Chapter 11
Headaches, Migraine, and Cluster Headache

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Introduction

Primary headaches are those that exist independent from any other medical condition. In contrast, secondary headaches are due to an underlying condition and are classified according to their cause. The primary headaches are discussed in this chapter. The International Headache Society (IHS) [1] classification breaks the primary headache disorders into four categories:

1. Tension-type headache (TTH)
2. Migraine
3. Cluster headache and other trigeminal autonomic cephalalgias
4. Other primary headaches

Tension-Type Headache

Clinical Presentation and Diagnosis

TTH is a common primary headache with tremendous socioeconomic impact. TTHs are so called because they cause a dull aching pain that people describe as a band around their heads radiating to their neck. TTHs are divided into *infrequent episodic*, *frequent episodic*, *chronic*, and *probable*. The categories are typically subdivided according to the presence or the absence of pericranial tenderness as assessed by manual palpation.

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TTH is described as a non-pulsating and a dull pain of mild-to-moderate intensity often manifesting as tightness, pressure, or soreness in a "band-like" distribution as if the patient were wearing a hat. The pain location is not specific, though it is often bilateral and may extend into suboccipital and the neck and occasionally the shoulders. Temporalis muscle involvement is most likely present, and mastication may be affected in some patients. TTH is not accompanied by nausea or vomiting, nor is it aggravated by routine physical activity, but it may be associated with sensitivity to light or noises.

The headaches may last from 30 min to 7 days. *Infrequent headaches* occur less than 1 day per month (less than 12 per year) and as *frequent* if they occur on more than 1 day per month but less than 15 days per month for at least 3 months. Chronic TTH evolves from episodic TTH and is diagnosed when headaches occur daily or more often than 15 days per month for at least 3 months. In contrast, if a new-onset daily or unremitting headache with tension-type characteristics develops, the headache is classified as *new daily persistent headache*. Sensitivity to light and/or noises and mild nausea may be present with these headaches. It may be difficult to distinguish between chronic migraine and chronic TTH, and these disorders may be present simultaneously.

Epidemiology

The diagnosis of TTH, a heterogeneous syndrome, is mainly based on the absence of typical features found in other headaches such as migraine. However TTH is the most common headache as about 80 % of the general population suffer from episodic TTHs and 3 % have chronic TTH (CTTH). In a cross-sectional population study of 740 adult subjects, 74 % had experienced TTH within the previous year, while 31 % of the same population had experienced TTH for more than 14 days during the previous year [2]. In another study, a 1-year prevalence rate for TTH in males was 63 % and in females 86 % [3]. The onset of the headaches is usually between 20 and 40 years of age.

Pathogenesis

For many years, TTH was thought to be directly related to muscle tension and was referred to as a *muscle contraction* or a *muscle tension* headache. Muscle tenderness may be present in some individuals; however, increased levels of electromyographic activity are not always associated with the condition [4]. Some studies [5] report that electromyography revealed increased activity in response to emotional stressors in patients compared with controls. It has been suggested, however, that this increase in electromyographic detected activity may not be the cause of the pain but, rather, a response to the pain. Emotional stress, anxiety, and depression seem to have causal relationships with TTHs [6].

A very controversial boundary exists between migraine and TTH. Some experts see these disorders as distinct entities, while others see them as opposite ends of a continuum, varying in severity and features but having a common pathogenesis [7]. At this time, the pathophysiology of TTH remains unclear. The latest theories include peripheral and central sensitization concepts, with a possible role for nitric oxide [8].

Treatment

Establishment of an accurate diagnosis is important before initiation of any treatment.

Simple analgesics are the mainstays for treatment of episodic TTH. Physical therapy and acupuncture are widely used, but the scientific evidence for efficacy is sparse. Nondrug management is crucial. Information, reassurance, and identification of trigger factors may be rewarding. Psychological treatments with scientific evidence for efficacy include relaxation training, EMG biofeedback, and cognitive therapy.

Patients with TTH tend to self-medicate with over-the-counter analgesics, antihistamines, caffeine, and other medications. Rarely do they consult their physician for relief unless the frequency or the severity of these headaches increases. Combination analgesics, triptans, muscle relaxants, and opioids should not be used, and it is crucial to avoid frequent and excessive use of simple analgesics to prevent the development of medication-overuse headache. The efficacy is modest, and treatment is often hampered by side effects. Thus, treatment of frequent TTHs is often difficult, and multidisciplinary treatment strategies can be useful. Since emotional stress plays an important role in TTHs, the patient should be assessed for any significant stressors; when significant stressors are identified, corrective behaviors or, when possible, avoidance should be encouraged. Stress management skills, relaxation training, and biofeedback techniques can be important therapies for TTHs [9], but patients must be willing to take time to work with these therapies. If anxiety disorder and major depression disorder are present, these conditions need to be managed by the proper health care professional.

Pharmacotherapy may be needed, but the patient should be aware of the potential complications. Nonsteroidal anti-inflammatory inhibitors are often effective. Tricyclic antidepressants, such as amitriptyline or nortriptyline, can be helpful in managing frequently occurring TTH but should be taken at bedtime because of their sedative effects.

When masticatory muscle disorders are present in association with TTHs, efforts should be first directed to treating the disorder. A nighttime occlusal appliance for nocturnal bruxism may help a headache that occurs upon awaking. During the day, the patient should practice techniques in cognitive awareness, habit reversal, and self-relaxation to reduce or eliminate tension and clenching or grinding of the teeth.

Often TTH is a heterotopic pain originating in the cervical muscles. When a cervical myofascial pain disorder is present, treatment should be oriented toward

resolving this disorder. If myofascial trigger points are the source of headache, the use of postural, stretching, and strengthening exercise programs combined with the use of a vapocoolant spray and/or trigger point injections may be effective [10].

Migraine Headaches

Migraine is a disorder of the trigeminal system. A diagnosis of *migraine* may be confirmed when certain IHS criteria are met after organic disease is excluded: (1) Patients need to have experienced at least five attacks, each lasting 4–72 h; (2) two of the following pain characteristics must be present: unilateral pain, pulsatile quality, moderate-to-severe intensity, and aggravation by routine physical activity; and (3) the attack must be accompanied by nausea (and/or vomiting) or photophobia and phonophobia.

Migraines may occur *with* or *without aura*. *Aura* is the presence of reversible focal neurologic symptoms that gradually develop over 5–20 min and last for no more than 1 h and a simultaneous reduction in regional cerebral blood flow. Aura may also occur in the absence of a typical migraine headache. Patients may experience premonitory symptoms hours to a day or two before a migraine attack (with aura or without aura). These include various combinations of fatigue, difficulty concentrating, neck stiffness, sensitivity to light or sound, nausea, blurred vision, yawning, and pallor. If migraine occurs on more than 15 days per month for at least 3 months in the absence of medication overuse, the migraine is called *chronic*. Chronic migraine typically evolves from episodic migraine over months to years in susceptible individuals. Headaches increase in frequency over time, becoming less intense but more disabling and less responsive to treatment. If migraine headaches last for more than 3 days, it is called *status migrainosus*. Serious complications of migraines are rare and include migrainous stroke, aura, or migraine-triggered seizures and persistent aura [11].

Epidemiology

Estimates of migraine prevalence vary, ranging from 4 % to about 20 % [12–16]. Before puberty onset, migraine is slightly more common in boys, with the highest incidence between 6 and 10 years of age. In females, the incidence is highest between 14 and 19 years of age. In general, females are more commonly affected than males. The prevalence of migraine in the United States is 17–18 % for women and 6 % for men [15–20].

Migraine prevalence is inversely proportional to income, with the low-income group having the highest prevalence. Race and geographic region are also influential factors; the prevalence is highest in North America and Western Europe and among those of European descent [16]. Because the condition usually affects people

during their most productive years, migraine is a burden to the patient and society. Not only does migraine affect the patient's quality of life by impairing his or her ability to participate in family, social, and recreational activities, but it also affects society in terms of direct costs (e.g., medical care) and indirect costs (e.g., absenteeism and reduced effectiveness at work).

Pathogenesis

Many mechanisms and theories explaining the causes of migraine have been proposed, although the full picture is still elusive. A strong familial association and the early onset of the disorder suggest a genetic component, which has led some to question whether it is a channelopathy. The trigeminal vascular model by Moskowitz [18] explains that trigeminal activation resulting in the release of neuropeptides produces neurogenic inflammation, increased vascular permeability, and dilation of blood vessels. Other pathophysiologic mechanisms behind migraine have been proposed, such as serotonin, calcitonin gene-related peptide, nitric oxide, dopamine, norepinephrine, glutamate, and other substances [19, 20] as well as mitochondrial [21] dysfunction. It has recently been recognized that central sensitization producing allodynia and hyperalgesia is an important clinical manifestation of migraine [22].

Treatment

Pharmacologic treatment of migraine may be abortive/symptomatic or prophylactic. Patients who experience frequent severe migraines often require both approaches. The choice of treatment should be guided by the frequency of the attacks. Infrequent attacks (two or fewer per week) may be treated with abortive medications [23], and more frequent attacks should be treated with prophylactic medications. If there is a concurrent illness, a single agent should be used to treat both when possible, and agents that might aggravate a comorbid illness should be avoided. Nonpharmacologic methods such as biofeedback, relaxation techniques, acupuncture, and other behavioral interventions can be used as adjunctive therapy [24]. Patient preferences should also be considered.

Several medications have been used for acute migraine treatment, including selective 5-$HT_{1B/D}$ (serotonin) agonists, analgesics, nonsteroidal anti-inflammatory drugs, antiemetics, anxiolytics, ergot alkaloids, steroids, neuroleptics, and narcotics. Drugs with proven statistical and clinical benefit according to the American Academy of Neurology should be given as first-line treatment [23].

When migraine becomes more frequent and the use of acute medications exceeds two to three times per week, preventive medications are used. Preventive treatments include a broad range of medications, most notably antidepressants,

anticonvulsants, and beta-blockers [23]. Serotonin antagonists [24, 25], nonsteroidal anti-inflammatory drugs, and calcium channel blockers appear to be less effective [26]. These medications are started at low doses and titrated to the desired effect to minimize the side effects and arrive at the minimal dose needed. In more refractory cases, polypharmacy may be necessary. Botulinum toxin type A is an alternative that continues to be studied [27, 28].

Patients can help themselves, too, by learning to identify and avoid headache triggers. Important triggers are environmental factors, including light, noise, allergens, and barometric changes; behavioral factors, such as missing meals or getting too much or too little sleep; and food/beverage items, such as cured meats, cheese, chocolate, and those containing aspartame, monosodium glutamate, and nitrites.

Cluster Headache

Clinical Presentation and Diagnosis

Cluster headaches are typically side fixed, remaining on the same side of the head for the patient's lifetime. This headache is a throbbing, sharp, or boring pain of severe intensity usually localized to the orbital, supraorbital, and/or temporal region. Only 15 % of patients will experience a side shift between cluster periods. To confirm the diagnosis, patients should have experienced at least five attacks of severe, unilateral, pain lasting from 15 to 180 min if left untreated [1]. The headache also needs to be associated with at least one of the following signs or symptoms: lacrimation, conjunctival injection, rhinorrhea, nasal congestion, forehead and facial sweating, miosis, ptosis, or eyelid edema.

Patients cannot and do not want to remain still during a cluster headache. They typically pace the floor or even bang their heads against the wall to try to alleviate the pain. Cluster headaches are short in duration compared with some of the other primary headache disorders, usually lasting an average of 45 min to 1 h, and patients will frequently have between one and three attacks per day. The headaches have a predilection for the first REM sleep phase, so the patient will awaken with a severe headache 60–90 min after falling asleep. This is an important distinguishing characteristic, as very few other pain problems are known to wake a person from sleep.

Cluster headaches can be of an *episodic* (greater than 1 month of headache-free days per year) or a *chronic* (occurring for more than 1 year without remission or with remissions lasting less than 1 month) subtype. Between 80 and 90 % of cluster patients have the episodic variety. Cluster periods, or the time when patients are experiencing daily cluster headache attacks, usually last between 2 and 12 weeks, and patients can have 1–2 cluster periods per year. It is common for a patient to experience a cluster period at the same time each year. This circadian periodicity suggests a hypothalamic generator for cluster headaches [29].

Epidemiology

Cluster headache was thought to affect primarily men; however, more recent studies have determined the ratio of men to women to be approximately 4:1 [30, 31]. Prevalence estimates vary between 0.09 and 0.32 % [32, 33].

Pathogenesis

The three defining aspects of cluster headache are the trigeminal distribution, periodicity of attacks, and one sided, but the primary mechanism associated with cluster headache is unknown; it is believed to be central. The rhythmic periodicity and the predilection for attacks to occur during sleep have implicated circadian and circannual rhythms, which indicate hypothalamic involvement [29, 34].

Studies have shown a close relationship between cluster headaches and sleep-disordered breathing and sleep apnea [35, 36]. This factor may explain the positive response of cluster headaches to oxygen as well as the relationship between cluster headaches and altitude and sleep apnea [37].

Treatment

The treatment of cluster headache is essentially pharmacologic, with the goal of shortening and alleviating the cluster headache attacks and shortening the cycle of attacks; therefore, like migraine therapy, it can be divided into symptomatic/abortive and prophylactic regimens. Due to the nature of cluster headaches, symptomatic treatment is rapid acting. Agents used are oxygen, serotonin receptor agonists (triptans), and dihydroergotamine. Individual attacks will usually respond to oxygen delivered at 7 L per minute for approximately 15 min. Due to the frequency of headaches, the use of ergotamine preparations is largely limited because of the hypertensive effects of the ergot alkaloid. Also, because of the rapid onset of pain and relatively short duration, oral narcotic analgesics should be limited.

Prophylactic therapies should be initiated as soon as the cycle begins. Verapamil may be used as first-line treatment [38, 40]. Corticosteroids are also very effective but should be used only as initiation therapy for a short period of time [42]. Others, such as lithium carbonate, Divalproex Sodium, and Topiramate, have shown superiority over placebo in several trials [39, 42]. There is insufficient evidence for the use of gabapentin at this time. More controlled trials are needed to establish the appropriate protocol for prophylactic treatment of cluster headaches. The preventive medications are usually continued for 1 month after the last cluster attack and then discontinued until the next cycle begins.

Limited information from small case series is available and indicates varying degrees of success on surgical intervention to treat cluster headaches. The procedures included sphenopalatine ganglion blockade [41, 42], trigeminal rhizotomy [41, 42], microvascular decompression of the trigeminal nerve [42], and gamma

knife radiation [43]. More recently, occipital nerve stimulation and deep brain stimulation of the hypothalamic area in patients with intractable chronic cluster headaches have been studied [43–46], and these small case series have yielded promising results. Surgical interventions are reserved for extreme unremitting cases of cluster headache when all medications have failed to provide relief.

Paroxysmal Hemicrania

Paroxysmal hemicrania is a headache with clinical characteristics similar to those of cluster headache, but the headache attacks are shorter lasting (2–30 min), more frequent, and occur more commonly in women [1]. The attacks are also strictly unilateral, predominantly in the periorbital region. The diagnosis is confirmed when the headache is accompanied by at least one of the following signs or symptoms: lacrimation, conjunctival injection, rhinorrhea, nasal congestion, forehead and facial sweating, miosis, ptosis, and eyelid edema. Attacks occurring in periods lasting 7 days to 1 year separated by pain-free periods lasting 1 month or more are classified as *episodic*, and attacks occurring for more than 1 year without remission or with remissions lasting less than 1 month are classified as *chronic*. Unlike with cluster headache, very little is known about the pathophysiologic mechanisms behind paroxysmal hemicrania, but it is thought that disturbances in the hypothalamus play a central role in this entity as well [47].

The disorder is peculiar in that it is 100 % responsive to indomethacin [46–48]. Contrasting reports are available about the efficacy of sumatriptan [49–51]. Topiramate appears to be promising [52].

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