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THE UNRELENTING PAIN OF THE CLUSTER HEADACHE: A HIDDEN BEAST

Dr. Zeenath Sheikh*

Lecturer of Biomedical Science Cihan University Erbil Kurdistan Region –Iraq.

***Corresponding Author: Dr. Zeenath Sheikh**

Lecturer of Biomedical Science Cihan University Erbil Kurdistan Region –Iraq.

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ABSTRACT

A primary headache disorder known as cluster headaches affects around 0.1% of the population. Cluster headaches can last anywhere from 15 to 180 minutes and can happen up to eight times a day. Significant unilateral cranial autonomic symptoms, agitation, and restlessness are associated with acute unilateral pain, especially in the first division of the trigeminal nerve. One severely incapacitating main headache condition is cluster headache (CH). Despite being rare—affecting only 0.1% of the population—it is among the most excruciating illnesses that have ever been discovered by humans. Abortive therapy, transitional therapy, and preventive therapy are the three approaches used to effectively treat CH. Due to the rarity of this ailment, there are few large-scale controlled trials, and the data supporting different therapy is derived from smaller research. The treatments with the best quality of evidence and newly developed treatments for CH are the main subjects of this review.

Synonyms and disease names

Cluster headache (CH) is also known by the following names: sphenopalatine, erythromelalgia of the head, ciliary or migrainous neuralgia, histaminic cephalalgia, petrosal neuralgia of Gardner, erythroprosopalgia of Bing, Vidian and Sluder's neuralgia, and hemicrania periodic neuralgiform. The French term for it is "algie vasculaire de la face," which is a little confusing considering that CH doesn't mainly involve artery or vein problems.

Epidemiology

Although cluster headaches are less common than migraines, it is challenging to determine their exact incidence in the community. However, given the unique characteristics of cluster headaches, probable patients can be identified in the local population by using questionnaires based on the ICHD criteria. To ascertain how prevalent cluster headaches are in the local population, studies have been conducted.

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Gender

Cluster headache has historically been thought to be differentiated between chronic cluster headache (CCH) and episodic cluster headache (ECH), affect mostly men, and have a high male-to-female ratio. Research involving 545 patients with ECH and CCH revealed a decrease in the preponderance of men between 1963 and 1997.

The male-to-female ratio in the study by Bahra et al. is 2.5:1, and it has remained steady over the past ten years. Some have argued that the declining male-to-female ratio is a reflection of how women's lifestyles have evolved over time, possibly as a result of increasing cigarette and alcohol consumption. The authors hypothesized that this might be connected to the regulation of sex hormones and environmental factors.

The clinical phenotypes of cluster headache attacks are similar in men and women. But during episodes of cluster headaches, women are more likely to experience nausea and vomiting. Cluster headaches affect both sexes about the same age on average, which is in their third decade of life. Women have a bimodal pattern for CCH, with peaks in the second and sixth decades, in contrast to men. Unlike migraines, there is insufficient data to definitively link estrogen to cluster headaches. This includes the use of oral contraceptives, hormone replacement therapy, menstruation, pregnancy, and menopause.

Pathophysiology

The pathophysiology of cluster headaches is complicated, and the underlying mechanisms are still unclear. Because the activation of the trigeminal-autonomic reflex causes vascular cerebral alterations, cluster headaches are neurovascular in nature as opposed to vascular. The trigeminal-autonomic reflex is a mechanism that involves a brainstem connection between the trigeminal nerve and the facial cranial nerve parasympathetic outflow. It is triggered by stimulating the trigeminovascular pathways.

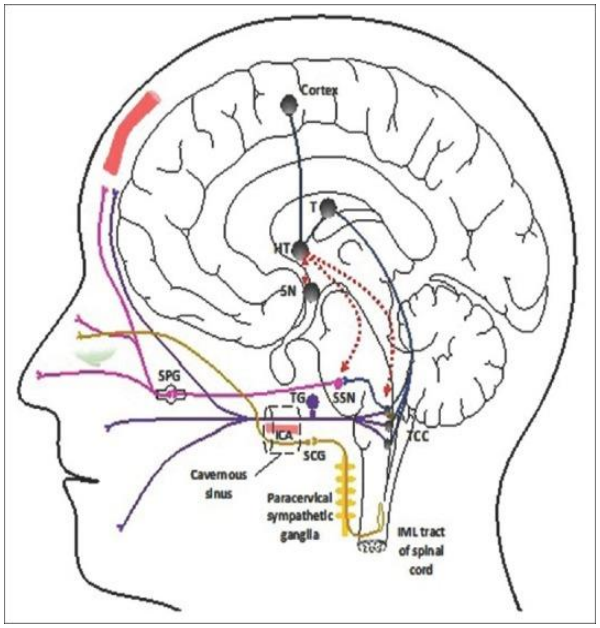

Figure 1.

The etiology of headache clusters. Trigeminal nerve ophthalmic division is where pain afferents from the trigeminovascular system receive signals from the dura mater (represented by purple fibers) and cranial arteries.

Pain perception is the result of these inputs, which synapse in the TCC and project to higher brain regions like the cortex and thalamus (T) (shown by blue fibers). The cranial parasympathetic autonomic vasodilator route's source of cells, the SSN within the pons, is activated when the trigeminovascular system is stimulated by stimulation of dural structures. The SSN outflow subsequently triggers this parasympathetic response, which is then conveyed via the SPG (shown by pink fibers) and the face (VIIth cranial) nerve (not shown).

The activation of both the trigeminal and autonomic nerves defines the trigeminal autonomic reflex arc, which is crucial to the pathophysiology of cluster headache and other TACs. The ipsilateral trigeminal system and other brain areas related to pain are functionally coupled to the HT.

The pathways by which the HT induces or regulates pain are shown by the red dashed lines. Sympathetic symptoms (incomplete Horner syndrome) can be elicited by a third-order sympathetic nerve lesion, which is indicated by yellow fibers and is thought to be caused by vascular alterations to the ICA in the cavernous sinus with subsequent stimulation of the local plexus of nerve fibers. Superior cervical ganglion (SCG) and the intermediolateral spinal cord tract (IML) SSN stands for Superior Salivatory Nucleus, SPG for Sphenopalatine Ganglion, HT for Hypothalamus, and TCC for Trigemino Cervical Complex.

Mechanism

Neurons in the trigeminal ganglion innervate the cerebral vessels and dura mater via cell bodies. The ganglion contains bipolar cells that have synaptic connections with the cerebral vessels and dura mater on the periphery and fibers that synapse in the trigeminocervical complex (TCC), which includes the trigeminal nucleus caudalis in the caudal brainstem and the high cervical cord in the dorsal horns of C1 and C2.

The thalamus, which receives projections from the TCC, activates cortical regions like the frontal cortex, insulae, and cingulate cortex that are involved in processing pain. Vasodilator peptides are abundant in the cell bodies of trigeminal ganglions, and they innervate blood vessels. These include substance P, calcitonin gene-related peptide (CGRP), and others.

The parasympathetic outflow from the superior salivatory nucleus, the cranial facial nerve, through the sphenopalatine ganglion causes vasodilation and parasympathetic activation, which in turn causes the associated cranial autonomic symptoms of cluster headache. The clinical manifestations include nasal congestion, conjunctival injection, and lacrimation. It has been documented that when the first division of the trigeminal nerve is stimulated by pain, as occurs with an injection of capsaicin, carotid vasodilation and parasympathetic activation occur.

These cluster headache clinical traits point to a central mechanism, specifically the hypothalamus. Kudrow discovered that cluster headaches reoccur at the same time every year in a cyclical fashion, particularly after the change in clocks to daylight savings time. He hypothesized that this was related to photoperiodism, or the length of daylight, and that it may be attributed centrally to the hypothalamus, implying an inability to synchronize the internal circadian pacemaker with external ambient light cues.Melatonin is produced in the pineal gland, and its secretion rate is 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 artery.Light intensity is the primary environmental stimulus for diurnal melatonin generation, with information reaching the suprachiasmatic nuclei of the hypothalamus via a direct pathway from the retina. Melatonin secretion has been reported to be reduced throughout bouts in ECH patients,

with the characteristic nocturnal peak being blunted due to aberrant melatonin metabolite excretion. Case reports, a small placebo-controlled trial, and a study looking at melatonin as an additional therapy in cluster headache prevention have all reported the effectiveness of melatonin replacement in the management of cluster headache. Further research into the role of other neuroendocrine hormones such as cortisol, testosterone, and orexin has provided more evidence for the hypothalamus's participation in cluster headache. Functional neuroimaging studies have shown that the posterior hypothalamus is active during both spontaneous and intravenous nitroglycerin-induced cluster headache episodes. The beneficial effects of deep brain stimulation targeted at the posterior hypothalamic gray in patients with cluster headaches further supported the role of the hypothalamus in cluster headaches.

The posterior hypothalamus is active during both spontaneous and intravenous nitroglycerin-induced cluster headache episodes; according to functional neuroimaging studies. The importance of the hypothalamus in cluster headaches was further demonstrated by the beneficial effects of deep brain stimulation directed towards the posterior hypothalamic gray in patients with cluster headaches.

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Signs and Symptoms

Excruciating pain that usually occurs in, behind, or around one eye but may spread to other parts of your face, head, and neck.

- One-sided discomfort Restlessness
- Tears that are excessive
- The affected side of your eye is red.
- On the affected side, a stuffy or runny nose
- Sweating on the affected side's forehead or face
- Pale skin (pallor) or facial flushing
- Swelling in the area around your affected eye
- Eyelid drooping on the affected side

Cluster headache sufferers, unlike migraine sufferers, are more likely to pace or rock back and forth. Some migraine-like symptoms, such as sensitivity to light and sound, might accompany a cluster headache, but only on one side.

Characteristics of the Cluster Period

The duration of a cluster phase can vary from a few weeks to several months. Every cluster period may have an identical start date and length from one period to the next. For instance, cluster periods can happen on an annual basis, like every spring or fall. Most individuals experience episodic cluster headaches. When a person has episodic cluster headaches, their migraines can last anywhere from a week to a year. After that, there is a period of painless remission that lasts for three months or more before the headaches return.

Future Therapy of Cluster Headache

Triptans

Although triptans are portable and inexpensive, the recommended dosage for them is only twice daily. However, many people with CH exceed this limit, in agreement with their neurologist, based on an individual assessment and lack of options.

Since the vasoconstrictive effect of triptans has been shown to increase the risk of stroke and acute myocardial infarction, they should not be used by anyone with certain cardiovascular diseases. Once more, after the efficacy of the thorough information administration route is impacted, people may still be so burdened that usage is still permitted. In 25 minutes, 75% of subjects who

received subcutaneous injectable sumatriptan reported being completely pain-free.

Ketamine

An NMDA receptor antagonist that is non-competitive is ketamine. Low doses of intravenous ketamine were administered every two weeks to treat 16 patients with episodic cluster headaches and 13 patients with chronic headaches in a 2016 study data.

Ketamine also had an effect on half of the chronic cluster headache patients. The study was not, however, placebo controlled. In an open trial, patients with chronic cluster headaches who had not responded to at least three preventive treatments were given a combination of ketamine and magnesium [65]. A single ketamine infusion (0.5 mg/kg over 2 hours) plus 3000 mg of magnesium sulfate was given to 17 patients.These findings suggest that ketamine might play a vital role. An experiment with a placebo control is required to verify this. But be aware that ketamine also carries a high risk of addiction. A proof-of-concept trial is being conducted in Denmark to assess the effectiveness of ketamine intranasal spray in treating chronic cluster headache.

Pasireotide

Somatostatin is involved in the pathophysiology of pain in a significant way. Because of its extremely short half-life, somatostatin is not a good choice for treating cluster attacks. Pasireotide's half-life is significantly longer than somatostatin's. In a phase II trial that was double-blind, placebo-controlled, and randomized, patients suffering from both episodic and chronic cluster headaches were included.

Onabotulinumtoxin

Patients with chronic cluster headaches participated in an open trial to study onabotulinumtoxin A. Twenty-eight male patients finished the 28-week study. In 59% of the participants, there was a decrease of more than 50% in the total number of headache minutes. The study comprised 496 participants' responses. Sodium oxybate was mentioned in case reports of patients with cluster headache and sleep disturbances. The indoleamine hallucinogens, psilocybin, lysergic acid diethylamide, and lysergic acid amide, were as effective as or more effective than most conventional medications. These agents shortened or aborted a cluster period.

Because of the intense pain attacks, cluster headaches are very distressing and have a significant negative impact on the quality of life for those who have them.

The only approved and readily available medications for attack therapy are oxygen, subcutaneous sumatriptan, intranasal sumatriptan, and zolmitriptan. Both subcutaneous sumatriptan and oxygen are still very costly, and many health care systems do not pay for them. As an illustration, of 399 patients with cluster headaches in a real-world study conducted in Denmark, only 30 received subcutaneous sumatriptan treatment for their attacks. By 20%, a 100% treatment effect was attained, and by another 10%, pain relief of 50%.

Preventive treatment

Topiramate

Only one open-label study using high doses (100–200 mg/day) and reported good efficacy in up to two thirds of patients provides evidence for topiramate's effectiveness in preventing cluster headaches. Topiramate side effects, particularly cognitive slowing, teratogenicity, nephrolithiasis, and low mood, pose a significant obstacle to its use. Additionally, topiramate may have an impact on the effectiveness of oral contraceptives, which can significantly influence preventive decision-making.

Lithium

Lithium has little evidence (33, 36, 37), but it's generally regarded as a good backup plan. Compared to episodic cluster headaches, chronic cluster headaches are treated with it more frequently; however, because of its possible effects on thyroid function and potential to interfere with diuresis, its use may be complicated and limited. Because of its narrow therapeutic index and potential for toxicity, which can manifest as a wide range of gastrointestinal and neurological symptoms, lithium therapy requires routine blood monitoring to maintain a serum concentration between 0.4 and 1.2 mEq/L.

Melatonin

There are numerous tenable explanations for the possible connection between melatonin and attacks of cluster headaches.38 Taking 10 mg of melatonin at night can help stop episodic cluster headache episodes. 10 mg of melatonin taken at night can help stop episodic cluster headache episodes. Replicate the favorable outcome. One could counter that there's a chance that the formulation or the timing of the dose were confusing variables. Melatonin is still frequently used to prevent cluster headaches because of its manageable side effect profile. Doses of 10 to 25 mg should be taken in the evening.

Verapamil

Two randomised clinical trials and an open-label study31 both found verapamil to be beneficial in the long run. preventive treatment for cluster headaches, usually 80 mg three times a day at first, with the possibility of increasing the dose every two weeks based on response; 320 mg three times a day is the maximum recommended dosage.

Physicians who treat patients should be informed that cardiac arrhythmia, bradycardia, or PR interval prolongation can occur in as many as one in five patients who take verapamil.33 As a result, it is advised to take a baseline 12-lead ECG before beginning treatment and again 10 days following each dosage increase.

Neuromodulation: For patients with cluster headaches in whom oral preventive therapy was either ineffective or inappropriate, neuromodulation is a useful development. We will concentrate on two neuromodulatory techniques in light of the data: Neuronal network and sphenopalatine ganglion microstimulator.

Non-invasive vagus nerve stimulation

Three 2-minute ipsilateral stimulations of the cervical branch of the vagus nerve have been shown to be effective in treating cluster headache attacks acutely in an open-label study46. Two double-blind sham-controlled randomised studies have also demonstrated the effectiveness of the gamma Core (nVNS) device (figure 2) in treating episodic cluster headaches acutely. Chronic cluster headache did not show the same benefit from attack treatment, which may be related to a high placebo response rate. A recent study explained this observation by claiming that the sham device had a modulatory effect on the trigeminal autonomic reflex. In a prospective observational study, the preventive effect of GammaCore was demonstrated, with nearly 75% of patients showing overall improvement. An open-label randomised trial employing Gamma Core as an adjuvant treatment48 with unilateral, three 2-minute stimulations administered twice daily showed comparable outcomes for chronic cluster headaches.

CONCLUSION

The high intensity of pain assaults associated with cluster headaches makes them exceedingly stressful, and they significantly lower the quality of life for those who have them. The only approved and readily available medications for attack therapy are oxygen, subcutaneous sumatriptan, intranasal sumatriptan, and zolmitriptan. Subcutaneous sumatriptan and oxygen are still quite costly and are not covered by many health insurance plans. For instance, just thirty of the 399 individuals with cluster headaches in a real-world study conducted in Denmark used subcutaneous sumatriptan to treat their attacks. There are only open study data available for the other drugs under investigation. As a result, the prevention of cluster headaches with these medicines is not authorized. In this case, randomized placebo-controlled trials would be required to provide evidence of efficacy. Designing and carrying out these studies, however, can be very challenging. For instance, it can be challenging to determine whether an improvement in episodic cluster headache occurs. because the cluster period terminates on its own initiative, or It's an effect of treatment.

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