Making the Diagnosis of Cluster Headache

Vince Martin, MD

DEFINITION OF CLUSTER HEADACHE

The International Classification of Headache Disorders, 3rd edition (ICHD-3) describes cluster headache (CH) as attacks of severe, strictly unilateral pain which is orbital, supraorbital, temporal, or in any combination of these sites, lasting 15 to 180 minutes and occurring from once every other day to eight times a day (TABLE 1). The pain is associated with one or more autonomic signs or symptoms ipsilateral to the headache and the intensity is often described as excruciating. Patients are usually unable to lie down and characteristically pace the floor. CH attacks occur in series lasting for weeks or months (so-called cluster periods or bouts) and are usually separated by remission periods lasting months or years. One-quarter of patients are reported to have only a single cluster period in their lifetime. Attacks tend to exhibit a circadian as well as circannual pattern, that is, occur at the same time(s) each year, particularly during the spring and fall. During a cluster period, attacks occur regularly and may be provoked by alcohol, histamine, or nitroglycerin. Other possible triggers include weather changes, smells, and bright or flashing lights.

CH is classified as either episodic or chronic. Episodic CH attacks occur in periods lasting from seven days to one year, although they usually last between two weeks and three months. In episodic CH, cluster periods are separated by pain-free periods lasting at least three months. Eighty-five to 90% of patients with CH meet the definition for episodic CH. In contrast, approximately 10% to 15% of patients with CH have chronic CH. Chronic CH attacks occur without a remission period, or with remissions lasting <3 months, for at least one year. Chronic CH may arise de novo or evolve from episodic CH. In some patients, chronic CH changes into episodic CH.

EPIDEMIOLOGY

CH is a rare headache disorder with a lifetime prevalence of approximately 0.12%. The age at first occurrence of CH is typically between 20 and 40 years, although onset has been observed earlier. In addition, a second, smaller peak in the incidence of onset has been shown in later decades of life in some studies. CH predominantly affects men with a men to women ratio of approximately 3 or 4 to 1. This ratio has decreased over the past few decades for reasons that remain unclear. Some evidence indicates a lower men to women ratio in cases of familial CH.

RISK FACTORS

Smoking

Cigarette smoking is strongly associated with CH. A review of the medical records of 374 men with CH showed that 88.8% of patients with episodic CH had a positive smoking history, with 78.9% of patients with episodic CH being current smokers. For chronic CH, 95.1% had a positive smoking history, with 87.8% smoking at the time they developed chronic CH. Findings from the US Cluster Headache Survey showed that 73% had a positive smoking history, with 51% indicating smoking at the time they developed CH.

Genetics

First- and second-degree relatives of people with CH are more likely to have CH than the general population. Epidemiologic evidence indicates the risk for CH is five to 18 times higher than the general population for first-degree relatives, and one to three times higher for second-degree relatives. For families in which several members have CH, the disorder can vary among them with respect to episodic or chronic presentation and the presence of autonomic symptoms.
CH, as well as areas that may be responsible for the restlessness observed with CH. Molecules modulated by the hypothalamus, such as melatonin, are altered in patients with CH.

The trigeminovascular system is responsible for the pain observed in CH. Pain input is first received through the ophthalmic branch from the forehead, eye, dura, and large cranial vessels. These inputs are projected to several nociceptive nuclei in the brainstem and upper cervical cord, then to the thalamus, and finally to the pain neuromatrix. The trigeminovascular system has several signaling molecules including calcitonin gene-related peptide and substance P, which are elevated during a CH attack.

Areas of the autonomic system involved in CH stem from the superior salivatory nucleus to the sphenopalatine ganglion. Autonomic features such as lacrimation, conjunctival injection, and other cranial autonomic features of CH involve either parasympathetic overactivation or sympathetic inactivation. Among several signaling molecules in the autonomic system, the levels of vasoactive intestinal peptide and pituitary adenylate cyclase-activating peptide are elevated during a CH attack.

DIAGNOSIS

CASE SCENARIO

MJ is a 31-year-old man seen in the office complaining of episodes of excruciating left-sided head pain. The headaches tend to occur at night and last a couple of hours. During the headache attacks, he has tearing and redness of his left eye and is very restless/agitated.

The diagnosis of CH is primarily a clinical one based on history and detailed neurological examination. A concomitant headache disorder may be observed since some patients with CH also experience another headache disorder. Laboratory evaluation is not useful in diagnosing CH except when needed to exclude a secondary headache disorder. Magnetic resonance imaging (MRI) of the brain can be used to rule out other etiologies. In patients with CH, MRI reveals significant enlargement of the anterior hypothalamic gray matter ipsilateral to the headache side compared with controls. Moreover, functional MRI has demonstrated significant cerebral activation in the ipsilateral hypothalamic gray matter during an attack.

Clinical features

CH attacks are unilateral, affecting the peri- and retro-orbital regions and the temple, sometimes involving the teeth.

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**TABLE 1. ICHD-3 diagnostic criteria for cluster headache.**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
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<tbody>
<tr>
<td>A.</td>
<td>At least five attacks fulfilling criteria B-D</td>
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<tr>
<td>B.</td>
<td>Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)</td>
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<tr>
<td>C.</td>
<td>Either or both of the following:</td>
</tr>
<tr>
<td>1.</td>
<td>at least one of the following symptoms or signs, ipsilateral to the headache:</td>
</tr>
<tr>
<td>a)</td>
<td>conjunctival injection and/or lacrimation</td>
</tr>
<tr>
<td>b)</td>
<td>nasal congestion and/or rhinorrhea</td>
</tr>
<tr>
<td>c)</td>
<td>eyelid edema</td>
</tr>
<tr>
<td>d)</td>
<td>forehead and facial sweating</td>
</tr>
<tr>
<td>e)</td>
<td>miosis and/or ptosis</td>
</tr>
<tr>
<td>2.</td>
<td>a sense of restlessness or agitation</td>
</tr>
<tr>
<td>D.</td>
<td>Occurring with a frequency between one every other day and eight per day</td>
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<tr>
<td>E.</td>
<td>Not better accounted for by another ICHD-3 diagnosis.</td>
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</tbody>
</table>


1During part, but less than half, of the active time-course of cluster headache, attacks may be less severe and/or of shorter or longer duration.

2During part, but less than half, of the active time-course of cluster headache, attacks may be less frequent.
The pain is excruciating, often described as severe, intense, sharp, and burning, with a clear onset and resolution.\(^2\) The pain may be compared to poking the eye with a white-hot needle or knife.\(^{18}\) During an attack, patients experience one or more cranial autonomic symptoms ipsilateral to the pain, including lacrimation, eye redness, eye discomfort such as grittiness, ptosis, nasal congestion, rhinorrhea, aural fullness, throat swelling, and flushing.\(^2\) Restlessness and agitation are prominent features during an attack and are highly sensitive and specific for CH.\(^2\) Patients are cognitively alert, but may be irritable and aggressive.\(^{18}\) Once an attack terminates, patients are usually symptom-free until their next attack.\(^2,18\)

Attacks tend to exhibit a circadian pattern, often occurring at night during sleep.\(^2,3\) For unknown reasons, recurrent cluster attacks or bouts also exhibit a circannual rhythm, often occurring in the spring and autumn.\(^4,5,18\) Similar to restlessness and agitation, circadian and circannual cyclicity are not observed in all patients with CH, but when present, they are very suggestive of CH.\(^{18}\)

### RESOURCES

The following are resources that may be helpful in diagnosing CH, as well as providing education to patients with CH.

- American Headache Society  
  - Case vignette, including signs/symptoms, diagnosis, and treatment  
- American Migraine Foundation  
  - Epidemiology, pathophysiology, symptoms and comorbidities  
  https://americanmigrainefoundation.org/resource-library/cluster-headache-and-other-medical-conditions/  
  - Symptoms and treatment  
  https://americanmigrainefoundation.org/resource-library/what-to-know-about-cluster-headache/
- Clusterbusters  
  - Symptoms, diagnosis, terms  
  https://clusterbusters.org/about-cluster-headache/

### MISDIAGNOSIS AND DIAGNOSTIC DELAY

CH is often a debilitating disorder that, during the worst attacks, causes excruciating pain.\(^1\) Patients with CH often experience a delay in diagnosis resulting in prolonged morbidity and exposure to unnecessary diagnostic procedures and treatments. A systematic review showed that the mean time to correct diagnosis in the United States ranged from 6.6 to 8.5 years, with one study showing that 42% of patients waited more than 5 years to receive a correct diagnosis of CH.\(^{22}\) A systematic literature review of US and non-US studies reported that diagnoses received prior to a CH diagnosis included a wide variety of headache and non-headache disorders.\(^{22}\) In the US, the number of diagnoses received prior to CH was 3.9. In addition to various investigations to diagnose a secondary headache such as radiologic procedures, patients received a wide spectrum of pharmacologic, surgical, and alternative medicine treatments.\(^{22}\)

Several factors may contribute to diagnostic delay including the nonspecific nature of many signs and symptoms. One study involving 1163 patients with CH found a diagnostic delay more likely in those with an episodic attack pattern, presence of nausea and/or vomiting during attacks, photophobia or phonophobia, nocturnal onset, and alternating attack side.\(^{23}\) Another study found that lower age at onset and pain that does not reach its peak intensity within the first five minutes were significant causes of diagnostic delay.\(^{24}\)

### TABLE 2. Common features of cluster headache\(^{1-4,18,21}\)

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
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<tbody>
<tr>
<td>Typical age of onset</td>
<td>20-40 years</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>M&gt;F</td>
</tr>
<tr>
<td>Quality of pain</td>
<td>Stabbing, piercing, sharp, burning</td>
</tr>
<tr>
<td>Pain intensity</td>
<td>Severe or very severe</td>
</tr>
<tr>
<td>Localization</td>
<td>Unilateral around the eye, above the eye, or near the temple</td>
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<tr>
<td>Duration of attacks</td>
<td>15-180 minutes</td>
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<tr>
<td>Frequency of attacks</td>
<td>Every one or two days up to 8 times per day</td>
</tr>
<tr>
<td>Periodicity</td>
<td>Attacks occur during cluster bouts; cluster bouts can follow circannual periodicity; attacks can follow circadian periodicity</td>
</tr>
<tr>
<td>Autonomic manifestations</td>
<td>Yes</td>
</tr>
<tr>
<td>Behavior</td>
<td>Restlessness, agitation</td>
</tr>
<tr>
<td>Triggers</td>
<td>Alcohol, histamine, nitroglycerin</td>
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</tbody>
</table>
• Cluster Headache Support Group
  - Patient experience
    https://chsg.org/2011/02/14/cluster-headache-attack/
  - Coping strategies
    https://chsg.org/guides/coping-strategies/
  - Disability laws, insurance, and employment rights
    https://chsg.org/guides/disability/
• International Classification of Headache Disorders
  - Diagnostic criteria for cluster headache
    https://www.ichd-3.org/3-trigeminal-autonomic-cephalalgias/3-1-cluster-headache/
• National Headache Foundation
  - Headache diary
  - Headache Impact Test
• National Organization for Rare Disorders
  - Description, signs/symptoms, causes, comorbidities, diagnosis, treatment
    https://rarediseases.org/rare-diseases/cluster-headache/

REFERENCES

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