

# CLINICAL REVIEW

## Cluster headache

Alexander D Nesbitt *research fellow*<sup>1,2</sup>, Peter J Goadsby *professor of clinical neurology*<sup>2</sup>

<sup>1</sup>Surrey Sleep Research Centre, University of Surrey, Guildford GU2 7XP, UK; <sup>2</sup>Department of Neurology, University of California, San Francisco, CA 94115, USA

Few, if any, medical disorders are more painful than cluster headache. Previously termed migrainous neuralgia, it was last reviewed in the *BMJ* nearly 50 years ago.<sup>1</sup> At that time, the authors stressed the importance of covering the topic in a general medical journal to aid recognition. Despite this remarkably prescient view, and the extreme and stereotyped nature of its presentation, cluster headache is still commonly misdiagnosed. Without a clear diagnosis, affected patients can wait many years before receiving adequate help, and they often endure unnecessary and unhelpful attempts at treatment before gaining any relief.<sup>2</sup>

Patients describe the pain of a single attack as being worse than anything else they have experienced, including childbirth. Many endure repeated attacks, lasting up to three hours, every single day. The severity of the pain has earned it the sobriquet “suicide headache,” although in our experience this is a rare occurrence in this exceptional patient group.

The management of this condition differs from that of other headache disorders. This article will review the clinical entity of cluster headache by highlighting its unique and defining characteristics as an aid to correct diagnosis, before critically appraising current treatment methods. In doing so, we outline an up to date streamlined management strategy aimed at limiting the considerable burden that this condition places on patients.

### What is cluster headache?

Cluster headache is a primary headache disorder classified with similar conditions known as trigeminal autonomic cephalalgias (table 1).<sup>3</sup> These conditions are typified by recurrent attacks of unilateral pain, which are very severe and usually involve the orbital or periorbital region innervated by the first (ophthalmic) division of the trigeminal nerve. Characteristic signs and symptoms of activation of the cranial autonomic pathways accompany the pain on the same side: lacrimation, conjunctival injection, nasal congestion or rhinorrhoea (or both), ptosis or miosis (or both), and periorbital oedema (box 1; fig 1).<sup>4</sup>

The term cluster headache originates from the tendency of attacks to cluster together into bouts that last several weeks. In the episodic form of the disorder, the bouts can occur at certain times of year, often with a seasonal predilection.<sup>4</sup> They are separated by periods of remission, which last at least a month

(box 2).<sup>3</sup> However, about 10% of patients have the chronic form of the disorder and have continuous attacks with no respite.

A well described physiological reflex arc, the trigeminovascular reflex, potentiates the trigeminal pain and cranial autonomic features of cluster headache by positive feedback mechanisms (fig 2).<sup>8</sup>

Functional imaging studies have detected activation ipsilateral to the pain in the region of the posterior hypothalamus (fig 2), which may have a pivotal role in integrating the pain, cranial autonomic features, and unique timing of cluster headache.<sup>11</sup>

### Who gets it?

Pooled data from epidemiological studies give cluster headache a lifetime prevalence of 0.12%, with data from a door to door study in Norway showing a one year prevalence of 0.3%.<sup>12</sup> The condition has a heritable tendency in some families, and first degree relatives of affected people have an estimated 14-48-fold increased risk of developing it.<sup>13</sup>

The male to female ratio varies between 2.5:1 and 3.5:1.<sup>4, 14</sup> Patients typically start to develop the attacks in their third to fifth decade, although patients as young as 4 years and as old as 96 years can be affected. There seems to be an association with smoking, with around 65% of patients being active smokers or reporting a history of smoking.<sup>14</sup> However, a causative link to smoking seems unlikely, because smoking cessation does not seem to alter the clinical course of the disorder and cannot easily account for the disorder in children.

The natural course of cluster headache can be difficult to predict, with some people showing a bidirectional transition between the episodic and chronic form of the condition. Less frequent bouts of attacks and more prolonged, and sometimes permanent, periods of remission can occur with advancing age.

### How is cluster headache diagnosed?

The diagnosis of cluster headache is made by a careful history that elicits the clinical features of short lasting unilateral pain with cranial autonomic disturbances (box 2), and the cyclical nature of the bouts in which the attacks occur. Descriptions of

### Summary points

Cluster headache is an excruciatingly painful primary headache disorder, which places an exceptional burden on those affected

Attacks are one sided, generally last 15 minutes to three hours, and have a characteristic set of cranial autonomic features, which are accompanied by agitation

Attacks occur from once every other day to eight times daily, in bouts that last several weeks, usually with complete remission between bouts

Treat acute attacks with high flow oxygen (12 L/min for at least 15 minutes) or parenteral triptans (or both), such as subcutaneous sumatriptan 6 mg, unless contraindicated

High doses of verapamil are often necessary as preventive treatment; electrocardiographic monitoring is mandatory when escalating doses

### Sources and selection criteria

We based this clinical review on personal reference archives, personal experience, and extensive literature searches of the PubMed and Cochrane databases using the search terms "cluster headache" and "trigeminal autonomic cephalgia". We also consulted management guidelines from the European Federation of Neurological Sciences and the British Association for the Study of Headache.

### Box 1 Cranial autonomic features of cluster headache attacks<sup>4 5\*</sup>

Ipsilateral lacrimation (91%)

Ipsilateral conjunctival injection (77%)

Ipsilateral nasal congestion or rhinorrhoea (75%/72%)

Ipsilateral ptosis† (74%)

Ipsilateral oedema of the eyelid or the face (or both) (74%)

Ipsilateral sweating of the forehead or the face (or both) (38%)

Ipsilateral miosis† (29%)

\*Features are ipsilateral to the side of pain; not all features need to be present

†A partial Horner's syndrome may persist to a lesser degree between attacks.

### Box 2 Diagnostic criteria for cluster headache<sup>3</sup>

A) At least five attacks fulfilling criteria B-D

B) Severe or very severe unilateral orbital, supraorbital, or temporal pain that lasts for 15-180 minutes if untreated

C) Headache accompanied by at least one of the following:

- Ipsilateral conjunctival injection or lacrimation (or both)
- Ipsilateral nasal congestion or rhinorrhoea (or both)
- Ipsilateral eyelid oedema
- Ipsilateral forehead and facial sweating
- Ipsilateral miosis or ptosis (or both)
- Restlessness or agitation

D) Attacks have a frequency of one every other day to eight each day

E) Not attributed to another disorder

*Episodic cluster headache:* Attacks occurring in periods that last seven days to one year separated by pain-free periods that last one month or longer

*Chronic cluster headache:* Attacks that occur for more than one year without remission or with remissions that last less than one month

the disorder are supported by three large prospective case series that use similar methods.<sup>4 5 14</sup>

### Where is the pain and what is it like?

The pain of cluster headache is unilateral in at least 97% of people with episodic disease and mainly focused behind the eye (88-92%), over the temple (69-70%), or over the maxilla (50-53%), although it may extend to other areas of the head and neck.<sup>4 5 14</sup> Between 14% and 18% of patients report that the pain shifts sides between bouts of attacks and less commonly during a bout, but never during the attack itself.<sup>4 14</sup> Patients often describe the pain as a sharp, piercing, burning, or pulsating sensation like "having a red hot poker forced through my eye," and they report that the intensity is so extreme it is unlike anything they have ever experienced ("11 out of 10").

### How long does an attack last?

The diagnostic criteria (box 2) state that attacks should last between 15 and 180 minutes, although on rare occasions they can last longer. In the British series, a mean untreated minimum duration of 72 minutes and maximum duration of 159 minutes was reported.<sup>4</sup>

The onset of pain is rapid, and the sensation increases from serious discomfort to excruciating pain over the course of a few minutes. The pain usually stays at maximal intensity for the duration of the attack, although it may wax and wane slightly, or be punctuated by super-intense stabs of pain. The attack will often end as abruptly as it started.

## How often do individual attacks occur?

The frequency of attacks is also a feature of the diagnostic criteria (box 2), and it varies from one attack every 48 hours to eight separate attacks in 24 hours, although less frequent attacks may occur at the beginning and end of bouts.

The British study found the mean maximum number of attacks each day to be 4.6, with 37% of patients reporting a predictable time of onset during the day and 72% reporting attacks occurring at predictable times during the night, waking them from sleep.<sup>4</sup>

## Which other symptoms occur with the attack?

Each attack is accompanied by one or more cranial autonomic symptom or sign on the same side as the pain (box 1; figs 1 and 2). All of these signs and symptoms are transient and resolve with the cessation of pain, although a partial Horner's syndrome or isolated ptosis may persist between attacks or even bouts as a result of local damage to oculosympathetic fibres during repeated attacks (fig 2).<sup>10</sup> The persistence of these signs in the context of the disorder need not cause undue alarm, unless they progressively worsen, in which case secondary causes should be considered and investigations or referral initiated.

Between 70% and 93% of patients describe a sense of restlessness and agitation during an attack and will often pace, rock back and forth, and bang their heads.<sup>4 14</sup> Most patients wish to isolate themselves and seek a cold environment. Between 28% and 50% report nausea,<sup>4 5 14</sup> and a further 23% may vomit during an attack.<sup>4</sup> More than half (54-64%) of patients have photophobia, often limited to the same side as the pain, with slightly fewer reporting an aversion to loud noise (43%) or strong smells (26%) during the attack.<sup>4 14 15</sup>

Aura phenomena, similar to those experienced during migraine, including visual phenomena and paraesthesia, precede attacks by up to 60 minutes in 14% of patients.<sup>4</sup>

Patients commonly have tenderness and cutaneous allodynia at and around the site of pain between attacks, including over the ipsilateral greater occipital nerve.<sup>16</sup>

## Does anything trigger the attacks?

In over half of patients (53-63%), small quantities of alcohol, particularly red wine (70%), will precipitate an attack, usually within an hour of ingestion.<sup>4 14 15</sup> However, this is only the case during a bout rather than when in remission.

In most patients (72%), attacks are related to nocturnal sleep, with daytime naps also being triggers in some.<sup>4</sup> Small case series have reported a raised apnoea-hypopnoea index in some patients, suggesting a higher incidence of obstructive sleep apnoea, although no convincing mechanistic or therapeutic insights currently exist to explain this.<sup>17</sup>

Some patients report that odours from volatile organic compounds, such as perfume and paint, can also trigger attacks. Nitrates may trigger attacks,<sup>18</sup> and glyceryl trinitrate is used to provoke attacks experimentally.<sup>11</sup> Sildenafil has also been reported to induce attacks during a bout.<sup>19</sup>

## How often do bouts of attacks occur?

Most people with cluster headache experience one bout a year, with a unimodal frequency distribution and mean bout duration of 8.6 weeks found in the British series. However, patients may go for several years without a bout (up to 20 in some cases), and others may have more frequent bouts each year.<sup>4</sup>

## Which conditions resemble cluster headache?

The table highlights the main features of cluster headache and the other trigeminal autonomic cephalalgias, which although rare are the main differential diagnoses.

Secondary (or symptomatic) cluster headache may be caused by several structural lesions, particularly pituitary tumours, in addition to carotid dissections and cavernous sinus pathology, so magnetic resonance imaging of the brain and, potentially, carotid arteries is a useful part of the diagnostic investigation.<sup>20</sup>

Attacks of migraine tend to be less severe and to last longer; cranial autonomic features, if present, are less prominent and more likely to be bilateral.<sup>21</sup> Nausea, vomiting, and bilateral photophobia are common. Migraine lacks the striking timing patterns and clustering effects, and most patients prefer not to move during the episode, in contrast to the agitation and restlessness experienced during a cluster attack. Alcohol ingestion may also precipitate migraine, typically after a time delay of several hours.

Trigeminal neuralgia tends to affect people over the age of 50 years and consists of sudden short lasting stabs of lancinating pain, usually affecting the second and third divisions of the trigeminal nerve. It is not associated with cranial autonomic features and is often precipitated by touch, chewing, swallowing hot or cold liquids, and cold wind.<sup>3</sup>

## How should patients with cluster headache be managed?

Effective management relies on shared responsibility between primary and secondary care, and all suspected cases should be initially referred for specialist neurological or headache assessment. Patients should be kept under long term follow-up and if possible be offered open appointments at times when bouts recur.

## Treatment of individual attacks

Standard analgesia is ineffective, and there is no evidence to support the use of non-steroidal anti-inflammatory drugs, paracetamol (acetaminophen), codeine, or opioids in the treatment of individual attacks. Prescription of such agents should therefore be avoided. The mainstay of abortive treatment consists of inhaled oxygen and parenteral triptans.

### Oxygen

A recent double blind randomised placebo controlled crossover trial found that 78% of subjects were pain free after inhalation of 100% oxygen at 12 L/min for 15 minutes ( $P<0.001$ ).<sup>22</sup> Patients should continuously inhale oxygen at this rate for at least 15 minutes through a non-rebreathing facemask. Guidelines for oxygen use, including a prefilled home oxygen order form for doctors of patients in the United Kingdom, are provided on the website of the Organisation for the Understanding of Cluster Headache.

### Triptans

Parenteral triptans have been shown to be an effective treatment for individual attacks, whereas orally administered triptans have not. A randomised double blinded placebo controlled crossover study of sumatriptan 6 mg subcutaneous injections showed freedom from pain or a reduction to mild pain in 74% of attacks 15 minutes after administration ( $P<0.001$ ).<sup>23</sup> The incidence of

rebound and tachyphylaxis is lower in patients with cluster headache than in those with migraine when sumatriptan is injected up to twice daily on a long term basis. Good randomised placebo controlled evidence also supports the use of sumatriptan nasal spray 20 mg (57% of patients reported adequate relief ( $P=0.002$ ) and 47% reported freedom from pain ( $P=0.003$ ) at 30 minutes)<sup>24</sup> and zolmitriptan nasal spray 10 mg (61% ( $P=0.002$ ) and 50% ( $P=0.003$ )).<sup>25</sup>

## Preventive treatment

Preventive treatment aims to suppress the attacks for the duration of the bout, or over longer periods in those with chronic cluster headache, with the fewest possible side effects.

Consensus evidence, based on observation and one small randomised controlled trial,<sup>26</sup> suggests that a tapering course of corticosteroids—such as 1 mg/kg prednisolone (maximum 60 mg) for five days, which is then reduced by 10 mg every three days—may temporarily reduce the frequency of headaches. A preventive agent, with longer latency until onset of action, should be started at the same time.<sup>27</sup>

The preventive drug of choice is verapamil. This is based on consensus agreement and a small double blinded multicentre placebo controlled study.<sup>28</sup> Baseline electrocardiography should be performed before starting verapamil at a dose of 80 mg three times a day and increasing this by 80 mg each fortnight. Electrocardiography should be repeated 10 days after the dose change and reviewed before each dose increase, paying particular attention to the PR interval. This is essential because of the relatively high incidence of heart block associated with verapamil.<sup>29</sup> For adequate control, at least 480 mg daily is usually needed, and doses of up to 960 mg daily are sometimes needed.<sup>28</sup> At higher doses, other side effects of verapamil include constipation, dizziness, and peripheral oedema.

Verapamil can be slowly withdrawn and stopped once the bout is assumed to have ended and lower doses do not allow breakthrough attacks. The maximum efficacious dose achieved can then be given at the beginning of subsequent bouts, as long as a baseline electrocardiogram remains within normal limits.

Although evidence from controlled trials is limited, there is consensus that lithium may be a useful preventive treatment, even though it is generally of less use than verapamil and it is associated with more side effects and the need for regular plasma monitoring.<sup>27</sup>

Observational studies from the 1960s suggest that methysergide can be efficacious, particularly for short bouts, but its use is restricted by serious fibrotic side effects, and it should therefore be given for short periods only under specialist supervision.<sup>27</sup> Melatonin can be useful in doses of 9–15 mg at night, and this is supported by a small double blind pilot study.<sup>30</sup>

Other agents such as topiramate, sodium valproate, pizotifen, and gabapentin are occasionally used with some success, although data from clinical trials are limited.<sup>27</sup>

## Nerve blocks and infusions

Data from a recent randomised controlled trial support the injection of a mixture of local anaesthetic and corticosteroid solution over the greater occipital nerve on the side of the pain.<sup>31</sup> This can be used as an effective bridging technique to allow an adequate dose of oral preventive drug to be achieved. Its use would normally be limited to once every eight to 12 weeks.

A repeated course of intravenous dihydroergotamine, when used according to established protocols in specialist centres only, was shown to break the cycle in a cohort study.<sup>32</sup>

## Neuromodulation

The small proportion of people with chronic cluster headache who gain no meaningful benefit from preventive drugs should be considered for surgical intervention. Occipital nerve stimulation involves the extracranial implantation of stimulating electrodes around the greater occipital nerve, situated below the scalp and overlying the occipital bones.<sup>33 34</sup> Long term follow-up of a small cohort showed improvement in 71%, with 64% stating that they would recommend the procedure to others. This safe and effective technique should be considered part of routine care in selected patients with drug refractory chronic cluster headache.<sup>35</sup>

Because functional imaging studies show activation in the region of the posterior hypothalamus during attacks,<sup>11</sup> deep brain stimulation of this area is also being used to treat refractory cases. This technique offers good efficacy in about 60% of patients,<sup>36</sup> although a small controlled trial was negative, and death has been reported as a complication of this approach.<sup>37</sup> Its use should be restricted to patients who have failed peripheral stimulation techniques.

Contributors: ADN initiated and planned the manuscript. ADN and PJG both contributed to the manuscript and provided figures. PJG critically revised drafts of the article and approved the content of the final version to be published. PJG is guarantor.

Competing interests: Both authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: ADN had financial support from the Patrick Berthoud Charitable Trust for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work. PJG has consulted for or lectured in sessions supported by Allergan, American Headache Society, Colucid, MAP Pharma, Merck, eNeura, Autonomic technologies, Boston Scientific, Eli-Lilly, Medtronic, Linde gases, Menarini, BristolMyersSquibb, and Pfizer, and had grant support from GlaxoSmithKline, MAP Pharma, Merck, eNeura, and Amgen.

Provenance and peer review: Commissioned; externally peer reviewed.

Patient consent obtained.

- 1 Balla JL, Walton JN. Periodic migrainous neuralgia. *BMJ* 1964;1:219-21.
- 2 Bahra A, Goadsby PJ. Diagnostic delays and mis-management in cluster headache. *Acta Neurol Scand* 2004;109:175-9.
- 3 Headache Classification Committee of the International Headache Society. The international classification of headache disorders (second edition). *Cephalalgia* 2004;24(suppl 1):1-160.
- 4 Bahra A, May A, Goadsby PJ. Cluster headache: a prospective clinical study in 230 patients with diagnostic implications. *Neurology* 2002;58:354-61.
- 5 Donnet A, Lanteri-Minet M, Guegan-Massardier E, Mick G, Fabre N, Geraud G, et al. Chronic cluster headache: a French clinical descriptive study. *J Neurol Neurosurg Psychiatry* 2007;78:1354-8.
- 6 Cittadini E, Matharu MS, Goadsby PJ. Paroxysmal hemicrania: a prospective clinical study of thirty-one cases. *Brain* 2008;131:1142-55.
- 7 Cohen AS, Matharu MS, Goadsby PJ. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA). A prospective clinical study of SUNCT and SUNA. *Brain* 2006;129:2746-60.
- 8 Goadsby PJ. Pathophysiology of cluster headache: a trigeminal autonomic cephalgia. *Lancet Neurol* 2002;1:37-43.
- 9 Akerman S, Holland P, Goadsby PJ. Diencephalic and brainstem mechanisms in migraine. *Nat Rev Neurosci* 2011;12:570-84.
- 10 Drummond PD. Mechanisms of autonomic disturbance in the face during and between attacks of cluster headache. *Cephalalgia* 2006;26:633-41.
- 11 May A, Bahra A, Buchel C, Frackowiak RS, Goadsby PJ. Hypothalamic activation in cluster headache attacks. *Lancet* 1998;352:275-8.
- 12 Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. *Cephalalgia* 2008;28:614-8.
- 13 Russell MB. Epidemiology and genetics of cluster headache. *Lancet Neuro* 2004;3:279-83.
- 14 Schurks M, Kurth T, de Jesus J, Jonic M, Roskopf D, Diener HC. Cluster headache: clinical presentation, lifestyle features, and medical treatment. *Headache* 2006;46:1246-54.
- 15 Irimia P, Cittadini E, Paemeleire K, Cohen AS, Goadsby PJ. Unilateral photophobia or phonophobia in migraine compared with trigeminal autonomic cephalalgias. *Cephalalgia* 2008;28:626-30.
- 16 Marmura MJ, Pello SJ, Young WB. Interictal pain in cluster headache. *Cephalalgia* 2010;30:1531-4.



### Tips for non-specialists

- Consider cluster headache in anyone who presents with a regularly occurring severe unilateral headache that lasts for three hours or less
- A marked sense of agitation and need to move about can help differentiate cluster headache from migraine, which usually compels the patient to remain calm and still
- Conventional analgesia is ineffective and not worth trying
- Offer all patients short burst oxygen therapy and parenteral (injectable or nasal) triptans to treat attacks
- Prefilled, cluster specific home oxygen supply order forms and guidelines on use are available to download at [www.ouchuk.org](http://www.ouchuk.org)

### Ongoing and future research

- Imaging studies using functional and high resolution anatomical approaches aim to provide more detailed information on the activating mechanisms of attacks
- Future randomised controlled trials may assess the efficacy of the calcitonin gene related peptide inhibitors or receptor antagonists, a new class of headache abortive drugs
- Further investigation of the sleep and circadian physiology of patients is providing important mechanistic information designed to help develop new proof of concept treatments
- Randomised controlled trials of different methods of oxygen delivery will provide information that can help rapidly abort individual attacks
- Needleless triptan injections are currently being marketed
- New modes of neurostimulation, such as sphenopalatine ganglion stimulation, are being explored
- Patient databases will help enable longitudinal assessment of the natural course of the disorder

### Additional educational resources

#### Resources for healthcare professionals

- Organisation for the Understanding of Cluster Headache (OUCH UK; [www.ouchuk.org/html/clusters\\_video5.asp](http://www.ouchuk.org/html/clusters_video5.asp))—Video of a patient enduring an attack, which shows the characteristic psychomotor agitation that accompanies an attack
- BMJ Learning (<http://learning.bmj.com/learning/module-intro/.html?moduleId=5004479&searchTerm=%E2%80%9Ccluster%20headache%E2%80%9D&page=0>)—A guide to diagnosis and management
- British Association for the Study of Headache ([www.bash.org.uk](http://www.bash.org.uk))—Guidelines on the diagnosis and management of a range of primary headaches, including cluster headache; also gives details of regular meetings and teaching weekends for GPs, specialist registrars, and consultants throughout the UK
- International Headache Society (<http://ihs-classification.org/en/>)—Useful diagnostic criteria that cover all forms of primary and secondary headache disorders; registered members may take advantage of an online learning resource centre and access to the journal *Cephalalgia*

#### Resources for patients

- Organisation for Understanding Cluster Headache (OUCH UK; [www.ouchuk.org](http://www.ouchuk.org))—A unique patient support group that offers practical advice and information for patients and supporters plus an online support forum and regular meetings throughout the UK

### A patient's perspective

I am careful not to wake the children as I make my way downstairs. If they were to witness my nightly cluster ritual, they would never see me the same way again. Their father, fearless protector, diligent provider, crawling about in tears, beating his head on the hard wood floor. The pain is so intense I want to scream, but I never do. I go down three flights of stairs where I can't be heard, and drop to my knees. I place my hands on the back of my neck and lock my fingers together. I bind my head between my arms and squeeze as hard as I can in an attempt to crush my skull. I begin to roll around, banging my head on the floor, pressing my left eye with the full force of my palm. I search for the telephone that has always been my weapon of choice for creating a diversion, and I beat my left temple with the hand piece. I create a rhythm as I strike my skull, cursing the demon with each blow.

With permission from [www.clusterheadaches.com](http://www.clusterheadaches.com)

- Chervin RD, Zellek N, Lin X, Hall JM, Sharma N, Hedger KM. Sleep disordered breathing in patients with cluster headache. *Neurology* 2000;54:2302-6.
- Ekbom K. Nitroglycerin as a provocative agent in cluster headache. *Arch Neurol* 1968;19:487-93.
- Evans RW. Sildenafil can trigger cluster headaches. *Headache* 2006;46:173-4.
- Wilbrink LA, Ferrari MD, Kruit MC, Haan J. Neuroimaging in trigeminal autonomic cephalgias: when, how, and of what? *Curr Opin Neurol* 2009;22:247-53.
- Lai T-H, Fuh J-L, Wang S-J. Cranial autonomic symptoms in migraine: characteristics and comparison with cluster headache. *J Neurol Neurosurg Psychiatry* 2009;80:1116-9.
- Cohen AS, Burns B, Goadsby PJ. High flow oxygen for treatment of cluster headache. A randomized trial. *JAMA* 2009;302:2451-7.
- Ekbom K; the Sumatriptan Cluster Headache Study Group. Treatment of acute cluster headache with sumatriptan. *N Engl J Med* 1991;325:322-6.
- Van Vliet JA, Bahra A, Martin V, Aurora SK, Mathew NT, Ferrari MD, et al. Intranasal sumatriptan in cluster headache—randomized placebo-controlled double-blind study. *Neurology* 2003;60:630-3.
- Cittadini E, May A, Straube A, Evers S, Bussone G, Goadsby PJ. Effectiveness of intranasal zolmitriptan in acute cluster headache. A randomized, placebo-controlled, double-blind crossover study. *Arch Neurol* 2006;63:1537-42.
- Jammes JL. The treatment of cluster headaches with prednisone. *Dis Nerv Syst* 1975;36:375-6.
- May A, Leone M, Afra J, Linde M, Sandor PS, Evers S, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol* 2006;13:1066-77.
- Leone M, D'Amico D, Frediani F, Moschiano P, Grazzi L, Attanasio A, et al. Verapamil in the prophylaxis of episodic cluster headache: a double-blind study versus placebo. *Neurology* 2000;54:1382-5.
- Cohen AS, Matharu MS, Goadsby PJ. Electrocardiographic abnormalities in patients with cluster headache on verapamil therapy. *Neurology* 2007;69:668-75.
- Leone M, D'Amico D, Moschiano P, Fraschini F, Bussone G. Melatonin versus placebo in the prophylaxis of cluster headache: a double-blind pilot study with parallel groups. *Cephalalgia* 1996;16:494-6.
- Leroux E, Valade D, Taïfas I, Vicaut E, Chagnon M, Roos C, et al. Suboccipital steroid injections for transitional treatment of patients with more than two cluster headache attacks per day: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2011;10:891-7.
- Nagy AJ, Gandhi S, Bhola R, Goadsby PJ. Intravenous dihydroergotamine (DHE) for inpatient management of refractory primary headaches. *Neurology* 2011;77:1827-32.
- Burns B, Watkins L, Goadsby PJ. Successful treatment of medically intractable cluster headache using occipital nerve stimulation (ONS). *Lancet* 2007;369:1099-106.
- Magis D, Allena M, Bolla M, De Pasqua V, Remacle JM, Schoenen J. Occipital nerve stimulation for drug-resistant chronic cluster headache: a prospective pilot study. *Lancet Neurol* 2007;6:314-21.
- Burns B, Watkins L, Goadsby PJ. Treatment of intractable chronic cluster headache by occipital nerve stimulation in 14 patients. *Neurology* 2009;72:341-5.

- 36 Leone M. Deep brain stimulation in headache. *Lancet Neurol* 2006;5:873-7.
- 37 Schoenen J, Di Clemente L, Vandenheede M, Fumal A, De Pasqua V, Mouchamps M, et al. Hypothalamic stimulation in chronic cluster headache: a pilot study of efficacy and mode of action. *Brain* 2005;128:940-7.

Cite this as: *BMJ* 2012;344:e2407

© BMJ Publishing Group Ltd 2012

## Table

**Table 1 | Comparison of the trigeminal autonomic cephalalgias based on cohorts studied,<sup>4 6 7</sup> the international classification of headache disorders,<sup>3</sup> and patients seen in practice\***

Characteristic	Cluster headache	Paroxysmal hemicrania	SUNCT/SUNA
Sex (M:F)	3:1	1:1	1.5:1
Pain:			
Quality	Sharp/stabbing/throbbing	Sharp/stabbing/throbbing	Sharp/stabbing/throbbing
Severity	Very severe	Very severe	Severe
Distribution	V1>C2>V2>V3	V1>C2>V2>V3	V1>C2>V2>V3
Attacks:			
Frequency per day	1 every other day to 8/day	1-40 (>5/day for more than half the time)	3-200 (typically 100/day)
Length	15-180 min	2-30 min	5-240 s
Triggers			
Alcohol	+++	+	–
Nitroglycerin	+++	+	–
Cutaneous	–	–	+++
Agitation or restlessness	90%	80%	65%
Episodic v chronic	90:10	35:65	10:90
Circadian or circannual periodicity	Present	Absent	Absent
Treatment effects:			
Oxygen	80%	No effect	No effect
Sumatriptan 6 mg subcutaneously	75%	20%	<10%
Indomethacin	No effect	100%	No effect
Migrainous features with attacks:			
Nausea	50%	40%	25%
Photophobia or phonophobia	65%	65%	25%

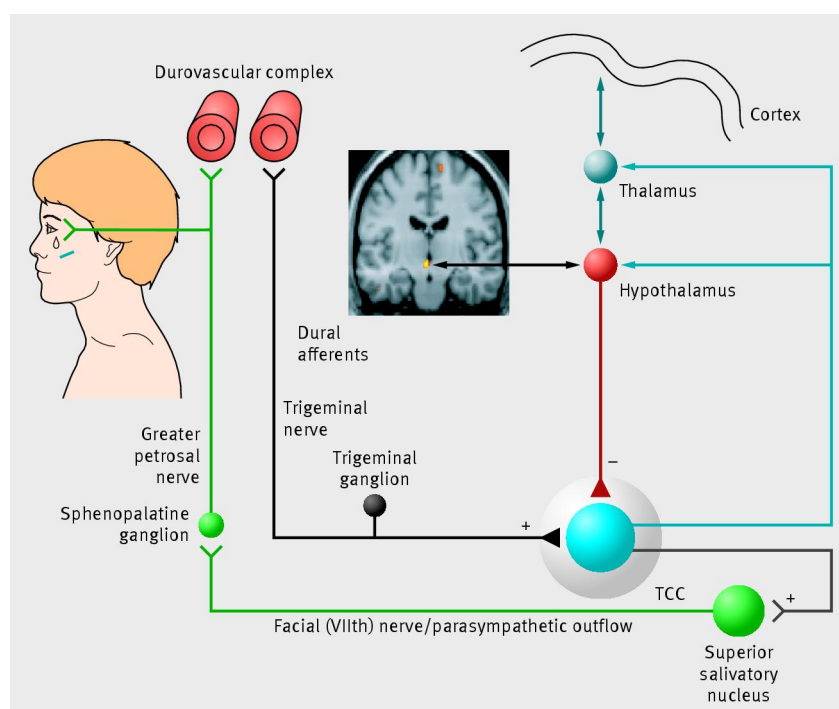
\*SUNCT/SUNA=short lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing/short lasting unilateral neuralgiform headache attacks with cranial autonomic features; C=cervical; V=trigeminal.

## Figures



**Fig 1** Cranial autonomic features during a cluster headache attack. This photograph was taken during an attack and clearly shows characteristic left periorbital oedema and left partial ptosis, with left conjunctival injection and tear formation. These signs reverted to normal when the attack stopped





**Fig 2** The trigeminovascular reflex. Nerve endings containing pain receptors innervate structures of the face and cranial vault, particularly the pain producing dura mater and cerebral blood vessels (the durovascular complex). This nociceptive information is carried to the brainstem in the trigeminal nerve, via the trigeminal ganglion. Within the brainstem, trigeminal fibres synapse in an area known as the trigeminocervical complex (TCC). From here, information ascends to the hypothalamus, thalamus, and cortex via pain processing pathways. In addition, the afferent trigeminal signals arriving at the TCC also stimulate the cranial parasympathetic system via the superior salivatory nucleus. This results in increased firing of parasympathetic fibres carried from the brainstem in the facial nerve and then greater superficial petrosal nerve, which synapse at the sphenopalatine ganglion. These fibres innervate facial structures (including the lacrimal gland and nasal mucosa, thus causing the lacrimation and rhinorrhoea seen with attacks) and the durovascular complex. Neurotransmitter release at these parasympathetic terminals (vasoactive intestinal polypeptide) causes further irritation of trigeminal sensory nerve endings and release of calcitonin gene related peptide, which potentiates the trigeminovascular reflex arc. It is this reflex that is responsible for the pain and facial parasympathetic signs of cluster headache attacks.<sup>9</sup> The ptosis and miosis seen with attacks arise from interruption of the oculosympathetic fibres that run with the internal carotid artery and through the cavernous sinus, where they are thought to be affected by local vascular distension.<sup>10</sup> The posterior hypothalamus, which shows a strong activation signal in functional imaging studies during attacks (insert), may modulate signalling through the TCC, perhaps providing a breaking mechanism to regulate the trigeminovascular reflex<sup>9</sup>