Narrative reviews based on author experience and a discretionary selection of articles.

Cluster headache

Cluster headaches are extremely painful. The condition is typified by recurrent attacks of intense, strictly unilateral pain centred about one eye, accompanied by autonomic symptoms on the ipsilateral side of the face. Time to correct diagnosis and treatment is often long, and we therefore wish to draw attention to this condition.

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MAIN MESSAGE

Cluster headache is an extremely painful primary headache

The condition is characterised by repeated attacks of strictly unilateral pain behind and around one eye, typically accompanied by restlessness and ipsilateral cranial autonomic phenomena

Attacks occur 1–8 times per day for periods lasting a number of weeks

The pathophysiology is unclear, but much suggests a central role for the hypothalamus

Cluster headache is a relatively rare type of headache, but nevertheless the most common of the so-called trigeminal autonomic cephalagias (*Gr*. *kephal*ē, head). The condition is characterised by brief episodes of pain behind and around one eye (in the area supplied by the 1st branch of the trigeminal nerve) and simultaneous autonomic symptoms affecting the ipsilateral side of the face (Box 1) (1).

Attacks occur in periods lasting a number of weeks (clusters). The intense pain, allegedly worse than that of both kidney stones and childbirth, means that the condition has become known colloquially as «suicide headache». In an internet-based American study, 55 % of the 1 134 participants stated that they had thought about suicide, while 2 % had attempted to take their own lives (2). In spite of the intense pain, the time to correct diagnosis is long; in a recent study in Northern Norway, it was 5.8 years (3). Many are seen by a number of specialists before the correct diagnosis is made. We therefore wish, in this article, to highlight the clinical and pathophysiological characteristics of cluster headache.

Incidence and predisposing conditions

Little is known about the incidence of cluster headache, but prevalence varies between studies from 0.05 % to 0.3 % (4). The only Norwegian survey of incidence was conducted by Dr Sjåstad via personal interviews with 1 838 people in the municipality of Vågå (5), seven of whom (0.38 %) were found to have cluster headache (5). A major Swedish study from the 1970s reported that 0.09 % of adult males in the population suffered from cluster headache (6). If the prevalence in the Norwegian population is estimated to be 0.5–1 per 1 000, this would mean that there are 2 500–5 000 Norwegians who suffer from this condition. By comparison, there are estimated to be just under 6 000 people in Norway with multiple sclerosis (7).

Whereas migraine most frequently affects women, men are affected three times more often than women by cluster headache (4). Onset is usually between the ages of 20 and 40 years (1), but has been reported at all ages, from three years to over 90 years. The risk of cluster headache is estimated to be 5–18 times higher in first-degree relatives than in the general population, and 1–3 times higher in second-degree relatives (8). An association has been demonstrated with the *alcohol dehydrogenase* gene and with a variant of the *hypocretin receptor 2* gene. Nevertheless, cluster headache that runs in families is relatively rare, and many genes and environmental factors probably play a role (9).

Historically, the cluster headache patient has been characterised, and to some degree stigmatised, as the prototypical «testosterone man» in both appearance and behaviour: a heavy user of tobacco and alcohol, but also ambitious and hard-working (10). A study from Northern Norway found that only a minority of cluster headache patients were non-smokers or had never smoked (3). Whether cluster headache patients have higher levels of alcohol consumption than others is less certain.

Clinical presentation

Cluster headache is characterised by relatively brief attacks of stereotyped, strictly unilateral and very intense pain in the eye region. Around 15 % of patients may experience their cluster headache switching sides, but never during an attack and very rarely within a single bout of headaches. Autonomic symptoms that affect the side of the face ipsilateral to the pain (Fig. 1) are a signature of both cluster headache and other rarer trigeminal autonomic headaches.

All symptoms and signs are principally transient and disappear when the pain resolves. A partial Horner's syndrome can, however, persist between attacks during an active disease period, and on rare occasions even become permanent. Restlessness and agitation are also typical of cluster headache attacks. Migrainous features such as photo- and phonophobia, nausea, vomiting and visual and sensory auras may occur (11). The syndrome is characterised by the fact

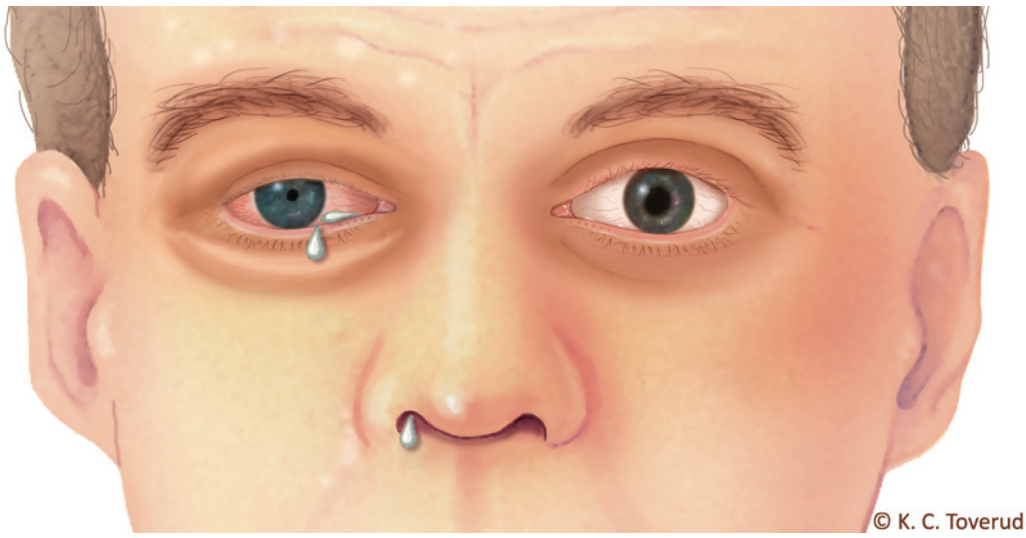

Figure 1 *Cranial autonomic signs during a cluster headache attack. Partial Horner's syndrome (ptosis, miosis), conjunctival injection and tears on the left side. A characteristic periorbital oedema can also be seen*

that attacks tend to cluster, and often occur at specific timepoints.

Bouts of cluster headaches usually last from weeks to months, 8.6 weeks on average in a British series (11), only for the headaches to disappear for months to years. Some patients experience only one bout of cluster headaches in their lives, while others have frequent relapses. A typical scenario is one bout per year with a couple of attacks each day, one of which often occurs early at night during sleep. If there is no remission after a year, or remission lasts less than a month, the patient has *chronic cluster headache*. This is true of approximately 10–15 % of patients (1). In active disease periods, attacks are triggered in the majority by small amounts of alcohol, usually within an hour of ingestion. Other (vasodilatory) agents such as histamine and nitroglycerin can also trigger attacks (1).

BOX 1

Diagnostic criteria (1)

At least 5 attacks that fulfil the following two requirements

Intense unilateral orbital, supraorbital pain and/or temporal pain which untreated lasts for 15–180 minutes

The headache is accompanied by one or both of the following:

1 At least one of the following symptoms or signs ipsilateral to the headache:
   - Conjunctival injection and/or lacrimation
   - Nasal congestion and/or rhinorrhoea
   - Eyelid oedema
   - Forehead or facial sweating
   - Forehead or facial flushing
   - Sensation of fullness in the ear
   - Miosis and/or ptosis

2 Restlessness or agitation

Attacks occur between once every other day and 8 times a day for more than half of the active disease period

No other disorder can better account for the clinical picture

Pathophysiology

The mechanisms that underlie cluster headache attacks are only partially known. An overview of existing knowledge is given in Figure 2 (12–15).

Step 1. Predisposition and attack onset

A small area of the anterior hypothalamus determines rhythmic diurnal fluctuations in a number of physiological functions. This part of the brain was believed early on to be responsible for generating cluster headache attacks, on the basis of their striking regularity. In the 1970s and 1980s, multiple studies revealed abnormal levels of pituitary hormones during bouts of cluster headaches, supporting a causal role for the hypothalamus (12).

In the late 1990s, positron emission tomography (PET) revealed marked activation of the posterior hypothalamus during nitroglycerin-induced attacks (16). It was long assumed that this was unique to cluster headaches, and then later to trigeminal autonomic headaches as a whole, but more recently hypothalamic activation has also been shown in migraine (17).

Step 2. Pain

The pain associated with cluster headache is mediated by the first branch of the fifth cranial nerve (trigeminal nerve). Why the nerve becomes activated is unknown, but when it does, a number of peptides are released from the free nerve endings (13). These can cause a local inflammatory response with histamine release, vasodilation and oedema. Increased levels of both calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) are detected during both spontaneous and nitroglycerin-induced cluster headache attacks.

Step 3. Lacrimation, rhinorrhoea, conjunctival injection and flushing

Parasympathetic nerve fibres follow the 7th cranial nerve and end in a ganglion behind the eye socket (sphenopalatine ganglion). Postganglionic fibres project to structures including the lacrimal glands, meninges and cranial blood vessels. It is assumed that strong activation of the trigeminal nucleus (pain signals) reflexively activates these fibres (14). Dilatation of intracranial vessels during attacks has been demonstrated using various techniques, and the temperature of the face increases on the affected side.

Step 4. Miosis, ptosis

In addition to symptoms that indicate increased parasympathetic activation during cluster headache attacks, many patients also show symptoms of sympathetic failure on the headache-affected side, in the form of a Horner-like syndrome. The most widely accepted theory is that this is the result of compression or stretching of the oculosympathetic fibres, which are in the adventitia of the internal

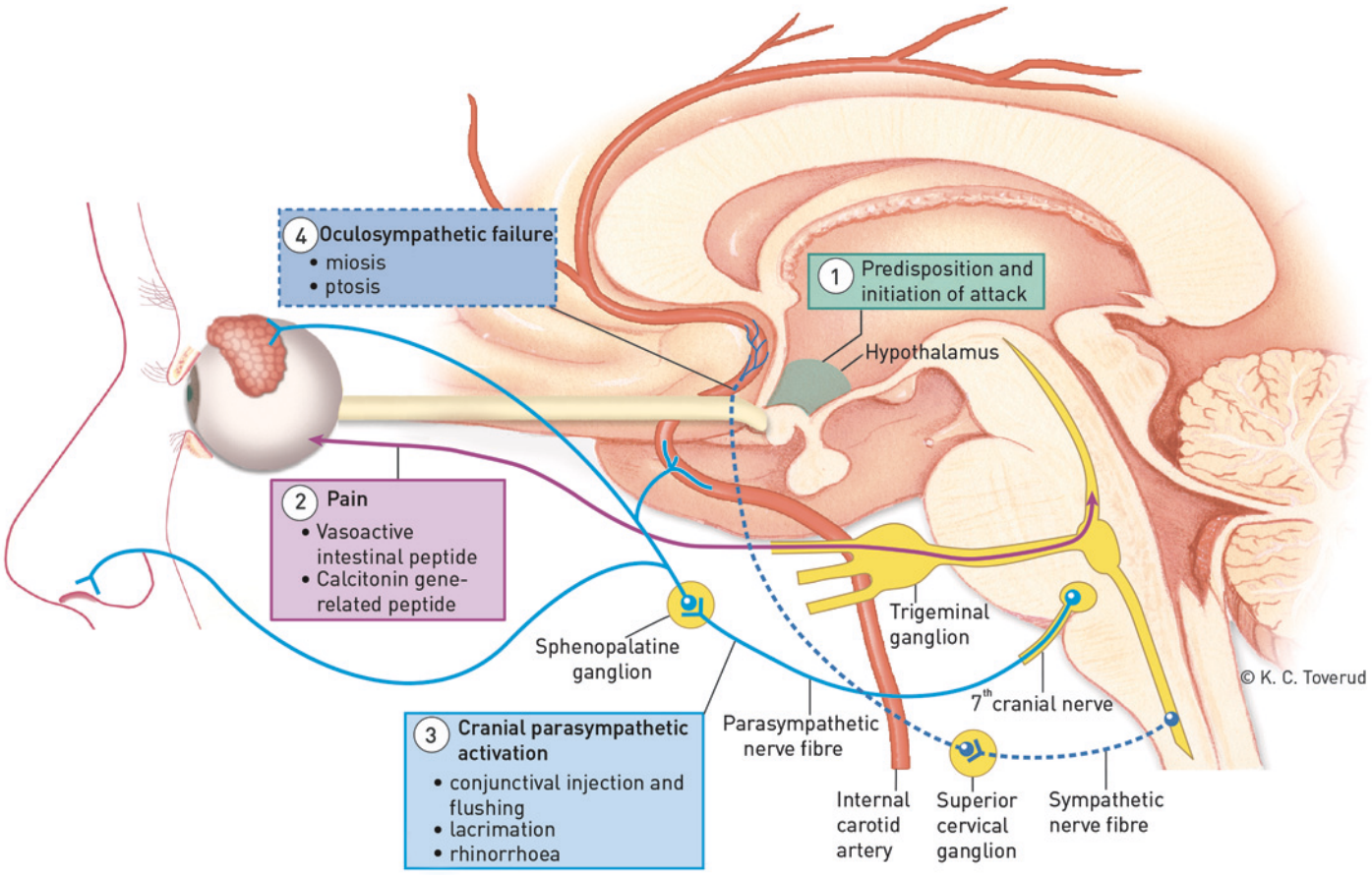

Figure 2 *Postulated pathophysiological mechanism. The cause of cluster headache is unknown, and the mechanisms that underlie the symptoms and signs are only partially understood. Illustrated are current theories regarding attack initiation (step 1) [12], pain activation (step 2) [13], cranial parasympathetic activation (step 3) [14] and oculosympathetic failure (step 4) [15]*

carotid artery, due to parasympathetic vasodilation (15).

Evaluation and differential diagnoses

A diagnosis of cluster headache is made on the basis of a thorough medical history that reveals symptoms and signs in accordance with diagnostic criteria (Box 1) (1). Symptomatic (secondary) forms are rare, but should be ruled out. In particular, one should be aware of the possibility of arterial dissection and of structural lesions of the pituitary gland and adjacent areas (18). Some recommend routine MRI of the pituitary gland. However, this risks uncovering incidental microadenomas, perhaps in as many as one in ten patients (19). Upon suspicion of carotid dissection, for example due to persistent Horner's syndrome, or pathology of the cavernous sinus, MRI should be supplemented with angiography. Eye diseases such as keratitis and glaucoma are also differential diagnoses that must be kept in mind.

Cluster headache and migraine are related conditions with overlapping clinical symptoms. In migraine attacks, the pain lasts longer, autonomic symptoms are less prominent and often bilateral, and accompanying symptoms such as phono-/photophobia and nausea are typical. Neither the strong association with sleep and alcohol nor the cyclical nature of attacks is as pronounced in migraine as in cluster headache. The typical migraine patient wishes to rest, preferably lying in a dark, cool and quiet room, whereas the cluster headache patient is agitated and will often pace restlessly with their hand pressed against the painful area.

Because of the intense pain, cluster headache is sometimes confused with trigeminal neuralgia. The pain of trigeminal neuralgia is, however, a stabbing pain (1–2 sec), almost always localised in the face (2nd or 3rd branches of the trigeminal nerve) and unaccompanied by autonomic phenomena (1). Trigeminal autonomic headaches other than cluster headache are rare (20). One should nevertheless note that both hemicrania continua and paroxysmal hemicrania can be prevented by use of indometacin, but that such treatment is poorly tolerated (20).

Treatment

The European guidelines for the treatment of cluster headache are from 2006 (21), but in our view there have been few more recent studies that are likely to change these to any notable degree. The scientific knowledge base for the recommendations is graded (A–C).

Treatment of attacks

Attacks are treated with parenteral triptan and/or 100 % oxygen via a mask (grade A). A couple of subcutaneous injections of sumatriptan daily are considered safe in younger patients in good cardiovascular health, also when used for extended periods (21). Experience suggests that many patients use more frequent doses, and our impression is that the risk of serious adverse effects is not high. Triptans are, however, contraindicated with cardiovascular and cerebrovascular disease, and should generally be used with caution (22), particularly in the elderly.

Nasal sprays containing sumatriptan (20 mg) or zolmitriptan (10 mg) also have documented efficacy, but with slower onset of

action than injection therapy (grade A); the same is true of peroral zolmitriptan (10 mg) (grade B). Local treatment with 1 ml lidocaine 4 % intranasally appears to have an effect in at least one third of patients, while in half, subcutaneous injection of 100 µg octreotide reduced the headache within 30 minutes (grade B).

Transitional treatment

Bridging therapy is generally used in a transitional phase until long-acting preventative medications start to work. Steroids can quickly reduce and sometimes temporarily eliminate attacks of cluster headache (grade A). The optimal treatment regime is unclear, but a high dose of prednisolone (60–80 mg/day) for five days with subsequent reduction by 10 mg every second or third day until discontinuation, is in keeping with most recommendations.

Methylprednisolone, 100–500 mg/day for five days with prednisolone taper, is another common recommendation. Suboccipital injections of steroids and local anaesthetic around the occipital nerve on the pain-affected side can also quickly reduce attack frequency in both episodic and chronic cluster headache (23).

Preventive treatment

The vast majority of patients should be offered preventive treatment. Verapamil is undoubtedly the first choice and has documented efficacy in a small placebo-controlled multicentre study (grade A). The usual dosage is 240–480 mg per day, divided into three doses. Some need up to 960 mg per day, but will often then experience side effects in the form of fatigue, nausea, dizziness, constipation, peripheral oedema and possibly cardiac arrhythmias. Because of the latter, ECG testing is recommended prior to the start of treatment, and should be performed regularly throughout the treatment period, for example ten days after a dose increase, to detect any lengthening of the PR interval (AV block).

Lithium has shown an equivalent but slower-onset effect to that of verapamil (360 mg) in a small double-blind placebo-controlled study (grade B). The consensus recommendation is lithium at a plasma concentration of 0.6–1.2 mmol/l (21), but because of its narrow therapeutic window with potential for poisoning in the event of small changes in fluid-electrolyte balance and renal function, this is mostly reserved for patients with chronic cluster headache in whom other therapies are contraindicated or ineffective.

A number of other medications have been tried and are used to some degree, but there is little evidence that they have any impact. Many patients could probably benefit from a moderate dose of verapamil in combination with another drug.

Treatment of chronic cluster headache

Verapamil is the first-line treatment also for those with chronic cluster headache. In addition, the consensus is that lithium may be tried (21). For patients with refractory chronic cluster headache, so-called neuromodulatory treatment should be considered. In recent years, deep brain stimulation of the lower posterior hypothalamus has shown promising results in some treatment-refractory patients (24). Peripheral stimulation of the occipital nerve or sphenopalatine ganglion seems to work in just over half (24).

Conclusion

Cluster headache is a relatively rare disorder. It is extremely painful and requires rapid diagnosis. In order to better survey the incidence of cluster headache, ensure equal provision of quality-assured treatment across health authorities, and facilitate research, we advocate the preparation of detailed national care guidelines and the establishment of a national patient/quality register.

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