

A hand holding a syringe with the word 'CLUS' overlaid in large white letters. The syringe is held in a way that the needle points upwards. The background is a soft, out-of-focus light green. The word 'CLUS' is in a bold, sans-serif font, with the 'S' partially cut off on the right edge of the image.

CLUS

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HEADACHE

update on a common neurological problem

Cluster headache (CH) is a strictly unilateral headache that occurs in association with cranial autonomic features and, in most patients, has a striking circannual and circadian periodicity. It is an excruciating syndrome and is probably one of the most painful conditions known to mankind, with female patients describing each attack as being worse than childbirth. The understanding of cluster headache, in pathophysiological terms, and the management strategies, have altered dramatically in recent years. Interested readers are referred to monographs for greater details (Kudrow 1980; Sjaastad 1992; Olesen *et al.* 1999).

PATHOPHYSIOLOGY

Any pathophysiological construct for cluster headache 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 trigeminocervical complex from whence nociceptive pathways project to higher centres. This implicates an integral role for the ipsilateral trigeminal nociceptive pathways in cluster headache. Secondly, the ipsilateral autonomic features suggest cranial parasympathetic activation (lacrimation and rhinorrhoea) and sympathetic hypofunc-

Fig. 1. Trigemino-autonomic reflex. Stimulation of the trigeminovascular pathways results in the activation of the cranial parasympathetic outflow, thus providing the anatomical basis for the expression of trigeminal pain and ipsilateral autonomic symptoms in cluster headache.

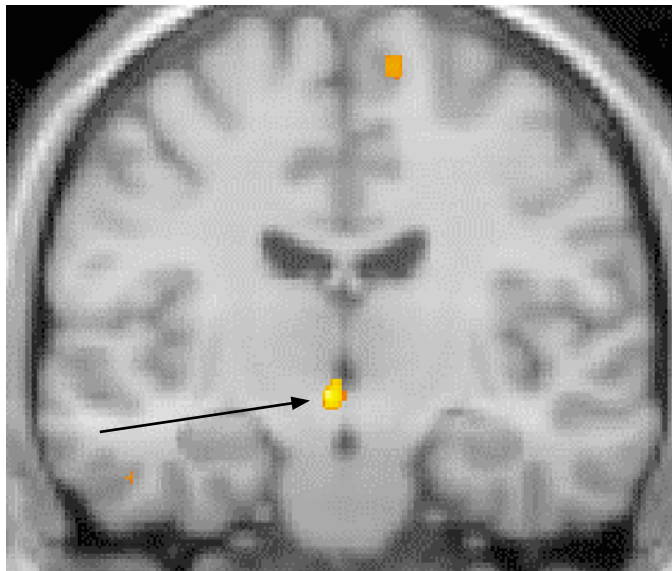
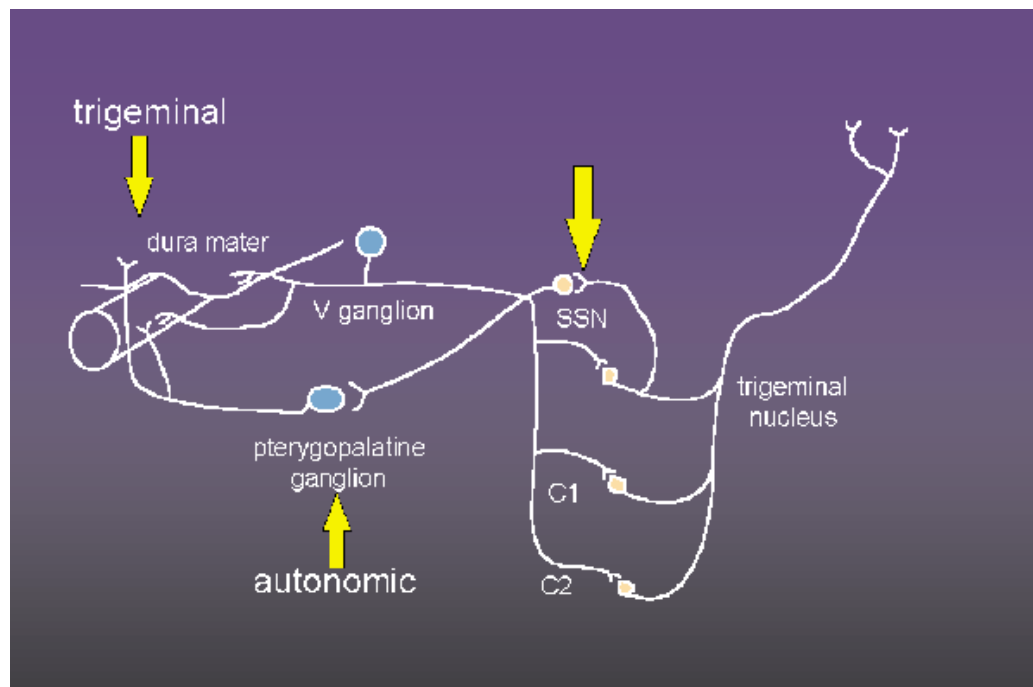


Fig. 2. Ipsilateral posterior hypothalamic activation in cluster headache demonstrated with functional Positron Emission Tomography.

tion (ptosis and miosis). These cranial autonomic symptoms are, partly, accounted for by the trigemino-autonomic reflex (Fig. 1). Finally, functional (May *et al.* 1998; May *et al.* 2000) and structural (May *et al.* 1999) 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 (Fig. 2). Hence, cluster headache is probably due to an abnormality in the hypothalamus

with subsequent trigeminovascular and cranial autonomic activation.

EPIDEMIOLOGY

The prevalence of CH is estimated to be one per 1000 population (D'Alessandro *et al.* 1986), approximately the same as that of multiple sclerosis in the UK. The male : female ratio is about 5 : 1 (Manzoni 1998; Bahra *et al.* 2001). It can begin at any age, although the most common age of onset is the third or fourth decade of life.

CLINICAL FEATURES

The terminology used to describe the features of CH can be confusing. 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 features are dealt with under two major headings: **the cluster attack** and **the cluster bout**.

The cluster attack

The attacks are strictly unilateral, though the

headache may alternate sides. The pain is excruciatingly severe. It is located mainly around the orbital and temporal regions though any part of the head can be affected. The headache usually lasts 45–90 min but can range from 15 min to 3 h. It has an abrupt onset and cessation.

The signature feature of CH is the association with autonomic symptoms, and it is extremely unusual for these not to be reported. The International Headache Society (IHS) classification diagnostic criteria (Headache Classification Committee of The International Headache Society 1988) 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, nasal blockage and forehead or facial sweating. The autonomic features are transient, lasting only for the duration of the attack, with the exception of a 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 a significant proportion of cluster patients (Silberstein *et al.* 2000; Bahra *et al.* 2000). The premonitory symptoms of tiredness and yawning, as well as the associated features of nausea, vomiting, photophobia, phonophobia and aura symptoms have all been described in relationship to cluster attacks. However, in contrast to migraine, CH sufferers are usually restless and irritable, preferring to move about; looking for a movement or posture that may relieve their pain.

The cluster attack frequency varies between one every alternate day to three daily, although some patients 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, or night.

Alcohol, nitroglycerine, exercise, and elevated environmental temperature are recognized precipitants of acute cluster attacks. Alcohol induces acute attacks, usually 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 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.

The cluster bout

CH is classified according to the duration of the bout. About 80–90% of patients have episodic cluster headache (ECH), which is diagnosed when they experience recurrent bouts, each with duration of more than a week and separated by remissions lasting more than 2 weeks. The remaining 10–20% of patients have chronic cluster headache (CCH), in which either no remission occurs within one year or the remissions last less than 14 days. The latter definition will probably be lengthened to one month when the current revision process for the IHS Classification is complete (Olesen 2000).

Most patients with ECH have one or two annual cluster periods, 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 individuals, these periods remain relatively consistent within the same individual.

NATURAL HISTORY

Although there is a paucity of 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 (Manzoni *et al.* 1991). An encouraging piece of information for CH sufferers is that a substantial proportion of them can expect to develop longer remission periods as they age (Igarashi & Sakai 1996).

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.

The pain of CH builds up very rapidly to such an excruciating intensity that most oral agents are too slowly absorbed to relieve the pain within a reasonable period of time.

Unilaterality 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 and cessation;
- circadian periodicity;
- precipitation within an hour, rather than several hours, by alcohol;
- clustering of attacks with intervening remissions in ECH.

Before a diagnosis of CH can be made, secondary headache disorders that mimic CH need to be excluded. Symptomatic CH has

been described with infectious, vascular and neoplastic intracranial lesions. Any atypical features in the history or abnormalities on neurological examination (with the exception of a partial Horner's syndrome) warrant further investigations to search for organic causes.

Paroxysmal hemicrania is a syndrome that is similar to CH except that it prevails in females and attacks are briefer and more frequent. Paroxysmal hemicrania is absolutely responsive to adequate doses of indomethacin thus underlining the importance of not misdiagnosing it as CH (Antonaci & Sjaastad 1989).

TREATMENT

The management of CH includes offering advice on general measures to patients, treatment with abortive and preventative agents, and rarely surgery.

General measures and patient education

Patients should be advised to abstain from taking alcohol during the cluster bout. Otherwise, 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. Patients should be advised to avoid afternoon naps as sleeping can precipitate attacks in some patients.

Abortive agents

The pain of CH builds up very rapidly to such an excruciating intensity that most oral agents are too slowly absorbed to relieve the pain within a reasonable period of time. The most efficacious abortive agents are those that involve parenteral or pulmonary administration.

Triptans

Subcutaneous sumatriptan 6 mg is the drug of choice in abortive treatment of a cluster attack. It has a rapid effect and high response rate (Ekbom & The Sumatriptan Cluster Headache Study Group 1991). 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 (Ekbom *et al.* 1992; Ekbom *et al.* 1995; Gobel *et al.* 1998). However, in this era of a cost-conscious UK National

Health Service (NHS), some practitioners are reluctant to prescribe this relatively expensive drug. We feel that, given the devastating morbidity associated with this excruciating pain syndrome, it is unethical to withhold treatment for cost reasons. Nasal sumatriptan 20 mg is a useful option that is superior to placebo in the treatment of acute cluster headache (van Vliet *et al.* 2001). There is no controlled evidence to support the use of oral sumatriptan in CH. Sumatriptan 100 mg three times daily taken prior to an anticipated onset of an attack or at regular times does not prevent the attack and therefore it should not be used for CH prophylaxis (Monstad *et al.* 1995).

Zolmitriptan provides meaningful pain relief after oral administration of 5 mg in the majority of patients with episodic CH, but not in chronic CH. However, its efficacy is modest and does not approach the efficacy or speed of subcutaneous sumatriptan or oxygen (Bahra *et al.* 2000).

Oxygen

Inhalation of 100% oxygen, at 7–12 L min⁻¹, is rapidly effective in relieving pain in the majority of sufferers (Fogan 1985). It should be inhaled continuously for 15–20 min via a nonbreathing facial mask. Patients need to be informed that they should cover any apertures on the facemask. A major problem in UK is that the high flow-rate oxygen regulator is not available on the NHS, and low flow oxygen is generally unhelpful. Thus, this treatment is an option only if the patient can afford to buy the high-flow rate regulator. The regulator and the 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*.

Topical lignocaine

Lignocaine solution 20–60 mg, given as nasal drops (4–6% 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 patients obtain complete pain relief (Robbins 1995). Therefore, intranasal lignocaine serves as a useful adjunct to other abortive treatments but is rarely adequate on its own.

SHORT-TERM	LONG-TERM
PREDNISOLONE (TRANSITIONAL ONLY)	VERAPAMIL
METHYSERGIDE	LITHIUM
ERGOTAMINE DAILY (NOCTURNAL)	

Ergotamine

Oral or rectal ergotamine is generally too slow in onset to provide meaningful relief in a timely manner.

Analgesics

Opiates, nonsteroidal anti-inflammatory drugs and combination analgesics have no role in the acute management of CH.

Preventative Treatments [Table 1]

The aim of preventative therapy is to produce a rapid suppression of attacks and to maintain that remission with minimal adverse effects until the cluster bout is over, or for a longer period in patients with chronic cluster headache. Preventative treatments can be divided into short-term preventatives, 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. This is a more practical distinction than treatment for ECH and CCH, as long bouts of ECH are effectively managed in the same way as CCH.

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.

Steroids: Corticosteroids are highly efficacious and the most rapid-acting of the preventative agents (Kudrow 1980; Couch & Ziegler 1978). However, caution has to be exercised in their use because of the potential for serious adverse effects. Treatment should be limited to a short intensive course of 2–3 weeks in tapering doses. We start patients on oral prednisolone 1 mg/kg, to a maximum of 60 mg, od for 5 days and thereafter de-

Table 1 Preventative Management of Cluster headache

Ergotamine
is an
effective
preventative
agent that is
particularly
useful in
short-term
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ECH when
attacks
occur
predictably
during the
day or at
night.

crease the dose by 10 mg every 3 days. Unfortunately, relapse almost invariably occurs as the dose is tapered. For this reason, steroids are used as an initial therapy in conjunction with preventatives, until the latter are effective.

Methysergide: Methysergide is a potent prophylactic agent for the treatment of CH (Kudrow 1987; Curran *et al.* 1967). It is an ideal choice in patients with short cluster bouts, which last less than 4–5 months. Doses up to 12 mg daily can be used if tolerated. Patients are started on 1 mg od and the daily dose then increased by 1 mg every 3 days (in a tds regime) until the daily dose is 5 mg; thereafter, the dose is incremented by 1 mg every 5 days. Prolonged treatment has been associated with fibrotic reactions (retroperitoneal, pulmonary, pleural and cardiac) though these are rare (Graham *et al.* 1966). Methysergide may be used in CCH, but a drug holiday for one month is necessary after every 6 months of treatment.

Ergotamine: Ergotamine is an effective preventative agent that is particularly useful in short-term management of ECH when attacks occur predictably during the day or at night (Symonds 1956). Ergotamine 1–2 mg orally or rectally can be taken at bedtime or about an hour before the attack is due. It is rarely suitable for use in CCH and complicates management of ECH as concomitant use of sumatriptan is contraindicated.

Long-term prevention

Some patients with either long bouts of episodic cluster headache or chronic cluster headache will require preventative treatment over many months, or even years. Verapamil and lithium are particularly useful in this setting.

Verapamil: Verapamil is the preventative drug of choice in both episodic and chronic CH (Gabai & Spierings 1989; Bussone *et al.* 1990; Leone *et al.* 2000). Clinical experience has clearly demonstrated that higher doses than those used in cardiological indications are needed. We employ dosages in a range from 240 to 960 mg 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 potential development of heart block. After performing a baseline ECG, patients are usually started on 80 mg bd and thereafter the total daily dose is increased in increments of 80 mg every 10–14 days. An ECG is performed prior to each increment. The dose is increased until the cluster attacks are suppressed, adverse effects intervene, or the maximum dose of 960 mg daily is achieved.

Lithium: Lithium is an effective agent for CH prophylaxis, though the response is less robust in ECH than CCH (Kudrow 1977; Ekbom 1981). Renal and thyroid function tests are performed prior to initiation of therapy. Patients are then started on 300 mg bd and the dose titrated using the protocol outlined in the British National Formulary, aiming for a serum lithium level in the upper part of the therapeutic range. Most patients will benefit from dosages between 600 and 1200 mg daily. The concomitant use of NSAIDs, diuretics and carbamazepine is contra-indicated.

Other Drugs: Though sodium valproate, pizotifen, topiramate, gabapentin and melatonin are often used, they are of as yet unproven efficacy. We feel that double-blind controlled trials should be conducted with the most promising of these substances, topiramate (Wheeler & Carrazana 1999) and gabapentin (Ahmed 2000) and are aware that a shortly to be published controlled trial of valproate will demonstrate that it is of no benefit in cluster headache.

Surgery

This is a last-resort measure in treatment-resistant patients and should only be considered when the pharmacological options have been fully exploited. Patients must be carefully selected. Only patients whose headaches are exclusively unilateral should be considered for surgery, as patients whose attacks have alternated sides are at risk of a contralateral recurrence after surgery. A number of procedures that interrupt either the trigeminal sensory or autonomic (parasympathetic) pathways can be performed though few are associated with long-lasting results while the adverse effects can be devastating. The procedures that have been reported to show some success include

trigeminal sensory rhizotomy via a posterior fossa approach (Kirkpatrick *et al.* 1993), radiofrequency trigeminal gangliorhizolysis (Mathew & Hurt 1988) and microvascular decompression of the trigeminal nerve with or without microvascular decompression of the nervus intermedius (Lovely *et al.* 1998). Complete trigeminal analgesia may be required for the best results. Complications include diplopia, hyperacusis, jaw deviation, corneal anaesthesia and anaesthesia dolorosa. Aggressive long-term ophthalmic follow-up is essential.

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