

Cluster headache: causes and current approaches to treatment

Manjit Matharu BSc, MRCP and Peter Goadsby MD, DSc

Cluster headaches have been described as one of the most painful human conditions. The authors discuss the causes and management, encompassing general measures, acute and preventive treatment and surgery.

Figure 1. Cluster headaches are strictly unilateral and usually orbital or temporal

Cluster headache (CH) is a unilateral headache that occurs in association with cranial autonomic features. It is an excruciating syndrome and one of the most painful conditions known to humans, with female patients describing each attack as being worse than childbirth. In most patients, it has a striking circannual and circadian periodicity. This disorder has a highly stereotyped clinical pheno-

type and responds to specific therapies, thereby underlying the importance of distinguishing it from other primary headache syndromes.

Epidemiology

The prevalence of CH is estimated to be 0.4 per cent.¹ The male:female ratio ranges from 3.5 to 7:1.² It can begin at any age, though the most common age of

onset is the third or fourth decade of life.

Clinical features

It is useful for both clinician and patient to standardise the terminology used in CH. A *cluster headache* or *attack* is an individual episode of pain that can last from a few minutes to some hours. A *cluster bout* or *period* refers to the duration over which recurrent

cluster attacks are occurring; it usually lasts some weeks or months. A *remission* is the pain-free period between two cluster bouts.

CH is a disorder with highly distinctive clinical features; these are dealt with under two major headings: *cluster attack* and *cluster bout*.

Cluster attack

The attacks have an abrupt onset and cessation. They are strictly unilateral, though they may alternate sides. The pain is excruciatingly severe and located mainly around the orbital and temporal regions, although any part of the head can be affected. The headache usually lasts 45-90 minutes but can range from 15 minutes to three hours.

The signature feature of CH is the association with cranial autonomic symptoms, and it is extremely unusual for these not to be reported. The International Headache Society (IHS) diagnos-

tic criteria³ require the cluster attacks to be accompanied by at least one of the following, which have to be present on the pain side: conjunctival injection, lacrimation, miosis, ptosis, eyelid oedema, rhinorrhoea, restlessness or agitation, nasal blockage and forehead or facial sweating (see Table 1). The autonomic features are transient, lasting only for the duration of the attack, with the exception of partial Horner's syndrome; ptosis or miosis may rarely persist, especially after frequent attacks.

Recently, there have been several descriptions of the full range of typical migrainous symptoms in significant proportions of cluster patients.^{2, 4} Premonitory symptoms (tiredness, yawning), associated features (nausea, vomiting, photophobia, phonophobia) and aura symptoms have all been described in relation to cluster

attacks. However, in contrast to migraine, CH sufferers are usually restless and irritable, preferring to move about and look for a movement or posture that may relieve the pain. This is such a prominent feature of the CH phenotype that it has recently been incorporated into the revised IHS diagnostic criteria.³

The cluster attack frequency varies between one every alternate day to three daily, although some have up to eight daily. The condition can have a striking circadian rhythmicity, with some patients reporting that the attacks occur at the same time each day.

Alcohol, nitroglycerine, exercise and elevated environmental temperature are recognised precipitants of acute cluster attacks. Alcohol induces acute attacks within an hour of intake in the vast majority of sufferers, contrasting with migraine sufferers who generally have headache some hours after alcohol intake. Alcohol also triggers attacks during a cluster bout but not in a remission. Allergies, food sensitivities, reproductive hormonal changes and stress do not appear to have any significant role in precipitating attacks.

Cluster bout

CH is classified according to the duration of the bout. About 80 to 90 per cent of patients have *episodic cluster headache* (ECH), which is diagnosed when they experience recurrent bouts, each with a duration of more than a week and separated by remissions lasting more than four weeks. The remaining 10 to 20 per cent of patients have *chronic cluster headache* (CCH), in which either no remission occurs within one year or the remissions last less than one month.³

Most patients with ECH have one or two annual cluster periods,

<p><i>Cluster headache has 2 key forms:</i></p> <ul style="list-style-type: none"> • episodic: occurs in periods lasting 7 days to 1 year separated by pain-free periods lasting 1 month or more • chronic: attacks occur for more than 1 year without remission or with remissions lasting less than 1 month
<p><i>Headaches* must have each of:</i></p> <ul style="list-style-type: none"> • severe, unilateral, orbital, supraorbital and/or temporal pain lasting 15-180 minutes untreated • frequency of attacks: from 1 every other day to 8 per day • headache associated with at least 1 of the following signs that have to be present on the pain side: <ul style="list-style-type: none"> – conjunctival injection – lacrimation – nasal congestion – rhinorrhoea – forehead and facial sweating – miosis – ptosis – eyelid oedema – sense of restlessness or agitation during headache
<p>*no reasonable secondary cause</p>

Table 1. Diagnostic features of cluster headache modified from the International Headache Society³

each lasting between one and three months. Often, a striking circannual periodicity is seen with the cluster periods, with the bouts occurring in the same month of the year. In others, the cluster periods tend to recur at regular intervals that are consistently different than 12 months. Although the duration of the cluster and remission periods varies between patients, these periods remain relatively consistent within individuals.

Pathophysiology

Any pathophysiological construct for CH must account for the three major features of the syndrome: trigeminal distribution pain, ipsilateral cranial autonomic features and the striking tendency to circadian and circannual periodicity.

Firstly, the pain-producing innervation of the cranium projects through branches of the trigeminal and upper cervical nerves to the trigemino-cervical complex, from whence nociceptive pathways project to higher centres. This implicates an integral role for the ipsilateral trigeminal nociceptive pathways in CH.

Secondly, the ipsilateral cranial autonomic features suggest cranial parasympathetic activation (lacrimation and rhinorrhoea) and sympathetic hypofunction (ptosis and miosis). These cranial autonomic symptoms are, partly, accounted for by the trigemino-autonomic reflex.⁵

Finally, functional⁶ and structural⁷ imaging studies point to the specific involvement of the posterior hypothalamus, a structure that is known to have a modulatory role on the nociceptive and autonomic pathways, and is the site of the circadian pacemaker cells (see Figure 2).

Hence, CH is probably due to an abnormality in the posterior hypothalamus with subsequent

trigeminovascular and cranial autonomic activation.

Natural history

Although there is limited literature on the long-term prognosis of CH, the available evidence suggests that it is a lifelong disorder in the majority of patients. In one study, about one-tenth of patients with ECH evolved into CCH whereas one-third of patients with CCH transformed into ECH.⁸

An encouraging piece of information for CH sufferers is that a substantial proportion of them can expect to develop longer remission periods as they get older.⁹

Differential diagnosis

In spite of the rather characteristic clinical picture, the differential diagnosis may be difficult in some cases as each of the features of CH can be mimicked by other headaches (see Table 2). The main differential diagnoses to consider are secondary causes of CH, migraine and paroxysmal hemicrania.

Before a diagnosis of CH can be made, secondary headache disorders that mimic CH need to be excluded. Symptomatic CH has been described after infectious, vascular and neoplastic intracranial lesions. Any atypical features in the history or abnormalities on neurological examination (with the exception of partial Horner's syndrome) warrant further investigation to search for organic causes.

Unilateralism of pain and presence of migrainous and autonomic symptoms are features common to both migraine and CH, and differentiating between them can be difficult in some cases. The features that can be useful in distinguishing CH from migraine include: relatively short duration of headache; rapid onset

<p><i>Primary headache syndromes</i></p> <ul style="list-style-type: none"> migraine paroxysmal hemicrania SUNCT syndrome hemicrania continua hypnic headache
<p><i>Secondary causes of cluster headache</i></p> <ul style="list-style-type: none"> vascular abnormalities tumours infection traumatic or surgery
<p><i>Secondary headache syndromes</i></p> <ul style="list-style-type: none"> Tolosa-Hunt syndrome temporal arteritis Raeder's paratrigeminal neuralgia

Table 2. Differential diagnoses of cluster headache

and cessation; circadian periodicity; precipitation within an hour, rather than several hours, by alcohol; restlessness or agitation during the attack; and clustering of attacks with intervening remissions in ECH.

Paroxysmal hemicrania is a syndrome that is similar to CH except that it is prevalent in females with shorter but more frequent attacks. It is exquisitely responsive to doses of indometacin, thus emphasising the importance of not misdiagnosing it as CH.¹⁰

Investigations

The diagnosis of CH is made entirely on the basis of a good clinical history and a detailed neurological examination. However, it is very difficult to clinically dissect the secondary causes from primary CH. A magnetic resonance imaging (MRI) scan of the brain is a reasonable screening investigation.

Treatment principles

Management of CH includes offering advice on general measures to patients, treatment with abortive and preventive agents and – rarely – surgery.

General measures and patient education

Patients should be advised to abstain from taking alcohol during the cluster bout but, other than that, dietary factors seem to have little importance in CH.

Anecdotal evidence suggests that patients should be cautioned against prolonged exposure to volatile substances such as solvents and oil-based paints, and should be instructed to avoid afternoon naps as sleeping can precipitate attacks in some patients.

Abortive agents

The pain of CH builds up rapidly to such an extent that most oral agents are too slowly absorbed to cure the pain within a reasonable amount of time. The most efficacious abortive agents are those that involve parenteral or pulmonary administration (see Table 3).

Triptans

Subcutaneous sumatriptan (Imigran) 6mg is the drug of choice in abortive treatment of a cluster attack. It has a rapid effect and high response rate.¹¹ In CH, unlike in migraine, subcutaneous sumatriptan can be prescribed at a frequency of twice daily, on a long-term basis if necessary, without risk of tachyphylaxis or rebound.¹²⁻¹⁴

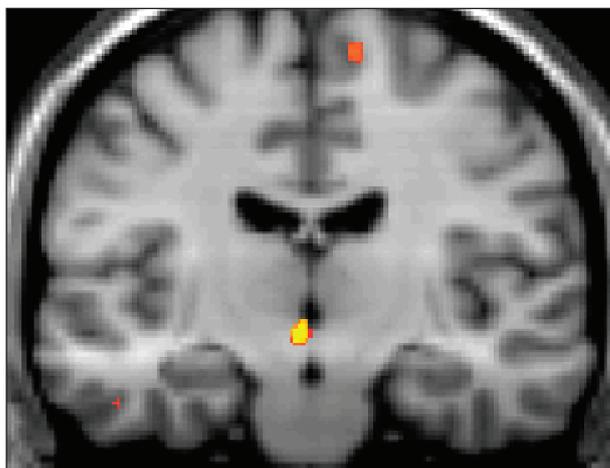


Figure 2. Hypothalamic activation during an acute attack

<i>Good efficacy</i>	<ul style="list-style-type: none"> oxygen 100 per cent at 7-12 litres per min for 15-30 minutes sumatriptan subcutaneous injection 6mg (maximum twice daily for the duration of the cluster bout)
<i>Moderate efficacy</i>	<ul style="list-style-type: none"> sumatriptan nasal spray 20mg (maximum 3 times daily for the duration of the cluster bout) octreotide subcutaneous injection 100µg zolmitriptan 5 or 10mg (for episodic cluster headache only)
<i>Poor efficacy or unproven</i>	<ul style="list-style-type: none"> ergotamine tablets or suppository intranasal lidocaine

Table 3. Acute management of cluster headache

However, in this era of a cost-conscious NHS, some practitioners are reluctant to prescribe this relatively expensive drug. The authors feel that, given the devastating morbidity associated with this excruciating pain syndrome, it is unethical to withhold treatment for cost reasons.

Though nasal sumatriptan 20mg is often used, it is considerably less efficacious than the subcutaneous formulation.¹⁵

There is no controlled evidence to support the use of oral sumatriptan in CH. Sumatriptan 100mg three times daily taken prior to an anticipated onset of an attack or at regular times does not prevent the attack and it should therefore not be used for CH prophylaxis.¹⁶

Zolmitriptan provides meaningful pain relief after oral administration of 5mg in the majority of patients with ECH, but not in CCH. However, its efficacy is modest and does not approach the efficacy or speed of subcutaneous sumatriptan or oxygen.¹⁷

Oxygen

Inhalation of 100 per cent oxygen, at 7-12 litres per minute, is effective in rapidly relieving pain in the majority of sufferers.¹⁸ It should be inhaled continuously

for 15-20 minutes via a non-rebreathing facial mask. Patients need to be informed that they should cover any apertures on the facemask.

A major problem in the UK is that the high flow rate oxygen regulator is not available on the NHS, and low flow oxygen is generally unhelpful. As a result, this treatment is only an option if the patient can afford to buy the high flow rate regulator. The regulator and facemask can be purchased from BOC Medical Gases (numerous branches throughout the UK). The BOC specifications are Multiflow Regulator Code 888842 and Face mask (variable) (005) Code 888845.

Octreotide

Subcutaneous octreotide 100µg has recently been demonstrated to be moderately effective in the treatment of acute CH attacks.¹⁹ In clinical practice, octreotide may be useful in patients who are unresponsive to – or intolerant of – triptans and oxygen.

Intranasal lidocaine

Lidocaine solution 20-60mg, given as nasal drops (4-6 per cent lidocaine solution) or a spray deep in the nostril on the painful side,

results in mild to moderate relief in most patients, though only a few obtain complete pain relief.²⁰ Therefore, intranasal lidocaine serves as a useful adjunct to other abortive treatments but is rarely adequate on its own.

Other drugs

Oral or rectal ergotamine is generally too slow in onset to provide meaningful relief in a timely manner. Opiates, NSAIDs and combination analgesics have no role in the acute management of CH.

Preventive treatments

The aim of preventive therapy is to generate a rapid suppression of attacks and to maintain that remission with minimal side-effects until the cluster bout is over, or for a longer period in patients with CCH.

Preventive treatments can be divided into short-term preventives, suitable for rapidly controlling the attack frequency but not for prolonged use, and long-term therapies that are required for prolonged medical management of cluster headache (see Table 4).

Short-term prevention

Patients with either short bouts, perhaps in weeks, or in whom one

wishes to quickly control the attack frequency can benefit from short-term prevention. These medicines are distinguished by the fact that they cannot be used in the long term and thus may require replacement by long-term agents in many patients.

Corticosteroids Corticosteroids are highly effective and the most rapid acting of the preventive agents.²¹ However, caution has to be exercised in their use because of the potential for serious side-effects. Treatment should be limited to a short, intensive course of two to three weeks in tapering doses.

The authors start patients on oral prednisolone 1mg per kg, to a maximum of 60mg once daily for five days, and thereafter decrease the dose by 10mg every three days. Unfortunately, relapse almost invariably occurs as the dose is tapered, so corticosteroids are used as an initial therapy in conjunction with preventives until the latter are effective.

Methysergide Methysergide (Deseril) is a potent prophylactic agent for the treatment of CH.²² It is an ideal choice in patients with short cluster bouts that last less than four to five months. Doses up to 12mg daily can be used if tolerated.

Patients are started on 1mg once daily and the daily dose is then increased by 1mg every three days (in a three times daily regimen) until the daily dose is 5mg. Thereafter, the dose is increased by 1mg every five days.

Prolonged treatment has been associated with fibrotic reactions (retroperitoneal, pulmonary, pleural and cardiac), though these are rare.²³ Though occasionally used in CCH, a drug holiday after every six months of treatment is necessary and neurological supervision entirely appropriate.

Long-term prevention

Some patients with long bouts of either ECH or CCH will require preventive treatment over many months, possibly even years. Verapamil and lithium are particularly useful in this setting.

Verapamil Verapamil is the preventive drug of choice in both ECH and CCH.²⁴⁻²⁶ Clinical experience has demonstrated that higher doses than those used in cardiological indications are needed, and dosages commonly employed range from 240 to 960mg daily in divided doses.

Verapamil can cause heart block by slowing conduction in the atrioventricular node. Observing for PR interval prolongation on ECG can monitor the potential development of heart block.

After performing a baseline ECG, patients are usually started on 80mg three times daily and thereafter the total daily dose is increased in 80mg increments every 10-14 days. An ECG is performed prior to each increment.

The dose is increased until the cluster attacks are suppressed, side-effects intervene or the maximum dose of 960mg daily is achieved.

Lithium Lithium is an effective agent for CH prophylaxis, though

Short-term prevention (for episodic cluster headache)	Long-term prevention (for prolonged bouts of episodic cluster headache or chronic cluster headache)
prednisolone/prednisone (transitional only) methysergide verapamil daily (nocturnal) ergotamine* topiramate† valproate (valproic acid)‡ pizotifen‡	verapamil lithium methysergide topiramate† gabapentin† valproate‡ pizotifen‡
* patients with predictable nocturnal headaches only † unproven but promising ‡ limited data or negative data	

Table 4. Prophylaxis of cluster headache

the response is less robust in ECH than CCH.^{25, 27}

Renal and thyroid function tests are performed prior to initiation of therapy. Patients are then started on 300mg twice daily and the dose titrated using the protocol outlined in the *BNF*, aiming for a serum lithium level in the upper part of the therapeutic range. Most patients will benefit from dosages between 600 and 1200mg daily.

The concomitant use of NSAIDs, diuretics and carbamazepine (Tegretol) is contraindicated.

Other drugs Though topiramate, sodium valproate, pizotifen (Sanomigran) and gabapentin are often used, they are of as yet unproven efficacy.

Surgery

This is a last-resort measure in treatment-resistant patients and should only be considered when the pharmacological options have been exploited to the fullest. There is an emerging distinction between destructive procedures, which have historically been the only option, and neuromodulatory procedures.

Destructive procedures

A number of destructive procedures that interrupt either the trigeminal sensory or autonomic (parasympathetic) pathways can be performed, though few are associated with long-lasting results while the side-effects can be devastating.

Neuromodulatory procedures

Based upon the finding of ipsilateral inferior posterior hypothalamic activation in CH6, several intractable CCH patients have been successfully treated by electrode implantation and stimulation of this region.²⁸

The procedures were generally well tolerated with no significant adverse events, except for one postoperative death secondary to intracerebral haemorrhage. This underlines the importance of appreciating that deep brain stimulation procedures are associated with a small risk of mortality.

There is a recent report of successful treatment of two patients with intractable CCH with continuous cutaneous neurostimulation of the occipital nerve.²⁹ This procedure is reversible and associated with relatively minor adverse events and no mortality.

With the emergence of neuromodulatory techniques, the authors feel that destructive approaches should not be pursued. The preferred procedure is sub-occipital nerve stimulation until it is clear what its place is when compared to posterior hypothalamic (deep brain) stimulation.

Role of GP and neurologist

All patients suspected of having cluster headaches should be referred to a neurologist to confirm the diagnosis and arrange any investigations that may be necessary. Once the management plan has been formulated, shared care is an excellent route by which it can be implemented.

Patient support group

Organisation for the Understanding of Cluster Headaches (OUCH-UK). Norham House, Mountenoy Road, Rotherham. S60 2AJ. Website: www.ouchuk.org.

References

1. Sjaastad O, Bakkeig LS. Cluster headache prevalence. Vaga study of headache epidemiology. *Cephalalgia* 2003;23:528-33.
2. Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study

- with diagnostic implications. *Neurology* 2002;58:354-61.
3. Headache Classification Committee of The International Headache Society. The International Classification of Headache Disorders (second edition). *Cephalalgia* 2004; 24:1-195.
 4. Silberstein SD, Niknam R, Rozen TD, *et al.* Cluster headache with aura. *Neurology* 2000;54:219-21.
 5. Goadsby PJ, Lipton RB. A review of paroxysmal hemicranias, SUNCT syndrome and other short-lasting headaches with autonomic feature, including new cases. *Brain* 1997;120: 193-209.
 6. May A, Bahra A, Buchel C, *et al.* Hypothalamic activation in cluster headache attacks. *Lancet* 1998;352: 275-8.
 7. May A, Ashburner J, Buchel C, *et al.* Correlation between structural and functional changes in brain in an idiopathic headache syndrome [see comments]. *Nature Medicine* 1999;5:836-8.
 8. Manzoni GC, Micieli G, Granella F, *et al.* Cluster headache – course over ten years in 189 patients. *Cephalalgia* 1991; 11:169-74.
 9. Igarashi H, Sakai F. Natural history of cluster headache. *Cephalalgia* 1996; 16:390-391.
 10. Matharu MS, Boes CJ, Goadsby PJ. Management of trigeminal autonomic cephalgias and hemicrania continua. *Drugs* 2003;63:1637-77.
 11. The Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. *New England Journal of Medicine* 1991; 325:322-6.
 12. Ekbom K, Waldenlind E, Cole J, *et al.* Sumatriptan in chronic cluster headache: results of continuous treatment for eleven months. *Cephalalgia* 1992;12:254-6.
 13. Ekbom K, Krabbe A, Micieli G, *et al.* Cluster headache attacks treated for up to three months with subcutaneous sumatriptan (6mg). Sumatriptan Cluster Headache Long-term Study Group [published erratum appears in *Cephalalgia* 1995 Oct;15(5):446]. *Cephalalgia* 1995;15:230-6.
 14. Gobel H, Lindner V, Heinze A, *et al.* Acute therapy for cluster headache with sumatriptan: findings of a one-year long-term study. *Neurology* 1998; 51:908-11.
 15. Van Vliet JA, Bahra A, Martin V, *et al.* Intranasal sumatriptan in cluster headache: Randomized placebo-controlled double-blind study. *Neurology* 2003;60:630-3.
 16. Monstad I, Krabbe A, Micieli G, *et al.* Preemptive oral treatment with sumatriptan during a cluster period. *Headache* 1995;35:607-13.
 17. Bahra A, Gawel MJ, Hardebo JE, *et al.* Oral zolmitriptan is effective in the acute treatment of cluster headache. *Neurology* 2000;54:1832-9.
 18. Fogan L. Treatment of cluster headache. A double-blind comparison of oxygen v air inhalation. *Archives of Neurology* 1985;42:362-3.
 19. Matharu MS, Levy MJ, Meeran K, *et al.* Subcutaneous octreotide in cluster headache: Randomized placebo-controlled double-blind crossover study. *Ann Neurol* 2004; 56:488-94.
 20. Robbins L. Intranasal lidocaine for cluster headache. *Headache* 1995;35: 83-4.
 21. Couch JR, Jr, Ziegler DK. Prednisone therapy for cluster headache. *Headache* 1978;18:219-21.
 22. Curran DA, Hinterberger H, Lance JW. Methysergide. *Research and Clinical Studies in Headache* 1967;1:74-122.
 23. Graham JR, Suby HI, LeCompte PR, *et al.* Fibrotic disorders associated with methysergide therapy for headache. *N Eng J Med* 1966;274: 360-8.
 24. Gabai IJ, Spierings EL. Prophylactic treatment of cluster headache with verapamil. *Headache* 1989;29:167-8.
 25. Bussone G, Leone M, Peccarisi C, *et al.* Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990; 30:411-7.
 26. Leone M, D'Amico D, Frediani F, *et al.* Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology* 2000; 54:1382-5.
 27. Ekbom K. Lithium for cluster headache: review of the literature and preliminary results of long-term treatment. *Headache* 1981;21:132-9.
 28. Franzini A, Ferroli P, Leone M, *et al.* Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: first reported series. *Neurosurgery* 2003; 52:1095-9; discussion 1099-101.
 29. Dodick D, Trentman T, Zimmerman R, *et al.* Occipital nerve stimulation for intractable chronic primary headache disorders. *Cephalalgia* 2003;23:701.

Dr Matharu is a specialist registrar in neurology at the Royal London Hospital, and Peter Goadsby is professor of clinical neurology at the Institute of Neurology and an honorary consultant neurologist at the National Hospital for Neurology and Neurosurgery, London