CME

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

Christina R. Lindemann, MS, PA-C

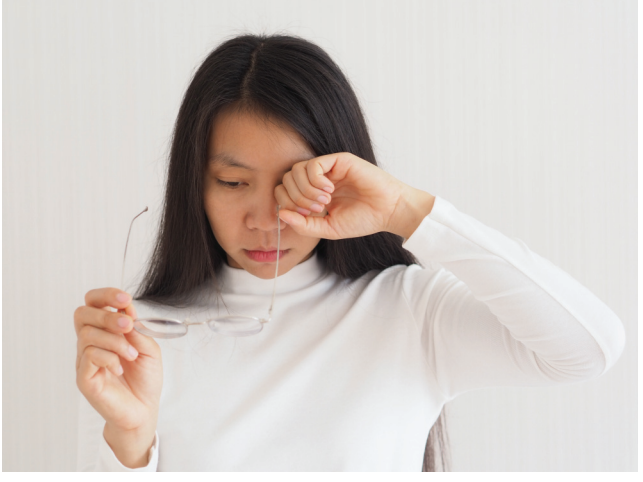
ABSTRACT

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]

Christina R. Lindemann practices in the Headache and Traumatic Brain Injury Center at the University of California San Diego. The author has disclosed no potential conflicts of interest, financial or otherwise.

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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.

Subcutaneous sumatriptan typically is dosed at 6 mg and a maximum frequency of twice daily. Sumatriptan also comes in oral and intranasal forms. However, there is no evidence for efficacy of the oral form in cluster headache. Furthermore, onset is more rapid via nonoral routes, which is important to consider when attacks are not only very severe but also can be relatively short in duration. Some evidence supports the efficacy of the intranasal form of sumatriptan, although evidence for zolmitriptan nasal spray is stronger.[17]

Zolmitriptan nasal spray typically is used in 5-mg or 10-mg doses. The spray usually is administered on the side contralateral to the headache because of the rhinorrhea and nasal congestion that can occur ipsilateral to the headache.

Warn patients that triptans may cause a sensation of chest pressure, throat tightness, nausea, and fatigue. Consider patient contraindications to sumatriptan and zolmitriptan before prescribing, including a history of coronary artery disease, coronary artery vasospasm, ischemic bowel disease, peripheral vascular disease, uncontrolled hypertension, stroke, or transient ischemic attack.[19,20]

nVNS is FDA-approved for acute use in episodic cluster headache but not in chronic cluster headache. This treatment involves a device placed at the neck that provides a mild electrical signal over the vagus nerve. Three 2-minute stimulations are performed at the onset of an attack. If pain continues after 3 minutes, the stimulations can be repeated. Therapy may be used for up to four attacks per day.

Other medications sometimes used for patients who cannot take or do not respond to first-line treatments include ipsilateral intranasal lidocaine and subcutaneous octreotide. Evidence for these is less established, however.[17]

Transitional treatment These treatments are used as a bridge to reduce cluster headache attack frequency while patients wait for preventive regimens to take effect. However, if a patient has a shorter cluster period, such as a few weeks in duration, sometimes these treatments can be used in a preventive manner. A tapering course of oral corticosteroids or ipsilateral suboccipital corticosteroid injections often are used for transitional treatment. Suboccipital corticosteroid injections have a positive level A recommendation by the AHS.[17] Prednisone is level U, indicating insufficient evidence to make a recommendation, but it often is used in practice.[17] The various prednisone and suboccipital corticosteroid injection protocols are beyond the scope of this article.

Preventive treatment These treatments are used to reduce the frequency of cluster headache attack, most often for patients with cluster periods that last for months or are without remission. With the exception of suboccipital corticosteroid injections, the AHS does not have any positive level A recommendations for treatments that reduce the frequency of cluster headache.[17] Verapamil and lithium typically are used in practice and both have positive level C recommendations, indicating possible effectiveness based on the quality of evidence in the literature.[17]

Verapamil often is used first-line. Typical dosing starts at 80 mg three times daily with titration by 80 mg every 2 weeks according to patient response. Doses can approach 400 mg per day. Because verapamil can cause PR interval prolongation and atrioventricular heart block, obtain a baseline ECG and further ECG monitoring with each dose increase. Obtain an ECG periodically after the patient reaches the target dose.

Lithium requires monitoring for toxicity, and adverse reactions including hypothyroidism, cardiac dysrhythmias, and neurotoxicity. Because of its multiple interactions, narrow therapeutic window, and adverse reaction profile, lithium is not used first-line. Typically, if lithium is being considered, referral to neurology is warranted.

Galcanezumab, an injectable monoclonal antibody targeting calcitonin gene-related peptide, received FDA approval in June 2019 for treatment of episodic cluster headache.[21] This medication is dosed subcutaneously in three 100-mg syringes (300 mg total) per month. Possible adverse reactions include injection-site reactions and hypersensitivity reactions. The last AHS recommendations were made in 2016; therefore, this medication does not have an AHS recommendation.

nVNS also is FDA-approved for preventive treatment in patients with chronic and episodic cluster headache. For prevention, three 2-minute stimulations are performed twice daily.

Other treatments sometimes used in clinical practice include topiramate, gabapentin, and melatonin. Melatonin 10 mg has a positive level C rating by AHS; studies of topiramate and gabapentin did not meet the AHS's inclusion criteria for forming its recommendations.[17]

Preventive treatment typically is continued until 2 to 3 weeks after a cluster period has subsided. The medication can then be stopped. At this time, there is no evidence to support that staying on a medication will prevent a new cluster period from occurring in the future.

CONCLUSION

Cluster headache is a disabling disorder that often takes years until it is properly diagnosed. It typically presents with severe orbital or periorbital pain combined with ipsilateral cranial autonomic features and a sensation of restlessness for 15 to 180 minutes. Attacks can cluster, by occurring in series for weeks or months at a time, to then be followed by a period of complete headache remission. Cluster headache often has a circadian and circannual rhythm that, combined with its duration, sensation of restlessness, and autonomic features, can be useful in differentiating it from other primary headache disorders. Some secondary causes can mimic a cluster headache phenotype, so careful evaluation is warranted. This evaluation typically includes MRI of the brain with contrast. Although FDA

approval is limited for cluster headache treatments, some evidence-proven options are available. Further research on treatments also is needed, given the lack of treatment options for targeted therapy.

By better understanding cluster headache, clinicians can help patients promptly obtain appropriate evaluation, treatment, and referrals and avoid unnecessary suffering, testing, and invasive interventions. **JAAPA**

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