Review Article

Cluster Headache: Epidemiology, Pathophysiology, Clinical Features, and Diagnosis

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Abstract

Cluster headache is a primary headache disorder affecting up to 0.1% of the population. Patients suffer from cluster headache attacks lasting from 15 to 180 min up to 8 times a day. The attacks are characterized by the severe unilateral pain mainly in the first division of the trigeminal nerve, with associated prominent unilateral cranial autonomic symptoms and a sense of agitation and restlessness during the attacks. The male-to-female ratio is approximately 2.5:1. Experimental, clinical, and neuroimaging studies have advanced our understanding of the pathogenesis of cluster headache. The pathophysiology involves activation of the trigeminovascular complex and the trigeminal-autonomic reflex and accounts for the unilateral severe headache, the prominent ipsilateral cranial autonomic symptoms. In addition, the circadian and circannual rhythmicity unique to this condition is postulated to involve the hypothalamus and suprachiasmatic nucleus. Although the clinical features are distinct, it may be misdiagnosed, with patients often presenting to the otolaryngologist or dentist with symptoms. The prognosis of cluster headache remains difficult to predict. Patients with episodic cluster headache can shift to chronic cluster headache and vice versa. Longitudinally, cluster headache tends to remit with age with less frequent bouts and more prolonged periods of remission in between bouts.

Keywords: Cluster headache, diagnosis, epidemiology, pathophysiology, trigeminal autonomic cephalalgias

Introduction

Cluster headache is a primary headache disorder, belonging to the trigeminal autonomic cephalalgias (TACs). Descriptions of the disorder in the literature dates as far back as 1641, where the Dutch physician Nicolaes Tulp, famous from Rembrandt's painting, "The anatomy lesson," described a recurring severe unilateral headache lasting no longer than 2 h in the Observationes Medicae.[1] However, cranial autonomic features were not described therein. Wilfred Harris (1869–1960), a Madras-born London neurologist, described cluster headache in his classic monograph *Neuritis and Neuralgia* in 1926;[2] this was probably the earliest clear recognition of it as a separate entity from migraine and trigeminal neuralgia.[3] In 1936, Harris named these headaches migrainous neuralgia or ciliary (migrainous) neuralgia,[4] where he recorded the unilaterality of attacks, severity, associated autonomic features, and frequency of attacks. His description was the first recorded reports of cluster headache in the English medical literature. The same clinical features are detailed in the International Classification Headache Disorder-3 (ICHD-3).[5] This review will cover the epidemiology, pathophysiology, clinical features, and diagnosis of the disorder.

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Epidemiology

Given the low prevalence of cluster headache compared to migraine, it is difficult to assess accurately the prevalence of cluster headache in the community. Nonetheless, given the specific features of cluster headache, it is possible to identify possible cases in the community, using questionnaires based on the ICHD criteria. Community-based studies have been performed to ascertain the prevalence of cluster headache. They are generally modeled on a two-step process. The first step is to screen for possible cluster headache cases either through mailed questionnaires or structured interviews based on the ICHD

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criteria. Following this, interviews are performed by neurologists or trained interviewers to assess cases further. Fischera *et al*. reviewed 16 population-based studies published up to August 2007, specifically looking at cluster headache prevalence in a meta-analysis and found that the 1-year prevalence varied greatly between the studies and ranged from 3 to 150/100,000. Their pooled lifetime prevalence was 0.12%.[6] The study with the highest prevalence found in this meta-analysis was the Vågå study in Norway where the principal investigator Sjaastad personally interviewed and examined 1828 inhabitants of Vågå. The study identified seven subjects with cluster headache, corresponding to a prevalence of 381 per 100,000 (95% confidence intervals: 153–783).[7] Since August 2007, there have been two further population-based studies, one from the Republic of Georgia with a prevalence of 87 per 100,000[8] and in rural Ethiopia with a prevalence of 1.3%.[9]

Sex

Cluster headache has been historically considered to have a male preponderance, with a high male-to-female ratio, and thought to be different between episodic cluster headache (ECH) and chronic cluster headache (CCH). In a study involving 545 patients with ECH and CCH examined between 1963 and 1997, it was observed that there was a downward trend in male preponderance over this period. Although there is still an overall male preponderance for cluster headache, this did not differ between ECH and CCH. Subanalysis of the gender ratio by the age of onset revealed that the male-to-female ratio was highest in patients where the age of onset was between 20 and 49 years old; in ECH, this was 7.2:1; and in CCH, this was 11.0:1. The male-to-female ratio was lowest when the age of onset was after 50, where the ratio was 2.3:1 in ECH and 0.6:1 in CCH.[10] The authors postulated that this could be related to sex hormone regulation and environmental factors. Others have suggested that the decreasing male-to-female ratio reflects the change in women's lifestyle over the decades, possibly related to the increase in cigarette smoking and alcohol use.[11] Bahra *et al*. found that the male-to-female ratio to be 2.5:1 and has been consistent through the decade.[12]

The cluster headache attack clinical phenotype is similar between men and women.[12-14] However, women with cluster headache tend to have more nausea and vomiting with their attacks.[13,14] The mean age of onset of cluster headache in both genders is similar, with the mean age of onset being in the third decade. For CCH, there is a bimodal pattern in women with peaks in the second and sixth decade as compared with men.[15]

Unlike in migraine,[16] no clear relationship between cluster headache, and estrogen has been established, in particular with oral contraception, hormone replacement therapy, menses, pregnancy, and the menopause.[12,13]

Genetics

In the last two decades, genetic links have been explored the following reports of cluster headaches in monozygotic twin pairs,[17-19] from twin registry survey,[20] and genetic epidemiological surveys,[21-24] suggesting a higher risk for family members compared with the general population. It is thought that first-degree relatives have a 5–18 times higher risk, and in second degree relatives, 1–3 times increased risk as compared to the general population.[25]

However, the inheritance and genetics of the disorder are complex, and thus far no confirmed gene has been found to be clearly associated with cluster headache. Initial studies suggest a possible relationship to the hypocretin receptor 2 gene.[26-28] However, a large study from The Netherlands and their meta-analysis could not confirm findings from earlier studies.[29] Similarly, the recent first genome-wide association study involving 99 Italian patients with cluster headache did not show a statistically significant association; however, a suggestive association with a variant of the pituitary adenylate cyclase activating peptide receptor gene[30] was reported. Much larger cohorts are clearly required to confirm these initial findings.

Race

The majority of the large-scale epidemiological studies have been performed in Caucasians. Consequently, less is known regarding the prevalence of cluster headache across the world. In the US, a retrospective study at an academic headache center found that African-American women seemed to develop cluster headache more often than African-American men (25% vs. 17.4%).[14] There have been community-based headache studies in Malaysia where they did not identify any cases of cluster headache in a population size of 595.[31] In rural Ethiopia, the prevalence of cluster headache between 1992 and 1993 was reported to be extremely rare at 0.03%,[32] whereas in 2011, the prevalence of cluster headache was found to be 1.3%,[9] reflecting the other prevalence from the meta-analysis mentioned above.

As compared to Caucasians, variations in clinical phenotype among eastern Asians have been reported. These studies were largely clinic based, and they reported that the sense of agitation during cluster headache attacks was less prominent. There was also a lower prevalence of CCH observed.[33-37]

Pathophysiology

The pathophysiology of cluster headache is complex and the underlying mechanisms are not fully elucidated. Cluster headache is a neurovascular rather than a vascular headache, with vascular cerebral changes being driven by the effects of trigeminal-autonomic reflex activation.[38,39] The trigeminal-autonomic reflex is a pathway which consists of a brainstem connection between the trigeminal nerve and facial cranial nerve parasympathetic outflow[39] and is activated with the stimulation of the trigeminovascular pathways [Figure 1].

The trigeminovascular pathway consists of neurons innervating the cerebral vessels and dura mater through cell bodies in the trigeminal ganglion. The ganglion contains bipolar cells,

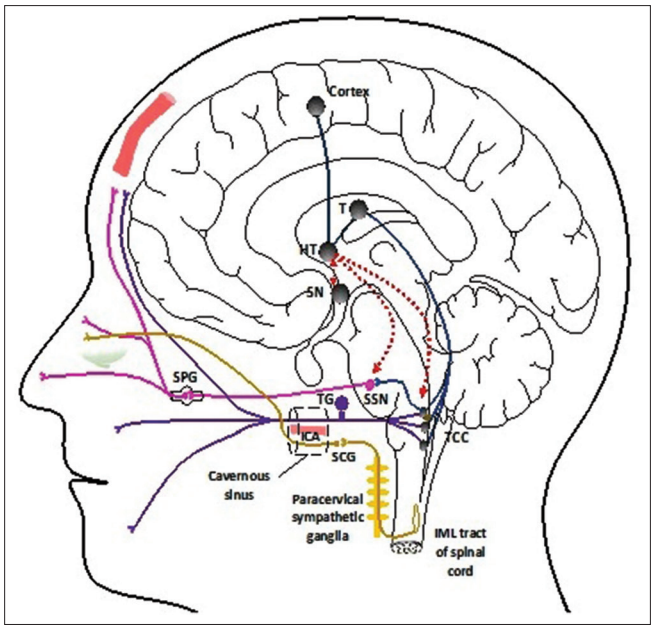

Figure 1: Cluster headache pathophysiology. Pain afferents from the trigeminovascular system traverse the ophthalmic division of the trigeminal nerve, taking signals from the cranial vessels and dura mater (shown by purple fibers). These inputs synapse in the TCC and project to higher brain structures such as the thalamus (T) and cortex resulting in pain perception (shown in blue fibers). Activation of the trigeminovascular system by stimulation of dural structures also causes neuronal activation in the SSN within the pons, which is the origin of cells for the cranial parasympathetic autonomic vasodilator pathway. There is subsequent activation of this parasympathetic reflex through the outflow from the SSN and is relayed through the SPG (shown by pink fibres), but also through the facial (VIIth cranial) nerve (not shown). Activation of both trigeminal and autonomic nerves defines the trigeminal autonomic reflex arc, which is integral to the pathophysiology of cluster headache and the other TACs. The HT is functionally connected to the ipsilateral trigeminal system and other brain areas of the pain matrix. Red dashed lines indicate the pathways by which the HT controls or triggers pain. A third-order sympathetic nerve lesion thought to be caused by vascular changes to the ICA in the cavernous sinus with subsequent irritation of the local plexus of nerve fibers, can give rise to sympathetic symptoms (incomplete Horner syndrome) (shown by yellow fibers). IML = Intermediolateral tract of spinal cord, SCG = Superior cervical ganglion, SN = Suprachiasmatic nucleus, TCC = Trigeminocervical complex, SSN = Superior salivatory nucleus, SPG = Sphenopalatine ganglion, HT = Hypothalamus, ICA = Internal carotid artery

with peripherally there are synaptic connection with the cerebral vessels and dura mater and centrally there are fibers synapsing in the trigeminocervical complex (TCC), which are the trigeminal nucleus caudalis in the caudal brainstem and high cervical cord in the dorsal horns of C1 and C2. There are projections from the TCC up to the thalamus, resulting in activation of cortical structures involved in pain processing, such as the frontal cortex, insulae, and cingulate cortex. The cell bodies of the trigeminal ganglion contain several vasodilator peptides that innervate the blood vessels. These include calcitonin gene-related peptide (CGRP), substance P, and neurokinin A. CGRP is elevated during both spontaneous[40] and nitroglycerin-triggered cluster headache attacks,[41] providing evidence that the trigeminovascular pathway is activated during attacks.

The associated cranial autonomic symptoms characteristic of cluster headache arise from the reflex activation of the trigeminal-autonomic reflex pathway through parasympathetic outflow from the superior salivatory nucleus,[42] the cranial facial nerve, through the sphenopalatine ganglion,[43] resulting in vasodilatation and parasympathetic activation. Clinically, this presents as lacrimation, conjunctival injection, and nasal congestion. When the first division of the trigeminal nerve is activated by pain, such as by capsaicin injection, carotid vasodilation and parasympathetic activation have been observed.[44]

These clinical features of cluster headache suggest a central mechanism, in particular, the hypothalamus. Kudrow observed that cluster headache bouts occur at the same time each year in a circannual pattern, particularly during the change in clocks to daylight savings in seasons. He postulated that this was linked with photoperiodism, otherwise known as length of daylight, and that this could be attributed centrally to the hypothalamus, suggesting an inability to synchronize the internal circannual pacemaker with the external environmental light cues.[45] Melatonin is produced in the pineal gland, and its rate of secretion has a strong circadian rhythm regulated by the suprachiasmatic nucleus, which receives sympathetic innervation from the hypothalamus and autonomic centers of the thoracic spinal cord, the sympathetic cervical plexus, and the carotid plexus. The main environmental stimulus for the diurnal production of melatonin is light intensity, with this information reaching the suprachiasmatic nucleus of the hypothalamus through a direct pathway from the retina.[46] During bouts in ECH patients, melatonin secretion has been found to be lower, with the characteristic nocturnal peak being blunted[47,48] with abnormal melatonin metabolite excretion.[48,49] The usefulness of melatonin replacement in the management of cluster headache has been reported from case reports,[50,51] a small placebo-controlled study,[52] and in a study looking at melatonin as an adjunctive therapy in cluster headache prevention.[53] Further studies looking at the role of other neuroendocrine hormones such as cortisol,[47,54] testosterone,[54-58] and orexin[59] have provided further evidence for the involvement of the hypothalamus in cluster headache.

From functional neuroimaging studies, the posterior hypothalamus has been observed to be activated during spontaneous cluster headache attacks[60,61] and cluster headache attacks triggered by intravenous nitroglycerin.[62] The role of the hypothalamus in cluster headache was further supported by the therapeutic effect of targeting the posterior hypothalamic gray through deep brain stimulation in cluster headache patients.[63-65]

Clinical Features and Diagnosis

As compared to other disorders within the TAC category, patients with cluster headache experience multiple attacks of relatively

short-lasting severe headaches [Table 1]. The headaches are characteristically excruciating, unilateral, and commonly involves the first division of the trigeminal nerve, over the peri- and retro-orbital regions and in the temple.[12] The pain can be perceived to have arisen from the sinuses or from the dentition, and patients often present to an otolaryngologist or dentist for this reason.[66] The quality of the pain is severe, intense, sharp, and burning and it is commonly described to be worse than childbirth. It is aptly also known as "suicide headaches." The attack generally builds up quickly in intensity resulting in a severe pain, which dissipates in a similar timeframe, with a clear onset and resolution to the attack. The attacks are strictly unilateral, however, on occasion attacks can switch sides within the same bout (14%), or a side-shift may occur from one bout to other (18%).[12]

Without treatment, cluster headache attacks may last from 15 min to 3 h, with an average of 45–90 min in duration.[67] During an attack, patients experience cranial autonomic symptoms, which include lacrimation, eye redness, eye discomfort such as grittiness, ptosis, nasal congestion, rhinorrhea, aural fullness, throat swelling, and flushing. These cranial autonomic symptoms are present on ipsilateral to the pain and is thought to be due to parasympathetic activation.[68,69] In addition, sympathetic impairment[70] presenting as miosis and partial Horner syndrome may occur. Wilfred Harris was the first to recognize that Horner syndrome could occur in cluster headache.[3]

Table 1: Cluster headache diagnostic criteria (adapted from International Classification of Headache Disorders, Third edition)

Cluster headache

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 one 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 rhinorrhea
   c. Eyelid edema
   d. Forehead and facial sweating
   e. Forehead and facial flushing
   f. Sensation of fullness in the ear
   g. Miosis and/or ptosis
2. A sense of restlessness or agitation

D. Attacks have a frequency between one every other day and 8/day for more than half of the time the disorder is active

E. Not better accounted for by another ICHD-3 diagnosis

Episodic cluster headache: Cluster headache attacks occurring in periods lasting from 7 days to 1 year, separated by pain-free periods lasting at least 3 months without preventive treatment

A. Attacks fulfilling criteria for 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

Chronic cluster headache: Cluster headache attacks occurring for >1 year without remission, or with remission periods lasting <3 months without preventive treatment

A. Attacks fulfilling criteria for cluster headache and criterion B below

B. Occurring without a remission period, or with remissions lasting <3 months, for at least 1 year

One prominent feature during attacks is the sense of restlessness and agitation. This is a useful feature that can help in distinguishing cluster headache from migraine. During an episode, migraine patients prefer to lie still. In contradistinction, cluster headache patients pace or rock during attacks and attempt to lessen the intensity of the pain by applying pressure to the affected area.[67,70] In general, once an attack terminates, patients are pain-free until their next attack. Patients may have attacks ranging once every other day up to 8 times a day.[5] There is a tendency for the attacks to occur at night and patients report a sleep association. A remarkable observation is that attacks seem to occur at the same time each day and have a circadian pattern.

The duration, in which patients have cluster headache attacks, is called a bout, and this can range on average between 6 and 12 weeks.[5] Patients with cluster headaches may experience bouts separated by months or even years of remission.[67,70] Episodic and chronic cluster headache is defined by the remission duration between bouts. CCH patients have persistent attacks occurring for more than one year without remission, or a remission period lasting less than three months, without preventive medication.[5] About 15%–20% of patients suffer from chronic cluster headache.[71] It is important to distinguish episodic from CCH s as it can help guide decisions regarding management. ECH patients may notice a pattern to their bouts, typically occurring around spring and autumn, at the time of the equinoxes. Some CCH patients may notice an increase in attacks during these times of the year.[45] This circannual phenomenon is not clearly understood but may implicate the hypothalamus in the pathogenesis.

Patients have noticed that their attacks may be triggered by various substances. These include alcohol, strong smells such as petroleum and nail varnish, and nitrate-containing foods such as cured meats.[72] Triggers may bring on attacks for ECH patients who are in a bout or for CCH patients. In the research context, the administration of intravenous nitroglycerin can induce cluster headache attacks in a reproducible way.[73,74]

Cluster headache is still underdiagnosed and suboptimally managed, and patients often have a delay to their diagnosis. The US cluster headache survey found that cluster headache patients on average have more than 5 years delay in diagnosis with only 21% receiving a correct diagnosis at the time of initial presentation.[75] Bahra and Goadsby found in their tertiary headache center that the mean time to diagnosis dropped from 22 years in the 1960s to 2.6 years in the 1990s in the UK although the mean number of general practitioners seen before a diagnosis was made remains at three.[66]

Prognosis

The natural history of cluster headache is difficult to predict. In patients with initial ECH, 13% may subsequently develop

CCH. On the contrary, 33% of patients with initial CCH may shift to the episodic pattern during the course of the disorder.[76] Anecdotally, cluster headache tends to remit[12] with age with less frequent bouts and more prolonged periods of remission between bouts.

Conclusion

Cluster headache is a primary headache disorder with distinct features of unilateral intense pain of a relatively short duration, with prominent cranial autonomic symptoms, and a circadian and circannual rhythm. It is one of the most painful and disabling disorders known to humans. The pathogenesis involving the trigeminal-autonomic reflex, the trigeminovascular pathway, and hypothalamus provides an explanation for the clinical phenotype. The advances in our understanding of the pathophysiology have led to the development of various novel treatments, ranging from deep brain stimulation of the posterior hypothalamus to CGRP monoclonal antibodies targeted at neuropeptides involved in the trigeminovascular pathway. These topics will be covered elsewhere in this series. Further studies are required to unravel the exact role of the hypothalamus in cluster headache and to understand the natural history of this devastating condition.

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Conflicts of interest

Peter James Goadsby reports grants and personal fees from Allergan, Amgen, and Eli-Lilly and Company; personal fees from Akita Biomedical, Alder Biopharmaceuticals, Avanir Pharma, Cipla Ltd., Dr Reddy's Laboratories, eNeura, Electrocore LLC, Novartis, Pfizer Inc., Quest Diagnostics Scion, Teva Pharmaceuticals, Trigemina Inc., Scion; personal fees from MedicoLegal work, Journal Watch, Up-to-Date, Massachusetts Medical Society, Oxford University Press; and in addition, Dr. Goadsby has a patent Magnetic stimulation for headache assigned, without fee, to eNeura.

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