

ORIGINAL ARTICLE

Four decades of experience with cluster headache: description of a series from a tertiary hospital

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KEYWORDS

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Abstract

Introduction: There are practically no series of cluster headache (CH) in our country. Our aim was to longitudinally describe the characteristics of patients with CH seen in our Hospital since 1980.

Methods: Retrospective analysis of the clinical charts of patients diagnosed as CH.

Results: We included 153 patients diagnosed as CH. 137 (89,5%) males, with a mean age (MA) at diagnosis of 39.5 years (mean deviation 11.4) and a MA at the beginning of the symptoms of 32.8 years (mean deviation 11.3). 128 suffered from episodic CH (eCH; 92.2% males) and 25 chronic CH (cCH; 76% males). The MA at the beginning was delayed in cCH as compared with eCH (37.6 versus 31.8; $p = 0.023$). Four patients (2.6%) had familial antecedents. Only 3 (2%) referred visual aura. At diagnosis, 66% were smokers and 15% heavy alcohol drinkers. The median duration of cluster period was 60 days, with a median frequency of every 2 years. 16 cases (10.5%) presented a benign course with only one cluster period.

Conclusions: The minimal prevalence of CH in our area was 0.05%, with eCH being the most frequent phenotype. Up to one out of 10 patients showed a benign form with just one cluster period. The diagnostic delay close to 7 years indicates an insufficient recognition of this entity. A high proportion of CH patients showed, already at diagnosis, unhealthy life habits. Cluster periods lasted an average of 2 months and occurred approximately every 2 years. A late beginning and being a woman were associated with the variant of cCH.

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PALABRAS CLAVE

Cefalea en racimos;
Clínica;
Epidemiología

Cuatro décadas de experiencia con la cefalea en racimos: descripción de una serie en un hospital de tercer nivel**Resumen**

Introducción: No existen prácticamente series de cefalea en racimos (CR) en nuestro país. Nuestro objetivo es describir longitudinalmente las características de los pacientes con CR atendidos desde 1980 en un hospital de tercer nivel.

Métodos: Revisión retrospectiva de historias de pacientes con CR en nuestro centro.

Resultados: Se incluyeron 153 pacientes diagnosticados de CR. 137 (89,5%) hombres, media de edad (ME) al diagnóstico 39,5 años (desviación media 11,4) y ME al inicio de los síntomas 32,8 (desviación media 11,3). 128 sufrían CR episódica (CRe; 92,2% hombres) y 25 CR crónica (CRc; 76% hombres). La ME al inicio fue más tardía en CRc que en CRe (37,6 vs 31,8; $p = 0,023$). Cuatro pacientes (2,6%) tenían antecedentes familiares. Sólo 3 (2%) referían aura (visual). Al diagnóstico, 66% eran fumadores y 15% bebedores. La mediana de duración del brote fue de 60 días, con una mediana de frecuencia de 2 años. 16 (10,5%) fueron casos benignos (racimo único).

Conclusiones: La prevalencia mínima de CR en nuestra área fue 0,05%, siendo el fenotipo más frecuente la CRe. Hasta uno de cada 10 pacientes presentó una forma benigna con un único racimo. El retraso diagnóstico de casi 7 años indica un insuficiente reconocimiento de esta entidad. Una elevada tasa de pacientes tenía hábitos de vida poco saludables ya al diagnóstico. Los racimos duraron una media de dos meses y ocurrieron aproximadamente cada 2 años. Un inicio tardío y ser mujer, se asoció con CRc.

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Introduction

Cluster headache (CH) is the most frequent type of trigeminal autonomic cephalalgia (TAC), with a prevalence of up to one case per 1000 population, depending on the study.^{1,2} It is the most disabling primary headache, and is underdiagnosed, despite its distinctive clinical features.^{3–6} According to the third edition of the International Classification of Headache Disorders (ICHD-3),⁷ diagnosis of CH requires at least 5 attacks of severe, unilateral, orbital, supraorbital, and/or temporal pain, lasting 15–180 minutes, with at least one cranial autonomic symptom and/or a sense of restlessness or agitation, occurring with a frequency between one every other day and 8 per day. Two subtypes have been described: episodic CH (eCH), characterised by occurrence of at least 2 cluster periods lasting 7 days to one year, separated by pain-free remissions of ≥ 3 months, and chronic CH (cCH), in which attacks occur for one year or longer without remission, or with remission periods lasting < 3 months.⁷

Some of the distinctive characteristics of CH include its circadian and circannual pattern, suggesting the involvement of a biological pacemaker, its male predominance, and its association with unhealthy lifestyle habits.^{3,8} In recent years, other symptoms have also been identified, such as the presence of aura (a classical symptom of migraine), which is most frequently visual and presents variable prevalence (it has been reported in up to 23% of cases).^{9–11} However, very few large series have been published, and in Spain, only one series has been published, prior to the adoption of the current criteria.¹²

The primary objective of this study was to describe the clinical and epidemiological characteristics of patients diag-

nosed with CH over a 40-year period at a tertiary hospital in Spain. As a secondary objective, we analysed differences between patients with eCH and those with cCH.

Methods

We recorded data from all patients with CH attended either by general neurologists or by headache specialists at our department's outpatient consultations, since 1980. We reviewed the medical records of patients diagnosed with CH up to May 2021. Diagnoses were reclassified according to the current criteria.⁷ Clinical and demographic variables were gathered using an ad hoc database. The use and publication of these data for scientific purposes was approved by the ethics committee of the region of Cantabria (code 2021.137). Given the nature of the study, informed consent was not required.

The following data were gathered from each patient: clinical record number, sex, current age, age at symptom onset, age at diagnosis, specific diagnosis (cCH or eCH), pain lateralisation, cluster frequency (clusters per year), and attack duration (in days). Other variables were also analysed, including family history of TAC, presence of symptoms compatible with aura, and copresence of migraine. We also recorded the presence of arterial hypertension, diabetes mellitus, dyslipidaemia, obesity, smoking, excessive alcohol consumption, cancer, and other comorbidities (cardiovascular, digestive, respiratory, psychiatric, and other neurological diseases).

A descriptive analysis was performed. Qualitative variables were expressed as absolute (n) and relative frequencies

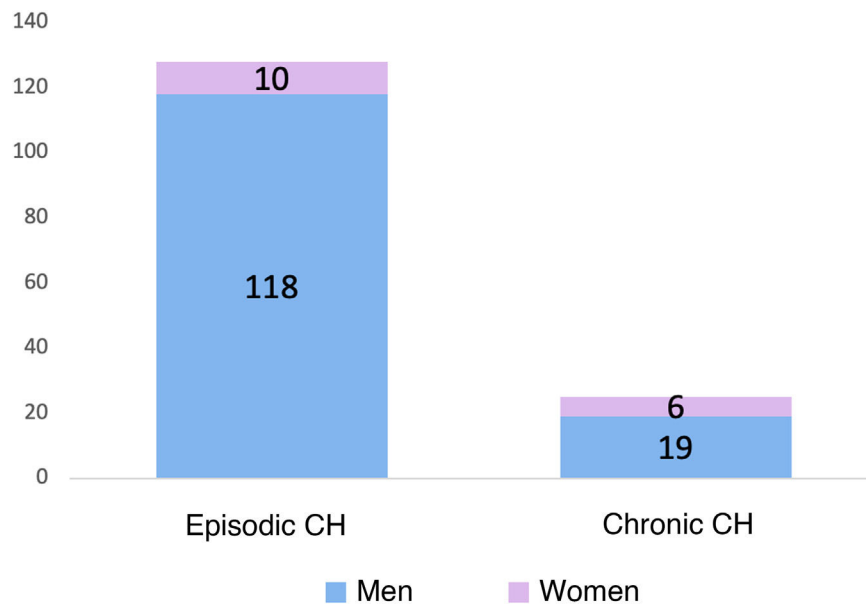


Figure 1 Distribution of our series of patients with cluster headache, by diagnosis and sex. CH: cluster headache.

(%) and quantitative variables as measures of central tendency (mean or median) and dispersion (standard deviation [SD] or interquartile range [IQR]), according to data distribution. The Kolmogorov–Smirnov test was used to analyse the distribution of quantitative variables. All variables followed a normal distribution, with the exception of age at diagnosis in the total sample of patients with CH and the eCH subgroup, as well as the variables cluster frequency and attack duration in the eCH subgroup. Baseline characteristics were calculated for the total sample and the eCH and cCH subgroups separately. We compared clinical and demographic characteristics between patients with eCH and cCH, based on the assumption that there were differences between groups. We used the *t* test for normally and non-normally distributed continuous variables (given that $n > 30$), and the chi-square test (or the Fisher exact test, when appropriate) for categorical variables. Statistical analysis was conducted using the SPSS® software. Statistical significance was set at $P < .05$.

Results

Demographic and clinical characteristics

ICHD-3 diagnosis, sex, and age

A total of 156 patients met the diagnostic criteria for CH. We excluded one patient due to insufficient clinical data, as well as 2 patients who had been followed up for less than one year, preventing classification into the eCH or cCH subgroup; the final sample therefore included 153 patients. After reclassification, 128 (83.7%) met criteria for eCH and 25 (16.3%) for cCH. A total of 137 patients were men (89.5%). By type of CH, 118 (92.2%) patients with eCH and 19 (76%) patients with cCH were men (Fig. 1); this difference was statistically significant ($P = .027$) (Table 1). Mean current

age was 60.6 years (SD: 13.8). Mean age at symptom onset was 32.8 years (SD: 11.3), and median age at diagnosis was 38 (IQR: 17.25). These data reflect a mean diagnostic delay of 6.7 years (39.5 vs 32.8; $t = 6.06$; 95% CI, 4.85–7.26; $P = .000$). Table 1 compares mean age at diagnosis and at symptom onset between patients with eCH and cCH, revealing a significantly older age at symptom onset in patients with cCH ($P = .023$).

Family history

Four patients (2.6%) reported family history of TAC in first-degree relatives. A woman with left-sided cCH had a first-degree relative diagnosed with left paroxysmal hemicrania. A man with eCH had a brother with CH. The remaining 2 patients were first-degree relatives of one another; both had eCH.

Clinical characteristics of headache

Pain lateralisation

Headache was strictly right-sided in 51.1% of patients, left-sided in 46.1%, and alternating in 2.8% (strictly unilateral, switching sides between attacks); no significant differences were observed between the eCH and cCH subgroups.

Cluster duration and frequency

In patients with eCH, median cluster duration was 60 days (IQR: 45). Regarding cluster frequency, the median was one cluster every 2 years (IQR: 1.33). Sixteen patients (10.5%) experienced a single cluster; 7 of these (4.6%) were followed up at the neurology department on an outpatient basis and subsequently by primary care (which demonstrates the

Table 1 Main demographic characteristics of our series of patients with cluster headache.

	Total (N = 153)	eCH (n = 128)	cCH (n = 25)	P*
Men, n (%)	137 (89.5%)	118 (92.2%)	19 (76.0%)	.027**
Age at diagnosis ^a	38 (17.25)	37 (17.25)	43 (21.25)	.096***
Age at symptom onset ^b	32.8 (11.3)	31.8 (10.8)	37.1 (13.0)	.023***

cCH: chronic cluster headache; eCH: episodic cluster headache.

^a Median (interquartile range).

^b Mean (standard deviation).

* Comparison between eCH and cCH.

** Fisher exact test.

*** t test for independent samples.

benign course of their condition), whereas 9 (5.9%) were lost to follow-up after the first episode.

Aura and migraine

Three patients (2%) reported typical symptoms of aura, which was visual in all cases. All met criteria for eCH, and none of them had migraine. Only one patient in our series (0.7%) had migraine in addition to eCH.

Comorbidities at diagnosis

The frequency of various comorbidities at diagnosis is shown in Table 2. Except for diabetes mellitus ($P = .019$), respiratory diseases ($P = .004$), and cancer ($P = .019$), which were more frequent in the cCH subgroup, no significant differences were observed in the frequency of any comorbidity between patients with eCH and those with cCH. It should be noted, however, that the prevalence of all comorbidities, except for smoking and alcohol consumption, was rather low.

Discussion

This is the first large series of Spanish patients diagnosed with CH according to the current diagnostic criteria, and one of the very few to include longitudinal follow-up of up to 4 decades. Our study confirms several well-established characteristics of CH and provides novel insights.

One finding that is common to all published series is the mean delay of 5–10 years^{4–6} between symptom onset and diagnosis. In our series, this diagnostic delay was greater than 6 years, which reveals insufficient recognition of this entity. Late and incorrect diagnosis leads to treatment delays, which is particularly concerning given that CH is one of the most disabling types of pain,^{3,13} causing a considerable loss of quality of life.

Although CH is less prevalent than other primary headaches,¹⁴ it is the most common TAC¹³ and its frequency is not negligible. The theoretical minimum prevalence of CH in our reference population of 320 000 is 0.05%, which is equivalent to 45.9 cases per 100 000 population, or one case per 2178 population. These rates fall within the broad ranges reported in epidemiological studies of CH, with prevalence ranging from 31 to 588 cases per 100 000 population.^{1,2} These

findings underscore the need to increase knowledge of this entity among primary care physicians, as the patient population assigned to each professional is highly likely to include at least one patient with CH; neurology departments, on the other hand, must adapt accordingly to plan the provision of the most appropriate care.

Our results confirm the male predominance described in the literature, with only 10% of patients in our series being women.¹⁵ However, recent studies have reported a less marked male predominance.^{16,17} It is unclear whether this trend results from a real increase in incidence among women, improved diagnostic accuracy due to greater awareness of this entity (as many women may previously have been misdiagnosed with migraine, which is more prevalent in this population), or the recent increase in tobacco and alcohol use among women.¹⁸

Regarding patient distribution by diagnosis and age at symptom onset, eCH is the most frequent phenotype, with only 15% of patients meeting criteria for cCH.^{3,6,13,15,19} Mean age at symptom onset is around 30 years,^{16,20} and tends to be higher in patients with cCH.^{2,16,21} An interesting finding from our study is the difference in the sex distribution by phenotype, with the male-to-female ratio for eCH being nearly twice that observed for cCH. This suggests that, in addition to older age at symptom onset, female sex is also associated with a diagnosis of cCH. This hypothesis is consistent with the results of the study by Manzoni et al.,¹⁶ who reported that the mean age at cCH onset was 5 years older in women, and the study by Ekbohm et al.,²² who found that late onset of CH is more frequent among women with chronic forms. Therefore, onset after the fourth decade of life in women should prompt suspicion of chronic forms of the condition.

In our sample, median cluster duration was 60 days (8.5 weeks) and median cluster frequency was one episode every 2 years. These findings are consistent with the few data currently available in the literature. Cluster duration has classically been reported to range from 6 to 12 weeks, with most patients experiencing clusters annually.^{3,17,23} Other studies have found that over 20% of patients present remission periods of over 2 years.²⁴ These findings have relevant implications for clinical practice, suggesting that patients in our setting have clusters lasting approximately 2 months, with remission periods of approximately 2 years.

Interestingly, 7 patients in our series experienced a single cluster over a long follow-up period (an additional 9 patients also experienced a single episode, but were lost to follow-

Table 2 Comorbidities at diagnosis of cluster headache.

Comorbidity n (%)	Total (N = 153)	eCH (n = 128)	cCH (n = 25)	P value*
AHT	15 (9.8)	12 (9.4)	3 (12.0)	.307***
Dyslipidaemia	7 (4.6)	6 (4.7)	1 (4.0)	.346***
DM	3 (2)	1 (0.8)	2 (8.0)	.019**
CVD	6 (3.9)	4 (3.1)	2 (8.0)	.251**
Smoking	101 (66.0)	88 (68.8)	13 (52.0)	.151***
Excessive alcohol consumption	23 (15.0)	19 (14.8)	4 (16.0)	1.000**
Gastrointestinal disorders (gastrointestinal bleeding, gastric ulcer)	8 (5.3)	8 (6.3)	0 (0)	.355**
Psychiatric disorders (schizophrenia, depression)	3 (2)	1 (0.8)	2 (8.0)	.070**
Other neurological diseases (stroke, parkinsonism)	4 (2.6)	3 (2.3)	1 (4.0)	.514**
Respiratory diseases (asthma, COPD)	3 (2)	0 (0)	3 (12.0)	.004**
Cancer (lung, pancreas)	3 (2)	1 (0.8)	2 (8.0)	.019***

AHT: arterial hypertension; cCH: chronic cluster headache; CH: cluster headache; COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease (including atrial fibrillation, ischaemic heart disease, and hypertrophic cardiomyopathy); DM: diabetes mellitus; eCH: episodic cluster headache.

* Comparison between eCH and cCH.

** Fisher exact test.

*** Chi-square test.

up). This finding suggests that approximately one in every 20 patients may not present recurrences, an observation also described by other authors.²⁵

Aura was not recognised as a symptom of CH until very recently. In 2000, Silberstein et al.¹¹ reported mainly visual aura in 6% of patients with CH, whereas other more recent retrospective studies have reported even higher frequencies.^{5,15,26} In our sample, 2% of patients presented symptoms of visual aura. This rate is similar to that reported in a recent prospective study (3.5%), which found that most patients with aura also presented migraine with aura.²⁷ The estimated prevalence of migraine among patients with CH is similar to that observed in the general population.²⁸ In our series, however, only one patient had migraine, which suggests that this information was not systematically recorded, with migraine probably being overshadowed by the severity of CH.

Only 2.6% of patients presented family history of TAC; this is consistent with previous studies reporting rates between 2.3% and 4.1%.^{29,30} These results do not support the hypothesis of a significant hereditary component of CH; however, due to the retrospective nature of the study, we cannot rule out a genetic influence, as other recent studies have suggested.^{31–33}

A frequent finding in the literature on CH is the high prevalence of unhealthy lifestyle habits, particularly smoking, which is reported in more than two-thirds of patients.^{5,34} Some studies have described longer cluster duration, greater attack frequency, and more severe pain among smokers.³³ In our series, 2 in every 3 patients were smokers at the time of diagnosis, which is twice as high as the rate of daily smokers in our region.³⁵ The same is true for alcohol use: 15% of our patients reported excessive alcohol use at diagnosis, a higher rate than that estimated for the general population of our region (11.8%) during the 2014–2018 period.³⁶ However, it should be noted that alcohol consumption could not be quantified as it was not consistently recorded in most medical records. Although the relationship between alcohol use and CH is unclear, alcohol is one of the main triggers during cluster periods.^{34,37} Some

studies suggest that alcohol and tobacco use may be linked to anxious or compulsive personality traits in patients with CH,^{38,39} whereas others have found no differences between comparison groups.^{40,41} This supports the need for further research into the psychological comorbidities of CH and how they can impact on pain coping, quality of life, and optimal treatment.

Our results may be subject to biases inherent to the retrospective nature of the study. For example, the periodicity of clusters may not have been accurately recorded, as some patients may not have sought medical attention during each episode or were lost to follow-up due to transfer to another centre. For the same reason, we were unable to calculate the rate of conversion from eCH to cCH, or to identify potential triggers or other clinical characteristics of this entity, such as attack intensity or duration, the association with trigeminal autonomic signs, or its circadian pattern. Future prospective studies should aim to deepen our knowledge of this entity. Despite these limitations, our results are consistent with previous evidence, suggesting that most of the clinical records analysed were of good quality and that our conclusions are valid.

Conclusions

- The theoretical minimum prevalence of CH in our sample was 0.05%. We observed a diagnostic delay of over 6 years, which reveals a lack of recognition of this entity.
- CH shows a clear male predominance, with a male-to-female ratio of 9:1, although sex differences are less marked in cCH.
- Later symptom onset and female sex were associated with greater likelihood of cCH.
- Patients presented a mean cluster duration of 2 months, at a mean frequency of approximately one cluster every 2 years. Copresence of aura was infrequent in our sample.
- At least 5% of our patients presented a “benign” course, with only one documented cluster.

- A considerable proportion of patients exhibited unhealthy lifestyle habits.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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