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Diagnosis of this excruciating, often debilitating headache type may be delayed five years or longer.

Cluster Headache

Hastening Diagnosis and Treatment

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Cluster headache is an extremely painful and potentially debilitating condition. It is underrecognized and often misdiagnosed, leading to a delay in appropriate treatment. Clinicians must be prepared to identify this uncommon headache type—then refer the patient or create a treatment plan that will optimize the patient's function and minimize cluster headache's disabling effects.

Headache is one of the health problems most commonly associated with significant morbidity, as well as considerable social and economic repercussions.[1,2] Headaches are classified into three main types:

- *Primary headaches,* or headaches without known organic causes
- *Secondary headaches,* or headaches manifesting with symptoms due to organic causes; and
- *Cranial neuralgias, facial pain,* and other headaches.[3]

Cluster headache (CH) is a type of primary headache—one of the headache types encompassed by the term *trigeminal autonomic cephalalgia*.[3] It is one of the most intense, excruciating headaches a patient can experience, and the diagnosis is often missed or delayed. Only 21% of patients receive a correct diagnosis of CH on first presentation, and the average patient visits three health care providers before the correct diagnosis is made.[4,5] According to recently published results from the US Cluster Headache Survey,[4] the diagnostic delay for CH averages five years or longer, limiting the patient's access to correct treatment.

Patients with CH are prone to significant physical, social, and economic disability; most patients, for example, find it difficult to work during a CH period.[1,2] Almost 20% of patients with CH report having lost a job because of their headaches, and about 8% are unemployed or on disability.[4]

Because of the pain severity and the associated impairment, the risk for suicide in the CH patient population is real.[2,6,7] Jürgens et al[7] report that 22% of patients with chronic CH and about 15% of those with episodic CH had suicidal tendencies; Rozen and Fishman[4] report suicidal ideation in 55% of CH patients.

CHARACTERISTICS OF CLUSTER HEADACHE

As the name implies, attacks of this headache type tend to "cluster" together. In 85% to 90% of patients, CH is *episodic,* with cluster periods of headache attacks commonly lasting for one week to one year, and intervening remission periods that may last from one month to years.[3,8] The remaining 10% to 15% of CH patients have the *chronic* CH type, in which cluster periods typically last for more than one year and are separated by remission periods lasting one month or less.[3,8]

Cluster headaches tend to occur in predictable patterns, often in the spring and fall.[9-11] Most headaches begin between early evening and early morning, and patients are often awakened by CH during the night; according to responses in the US Cluster Headache Survey,[4] onset times peak between midnight and 3 AM. Attacks can occur when the neck is rotated or flexed in specific ways; external pressure to the transverse processes of C4 or the nerve root of C2 can trigger a CH attack.[12]

Other CH triggers include alcohol (especially beer and red wine[4,13]), histamine, nitroglycerine, carbon dioxide, certain odors, and weather changes.[3,4,11,14] Eighty percent or more of CH patients have a history of prolonged tobacco use, and at least 60% of CH patients who do

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TABLE
The Differential Diagnosis for Cluster Headache[1,3,8,13,26,28]

Headache type	Severity	Location	Quality	Onset	Duration	Attack frequency	Autonomic symptoms?	Nocturnal headaches?	Gender ratio
Cluster headache	Severe, excruciating	Unilateral orbital or temporal	Stabbing	Rapid	15 – 180 min	1 every other day to 8/d	Yes	Yes	M > F
Paroxysmal hemicrania	Severe, excruciating	Unilateral orbital or temporal	Throbbing, stabbing	Rapid	2 – 30 min	≥ 5/d	Yes	Yes	F > M
SUNCT	Moderate	Unilateral periorbital	Throbbing, burning, electric	Rapid	5 – 240 sec	3 – 200/d	Yes	Yes	M ≈ F
Migraine	Moderate to severe	Unilateral	Throbbing	Gradual	4 – 72 h	No specific pattern	No	Yes	F > M
Tension	Mild to moderate	Bilateral	Steady, "tightening band"	Gradual	Varies	No specific pattern	No	No	F > M (slightly)
Trigeminal neuralgia	Moderate to severe	Unilateral, trigeminal nerve distribution	Intense, electric shock–like, stabbing	Rapid	Seconds to minutes	No specific pattern	No	No specific pattern	F > M

Abbreviation: SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing

Sources: Stovner et al. *Cephalalgia.* 2007[1]; Headache Classification Subcommittee, International Headache Society. *Cephalalgia.* 2004[3]; Scottish Intercollegiate Guidelines Network. *Diagnosis and Management of Headache in Adults.* 2008[8]; Nesbitt and Goadsby. *BMJ.* 2012[13]; Leone et al. *Lancet Neurol.* 2009[26]; Bendtsen and Jensen. *Neurol Clin.* 2009.[28]

not smoke were the children of smokers.[15] No clear relationship has been found between CH and hormones.[9,10]

EPIDEMIOLOGY

Cluster headache is relatively rare, affecting about 0.1% of the population.[8-10,16] Onset of the condition usually occurs between ages 20 and 40, and men are three to four times more likely to be affected than are women.[3,16] A familial/genetic relationship may exist.[10,17,18]

DIAGNOSIS

Patient History

Diagnosis of headache relies heavily on the patient's clinical history and physical exam.[3,8,10] A detailed history should include the initial onset of CH, progression of the condition, and information about any precipitating event(s) and prodromal symptoms. Clinicians should document the pattern of pain by including specific information regarding its location, severity, quality, frequency, and duration. Of considerable value is the patient's use of an accurate headache diary, which clinicians should encourage headache patients to maintain; in these, patients should be instructed to record the headache characteristics mentioned.[3,8]

Associated symptoms (assessed by conducting a complete review of systems), aggravating and alleviating factors, previous medical history, and psychosocial and family history are important in formulating the differential diagnosis, as misdiagnosis of CH is often related to inadequate history intake.[13]

Presentation

Cluster headaches share three main features: they are unilateral; they are associated with autonomic symptoms; and attacks tend to "cluster" in a circannual pattern (ie, clusters occurring at the same time of year) and/or circadian pattern (headache at the same time of day).[8,19] The most common locations for cluster headaches are unilateral orbital, supraorbital, temporal, or a combination of these locations.[3,8]

About 30% of patients describe the pain as "stabbing,"[3] and it is often compared to "a hot poker in the eye." Pain peaks rapidly, usually within five to 10 minutes. It may radiate to the ipsilateral forehead, jaw, cheek, and/or teeth.[3] Patients appear restless and agitated, unable to lie still.[2,10] They often sit, holding their heads, and may pace the floor or bang their heads against the wall.

CH is associated with at least one of the following autonomic symptoms, occurring in the ipsilateral side of the head: conjunctival injection, nasal congestion, forehead and facial sweating, eyelid edema, lacrimation, rhinorrhea, ptosis, and miosis.[3,13] Headaches may occur on one side of the head throughout one cluster episode, then shift to the contralateral side in subsequent periods.[10] Aura occurs in 14% to 20% of patients,[13,20-22] and nausea, as well as ipsilateral visual, sensory, and speech/language disturbances have also been reported.[3] Each CH attack lasts between 15 minutes and three hours, and attacks may range in frequency from one every other day to eight per day.[3,13]

>PRIMARYPOINT

Cluster headaches are unilateral and accompanied by autonomic symptoms, and they tend to "cluster" in circannual or cirdadian patterns.

Patients who have experienced at least five episodes of these headache symptoms, with severe pain in the specified areas and duration, accompanying autonomic symptoms, specified attack frequency, and symptoms not attributed to another disorder meet the diagnostic criteria for cluster headache given in the second edition of the *International Classification of Headache Disorders (ICHD-II,* 2004).[3] The *ICHD-II* criteria, based on clinical and epidemiologic research, are recognized as a consensus guideline that is accepted worldwide to facilitate clinical practice.[3] Patients who have experienced attacks fulfilling all but one of the *ICHD-II* criteria for CH are diagnosed with *probable CH*[3] or *cluster-like headache* (CLH).[23]

Physical Examination

A thorough physical examination, including an investigation of the neurologic system, is essential to differentiate among primary, secondary, and other headache types. In the patient with CH, no neurologic deficits or deficits that suggest underlying disorders are usually found.[3,10]

Differential Diagnosis

In the evaluation of headache, it is important to differentiate CH from the other trigeminal autonomic cephalalgias: *paroxysmal hemicrania* (PH), *short-lasting unilateral neuralgiform headache with conjunctival injection and tearing* (SUNCT), and possibly *hemicrania continua*.[3,24,25] As in CH, the pain of PH is severe, unilateral, and stabbing in quality; it, too, is associated with autonomic symptoms, often occurs at night, and can be episodic or chronic.[3] However, PH headache lasts for only 2 to 30 minutes and can occur five times or more per day. Though difficult to distinguish from CH patients, those with PH usually respond to indomethacin, whereas those with CH ordinarily do not.[3,8]

As in patients with CH, those affected by SUNCT experience autonomic symptoms—most commonly, conjunctival injection and tearing.[3,26] SUNCT differs from CH, however, in that the pain is moderate in severity, with a pulsating, burning, electric-like quality. Duration is much shorter, with episodes lasting between 5 seconds and 4 minutes.[3,26]

Hemicrania continua, though unilateral, is described as continuous and moderate in intensity. Like PH, it is also indomethacin-responsive.[8,25,27]

A broader differential diagnosis for CH, as detailed in the table,[11,3,8,13,26,28] includes the other primary headaches: tension headache, migraine headache, and trigeminal neuralgia.[3,26] *Tension headache,* which affects 30% to 78% of the general population,[3] is subdivided into *infrequent episodic, frequent episodic,* and *chronic tension-type headache.* Unlike CH, tension headache is mild to moderate in intensity and occurs bilaterally, with nonpulsating pres-

	Comments
	Associated restlessness, agitation; triggers include alcohol, histamine, nitroglycerine, carbon dioxide, certain odors, weather changes
	Responsive to indomethacin
	Usually presents with conjunctival injection and tearing but may manifest with other autonomic symptoms
	May present with or without aura; patient prefers to be quiet, still
	Tenderness on palpation of pericranial muscles
	Abrupt onset and termination; often triggered by washing, shaving, smoking, brushing teeth

sure or a tightening sensation. It is not aggravated by routine physical activity, nor is it associated with nausea, vomiting, or photophobia.

Migraine headache, also a more common primary headache type than CH,[3] occurs unilaterally, is moderate to severe in intensity, and is often described as throbbing. More gradual than CH in onset, migraine is often associated with nausea, vomiting, photophobia, phonophobia, and/or visual aura. Migraine headache lacks the ipsilateral autonomic manifestations of CH, and migraineurs prefer to rest or sleep—in contrast to the extreme restlessness or agitation seen in CH patients.[3]

Also like CH, *trigeminal neuralgia* is unilateral with a trigeminal nerve distribution, and the pain can be severe and stabbing.[3] However, trigeminal neuralgia lacks the autonomic symptoms associated with CH, and the pain lasts from only seconds to minutes. This headache type is often triggered by washing, shaving, or brushing teeth.[3]

It is also critical to exclude secondary headaches, especially those with serious causes, including meningitis, subarachnoid hemorrhage, epidural or subdural hematoma, glaucoma, tumors, temporal arteritis, or purulent sinusitis.[27] Red flags associated with these conditions are:

- A complaint of the patient's "worst headache ever" *(thunderclap headache)*
- First severe headache
- A subacute headache worsening over days or weeks
- An abnormal neurologic examination
- Fever or other unexplained systemic signs
- A headache preceded by vomiting
- Headache that is induced by bending, lifting, or coughing
- Headache that disturbs the patient's sleep or presents immediately upon awakening
- History of known systemic illness
- Headache onset after age 55; and
- Pain associated with local tenderness, for example, near the temporal artery.[27]

➤PRIMARYPOINT

It is essential to rule out headaches caused by meningitis, subarachnoid hemorrhage, temporal arteritis, tumors, and other serious underlying conditions.

DIAGNOSTIC TESTING

Since, by definition, primary headaches are those without underlying organic causes, diagnostic tests and neuroimaging studies are generally not recommended,[10,29] especially when the patient history and presentation confirm the required *ICHD-II* diagnostic criteria. However, neuroimaging is often recommended for a patient with CH or CH-like presentations.[8,23,30-32]

In a literature review published in 2006, Detsky et al[30] examined the correlation between clinical features of headache (as described in the *ICHD-II* criteria) and intracranial abnormality (as found on CT or MRI). They found an increased risk for serious intracranial abnormalities among study subjects with cluster-type headache. In any patient with chronic headache, they found, abnormal neurologic findings on physical exam represent the greatest predictor for intracranial pathology.[30]

In a similar study of 1,872 consecutive patients with nonacute headaches who underwent CT or MRI, one of 20 patients with CH was found to have a pituitary adenoma.[33] When Favier et al[34] reviewed 31 cases of trigeminal autonomic cephalalgia (TAC), including 10 with atypical symptoms, they found that even typical TAC can result from underlying pathologies with rare warning signs and symptoms. In some patients, neuroimaging study results were normal on initial diagnosis, but pathologies were discovered later after symptoms worsened or treatments ceased to be effective, prompting further imaging studies.

In a review of case studies of patients with CLH, Mainardi et al[23] found that of 38 patients who fulfilled the *ICHD-II* criteria for CH, 12 patients (31.6%) had vascular pathologies, 12 (31.6%) had tumors, and five (13.2%) had inflammatory or infectious pathologies. The researchers recommended that all patients with symptoms of CH or CLH undergo cerebral MRI with contrast medium, even though the yield for abnormal findings would likely be low.[23] Wilbrink et al[32] also found a wide range of pathologies without typical warning signs or symptoms among 56 case studies of TAC and TAC-like syndromes—and recommended that all such patients be considered candidates for neuroimaging.

Recommendations from both the Scottish Intercollegiate Guidelines Network (SIGN)[8] and the Taiwan Headache Society treatment guidelines[31] include neuroimaging of patients with CH or CLH.

MANAGEMENT

Clinicians may wish to consider referring patients to a neurologist at the initial diagnosis of CH. Patients with atypical symptomatology or neurologic abnormalities, and those who respond insufficiently to treatment warrant a neurology referral for further investigation.

The two treatment strategies for CH are *first,* symptomatic treatment for acute attacks; and *second,* intervention to prevent or reduce further attacks and to shorten the cluster period.[8,11,14,35,36]

Acute Treatment

Acute symptomatic treatment is aimed at aborting the pain within 15 to 30 minutes from headache onset.[14,35,36] Currently, it is generally accepted that 100% oxygen and parenteral triptans (5-$HT_{1B/1D}$, not through the alimentary tract) are considered first-line treatment options.[8,11,13,14,35,36]

For the majority of patients (particularly those with episodic CH), inhaled normobaric oxygen effectively relieves CH pain within 15 minutes.[14,37-39] Oxygen is administered at 6 to 12 L/min with a nonrebreather mask for at least 15 to 20 minutes.[8,14,13] Although associated adverse events are rare, oxygen is inconvenient to transport, and it poses a fire hazard. Additionally, high-flow oxygen is contraindicated in patients with chronic obstructive pulmonary disease, as these patients depend on the hypoxic drive and run the risk of respiratory depression.[14,40,41]

Triptans, too, have been found effective in the acute treatment of CH; administration by subcutaneous injection or intranasal delivery is considered more effective than the oral route due to faster onset of action,[11,14,35] and oxygen use may enhance triptans' efficacy.[38] In two 2010 reviews of the relevant literature, subcutaneous sumatriptan, dosed at either 6 mg or 12 mg, provided effective pain relief within 15 minutes for most patients, with no statistical between-dosage differences.[11,35] The most common adverse effects were injection-site reactions, nausea, vomiting, dizziness, fatigue, and paresthesias.[35]

Intranasal zolmitriptan (5 mg and 10 mg) and intranasal sumatriptan 20 mg were also found effective, with significant pain relief within 30 minutes. Bad taste is a common complaint.[35] Of note, both sumatriptan and zolmitriptan are contraindicated in patients with

cardiovascular or cerebrovascular disease.[14]

In an older study of efficacy, safety, and tolerability of subcutaneous sumatriptan, almost 70% of patients averaging between one and six CH attacks per day were found to be using more than the 12-mg maximum recommended daily dosage—as much as 36 mg in a 24-hour period.[42] Nevertheless, the researchers concluded that subcutaneous sumatriptan was effective and well tolerated without decreased efficacy over one year in patients with CH.

➤PRIMARYPOINT

Invasive procedures, such as greater occipital nerve block and deep brain stimulation, should be reserved for a select patient population.

Ergotamine, once commonly used for the acute treatment of CH, has fallen out of favor in recent years due to its vasoconstrictive effects and serious adverse effects profile.[14,35] Dihydroergotamine (DHE) is most effective when administered by IV (though not easily accessible for an acute attack); however, evidence regarding its efficacy and tolerability in other forms is insufficient to recommend DHE for acute CH therapy.[14,35]

Intranasal lidocaine, somatostatin by infusion, and subcutaneous octreotide are considered second-line treatment choices for patients who are resistant to first-line therapies or who cannot tolerate them.[14,35,43,44]

Cluster Headache Prophylaxis

A CH period can last for weeks to months. Prophylactic modalities, which are intended to shorten this period and to reduce the frequency and severity of headache attacks, are categorized into transitional and maintenance prophylaxis treatments.[14,35]

Transitional prophylaxis, a shorter course of treatment, is often started with *maintenance prophylaxis* (which is used throughout each cluster period) to hasten the response to the maintenance treatment. Corticosteroids are commonly used as a transitional treatment modality. In prednisone use, a starting dose of at least 40 mg/d by mouth is often required to provide benefit.[14] The peak dose is usually given for three to 10 days, then gradually tapered over the succeeding 10 to 30 days. Headache recurrence is common during the prednisone taper. Ergotamine tartrate and DHE are also used as transitional prophylaxis treatment for CH.[14]

Verapamil is considered the maintenance prophylaxis drug of choice due to its efficacy and safety.[14,35,45] The dosage required for adequate response ranges from 200 mg to 960 mg/d, in divided doses or in extended-release formulation. Most patients respond to daily doses between 200 mg and 480 mg.[14,46,47] Constipation is the most common adverse effect. Slow titration and frequent ECG monitoring, particularly when dosing is increased, are necessary to avoid heart block, bradycardia, hypotension, and peripheral edema.[13]

Lithium is often used as second-line therapy for maintenance prophylaxis, possibly in combination with verapamil or topiramate, to improve pain control.[35] Lithium carbonate, given at a dosage of 600 to 900 mg/d to maintain a serum level of 0.4 to 0.8 mEq/L, and topiramate, at dosages ranging from 50 to 200 mg/d, may be needed to achieve an adequate response.[14]

In at least one small study, melatonin (10 mg/d) has been associated with CH remission in 50% of treated patients.[14,48] It may be used in combination with other prophylactic medications.[14]

Among numerous other agents that have been used for CH prophylaxis, neither sodium valproate, sumatriptan, cimetidine/chlorpheniramine, misoprostol, nor oxygen is recommended for prevention of CH.[35]

Narcotics

Because of its excruciating pain, CH has been referred to as "suicide headache."[2,6,7,10,13] Acute and prophylactic treatments for CH will likely reduce the number of headache attacks; however, with CH attacks as frequent as eight times per day, these treatments may not be adequate.[24,49]

The use of any narcotic is not ideal due to its potential for addiction, and it may cause medication-overuse headache. Furthermore, in oral form, a narcotic may not relieve CH pain quickly enough. Low-dose levomethadone is an opioid that has been used prophylactically with some success in patients with chronic CH.[24,49] However, the primary care provider whose CH patient finds pain control inadequate should refer to a neurologist or a pain management specialist for evaluation—and possibly for treatment with an invasive procedure.

Invasive Procedures

Greater occipital nerve block has shown promise in the treatment of CH.[50,51] In a small, double-blind study, patients with episodic or chronic CH were randomized to receive a suboccipital injection, of either combined long- and rapid-acting betamethasone or saline (placebo), in the area of the greater occipital nerve.[50] Eighty-five percent of treated patients were free of headache attacks within 72 hours, compared with none in the control group. Use of lidocaine with triamcinolone was found somewhat less effective.[51]

Occipital nerve stimulation has also shown promise for patients with chronic CH who become resistant or are unresponsive to conventional treatments, or who cannot tolerate them.[14,24] It appears to induce gradual neuromodulation, with gradual benefits (after six to 30 months). Deep brain stimulation (ie, of the posterior hypothalamus), delivered via implanted electrodes, and other procedures have produced results ranging from "excellent" to "transient remission," reducing the use of ablative surgeries.[14,52] Because invasive modalities carry a risk for serious adverse effects,[14] their use should be reserved for a select patient population.

PATIENT/FAMILY EDUCATION

Patients with CH need to be educated regarding the nature, signs and symptoms, and triggers of CH. The indications for acute and prophylactic treatments and the adverse effects associated with each therapy must also be reviewed. Clear follow-up instructions are essential, including what conditions warrant further evaluation: worsening of the condition, changes in symptoms (impaired alertness, vision, movement, or sensation; onset of seizures), or treatment failure.

CONCLUSION

Cluster headache, a relatively uncommon primary headache that can cause excruciating and debilitating pain, is often misdiagnosed and inappropriately treated, with serious physical, social, and economic ramifications. This headache type is unilateral, associated with autonomic symptoms, and characterized by clustering of headache/remission periods in a circannual and/or circadian pattern. Diagnosis is made through the health history and physical exam, based on criteria from the *ICHD-II*. Neuroimaging may not be necessary, but given the evidence that CH and TAC are often associated with serious underlying pathology, MRI with contrast should be considered, and consultation with a neurologist at initial di-

agnosis is recommended.

Treatment is aimed at aborting the pain within 15 to 30 minutes of an acute headache attack and preventing further episodes through transitional and maintenance prophylaxis. Newer invasive options that are showing great promise may be considered for a select patient population. Clinicians should involve patients in treatment decisions that will address their individual needs, improving function and optimizing outcomes. **CR**

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