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Migraine and Cranial Autonomic Symptoms in Children and Adolescents: A Clinical Study

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Abstract

The frequency of cranial autonomic symptoms in children affected by primary headaches is uncertain. The aim of our study was to estimate the frequency of symptoms in pediatric headaches and correlate it with main migraine characteristics. A questionnaire investigating the presence of cranial autonomic symptoms was administered to all children with primary headache for 2 years. A total of 230 children with primary headache (105 males, 125 females) were included. Two hundred two children were affected by migraine and 28 (12.2%) by other primary headaches. Cranial autonomic symptoms were significantly complained by migraineurs (55% vs 17.8%) ($P < .001$) and by children with higher frequency of migraine attacks (odds ratio = 2.6, confidence interval = 1.4-4.7, $P = .001$). Our findings show that cranial autonomic symptoms are rather common during pediatric migraine attacks. The association between cranial autonomic symptoms and higher frequency of attacks might suggest the role of the trigeminal-autonomic reflex in migraine pathophysiology.

Keywords

migraine, trigemino-autonomic reflex, cranial autonomic symptoms, children, primary headaches

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Background and Aims

Migraine, in pediatric population, is a common and disabling neurological disorder. Though migraine is a complex disorder,[1] the trigeminal-vascular activation is considered an important pathophysiological mechanism explaining the pain phase of migrainous attacks,[2] as opposed to the trigeminal-autonomic reflex that is involved in the determinism of the trigeminal autonomic cephalalgias, where the unilateral cranial autonomic signs are the main clinical expression.[3]

The diagnostic differentiation between migraine and trigeminal autonomic cephalalgias, based on the presence of cranial autonomic signs, however, has not been clearly established.[4] They have been in fact described in some studies also in adult migraineurs, with frequencies ranging from 27% to 73%.[5-9] Some of these studies also found an association between cranial autonomic symptoms and some features of migraine attack, hypothesizing possible pathogenetic mechanisms. On the contrary, in pediatric migraineurs, their frequencies and possible association with migraine characteristics have been only recently reported in a study by Gelfand et al.[10]

On the basis of these considerations, and on suggestion of a cranial parasympathetic activation in a subgroup of pediatric migraineurs,[11] we evaluated the frequency of cranial autonomic signs during cephalalgic attacks in a population of children and adolescents with primary headaches and correlated the signs to main symptoms of migraine.

Methods

Inclusion and Exclusion Criteria

All patients with primary headache consecutively seen between June 2010 and May 2012, in the outpatient service for diagnosis and treatment of headache in the Child and Adolescent Neuropsychiatry Department, were invited to participate to the study. Our service is

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Table 1. Frequency of cranial autonomic Symptoms in Young Migraineurs.

Cranial autonomic symptoms	No. of CAS-positive subjects (%)
Red ear	43 (21.3)
Facial flushing	42 (20.8)
Conjunctival injection	37 (18.3)
Lacrimation	34 (16.8)
Nasal obstruction	29 (14.4)
Facial sweating	26 (12.9)
Ptosis	22 (10.9)
Rhinorrhea	17 (8.4)
Eyelid edema	16 (7.9)
Miosis	7 (3.5)

Abbreviation: CAS, cranial autonomic symptoms.

open to all young patients with headache, independently from difficulty in diagnosis and severity of symptoms. This service is one of the 2 services for diagnosis and treatment of headache in this age group of our district, and patients are sent by general pediatricians.

All patients were classified according to the 2004 International Headache Society criteria.[12] To be included, patients needed to have a headache history of at least 3 months and more than 10 episodes of headache in their life. Informed consent was obtained from the parents of all children. All data collected were part of the patient's standard medical files. According to local ethical policies, no formal approval by the hospital ethics committee was needed.

Diagnostic Investigations

A semistructured interview[13] investigating main characteristics of headache attacks was administered to all patients. We collected information on the demographic and headache characteristics and categorized them as follows: age, sex, family migraine history (presence/absence), frequency (>8 vs ≤8 headache days per month) and duration (>4 vs ≤4 hours) of the attacks, duration of migraine (>4 vs ≤4 years), quality (pulsating vs not pulsating), intensity (severe vs mild/moderate) and lateralization (unilateral vs bilateral) of the pain, the influence of physical activity (yes/no), occurrence of nausea (yes/no), vomit (yes/no), photophobia (yes/no), phonophobia (yes/no), osmophobia (yes/no), occurrence of aura (yes/no) and allodynia (yes/no). A short supplementary questionnaire, investigating the presence of cranial autonomic symptoms during migraine attack (conjunctival injection, lacrimation, nasal congestion, eyelid oedema, forehead/facial sweating, flushing facial, rhinorrhea, red ear, ptosis and miosis) was administered to all children and their parents at the same time. Finally, in order to study if migraineurs with cranial autonomic symptoms compared to those who did not complain them had a general hyperactivity of the vegetative system, a short questionnaire[14] investigating the presence of general autonomic symptoms was administered to a random sample of 50 cranial autonomic symptoms–positive and fifty cranial autonomic symptoms–negative migraineurs. Child was considered positive for presence of General Autonomic symptoms when, independently from migraine attacks, reported at least 1 of these autonomic general symptoms: vasomotor (sweating, heat intolerance, coldness, skin discoloration), symptoms of orthostatic hypotension (dizziness, syncope, lipotimia), gastrointestinal disorders (abdominal pain/cramping, diarrhea/obstinate constipation, early satiety, persistent fullness), and secretomotor (dry mouth, dry eyes, excessive salivation/secretion).

General and neurologic examinations were carried out in all children. Other diagnostic investigations (eg, blood tests, neurophysiological and neuroimaging studies, other specialist visits) were performed, if required.

Statistics

Chi-square and t tests were used to compare the nominal and the continuous variables, respectively. Odds ratios calculated by means of a logistic regression analysis were used as measure of association between cranial autonomic symptoms and migraine characteristics. A P value <.05 was considered statistically significant. Data were processed using SAS software (version 9.1.3 for Windows; SAS, Cary, NC).

Results

Two hundred thirty children (105 males, 125 females, mean age10.7 $\pm$ 3.1), fulfilling the inclusion criteria, were seen during the study period and they all agreed to participate to the study. Two hundred two children (87.8%; 96 males, 106 females) were affected by migraine with/without aura and 28 (12.2%; 9 males, 19 females) by other Primary Headaches (2 primary stabbing headache, 17 episodic, and 9 chronic tension-type headache). Cranial autonomic symptoms occurred significantly more frequently among migraineurs (111, 55%) than in patients with other primary headaches (5, 17.9%; $\chi^2 = 12\ 092$; $P < .001$). In migraineurs with cranial autonomic symptoms, the autonomic symptoms were present bilaterally in 70% (77 patients), unilaterally in 15% (17 patients), and uncertain in 15% (17 patients), and the 3 most frequent symptoms were red ear, facial flushing, and conjunctival injection (Table 1). In migraineurs with cranial autonomic symptoms, 30.6% of patients (34/111), 25.2% (28/111), and 40.5% (45/111) complained respectively 1, 2, or at least 3 cranial autonomic symptoms. In migraineurs, cranial autonomic symptoms were more frequent in children with higher frequency of migraine attacks (>8 per month) (odds ratio = 2.6, 1.4-4.7, $P = .001$) compared to those with lower frequency (≤8; see Table 2). General autonomic symptoms were significantly more frequent in migraineurs with cranial autonomic symptoms (38/50, 76%) compared to patients without cranial autonomic symptoms (23/50, 46%) ($\chi^2 = 8239$, $P < .0038$), with vasomotor (28 patients, 56%) and gastrointestinal (21 patients, 42%) the most frequently reported symptoms.

Discussion

Our study shows that in pediatric migraineurs, cranial autonomic symptoms are common and significantly more frequent than in other primary headaches, excluding the trigeminal autonomic cephalalgias, which however are very rare in the pediatric population and were absent in our sample.

Recently, a study[10] found high frequency of cranial autonomic symptoms in pediatric migraineurs (ie, 62%, which can rise to 70% with inclusion of new proposed International Headache Society criteria).[15] In our population, cranial autonomic symptoms were reported in almost half of the migraineurs;

Table 2. Association Between Cranial Autonomic Symptoms and Some Demographic or Migraine Characteristics.

Variable (202)	CAS+ (111)	CAS– (91)	OR (95% CI)	*P*
Gender				
Male	58 (60.4)	38 (39.6)	1.5 (0.9, 2.7)	.14
Female	53 (50)	53 (50)		
Age (y)				
≤10.9	59 (56.7)	45 (43.3)	1.2 (0.7, 2.0)	.6
>10.9	52 (53.1)	46 46.9)		
Duration disease (y)				
>4	21 (58.3)	15 (41.7)	1.2 (0.6, 2.5)	.65
≤4	90 (54.2)	76 (45.8)		
Duration episodes (h)				
>4	47 (60.3)	31 (39.7)	1.4 (0.8, 2.5)	.23
≤4	64 (51.6)	60 (48.4)		
Frequency of attacks (per month)				
>8	55 (68.8)	25 (31.2)	2.6 (1.4, 4.7)	.001
≤8	56 (45.9)	66 (54.1)		
Family history				
Yes	98 (53.3)	86 (46.7)	0.4 (0.2, 1.3)	.13
No	13 (72.2)	5 (27.8)		
Aura				
Yes	19 (70.4)	8 (29.6)	2.1 (0.9, 5.2)	.08
No	92 (52.6)	83 (47.4)		
Phonophobia				
Yes	80 (52.3)	73 (47.7)	0.6 (0.3, 1.2)	.18
No	31 (63.3)	18 (36.7)		
Photophobia				
Yes	79 (55.2)	64 (44.8)	1.0 (0.6, 1.9)	.91
No	32 (54.2)	27 (45.8)		
Osmophobia				
Yes	33 (61.1)	21 (38.9)	1.4 (0.8, 2.7)	.28
No	78 (52.7)	70 (47.3)		
Allodynia				
Yes	45 (60)	30 (40)	1.4 (0.8, 2.5)	.26
No	66 (52)	61 (48)		
Location pain[a]				
Unilateral	31 (54.4)	26 (45.6)	1.0 (0.5, 1.8)	.95
Bilateral	74 (54.8)	61 (45.2)		
Physical activity				
Yes	69 (57.5)	51 (42.5)	1.3 (0.7, 2.3)	.37
No	42 (51.2)	40 (48.8)		
Vomiting				
Yes	38 (50.7)	37 (49.3)	0.8 (0.4, 1.3)	.34
No	73 (57.5)	54 (42.5)		
Nausea				
Yes	77 (57.9)	56 (42.1)	1.4 (0.8, 2.5)	.24
No	34 (49.3)	35 (50.7)		
Intensity pain				
Severe	84 (52.2)	77 (47.8)	0.6 (0.3, 1.2)	.11
Mild/moderate	27 (65.9)	14 (34.1)		
Quality[b]				
Pulsating	61 (53)	54 (47)	0.8 (0.5, 1.4)	.47
Other	50 (58.1)	36 (41.8)		

[a]Information unavailable for 10 patients.
[b]Information unavailable for 1 patient.
Abbreviations: CAS, cranial autonomic symptoms; CI, confidence interval; OR, odds ratio.

positive subjects had frequently more than 1 symptom, and further beyond the cranial autonomic activation, these patients had general autonomic symptoms significantly more common than migraineurs without cranial autonomic symptoms. Among cranial autonomic symptoms, we included symptoms (facial flushing and red ear) that are not included in International Headache Society criteria for trigeminal autonomic cephalalgias as well. These symptoms are however frequently reported

in clinical cases,[16,17] and considering anatomic and physiological evidence,[18,19] it is reasonable to include them among cranial autonomic symptoms. The decision to include facial flushing and red ear among them is further supported by the finding that these, together with conjunctival injection and lacrimation, were in our population among the most frequent symptoms, similarly to Gelfand's study[10] where flushing and conjunctival injection were among the most frequent symptoms. Overall, these findings support the hypothesis that in pediatric migraineurs, similarly to the adult population,[5-9] local signs of parasympathetic activation are present in the course of migraine attacks.

A possible general autonomic hyperactivity (especially parasympathetic) is also suggested by the evidence that in our population, cranial autonomic symptoms–positive migraineurs compared to cranial autonomic symptoms–negative migraineurs reported more frequent general autonomic symptoms.

Finally, among migraineurs, we observed that cranial autonomic symptoms were more common in subjects with higher frequency of migraine attacks. This result supports the hypothesis that their presence, as it has been postulated for adult migraineurs,[5,6,9] seems to be related to some features of migrainous pain.

Differences with a previous study,[10] where no significant correlation between cranial autonomic symptoms and migrainous features was reported, are possibly attributable to factors such as age difference (our children are younger), sample size (our sample is nearly 60% larger), difference in gender frequency, and finally the absence or different categorization of some migraine features (eg, number of attacks).

The association of cranial autonomic symptoms with characteristics of migraine pain is consistent with findings of studies performed in the adult population,[5,6,9] showing a correlation with intensity, duration, and history of illness.

The main limitation of our study is probably related to its retrospective nature, which possibly might underestimate the occurrence of some clinical manifestations compared to others more easily reported. For example, some cranial autonomic symptoms (miosis, mild palpebral ptosis) might be more difficult to remember compared to others (facial flushing and lacrimation). Further, results of our study cannot be extended to the general pediatric population. However, as our service is one of the 2 outpatient services for diagnosis and treatment of headaches in Palermo province, the great number of children with headaches seen makes it unlikely that those enrolled in this study are characterized by more severe symptoms or more difficult headache diagnosis. Finally, the large examined sample, the analysis of general autonomic symptoms, and the consecutive recruitment of patients helped to reduce this limit, and the results are consistent with previous studies in adults.

Pathophysiological Considerations

Our results, together with findings from previous literature, suggest an involvement of the trigeminal autonomic reflex in migraine attack.

Similarly to the trigeminal autonomic cephalalgias, where pain is very severe, the relationship between cranial autonomic symptoms and intensity of pain has been explained[5] by a severity of migraine pain above a threshold activating the efferent arm of trigeminal-autonomic reflex. In a following study, cranial autonomic symptoms were more common in subjects with a longer history of disease and longer migraine attacks,[6] suggesting that the activity of the trigeminal autonomic reflex was linked to trigeminal nucleus sensitization. Frequent subthreshold or threshold stimuli (longer and/or frequent migrainous attacks) might therefore facilitate central sensitization of the trigeminal nucleus and consequently the activation of the trigeminal autonomic reflex. This theory, considering the relation between frequency attacks and positivity to cranial autonomic symptoms, seems confirmed by our findings. However, it is possible to formulate a third alternative hypothesis: the parasympathetic activation, in a specific migraineurs subgroup, can be primary, and not secondary to central sensitization of trigeminal nucleus. This hypothesis is based on some considerations: (1) many subjects with very severe and frequent migraine attacks do not ever have cranial autonomic symptoms in the course of migraine; (2) parasympathetic activation seems to be related to lateralization of pain,[20] a feature that would be difficult to explain with a frequent overstimulation of the trigeminal nucleus; (3) anatomic and physiological observations[21] allow to hypothesize that exogenous and endogenous triggers in migraineurs primarily could activate brain centers projecting to the parasympathetic nucleus and successively determine a nociceptive activation, and finally, (4) in the pathophysiology of migrainous pain, it has been suggested the role of parasympathetic system, as the efferent arm of nociception activation in perivascular nerves from brain centers.[22,23]

To our opinion, in the positive cranial autonomic symptoms subgroup of patients, parasympathetic activation facilitates triggers to activate the pain, by parasympathetic fibers together or as an alternative to the antidromic discharges of trigeminal sensitive fibers.

Conclusions

Our study shows that a discrete group of children with migraine presents cranial autonomic symptoms during their painful attacks more frequently than in other primary headaches, with more than 1 often occurring at each migraine attack. These data could suggest therefore (1) the presence of a subgroup of patients with migraine with different clinical picture (greater intensity, longer duration and greater frequency of episodes) and possibly different therapeutic response, as just suggested for adult migraineurs,[24,25] (2) characterized by a more general autonomic arousal, in particular parasympathetic, (3) suggesting a possible primary role of the autonomic system in the pathogenesis of migraine pain. The observation of cranial autonomic symptoms in subjects with higher frequency of attacks might be explained[21,22] considering the cascade of events preceding migraine pain. In fact, cortical and subcortical structures activated by migraine exogenous and endogenous trigger

factors would in turn activate the parasympathetic nuclei, that innervating the blood vessels can enhance directly or indirectly the responsiveness of meningeal nociceptors sending signals to the trigeminal sensory fibers. For this reason, greater parasympathetic hyperactivity in these patients would activate the nociceptive response to a lower threshold, resulting in higher frequency of attacks, and at the same time via the trigeminal-autonomic reflex cause the appearance of cranial autonomic symptoms during the attack.

Author Contributions

VR and MD conceived and designed the study. VR, GG, CS, FC, DB, GSan, and MD analyzed and interpreted the data. GG, CS, FC, and DB were responsible for acquisition of data. VR, FC, DB, GSan, GSav, FV, and MD drafted the article. GSav and FV revised the intellectual content.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

All the data were part of the patient's standard medical files. According to local ethical policies, no formal approval by the Hospital Ethics Committee was necessary and required. Database has been stored in excel file.

References

1. Charles A. Migraine. A brain state. *Curr Opin Neurol*. 2013;26: 235-239.
2. Pietrobon D, Moskowitz MA. Pathophysiology of migraine. *Annu Rev Physiol*. 2013;75:23.1-23.27.
3. Waldelind E, Drummond PD. The synthesis of cluster headache. In: Olesen J, Tfelt-Hansen P, Welch KM eds. *The Headaches*. Baltimore, MD: Lippincott Williams &Wilkins; 2001:708-715.
4. Blau JN. Adult migraine: the patient observed. In: Blau JN, ed. *Migraine*. London: Chapman & Hall; 1987:3-30.
5. Barbanti P, Fabbrini G, Pesare M, Vanacore N, Cerbo R. Unilateral cranial autonomic symptoms in migraine. *Cephalalgia*. 2002; 22:256-259.
6. Gupta R, Bhatia MS. A report of cranial autonomic symptoms in migraineurs. *Cephalalgia*. 2007;27:22-28.
7. Obermann M, Yoon MS, Dommes P, et al. Prevalence of trigeminal autonomic symptoms in migraine: a population-based study. *Cephalalgia*. 2007;27:504-509.
8. Lai TH, Fush JL, Wang SJ. Cranial autonomic symptoms in migraine: characteristics and comparison with cluster headache. *J Neurosurg Psychiatry*. 2009;80:1116-1119.
9. Guven H, Cilliler AE, Comoğlu SS. Unilateral cranial autonomic symptoms in patients with migraine. *Acta Neurol Belg*. 2013;113: 237-242.
10. Gelfand AA, Reider AC, Goadsby PJ. Cranial autonomic symptoms in pediatric migraine are the rule, not exception. *Neurology*. 2013;81:1-6.
11. Raieli V, Compagno A, Brighina F, Puma D, Ragusa D, Savettieri G, D'Amelio M. Prevalence of red ear syndrome in juvenile primary headaches. *Cephalalgia*. 2011;31:597-602.
12. Headache Classification Subcommittee of the International Headache Society. *The International Classification of Headache Disorders*. 2nd edition. *Cephalalgia*. 2004;24(suppl 1): 9-160.
13. Raieli V, Eliseo GL, Pandolfi E, Puma D, Ragusa D, Eliseo M. Il processo diagnostico nelle cefalee: uso di una intervista semistrutturata per una popolazione in età evolutiva [in Italian] [The diagnostic flow-chart in headaches: use of semistructured interview in pediatric population]. *Riv Neurologia*. 1998;8:77-82.
14. Low PA, Sandroni P, Benarroch E. Clinical autonomic disorders. Classification and clinical evaluation. In: Low PA, Benarroch E, eds. *Clinical Autonomic Disorders*. Baltimore, MD: Lippincott Williams & Wilkins; 2008:1-16.
15. International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33:629-808.
16. Al-Din AS, Mir R, Davey R, Lily O, Ghaus N. Trigeminal cephalgias and facial pain syndromes associated with autonomic dysfunction. *Cephalalgia*. 2005;25:605-611.
17. Purdy RA, Dodick DW. Red ear syndrome. *Curr Pain Headache Rep*. 2007;11:313-316.
18. Drummond PD, Lance JW. Facial flushing and sweating mediated by the sympathetic nervous system. *Brain*. 1987;110:793-803.
19. Brennan KC, Charles A. An update on the blood vessel in migraine. *Curr Opin Neurol*. 2010;23:266-274.
20. Avnon Y, Nitzan M, Sprecher E, Rogowski Z, Yarnitsky D. Different patterns of parasympathetic activationin uni- and bilateral migraineurs. *Brain*. 2003;126:1660-1670.
21. Burstein R, Jakubowski M. Unitary hypothesis for multiple triggers of the pain and strain of migraine. *J Comp Neurol*. 2005;493:9-14.
22. Olesen J, Burstein R, Ashina M, Tfelt-Hansen P. Origin of pain in migraine: evidence for peripheral sensitisation. *Lancet Neurol*. 2009;8:679-690.
23. Janig W. Relationship between pain and autonomic phenomena in headache and other pain conditions. *Cephalalgia*. 2003; 23(suppl 1):43-48.
24. Barbanti P, Fofi L, Dall'Armi V, et al. Rizatriptan in migraineurs with unilateral cranial autonomic symptoms: a double-blind trial. *J Headache Pain*. 2012;5:407-414.
25. Khan S, Schoenen J, Ashina M. Sphenopalatineganglion neuromodulation in migraine: what is the rationale? *Cephalalgia*. 2014;34:382-391.