

Prevalence of cranial autonomic symptoms in frequent episodic tension-type headache: A post hoc analysis of the cross-sectional Migraine in Poland study

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Conflict of interest

In the past 24 months, Marcin Straburzyński, PhD, Magdalena Nowaczewska, PhD, and Ewa Katarzyna Czapinska-Ciepiela, PhD, have received honoraria for lectures (Pfizer, AbbVie, Bausch Health Poland, Teva; Pfizer, Teva; Teva, Angelini Pharma Polska, Pfizer, respectively) and compensation for participation in clinical trials (Amgen; Amgen, AbbVie; SK Life Science, AbbVie, Cerevel, respectively). Marcin Straburzyński has also received compensation for scientific consulting (NEUCA Group). Marta Waliszewska-Prosół, PhD, has received honoraria for lectures (Pfizer, AbbVie, Teva). Anna Gryglas-Dworak, PhD, has received compensation for conducting clinical trials (Lundbeck Poland, Amgen, Pfizer, AbbVie, Teva).

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Abstract

Background. Cranial autonomic symptoms (CASs) include lacrimation, conjunctival injection, rhinorrhea, nasal congestion, facial flushing or sweating, ptosis, and myosis. These symptoms may be associated with trigeminal autonomic cephalalgias (TACs) and migraine.

Objectives. The aim of the study was to assess whether CASs are also reported by patients with frequent episodic tension-type headache (eTH).

Material and methods. A cross-sectional online survey of a large Polish population was conducted between August 2021 and June 2022. The analysis assessed diagnostic criteria for migraine and eTH, as well as the presence of allodynia, headache-related disability and symptoms of depression.

Results. The survey involved 3,225 respondents (age: 13–80 years, mean (M) = 38.9 years; 87.1% female). A total of 166 individuals met the diagnostic criteria for isolated frequent eTH without migraine or probable migraine with or without aura. Allodynia was present during the majority of attacks in 40 (24.1%) eTH subjects, while 86 (51.8%) eTH respondents reported at least 1 CAS during their headache attacks. The presence of at least 1 CAS was more prevalent in migraine than in eTH ($p = 0.001$). The respondents with at least 1 CAS during eTH attacks reported a higher burden associated with pain ($p = 0.024$) and higher Patient Health Questionnaire-9 (PHQ-9) scores ($p = 0.016$).

Conclusions. The prevalence of retrospectively reported CASs was high among individuals with eTH, which may potentially contribute to diagnostic errors. Cranial autonomic symptoms in eTH do not appear to be caused by severe pain or central sensitization.

Keywords: pain, migraine, tears, trigeminal nerve

Introduction

Headache and facial pain are highly prevalent in the general population.¹ However, these conditions are often accompanied by other symptoms and are rarely limited to pain alone. Trigeminal autonomic cephalalgias (TACs) and migraine may be accompanied by cranial autonomic symptoms (CASs) such as lacrimation, conjunctival injection, rhinorrhea, nasal congestion, facial flushing or sweating, ptosis, and myosis.^{2–6} The latter three are considered manifestations of sympathetic pathway activation, while the remaining CASs result from parasympathetic mechanisms.^{4,7} There is increasing evidence that parasympathetic CASs may include dysphonia, aural fullness, sneezing, and throat swelling.^{6,8} However, these symptoms are not included in the diagnostic criteria for TACs.^{9,10} Neurogenic disorders are often associated with symptoms of eye, nose or skin disorders.

At present, the understanding of the mechanisms behind CASs in primary headache disorders points to the superior salivatory nucleus (SSN) as a key region.^{7,11} Electrophysiological evidence indicates a direct connection between the trigeminocervical complex (TCC) and SSN in the pons.^{6,7} This connection is a fragment of the trigeminal-autonomic reflex (TAR), in which sensory input from trigeminal afferents provokes CASs.¹² By itself, TAR is an important reaction that protects the eyes and upper respiratory tract from harmful situations (e.g., foreign bodies). When triggered by noxious stimuli, the activation spreads from TCC to SSN and further via parasympathetic efferents to the lacrimal glands and nasal mucosa. However, the parasympathetic function is also modulated by input from higher brain structures, including the hypothalamus and limbic and cortical areas,^{7,13} which may explain why CASs can occur in primary headache disorders even in the absence of pain (e.g., in the premonitory phase).^{14–16} However, CASs are more pronounced when the nociceptive and top-down inputs are combined.⁶

With the exception of trigeminal neuralgia, there is limited evidence to suggest that CASs occur in headache disorders other than TACs and migraine.¹⁷ However, if these symptoms are secondary to TCC activation and subsequent SSN stimulation, then CASs should also be present in tension-type headache (TTH), the most prevalent primary headache disorder. Tension-type headache shares many similarities with migraine, including pain located mainly within the distribution of the first branch of the trigeminal nerve, a paroxysmal and recurring timeline, patient demographics, triggers, and comorbidities.¹⁸ Therefore, CASs in TTH would further support an overlapping etiopathogenesis of these disorders.

The aim of this study was to assess the prevalence of CASs, namely lacrimation, conjunctival injection, ptosis, nasal congestion, rhinorrhea, myosis, and facial flushing or sweating among subjects who meet the diagnostic criteria for frequent episodic TTH (eTTH).

Material and methods

The Migraine in Poland study is a cross-sectional survey registered in the ClinicalTrials.gov database (registration No. NCT05087420). Data was collected through an online questionnaire distributed via various channels from August 2021 to June 2022, including social media (Facebook, Instagram and Twitter) and national mass media (radio, television, newspapers, websites). The questionnaire was also distributed to employees of Poland's largest state-owned and private companies, state and religious institutions, secondary schools and universities, scientific societies, trade unions and non-governmental organizations, and outpatient service providers in primary and secondary care. The target group was not limited to individuals diagnosed with migraine, although the invitation headline implied a focus on that disorder. The survey assessed diagnostic criteria for migraine and TTH based on the International Classification of Headache Disorders, 3rd edition (ICHD-3). Moreover, the questionnaire examined the presence of CASs listed in the ICHD-3 chapters dedicated to TACs and their relationship to headache attacks. The questionnaire was based on the American Migraine Prevalence and Prevention (AMPP) Study, which enabled the evaluation of respondents' demographic characteristics, headache features and the presence of allodynia.¹⁹ Allodynia was defined as an interictal exacerbation of headache or skin discomfort during normal activities involving sensory stimulation (i.e., combing or pulling hair, face shaving, wearing eyeglasses, contact lenses or earrings, taking a shower, resting face or head on a pillow, and exposure to heat or cold). The study evaluated disease burden using the Migraine Disability Assessment (MIDAS) and assessed the presence and severity of depression using the Patient Health Questionnaire-9 (PHQ-9). The protocol description for the Migraine in Poland study was presented in detail in a previous publication.²⁰

Statistical analysis

Statistical calculations were performed using the R v. 3.6.0 software (<https://cran.r-project.org/>), PSPP software (<https://www.gnu.org/software/pspp/>) and Microsoft Office 2019 (Microsoft Corporation, Redmond, USA). The differences between groups were evaluated using a significance level of $p \leq 0.05$. The tests were selected based on the distribution of values, which was verified with the Shapiro–Wilk test. The Pearson's χ^2 test was used to analyze data expressed at the nominal level, with continuity correction applied for 2×2 tables. Fisher's exact test was used for tables larger than 2×2 when the conditions for the χ^2 test were not met. Quantitative data broken down into groups was analyzed using the Mann–Whitney–Wilcoxon test.

Results

The survey involved 3,225 respondents (age: 13–80 years, mean (M) = 38.9 years; 87.1% female). Of the 1,141 subjects who met the criteria for TTH, 166 respondents met the diagnostic criteria for isolated frequent eTTH according to the ICHD-3 (without co-occurring migraine attacks or probable migraine with or without aura). The ICHD-3 diagnostic criteria for migraine without aura (MwoA) were present in 1,679 participants. Allodynia accompanied the majority of attacks in 40 (24.1%) eTTH subjects.

In the eTTH cohort, 86 (51.8%) respondents reported experiencing at least 1 CAS during their headache attacks. The prevalence of specific CASs and its comparison to the MwoA cohort is presented in Fig. 1. The presence of at least 1 CAS and the presence of at least 2 CASs were significantly more prevalent in respondents with migraine ($p = 0.001$; $\chi^2 = 46.656$; degrees of freedom (df) = 10). Although all CASs were more prevalent in the MwoA group, only conjunctival injection, ptosis and myosis reached statistical significance ($p = 0.001$).

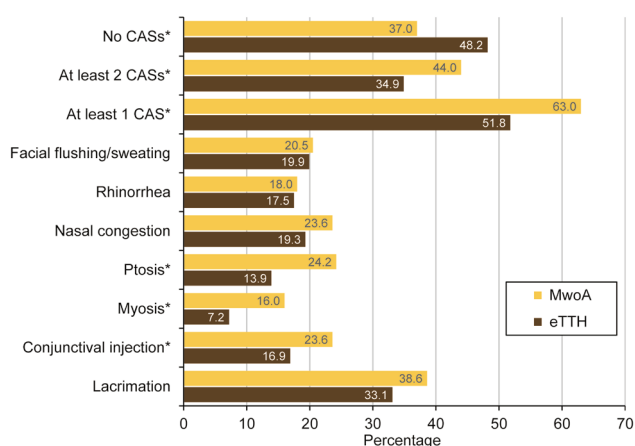


Fig. 1. Interictal cranial autonomic symptoms (CASs) in individuals with episodic tension-type headache (eTTH) and migraine without aura (MwoA)

*statistically significant difference between the eTTH and MwoA groups ($p = 0.001$; $\chi^2 = 46.656$; degrees of freedom (df) = 10).

There were no significant differences in headache intensity expressed on the Numerical Rating Scale between eTTH respondents with and without CASs ($p = 0.285$; median (Me) = 6.0 in both groups; $U = 3113.0$). Headache frequency did not differ between these groups ($p = 0.106$; $Me = 14.0$ vs. $Me = 10.0$, respectively; $U = 2939.5$). Moreover, allodynia in eTTH was not associated with interictal CASs ($p = 0.657$; $\chi^2 = 0.197$; $df = 1$). However, patients with at least 1 CAS during an eTTH attack reported a greater burden associated with pain in the MIDAS test ($p = 0.024$) (Fig. 2). Additionally, subjects with at least 1 CAS had significantly higher PHQ-9 scores ($p = 0.016$) (Fig. 3).

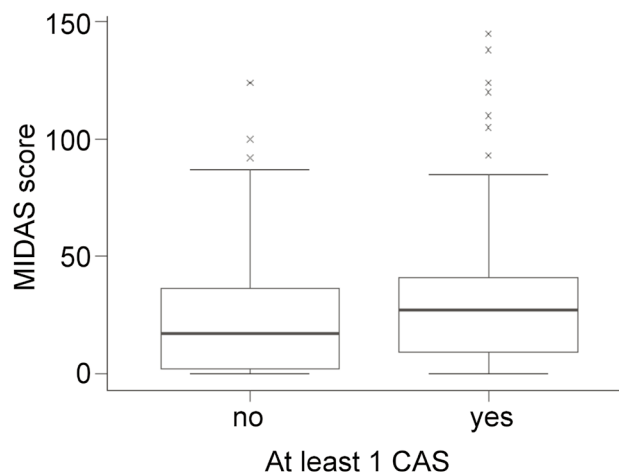


Fig. 2. Distribution of Migraine Disability Assessment (MIDAS) scores in the eTTH group with and without at least 1 CAS ($p = 0.024$; $U = 2640.5$)

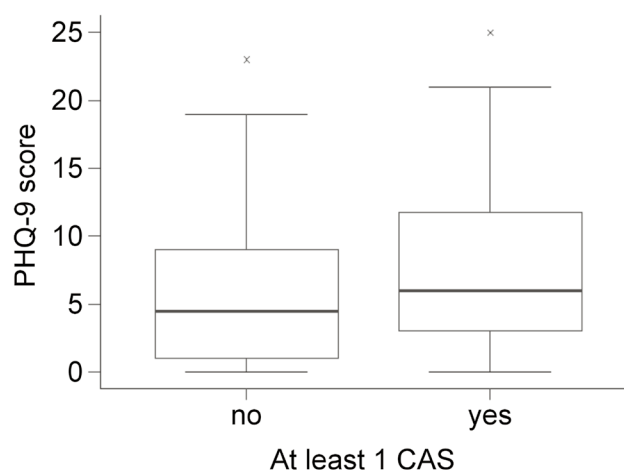


Fig. 3. Distribution of Patient Health Questionnaire (PHQ-9) scores in the eTTH group with and without at least 1 CAS ($p = 0.016$, $U = 2695$)

Discussion

Although less common than in MwoA, CASs can also accompany headaches in eTTH. To the best of our knowledge, only 1 study has assessed the prevalence of CASs in TTH.²¹ The study compared a selection of CASs (i.e., conjunctival injection, lacrimation, periorbital edema, and nasal symptoms) in 50 subjects with migraine and TTH, and found that only lacrimation and conjunctival injection were reported by TTH subjects. In our study, all canonical CASs were reported interictally by at least some patients with eTTH.

Although our study used convenience sampling, the obtained results are comparable to findings from population-based studies.²⁰ A recent Danish study reported that 57% and 31% of people with migraine experienced 1 or 2 CASs, respectively.⁴ In our study, 1 or 2 CASs interictally were experienced by 63% and 44% of MwoA respondents, respectively. However, in a study by Christensen et al., further cohort validation through telephone interviews

indicated that online questionnaires may overestimate the presence of these symptoms.⁴ Future prospective studies using electronic diaries could specify the true prevalence of CASs in migraine or TTH. Nevertheless, the overreporting of CASs is important in clinical practice, as most headache diagnoses rely on retrospective symptom analysis. Therefore, clinicians should be aware that approx. half of patients with TTH or MwoA may report CASs when specifically asked about them. The proposal of the Danish group to require at least 2 interictal CASs may help eliminate overreporting and increase specificity.⁴

Cranial autonomic symptoms in eTTH appear to follow similar patterns as CASs in migraine. For example, Ray et al. found that these symptoms are linked to depression and anxiety in migraine.²² Similarly, in our study, the presence of CASs was associated with higher PHQ-9 scores. The relationship between depression and pain is well-established in the literature.²³ Cases of CASs in eTTH might be an effect of symptom overreporting by patients with depression or an overlap in etiopathogenesis. Several hypothalamic regions implicated in primary headache disorders with CASs are also involved in mechanisms of depression (e.g., paraventricular²⁴ and dorso-medial²⁵ nuclei). Therefore, it is possible that depression contributes to CASs in TTH through hypothalamic involvement and subsequent top-down SSN stimulation.

Some studies indicated that CASs accompany headaches in patients with more severe attacks.^{2,5,26–28} If the correlation between pain intensity and CASs is valid, it could explain why these symptoms are more prevalent in migraine than in TTH. Tension-type headache is typically characterized by mild to moderate intensity headaches. Several studies have shown that CASs may also occur in the preictal or postictal phase in cluster headache¹⁴ or migraine,¹⁶ indicating mechanisms other than direct SSN stimulation by TCC.⁷ In TTH, where headache intensity is milder, these other mechanisms may come to the forefront since no significant associations were found between headache intensity in TTH and the presence of CAS.

Another important difference between CASs in migraine and TTH is related to central sensitization, which may contribute to chronic TTH mechanisms.²⁹ Some studies have shown that CASs occur in migraine more often in people with allodynia and other indicators of central sensitization,^{13,27} though this observation was mostly valid for patients with very pronounced or multiple CASs.¹³ However, allodynia is less prevalent in TTH than in migraine,³⁰ indicating that central sensitization plays a less important role, at least in episodic cases. In our group, only 24% of patients reported this symptom, and no association with CASs was found.

Questionnaire studies have unavoidable limitations, including recall or cognitive bias. Our survey used convenience sampling, although this was reduced by the broad distribution of the questionnaire. The main study results are similar to population-based surveys, indicating that our

sample may be representative. It is important to note that CASs are not specific to headache disorders and may occur in various non-neurological situations (e.g., infections³¹). For example, allergic rhinitis (rhinorrhea and nasal congestion) has a prevalence of 36% in the Polish population,³² and conjunctivitis (lacrimation and conjunctival injection) occurs in 6–30% of the general European population.³³ These confounding factors may contribute to an overestimation of CAS prevalence. The online nature of the survey may have limited differentiation with less prevalent painful disorders, which could have led to diagnostic inaccuracy, particularly when there is a high overlap of these conditions.^{34,35} In an online survey, only the co-occurrence of CAS with headache indicates that what the patient reports is the result of a neurological disorder. Finally, the study was limited by the small number of participants with eTTH, which may be attributed to the fact that the study was advertised as an assessment of migraine. Consequently, patients with eTTH were less likely to participate in the survey.

Conclusions

The prevalence of retrospectively reported CASs is high in eTTH. Our study results are mostly relevant to the diagnostic side of everyday clinical practice. Cranial autonomic symptoms in patients with TTH may contribute to diagnostic difficulties, as patients and healthcare providers may mistake TTH for other disorders, such as rhinosinusitis (in people with TTH and nasal congestion or rhinorrhea), conjunctivitis (in people with TTH and conjunctival injection or lacrimation) or TAC. Therefore, healthcare providers must be aware that CASs may also be a symptom reported by TTH patients.

The study findings suggest several directions for future research. Firstly, the prevalence of CASs in TTH should be confirmed by prospective diary-based assessment in a clinical setting to exclude recall bias and identify any previously unrevealed concomitant disorders. Secondly, this study highlights neurobiological mechanisms that were not previously assessed in TTH. Therefore, future research should investigate how the activation of TCC may lead to parasympathetic pathway stimulation in TTH.

Ethics approval and consent to participate

The study was approved by the Bioethics Committee of Wrocław Medical University, Poland. Participants were required to provide electronic informed consent before starting the questionnaire.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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