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Managing patients with cluster headache in primary care

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What are the distinctive clinical features?

How should diagnosis be confirmed?

What are the treatment strategies?



CLUSTER HEADACHE IS A STRICTLY UNILATERAL HEADACHE THAT OCCURS IN ASSOCIATION WITH

cranial autonomic features. It is an excruciatingly painful syndrome, female patients will describe the pain as worse than childbirth. In most patients there is a striking circannual and circadian periodicity. The disorder has a highly stereotypic clinical phenotype and responds to specific therapies, highlighting the importance of distinguishing it from other primary headache conditions.

EPIDEMIOLOGY

The prevalence of cluster headache is estimated to be 0.2%.¹ The male:female

ratio is 3.5–7:1.² Although it can begin at any age, the most common age of onset is in the third or fourth decade of life. There is a lack of literature on the long-term prognosis, but the available evidence suggests that it is a lifelong disorder. However, one study suggests that a substantial proportion of patients can expect to develop longer remission periods as they grow older.³

CLINICAL FEATURES

It is critical that both the clinician and patient understand the terminology used in cluster headache and employ it appropriately. A cluster attack is an individual episode of pain whereas a cluster bout or period refers to the duration over which recurrent attacks

are occurring. A remission is the pain-free period between cluster bouts.

The diagnosis of cluster headache is purely clinical and it is therefore crucial to take a good history looking for its distinctive features, see table 1, p16. Cluster attacks are strictly unilateral, although they may alternate sides. Pain is excruciating and located mainly around the orbital and temporal regions though any part of the head may be affected. Attacks have an abrupt onset and offset and usually last around 45–90 minutes but can range from 15 minutes to three hours. Attack frequency generally varies from one every alternate day to three a day, although the International Headache Society criteria state there »

Table 1
Clinical features and differential diagnosis of cluster headache

	Cluster headache	Migraine	Paroxysmal hemicrania
Pain location	Unilateral	Bilateral or unilateral	Unilateral
Pain quality	Variable (sharp, burning, pressing, boring)	Throbbing or pulsating	Variable (sharp, burning, pressing, tight, throbbing)
Pain intensity	Severe or excruciating	Moderate to severe	Severe
Duration of headache	15–180 min	4–72 hours	2–30 min
Frequency of headache	One every other day to eight per day	Episodic: < 15 days per month	> 5 attacks daily for > 50% of the time
	Episodic: remission periods > 1 month	Chronic: > 15 days per month for > 3 months	Episodic: remission periods > 1 month
	Chronic: remission periods < 1 month over the course of a year		Chronic: remission periods < 1 month over the course of a year
Behaviour during attack	Restless or agitated	Patient wants to remain still	Restless or agitated
Cranial autonomic features	● Red and/or watery eye ● Nasal congestion and/or runny nose ● Swollen eyelid ● Forehead and facial sweating ● Constricted pupil ● Drooping eyelid ● Sensation of fullness in ear	May be present	● Red and/or watery eye ● Nasal congestion and/or runny nose ● Swollen eyelid ● Forehead and facial sweating ● Constricted pupil ● Drooping eyelid ● Sensation of fullness in ear
Migrainous symptoms	● Nausea common ● Ipsilateral photophobia and phonophobia ● Aura (often visual) in 14% of cases	● Photophobia and phonophobia (bilateral) ● Osmophobia ● Nausea and vomiting ● Aura - symptoms can occur without headache, are fully reversible, develop over 5 min or more and last up to an hour ● Typical aura symptoms: - Visual – flickering lights, spots, lines and/or partial loss of vision - Sensory – pins and needles, often spreading over face or up arm - Speech – slurred, muddled, dysphasic	● Ipsilateral photophobia and phonophobia ● May have nausea
Triggers	● Alcohol (within an hour of ingestion) ● Warm environment ● Sleep ● Strong smells ● No cutaneous trigger	● Sleep disturbance ● Hunger or dehydration ● Menstrual period ● Alcohol (several hours after ingestion) ● Bright lights ● Strong smells ● Physical exertion ● Stress ● Dietary factors e.g. citrus fruit	● Alcohol ● Physical exertion ● Stress ● Strong smells ● No cutaneous trigger
First-line preventive treatments	Verapamil	Beta-blockers Antidepressants Topiramate	Indometacin – attacks will resolve completely on therapeutic doses
First-line acute treatments	Oxygen (100% ≥ 12 L/min) Subcutaneous sumatriptan	High-dose NSAID + triptan + antiemetic	Nil

may be up to eight attacks a day.⁴

The key feature of cluster headache is the presence of at least one cranial autonomic symptom during an attack. These symptoms occur on the same side as the pain and include: lacrimation, conjunctival injection, miosis, rhinorrhoea or stuffiness of the nose, facial sweating or redness, ptosis and a prominent sense of agitation or restlessness.

Patients can often predict the timing of their attacks, as they occur at the same time of night or day, a feature called circadian periodicity.

Alcohol, physical exertion, warm environments, sleep and the smell of volatile substances (e.g. perfume, petrol etc) can all trigger acute cluster attacks. It is worth noting that in cluster headache sufferers, alcohol will induce an attack within an hour of ingestion, contrasting with migraine sufferers where attacks usually start many hours later.

Migrainous features can be seen in a number of cluster headache patients with typical aura (14%), nausea (50%), photophobia (56%) and phonophobia (43%) commonly reported.²

However, with a thorough clinical history searching for the key features of cluster headache the diagnosis should be clear in most patients (see the section on differential diagnosis, below and table 1, opposite).

The majority (80-90%) of patients will have episodic cluster headache with recurrent bouts separated by remission periods of more than a month. The remaining 10-20% have chronic cluster headache and have no significant remission periods over the course of a year.⁴ Most patients with episodic cluster headache will have one or two annual cluster bouts, lasting between one and three months. Often, the bouts will occur predictably in the same months each year (circannual periodicity). Although the duration of bouts and remissions varies widely between individuals, these periods tend to remain constant within an individual.

PATHOPHYSIOLOGY

The pathogenesis is complex and not completely understood. The three major features of the syndrome are:

- Trigeminal distribution of pain
- Ipsilateral cranial autonomic features
- Circadian/circannual pattern of attacks

There is a well described physiological reflex arc, the trigemino-parasympathetic reflex, that is thought to explain the

pain location and autonomic features of cluster headache.⁵ Nociceptive information from pain-sensitive structures in the face, the dura and cerebral blood vessels is carried via the trigeminal nerve to a region of the brainstem called the trigeminocervical complex (TCC). Information is relayed from here to the hypothalamus, thalamus and cortex.

Signals in the TCC activate the cranial parasympathetic system and cause the autonomic features of a cluster attack. Neurotransmitters released at the parasympathetic nerve endings cause irritation and activation of the trigeminal sensory nerves which results in a feedback loop further potentiating the reflex arc.

‘Unilateral pain and the presence of both autonomic and migrainous symptoms are common to migraine and cluster headache’

The periodicity of attacks and the prominent agitation with attacks led to the belief that the hypothalamus was involved in the pathogenesis of cluster headache. Imaging studies have pointed to the specific involvement of the posterior hypothalamic region,⁶ a structure known to modulate nociceptive and autonomic pathways, and the site of the body's circadian pacemaker. As mentioned above, there are also direct hypothalamic-trigeminal connections. Hence, cluster headache is regarded as an abnormality in the posterior hypothalamus with subsequent trigeminovascular and cranial autonomic activation.

DIFFERENTIAL DIAGNOSIS

Because of the distinctive clinical features of cluster headache, the headache history will usually point to the diagnosis. However, the differential diagnosis may be more difficult if atypical features or multiple headache types are present. The main differential

diagnoses to consider are secondary causes of cluster headache (e.g. vascular or neoplastic lesions), paroxysmal hemicrania and most commonly migraine. The main clinical features of these conditions are outlined in table 1, opposite.

The unilateral pain and the presence of both autonomic and migrainous symptoms are common to migraine and cluster headache. Differentiating between them can be difficult in a small number of cases.

The clinical features that are most useful in distinguishing cluster headache from migraine include:

- Relatively short duration of headache attack
- Rapid onset and offset of attacks
- Clear circadian periodicity (headache diaries are often useful here)
- Rapid precipitation with alcohol within an hour compared with several hours in migraine
- Agitation during an attack
- Clustering of attacks with intervening remission periods.

Paroxysmal hemicrania is a rare syndrome similar to cluster headache but with briefer and more frequent attacks. It shows an absolute response to adequate doses of indometacin. The excellent treatment response emphasises the importance of considering the condition in all patients with frequent unilateral headache attacks and referring them to specialists for consideration of a trial of indometacin.

A headache diary documenting daily attack frequency, severity and duration will be crucial in differentiating between many headache types and patients should be encouraged to keep these where possible.

INVESTIGATIONS

The diagnosis of cluster headache is purely clinical and cannot be made on imaging.

The NICE guideline on headache⁷ recommends that the need for neuroimaging in patients with a first bout of cluster headache is discussed with a specialist.

The reason for caution when considering neuroimaging is that incidental pathology is found in 10% of patients with headache sent for CT scans by GPs.⁸ This can lead to unnecessary anxiety and investigations for patients. Furthermore, there is no evidence that using imaging as a management tool reduces patient anxiety. Therefore, we advise that »

Table 2

Abortive management of cluster headache

Good efficacy	● Oxygen 100% $\geq$ 12 L/min for 15–30 min¹³ ● Sumatriptan subcutaneous injection 6 mg (maximum twice daily for the duration of the cluster bout)²¹
Moderate efficacy	● Sumatriptan nasal spray 20 mg (maximum thrice daily for the duration of the cluster bout)²³ ● Zolmitriptan 5 or 10 mg (for episodic cluster headache only)^{21,22}

imaging is only carried out with specialist advice and should not be repeated on a regular basis because the patient continues to have headaches. If imaging is considered necessary then an MRI scan of the brain is the most appropriate form.

TREATMENT

The GP is pivotal in making a prompt diagnosis, supplying general information and advice about the condition and starting appropriate abortive and preventive agents. Specialist advice should be sought at first presentation, for confirmation of diagnosis and development of a plan for managing current and future cluster bouts, and where first-line treatments fail. However, primary care has a key role in implementing plans and monitoring patients.

Patient education

Patients should be advised to abstain from alcohol during the cluster bout. Dietary factors seem to have little importance in cluster headache. 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.

Acute treatments

The aim of these treatments is to provide prompt relief from the individual cluster attacks. Standard painkillers are ineffective and there is no evidence to support the use of drugs such as opioids, NSAIDs, paracetamol or even oral triptans in these patients. The only evidence-based acute treatments are subcutaneous or nasal triptans and oxygen, see table 2, above.

Subcutaneous and nasal triptans

The pain of a cluster headache attack builds up so rapidly that oral triptans

Table 3

Bridging treatment for cluster headache

Oral corticosteroids	● 70–80% respond within 24–48 hours²³ ● Prednisolone 60 mg daily max (1 mg/kg/day) for 5 days, thereafter reducing dose by 10 mg every 3 days until stopped ● Maximum 3 courses in a year
Greater occipital nerve block	● Two thirds of patients pain free at 4 weeks¹⁷ ● Specialist centres only ● Can be carried out every 3 months if needed

have no place in the treatment as they are absorbed far too slowly to be of any use. Therefore, as the NICE guideline recommends, subcutaneous sumatriptan or nasal triptans (sumatriptan or zolmitriptan) should be offered to patients for the acute treatment of attacks.

Subcutaneous sumatriptan at a dose of 6 mg is the drug of choice, with most patients reporting mild or no pain within 15 minutes of administration.⁹ In contrast to migraine, subcutaneous sumatriptan can be taken at a frequency of twice a day on a long-term basis without the risk of tachyphylaxis or medication overuse headache.^{10–12}

Although nasal sumatriptan 20 mg and nasal zolmitriptan 5 mg can be used up to three times daily, their efficacy is much less than the subcutaneous triptan and they should only be used if there is a good reason not to use the injectable form e.g. severe needle phobia, bleeding tendency.

In the past, some doctors were reluctant to prescribe triptans, especially subcutaneous sumatriptan, because of the expense. This led to patients with excruciating pain being denied treatment.

NICE has taken important steps to deal with this by stating clearly that not only should triptans be offered to all cluster headache patients, but that adequate supplies are made available to the patient calculated according to their history of cluster bouts and the maximum daily dose of two injections or three nasal sprays, see box 1, opposite. For example, a patient who has a typical bout lasting four weeks with an average of three attacks a day should be supplied with at least 56 injections to take through the cluster bout period.

Triptans are vasoconstrictors and should be avoided in patients with known cardiovascular disorders or uncontrolled hypertension.

Oxygen

Inhalation of 100% oxygen at a rate of at least 12 L/min given through a non-rebreathing mask and reservoir bag is rapidly effective in relieving pain in most sufferers.^{13–15}

Patients should be instructed to inhale continuously for at least 15–20 minutes. It is important to ensure the right flow rate and mask are used. NICE guidance now states that all cluster headache sufferers should have a provision of home and ambulatory oxygen.

The GP or headache specialist should use a home oxygen order form (HOOFF) to ensure that the oxygen is made available as soon as possible at the onset of a cluster bout.

‘Inhalation of 100% oxygen at a rate of at least 12 L/min through a non-rebreathing mask and reservoir bag is rapidly effective in relieving pain in most sufferers’

Transitional therapies

Given that preventive medications can take a number of weeks to exert their full effect, patients with short bouts or patients in whom one wishes to control attack frequency quickly may benefit from a transitional or bridging treatment. These interventions are not suitable for long-term use and so patients often require concurrent treatment with traditional preventive agents. A short course of steroids is the most commonly used transitional

Table 4**Preventive treatment in cluster headache**

Good evidence	● Verapamil: starting dose of 120 mg two times a day, and increase dose in increments of 120 mg every two weeks (in three times daily regimen); maximum dose 960 mg daily (ECGs to be taken before every dose increase)
Moderate or poor evidence	● Lithium ● Topiramate ● Gabapentin ● Melatonin ● Sodium valproate ● Baclofen

Table 5**Surgical treatment for cluster headache****Occipital nerve stimulation**

- Subcutaneous electrodes placed over the occiput and continuous stimulation applied
- Two thirds of patients show good clinical response²⁴

Sphenopalatine ganglion stimulation

- Still in experimental stage
- Electrode placed within the pterygopalatine fossa ipsilateral to headache side
- Stimulation applied during acute attacks
- 78% of patients report $\geq 50\%$ reduction in pain severity (60% pain free) within 3 min stimulation²⁵
- Some suggestion that it may be useful as a preventive treatment

Deep brain stimulation

- Electrode placed in the posterior hypothalamic region of the brain on the side of the headache and continuous stimulation applied
- 60% of patients report $\geq 50\%$ reduction in headache attack frequency or severity²⁴

Box 1**Summary of NICE recommendations on cluster headache⁷****Diagnosis**

- Discuss the need for neuroimaging with a headache specialist

Acute treatment

- Offer oxygen and/or subcutaneous OR nasal triptan for acute treatment
- Oxygen must be given at 100% at a flow rate of at least 12/L min via a non-rebreathing mask
- Both ambulatory and home oxygen should be supplied
- Patients must be supplied with adequate amounts of triptans based on their history of cluster bouts
- Subcutaneous sumatriptan can be used a maximum of twice a day
- Nasal triptans can be used a maximum of three times a day
- Paracetamol, opiates and NSAIDs should not be used

Preventive treatment

- Verapamil should be considered as a prophylactic agent in cluster bouts (ensuring adequate ECG monitoring is undertaken)
- Specialist advice should be sought if the prescribing doctor is unfamiliar with verapamil in cluster headache or if the patient fails to respond to verapamil
- Pregnant patients must be referred to a specialist

agent in primary care but referral to specialists for greater occipital nerve (GON) block is another option where available, see table 3, opposite.

Corticosteroids

Corticosteroids are highly effective and act rapidly¹⁶ but caution should be taken in their use because of the potential side effects, and no more than three courses should be given in a year. Treatment should be limited to a short intensive course tapered over two to three weeks.

Our preference is to give oral prednisolone at a maximum of 60 mg daily (1 mg/kg daily) for five days and then taper the dose by 10 mg every three days until stopped.

Relapse is common as the dose is decreased and therefore they are often used to cover the time taken for a preventive drug to take effect.

Greater occipital nerve block

GON blocks, although not available in most primary care settings, may be obtained through specialist referral. They involve subcutaneous injections of a mixture of local anaesthetic and steroid into the area of the greater occipital nerves on the back of the scalp. They can be highly effective with up to two thirds of patients pain free at four weeks.¹⁷

Patients in whom steroids are contraindicated or who have previously failed to respond to steroids should be considered for referral at the start of a bout. GON blocks can also be used on a regular basis, every three to four months, but this should be considered a specialist treatment.

Preventive treatment

Patients with long cluster bouts or with cluster headache will require preventive treatment over a long period. The aim of such therapy is to induce remission or control attack frequency as rapidly as possible. In episodic forms, when patients are out of a bout and have been pain free for at least two weeks, the preventive agent should be slowly withdrawn but in the chronic form the medications are often needed indefinitely. The most common drug used in this setting is verapamil and the NICE guideline focuses on this drug.⁷ Under specialist advice, other drugs such as lithium, topiramate or melatonin may be used, see table 4, above left.

Verapamil: Verapamil is the first-line preventive treatment for both episodic and chronic cluster headache and »

key points

SELECTED BY

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Cluster headache is a strictly unilateral headache that occurs in association with cranial autonomic features. The male:female ratio is 3.5–7:1. Although it can begin at any age, the most common age of onset is in the third or fourth decade of life. The diagnosis is purely clinical and it is therefore crucial to take a good history looking for its distinctive features.

Although cluster attacks are unilateral, they may alternate sides. Pain is excruciating and located mainly around the orbital and temporal regions though any part of the head may be affected. Attacks have an abrupt onset and offset and usually last around 45–90 minutes but can range from 15 minutes to three hours. Attack frequency generally varies from one every other day to three a day, although the International Headache Society criteria state there may be up to eight attacks a day. The key feature of cluster headache is the presence of at least one cranial autonomic symptom during an attack.

Alcohol, physical exertion, warm environments, sleep and the smell of volatile substances can all trigger acute attacks. The majority (80–90%) of patients will have episodic cluster headache with recurrent bouts separated by remission periods of more than a month. The other 10–20% have chronic cluster headache and no significant remission periods over the course of a year.

Diagnosis is purely clinical and cannot be made on imaging. However, the NICE guideline on headache recommends that the need for neuroimaging in patients with a first bout of cluster headache is discussed with a specialist. If imaging is considered necessary then an MRI scan of the brain is the most appropriate form. The main differential diagnoses to consider are secondary causes (e.g. vascular or neoplastic lesions), paroxysmal hemicrania and most commonly migraine. The clinical features that are most useful in distinguishing cluster headache from migraine include: relatively short duration of attack; rapid onset and offset of attacks; clear circadian periodicity; rapid precipitation with alcohol; agitation during an attack; and clustering of attacks with intervening remission periods.

Specialist advice should be sought at first presentation for confirmation of diagnosis, development of a plan for managing current and future cluster bouts and where first-line treatments fail. Subcutaneous sumatriptan or nasal triptans should be offered to patients for the acute treatment of attacks. Inhalation of 100% oxygen at a rate of at least 12L/min given through a non-rebreathing mask and reservoir bag is rapidly effective in relieving pain in most sufferers. Corticosteroids are highly effective as preventive agents and act rapidly but caution should be taken in their use because of potential side effects, and no more than three courses should be given in a year. Verapamil is the first-line preventive treatment and should be considered in all patients where appropriate.

should be considered in all patients where appropriate.^{7,18–20}

If the reviewing physician is unfamiliar with its use then a specialist opinion including advice on ECG monitoring should be undertaken.⁷ Clinical experience is that higher doses than those used in cardiology patients are needed to control cluster headache. Doses of 240–960 mg daily are not uncommon in cluster headache treatment.

An ECG must be carried out before starting verapamil and if this is normal then our practice is to start at 120 mg two times daily. The total daily dose should then be increased by 120 mg every two weeks with an ECG being taken before every dose increase.

Any indication of a prolonged PR or QT interval should prompt discussion with a specialist and the dose should be decreased to the last known dose at which the ECG was normal. If ECG monitoring is normal and side effects allow, the dose should be increased to a point where attacks are suppressed or a maximum dose of 960 mg is achieved. Commonly reported side effects include: fatigue, ankle swelling, nausea and abdominal pain.

Surgical measures

There is an increasing evidence base emerging for the use of surgical procedures involving neuromodulation to control medically intractable cluster headache. These procedures are only used in highly specialised centres and are aimed at patients who have failed all available medical treatments. A brief overview of these procedures is given in table 5, p19.

CONCLUSION

All patients with cluster headache should have the acute and preventive treatments implemented as outlined by the NICE guideline for headache disorders, see box 1, p19.

GPs should also consider referring all patients to a neurologist to confirm the diagnosis, arrange any investigations that may be necessary, and formulate a management plan. Once the management plan has been formulated, shared care is an excellent route by which it can be implemented.

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