Review paper

Archives of Psychiatry Research 2023;59:75-86
DOI:10.20471/may.2023.59.01.10

Cluster Headache: Literature Review with Reference to Sex Differences

Darija Mahović[1,2], Matea Bračić[2]

[1]Department of Neurology, University Hospital Center Zagreb, Croatia [2]School of Medicine, University of Zagreb, Zagreb, Croatia

Abstract – Cluster headache is a pain syndrome characterized by severe, unilateral and predominantly orbital pain which lasts 15 - 180 minutes. It is accompanied by a range of ipsilateral autonomic symptoms, such as lacrimation, rhinorrhoea and myosis. Cluster headaches can be episodic with periods of remission or chronic. Even though it is a relatively rare condition, the excruciating pain causes significant disruption of patients' daily life. The pathophysiology behind cluster headaches is complex and despite making significant progress, the pathogenetic cascade of events hasn't been entirely elucidated yet. However, research into this subject has discovered brain structures, peripheral pathways and neuropeptides which have key roles in pathogenesis. The basis of diagnosing cluster headaches is a detailed patient history and the exclusion of other primary headaches and potential secondary causes. Sex differences in clinical presentation need to be taken into consideration in order to avoid misdiagnosis. Treatment options are divided into three categories: acute, transitional and prophylactic treatment. Although there are a lot of treatment modalities available, further research is necessary in order to find new therapeutic targets and more effective prophylaxis, especially for chronic cluster headache.

Key words: cluster headache; diagnosis; pathology; physiology; therapeutics

e-mail: apr.kbcsm@gmail.com • www.http://apr.kbcsm.hr

Introduction

Cluster headache is a type of trigeminal autonomic cephalalgia (TAC) which is characterized by attacks of severe, unilateral pain, predominantly localized in the orbital, supraorbital or temporal area [1]. These attacks can last from 15 minutes up to three hours, and the severity of the pain causes significant disability in patients' daily functioning [2,3]. In fact, an attack of cluster headache has often been described as the worst pain imaginable, more painful than childbirth, pancreatitis or kidney stones [4]. The pain is accompanied by ipsilateral autonomic symptoms, such as lacrimation, myosis, nasal congestion and sweating, as well as restlessness and agitation [1].

The prevalence of cluster headache is fairly low and estimates vary from a 0.1 % to 0.3 % lifetime prevalence, with regional differences throughout the world [2,5,6]. Cluster headaches are more common in men, with the male to female ratio ranging from 2.5 : 1 to 4.3 : 1 [7,8]. This ratio has decreased over the years, possibly due to a better application of diagnostic criteria, thereby reducing the possibility of misdiagnosing cluster headaches as other headache disorders in women [9-11]. Average age at onset is 20 - 40 years, but the first attack can occur earlier or later in life [1,9,12,13].

Correspondence to:
Darija Mahović, MD, PhD, Department of Neurology, University Hospital Center Zagreb, Kišpatićeva 12, 10 000 Zagreb, Croatia
E-mail: darija.mahovic@mef.hr

Men predominantly report their first cluster headache between the ages of 21 and 30, while women have two peaks of incidence: in the second decade of life and around the age of 50 [10,14,15]. Possible risk factors include smoking, genetics and previous head trauma [16,17].

In this review, we aim to summarize the main clinical features of cluster headaches (including sex differences in presentation), possible pathophysiological processes behind the illness and current treatment options.

Pathophysiology

The pathophysiological processes underlying cluster headache are complex and still not entirely elucidated. The current theories explaining the cascade of events that triggers a cluster attack include the involvement of structures of the central nervous system, such as the hypothalamus, peripheral structures, such as the trigeminal nerve and cranial blood vessels, and neuropeptides [9,17].

Key components and pathways

The trigeminal nerve has a prominent role in the pathophysiology of cluster headache. The activation of nociceptive processes of its first branch, the ophthalmic nerve, results in ipsilateral pain, but also produces a reflex parasympathetic response [17,18]. This is a result of triggering two key nervous pathways: the trigeminovascular pathway and trigeminal autonomic reflex [9,17,19]. The centre of the trigeminovascular pathway is in the trigeminal ganglion, where the bodies of pseudounipolar sensory neurons are located [20]. These neurons supply afferent fibres towards cerebral and meningeal vasculature, while the fibres leading to the midbrain synapse in the trigeminocervical complex (TCC), comprised of the caudal part of the spinal trigeminal nucleus and the dorsal horns of the C1 and C2 spinal nerves [19,21]. The stimulated afferents from meningeal blood vessels transfer nociceptive signals via pseudo unipolar neurons towards the TCC [19]. The projections from the TCC lead towards the thalamus and subsequently to higher cortical structures, such as the frontal cortex and insulae, which participate in pain processing [9,19]. As a result, this signal is perceived as a headache [19]. The TCC also participates in the parasympathetic portion of symptoms by acting as the relay point, transferring the signal coming from trigeminal nerve endings towards the superior salivatory nucleus (SSN) [9,17,19]. The parasympathetic fibres from the SSN synapse in the sphenopalatine ganglion (SPG) via the facial nerve, and then finally end in target organs [9,19]. Thus, the signal that started as trigeminal irritation elicits a parasympathetic response and causes symptoms such as rhinorrhoea and lacrimation, as well as cerebral vasodilation [9,17,19,22]. Furthermore, the vasodilatory effects of this reflex pathway cause further trigeminal irritation, perpetuating the cycle of painful stimuli and further increasing parasympathetic activity via the SPG [22,23]. A double-blind, randomized cross-over study demonstrated that stimulating the SPG provokes cluster-like attacks, which points to its importance in cluster pathophysiology [24]. SPG stimulation also causes a rise in sympathetic tonus directly preceding a cluster attack, while the attack itself is characterized by parasympathetic overactivity [25].

The transfer of impulses between different components of the trigeminovascular pathway and trigeminal autonomic reflexes are mediated by numerous neuropeptides, such as calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide 38 (PACAP-38) and vasoactive intestinal polypeptide (VIP) [17]. CGRP is one of the most widely researched and targeted neuropeptides in the pathogenetic cascade of cluster headaches. CGRP levels are elevated in plasma samples of patients during acute attacks and decrease once the attack stops [26,27]. However, CGRP levels in chronic cluster headache patients are significantly lower than those with episodic cluster headache [28]. Exogenous CGRP can cause cluster headache in patients who are currently in a cluster bout or in chron-

ic cluster headache patients who have recently had an attack, but not in those who are in remission [29]. PACAP-38 is a neuropeptide found in the trigeminal ganglion, the SPG and the SSN [9,19]. Similarly to CGRP, PACAP-38 levels are elevated in acute cluster attacks, normalize between bouts and are lower in chronic cluster headache patients [26,28]. In addition, intravenous PACAP-38 application has been shown to increase CGRP release in animal models [30]. VIP may also play a role in cluster pathogenesis, as demonstrated by a study where increased levels of this neuropeptide were found during an acute attack [26].

The cyclic nature of cluster headache points to the hypothalamus as a possible culprit in the pathogenetic process, mainly due to its role in circadian rhythmicity [17,19]. Furthermore, the hypothalamus participates in neuroendocrine balance, autonomic nervous system regulation and trigeminal nociception, all of which are affected in cluster headache [19]. The most recent evidence for hypothalamic involvement comes from neuroimaging studies, where the ipsilateral posterior hypothalamus was found to be active during acute attacks [31]. A PET study which investigated hypothalamic activation in and out of bouts showed that activation happened only in a cluster period [32]. Another study which used voxel-based magnetic resonance imaging (MRI) demonstrated significantly increased density and volume of grey matter in the posterior hypothalamus compared to healthy controls [33]. Another key hypothalamic structure is the suprachiasmatic nucleus (SCN), which regulates the circadian rhythm [19,34]. The amount of light which stimulates the retinohypothalamic tract affects the activation level of neurons within the SCN, which then determines the amount of melatonin secreted by the pineal gland [19,35,36]. Studies have shown that patients with cluster headache have lower levels of melatonin when compared to healthy controls [17,37-39]. Additionally, some patients have disturbances in hormones regulated by the hypothalamus, such as increased secretion of cortisol, altered rhythmicity of prolactin secretion and reduced response to thyrotropin releasing hormone [9,17,39].

Neuroimaging studies have also shown increased activity and changes in higher cortical areas. One PET study demonstrated increased glucose metabolism in the prefrontal and anterior cingulate cortices, as well as in the insulae and temporal cortex, during a cluster bout, while there were no changes during out-of-bout periods [40]. Furthermore, a voxel-based study showed a reduction in grey matter volume in the middle frontal, medial frontal and left superior gyri during cluster periods, in comparison with healthy controls [41].

Sex-specific hormonal variations

Physiological shifts of female sex hormones seem to affect cluster headache severity and frequency in different ways [11,13,14]. In a study by Allena and associates 61 % of female patients reported that their first attack of cluster headache occurred around a period of hormonal fluctuation, i.e. at menarche, post-partum, menopause or while taking hormonal birth control [11]. Only a minority of women report worsening or improvement in their headaches during menses or menopause, while most women experience either a significant improvement or no change at all during pregnancy [13,14]. Cluster headaches in men are also susceptible to hormonal shifts, exemplified by lower levels of serum testosterone during cluster bouts [42].

Genetic predisposition

There are some indications that genetic factors may have an important role in pathogenesis of cluster headaches [9]. In some families cluster headaches are more common and appear in every generation, which might suggest an autosomal dominant inheritance pattern in some cases of cluster headache [6]. In fact, it is speculated that around 5 % of cluster headaches are autosomal dominant [1]. Various genes have been suggested as the potential culprits in cluster headache pathogenesis (CACNA1A, MTHFR, CLOCK, HCRTR2,

ADH4, NOS1, CRY1 etc.), but the results of genetic studies were either negative or haven't been conclusively replicated [43-45]. A few genome-wide association studies (GWAS) have also been conducted in order to link single-nucleotide polymorphisms (SNPs) to susceptibility to cluster headaches. Some of those studies have yielded statistically significant results, but the findings haven't been confirmed in similar studies [43,46,47].

Diagnosis

Clinical presentation

Cluster headaches are characterized by severe, even excruciating, unilateral pain [1]. This sharp or pulsating pain can be so severe that patients often pace around the room or even hit themselves [14,18]. The localization is mostly retro-orbital (around 90 %) and/or temporal (around 70 %), but pain can originate in or spread to other locations (maxilla, forehead, cheek, occiput) [13,48]. The pain is unilateral in almost all cases, though a small proportion of patients report bilateral headaches as well [12,48]. The right side is slightly (50 - 60 %) more affected than the left, and the side of the attack tends to remain unchanged during a bout [12,13,48]. Aside from pain, clinical presentation includes one or more accompanying autonomic symptoms, which present on the same side as the headache: conjunctival injection and/or lacrimation (most common), nasal congestion and/or rhinorrhoea, eyelid oedema, forehead and facial sweating, and myosis and/or ptosis [1,13,48]. Another frequent symptom is a general feeling of restlessness, or even agitation, during an attack [1,19]. Some patients may experience photophobia, phonophobia, nausea or even aura, which can potentially lead to a misdiagnosis as migraine [9,49].

Attacks typically start and cease abruptly, with a duration from 15 minutes to 3 hours and a frequency of up to 8 times a day [1,49]. Most patients report a circadian and/or circannual rhythmicity of their attacks [17]. Attacks occur predominantly at fixed times during the night and/or soon after falling asleep [13,17,49]. Spring and autumn are the times of year when most headache cycles (bouts) occur [9,13,17,49]. These attack cycles are the fundamental characteristic of episodic cluster headaches. They can span months or even years and are separated by a remission period of at least 3 months [1,17]. On the other hand, chronic cluster headaches have very short or no remission periods at all, but may retain circannual rhythmicity [1,49]. Cluster headache attacks primarily occur unprovoked, but can also be caused by triggers. The most common triggers are alcohol (particularly beer and wine), histamine, nitro-glycerine, strong smells, stress, sleep and changes in temperature [18,48,49].

Sex differences

Bearing in mind the complexity of the pathophysiology of cluster headache, it is not surprising that there are sex differences in clinical presentation. Pain intensity is generally identical, but women seem to have a higher daily attack frequency than men [14]. It is not clear whether the duration of an untreated attack is longer in women or men [11,15]. Pain location also differs between sexes, with women having a more diffuse pain distribution towards the jaw, zygomatic area and ear [11,14]. Several studies have pointed to differences in associated symptoms–men are generally more likely to have cranial autonomic symptoms, while migraine-like features appear more frequently in women, but this distinction hasn't been consistently proven [14]. Several studies report that lacrimation and facial sweating are more frequent in men, while ptosis, nasal congestion and nausea are more frequently found in women [10,11,14,15]. However, the frequency of individual symptoms differs between studies and is inconsistent. Aura symptoms may be present in both sexes, with a significant difference in type: visual auras are more common in men, while women are more likely to have language and brainstem auras [14].

Alcohol is a trigger in both sexes, more frequently so in men [14,15]. A history of cigarette smoking is more prevalent in men, but one survey demonstrated a similar level of exposure to second-hand smoke during childhood in both sexes, possibly pointing to the role of early exposure to cigarette smoke in cluster pathogenesis [14,15]. As for family history, some studies report that women are more likely to have an affected family member [14], while others have shown no conclusive difference between sexes [11]. However, there is a consistently more prevalent family history of migraine in women than men [11,13,14].

Diagnostic algorithm

According to the 3rd edition of the International Classification of Headache Disorders (ICHD-3) of the International Headache Society (IHS), if a patient has had at least 5 attacks that fit the diagnostic criteria listed in Table 1, they can be diagnosed with cluster headache. Furthermore, determining whether a patient is suffering from episodic or chronic cluster headache is based on the existence and length of remission [1]. The diagnostic criteria all rely on subjective patient reports, which is why thorough history taking is the key to diagnosis. Additionally, secondary causes of headaches, such as those related to cerebrovascular disease, intracranial tumours and trauma, must be excluded before a definitive diagnosis is made [9]. The European Headache Federation (EHF) recommends the following investigative studies: brain MRI, ultrasound of the carotid and vertebral arteries and/or magnetic resonance angiography (MRA), pituitary function studies, and in some cases polysomnography [50].

Differential diagnosis

The majority of differential diagnoses are other primary headaches. Due to the similarity in presentation, cluster headaches might be misdiagnosed as other types of TACs. However, that can be avoided by inquiring about

Table 1. ICHD-3 diagnostic criteria for cluster headache

Cluster headache
• At least five attacks fulfilling the following criteria: • Severe to very severe unilateral orbital, supraorbital and/or temporal pain that lasts 15 - 180 minutes when left untreated • One or both of the following: − at least one of the following, ipsilateral to the headache: conjunctival injection and/or lacrimation, nasal − congestion and/or rhinorrhoea, eyelid oedema, forehead and facial sweating, myosis and/or ptosis • A sense of restlessness or agitation • Occurring with a frequency between once every other day and eight times per day • Cannot be better accounted for by another ICHD-3 diagnosis.
Episodic cluster headache
• Attacks fulfilling criteria for cluster headache and occurring in bouts • At least two bouts lasting from 7 days to one year when untreated, separated by remission periods of ≥ 3 months
Chronic cluster headache
• Attacks fulfilling criteria for cluster headache • Occurring without a remission period or with remissions lasting < 3 months, for at least one year

ICHD-3 – International Classification of Headache Disorders, third edition [1]

the frequency and length of the attacks, as well as testing if the pain responds to indomethacin [9]. Trigeminal neuralgia can be a potential differential diagnosis, but it can also occur concurrently with cluster headache, which is a clinical entity known as cluster-tic syndrome [1,18]. Moreover, cluster headaches are often mistaken for migraines, particularly in patients who report auras, photophobia and/or phonophobia [9,18]. Women are more frequently misdiagnosed and are more likely to have a diagnostic delay than men [10,14]. Secondary causes must also be excluded using appropriate imaging and investigative methods, as stated in section Diagnostic algorithm [50,51].

Treatment

Acute treatment

Subcutaneous sumatriptan is considered to be the one of the most effective drugs in the treatment of acute cluster attacks, with a level A recommendation in both the American Headache Society (AHS) and the European Federation of Neurological Societies (EFNS) guidelines [19,52,53]. A randomized, double-blind, placebo-controlled study of sumatriptan 6 mg from 1991 demonstrated a decrease in severity in 74 % of participants' attacks within 15 minutes of treatment, compared to only 26 % in those receiving placebo [54]. The recommended dose of subcutaneous sumatriptan is 6 mg up to twice daily at any point during an attack [9,19]. Although a dose-comparison study by Ekbom and associates showed that a dose increase to 12 mg provided 80 % of patients pain relief after 15 minutes, there was no significant difference in pain mitigation in comparison to sumatriptan 6 mg, which is why a higher one-time dose isn't recommended [55]. Sumatriptan is mostly well-tolerated, with the most frequent adverse effects being injection site reactions (erythema, swelling, tingling and burning), neurological manifestations (dizziness, tiredness, paraesthesia, numbness), chest pain and nausea/vomiting [54,55]. Due to its vasoactive effect, sumatriptan is contraindicated in patients with cardiovascular and cerebrovascular illnesses [9]. Sumatriptan can also be administered intranasally at a dose of 20 mg [52,53]. A double-blind, placebo-controlled study showed significant efficacy of intranasal sumatriptan over placebo (57 % vs 26 %) after 30 minutes, while the most common adverse effect was bitter taste [56]. Zolmitriptan is also effective as an acute therapeutic and is administered orally or intranasally [51-53]. A study by Cittadini and associates analysed the pain relief of patients who were given intranasal zolmitriptan, and they were able to demonstrate significant efficacy of zolmitriptan over placebo at 5 and 10 mg [57]. The recommended dose for intranasal application is 20 mg, while 5 and 10 mg are given both orally and intranasally [52,53]. The side-effect profile is similar to that of sumatriptan [47,53].

High-frequency oxygen has been used as an abortive treatment for cluster headaches for decades and has the highest level of recommendation [52,53]. Inhalations of oxygen at 100 % should be delivered at a rate of 12 l/min for 15 minutes [9]. A 2009 randomized placebo-controlled study demonstrated significant efficacy of 100 % oxygen 12 l/min delivered via a non-rebreather mask in comparison with air (78 % vs 20 %) after 15 minutes of treatment, with no significant adverse effects related to treatment [58]. When comparing flow rates, Dirkx and associates reported no significant difference in effect between a lower rate of 7 l/min and the standard flow rate, and noted that 12 l/min should consequently be used in all patients [59]. The preferred method of oxygen delivery should be non-rebreather masks or demand valve oxygen (DVO) masks where possible [9,60].

Non-invasive vagus nerve stimulation (nVNS) is a newer type of non-drug acute treatment for cluster headaches. The non-invasive nature of the treatment presents an advantage over more aggressive methods of nerve stimulation. The device produces a 5 kHz wave burst which lasts about 1 millisecond and repeats every 40 milliseconds [19,61]. The ACT1 study investigated the efficacy

of nVNS in acute attacks in both episodic and chronic cluster headache. Their findings showed a significant difference in efficacy between nVNS and sham stimulation (26.7 % vs 15.1 %), with the episodic cluster group showing a better acute and sustained response to treatment [61]. In the ACT2 study, there were no significant differences in efficacy between nVNS and sham in the total study population. However, when analysing the episodic cluster group separately, nVNS was significantly more effective (48 % vs 6 %), which indicates that chronic cluster headache patients are more resistant to this treatment modality [62]. According to the findings of the PREVA study, nVNS could have a place in the treatment of chronic cluster headache as an add-on treatment option, as the addition of nVNS was more effective in attack frequency reduction than standard-of-care alone [63,64]. Possible adverse effects are mostly mild or moderate, the most frequent being burning or tingling at the application site, lip or facial drooping and twitching, dizziness, headache and neck pain [61,64].

There are several other acute treatments available, but the evidence for their efficacy is either inconsistent or lacking. Subcutaneous octreotide was shown to be more effective than placebo in a 2004 randomized trial [65], but the recommendations for its use are still inconsistent (EFNS level B vs AHS level C) [52,53]. Somatostatin receptor agonists may also have treatment potential due to the role of endogenous somatostatin in nociception [19]. Ergot alkaloids, predominantly ergotamine, are an antiquated method of cluster headache treatment and there is a lack of randomized studies that would confirm their effectiveness in acute treatment [9].

Transitional ("bridging") treatment

Corticosteroids have been used in the treatment of cluster headaches since the 1950s, with varying success [19], which is reflected in different recommendation levels (EFNS level A vs AHS level U) [52,53]. The most commonly used compounds are prednisone and methylprednisolone. The possible mechanism of action behind steroid therapy is the disruption of trigeminal and hypothalamic activation routes via its effect on CGRP and melatonin levels [66]. There is a lack of randomized control trials to prove efficacy, but case series and observational studies report significant pain relief and decrease in headache frequency [67,68]. However, the doses used to treat cluster headache are too high to use as chronic treatment, considering the various side-effects of long-term use, which is why steroids should be applied only as a bridging therapy for 2-3 weeks [9,19].

Steroids can also be used locally as a blocking agent, mostly together with lidocaine, in another type of transitional therapy - greater occipital nerve (GON) injection [19,51]. The effect of this treatment lasts around 4 weeks and can be repeated several times after a 3-month pause [19]. A double-blind, placebo-controlled study showed that a significant portion of the participants (85 %) responded well to the treatment, while the effect was sustained for at least 4 weeks [69]. A prospective study by Lambru and associates confirmed the efficacy and response consistency after multiple GON injections, albeit with a shorter median response duration (21 days) [70]. A retrospective, comparative study of oral steroids and GON demonstrated that both therapies are effective, with oral steroids having a slight advantage [71]. The possible adverse effects of GON block are tenderness at injection site, dizziness and neck stiffness [70].

Prophylactic treatment

The first-line prophylactic treatment for cluster headaches is verapamil, a calcium channel blocker which has a level A recommendation [52]. The usual starting dose is 80 mg three times a day, while the maintenance dose can go up to 320 mg three times per day [19]. There haven't been many randomized trials for this indication, but those that were conducted showed that verapamil causes a sig-

nificant reduction in the number of attacks [72]. In one such study, Leone and associates reported a significant reduction in both attack frequency and use of analgesics in comparison to placebo [73]. The most frequent side-effects of verapamil are constipation, leg oedema and headache. Caution is necessary in patients with cardiovascular disorders, particularly those with arrhythmias [9].

As in other headache disorders, antiepileptic medication is used in cluster headache prophylaxis. Topiramate has shown promising results and currently has a level B recommendation [52]. However, the efficacy results are not consistent and are based largely on open-label studies with a small sample size [74-76]. Other proscribed antiepileptic medications include valproate and gabapentin [9].

The discovery of the role of the hypothalamus in pathophysiologic processes behind cluster headache has opened the door for melatonin as a preventive therapeutic. The current evidence for the use of melatonin is not particularly solid (level C) [52,53]. One double-blind study demonstrated a significant reduction in headache frequency versus placebo [77], whereas another, newer study, showed no difference in endpoints at all [78]. The safety profile is favourable, with very few mild adverse effects [19].

As we have stated previously, CGRP is another key component in the pathophysiology of cluster headaches, which is why CGRP monoclonal antibodies (mAbs) can be used as a prophylactic option. A placebo-controlled trial from 2019 established the basis for the use of galcanezumab 300 mg in episodic cluster headache by demonstrating a significant reduction in weekly attack frequency in comparison to placebo (a difference of 3.5 attacks/week). The adverse effects were mild to moderate, mostly injection-site pain and nasopharyngitis [79]. These results were supported by the results of a post-hoc analysis of a Phase 3 randomized study, which showed both a significant reduction in attack frequency and in acute medication use [80]. However, the same efficacy endpoints haven't been reproduced in the population of chronic cluster headache patients [81]. A newer CGRP mAb, fremanezumab, hasn't been proven to be effective in the therapy of cluster headache [51].

Lithium and methysergide are two prophylactic options that have been used for decades, but have few well-designed studies to back up their efficacy [19,52,53]. Ultimately, even though lithium or methysergide might be effective in some patients, both have a significantly worse safety profile than equally effective treatment [82-84].

Sphenopalatine ganglion (SPG) stimulation is an invasive method of preventive treatment which uses a pulse generator as a stimulator. The micro stimulator itself requires implantation and is attached to a zygomatic arch, while the remote control unit is external [19]. A double-blind sham-controlled study demonstrated significant efficacy in pain relief 15 minutes after starting treatment when compared to sham stimulation (62.46 % vs 38.87 %). The most common adverse effects were numbness, swelling, headache, paraesthesia and trismus, while all the serious adverse events were related to the implantation procedure itself [85]. In terms of long-term efficacy, a follow-up study of the Pathway CH-1 study showed that SPG stimulation provided periods of complete remission in 30 % of participants and a significant improvement in disability measurements and preventive medication use [86]. In fact, the results of some long-term studies point to SPG stimulation as an effective preventive treatment in chronic cluster headache, but more data is still necessary for definitive conclusions [87].

Deep brain stimulation (DBS), predominantly of hypothalamic and some midbrain structures, has been used as a last resort treatment in drug-resistant chronic cluster headaches [19]. Even though the results of some smaller-scale studies suggest DBS could be effective in this difficult-to treat population [88], the results haven't been consistent [89]. Furthermore, the invasiveness of the procedure brings forth the possibility of serious adverse events, such as infections, loss of conscious-

ness and even fatal cerebral haemorrhage, which is why this treatment modality is avoided if there are other options [19,89,90].

Conclusion

Despite being the most common TAC, cluster headache is still a fairly uncommon illness. However, the severity of the pain and the significant disability it produces warrants a continuing investigation into possible new treatment targets and therapeutic modalities. The diagnostic delay is still significant, especially in women. There have been some encouraging developments with the introduction of mAbs and non-invasive stimulation methods, but there is still room for improvement, particularly when it comes to treating chronic cluster headache.

Acknowledgements

None.

Conflict of interest

None to declare.

Funding Sources

None.

References

1. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38:1-211.
2. Steinberg A, Josefsson P, Alexanderson K, Sjöstrand C. Cluster headache: prevalence, sickness absence, and disability pension in working ages in Sweden. Neurology. 2019;93:e404-13.
3. D'Amico D, Raggi A, Grazzi L, Lambru G. Disability, quality of life, and socioeconomic burden of cluster headache: a critical review of current evidence and future perspectives. Headache. 2020;60:809-18.
4. Burish MJ, Pearson SM, Shapiro RE, Zhang W, Schor LI. Cluster headache is one of the most intensely painful human conditions: results from the international cluster headache questionnaire. Headache. 2021;61:117-24.
5. Stovner LJ, Andree C. Prevalence of headache in Europe: a review for the eurolight project. J Headache Pain. 2010;11:289-99.
6. Russell MB. Epidemiology and genetics of cluster headache. Lancet Neurol. 2004;3:279-83.
7. Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. Cephalalgia. 2008;28:614-8.
8. Nesbitt AD, Goadsby PJ. Cluster headache. BMJ. 2012;344:e2407.
9. May A, Schwedt TJ, Magis D, Pozo-Rosich P, Evers S, Wang SJ. Cluster headache. Nat Rev Dis Prim. 2018;4:18006.
10. Lund NLT, Snoer AH, Jensen RH. The influence of lifestyle and gender on cluster headache. Curr Opin Neurol. 2019;32:443-8.
11. Allena M, De Icco R, Sances G, Ahmad L, Putortì A, Pucci E, et al. Gender differences in the clinical presentation of cluster headache: a role for sexual hormones? Front Neurol. 2019;10:1220.
12. Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. Headache. 2012;52:99-113.
13. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study with diagnostic implications. Neurology. 2002;58:354-61.
14. Rozen TD, Fishman RS. Female cluster headache in the United States of America: What are the gender differences?: Results from the United States cluster headache survey. J Neurol Sci. 2012;317:17-28.
15. Rozen TD, Niknam RM, Shechter AL, Young WB, Silberstein SD. Cluster headache in women: clinical characteristics and comparison with cluster headache in men. J Neurol Neurosurg Psychiatry. 2001;70:613-7.
16. Rozen TD. Linking cigarette smoking/tobacco exposure and cluster headache: a pathogenesis theory. Headache. 2018;58:1096-112.
17. Nahas SJ. Cluster Headache and other trigeminal autonomic cephalalgias. Continuum (Minneap Minn). 2021;27:633-51.
18. Ljubisavljevic S, Zidverc Trajkovic J. Cluster headache: pathophysiology, diagnosis and treatment. J Neurol. 2019;266:1059-66.
19. Wei DY, Goadsby PJ. Cluster headache pathophysiology - insights from current and emerging treatments. Nat Rev Neurol. 2021;17:308-24.
20. Messlinger K, Russo AF. Current understanding of trigeminal ganglion structure and function in headache. Cephalalgia. 2019;39:1661-74.
21. Arbab MAR, Delgado T, Wiklund L, Svendgaard NA. Brain stem terminations of the trigeminal and upper spinal ganglia innervation of the cerebrovascular system: WGA-HRP transganglionic study. J Cereb Blood Flow Metab. 1988;8:54-63.
22. Goadsby PJ. Pathophysiology of cluster headache: a trigeminal autonomic cephalgia. Lancet Neurol. 2002;1:251-7.
23. May A, Goadsby PJ. The trigeminovascular system in humans: pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. J Cereb Blood Flow Metab. 1999;19:115-27.
24. Schytz HW, Barløse M, Guo S, Selb J, Caparso A, Jensen R, et al. Experimental activation of the sphenopalatine ganglion provokes cluster-like attacks in humans. Cephalalgia. 2013;33:831-41.
25. Barloese M, Petersen AS, Guo S, Ashina M, Mehlsen J, Jensen RH. Sphenopalatine ganglion stimulation induces changes in cardiac autonomic regulation in cluster headache. Clin Physiol Funct Imaging. 2018;38:808-15.

26. Goadsby PJ, Edvinsson L. Human in vivo evidence for trigeminovascular activation in cluster headache neuropeptide changes and effects of acute attacks therapies. Brain. 1994;117:427-34.
27. Belin AC, Ran C, Edvinsson L. Calcitonin Gene-Related Peptide (CGRP) and cluster headache. Brain Sci. 2020;10:30.
28. Snoer A, Vollesen ALH, Beske RP, Guo S, Hoffmann J, Fahrenkrug J, et al. Calcitonin-gene related peptide and disease activity in cluster headache. Cephalalgia. 2019;39:575-84.
29. Vollesen ALH, Snoer A, Beske RP, Guo S, Hoffmann J, Jensen RH, et al. Effect of infusion of calcitonin gene-related peptide on cluster headache attacks: a randomized clinical trial. JAMA Neurol. 2018;75:1187-97.
30. Uddman R, Goadsby PJ, Jansen I, Edvinsson L. PACAP, a VIP-like peptide: immunohistochemical localization and effect upon cat pial arteries and cerebral blood flow. J Cereb Blood Flow Metab. 1993;13:291-7.
31. Yang FC, Chou KH, Kuo CY, Lin YY, Lin CP, Wang SJ. The pathophysiology of episodic cluster headache: insights from recent neuroimaging research. Cephalalgia. 2018;38:970-83.
32. May A, Bahra A, Büchel C, Frackowiak RSJ, Goadsby PJ. Hypothalamic activation in cluster headache attacks. Lancet. 1998;352:275-8.
33. May A, Ashburner J, Büchel C, McGonigle DJ, Friston KJ, Frackowiak RSJ, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. Nat Med. 1999;5:836-8.
34. Burish MJ, Chen Z, Yoo SH. Cluster headache is in part a disorder of the circadian system. JAMA Neurol. 2018;75:783-4.
35. Naber WC, Fronczek R, Haan J, Doesborg P, Colwell CS, Ferrari MD, et al. The biological clock in cluster headache: a review and hypothesis. Cephalalgia. 2019;39:1855-66.
36. Hastings MH, Maywood ES, Brancaccio M. Generation of circadian rhythms in the suprachiasmatic nucleus. Nat Rev Neurosci. 2018;19:453-69.
37. Chazot G, Claustrat B, Brun J, Jordan D, Sassolas G, Schott B. A Chronobiological study of melatonin, cortisol growth hormone and prolactin secretion in cluster headache. Cephalalgia. 1984;4:213-20.
38. Pringsheim T. Cluster headache: evidence for a disorder of circadian rhythm and hypothalamic function. Can J Neurol Sci. 2002;29:33-40.
39. Leone M, Bussone G. A Review of hormonal findings in cluster headache. evidence for hypothalamic involvement. Cephalalgia. 1993;13:309-17.
40. Sprenger T, Ruether KV, Boecker H, Valet M, Berthele A, Pfaffenrath V, et al. Altered metabolism in frontal brain circuits in cluster headache. Cephalalgia. 2007;27:1033-42.
41. Yang FC, Chou KH, Fuh JL, Huang CC, Lirng JF, Lin YY, et al. Altered gray matter volume in the frontal pain modulation network in patients with cluster headache. Pain. 2013;154:801-7.
42. Romiti A, Martelletti P, Gallo MF, Giacovazzo M. Low plasma testosterone levels in cluster headache. Cephalalgia. 1983;3:41-4.
43. Cargnin S, Sances G, Shin J Il, Tassorelli C, Terrazzino S. Gene polymorphism association studies in cluster headache: A field synopsis and systematic meta-analyses. Headache. 2021;61:1060-76.
44. Gibson KF, Dos Santos A, Lund N, Jensen R, Stylianou IM. Genetics of cluster headache. Cephalalgia. 2019;39:1298-312.
45. Fourier C, Ran C, Sjöstrand C, Waldenlind E, Steinberg A, Belin AC. The molecular clock gene cryptochrome 1 (CRY1) and its role in cluster headache. Cephalalgia. 2021;41:1374-81.
46. O'Connor E, Fourier C, Ran C, Sivakumar P, Liesecke F, Southgate L, et al. Genome-wide association study identifies risk loci for cluster headache. Ann Neurol. 2021;90:193-202.
47. Harder AVE, Winsvold BS, Noordam R, Vijfhuizen LS, Børte S, Kogelman LJA, et al. Genetic susceptibility loci in genome-wide association study of cluster headache. Ann Neurol. 2021;90:203-16.
48. Donnet A, Lanteri-Minet M, Guegan-Massardier E, Mick G, Fabre N, Géraud G, et al. Chronic cluster headache: a french clinical descriptive study. J Neurol Neurosurg Psychiatry. 2007;78:1354-8.
49. Burish M. Cluster headache and other trigeminal autonomic cephalalgias. Continuum (Minneap Minn). 2018;24:1137-56.
50. Mitsikostas DD, Ashina M, Craven A, Diener HC, Goadsby PJ, Ferrari MD, et al. European headache federation consensus on technical investigation for primary headache disorders. J Headache Pain. 2015;17:5.
51. Suri H, Ailani J. Cluster Headache: A review and update in treatment. Curr Neurol Neurosci Rep. 2021;21:31.
52. May A, Leone M, Áfra J, Linde M, Sándor PS, Evers S, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. Eur J Neurol. 2006;13:1066-77.
53. Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. Treatment of cluster headache: the american headache society evidence-based guidelines. Headache. 2016;56:1093-106.
54. Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. N Engl J Med. 1991;325:322-6.
55. Ekbom K, Monstad I, Prusinski A, Cole JA, Pilgrim AJ, Noronha D. Subcutaneous sumatriptan in the acute treatment of cluster headache: a dose comparison study. Acta Neurol Scand. 1993;88:63-9.
56. van Vliet JA, Bahra A, Martin V, Ramadan N, Aurora SK, Mathew NT, et al. Intranasal sumatriptan in cluster headache: Randomized placebo-controlled double-blind study. Neurology. 2003;60:630-3.
57. Cittadini E, May A, Straube A, Evers S, Bussone G, Goadsby PJ. Effectiveness of intranasal zolmitriptan in acute cluster headache: A randomized, placebo-controlled, double-blind crossover study. Arch Neurol. 2006;63:1537-42.
58. Cohen AS, Burns B, Goadsby PJ. High-flow oxygen for treatment of cluster headache: a randomized trial. JAMA. 2009;302:2451-7.
59. Dirkx THT, Haane DYP, Koehler PJ. Oxygen treatment for cluster headache attacks at different flow rates: a double-blind, randomized, crossover study. J Headache Pain. 2018;19:94.
60. Petersen AS, Barloese MCJ, Lund NLT, Jensen RH. Oxygen therapy for cluster headache. a mask comparison trial. A single-blinded, placebo-controlled, crossover study. Cephalalgia. 2017;37:214-24.
61. Silberstein SD, Mechtler LL, Kudrow DB, Calhoun AH, McClure C, Saper JR, et al. No–invasive vagus nerve stimulation for the acute treatment of cluster headache: findings from the randomized, double-blind, sham-controlled ACT1 study. Headache. 2016;56:1317-32.
62. Goadsby PJ, de Coo IF, Silver N, Tyagi A, Ahmed F, Gaul C, et al. Non-invasive vagus nerve stimulation for the acute treatment of episodic and chronic cluster headache: a randomized, double-blind, sham-controlled ACT2 study. Cephalalgia. 2018;38:959-69.

63. Gaul C, Magis D, Liebler E, Straube A. Effects of non-invasive vagus nerve stimulation on attack frequency over time and expanded response rates in patients with chronic cluster headache: a post hoc analysis of the randomised, controlled PREVA study. J Headache Pain. 2017;18:22.
64. Gaul C, Diener HC, Silver N, Magis D, Reuter U, Andersson A, et al. Non-invasive vagus nerve stimulation for PREVention and Acute treatment of chronic cluster headache (PREVA): a randomised controlled study. Cephalalgia. 2016;36:534-46.
65. Matharu MS, Levy MJ, Meeran K, Goadsby PJ. Subcutaneous octreotide in cluster headache: randomized placebo-controlled double-blind crossover study. Ann Neurol. 2004;56:488-94.
66. Neeb L, Anders L, Euskirchen P, Hoffmann J, Israel H, Reuter U. Corticosteroids alter CGRP and melatonin release in cluster headache episodes. Cephalalgia. 2015;35:317-26.
67. Mir P, Alberca R, Navarro A, Montes E, Martínez E, Franco E, et al. Prophylactic treatment of episodic cluster headache with intravenous bolus of methylprednisolone. Neurol Sci. 2003;24:318-21.
68. Couch JR Jr, Ziegler DK. Prednisone therapy for cluster headache. Headache. 1978;18:219-21.
69. Ambrosini A, Vandenheede M, Rossi P, Aloj F, Sauli E, Pierelli F, et al. Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: A double-blind placebo-controlled study. Pain. 2005;118:92-6.
70. Lambru G, Abu Bakar N, Stahlhut L, Mcculloch S, Miller S, Shanahan P, et al. Greater occipital nerve blocks in chronic cluster headache: a prospective open-label study. Eur J Neurol. 2014;21:338-43.
71. Wei J, Robbins MS. greater occipital nerve injection versus oral steroids for short term prophylaxis of cluster headache: a retrospective comparative study. Headache. 2018;58:852-8.
72. Petersen AS, Barloese MCJ, Snoer A, Soerensen AMS, Jensen RH. Verapamil and cluster headache: still a mystery. a narrative review of efficacy, mechanisms and perspectives. Headache. 2019;59:1198-211.
73. Leone M, D'Amico D, Frediani F, Moschiano F, Grazzi L, Attanasio A, et al. Verapamil in the prophylaxis of episodic cluster headache: A double-blind study versus placebo. Neurology. 2000;54:1382-5.
74. Láinez MJA, Pascual J, Pascual AM, Santonja JM, Ponz A, Salvador A. Topiramate in the prophylactic treatment of cluster headache. Headache. 2003;43:784-9.
75. Huang WY, Lo MC, Wang SJ, Tsai JJ, Wu HM. Topiramate in prevention of cluster headache in the Taiwanese. Neurol India. 2010;58:284-7.
76. Leone M, Dodick D, Rigamonti A, D'Amico D, Grazzi L, Mea E, et al. Topiramate in cluster headache prophylaxis: an open trial. Cephalalgia. 2003;23:1001-2.
77. Leone M, D'Amico D, Moschiano F, Fraschini F, Bussone G. Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. Cephalalgia. 1996;16:494-6.
78. Pringsheim T, Magnoux E, Dobson CF, Hamel E, Aubé M. Melatonin as adjunctive therapy in the prophylaxis of cluster headache: a pilot study. Headache. 2002;42:787-92.
79. Goadsby PJ, Dodick DW, Leone M, Bardos JN, Oakes TM, Millen BA, et al. Trial of galcanezumab in prevention of episodic cluster headache. N Engl J Med. 2019;381:132-41.
80. Kudrow D, Andrews JS, Rettiganti M, Oakes T, Bardos J, Gaul C, et al. Treatment outcomes in patients treated with galcanezumab vs placebo: post hoc analyses from a phase 3 randomized study in patients with episodic cluster headache. Headache. 2020;60:2254-64.
81. Dodick DW, Goadsby PJ, Lucas C, Jensen R, Bardos JN, Martinez JM, et al. Phase 3 randomized, placebo-controlled study of galcanezumab in patients with chronic cluster headache: results from 3-month double-blind treatment. Cephalalgia. 2020;40:935-48.
82. Steiner TJ, Hering R, Couturier EGM, Davies PTG, Whitmarsh TE. Double-blind placebo-controlled trial of lithium in episodic cluster headache. Cephalalgia. 1997;17:673-5.
83. Bussone G, Leone M, Peccarisi C, Micieli G, Granella F, Magri M, et al. Double blind comparison of lithium and verapamil in cluster headache prophylaxis. Headache J Head Face Pain. 1990;30:411-7.
84. Boiardi A, Bussone G, Merati B, Tansini E, Boeri R. Course of chronic cluster headache. Ital J Neurol Sci. 1983;4:75-7.
85. Goadsby PJ, Sahai-Srivastava S, Kezirian EJ, Calhoun AH, Matthews DC, McAllister PJ, et al. Safety and efficacy of sphenopalatine ganglion stimulation for chronic cluster headache: a double-blind, randomised controlled trial. Lancet Neurol. 2019;18:1081-90.
86. Barloese MCJ, Jürgens TP, May A, Lainez JM, Schoenen J, Gaul C, et al. Cluster headache attack remission with sphenopalatine ganglion stimulation: experiences in chronic cluster headache patients through 24 months. J Headache Pain. 2016;17:67.
87. Láinez JM, Marti AS. Sphenopalatine ganglion stimulation in cluster headache and other types of headache. Cephalalgia. 2016;36:1149-55.
88. Nowacki A, Schober M, Nader L, Saryyeva A, Nguyen TAK, Green AL, et al. Deep brain stimulation for chronic cluster headache: meta-analysis of individual patient data. Ann Neurol. 2020;88:956-69.
89. Fontaine D, Lazorthes Y, Mertens P, Blond S, Géraud G, Fabre N, et al. Safety and efficacy of deep brain stimulation in refractory cluster headache: a randomized placebo-controlled double-blind trial followed by a 1-year open extension. J Headache Pain. 2010;11:23-31.
90. Vyas DB, Ho AL, Dadey DY, Pendharkar AV, Sussman ES, Cowan R, et al. Deep brain stimulation for chronic cluster headache: a review. Neuromodulation. 2019;22:388-97.