the number of CAS present. Forty-five (30.4%) patients reported only ‘one CAS’, 37 (25%) ‘two CAS’, 20 (15.5%) ‘three CAS’, 18 (12.2%) ‘four CAS’, 17 (11.5%) ‘five CAS’, 9 (6.1%) ‘six CAS’ and 2 (1.4%) patients had ‘seven CAS’. Thus, two or more CAS was present in 70% of migraineurs [Figure 2].

Laterality
Bilateral CAS was present in 129 (87%) patients- a) Unilateral headache - 16 (11 right sided, 5 left sided) and b) Bilateral...
headache – 113. Unilateral CAS was present in – a) Headache and CAS side same and fixed - 3, b) Headache and CAS side same but both changing (ipsilateral) – 15 and c) Headache side and CAS side opposite (contralateral) – 1 [Table 2].

Comparison (CAS Vs. without CAS)

On segregating patients in those with CAS and without CAS in two groups, we tried to observe any association with demographic features and headache characteristics. Analysis for association was done with age, gender, family history, frequency and intensity of headache, duration of illness, nausea, vomiting, photophobia, phonophobia, aura, and aggravating factors like sunlight, noise, travel, and fasting.

When analyzed for the association of CAS with other factors aggravation with sunlight was observed in all patients of migraine with CAS. However, no factor was found to be significantly associated with cranial autonomic symptoms [Table 1].

**Discussion**

CAS is often under-reported and less discussed occurrence in migraine. It is established that trigemino-cervical complex (TCC) plays role in cranial autonomic symptoms by trigeminal autonomic reflex (TAR) or trigemino-facial reflex (superior salivatory nucleus fibers through facial nerve). This pathway is connected to brainstem nuclei in the midbrain (the lateral periaqueductal grey matter (PAG) and dorsal raphe nucleus (DRN)) and pons (the locus coeruleus). SSN (superior salivatory nucleus) has a connection to locus coeruleus and bilateral connections with trigeminal. Normally locus coeruleus nuclei inhibit each other. Brainstem nuclei have higher connections directly or indirectly to the posterior hypothalamus and many cortical areas.

It is also evident by previous studies that CASs can occur in headaches irrespective of underlying etiology. However, CASs had been considered a hallmark of TACs.

Diagnostic confusion arises when CAS is observed in other primary headache patients. Studies showed the presence of CASs in patients of migraine. At present, the treatment received by two groups (TACs vs. migraine) is different, so the correct diagnosis is important in these cases.

| Characteristics | CAS Present | CAS absent | P |
|-----------------|-------------|------------|---|
| Gender          |             |            |   |
| Male            | 28 (19)     | 15 (29)    | 0.13 |
| Female          | 120 (81)    | 37 (71)    |    |
| Diagnosis       |             |            |   |
| MoA*            | 142 (96)    | 50 (96)    | 0.94 |
| MA**            | 6 (04)      | 2 (04)     |    |
| Family history  |             |            |   |
| (74)            | 60 (55)     | 14 (27)    | 0.08 |
| Frequency       |             |            |   |
| <5/month        | 14 (10)     | 6 (12)     | 0.87 |
| 5 to 15/month   | 93 (62)     | 33 (63)    |    |
| >15/month       | 41 (28)     | 13 (25)    |    |
| Severity***     |             |            | 0.43 |
| Moderate        | 57 (39)     | 21 (40)    |    |
| Moderate to severe | 14 (09) | 2 (04) |    |
| Severe          | 77 (52)     | 29 (56)    |    |
| Associated symptoms |         |            |   |
| Nausea          | 133 (90)    | 42 (81)    | 0.08 |
| Vomiting        | 83 (56)     | 33 (63)    | 0.35 |
| Photophobia     | 147 (99)    | 50 (96)    | 0.10 |
| Phonophobia     | 145 (98)    | 51 (98)    | 0.96 |
| Aggravating factors |         |            |   |
| Sunlight        | 148 (100)   | 49 (94)    |    |
| Noise           | 145 (98)    | 49 (94)    | 0.17 |
| Fasting         | 37 (25)     | 09 (17)    | 0.25 |
| Travel          | 24 (16)     | 05 (10)    | 0.24 |

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**Table 2: Laterality of cranial autonomic symptoms in migraine patients**

| Unilateral (U/L) | B/L @ |
|------------------|-------|
| U/L**            | U/L***| I/L $^3$ |
| CAS*             | 3     | 1       | 15  |
| Conjunctival injection | 3 | 4 (3R,1L) | B/L |
| Lacrimation      | 1     | 1 (1L)  | 12  |
| Nasal congestion | 1     | 0      | 3   |
| Rhinorhea        | 0     | 0      | 1   |
| Eyelid edema     | 2     | 0      | 06  |
| Facial sweating  | 1     | 0      | 07  |
| Facial flushing  | 0     | 1 (1L) | R   |
| Aural fullness   | 2     | 4 (2,2,R) | B/L |
| Ptosis           | 2     | 1 (1L) | V   |

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*B/CAS – Cranial Autonomic Symptoms, R - right, L - left, V - vertex** **U/L - strictly Unilateral ***U/L; headache side – CAS were present on one side but headache location was bilateral or on opposite side*** I/L – Ipsilateral CAS (CAS were unilateral and on the side of headache but the headache side was changing) B/L - Bilateral CAS
Our study observed that seventy-four percent (74%) of patients had at least one CAS during headache attacks. This frequency suggests that in migraine, CAS is commoner than thought previously. In literature, there is wide variation in results ranging from 26% to 73% in migraine patients. A population-based study by Obermann et al.\(^\text{[10]}\) reported CAS in 26% of patients. Lai et al.\(^\text{[12]}\) reported CAS in 56% of patients. In contrast, Gupta R and Bhatia MS reported in 73% of patients with migraine. Using a scale for not missing even mild symptoms, one study by Riesco et al.\(^\text{[24]}\) reported it in 80% of chronic migraine patients. Another study by Gelfand et al.,\(^\text{[13]}\) however, in a pediatric population, reported CAS in 73% of patients.

This wide variation in reporting might be because of multiple factors playing a role in initial studies, including researchers’ bias that CAS is the hallmark of TACs and present unilaterally. Factors related to CAS itself like their variable intensity in migraine, bilateral occurrence making them less noticeable, not bothersome feature for patients. Study types, like population-based studies might be having the disadvantage of the less rigorous/focused interview where symptoms are not revealed due to lack of any leading questions.

But recent studies, probably by looking beyond the discussed factors in preceding lines, are pointing CAS as a rule rather than the exception.

Ocular CAS was observed in 125 (84.5%) patients compared to that of nasal CAS, 18 (12%). In experiments for TAR, after sectioning the seventh nerve, 20% vasodilatation still remains, attributed to antidromic-activation of trigeminal division contributing to CAS. Probably this is because of the predominant activation of ophthalmic division in migraine.\(^\text{[5]}\) Other studies have made similar observations. R Gupta and MS Bhatia reported nasal symptoms in 10.3%, Lai et al. reported it in 35.9% of cases, but still, it was considerably lower than that of ocular.\(^\text{[12]}\) So it is observed that nasal CAS is less common in patients with a migraine diagnosis.

Lacrimation (45.5%), conjunctival injection (34.5%), and eyelid edema (34%) were the three most common symptoms, followed by facial sweating (25%), facial flushing (17.5%), nasal congestion (9%), rhinorrhea (5%) and ptosis (4%). Lacrimation, being both an easily perceptible and observable feature inpatient with pain, has been observed most commonly in studies, as is the case in our study. But presence of unilateral and ipsilateral lacrimation in 14 (10%) patients suggests selective activation of efferent arm of TAR. Further, bilateral presentation is in line with the findings that bilateral headaches have more autonomic dysfunction than unilateral and supports that the superior salivatory nucleus has bilateral innervations from the trigeminal system. What factors decide bilateral salivatory nucleus stimulation by trigeminal is not clear. Findings are in concordance with previous studies. However, the study by Lai et al. showed facial sweating (28.8%) and lacrimation (24.6%) as the most commonly reported symptom and eyelid edema as the least.\(^\text{[12]}\) This study was done before the inclusion of aural fullness as CAS and in a different population. One study at the time of the start of ICHD 3 beta, which included aural fullness as CAS found it as the most common CAS in pediatric migraineurs. However, the study by R Gupta and MS Bhatia showed the same trend and showed lacrimation (43.6%), redness of eye (37.2%), periorbital swelling (25.6%) followed by nasal symptoms (10.3%). Observing facial autonomic symptoms among different CAS items is unique as it probably originates from both parasympathetic hyper-functioning and sympathetic deficit simultaneously. This was the second most common CAS group showing facial flushing (parasympathetic) in 17.5% and facial sweating (sympathetic) in 25% of patients. This higher frequency might be because of similar neuro-anatomical innervations like that of ocular. Parasympathetic activation causes vasodilatation of ICA, which leads to flushing and increased facial skin temperature. Following this, compression of sympathetic fibers around the ICA (oculo-sympathetic fibers) supplying medial forehead skin occurs. However, sweating in sympathetic dysfunction is thought to be explained by parasympathetic response of partially denervated muscarinic sweat glands. In experiments, exogenous CGRP has also been shown to increase sweat rate, present at trigeminal endings.\(^\text{[19]}\) Lai et al.\(^\text{[12]}\) reported it in 51% of cases. Amy et al.\(^\text{[13]}\) reported facial symptoms in 24% of pediatric patients, similar to our study. The reason for discordance with other studies is not apparent to us. Aural symptoms observed in 55 (27.5%) patients, supports the inclusion of this symptom in ICHD 3 beta. The trigeminal nerve also innervates the cochlear nucleus and superior olivary complex as per a study by Shore et al.\(^\text{[20]}\) Such connections have also been shown by Marano et al.\(^\text{[21]}\) However, observations by Gelfand et al. in the pediatric population showed aural fullness as the most common CAS.\(^\text{[13]}\) Differential activation of the trigeminal autonomic pathway (affecting more to cochlea-vestibular connections compared to ophthalmic division) in children or a common occurrence of ear and throat problems in childhood might be the cause of such discrepancy.

CAS was observed bilaterally in 87 percent of patients. Although previous studies have suggested that unilateral pain is common in subjects with cranial autonomic symptoms (Kaup
In our study, 129 (87%) patients had bilateral symptoms, 19 (13%) had unilateral/ipsilateral CAS. This tendency for bi-laterality may explain why studies examining only for unilateral cranial autonomic symptoms in patients of migraine reported a lower prevalence of cranial autonomic symptoms (26.9%–45.8%) (Obermann et al., 2007). Dysfunction in the normal inhibitory capacity of locus ceruleus to each other and bilateral activation of superior salivatory nucleus appears to be the mechanisms involved in migraine. However, factors deciding unilateral vs. bilateral activation are still not clear. Inherent or genetic predisposition in migraineurs, pain/noceception threshold, pain matrix connections, and modulation by hypothalamic or cortices need to be explored. The association between unilateral migraine pain and cranial autonomic symptoms is not consistent (Lai et al. 2009). Observing the presence of, sensory sensitivity symptoms, such as photophobia and phonophobia more often bilaterally in migraineurs and unilateral in trigeminal autonomic cephalalgias (Irimia et al., 2008), it is not illogical to assume that cranial autonomic symptoms would also occur on both sides in patients of migraine. However, another possibility might be that sample was having bilateral headaches. One patient reported contralateral CAS, however, importance and mechanism, if any, is not clear to us.

On segregating patients in those with CAS and without CAS in two groups, we tried to observe any association with demographic and headache characteristics. We analyzed any association with age, gender, family history, frequency and intensity of headache, duration of illness, nausea, vomiting, photophobia, phonophobia, aura, and aggravating factors like sunlight, noise, and fasting. Our study observed that patients of “migraine with CAS” were having more of these symptoms compared to that of “migraine without CAS” and we observed nausea in 76% vs. 24%, vomiting in 72% vs. 28%, photophobia in 75% vs. 25%, phonophobia in 74% vs. 26%. In aggravating factors with sunlight, it was 75% vs. 25%, noise 75% vs. 25%, fasting 80% vs. 20%, travel 83% vs. 17%.

Chronic migraine patients were more in CAS positive group (76% vs. 24%). Unexpectedly high number of chronic migraineurs in our study was probably due to an inherent bias of specialized site of data collection i.e., headache clinic at a tertiary care center (in which more resistant and non-responsive patients are followed). Headache was severe in CAS-positive patients (73% vs. 27%). When analyzed for the association of CAS with these factors, sunlight was observed as aggravating factor of headache in all CAS-positive patients. This means, all patients having “migraine with CAS” were having aggravation of their headache on sunlight exposure. No factor was found to be significantly associated with cranial autonomic symptoms. In some studies, headache was severe and associated symptoms (nausea, photophobia and phonophobia) were more in cranial autonomic symptom positive group (Lai et al. 2009) and some have reported a high number of patients with photophobia (Gupta R, Bhatia MS, 2007). This observation appears to be new in our study and possibly can be explained by light aversive behavior, a surrogate of photophobia, induced by CGRP in migraine patients. Another entity to be ruled out in these patients is ictal epileptic headache (IEH). CAS-positive patients may have a predisposition for pure cranial autonomic activation (sunlight as a trigger). According to previous studies, neuronal activation at a particular threshold can activate only the autonomic system (in the absence of nonautonomic activation) and manifest as headache (IEH). However, sunlight also aggravated headaches in patients without CAS. Such assumptions need further confirmation with ictal EEG recordings and response to anti-epileptics but obviously, open an area for further research.

Limitations and future research
As the study was interview-based recall bias cannot be ruled out. Combination of local language questionnaires, recording of videos, or interviews by showing analogous videos might improve documentation of subjective symptoms which we came to know by experience of this study. Simultaneous objective documentation of autonomic activation and its correlation with clinical history is needed in future studies.

CONCLUSION
Our study showed that CASs in migraine are commoner (74%) than thought before of which a good number (70%) have two or more CAS, commonly seen bilaterally (87%), ocular and facial CAS are observed more (compared to that of nasal), non-ocular CAS rarely present alone and sunlight triggers headache in almost all CAS positive patients however no significant association observed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Table S1: Odds Ratio (95% Confidence interval) for Co-occurrence of cranial autonomic symptoms in patients of migraine.

|                | Eye related symptoms | Nose related symptoms | Ear symptoms | Facial Symptoms |
|----------------|----------------------|-----------------------|--------------|----------------|
| Conjunctival   |                      |                       |              |                |
| injection      | L.                    | E.                    | N.           | F.             |
| Conjunctival   | -                    | 2.888                 | 1.148        | 3.136          |
| Injection      | (1.387-6.015)        | (1.745-7.410)         | (527-2.501)  | (1.351-7.277)  |
| L.             | 0.953(1.186-4.890)   | 1.628(1.293-9.045)    | 0.960(1.04-8.884) | 1.228(0.464-3.252) |
| E.             | 3.596(1.745-7.410)   | 2.455(1.036-31.445)   | 3.531(1.624-19.972) | 2.240(0.988-5.080) |
| N.             | 5.708 (1.036-31.445) | 3.531(1.624-19.972)   | 1.622(1.157-16.716) | 4.714 (1.783-12.464) |
| F.             | 0.953(1.186-4.890)   | 1.628(1.293-9.045)    | 0.960(1.04-8.884) | 1.228(0.464-3.252) |

- Significant values are highlighted.
Figure S2: Flow chart showing patients flow in the study