CLUSTER HEADACHE

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ABSTRACT

Any pain in the head, and especially in the face, requires careful evaluation for appropriate diagnosis and treatment. Clinical factors that must be considered in the differential diagnosis are the location of the pain, the quality and intensity of the pain, the behavior of the patient during a headache attack, the autonomic features that are present, any trigger factors that can be identified, and the temporal profile. This article looks at the clinical hallmarks of cluster headache and what differentiates it from other head pain and migraine.

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Cluster headache is characterized by severe unilateral orbital and temporal pain of rapid onset, usually 5 minutes to 15 minutes, and of short duration, usually 45 minutes to 90 minutes. Unlike patients with migraine, who typically look for a quiet and/or dark place to lie down during an attack, patients with cluster headache are restless and agitated, often given to pacing. Although cluster headaches are not associated with migrainous symptoms such as nausea, photophobia, phonophobia, aura, and gastrointestinal symptoms, they may occur, as demonstrated by recent reports of patients with cluster headache who also had migrainous or migrainelike aura and vision changes.

Cluster headache is associated with a number of autonomic features, most commonly conjunctival injection, lacrimation, nasal congestion, and runny nose on the patient’s affected side. Facial flushing, sweating, and edema of the eyelid on the affected side are sometimes present, and systemic signs such as bradycardia may also occur. Cold spots have been noted on tomographic images taken of a patient during a cluster headache attack, and the patient’s affected side may be colder to the touch than the unaffected side. Other associated features are high alcohol and/or tobacco usage, peau d’orange skin, hazel eyes, andleonine features. While many physicians think the latter is typical of cluster headache, it is not pathognomonic.

Alcohol use is a precipitating or aggravating factor for both cluster and migraine headaches, often triggering a cluster headache within 20 to 30 minutes and a migraine within 2 hours. Nitroglycerin use can also precipitate migraine and cluster headaches. While triggers such as trivial touch and facial movements can precipitate trigeminal neuralgia, they are not typical for cluster headache.

The circadian clustering of headache attacks gives cluster headache its name. Typically, there are 1 to 3 attacks a day, although up to 8 attacks per day can occur, with peak time periods that tend to occur at the same time in the same patient. Attacks often occur during rapid-eye movement sleep (ie, 2 AM), at 3 PM, 9 PM, early morning, evening, or after a nap. In some

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In some patients, attacks cluster at the same time of the year. For those living in the northern hemisphere, attacks usually occur during the early months of the year and autumn, when there is less daylight. For those living in the southern hemisphere, attacks occur during the late months of the year and spring.

The International Headache Society recognizes 2 forms of cluster headache: episodic, which affects 90% of patients, and chronic, which affects the remaining 10%. Chronic cluster headache is characterized by the absence of a remission that lasts for more than 2 weeks between attack clusters or by a cluster period that lasts for more than 1 year without remission. Transformation from episodic to chronic cluster headache may occur in 13% of patients, while transformation from chronic to episodic cluster headache may occur in 33%. Cluster-free intervals vary between 1 year and several years.

Unlike migraine, which is relatively common, cluster headache is rare, with a prevalence of 0.1% to 0.4%. Whereas migraine headache is more common in females, cluster headache is more common in males, with a male-to-female ratio ranging from 3.5:1 to 7:1. The average age at onset is 27 to 31 years of age and is extremely rare before the age of 10.

**Related Syndromes**

There are at least 3 syndromes that are related to cluster headache: chronic paroxysmal hemicrania (CPH), episodic paroxysmal hemicrania (EPH), and short unilateral neuralgic pain with conjunctival tearing (SUNCT). Because these trigeminal/autonomic cephalalgias involve autonomic features and share several presenting symptoms with cluster headache, the diagnosis can be confounded. The major differences between these syndromes and cluster headache are shown in the Table.

**Pathophysiology**

The pathophysiology of cluster headache has been a subject of considerable research interest in recent years, with several major advances in the areas of pain, autonomic symptoms, and periodicity. There are now human data on the vessels and cavernous sinus and on the trigeminal system, as well as neuroimaging data on periodicity and hypothalamic function.

In the area of pain and autonomic signs, one investigation in patients with cluster headache found that increased levels of calcitonin gene-related peptide in the jugular vein reflected trigeminovascular activation, while increased levels of vasoactive intestinal peptide reflected cranial parasympathetic activation. Other investigations have suggested that vasodilation of the internal carotid artery during a cluster headache attack might be involved or that inflammation leading to compression of nerves in the carotid sinus might be the underlying cause of the pain.

Studies in patients with migraine and cluster headache have shown similarities between the 2 disorders. One similarity is that nitroglycerin can induce headache in both populations. However, the time frames are different, as are the underlying mechanisms. Whereas nitroglycerin induces a migraine attack in approximately 5 hours by neuronal sensitization, it induces a cluster attack in about 30 minutes, possibly by a vascular effect. Other similarities between migraine and cluster headache include impaired mitochondrial energy reserves, impaired serotonin metabo-

<table>
<thead>
<tr>
<th></th>
<th>CPH</th>
<th>EPH</th>
<th>SUNCT</th>
<th>Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female-to-male ratio</td>
<td>3:1</td>
<td>1:1</td>
<td>1:2.3</td>
<td>1:4</td>
</tr>
<tr>
<td>Attacks/day</td>
<td>1-40</td>
<td>3-30</td>
<td>1/day-30/hour</td>
<td>0-8</td>
</tr>
<tr>
<td>Attack duration</td>
<td>2-45 min</td>
<td>1-30 min</td>
<td>15-200 sec</td>
<td>15-180 min</td>
</tr>
<tr>
<td>Indomethacin response</td>
<td>++</td>
<td>++</td>
<td>No</td>
<td>±</td>
</tr>
</tbody>
</table>

CPH = paroxysmal hemicrania; EPH = episodic paroxysmal hemicrania; SUNCT = short unilateral neuralgic pain with conjunctival tearing; ++ = marked response; ± = variable response.

lism, abnormalities of evoked potentials, a therapeutic response to triptans, and a family history of migraine in first-degree relatives of patients with either migraine or cluster headache.

An important advance in the area of periodicity was the finding of structural changes in the brains of patients with cluster headache. Other important advances in this area include abnormal activation of the hypothalamus, suggesting that the neuroendocrine system is involved (with the hypothalamus as the generator), and dysfunction of the hypothalamic pacemaker.

**ACUTE AND PREVENTIVE TREATMENT**

Several regimens are available for acute and preventive treatment of cluster headache. The most effective is a subcutaneous injection of a 6-mg dose of sumatriptan. Other regimens with high efficacy in the acute treatment setting are oxygen (7-10 L/min for 10-15 minutes), and intravenous, intramuscular, or subcutaneous injections of dihydroergotamine mesylate 0.5-1.0 mg, ergotamine 1-2 mg (either orally or by suppository), and intranasal lidocaine and/or cocaine.

While several drugs are effective in preventing cluster headache attacks, there is no consensus as to which is best. These drugs include prednisone (60 mg/day for 3 days, then tapered in 10-mg decrements every 3 days), ergotamine (1-2 mg orally or by suppository), dihydroergotamine mesylate (0.5-1.0 mg subcutaneously or intramuscularly every 8 to 12 hours), verapamil (which is probably most effective for prevention), methysergide, and lithium (particularly for the chronic form of cluster headache). Occipital nerve block is also an option.

To induce remission from cluster headache, a single suboccipital injection of a combination of a short- and a long-acting steroid is quite effective and has a remission rate of about 50%. If there is no remission after 48 hours, 240 mg of verapamil twice a day is tried, resulting in remission in an additional 20% of patients. If attacks continue, the verapamil dose is increased (in increments of 120 mg) to 600 mg to 1040 mg, causing remission in an additional 10% of patients. If this approach is unsuccessful, methysergide plus lithium or verapamil plus lithium is given. If this also fails to induce remission, topiramate (100 mg -400 mg) or gabapentin (900 mg -1200 mg) can be tried. If there is still no remission, the patient is considered drug resistant and a traumatic procedure, such as a radiofrequency-induced lesion of the gasserian ganglion, should be discussed with the patient.

**REFERENCES**


