Cluster headaches

Synonyms: migrainous neuralgia; histamine headache; 'alarm clock headache'; ciliary neuralgia; hemicrania neuralgiformis chronica; Horton's headache; petrosal neuralgia; Bing's erythroprosopalgia; suicide headache

Recognised over 100 years ago, this condition is different from migraine - clinically, aetiologically and genetically. This is reflected in the fact that the latest version of the International Classification of Headache Disorders third edition (ICHD-3) moves cluster headache from Migraine to Trigeminal Autonomic Cephalgias [1] .

It is a disorder producing severe unilateral pain, localised in or around the eye and accompanied by ipsilateral autonomic features. It is quite rare, often misdiagnosed and frequently poorly managed [2] .

Although short-lasting, the extremely painful nature of the headache causes patients very great distress and has earned the name 'suicide headache'. It is described as one of the most painful conditions known to man [3] . The clustering of attacks means that there is significant interruption to life and work. The underlying mechanism of headache is poorly understood and prophylactic treatments are therefore empirical.

Episodic cluster headaches (CHs)

These are CHs occurring in periods lasting from seven days to one year. The National Institute for Health and Care Excellence (NICE) specifies a pain-free period lasting a month or longer; the International Headache Society (IHS) specifies at least three months [1] [4] . Cluster periods usually last between two weeks and three months [4] .

Chronic CHs

These are defined as CHs occurring for one year without remissions or with short-lived remissions. The NICE definition specifies a remission period of less than one month, whilst the IHS classification specifies less than three months [1] . Chronic CH may arise de novo or develop from episodic CH [4] .

Epidemiology[5]

- CH has an estimated one-year prevalence of 53 per 100,000 adults. The lifetime prevalence is 124 per 100,000.
- The typical age of onset of CH is 20 to 40 years. About 7 out of 10 patients report onset before the age of 30.
- About 4 times more males are affected than females. The male-to-female ratio is significantly higher for chronic CH (15:1) than for episodic CH (3.8:1).
- About 80-90% of people with episodic cluster headache have recurrent bouts separated by remission periods of more than a month.
- Progression from episodic to chronic CH is associated with late onset, occurrence of sporadic attacks, higher frequency of cluster periods and shorter periods of remission[6] .
- Head injury, cigarette smoking and alcohol use are also associated with a worse prognosis[7] [8] .

Pathophysiology[7]

Imaging studies suggest these syndromes inappropriately activate a normal trigeminal-parasympathetic reflex. An autosomal dominant form has been identified in about 5% of cases[1] .

A complete picture of the pathophysiological processes which cause a CH has been difficult to elucidate, particularly because the condition is rare and sample sizes are small. Vasodilation is known to occur during an attack. This is associated with activation of the trigeminovascular system causing perivascular afferent nerves to activate. The activation of the trigeminal nerve is believed to be unilateral, although this has not been confirmed by imaging. Complete trigeminal nerve root section does not affect the number or frequency of attacks, so clearly this is not the whole story.

An association with the hypothalamus has been confirmed. Attacks have a circadian periodicity, and occur most often at night. PET scans demonstrate activation of the inferior hypothalamic grey matter while the patient is having an attack. Anatomical abnormalities have been detected within this same region of the hypothalamus. Stimulation of the hypothalamus does not, however, trigger attacks. In fact, some research suggests that stimulation of the hypothalamus may abort an attack.

Parasympathetic nerve fibres are involved, and cause the autonomic symptoms, including conjunctival injection or lacrimation, rhinorrhoea, and facial vasodilation. How these are activated as part of the trigeminal reflex is activated is uncertain.

Clinical features [1] [4] [5] [7]

It is important to distinguish between cluster attacks (individual episodes of pain) and cluster bouts (the time over which recurrent attacks occur). It is also important to distinguish between episodic CH and chronic CH.

Pattern of occurence

- Episodic CHs occur from once every other day to eight times a day with a pain-free period of greater than one month. Chronic CHs occur from once every other day to eight times a day with a continuous pain-free period of less than one month in a 12-month period.
- The headache typically occurs at the same time of the night or day.
- A circadian pattern is accompanied in 85% of patients (episodic CH) with remissions lasting for months or years.
- About 10-15% of patients have CH chronically with no remission. Often the interval between bouts is the same and there is a tendency for the interval to lengthen with age.
- 10% of those with episodic CH go on to develop chronic CH.
- About a third of those with chronic CH become episodic.

Nature of symptoms

- The pain comes on rapidly (without aura) over about 10 minutes.

- The pain maintains an intensity, is excruciating, sharp and penetrating (not pulsatile as with migraine).
- The pain is centred around or behind the eye, temple or forehead, although the neck and other parts of the head can be involved.
- Pain is unilateral and mostly stays on the affected side with each attack.
- It can last from 15 minutes to three hours.
- Attacks of pain occur once- or twice-daily (occasionally more often, even up to eight times daily).
- Wakened patients may beat their heads against the wall in distress.
- Associated autonomic features of ipsilateral lacrimation, rhinorrhoea, nasal congestion, eyelid swelling, facial sweating or flushing and conjunctival injection and a partial Horner's syndrome with miosis and ptosis may be present: two or more in the presence of the extremely severe periocular headache will secure the diagnosis.
- Nausea may accompany the pain, but is much less of a feature than with migraine.
- Sufferers, unlike with migraine, cannot keep still and are described typically as restless.
- Patients pace around, occasionally banging their heads on walls and furniture.

Triggers

- Alcohol is a potent precipitant of attacks. However, in episodic CH, normal alcohol consumption can be resumed once the cluster period is over.
- Histamine and nitroglycerine are also provokers of attacks in chronic CH and during cluster periods in episodic CH.
- For some patients, heat, exercise and solvents can precipitate attacks.
- Disruption to sleep patterns (for example, by shift work, jet lag, etc) can also exacerbate or trigger CHs.

Diagnosis[1]

The diagnosis is made from the history. The IHS guidelines have suggested the following diagnostic criteria:

- At least five attacks fulfilling the criteria below.
- Severe, or very severe, unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes if untreated.
- Headache accompanied by at least one of:
    - Ipsilateral conjunctival injection and/or lacrimation.
    - Ipsilateral nasal congestion and/or rhinorrhoea.
    - Ipsilateral eyelid oedema.
    - Ipsilateral forehead and facial sweating.
    - Ipsilateral miosis and/or ptosis.
    - A sense of restlessness or agitation.
- Attacks occur from one every other day to eight times daily.
- Not attributable to another disorder.

Differential diagnosis

This could include a longer list of causes of headache but those most similar to CH in the IHS guidelines are[9] :

- Paroxysmal hemicrania.
- Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT).
- Probable diagnoses (of CH, SUNCT and paroxysmal hemicrania) where insufficient attacks have occurred or diagnostic criteria are not fulfilled.

Investigations[4]

The diagnosis is usually made from history and neurological examination. As with any primary headache, some patients may need imaging, and the red flags of headache indicating the need to search for a secondary cause are:

- Worsening headache with fever.
- Sudden-onset headache reaching maximum intensity within five minutes.
- New-onset neurological deficit.
- new-onset cognitive dysfunction
- Change in personality.
- Impaired level of consciousness.
- Recent (typically within the past three months) head trauma.
- Headache triggered by cough, Valsalva manoeuvre (trying to breathe out with the nose and mouth blocked) or sneeze.
- Headache triggered by exercise.
- Orthostatic headache (headache that changes with posture).
- Symptoms suggestive of giant cell arteritis.
- Symptoms and signs of acute narrow-angle glaucoma.
- A substantial change in the characteristics of their headache.

Management

It should be remembered that:

- Some patients will have found medical interventions unhelpful or hard to tolerate.
- Patients may not have had the benefit of up-to-date review of treatment.
- Patients may be depressed or despondent about the condition.

- Patients experiencing their first attacks will be greatly distressed and will need reassurance.
- Drug treatment is always necessary for effective control.
- The realistic aim of treatment is suppression of the attack and reduction in frequency and severity of attacks. There is no likely prospect, at present, of curative medical treatment.
- Prophylaxis should begin as soon as possible after the start of a new cluster period, as there is evidence that it is most effective at this point[9] .
- Failure of one drug does not predict failure of another.
- All treatments are potentially toxic and shared risk/benefit evaluation is an essential part of management.
- Partial relief presents a dilemma, as using two drugs together is potentially of greater toxicity that one alone, but it may be hard for patients to sacrifice what has been gained in order to try another treatment which may be more or less effective.
- When benefit is not seen within one week of reaching the maximum dose of a drug then it should be changed or supplemented.
- Acute therapy may be used in addition to prophylactic therapy if breakthrough attacks continue.

It is therefore important to:

- Establish rapport, based on knowledge and understanding of the condition generally and the patient's particular experience.
- Anticipate that polypharmacy is likely to be required.
- Be prepared to follow up closely to monitor efficacy of treatments, side-effects, etc.
- Consider drawing up a programme of measures, perhaps with a patient-held record book or diary.

General advice

- Be prepared for attacks. Patients should be encouraged to have both acute and preventative treatments available. This may involve completion of Home Oxygen Order Forms (HOOFs) if oxygen is to be used.
- Stop smoking, as this can increase the risk of chronic CH developing.
- Abstain completely from alcohol during periods of CH and in chronic CH.
- There is no evidence that abstinence from smoking during attacks affects CH[9] .
- Maintain a regular sleep routine and good sleep hygiene (avoiding tea, coffee, etc).

Acute attack

A triptan and oxygen are likely to be the mainstay of treatment for most patients[4] [10] :

- Offer oxygen and/or a subcutaneous or nasal triptan (eg, sumatriptan) for the acute treatment of a cluster attack.
- Subcutaneous triptans are not recommended for patients under the age of 18 years.
- A sumatriptan or zolmitriptan nasal spray should be offered if the subcutaneous route is unacceptable (both are unlicensed for this use).
- Oxygen - use 100% oxygen at a flow rate of at least 12 litres per minute with a non-rebreathing mask and a reservoir bag. It is particularly useful for night attacks. Standard high flow oxygen and demand valve oxygen types are available. Useful guidance for patients is available on the OUCH (UK) website[2] .

Other possible treatments for acute attacks include:

- **Ergotamine** - not advocated by NICE, but the British National Formuarly (BNF) recommends it for short-term use only in patients who do not get prolonged attacks.
- **Metoclopramide** - may be useful as an adjunct to acute treatments.

- **Lidocaine** - 1 ml of 4% lidocaine, which can be given intranasally to the affected side [11]
- NHS England has recently agreed to fund the provision of a device called gammaCore® which delivers a low-level electric current to the vagus nerve via the neck [12] .

Prophylaxis

Verapamil

- This should be considered for prophylaxis of CH (unlicensed use) [4] . It is the first-line choice for both episodic and chronic CH.
- The BNF recommends a dosage range for adults of 240-480 mg daily in 2-3 divided doses [10] .
- Side-effects of constipation and flushing may limit use in some.
- ECG monitoring (for AV block) is required at doses over 120 mg daily and fortnightly ECG monitoring is required with successive dose increases (because of the risk of dysrhythmias).
- Some experts believe that standard-release verapamil formulations are more effective in CH than the modified-release versions.
- If unfamiliar with this use of verapamil, or if the patient does not respond to treatment, the GP should seek specialist advice.

NICE only recommends verapamil for the prophylaxis of CHs. Other medications have been tried, with varying degrees of success [7] . These include lithium, oral steroids, valproic acid, melatonin, topiramate, ergotamine, methysergide and nifedipine.

It is suggested that if a patient does not respond to prophylactic verapamil, a neurologist should be involved.

Deep brain stimulation [7]

- This may have a place in intractable chronic CH. It has been quite useful in drug-resistant patients.
- The ipsilateral posterior hypothalamus is targeted for electrical stimulation.

Surgery

Trigeminal nerve resection has not been shown to be helpful but decompression of the nerve has been shown to be temporarily effective in a small series of patients [13] .

More invasive procedures

These are used as a last resort. They involve chemical or physical ablation to parts of the trigeminal nerve. These can be effective but are likely to be reserved for refractory chronic CH. Cases require referral for consideration of neuromodulation and more invasive treatments [14] .

Alternative therapies

Therapies such as acupuncture have anecdotally been very helpful to some patients. One study found that it was more beneficial when the acupuncture points stimulated were those used for trigeminal neuralgia, rather than migraine [15] .

Referral guidance

Urgent referral is recommended for all people with suspected CH - for confirmation of the diagnosis, investigation of secondary causes of CH, and initiation of preventative treatment [4] [5] .

Referral should be to a neurologist interested and expert in this condition. Other indications include:

- Diagnostic uncertainty.
- Imaging or further investigation.
- Failure of treatment.
- For new or invasive treatments [14] .

Treatment review

- The intermittent occurrence of clusters in some patients may mean that they 'fall off' the practice system for regular review, and lack continuity in primary care.

- It is good practice to review CH patients at least annually, both to discuss their medication and to enable planning for attack management: the average GP will have fewer than 1 in 1,000 affected patients.
- Reviewing patients when they are well and discussing how they might manage possible attacks, offering them easy routes to contact you in the case of a new cluster of headaches, is likely to increase patient confidence and compliance.
- Encourage patients to be better informed by, or example, joining OUCH (UK).

Prognosis [5] [7]

There is an absence of good-quality evidence regarding prognosis. Available data suggest that about 25% of patients experience a CH as an isolated incident. Another 15-20% of patients will have chronic CHs, Of those, 10-20% develop resistance to medication. The condition was once thought to be lifelong but it is now known that it often resolves in approximately 15 years.

Periods of remission tend to increase as people get older.

Chronic CH has been known to evolve into episodic CH, and vice versa.

Dr Mary Lowth is an author or the original author of this leaflet.

Further reading

- Implantation of a sphenopalatine ganglion stimulation device for chronic cluster headache; NICE Interventional procedure guidance, June 2015
- Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine; NICE Interventional Procedure Guidance, March 2016

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