Chronic cluster headache: a French clinical descriptive study

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Background: Cluster headache (CH) is a relatively rare disease and episodic CH is more frequent than chronic CH. Few studies have described the characteristics of patients with chronic CH.

Methods: This was a descriptive study carried out by eight tertiary care specialist headache centres in France participating in the Observatory of Migraine and Headaches (OMH). From 2002 to 2005, OMH collected data from 2074 patients with CH, of whom 316 had chronic CH. From January to June 2005, 113 patients with chronic CH were interviewed using standardised questionnaires during a consultation.

Results: The male to female ratio was 4.65:1. Median age was 42 years. The majority of patients were smokers or former smokers (87%). 46% had primary chronic CH (chronic at onset) and 54% secondary chronic CH (evolving from episodic CH). Most patients had unilateral pain during attacks and 7% had sometimes bilateral pain during an attack. 48% reported a persisting painful state between attacks. Symptoms anteceding pain onset (mainly discomfort/diffuse pain, exhaustion, mood disorders) and auras were reported by 55% and 20% of patients, respectively. The functional impact of chronic CH was estimated as severe by 74% of patients, and 75.7% suffered from anxiety, as assessed by the Hospital Anxiety and Depression scale. There was no substantial difference in clinical presentation between primary and secondary CH.

Discussion: This study confirms the existence of auras and interictal signs and symptoms in patients with chronic CH, and male sex and smoking as CH risk factors. Primary and secondary chronic CH appear equally prevalent. Male sex does not appear to favour the shift from episodic to chronic CH.

Recent epidemiological studies indicate that the prevalence of cluster headache (CH) is about 0.2–0.4%.^{1–3} In contrast with migraine, it is more common in men than in women.^{3,4} Two forms of CH have been distinguished, depending on whether the attacks occur in bouts lasting more than 1 year with remission periods of less than 1 month (chronic CH) or in bouts of 1 week to 1 year separated by pain free periods of 1 month or longer (episodic CH).⁵ Episodic CH is much more frequent than chronic CH, with an episodic to chronic ratio estimated at 3.5–4.0.^{6–8}

Much effort has been devoted to the elucidation of the pathogenesis of the disease.⁹ In contrast, relatively few studies have aimed to describe the characteristics of samples of patients with CH. This may be of interest as this headache syndrome may be under recognised in primary care and thus suboptimally managed because of its low frequency.⁸ One UK study described the characteristics of a large sample of 230 non-clinic based patients with CH.⁷ Another joint German and US large study described clinical features and medical treatments in 246 patients with CH.¹⁰ The long term follow-up study by Kunkel and Frame (1994) of 109 patients with chronic CH focused essentially on the evolution of the disease over years.⁶ In 2002, the French Headache Society (SFEMC) decided to set up a French clinical research network on headaches and facial pains (Observatory of Migraine and Headaches (OMH)) based on the International Headache Society (IHS) classification (initially the first and then the second edition of the IHS classification).^{5,11} The network involves 13 tertiary care headache clinics and one specialised emergency department, and covers approximately two-thirds of the French metropolitan territory.¹² The setting up of the OMH database was declared and approved by the French Commission on Data Processing and Liberties (CNIL). The objective of this article is to present the data collected between 2002 and 2005 that concern specifically

the clinical characteristics of the patients included in OMH with a diagnosis of chronic CH.

METHOD

Subject recruitment

At the beginning of 2005, the centres participating in OMH had collected data from a total of 2074 patients diagnosed with CH according to IHS criteria, of whom 316 had the chronic form of the disease. During the period from January to June 2005, neurologists from eight OMH centres (emergency headache centre of Lariboisière Hospital in Paris, centres in Lille, Marseille, Lyon, Nice, Rouen, Toulouse, Saint-Etienne) contacted known patients with chronic CH in their respective area for a face to face interview during which patients were administered a standardised 44 item questionnaire. New consulting patients diagnosed with chronic CH were also interviewed. In each centre, all patients participating in the study were interviewed during a consultation by the same physician.

Study questionnaires

- Patients were queried about their medical and surgical history, and for women hormonal status and hormonal treatments—5 items;
- social habits (smoking, alcohol consumption, use of illicit drugs)—10 items;
- possible evolution from episodic to chronic CH (age, periodicity before and after evolution)—7 items;
- characteristics of the disease (existence of premonitory symptoms, existence of aura, pain localisation, laterality

Abbreviations: CH, cluster headache; HAD scale, Hospital Anxiety and Depression scale; IHS, International Headache Society; OMH, Observatory of Migraine and Headaches

- and periodicity, trigger factors, duration of attacks before and after evolution to chronic CH, associated signs and symptoms, existence of a painful state or isolated autonomic signs persisting between the attacks—12 items;
- medical treatments used (abortive and prophylactic treatments)—4 items;
 - neurological examination (normal/abnormal)—1 item;
 - radiological examinations (CT scan, MRI)—1 item;
 - family history of headaches in relatives of first or second degree, and corresponding diagnoses—4 items.

In addition, the functional impact of the disease was evaluated using a French version of the 6 item HIT questionnaire,^{13 14} and the possibly existing emotional impact was evaluated using the French version of the widely used Hospital Anxiety and Depression (HAD) scale.^{15 16} HIT-6 quantifies headache impact using a score of 36–78 (a score of 36–49 corresponding to no or little functional impact, 50–55 to moderate impact, 56–59 to substantial impact and ≥60 to severe functional impact). For the HAD scale, the original scale has been validated against face to face interviews by psychiatrists, and the anxiety and depression scores have been shown not to be interrelated. Furthermore, the HAD anxiety and depression subscales are well correlated with other widely used anxiety and depression scales.^{17 18} The HAD scale involves seven anxiety items alternating with seven depression items. Anxiety and depression were both defined by anxiety (HAD-Anx) and depression (HAD-Dep) scores ≥8.

Statistical analysis

Statistical analysis was essentially descriptive. Data from subgroups of patients were summarised by the number and relative proportion of patients in each relevant category (demographic, social, diagnostic or clinical). Quantitative data (age, HIT-6 and HAD scores) were summarised by the corresponding median and range.

RESULTS

A total of 113 patients, all with chronic CH, recruited by the eight participating OMH centres, made up the study sample. The Paris centre enrolled 44 patients, the Rouen centre 21 patients, the Marseille centre 20 patients, the Nice centre 10 patients, the Lyon centre seven patients, the Toulouse centre five patients, the Lille centre four patients and the Saint-Etienne centre two patients.

Demography, social habits and family history

There were 93 men and 20 women (male:female ratio 4.65:1). Median age at the time of consultation was 42 years with no difference between men and women (range 19–80 years). The

Figure 1 Distribution of patients according to age at onset of chronicity.

Table 1 Sites of pain in patients with chronic cluster headache

Site	Present study (n = 113) (n (%))	Study by Bahra ⁷ (n = 48) (%)
Retro-orbital	99 (88)	(94)
Temporal	78 (69)	(81)
Maxillary	60 (53)	(67)
Frontal	53 (47)	(42)
Occipital	36 (32)	(8)
Neck	35 (31)	(35)
Nose	30 (27)	(29)
Ear	28 (25)	(27)
Parietal	27 (24)	(0)
Jaw	23 (20)	(65)
Cheek	23 (20)	(63)
Vertex	18 (16)	(8)
Shoulder	8 (7)	(25)

distribution of patients according to age at occurrence of chronic CH is shown in fig 1. The majority of patients were current smokers (77 patients: 68%; 70 men, seven women) or former smokers (22 patients: 19%; 19 men, three women). Only 14 patients had never smoked (12%; four men, 10 women). Forty-eight patients were regular alcohol consumers (42%; 42 men, six women) and 29 were regular cannabis consumers (26%; 26 men, three women). Of the 20 women of the sample, eight presented with primary chronic CH and 12 (60%) with secondary chronic CH, nine were smokers or former smokers (no response: one) and six were alcohol consumers (no response: two).

A family history of headaches existed in 58 (53%) of 110 respondents (no response: three patients). The headache disorder reported among relatives was migraine without aura for 32 patients (29%), migraine with aura for one patient (1%), probable migraine for 21 patients (19%), episodic CH for six patients (5%) and/or other for five patients (5%).

Clinical characteristics

Fifty-two patients (46%; 44 men and eight women) had primary chronic CH (unremitting from onset) and 61 patients (54%; 49 men and 12 women) had secondary chronic CH (that evolved from an initially episodic pattern).

The sites of pain were retro-orbital in nearly all patients, and temporal, maxillary and/or frontal in the majority (table 1). The pain always occurred on the same side in 79% of patients (right side: 47 patients; left side: 38 patients; no response as to the side of pain: six patients) while the side varied for 14% (15 patients). Seven patients (7%) sometimes had bilateral pain during an attack. Attacks occurred regularly at the same time of

Table 2 Trigger factors for cluster headache attacks in patients with chronic cluster headache

Trigger factor	No (%) of patients
Stress, annoyance	44 (40)
Alcohol, wine	34 (31)
Weather, ambient temperature	32 (29)
Fatigue	30 (27)
Effort, physical activity	19 (17)
Tobacco	18 (16)
Rest, weekend, holidays	16 (14)
Smells	15 (14)
Food, meals	11 (10)
Altitudes, flight	10 (9)
Menses	3 (3)

Total number of patients = 111 (no response: two patients).

Table 3 Signs and symptoms associated with attacks in patients with chronic cluster headache

Associated signs and symptoms	No (%) of patients
Lacrimation	103 (93)
Conjunctival injection	82 (74)
Eyelid ptosis	76 (68)
Nasal congestion	73 (66)
Phonophobia	72 (65)
Photophobia	71 (64)
Rhinorrhoea	69 (62)
Nausea, vomiting	54 (49)
Eyelid swelling	50 (45)
Agitation	50 (45)
Sweating (face, front)	42 (38)
Prostration	41 (37)
Miosis	32 (29)
Abdominal pain	14 (13)

Total number of patients = 111 (no response: two patients).

day for 71 patients (72%; no response: 15 patients), mostly at night for 17% of respondents, equally at night or during the day for 45% and preferentially during the day for 38%. Since the onset of CH chronicity, the frequency of attacks was reported to be fluctuating by 79 of 100 patients with available data (79.0%; 67 men, 12 women). Forty-eight patients (42%) reported a painful state persisting between attacks and 27 patients persisting isolated autonomic signs (27%; no response: 13 patients).

In the 61 patients with secondary chronic CH, the average duration of attacks during the antecedent period of episodic CH was <30 min for 18 patients (16%), 30–60 min for 20 patients (18%), 60–120 min for 11 patients (10%) and >120 min for 10 patients (8%) (no response: two patients). Compared with the previous period of episodic CH, attack duration was deemed longer during chronic CH by 27 of the 59 patients with secondary chronic CH and available data.

Known trigger factors were reported by a proportion of patients (table 2). Most frequently mentioned trigger factors were stress or annoyance, drinking alcohol or wine, unpleasant weather or elevated ambient temperature. Many patients reported associated signs and symptoms, most frequently lacrimation, conjunctival injection, eyelid ptosis, nasal congestion, phono- or photophobia and rhinorrhoea, while gastrointestinal symptoms were mentioned by half of the patients (table 3).

Premonitory signs and symptoms were reported by a substantial proportion of patients ($n = 63$). The most frequent premonitory symptoms were feelings of discomfort, tension or diffuse pain (one-third of patients), exhaustion (a quarter of patients) and mood disorders (one-fifth of patients) (table 4). Occurrence of auras was mentioned by 20% of 109 responding patients: the aura was visual in 18 patients (positive in 11 patients, negative in seven), paraesthetic in nine and/or aphasic in one. Three women reported auras.

Functional and emotional impact of cluster headache

The functional impact of CH was assessed in 112 patients using the HIT-6 questionnaire. Median HIT-6 score was 65 (range 36–78), corresponding to severe functional impact. The proportions of patients with no or little, moderate, substantial or severe functional impact are depicted in fig 2: the majority of patients with chronic CH (74%) exhibited severe functional impact.

Anxiety and depression were evaluated by the HAD-Anx and HAD-Dep scores in 107 patients. The number of patients with HAD-Anx score ≥ 8 was 81 (75.7%) and that of patients with HAD-Dep score ≥ 8 , 46 (43.0%).

Table 4 Premonitory signs and symptoms in patients with chronic cluster headache

Premonitory signs and symptoms	No (%) of patients
Discomfort, tension, diffuse pain	41 (36)
Feeling of exhaustion	27 (24)
Mood disorders, irritability, dysphoria	22 (22)
Paraesthesias	15 (13)
Yawning, sighs	10 (9)
Changes in feeding behaviour	9 (8)
Polyuria, polydipsia	8 (7)

Subgroups of patients with primary or secondary chronic CH

There were few differences between the clinical features of patients with primary or secondary chronic CH. The only noteworthy differences concerned:

- the male to female ratio: 5.5:1 for patients with primary chronic CH compared with 4.1:1 for those with secondary chronic CH;
- mean age at onset of chronic CH: 32.6 years for patients with primary chronic CH compared with 38.1 years for those with secondary chronic CH;
- the number of patients with premonitory thymic symptoms: 16 patients with the primary form versus six patients with the secondary form;
- the proportion of patients with persisting painful state between attacks: 39% of patients with primary CH compared with 49% of those with secondary chronic CH.

Other characteristics (other premonitory symptoms, aura, sites of pain, rhythmicity, smoking, trigger factors (except weather), associated signs and symptoms, family history) were all comparable between the two subgroups of patients (data not shown).

DISCUSSION

To the best of our knowledge, this description of a clinic based series of patients with chronic CH is the largest reported to date: the study of 230 patients with CH carried out by Bahra *et al* (2002) involved mostly patients with episodic CH (182 patients with episodic CH vs 48 patients with chronic CH); the

Figure 2 Distribution of patients according to the functional impact of chronic cluster headache, as assessed by the HIT-6 questionnaire.¹³ No or little impact is defined by a HIT-6 score of 36–49, moderate impact by a score of 50–55, substantial impact by a score of 56–59 and a severe impact by a score ≥ 60 . No response: six patients.

study by Blau and Engel (1998) of 150 patients with CH involved 26 patients with chronic CH; the study by Schürks *et al* (2006) of 246 patients with CH involved 41 patients with chronic CH.^{7 10 19} In their long term follow-up study of 109 patients with chronic CH, Kunkel and Frame (1994) gave very few details on patient characteristics and focused essentially on the evolution of the disease.⁶ The survey by van Vliet *et al* (2003 and 2006) was based on a postal questionnaire.^{8 20} All patients included in the present study were interviewed by a physician during a consultation.

One salient finding of this study is the confirmation of data from Blau and Engel (1998) indicating that many patients with CH experience typical symptoms preceding pain onset in most, but not all, CH attacks when patients are not asleep. These authors divided premonitory symptoms into a local vasomotor group (nasal and ocular congestion, similar to the signs occurring during the attacks), a muscular group (flaccidity of eyelids but neck stiffness) and a neurological group (diffuse cerebral disturbance including mood alterations and alimentary symptoms).¹⁹ As suggested by Blau and Engel, the autonomic features anteceding pain onset are not necessarily premonitory but might have other pathogenetic implications, in particular indicating that parasympathetic hyperactivity does not necessarily occur as a reflex response to pain. Furthermore, we confirm many of the mood and neurological changes reported by Blau and Engel: tiredness, dysphoria, yawning and changes in alimentary behaviour. Existence of premonitory symptoms is well in keeping with the identification of the hypothalamus as the site of initiation of CH attacks.^{9 21} Auras (visual, paraesthetic and/or aphasic) were also reported by 20% of our patients with chronic CH. This elevated figure is in striking contrast with the previously reported rarity of auras among patients with CH or other trigeminal autonomic cephalalgias,^{22 23} while other reports did not even mention the existence of auras.²⁰ However, our observation of 20% of patients with chronic CH experiencing auras tallies accurately with the frequency of auras (20–23% of patients) reported in two published series of 100 and 246 patients with CH, respectively,^{10 24} and is comparable with the proportion of 14% of patients with CH with auras in the study of Bahra and colleagues.⁷ Information on auras, as well as about possible autonomic signs without headache (interictal signs) has to be specifically elicited from patients who generally do not spontaneously complain of them.

In our patient sample, the frequencies of primary and secondary chronic CH were close to each other (46% vs 54%, respectively). This result is in contrast with previous data suggesting a higher frequency of primary chronic CH. Kunkel and Frame observed 64% of patients with primary chronic CH and 36% with secondary chronic CH.⁶ Likewise, in their prospective study of 230 patients with CH of whom 48 had chronic CH, Bahra *et al* observed 63% of patients with primary and 37% with secondary chronic CH.⁷ The male to female ratio (4.65:1) in our sample of patients with chronic CH was much higher than the ratio (2.5:1) observed in the study by Bahra *et al* of both episodic and chronic CH, while age at onset was comparable in both studies.⁷ These authors noted a great difference in mean age at onset of chronic CH between men (33.9 years) and women (44.1 years). Male sex may thus be linked with an increased proportion of secondary chronic CH. In our patient sample, the male to female ratio among patients with primary chronic CH remained greater than in patients with secondary chronic CH (5.5:1 vs 4.1:1). This does not support the statements of Favier *et al* who quoted male sex among factors predicting transition to the chronic condition.²⁵

Age at disease onset is classically earlier for episodic CH than for chronic CH.^{6 8 26} However, because of the length of time before

transition to chronicity, age at onset of chronic CH may be later for secondary CH compared with primary CH. This is what we observed, with transition to chronic CH at a mean age of 38.1 years for secondary chronic CH compared with onset of primary chronic CH at a mean age of 32.6 years for primary CH. Kunkel and Frame reported a mean age of 38.9 years at onset of secondary chronic CH compared with 36.0 years at onset of primary chronic CH, versus 28.6 years at onset of primary episodic CH.⁶

Finally, we found no striking difference in clinical presentation between patients presenting with primary CH or episodic CH evolving into chronic CH, justifying the absence of distinction between these two forms of chronic CH in ICHD-II.⁵

Since the first descriptions of the disease, the male to female ratio in patients with CH has been observed to decrease over the years, in parallel with the male to female ratio for smoking habits.⁴ In 1956, Horton reported a CH male to female ratio of 6.7:1 while in 2002 Bahra *et al* found a ratio of 2.5:1.^{7 27} Whereas the male to female ratio in our patient sample was much higher than in the study of Bahra *et al*,⁷ the proportion of smokers or former smokers was very similar (current smokers: 68% vs 67%; former smokers: 19% vs 17%, respectively), which is in favour of smoking habits being a consistent risk factor for CH.

In most of our patients with CH, the spread of the pain was limited to the retro-orbital, temporal, maxillary and frontal regions. In contrast with the patients with chronic CH included in the study of Bahra and colleagues,⁷ only a small proportion of our patients experienced pain in the jaw, cheek or shoulder. The other pain localisations were observed with similar frequencies in both studies, except for occipital pain which was observed in a greater proportion of our patients. The reasons for these differences are not known.

Forty-two per cent of patients in our sample reported a painful state between attacks. This might reflect the existence in CH of a persistent state of central sensitisation similar to allodynia. Allodynia is an increase in the responsiveness (ie, sensitisation) of central pain neurons that process information arising from intracranial structures and skin, resulting in pain in response to non-noxious stimuli to normal skin. Allodynia has been observed during migraine and was also described during CH attacks.^{28–30} However, in a meticulous quantitative study of skin (cheeks, back) thermal and mechanical sensory thresholds in 16 patients with CH (eight with episodic CH and eight with chronic CH), Ladda *et al* found no evidence of skin hypersensitivity during CH attacks (triggered by nitroglycerin) compared with in-bout and out-of-bout pain free intervals.³¹ In his commentary on this work, Burstein suggested that three mechanisms might explain this difference between trigeminovascular headaches such as migraine and CH: firstly, activation of somatic nociceptors in CH versus visceral nociceptors in migraine; secondly, involvement of lamina II of the dorsal horn (which contains inhibitory interneurons) for somatic nociceptors as opposed to visceral nociceptors; and thirdly, increased and decreased activity in CH and migraine, respectively, of inhibitory descending modulatory pathways that regulate the output of nociceptive dorsal horn neurons.³² The subjectively assessed interictal painful state reported by our patients with CH may thus be related to mechanisms different from true allodynia. Persistence of interictal local autonomic dysfunction associated with some degree of painful state suggests the existence of a background of cerebral abnormalities between CH attacks and pain upsurges.

One limitation of our study may be the population of patients which consisted only of patients consulting tertiary care specialist headache centres. Thus our results may not be entirely applicable to all patients with chronic CH, in particular those with milder forms of the disease. Evaluation of the functional impact of chronic CH using the HIT-6 questionnaire showed that 74% of patients in this study endured severe impact, and 73% suffered

from anxiety. A study of 56 consecutive patients with CH seen in a specialist headache centre (34 with episodic CH during an active period and 22 with chronic CH) similarly found high morbidity in these patients and concluded that the impact of the disorder on their health related quality of life is likely to be greater than that in the general population of patients with CH.³³ Comparative data in other populations of patients with chronic CH are thus desirable. Furthermore, some patients with secondary chronic CH (16%) reported attacks of less than 0.5 h duration during the antecedent period of episodic CH. As no attempt was made to rule out chronic paroxysmal hemicrania using an indomethacin test,⁵ the possibility exists of a small confounding effect due to such patients.

CONCLUSION

This study provides detailed information on a large sample of patients with chronic CH consulting specialist headache centres in different regions of France. It confirms the predominance of male sex and smokers among these patients. One-fifth of patients with chronic CH experienced auras, mainly visual or paraesthetic, rarely aphasic. The autonomic features anteceding pain onset may be not only premonitory but may have specific pathogenetic implications in relation to the role of the hypothalamus in the genesis of CH attacks. Some degree of painful state and autonomic signs between attacks is suggestive of a persisting background of cerebral abnormalities between attacks. Male sex does not seem to influence the risk of transition from episodic to chronic CH. The primary and secondary forms of chronic CH appear equally prevalent and there was no obvious difference in clinical presentation between the two forms of chronic CH, which justifies the absence of distinction between them in the current classification of headache disorders.

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