Cluster Headache: What's New?

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Prepared For: Neurology India

Title character count: 29 characters

Abstract word count: 140

Main body word count: 5510

Total number of pages: 37

Tables: 3

Figures: 1

References: 90

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Abstract

Cluster headache is a severely disabling disorder affecting approximately one in 1000 of the population. It is characterised by attacks of excruciating unilateral head pain associated with ipsilateral cranial autonomic symptoms, with a tendency for attacks to occur with circadian and circannual periodicity. It is widely described as the most painful condition a human can experience. Recent clinical, imaging, and biochemical evidence has shed light on the underlying mechanisms of this disorder. This review describes the clinical characteristics, epidemiology, risk factors, and differential diagnosis of cluster headache, and discusses the current understanding of its pathophysiology. The established treatment options for the acute, preventive, and transitional treatment of cluster headache are outlined, and the evidence is evaluated for newer pharmacological and neuromodulatory therapies, which have been developed based on recent greater pathophysiological understanding of cluster headache and other primary headache disorders.

Introduction

Cluster headache is a primary headache disorder classed as a trigeminal autonomic cephalalgia. It is distinguished by the severe nature of the pain, length of attacks, presence of cranial autonomic symptoms such as lacrimation and conjunctival injection, and tendency of attacks to occur with circadian and circannual periodicity. There are a number of effective acute and preventive treatment options, however there is often a delay until the correct diagnosis is made and targeted treatment started. The pathophysiology of cluster headache is still poorly understood, but recent advances in the understanding of the primary headache disorders have led to newer treatments which may help those patients who do not respond to the established ones.

Clinical characteristics

Cluster headache is characterised by attacks of severe unilateral head pain in the orbital, supraorbital or temporal region lasting between 15 minutes and three hours if untreated. The pain is associated with ipsilateral cranial autonomic symptoms such as conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, ptosis, meiosis, and eyelid oedema. Attacks are usually accompanied by restlessness or agitation.[1]

Cluster headache is so called because attacks usually occur in ‘clusters’ (also called bouts or periods) lasting a few weeks or months, during which time attacks occur between once every other day and eight times per day. There is often striking circannual periodicity with bouts occurring predictably during certain times of the year, and circadian periodicity during bouts with attacks occurring predictably at the same time(s) of day, often at night.

Patients are said to have episodic cluster headache if bouts are separated by pain-free remissions of at least three months, and chronic cluster headache if attacks occur for one year or longer without remission or remissions last less than three months.[1] Approximately 85% patients have episodic cluster headache. In some patients, cluster headache attacks can be triggered by alcohol, strong smells, exercise, warm environment, or nitrate containing medications whilst they are within a bout. Between attacks there is usually no background pain, although some patients can have background pain of lower severity, with either tension-type or migraine phenotype.

Cluster headache is widely described as the most painful condition a human can experience. In females with cluster headache the pain is often described as worse than childbirth. Cluster headache leads to a high degree of headache-related disability, probably the highest of all headache disorders.[2] Depression and anxiety commonly develop after the onset of cluster headache. Individuals with cluster headache are 5.6 times more likely to be depressed,[3] and suicidal ideation was found to occur in 55% of sufferers in a large survey.[4] Fortunately, despite the severity of the pain, cluster headache is not life-threatening or physically damaging to the brain.

Diagnosis

Like all primary headache syndromes, the diagnosis of cluster headache is made clinically based on the patient's history according to consensus criteria. Diagnosis will be aided by observation of an attack or photograph or video of an attack demonstrating cranial autonomic symptoms. Between attacks neurological examination is usually normal though some patients can have a partial Horner's syndrome.

Primary headache syndromes are currently classified according to the International Classification of Headache Disorders, 3rd Edition.[1] In this classification cluster headache belongs to the group of trigeminal autonomic cephalalgias, which also includes paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with autonomic symptoms, and hemicrania continua (see Table 1).

Table 1. Comparison of the typical clinical features of trigeminal autonomic cephalalgias

	Cluster headache	**Paroxysmal hemicrania**	**SUNHA**	**Hemicrania continua**
Sex ratio F:M	1:4	1:1	1:1.5	2:1
Quality of pain	Throbbing, stabbing, boring	Throbbing, stabbing, boring	Sharp, stabbing (neuralgiform)	Dull, throbbing, sharp
Severity of pain	Very severe	Very severe	Very severe	Variable
Site of pain	Orbital, supraorbital, temporal	Orbital, supraorbital, temporal	Trigeminal distribution	Orbital, supraorbital, temporal
Frequency of attacks	Alternate days to 8 per day	1-40 per day (usually >5 per day)	>1 per day (range 1-200)	Continuous
Duration of attack	15-180 minutes	2-30 minutes	1-600 seconds	Continuous
Autonomic features	Yes	Yes	Yes*	Yes
Migrainous features	Yes	Yes	Rarely	Yes
Alcohol trigger	Yes	Occasional	No	Yes
Cutaneous trigger	No	No	Yes	No

Indomethacin response	No	Yes	No	Yes
Abortive treatment	Triptans Oxygen	Nil	Nil	Nil
Preventive treatment	Verapamil Lithium Topiramate Melatonin	Indomethacin	Lamotrigine Carbamazepine Oxcarbazepine Topiramate	Indomethacin

*Both conjunctival injection and lacrimation (tearing) must be present for diagnosis of SUNCT; not more than one of conjunctival injection and lacrimation (tearing) may be present for diagnosis of SUNA

Abbreviations: SUNHA, short-lasting unilateral neuralgiform headache attacks with autonomic symptoms (includes SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; and SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms)

Frequently there is a long diagnostic delay before the diagnosis of cluster headache is made and targeted treatment started, and patients are often not given the correct diagnosis on first presentation to a healthcare professional.[4] The main differential diagnoses of cluster headache are other primary headache disorders, particularly migraine and paroxysmal hemicrania. A variety of secondary causes may rarely present with a cluster headache phenotype. Accurate diagnosis is important to determine the optimal treatment.

In comparison with cluster headache, migraine attacks are typically longer in duration (longer than four hours) and associated with prominent migrainous features (i.e. nausea and vomiting, photophobia, phonophobia). Cranial autonomic features can be present in migraine but are more prominent in cluster headache.

Paroxysmal hemicrania is characterised by attacks which are also strictly unilateral and associated with cranial autonomic features, but attacks are of a shorter duration (2-30 minutes) and usually occur more than five times per day.[1] The importance of this diagnosis is that unlike cluster headache, paroxysmal hemicrania responds absolutely to the drug indomethacin. We recommend a trial of indomethacin in patients with probable cluster headache if attacks are shorter than 30 minutes or there are more than five attacks per day, but not all patients as the diagnostic yield is low and indomethacin may in some cases worsen cluster headache. We use a trial of oral indomethacin starting at a dose of 25mg three times a day for three days, followed by 50mg three times a day for three days, followed by 75mg three times a day for seven days, taken with a proton-pump inhibitor for gastric protection.

Rarely a patient can present with a clinical syndrome resembling primary cluster headache due to secondary pathology. This may include pituitary tumour, cavernous sinus pathology, arterial dissection or aneurysm.[5] Our practice is to perform magnetic resonance imaging (MRI) to exclude secondary causes in all patients who present during the first bout. In those presenting in the second bout or later a secondary cause is extremely unlikely, and risk of incidental findings is not insignificant, but it is reasonable to perform imaging as the devastatingly disabling attacks frequently provoke concern about secondary causes and imaging is often reassuring. Dedicated pituitary imaging does not need to be routinely organised unless any clinical features of pituitary tumour are present, as the risk of pituitary tumour in this population does not appear to be higher than the background risk.[6]

Epidemiology and risk factors

Cluster headache affects approximately 0.1% of the population.[7] In contrast to migraine which is more common in females, cluster headache is approximately four times commoner

in males.[7] The onset is typically in the third decade of life. The clinical phenotype is similar in men and women, although women may suffer more nausea and vomiting with attacks.[8] Unlike migraine, there is not usually any relationship to the menstrual cycle, pregnancy, or menopause.[9]

There appear to be both genetic and environmental risk factors for the development of cluster headache. Approximately 6% of patients of cluster headache have a family history in a first or second degree relative,[10] and there are several reports of cluster headache in identical twins. A polymorphism in the hypocretin receptor-2 gene was demonstrated to increase the risk of cluster headache,[11] however this has not been supported by other more recent studies.[12] No other gene has consistently been shown to be strongly associated. However, the genetics studies conducted thus far were relatively small and underpowered. The International Consortium for Cluster Headache Genetics (ICCG) is currently conducting a large genome wide association study which is due to report shortly and will likely identify some cluster headache susceptibility loci.

Cigarette smoking is extremely common in those with cluster headache, and in most cases the smoking habit precedes the onset of cluster headache. In non-smokers there is often a history of passive smoking during childhood. It is possible smoking contributes to the onset of cluster headache via a toxic compound in cigarette smoke. Use of other illicit drugs prior to the onset is also higher in men with cluster headache than the general population, so alternatively the association may be due to a shared risk factor for both cluster headache and addictive behaviour.[13] Some studies have also shown a higher rate of excess of both caffeine and alcohol intake in patients with cluster headache, however many patients' alcohol intake will decrease during bouts due to its ability to trigger attacks.

Previous head injury is commonly reported by patients with cluster headache. Often this is not in sufficient close temporal relation to the head injury to meet criteria for a true post-traumatic headache. When a post-traumatic headache with cluster headache phenotype does occur, it is more likely to be chronic and refractory to treatment.[14]

Pathophysiology

The pathophysiology of cluster headache remains poorly understood. The key features which would be accounted for by a comprehensive pathophysiological model include the trigeminal distribution of the pain, the presence of cranial autonomic symptoms, the periodicity of attacks, and the response to treatments such as triptans and oxygen. Overall there is no universal consensus on the pathophysiology of cluster headache. The current leading view suggests that during attacks the trigeminovascular system and trigeminal-autonomic reflex become activated via a trigeminal-hypothalamic pathway under fluctuating control from the hypothalamus and other central pain-processing regions.

Vascular hypotheses

Cluster headache has in the past been described as a "vascular headache", as vasodilation of intracranial arteries ipsilateral to the pain is seen during attacks. Experimental studies using induced forehead pain by capsaicin injection have suggested that pain induces vasodilation, not vice-versa.[15] Current thinking is that the attacks originate in the nervous system rather than due to a primary vascular aetiology.

It has been hypothesised that cluster headache may be caused by a lesion in the cavernous sinus, a region where incoming trigeminal nociceptive fibres, and outgoing sympathetic and

parasympathetic fibres are adjacent.[16, 17] Evidence from imaging, angiography and biochemical studies has not shown any evidence of inflammation or other lesion in this region in cluster headache patients.

Trigeminal nerve

The pain of cluster headache is usually felt in the dermatome of the first division of the trigeminal nerve (V1). The location of the pain in cluster headache and other primary headache syndromes therefore implicates the trigeminal nerve as involved as least in the pain component of attacks. V1 provides sensory innervation to the eye, skin of the upper face and front part of scalp, as well as the frontal sinuses, cranial vessels and dura mater.

The assumed importance of the trigeminal nerve to the pain of cluster headache has led some to perform complete trigeminal nerve section or radiofrequency ablation in patients with chronic cluster headache that is refractory to other treatments. This can be effective in some patients,[18] but not all,[19] indicating that the peripheral trigeminovascular system cannot be the sole explanation for attacks. It is also possible for a syndrome which is otherwise indistinguishable from cluster headache to have attacks outside the trigeminal nerve distribution (for example occipital, parietal and cervical regions).[20]

Trigeminovascular system

The trigeminovascular system is a term used to describe the trigeminal neurons which innervate cerebral blood vessels. The headache phase of migraine has been proposed to develop as the result of an abnormal release of neurotransmitters or peptides in the trigeminovascular system. Peptides involved in this system include calcitonin gene-related peptide (CGRP), substance P and vasoactive intestinal peptide. Elevated levels of CGRP

have been found in patients with migraine and cluster headache, both during spontaneous and nitroglycerine-induced attacks.[21, 22] A specific marker for cluster headache, different to migraine or other headache disorders has not been identified.

Infusion of CGRP can trigger attacks in those with chronic cluster headache, and with episodic cluster headache exclusively whilst within a bout.[23] Similar findings in patients with migraine have led to the development of anti-CGRP monoclonal antibodies, which have recently also been trialed in patients with cluster headache.

Trigeminal-autonomic reflex

The autonomic symptoms during attacks of cluster headache and other trigeminal autonomic cephalalgias are thought to result from activation of a trigeminal-autonomic reflex. This is a physiological reflex by which a painful stimulus in the trigeminal region results in reflex activity in the ipsilateral facial parasympathetic system, producing symptoms which may be expected from physical damage to that side of the head or eye such as lacrimation, conjunctival injection, rhinorrhoea, and facial swelling.

The trigeminal-autonomic reflex, which has been studied in animals, has the afferent limb of the trigeminal sensory neurons, and efferent limb of the parasympathetic neurons travelling with the facial nerve from the superior salivatory nucleus via the sphenopalatine ganglion. Various therapies which are effective in trigeminal autonomic cephalalgias have been shown experimentally able to modulate this reflex, although it is not known whether they do this directly or indirectly e.g. via the hypothalamus.[24]

The symptoms of rhinorrhoea, lacrimation, conjunctival injection and nasal congestion in association with cluster headache are related to increased parasympathetic activation. Conversely the symptoms of ptosis and meiosis are related to reduced sympathetic function.

Hypothalamus

The marked circadian and circannual periodicity observed in cluster headache patients suggests that neuronal populations which have circadian and circannual fluctuations must play a role in the pathophysiology. The human "biological clock" is the suprachiasmatic nuclei located in the anterior hypothalamus. Cells in this area generate a self-sustaining rhythm which is entrained by light signals from the retina via the retinohypothalamic tract and melatonin secreted by the pineal gland. The outputs from the suprachiasmatic nuclei in turn entrain various parts of the body and brain which have diurnal rhythms, including the secretion of pituitary hormones.

A number of studies have found abnormal levels of pituitary hormones in patients with cluster headache suggesting hypothalamic dysfunction.[25] It is not known whether these changes are specific to cluster headache as abnormal pituitary hormone levels have also been found in migraine and other non-headache chronic pain conditions,[26] and may also be affected by chronic stress or interrupted sleep. The circadian secretion of melatonin has also been found abnormal in patients with cluster headache during bouts.[27]

Orexin-A and -B (also known as hypocretins) are neuropeptides which are produced exclusively by a small area of neurons in the posterior and lateral hypothalamus. They are involved in the regulation of wakefulness and food intake. A polymorphism in an orexin receptor gene has been demonstrated to increase the risk of cluster headache in some genetic

studies.[11] Animal experiments have shown that orexin-A and orexin-B given via injection into the posterior hypothalamus or intravenous infusion can differentially modulate the response of trigeminal neurons to dural stimulation, indicating that the posterior hypothalamus can alter the trigeminal nociceptive response to meningeal inputs.[28, 29]

Imaging studies have supported the importance of the hypothalamus in cluster headache. Functional imaging studies using positron emission tomography (PET) and functional MRI have shown activation in the ipsilateral hypothalamic grey matter during attacks.[30-32]

Functional imaging studies in other trigeminal autonomic cephalalgias have also shown activation in a similar region.[33, 34] This activation may not be specific for trigeminal autonomic cephalalgias as hypothalamic activation has been also seen in spontaneous migraine attacks,[35] and other acute pain states such as induced angina pectoris.[36]

A structural MRI study using voxel-based morphometry reported an increase in bilateral inferior posterior hypothalamic gray matter volume in patients with cluster headache in the same region activated on functional MRI.[37] This structural change has not been supported by other studies using similar methodology.[38]

Magnetic resonance spectroscopy has shown reduced altered metabolite ratios in the hypothalamic region in patients with cluster headache. In a study of 47 patients there was a significantly lower NAA/Cr and Cho/Cr ratio in patients with cluster headache compared with healthy controls and those with chronic migraine. There was no difference in those with episodic cluster headache between inside and outside a bout.[39]

Functional connection between the trigeminal nerve and hypothalamus is likely important for co-ordinating endocrine, autonomic and behavioural responses to stimuli and pain in the head and face, blood vessels and meninges. A "trigeminohypothalamic" tract connecting the hypothalamus and trigeminal nucleus has been shown to exist in animal studies.[40, 41] Connection between the hypothalamus and brainstem regions including the trigeminal nucleus has been demonstrated in humans using probabilistic tractography imaging in patients who underwent deep brain stimulation for refractory chronic cluster headache.[42]

Cortical factors

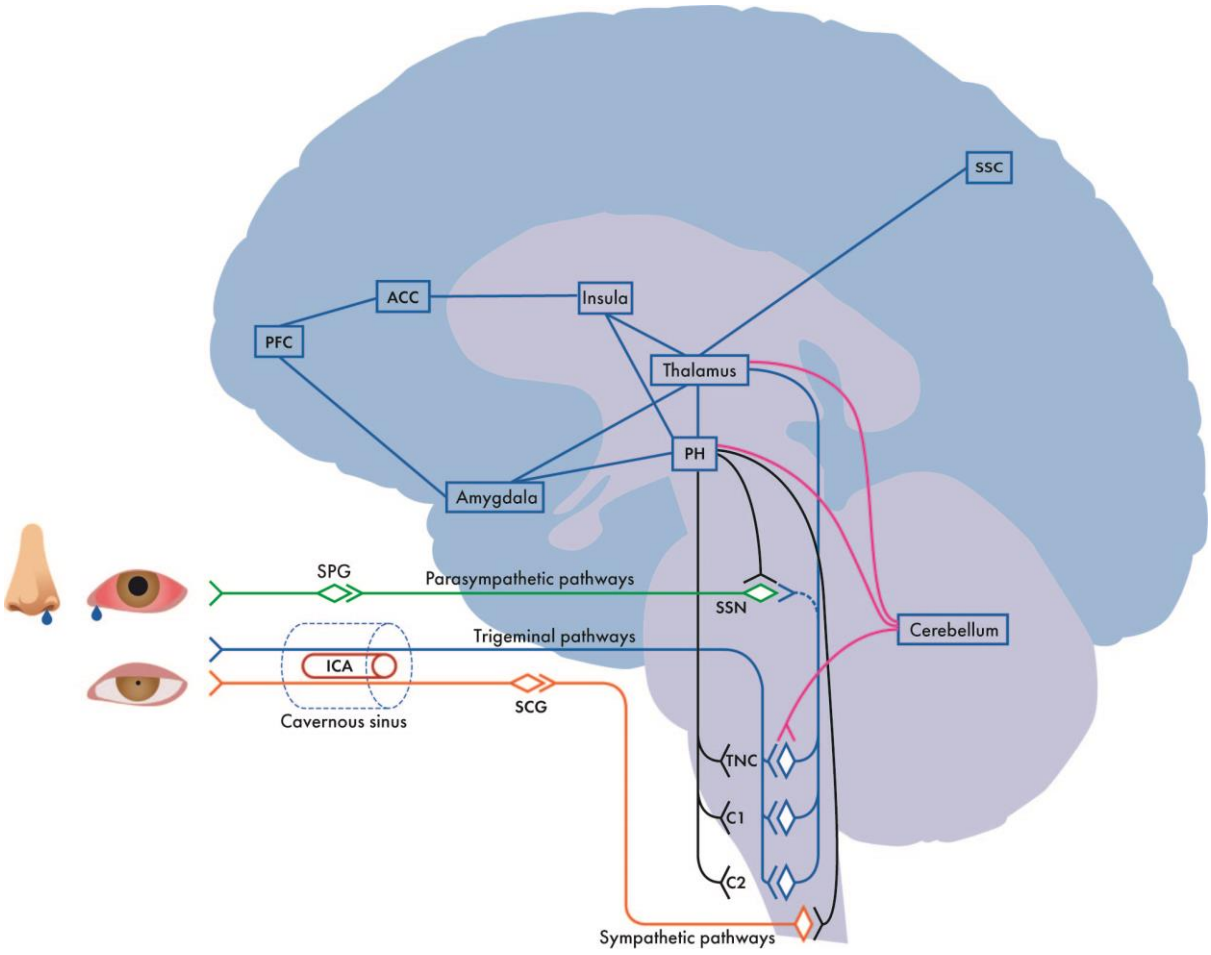
The perception of pain is presumed to occur in the cerebral cortex via projections from the thalamus. Cortical processing of pain is incompletely understood and there is no central area for the processing of pain, but most studies have implicated the bilateral insula, anterior cingulate cortex and regions of the frontal cortex as pain processing regions.

Structural neuroimaging studies have shown reduced grey matter volume in cortical pain processing regions in patients with cluster headache,[38, 43] which in one study depended on whether the patient was within or outside a bout.[44] Functional imaging studies have shown activation in central pain processing regions during attacks,[32] and a PET study has shown hypometabolism in the anterior cingulate cortex and prefrontal cortex, suggesting deficient top-down modulation of antinociceptive circuits in cluster headache patients.[45]

Pain is an unpleasant sensory and emotional experience. The perception of pain is complex and influenced by multiple cognitive, emotional and behavioural factors. Psychosocial factors including mood, personality traits, social support and 'stress' unrelated to cluster headache

itself anecdotally affect the course of cluster headache or trigger attacks in individuals by unclear mechanisms.

Figure 1. Schematic diagram of the central and peripheral pathways involved in the pathophysiology of cluster headache



Abbreviations: ACC, anterior cingulate cortex; C1, first cervical nerve root; C2, second cervical nerve root; ICA, internal carotid artery; PFC, prefrontal cortex; PH, posterior hypothalamus; SCG, superior cervical ganglion; SPG, sphenopalatine ganglion; SSC, somatosensory cortex; SSN, superior salivatory nucleus; TNC, trigeminal nucleus caudalis

Management

The management options in cluster headache are divided into acute, preventive and transitional treatments. The true effectiveness of any cluster headache treatment is difficult to determine without comparison to a placebo group, as cluster attacks and cluster bouts will spontaneously terminate after an unpredictable amount of time. There is good quality evidence for acute treatment with parenteral triptans and high flow oxygen; transitional treatment with oral corticosteroids and greater occipital nerve blocks including corticosteroids; and preventive treatment with verapamil. Newer drug and neuromodulatory treatments are showing promising results and may soon become established in clinical practice.

Acute treatments

Acute treatments aim to terminate an individual attack, should be taken at the onset of the attack, and ideally should work within seconds or minutes, hence parenteral rather than oral treatments are required. The most established effective acute treatments for cluster attacks are subcutaneous/intranasal tripans and inhaled high-flow oxygen.

Triptans

Subcutaneous sumatriptan is the most effective triptan for cluster headache and can be given up to twice per day. In a randomised controlled trial subcutaneous sumatriptan was effective at aborting 46% attacks and reducing pain level to mild in 74% of attacks within 15 minutes.[46] Intranasal sumatriptan and intranasal zolmitriptan are also available as alternatives, but have lower efficacy rates and should be reserved for patients who are not able to use a subcutaneous injection. Due to their vasoconstrictive effect, triptans should not be used in those with significant vascular disease or uncontrolled hypertension.

The mechanism of action of triptans in headache disorders is attributed to their selective agonist effect on 5-HT_{1B} and 5-HT_{1D} serotonin receptors on blood vessels causing vasoconstriction, and/or effect on peripheral nociceptors inhibiting the release of neuropeptides such as CGRP and substance P. Recently an animal study has shown that as soon as 1 minute after subcutaneous injection of sumatriptan it can be observed in the hypothalamus at a higher concentration than in both the trigeminal ganglion and the dura, suggesting that triptans may instead work in the central nervous system rather than peripherally.[47]

Oxygen

High flow oxygen is also effective at terminating attacks. One hundred percent oxygen should be given at 7-15 litres per minute (L/min), lower concentration oxygen is unlikely to be effective. In a randomised controlled trial of inhaled 100% oxygen at 12 L/min, 78% patients were pain free after 15 minutes, compared to 20% with placebo air.[48] The mechanism of action of oxygen in cluster headache is not understood. An experimental study has shown it does not affect trigeminal afferents but can inhibit cranial parasympathetic neurons.[49]

Other acute treatments

Alternative acute treatments used but are less effective include intranasal lidocaine spray, intranasal dihydroergotamine, intranasal cocaine, and intranasal capsaicin. Conventional analgesics such as paracetamol, aspirin and nonsteroidal anti-inflammatory drugs are almost never effective in terminating attacks.

Octreotide, a somatostatin analogue has been shown to be effective in the acute treatment of cluster headache when compared with placebo.[50] It is potentially useful in those patients unable to take triptans, but not used in clinical practice as it is expensive, needs to be stored in a fridge, and is not licensed for use in cluster headache. There is an ongoing phase II study of an analogue pasireotide.

Non-invasive vagus nerve stimulation

A hand-held device which is held against the neck and delivers an electrical current in order to stimulate the vagus nerve (gammaCore®) has been investigated in two randomised sham-controlled trials for the acute treatment of cluster headache attacks. In both trials the primary endpoint was negative, but post-hoc analysis showed that it was significantly effective in patients with episodic cluster headache but not chronic cluster headache.[51, 52]

Non-invasive neuromodulatory therapies, which aim to alter nerve activity through targeted delivery of electrical stimulation, are an attractive option as they do not typically cause systemic side effects. Vagus nerve stimulation is thought to modulate the trigeminal-autonomic reflex but may alternatively work via connection from the nucleus tractus solitarius to the hypothalamus.

Preventive medications

Preventive treatments aim to prevent further attacks from occurring and usually do not have their full effect for a number of weeks after being started. The most established and well evidenced preventive treatment for cluster headache is verapamil and this should be used as the first line preventive medication. A number of other medications have shown benefit but

generally only in small open label trials, and in clinical practice are less effective and/or more likely to cause side effects.

Verapamil

Verapamil is a calcium channel blocker. In a randomised controlled trial verapamil was significantly more effective than placebo at a dose of 120mg three times per day for fourteen days, [53] and in an open label study 69% patients improved more than 75%.[54]

Verapamil is usually given starting at a dose of 240mg daily in two or three divided doses and increased in 80-120mg increments in two weekly intervals, up to a maximum dose of 960mg daily. In patients with episodic cluster headache our practice is to continue verapamil for the duration of the cluster bout and if subsequently pain-free for at least one month to gradually decrease the dose in steps of 80-120mg every five days. Due to its effect on cardiac conduction, before verapamil is started, and prior to each dose increase, electrocardiography (ECG) should be performed. In an audit of ECGs in patients who had received verapamil for cluster headache, 19% had arrythmias, and in another 4% of patients verapamil had to be stopped due to bradycardia.[55]

The mechanism of verapamil in cluster headache is incompletely understood. It has been hypothesised to be due to effects on CGRP release, circadian rhythms, or by reducing vasodilation. A recent study using machine learning techniques has shown that responsiveness to verapamil can be predicted with moderate accuracy based on high dimensional modelling of routinely collected clinical and imaging data. In this study an area in lobule VI of the cerebellum, an area is known to be activated with trigeminal nociceptive

stimulation, was found to have higher gray matter concentration in verapamil non-responders compared to responders.[56]

Lithium

Lithium has been used for cluster headache since the 1970s. A comparison trial of lithium and verapamil showed that both were similarly effective, but verapamil caused fewer side effects.[57] One small, short, placebo controlled trial of lithium did not show a significant improvement over placebo.[58] Therapeutic drug monitoring is required due to its narrow therapeutic range and possibility of toxicity.

Topiramate

Topiramate is an anti-epileptic drug which is widely used as a preventive treatment in migraine. It appears to also be effective in some patients with cluster headache. A number of open trials and case series have reported its efficacy,[59, 60] but no randomised placebo-controlled trials have been conducted.

Melatonin

Melatonin is a hormone naturally secreted from the pineal gland in response to darkness and involved in regulation of sleep-wake cycles. Melatonin has been shown to be beneficial in cluster headache in case studies and a small double blind placebo controlled study,[61] however this was not confirmed in another study.[62] Melatonin is safe with minimal side effects.

Other preventive medications

A variety of other medications have been reported to be helpful in patients with cluster headache, but generally in small series of patients and not compared to placebo. Gabapentin has been reported as effective in two small open label series.[63, 64] Sodium valproate also has open label evidence, but there was no difference to placebo in a randomised controlled double-blind trial.[65] The ergot derived drug methysergide was recognized as an effective treatment in some patients, but is no longer available due to safety concerns. Other treatments reported include baclofen, pregabalin, levetiracetam, chlorpromazine, candesartan, pizotifen, tizanidine, and transdermal clonidine.

Botulinum toxin injections have also been reported as effective in open label studies and case reports, but again no randomised controlled trials have been performed. The local injection of botulinum toxin towards the sphenopalatine ganglion has also been trialed in patients with refractory chronic cluster headache.[66]

Table 2. Preventive medications for cluster headache

Medication	**Daily dose range**	**Common side effects**	**Monitoring**
Verapamil	240-960mg	Hypotension, bradycardia, constipation, peripheral oedema	Electrocardiogram before starting and before dose increases
Lithium	300-1200mg	Nausea, anorexia, diarrhoea, fine tremor, polyuria	Lithium levels; renal function, electrolytes and thyroid function
Topiramate	50-200mg	Cognitive impairment, mood change, renal stones, weight gain, teratogenicity	Nil
Melatonin	3-15mg	Fatigue	Nil

Gabapentin	900-3600mg	Fatigue, dizziness, nausea, diarrhoea, dry mouth, constipation, ataxia	Nil
Sodium valproate	500-1200mg	Abdominal pain, nausea, weight gain, hair loss, tremor, teratogenicity	Full blood count, liver function

CGRP monoclonal antibodies

Monoclonal antibodies targeting CGRP or its receptor have recent good quality evidence for the treatment of episodic and chronic migraine in multiple large randomised controlled trials. They have also recently been investigated for use in cluster headache. A randomised controlled trial of the anti-CGRP humanized monoclonal antibody galcanezumab given subcutaneously at a dose of 300mg once per month in patients with episodic cluster headache showed a small but significant reduction in headache frequency compared with placebo, with a good safety profile.[67] A trial in chronic cluster headache did not show a significant reduction in attack frequency versus placebo.[68] Fremanezumab has also been trialled in episodic and chronic cluster headache, however the trial was discontinued early as interim analysis showed it was unlikely to meet its primary endpoint.

Non-invasive vagus nerve stimulation

Non-invasive vagus nerve stimulation with the gammaCore® device has been also trialled as a preventive treatment for chronic cluster headache. In an open label trial compared with standard care there was a significant reduction in number of attacks per week compared to the control group (-5.9 vs. -2.1 respectively).[69] Sham controlled studies are required, similarly to those performed to assess its use in acute treatment.

Transitional treatments

Transitional treatments have an intermediate onset and duration of action and are usually used either whilst waiting for a preventive treatment to be uptitrated, or in an attempt terminate a bout in patients with episodic cluster headache, especially those with short and infrequent bouts.

Oral steroids

Short term use of high dose corticosteroids has been used as a transitional treatment for many years with good effectiveness in clinical practice. A recent placebo-controlled trial has confirmed the efficacy of corticosteroids using prednisone 100mg for five days then tapered by 20mg every three days.[70] Our usual practice is to use oral prednisolone starting at 60mg and reducing by 10mg every three days until stopped. Dexamethasone and intravenous methylprednisolone have also been used.

Due to the many long-term side effects of corticosteroids, they should be used sparingly and for short time period: a maximum of four weeks (including taper) per course, and maximum two courses per year. Attacks often recur once the steroid dose is tapered, meaning their use should usually be accompanied by starting a longer acting preventive medication such as verapamil. The mechanism of action of corticosteroids in cluster headache is not known but has been hypothesised to be due to their influence on inflammatory, hypothalamic, histaminergic, or opioid systems.

Greater occipital nerve injection

Suboccipital injection targeting the greater occipital nerve (GON) using local anaesthetic agents and/or corticosteroids are well tolerated and effective in the transitional treatment of cluster headache. Two placebo-controlled trials have been conducted in cluster headache,

both of which used steroid injections without the addition of local anaesthetic, and both showed significant improvement in the treatment group compared with placebo injection.[71, 72] GON injection is relatively easy to perform and preferred to oral steroids due to similar clinical effectiveness and avoidance of systemic steroid side effects. The mechanism of action is thought to be an interruption of the pathways involved in the trigeminal autonomic reflex via functional connectivity between the trigeminal and occipital nerves.[73]

Other transitional treatments

Multiple cranial nerve blocks targeting the greater and lesser occipital, supraorbital, supratrochlear, and auriculotemporal nerves have also been used. In an open label report 36/52 (69%) of patients with chronic cluster headache responded.[74] Sphenopalatine ganglion blockade has been used, with various approaches requiring technical expertise.[75, 76] Intravenous dihydroergotamine is also occasionally used as a transitional treatment, and is usually effective within a few days. Rarely it is given periodically in patients with treatment refractory chronic cluster headache.

Lifestyle factors

No lifestyle factor has strong suggestion of benefit in cluster headache, other than avoidance of triggers, especially alcohol. Patients are usually recommended to stop smoking, but this rarely improves their headaches.

Medication overuse headache, which is a common problem in migraine, may also rarely occur in patients with cluster headache, usually those who have a personal or family history of migraine.[77] Due to the excruciating nature of the pain, acute treatments should not usually be rationed in patients with cluster headache, but it should be considered in patients who

develop a chronic daily headache in temporal association with regular use of acute treatments.

Surgical treatments and invasive neurostimulation

Destructive surgery of the trigeminal nerve originally used for trigeminal neuralgia has be attempted in those with cluster headache. This has included trigeminal nerve section, glycerol rhizotomy and radiosurgery of the trigeminal nerve. The results have been mixed and side effects potentially serious, which can include infection, cerebrospinal fluid leak, corneal anaesthesia and anaesthesia dolorosa.

More recently, neuromodulatory therapies have been preferred which deliver electrical stimulation with the aim of manipulating central or peripheral pain pathways. Due to the surgical risks these treatments are reserved for patients with chronic cluster headache who are refractory to multiple medical preventive treatments.

Occipital nerve stimulation

Occipital nerve stimulation (ONS) involves peripheral stimulation of the occipital nerves by implanted suboccipital electrodes, which are connected to an implantable pulse generator sited in the subcutaneous tissue of the chest or abdomen. The largest open label reports of ONS in cluster headache have shown a response rate of 53-67% at long term follow up.[78, 79] Placebo controlled trials of ONS in chronic cluster headache have not been conducted. Placebo controlled trials of ONS in chronic migraine have shown a small but statistically significant improvement in headache days compared with sham stimulation,[80] although trials are limited by difficulty in blinding as paraesthesia is usually felt whilst the stimulator is

active. There are potential complications of ONS surgery including infection and need for revision surgery for lead migration.

Sphenopalatine ganglion stimulation

An implantable sphenopalatine ganglion stimulator has been developed for aborting cluster attacks. Two randomised sham-controlled trials have been performed in patients with medically refractory chronic cluster headache, showing effectiveness both for abortion of attacks and preventive reduction in attack frequency.[81, 82] In a large open label registry 55% patients had a >50% reduction in attack frequency and 32% patients benefited acutely.[83] There are risks from the implantation procedure as with any surgical procedure. Unfortunately, the manufacturer of this device has recently gone out of business, therefore this is not a current treatment option.

Deep brain stimulation

Informed by the neuroimaging studies showing activation of the posterior hypothalamus during attacks, deep brain stimulation (DBS) of the posterior hypothalamic region has been attempted.[84] Though many of the reports describe the procedure as posterior hypothalamic DBS, the electrodes are in fact implanted in the ventral tegmental region.[85] Open label studies have shown that DBS is effective in 60-80% patients.[86, 87] Only one randomised sham-controlled controlled trial has been performed, which included 11 patients.[88] During the randomised phase there was no significant difference between active and sham stimulation, however the duration of the blinded trial was only 1 month. Open label studies have shown that some patients may take longer than this time to respond, and in the open 1-year extension of the trial a number of patients did become responders. The delayed response argues against a simple deactivation of the region of the electrode. A PET study has shown

altered activity in central pain processing regions such as the anterior cingulate cortex and insula in patients treated with DBS.[89] This procedure should only be performed in a specialist centre and considered when all other treatments have failed. Serious adverse effects such as intracerebral haemorrhage are possible but rare. The most common side effects are transient dizziness or diplopia.

Table 3. Summary of established and emerging treatments for cluster headache

	Established treatments	**Emerging treatments**
Acute	Triptans Oxygen	
Preventive	Verapamil Lithium Topiramate Melatonin Gabapentin	Anti-CGRP monoclonal antibodies
Transitional	Greater occipital nerve block Corticosteroids Intravenous dihydroergotamine	Multiple cranial nerve blocks
Non-invasive neuromodulation		Vagus nerve stimulation
Invasive neuromodulation	Occipital nerve stimulation Deep brain stimulation	Sphenopalatine ganglion stimulation

Abbreviations: CGRP, calcitonin gene-related peptide

Prognosis

In the majority of patients, cluster headache has a long duration, and can be lifelong. In a ten year follow up study 81% of patients with episodic cluster headache had remained in that state and 12.9% had transitioned into chronic cluster headache; 52.4% of patients with

chronic cluster headache had remained in that state, and 32.6% had improved to episodic; and in only 10% patients it appeared to have resolved with no attacks for the prior three years.[90]

Conclusion

Cluster headache is an excruciatingly painful and severely disabling primary headache disorder. Clinical, biochemical and imaging evidence points towards the hypothalamus and trigeminovascular system as being central to its pathophysiology. The current core of management should include parenteral triptans and oxygen as acute treatments, GON injection as a transitional treatment, and verapamil as a preventive treatment. Newer therapies such as anti-CGRP monoclonal antibodies, non-invasive vagus nerve stimulation, and deep brain stimulation are showing promise, especially for those with treatment refractory chronic cluster headache.

Disclosures:

SC has no disclosures. MSM serves on the advisory board for Abbott, Allergan, Eli Lilly, Medtronic, Novartis and TEVA and has received payment for the development of educational presentations from Allergan, electroCore, Eli Lilly, Novartis and TEVA.

The authors hereby certify that the work shown here is genuine, original and not submitted anywhere, either in part or full. They transfer the full rights of the video to Neurology India.

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