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REVIEW

Cluster headache: pathophysiology, diagnosis and treatment

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Abstract
Cluster headache (CH) is characterized by attacks of severe, strictly unilateral pain that is orbital, supraorbital, temporal, or any combination of these, lasts 15–180 min, and occurs from once every other day to eight times a day. The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid edema, and/or with restlessness or agitation. The understanding of the pathophysiological mechanisms behind CH is far from complete, but CH is considered to be a neurovascular and chronobiologic headache disorder, with a pivotal role played by the central brain mechanisms. The diagnosis of CH is based on a careful history that elicits the clinical features of attacks, ipsilateral autonomic phenomena, and the cyclical nature of the bouts in which the attacks occur. Additional diagnostic interventions are needed to rule out secondary causes of CH. The main focus of therapy is to abort attacks once they have begun and to prevent future attacks. Alternative interventions in patients with CH who have not experienced any meaningful benefit from preventive drugs are well defined. Although there have been advances in the diagnosis and therapy of CH, a significant number of CH patients experience misdiagnoses and diagnostic delay, which stalls the possibility of the timely application of adequate abortive and preventive therapy.

Keywords Cluster headache · Pathophysiology · Diagnosis · Therapy

Definition

Trigeminal autonomic cephalalgia (TAC) is a type of primary headache disorder characterized by pain in the distribution of the first division of the trigeminal nerve in parallel with cranial autonomic features on the same side of the head. CH is the most common and best studied TAC.

CH is characterized by attacks of severe, strictly unilateral pain that is orbital, supraorbital, temporal, or any combination of these, lasts 15–180 min, and occurs from once every other day to eight times a day. The pain is associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis and/or eyelid edema, and/or with restlessness or agitation, Table 1 [1].

Epidemiology

CH is more rare than other primary headache disorders (migraine and tension type headache), with a population prevalence up to 0.1%. Although data from epidemiological studies give CH a lifetime prevalence of 0.12%, there are data showing a 1-year prevalence of 0.3% [2]. The male-to-female ratio varies between 2.5:1 and 3.5:1 [3]. Despite a similar clinical phenotype, diurnal attack cycle is advanced by 1 h in men compared to women. Women are more often misdiagnosed and have chronic CH more frequently than men [4]. Although patients can be affected at any age, CH attacks typically start between the 20 and 40 s [5]. Interestingly, one study showed that patients with CH onset after 40 years of age reported a lower number of autonomic features and less frequently had conjunctival injection and nasal congestion/rhinorrhea phenomena during their attacks; the diagnostic delay was the longest in the patients with CH onset before 20 years of age [5].

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Table 1 Diagnostic criteria for CH

A. At least five attacks fulfilling criteria B–D
B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 min (when untreated)
C. Either or both of the following
1. At least one of the following symptoms or signs, ipsilateral to the headache
(a) Conjunctival injection and/or lacrimation
(b) Nasal congestion and/or rhinorrhoea
(c) Eyelid oedema
(d) Forehead and facial sweating
(e) Miosis and/or ptosis
2. A sense of restlessness or agitation
d. Occurring with a frequency between one every other day and eight per day
e. Not better accounted for by another ICHD-3 diagnosis

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CH causes high healthcare costs that are associated with inpatient admissions, pharmacy fulfillments, absenteeism and short-term disability [6, 7]. Unhealthy lifestyle factors and lifestyle-related diseases are more prevalent in CH patients [8].

In some families, CH has a heritable tendency. First-degree relatives of CH patients have an estimated 10- to 50-fold increased risk of developing CH [5]. Increasing evidence suggests an association between CH and smoking, with around 65% of patients being active smokers or reporting a history of smoking [9]. Recent published data suggest higher smoking rate of 88% among CH patients [10]. The clinical phenotype of CH is a more severe based on attack frequency, cycle duration, headache related disability and chronification in smoking exposed patients, while nonexposed smoking CH patients have an earlier age of onset, higher rate of familial migraine, and less circadian periodicity and daytime entrainment [10]. The natural course of CH can be difficult to predict, with some people showing a bidirectional transition between the episodic and chronic forms of the condition. Less frequent bouts of attacks and more prolonged, and sometimes permanent, periods of remission can occur with advancing age [11].

Pathophysiology

The understandings of the pathophysiological mechanisms behind CH are far from complete. CH is considered to be a neurovascular and chronobiological headache disorder, with a pivotal role played by the central brain mechanisms [12, 13]. From a clinical point of view, the recognition of CH pathophysiology is useful in understanding the main clinical features of CH, such as the trigeminal distribution of pain, ipsilateral cranial autonomic features, and episodic patterns of attacks.

Calcitonin gene-related peptide (CGRP) is recognized as a key signaling molecule involved in CH. The human experimental studies reported elevated plasma CGRP levels during spontaneous and induced cluster attacks. The exact role of CGRP and its mechanism of action in CH have not been fully clarified but CGRP is considered as a validated therapeutic target for CH [14].

While the severe unilateral pain is mediated by the activation of the first (ophthalmic) division of the trigeminal nerve, the associated autonomic symptoms are due to the activation of the cranial parasympathetic outflow from the seventh cranial nerve [12]. Evidence suggests that the autonomic symptoms in CH can be the consequence of the central autonomic dysregulation due to hypothalamic disturbance; the consequence of vasodilation and perivascular edema due to the trigeminal parasympathetic overactivity during attacks that compromises the carotid canal and the traversing sympathetic fibers; or the autonomic symptoms may appear secondary to trigeminal discharge [15]. The higher sympathetic tone has been shown during neurostimulation of the sphenopalatine ganglion preceding cranial autonomic symptoms or cluster pain, while during cluster pain increased parasympathetic activity has been observed [16]. It is important to note that a small percentage of CH patients (3–5%) have no autonomic symptoms; in rare cases, pain and autonomic symptoms may fully dissociate [17].

The relapsing-remitting course and seasonal variation as well as the clockwise regularity of single episodes are the main features of CH that suggest that the hypothalamus is involved in CH pathogenesis. Novel data suggest differences in the hypothalamus' influence on CH attacks occurrence between the genders [4].

In their neurovascular theory, Goadsby and Edvinsson [18] superseded the previous clear vascular theory that an inflammation of the walls of the cavernous sinus (the only peripheral anatomical location where a single pathology could involve trigeminal C-fibers and sympathetic fibers)

underlies CH pathogenesis [19], showing that neurovascular events and some central impulse generators are more potent. There are results of lowered concentrations of testosterone in the plasma of men with CH, which was accompanied by a reduced response to thyrotropin-releasing hormone [20]. Further, a blunted nocturnal peak in melatonin and complete loss of circadian rhythm of melatonin have been reported in patients with CH [21]. As melatonin is considered as the main biomarker of circadian rhythmicity, this change in the plasma concentration directly suggests desynchronization of the circadian rhythms in CH. It has been shown that the circadian pattern of melatonin and cortisol, as well as other hormones, is altered in CH patients [12]. The endogenous circadian control by the hypothalamus, actually by its structures such as the suprachiasmatic nuclei stimulated by light conditions via a retino-hypothalamic pathway, etc., represents the strongest trigger for the pathogenesis of CH. The suprachiasmatic nuclei are situated in the anterior hypothalamus and work as an endogenous pacemaker responsible for controlling the circadian rhythmicity of hormone release and sleep-wakefulness cycles. It has extensive projections to other hypothalamic nuclei and a polysynaptic pathway to the pineal gland, responsible for melatonin production [13]. There are results which also suggest a functional involvement of the hypothalamic hypocretinergic system in the pathogenesis of CH, although the same results show that the hypocretin-1 levels in CSF do not influence the clinical course of CH [22]. Significantly reduced hypocretin-1 level concentrations in CH patients were considered as an insufficient antinociceptive activity of the hypothalamus in CH pathogenesis [23].

A growing number of neuroimaging studies have also shown specific hypothalamic involvement in CH. Neuroimaging has suggested an abnormal or dysfunctional posterior hypothalamus in CH. A positron emission tomography study performed to visualize regional cerebral blood flow in CH patients both in and out of cluster showed significant activation of the ipsilateral, posterior, and hypothalamic gray matter, but only in CH patients in a cluster period [24]. A voxel-based, morphometric, magnetic resonance study found a significantly increased density and volume of the gray matter region in the inferior posterior hypothalamus in CH patients compared to healthy controls [25]. A proton MR spectroscopy study measured *N*-acetylaspartate/creatine ratios (NAA/Cr) in CH patients in and out of cluster periods as compared to healthy individuals and migraine patients, and found lower NAA/Cr in the hypothalamus of all CH patients without differences between episodic and chronic CH [26]. A functional magnetic resonance imaging study of CH patients also showed significant hypothalamic activation ipsilaterally, attributable to cluster attacks [27]. Recent progress in neuroimaging provides additional insights into structural and functional connectivity changes in the pain neuromatrix with an emphasis on central descending pain modulation, and non-traditional pain processing networks including the occipital and cerebellar networks which are dynamically altered between in-bout and out-of-bout periods in episodic CH [28]. The important role of the anterior hypothalamus in CH has been also proven [29].

Diagnosis

The diagnosis of CH is based on a careful history that elicits the clinical features of attacks: severe, strictly unilateral pain that is orbital, supraorbital, temporal, or any combination of these, duration, ipsilateral autonomic phenomena, and the cyclical nature of the bouts in which the attacks occur. The local painful and painless pre-attack symptoms occur in CH. These symptoms are significantly frequent in men with episodic CH compared with women and chronic CH [30].

CH attacks occur in series lasting for weeks or months separated by remission periods usually lasting months or years. About 10–15% of patients have chronic CH, without remission periods [1]. The pain of CH is unilateral in almost all patients with episodic CH. It is mainly focused behind the eye and maxilla, but may spread to other regions of the head and neck. Pain can shift sides between bouts of CH attacks (less commonly during a bout; never during the attack itself). Patients describe the pain as extreme, the worst they have ever experienced, and as a sharp, burning or pulsating sensation [31, 32]. During attacks, patients are usually unable to lie down, and they characteristically pace the floor. During some part of a bout, less than half of the active time-course of CH, attacks may be less severe and/or of shorter or longer duration and may be less frequent [1].

Attacks occur spontaneously and may be provoked by alcohol, histamine, nitroglycerin, or organic compounds such as perfume and paint. In over half of patients, small quantities of alcohol, particularly red wine, will precipitate an attack, usually within an hour of ingestion [33].

The diagnostic criteria propose that attacks last between 15 and 180 min, although on rare occasions they can last longer. The attack will often end as abruptly as it started. The frequency of attacks varies, although less frequent attacks may occur at the beginning and end of bouts. CH attacks often occur during the night, waking patients from sleep [31]. The attacks are accompanied with psychomotor agitation which is one of the key features of CH [3].

The cranial autonomic symptoms or signs appear on the same side as the pain and resolve with the cessation of pain. Horner's syndrome or isolated ptosis may persist between attacks or even bouts as a result of local damage to oculosympathetic fibers during repeated attacks [34]; its persistence indicates increased alertness towards secondary causes. Patients commonly have tenderness and cutaneous

allodynia at and around the site of pain between attacks, including over the ipsilateral greater occipital nerve [35].

CH attacks may present with migraine-like features such as nausea, vomiting, phono/photophobia, and aura phenomena similar to those experienced during migraine, as well as symptoms often limited to the same side as the pain; slightly fewer patients report an aversion to loud noise or strong smells during an attack [3, 36]. The majority of the unconfirmed cases of CH have been identified as migraine headache. This might be secondary to the common finding of unilateral autonomic symptoms which are accompanied by migraine-like symptoms in almost a third of CH patients [32, 37].

Most CH patients experience one bout a year, although some patients may go for several years without a bout and others may have more frequent bouts [31]. There are two clinical forms of CH, episodic and chronic, based on the duration of pain-free periods between cluster periods (less or more than 3 months), Table 2. In episodic CH, cluster periods usually last between 2 weeks and 3 months. Chronic CH may arise de novo or evolve from episodic CH. Some CH patients change from chronic to episodic CH [1].

The available evidence suggests that CH represents a lifelong disorder in most patients, evolving from episodic into chronic CH in one out of ten patients and transforming from chronic to episodic in one out of three patients [3].

Differential diagnosis

Table 3 summarizes the main features of CH compared to other TAC, as shown in a previous study [38]. Several structural lesions in the mid and posterior cranial fossa, particularly pituitary tumors, carotid dissections, and cavernous sinus pathology can be clinically presented mimicking CH. Brain MRI with detailed study of the pituitary area and cavernous sinus, is recommended for all TACs including CH, because even clinically typical CH can be caused by structural lesions [32, 39].

When three consecutive preventive treatments fail (refractory CH), additional magnetic resonance angiography of the brain and carotid/vertebral arteries may be required. In the presence of Horner's syndrome, additional imaging of the apex of the lung may be warranted, especially in smokers. Pituitary function testing should be considered in all refractory CH patients. Despite these recommendations, CH patients with a long history of CH bouts separated by asymptomatic periods that respond to preventive treatment do not need neuroimaging [40].

Comorbidity with trigeminal neuralgia (TN) (CH-tic syndrome) should be ruled out in cases of refractory CH. As in other TAC [41], some CH patients have been described having both CH and TN (sometimes referred to as cluster-tic syndrome). They should receive both diagnoses. The importance of this observation is that both conditions must be treated for the patient to become pain free [1].

A study conducted to investigate the occurrence of diagnostic errors in CH-affected patients suggested that CH patients often consult various specialists (neurologists, primary care physicians, ENT specialists, dentists, etc.) prior to receiving the final and true diagnosis of CH. Misdiagnoses at the first consultation were recorded in more than two-third of CH patients (trigeminal neuralgia, migraine without aura, sinusitis, etc.); in the majority, instrumental and laboratory investigations were conducted, and the diagnostic delay was more than 5 years [42]. Migraine attacks tend to be less severe and to last longer, the cranial autonomic features of migraine are less prominent and more likely to be bilateral, and nausea, vomiting, and bilateral photophobia are common. Migraine patients prefer not to move during the episode, in contrast to the agitation and restlessness experienced during CH. Trigeminal neuralgia tends to affect people over the age of 50 and consists of sudden short-lasting stabs of lancinating pain, usually affecting the second and third divisions of the trigeminal nerve. It is usually not associated with cranial autonomic features and is often precipitated by touch, chewing, swallowing hot or cold liquids, and cold wind [43]. As we noted previously, the coexistence of migraine or TN with CH, although rare, is possible.

Table 2 Diagnostic criteria for episodic and chronic CH

Diagnostic criteria for episodic CH
Cluster headache attacks occurring in periods lasting from 7 days to 1 year, separated by pain-free periods lasting at least 3 months.
A. Attacks fulfilling criteria for 3.1 Cluster headache and occurring in bouts (cluster periods)
B. At least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥ 3 months
Diagnostic criteria for chronic CH
Cluster headache attacks occurring for 1 year or longer without remission, or with remission periods lasting less than 3 months
A. Attacks fulfilling criteria for 3.1 Cluster headache, and criterion B below
B. Occurring without a remission period, or with remissions lasting < 3 months, for at least 1 year

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Table 3 Comparison of the clinical features of TAC

Characteristic	Cluster headache	Paroxysmal hemicrania	SUNCT/CUNA
Gender (M/F)	3:1	1:1	1.5:1
Pain			
Severity	Very severe	Very severe	Severe
Distribution	V1 > C2 > V2 > V3	V1 > C2 > V2 > V3	V1 > C2 > V2 > V3
Quality	Stabbing/sharp	Stabbing/sharp	Stabbing/sharp
Attacks			
Length	15–180 min	2–30 min	1–600 s
Number/day	1/2 days–8/day	> 5/day	100/day (3–200/day)
Agitation/restlessness	+++	++	+
Triggers			
Alcohol	+++	+	–
Cutaneous	–	–	+++
Nitroglycerin	+++	+	–
Circadian/circannual periodicity	+	–	–
Therapy			
Oxygen	> 80%	–	–
Triptans	> 70%	20%	< 10%
Indomethacin	–	100%	–
Migraine like features (nausea, vomiting, photo/phonophobia)	50–65%	40–65%	25%

Based on the International Classification of Headache Disorders, 3rd edition, 2018 and modified according to Nesbitt and Goadsby, 2012

SUNCT/SUNA short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/short lasting unilateral neuralgiform headache attacks with cranial autonomic features

Comorbidities

Most studies addressing psychiatric comorbidity in CH have focused on depression and anxiety, although they vary widely. The rate of bipolar disorder in CH patients is largely unknown [44]. Aggression is commonly seen in CH patients ictally; in fact, a sense of restlessness or agitation is one of the cardinal features of the CH attack. Restless leg syndrome may also co-exist with CH. Although CH often carries the nickname of "suicide headache", reports of suicide in these patients are rare [45–47]. There is study which results suggest the rate for suicide ideations is 55% among CH patients, and the rate for CH patients who have actually tried to commit suicide is 2% [48].

REM sleep is affected in CH [49, 50]. Some results suggest a higher incidence of obstructive sleep apnea in CH patients [51]. Reports indicate that CH and obstructive sleep apnea are associated with an improvement in CH upon following treatment for sleep apnea [49]. There is no association between apnea events or specific sleep stages in CH [50]. In our previous research, we noticed that comorbid disorders in CH patients were frequent and similar to those noticed in migraine patients, except chronic sinusitis and diabetes mellitus [52].

Therapy

The main focus of intervention is to abort attacks once they have begun and to prevent future attacks. Standard analgesia is ineffective, and there is no evidence to support the use of non-steroidal anti-inflammatory drugs, paracetamol (acetaminophen), codeine, or opioids in the treatment of individual attacks. There are, however, abortive and preventive treatments for CH.

The mainstay of abortive treatment consists of inhaled oxygen and parenteral triptans. There is consensus that high-dose and high-flow-rate oxygen is effective for the abortive treatment of episodic or chronic CH acute attacks [53]. The majority of CH patients are pain free after inhalation of 100% oxygen at 12 L/min for 15 min through a non-rebreathing facemask [54]. Oxygen mask type is also of importance. There is study designed to investigate possible differences in effect between different types of masks in the acute treatment of CH which results suggest that therapy by O_2ptimask and Demand Valve Oxygen resulted in a decreased need for rescue medication [55]. Parenteral triptans have been shown to be an effective treatment for individual attacks; orally administered triptans have not. Sumatriptan, used subcutaneously or intranasally, and zolmitriptan used intranasally reduce the severity and duration of CH attacks once

they have begun [54, 56]. Oral zolmitriptan reduces attack severity in episodic CH, but its effectiveness is not known in chronic CH as well as the effectiveness of oral sumatriptan [53]. There is consensus that subcutaneous octreotide is effective for abortive treatment of CH. The effectiveness of intranasal lidocaine and hyperbaric oxygen for abortive treatment of CH is unknown [53].

Preventive treatment aims to suppress the attacks for the duration of the bout, or over longer periods in those with chronic CH, with the fewest possible side effects [57]. There is consensus that corticosteroids such as 1 mg/kg prednisolone (maximum 60 mg) for 5 days, which is then reduced by 10 mg every 3 days, may temporarily reduce the frequency of headaches; a preventive agent, with a longer latency until onset of action, should be started at the same time [58, 59]. There is evidence that greater occipital nerve injections (betamethasone plus xylocaine) are effective for preventive treatment of CH. This can be used as an effective bridging technique to allow an adequate dose of oral preventive drug to be achieved. Its use would normally be limited to once every 8–12 weeks [53]. There is consensus that both verapamil and lithium prevent CH, but that verapamil is more effective than lithium, and causes fewer adverse effects [59]. Lithium in dose of 900 mg is effective in reducing attacks frequency in both episodic and chronic CH, while verapamil is effective in reducing attack frequency in dose of 360 mg daily [60]. Before starting verapamil at a dose of 80 mg three times a day and increasing this by 80 mg each fortnight, baseline and repeated electrocardiography should be performed because of the relatively high incidence of heart block associated with verapamil. The preventive effects of baclofen, botulinum toxin, capsaicin, chlorpromazine, clonidine, ergotamine or dihydroergotamine, gabapentin, leuprolide, melatonin, methysergide, pizotifen, sodium valproate, oral sumatriptan, topiramate, and tricyclic antidepressants are not well documented [53].

Patients with chronic CH who gain no meaningful benefit from preventive drugs should be considered for alternative intervention [40]. There are results for the effective treatment with onabotulinum toxin A in refractory CH patients [61]. Recent results show that sphenopalatine ganglion stimulation is an effective therapy for CH patients providing therapeutic benefits and improvements in use of medication as well as headache impact and quality of life [62]. Neurostimulation seems to offer a novel, superior alternative therapy for CH. Hypothalamic deep brain stimulation, occipital nerve stimulation, and other interventions all seek to provide adaptive therapy for CH patients. Also, occipital nerve blockade is a safe and effective transitional treatment option in case of insufficient response of CH in both episodic and chronic CH, while patients with episodic CH have a better and more sustainable treatment response. Side effects of occipital nerve blockade are mild and occur with low frequency [63]. The sphenopalatine ganglion blocking can also successfully resolve CH [64]. Percutaneous radiofrequency ablation of the sphenopalatine ganglion has been shown to be an effective modality of treatment for patients with intractable chronic CH [65]. All these procedures can be abortive and preventive. Although the exact methods of action of these therapies are not yet completely understood, they are effective in up to 60% of CH patients [66].

Efficacy of CGRP monoclonal antibodies and antagonists in migraine treatment increased the interest in the prospect of treating CH with CGRP antagonism. The results from many RCTs may reveal the therapeutic potential of CGRP monoclonal antibodies and antagonists for CH treatment, although future investigations should shed light on predictive factors of good CGRP monoclonal antibodies and antagonists responsiveness [14, 67].

Conclusion

CH presents a relatively rare primary headache disorder, but it should be considered in all clinical settings when pain occurs in the disturbance of the first branch of the trigeminal nerve associated with ipsilateral autonomic phenomena with a circadian and circannual rhythm. The secondary causes of CH must be excluded particularly in cases with atypical presentation, late onset, debut of chronic CH and abnormal neurological examination. Although there have been advances in the diagnosis and therapy of CH, a significant number of patients still have a delayed diagnosis of CH, which postpones the possibility of a timely application of adequate abortive and preventive therapy.

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Compliance with ethical standards

Conflicts of interest No conflict of interest exists for any of the authors listed in the article.

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