Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: November 30, 2022

Citation: Gosalia H, Wei DY, et al., 2022. Cluster Headache: Epidemiology, Pathophysiology, Clinical Features, and Diagnosis, Medical Research Archives, [online] 10(11). https://doi.org/10.18103/mra.v10i11.3363

DOI
https://doi.org/10.18103/mra.v10i11.3363

ISSN: 2375-1924

REVIEW ARTICLE

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

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ABSTRACT
Cluster headache is a primary headache disorder and is the most prevalent of the trigeminal autonomic cephalalgias. Cluster headache significantly impacts those affected, necessitating early diagnosis and management. Despite unique clinical features, such as patients experiencing attacks in a circannual pattern and often with a circadian rhythm within bouts, cluster headache patients often are misdiagnosed, mismanaged and have a delay in diagnosis. Preclinical, neuroimaging and clinical studies have advanced our understanding of cluster headache pathophysiology. The trigeminovascular system, the trigeminal autonomic reflex, and the hypothalamus are all involved in the pathophysiology of cluster headache. As our understanding of the pathophysiology of cluster headaches has evolved, new therapeutic options, such as calcitonin gene-related peptide monoclonal antibodies, non-invasive vagal nerve stimulation and sphenopalatine ganglion stimulation, have proved to have efficacy in the treatment of cluster headache. Herein, we aim to review developments to aid readers in their understanding of this debilitating disorder.

Keywords: Cluster headache, pathophysiology, diagnosis, clinical, calcitonin-gene related peptide

Introduction

Primary headache disorders, particularly cluster headache, impose a profound burden upon the patient population. Cluster headache is a primary headache disorder and is the most common of the trigeminal autonomic cephalalgias (TACs)[1,2]. Cluster headache is defined as attacks of severe, strictly unilateral pain, lasting 15-180 minutes and occurring up to eight times a day, accompanied with at least one cranial autonomic symptom[2]. Cluster headache has distinct manifestations, including lacrimation, conjunctival injection, nasal congestion, rhinorrhoea, forehead and facial sweating, ptosis and miosis[2]. Patients also report a sense of agitation or restlessness[2], this characteristic facilitates the diagnosis. Early reports by Ekbom compared the clinical presentation of cluster headache to migraine, a sense of restlessness and agitation was unique to cluster headache[3].

Cluster headache patients report the attacks as the most painful affliction they have experienced[4]. Patients will describe the pain as 'someone trying to rip your eye out' or 'giving birth four times a day, for eight weeks.' The intensity and severity of the pain have given the disorder the epithet 'suicide headache.' Cluster headache is often associated with consequential psychiatric issues[5], such as depression and anxiety[6-8]. These seem likely to be co-morbidities. Further to the personal burden, cluster headache imposes a substantial economic burden. A recent paper by Petersen and colleagues found a significant loss in output from missed work, which resulted in indirect costs of €11,809 per patient per year for the chronic subtype and €3,558 per patient per year for episodic subytype[9]. The indirect costs and direct costs of the disorder were significantly higher for chronic patients, perhaps due to the greater disability. Interestingly, episodic cluster headache patients rated their own health poor/very poor even outside of their bouts. This study suggests that the impact of the disorder is beyond a personal burden and has a wider economic and financial repercussion. The disorder's incapacitating nature justifies early detection and pain management measures.

History of cluster headache

Complex yet sometimes indistinct headache cases have been described in ancient Greek and Roman medical books. Reports of cluster headache date as early as 1641; Nicholas Tulp, a Dutch physician, widely known from Rembrandt's painting, 'The Anatomy Lesson,' reported what is now medically diagnosed as cluster headache in the Observations Medicae[10]. To our knowledge, this is the first medical description of cluster headache. He described a 'recurring headache' rarely lasting longer than two hours[10]. Additionally, Gerard van Swieten, a Dutch physician and the creator of the Vienna School of Medicine, provided an early, thorough explanation in 1745[11]. He described the patient's clinical presentation which could fit the International Classification of Headache Disorders' classification, 3rd edition (ICHD-3)[2] criteria for the disorder. It was not until 1926 that Wilfred Harris, a London neurologist, described what he called migrainous neuralgia that modern-day cluster headache could be recognised[12]. Wilfred Harris' work was an influential early account of what is now accepted as cluster headache. Harris described unilateral attacks, frequency of attacks and even autonomic features[13]. It is important to note that Bayard T. Horton, an American physician, also significantly contributed to the early recognition of cluster headache[14]. Horton's primary work facilitated the medical community's early understanding of cluster headache. Moreover, Kunkle and colleagues established cluster headache's periodicity of attacks and cycling pattern while coining the name 'cluster headache'[15].

Epidemiology

It is challenging to determine the epidemiology of this disorder due to its relatively low reported prevalence. Cluster headache seems indeed relatively rare and thus may be missed particularly in primary care. Bahra and Goadsby reported that a typical sufferer would be seen by three medical professionals, along with improper management, before the correct diagnosis is established[16]. However, diagnosis timelines are improving in the UK[16], and the growing awareness of the disorder facilities an early intervention. A more recent study in Denmark showed this continued improvement in diagnosis timeline throughout the decades from 1950 until 2010[17]. When patients are seen in a tertiary headache centre, the cases and numbers captured are biased, one way of capturing the number of cases in the community is through cluster headache-specific population-based questionnaires[18] or directly interviewing the patient population[19] to identify the number of cases in the community. Based on epidemiological studies, cluster headache has a prevalence of around 0.1%[19,20]. Cluster headache has been regarded to have a male preponderance, with a male to female ratio of approximately 2.5:1[21]. A Norwegian epidemiology study recently deduced the prevalence of cluster headache to be 48.6 per 100,000 and the estimated incidence to be 3.0 per 100,000/year[22]. The authors postulated that this

might underestimate the true prevalence based on small-scale studies conducted in the Scandinavian regions, and misdiagnosis. More extensive epidemiological investigations are necessary to estimate the true prevalence and confirm the gender ratio of this disorder.

Genetics

The scientific community has sought to gain insight into the genetics of cluster headache in order to understand the mechanisms involved and improve treatment targets. The genetic basis of cluster headache was identified in twin studies. In 1991, Couturier and colleagues reported a case of monozygotic twins both suffering from cluster headache, the similarities in attack frequency and clinical presentation sparked an interest into the genetics of cluster headache[23]. Epidemiology studies investigating the familial genetic cause followed as families reported cluster headache[24,25]. These studies implied that cluster headache had a plausible genetic component, after which candidate gene studies have been conducted. Due to some clinical similarities to migraine, a shared genetic contribution was investigated. The *CACNA1A* gene, which can cause familial hemiplegic migraine, type 1[26], was studied[27]. No involvement of this gene was found. Moving forward, after various studies investigated genetic causes[28-31], some studies focused on the circadian rhythm aspect of cluster headache by studying genes known to play a role in circadian rhythm: *PER3*[28], *CLOCK*[29] and *HCRTR2*[30,32]. Yet, these studies displayed inconclusive results and did not suggest an association when replicated in a larger sample[33]. Cluster headache genetics is likely complex; genome-wide association studies (GWAS) were performed to investigate this. The first GWAS study in cluster headache was conducted in 99 Italian patients, they found a suggestive association, but nothing significant[34] and the risk loci could not be replicated in a Swedish study with 542 cluster headache patients and 581 controls[35]. In 2021, two extensive GWAS studies in cluster headache were presented. A Dutch-Norwegian GWAS study found four risk loci and successfully replicated them in the Norwegian cohort[33]. Another Swedish-UK study found four risk loci for cluster headache and successfully replicated these loci, substantiating a genetic predisposition to cluster headache[36]. Both studies had very large odds ratios, which led to the successful risk loci due to the large effect size. Notably, *FHL5* was a risk locus found in both studies[33,36]. Interestingly, there is an overlap with migraine; *FHL5* is found in migraine[37], as a risk locus, which may simply represent the background of migrainous biology in the population[38]. RNA sequencing results showed that cluster headache patients had altered expression of the genes *POLR1B* and *TMEM87B*[33]. However, in order to extrapolate findings from these pathways, further studies are necessary.

Race

To date, there has been a paucity of literature studying the racial differences in cluster headache. Very little is known about race in cluster headache and what is known, or instead studied, is predominately from Caucasian populations where research resource is dominant. Interestingly, a study conducted by Peng and colleagues concluded that regional differences in the presentation of cluster headache exist[39]. This recent review suggested that Asian patients have a greater male preponderance when compared to the European and North American patient population, and a lower prevalence of chronic cluster headache was observed. Furthermore, in terms of clinical presentation, patients in the Asian region may have a lower prevalence of chronic cluster headache, less circadian periodicity and less restlessness[39]. The reason for these differences may include climate, latitude, differing medical systems or race. Further studies are necessary to validate the observations. Given the lack of confidence in existing data, large-scale epidemiology studies looking into possible racial differences are warranted.

Sex

A retrospective study conducted at an academic headache centre deduced that African-American women were more likely to have cluster headache than African-American men, 25% and 17.4%, respectively[40]. Over the years, attention has been drawn to cluster headache's male preponderance. For many years, there was a reported strong male preponderance; in recent years, this has been reviewed and this may be due to misdiagnosis in women. Based on existing research, a study led by Lund and colleagues deduced that women comparatively were more misdiagnosed than men (61% and 46%, respectively)[41]. Regarding clinical presentation, two studies established that chronic cluster headache was more prevalent in females than males[41,42]. An explanation for this could be differences in disorder biology. Another interesting aspect of sex in cluster headache is the management of cluster headache in pregnant women. The treatment of cluster headache during pregnancy is challenging, and this may further contribute to the disease burden. The use of high-flow oxygen is the safest acute treatment in

pregnant women[43-45]. It is recommended that sumatriptan administered subcutaneously or intranasally may be explored if oxygen therapy is insufficient[46]. Furthermore, in terms of preventive treatment, verapamil and prednisolone have been suggested in pregnant women with cluster headache[46]. However, it is recommended that the dosage of the drug should be as low as feasible[46]. Further research must be devoted to this area, as the disease burden may affect pregnant women mentally and during the childbearing period. Interestingly, a case report underlined the necessity for relevant guidelines to be established for pregnant women with cluster headache[47]. Clinically, treating pregnant or lactating women can be quite complex from a therapeutic standpoint. This aspect of cluster headache has not received enough study attention, and knowledge would assist the medical community in better understanding the condition and treating patients.

Age

The age of onset of this disorder has been reported at varying ages. Apropos onset of cluster headache, the average onset has been reported at around 30 years of age[20]. The results from an International Cluster Headache Questionnaire study revealed that the average age of onset was 27.3 +-12.5 years and 27.5% of the studies sample had paediatric onset[48]. To distinguish the age of onset, the results reported that the age of onset peaked for episodic patients between 16-20 years, for both males and females. Comparatively, the peak age onset for chronic patients varied from teenage years to 50s. The results from this research suggested that cluster headache frequently initiates during childhood and adolescence. However, due to diagnostic delays and perhaps lack of disorder acknowledgement, it is not fully diagnosed until adulthood. This study, and current literature, urge the necessity for further exploration to be devoted to this sector of cluster headache research.

Diagnosis and Clinical Presentation

Patients with cluster headache describe recurrent attacks of severe unilateral pain in the trigeminal distribution, mainly in the periorbital region of V1. The pain can last from 15 minutes until 3 hours when untreated. These attacks can occur once every other day to up to eight times a day[2]. Besides the pain, the patient will experience ipsilateral cranial autonomic symptoms and a sense of restlessness or agitation. It is this sense of restlessness and agitation that sets it apart from migraine, where patients will not be able to lie or sit still, whereas, during a migraine, patients would prefer to lie in a dark, quiet room. Furthermore, the pain is often so severe that it is comparable to gunshot wounds and for women who have had children, comparable to childbirth[4].

A particularly interesting aspect of cluster headache is the circadian and circannual pattern noted by patients and clinicians[49]. The circadian pattern is used to describe the cluster headache attacks occurring at roughly the same time each day, whereas the circannual pattern is when bouts occur around the same time each year, typically around the time of changing of daylight length (photoperiodism)[50].

Cluster headache is subdivided into episodic and chronic cluster headache depending on the period without attacks. Episodic cluster headache patients will experience a cluster or 'a bout' lasting on average 6 to 12 weeks during which they would have attacks[51]. In episodic cluster headache, the period of remission is more than three months, and in chronic cluster headache the remission is less than three months. The differentiation between the subtypes is arbitrary and would be more helpful in all respects if this reflected the pathophysiological differences between the two subtypes. There is some evidence that the subtypes respond differently to treatments, and to the ability to trigger attacks using human triggering models and chronobiology. Lithium is a preventive treatment that is useful in chronic cluster headache[52] but not episodic cluster headache[53]. In more recent clinical trials using calcitonin gene-related peptide (CGRP) monoclonal antibodies, trials showed it was effective in episodic cluster headache[54] but not in chronic cluster headache[55]. Differences between episodic and chronic cluster headache are also apparent from CGRP triggering cluster headache attacks. CGRP infusion can trigger attacks in episodic cluster headache patients in bout, and in chronic cluster headache patients, those with a low frequency of attacks in the previous 30 days did not have an attack triggered[56]. When comparing the chronorisk of episodic cluster headache and chronic cluster headache, which is the probability distribution of attacks throughout the day, episodic cluster headache attacks followed a circadian pattern, whereas in chronic cluster headache attacks followed an ultradian pattern[57]. This could be explained by the suprachiasmatic nucleus (SCN) influenced by external light being a strong driving force in episodic cluster headache attacks, as the SCN maintains a spontaneous firing rate not exactly 24 hours, therefore without external cues, the SCN

will follow its free-running pattern rather than the circadian one.

Although the ICHD-3 definition of the attack is from 15 minutes up to 3 hours, this does not take into account the non-headache symptoms that patients experience before the onset of their pain. These include a heterogenous group of homeostatic, mood, cognitive and sensory processing symptoms similar to those experienced by patients with migraine[58,59], cluster headache patients experience non-headache symptoms in the lead-up to their attacks[60,61], however, in a shorter duration than in migraineurs.

The diagnosis of cluster headache is made on the clinical history. Paroxysmal hemicrania is a condition within the trigeminal autonomic cephalalgia group that can closely resemble cluster headache. Paroxysmal hemicrania attacks are also unilateral and last between 2 and 30 minutes[2] which overlaps with the ICHD-3 duration of cluster headache attacks, therefore, cluster headache attacks that are on the shorter side of the range can be mistaken for paroxysmal hemicrania. However, paroxysmal hemicrania attacks do not tend to have the nocturnal tendency as in cluster headache. The absolute key differentiation is that paroxysmal hemicrania responds persistently to an adequate dose of indomethacin[62], whereas cluster headache would not.

As mentioned, there is no biomarker or investigation that can diagnose cluster headache, however, patients with cluster headache should undergo an MRI scan of the brain at their first consultation to ensure there is no secondary cause and no associated pituitary abnormality as the cause for their symptoms.

Pathophysiology

The pathophysiology of cluster headache is yet to be fully elucidated. Our understanding of cluster headache pathophysiology to date, is largely based on animal models, neuroimaging studies and clinical insights. Cluster headache is a neurovascular disorder[63] where the pathophysiology collectively involves, the trigeminovascular system, the trigeminal autonomic-reflex and hypothalamic activation. These structures are thought to be pivotal in attack initiation[63,64].

Hypothalamus

The hypothalamus, situated deep within the brain, the human body's 'biological clock', is understood to be a key component in cluster headache pathophysiology. The aforementioned circadian periodicity supports the involvement of the hypothalamus[63]. Kudrow remarked that cluster headache attacks occur at the same time annually, in a circannual pattern[50]. This mechanistic remark aligns with the clinical observation where patients tend to have attacks in a circannual pattern associated with photoperiodism[50] and this, in turn, could be the workings of the hypothalamus. The SCN, located in the anterior segment of the hypothalamus, is the primary circadian clock of the human body[65]. The SCN can calibrate the circadian clock to account for changes in the light it receives from the retina[65], for example, adjusting to time zones. The retinohypothalamic tract is the pathway by which this information is relayed from the retina to the SCN[66]. Melatonin is synthesised by the pineal gland[67] and facilitates control of the sleep-wakefulness cycle, which is regulated by the suprachiasmatic nucleus. In terms of the biology, melatonin levels increase at night as it spikes in response to darkness[68]. Interestingly, during active periods of attacks, research has shown that melatonin levels are comparatively lower in cluster headache patients[69-71]. Apropos melatonin, it is an efficacious preventive treatment for episodic cluster headache[72], and interestingly it has conflicting results in chronic patients[72,73]. We prescribe melatonin for our cluster headache patients, as case reports have shown efficacy[74] and evidence suggests that melatonin at high doses is also safe[75,76]. Overall, it is well tolerated as a preventive treatment for cluster headache[72]. The use of melatonin in cluster headache indicates an association of the SCN and thus, the hypothalamus, in cluster headache pathophysiology.

Further to Kudrow's theory[50] and clinical presentations, neuroimaging studies can be used to explore the role of the hypothalamus in cluster headache pathophysiology. A positron emission tomography (PET) study revealed activation in the ipsilateral inferior hypothalamic grey matter[64]. This activation was observed in chronic cluster headache patients, in an active pain state of a nitroglycerin triggered attack, but not for the control group who were episodic cluster headache patients out of bout[64]. This further alludes to the intrinsic role of the hypothalamus to cluster headache pathophysiology, predominantly during acute attacks. To support further the role of the hypothalamus, research has shown that bilateral deep brain stimulation (DBS) of the hypothalamus is an efficacious preventive treatment[77-79]. However, the role of DBS in cluster headache should be

reconsidered in the changing landscape of treatment options in the last ten years, particularly with the emergence of less invasive treatment options.

Trigeminal autonomic reflex

The trigeminal-autonomic reflex has an important role in the pathophysiology of cluster headache. The trigeminal-autonomic reflex is activated via irritation of the trigeminal nerve endings[5]. The afferent branch is the trigeminal nerve. The efferent branch of this arc comprises parasympathetic fibres that emerge from the superior salivatory nucleus, travel via the seventh cranial nerve, and connect to postganglionic parasympathetic neurons in the sphenopalatine ganglion (SPG)[63,80]. This reflex induces associated cranial autonomic symptoms such as lacrimation, conjunctival injection, ptosis and miosis. To review this experimentally, May and colleagues deduced that when the ophthalmic division of the trigeminal nerve is triggered via a painful stimulus, such as a capsaicin injection, vasodilation of the carotid artery is observed as well as activation of the ophthalmic division of the trigeminal nerve[81,82]. These findings further suggest that these structures are pivotal to cluster headache pathophysiology. Additionally, studies have shown that the use of a microstimulator at the SPG is an efficacious preventive treatment for cluster headache. Two trials showed that pain relief was achieved in more patients with active treatment than a sham and reduced attack frequency[83,84]. Conversely, given the minimally-invasive procedure involved in the microstimulator implantation, the most common side effects were transient pain and swelling at the site of implantation, nausea, vomiting and paraesthesia. However, there were no reports of unexpected serious adverse events and overall the stimulator was well tolerated[83,84]. A case report described a patient in which percutaneous radiofrequency ablation (RFA) of the SPG provided an effective treatment response for patients presenting with intractable chronic cluster headache[85]. Furthermore, investigations carried out by Amighi and colleagues reported that SPG block and radiofrequency denervation decreased the intensity of pain in the studied cohort[86]. Larger datasets would be required for widespread use of ablation strategies bearing in mind that ablation would make an SPG stimulator useless. An interesting pilot study investigated the safety and efficacy of injecting onabotulinumtoxinA (BTA) towards the SPG in order to treat intractable chronic cluster headache[87]. The results suggested a reduction in attack frequency, after treatment with a good tolerability and safety profile[87]. It should be said the study was small, with a limited study design and protocol violations, so a larger controlled study would be warranted. Above all, it is important to note that stimulation of the SPG plays an important role in producing cranial autonomic symptoms, through increasing parasympathetic outflow[88]. However, stimulation of the SPG alone is insufficient for attack genesis[88,89].

Trigeminovascular system

The trigeminovascular system consists of the neurons innervating the cerebral vessels and dura matter that have cell bodies in the trigeminal ganglion[63]. The trigeminal ganglion innervates the cerebral vessels and dura matter through branches of the trigeminal nerve, and centrally fibres are synapsing in the trigeminocervical complex (TCC)[5,63,90], encompassing the trigeminal nucleus caudalis and the dorsal horns of the spine nerves 1 and 2[90,91]. Rostral projections from the TCC to the thalamus result in the activation of structures pivotal to pain processing, such as insulae, cingulate cortex and frontal cortex. Following this activation CGRP[92] and pituitary adenylate cyclase activating polypeptide (PACAP)[93] are released. Tuka and colleagues demonstrated that PACAP38 is released during the course of an episodic cluster headache attack[93]. In terms of CGRP, from a preclinical perspective, CGRP levels have been shown to be elevated during both sporadic[92] and nitroglycerin (NTG) induced attacks[94]. A recent study from the Danish Headache Center, Denmark, deduced that CGRP infusions trigger cluster headache attacks for episodic patients during their active state and chronic cluster patients. Such findings demonstrate that the trigeminovascular pathway is stimulated during an attack, to clarify its role, further studies, both preclinical and clinical, are essential. Moving from bench to bedside, a CGRP humanised monoclonal antibody, galcanezumab, has been approved in the US as a preventive treatment for episodic cluster headache. A clinical trial deduced that compared to placebo, galcanezumab reduced the frequency of attacks in episodic cluster headache patients[54]. The treatment was well tolerated, with no deaths or serious adverse effects occurring. There is currently a lack of evidence for an efficacious response to CGRP monoclonal antibodies for the indication of chronic cluster headache. Further work evaluating its response in chronic patients is required and a number of factors may need to be explored, such as dosage, titration and time intervals. Intriguingly, patients with chronic cluster headache were shown to have lower plasma levels of CGRP than those with episodic cluster headache[95]. Whether there are differences in the

mechanistic and pathophysiological pathways between episodic and chronic cluster headache, and if this affects treatment response is yet to be elucidated. Research focusing on underpinning the possible differences in the biology of the two forms of this disorder may yield stimulating results. Whilst the medical and scientific community have made progress in our understanding of the constituents involved in cluster headache pathophysiology, further research in building an understanding of attack origin is warranted.

Conclusion

Cluster headache is a highly disabling primary headache disorder and presents with distinct clinical manifestations. It is one of the most painful conditions reported and this alone is motivation to improve the lives of those suffering. An enriched understanding of cluster headache attack genesis is yet to be elucidated; a distinction of the attack initiation will allow future therapeutic targets to be derived. A wider understanding of the pathophysiology may facilitate research on essentially manipulating the biology during the infancy of an attack and open treatment pathways that avert cluster headache attacks. CGRP monoclonal antibodies have been the centre of attention as the treatment target for primary headache disorders, their potential role as a preventive treatment in cluster headache and its associated research may provide a hopeful overture. However, the exploration of other targets from the pathophysiology of cluster headache is required and encouraged to provide as many options as possible to help manage this debilitating headache disorder for our patients.

Conflicts of Interest Statement

Helin Gosalia has nothing to declare. Diana Y. Wei reports receiving consulting fees from Lundbeck. Peter J. Goadsby reports, over the last 36 months, grants and personal fees from Eli-Lilly and Company, grant from Celgene, and personal fees from Aeon Biopharma, Allergan/Abbvie, Amgen, Biodelivery Sciences International, Biohaven Pharmaceuticals Inc., CoolTech LLC, Dr Reddys, Epalex, GlaxoSmithKline, Impel Neuropharma, Lundbeck, Novartis, Praxis, Sanofi, Satsuma and Teva Pharmaceuticals, and personal fees for advice through Gerson Lehrman Group, Guidepoint, SAI Med Partners, Vector Metric, and fees for educational materials from CME Outfitters, Omnia Education, WebMD, and publishing royalties or fees from Massachusetts Medical Society, Oxford University Press, UptoDate and Wolters Kluwer, and for medicolegal advice in headache, and a patent magnetic stimulation for headache (No. WO2016090333 A1) assigned to eNeura without fee.

Funding Statement

The work described here was, in part, funded by the National Institute of Health and Social Care Research.

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