Making the Diagnosis of Cluster Headache

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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**).[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.[1]

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.[1] One-quarter of patients are reported to have only a single cluster period in their lifetime.[1] 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.[2-4] During a cluster period, attacks occur regularly and may be provoked by alcohol, histamine, or nitroglycerin.[1] Other possible triggers include weather changes, smells, and bright or flashing lights.[5]

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.[1]

In contrast, approximately 10% to 15% of patients with CH have chronic CH.[1] Chronic CH attacks occur without a remission period, or with remissions lasting <3 months, for at least one year.[1] Chronic CH may arise *de novo* or evolve from episodic CH. In some patients, chronic CH changes into episodic CH.[1]

EPIDEMIOLOGY

CH is a rare headache disorder with a lifetime prevalence of approximately 0.12%.[6] The age at first occurrence of CH is typically between 20 and 40 years, although onset has been observed earlier.[1,7,8] In addition, a second, smaller peak in the incidence of onset has been shown in later decades of life in some studies.[9,10] CH predominantly affects men with a men to women ratio of approximately 3 or 4 to 1.[1,3,6] This ratio has decreased over the past few decades for reasons that remain unclear.[4] Some evidence indicates a lower men to women ratio in cases of familial CH.[11]

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.[12] 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.[5]

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.[13] 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.[13]

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DISCLOSURES

Dr. Martin discloses that he serves on the advisory board for Amgen, Eli Lilly, Alder, Teva, Allergan, and Biohaven. He serves on the speakers' bureau for Amgen, Eli Lilly, Allergan and Teva. He has received grant funding from Allergan.

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TABLE 1. ICHD-3 diagnostic criteria for cluster headache.[1]

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

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[1]During 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.

[2]During part, but less than half, of the active time-course of cluster headache, attacks may be less frequent.

Head trauma

Some evidence suggests there may be an association between head trauma and CH.[14] Results of the US Cluster Headache Survey showed a history of head trauma in 18% of patients who subsequently developed CH.[5] Another investigation involving retrospective review of the medical records of all men with CH referred to one headache center over a 20-year period (N=374) showed that 35.9% of patients with episodic CH and 54.7% of patients with chronic CH had a history of head trauma.[12] In more than 75% of men whose head trauma preceded CH onset, the average time interval between the two events was 10.1 years, suggesting no association between the two.[12]

PATHOPHYSIOLOGY

CH is a primary headache disorder that involves interaction of three key structures within the central nervous system. These include the trigeminovascular system, autonomic nervous system (trigeminal autonomic reflex), and hypothalamus.[2,4,15] The trigeminovascular system consists of neurons of the trigeminal nerve that innervate cerebral blood vessels and dura mater.[2] The hypothalamus appears to play a large role in CH and is activated first, followed by the trigeminovascular and autonomic nervous systems.[15]

The hypothalamus includes the circadian system thought to be responsible for the clocklike regularity of CH, as well as areas that may be responsible for the restlessness observed with CH.[15] Molecules modulated by the hypothalamus, such as melatonin, are altered in patients with CH.[15]

The trigeminovascular system is responsible for the pain observed in CH.[15] 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.[15,16]

Areas of the autonomic system involved in CH stem from the superior salivatory nucleus to the sphenopalatine ganglion.[15] 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.[15-17]

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.[7,18] A concomitant headache disorder may be observed since some patients with CH also experience another headache disorder.[1] 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.[7] In patients with CH, MRI reveals significant enlargement of the anterior hypothalamic gray matter ipsilateral to the headache side compared with controls.[19] Moreover, functional MRI has demonstrated significant cerebral activation in the ipsilateral hypothalamic gray matter during an attack.[20]

Clinical features

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

TABLE 2. Common features of cluster headache[1-4,18,21]

Typical age of onset	20-40 years
Sex ratio	M>F
Quality of pain	Stabbing, piercing, sharp, burning
Pain intensity	Severe or very severe
Localization	 Unilateral around the eye, above the eye, or near the temple
Duration of attacks	15-180 minutes
Frequency of attacks	Every one or two days up to 8 times per day
Periodicity	Attacks occur during cluster bouts; cluster bouts can follow circannual periodicity; attacks can follow circadian periodicity
Autonomic manifestations	Yes
Behavior	Restlessness, agitation
Triggers	Alcohol, histamine, nitroglycerin

(**TABLE 2**).[1-4,18,21] 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]

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]

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
    https://americanheadachesociety.org/wp-content/uploads/2018/05/AHSProfilesIssue4.pdf
- 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/

- 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
    https://headaches.org/wp-content/uploads/2018/08/HEADACHE-DIARY.pdf
  - Headache Impact Test
    https://headaches.org/wp-content/uploads/2018/02/HIT-6.pdf
- National Organization for Rare Disorders
  - Description, signs/symptoms, causes, comorbidities, diagnosis, treatment
    https://rarediseases.org/rare-diseases/cluster-headache/ ●

REFERENCES

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
2. Wei DY, Yuan Ong JJ, Goadsby PJ. Cluster headache: Epidemiology, pathophysiology, clinical features, and diagnosis. *Ann Indian Acad Neurol*. 2018;21(Suppl 1): S3-S8.
3. May A, Leone M, Afra J, et al. EFNS guidelines on the treatment of cluster headache and other trigeminal-autonomic cephalalgias. *Eur J Neurol*. 2006;13(10):1066-1077.
4. Hoffmann J, May A. Diagnosis, pathophysiology, and management of cluster headache. *Lancet Neurol*. 2018;17(1):75-83.
5. Rozen TD, Fishman RS. Cluster headache in the United States of America: demographics, clinical characteristics, triggers, suicidality, and personal burden. *Headache*. 2012;52(1):99-113.
6. Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: a meta-analysis of population-based studies. *Cephalalgia*. 2008;28(6): 614-618.
7. Matharu MS, Goadsby PJ. Trigeminal autonomic cephalgias. *J Neurol Neurosurg Psychiatry*. 2002;72(Suppl 2):ii19-ii26.
8. Majumdar A, Ahmed MA, Benton S. Cluster headache in children – experience from a specialist headache clinic. *Eur J Paediatr Neurol*. 2009;13(6):524-529.
9. Manzoni GC, Taga A, Russo M, Torelli P. Age of onset of episodic and chronic cluster headache – a review of a large case series from a single headache centre. *J Headache Pain*. 2016;17:44.
10. Rozen TD, Fishman RS. Female cluster headache in the United States of America: what are the gender differences? Results from the United States Cluster Headache Survey. *J Neurol Sci*. 2012;317(1-2):17-28.
11. Taga A, Russo M, Manzoni GC, Torelli P. Familial cluster headache in an Italian case series. *Neurol Sci*. 2015;36(Suppl 1):S141-S143.
12. Manzoni GC. Cluster headache and lifestyle: remarks on a population of 374 male patients. *Cephalalgia*. 1999;19(2):88-94.
13. Russell MB. Epidemiology and genetics of cluster headache. *Lancet Neurol*. 2004;3(5):279-283.
14. Lambru G, Matharu M. Traumatic head injury in cluster headache: cause or effect? *Curr Pain Headache Rep*. 2012;16(2):162-169.
15. Burish M. Cluster headache and other trigeminal autonomic cephalalgias. *Continuum (Minneap Minn)*. 2018;24(4, Headache):1137-1156.
16. Buture A, Boland JW, Dikomitis L, Ahmed F. Update on the pathophysiology of cluster headache: imaging and neuropeptide studies. *J Pain Res*. 2019;12:269-281.
17. Tuka B, Szabo N, Toth E, et al. Release of PACAP-38 in episodic cluster headache patients – an exploratory study. *J Headache Pain*. 2016;17(1):69.
18. Leroux E, Ducros A. Cluster headache. *Orphanet J Rare Dis*. 2008;3:20.
19. Arkink EB, Schmitz N, Schoonman GG, et al. The anterior hypothalamus in cluster headache. *Cephalalgia*. 2017;37(11):1039-1050.
20. Morelli N, Pesaresi I, Cafforio G, et al. Functional magnetic resonance imaging in episodic cluster headache. *J Headache Pain*. 2009;10(1):11-14.
21. May A. Hints on diagnosing and treating headache. *Dtsch Arztebl Int*. 2018;115(17): 299-308.
22. Buture A, Ahmed F, Dikomitis L, Boland JW. Systematic literature review on the delays in the diagnosis and misdiagnosis of cluster headache. *Neurol Sci*. 2019;40(1): 25-39.
23. van Vliet JA, Eekers PJ, Haan J, Ferrari MD. Features involved in the diagnostic delay of cluster headache. *J Neurol Neurosurg Psychiatry*. 2003;74(8):1123-1125.
24. Van Alboom E, Louis P, Van Zandijcke M, Crevits L, Vakaet A, Paemeleire K. Diagnostic and therapeutic trajectory of cluster headache patients in Flanders. *Acta Neurol Belg*. 2009;109(1):10-17.