Chapter 93

Diagnosis, Differential Diagnosis, and Prognosis of Cluster Headaches

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DIAGNOSIS

Most patients with cluster headache (CH) seek medical help between attacks, and it is relatively seldom that the physician has an opportunity to witness an actual attack of headache. Results of a physical and neurologic examination are negative, with the exception of a possible partial Horner syndrome on the symptomatic side. Consequently, the diagnosis is based mainly on the history of the patient. If there is only a short history of disease, the diagnosis may be difficult, but if the patient has suffered previously from several identical periods of headache, it is easy to establish a correct diagnosis.

Some features of the pain of CH are of special diagnostic importance: (a) strict unilaterality; (b) very severe intensity; (c) orbital/supraorbital and/or temporal localization (i.e., predominantly first-division trigeminal pain); (d) prominent ipsilateral autonomic features; (e) short duration of attacks (15 to 180 minutes); (f) periods of susceptibility to attacks. Most commonly there is a characteristic periodicity to the attacks that helps to distinguish CH from other types of head pain, but as is well established about 15% of patients suffer from chronic symptoms (so-called chronic cluster headache). Sometimes a diagnosis may be obscure, especially at the beginning of the course of disease. CH commonly can be unrecognized or misdiagnosed (2,47); this most likely arises because the condition is uncommon (prevalence ~0.1%), and most of these patients have relatively infrequent attack-susceptible periods. Some patients may at times suffer from sporadic attacks having neither typical cluster nor chronic patterns, and it can be helpful to observe the patient directly in the hospital ward. The physician can obtain valuable information of the attacks and their time pattern if the patient keeps a record during the cluster period. The intensity, duration, and time of day of the attacks should be recorded, along with the effects of any medications.

In most individuals the pain is almost invariably strictly unilateral. There have, however, been exceptional case reports of bilateral pain in CH (2,20,40,49) and, even more rare, a change in side within the same attack (2). Individuals can experience attacks on both the right and left sides, more commonly in different bouts, but also during the same bout (6,20,23,26). The pain is predominantly in the distribution of the first division of the trigeminal nerve but can radiate over a wide area that includes the cheek, jaw, upper and lower teeth, nose, ear, occiput, neck, shoulder, or whole hemicranium (2,6,11,20,23,26). During attacks, there are accompanying autonomic features: a parasympathetic discharge and lacrimation with conjunctival injection, nasal congestion, rhinorrhea, and frontal sweating, as well as a sympathetic deficit: miosis and ptosis. The partial Horner syndrome occurs during acute attacks but may persist between attacks. However, in a few patients headaches are never accompanied by these autonomic symptoms or signs (7,31). There are a number of clinical features in CH that more typically occur in migraine. Up to 50% if individuals can experience nausea, less commonly with vomiting, and a similar number can experience photophobia and phonophobia (2,20). Aura symptoms are commonly not associated with CH attacks (6), but according to a recent large study, up to 14% of individuals can experience aura symptoms associated with their acute attacks (2). Most distinctive to CH is the characteristic of restlessness or agitation (2,3,6,9,45) that is now included as diagnostic criteria in the recent revised International Headache Society (IHS) classification (17). The patient often rocks the body to and fro, or he or she wanders restlessly back and forth across the floor. A simple diagnostic test (3) is to invite patients to demonstrate how they behave during severe attacks.

Clinical examination during spontaneous or provoked attacks is an additional valuable aid to diagnosis. An attack is readily provoked by giving nitroglycerin 1 mg sublingually during an active CH period (8). Preferably, the

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provocation should be carried out when the patient has not had a spontaneous attack within the previous 8 hours. The test result is accounted positive if a pain attack is induced with clinical features identical to those of a spontaneous attack. The induced attack is usually preceded by a lag of 30 to 50 minute after administration of nitroglycerin and is followed by a refractory phase lasting a few hours. The test reproducibility is good, attacks being provoked repeatedly on different occasions with an identical dose. This susceptibility decreases at either end of the bout, and an attack cannot be triggered outside of a bout (8).

Routine Investigations

The diagnosis of CH is based mainly on clinical criteria, and there is generally no indication for a radiologic investigation if the history and neurologic examination are unremarkable. Special investigations are, however, occasionally necessary in the following conditions: (a) an onset of first headaches in the elderly patient; (b) a short history of illness (e.g., in cases when the periodicity of headaches is still undetermined); (c) an atypical clinical picture (e.g., in cases with long-standing or even continuous headache); (d) a protracted course of disease, especially when the headache is progressively worsening; (e) a headache that is accompanied by confusion, loss of consciousness, or convulsions; or (f) any significant pathologic findings at neurologic examination or in laboratory tests.

As mentioned above, unilateral signs of miosis, ptosis, or both may be recorded in a substantial number of cases, but in clinical practice it is not necessary to perform a special ophthalmologic examination. In diagnosing structural brain lesions, computed tomography (CT) and magnetic resonance imaging (MRI) are the imaging procedures of first choice. An otologic examination and radiographs of the paranasal sinuses may occasionally be necessary in cases when sinusitis is being considered. Such laboratory procedures as lumbar puncture, evoked responses, or electroencephalography have no place in the routine investigation of CH.

DIFFERENTIAL DIAGNOSIS

CH is a stereotyped and very homogenous disorder. Despite sharing a number of clinical features with migraine, these features are not prominent attributes and the differential diagnosis from migraine should not be problematic. The most common problems encountered in the differential diagnosis are those of other pain syndromes that share the characteristic of strictly unilateral first-division trigeminal pain and ipsilateral autonomic features, termed the trigeminal autonomic cephalgias (13) and secondary CH. Other pain syndromes that are encompassed by the trigeminal autonomic cephalgias include paroxysmal hemicrania and SUNCT syndrome (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing). Some additional primary headaches in the differential diagnosis are hemicrania continua and hypnic headache (see Table 93-1).

Paroxysmal hemicrania (PH). The differentiation between CH and PH is that the latter is characterized by shorter and more frequent attacks and an absolute response to indomethacin. PH is characterized by strictly unilateral attacks with ipsilateral autonomic features, lasting 5 to 20 minutes and usually recurring at least 15 times per day. It is more common in women and chronic PH predominates over the episodic form (4:1). The pain disappears promptly with indomethacin (150 mg/day or less), an important diagnostic criterion. Parenteral indomethacin 100 mg intramuscularly (the "indotest") is a useful tool (1) for clinical assessment of unilateral headache with

TABLE 93-1 Differential Diagnosis of Cluster Headache

	Cluster Headache	*Paroxysmal Hemicrania*	*SUNCT*	*Hemicrania Continua*
Sex ratio M:F	3:1	1:2	2:1	1:2
Attack duration	15–180 min	2–30 min	5–240 sec	20 min–days Constant
Attack frequency	1 alternate days– 8/day	5–40/day	3–200/day	—
Chronic/episodic	Episodic (85%)	Chronic	Chronic	Chronic
Characteristics	Restless during attacks Periodicity GTN/alcohol susceptibility		Triggered and spontaneous attacks	
Prophylactic treatment	Verapamil Corticosteroids Lithium	Indomethacin Rofecoxib	Carbamazepine (partial response) Lamotrigine Gabapentin	Indomethacin Rofecoxib

GTN = glyceryl trinitrate; SUNCT = short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

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relatively short-lasting attacks when problems of classification arise. Requirement of higher doses up to 350 mg have been associated with secondary PH (42). Some patients who are not helped by indomethacin may respond to a COX II inhibitor (24).

SUNCT syndrome. This is now regarded as a separate, although very rare, clinical entity (41). The attacks are shorter and more frequent than both CH and PH. Typical symptoms are moderate to severe strictly unilateral pain predominantly in the distribution of the first-division trigeminal nerve, lasting from 5 to 240 seconds. Ipsilateral autonomic symptoms are most prominent during attacks and seem to be related to the severity of pain. Frequency of attacks may be as high as 200 per day. The attacks can be spontaneous or triggered by trigeminal or extratrigeminal maneuvers, such as chewing, brushing teeth, and talking. SUNCT and CH should be differentiated from first-division (V_1) trigeminal neuralgia (TN), which is characterized by brief paroxysmal, electric shock–like pains within the V_1 area, usually lasting a few seconds or less (39). The pain of TN can typically be provoked by superficial stimulation of so-called trigger zones within the distribution of V_1. Autonomic symptoms are commonly not a feature of classical TN (17) but may occur during particularly severe and long-lasting V_1 attacks in the later stages of disease (39). Autonomic features in SUNCT are, as mentioned, a prominent accompaniment to the pain (39,41). About 70 to 80% of patients with TN show an immediate, excellent response to carbamazepine. Patients with SUNCT syndrome appear, on the other hand, to be resistant to most medical and surgical treatments, at best showing a partial response only to carbamazepine (32). Recently, however, lamotrigine (4) and gabapentin (14,35) have shown rather promising results in SUNCT.

Hemicrania continua (HC) is a strictly unilateral pain that is continuous. It waxes and wanes in intensity. With more severe exacerbations, there may be accompanying ipsilateral autonomic features. These exacerbations may last from 20 minutes to several days. Patients with CH may experience a persistent background pain in between attacks. However, individuals with HC show an absolute response to therapeutic doses of indomethacin. As with PH, some patients who are not relieved by indomethacin have responded to a COX II inhibitor (34).

Hypnic headache syndrome (HHS) was first described by Raskin (37) in six elderly patients that were regularly awakened from sleep by short-lasting *diffuse* headaches, which were remarkably responsive to lithium carbonate. There are some similarities between HHS and CH: (a) attacks appear during the night, commonly with a clockwise regularity; (b) they seem to be associated with rapid eye movement (REM) sleep; (c) they are short lasting and occur on a daily basis; and (d) both CH and HHS are responsive to lithium carbonate. However, there are obvious diagnostic differences: the pain of HHS is bilateral, diffuse, and moderately severe and lacks local autonomic symptoms and signs. HHS is generally a syndrome in the elderly and is regarded as a benign, often self-limited disorder. It responds to indomethacin, flunarizine, and caffeine (10).

Secondary headaches. Pathologic conditions that secondarily give rise to symptoms akin to those of CH can be divided into two categories: those in which there may be an overlap in clinical features and those in which the typical syndrome of CH occurs in close temporal relationship with another pathology.

A number of studies have shown that there is often a significant delay in the diagnosis of CH (2,47). Patients may, in the meantime, have been seen, investigated, and treated by, for example, a dentist, an ear, nose and throat specialist, or an ophthalmologist. The location of the pain and in particular the radiation to the jaw, cheek, teeth, and ear often precipitate such referrals. However, the recurrent and stereotyped nature of CH with lack of additional local features (e.g., purulent nasal discharge in sinusitis or fixed but dilated and irregular pupil in acute glaucoma) should allow a physician to make the diagnosis with relative ease.

CH associated with intracranial pathology (symptomatic CH) has been reported for different lesions at different anatomic sites. These include pituitary tumors (15,36,44); parasellar meningioma (22); trigeminal neurinoma (27); aneurysm of the anterior communicating artery (15), posterior communicating artery (29), and vertebral artery (48); arteriovenous malformations (12,30); nasopharyngeal carcinoma at the skull base (28); or even an upper cervical meningioma (40). The occurrence of the intracranial lesion has been reported in close temporal relation to the onset of CH attacks or worsening of existing symptoms, with resolution of the attacks with treatment of the lesion. Of particular note is that some of these cases did not respond to appropriate medical treatments for CH (15,22,27,29) while others did (12,27,44). In addition, the symptoms are commonly consistent with IHS classification criteria (15,22,44), although there may be atypical features such as longer duration of attacks. If there is a short history of headache disease, a careful follow-up and proper investigations are thus to be recommended.

PROGNOSIS

Knowledge is rather sparse concerning the natural history of CH (18,19,21,25,33,38). Most of the information has been gained retrospectively and largely in patients attending specialist clinics. However, despite this, data from contacting those patients who have been lost to follow-up ("drop-outs") (21) show the same trends. In the majority of individuals, the natural course of the disease remains unchanged, although prolonged remissions may be a feature of episodic CH (19). These tend to occur in those

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individuals who have previously experienced episodic CH with a tendency toward infrequent bouts. Up to 26% of patients may only have a single CH bout (mean observation period 9 years) (43). Episodic CH may tend to worsen from year to year, but the opposite pattern may also be experienced. Late onset, especially in women (5,46), and high frequency of CH periods seem to related to a negative course, and, among others, are possible predictive factors in the evolution of episodic to chronic CH (46). However, it is also striking that "active" CH is seldom seen after the age of 75 years. The prognosis of the chronic form appears to be better than has been previously thought, changing in many patients into an episodic form (18,19,21,25).

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