Research Submissions

Cluster Headache Without Autonomic Symptoms: Why Is It different?

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Background.—Some patients with otherwise typical cluster headache (CH) have persistent attacks free of cranial autonomic symptoms (CAS). The factors responsible for this atypical presentation are not known.

Objectives.—To identify factors associated to the absence of CAS in patients with CH.

Methods.—A prospective series of 157 patients with the diagnosis of CH was analyzed, comparing 148 typical CH patients with 9 CH patients without CAS.

Results.—Patients without CAS reported significantly less intense attacks ($P = .003$) when compared to those with CAS. There was also a tendency (not reaching statistical significance) for a higher frequency of females and chronic CH among those without CAS. Otherwise, there were no differences between the two groups (in age, duration of illness, follow-up time, attack duration or frequency, nor side or site of pain). A logistic regression analysis showed that only pain intensity could explain the difference between the two groups, since the other explanatory variables were also associated with different intensity of attacks.

Conclusions.—These results support the hypothesis that CH without cranial autonomic symptoms represents a milder form of CH.

Key words: atypical cluster headache, cranial autonomic symptoms, trigemino-autonomic cephalalgia

Abbreviations: CH cluster headache, CAS cranial autonomic symptoms

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There are patients with short lasting recurring unilateral headaches, in all identical to CH, with the exception that they never have autonomic symptoms during the attacks. They represent 3% to 7% of cases in large CH series[1-3] and some of them have been described in detail.[4] The International Classification of Headache Disorders (ICHD-II)[5] recently acknowledged that fact, by allowing patients to be included in this diagnostic category in the absence of any associated autonomic symptoms, if they reported agitation or restlessness during the attacks.

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Some authors[6] postulated that cluster without autonomic symptoms represent a milder form of CH. However, factors associated with the absence of autonomic manifestations have not been specifically addressed so far.

This study was conducted to identify the clinical profile of cluster patients without cranial autonomic symptoms (CAS) in order to understand if it indeed represents a milder form of CH or if it is characteristic of a particular patient subgroup. With this purpose, we analyzed a series of 157 patients with the clinical diagnosis of CH, comparing cases with the complete syndrome with those lacking CAS in their demographic and clinical features.

METHODS

The clinical data of 165 patients with the clinical diagnosis of CH, followed in the Headache Outpatient Clinic of a University Hospital were analyzed. All data has been collected prospectively and assembled in a database (Microsoft Access® 2000) since 1995.

A total of 131 patients fulfilled all diagnostic criteria of CH (code 3.1) according to the ICHD-II, 2004.[5] The majority (90.8%) had episodic CH (code 3.1.1) and 9.2% had chronic CH (code 3.1.2). Most patients, 96.9% (127/131), experienced at least one or more of the required CAS, but 4 (3.1%) did not report any autonomic symptom, fulfilling the ICHD-II diagnostic criteria because of agitation or restlessness during the attacks.

Twenty-six cases were classified as probable CH (code 3.4.1), because they fulfilled all but one of the ICHD-II diagnostic criteria. Missing criteria were: lack of CAS in 5 patients (19.2%), atypical pain localization (outside the fronto-orbito-temporal region) in 7 patients (26.9%), moderate pain intensity in 2 (7.7%) patients, atypical attack duration in 9 (34.6%) (shorter than 15 minutes in one and longer than 180 in eight), attacks recurring at a low frequency (less than one attack every other day, on average) in 2 cases (7.7%), and one patient had less than five attacks in total (this patient began prophylactic therapy at his first attack).

Eight patients lacked two or more ICDH-II diagnostic criteria and were therefore excluded from this analysis.

Patients with definite or probable CH (n = 157) were divided in two groups, according to the presence or absence of CAS. These two groups were compared in relation to a number of demographic and clinical variables in order to identify factors associated with a less likelihood of autonomic symptoms to develop: age at first consultation (in years), gender, duration of illness (since their first episode to February 2004), follow-up time (from their first to their last visit to the clinic), pattern (episodic or chronic), seasonal periodicity (yes/no), average number of episodes per year (if there was no regular periodicity, mean was obtained by the quotient between the number of episodes and number of years of illness), average duration of cluster periods in days (only for episodic CH patients), average number of attacks per day, usual attack duration (in minutes), circadian rhythm (yes/no), site of pain (first versus second/third division of the trigeminal nerve and extratrigeminal), side of pain (nonshifting versus alternating), pain severity (moderate/severe or excruciating, as quantified by the patient during the typical bout), behavior during attacks (calm or agitated), and alcohol as a known precipitant (yes/no). Whenever the patient was seen outside an episode and had doubts or difficulty in remembering any clinical detail, or stated that there was a marked variability between attacks and/or bouts the information was coded as "missing." Patients who did not regularly drink alcoholic beverages were also coded "missing" in relation with that specific variable. Twelve patients were seen once during their first bout and had no further follow-up, and hence could not be classified as chronic or episodic. This accounts for missing cases in some of the variables studied.

Three compound indexes of severity were also calculated: attack burden (attack duration $\times$ number of daily attacks) was applied to all patients; bout burden (number of bouts/year $\times$ bout duration in days); and disease burden (bout burden/disease duration in years) were calculated only for episodic cluster patients.

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) for Windows Software v11.5. Frequency analysis was performed using a nonparametric test (chi-square or Fisher's exact test), and hypothesis on differences in means between groups were tested by the independent samples *t*-test. Protection against type 1 errors was made by adjusting the significance level to <0.01, due to the number of comparisons performed. For multivariate analysis we used enter and stepwise logistic regression, to select and describe the relation between explanatory variables and the dependent binary variable (presence or absence of autonomic symptoms). For that purpose, we entered all independent variables with a $P \leq .15$ obtained in the univariate analysis (sex, pain intensity, cluster type, calendar, and attack burden). A $P \leq .05$ was considered statistically significant.

RESULTS

There were 157 patients with the diagnosis of definite or probable CH, 125 (79.6%) males and 32 (20.3%) females, with an average age at the time of the first consultation of 40.5 years (SD, 12.7). A total of 148 patients had CAS and 9 (5.7%) did not.

Definite and Probable CH.—There were no statistically significant differences between those with

probable versus those with definite CH in the above mentioned variables except that patients with probable CH had more often pain located outside the V1 territory (V1 was compared to V2 + V3 + extratrigeminal localization [$\chi^2 = 17.28$, $P = .000$]), and a higher disease burden (6.8 on average, in patients fulfilling all diagnostic criteria compared to 24.6 in patients with probable CH [$t = -2.94$, $P = 0.004$]). Patients with probable CH were more often females, but the difference was not considered significant ($\chi^2 = 6.28$, $P = .012$).

CH With and Without CAS.—Clinical features of patients without CAS are presented in the Table, and are compared with 148 patients with typical CH. Of nine patients without CAS, four fulfilled the ICHD-II diagnostic criteria for definite CH (3 episodic and 1 chronic) and five were classified as probable CH (2 episodic and 3 chronic). There were five women and four men with an average age of 43.8 years old (SD, 16.2).

The comparison between patients with and without CAS showed that patients without CAS tended to have less severe pain than patients with the typical syndrome; excruciating pain was reported by 73.0% of subjects with CAS compared to 22.2% of individuals with no such symptoms (Fisher's exact test = 7.98, $P = .003$). Patients without CAS were more frequently females (15.6% females had no CAS com-

Table.—Cluster With and Without Cranial Autonomic Symptoms

		Cranial Autonomic Symptoms		
		No	Yes	
n		9	148	Test and significance
Age average (years)		43.8	40.3	$t = 0.82$, $P =$ n.s.
Sex	Male	4	121	Fisher's exact test = 7.27
	Female	5	27	$P = 0.018$
	Average disease duration (years)	13.7	15.4	$t = -0.54$, $P =$ n.s.
	Average follow-up time (years)	2.2	2.8	$t = -0.42$, $P =$ n.s.
Cluster type	Episodic	5	123	Fisher's exact test = 6.84
	Chronic	4	13	$P = 0.012$
Calendar	No	9	97	Fisher's exact test = 4.59
	Yes	0	51	$P = 0.032$ n.s.
	Average number cluster periods per year	2.0	2.2	$t = -0.41$, $P =$ n.s.
	Average duration of cluster period (days)	57.0	46.8	$t = 0.43$, $P =$ n.s.
	Average number of daily attacks	1.5	1.8	$t = -0.69$, $P =$ n.s.
	Average duration of attacks (minutes)	47.5	67.9	$t = -1.23$, $P =$ n.s.
Schedule	No	1	32	$\chi^2 = 0.11$, $P =$ n.s.
	Yes	8	116	
Pain side	NonShifting	8	121	$\chi^2 = 0.41$, $P =$ n.s.
	Alternating	1	27	
Maximum pain site	V1 territory	8	140	$\chi^2 = 0.76$
	Outside V1 territory	1	7	$P =$ n.s.
Type of pain	Throbbing	3	41	$\chi^2 = 0.2$, $P =$ n.s.
	Nonthrobbing	2	38	
Pain intensity	Moderate/severe	7	34	Fisher's exact test = 7.98
	Excruciating	2	92	$P = 0.003$*
Behavior during attacks	Calm	2	21	$\chi^2 = 1.52$
	Agitated	3	96	$P =$ n.s.
Precipitated by alcohol	No	0	15	$\chi^2 = 1.22$
	Yes	3	36	$P =$ n.s.
	Attack burden	60.0	115.3	$t = -1.72$, $P =$ n.s.
	Bout burden	232.5	90.7	$t = 0.74$, $P =$ n.s.
	Disease burden	25.8	8.8	$t = 1.45$, $P =$ n.s.

$t =$ independent samples t-test; *significant with $P < 0.01$.

pared to 3.2% of men) (Fisher's exact test = 7.27, $P = .018$), and tended to suffer from chronic rather than episodic CH (Fisher's exact test = 6.84, $P = .012$) but the differences were not considered significant. However, both gender and type of cluster were associated with attack severity, since only 46.6% (7/15) of chronic CH patients reported excruciating pain compared to 73.2% (82/112) of episodic CH ($\chi^2 = 4.45$, $P = 0.04$), and females reported more infrequently excruciating attacks (51.9%) than males (74.1%) ($\chi^2 = 5.04$, $P = 0.025$). These differences were not considered significant.

There were no differences between the two groups concerning all other variables in study, namely no significant differences were found regarding the location of pain.

The logistic regression analysis showed that only pain intensity was retained in the model (Nagekerkel $R^2 = 0.172$), OR = 9.43 (95%CI 1.8 to 47.6).

DISCUSSION

Pain intensity is significantly associated with the presence or absence of autonomic manifestations during attacks of CH. Autonomic symptoms are less likely to occur in patients with moderate-to-severe, rather than excruciating, attacks of pain.

CH is a trigemino-autonomic cephalalgia (TAC),[5,7] a group of headaches that elicit the trigemino-autonomic reflex, a physiological response to nociceptive stimulation of the trigeminal nerve. The severity of pain has been considered one of the main triggers of that reflex.[6] Indeed, its symptoms (lacrimation, conjunctival injection, vasodilation of the cranial vessels, and ipsilateral miosis and ptosis) have been described in other intense spontaneous or experimental cranial pains such as the painful stimulation of the cutaneous area of the temple by capsaicin injection in healthy volunteers,[8] thermocoagulation of the trigeminal ganglion in humans treated for trigeminal neuralgia,[9] experimental CH,[10] and during severe spontaneous migraine attacks.[11] According to the model proposed by Goadsby and Lipton for the TACs, "there should be a pain threshold above which autonomic symptoms occur."[7] Our findings corroborate this hypothesis.

It is interesting that measures of pain duration or recurrence (disease duration, frequency and duration of the episodes or attacks, or compound severity indexes) were not significantly different between the two groups. Although there was a trend for patients with chronic cluster to have no CAS, chronic CH was also associated with less severe attacks, possibly because these patients tend to be on permanent prophylactic medication. Thus, an intense (but not prolonged or repeated) stimulation of the trigeminal nucleus, facilitates, sensitizes, or decreases the threshold for autonomic activation. Similar results were found on longitudinal studies of CH patients whose attacks changed pattern over time (from episodic to chronic and vice versa) but maintained CAS, albeit different in quality.[12,13]

There was also a tendency for cluster without CAS to be more frequent in females than male patients. This gender difference was probably due to the different severity of attacks with gender, for women reported less severe attacks than men. Previous studies have pointed out differences in symptom presentation of CH with gender. In the series reported by Torelli et al,[3] the percentage of females in the CH group without CAS reached 37.5%, which was 10% higher than that found in the whole series. Two studies of CH in female patients[14,15] have shown that women are less likely to report ptosis and miosis than man and have attacks of shorter duration. Besides, women are more likely to experience nausea, vomiting, photophobia, and phonophobia during CH, symptoms that are associated with diagnostic delays in this syndrome.[16] These results may indicate gender differences in the phenotypic expression of this disorder that is associated with hormonal factors, namely with fluctuations of male hormones[17] and female infertility.[15]

It is interesting that there were no differences in pain localization between the two groups, although there are clinical and experimental reports suggesting that pain in the ophthalmic distribution of the trigeminal nerve tends to elicit the trigemino-autonomic reflex more often than outside the V1 territory[8,18] Yet, a study comparing upper and lower CH syndromes also did not report differences in autonomic manifestations between the two.[19]

The present findings need to be corroborated by direct observation of the attacks and tests of autonomic dysfunction, since our results were based on patient's recall. The large majority of patients were repeatedly examined during bouts (between attacks), and the time gap between attacks and the consultation, in that case, is usually short given the fact that patients are having several attacks per day. However, relying on patient's memory for the episodes may introduce a recall bias, since patients with more severe attacks may eventually remember their attacks with a greater detail and pay more attention to associated symptoms.

The inclusion of patients with probable CH in the presented analysis may also raise methodological concerns, for they may be atypical of the cluster population. Yet cases with "probable" diagnosis differed from the "definite" cases by the lack of any one of the ICHD-II diagnostic criteria, either CAS or other, avoiding a selection bias toward the absence of autonomic phenomena. In addition, those patients: (a) were diagnosed by neurologists with experience in headache, (b) did not differ significantly from typical CH patients regarding the main demographic and clinical variables, except for main site of pain (which is inherent to the diagnostic criteria).

The present study favors the hypothesis of Drummond[6] that CH without CAS represents a less intense subtype of the same headache. Therefore, the inclusion of CAS-lacking cases in the new ICDH-II seems to correspond to clinicians and investigators needs, when evaluating these patients. However, the recent description of cases of recurring CAS without pain (Cluster *Sine* Headache)[20-22] challenges this view. Those cases suggest that although pain and autonomic modules are linked by a putative "pain-autonomic" excitatory pathway, there may be a reciprocal inhibitory pathway (activated by genetic or anatomical variants), causing these unusual dissociations.

We hope that larger CH series can reproduce our findings. Further studies are necessary to understand the role of other variables in this phenomenon, so that these factors can be taken into account when establishing a CAS-lacking CH diagnosis. Other studies may help isolating different patterns of autonomic symptoms in CH patients, which may contribute to understand the pathogenesis of those symptoms and their relation with pain intensity.

REFERENCES

1. Nappi G, Micieli G, Cavallini A, Zanferrari C, Sandrini G, Manzoni GC. Accompanying symptoms of cluster attacks: their relevance to the diagnostic criteria. *Cephalalgia*. 1992;12:165-168.
2. Ekbom K. Evaluation of clinical criteria for cluster headache with special reference to the classification of the International Headache Society. *Cephalalgia*. 1990;10:195-197.
3. Torelli P, Cologno D, Cademartiri C, Manzoni GC. Application of the International Headache Society classification criteria in 652 cluster headache patients. *Cephalalgia*. 2001;21:145-150.
4. Vigl M, Zebenholzer K, Wessely P. Cluster headache without autonomic symptoms? *Cephalalgia*. 2001;21: 926-927.
5. The International Classification of Headache Disorders, 2nd edition. (ICHD-II, 2004). *Cephalalgia*. 2004;24(suppl 1):1-150.
6. Drummond PD. Dissociation between pain and autonomic disturbances in cluster headache. *Headache*. 1990;30:505-508.
7. Goadsby PJ, Lipton RB. A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic features, including new cases. *Brain*. 1997;120:193-209.
8. Frese A, Evers S, May A. Autonomic activation in experimental trigeminal pain. *Cephalalgia*. 2003;23:67-68.
9. Goadsby PJ, Edvinsson L, Ekman R. Release of vasoactive peptides in the extracerebral circulation of humans and the cat, during activation of the trigeminovascular system. *Ann Neurol*. 1988;23:193-196.
10. May A, Bahra A, Buchel C, Frackowiak RSJ, Goadsby PJ. Pet and MRA findings in cluster headache and MRA in experimental pain. *Neurology*. 2000;55:1328-1335.
11. Barbanti P, Fabbrini G, Pesare M, Vanacore N, Cerbo R. Unilateral cranial autonomic symptoms in migraine. *Cephalalgia*. 2002;22:256-259.
12. Bahra A, May A, Goadsby PJ. Cluster Headache. A prospective clinical study with diagnostic implications. *Neurology*. 2002;58:354-361.

13. Manzoni GC, Miceli G, Granella F, Tassorelli C, Zanferrari C. Cluster headache-course over ten years in 189 patients. *Cephalalgia*. 1991;11:169-174.
14. Rozen TD, Niknam R, Shechter AL, Young WB, Silberstein SD. Cluster headache in women: clinical characteristics and comparison to cluster headache in men [abstract]. *Neurology*. 1999;52:A471.
15. Manzoni GC, Miceli G, Granella F, Martignoni E, Farina S, Nappi G. Cluster headache in woman: clinical findings and relationships with reproductive life. *Cephalalgia*. 1988;8:37-44.
16. Vliet JA, Eekers PJE, Haan J, Ferrari MD, for the Dutch RUSSH study group. Features involved in the diagnostic delay of cluster headache. *J Neurol Neurosurg Psychiatry*. 2003;74:1123-1125.
17. Bussone G, Leone M, D'Amico D, Grazzi L, Attanasio A, Ferraris A. Endocrinology of cluster headache. In: Olesen J, Goadsby PJ, eds. Cluster Headache and Related Conditions. Oxford: Oxford University Press; 1999:179-185.
18. Pareja JA, Baron M, Gili P, et al. Objective assessment of autonomic signs during triggered first division trigeminal neuralgia. *Cephalalgia*. 2002;22:251-255.
19. Cademartiri C, Torelli P, Cologno D, Manzoni GC. Upper and lower cluster headache: clinical and pathogenetic observations in 608 patients. *Headache*. 2002;42:630-637.
20. Salvesen R. Cluster headache sine headache: case report. *Neurology*. 2000;55(3):451.
21. Leone M, Rigamonti A, Bussone G. Cluster headache sine headache: two new cases in one family. *Cephalalgia*. 2002;22:12-14.
22. Martins IP, Gouveia RG, Antunes JL. Double dissociation between autonomic symptoms and pain in cluster headache. *Cephalalgia*. 2004; in press.