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Review Article

Cluster Headache

Clinical Features and Therapeutic Options

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Abstract

Background

Cluster headache is the most common type of trigemino-autonomic headache, affecting ca. 120 000 persons in Germany alone. The attacks of pain are in the periorbital area on one side, last 90 minutes on average, and are accompanied by trigemino-autonomic manifestations and restlessness. Most patients have episodic cluster headache; about 15% have chronic cluster headache, with greater impairment of their quality of life. The attacks often possess a circadian and seasonal rhythm.

Method

Selective literature review

Results

Oxygen inhalation and triptans are effective acute treatment for cluster attacks. First-line drugs for attack prophylaxis include verapamil and cortisone; alternatively, lithium and topiramate can be given. Short-term relief can be obtained by the subcutaneous infiltration of local anesthetics and steroids along the course of the greater occipital nerve, although most of the evidence in favor of this is not derived from randomized clinical trials. Patients whose pain is inadequately relieved by drug treatment can be offered newer, invasive treatments, such as deep brain stimulation in the hypothalamus (DBS) and bilateral occipital nerve stimulation (ONS).

Conclusion

Pharmacotherapy for the treatment of acute attacks and for attack prophylaxis is effective in most patients. For the minority who do not gain adequate relief, newer invasive techniques are available in some referral centers. Definitive conclusions as to their value cannot yet be drawn from the available data.

Cluster headache is the most common type of trigemino-autonomic headache (1), affecting some 120 000 patients in Germany alone. This review article explains the clinical characteristics, diagnostic criteria, diagnostic approaches, differential diagnoses, and treatment options for cluster headache, so as to avoid delays to reaching the correct diagnosis and initiating adequate treatment. The mean time period to diagnosis has been reported to be 44 months (e1). In addition to the established medications for acute therapy and prophylaxis, newer options under discussion include neuromodulation treatment for patients with chronic refractory cluster headache and are provided in specialist centers.

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Methods

Selective review based on the authors' scientific and clinical activities in the field.

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Epidemiology

The prevalence of cluster headache on the basis of population based samples is reported to be 7–119/100 000 (e2, e3). The epidemiological study of the German Migraine and Headache Society (*Deutsche Migräne- und Kopfschmerzgesellschaft*, DMKG) found a 12-month prevalence of 0.15%, the equivalent of about 120 000 people in Germany (2). This means that cluster headache is as common as multiple sclerosis (e4). More men are affected than women, with a ratio of 3.5:1 (3). The age of onset is around the 30th year of life, but cluster headache can also occur in children (4, e5). First-degree relatives have an 18-fold increased risk and second-degree relatives are at up to three times the risk of also developing the disease (e2).

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Clinical features

The common characteristic of trigemino-autonomic headache disorders consists of brief, one-sided headache attacks and/or attacks of facial pain with ipsilateral autonomic symptoms. Typical comorbid symptoms include lacrimation from the eye on the affected side, conjunctival reddening, rhinorrhea and/or nasal congestion, miosis and ptosis; in rare cases, contralateral sweating has been observed. More than 90% of those affected display pronounced restlessness during the attack, incessantly pacing the room or rocking the head and/or upper body (4). Ipsilateral Horner syndrome or permanent headache may persist between attacks if these are very frequent and intense (e6). In 15% to 20% of patients, the headache changes sides during the course of their illness, but cluster headache never strikes bilaterally (4). In our patient collective, which we studied prospectively (n = 209), the average duration of an attack was 97 minutes. The attacks were primarily localized retro-orbitally or periorbitally and were described as stabbing and of the most severe intensity (“like a knife penetrating behind the eye”). Some patients experience pain in the face or even the teeth (orofacial cluster headache) (5). The severity of the pain and the frequency of the attacks seriously impair patients' quality of life; 25% of patients reported suicidal intentions during the course of

their illness (6). Aversion to light or sensitivity to noise are possible side effects, as are nausea and, rarer, visual aura (4). Particularly if symptoms are untypical, the diagnosis may be delayed, effective treatment not given, or even potentially harmful interventions administered; more than 20% of patients had surgery to their teeth or nasal sinuses (for example, if sinusitis was the suspected diagnosis) (e7).

The diagnostic criteria stipulate the occurrence of at least one attack every other day and up to eight attacks per day (Box 1, Table 1). Mostly, attacks follow a circadian pattern (mostly nocturnal attacks) or a seasonal rhythm (episodes mostly in spring and autumn). 85% of patients have episodic cluster headache, and some 15% chronic cluster headache, which develops secondary to episodic cluster headache or, more rarely, as primary chronic headache. Chronic cluster headache is defined as headache for at least one year, with attack-free intervals of less than one month (1). In more than 80% of cases, cluster headache occurs episodically over many years (4). Cluster attacks are typically triggered by alcohol consumption. It is also of note that most of the patients with cluster headache are tobacco smokers (3). Whether smoking cessation has a favorable effect on the disease outcome is not known.

BOX 1

Diagnostic criteria for cluster headache*

- A. At least 5 attacks fulfilling criteria B–D
- B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes if untreated.
- C. Headache is accompanied by at least 1 of the following:
 - ipsilateral conjunctival injection and/or lacrimation
 - ipsilateral nasal congestion and/or rhinorrhea
 - ipsilateral eyelid edema
 - ipsilateral forehead and facial sweating
 - ipsilateral miosis and/or ptosis
 - a sense of restlessness or agitation
- D. Attacks have a frequency from 1 every other day to 8/day
- E. Not attributed to another disorder.

*according to the International Classification of Headache Disorders (ICHD-II).

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	Cluster headache	Paroxysmal hemicrania	SUNCT syndrome ¹⁾
Duration of attacks	15–180 min	2–30 min	5–240 sec
Frequency of attacks	1–8/day	5–15/day	3–200/day
Associated autonomic symptoms ²⁾	++	++	+
Particularities	Oxygen is mostly effective	Response to indomethacin required	Lamotrigine effective

Table 1
Differential diagnostic overview

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Pathogenesis of cluster headache

The pathophysiology of cluster headache is not fully understood to date. Imaging procedures and hormone tests disproved the neurovascular theory of an inflammatory process of the cavernous sinus and gave rise to the idea that high-level central dysregulation is the crucial pathomechanism of the disorder (7, 8, e8). The posterior hypothalamus has a key role in this, which might explain the circadian and seasonal pattern of the disorder. While the hypothalamus as the supraordinate center is responsible for initiating attacks, the pain in the cranial

autonomic nervous system is introduced and sustained by activation of parasympathetic and trigeminal nuclei (7, 8).

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Diagnostic evaluation and differential diagnosis of cluster headache

The diagnosis of cluster headache is made clinically according to the criteria set out in the International Classification of Headache Disorders (ICHD-II) (Box 1). An additional criterion is a normal clinical-neurological finding (1). Secondary manifestations of cluster headache as a result of inflammatory or neoplastic processes in the cavernous sinus, the hypophyseal fossa, or adjacent structures have to be excluded by means of magnetic resonance imaging and, if required, computed tomography scanning of the skullbase. Especially adenomas of the pituitary gland need to be ruled out (e9, e10). As aneurysms close to the midline, arteriovenous malformations and dissections can also cause symptomatic cluster headache, MRI angiography is useful to exclude vascular pathologies (e11). Signs of symptomatic cluster headache are an untypical time pattern, pathological findings on neurological examination, and a lack of, or unsatisfactory, response to otherwise effective therapies. In terms of differential diagnoses, cluster headache needs to be distinguished from paroxysmal hemicrania, which typically responds to treatment with indomethacin. In patients with accompanying pronounced autonomic symptoms, migraine should also be considered as a differential diagnosis. However, migraine attacks usually last longer than four hours and do not occur several times a day. Up to 30% of migraine patients do, however, report accompanying trigemino-autonomic symptoms—albeit less pronounced ones—mostly lacrimation (9). In 25% of patients, cluster headache coincides with other headache types. Overlaps with migraine are known as cluster migraine; the simultaneous occurrence of cluster headache with trigeminal neuralgia is known as cluster-tic syndrome (e12). Trigeminal neuralgia can also be accompanied by autonomic symptoms, but, as a neuralgia, it is not classified as a trigemino-autonomic headache. A distinction has to be drawn from nocturnal attacks of primarily sleep-related headache, which mostly develops after the 50th year of life (e13). (Table 1) provides an overview of the most important differential diagnoses.

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Treating cluster headache

Therapeutically, the treatment of acute attacks needs to be distinguished from continuous treatment that aims to reduce the frequency and severity of the cluster attacks. Most therapies are empirically based; only few controlled studies exist, and the therapeutic recommendations of this article are based on our own experience, national and international therapeutic guidelines, small studies, and case series. Systematic reporting of effect sizes is therefore not possible (10– 12) (Tables 2 and 3).

		Important side effects	Evidence of the therapeutic recommendation
Acute therapy First-line treatment	Oxygen inhalation	–	11 Effect proved in 2 RCTs (1, 3)
	Sumatriptan 5 mg s.c.	Sensation of lightness around the thorax	11 Effect proved in 2 RCTs (9, 10)
	Zolmitriptan 5mg intranasally	Sensation of lightness around the thorax	11 Effect proved in 2 RCTs (41, 42) ¹
Acute therapy/Second-line treatment	Irrigation of lidocaine nasal spray (1%)	–	1 Effect proved in 1 RCT (11)

Table 2

Therapeutic recommendations for the treatment of cluster attacks (modified from [12])

		Important side effects	Evidence of the therapeutic recommendation
Prophylaxis First-line treatment	Verapamil up to 560 mg ¹	Cardiac conduction impairment (AV blockade), constipation, edema	11 Effect proved in 2 RCTs, important for treatment (e13, e17)
	Corticoids (prednisolone, methylprednisolone) 100 mg, higher dose if required	Blood glucose imbalance, hypertension, sleep disturbance, aseptic bone necroses	11 Effect not proved in RCT, important for treatment despite lack of RCTs (11)

Table 3
Therapeutic recommendations for the prophylaxis of cluster attacks (modified from [12])

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Acute treatment of cluster attacks

Inhaling oxygen (8–12 L/minute) through a close-fitting mouth-nose mask renders 78% of patients free of pain within 15 minutes (13). Oxygen can be prescribed in Germany as a medication that is covered by the statutory health insurers. Inhaling in a sitting position is said to be most effective; a rapid rebound and unsatisfactory effect in severe attacks are possible if oxygen inhalation is not begun immediately at the onset of the attack.

Triptans have shown a very beneficial and rapid effect; they can be administered subcutaneously (sumatriptan 6 mg) or intranasally (zolmitriptan 5 mg or sumatriptan 20 mg). The number needed to treat (NNT) for pain reduction within 15 minutes is 2.4 for subcutaneously administered sumatriptan 6 mg and 2.8 for intranasal administration of 10 mg zolmitriptan (14). Pre-existing cardiac and cerebrovascular disorders, as well as severe arterial hypertension are contraindications for triptan use. If triptans are administered on a daily basis, a dull and pressing headache may develop that should be categorized as headache due to triptan overuse. This mostly affects patients with migraines or familial predisposition to migraines (e14).

To treat attacks, 4% to 10% lidocaine solution or 10% cocaine solution can be administered deep into the nostril, with the patient's head reclining and rotated to the affected side. The effect is due to a local anesthetic block of the sphenopalatine ganglion (e15) by inhibition of parasympathetic reflex pathways. The effectiveness is inferior to that of triptans, and many patients have reported a disagreeable burning sensation in their nose. (Table 2) provides an overview of acute therapy.

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Prophylaxis of cluster headache

Prophylactic treatment of cluster headache is indicated in a setting of frequent and severe attacks; the aim is to shorten cluster episodes and reduce the number of attacks. Sufficient prophylaxis can help reduce triptan use and therapeutic expenditure. The prophylactic medications should be selected on the basis of therapeutic experience, contraindications, and comorbidities; often, several prophylactic drugs are required. (Table 3) provides an overview of prophylactic medications.

Verapamil is the drug of choice for the treatment of cluster headache. Because of its effects on cardiac conduction, control ECGs are essential before and during therapy. The recommendations how rapidly the dose should be stepped up are inconsistent and are based on effectiveness and tolerability. The recommended maximum daily dose is 560 mg. Higher dosages (up to 960 mg) should be given only once sufficient experience has been gained. Verapamil becomes effective within the first week of treatment and is superior to lithium in this respect

([e16](#), [e17](#)). Lithium is an alternative to verapamil especially in the treatment of chronic cluster headache. Blood levels of lithium as well as of thyroid hormones should be measured regularly.

Corticoids are highly effective as the exclusive treatment in patients whose history has shown brief cluster episodes, or as temporary treatment until verapamil or lithium becomes effective, and for temporary treatment of a severe episode in chronic cluster headache ([10](#)). We have seen good results after administration of prednisone 100 mg over 5 days with subsequent gradual reduction (for example, reducing the dose by 20 mg on every third day). Depending on the experience gleaned from preceding cluster episodes, markedly higher dosages may be required. In the short term, prednisone can be used at higher dosages and intravenously ([10](#), [e18](#)). Because of their side effect profile, the long-term use of steroids is contraindicated.

Oral ergotamines have been found to be effective, but their variable gastrointestinal resorption, vasoconstrictive potential, and the potentially threatening side effects associated with ergotism constitute problems. Because of synergistic side effects, they should not be administered simultaneously with triptans. Ergotamines can be taken in the evening as a prophylactic measure for nocturnal attacks ([e14](#)). The ergotamine alkaloid methysergide (8–12 mg) can be purchased from the international pharmacy. A combination with triptans, however, is problematic because of synergistic vasoconstrictive effects. Rare but potentially serious complications in long-term use are retroperitoneal, pleural, and cardiac valve fibrosis, so that laboratory controls, thoracic radiography, ECG, and abdominal ultrasonography should be undertaken after 4 to 6 months' treatment. The treatment should be given for a maximum of 6 months ([e19](#)). Because of the problematic side effects in long-term therapy, methysergide should be used only as third line pharmacotherapy and only by experienced practitioners.

Topiramate seems effective for cluster headache, but in our experience this is the case only for higher daily dosages (>100–150 mg/day) or in combination with verapamil and/or lithium. Adverse effects of topiramate include paresthesias and mental and cognitive impairments. Topiramate should not be used in patients with nephrolithiasis. Not enough study data are available, and topiramate is not licensed in Germany for use in cluster headache ([e20](#)). This is equally true for valproate, gabapentin, melatonin, and pizotifen. Our own experiences with these substances have been disappointing ([e21](#), [e22](#)), and they have hardly been included in routine clinical practice.

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Nerve block anesthesia for the treatment of cluster headache

Occipital nerve block using a corticoid and a local anesthetic may yield temporary relief. In a double blind, placebo controlled study, cluster attacks receded in some 85% of patients ([15](#)).

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Cluster headache that is refractory to treatment

To date, there is no uniform definition for treatment-refractory cluster headache ([16](#), [17](#)). It is therefore not possible to give an estimate of how many people are actually affected. The DMKG guidelines define cluster headache as refractory if the disease takes a chronic course over 24 months with significant impairments to the patient's quality of life and socioeconomic situation. The guidelines recommend minimum dosages (verapamil >400 mg, lithium carbonate >800 mg and serum concentrations in the therapeutic range, topiramate >100 mg, indomethacin >150

mg to exclude paroxysmal hemicranias or hemicrania continua, methysergide >8 mg, corticosteroids such as prednisolone >100 mg) (17).

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Invasive and interventional therapeutic approaches in cluster headache

Invasive procedures do not represent an “alternative” treatment option to pharmacotherapy but an additional back-up option for treating severely impaired patients whose headaches are refractory to treatment.

Ablative procedures such as rhizotomy of the root exit zone of the trigeminal nerve or destructive procedures to the Gasserian ganglion have been abandoned because of severe irreversible side effects (anesthesia dolorosa). Stereotactic radiosurgical interventions (gamma knife) have proved effective in a small case series, albeit at the cost of persistent hyposensitization (e23).

Neuromodulation procedures provide a source of hope for patients with treatment-refractory cluster headaches in terms of reducing the number and severity of attacks.

Case reports and case series have been published on deep brain stimulation at the posterior hypothalamus at the transition to the upper tegmentum. Since the effect often sets in only after weeks or months, the mechanism of action is assumed to be due to complex neuroplastic restructuring processes (18, e24). The initially published excellent response rates were reproduced at slightly lower rates as the procedure became more widely available (average success rate about 50%) (18, 19, e25). A recent blinded study found no superiority of stimulation in the first month but a 50% reduction in attacks when stimulation was continued (e26). In one case, lethal hemorrhage occurred as a complication after deep brain stimulation, which reflects the potential risks of stereotactic intervention independently of the indication (e27, e28).

Similarly good results were noted for stimulation of the occipital nerve. Modulation at the level of the spinal cord via convergence of afferences of the trigeminal nerve and the upper cervical marrow (C2/C3) in the trigemino-cervical complex is being discussed as a mechanism of action for bilateral chronic stimulation of the occipital nerve (e29– e31). The first successfully treated series of patients with chronic cluster headache reported a reduction in the intensity of pain and the frequency of attacks of 20% to 90%. Our own prospective studies have confirmed this; the effect can be expected to manifest after 4 to 6 weeks (20, 21). Because of the lower invasiveness of the procedure, we prefer bilateral stimulation of the occipital nerve to deep brain stimulation.

In spinal cord stimulation (SCS), an electrode is inserted epidurally high up in the cervical spine for the purpose of stimulation, but thus far only one case report has become available (e32); a scientific assessment of the procedure is currently not possible.

Therapeutic attempts have also been made using vagus nerve stimulation (VNS). A small case series showed an effect for migraine and cluster headache (e33, e34). However, so far the data do not permit any assessment of the short-term and medium-term effectiveness.

Stimulation of the sphenopalatine ganglion (SPG) is intended to enable treatment of attacks on the basis of ablative or local anesthetic effects (e35– e37). Initial results using external stimulation units have been promising (22, 23). However, it remains to be seen whether this technology is also suitable for prophylactic treatment. These procedures should not be used outside a clinical trial setting.

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Conclusions

In most patients it is possible by means of medication to satisfactorily treat and even prevent attacks of cluster headache, which is classed as the most severe headache disorder. Delays in reaching a diagnosis and therefore in administering treatment cause problems in this often underdiagnosed disorder. Neuromodulation therapies are available for patients with chronic cluster headache or for those whose headache is refractory to treatment, but their value is currently not clear. However, these treatment modalities give hope for improvements to the therapy of cluster headache, although they should be administered according to current guidelines in centers in the context of prospective studies (17).

Key Messages

- Cluster headache is the most severe type of primary headache and is characterized by brief, one-sided attacks that are typically accompanied by trigeminoautonomic manifestations and restlessness.
- Successful treatment of the attacks with triptans (nasal or subcutaneous) or inhalation of pure oxygen has a sound scientific evidence base.
- High-dose verapamil (also suitable for long-term treatment) and a short course of corticosteroids are the therapies of choice for the prophylaxis of cluster headache. Lithium has become an established treatment modality for chronic cluster headache.
- Topiramate, ergotamine, melatonin, valproate, and methysergide represent further medication treatments; however, the evidence base is limited.
- Stimulation of the occipital nerve can be offered in centers to patients with chronic cluster headache that is refractory to treatment and is a less invasive approach to therapeutic neuromodulation than deep brain stimulation in the hypothalamic region.

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Footnotes

Conflict of interest statement

Dr Gaul has received honoraria for participating in an advisory board from Desitin and Allergan. He has received honoraria in the context of a publication from Boehringer Ingelheim. He has received travel and hotel expenses and honoraria for speaking from Berlin Chemie, MSD, and Allergan. He has been reimbursed for conducting commissioned clinical studies from MSD, Novartis, Complien Health, CoLucid Pharmaceuticals, and Bial.

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