CME

Cluster headache: A review of clinical presentation, evaluation, and management

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ABSTRACT

Cluster headache is a primary headache disorder that leads to attacks of excruciating unilateral head pain with ipsilateral cranial autonomic features. These attacks can cluster, with frequent occurrences for weeks or months at a time followed by a period of complete remission. The excruciating pain of these attacks often is accompanied by increased suicidality, delays in diagnosis, and unnecessary invasive interventions. This article reviews the clinical presentation, differential diagnosis, evaluation, and treatment of cluster headache.

Keywords: cluster headache, trigeminal autonomic cephalalgias, TAC, treatment, cranial autonomic features, cluster period

Learning objectives

- Identify the clinical manifestations of cluster headache.
- Recognize clinical features that can assist in differentiating cluster headache from other headache disorders.
- Describe the role of imaging and other testing in evaluation of patients with a clinical picture of cluster headache.
- List possible treatment options in cluster headache.

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Cluster headache is a primary headache disorder that involves attacks of unilateral head pain with accompanying ipsilateral cranial autonomic features. Attacks often cluster and can occur in series for weeks or months at a time followed by a period of complete remission. With its unilateral head pain and autonomic features, cluster headache falls under the umbrella of trigeminal autonomic cephalalgias (TACs). Other TACs include hemicrania continua, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks. Of the TACs, cluster headache is the most common and has the longest episodic attack duration.[1]

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The pain of cluster headache attacks is unmatched. In a survey of 1,604 patients with cluster headache, responders were asked to rate different experiences on a pain scale of 1 (least painful) to 10 (most painful). Cluster headache was rated at 9.7, followed by labor pain at 7.2, pancreatitis at 7, and kidney stones at 6.9. Migraine, in comparison, was rated at 5.4.[2]

This significant pain is accompanied by increased suicidality during cluster periods, particularly during the time of the headache. In a study of 175 patients with cluster headache, 64.2% reported passive suicidal ideation and 35.8% reported active suicidal ideation during an attack, compared with 4% and 3.5%, respectively, outside an attack.[3]

Furthermore, patients with cluster headache often undergo delays in diagnosis, misdiagnosis, and improper treatment. In the United States, the average delay to correct diagnosis is 6.6 to 8.5 years.[4] This delay has been seen across multiple countries, including those with well-developed healthcare resources.[4] Misdirected referrals and lack of knowledge of the condition can further lead to improper diagnoses and unnecessary treatments. For example, many patients with cluster headache are referred to a dentist or otolaryngologist, with 52% of these patients having an invasive procedure performed for their pain.[5]

With increased clinician awareness of cluster headache presentation, evaluation, and management, time to diagnosis and proper treatment can be expedited to improve

Key points

- Cluster headache is a primary headache disorder that involves attacks of severe unilateral head pain with accompanying ipsilateral cranial autonomic features. Headaches often occur in clusters for weeks or months at a time, followed by periods of complete remission.
- Features of cluster headache that can help differentiate it from other primary headache disorders include its severity, duration, unilateral cranial autonomic features, associated restlessness or agitation, and rhythmicity.
- Because secondary causes can mimic a cluster headache phenotype, MRI of the brain is often ordered for evaluation.
- First-line acute treatment includes 100% oxygen via a non-rebreather mask and nonoral routes of triptans, namely sumatriptan subcutaneously.

patient outcomes and quality of life. This article summarizes the classic presentation, differential diagnosis, evaluation, and treatment of cluster headache.

EPIDEMIOLOGY

The pooled lifetime prevalence of cluster headache is 0.12%.[6] The textbook presentation of cluster headache usually involves a man age 20 to 40 years. A meta-analysis quantified the male-to-female ratio of patients with cluster headache to be about 4.3:1.[6]

Cluster headache can be chronic or episodic. The chronic form involves less than 3 months of headache remission over a year.[1] Between 10% and 15% of patients with cluster headache have the chronic form.[1]

CLINICAL MANIFESTATIONS

The classic presentation of cluster headache is excruciating, unilateral, periorbital pain that lasts 15 to 180 minutes and is accompanied by a sensation of restlessness or agitation.[1] Patients also may have ipsilateral cranial autonomic features such as conjunctival injection, ptosis, lacrimation, rhinorrhea, congestion, eyelid edema, miosis, or forehead sweating.[1] The International Classification of Headache Disorders, 3rd edition (ICHD-3), a resource that provides diagnostic criteria for a plethora of headache and facial pain disorders, includes these characteristics in its diagnostic criteria (**Table 1**).[1]

Cluster headache derives its name from its attacks occurring in groups, or cluster periods. Cluster periods involve repeated attacks, often over weeks or months, followed by complete remission of symptoms. These remissions often can last for extended periods of time, with some patients going years without return of their cluster headache symptoms. A Danish study found that 56% of patients have annual rhythmicity, with cluster periods starting at particular times of year.[7] Cluster headache frequency in this study was found to peak between August and March.[7]

TABLE 1. Cluster headache diagnostic criteria[1]

- Frequency: every other day to eight times per day
- Duration: 15-180 minutes
- Location of pain: unilateral; around the eye and temple
- Pain intensity: severe
- Associated with:
  - cranial autonomic symptoms on same side as headache, such as: ptosis, lacrimation, rhinorrhea or congestion, conjunctival injection, miosis, forehead or facial sweating, or eyelid edema

  and/or
  - restless/agitation during an attack

Frequency of headache varies during a cluster period, from every other day to up to eight times in a day.[1] Cluster headache also has a circadian rhythm, often awakening patients at night.[7] The Danish study noted that the highest frequency of cluster headache attacks in the early hours of the morning, with 2 a.m. being the most common hour for an attack.[7]

PATHOPHYSIOLOGY

The pathophysiology of cluster headache is complex and has yet to be fully elucidated. Theories are derived from the clinical features of cluster headache, including the trigeminal nerve distribution of pain, cranial autonomic features, and circadian periodicity. Given these features, the trigeminovascular system, trigeminal autonomic reflex, and hypothalamus are postulated to be involved.

The trigeminovascular system is thought to be involved in the sensation of pain in cluster headache. This system consists of neurons from the trigeminal ganglion that innervate the cerebral blood vessels and dura mater.[8] Projections also are sent to the trigeminocervical complex, a region in the caudal brainstem and upper cervical spinal cord where upper cervical nerve root and trigeminal ganglion projections converge. From here, signals are sent to the thalamus, which then results in activation of cortical structures involved in pain processing.[9]

The trigeminal autonomic reflex is thought to be involved in the ipsilateral cranial autonomic features in cluster headache. This reflex results in cranial parasympathetic symptoms such as lacrimation and congestion.[10] The mechanism behind its activation in cluster headache is not clear.

Involvement of the hypothalamus is supported by its neuroendocrine functions and regulation of circadian rhythm. Keeping in mind the role of the hypothalamus in the hypothalamic-pituitary axis, one study found that some men have lowered testosterone during cluster periods.[11] Another study noted that patients with cluster headache had reduced response to thyrotropin-releasing hormone during their cluster periods.[12] Furthermore, the hypothalamus controls circadian rhythm, which may explain the seasonal features and clockwise regularity of attacks. Involvement of the hypothalamus is further supported by functional

TABLE 2. Frequency and duration of TACs[1]

	Frequency	Duration
Cluster headache	Every other day to 8 times/day	15 to 180 minutes
Paroxysmal hemicrania	More than 5 times/day	2-30 minutes
Short-lasting unilateral neuralgiform headache attacks	At least once per day	1 to 600 seconds
Hemicrania continua	Constant (with exacerbations)	More than 3 months

neuroimaging showing activation of the ipsilateral posterior hypothalamus during a cluster headache attack.[13]

DIFFERENTIAL DIAGNOSIS

Migraine As with migraine, cluster headache can sometimes be accompanied by photophobia, phonophobia, or nausea. Furthermore, migraine can sometimes be accompanied by autonomic features such as lacrimation, conjunctival injection, or rhinorrhea. However, these autonomic features in migraine often are less prominent and/or bilateral.

Patients with migraine typically want to stay still because movement aggravates their pain. In contrast, patients with cluster headache often are restless and pace the room. In adults, migraine typically lasts 4 to 72 hours, but cluster headache attacks last up to 3 hours.[1]

Other TACs All of the TACs involve significant unilateral head pain and autonomic features. However, they are mainly differentiated by headache frequency and duration (**Table 2**). Paroxysmal hemicrania has the most overlap in duration with cluster headache: 2 to 30 minutes for paroxysmal hemicrania versus 15 to 180 minutes for cluster headache.[1] However, paroxysmal hemicrania is completely responsive to indomethacin, with this feature being included in its ICHD-3 diagnostic criteria.[1] Cluster headache does not respond to indomethacin. Paroxysmal hemicrania also typically occurs more frequently in a day, with a mean attack frequency of 11 times per day.[14]

Hypnic headache Sometimes called *alarm clock* headache, hypnic headache involves recurrent head pain that awakens a patient from sleep, and typically is seen in patients older than age 50 years.[15] These headaches are variable in presentation but are most commonly bilateral, mild to moderate in severity, and without autonomic features.[15] This differs from the severe, unilateral pain accompanied by cranial autonomic features that is typically seen in cluster headache. Hypnic headache also exclusively occurs at night, unlike cluster headache, which also can occur during the day.[1]

Consider secondary causes in the differential diagnosis of cluster headache, including vascular causes (cervical artery dissection, arteriovenous malformation, cerebral venous sinus thrombosis), trauma, tumors (pituitary adenoma, parasellar meningiomas), infections (sinusitis, herpes zoster ophthalmicus), and ophthalmic disease (glaucoma, orbital pseudotumor). Differentiation from cluster headache depends on the disease process. However, some secondary causes can present with typical cluster headache features and may be difficult to differentiate from symptom presentation alone.[16]

EVALUATION

Perform a thorough neurologic examination when evaluating a patient who may have cluster headache. If a patient has a headache at the time of the appointment, cranial autonomic features may be seen, such as ptosis, lacrimation, or conjunctival injection. Between headaches, the examination typically is normal, but obtain an MRI of the brain with contrast to rule out intracranial secondary causes that may mimic a cluster headache phenotype.

If arterial causes are a concern, such as in patients with Horner syndrome, magnetic resonance or CT angiography often are used. Magnetic resonance or CT venography may be considered if cerebral venous sinus thrombosis is a concern, such as in a patient with papilledema. Deciding between these imaging modalities and specific further testing is case-dependent and beyond the scope of this article. However, further testing is warranted if the patient has an abnormal neurologic examination beyond the typical transient ipsilateral cranial autonomic features during an attack, with assessment geared toward evaluating the noted abnormality. Any doubt in diagnosis, difficulty with management, or abnormal findings on testing warrant referral to neurology.

TREATMENT

Treatment for cluster headache typically is divided into acute, transitional, and preventive treatment. None of the treatments discussed in this article, except for galcanezumab, noninvasive vagus nerve stimulation (nVNS), and subcutaneous sumatriptan, are FDA-approved for use in cluster headache at this time.

Acute treatment These treatments are used to abort individual cluster headache attacks. The American Headache Society (AHS) gives a positive level A recommendation, which is indicative of established efficacy in the literature, for only three abortive treatments: supplemental oxygen, subcutaneous sumatriptan, and zolmitriptan nasal spray.[17] A noninvasive vagus nerve stimulator also is used acutely but was not available at the time these recommendations were made.

Supplemental oxygen is delivered at 10 to 15 L/minute as 100% oxygen for a total of 15 minutes.[18] It should be administered via a non-rebreather mask with the patient in the upright position. Oxygen generally is safe but is contraindicated in patients with significant chronic obstructive pulmonary disease because of the risk of developing severe hypercapnia.