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## Chronic cluster headache: a review

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**Abstract** Cluster headache (CH) is a rare but severe headache disorder characterised by repeated unilateral head pain attacks accompanied by ipsilateral autonomic features. In episodic CH, there are periods of headache attacks with pain-free intervals of weeks, months or years in between. A minority of patients have the chronic form, without pain-free intervals between the headache attacks. Chronic CH can occur as primary or secondary chronic CH; the rarest form is

episodic CH arising from chronic CH. In this article, we give a review of the chronic forms of CH and focus on demographics, clinical manifestations, social habits, predictive factors, head injury, genetics, neuroimaging and therapy. It is remarkable that little is known about risk factors that make CH chronic.

**Key words** Chronic cluster headache • Review

### Introduction

Cluster headache (CH) is characterised by short-lasting, unilateral severe pain attacks, usually located in the orbitotemporal region, accompanied by ipsilateral autonomic phenomena and/or restlessness or agitation [1]. Untreated, the pain lasts 15 min to 3 h and can occur from once every other day to 8 times a day. It is an excruciating pain, driving some patients to thoughts of suicide.

In episodic CH (ECH), the attacks occur in cluster periods lasting from one week to one year and are separated by remission periods of at least one month (Table 1). In chronic CH (CCH) the attacks occur almost every day for more than one year without remission or with remissions lasting less than one month. The chronic form can be unremitting from onset, primary chronic cluster headache (PCCH), or can evolve from the episodic form, secondary

chronic cluster headache (SCCH). The rarest variety is the secondary episodic form (SECH), which begins as chronic and becomes episodic.

In this review, we give an overview of demographics, clinical manifestations, social habits, predictive factors, head injury, genetics, neuroimaging and therapy of CCH. In the separate sections, we will first compare ECH with CCH, followed by a comparison of PCCH and SCCH.

### Demographics

The exact prevalence of CH (and its subforms) is uncertain. In some epidemiological surveys, the prevalence of CH varies from 56 to 401 per 100 000 [2]. The highest prevalence of 401 per 100 000 was found in a study in which the diagnosis of CH was based on a review of

**Table 1** Diagnostic criteria for CH [1]

CH	
A.	At least 5 attacks fulfilling criteria B–D
B.	Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min if untreated
C.	Headache is accompanied by at least one of the following: <ol style="list-style-type: none"> <li>1. Ipsilateral conjunctival injection and/or lacrimation</li> <li>2. Ipsilateral nasal congestion and/or rhinorrhoea</li> <li>3. Ipsilateral eyelid oedema</li> <li>4. Ipsilateral forehead and facial sweating</li> <li>5. Ipsilateral miosis and/or ptosis</li> <li>6. A sense of restlessness or agitation</li> </ol>
D.	Attacks have a frequency from one every other day to 8 per day
E.	Not attributed to another disease
ECH	
A.	Attacks fulfilling criteria A–E for CH
B.	At least two cluster periods lasting 7–365 days and separated by pain-free remission periods of $\geq 1$ month
CCH	
A.	Attacks fulfilling criteria A–E for CH
B.	Attacks recur $>1$ year without remission periods or with remission periods lasting $<1$ month

charts from patients who had been seen and diagnosed by a wide variety of clinicians [3]. So, this high figure may be biased.

The episodic form of CH is much more prevalent than the chronic form. The exact ratio between chronic and episodic CH, however, is unknown. Figures in the literature differ [4–6] (Table 2), probably because there is a difference in patient selection. Within the group of patients with CCH, the prevalence of the subgroups (PCCH, SCCH, SECH) is also not exactly known. In a follow-up study of 109 CCH patients during at least 5 years, 64% could be classified as PCCH and 36% as SCCH [7].

As to the course of CH, Pearce [8] conducted a follow-up study of 101 patients with ECH and 7 patients with CCH during 16 years. Four patients (3.96%) in the episodic group changed to a chronic pattern, whereas in the chronic group, 2 patients (28.6%) changed to an episodic pattern. Another study followed 189 patients with CH over a period longer than 10 years [9]. Almost 13% of ECH patients became secondarily chronic and 32.6% of CCH patients became secondarily episodic.

In 1956, Horton [10] reported a male-to-female ratio of CH of 6.7:1 and this was used in clinical practice for years. Recently, the male-to-female ratio was found to be much lower, namely 2.5:1 [5]. This decrease in ratio might be explained by the fact that specific male behavioural traits are possible cluster triggers and that more women are taking over these traits. Also, more women are contributing to household incomes and therefore seek treatment sooner. Another explanation might be that in the past, many women

**Table 2** Episodic-to-chronic ratio

Study	Number of patients	Episodic-to-chronic ratio
Manzoni (1997) [4]	482	7.5:1
Bahra et al. (2002) [5]	230	4:1
Van Vliet et al. (2003) [6]	1163	3.5:1

with CH were first diagnosed with migraine, because of atypical features of the CH, such as longer duration of an attack. A male to female ratio of 3.6:1 was found for ECH and 4.2:1 for CCH [4]. Another study found a male to female ratio of 3.2:1 in PCCH and 2.4:1 in SCCH [11].

Mean age at onset appeared to be later in CCH than in ECH: 38 *vs.* 32 years [6]. Mean age at onset was later in PCCH compared to SCCH: approximately 37 *vs.* 29 years [11, 12].

In conclusion, the exact prevalence of CH and its subforms is uncertain, but it is clear that episodic CH is much more prevalent than chronic CH. There is a male preponderance in CH, especially in the chronic form. In chronic CH, the mean age at onset appeared to be about 6 years later than in episodic CH. The mean age at onset is especially late in primary chronic CH.

### Clinical manifestations

The diagnostic criteria for CH do not differentiate between ECH and CCH in the clinical features of the attacks. The distinction is only made in the occurrence and duration of remission periods, but clinical studies also found some differences in the characteristics of ECH and CCH.

First, patients with CCH appear to have a mild, continuous headache between the attacks more often than patients with ECH [6]. Second, a significant difference in the site of pain appears to exist [5]. In both forms the site of pain was predominantly retro-orbital and temporal, but in CCH, more patients reported pain also in the upper teeth, jaw, cheek, ear and shoulder. Besides, in CCH there was more often a side change of the pain. Third, differences in autonomic features were found between ECH and CCH. Lacrimation is the most often reported symptom in both conditions, but rhinorrhoea occurred significantly less in CCH. Osmophobia occurred more in CCH. Finally, the reported attack duration between ECH and CCH was shorter in the chronic group.

There are also some differences in characteristics between PCCH and SCCH [11]. First, patients with PCCH more often reported right-sided pain than patients with

SCCH, a finding that is not easily explained. Second, in PCCH and SCCH, attack duration was most often between 15 and 120 min, but there was a statistically significant larger proportion of patients with SCCH who reported attacks lasting 120–180 min. Finally, patients with SCCH were more likely to have their headache associated with lacrimation, nasal congestion, rhinorrhoea and ptosis while patients with PCCH more frequently reported facial sweating and eyelid oedema.

In conclusion, there are some clinical differences between episodic and chronic CH and also between the two chronic forms.

### Social habits

Some studies have looked at lifestyle habits in episodic vs. chronic CH. Up to 90% of CH patients are smokers or former smokers [12] and there seem to be some differences between the episodic and chronic forms (Tables 3 and 4). In an Italian study, more male CCH patients smoked compared to ECH patients and the chronic patients also smoked more cigarettes a day [12]. Comparing the two chronic forms, there were more and also more heavy smokers in the SCCH group [11].

**Table 3** Social habits in ECH vs. CCH [12]

Social habit	ECH, %	CCH, %
Smoking habit		
No. of patients	78.9	87.8
>20 cig/day	57.8	66.7
Alcohol intake		
No. of patients	84.2	90.2
>100 g/day	19.2	29.7
Coffee intake		
No. of patients	94.4	100
>6 cups/day	7.3	36.6

**Table 4** Social habits in PCCH vs. SCCH [11]

Social habit	PCCH, %	SCCH, %
Smoking habit		
No. of patients	65.8	87.1
>20 cig/day	21.1	48.4
Alcohol intake		
No. of patients	76.3	64.5
50–100 g/day	27.6	15
Coffee intake		
No. of patients	89.5	90.3
5–7 cups/day	57.9	32.3

There were a few more alcohol drinkers in CCH compared to ECH, but the chronic patients were evidently heavier drinkers [12]. PCCH patients were more frequently heavy drinkers compared to SCCH patients [11].

A minor difference was found in the number of ECH and CCH patients consuming coffee, but the chronic patients drank more cups of coffee a day [12]. The percentage of regular coffee drinkers was the same in both chronic conditions, however PCCH patients drank more cups of coffee a day [11].

In conclusion, lifestyle habits such as smoking and the consumption of alcohol or coffee are common habits in CH, especially in chronic CH. Comparing the two chronic conditions, smoking is a more common habit in SCCH patients while consuming alcohol or coffee is more common among PCCH patients.

### Secondary chronic cluster headache: predictive factors

Three factors were discovered that seemed to predict a shift from ECH to CCH [9]. Firstly, the shift was associated with the duration of the disease. In 20.5% of episodic patients with a course of CH longer than 20 years, there was a shift towards the chronic form, versus a shift in 9.4% of patients with a shorter course than 20 years. Secondly, a late age at onset appeared to predict a pattern change. Mean age at onset was 27.1 years in ECH, while the mean age at onset was 34.9 years in SCCH. Thirdly, male sex was slightly related to a shift to a chronic condition: in SCCH, the percentage of females was 9.1% and the percentage of males was 13.6%.

The characteristics of cluster and remission periods were also found to be predictive factors in the shift from ECH to SCCH (Table 5). More SCCH patients reported cluster periods lasting more than 8 weeks before the CH became chronic, compared to ECH patients who stayed episodic [13]. Also, a larger proportion of SCCH patients reported remission periods lasting less than 6 months. More SCCH patients reported more than one cluster period a year and more frequently reported sporadic attacks.

**Table 5** Characteristics of cluster and remission periods in ECH and SCCH [13]

	ECH, %	SCCH, %
Cluster periods >8 weeks	8.5	25
Remission periods <6 months	6.6	28.6
More than 1 cluster/year	18.2	28.6
Sporadic attacks	5	25

In conclusion, factors that were found to predict a shift from episodic to chronic CH are: a longer course, a late age at onset, male sex, longer cluster periods, shorter remission periods, more cluster periods per year and more frequent sporadic attacks.

### Secondary episodic cluster headache: predictive factors

Four factors were found that favoured the evolution of CCH into SECH [9]. The first one was the use of prophylactic treatment (usually lithium). Of the chronic patients who became secondary episodic, about 56% used prophylactic medication. The second factor was an earlier headache onset. CH onset was 26 years for SECH and almost 35 years for PCCH. Thirdly, duration of the disease longer than 20 years was positively related to the evolution from CCH to ECH. Only in 46.6% of patients with CCH and a course longer than 20 years did the chronic form persist. Fourthly, male sex appeared to relate positively to a shift from CCH to ECH: all of the patients in the SECH group were men.

In conclusion, factors that were found to predict a shift from chronic to episodic CH are: the use of prophylactic treatment, an earlier age at onset, a longer course and male sex.

### Head injury

Head injury and CH have been frequently associated. In a case-control study [14], significantly more CH patients had a previous head trauma compared to the control group (30.8% vs. 15.8%), and in another study, almost 37% of CH individuals reported head injury vs. almost 17% of age- and gender-matched migrainous controls [12]. Patients with CCH reported a head injury more often, whether with or without loss of consciousness, compared to patients with ECH (Table 6). Also, head injury occurred more often on the same side as the headache in chronic patients. Head injury preceded the onset of CH more often in chronic patients [11] than episodic patients [13].

Individuals with PCCH reported head injury in their history less frequently compared to SCCH [11], but in a

**Table 6** Head injury in CH [11–13]

Head injury	ECH, %	CCH, %	PCCH, %	SCCH, %
No. of patients	35.9	54.7	34.2	54.8
Pre-CH	45.3	70.0	76.9	64.7

higher percentage of PCCH patients, the head injury preceded onset of CH. A significant difference was found in the average number of years elapsing between head injury and onset of CH when the analysis was restricted to head-injured males with loss of consciousness. The average latency period was 21.8 years for PCCH men and 5.5 years for SCCH men. Four of 28 SCCH patients had a second head injury and in all these 4 patients, the second head injury preceded the evolution from episodic to chronic [13]. The mean latency period between the second head injury and the evolution into SCCH was 11.0 years.

In conclusion, many CH patients report a head injury in their medical history. The frequency of head injury is higher in chronic than episodic patients and also higher in SCCH patients compared to PCCH patients. In most chronic patients, the head injury preceded the onset of CH.

### Genetics

It has been suggested that there is a genetic influence in CH. CH has been described in monozygotic twins and also in families in consecutive generations. In a French study [15], a positive family history was found in 10.75% of CH patients. Familial CH was found in 9.52% of ECH patients and in 20% of CCH patients; the difference was not statistically significant. Different forms of CH can occur within the same family. Spierings et al. [16] described a family with the occurrence of CH in three generations: an 8-year-old boy with PCCH, his 42-year-old father with SCCH and his 73-year-old paternal grandfather with ECH.

In conclusion, no difference in genetic factors seems to exist between the episodic and chronic form. Different forms of CH can occur in the same family.

### Neuroimaging

PET studies in CH patients revealed that the ipsilateral inferior posterior hypothalamus is activated during a CH attack [17]. No difference was made between CCH and ECH, because the ECH patients were used as controls while they were not in a cluster period.

With voxel-based morphometry, a significant structural difference in grey matter density bilateral in the inferior posterior hypothalamus was found between CH patients and healthy volunteers [18]. No comparison was made between CCH and ECH patients.

In conclusion, the difference between ECH and CCH in hypothalamic function and grey matter density has not been studied yet.

## Therapy

More patients with ECH than with CCH had success with oxygen: 78.8% vs. 68.4% [19]. The greatest difference was found when comparing ECH patients under 50 years of age (92.9%) with CCH patients over 49 years of age (57.1%). CH can also be treated with a hyperbaric form of oxygen. In a placebo-controlled study, the treatment of CCH patients with hyperbaric oxygen in 15 sessions every other day for 4 weeks was more effective than placebo [20]. The number of attacks and the analgesic consumption declined in the group treated with hyperbaric oxygen, while there was no change in the placebo group. However, it is difficult to treat patients with this therapy, because it requires hyperbaric chambers.

Patients with CCH responded well to the use of subcutaneous sumatriptan, but to a lesser extent than ECH patients: 72.9% of ECH patients were pain free within 15 min compared to 60% of CCH patients [21]. Also, CCH patients responded more slowly than patients with ECH.

In an open-label study [22], intranasal sumatriptan was more effective in ECH than in CCH, but only 4 patients with CCH and 6 with ECH participated. Within 30 min, 42% of headache attacks improved in ECH patients compared to only 16% of headache attacks in CCH patients. In a placebo-controlled study [23], no difference in efficacy of sumatriptan nasal spray was found between episodic and chronic patients. Unfortunately, no percentages were given.

Dihydroergotamine was more effective for ECH than for CCH [24]: there was complete resolution in 73% of ECH patients and in 46% of CCH patients. Dihydroergotamine appeared to induce transformation from CCH to ECH: of the 17 patients with CCH who achieved complete success with dihydroergotamine, 3 experienced a transformation to ECH.

In a double-blind crossover study, significantly more patients with ECH reported efficacy of oral zolmitriptan than placebo (46.8% vs. 28.9%) [25]. In CCH however, there was no significant difference.

In an open study with 48 patients [26], it was found that ECH patients more often improved than CCH patients on verapamil prophylaxis (73% vs. 60%), but this difference was not significant. Headache relief was obtained after an average of 1.7 weeks in the episodic group and after an average of 5 weeks in the chronic group. The required average daily dose of verapamil was 354 mg in ECH and 572 mg in CCH.

In an open study [27], 19 male CH patients (8 with CCH and 11 with ECH) were treated with lithium. In all chronic patients, there was at least a 75% improvement within 2 weeks after starting the treatment. In the episodic patients, there was an average improvement of only 15% with no improvement in 3 patients. Lithium was

compared with verapamil in a double-blind crossover trial in CCH patients [28]. It appeared that both medications were efficacious in preventing CCH, without significant differences.

Methysergide appeared effective in approximately 65% of ECH patients and in only 20% of CCH patients [29].

In an open-label study with 77 episodic and 15 chronic patients, there was a marked relief with prednisone therapy in 76.6% of patients with ECH and in 40% of patients with CCH [29].

In an open-label study, topiramate rapidly induced cluster remission in 64.3% of CCH patients and in 50% of ECH patients [30]. All chronic patients and 75% of episodic patients had poor or no response to other preventive treatments.

Serum melatonin levels are reduced in CH patients during a cluster period [31, 32]. In a double blind, placebo-controlled trial in 18 ECH and 2 PCCH patients, melatonin appeared only effective in the prophylaxis of ECH [33]. In another study, in 6 CCH patients and 3 ECH patients who did not react to conventional therapy, there was no effect of melatonin [34]. The lack of response in CCH may reflect a fundamental difference between the chronic and episodic condition.

In a placebo-controlled trial, capsaicin was superior to placebo in reducing headache severity when delivered twice a day in the ipsilateral nostril for seven days [35]. Episodic patients appeared to benefit more than chronic patients.

In CCH cases resistant to medical management, surgery could be a feasible option. Of 17 patients with intractable CCH who underwent a partial or complete section of the trigeminal nerve, 15 (88%) had complete or near-complete relief of their CH in the immediate postoperative period [36]. Complete section produced better results than partial section, but this difference was not significant. Two patients had recurrence of the CH after initial complete relief.

In another study, 28 CCH patients underwent in total 39 microvascular decompression procedures of the trigeminal nerve, alone or in combination with section and/or microvascular decompression of the nervus intermedius [37]. In 22 of 30 (73.3%) first time procedures, there was a 50% relief or better. At follow-up, this success rate dropped to 46.6%. Repeating the procedure was ineffective. Stimulation of the ipsilateral posterior hypothalamus with stereotactic implants in five patients with medically refractory CCH was successful [38]. All patients achieved complete pain relief. The relief of pain occurred in two patients after a couple of hours, in three patients in 1–4 weeks. Three patients remained pain free with prophylactic medication, the other two patients stayed pain free without medication. There were no adverse side effects of the stimulation and there were no acute complications from

the electrode implant procedure. Of course, these results are from a limited number of patients. In a long-term follow-up study of a patient with bilateral hypothalamic stimulation, the stimulation appeared very successful, but there were some adverse events, consisting of transient vertigo and bradycardia [39]. Besides, the hypothalamus is important for internal metabolic homeostasis and circadian rhythms, so an extremely cautious patient selection for hypothalamic stimulation is mandatory. Recently, proposals for patient selection are published [40].

In conclusion, symptomatic treatment with oxygen and subcutaneous sumatriptan is more effective in ECH than in CCH. Prophylactic medications are also more effective in ECH than in CCH with the exception of topiramate and especially lithium. Dihydroergotamine is more effective in ECH, but appears to induce transformation from CCH to ECH. Surgery could be a feasible option for CCH patients resistant to medical management. Stimulation of the posterior hypothalamus seemed to be very effective in medically refractory CCH, but the results are from a very limited number of patients.

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## Conclusions

CH is a severe headache disorder. Especially its chronic forms are very disabling and difficult to treat. In approximately 4–13% of cases, the episodic condition can develop to a chronic form of CH. It is remarkable that little is known about factors that influence the evolution of ECH to CCH. Such knowledge can, however, be of great value, as it may lead to treatment or preventive measures to

avoid this evolution. In our present review of (mainly retrospective) studies, three factors seemed to predict the shift from ECH to CCH: a longer course of CH, a late age at onset and male sex. The influence of male sex may have been overestimated, as there were not many women examined in these studies. The role of a long duration of CH is also not very strong, because the longer the duration of a disease, the more time there is for a pattern change. The characteristics of cluster and remission periods also seemed to predict a shift from ECH to CCH.

When comparing ECH with CCH, there did not appear to be many clinical differences. The main difference we found was the effect of prophylactic medication, which is larger in ECH than in CCH, with the exception of topiramate and lithium. Selection bias is a likely cause for these findings. It is striking that dihydroergotamine, although more effective in ECH, appears to induce transformation from CCH to ECH.

The comparison of PCCH with SCCH revealed a male preponderance in PCCH, but not many clinical differences.

Not much is known about the pathophysiology of CH. Even less is known about the chronic forms of CH. Patients with CCH more often report a head injury and some studies point to differences in social habits between ECH and CCH. These social habits are more often displayed by chronic patients. But are these habits secondary phenomena to the suffering of chronic CH, or do they play a role in the onset? Also, are there more factors that could favour the development of chronic CH, besides a head injury and lifestyle habits? For instance, does the frequent use of triptans play a role? Further research, for example by means of prospective and longitudinal studies, might lead to more insight in the pathophysiology of CCH.

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